AZAXYLYLENES AND THEIR HETEROCYCLIC ANALOGUES

by

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To Loraine and Rebecca

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ABSTRACT

This study is mainly concerned with the generation and chemistry of o-azaxylylenes. The thesis is, therefore, introduced by a review of the extensively studied o-xylylenes and their hetero-analogues.

Benzazetidines should be ideal precursors to o-azaxylylenes but no general route to these heterocycles is available. The reaction of benzyne with imines and amidines was, therefore, investigated and was shown to proceed through unstable benzazetidines but not to be a synthetically useful route to these compounds.

Flash vacuum pyrolysis of 2-N-tert-butoxycarbonyl-benzyl alcohols produced from tert-butoxycarbonylaniline by dilithiation and reaction with an aldehyde has been developed as a route to C-substituted o-azaxylylenes. Where the C-substituent is phenyl or thienyl, electro-cyclisation occurs to give acridine or thienoquinoline. With a pentenyl or hexenyl substituent intramolecular Diels-Alder reactions are observed. This work was extended to produce the first examples of pyridine, pyrazine, and thiophene based azaxylylenes which show similar reactions. The tert-butoxycarbonyl amino alcohols were compared with amino alcohols and dihydrobenzoxazinones as azaxylylene precursors and their relative merits evaluated. A clear picture has emerged as to the requirements for successful application of o-azaxylylenes in organic synthesis.

The generation of N-diarylazirinylazaxylylenes led to dihydroquindolines via N-indolylazaxylylenes, and 2-arylindoles possibly via 5H-1,3 or 1,4-benzodiazepines. A mechanistic investigation of this last reaction led to a new route to indoles by flash vacuum pyrolysis of 2-alkylbenzimidoyl chlorides and 2-alkylbenzamidines.

CONTENTS

INTRODUCTION

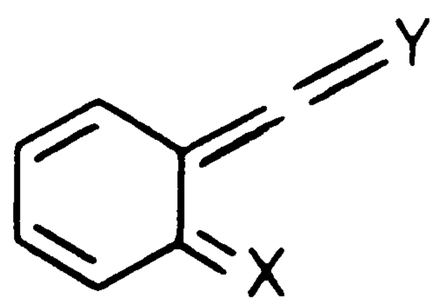
1. o-XYLYLENES AND RELATED SYSTEMS

(I) (II)

The o-xylylene system (I, X = CR^1R^2) has been extensively studied and has found wide application in the field of organic synthesis. This system is, in fact, just one member of a general class of o-quinonoid species which includes the o-thioquinone methides (I, X = S), the o-azaxylylenes (I, X = NR), and the o-quinone methides (I, X = O). Formally, all three systems can be regarded as the ring opened valence tautomers of the corresponding bicyclic structures (II).

The aim of the following review is to outline briefly the main trends in relative stability of the systems (I) and (II) for the series X = CR^1R^2, NR, S and O, and to survey the known methods of generation of the reactive quinonoid species (I). A comparative account of the reactions of these species is presented and their widespread application in organic synthesis, especially of natural products, is discussed from the point of view of the synthetic targets.

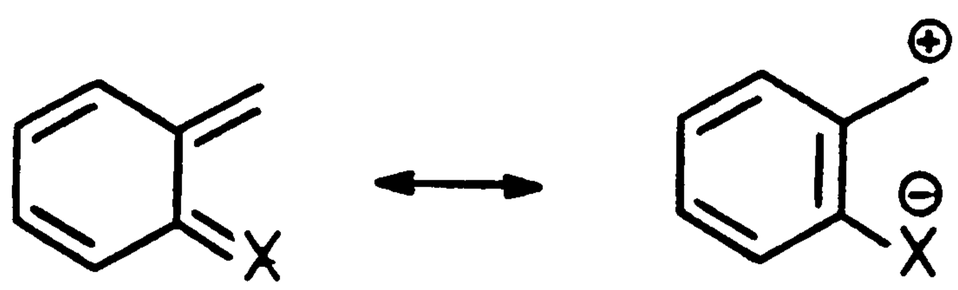
Throughout this review, o-quinonoid systems of type (III) which contains a cumulene moiety have been included where appropriate, as often, their methods of generation and their chemistry tend to parallel those of the non-cumulated systems (I).



(III)

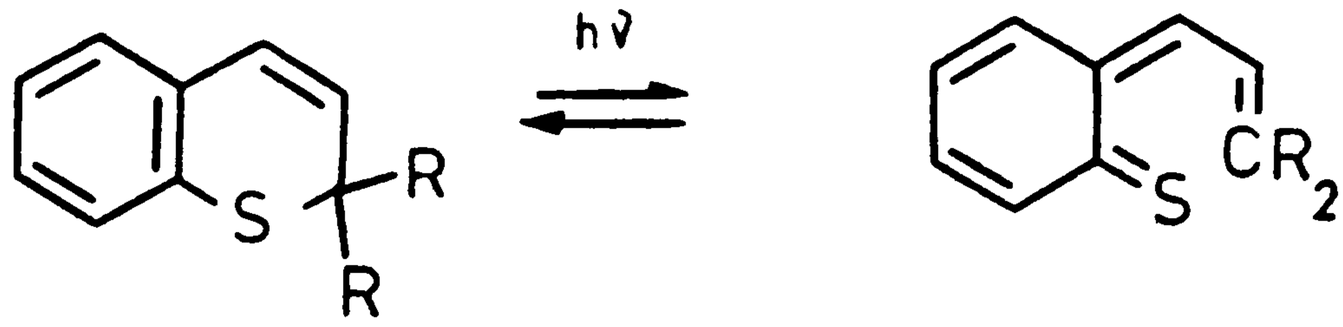
1.1 TRENDS IN STABILITY FOR o-QUINONOID SPECIES

Calculations by Kolshorn and Meier[1] suggest that the ring open form (I) is always more stable than the ring closed form (II) and that this energy difference increases as the electronegativity of X increases. Whilst it is likely that the open form (I) is more stable for highly polarised systems, for example X = O or CR^1R^2 bearing donor and acceptor substituents at either end of the diene, it is clearly not the case for unpolarised systems such as the parent o-xylylene (I, X = CH_2). In this case, experimental evidence[2] indicates that benzocyclobutene (II, X = CH_2) is 10.5 $Kcal.mol^{-1}$ more stable than o-xylylene. In addition, we can predict that the relative stability of the o-quinonoid systems (I) should increase as we traverse the series from (I, X = CR^1R^2) to (I, X = O), due to the increasing importance of the zwitterionic canonical form (Ia).

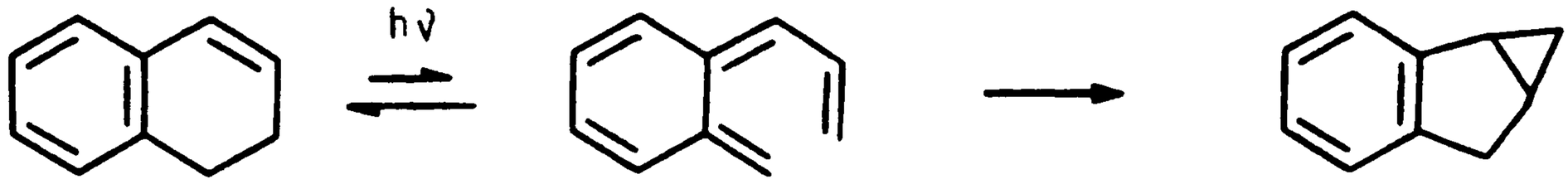


(I) (Ia)

A number of experimental facts seem to support this prediction. For example, irradiation of 2H-thiochromene (1) at -135° gives rise to a blue green colouration which is postulated to result from the presence of o-thioquinone methide (2).[3] In contrast, photolysis of dihydronaphthalene (3) at -196° did not give a measurable amount of o-xylylene

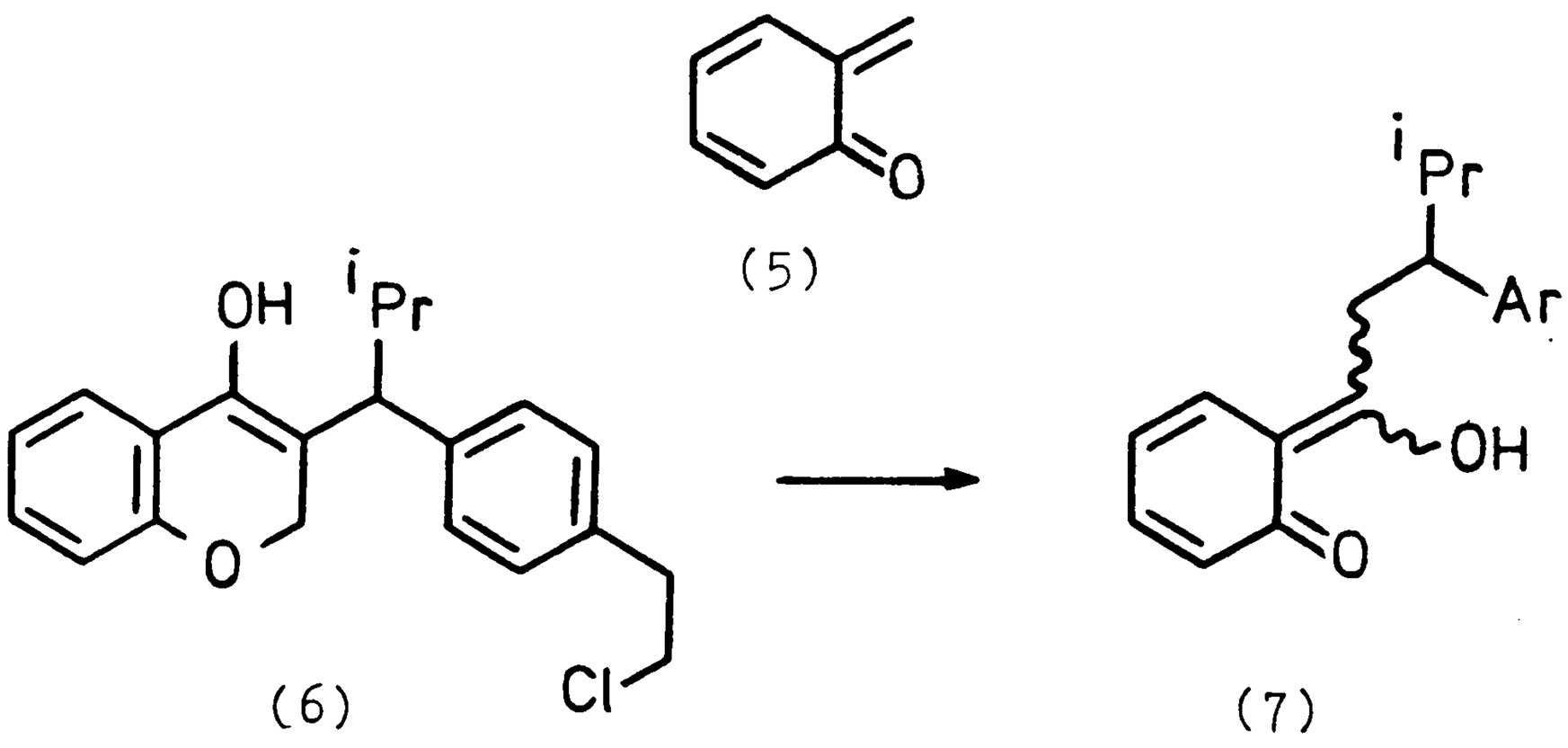


(1) (2)



(3) (4)

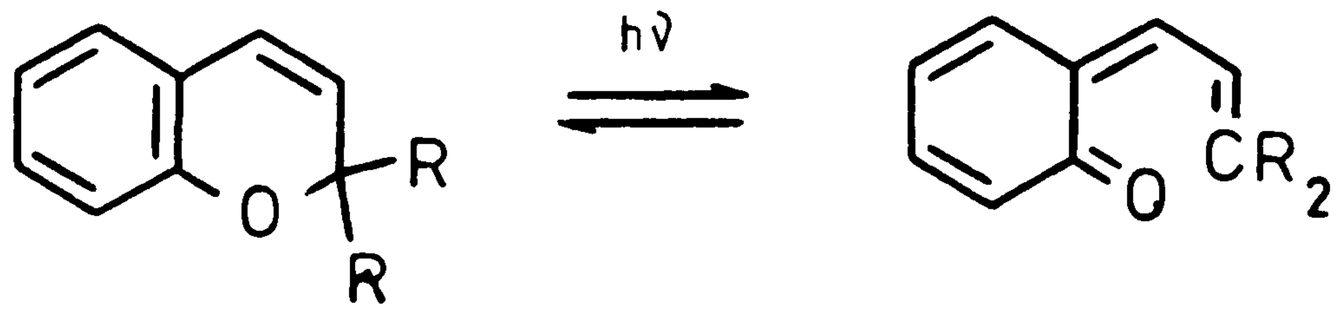
(4), although the formation of the observed product suggests its intermediacy.[4] This photochromic behaviour provides an indication of the relative stability of the o-thioquinone system compared to that of the o-xylylene system. This trend is even more apparent if we consider the most electro-negative member of the series, the o-quinone methide system. Whilst simple o-quinone methides such as the parent (5) are highly reactive and dimerise or trimerise below 0°C, many stable derivatives are known. For instance the stable o-quinone methides (7, E and Z) are formed from the *in vitro* metabolism of the anticoagulant compound clocoumarol (6) by rat liver microsomes.[5]



(5)

(6) (7)

By analogy with the 2H-thiochromene system (1), the 2H-benzopyrans (8) also exhibit photochromic behaviour with the coloured photoproduct being o-quinone methide (9).[6,7,8] This system has also been postulated as an intermediate in the biosynthesis of 2,2-dimethylchromene (9, R = Me).[9]



(8) (9)

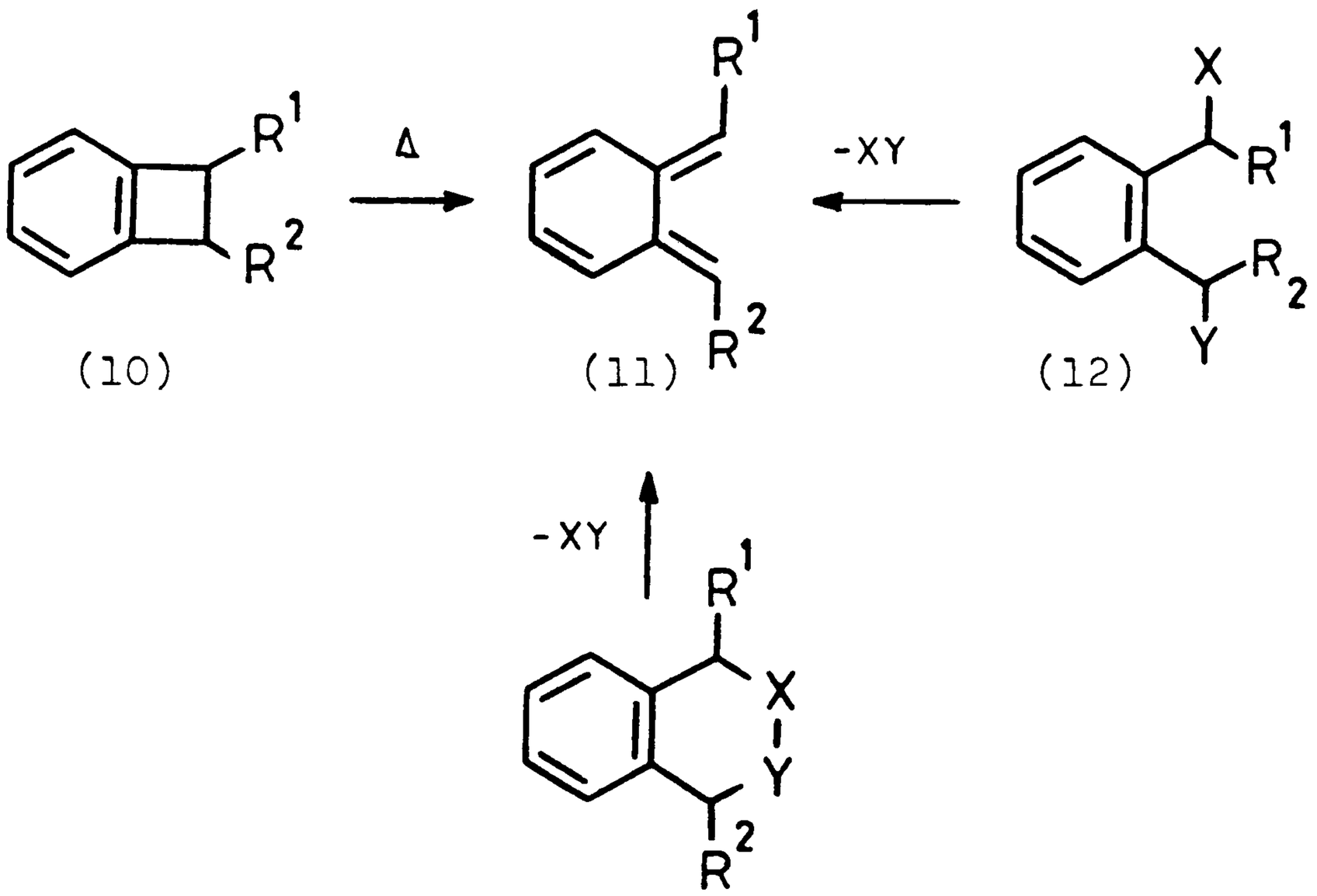
Because of this trend of increasing stability of the ring open form (I) over the ring closed form (II) as we traverse the series in order of increasing electro-negativity, we find that the number of reports of the isolation of the ring closed species (II) decreases rapidly across the same series. Thus, in the all carbon system (II), X = CR^1R^2) there are a large number of benzocyclo-butenes known, the majority of which result from the ring closure of an o-xylylene, and their chemistry has been well studied (Section 1.1(a)). Although benzothietes (II, X = S) are thermodynamically stable, they are much less well known, but again, the majority appear to originate from ring closure of o-thioquinone methides. Moving to the nitrogen analogues, there are few benzazetidines known, and only two of these appear to arise from ring closure of o-azaxylylenes (see Section 1.5(c)). For the case of oxygen, there are no reports of the isolation

of the benzoxete system (II, X = O), and only one report concerning the spectroscopic observation of a photolytic ring closure reaction of an o-quinone methide to a benzoxete at low temperature (Section 1.2(d)).

1.2 GENERATION

(a) o-XYLYLENES

The most widely used methods for the generation of o-xylylenes are summarized below (Scheme 1). As we



SCHEME 1

shall see later, most of these methods may be extrapolated to the generation of other o-quinonoid systems, and they are therefore examined here in detail.

The most general method for the generation of o-xylylenes (11) is thermal ring opening of benzocyclobutenes (10). These important starting materials can be synthesized in a

variety of ways. For example by:-

(a) The base induced cyclisation of o-chlorodihydocinnamonitriles[11].

(b) The ring closure of 1-bromo-2-(2-bromophenyl)-ethane.[12]

(c) The cobalt catalysed co-oligomerization of acetylenes.[13]

(d) Oxidation of N-aminodihydroisoindoles[14], or

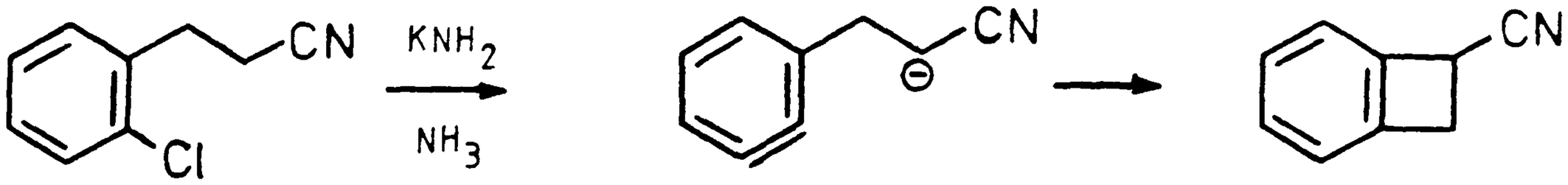
(e) Treatment of the derived sulphonamides with base.[15]

(f) Wolff rearrangement of α-diazoindanones[16]

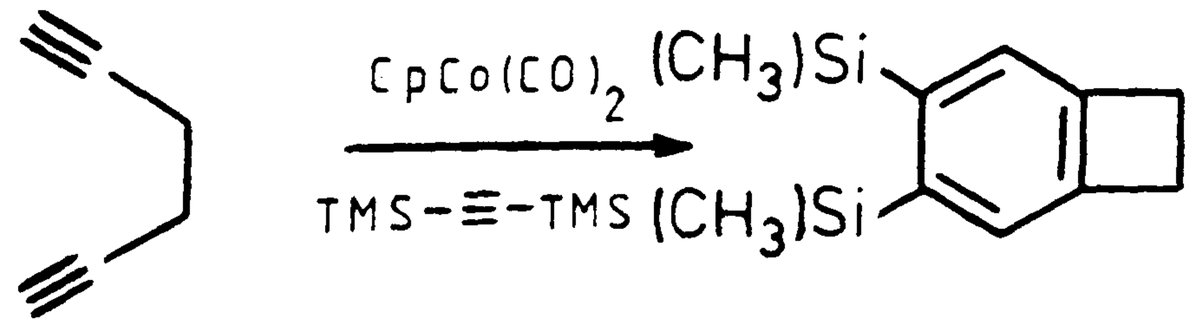
(g) Photoenolization.[17]

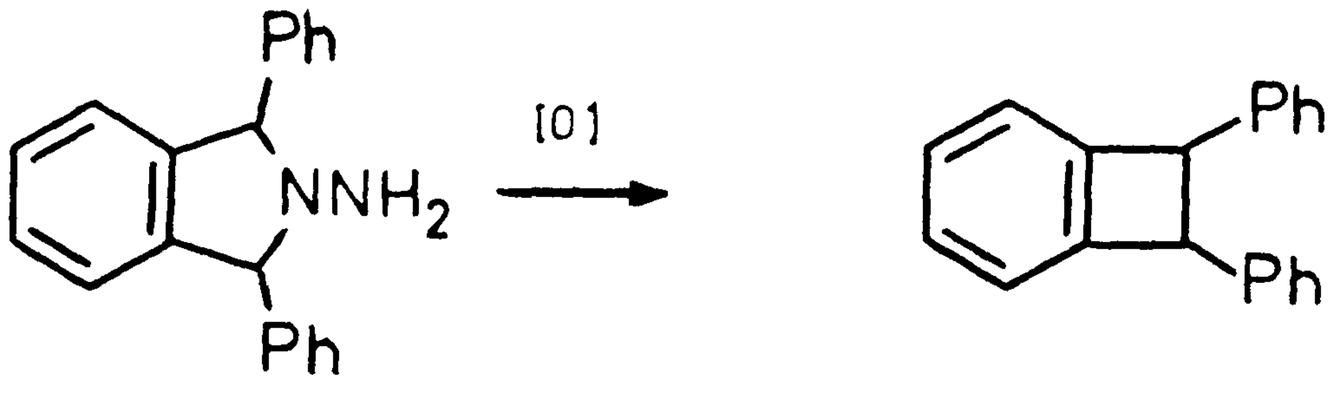
(h) Cycloaddition of benzyne to activated olefins[18] (Scheme 2).

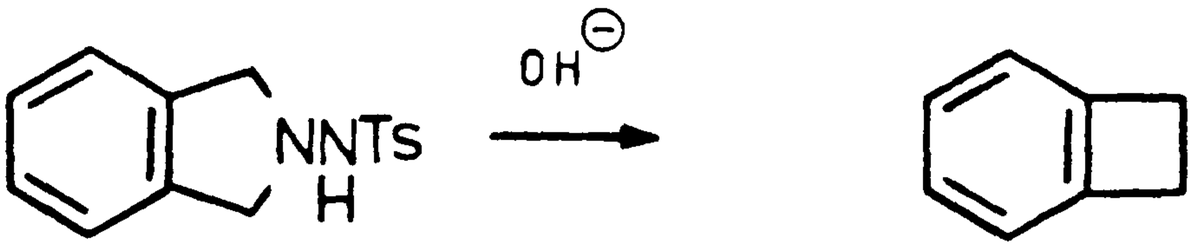
The ease of opening of the benzocyclobutene is dependent on the nature of the substituents present in the four-membered ring as illustrated in Table 1[19]. A small number of heterocyclic-fused cyclobutene derivatives have been reported. For example, cyclobutapyridines (15) and (16) were made by the flash-vacuum pyrolysis of propyl ether (14).[20] This reaction is analogous to the earlier reported synthesis of benzocyclobutenes by FVP of the phenyl substituted propargyl ether.[21] The quinoline system (17) is readily available from base catalysed condensation of o-amino benzaldehyde with cyclobutanone.[22] In addition, cyclobuta[c]thiophene (19) has been obtained in low yield from reaction of the bis-ylide (18) with cyclobutane-1,2-dione.[23]

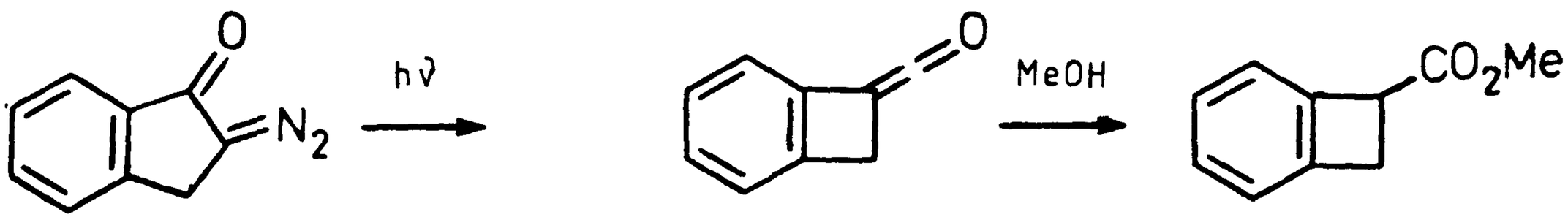
(a) 

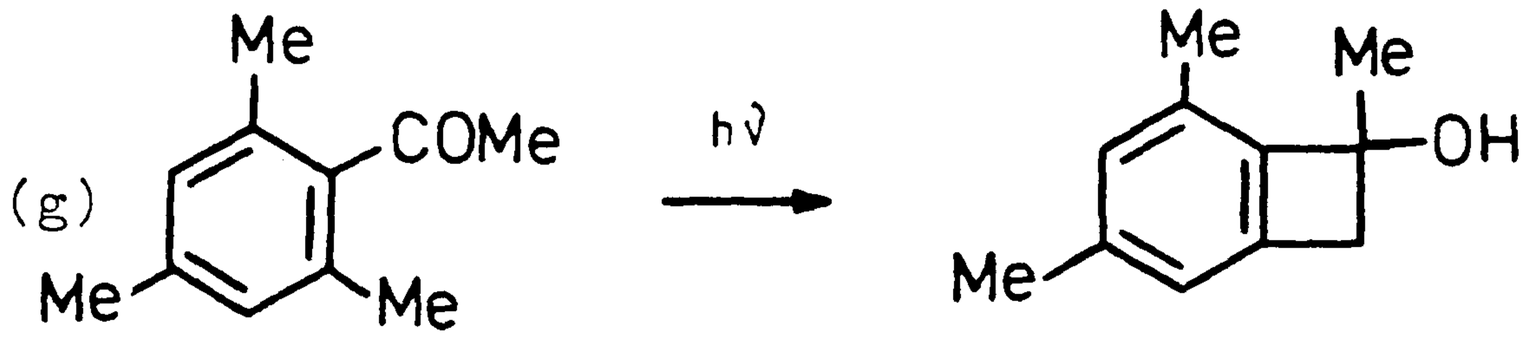
(b) 

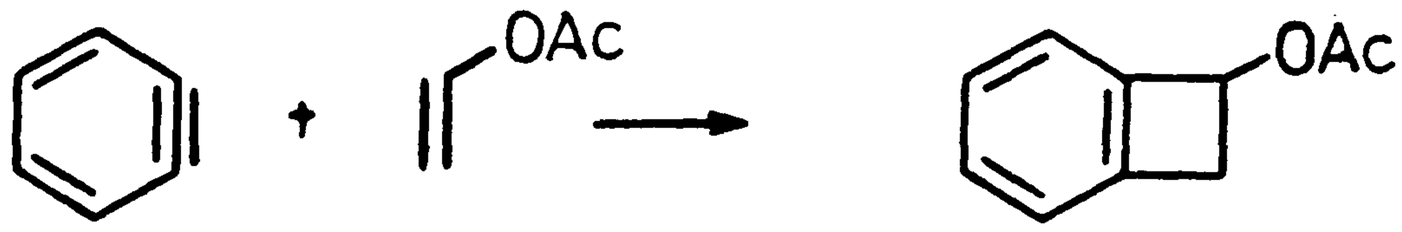
(c) 

(d) 

(e) 

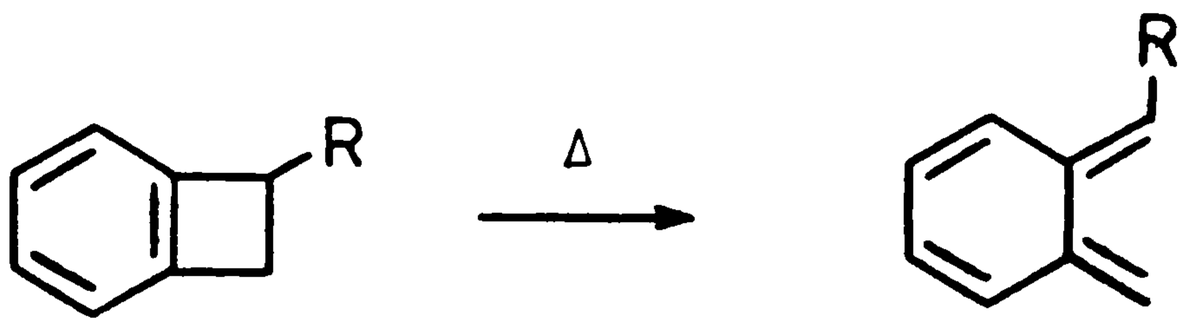
(f) 

(g) 

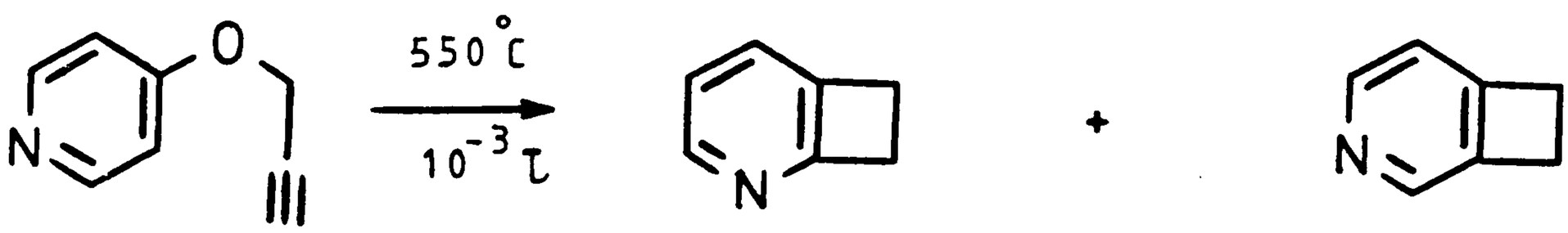
(h) 

SCHEME 2

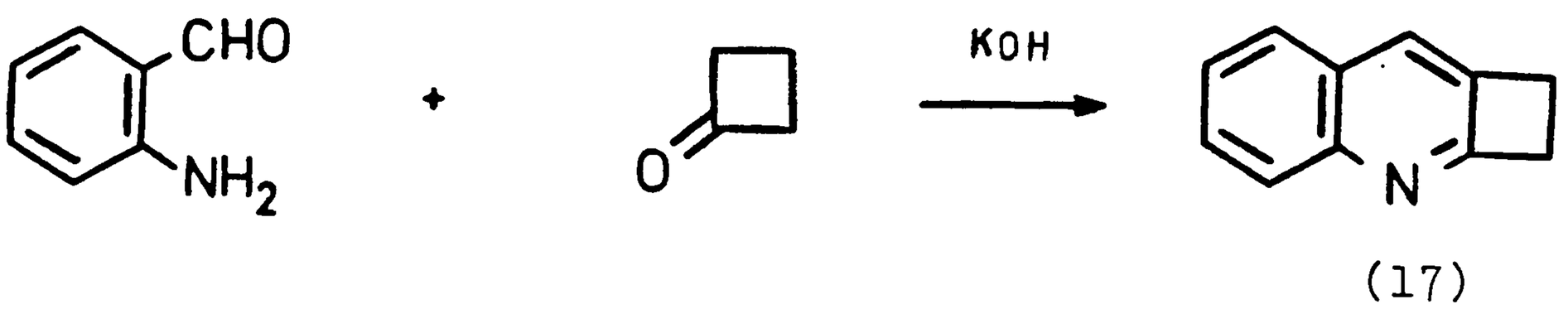
TABLE 1 Minimum temperature of ring opening of substituted benzocyclobutenes.



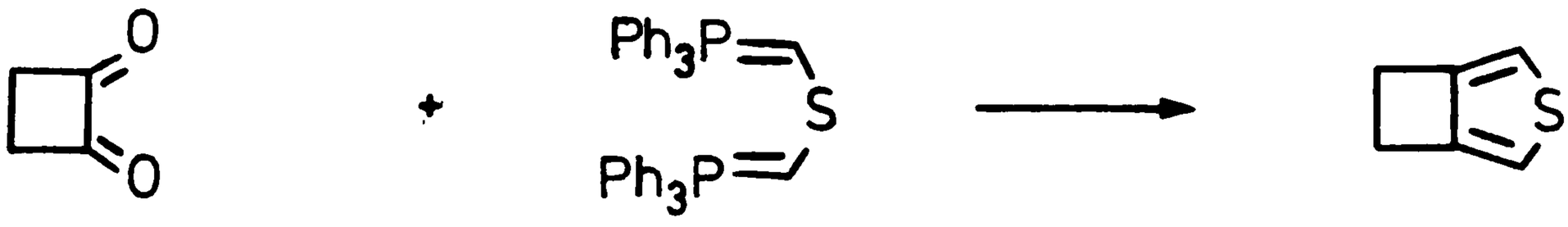
SUBSTITUENT R	TEMPERATURE (°C)
NH_2	25
OH	80
$NHCOR^1$	110
$\overset{O}{\overset{\|\|}{C}}R^1$	150
CH_2R^1	180
H	200



(14) (15) (16)



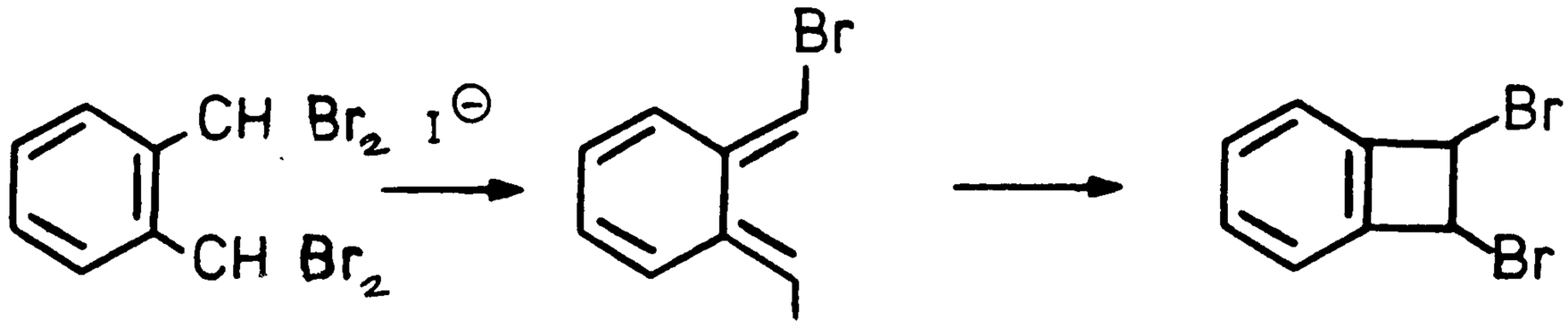
(17)



(18) (19)

No reports concerning the thermal ring opening of these systems to the corresponding o-xylylene species have appeared.

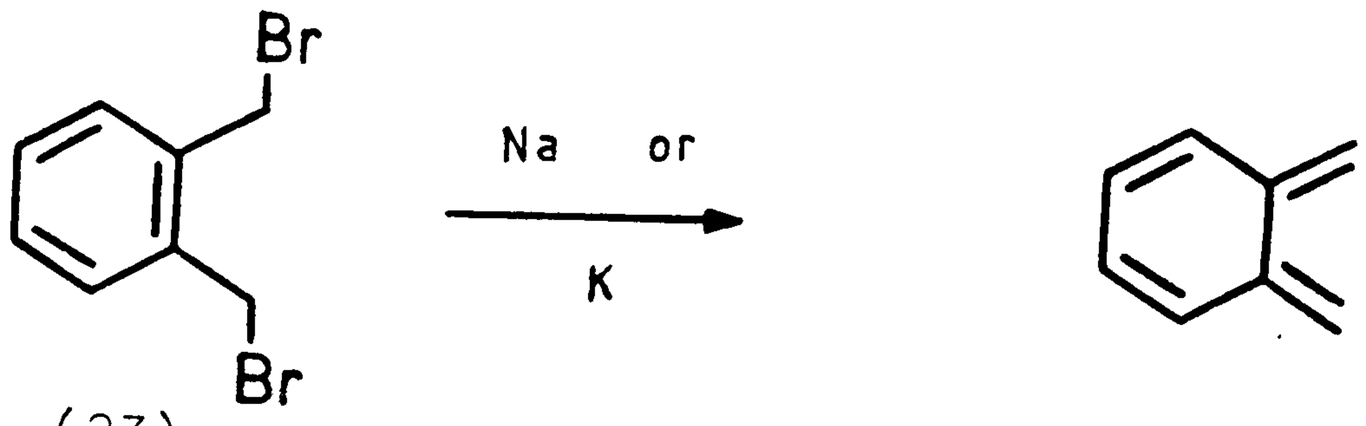
Another widely used method for the generation of o-xylylenes is 1,4-elimination of a fragment XY from a molecule of type (12) (Scheme 1). In fact, this approach was used in the earliest generation of an o-xylylene. Thus, in 1910 Finkelstein synthesised (22) by debromination of (20), a reaction shown later by Cava to involve the intermediacy of o-xylylene (21).[25]



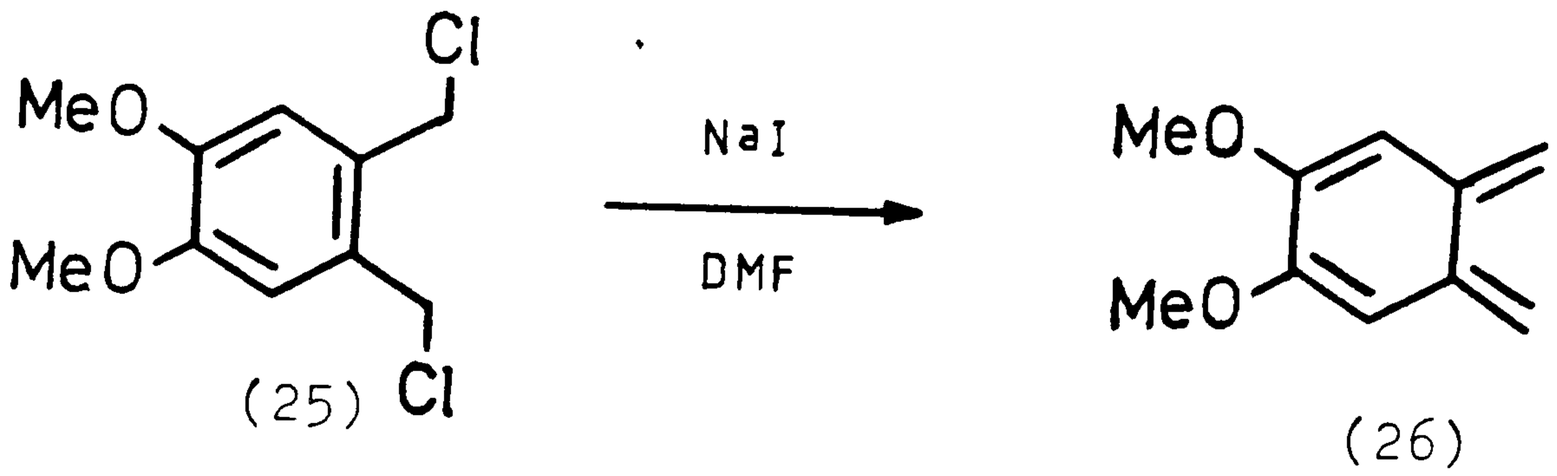
(20) (21) (22)

A similar dehalogenation route has been used to produce o-xylylenes (24),[26] (26),[27] and (28)[27] from bromides (23), (25) and (27) respectively, and has been extended to the formation of indole-2,3-quinodimethane (30) from the dibromide (29).[28]

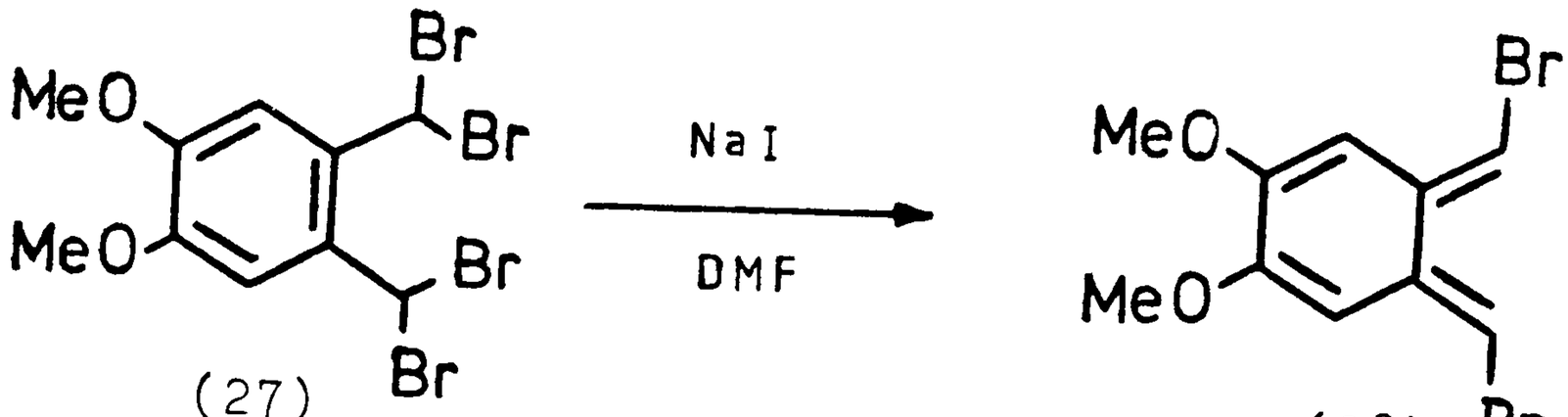
Dehydrohalogenation reactions (usually at elevated temperatures) have also been used to generate o-xylylenes. Thus, flash-vacuum pyrolysis of dichloride (31) yields o-xylylene (32) which ring closes to chlorobenzocyclobutene (33).[29] Similarly, thermolysis of trichloride (34) gives dichloride (36) via ring closure of o-xylylene (35)[30] (see Section 1.4(a)).



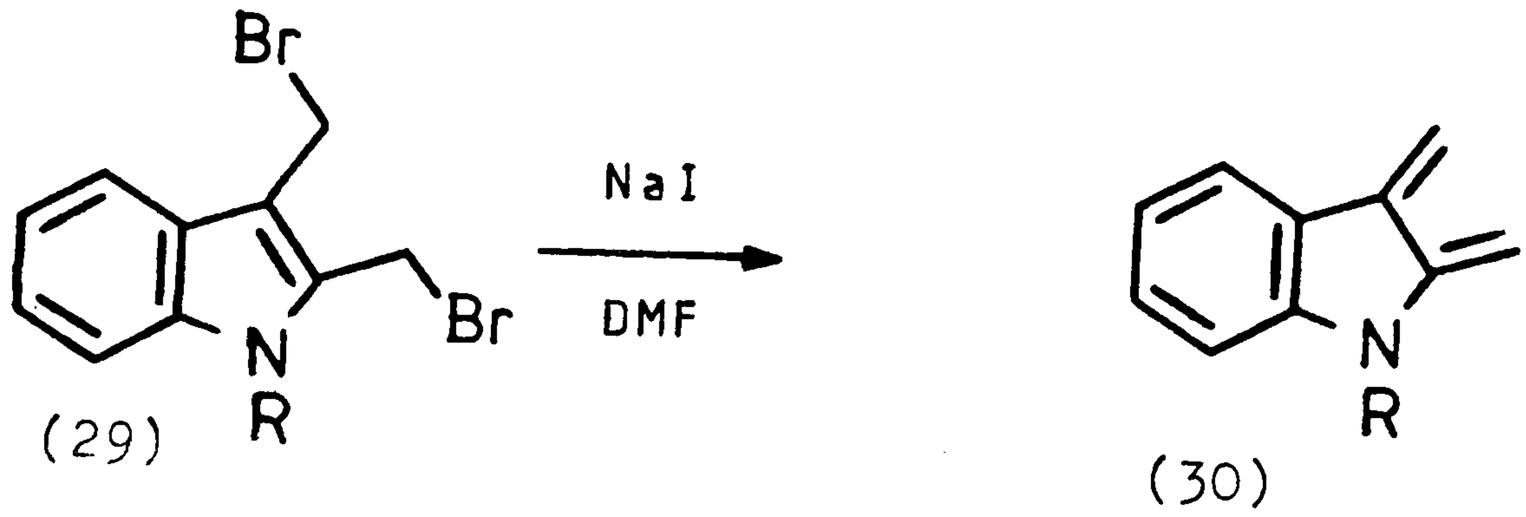
(23) (24)



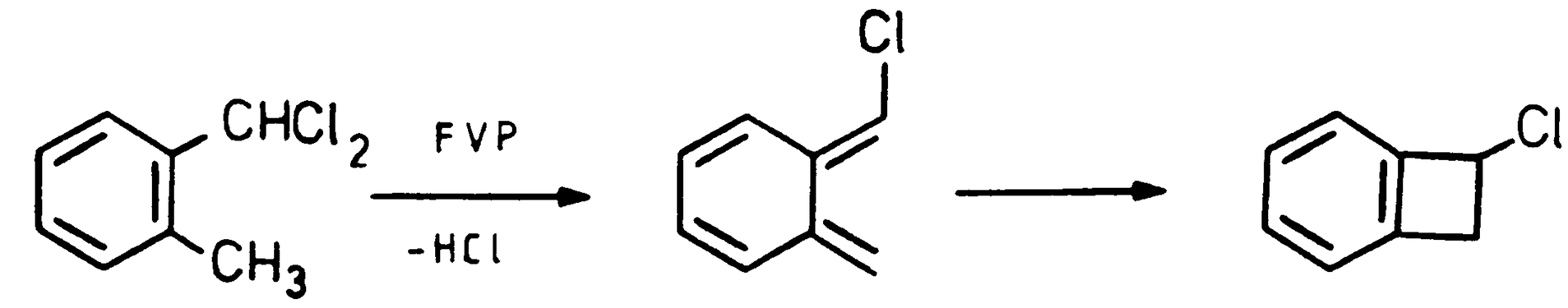
(25) (26)



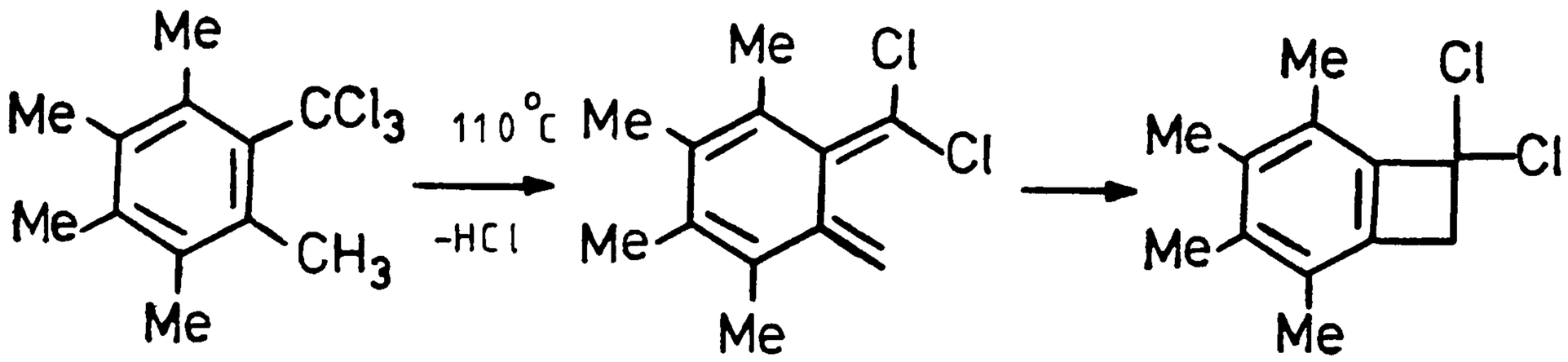
(27) (28)



(29) R (30) R

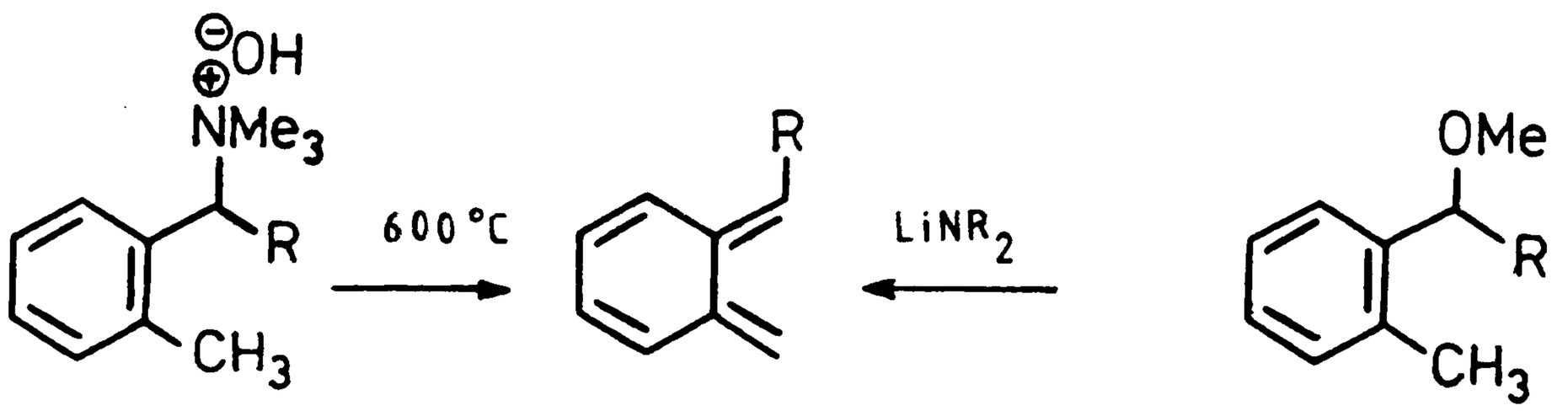


(31) (32) (33)



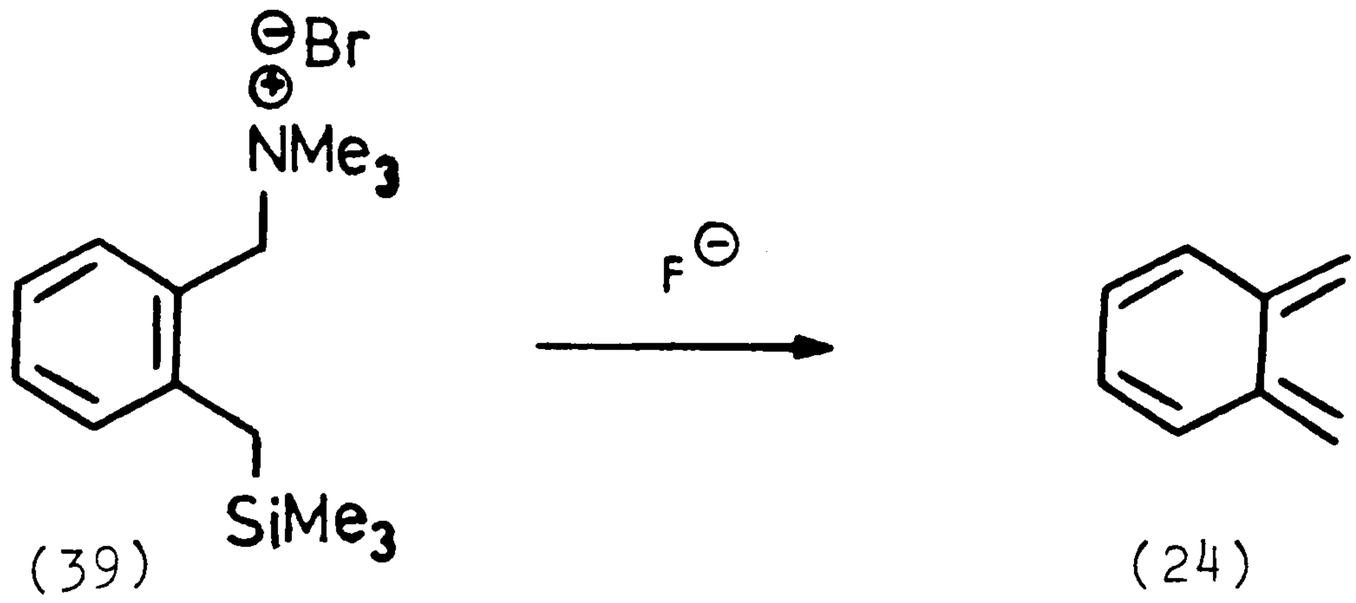
(34) (35) (36)

Other 1,4-eliminations include thermal elimination of trimethylamine and water from ammonium salt (37, R = H)[31] and base induced loss of methanol from ether (38, R = H)[32] to generate the parent o-xylylene (24, R = H) and from the acetal (38, R = OMe) to give the methoxy o-xylyene (24, R = OMe).[33]

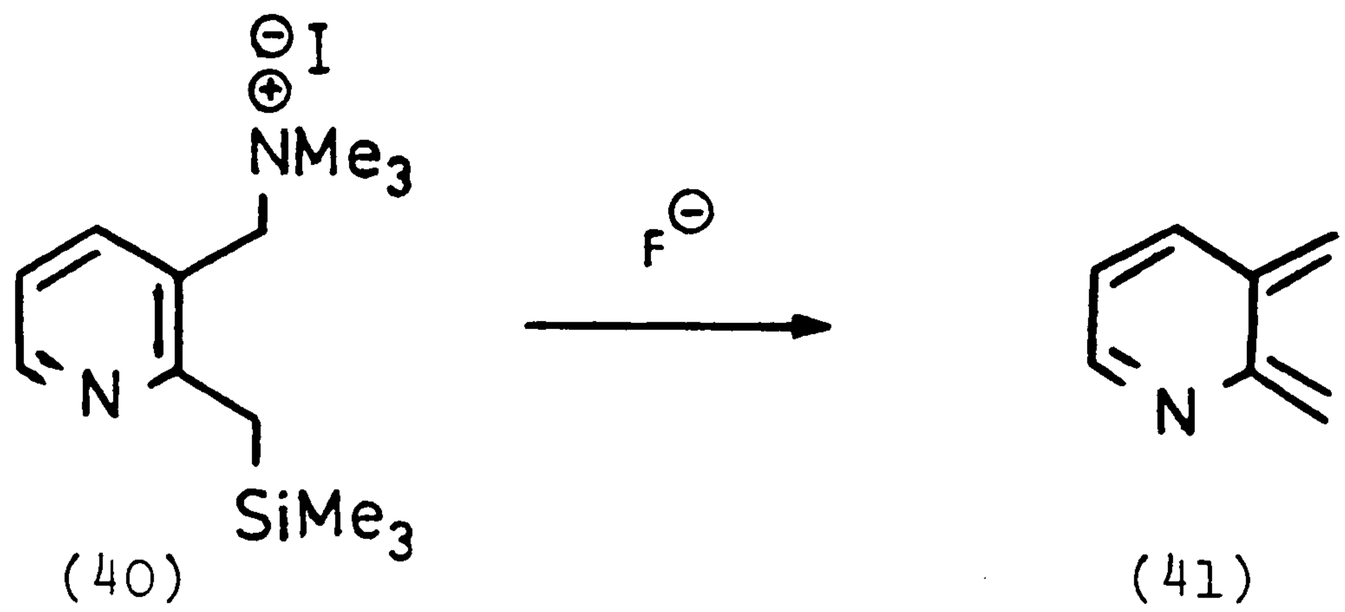


(37) (24) (38)

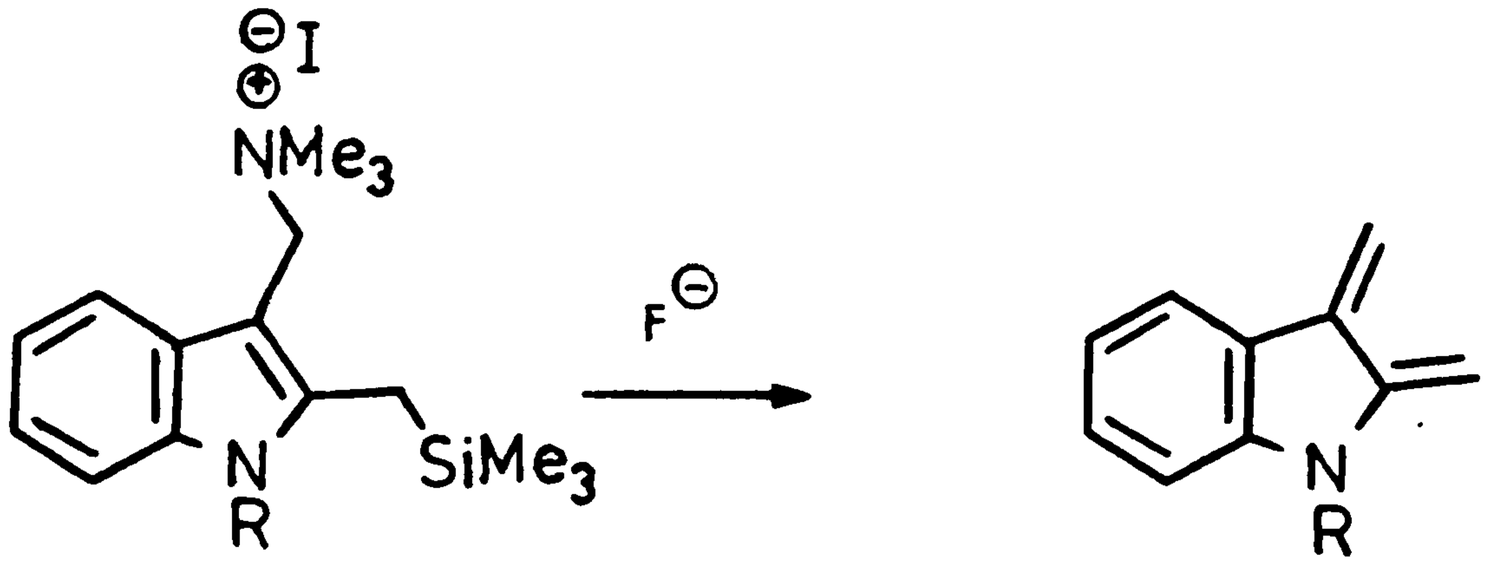
Recently, Saegusa and his co-workers have developed an elegant method for the generation of o-xylylenes based on the fluoride induced desilyation and loss of trimethylamine from ammonium salt (39). This approach was also extended to the generation of pyridine-2,3-quinodimethane (41) and indole-2,3-quinodimethane (43) from salts (40)[34] and (42)[35] respectively.



(39) (24)

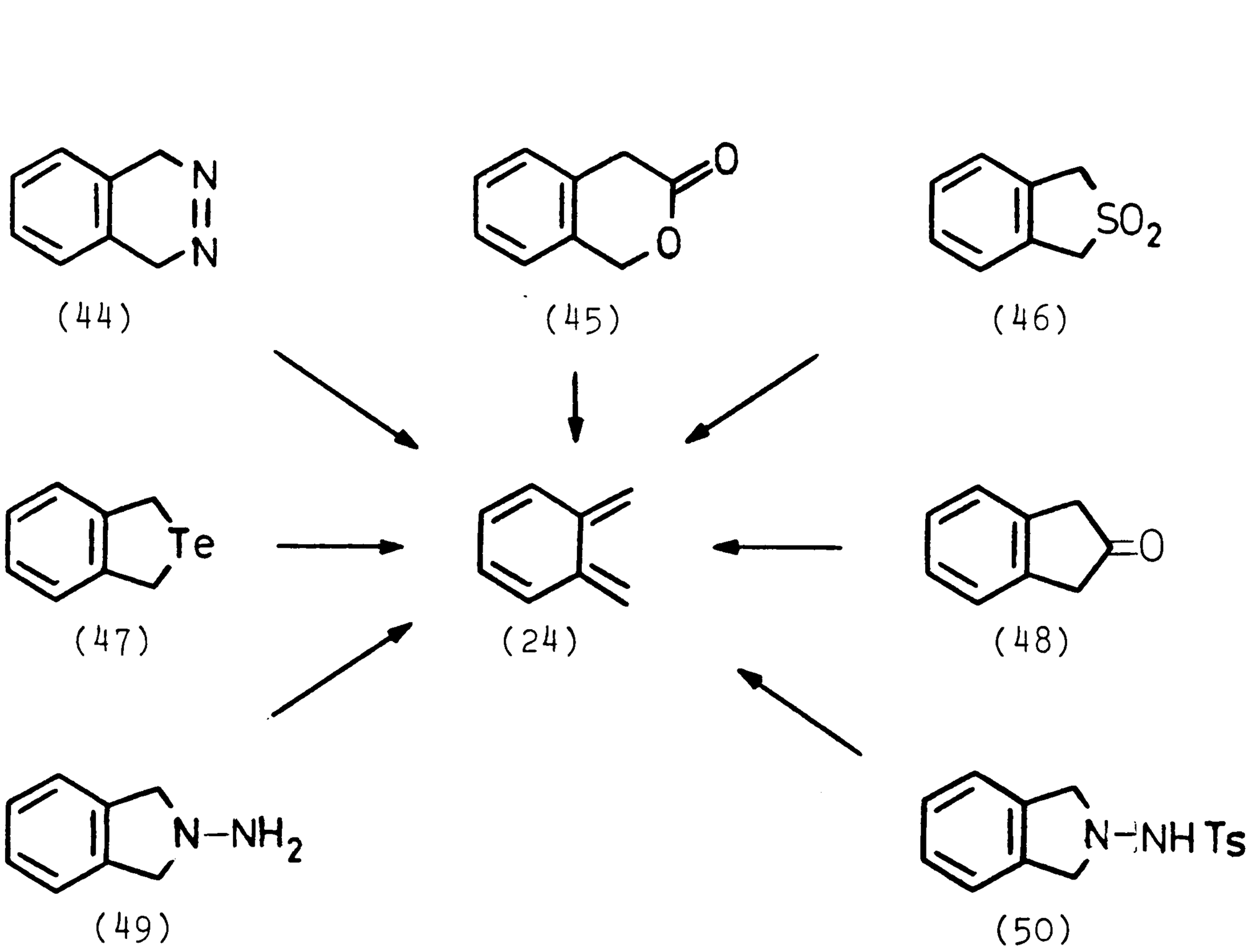


(40) (41)



(42) (43)

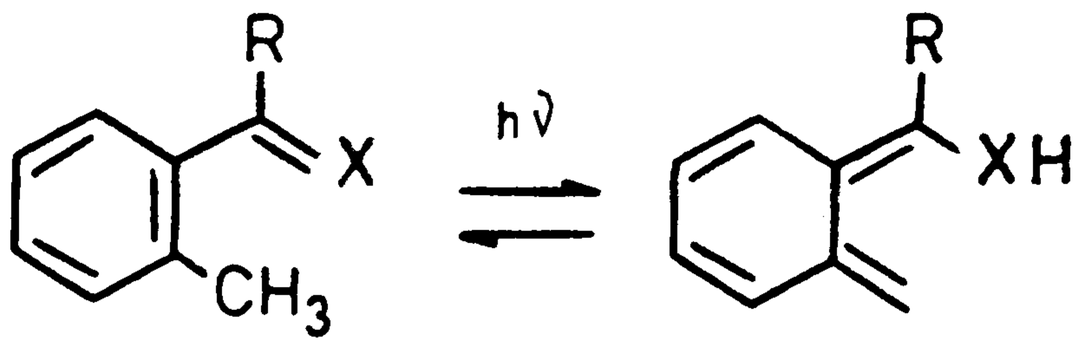
o-Xylylenes have also been obtained by the fragmentation of heterocycles of type (13), (Scheme 1). For example, irradiation of (44) in an argon matrix produces o-xylylene (24) in good yield under conditions where it can be studied spectroscopically.[36] Using flash vacuum pyrolysis, o-xylylene may be generated from a variety of heterocycles, such as (45),[37], (46)[38] and (47).[39] Loss of nitrogen from the hydrazine derivatives (49)[40] and (50)[41] to give o-xylylenes occurs on oxidation and treatment with base respectively. The photochemical elimination of carbon monoxide from derivatives of indanone (48) has been extensively used to generate o-xylylenes,[42] although this has been shown to be a non-cheletropic process.[43] (Scheme 3).



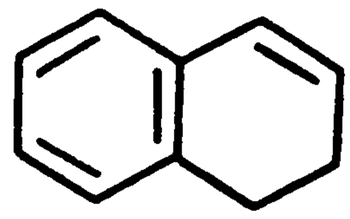
(44) (45) (46) (47) (24) (48) (49) (50)

SCHEME 3

A rather specialised case of o-xylylene generation is the phototautomerism of carbonyl compounds (51),[44] and o-tolyl styrenes (52).[45]



(53)



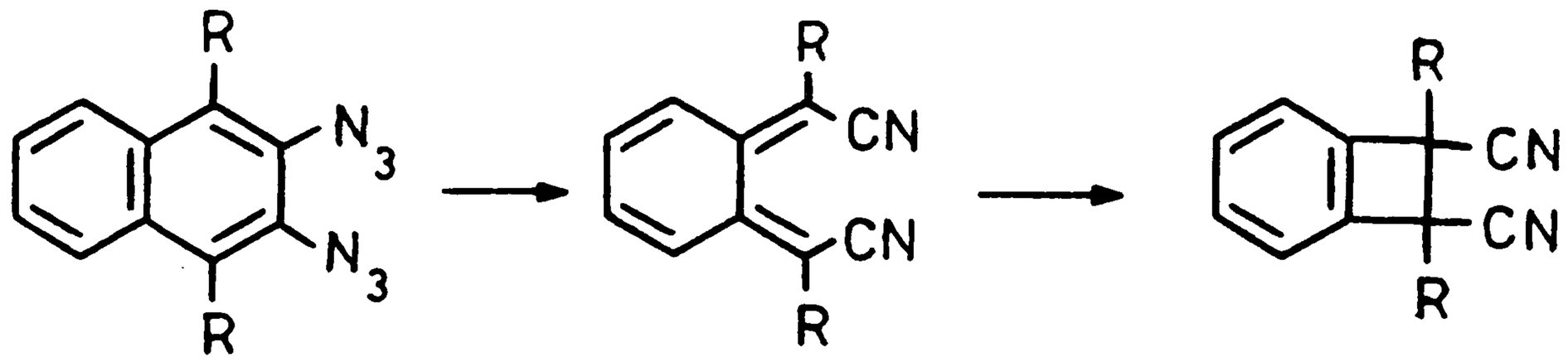
(3)

(51) X = O

(52) X = CH_2

If not trapped with dienophiles, o-xylylenes (53) isomerize back to the starting materials (51) and (52). An o-xylylene has also been implicated in the photochemistry of 1,2-dihydronaphthalene (3)[4] (see Section 1.1).

Finally, evidence for the formation of the dicyano-o-xylylenes (55) from the low temperature photolysis of diazidonaphthalenes (54) has been reported.[46] o-Xylylenes (55a) and (55b) have been postulated as intermediates in the flash pyrolysis of (54a)[47] and the thermolysis in o-dichlorobenzene of (54b)[48] respectively. In both cases, the corresponding dicyanobenzoxycyclobutenes (56) could be isolated at the end of the reactions.

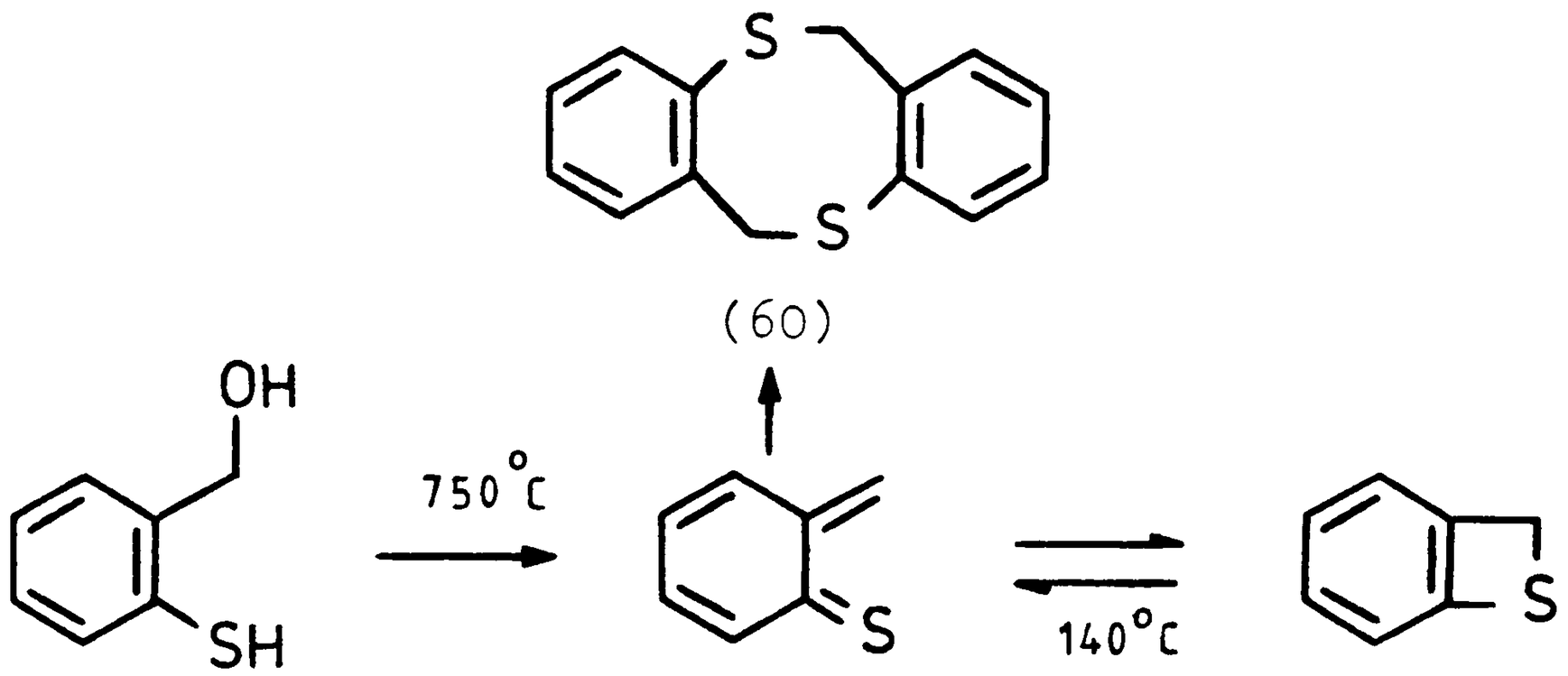


(54) (55) (56)

a; R = H b; R = OCOMe c; R = OMe

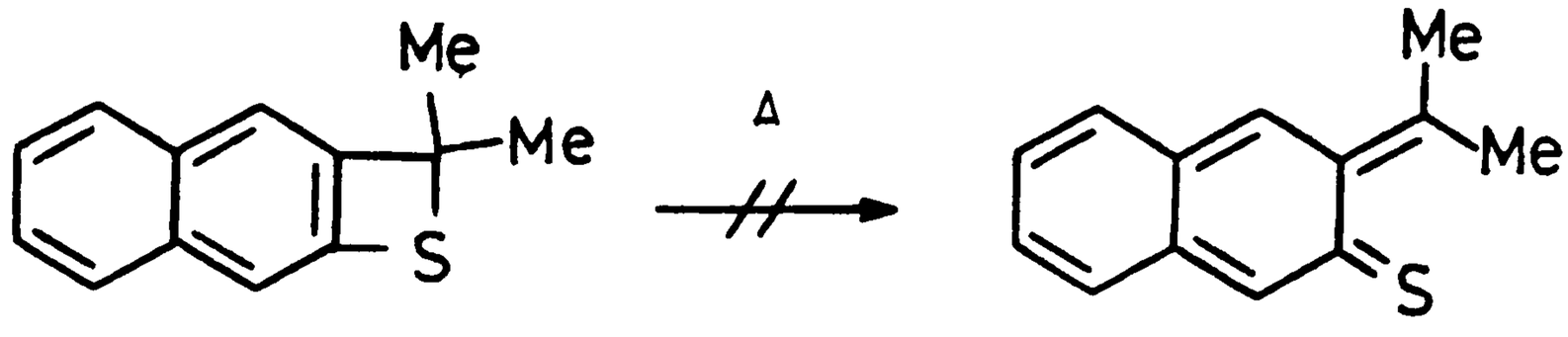
(b) o-THIOQUINONE METHIDES

In principle, most of the routes mentioned previously for the generation of o-xylylenes may be extended to the generation of the o-thioquinone methides. For example, flash pyrolytic 1,4-elimination of water from o-mercaptobenzyl alcohol (57) results in the formation of benzothiete (59) from electrocyclic ring closure of the transient o-thioquinone methide (58)[49] (see Section 1.4(b)).



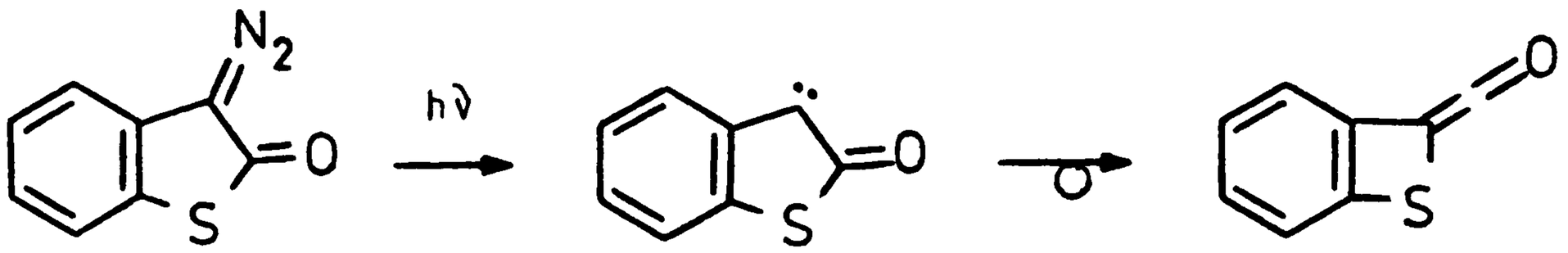
(57) (58) (59)

By analogy with benzocyclobutenes, benzothietes themselves should be valuable precursors to o-thioquinone-methides. Indeed, when heated to temperatures in excess of 100°C, benzothietes undergo ring opening to yield o-thioquinonemethides which in the absence of trapping agents, dimerize to give the head-to-tail dimer (60).[49] (A full discussion of the dimerization of o-thioquinone methides is presented in Section 1.3(b).) In contrast however, naphthothiete (61)[50] shows no tendency to undergo ring opening to the o-thionaphthoquinone methide (62), probably because this would involve the disruption of the aromaticity of two benzenoid rings.

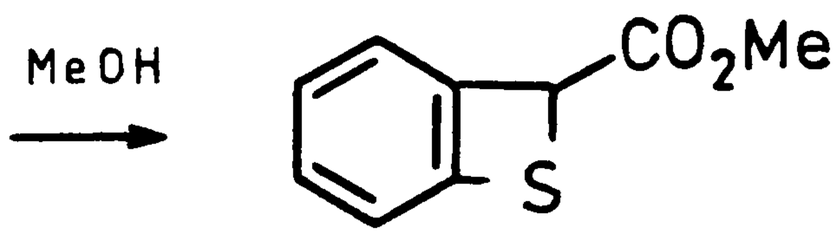


(61) (62)

However, although benzothietes have been shown to be useful precursors to o-thioquinone methides, only a relatively small number of routes for their synthesis have been reported compared to the large number of synthetic methods that exist for benzocyclobutenes. For instance, irradiation of (63) leads to benzothiete ester (66) by loss of nitrogen, and Wolff rearrangement of the resulting carbene (64) to ketene (65) which is trapped in situ with methanol.[51]

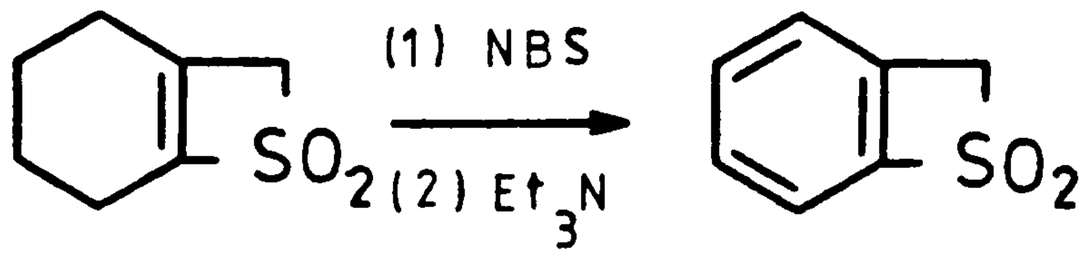


(63) (64) (65)

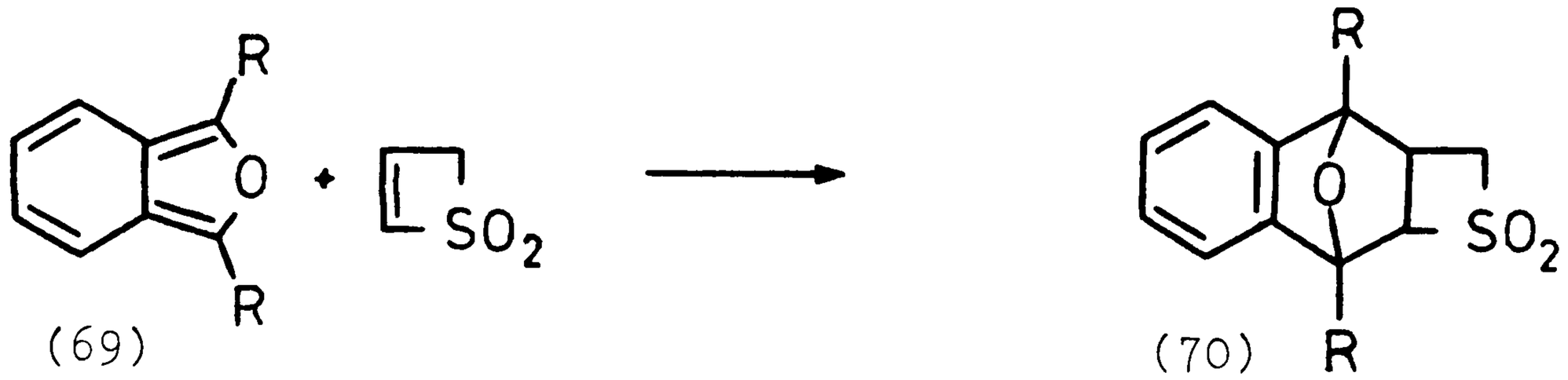


(66)

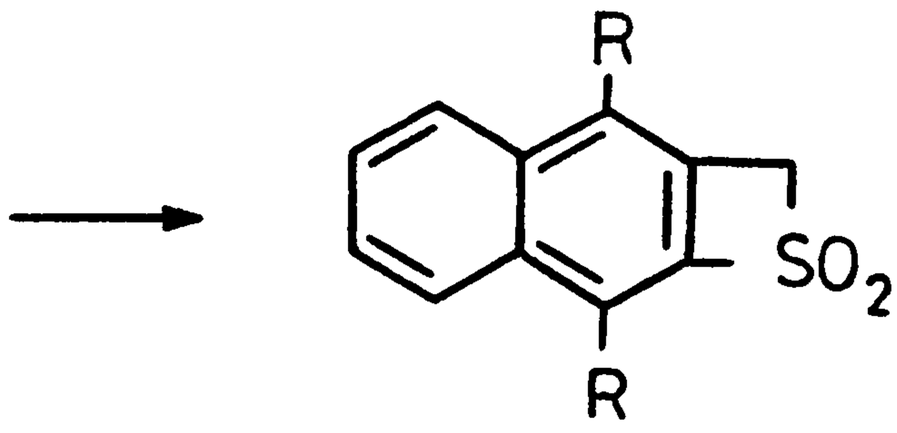
Benzothiete-1,1-dioxide (68) is formed in low yield from the dehydrogenation of sulphone (67). In addition, naphthothiete-1,1-dioxides (71, R = H)[52] and (71, R = Ph)[53] can be obtained by Diels-Alder trapping of isobenzofurans (69)



(67) (68)



(69) (70)

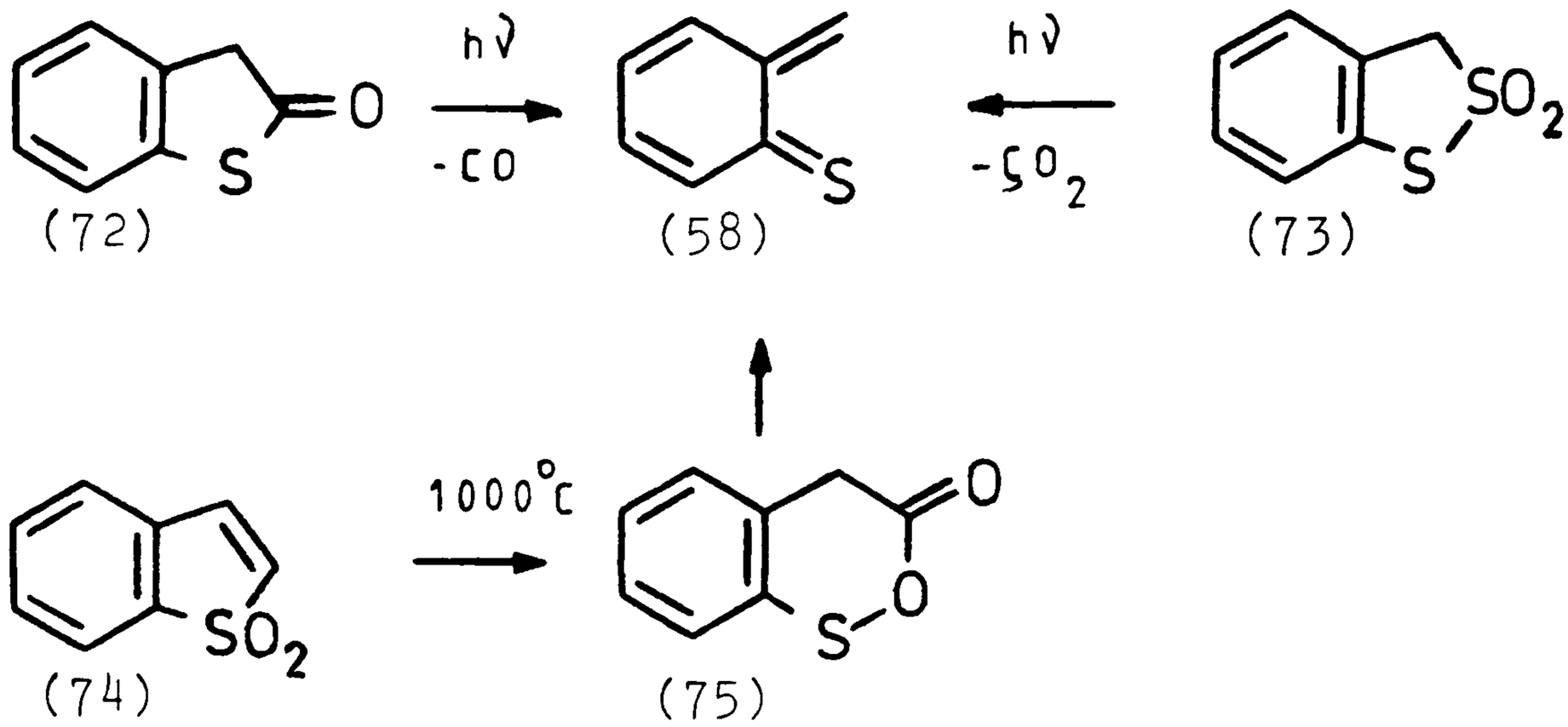


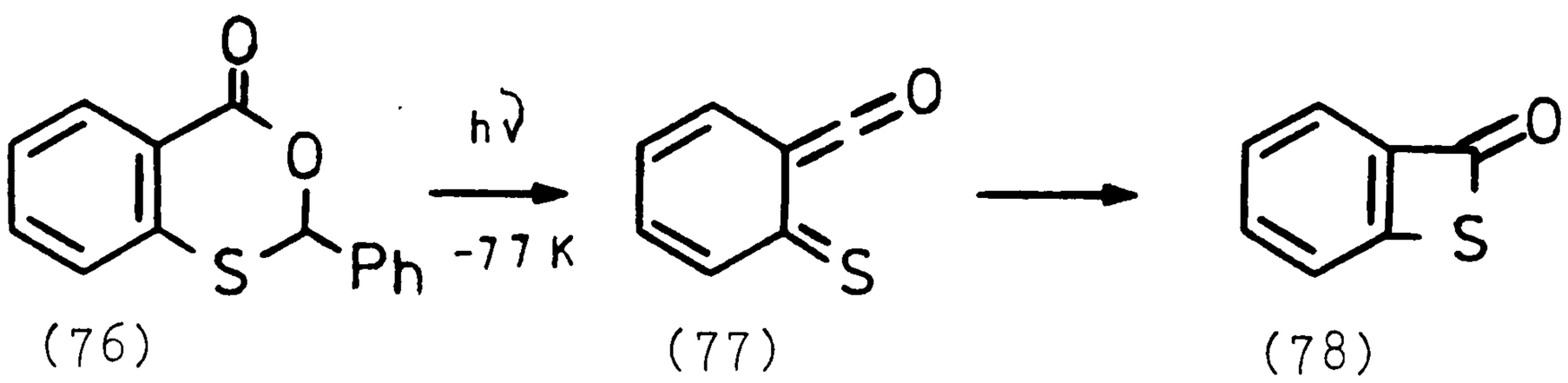
(71)

with thiete-1,1-dioxide followed by acid catalysed dehydration of the resulting adduct (70).

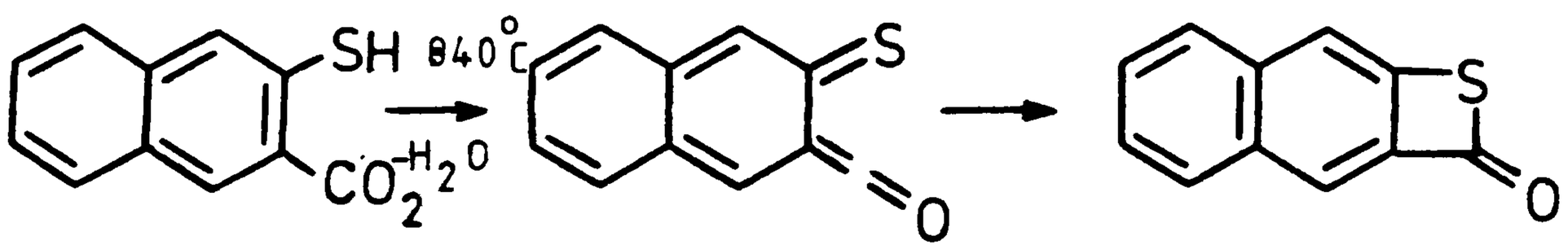
o-Thioquinone methides like o-xylylenes, can also be generated by the fragmentation of heterocycles. Thus, photolytic decarbonylation of benzothiophene-2-one (72) gives o-thioquinone methide (58), which could be trapped with dienophiles to give the corresponding adducts in high yield[54] (see also Section 1.3(b)).

o-Thioquinone methide (58) can also be generated by photochemical extrustion of SO_2 from (73)[55] and by loss of CO_2 from (75) which is an intermediate in the FVP of benzothiophene-1,1-dioxide (74).[56] Also, ketene (77) can be generated by irradiation of 2-phenyl-3,1-benzothian -4-o (76). If the photolysis is performed at low temperatures ring closure of (77) occurs to yield thiolactone (78).[57]



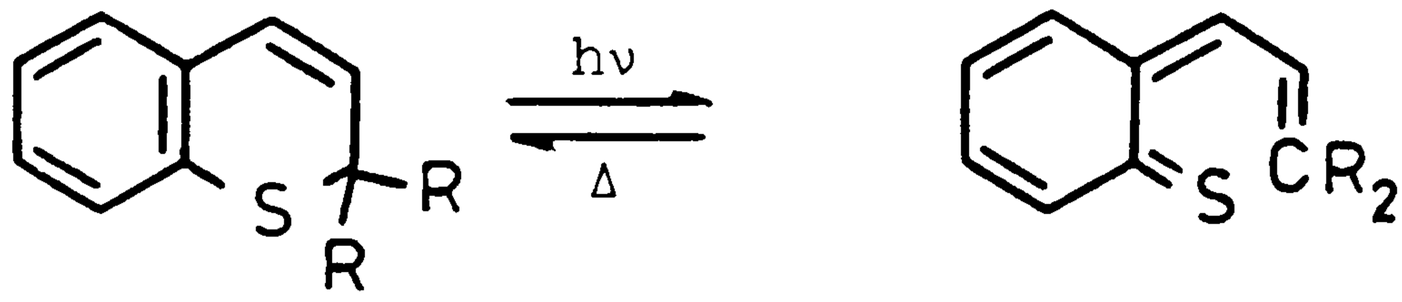


o-Thioquinone methides are also available from 1,4-elimination reactions but here too only a small number of cases have been reported compared to the large number of 1,4-elimination routes that exist for o-xylylenes. Thus, flash pyrolytic dehydration of carboxylic acid (79) gives naphthothietone (81) which is stable below 0°C.



(79) (80) (81)

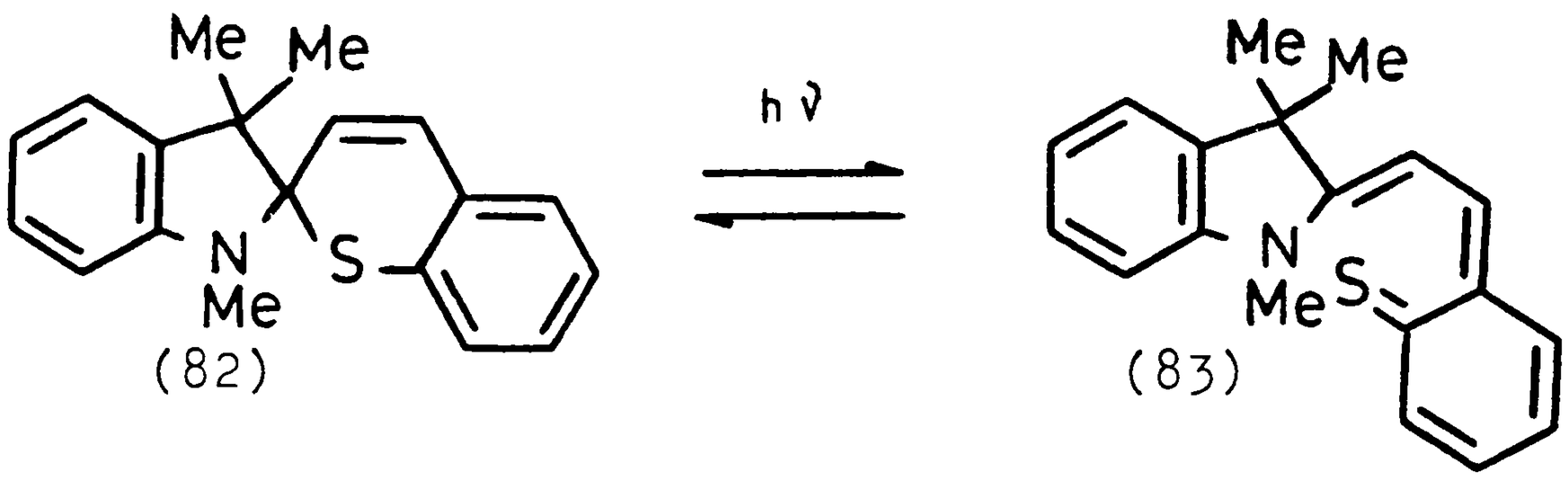
Phototautomerism reactions have also found application in the generation of o-thioquinone methides, indeed the first reported example (2), was invoked to explain the



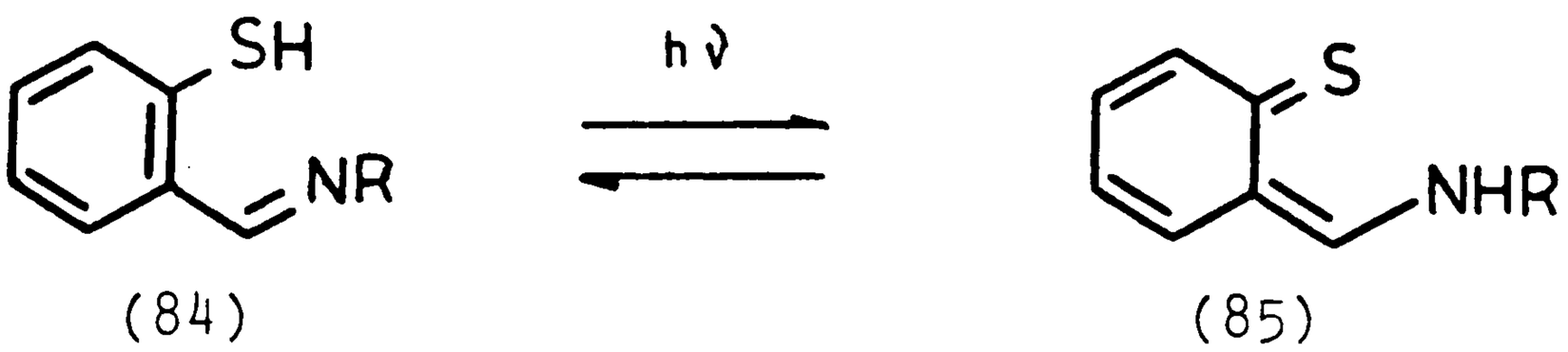
(1) R = H, ph (2)

photochromic behaviour of 2H-thiochromene derivatives (1),[3] (also see Section 1.1).

Similar behaviour was observed for the spiro compound (82). The tautomerism of mercaptobenzaldimines (84) to o-thioquinone methides has also been studied and the quinonoid tautomer (85) has been detected spectroscopically,[59] although there are no reports of chemical trapping. The observed ultra-violet absorption bands correspond closely to those predicted by molecular-orbital theory.[60]

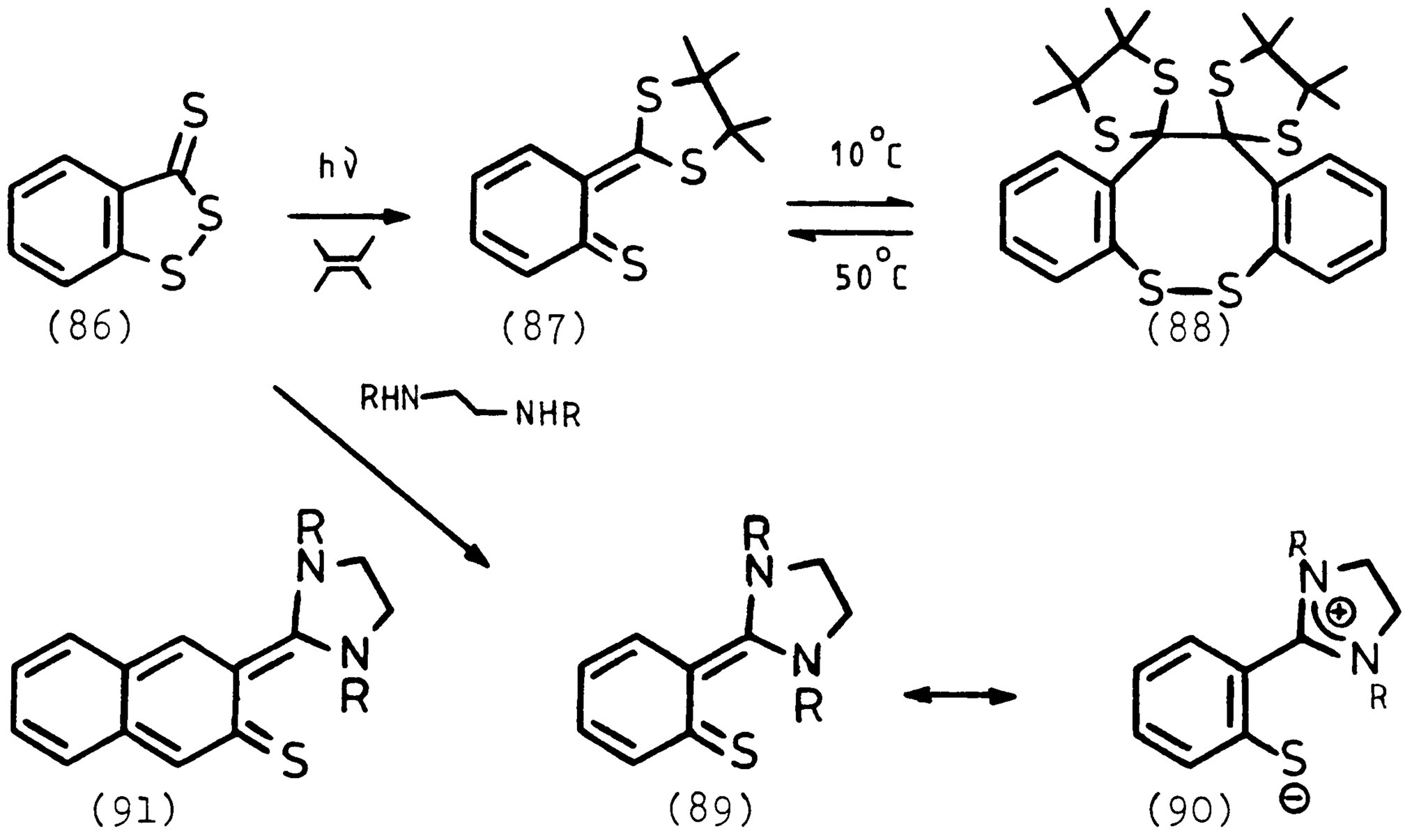


(82) (83)



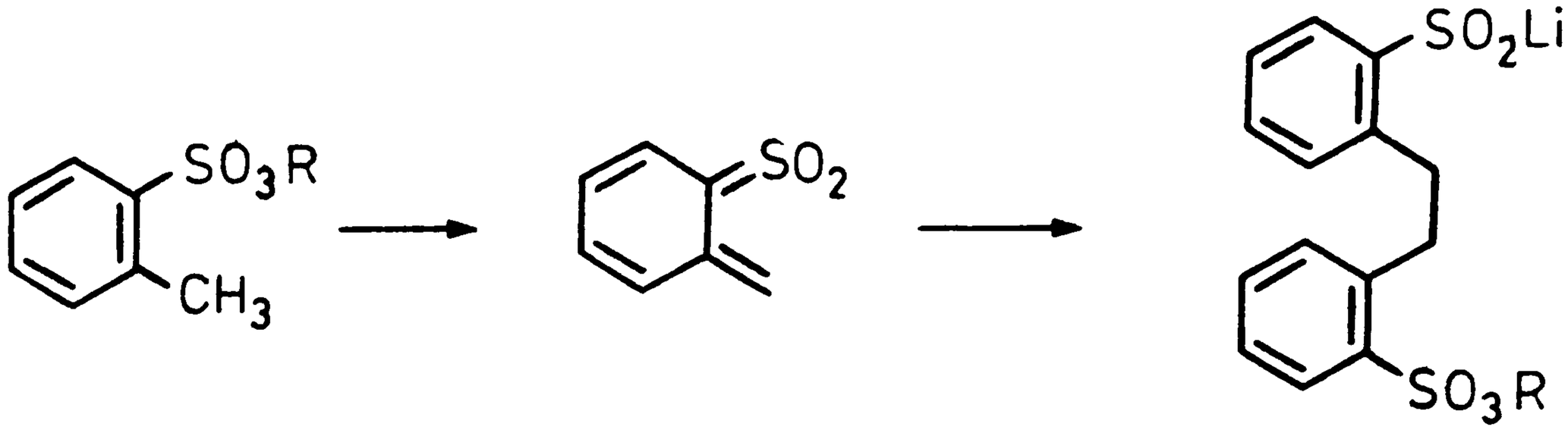
(84) (85)

Photolysis of benzo-1,2-dithiole-3-thione (86) in the presence of olefins yields the relatively stable deep blue o-thioquinone methide (87).[61] This system undergoes a reversible dimerization to give the colourless dimer (88). Alternatively, treatment of (86) with an ethylene diamine results in the formation of stable, monomeric o-thioquinone methides (89), in which a large contribution from the zwitterionic canonical form (90) is indicated by the NMR spectrum. In addition, naphthothioquinone methide (91) can also be obtained by this route.[62] This is noteworthy, since the 2,3-naphthoquinone methide moiety is normally highly destabilised by 2,3-naphtho fusion.



(86) (87) (88) (91) (89) (90)

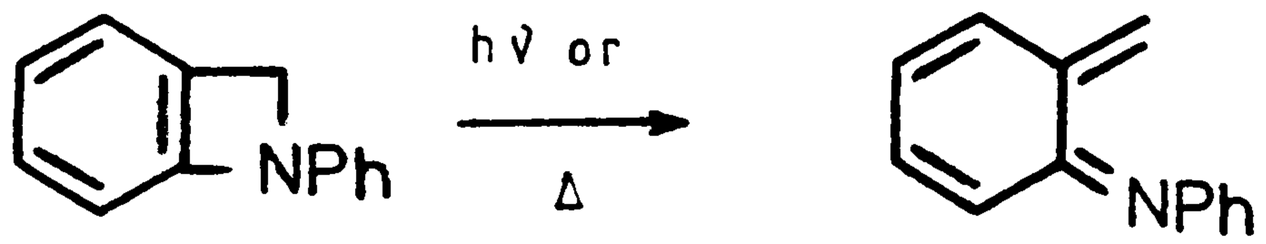
Finally, sulphene (93) has been proposed as an intermediate in the reaction of (92) with butyl lithium to give the dimeric salt (94), although it could not be trapped with enamines.[63]



(92) (93) (94)

(c) o-AZAXYLYLENES

Most of the synthetic routes previously described for o-xylylenes and o-thioquinone methides may be extended to the generation of o-azaxylylenes. For example, thermal or photochemical ring opening of N-phenylbenzazetidine (95) leads to the transient o-azaxylylene (96) which can be trapped with N-phenylmaleimide,[64] (see Section 1.4(c)).



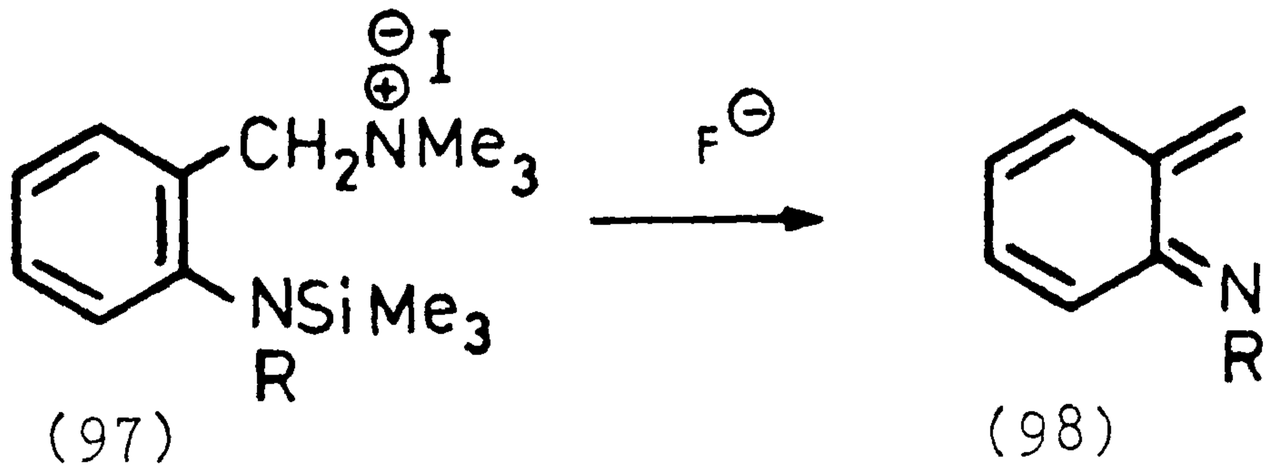
(95) (96)

This reaction is analogous to the generation of o-xylylenes from benzocyclobutenes examined earlier

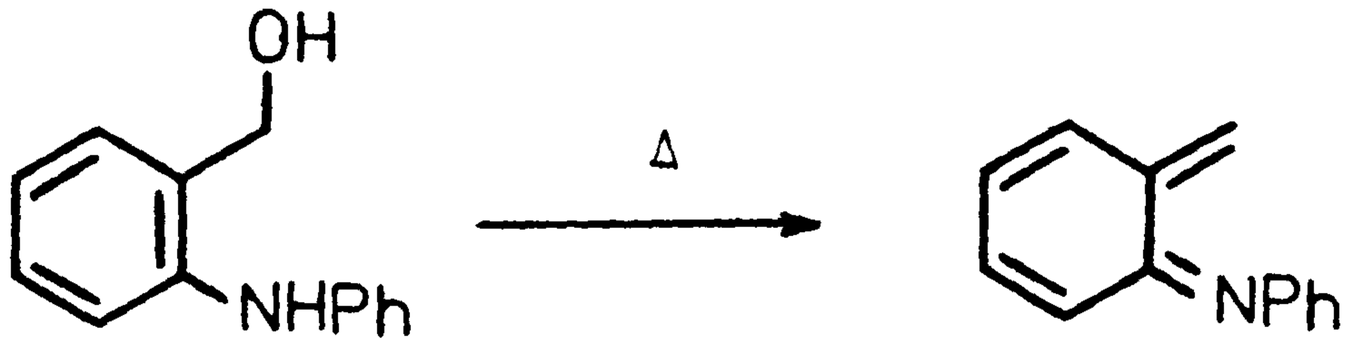
(Section 1.2(a)). However, unlike the case of benzocyclobutenes, unfortunately, no good route to benzazetidines exists and this tends to severely limit this approach. The synthesis of benzazetidines and their application to the generation of azaxylylenes is discussed in detail in the Discussion on approaches to benzazetidines (Section 2.1).

The 1,4-elimination can also be applied to o-azaxylylene generation. Thus Seagusa's method for the generation of o-xylylenes (39 → 24) can be extended to give a range of N-substituted o-azaxylylenes (98) from the N-trimethylsilyl salts (97).[65] This followed an earlier report that (96) was produced by 1,4-elimination of water in the flash pyrolysis of N-phenyl alcohol (99)[66] or the corresponding methyl ether.[102] Similarly, o-azaxylylene (101) has been obtained from the flash-pyrolysis of N-phenylanthranilic acid (100).[66]

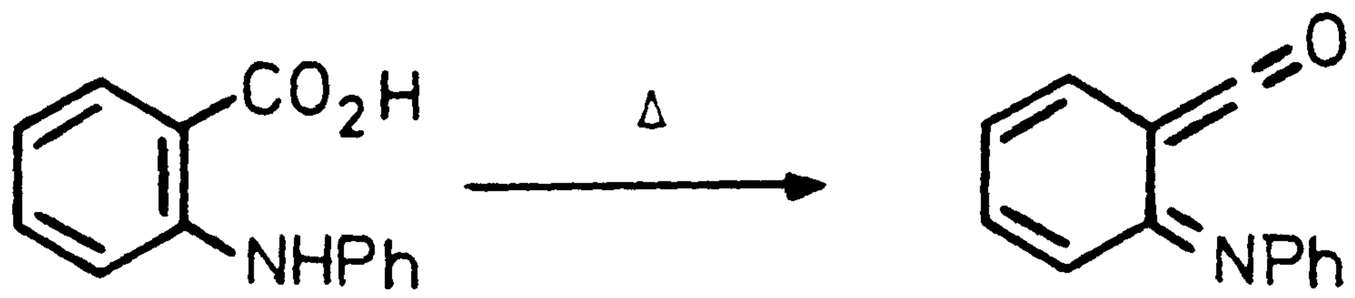
The parent o-azaxylylene (103) has been postulated as an intermediate in the reaction of o-aminobenzyl methyl ether (102) with phenyl magnesium bromide. The ultimate formation of amine (104) was explained by nucleophilic attack of a second mole of Grignard reagent on o-azaxylylene (103).[67] The 1,4-elimination approach is examined in depth in the Discussion on the generation of o-azaxylylenes (Section 2.).



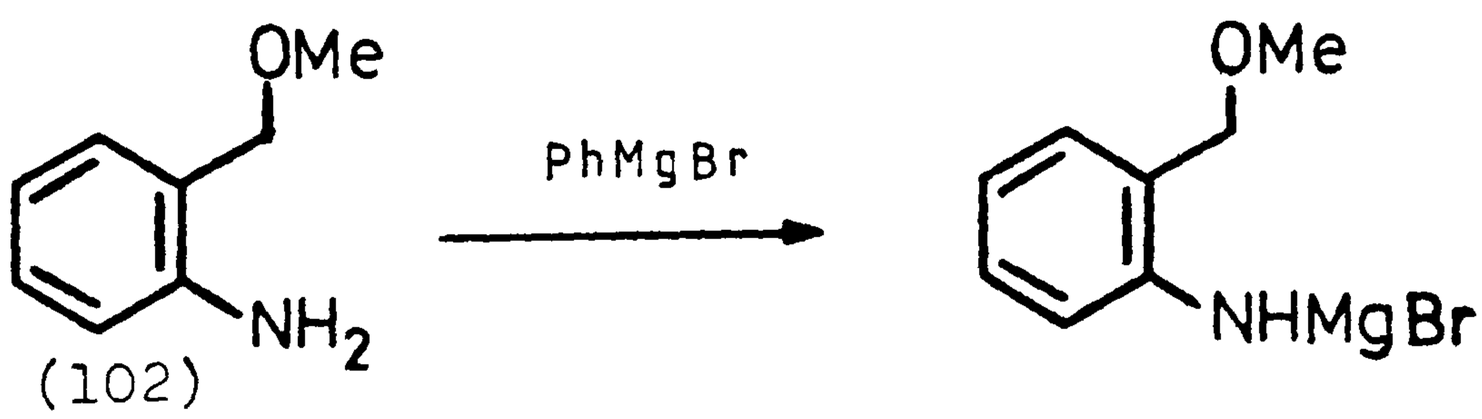
(97) (98)



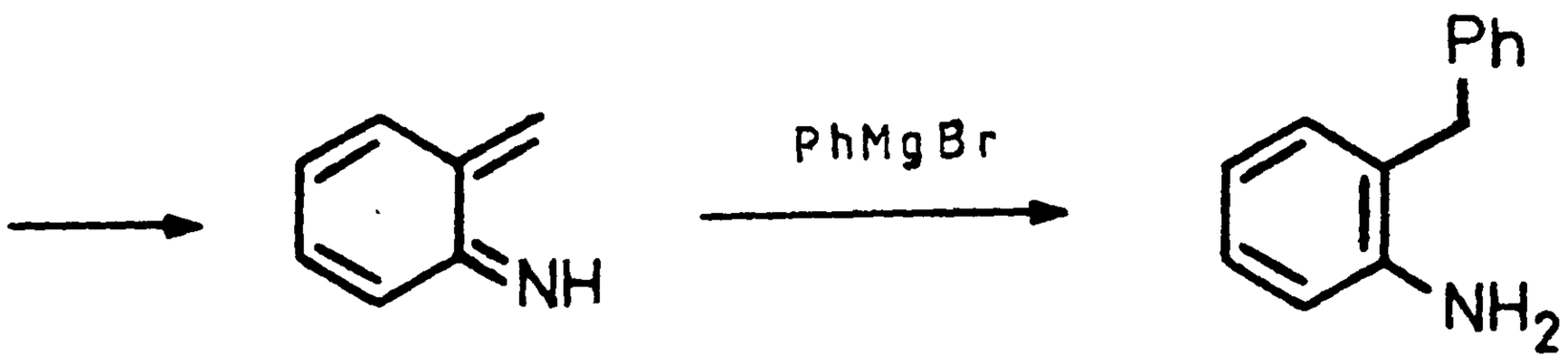
(99) (96)



(100) (101)

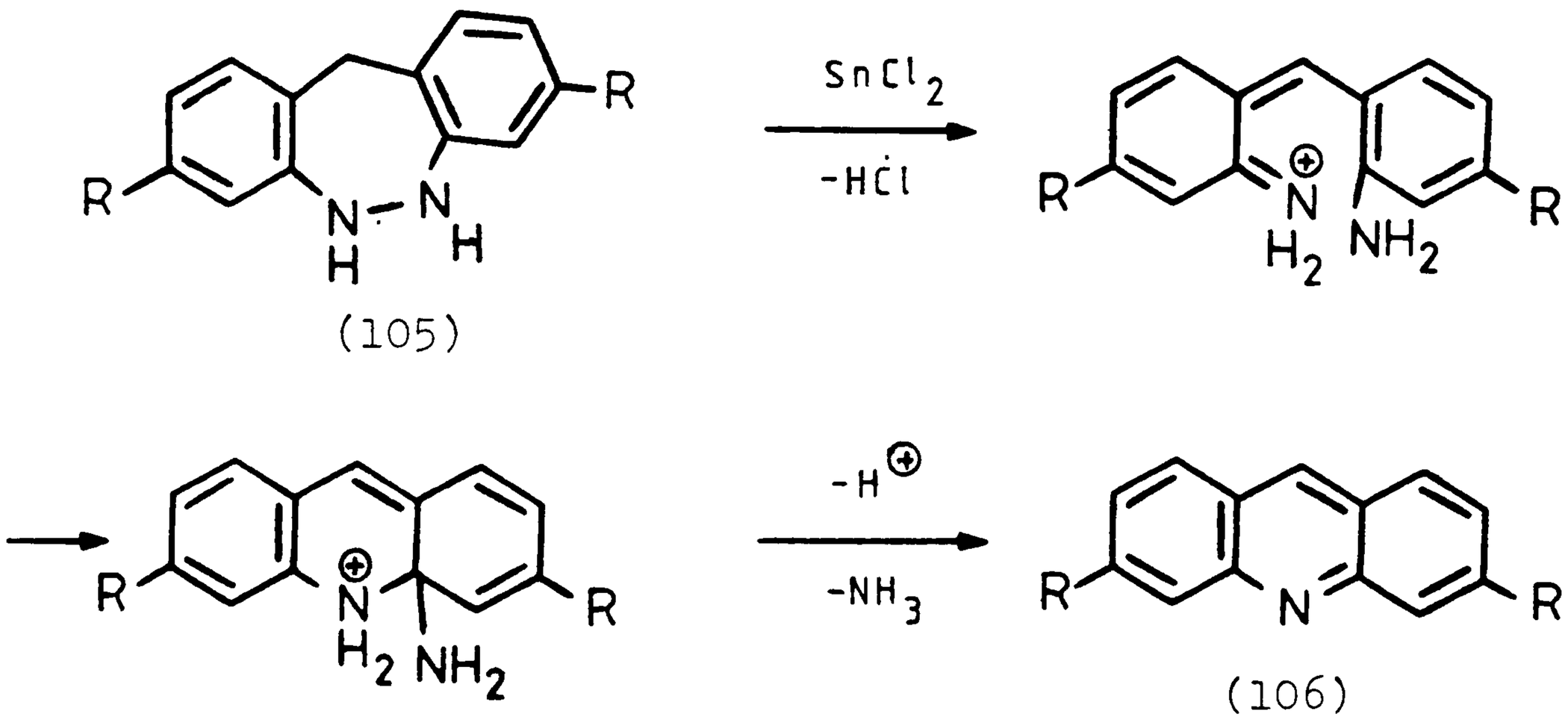


(102)



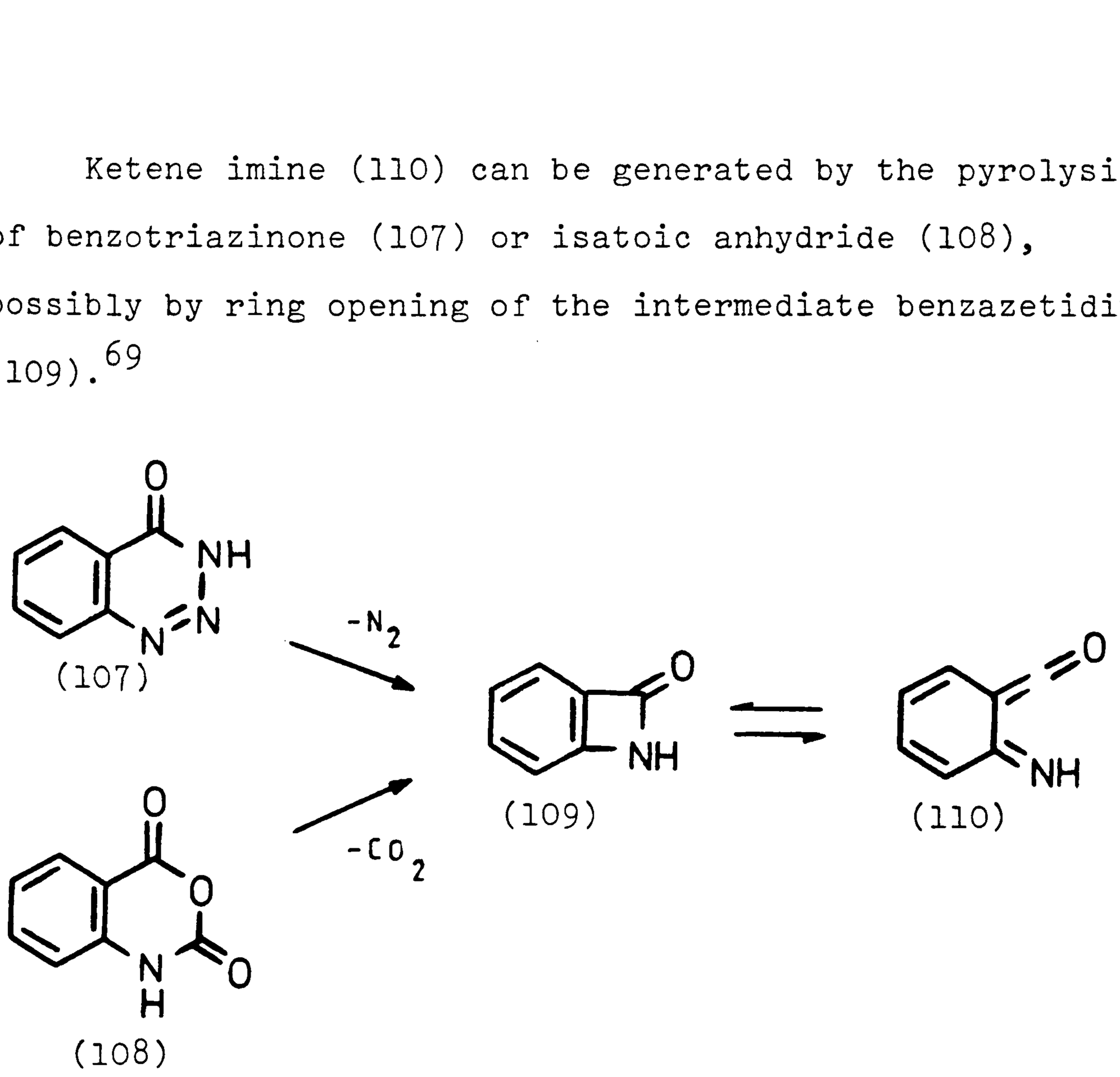
(103) (104)

There are also a number of reports concerning the generation of o-azaxylylenes by the fragmentation of various heterocycles. For example, o-azaxylylenes have been suggested as intermediates in the preparation of acridines (106) from the dihydrobenzodiazepines (105).[68]



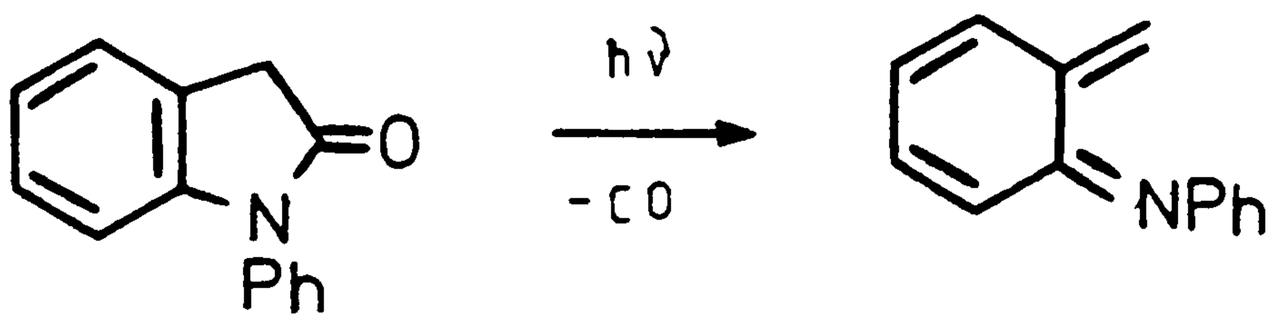
(105) (106)

Ketene imine (110) can be generated by the pyrolysis of benzotriazinone (107) or isatoic anhydride (108), possibly by ring opening of the intermediate benzazetidinone (109).[69]

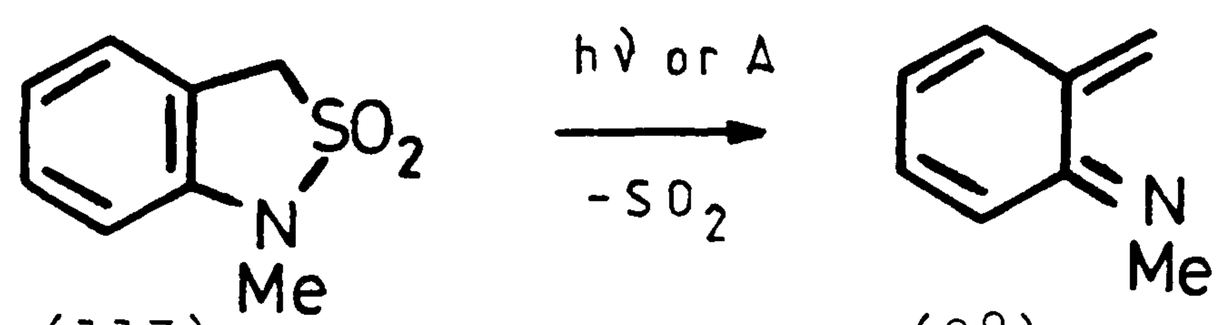


(107) (108) (109) (110)

Further examples of the fragmentation approach include the generation of o-azaxylylene (96) by the photo-decarbonylation of N-phenyloxindole (112),[70] and the thermal or photochemical extrusion of SO_2 from sultam (113) to yield azaxylylene (98).[71]

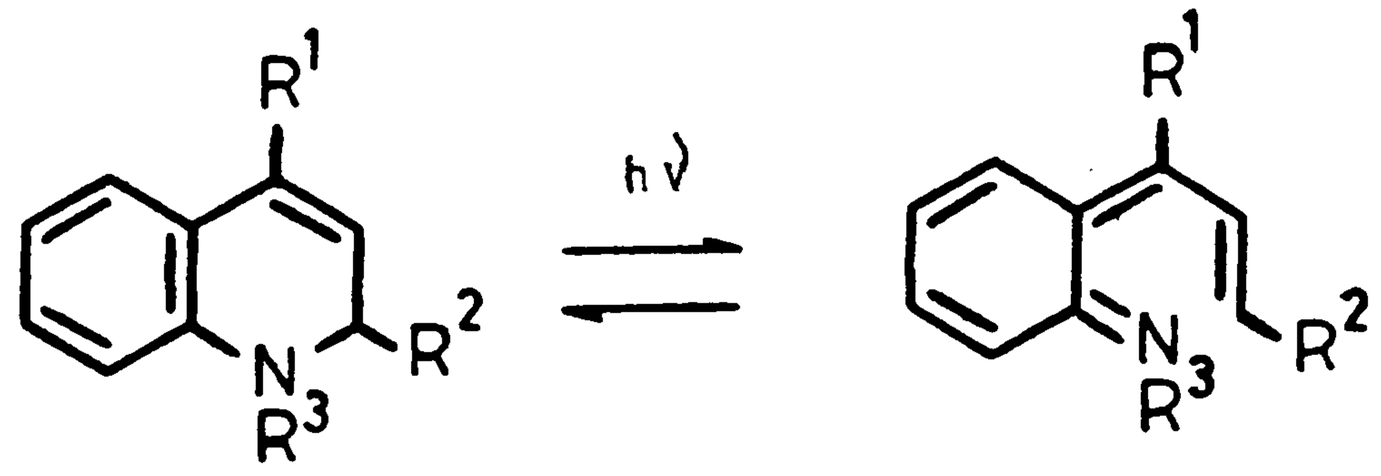


(112) (96)



(113) (98)

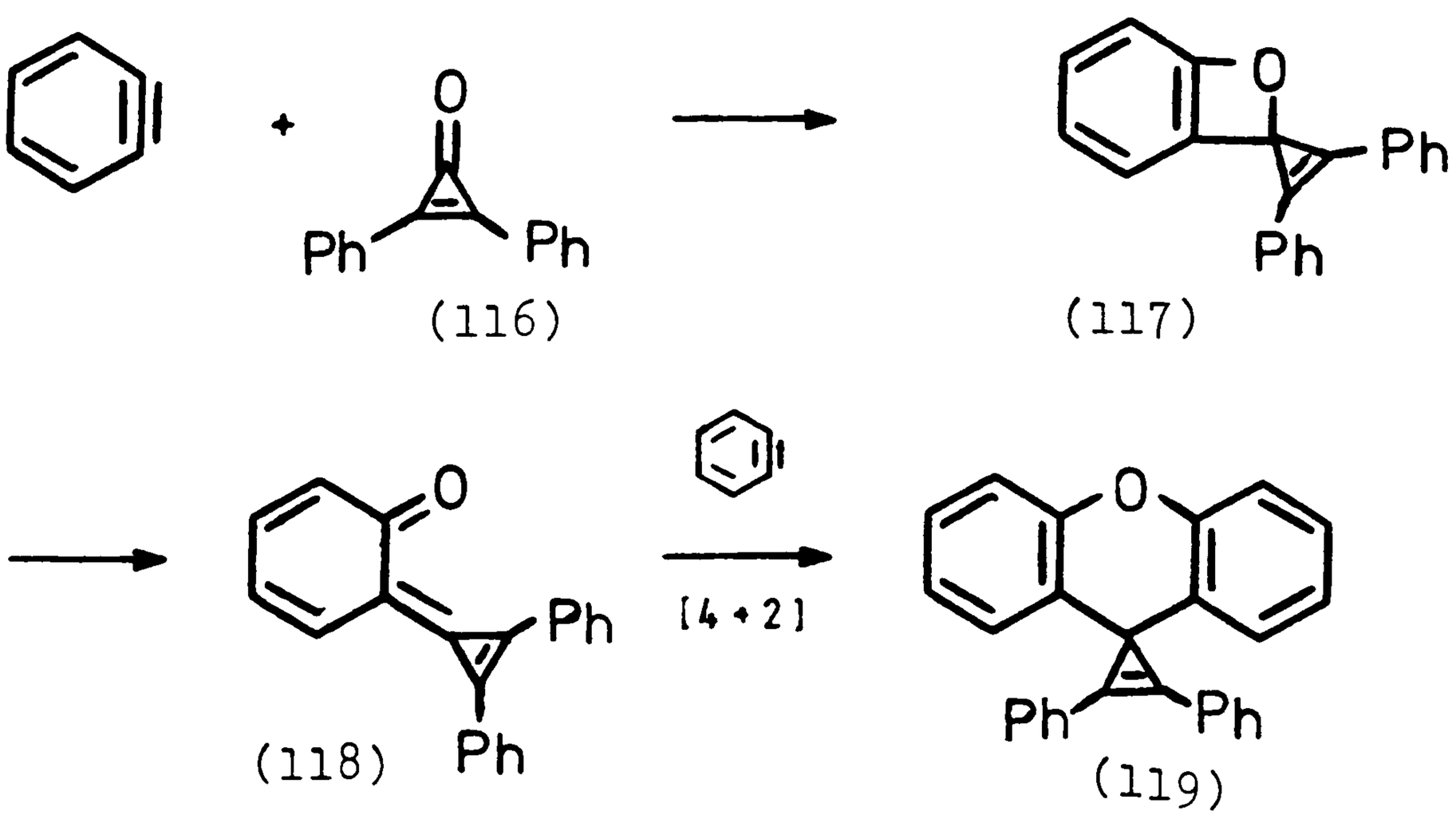
o-Azaxylylenes have also been postulated as intermediates in certain phototautomerism reactions. For example, 1,2-dihydroquinoline derivatives (114), have been observed to exhibit photochromism, in which the coloured photoproducts are thought to be azaxylylenes (115).[72,73]



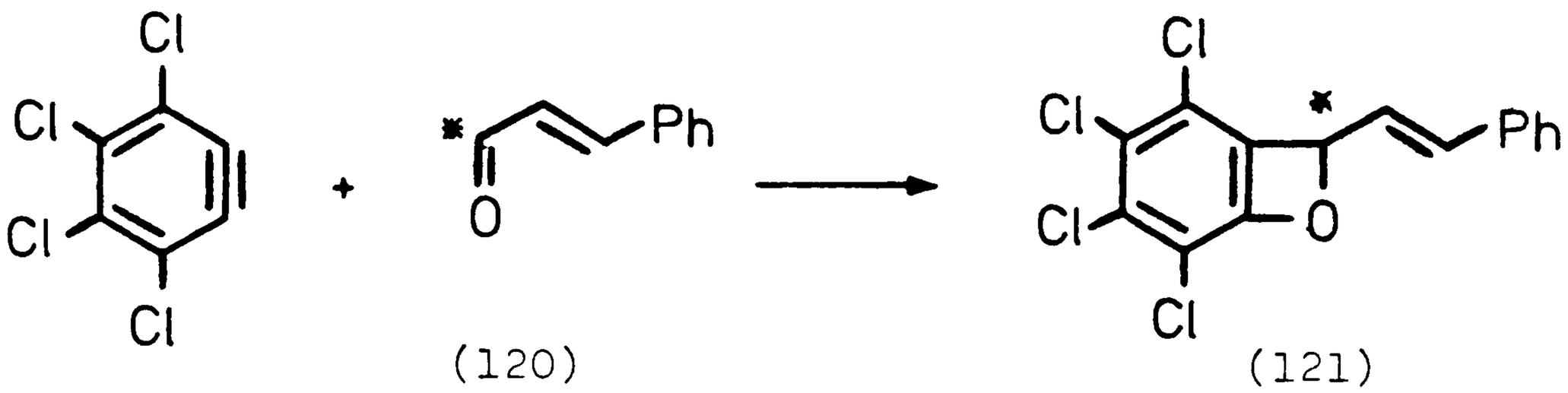
(114) (115)

(d) o-QUINONE METHIDES

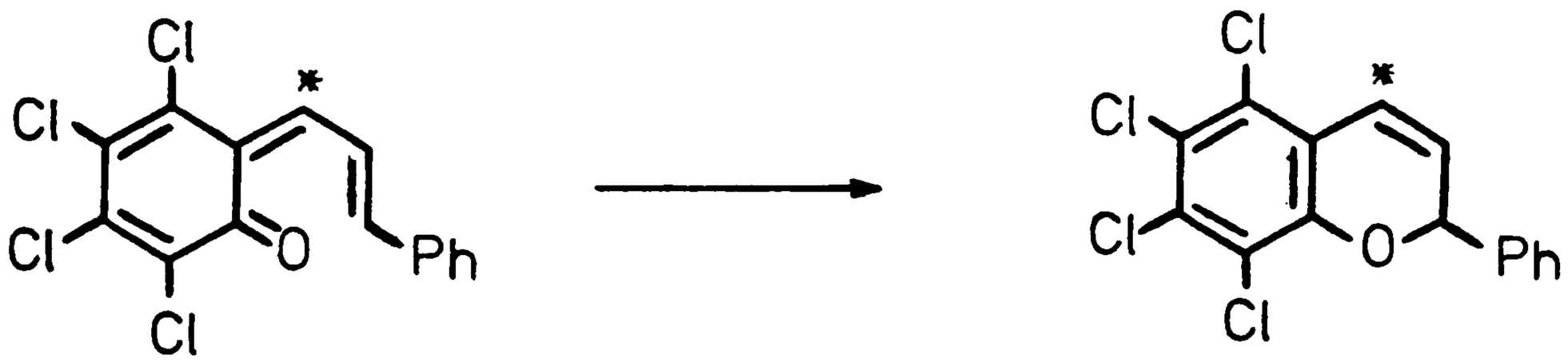
The range of synthetic methods described for the generation of o-xylylenes, o-thioquinone methides, and o-azaxylylenes broadly parallels those available for the generation of o-quinone methides.[74] However, Kolshorn and Meier[1] have predicted that o-quinone methide is approximately 80 Kcal.mol^{-1} more stable than the corresponding ring closed form, benzoxete. Indeed, experimental evidence certainly supports this prediction as the benzoxete system has never been isolated. It is, therefore, of little surprise that this instability invokes severe limitations on the utilization of benzoxetes for the generation of o-quinone methides. However, ring opening of transient benzoxetes has been postulated in a number of reactions. For instance, the addition of diphenylcyclopropenone (116) to benzyne leads ultimately to (119) and it has been suggested that this involves an initial [2+2] cycloaddition to produce benzoxete (117) which immediately ring opens to yield o-quinone methide (118) which then undergoes Diels-Alder reaction.[75]



In a similar reaction, the addition of ketone (120) to tetrachlorobenzyne has been shown to lead to chromene (123).Labelling experiments indicate that the reaction proceeds by the initial formation of benzoxete (121) followed by ring opening and electrocyclisation.[76]

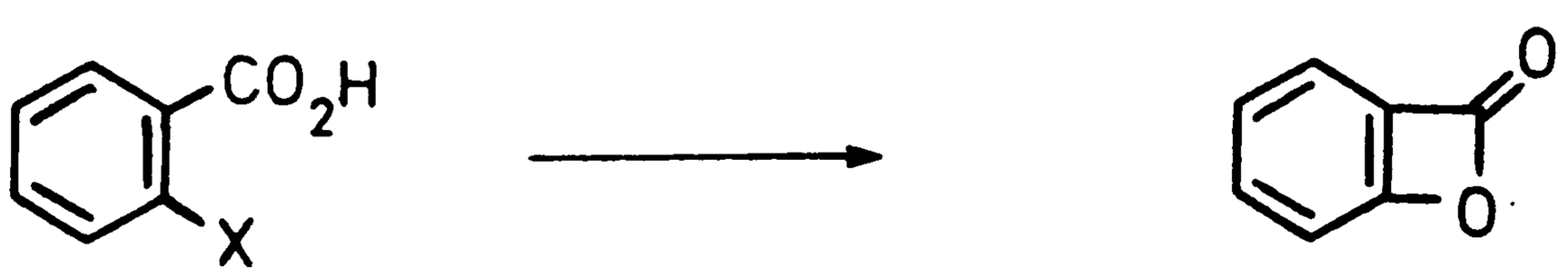


(120) (121)



(122) (123)

In addition, benzoxete (126) has been suggested as an intermediate in the decomposition of benzenediazonium-2-carboxylate (124)[75] or diphenyl iodonium-2-carboxylate (125)[77] to benzyne.

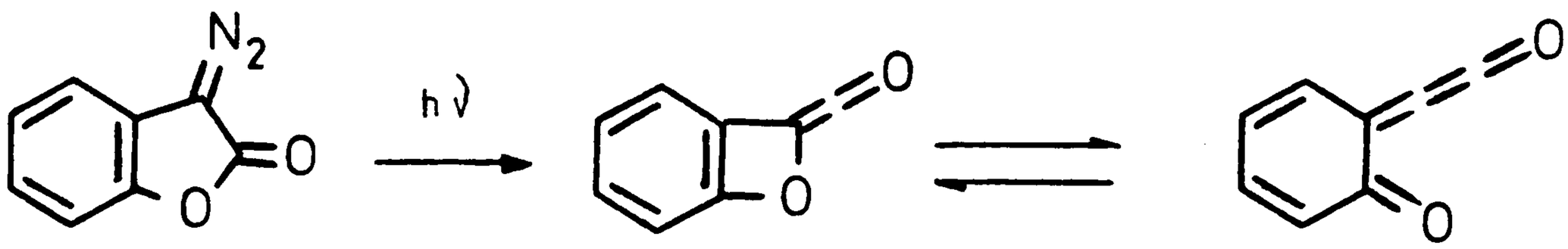


(126)

(124) X = N_2^+

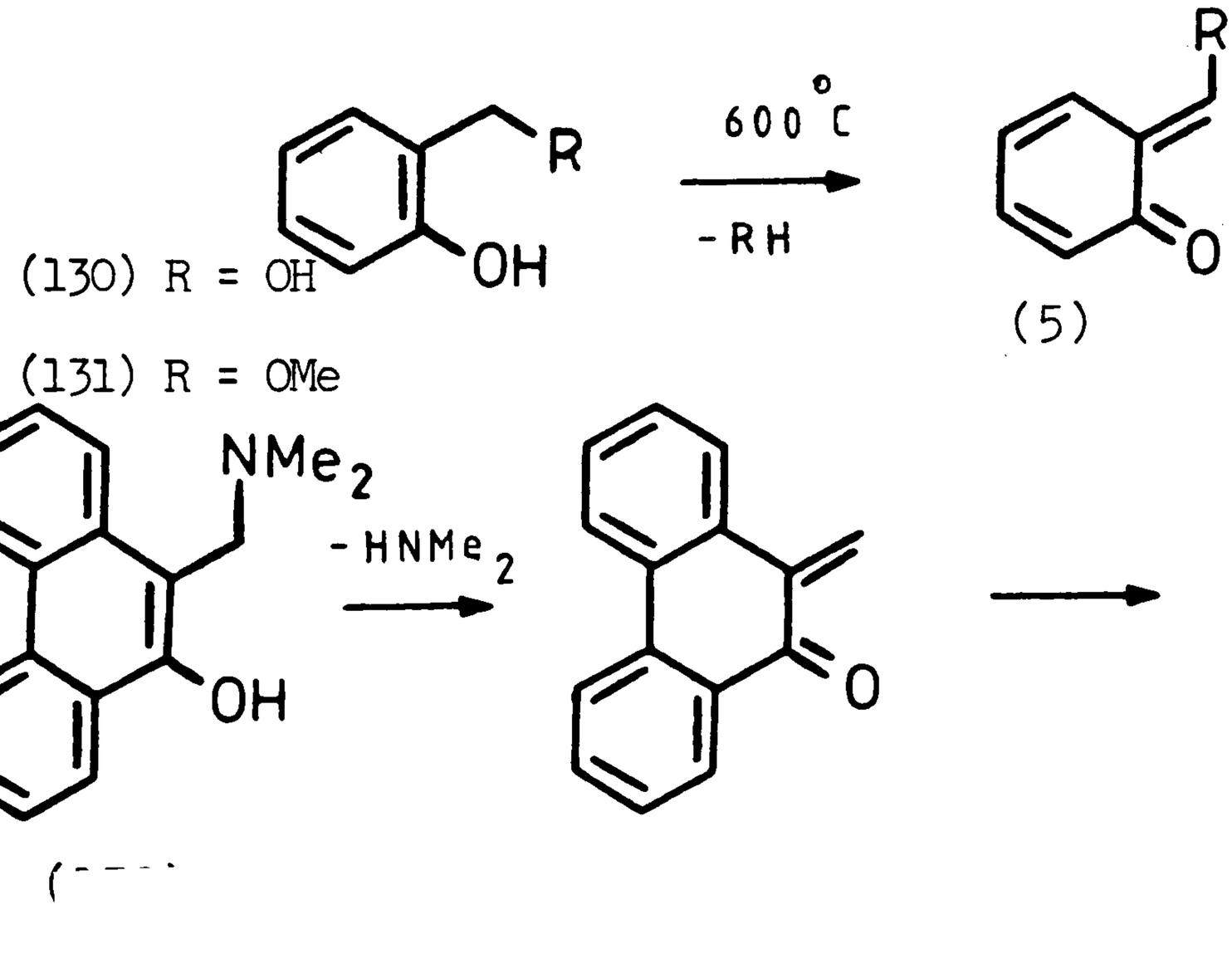
(125) X = I^+Ph

However, there has been one report in which the open and closed forms could be interconverted photochemically and both forms could then be detected spectroscopically. Thus, irradiation of 3-diazobenzofuranone (127) in an argon matrix at 8K,gave rise to two primary products (128) and (129),which could be interconverted photochemically. Prolonged irradiation led to the decarbonylation of (127) to give benzyne.[78]



(127) (128) (129)

The most widely used approach to o-quinone methides is 1,4-elimination. For instance, the parent o-quinone methide (5) has been generated by the flash-pyrolysis of either the alcohol (130)[79] or ether (131).[80] Elimination of dimethylamine from amine (132) yields the highly unstable o-quinone methide (133) which undergoes rapid dimerization to give (134).[81]



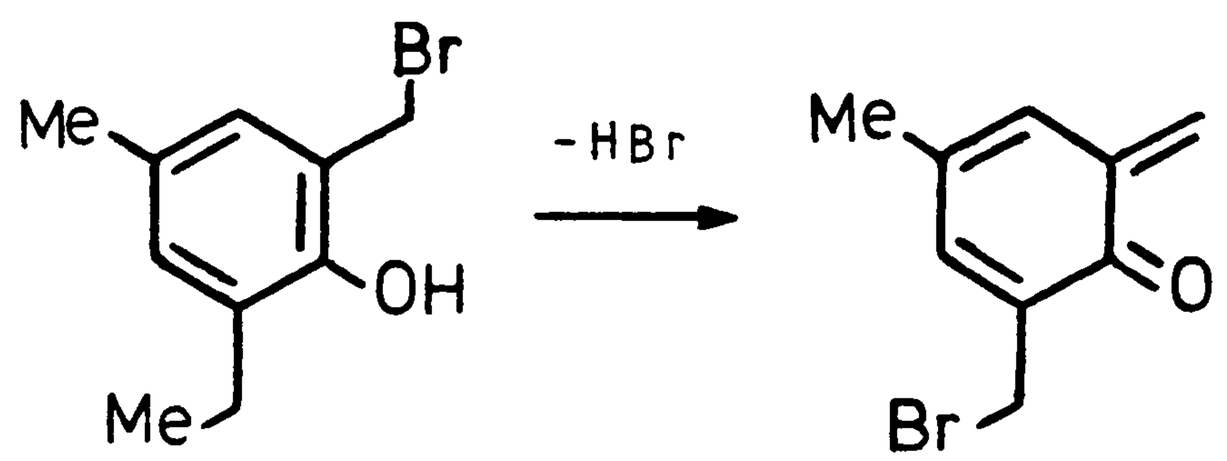
(130) R = OH

(131) R = OMe

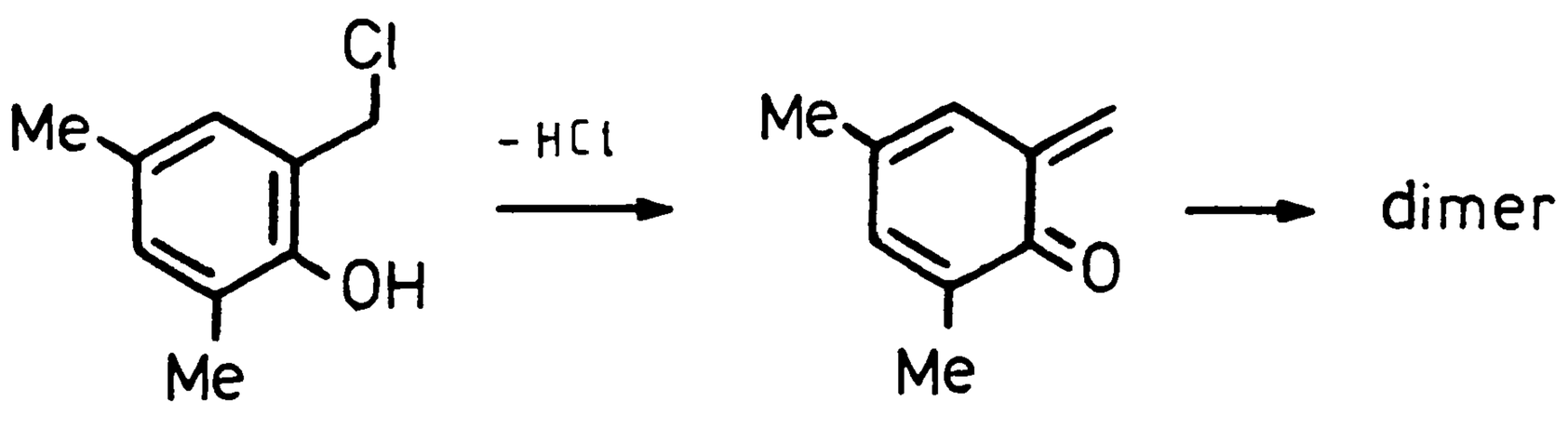
(5)

(134)

Also, elimination of HBr from phenol (135) has been reported to lead to o-quinone methide (136) during the vulcanization of rubber with phenol (135).[82] Similarly, o-quinone methide (138) has been postulated as an intermediate from the elimination of HCl from phenol (137).[83]



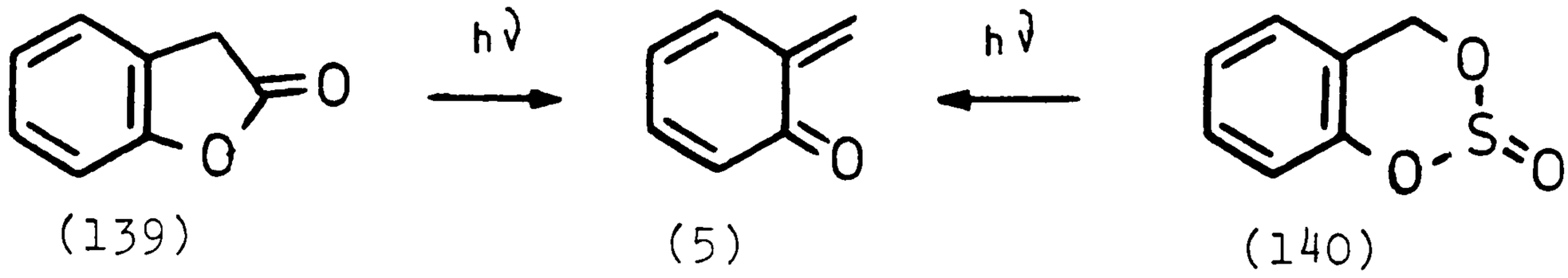
(135) (136)



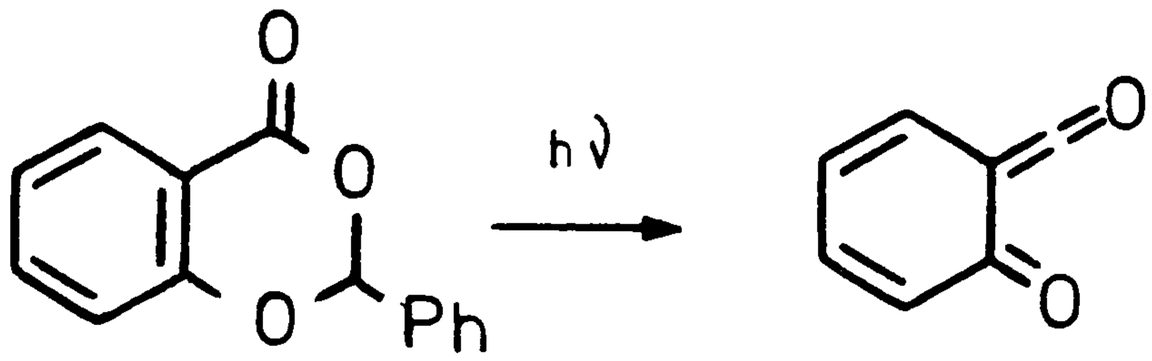
(137) (138)

o-Quinone methides have also been produced by the fragmentation of heterocycles. For example, photochemical extrusion of CO from lactone (139) and SO_2 from (140) generates the parent o-quinone methide (5).[84] In addition the photolysis of lactone (141) leads to ketene (142) by loss of benzaldehyde.[62]

One approach to the generation of o-quinone methides which has no counterpart in the generation of other o-quinonoid analogues discussed earlier, is the oxidation of suitably substituted phenols such as (143).[85a,85b] A substituent with no α-hydrogens is necessary in order to prevent radical coupling or formation of the p-quinone

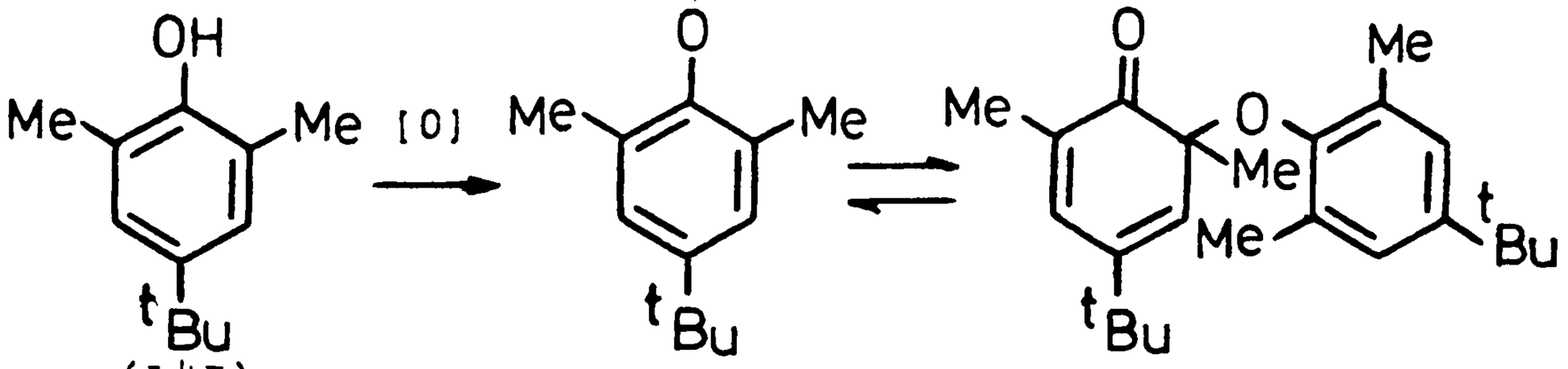


(139) (5) (140)

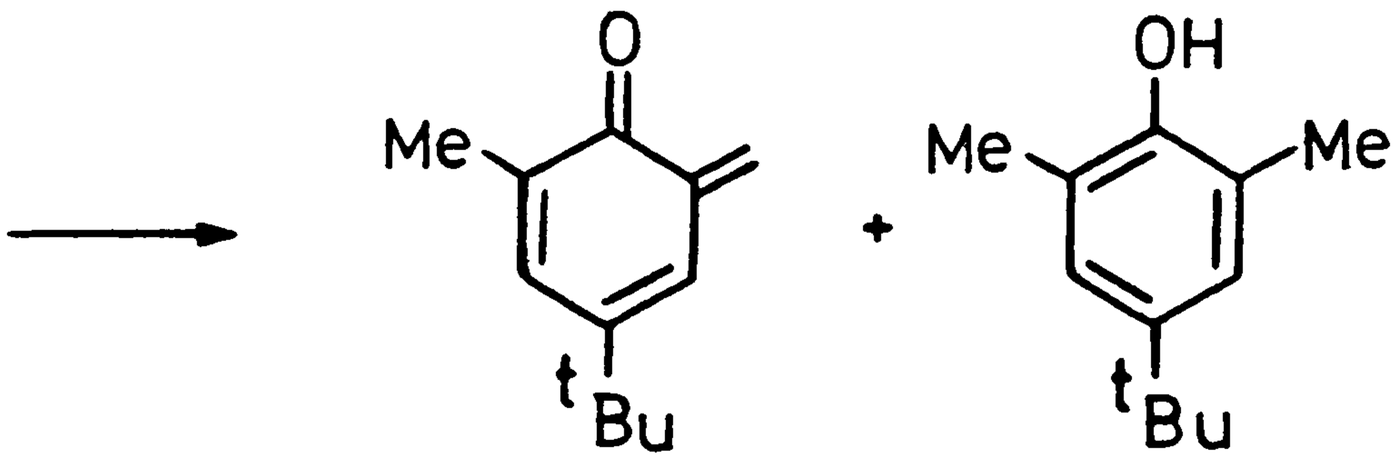


(141) (142)

methide.[86a] The proposed mechanism[85a] for the formation of o-quinone methide (144) is given in Scheme 4 below.



(143)

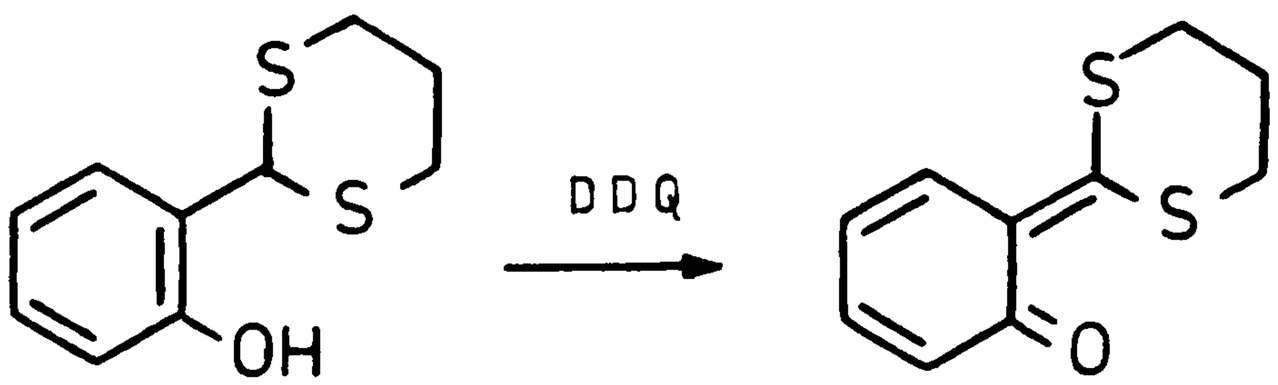


(144)

SCHEME 4

In the absence of a trap, (144) trimerizes, but in the presence of dienophiles, (144) may be trapped with the production of chromans.[86b]

A second oxidative method for the generation of o-quinone methides involves oxidation of dithiane (145) with DDQ. Chromatography of the resulting reaction mixture yields a red solid to which structure (146) has been assigned.[86c]

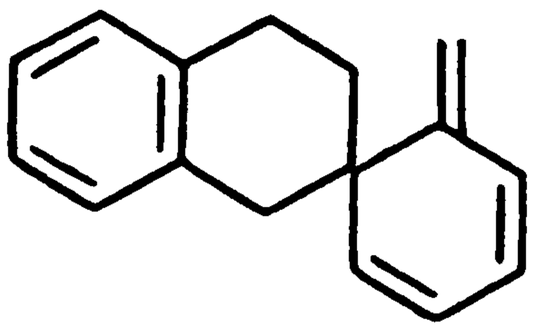


(145) (146)

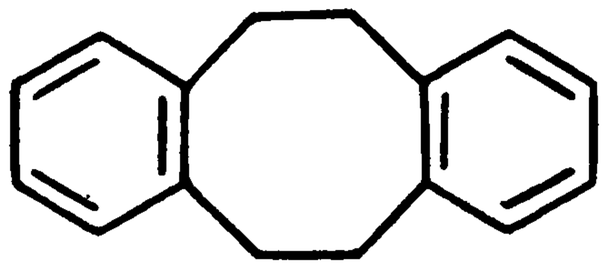
1.3 DIMERIZATION

(a) o-XYLYLENES

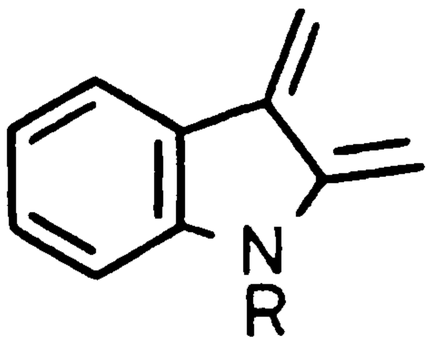
Very few examples of dimerization of o-xylylenes have been reported as isomerization to benzocyclobutenes (see Section 1.4(a)) or other reactions often occur much more readily. However, the few cases that have been reported reveal that o-xylylene can form two dimers, a spiro dimer (147), and a linear dimer (148). At temperatures below $0^{o}C$, formation of the spiro dimer occurs. This molecule is however, unstable and polymerizes at room temperature or upon attempted distillation.[36] A recent example of formation of this type of dimer has been described by Marinelli[35] in the case of indole-2,3-quinodimethanes (42) which in the absence of a trap afford the spiro dimers (149).



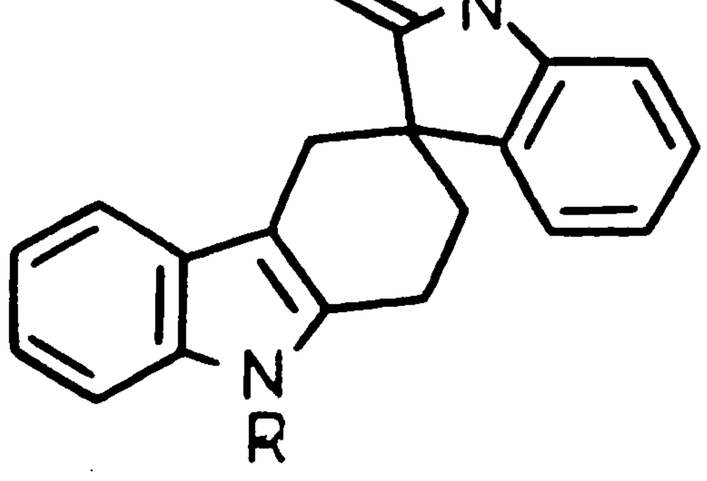
(147)



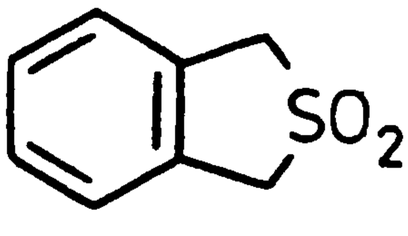
(148)



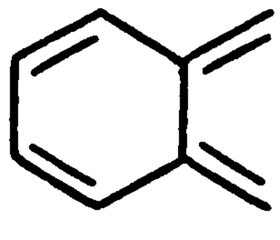
(42)



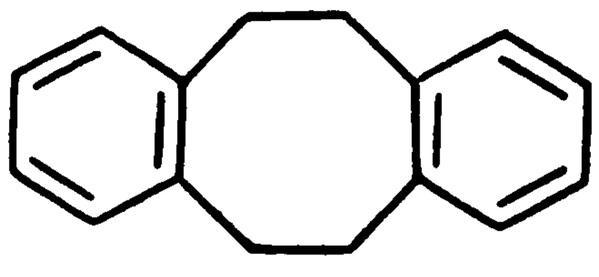
(149)



(46)



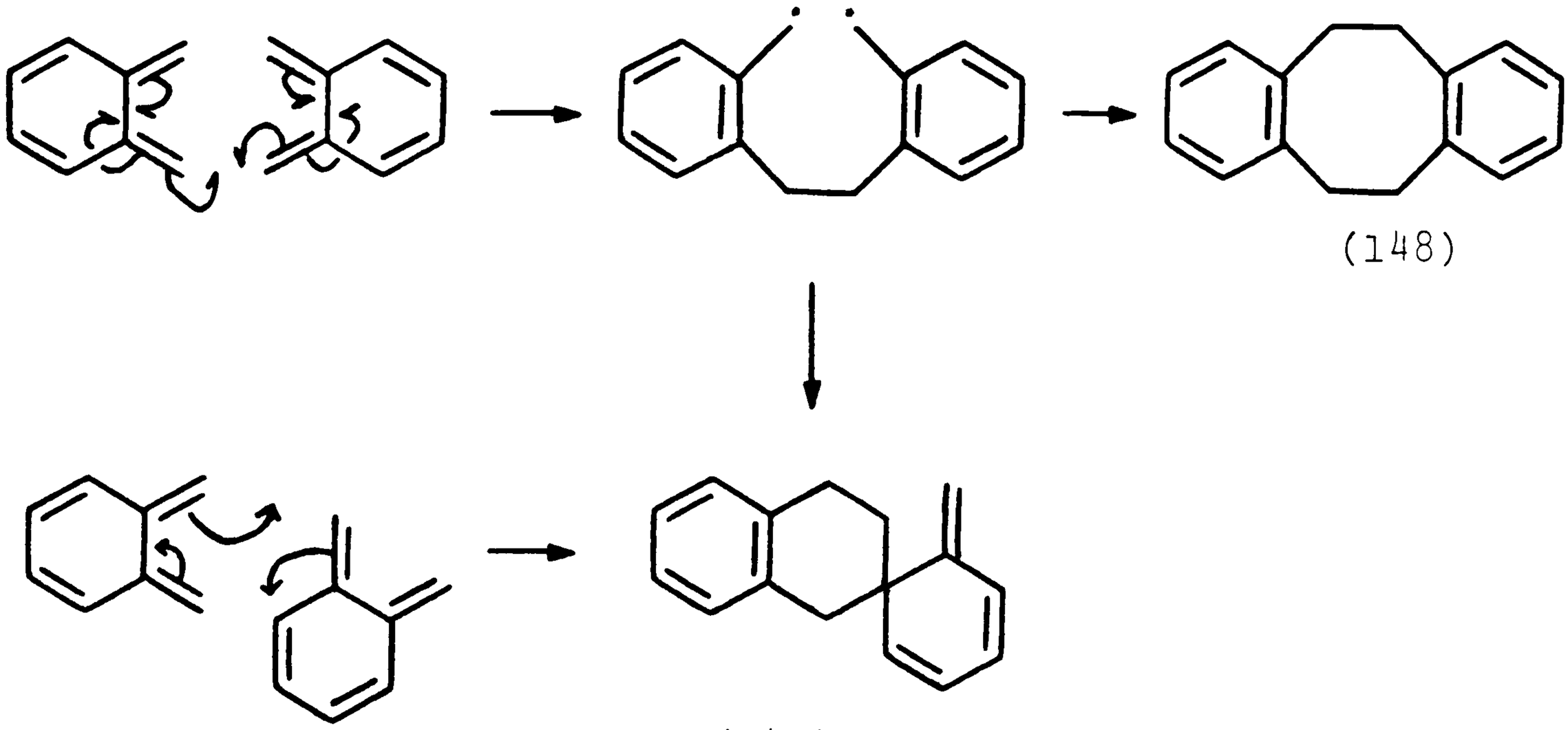
(24)



(148)

The linear dimer is formed when o-xylylenes are produced at higher temperatures. For example, o-xylylene (24) at 300°C in solution, produces the linear dimer (148) in good yield.[38] At intermediate temperatures a mixture of the two dimers may be obtained.[32,87] Because of this temperature dependence of dimer formation, it has been suggested[31] that dimerization of o-xylylenes may occur by a radical pathway, although the formation of the spiro dimer (147) can also be rationalized as a Diels-Alder reaction (Scheme 5).

In addition the dimerization of certain functionalised o-xylylenes (150) provides further support for the radical pathway.[88,89,90,91]

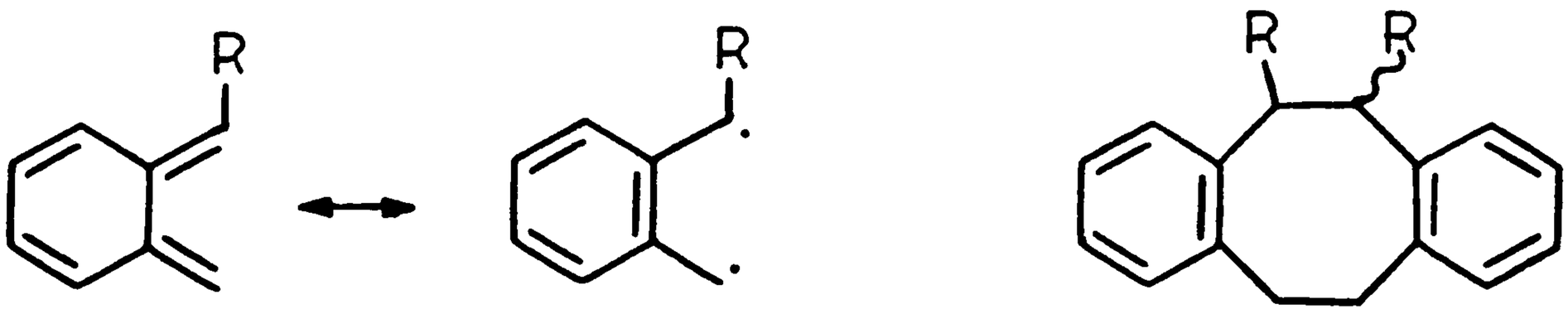


(148)

(147)

SCHEME 5

All of these xylylenes dimerize in a linear head-to-head fashion which is consistent with the most stable diradical. It is noteworthy that o-xylylene (150, R = SMe) also dimerizes to give a spiro dimer which isomerizes on heating to the linear dimer (151, R = SMe).

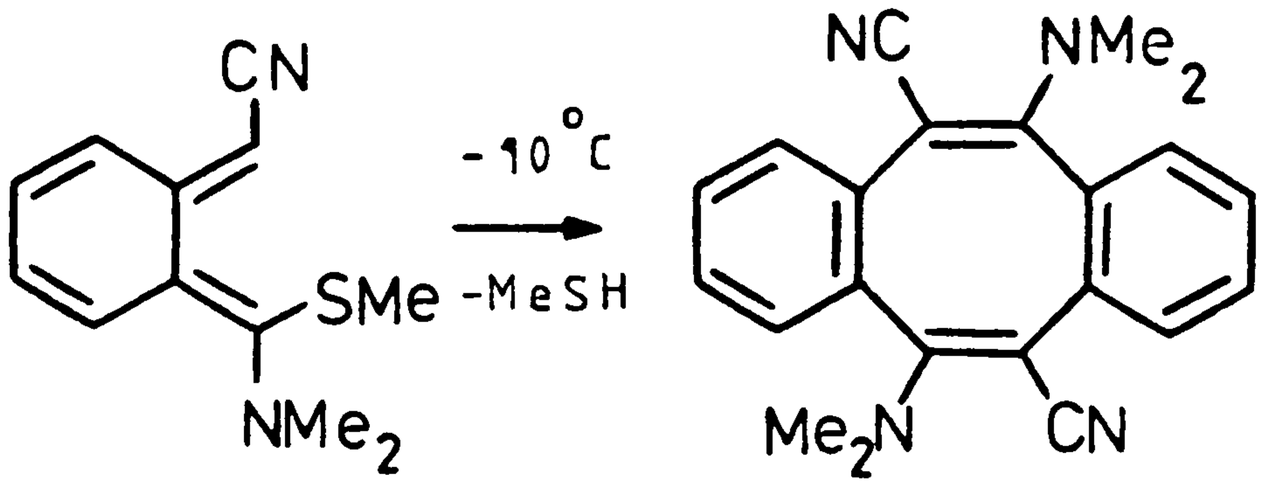


(151)

(150) R = SMe, $PO(OR)_2$

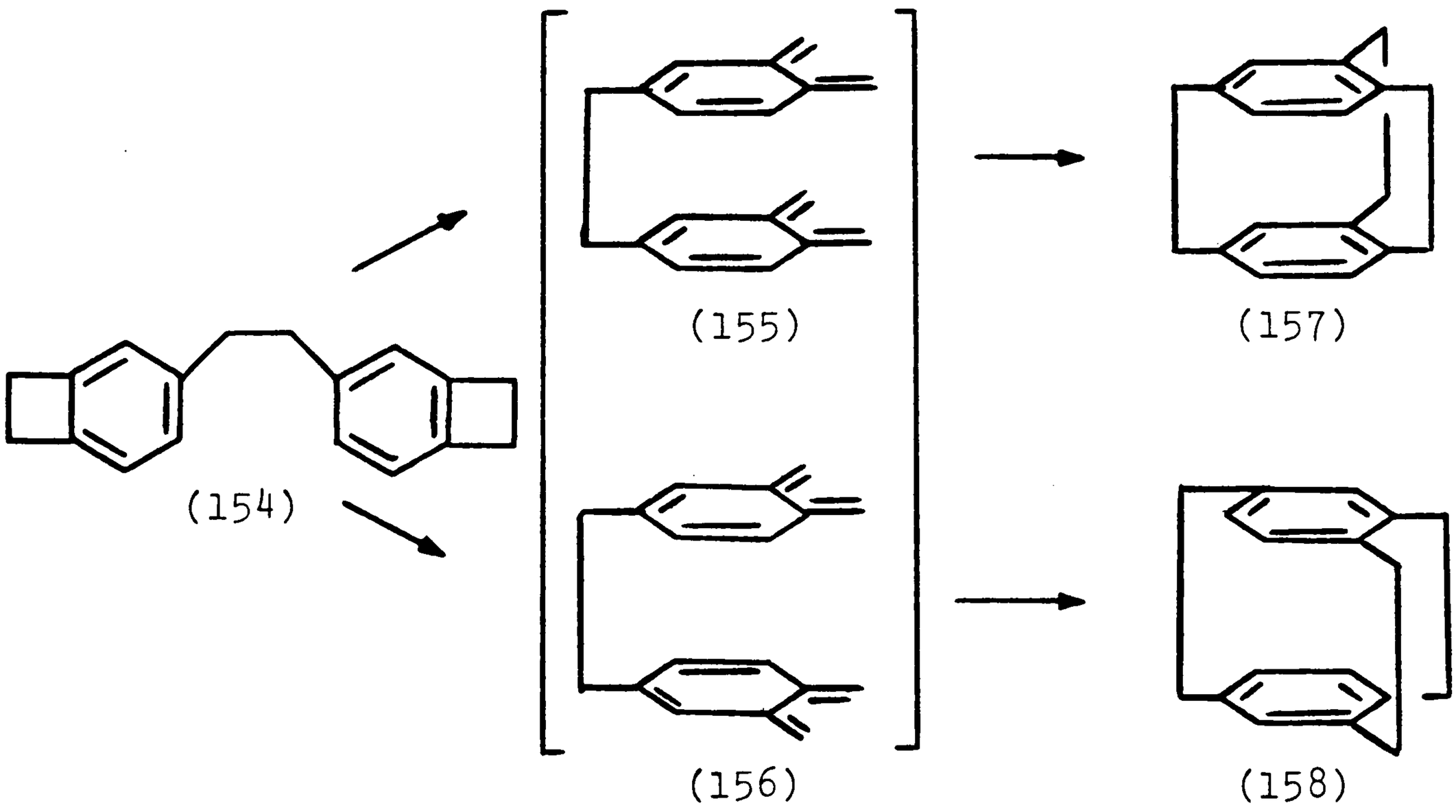
CN, $CONH(CH_2)_3CH=CH_2$

In contrast, the highly stabilised o-xylylene (152) dimerises to form a linear head-to-tail dimer (153), probably via a zwitterionic intermediate.[92]



(152) (153)

An interesting application of the dimerization of o-xylylenes has been reported by Vollhardt. Flash pyrolysis of bis-benzocyclobutene (154) produces para-cyclophane (157) in high yield, presumably through the bis-xylylene (155).[93] None of the chiral isomeric paracyclophane (158) was observed, presumably due to the higher energy transition state involved in the cyclization of (156).[93]



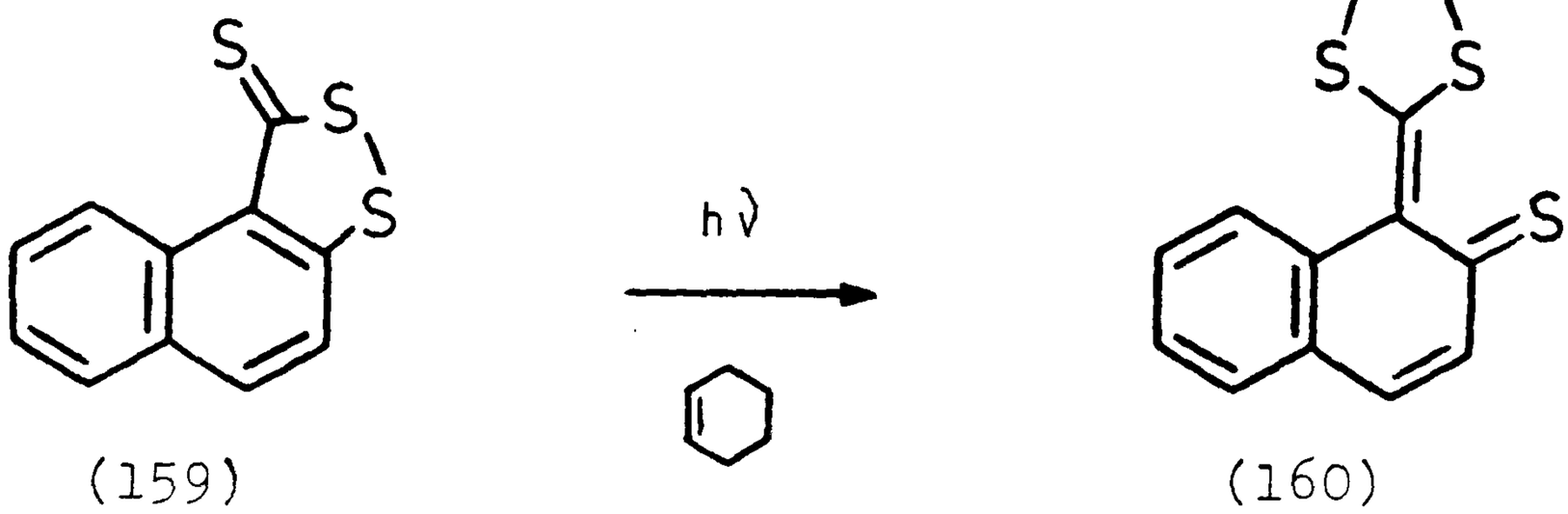
(154) (155) (156) (157) (158)

(b) o-THIOQUINONE METHIDES

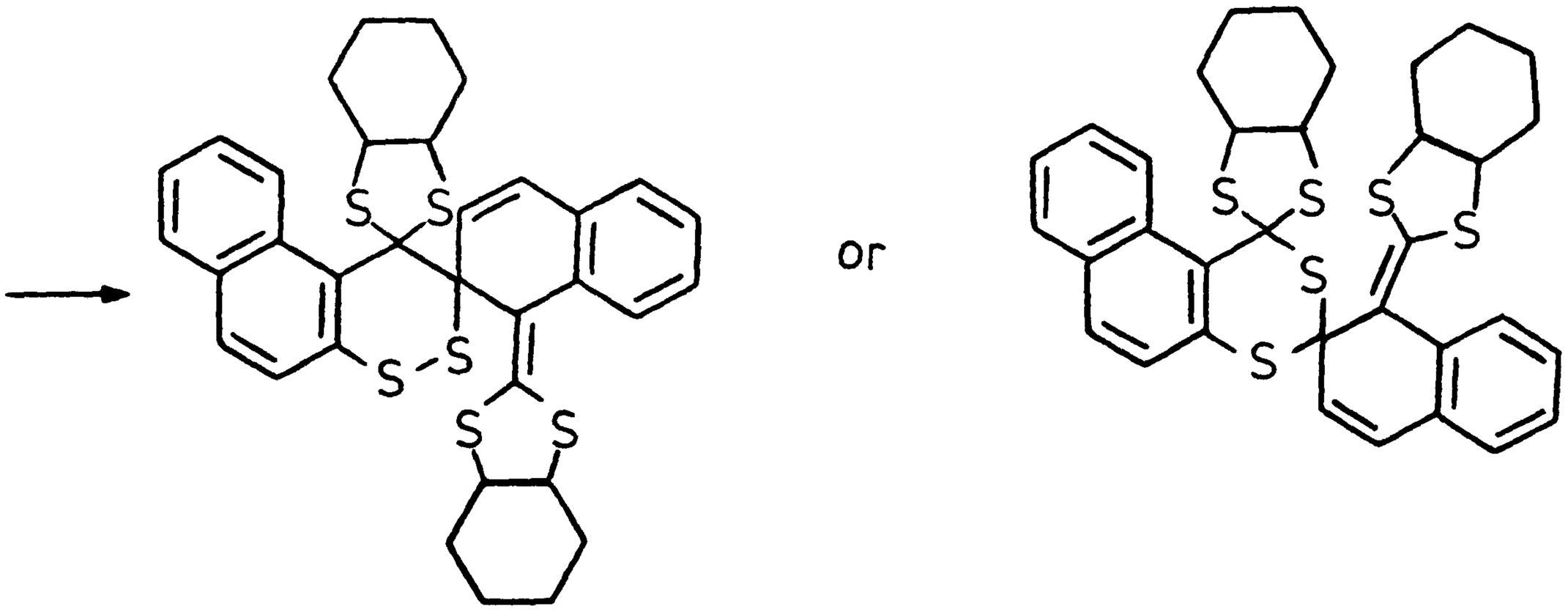
Although there are a number of reports concerning the dimerization of o-thioquinone methides, these are almost exclusively concerned with the formation of the linear dimer and it appears that in contrast to o-xylylenes, o-thioquinone methides do not generally form the spiro dimer. However, stable naphthothioquinone methide (160) formed from irradiation of thione (159) in the presence of cyclohexene is the only exception giving a dimer for which spectroscopic and analytical data are consistent with either of the spiro structures (161) or (162). Interestingly, the isomeric naphthothioquinone methide (163) shows no tendency to dimerize. This difference in behaviour was suggested to be due to the increased reactivity of (160) over (163) due to the steric interaction of the dithiane group with the hydrogen at the peri position of (160).[94]

The parent o-thioquinone methide (58) is reported to dimerize to give the head-to-tail dimer (60).[49,56] However, with other examples of dimerization of o-thioquinone methides there appears to be some confusion as to the regiochemistry of the observed dimers.

Chapman[57b] reports that the generation of ketene (77) by photolysis of lactone (76) at 77K gives rise to IR absorptions due to the presence of thiolactone (78). On warming to -40° these disappear and the head-to-tail dimer (164) is isolated. However, Pedersen[57a] reports that photolysis of (76) at 77K yields the head-to-head



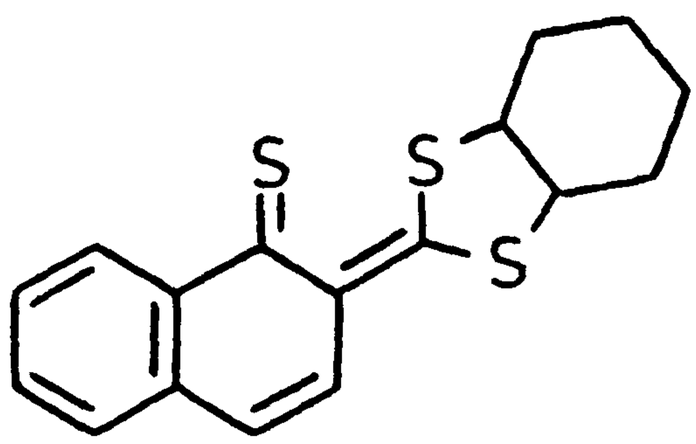
(159)



(161)

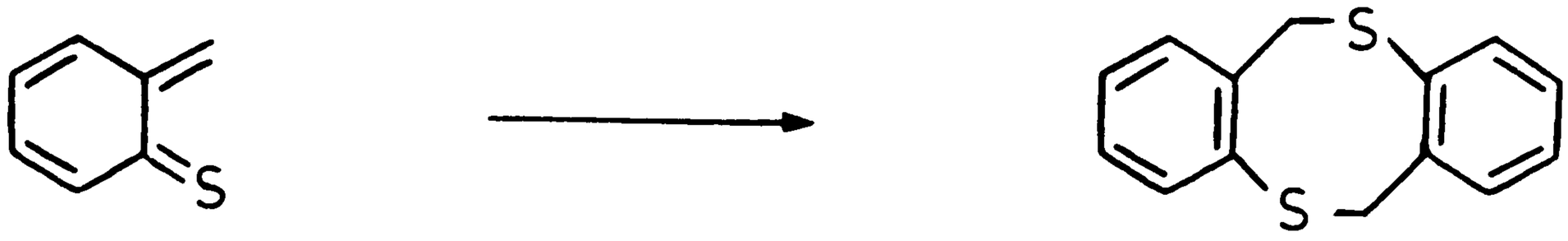
or

(162)

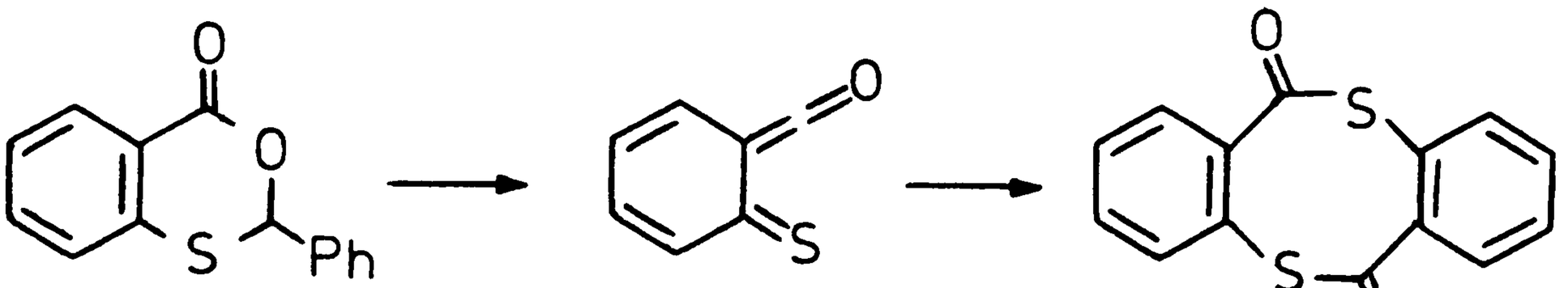


(163)

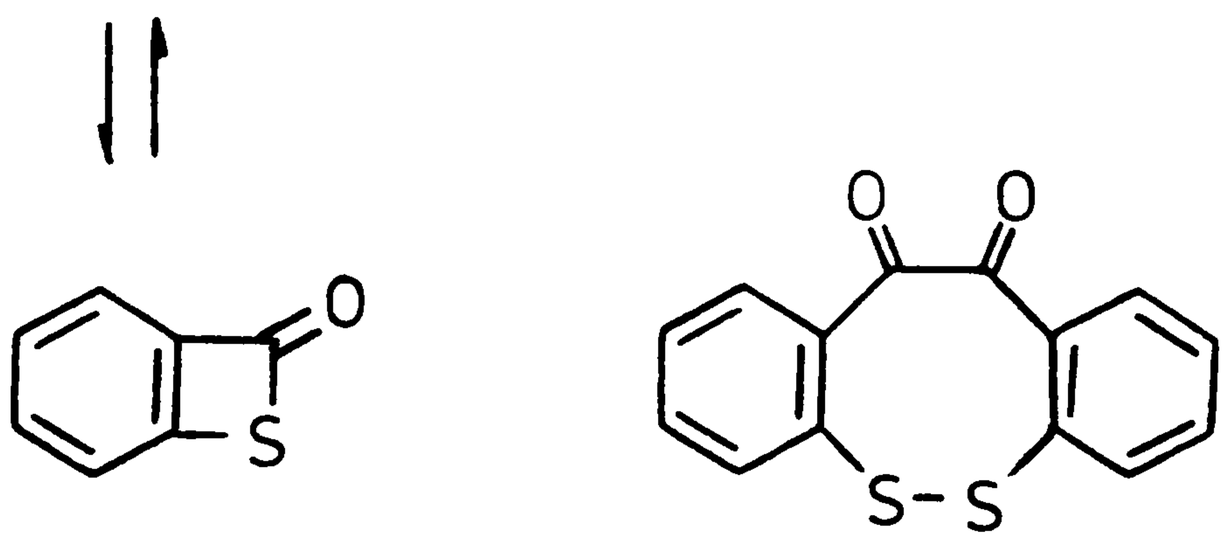
dimer (165), the main evidence for its identity being its desulphurisation with Raney nickel to benzoin and benzil, and its non-identity with an authentic sample of (164).



(58) (60)

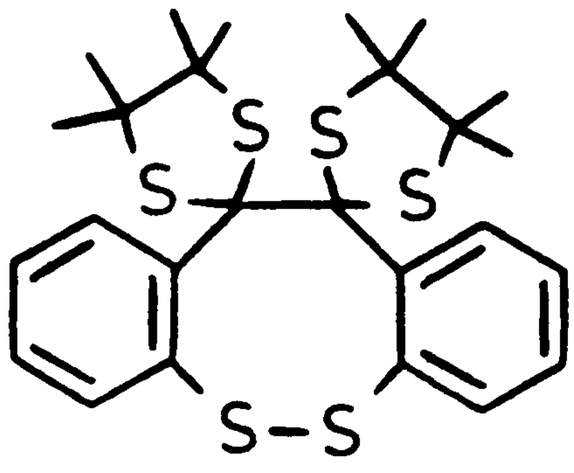


(76) (77) (164)

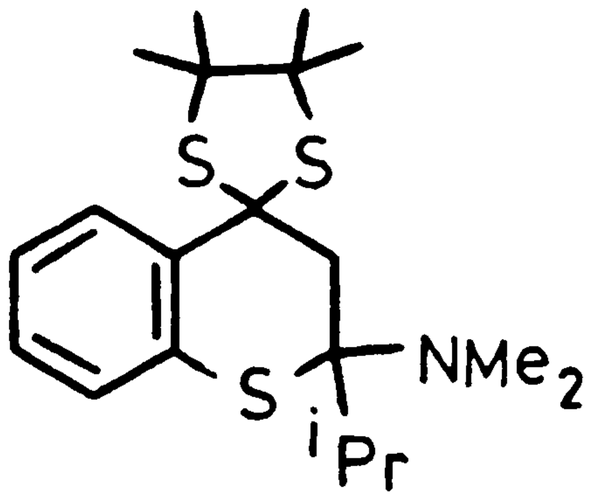


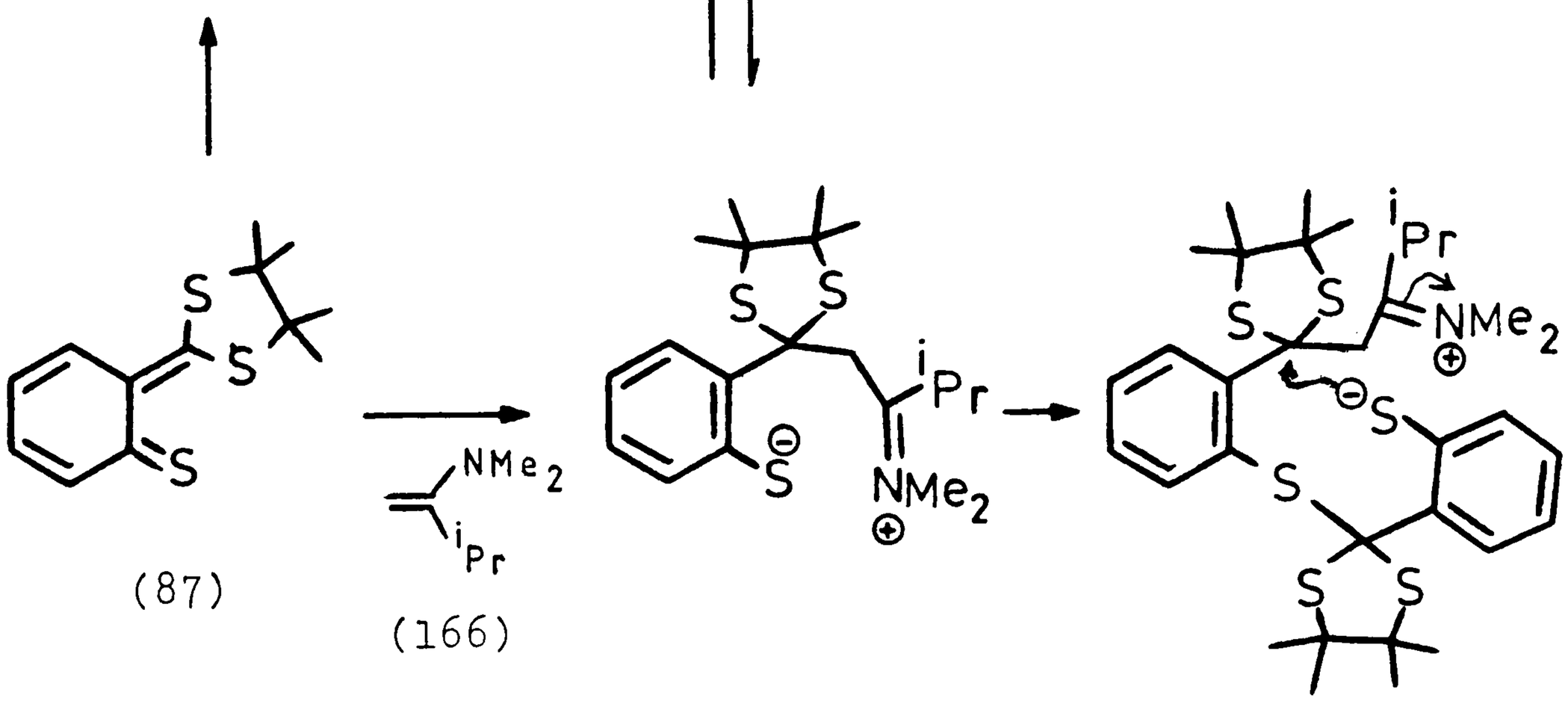
(78) (165)

In addition, it appears that highly stabilised o-thioquinone methides such as (87) can dimerize to give either the head-to-head or head-to-tail linear dimer. For example, under normal conditions (87) dimerizes to yield the head-to-head dimer (88), (see Section 1.2(b)). However, upon treatment of (87) with a hindered amine such as (166), the head-to-tail dimer (167) is obtained.[61b]



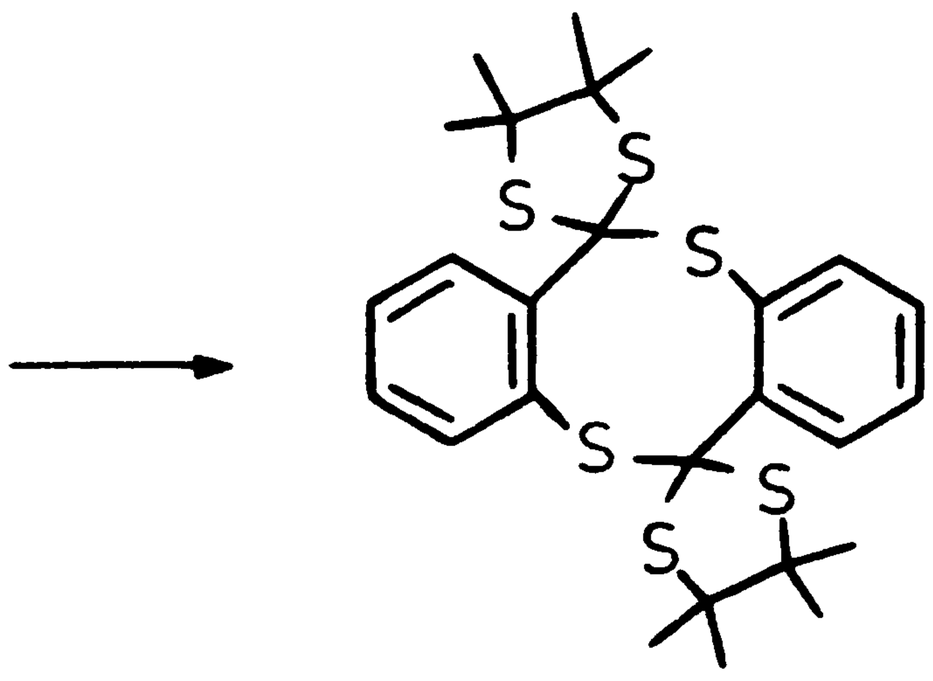
(88)





(87)

(166)



(167)

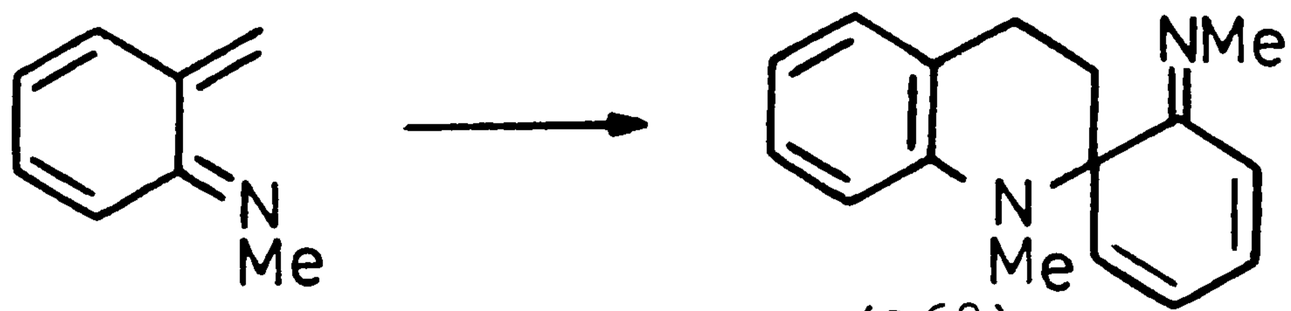
This behaviour seems to parallel that observed for o-xylylenes and the head-to-head dimers appear to be formed by a diradical reaction mechanism. The zwitterionic pathway seems to best explain the formation of the head-to-tail dimers, although in the last example, the ambiphilic

nature of the dithiane moiety is consistent with a zwitterionic pathway for formation of the head-to-head dimer.

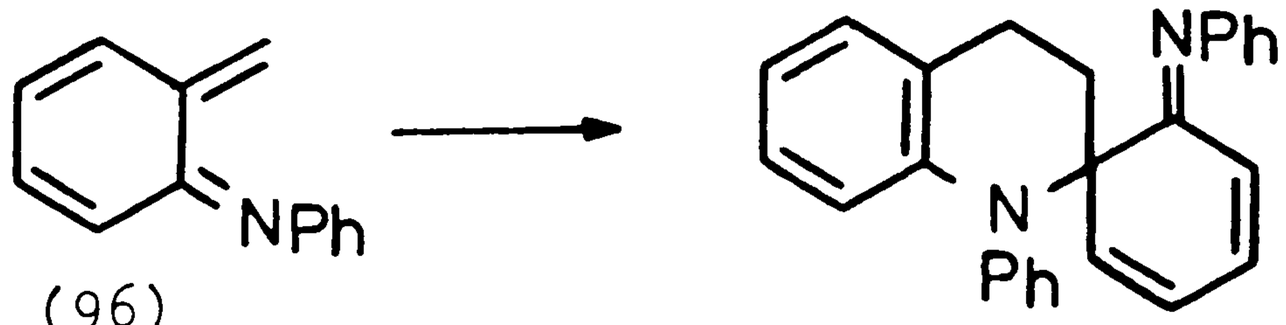
(c) o-AZAXYLYLENES

Once again, only a few reports concerning the dimerization of o-azaxylylenes have appeared. These reveal that o-azaxylylenes dimerize to form only the spiro dimer; this is in sharp contrast to the behaviour of the o-thioquinone methides.

Thus N-methylazaxylylene (113) undergoes dimerization even in the presence of reactive dienophiles to give the spirodimer (168)[65]. Similarly, the spirodimer (169)[70] is formed when N-phenylazaxylylene (96) is generated in solution in the absence of trapping reagents from photolysis of either N-phenylbenzazetidine or N-phenyl-oxindole (see Section 1.2(c)).

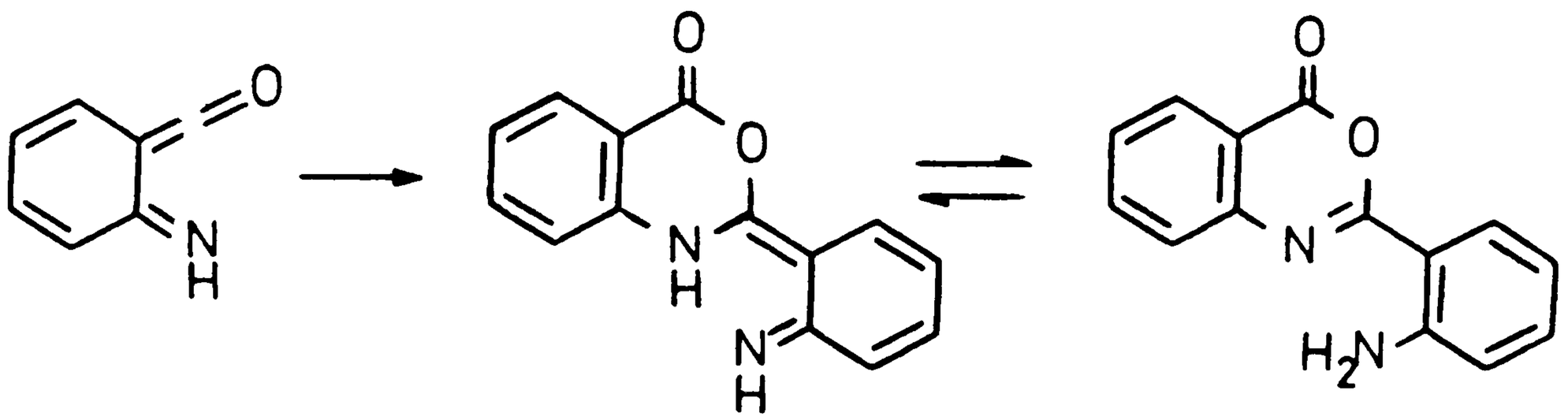


(113) (168)



(96) (169)

Also, ketene (110) dimerizes to give (170);[69] this presumably involves [4+2] cycloaddition with the carbonyl of another molecule to give the observed product. This reaction is in marked contrast to the behaviour of the corresponding o-thioquinone methide analogue of ketene (110) which only gives the linear dimer structures.[57]



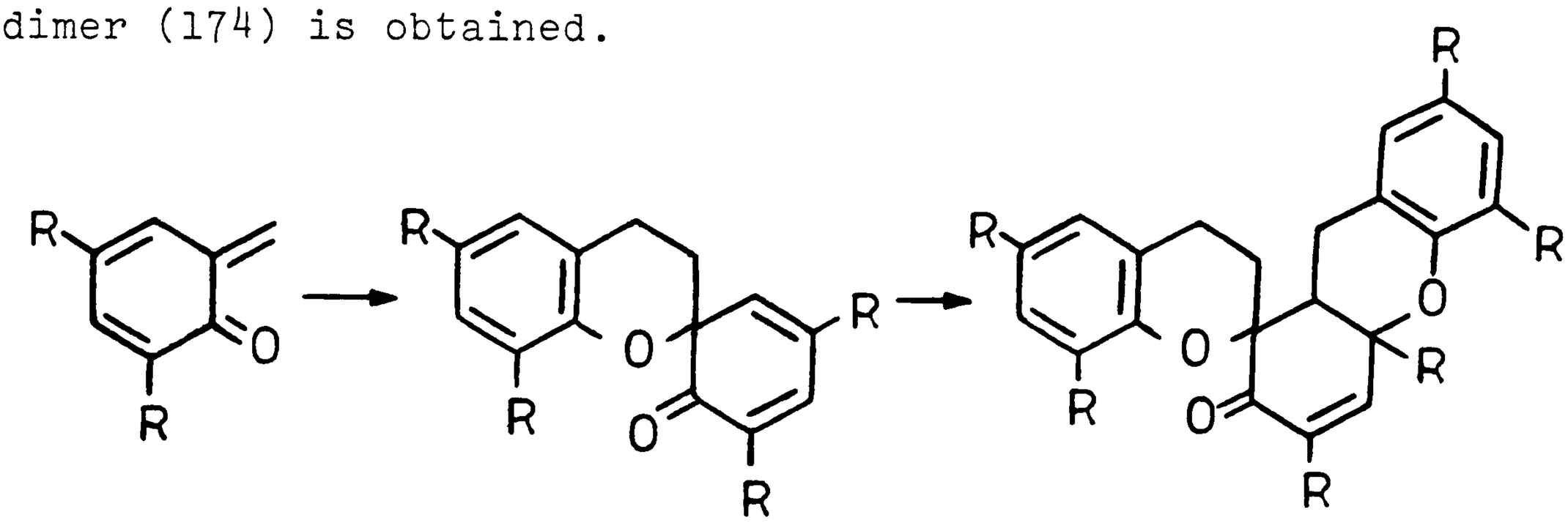
(110) (170a) (170b)

The difference in behaviour between the nitrogen and sulphur analogues may be due to poor 2p - 3pπ overlap in the C=S exocyclic bond. This would allow stepwise reactions to occur because of the enhanced ionic or diradical character of the o-thioquinone methide system.

(d) o-QUINONE METHIDES

The behaviour of o-quinone methides in dimerization reactions is similar to that of o-azaxylylenes in that there have been no reports of the formation of linear dimers from o-quinone methides. However, unlike all the quinonoid species discussed previously, simple o-quinone methides can lead to the formation of trimers. For example, the parent o-quinone methide (5) which is stable

below -20°C, leads to a mixture of dimer (171) and trimer (172) on warming. It is likely that this reaction proceeds by initial formation of the spirodimer (171) by [4+2] addition, followed by further reaction of this dimer with another molecule of o-quinone methide (5).[47,76,77] With the more hindered di-t-butyl species (173), only the dimer (174) is obtained.

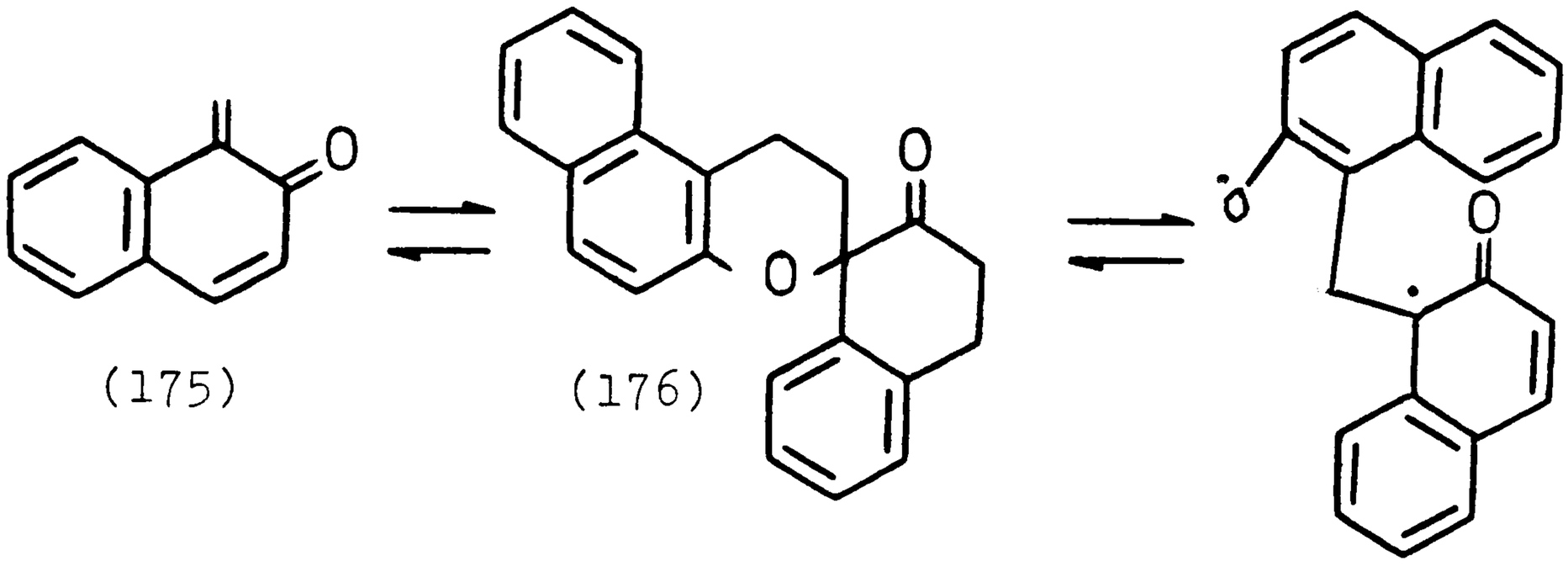


(5) R = H (171) R = H (172) R = H

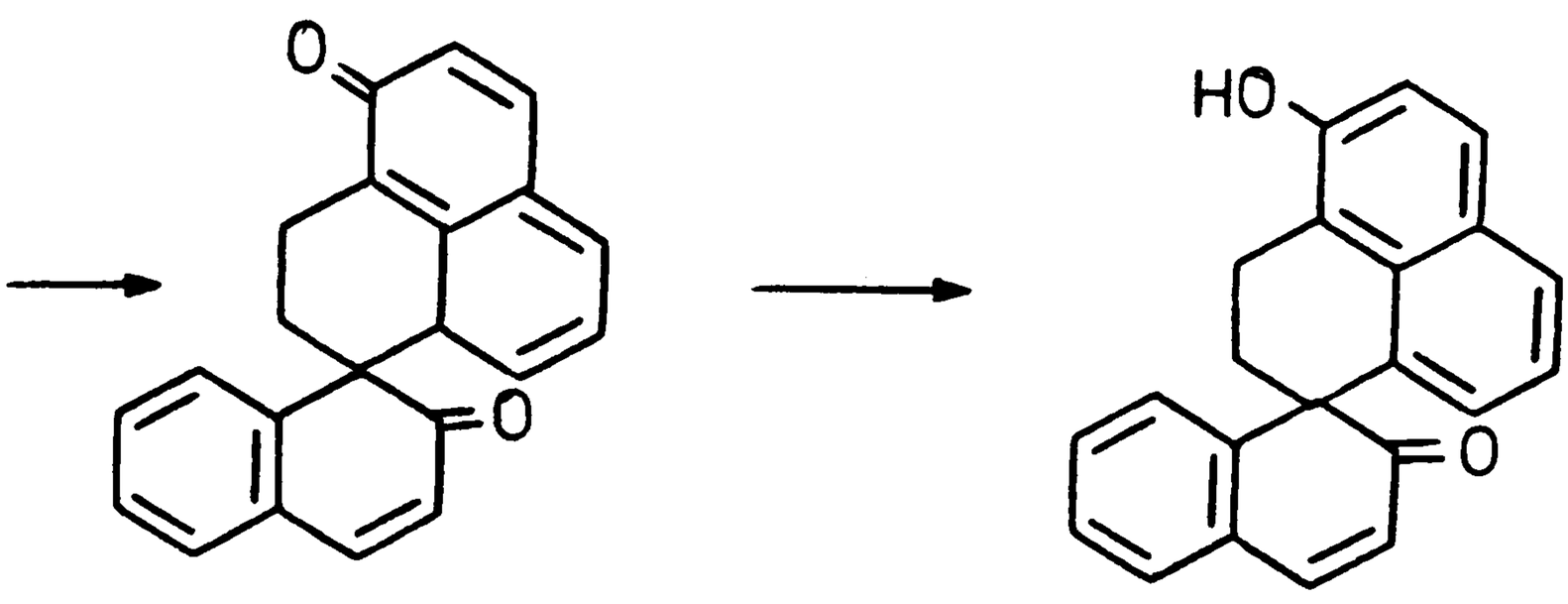
(173) R = ^{t}Bu (174) R = ^{t}Bu

Naphthoquinone methide (175) also forms only the spiro dimer (176), in this case reversibly.[95] However, generation of (175) from the dimer is complicated by the slow isomerization of dimer (176) to (177) at temperatures above 80°C.[85b]

Because there appear to be no reports concerning the formation of linear dimers, it is likely that the dimerization of o-quinone methides is a concerted process. This is consistent with there being a greater separation of HOMO and LUMO in the o-quinone methide and therefore less biradicaloid character. An apparent contradiction



(175) (176)



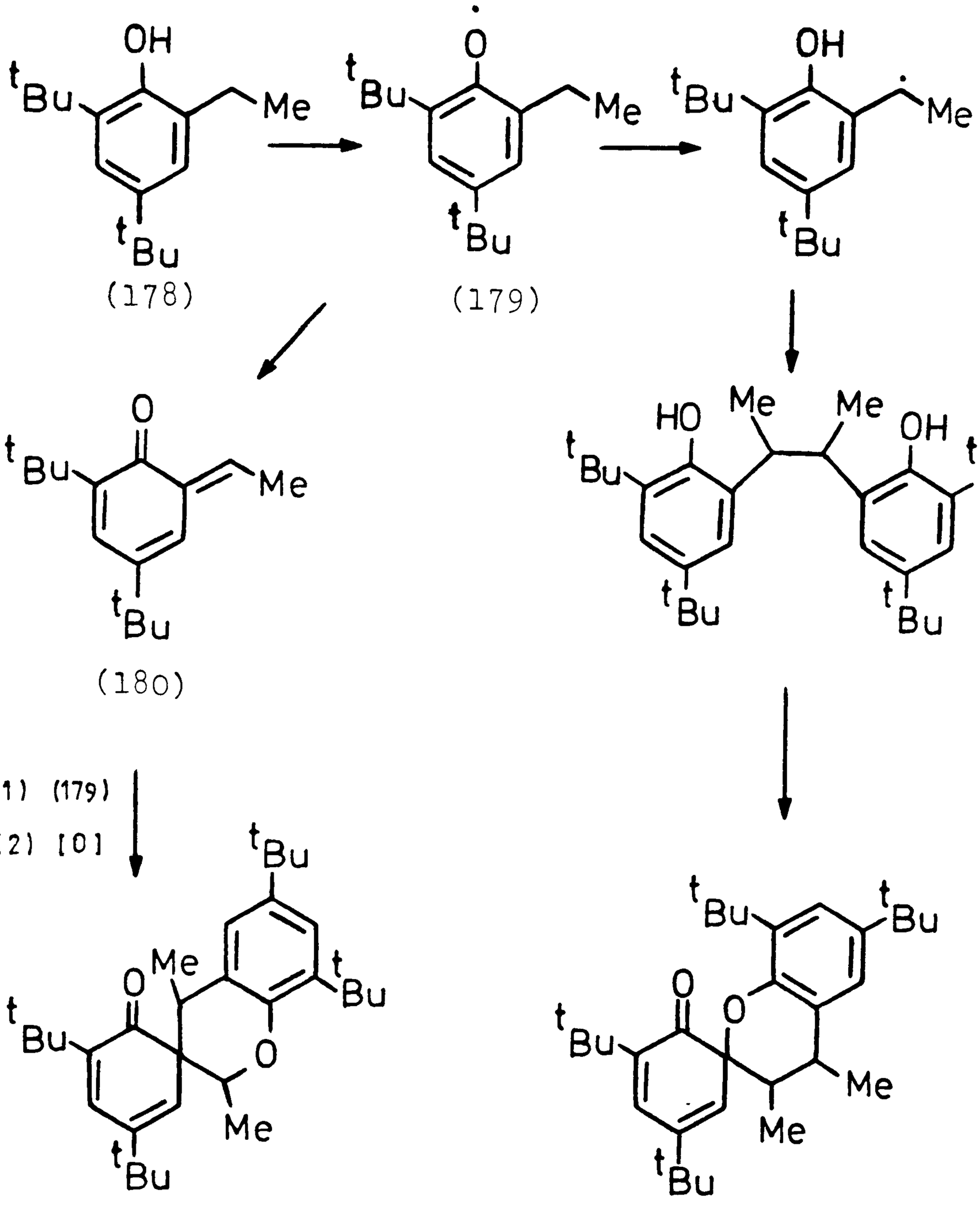
(177)

to this is the formation of two spirodimers (181) and (182) from the phenolic oxidation of (178).[96] For the reaction to be concerted in this case, it is necessary to postulate that o-quinone methide (180) reacts in a non-regiospecific manner. Since normally only dimers analogous to (182) are formed,[94,85b,96,97] an alternative mechanism could be that shown in Scheme 6.

1.4 NUCLEOPHILIC ADDITION

(a) o-XYLYLENES

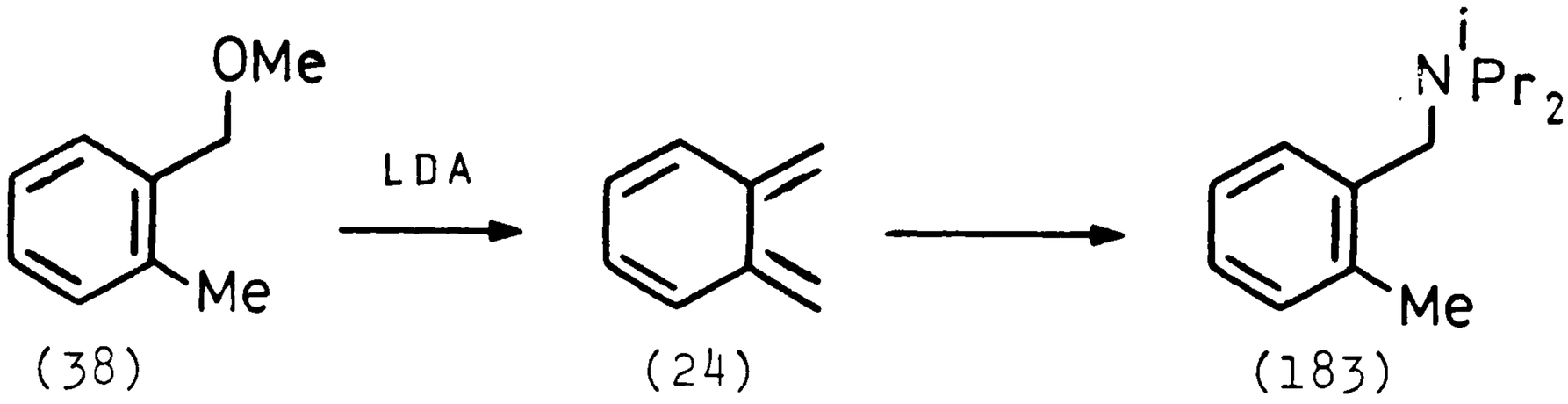
Although o-xylylenes are extremely reactive dienes, those systems with simple substituents do not possess any significant degree of polarization and therefore even



SCHEME 6

in the presence of reactive nucleophiles might well be expected to undergo dimerization or electrocyclic ring closure to benzocyclobutenes (see Section 1.5(a)) rather than participate in nucleophilic addition. Indeed, there

seems to be only one report of such a reaction. Thus treatment of ether (38) with LDA at room temperature produces amine (183). The direct displacement of methoxide was excluded by the observation that methyl benzyl ether itself is unchanged when exposed to similar conditions. The reaction was rationalized as involving elimination of methanol to give the parent o-xylylene (24) followed by addition of the LDA/diisopropylamine reagent to yield amine (183).[32]

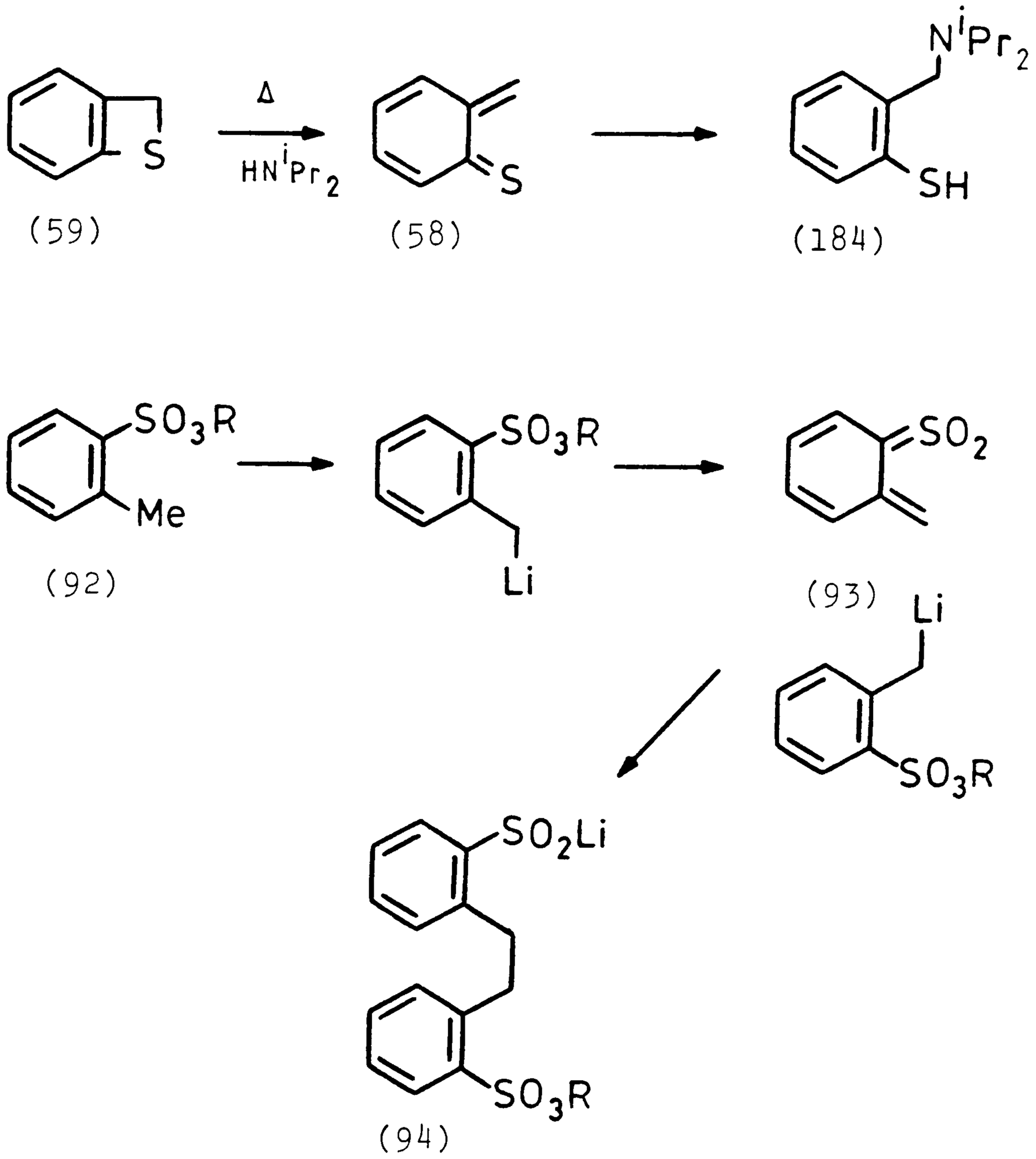


(38) (24) (183)

(b) o-THIOQUINONE METHIDES

The presence of a heteroatom in the exocyclic diene has the effect of polarizing the system and therefore renders the species prone to attack by nucleophiles. Indeed, despite there being only a few reported cases, this seems to be true for o-thioquinone methides. For instance, if benzothiete (59) is heated in the presence of diisopropylamine, the product is (184), presumably originating from nucleophilic addition of the amine to the carbon terminus of o-thioquinone methide (58).[49]

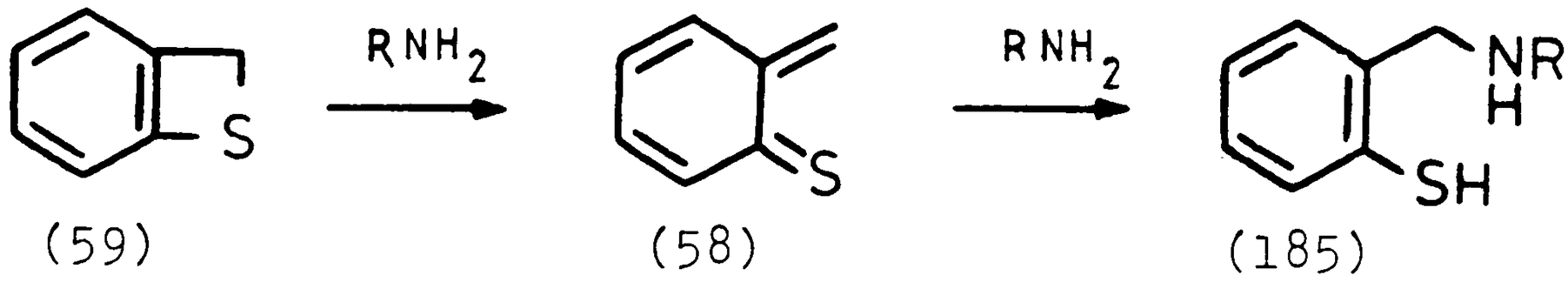
A less clear cut example involves the formation of salt (94) by treatment of sulphonate (92) with ^{n}BuLi which is postulated to proceed as shown.[63]



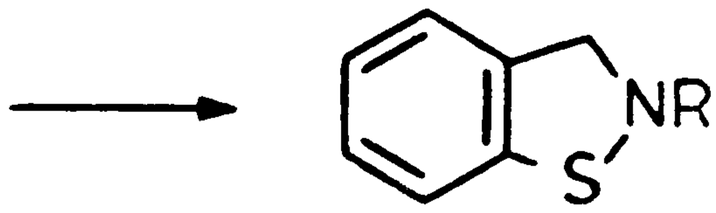
(59) (58) (184)

(92) (93) (94)

A recent report describes the formation of 2,3-dihydro-benzisothiazoles (186) by heating benzothiete (59) with various primary amines. Again, the reaction may be rationalized as involving nucleophilic attack of o-thioquinone methide (58) by a molecule of amine followed by auto-oxidation of the resulting thiol (185) to give (186).[98]

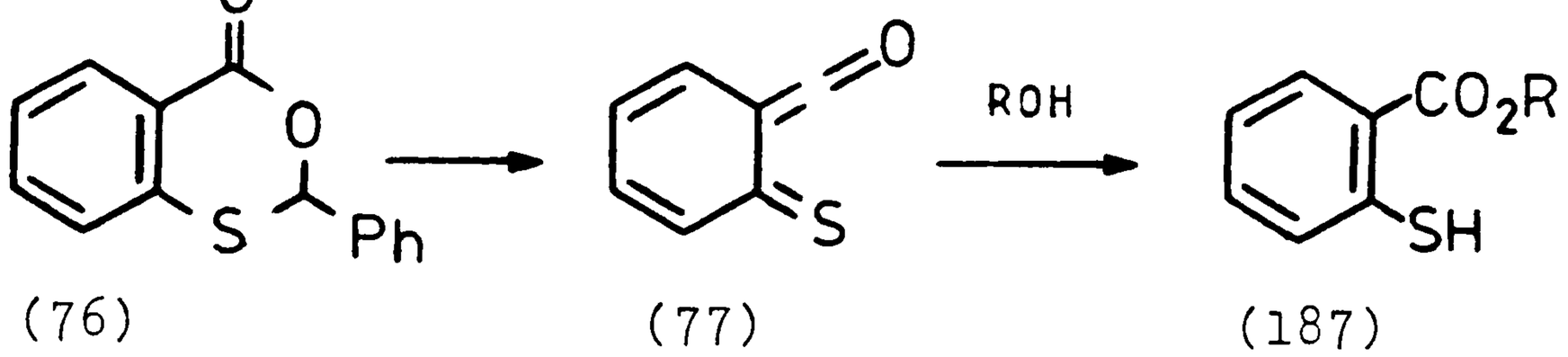


(59) (58) (185)



(186)

Finally, if ketene (77) is generated by photolysis of benzothianone (76) in either methanol[57a] or ethanol,[57b] the esters (187) are produced presumably by nucleophilic attack on (77) by a molecule of alcohol.

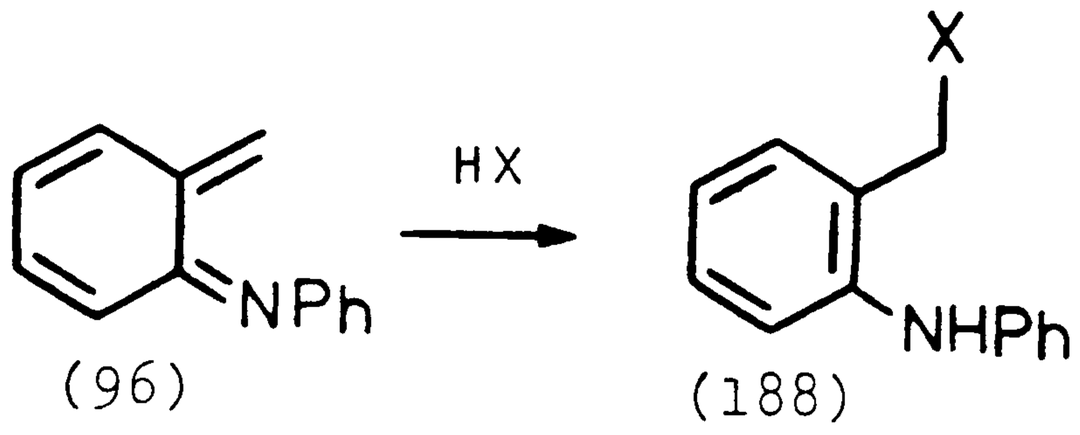


(76) (77) (187)

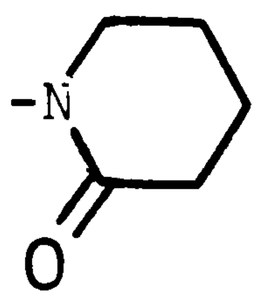
(c) o-AZAXYLYLENES

o-Azaxylylenes behave like very reactive conjugated imines in the presence of nucleophiles and are readily attacked at the exocyclic methylene position. Thus generation of N-phenylazaxylylene (96) from photolysis of N-phenyloxindole[70] in the presence of a variety of nucleophiles gives good yields of the corresponding adducts (188). These results are summarized in Table 2.

TABLE 2

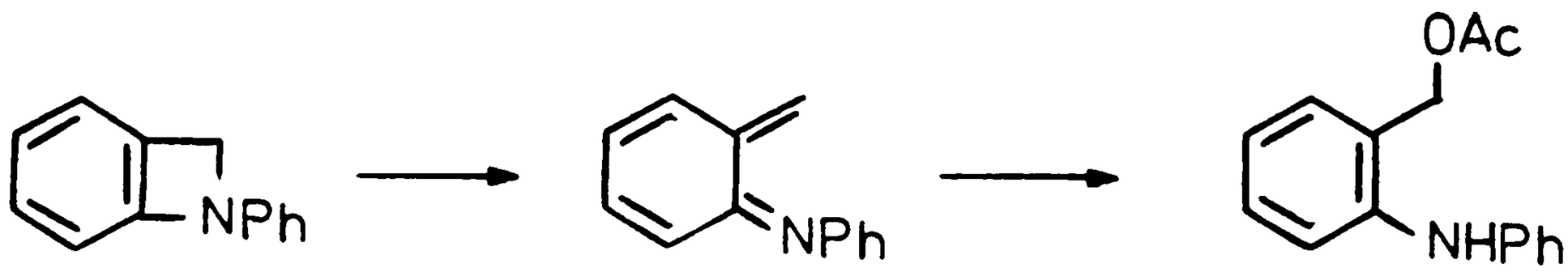


(96) (188)

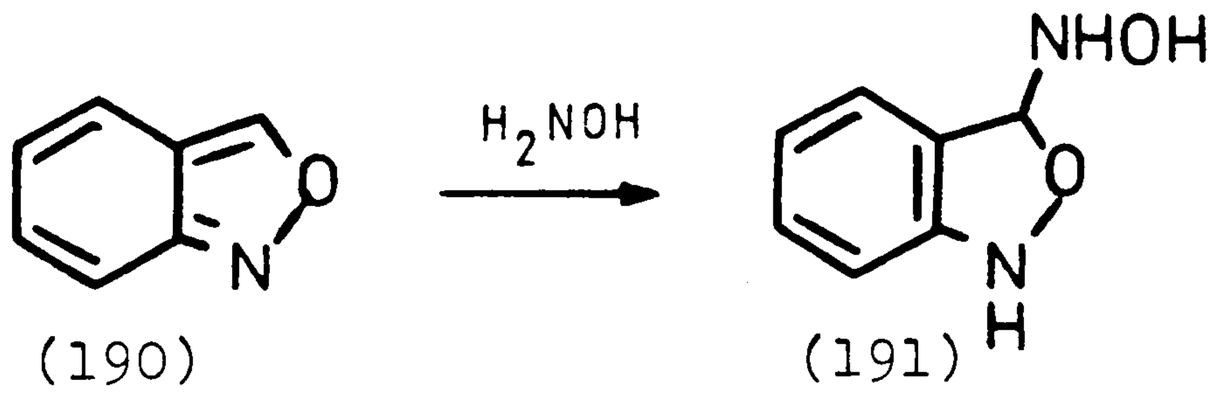
(188)	X	Yield%	REFERENCE
a	NHMe	65	99
b	NHPh	94	54,99
c	NH^nBu	92	99
d	NMe_2	92	99
e		97	99
f	OH	"High"	54
g	OEt	61	99
h	OCOMe	75	54,99
i		98	99

In addition, if N-phenylbenzazetidine is heated or photolysed in the presence of a nucleophile, for example acetic acid, the resulting product is (189) which can be rationalised as resulting from nucleophilic addition to an intermediate o-azaxylylene (96).[64] A nucleophilic addition to an o-azaxylylene has also been invoked to explain the

formation of amine (104) from ether (102) upon treatment with phenyl magnesium bromide[67] (see Section 1.2(c)). Certain stabilised o-azaxylylenes can also undergo nucleophilic additions. For instance whilst anthranil (190) appears to contain the azaxylylene moiety, it is in fact a rather unreactive system. However, this molecule is fairly susceptible to nucleophilic attack at the 3-position and for example with hydroxylamine, produces (191) which then undergoes further reaction upon ring opening.[100]

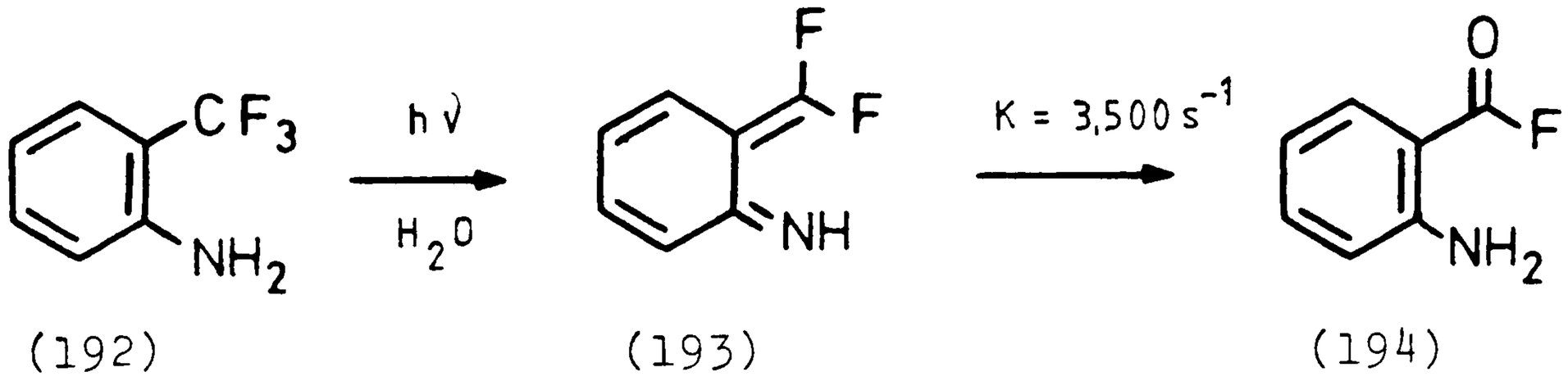


(95) (96) (189)

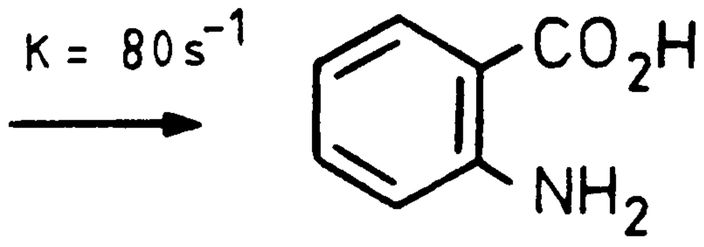


(190) (191)

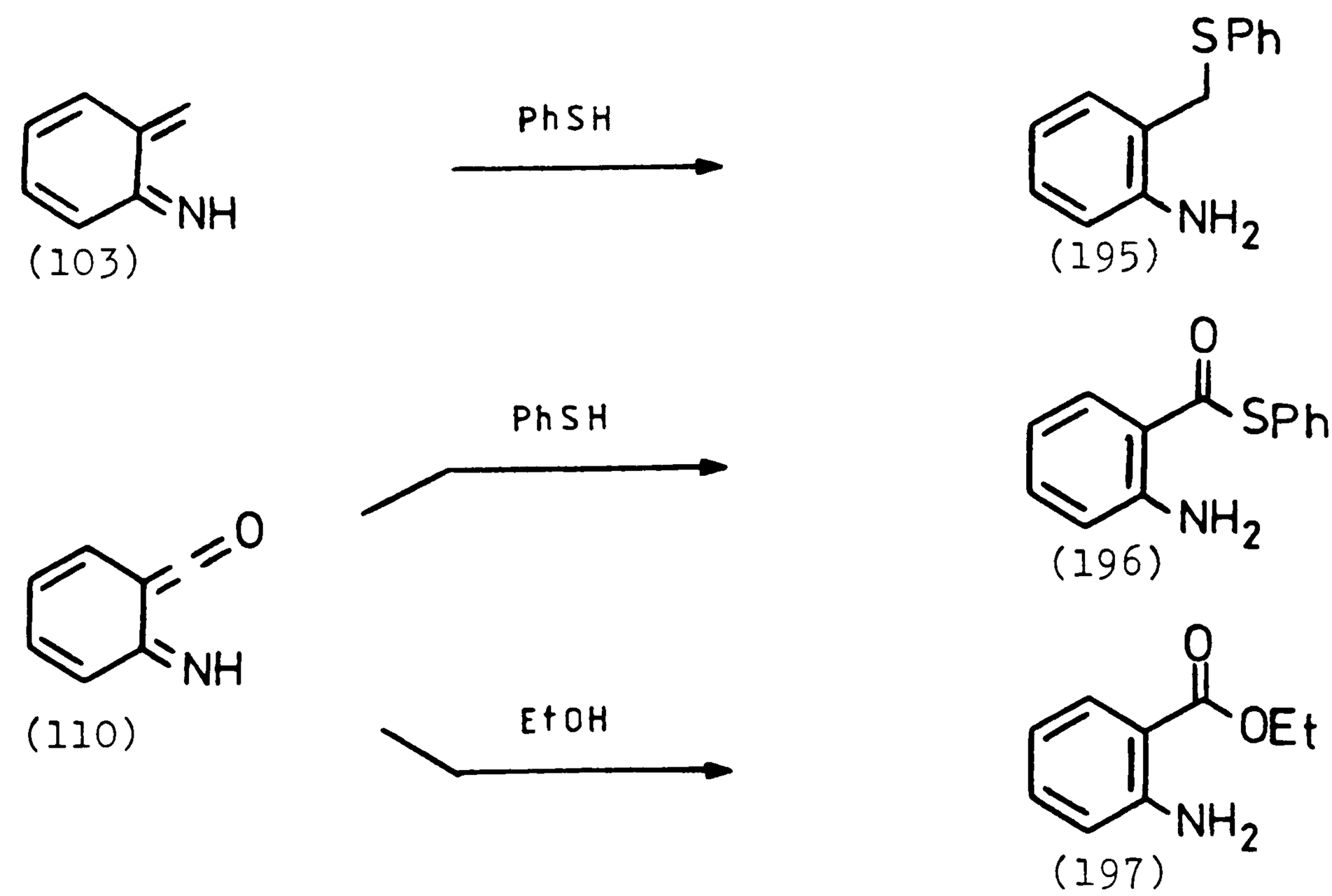
The kinetics of nucleophilic attack on o-azaxylylene (193) have been reported.[101] Generation of (193) by photolysis of amine (192) in aqueous solution results in the formation of acyl fluoride (194) by rapid attack of water. Amine (194) then slowly hydrolyses to yield anthranilic acid.[101]



(192) (193) (194)



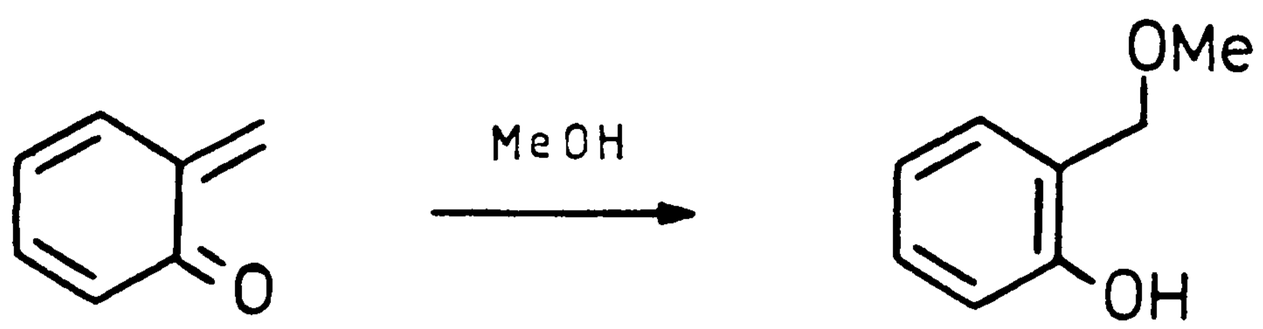
Nucleophilic addition of thiophenol to the parent o-azaxylylene (103) has been reported to give sulphide (195) in good yield.[102] Finally, the trapping of ketene (110) by thiophenol and ethanol yields thioester (196) and ester (197) respectively.[102]



(103) (195) (110) (196) (197)

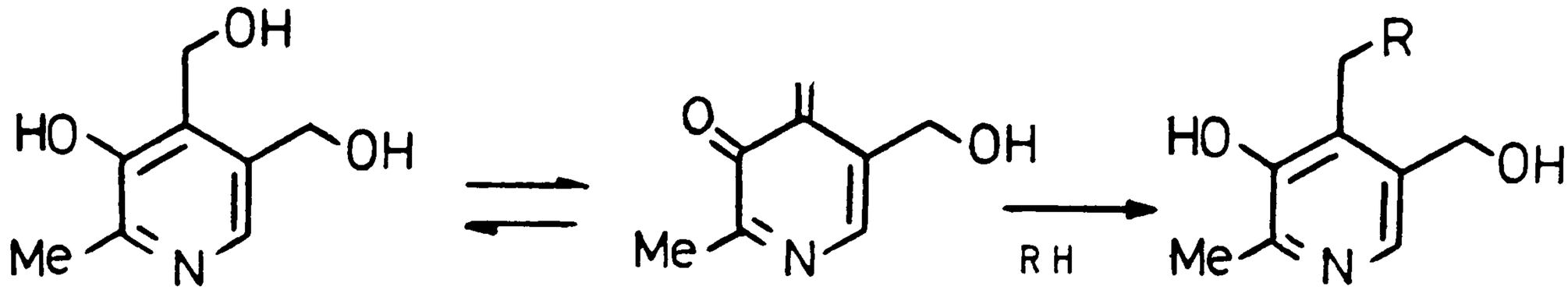
(d) o-QUINONE METHIDES

In view of the high reactivity of o-thioquinone methides and o-azaxylylenes to nucleophilic addition, it is not surprising that o-quinone methides also show a high degree of reactivity towards nucleophiles. For example, generation of the parent o-quinone methide (5) in the presence of methanol results in the formation of ether (198) by nucleophilic addition.[84]

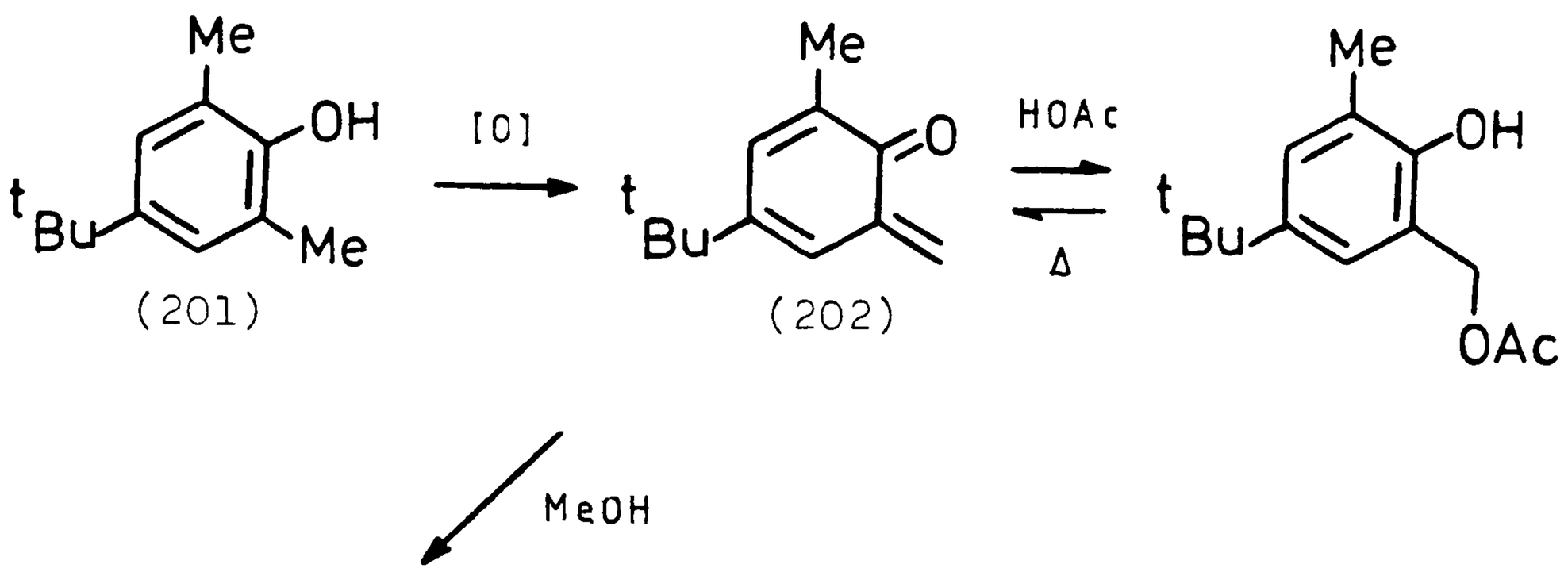


(5) (198)

Nucleophilic addition to the pyridine-quinone methide (200) formed from pyridoxine (199) has been reported,[103] and it has been suggested that the potent alkylating activity of (200) may be involved in the enzymatic reactions of vitamine B_6 and in certain toxicological reactions induced by pyridoxine.[103] In addition, oxidation of phenol (201) in the presence of nucleophilic species such as acetic acid or methanol affords products resulting from nucleophilic attack on an intermediate o-quinone methide (202). However, in the case of methanol, if an excess of oxidant is present, the adduct resulting from attack of methanol (203) may itself be oxidized to o-quinone methide (204) and attacked by a second mole of nucleophile.[85a]



(199) (200)



(201) (202) (203) (204)

1.5 PERICYCLIC REACTIONS

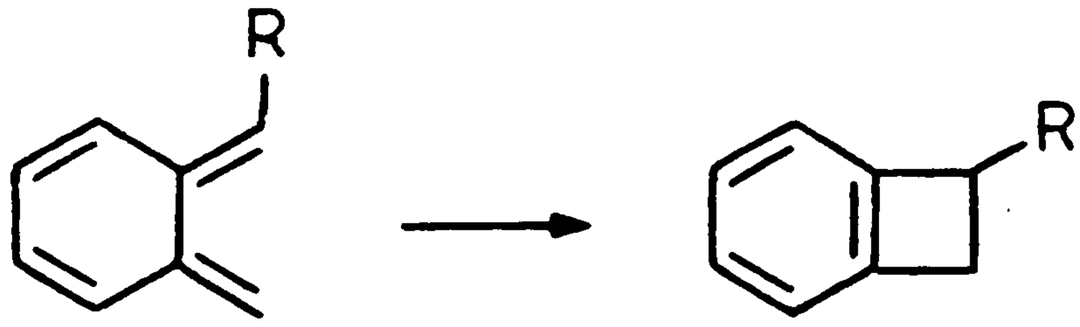
In previous chapters, we have already observed the ready participation of o-quinonoid species in pericyclic processes. For example, in discussing the methods for the generation of o-xylylenes (Section 1.2(a)) and o-thioquinone methides (Section 1.2(b)) we observed that a good way of generating these species was the thermal ring opening of the corresponding four-membered ring system:- itself a pericyclic reaction. In addition,

we have seen that certain o-quinonoid systems for example o-azaxylylenes can dimerize to give spirodimers, a process which is likely to involve a concerted [4+2] cycloaddition (Section 1.3(c)).

The following section will attempt to illustrate the ready participation of o-quinonoid species in these sorts of processes. In addition, Section 1.6 provides some examples of the elegant use of the pericyclic reactions of o-quinonoid systems in the synthesis of natural products.

(a) o-XYLYLENES

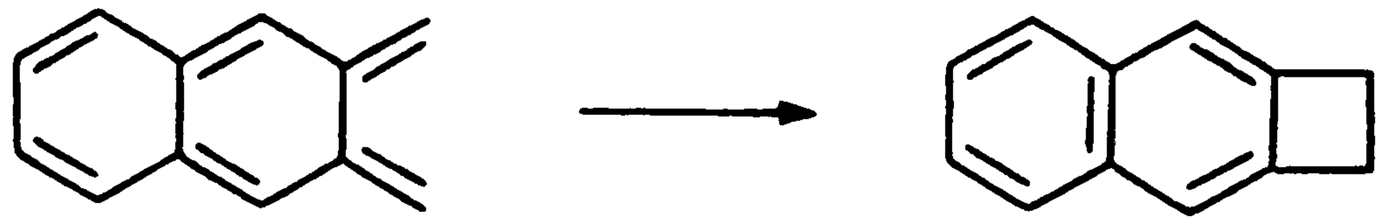
In the absence of other possible modes of reaction such as reaction with electrophiles or nucleophiles, most o-xylylenes readily undergo electrocyclic ring closure to give benzocyclobutenes, although for the parent system, photolysis[36] or high temperatures and dilution conditions[38] are required. For example, generation of o-xylylenes (24) and (32) under flash vacuum pyrolytic conditions gives good yields of the corresponding benzocyclobutenes (205)[104] and (33).[29]



(24) R = H (250) R = H

(32) R = Cl (33) R = Cl

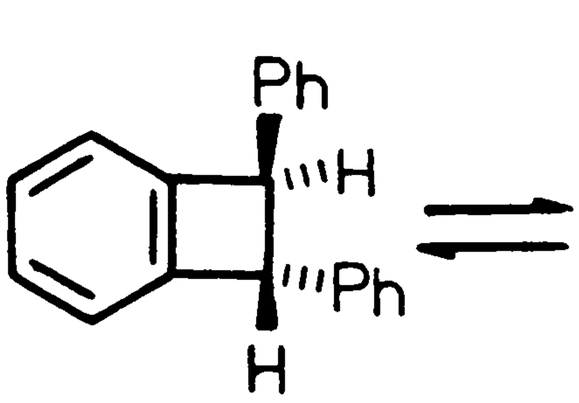
Similarly, generation of naphtho-xylylene (206) in the absence of dienophiles at 300°C yields naphtho-cyclobutene (207).[105]



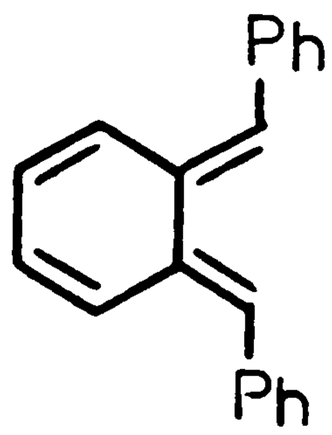
(206) (207)

Most substituted o-xylylenes undergo ring closure much more readily. This ring closure to benzocyclobutenes has been shown to be a stereospecific, conrotatory reaction,[106,107] which is what would be predicted in terms of orbital symmetry. Thus, benzocyclobutene (208) gives the E,E-o-xylylene (209) on pyrolysis. The Z,Z-isomer (210) is also an allowed product, but is sterically disfavoured. A similar stereospecificity has also been observed for (211) which ring opens to yield the E,Z-species (212).[106,107] Heavily substituted o-xylylenes such as (214) undergo rapid ring closure, the half life of (214) at 23°C being 3.2×10^{-15}s, to yield tetraphenylbenzocyclobutene (213). In this case, an electrocyclization reaction also competes to yield isoanthracene (215), but this occurs much more slowly.[108]

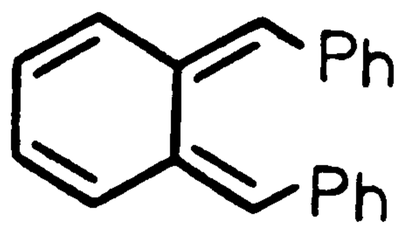
There are also a number of reports concerning the electrocyclization and sigmatropic shift reactions of o-xylylenes. For example, flash vacuum pyrolytic elimination of HCl from dichloride (216) produces o-xylylene (217) which



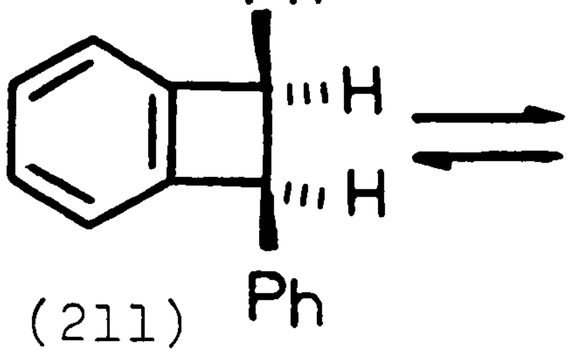
(208)



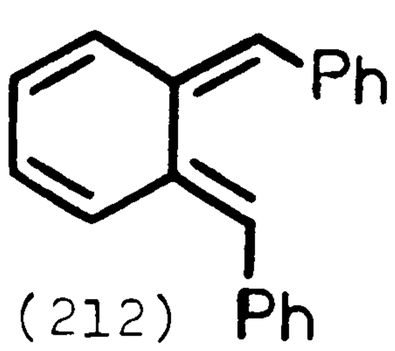
(209)



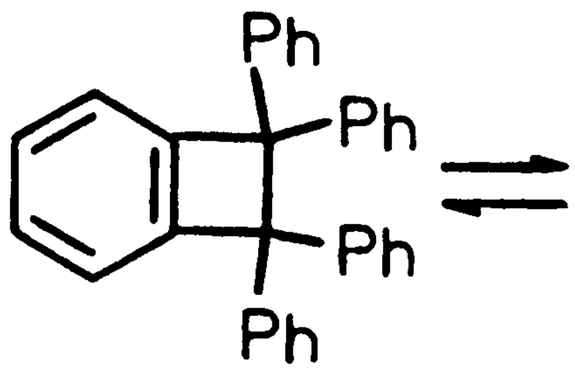
(210)



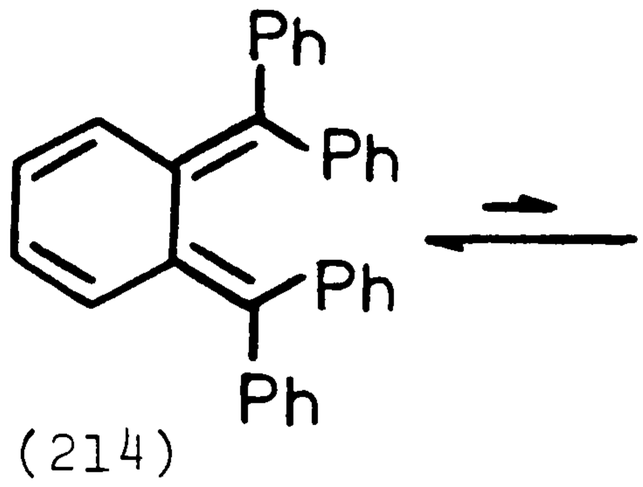
(211)



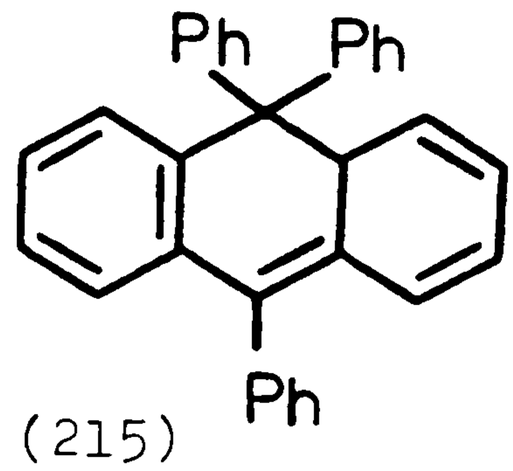
(212)



(213)

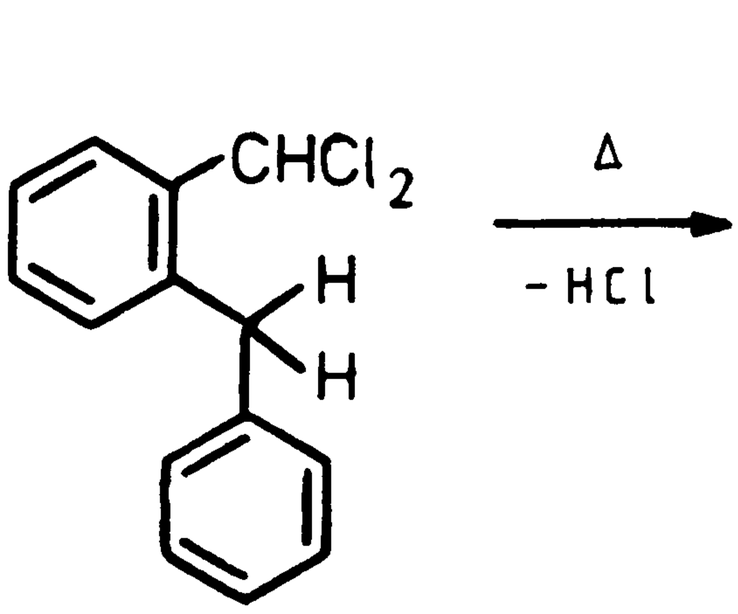


(214)

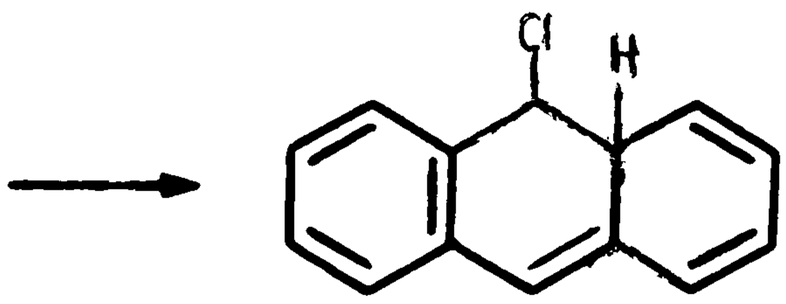


(215)

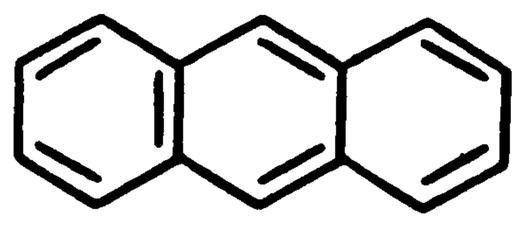
then undergoes electrocyclization with the phenyl substituent, followed by loss of a second mole of HCl to produce anthracene (218).[29]



(216)

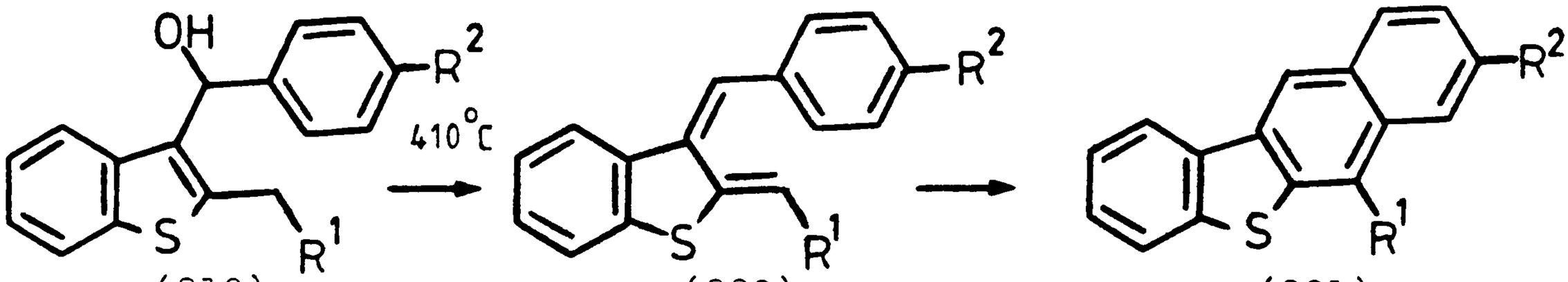


(217)



(218)

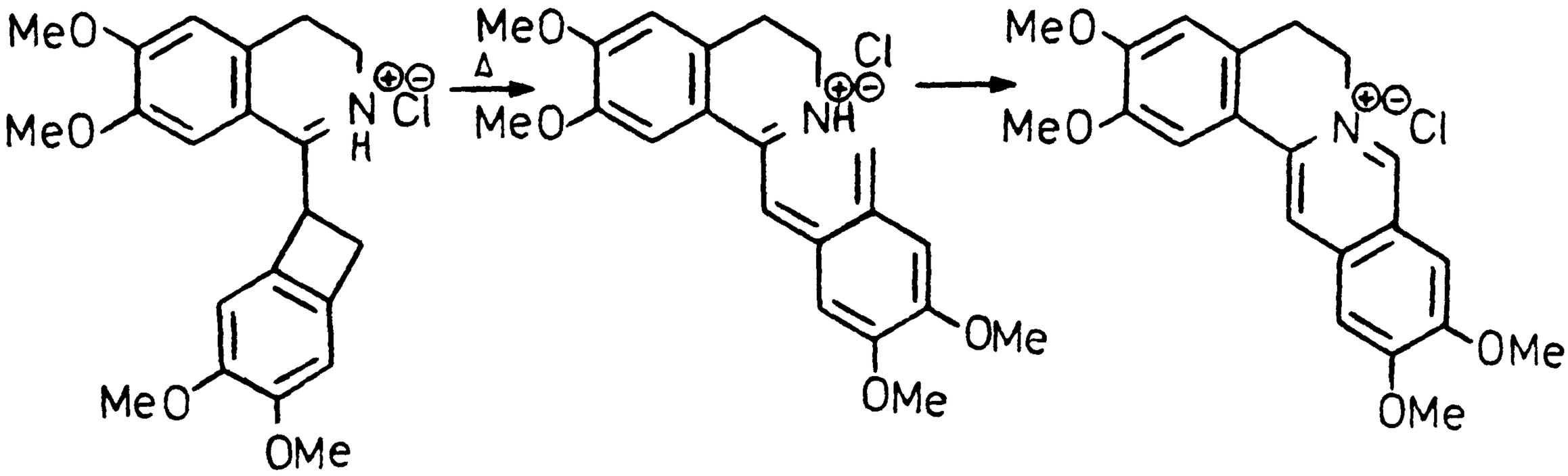
Similarly, benzothiophene-2,3-xylylene (220), generated by dehydration of alcohol (219) undergoes electrocyclization with the phenyl ring followed by dehydrogenation to give naphthobenzothiophene (221).[109]



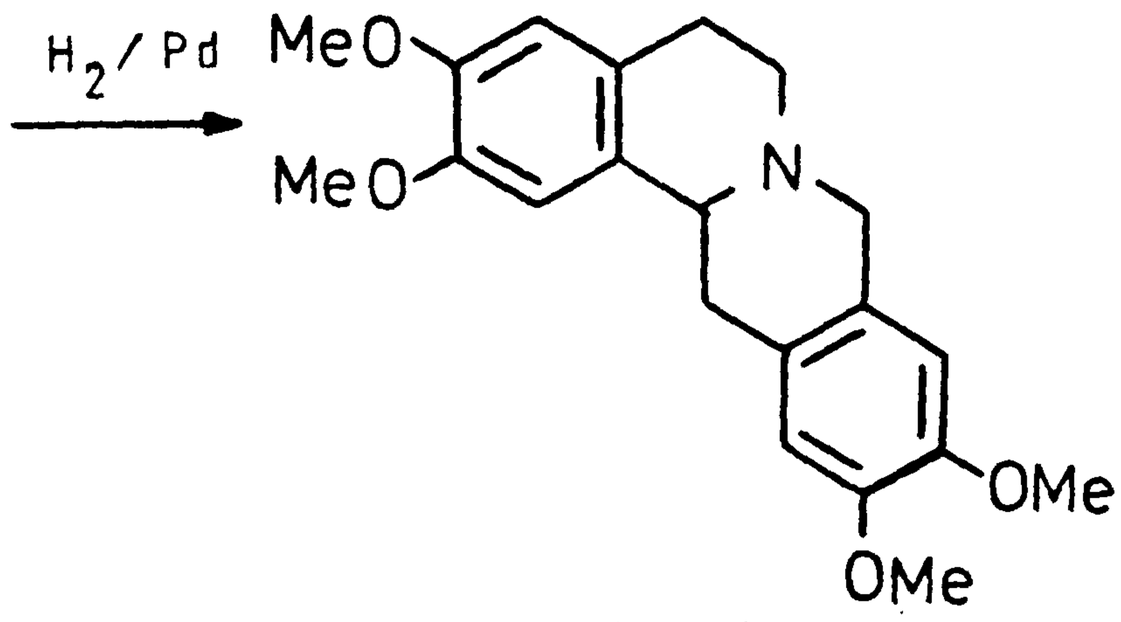
(219) (220) (221)

There are a number of reports concerning the electrocyclization of o-xylylenes with hetero-olefinic and hetero-aromatic substituents. For example, in a biomimetic synthesis of the alkaloid discretine (225), generation of o-xylylene (223) by thermal ring opening of benzocyclobutene (222) produces salt (224) by electrocyclization. This was then converted into discretine (225) by catalytic hydrogenation.[110] (Further illustrations of electrocyclic reactions of o-xylylenes in organic synthesis are presented in Section 1.6(b).)

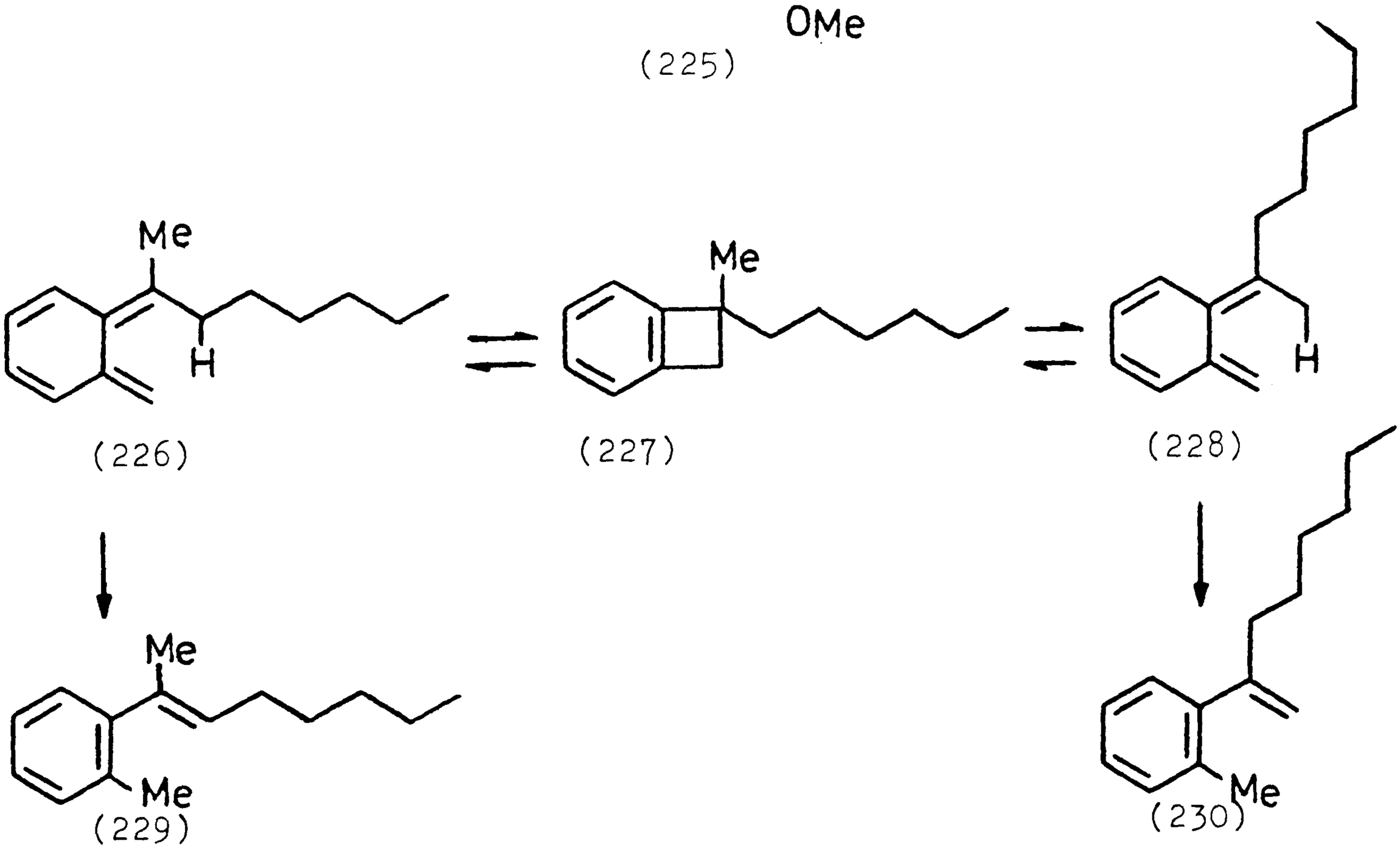
Certain alkyl-substituted o-xylylenes can undergo 1,5 -hydrogen shift reactions. For example, pyrolysis of benzocyclobutene (227) produces the o-methyl styrenes (229) and (230) by 1,5 -hydrogen shift of a hydrogen from a methylene directly attached to an exocyclic carbon in the o-xylylenes (226) and (228) respectively.[111]



(222) (223) (224)



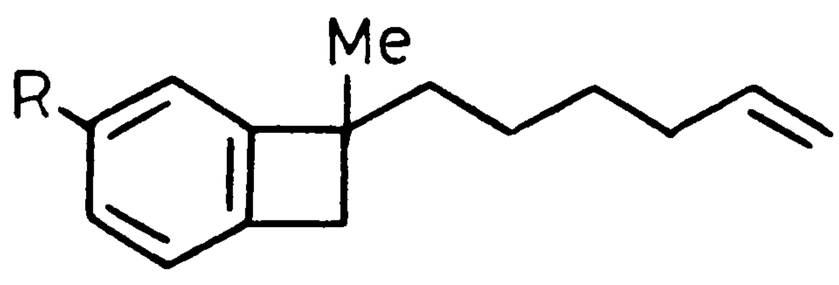
(225)



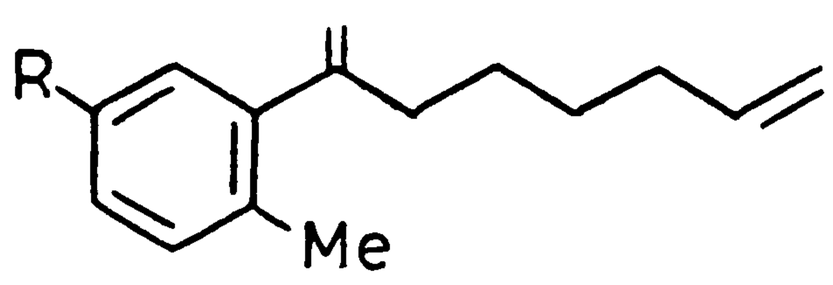
(226) (227) (228)

(229) (230)

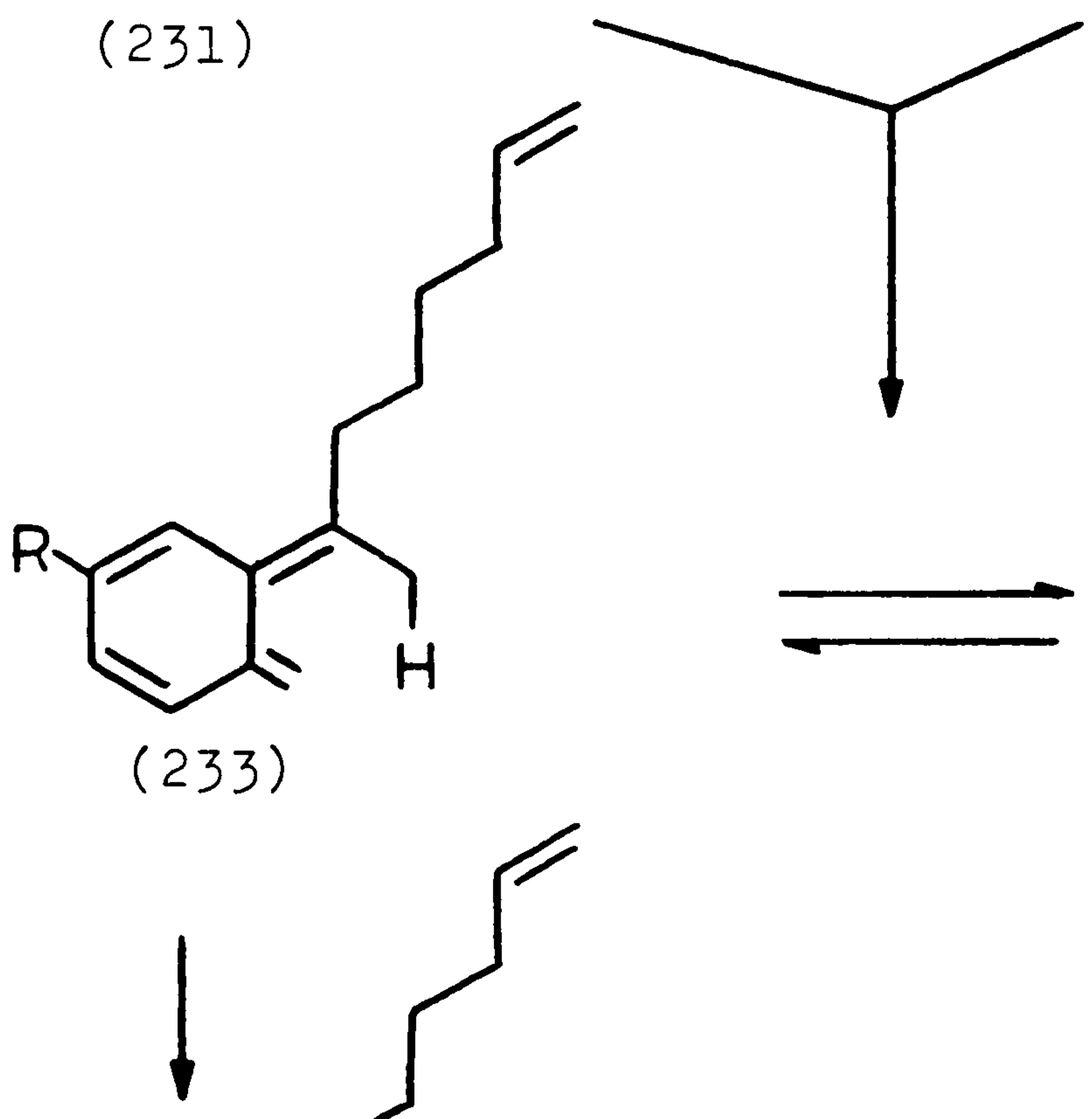
Similarly, generation of o-xylylenes (233) and (234) by either ring opening of benzocyclobutene (231)[111] or by photolysis of styrene (232)[112] produces styrenes (235) and (236) by 1,5 -hydrogen shift in both o-xylylenes respectively. However, a moderate yield of the trans-fused intramolecular cycloadduct (237) was also obtained from the photolysis reaction, whereas this was completely absent in the analogous reaction from benzocyclobutene (231).



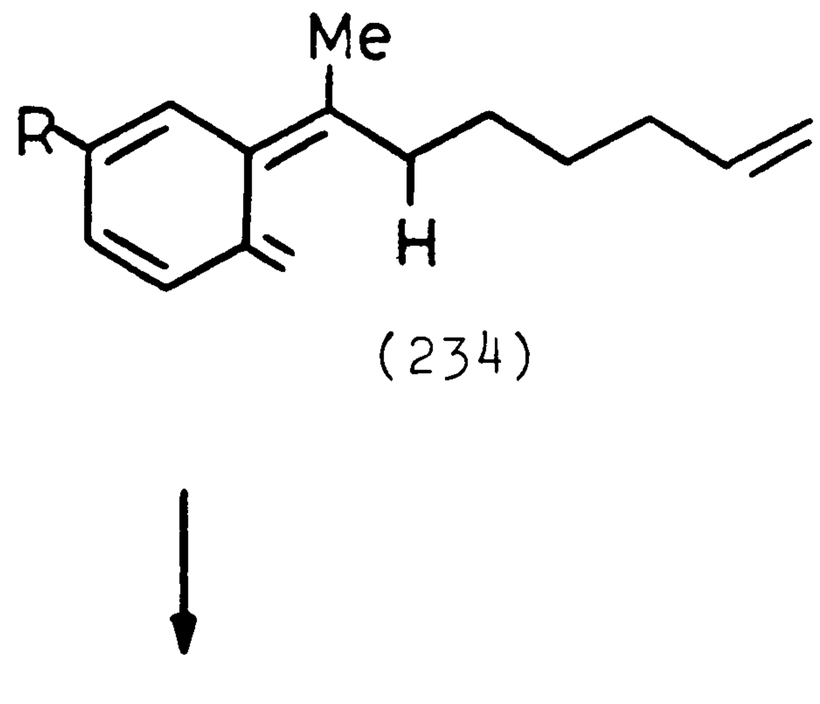
(231)



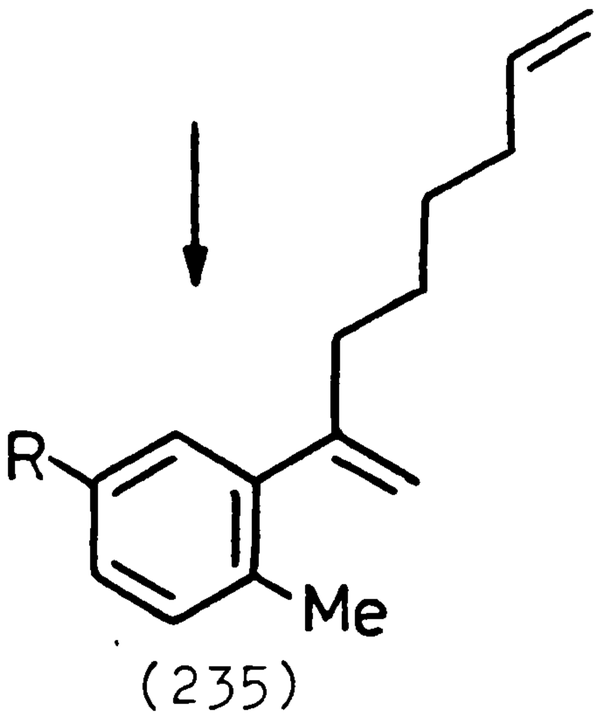
(232)



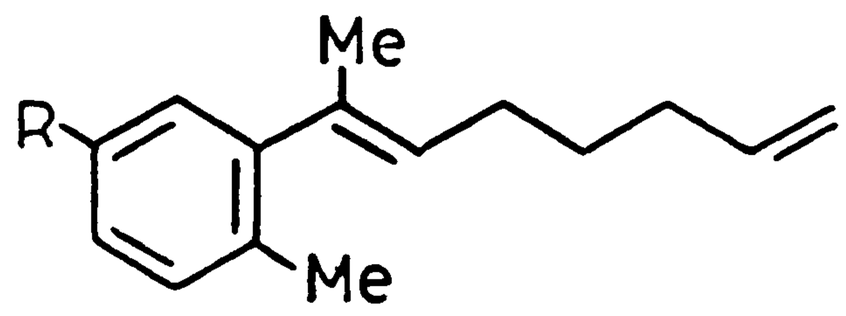
(233)



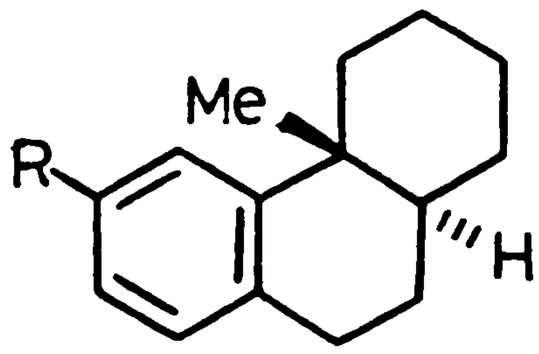
(234)



(235)

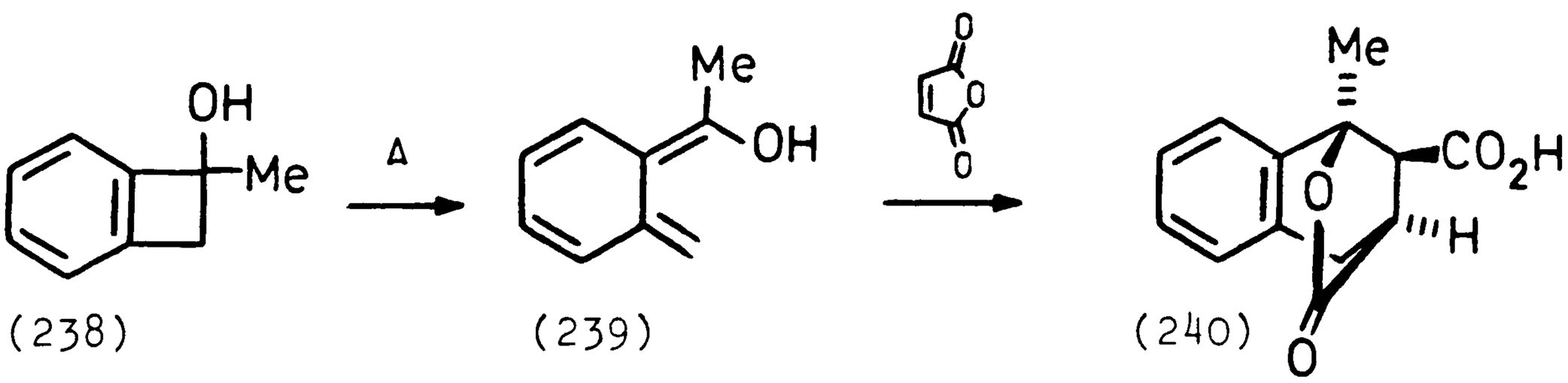


(236)



(237)

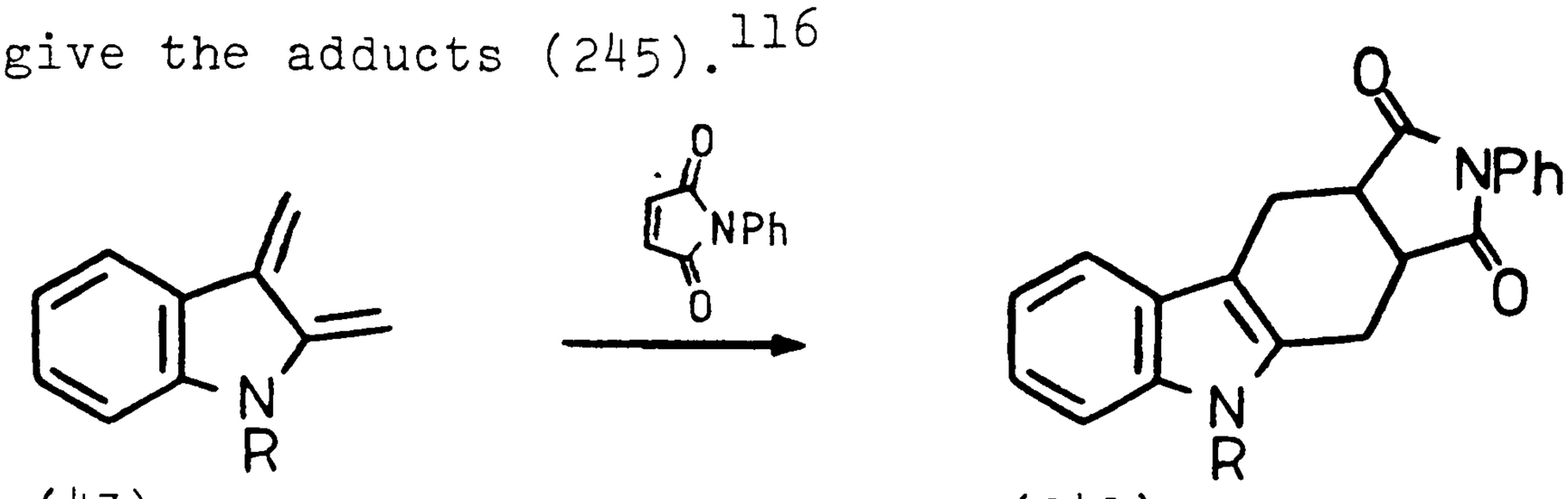
By far the most widely used and perhaps most well known reactions of o-xylylenes are their Diels-Alder reactions, in which they show a high degree of reactivity. The cycloaddition reactions of o-xylylenes appear to be concerted and the products obtained are those predicted by Frontier Orbital Theory.[113] Thus the Diels-Alder reactions of o-xylylenes are highly stereoselective. For example, heating benzocyclobutene (238) in the presence of maleic anhydride gives the lactone (240).[114] The relative configuration, of substituents in this adduct supports the stereoselective nature of the reaction. This also suggests that the configuration of the intermediate o-xylylene is that of (239). It has been suggested that electronic factors such as the presence of non-bonding electrons on substituents plays a part in governing the direction of ring opening of benzocyclobutenes, although no further investigation into this proposed effect has appeared.[114]



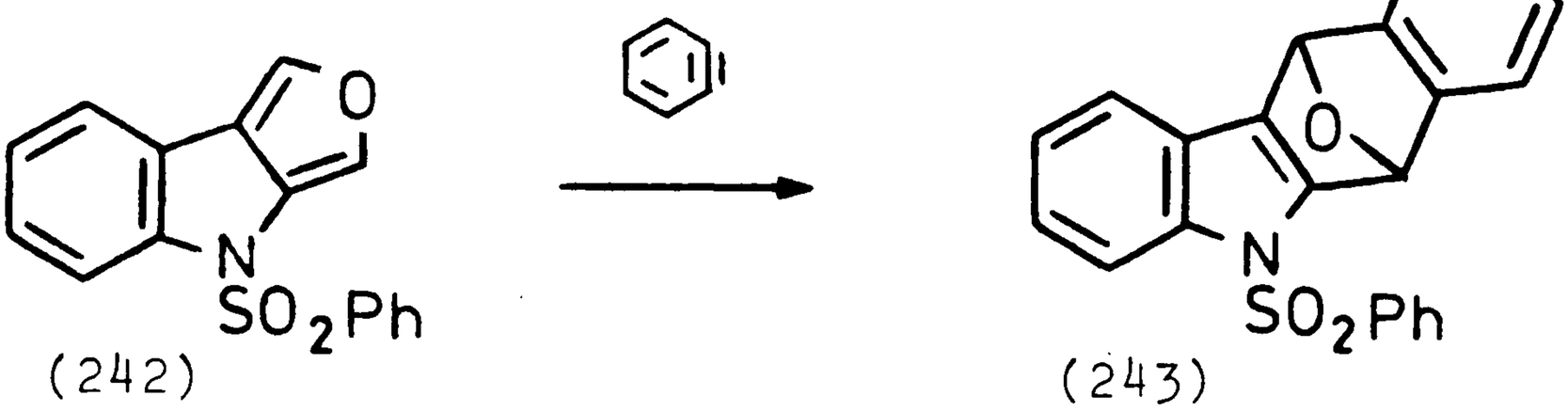
(238) (239) (240)

Other examples of intermolecular Diels-Alder reactions of o-xylylenes include trapping of indole-2,3-xylylene (43) with N-phenylmaleimide to yield adduct (241),[35]

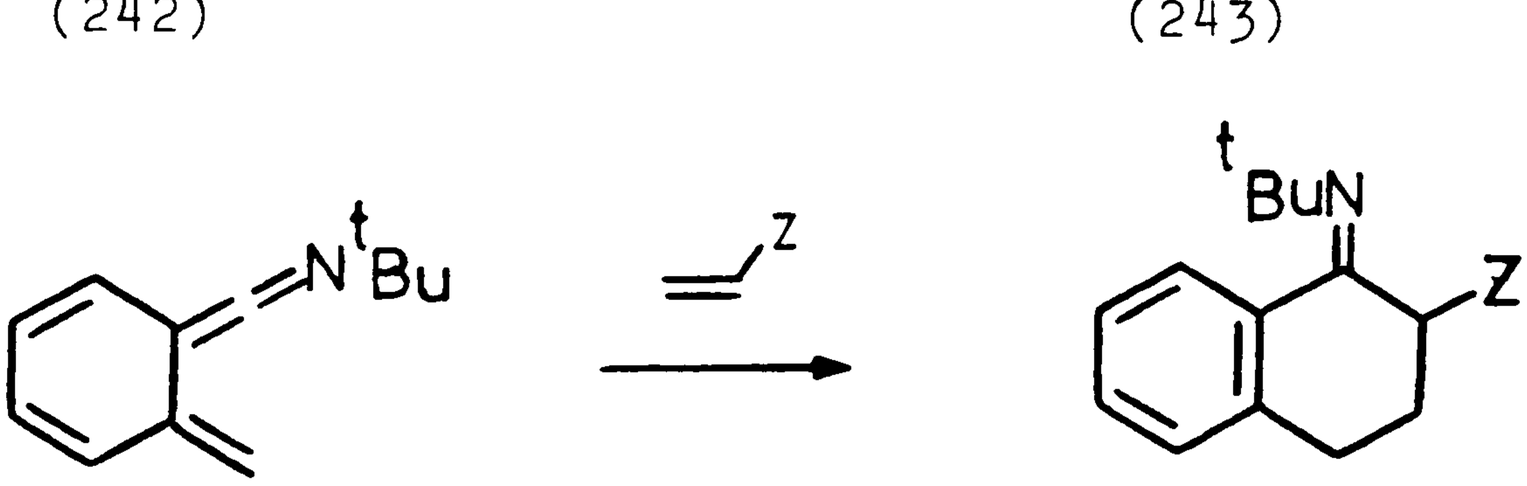
and of stable indole-2,3-xylylene analogue (242) with benzyne to give (243).[115] In addition, the novel o-xylylene-imine (244) adds to a variety of dienophiles to give the adducts (245).[116]



(43) (241)



(242) (243)

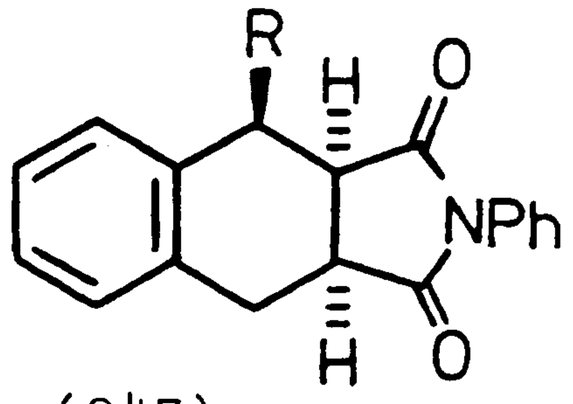


(244) (245)

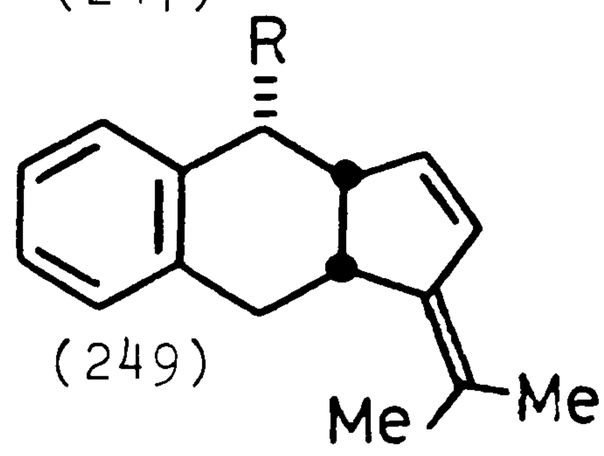
o-Xylylenes also show a high degree of endo selectivity in the Diels-Alder reaction. For example, o-xylylenes (246) add to N-phenylmaliemide to give only the endo adducts (247).[117] Surprisingly, o-xylylene (246, R = CN), shows no selectivity in its reaction with methyl acrylate, producing a 1:1 mixture of exo and endo adducts. This has been attributed to a stepwise, possibly diradical reaction pathway which is favoured by the substituents.[118]

The intermolecular cycloadditions of o-xylylenes (248) with 6,6-dimethylfulvene have also been reported. Reaction of the urethane substituted o-xylylene (248, R = $NHCO_2Me$) with this fulvene yields the [4+2] adducts (250) and (249) respectively. However, the o-xylylene (248, R = Me) under the same reaction conditions yields the [6+4] adduct (251) in addition to (249) and (250).[119]

(246) R = CN, CO_2Me

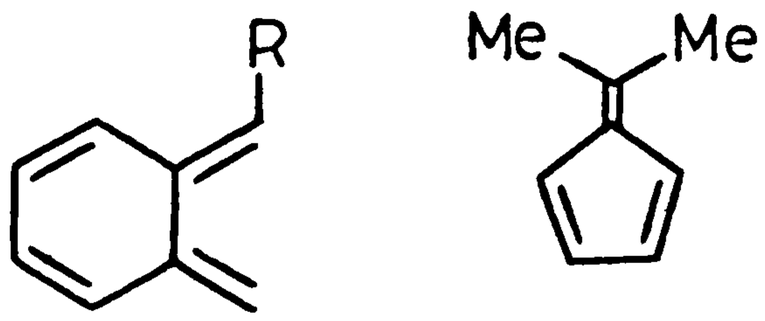


(247)

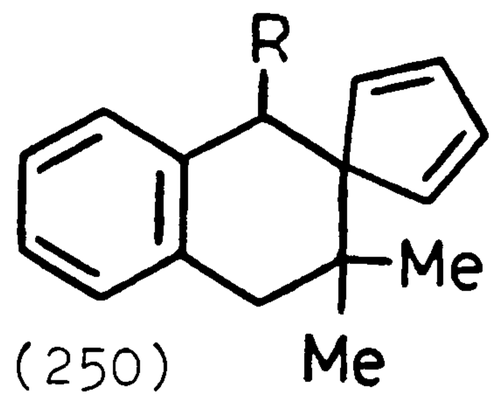


(249)

[4 + 2]

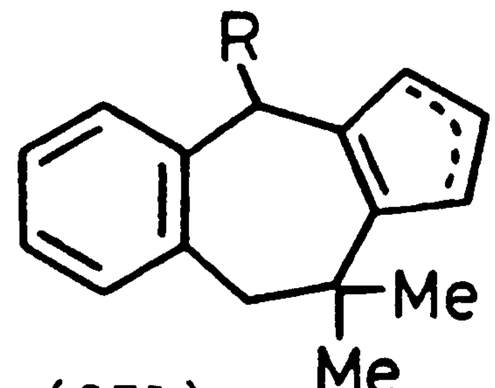


(248) R = $NHCO_2Me$, Me



(250)

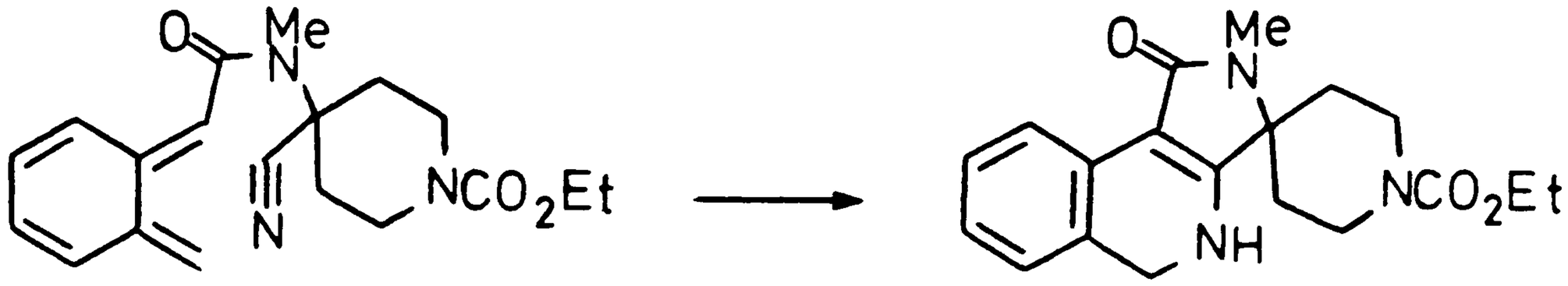
[6 + 4]



(251)

Synthetically, the most useful reactions of o-xylylenes are their intramolecular Diels-Alder reactions.[120] This is effectively demonstrated by the intramolecular cycloaddition

of a normally inert nitrile in o-xylylene (252) to produce dihydroisoquinoline (253) in high yield.[121]



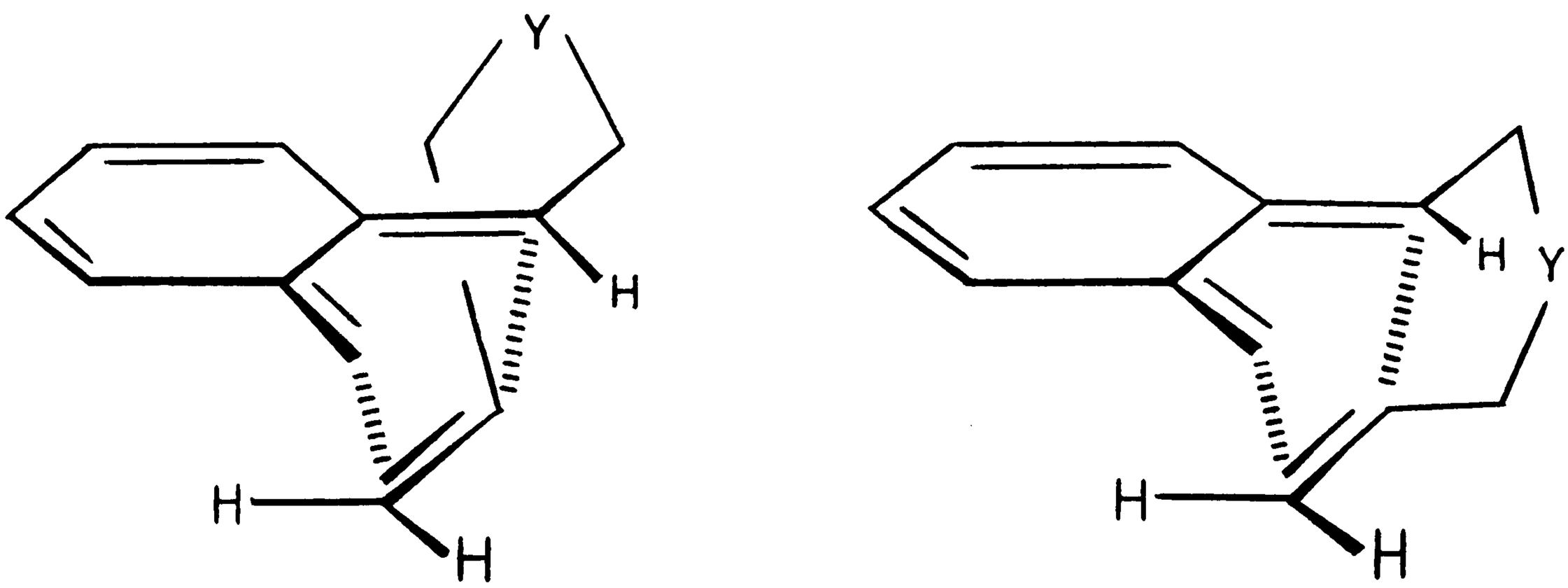
(252) (253)

Obviously, when the dienophile is itself cyclic or substituted, then complex multicyclic arrays such as those contained in certain natural products, can be constructed in a single step (see Section 1.6(a) and (b)).

The additional advantages gained in the intramolecular Diels-Alder reactions of o-xylylenes due to entropy, reactivity, regio, stereo and diastereoselectivity account for the large number of reports concerning this reaction that have appeared in the recent chemical literature. These reactions, in which the product does not constitute a natural product or an intermediate in the synthesis of natural products, are listed in Table 3.

The stereochemical outcome of a concerted intramolecular cycloaddition is a direct result of the configuration of the transition state in the cycloaddition, assuming no isomerization of the resulting products occurs. We assume that in these cycloadditions, the o-xylylene reacts whilst in the E-configuration (thus locating the bulkiest substituent in the least sterically hindered

position away from the diene system, Figure 1). Thus the endo transition state (A) will lead exclusively to a cis fused product, whereas the exo transition state (B) gives the trans fused product (Figure 1).



E-Configuration

(A) Endo (B) Exo

FIGURE 1

Although no firm rules seem to exist for predicting the stereochemical outcome of these intramolecular Diels-Alder reactions, in certain cases, the stereochemistry of the products seems to be a function of the substituents present on the chain connecting diene to dienophile. From a study of the product distributions of the o-xylylenes listed in Table 3, the following generalizations can be made. Simple o-xylylenes with three sp^3 carbons in the chain connecting diene to dienophile give both cis and trans products

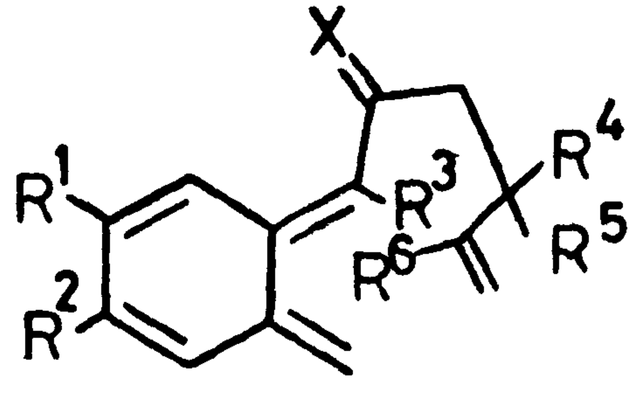
(entries 1, 3, 4, 5 and 63). However, if a ketone function is present at the carbon which is directly attached tothe xylylene system, the o-xylylene cyclizes through the endo transition state (A), giving exclusively cis fused products (entry 2). The majority of o-xylylenes with four carbon atoms in the connecting chain cyclize preferentially or exclusively via the exo transition state (B) to give trans fused products, irrespective of any Sp^2 centres present on the connecting chain or the substituent pattern on the chain or dienophile (entries 7 - 20). Ithas been suggested[183] that this selectivity is due to steric repulsion in the endo transition state (A) between the cyclohexadiene ring of the o-xylylene and bulky substituents in the connecting chain (for example, a cyclopentane ring as is found in certain steroid syntheses; see Section 1.6(a)). However, substrates with no substitution in the chain (entries 7 - 17) also give predominantly trans fused products. There do seem to be some exceptions to this exo selectivity for the formation of six-membered carbocyclic rings. For instance, a number of o-xylylenes containing nitrile groups directly attached to the diene system yield only the cis fused products (entries 15, 18 and 19) although the reason for this is not clear.

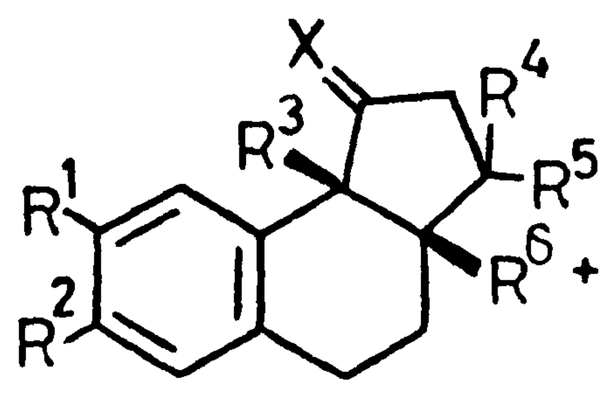
o-Xylylenes with three-membered nitrogen-containing chains appear to cyclize via the endo transition state (A) to give cis fused products regardless of the location of the nitrogen atom or the presence of carbonyl groups in

the chain (entries 21, 29 - 38). However, for the case of o-xylylenes containing four linking atoms in the chain, one of which is a nitrogen atom, then cyclization preferentially takes place via the exo transition state (B) giving trans fused products (entries 45, 46, 49, 50, 51, 53 and 57). However, the corresponding amides seem to prefer to cyclize via the endo transition state (A), (entries 47, 48, 52 and 58).

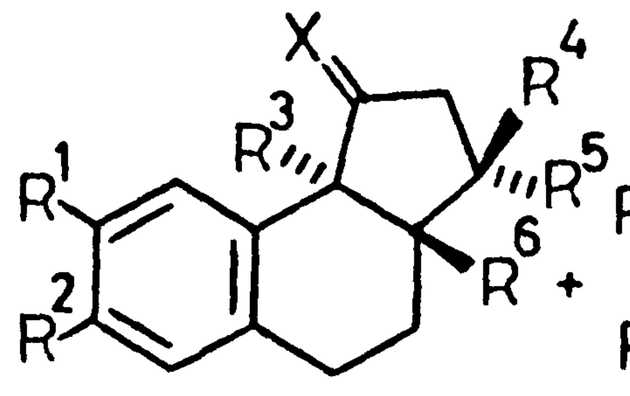
TABLE 3 Intramolecular Diels-Alder reactions of o-xylylenes

ENTRY	SUBSTRATE	PRODUCT(S) AND YIELD(S) %	REFERENCES

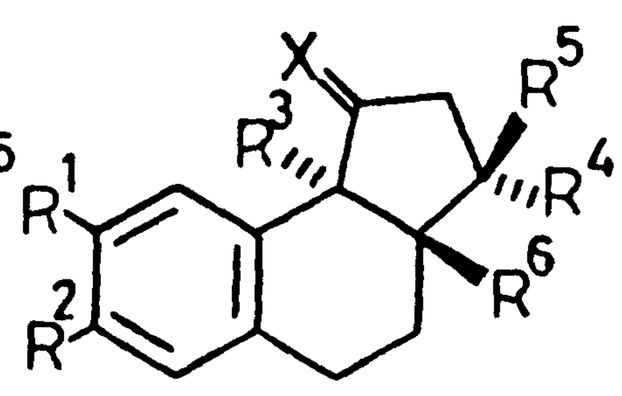




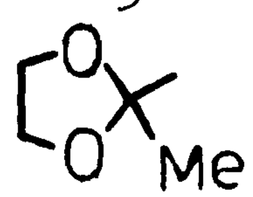
A



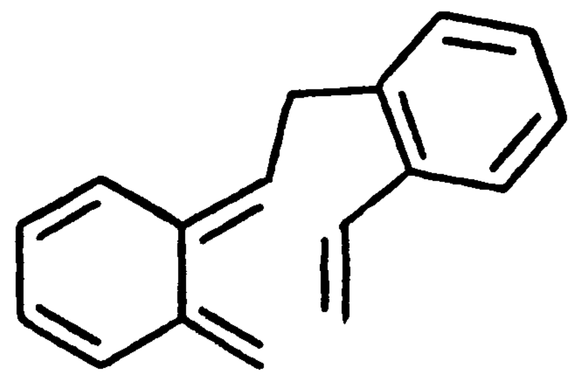
B

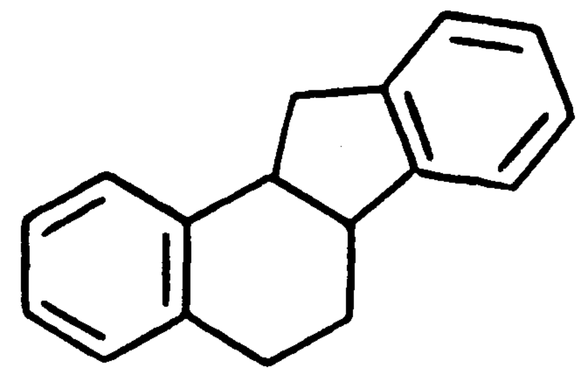


C

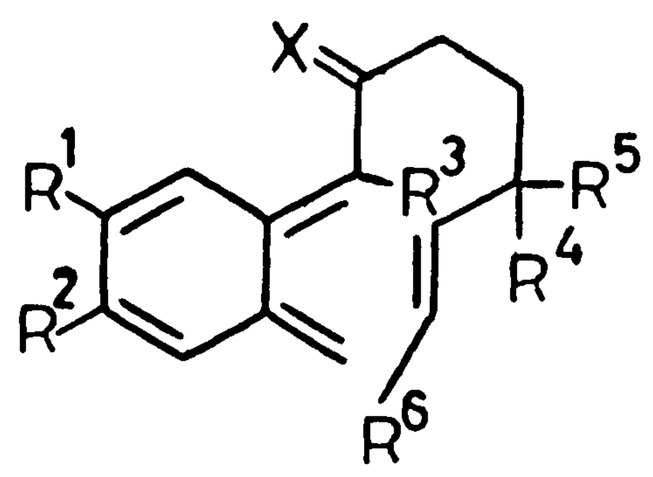
	R^1	R^2	R^3	R^4	R^5	R^6	X	A	B	C	
1	H	H	H	H	H	H	H_2[a,c,k]	(80)[b]			131, 125, 126, 138
2	H	H	H	H	H	H	O[a]	(70)	(0)	(0)	127
3	H	CH_3O	H	H	OH	CH_3	H_2[c]	(0)	(43)	(43)	124, 136
4	CH_3O	H	NC	CH_3	CH_3	H	H_2[c]	(81)[d]			139
5	H	CH_3O	H	H		CH_3	H_2[c]	(0)	(58)[e]	(6)[e]	124

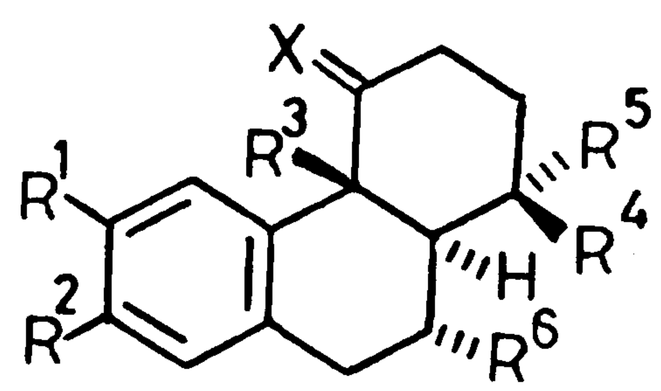
6

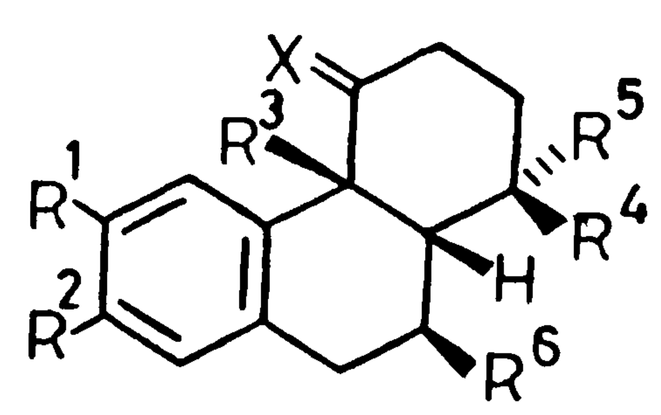




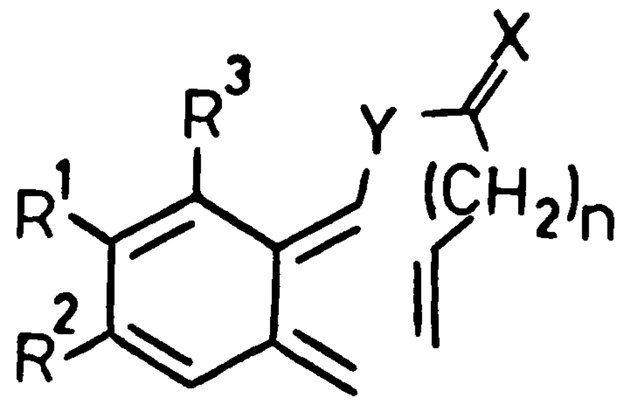
(85)[d]

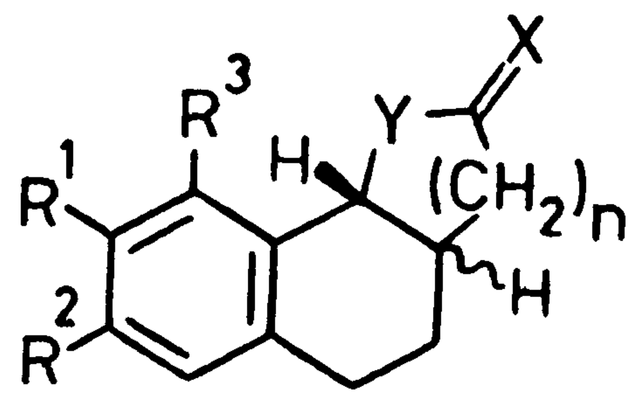




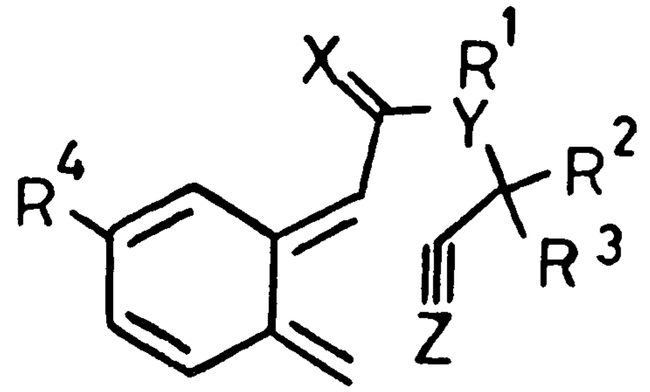


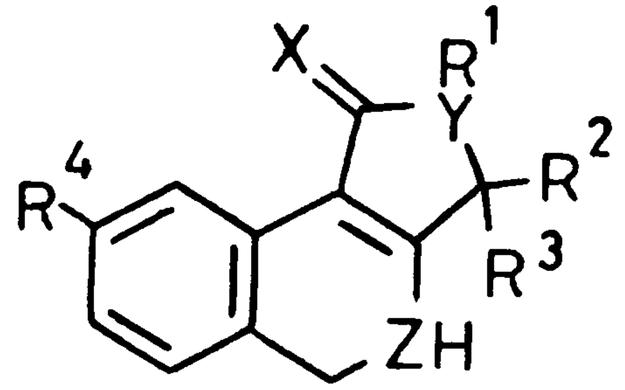
	R^1	R^2	R^3	R^4	R^5	R^6	X	A	B	REFERENCES
7	H	H	H	H	H	H	H_2[a,c,f,i,k]	(60)	(5)	125,123,126,131,132,138
8	H	H	H	H	H	H	O[a]	(80)[d]		127
9	H	H	CH_3	H	H	H	H_2[j]	(24)	(0)	112
10	CH_3O	H	H	H	H	H	H_2[f]	(75)	(0)	141,128
11	H	CH_3O	H	H	H	H	H_2[a,f]	(90)	(0)	128
12	H	NC	H	H	H	H	H_2[a]	(95)	(0)	135
13	$-OCH_2O-$		H	H	H	H	H_2[f]	(52)	(0)	128
14	CH_3O	CH_3O	H	H	H	H	H_2[f]	(60)	(0)	128
15	CH_3O	H	NC	H	H	H	H_2[c]	(80)[d]		111
16	H	$(Et)_2NSO_2H$		H	H	H	H_2[a]	(98)[d]		142
17	H	H	H	H	H	EtO_2C	H_2[a]	(69)	(6)	125
18	CH_3O	H	NC	MeO_2C	CH_3	H	H_2[c]	(0)	(40-50)	133,134
19	H	CH_3O	NC	MeO_2C	CH_3	H	H_2[c]	(14)[g]	(47)[h]	143
20	Me_3Si	Me_3Si	H	H	H	H	H_2[c]	(97)	(<5)	123



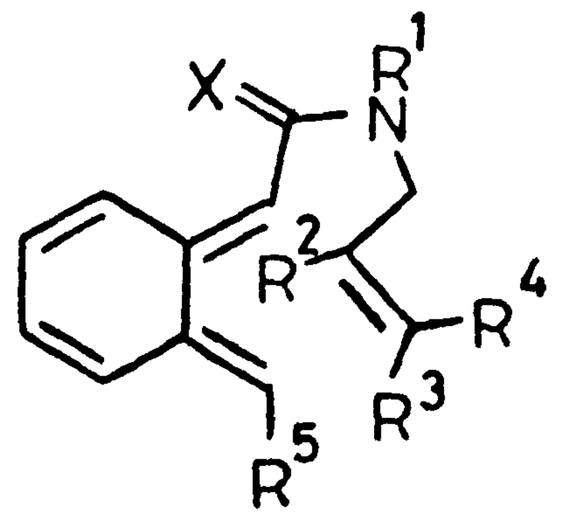


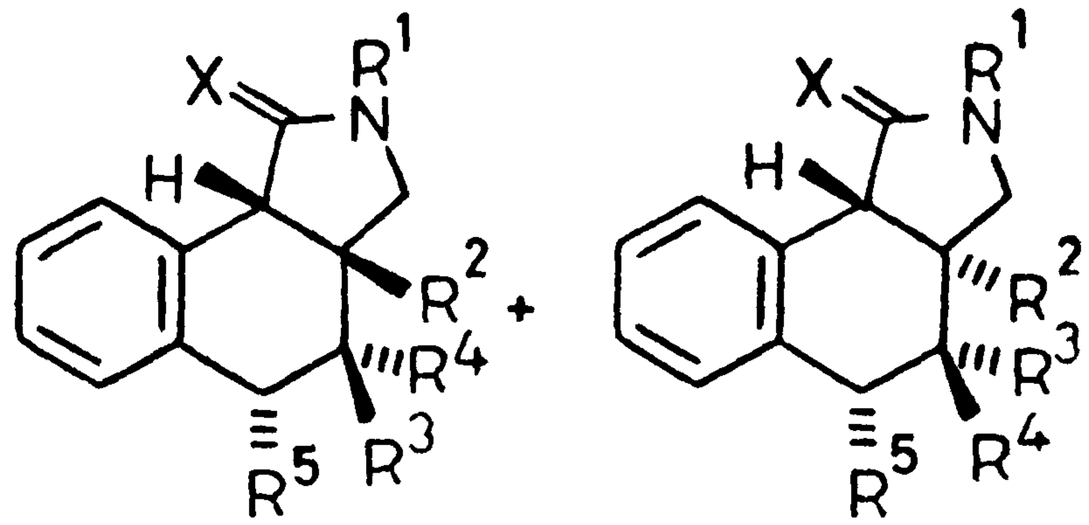
	R^1	R^2	R^3	N	X	Y	CIS	TRANS	REFERENCES
21	H	H	H	1	O	NH^c	(80)	(17)	129, 19
22	H	H	OMe	1	O	O^c	(61)		147
23	Me_3Si	Me_3Si	H	2	H_2	O^c	(0)	(60)	123





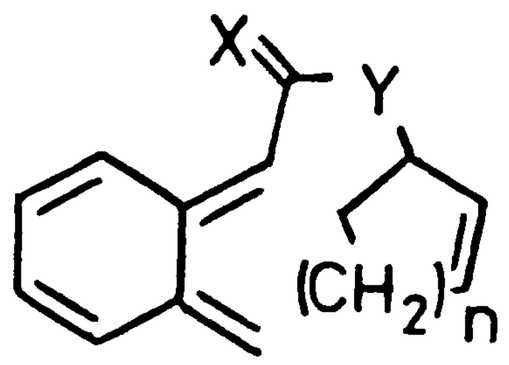
	R^1	R^2	R^3	R^4	X	Y	Z	CIS	TRANS	REFERENCES
24	H	H	H	H	O	N	CH^c		(95)	133
25	Me	H	H	H	O	N	N^c		(76)	113
26	$-(CH_2)_4-$		H	H	O	N	N^c		(-)	113
27	Me	$-(CH_2)_2\overset{CO_2Et}{N}(CH_2)_2-$		H	O	N	N^c		(82)	113
28	-	H	H	OMe	O	O	CH^c		(42)	147

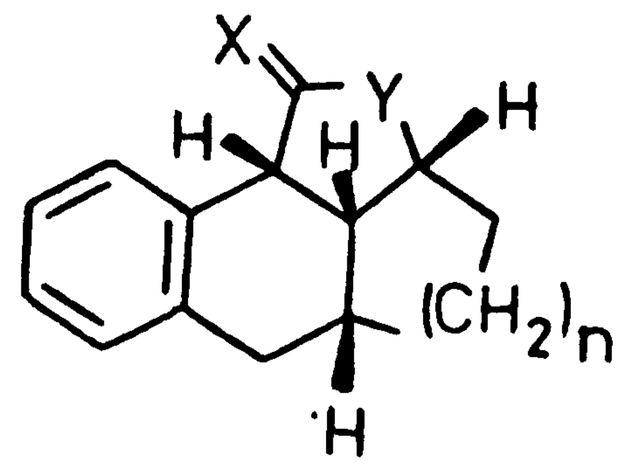




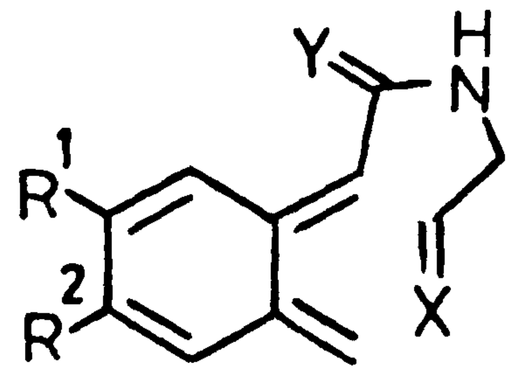
A B

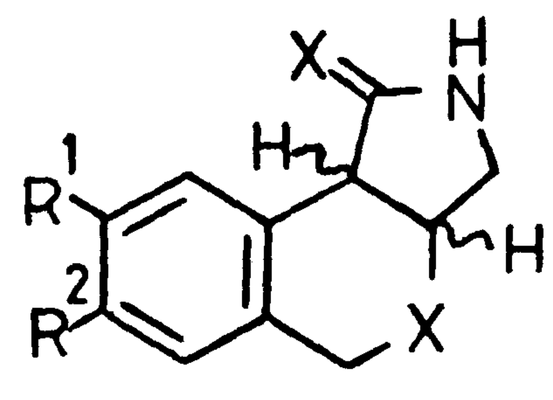
	R^1	R^2	R^3	R^4	R^5	X	A	B	REFERENCES
29	H	H	H	H	H	O[c]	(85)	(-)	91, 113, 144
30	H	H	Cl	H	H	O[c]	(77)[1]		91, 19
31	H	H	H	Cl	H	O[c]	(73)[1]		91
32	Me	H	Cl	H	H	O[c]	(-)[1]		144
33	Me	H	H	Cl	H	O[c]	(-)[1]		144
34	EtO_2C	H	H	H	OH	H_2[m]	(52)	(17)	130
35	Me	H	Ph	H	H	O[m]	(56)	(9)	144, 19
36	H	$-(CH_2)_2N(CH_2Ph)-CH_2-$		H	H	O[c]	(64)	(0)	91



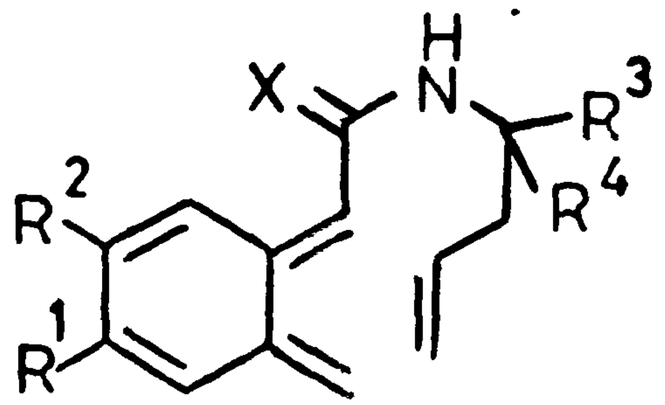


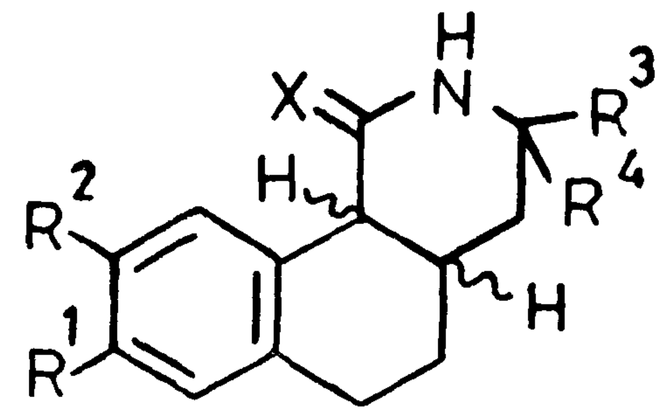
	N	X	Y		REFERENCES
37	1	O	NH[c]	(80)	19, 91, 144
38	2	O	NH[c]	(65)	19, 91, 144
39	1	H_2	CH_2[a]	(67)[d]	126
40	1	O	CH_2[a]	(45)	126



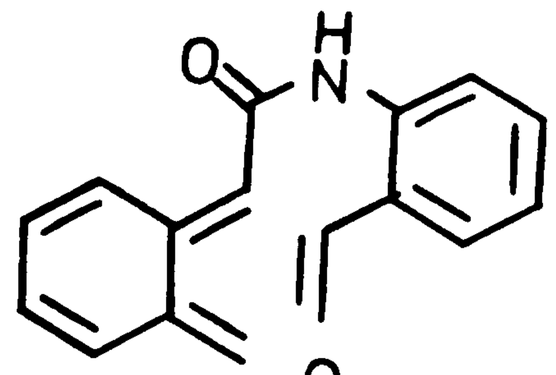


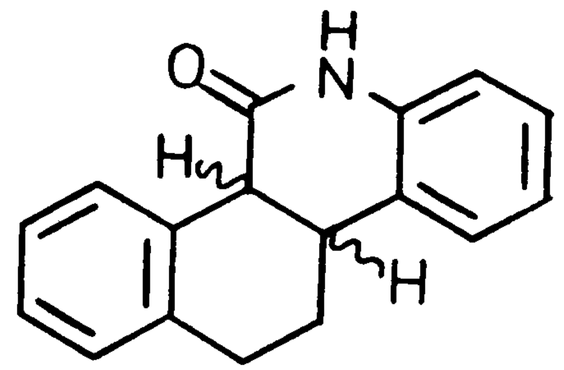
	R^1	R^2	X	Y	CIS	TRANS	REFERENCES
41	H	CH_3	O	O[c]	(25)[1]		113, 19
42	H	H	CH_3ON	O[c]	(58)[1]		113, 19
43	CH_3O	CH_3O_2C	O	H_2[c]	(0)	(41)	145
44	$PhCH_2O$	$Ph(CH_2)_2O$	O	O[c]	(12)	(70)	145





	R^1	R^2	R^3	R^4	X	CIS	TRANS	REFERENCES
45	H	H	H	H	H_2^c	(27)	(72)	146,19
46	H	Cl	H	H	H_2^c	(0)	(98)	19
47	H	H	H	H	O^c	(85)	(0)	144,19,91,146
48	H	H	O=		H_2^c	(64)	(31)	146
49	H	CH_3O	H	H	H_2^c	(0)	(54)	146
50	H	Cl	CH_3	H	H_2^c	(0)	(75)	19
51	CH_3O	CH_3O	H	H	H_2^c	(12)	(59)	19
52	CH_3O	CH_3O	O=		H_2^c	(57)	(0)	137, 19
53	$PhCH_2O$	H	H	H	H_2^c	(0)	(75)	19

54  c

144 

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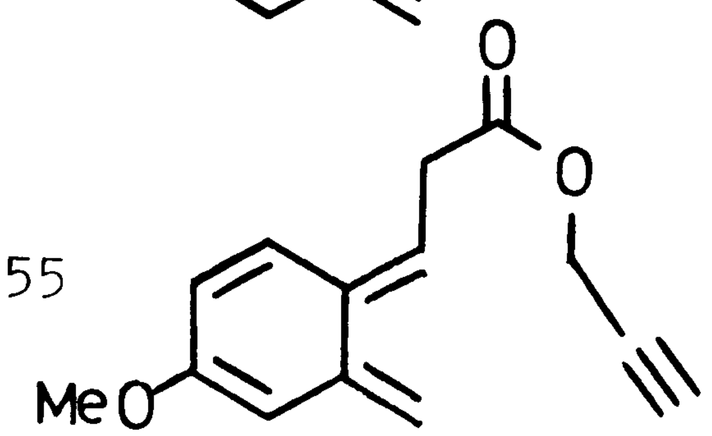
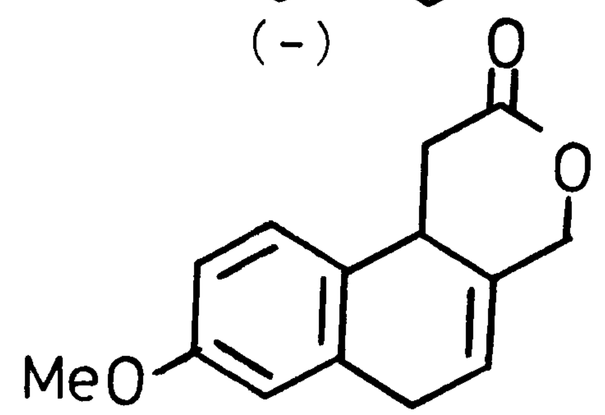
55  c

147 

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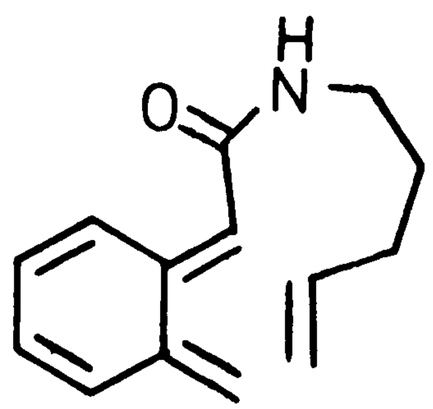
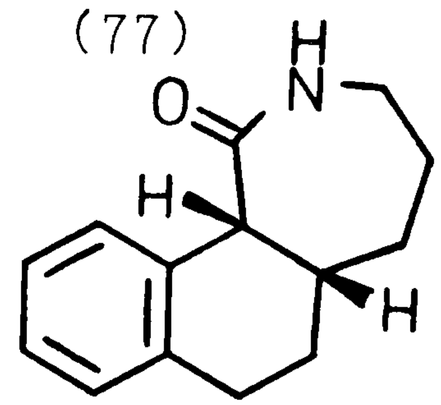
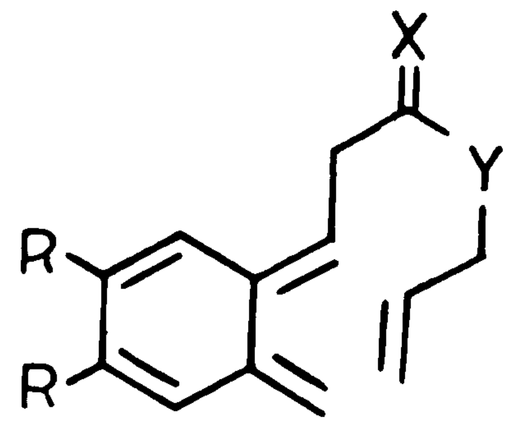
56  c

91 



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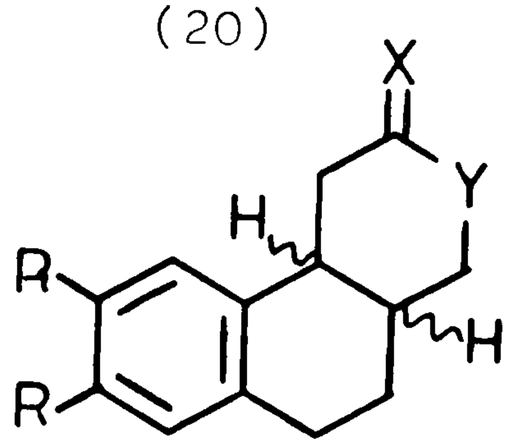
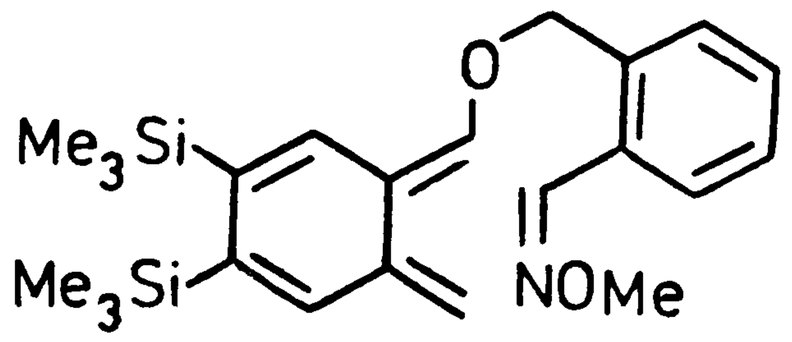
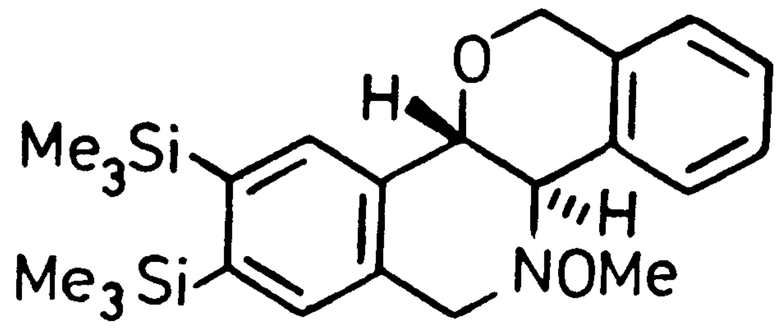


	X	Y	R
57	H_2	NH	H^c
58	O	NH	H^c
59	H_2	O	H^c
60	H_2	O	Me_3Si ^{c}

TRANS	CIS	REFERENCES
(87)	(12)	146
(13)	(79)	146
(-)	(-)	123
(74)	(19)	123

61 

c 

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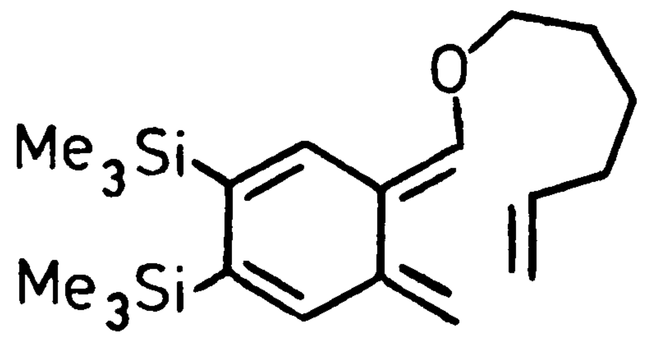
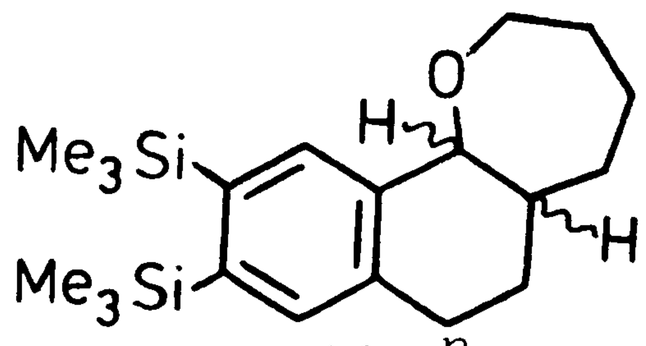
62 

c 

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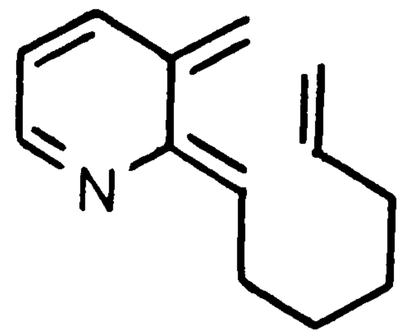
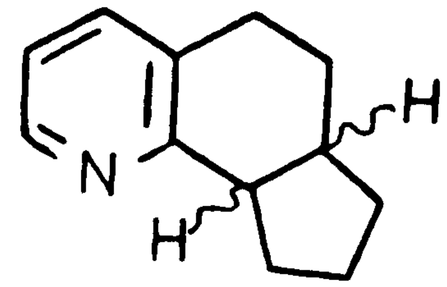
63 

i 

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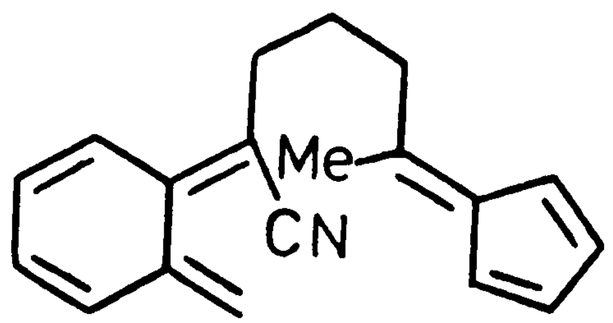
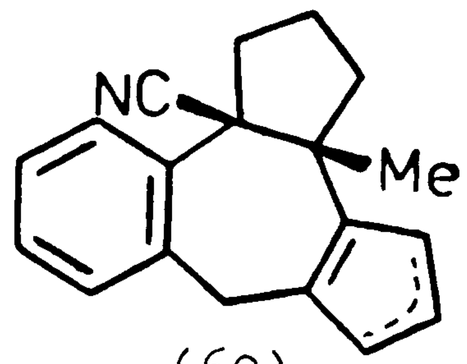
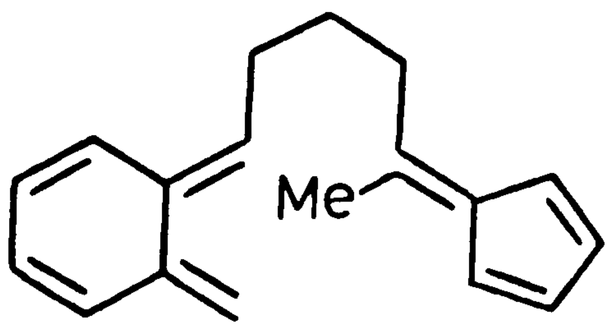
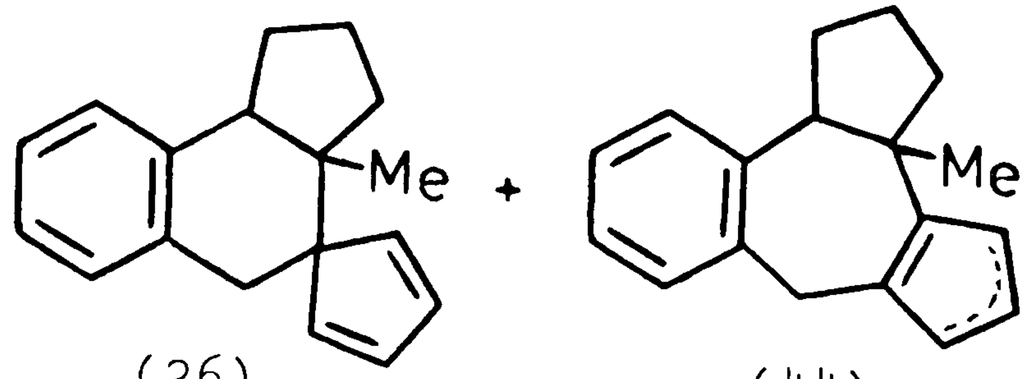
64 

c 

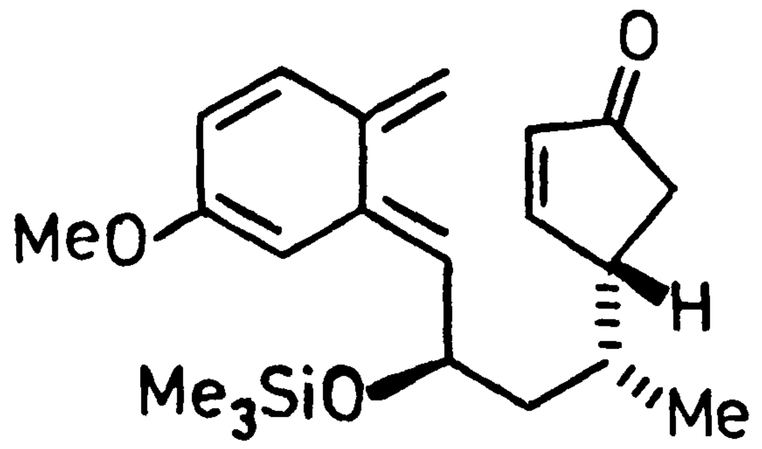
(60) 140

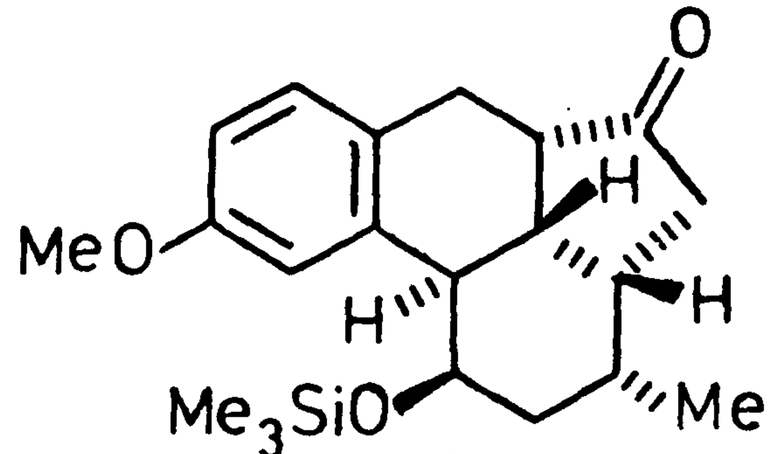
65 

c 

(26) (44) 140

66





(61)

148

(a) The substrate was generated by elimination of SO_2 from the corresponding 1,3-dihydroisothionaphthene-2,2-dioxide.

(b) The product was a mixture of two isomers in a ratio 3:1; the stereochemistry was not stated.

(c) The substrate was generated from the benzocyclobutene.

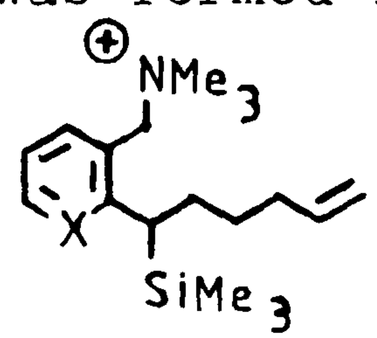
(d) The stereochemistry was not reported.

(e) The structure assignment is tentative.

(f) The substrate was generated by elimination of CO_2 from the corresponding 4-(5-hexenyl)isochroman-2-one.

(g) Isomer A with R^4/R^5 interchanged was formed in 3% yield.

(h) Isomer B with R^4/R^5 interchanged was formed in 34% yield.

(i) The substrate was generated from 

and $^nBu_4NF$; A was formed exclusively.

78

(j) The substrate was generated by photolysis of 2-(2-methylphenyl)-1,7-octadiene.

(k) The substrate was generated from the appropriate o-methylbenzyl ether by lithium tetramethylpiperidide induced 1,4-elimination.

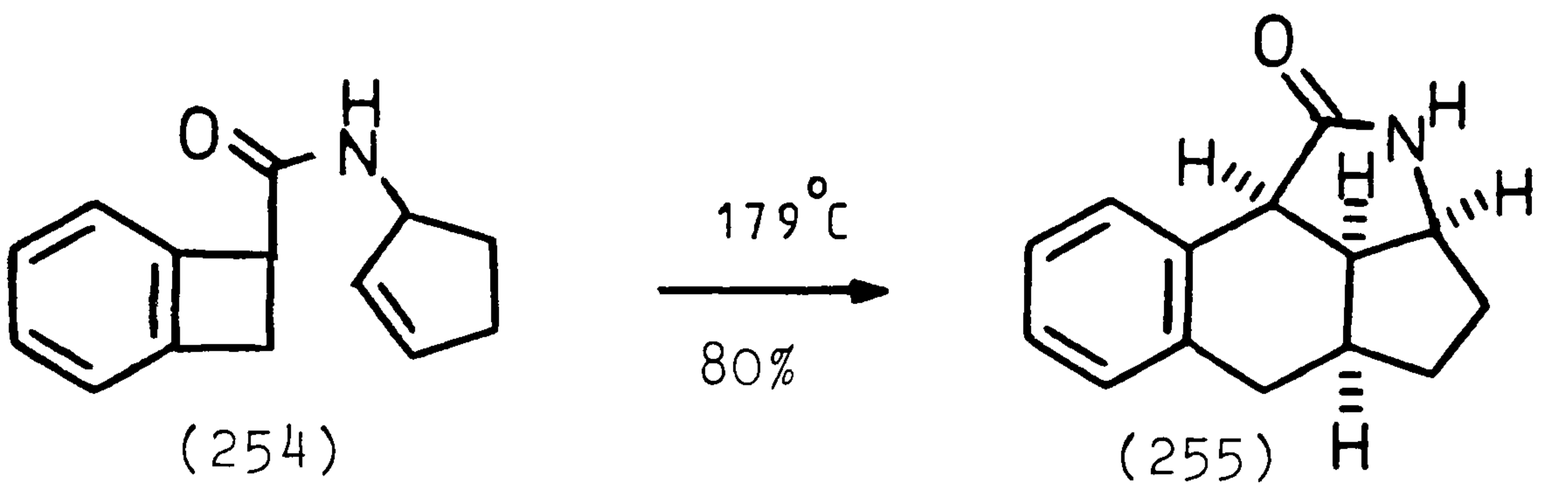
(l) The product was a mixture of cis/trans isomers; the isomer ratio was not determined.

(m) The substrate was generated by irradiation of 2-(N-allyl-N-carbethoxy)aminoethyl-benzaldehyde.

(n) The product was a mixture of fused and bridged isomers.

(o) The product was a 1:1 mixture of cis and trans isomers.

The remarkable control of stereochemistry that can be obtained from these cycloadditions is exemplified by the formation of the tetracyclic adduct (255) from olefin (254),[91] which involves formation of four adjacent chiral centres in one step (entry 37).



(254) (255)

The intramolecular cycloadditions of a fulvene dienophile have also been examined. With an o-xylylene substituted with a nitrile, the [6+4] adduct is obtained (entry 64). However, if the nitrile group is not present, a mixture of the [6+4] and [4+2] adducts is obtained (entry 65).

There are also a small number of examples of o-xylylene undergoing other modes of cycloaddition. These include the reaction of the parent o-xylylene (24) with SO_2. This reaction provides the second reported example of a diene reacting with SO_2 in a Diels-Alder mode[149] to give oxathiin-2-oxide (256). A minor product is (46) resulting from the more usual cheletropic mode of reaction.[150] In addition, tropone adds to o-xylylene to yield (257) and (258).[151] The product (257) which arises from a [2+4] cycloaddition is the first clear example of tropone reacting at its 4,5-positions, although a cycloadduct of this type has been postulated as an intermediate in the

reaction of tropone with nitrile oxides[152] and is probably due to the high reactivity of o-xylylene. The more usual [4+6] product (258) was also isolated. As can be seen from Figure 2, the orbital coefficients of tropone[153] at the 4,5-positions are relatively close to those of the 2,7-positions and therefore we may expect reactions across both of these sets of positions with a reactive diene.

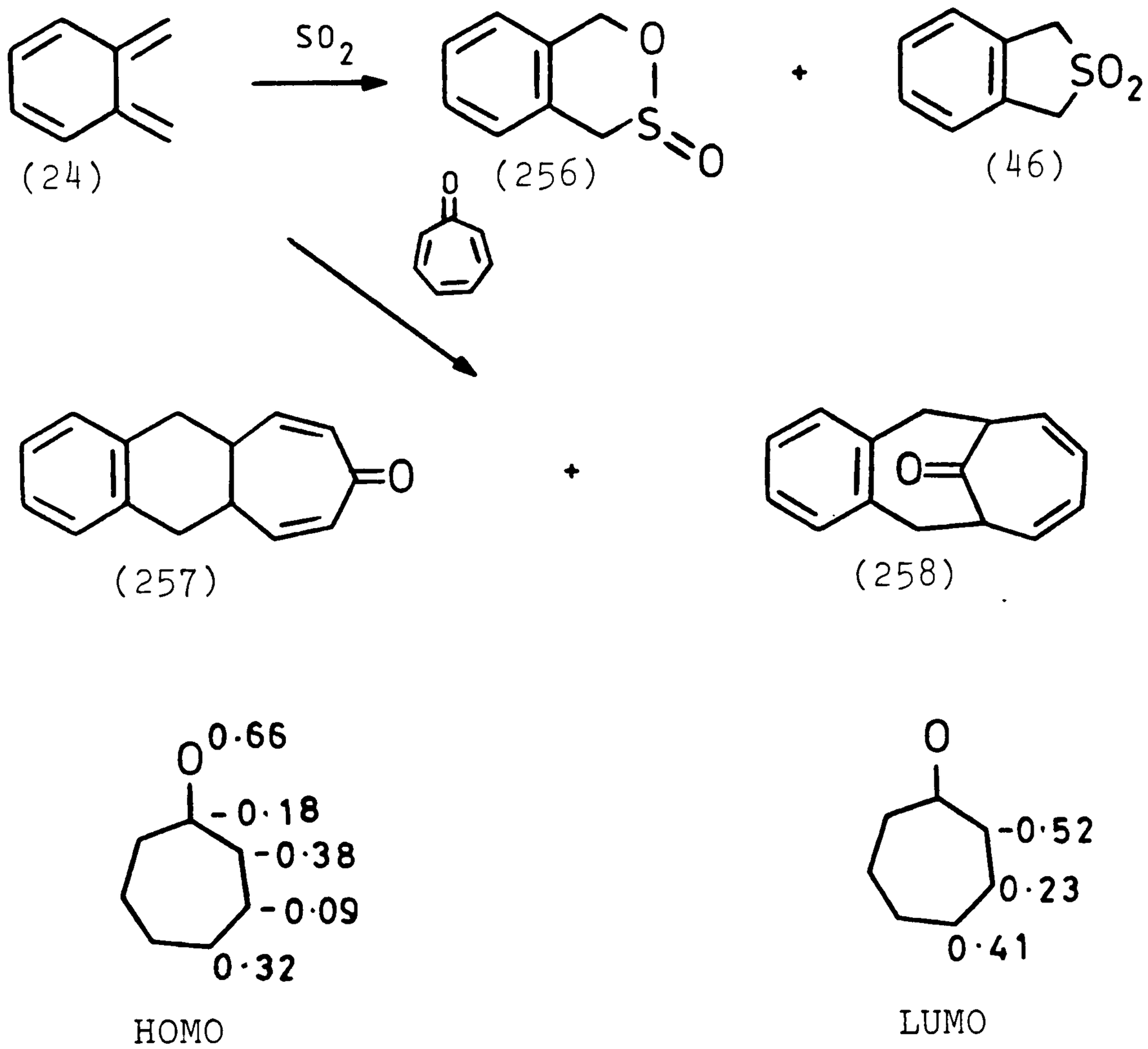
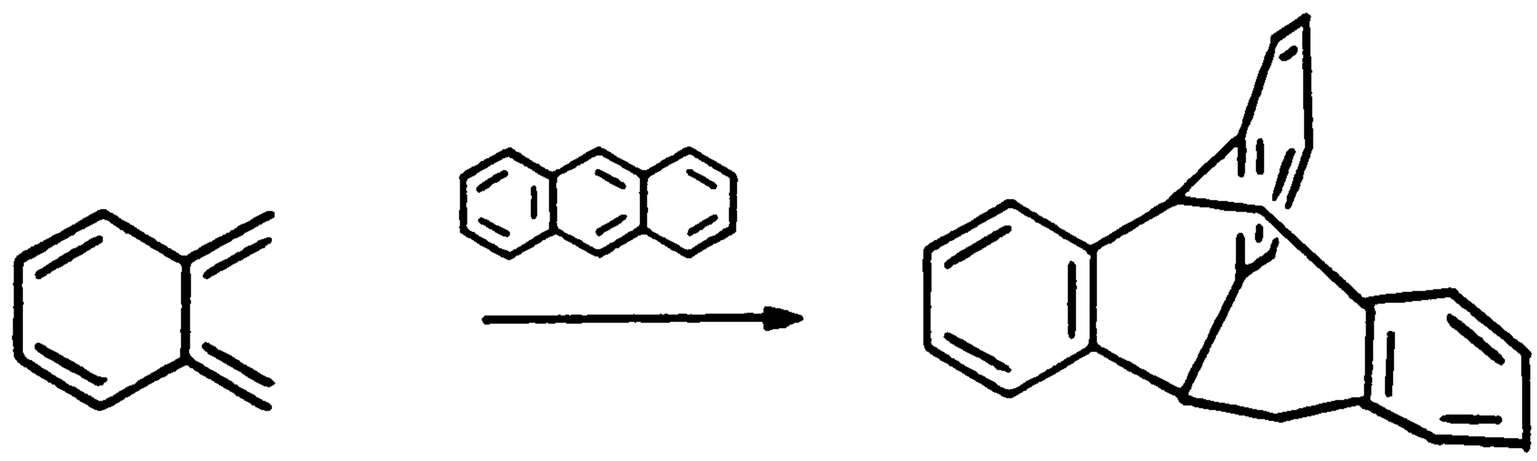


FIGURE 2

Generation of o-xylylene (24) in the presence of anthracene produces adduct (259) in low yield.[152,154] This would appear to arise from a dissallowed [4+4] addition of o-xylylene. It is, therefore, likely that (259) is the product of a radical reaction pathway. Since anthracene may be regarded as a highly stabilised o-xylylene, this example may lend further support to the theory of radical involvement in the dimerization of o-xylylenes (Section 1.3(a)).

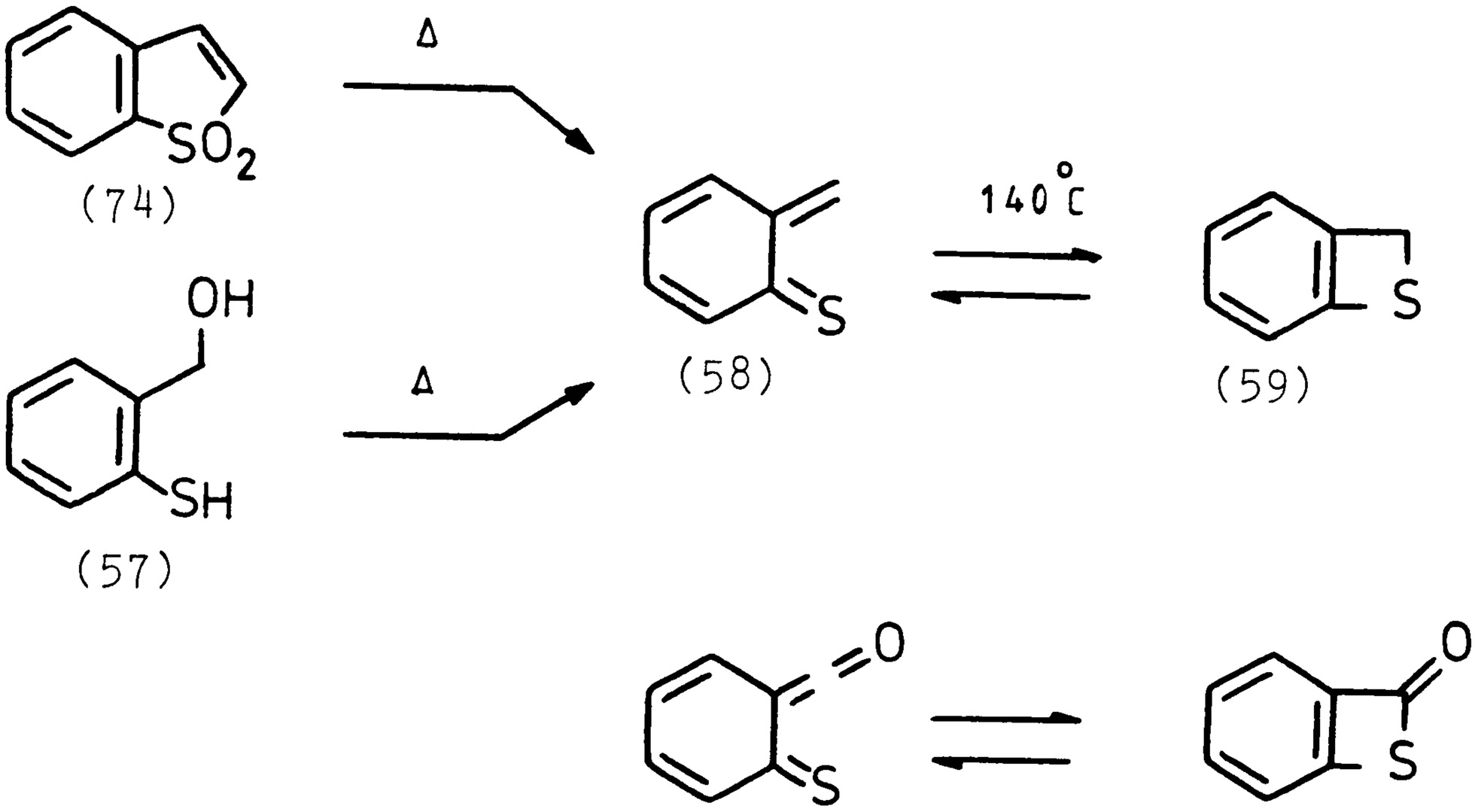


(24) (259)

(b) o-THIOQUINONE METHIDE

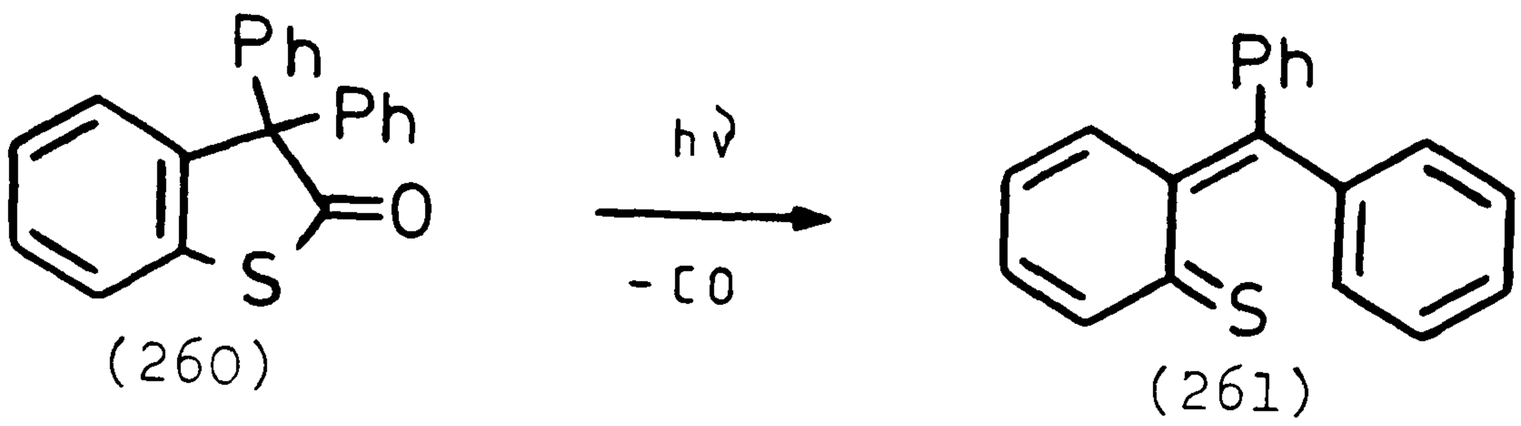
In view of the similar energy difference between the ring opened and closed forms of the carbon and sulphur systems,[1] it is surprising that there are few reports of ring closure of o-thioquinone methides to benzothietes. If the parent o-thioquinone methide (58) is generated under high dilution conditions by flash vacuum pyrolysis of either benzothiophene-1,1-dioxide (74),[56] or o-mercaptobenzyl alcohol (57),[49] the isolated product is benzothiete (59). o-Thioquinone methide (58) can be regenerated from benzothiete, (59) by heating to temperatures in excess of 100°C when,

in the condensed phase, it dimerizes. There is also evidence for this type of valence tautomerism between the ketene system (77) and the thiolactone (78).[57b,69]

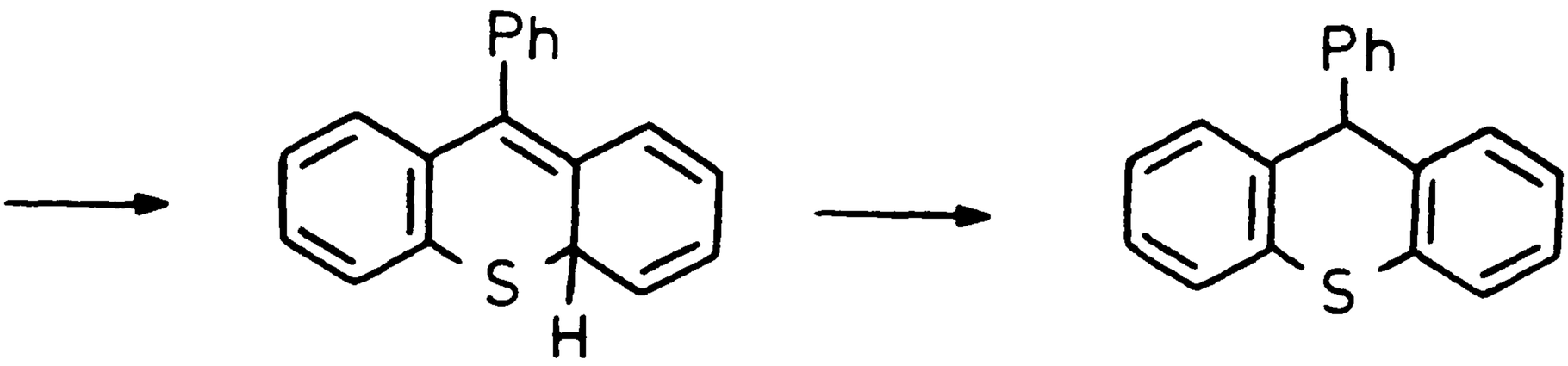


The highly stabilised o-thioquinone methides (such as (87), Section 1.1(b)) do not show any tendency to undergo ring closure, probably due to the high degree of benzenoid character from the polarization of the system.

Other pericyclic reactions of o-thioquinone methides have been reported. Appropriately substituted o-thioquinone methides can also undergo electrocyclization reactions. For instance, irradiation of benzothiophene-2-one (260) leads to the formation of (262) which slowly isomerizes to (263).[54,155] This reaction is rationalized as involving formation of the o-thioquinone methides (261)



(260) (261)

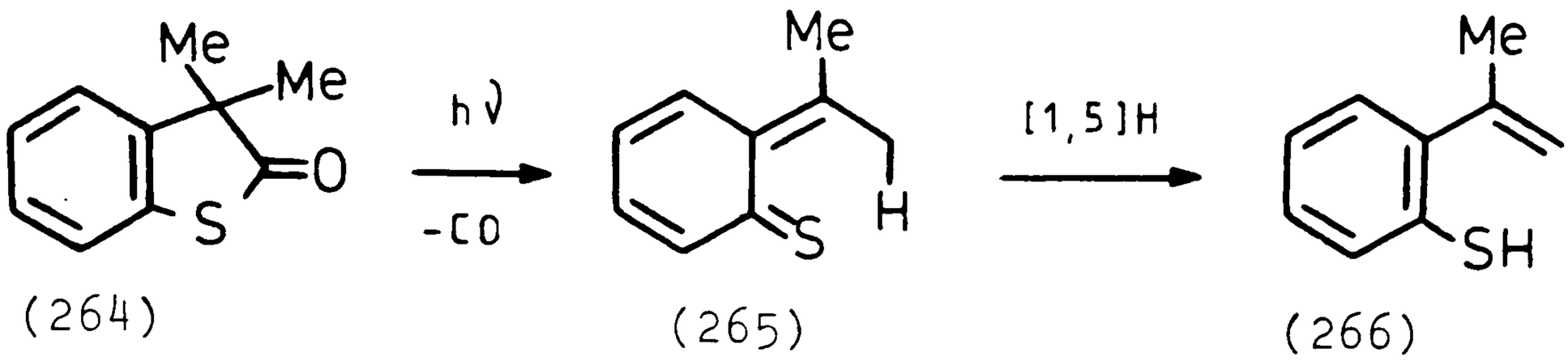


(262) (263)

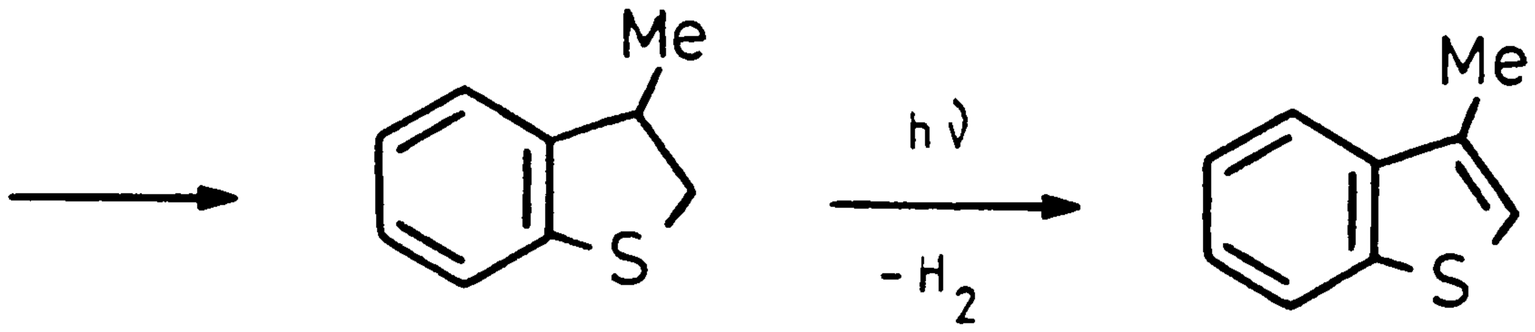
by decarbonylation of (260), followed by electrocyclization to (262).

o-Thioquinone methides can also undergo 1,5-H-shift reactions when generated photochemically. For example, irradiation of 3,3-dimethylbenzothiophen-2-one (264) gives rise to 3-methylbenzothiophene (267). Presumably, the reaction proceeds by way of o-thioquinone methide (265) which then undergoes a 1,5-hydrogen shift to yield styrene (266). This H-shift must necessarily be extremely facile as the proposed intermediate (265) could not be trapped with dienophiles such as N-phenyl maleimide.[54a]

Like o-xylylenes, o-thioquinone methides readily undergo cycloaddition reactions such as the Diels-Alder reaction. For example, trapping of the parent o-thioquinone methide (58) with N-phenylmaleimide, gave adduct (268) in good yield,[49,54,55] and provided the

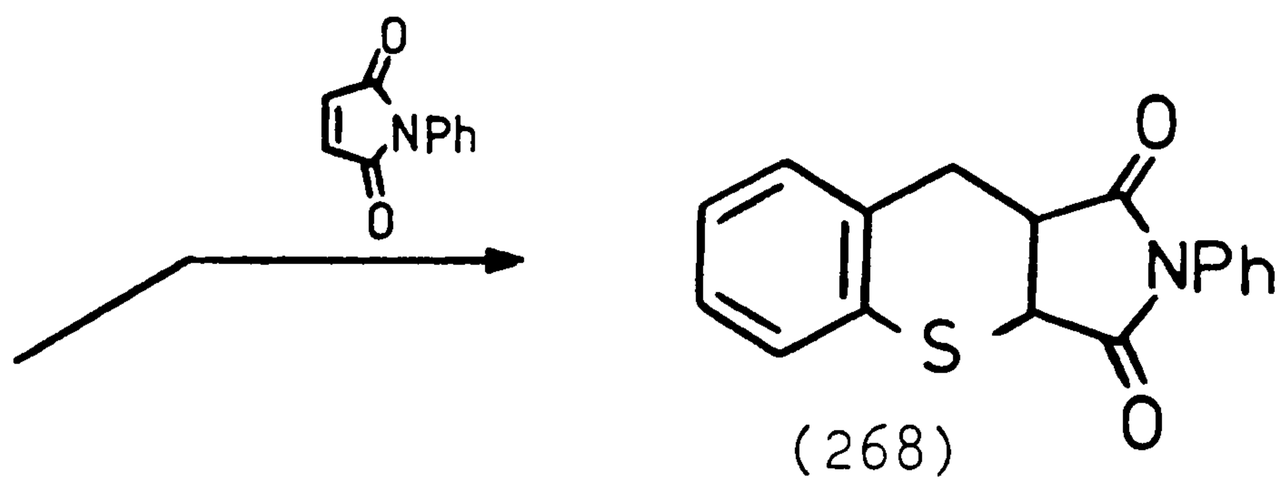


(264) (265) (266)

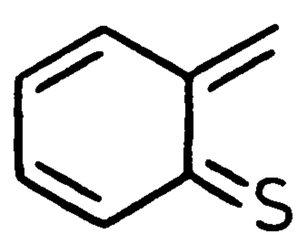


(267)

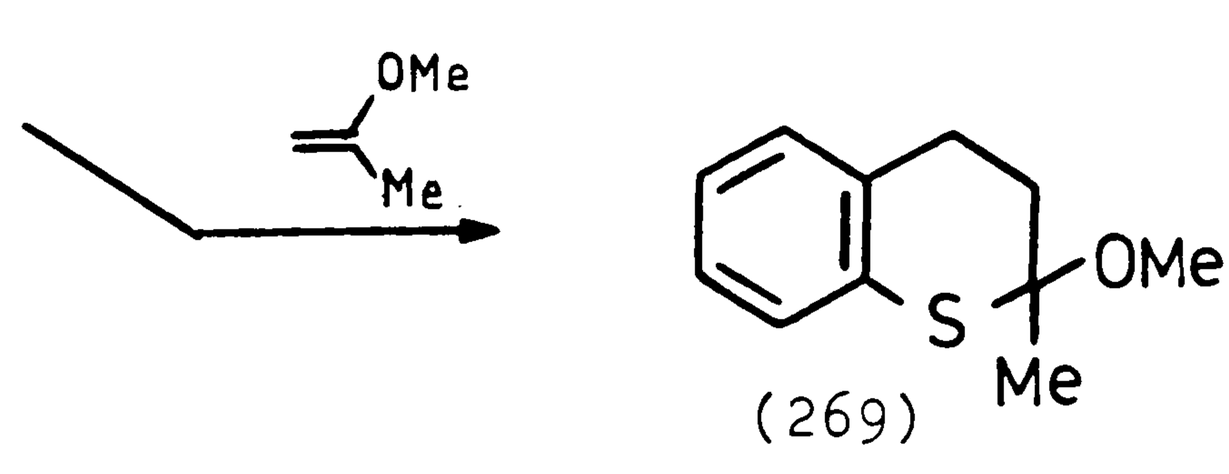
first example of a [2+4] cycloaddition to a heterodiene containing a sulphur atom.[54a] Cycloadditions with electron-rich dienophiles are also possible, for example, cycloaddition of (58) with isopropenyl methyl ether produces adduct (269) in moderate yield.[49]



(268)



(58)



(269)

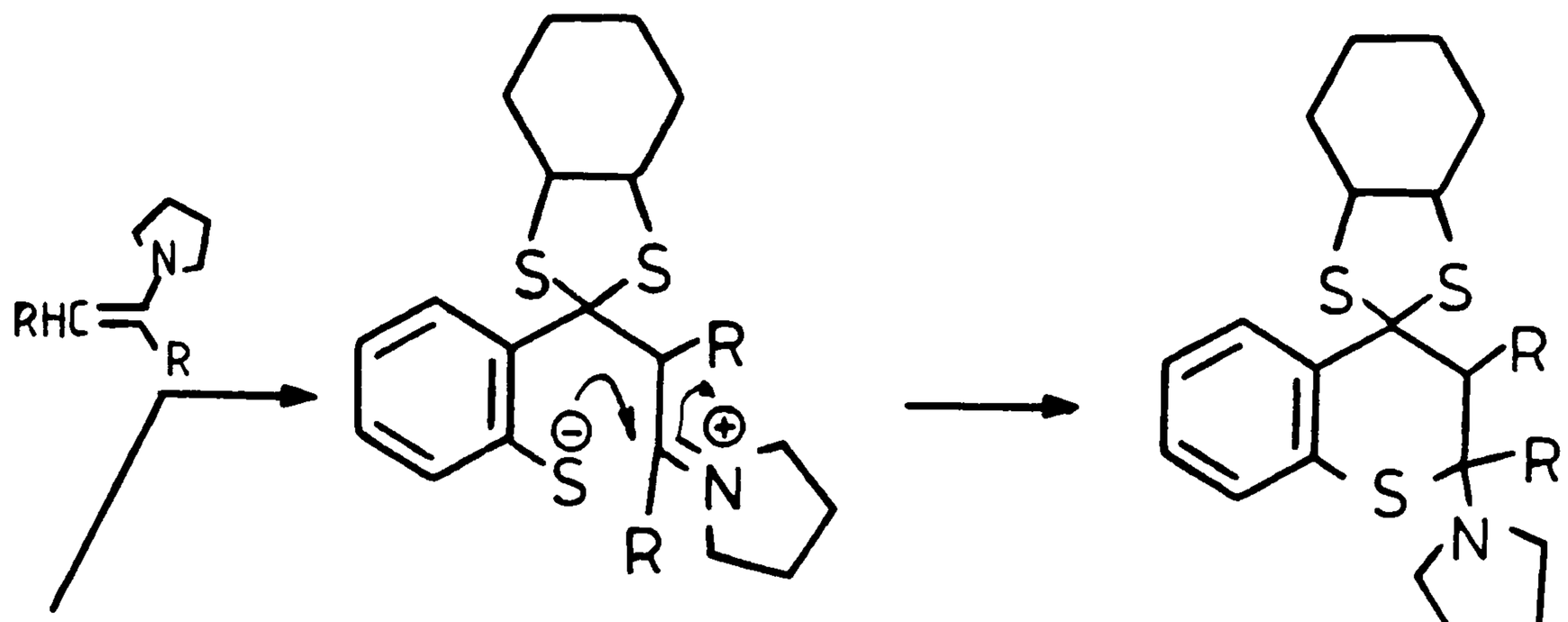
No data is yet available as to whether endo or exo addition is preferred with o-thioquinone methides. Also, stabilised o-thioquinone methides readily undergo cycloaddition. For example, o-thioquinone methide (270) adds to enamines to give the adducts (271) in good yield,[155,156] probably by a stepwise, ionic reaction mechanism.

With electron deficient olefins such as maleonitrile or fumaronitrile, the cycloaddition reactions appear to be concerted, as indicated by the retention of stereochemistry in the adducts (272) and (273).[155,156]

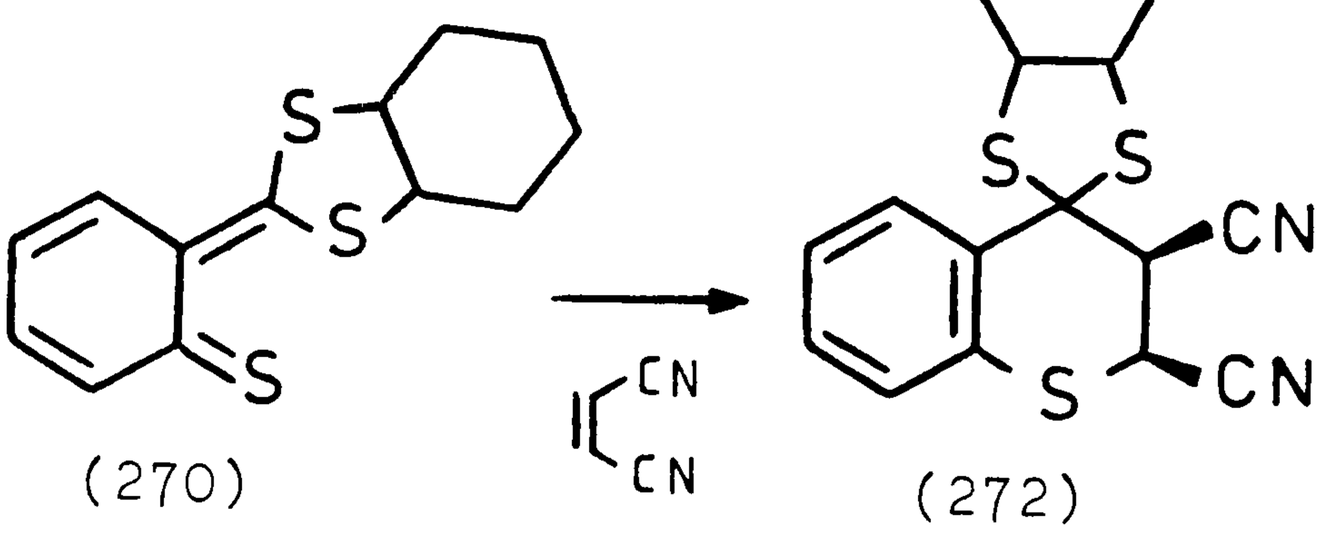
There appear to be no reports concerning the intramolecular Diels-Alder trapping of an o-thioquinone methide.

(c) o-AZAXYLYLENES

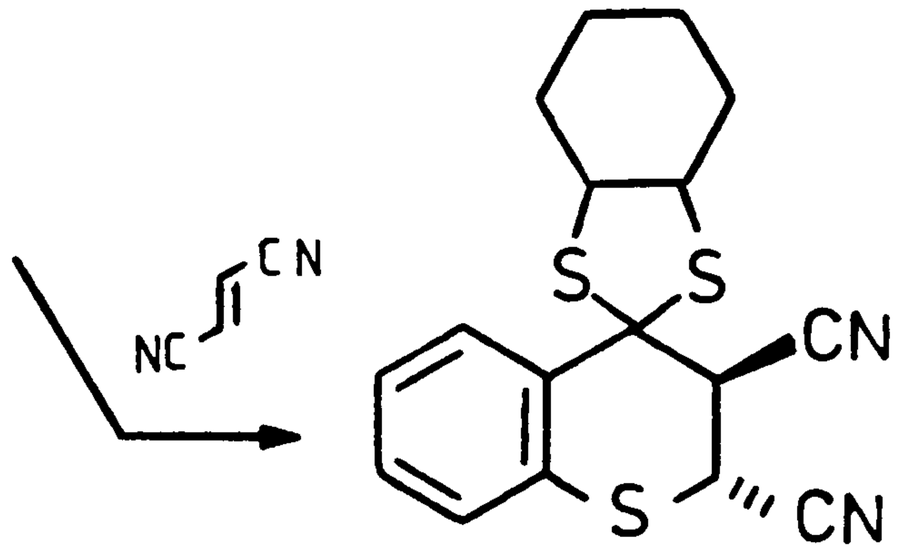
Theoretical calculations[1] have predicted that the energy difference between o-azaxylylene and benzazetidine is approximately 30 $KJ.mol^{-1}$ larger than that for the carbon and sulphur systems. Thus we would predict that ring closure of o-azaxylylenes to benzazetidines is much less favourable than for the carbon and sulphur analogues. This prediction appears to be correct as of the few benzazetidines that are known, only two have been formed via ring closure of an o-azaxylylene. Thus, o-azaxylylene (275) has been postulated as an intermediate in the photolysis of the N-acyldihydroquinoline (274). Interestingly, after a short period of irradiation, it was



(271)

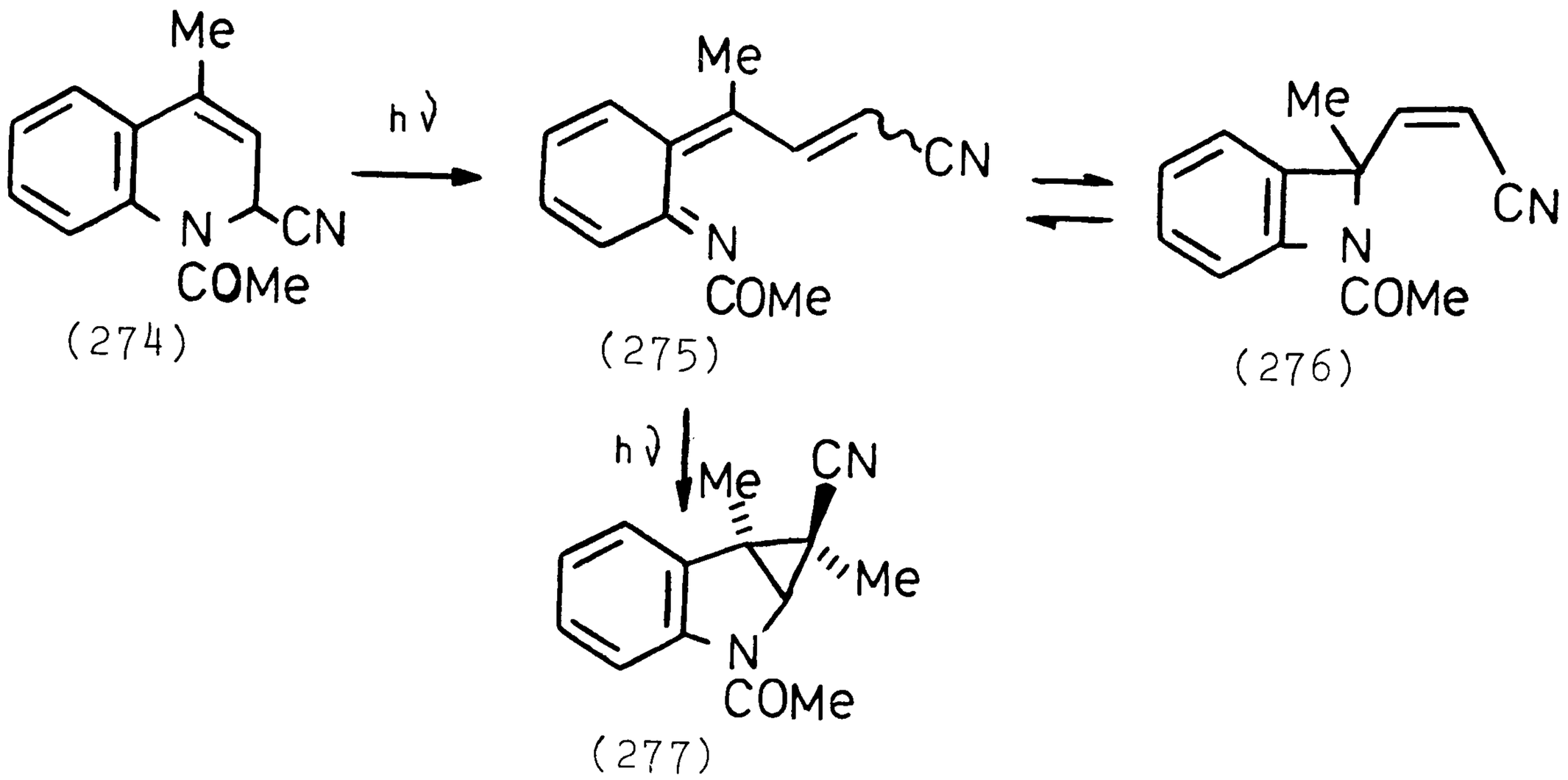


(270) (272)



(273)

reported that a mixture of benzazetidine (276) and indole (277) could be isolated from the reaction mixture, with (276) as the major product. Irradiation for a longer period resulted in the disappearance of benzazetidine (276) and gave indole (277) as the sole product. This was rationalized as involving a photochemical equilibrium between o-azaxylylene (275) and benzazetidine (276) with a slow, irreversible cyclization to indole (277).[73]

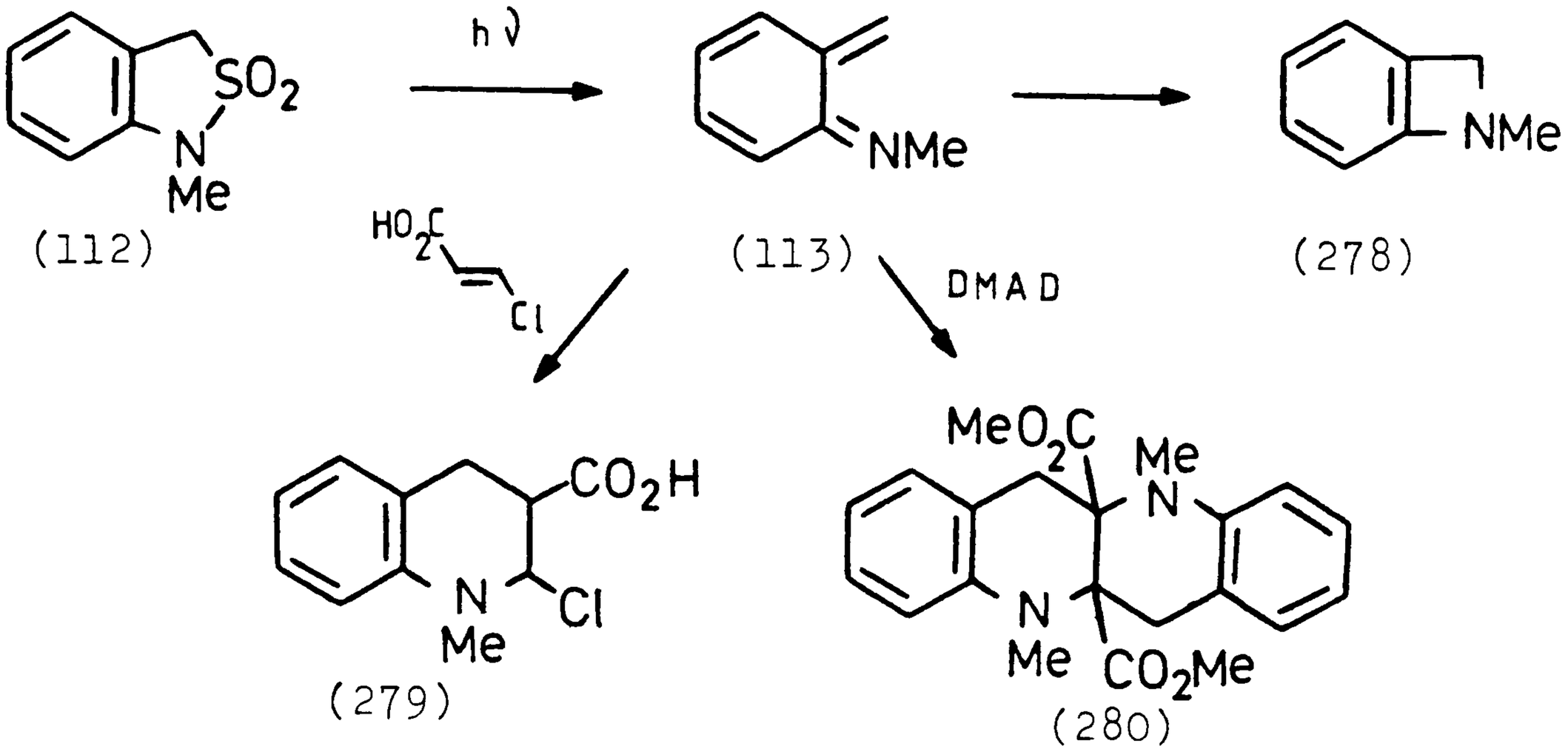


(274) (275) (276) (277)

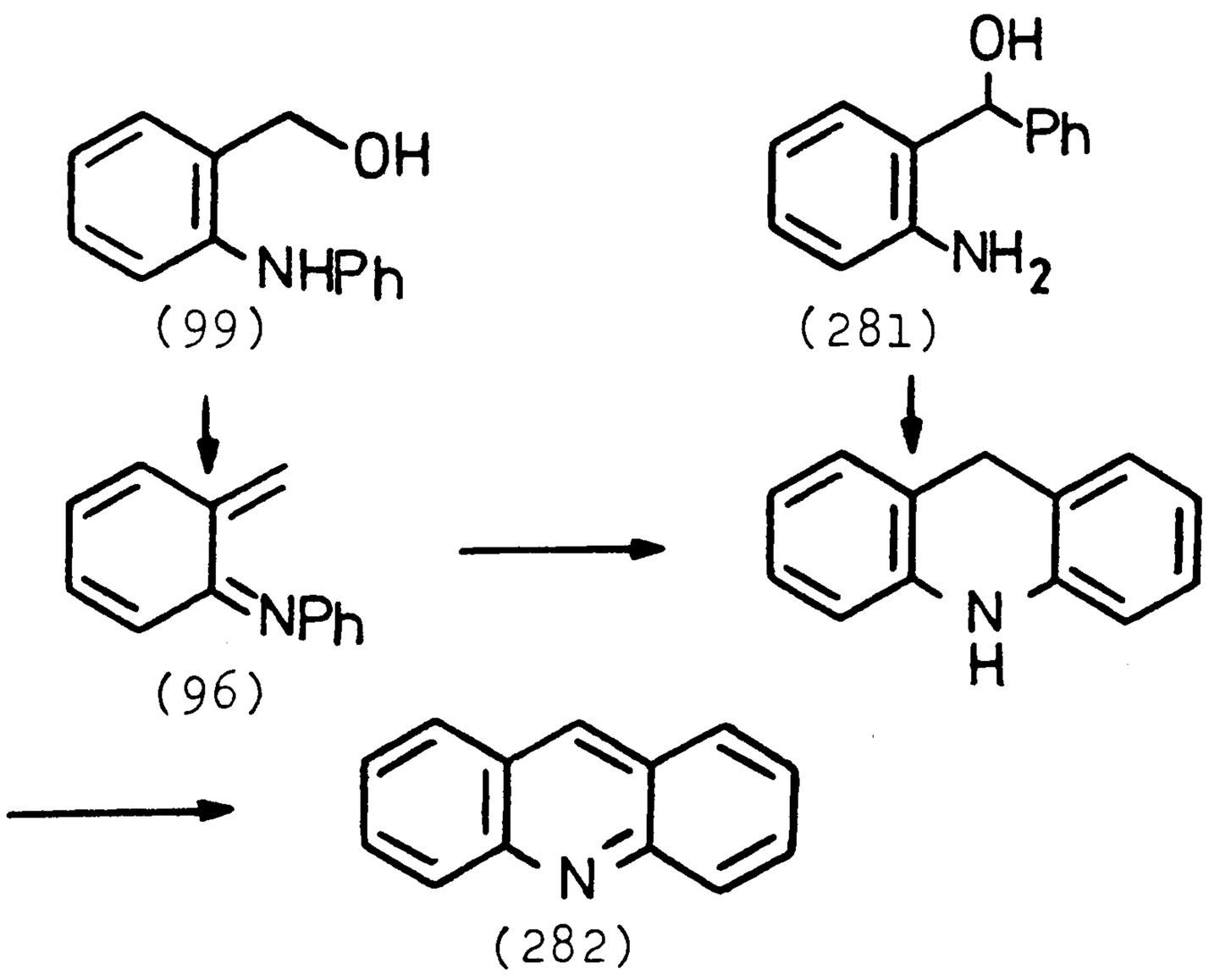
The second report of the ring closure of an o-azaxylylene results from the extrusion of sulphur dioxide from sultam (112) to yield benzazetidine (278).[71] The intermediacy of azaxylylene (113) was further implicated by the formation of cycloadducts (279) and (280) with chloroacrylic acid and dimethyl acetylene dicarboxylate respectively.[71]

Other reports of the valence tautomerism of the benzazetidine/o-azaxylylene system are limited to the ring opening reactions of benzazetidines (see Section 1.1(c)).

There are a number of reports concerning the electrocyclization reactions of o-azaxylylenes. For example, generation of N-phenyl azaxylylene (96) by flash pyrolytic dehydration of alcohol (99) produces acridine (282) in good yield presumably by electrocyclization of the intermediate o-azaxylylene (96) and dehydrogenation of the initially formed dihydroacridine.[64]

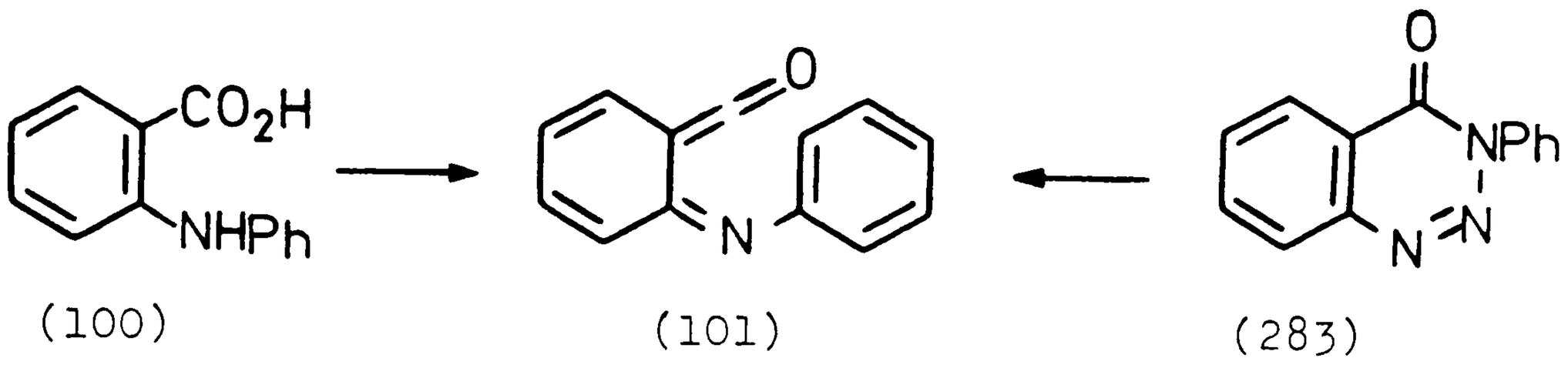


The same observation was made independently in these laboratories.[157] Similar pyrolysis of alcohol (281), again produces acridine (282) presumably by electro-cyclization of an intermediate C-phenylazaxylylene,[157] (see Discussion Section).



Similarly, acridone (284) results from the flash pyrolysis of N-phenylanthranilic acid (100)[66] or

N-phenylbenzotriazinone (283).[158] Again, it has been postulated that the reaction proceeds via electrocyclization of an intermediate o-azaxylylene-ketene (101).

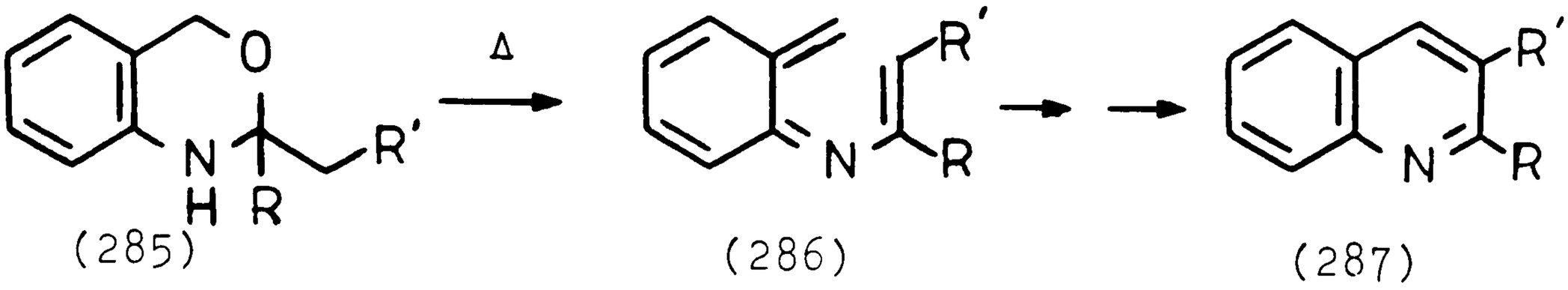


(100) (101) (283)

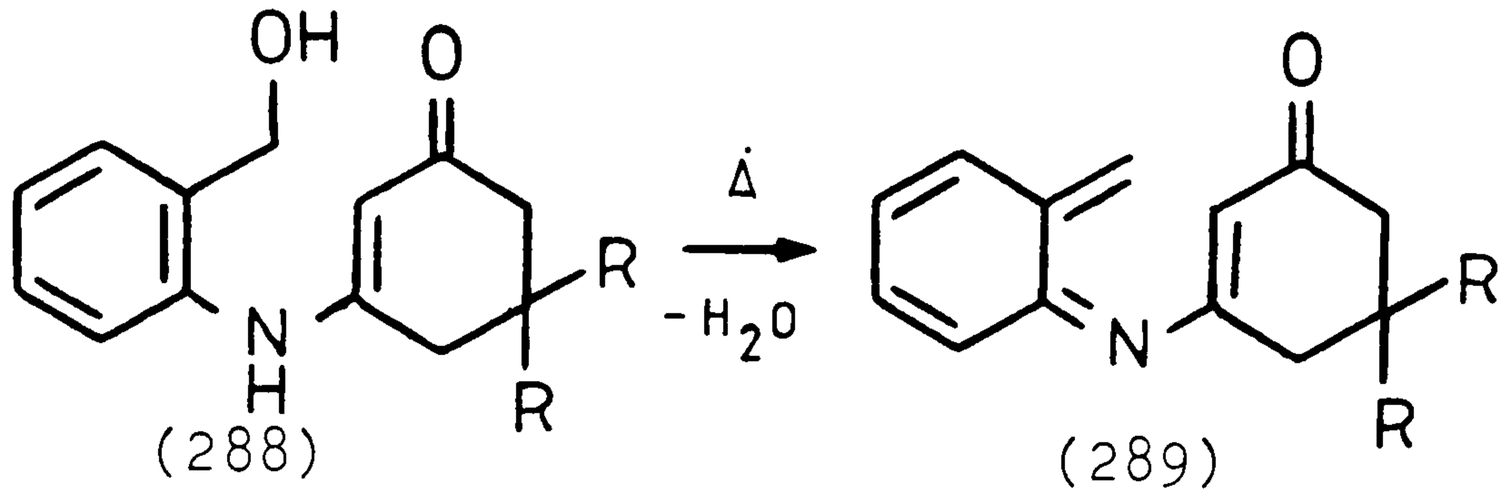
(284)

Electrocyclization of o-azaxylylene (286) is thought to occur in the flash vacuum pyrolysis of oxazine (285) which gives quinoline (287), again after dehydrogenation of the initially formed dihydro species.

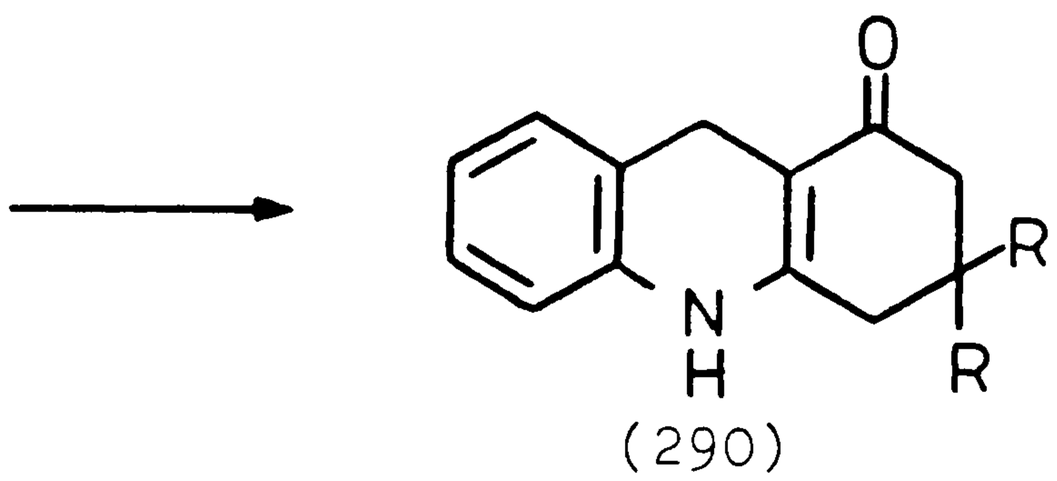
Similarly, flash pyrolytic dehydration of alcohol (288) produces the dihydro acridines (290) in good yield, again, the most plausable mechanism for formation of (290) is electrocyclization of an intermediate o-azaxylylene (289).[157]



(285) (286) (287)



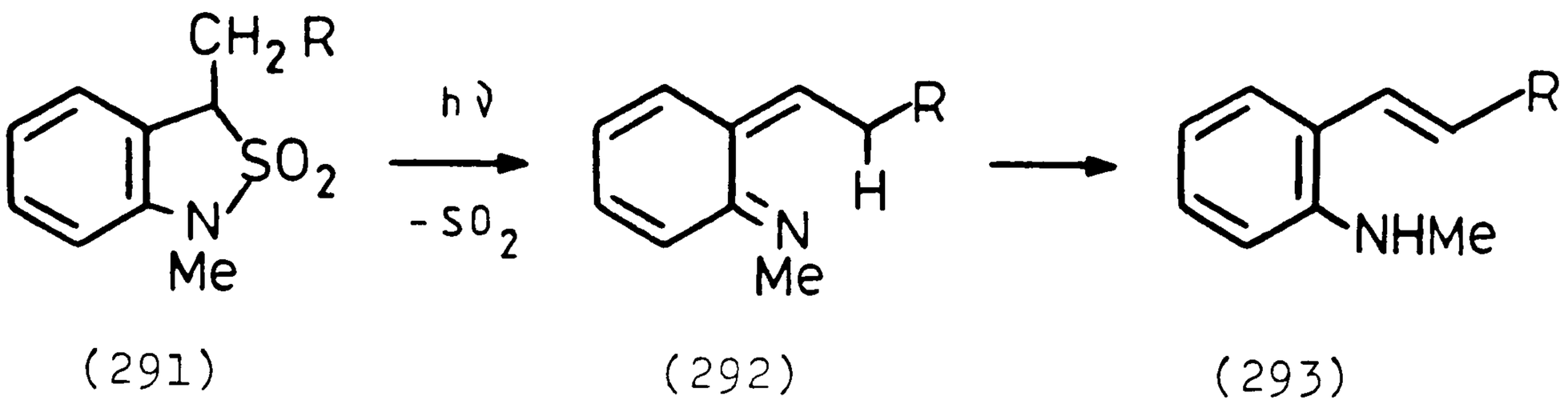
(288) (289)



(290)

Again, as was observed with certain alkyl substituted o-xylylenes, 1,5 -hydrogen shifts can be observed with alkyl o-azaxylylenes. However, the majority of these reports seem limited to alkyl substituted o-azaxylylenes generated under the conditions of flash vacuum pyrolysis[157] (see Section 2). An exception is the photolysis of sultams (291) which yields the o-amino styrenes (293), presumably by a 1,5 -H shift in the intermediate o-azaxylylene (292).[71]

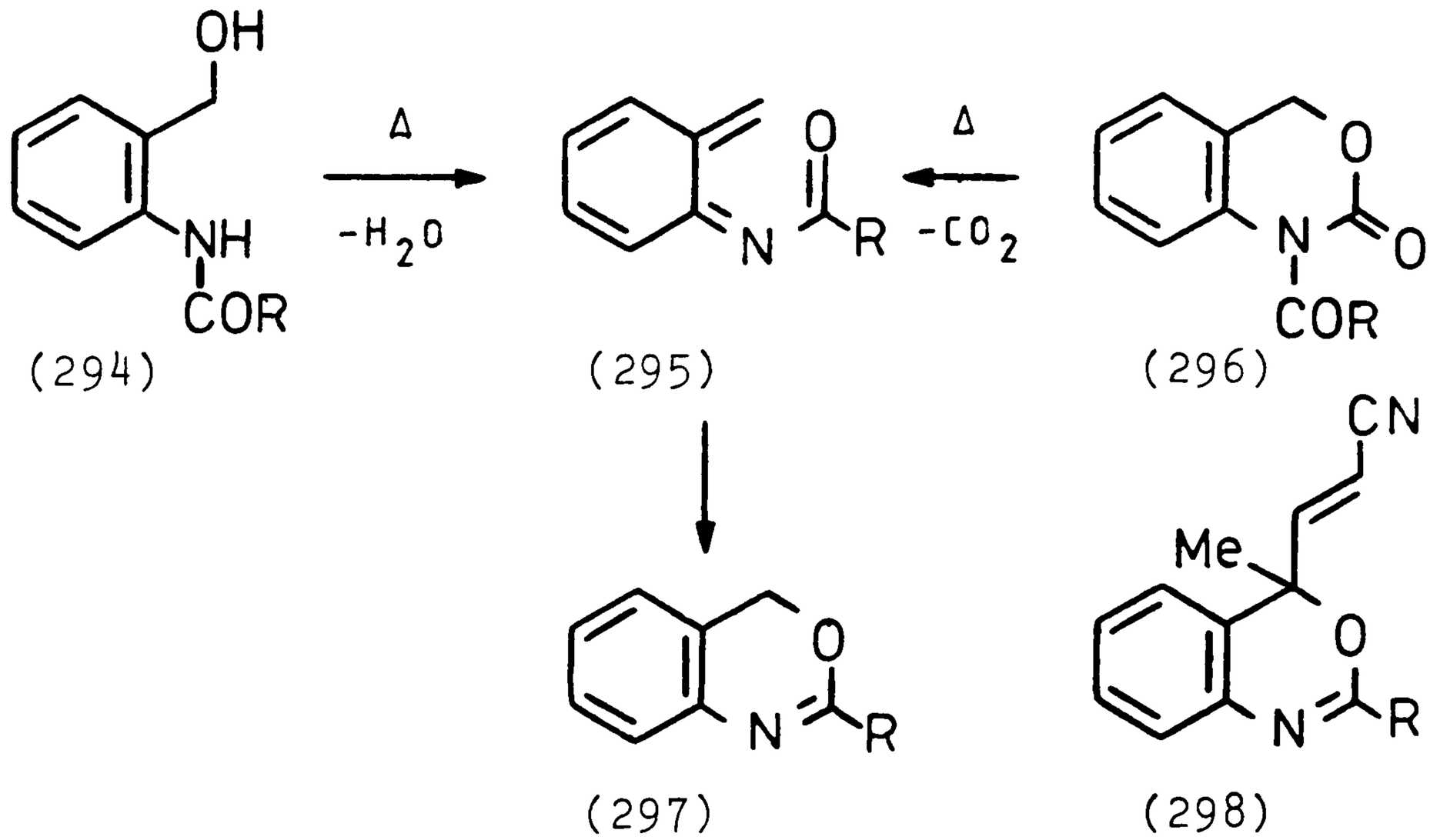
It has also been reported that N-acylazaxylylenes can undergo electrocyclization. Thus flash vacuum pyrolysis of amides (294) or benzoxazinones (296) produces



(291) (292) (293)

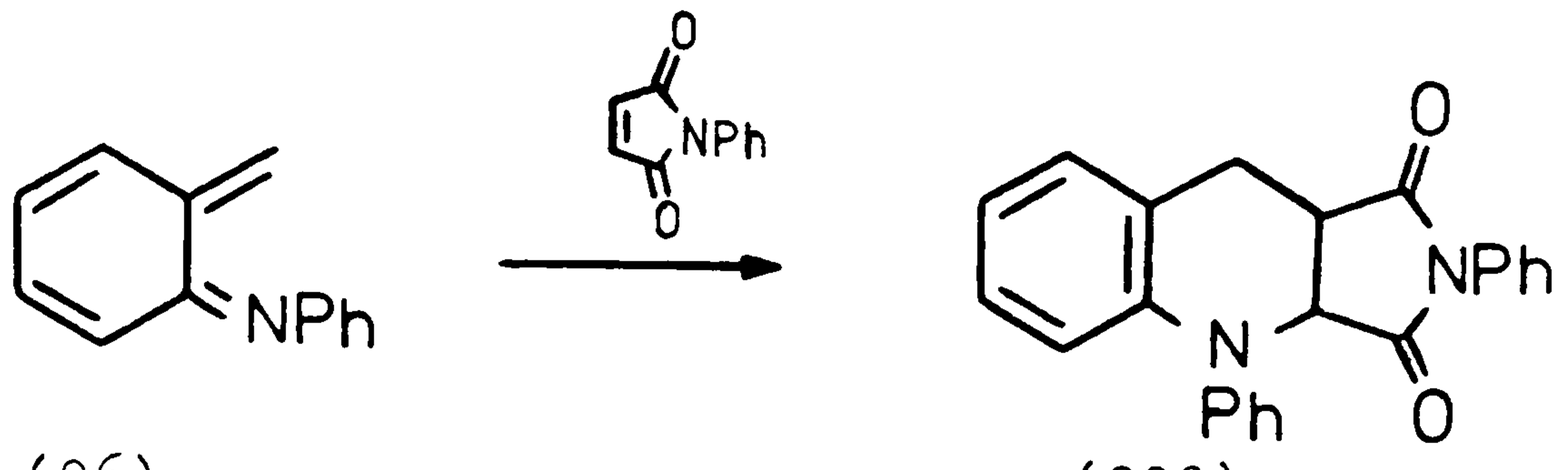
R = H, Ph, CH = CH_2

N-acylazaxylylene (295). This undergoes electrocyclization to afford oxazines (297).[157] In view of this observation, the previously mentioned report[73] concerning the photolysis of quinoline (274) merits reconsideration as it is possible that the N-acylazaxylylene (275) is in equilibrium with oxazine (298) formed by electrocyclization.



(294) (295) (296) (297) (298)

o-Azaxylylenes, like their carbon and sulphur analogues are very reactive towards dienophiles. Thus, N-phenyl-azaxylylene (96) readily undergoes intermolecular Diels-Alder reaction with N-phenylmaleimide to give the adduct (299) in good yield.[64]

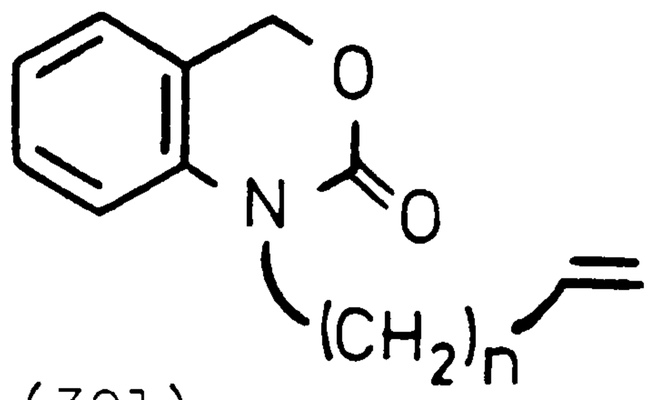


(96) (299)

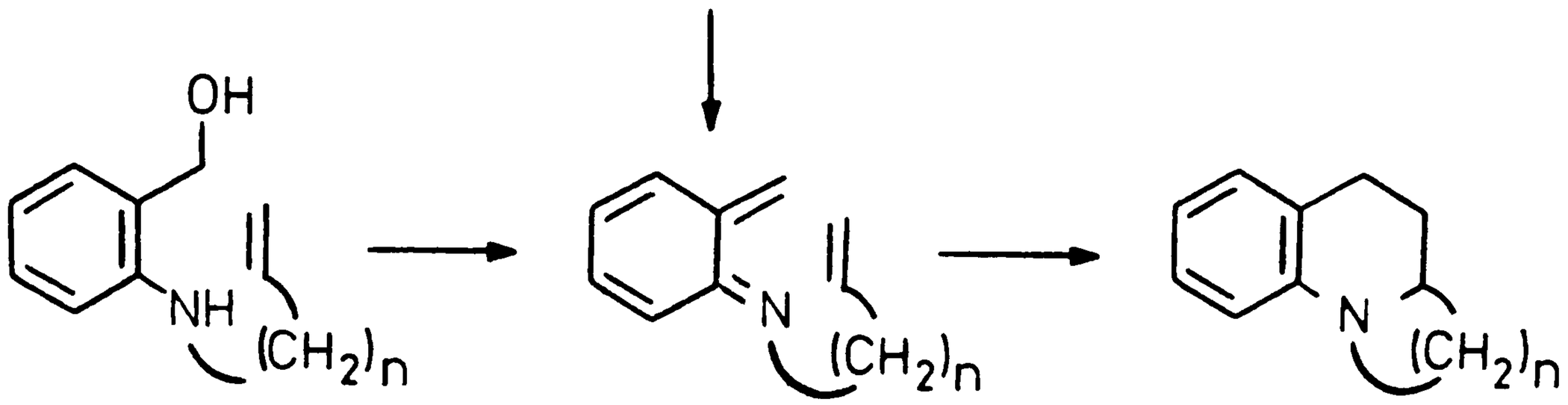
Other cases are the previously mentioned intermolecular cycloadditions of N-methyl azaxylylene (98) → (279) and (280).[71] Intramolecular Diels-Alder cycloadditions of azaxylylenes have also been reported where the chain connecting diene to dienophile is attached to the nitrogen of the system. For example, flash pyrolysis of amino alcohols (300) or benzoxazinones (301) produces tricycles (304) by intramolecular Diels-Alder trapping of the intermediate o-azaxylylenes (303).[157] Also, o-azaxylylenes (303) can be generated in solution from desilylation of salts (302) again, producing tricycles (304).[65]

(d) o-QUINONE METHIDE

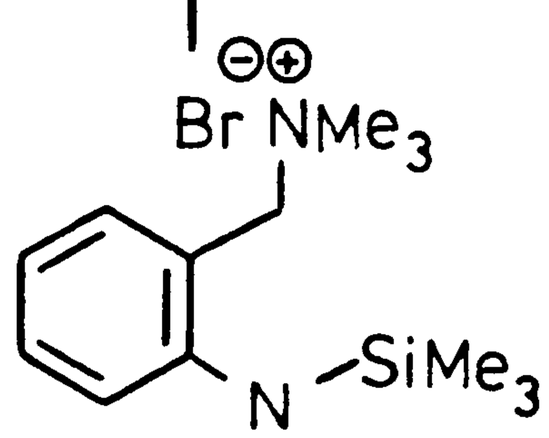
Because of the large energy difference which has been calculated[1] for the o-quinone methide/benzoxete system, we would predict that ring closure of an o-quinone methide to the much higher enegy benzoxete system is an extremely unfavourable process. Indeed apart from one



(301)



(300) (303) (304)

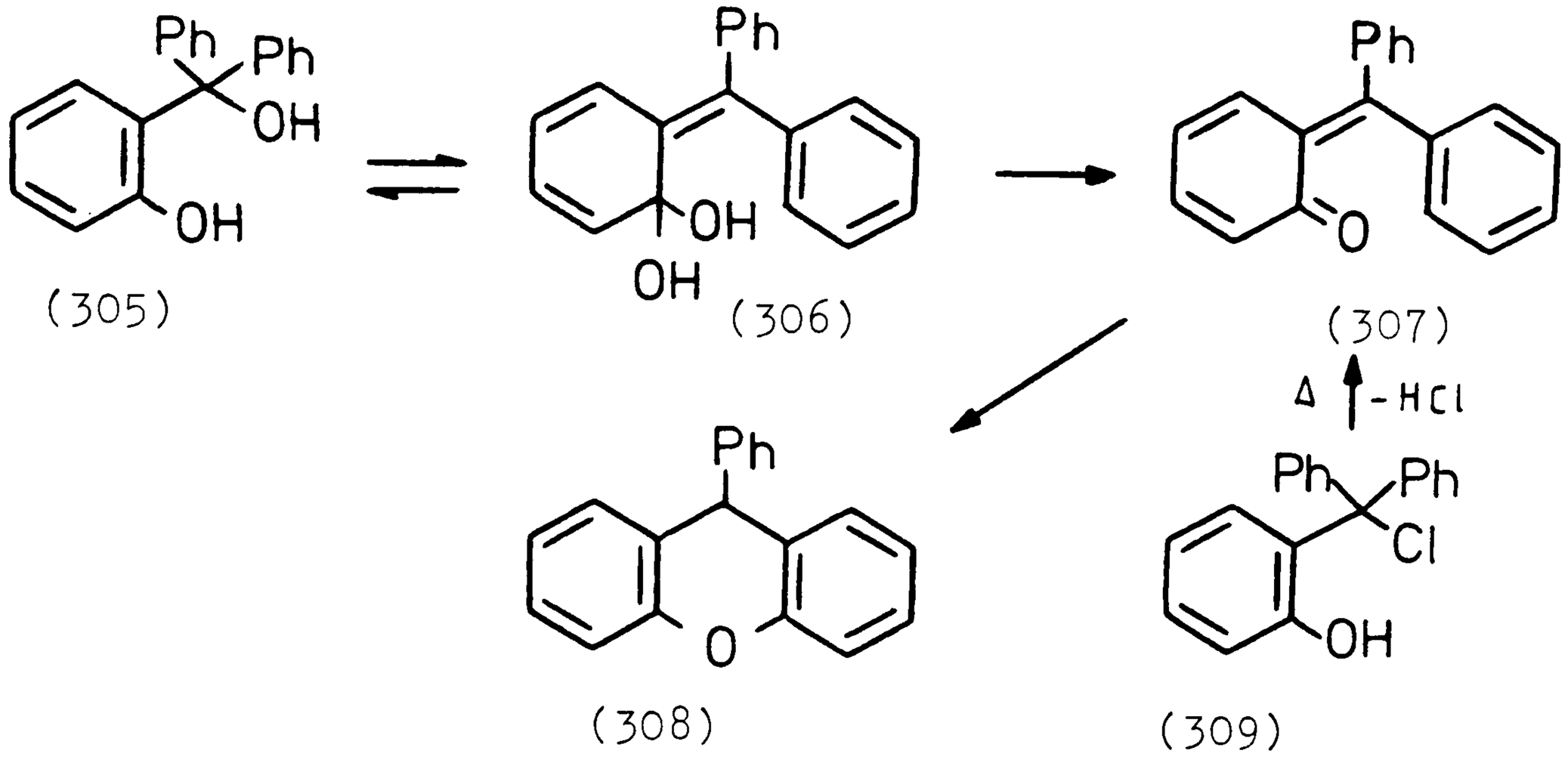


(302)

report concerning the photochemical interconversion of ring closed and ring open forms at low temperature[78] (reaction (128) → (129), Section 1.2(d)), there have been no reports concerning the ring closure of an o-quinone methide to a benzoxete.

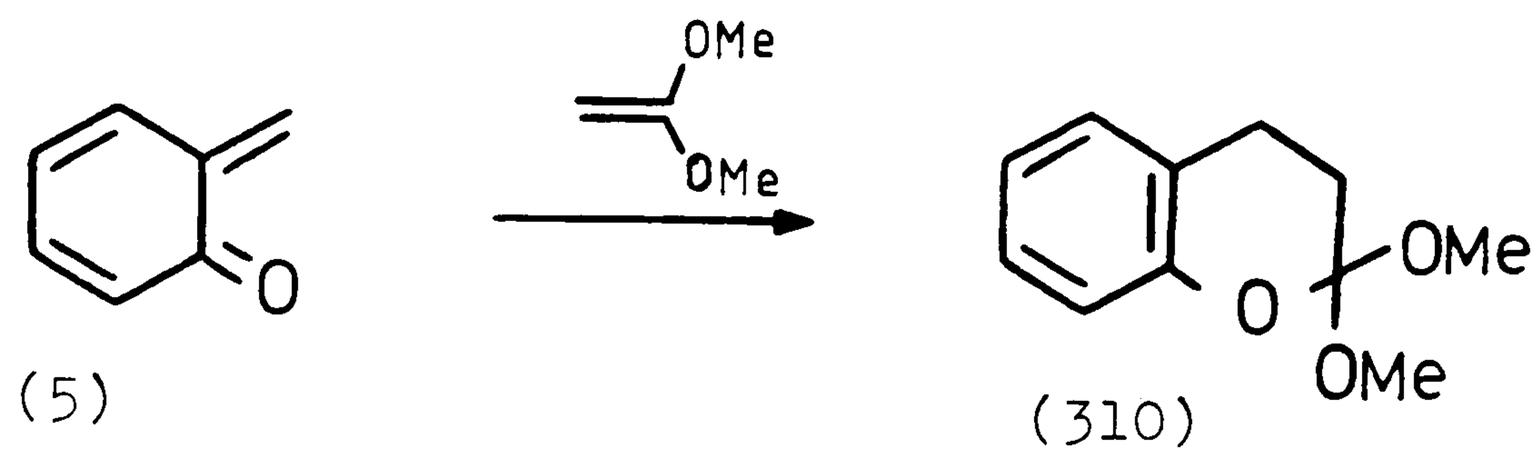
However, most of the other pericyclic reactions observed with the carbon, sulphur and nitrogen systems also occur with o-quinone methides. For example, if the tri-aryl carbinol (305) is heated to between 50° - 100°, tautomerism to (306) occurs. On stronger heating (306) loses water to yield xanthene (308) presumably by electrocyclization of o-quinone methide (307).[159]

Similar dehydrohalogenation of phenol (309) affords (308), presumably by the same mechanism.[159]

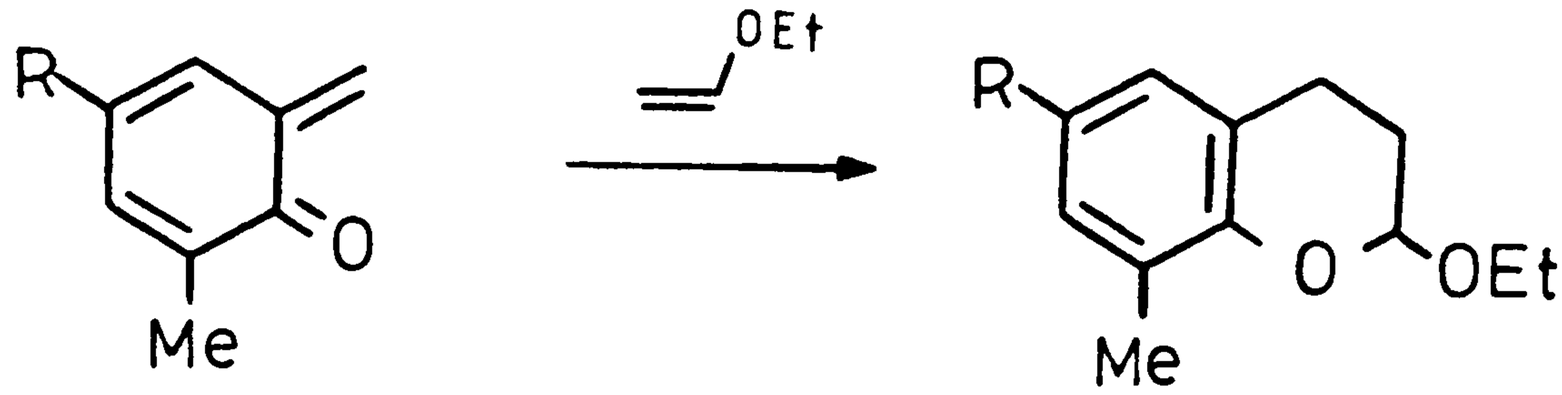


o-Quinone methides are also very reactive dienes in the Diels-Alder reaction and add efficiently to electron-rich olefins as exemplified by the intermolecular trapping of the parent o-quinone methide (5) by vinyl ether to give ortho ester (310).[84] Similarly, reaction of o-quinone methide (311) with an excess of ethyl vinyl ether produces chroman (312) in quantitative yield.[86b] If however, an electron donating substituent is present on the o-quinone methide, the reactivity is markedly reduced. For example, the generation of (313) in ethyl vinyl ether as solvent leads to trimer and no chroman.[86b]

o-Quinone methide (5) also adds to fairly unactivated olefins such as styrene to produce chroman (314).[86b]



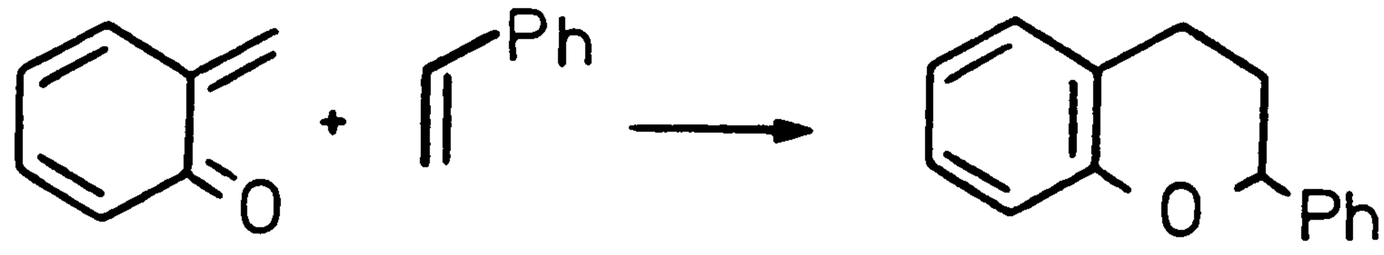
(5) (310)



(312)

(311) R = ^{t}Bu

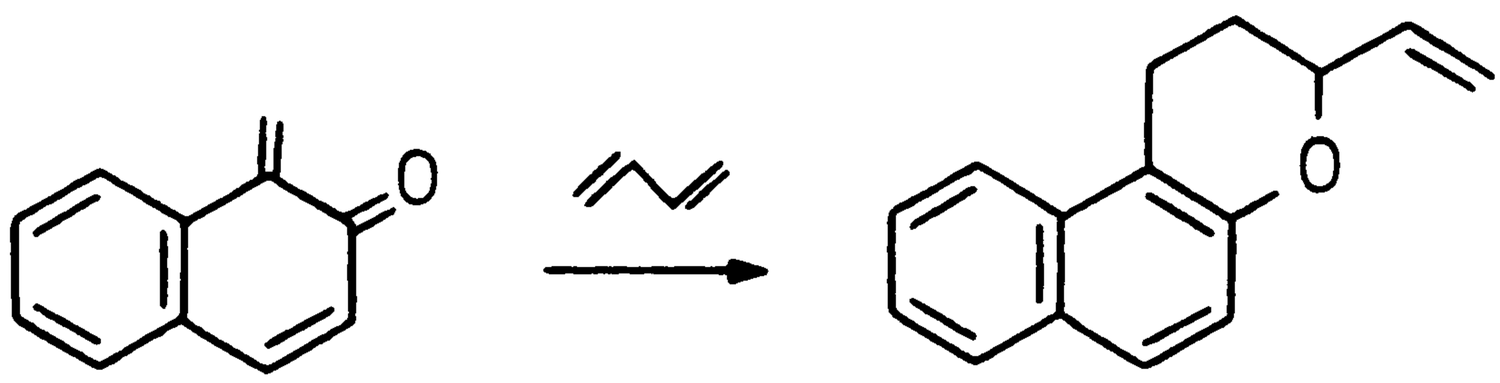
(313) R = OMe



(5) (314)

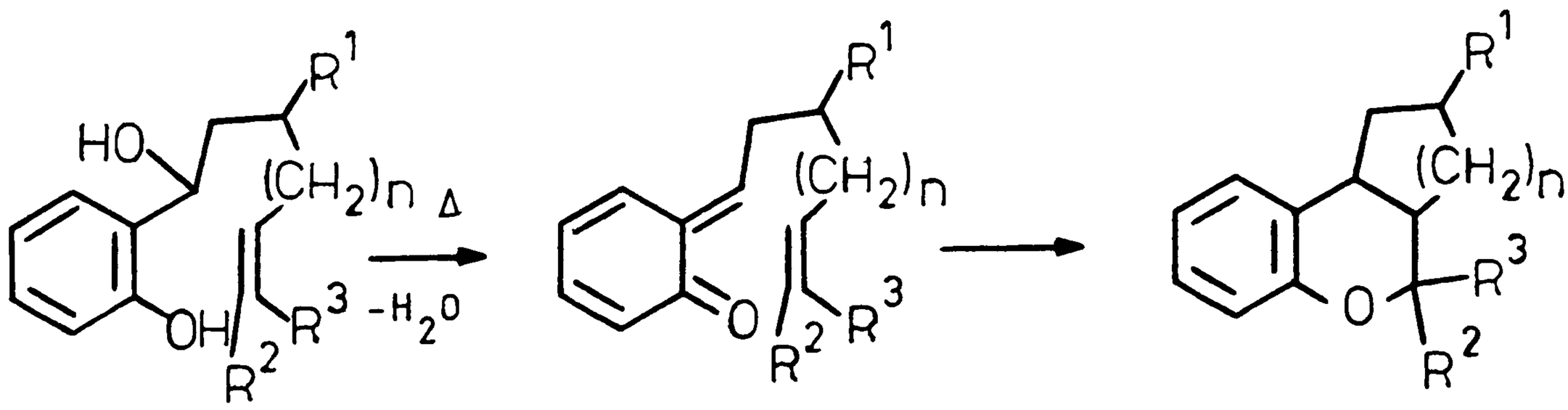
In addition, naphthoquinone methide (174) undergoes cycloaddition to one of the double bonds of butadiene to produce the vinyl substituted chroman (315) in good yield.[160]

Boekelheide has reported the intramolecular Diels-Alder trapping of o-quinone methide (317) to give cis-fused product (318) from flash pyrolysis of diol (316)[49]. Alternatively, heating alcohol (316) in solution at 270°C affords adduct (318), 40%, as a 3:1 mixture of cis and



(174) (315)

trans-isomers.[161] Also, the gas phase pyrolysis of alcohol (319) gives adduct (321) in good yield.[162] Finally, it has been reported recently that generation of o-quinone methide (323) from the thermolysis of diol (322) at 180°C gives the trans fused adduct (324) in high yield.[163]



(316) $R^1=R^2=R^3=H$, n = 1 (317) $R^1=R^2=R^3=H$, n = 1 (318) $R^1=R^2=R^3=H$ n = 1

(319) $R^1=R^2=H, R^3=Ph$, n = 1 (320) $R^1=R^2=H, R^3=Ph$, n = 1 (321) $R^1=R^2=H$, $R^3=Ph$, n = 1

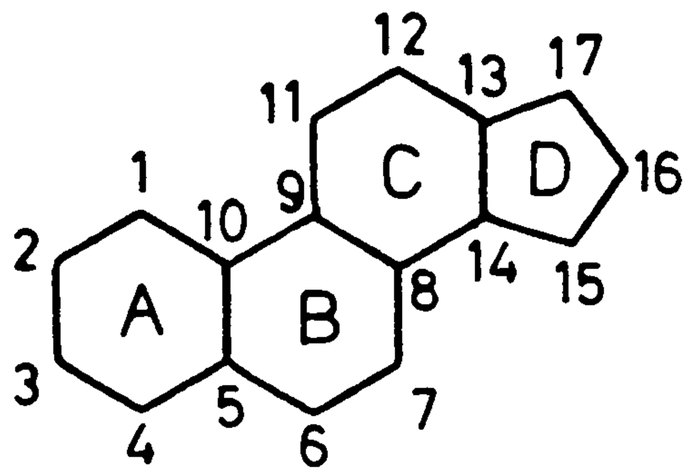
(322) $R^1=R^2=R^3=Me$, n = 2 (323) $R^1=R^2=R^3=Me$, n = 2 (324) $R^1=R^2=R^3=Me$ n = 2

1.6 SYNTHETIC APPLICATIONS

The most significant and challenging test of the preparative value of a synthetic method must be its rational and successful application to the synthesis of complex molecules. Indeed, Oppolzer was the first to exploit the synthetic potential of the cycloadditions of o-xylylenes in a total synthesis of the alkaloid chelidonine reported in 1971.[205] Since this report, a number of groups have realised the potential of the cycloadditions of o-quinonoid intermediates, and as a direct result, a large number of syntheses utilizing such cycloadditions have been published. These reports seem to be limited to o-xylylenes, o-azaxylylenes and o-quinone methides and to date, no use has been made of o-thioquinone methides in organic synthesis. A table summarizing the molecules synthesized by this method is included at the end of each section of the following review.

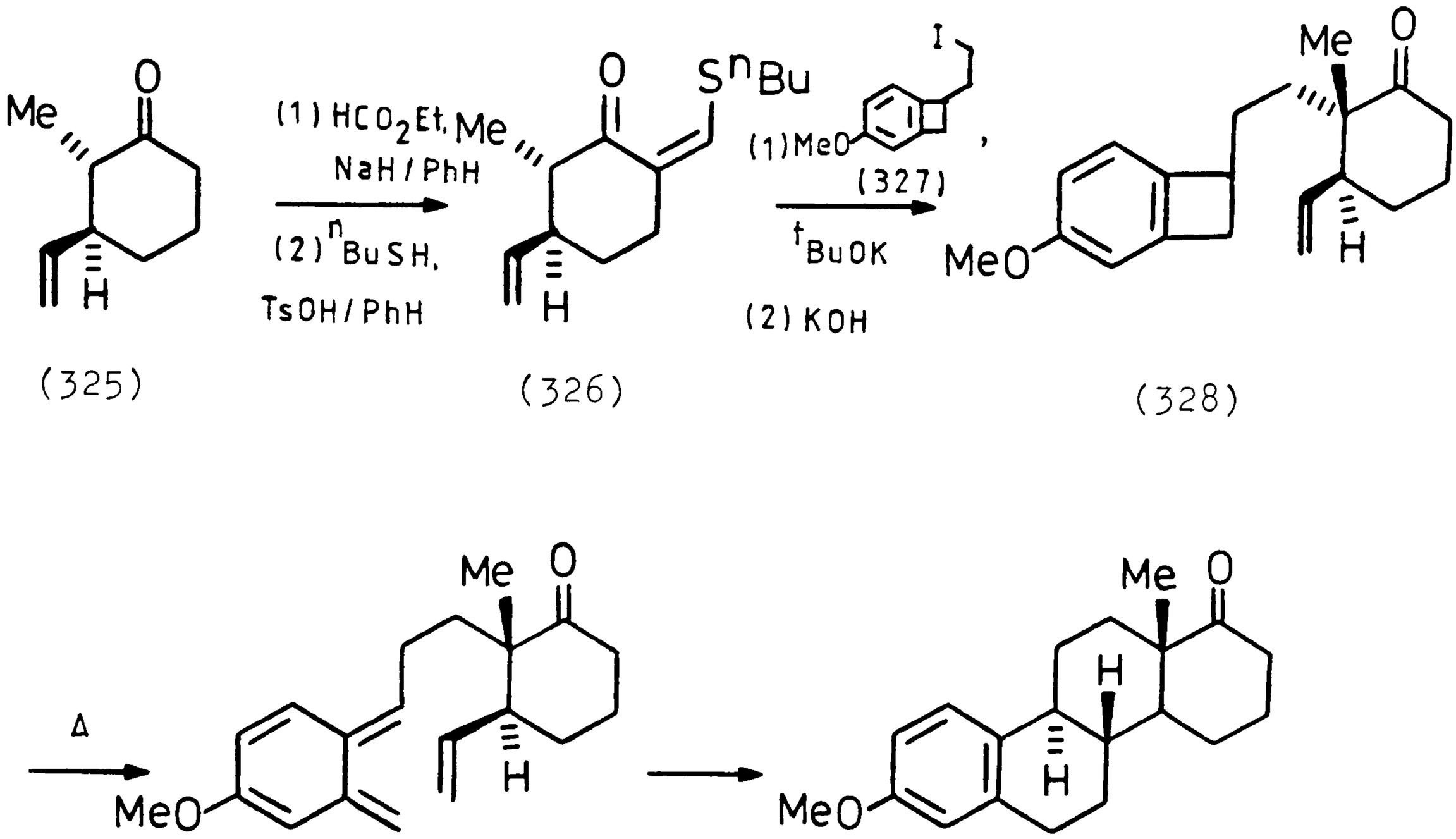
(a) THE TOTAL SYNTHESIS OF STEROIDS

The pronounced physiological activity of the steroid nucleus has made it the target of numerous, often ingenious synthetic strategies.[164] The various successful synthetic routes may be conceptualized in an abbreviated fashion as AB → ABCD, BC → ABCD, etc., based on the standard notation of the four annulated rings of the steroid nucleus shown below.



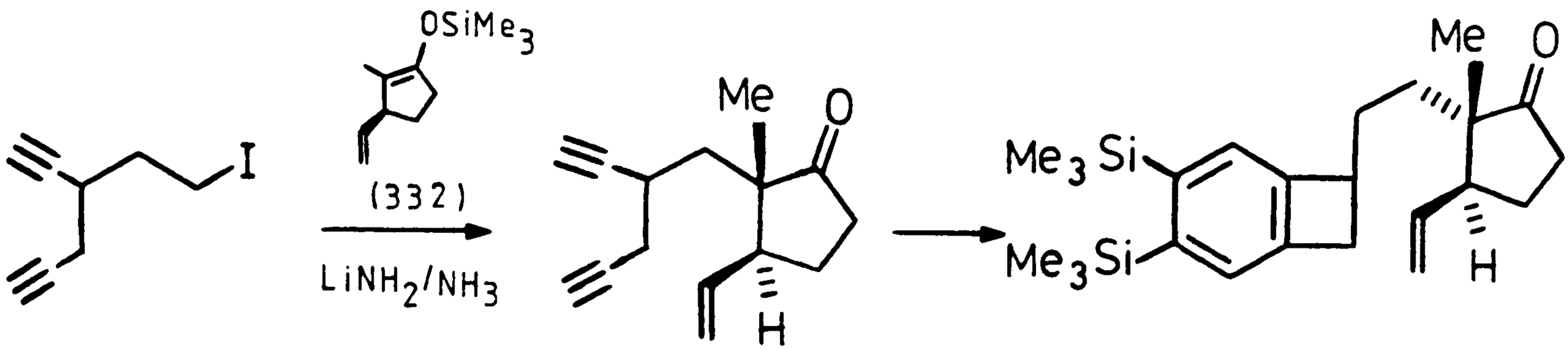
The use of o-quinonoid systems for the synthesis of A-ring aromatic steroids utilizes the AD → ABCD approach.[164] For example, the stereoselective synthesis of D-homoestrone (330) is based on the intramolecular Diels-Alder cyclo-addition of o-xylylene (329), generated by thermolysis of benzocyclobutene (328), (entry 21). The synthesis of precursor (328) involved the protection of ketone (325) (made by copper catalysed Michael addition of vinyl magnesium bromide to 2-methyl cyclohexenone) as its ^{n}butyl thiomethylene derivative. Enone (326) which will eventually form the D-ring of the steroid was coupled with iodide (327), followed by removal of the thiomethylene protecting group to yield (328).[179]

The majority of steroid syntheses involve elaboration of a simple benzocyclobutene as starting material, but there are some exceptions. Vollhardt has reported the synthesis of racemic estrone (334) by a cobalt-catalysed co-oligomerization route. Thus, alkylation of enolate (322) with iodide (331) gave the diene (333) in good yield. Cobalt catalysed cyclization of (333) with bis-trimethylsilyl acetylene gave benzocyclobutene (334) which was converted

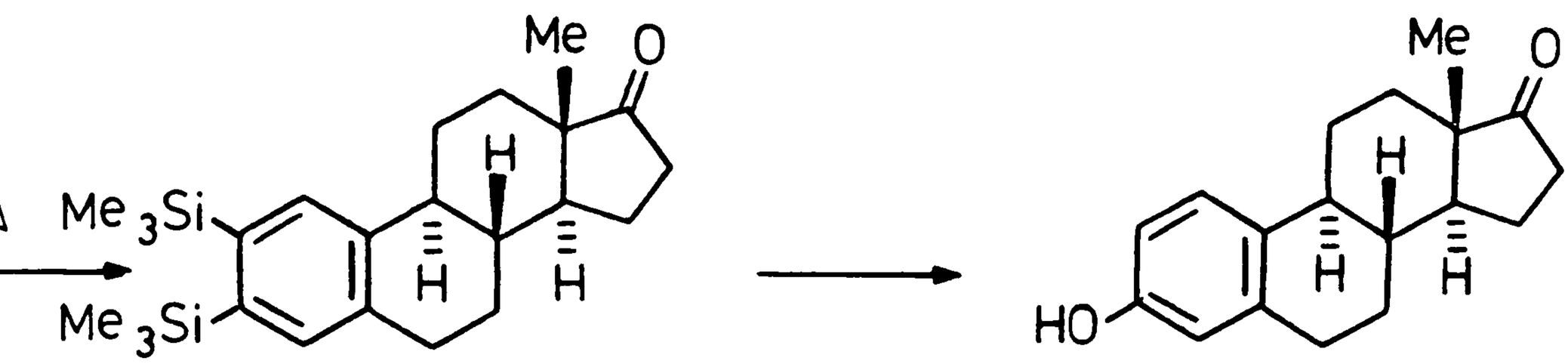


in situ to steroid (335) by heating in decalin presumably through the intermediate o-xylylene. Selective, oxidative protodesilylation of (335) yielded estrone (336) in 21% overall yield[171] (entries 9,14).

Steroids have also been synthesized via cyclization of o-xylylenes generated by cheletropic elimination of SO_2 (entry 1); and by fluoride induced 1,4-eliminations

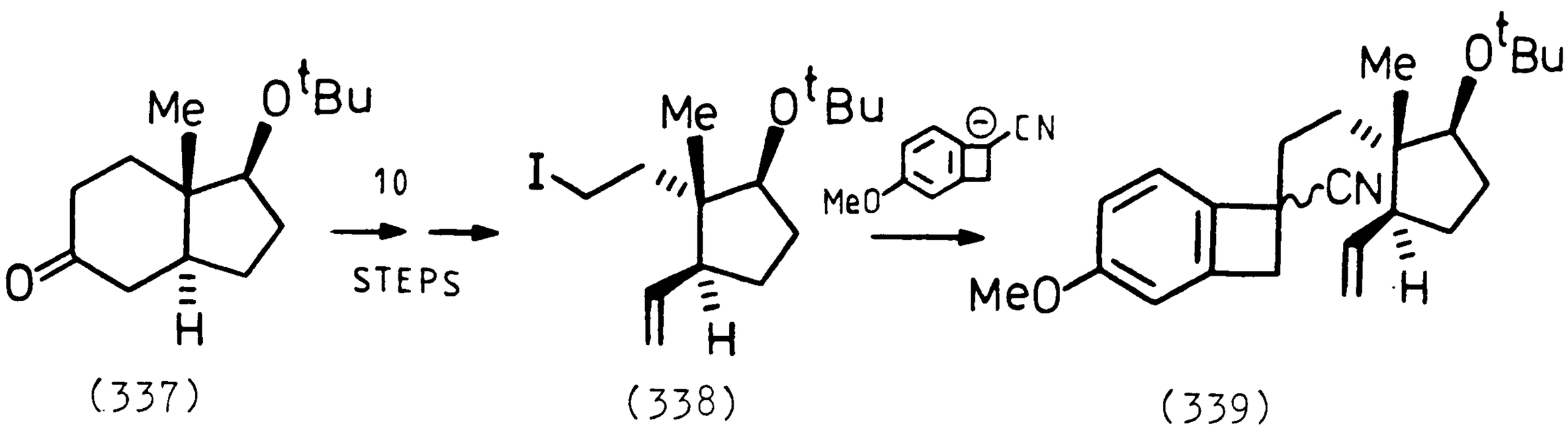


(331) (333) (334)

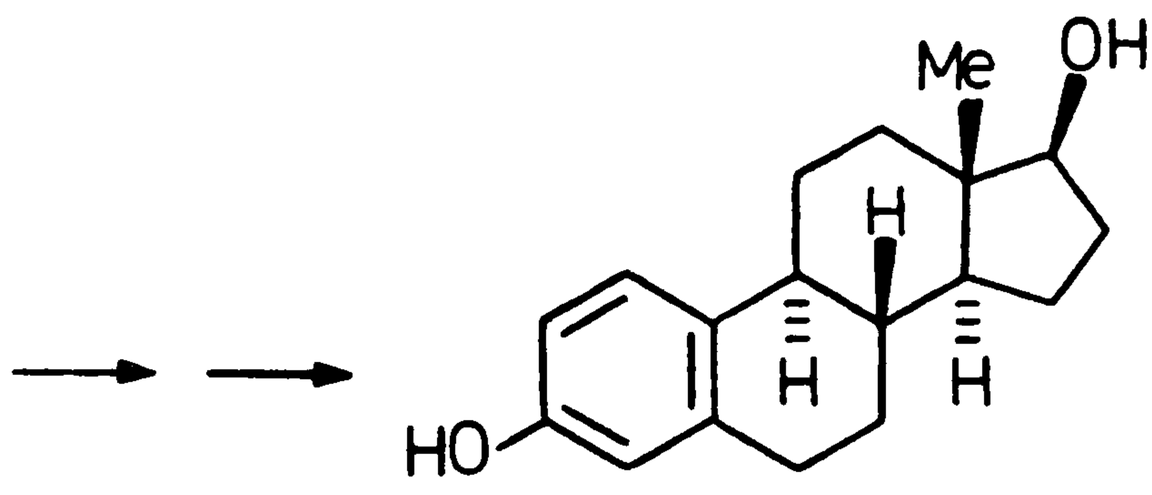


(335) (336)

(entries 2 and 8). A number of groups have developed enantioselective syntheses of steroids by generation of o-xylylenes containing a chiral cyclopentane D-ring, (entries 3, 12 and 15). For example, Kametani, using the readily available optically active ketone (337) achieved an asymmetric synthesis of estradiol (340) in high optical yield. The main features of the synthesis were conversion of (337) to iodide (338) and reaction with the 1-cyano-4-methoxy-benzocyclobutenyl anion to give (339) which after cyclization, and deprotection, afforded (+)-estradiol (340, entry 12).

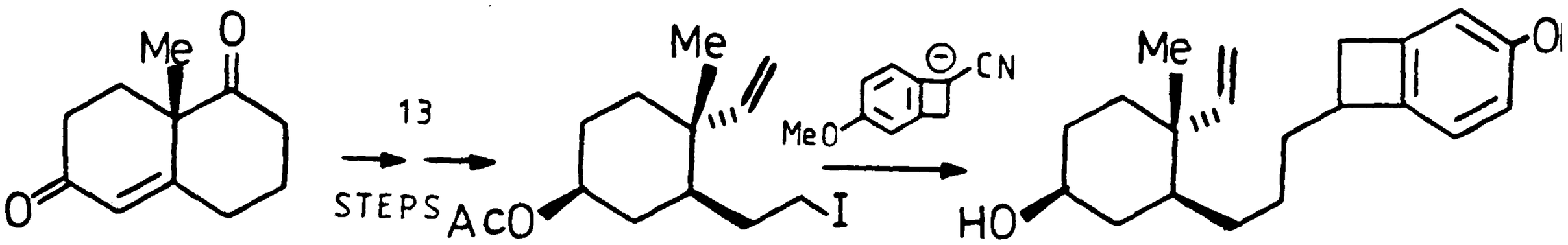


(337) (338) (339)

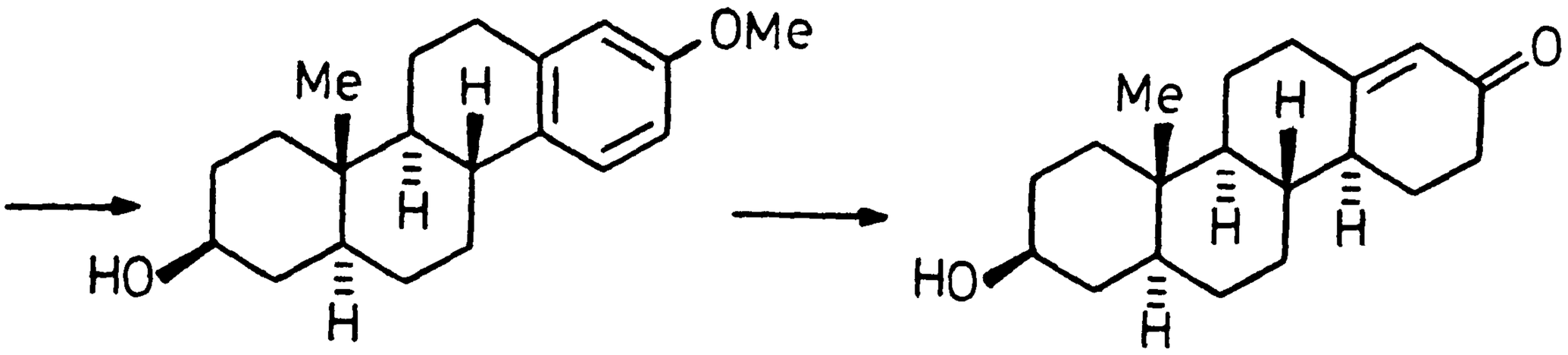


(340)

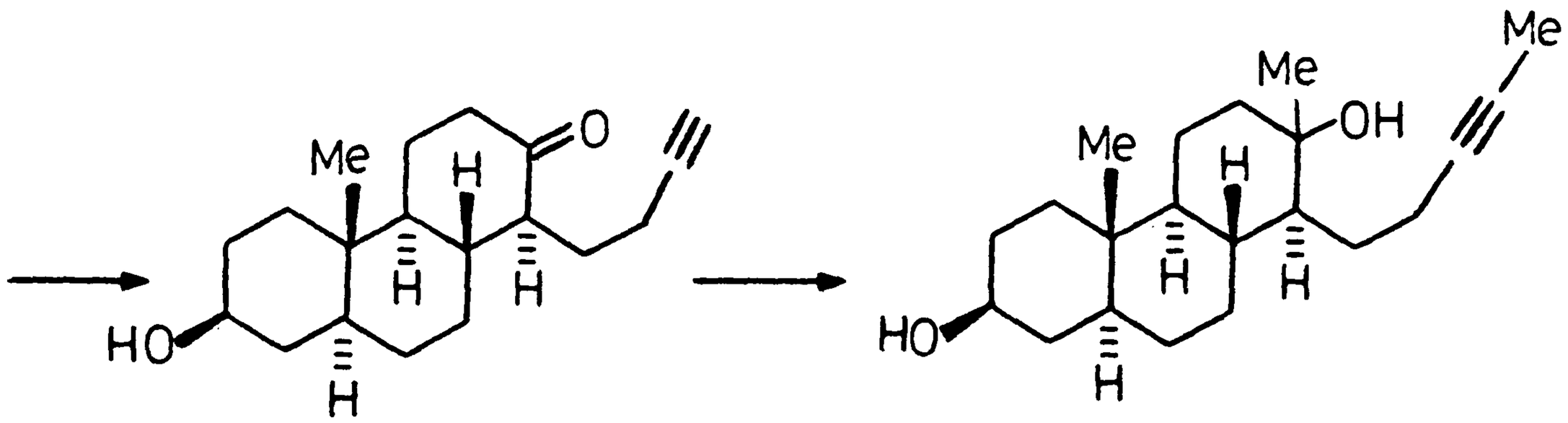
Kametani has also utilized the intramolecular Diels-Alder trapping of o-xylylenes for the synthesis of pregnane type steroids where the A-ring is a non-aromatic carbocyclic ring, (entries 22 - 24). Thus, optically active iodide (342) made in thirteen steps from optically active ketone (341) was coupled with the methoxy benzocyclobutenyl anion to give benzocyclobutene (343) after deprotection of the secondary alcohol. Cyclization then yields steroid (344) which is reduced to enone (345). Ring opening of (345) to yield acetylenic ketone (346) was followed by conversion to alcohol (347). Cyclization of (347) using trifluoroacetic anhydride and trifluoroacetic acid then gave (+)-5α-dihydropregnenolone (348).[180]



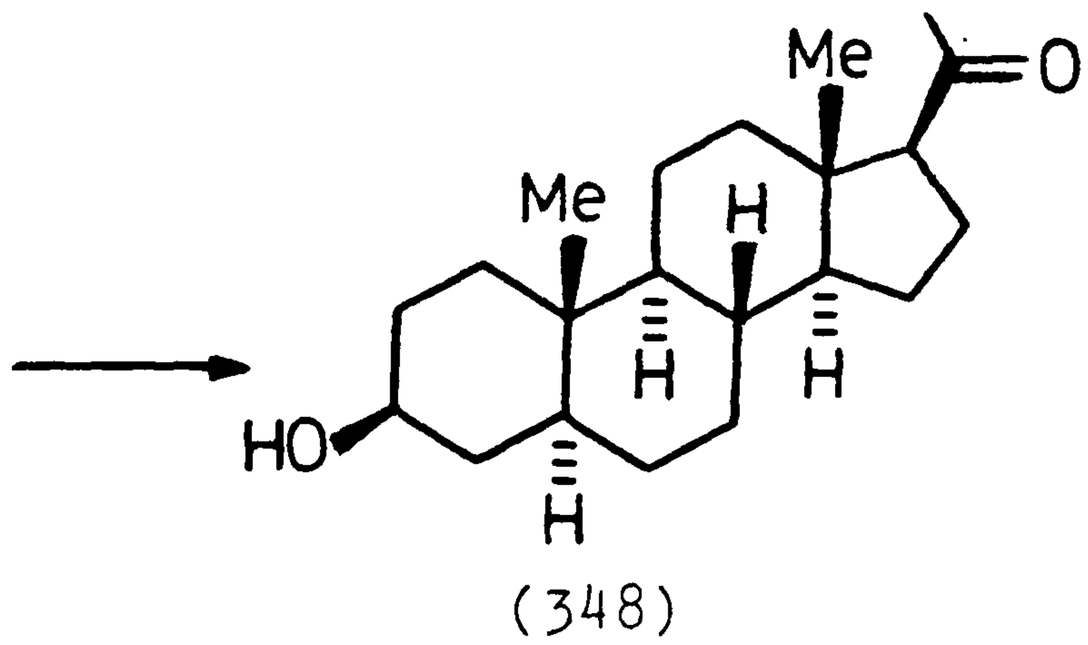
(341) (342) (343)



(344) (345)

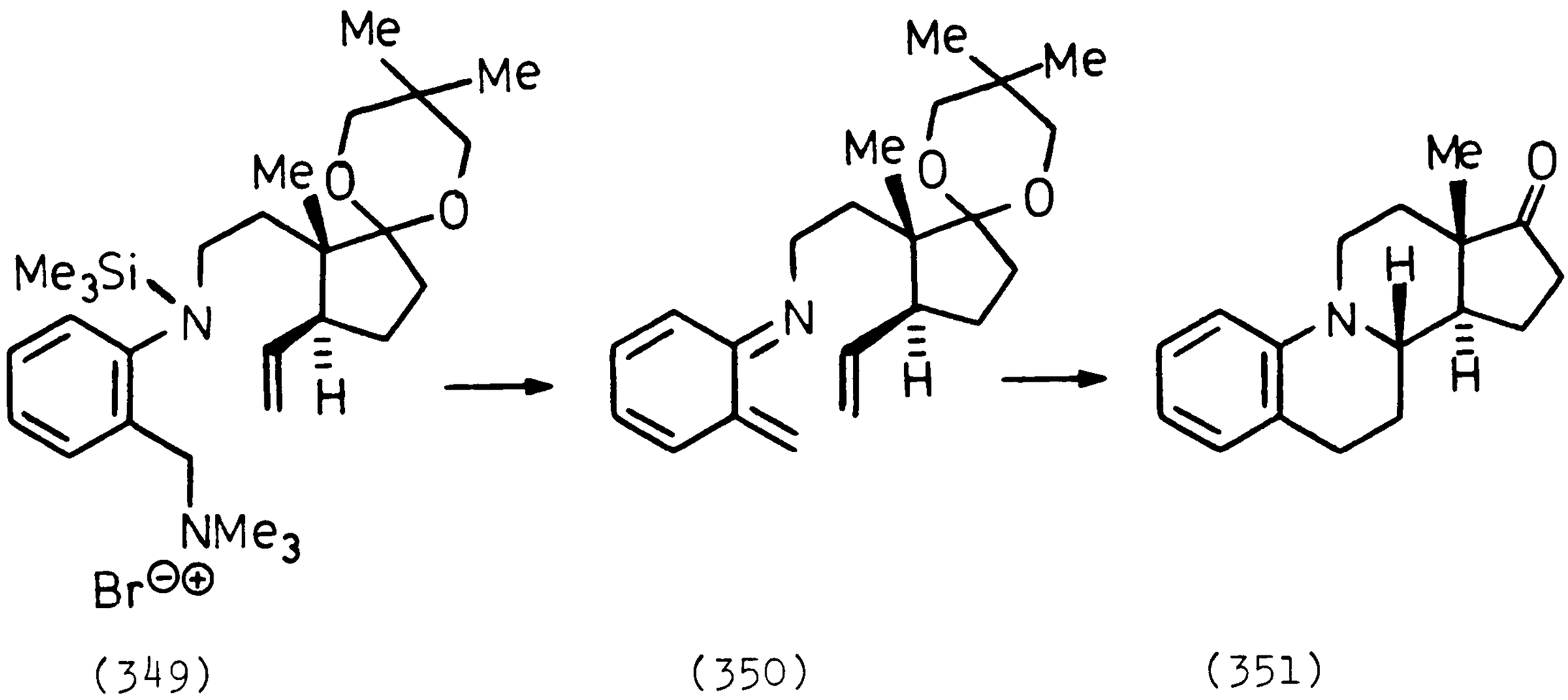


(346) (347)



(348)

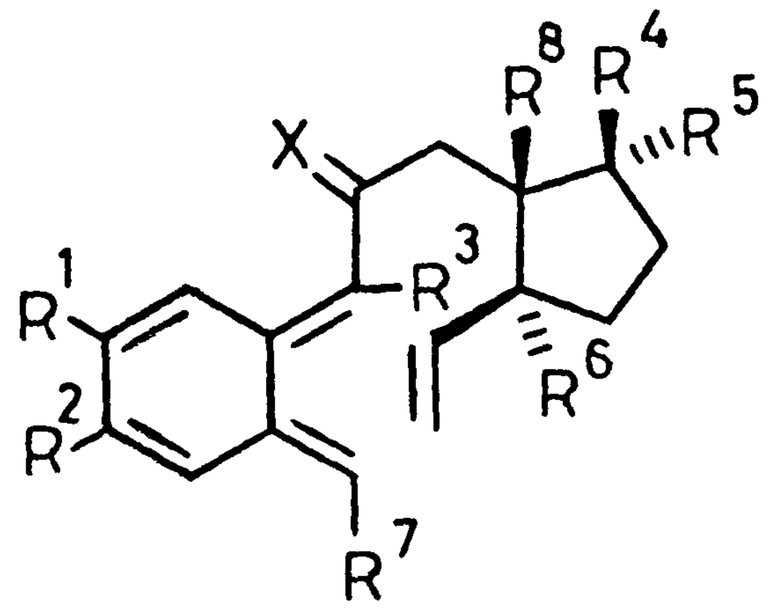
Finally, there has been one report concerning the use of an o-azaxylylene in the synthesis of an aza-steroid. Thus, Ito and co-workers,[65] produced 9-azaestrone (351) from cycloaddition of o-azaxylylene (350), generated by fluoride anion induced 1,4-elimination of salt (349), (entry 30).

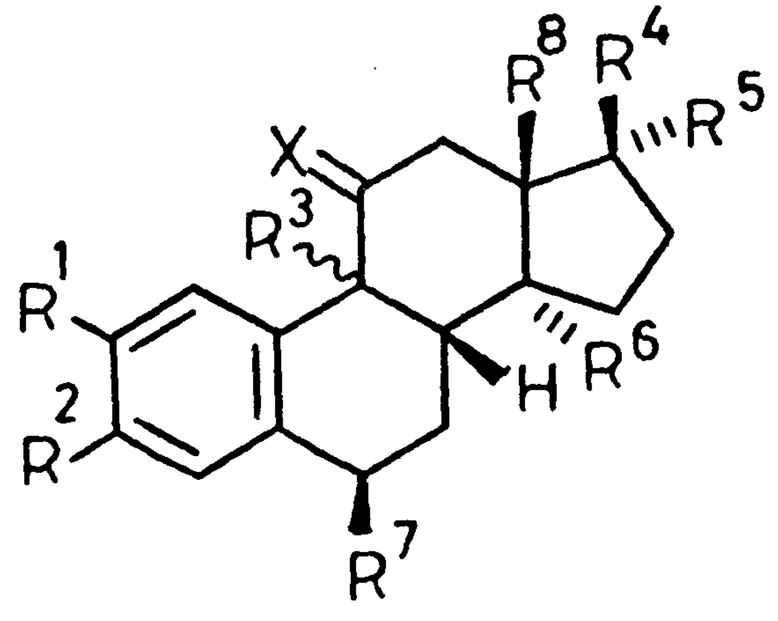


(349) (350) (351)

TABLE 4 o-QUINONOID INTERMEDIATES IN THE SYNTHESES OF STEROIDS

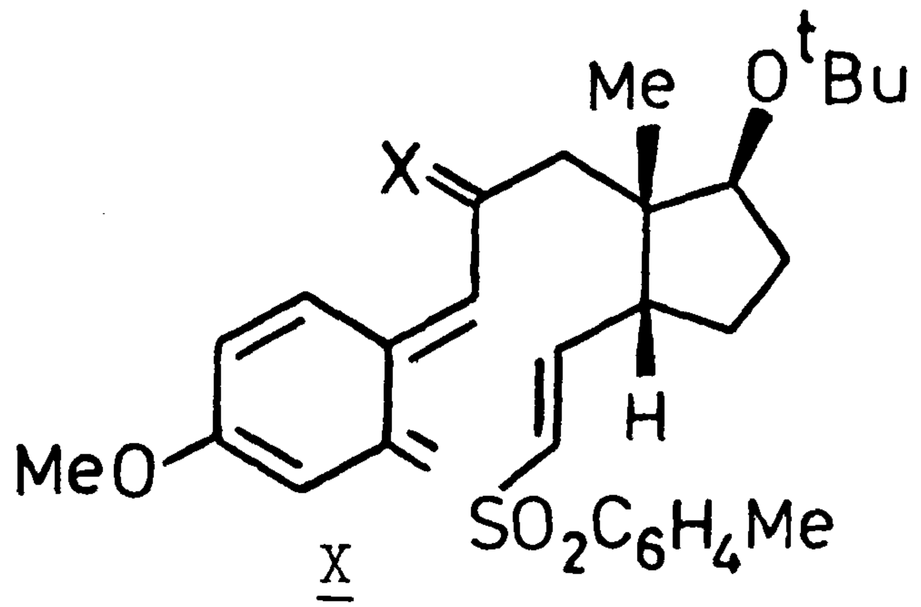
ENTRY	SUBSTRATE	PRODUCT(S) AND YIELD(S) (%)	REFERENCES



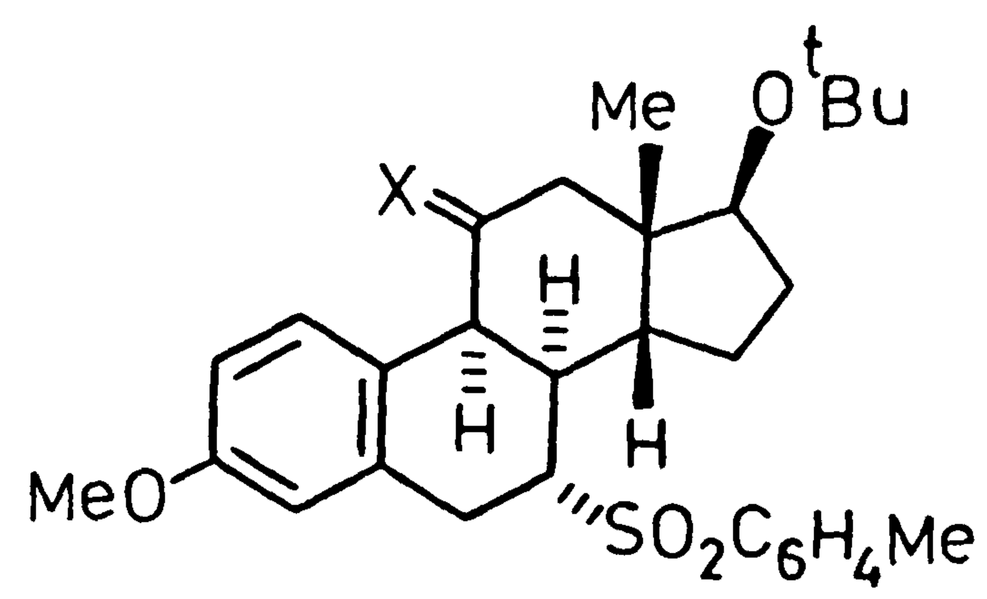


	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	X	TRANS	CIS	
1	H	H	H	O =		H	H	Me	H_2[a]	(85)	(0)	125
2	H	MeO	H	O =		H	H	Me	H_2[e]	(86)	(0)	172
3	H	MeO	H	O =		H	H	Me	O[d]	(56)	(5)	165
4	H	MeO	H	O =		H	H	Me	H,OH[g]	(70)	(0)	169
5	H	MeO	H	O =		OH	H	Me	H_2[b]	(45)	(0)	174
6	H	MeO	OH	O =		H	H	Me	H_2[f]	(Major)	(Minor)	168,176
7	H	MeO	H	OH	H	H	H	Me	H_2[b]	(78)	(0)	177
8	H	H	H	O =		H	Me	Me	H_2[e]	(95)	(0)	172
9	MeO	Me_3Si	H	O =		H	H	Me	H_2[b]	(11)	(0)	170,171
10	H	MeO	H			H	H	$OHCH_2$	H_2[b]	(75)	(0)	178

11	Me_3Si	MeO	H	O =	H	H	Me	H_2[b]	(22)	(0)	171,184
12	H	MeO	H	^tBuO H	H	H	Me	H_2[d]	(84)	(0)	173
13	H	MeO	H		H	H	MeO_2	CH_2[b]	(60)	(15)	178
14	Me_3Si	Me_3Si	H	O =	H	H	Me	H_2[b]	(95)	(0)	171,184
15	H	NC	H	^tBu H	H	H	Me	H_2[a,d]	(80)	(0)	135
16	H	MeO	H	O =	H	H	Me	$PhCH_2ON$[b]	(0)	(50)	166
17	Me_3Si	Me_3Si	H		H	H	Me	H_2[b]	(81)	(4)[c]	170,171
18	H	MeO	H	O =	OH	H	Me	PhCHO , H[b]	(37)	(0)	176



	X			
19	H_2[c]	(62)	167	
20	O[c]	(-)	167	



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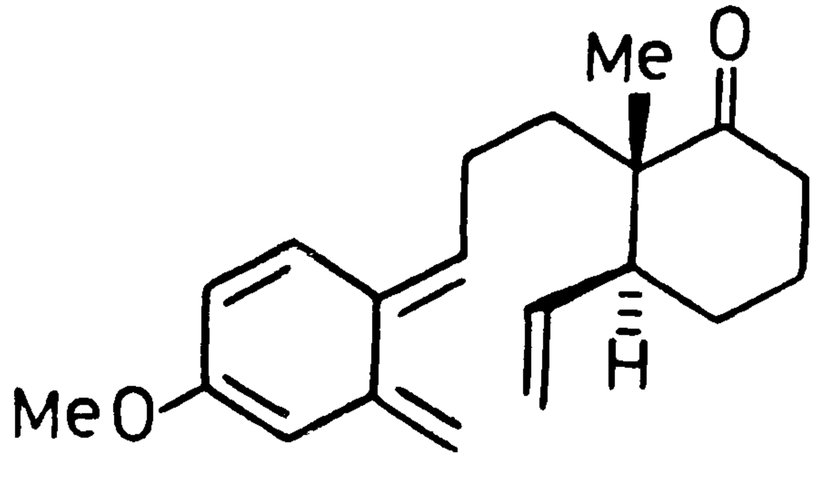
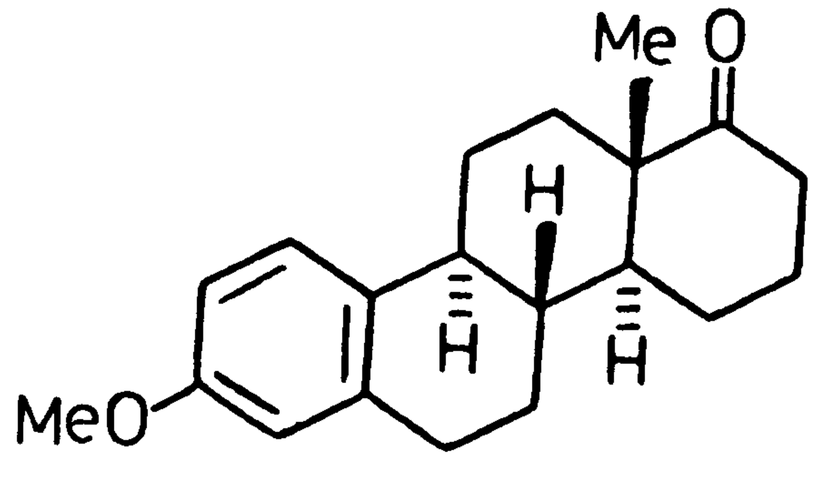
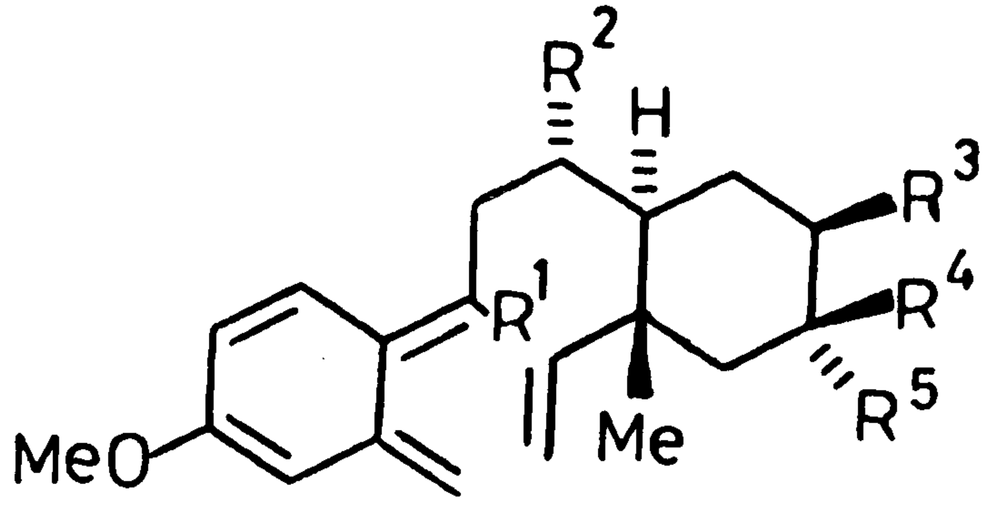
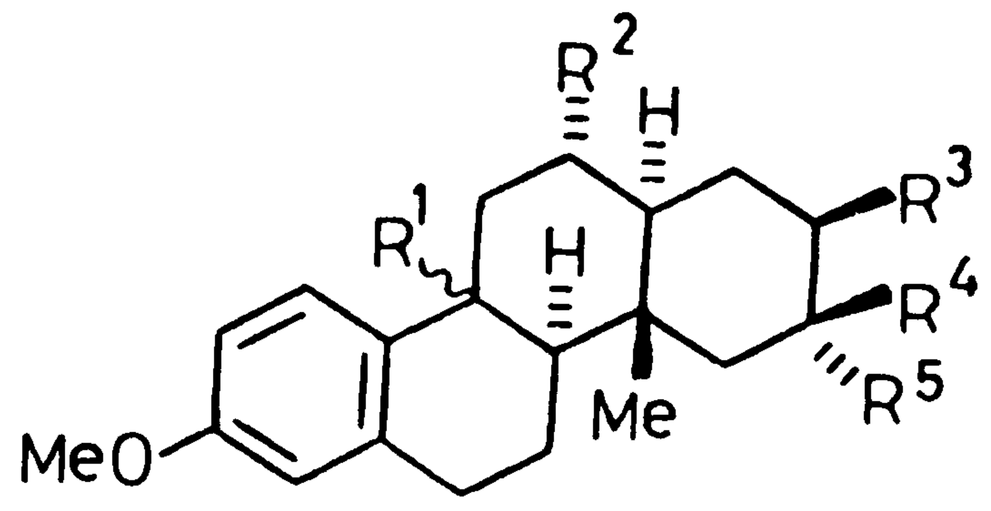




(95)

179

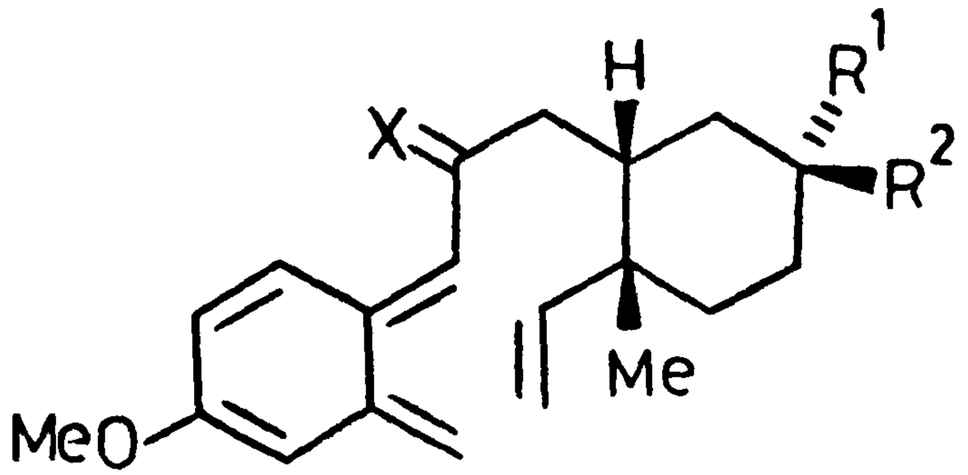


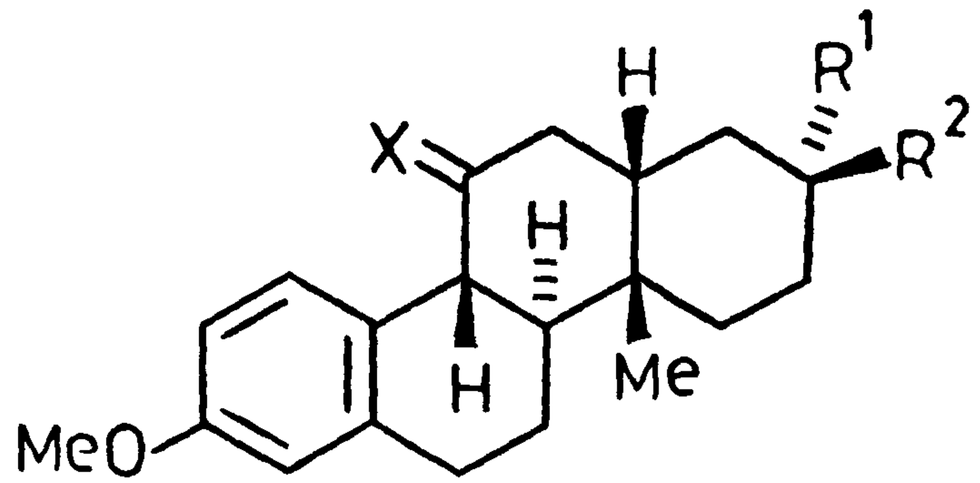


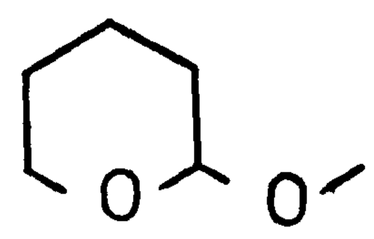
107

	R^1	R^2	R^3	R^4	R^5
22	H	H	OH	H	H[b]
23	NC	O_2N	H	CH_3CO_2	H[b]
24	NC	O_2N	H		[b]

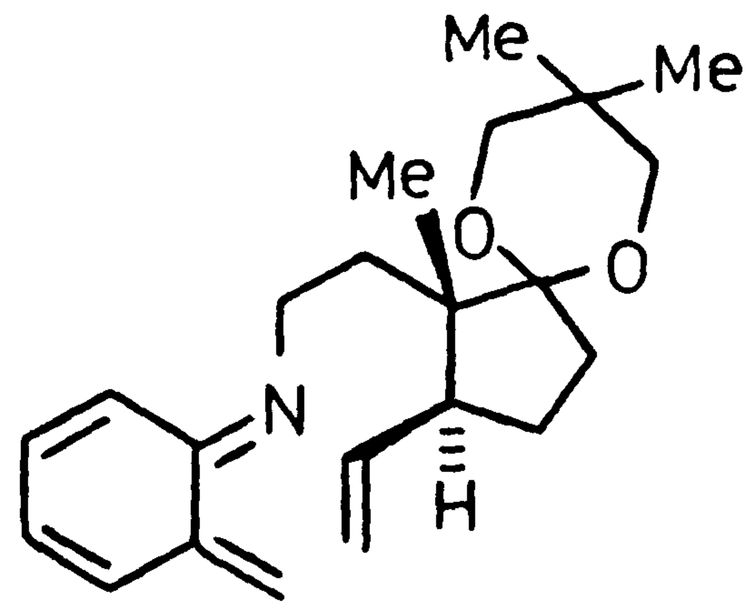
TRANS	CIS	REFERENCES
(93)	(0)	180
(0)	(94)	181,182
(0)	(96)	181





	R^1	R^2	X		
25	OH	H	O[i,b]	(-)[j]	183
26	O =		O[i,b]	(46)[k]	183
27	CH_3CO_2	H	O[i,l,b]	(43)	183
28		H	O[b,i]	(0)[j]	183
29	$PhCH_2O$	H	H,$PhCH_2O$[b,i]	(65)[m]	183

30



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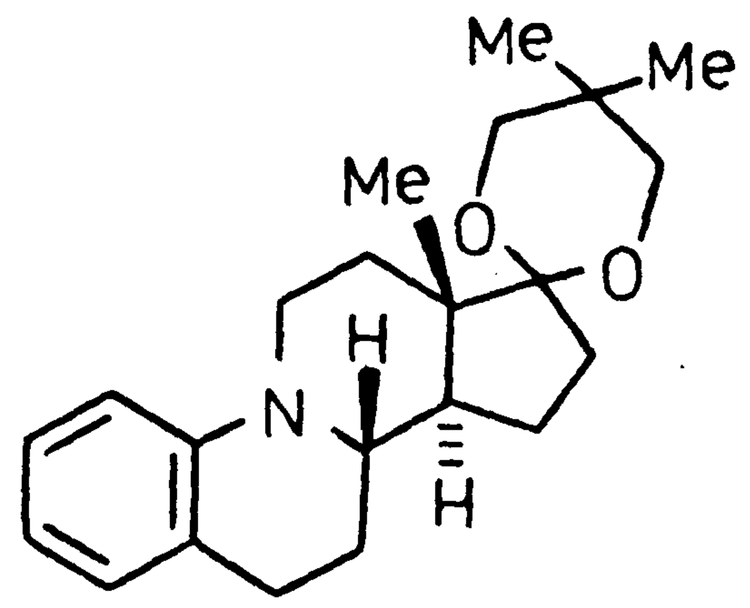


(60)

65

a. The substrate was generated by elimination of SO_2 from the corresponding 1,3-dihydro-isothionaphthene-2,2-dioxide.

b. The substrate was generated from the benzocyclobutene.

c. The structure assignment is tentative.

d. The reaction was carried out with a chiral cyclopentane ring corresponding to the natural steroid.

e. The substrate was generated by fluoride catalysed 1,4-elimination of the corresponding o-(α-trimethylsilyl alkyl)benzyltrimethyl ammonium iodide.

f. The substrate was generated by irradiation of the corresponding 3-methyl-4-acyl anisole.

g. See original work for precursor.

h. The benzyl group is α.

i. The substrate contained a chiral cyclohexane ring.

j. The hemiketal was formed in high yield.

k. The cis-fused product was formed in 28% yield.

l. The corresponding ethylene ketal failed to undergo the intramolecular Diels-Alder cycloaddition.

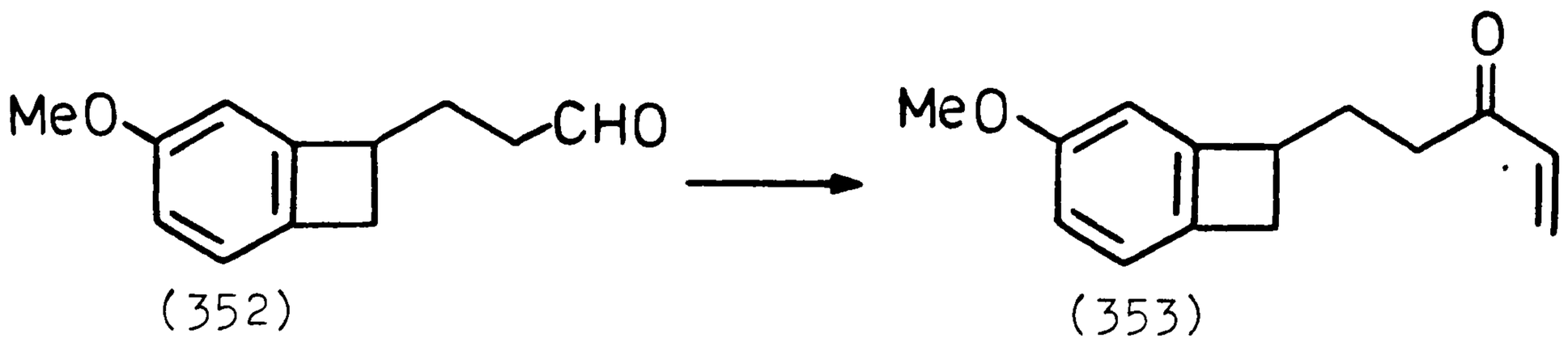
m. The $PhCH_2O$ group in X is β.

(b) THE TOTAL SYNTHESIS OF ALKALOIDS AND TERPENES

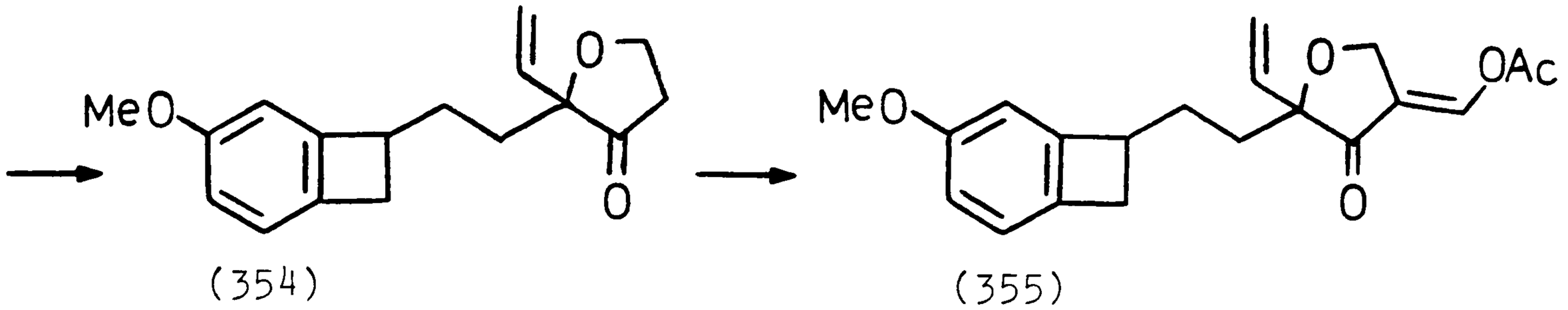
The varied and often complex structures to be found amongst this class of natural products have provided some of the most interesting examples of syntheses that utilize an intramolecular cyclization of an o-quinonoid species.

In the earliest examples, Kametani synthesized the alkaloids protoberberine, discretine and yohimbane based on the electrocyclization reactions of o-xylylenes with an imminium moiety (entries 1 - 4). In addition, the antitumor alkaloid ellipticene and related systems have been produced by electrocyclization involving indole, pyridine, and benzothiophene based o-xylylenes (entries 5 - 15). In an approach to the antitumour compound bruceantin, Kametani[221] utilized the stereoselective intramolecular cycloaddition of o-xylylene (356), generated from benzocyclobutene (355), to obtain ketone (357) which contains the main polycyclic ring structure of the target natural product (entry 16). Precursor (355) was made via conversion of aldehyde (352) to enone (353). This was then converted to dihydrofuranone (354) by sequential 1,2-addition of α-lithio-α-methoxy allene, base induced cylization, and acid hydrolysis of the resulting enol ether. Standard chemical manipulation of (354) then yields (355).[221]

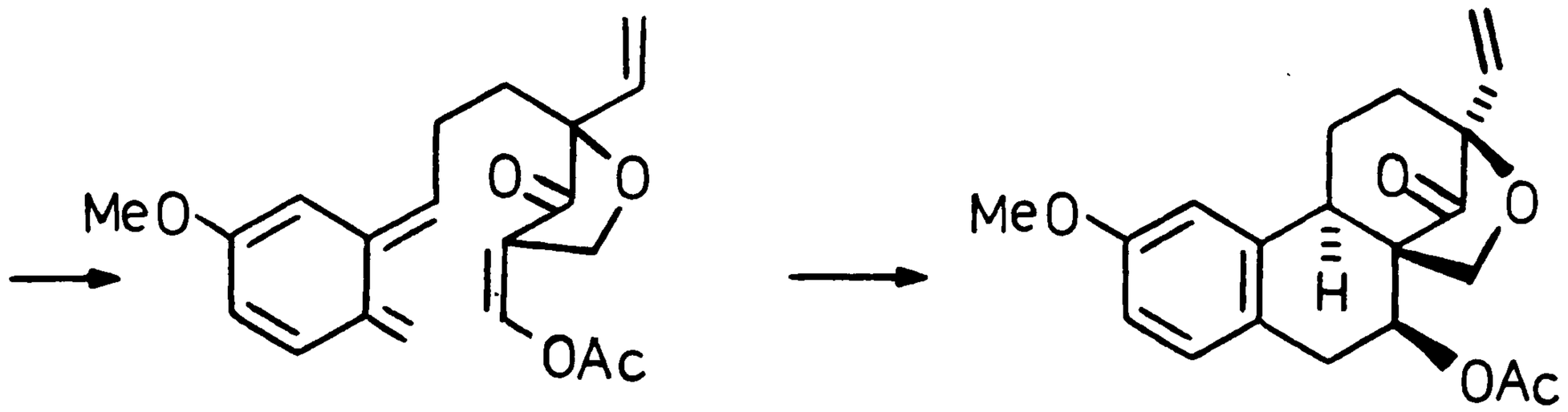
An elegant example of the use of intramolecular o-xylylene cycloadditions is provided by Magnus and co-workers in the synthesis of several indole based alkaloids. Their basic strategy involved the intramolecular



(352) (353)

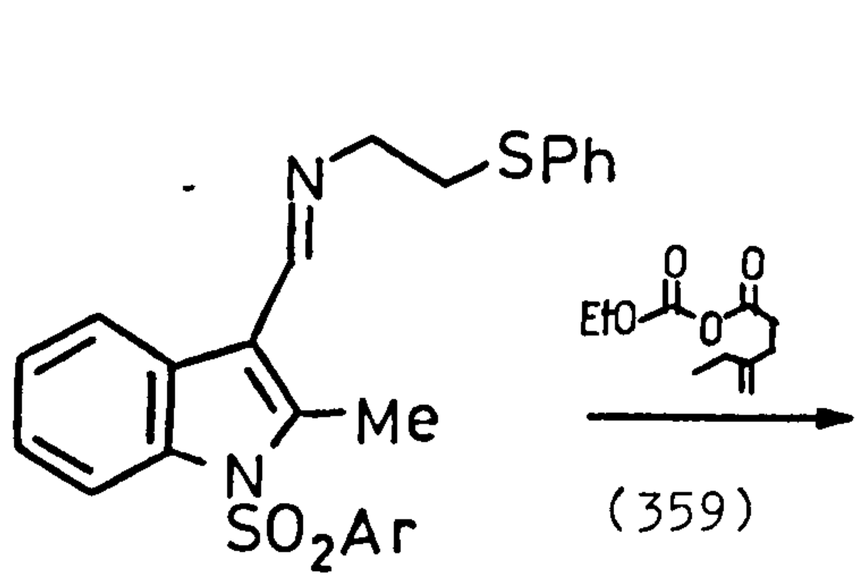


(354) (355)

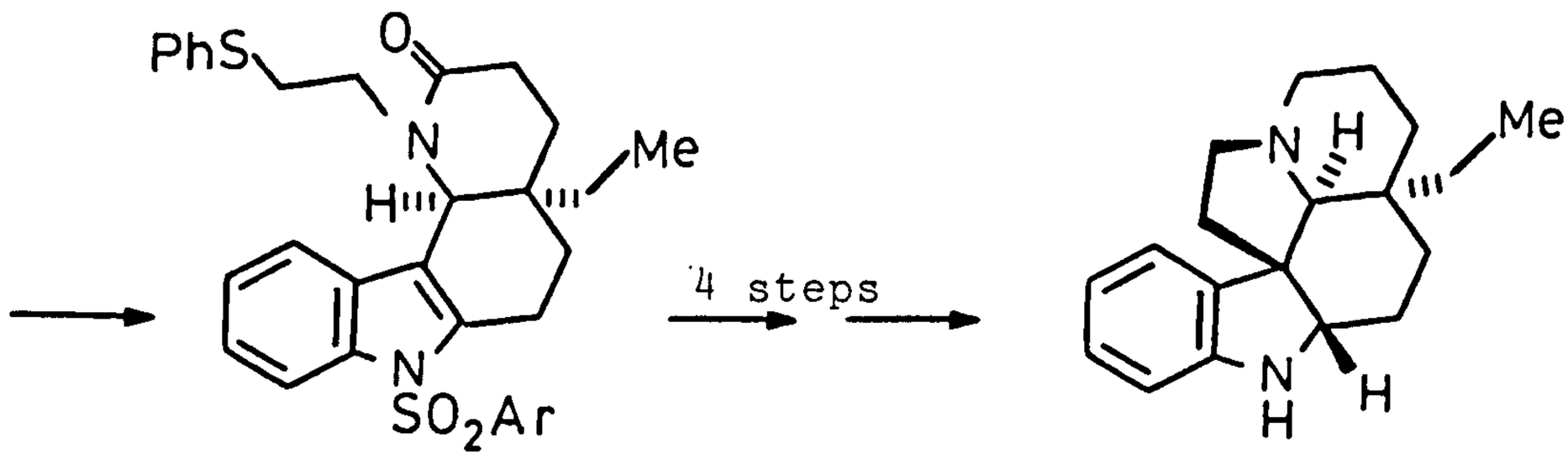


(356) (357)

trapping of an indole based o-xylylene generated in a 1,4-elimination step, (entries 29 - 52). For example, when imine (358) was heated in the presence of mixed anhydride (359), the tetracyclic indole (361) was obtained in good yield. Presumably, the reaction involves acylation of the imine followed by loss of a proton to give indole-xylylene (360), cyclization then gives (361), (entry 51). This was then converted into racemic aspidospermidine (362) in four steps with an overall yield of 12%.[206,211]



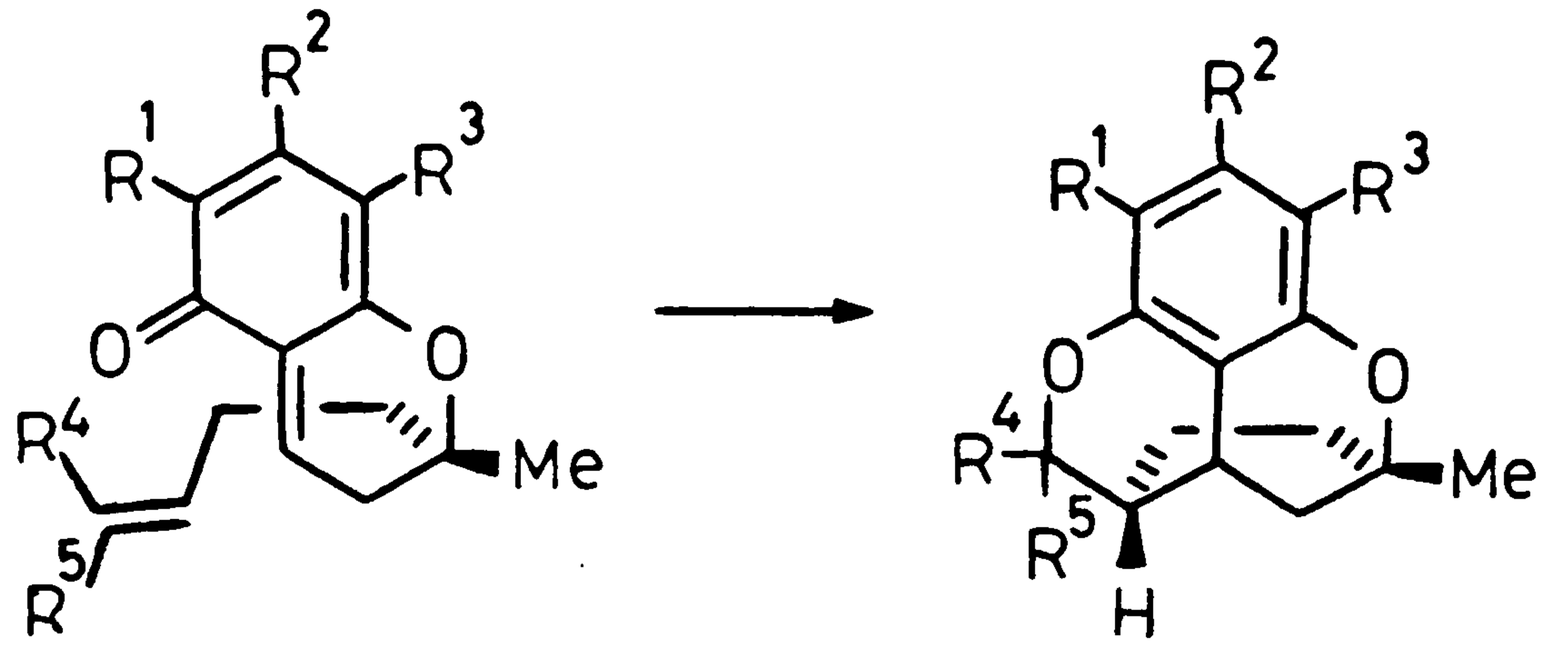
(358) (360)



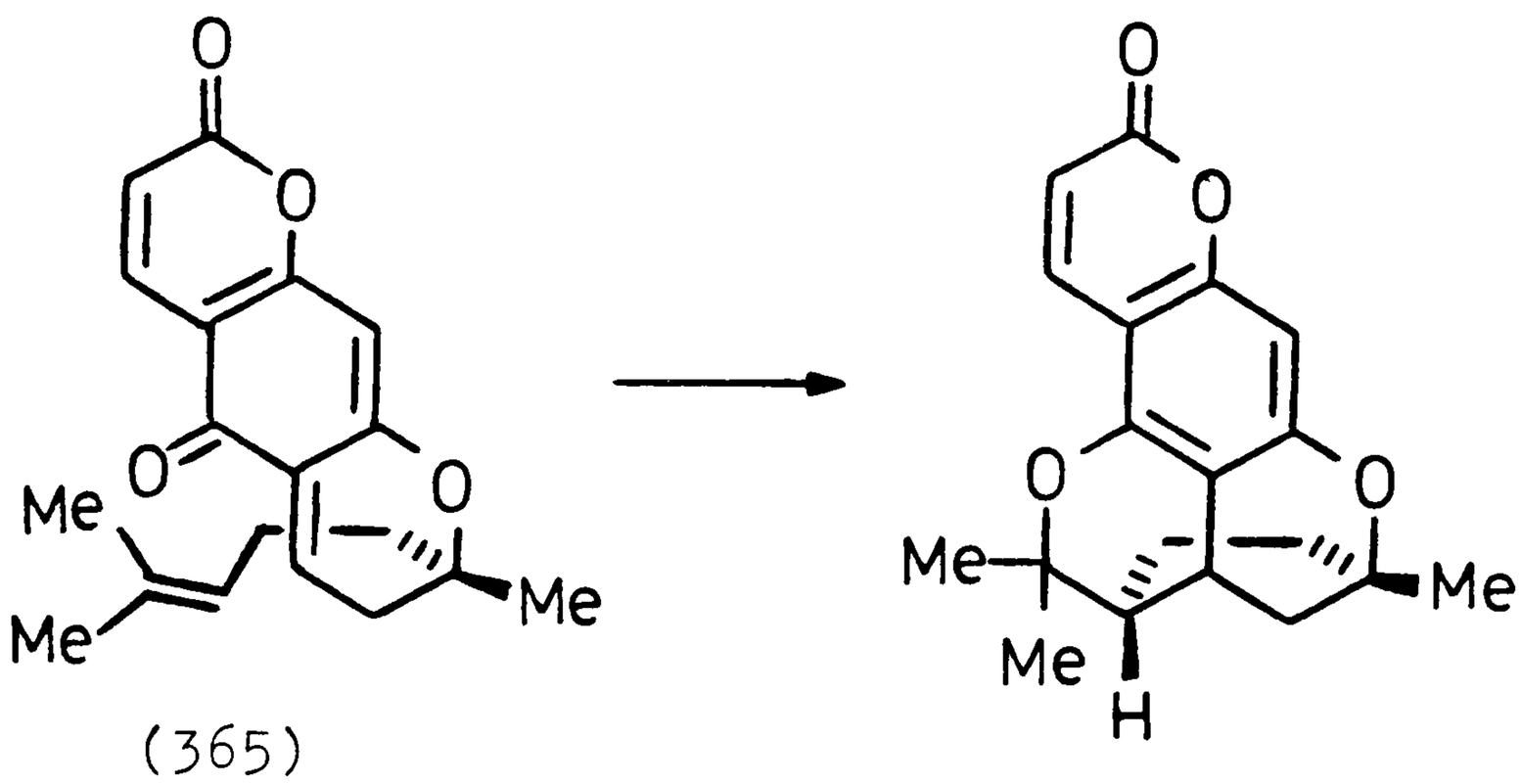
(361) (362)

There have been a number of reports concerning the use of other o-quinonoid species for the synthesis of alkaloids and terpenes. For example, the o-quinone methides (363) and (365) have been used to yield a range of citrans (364) and (366) by intramolecular cycloaddition (entries 56 - 70).

Also, the complex lignan carpanone (369) has been produced in just one step from phenol (367) by phenolic coupling (entry 56). This reaction is rationalized as proceeding via phenolic coupling to yield o-quinone methide (368) which cyclizes to afford (369) in good yield.



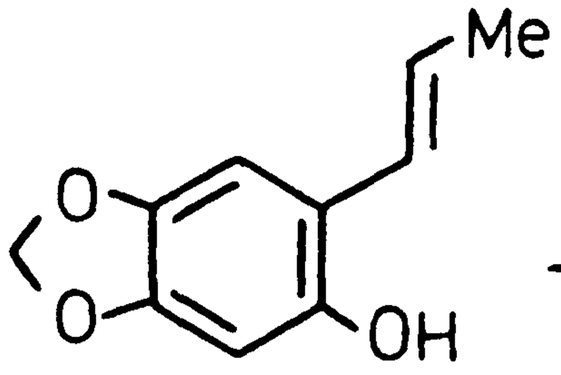
(363) (364)



(365) (366)

This is a striking example of the stereoselectivity that can be obtained with this type of intramolecular cyclo-addition reaction, as here, five asymmetric centres having the correct relative stereochemistry, have been introduced in a single reaction step.

There are a small number of reports of the use of o-azaxylylenes as key intermediates in the synthesis of alkaloids and terpenes (entries 53 - 56). For instance, treatment of salt (370) with fluoride anion generates o-azaxylylene (371) which cyclizes to (372). This was then converted in two steps to diol (373) which is a known precursor to gephyrotoxin (374), (entries 71 and 72).



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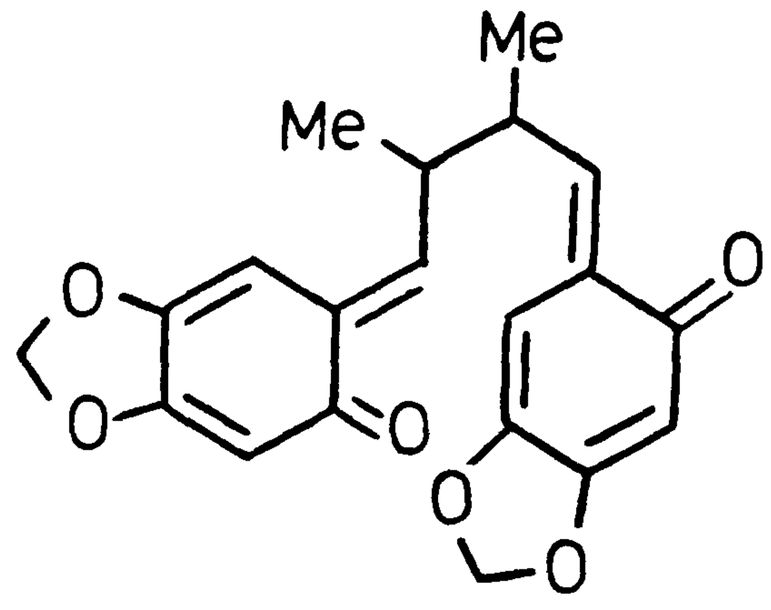

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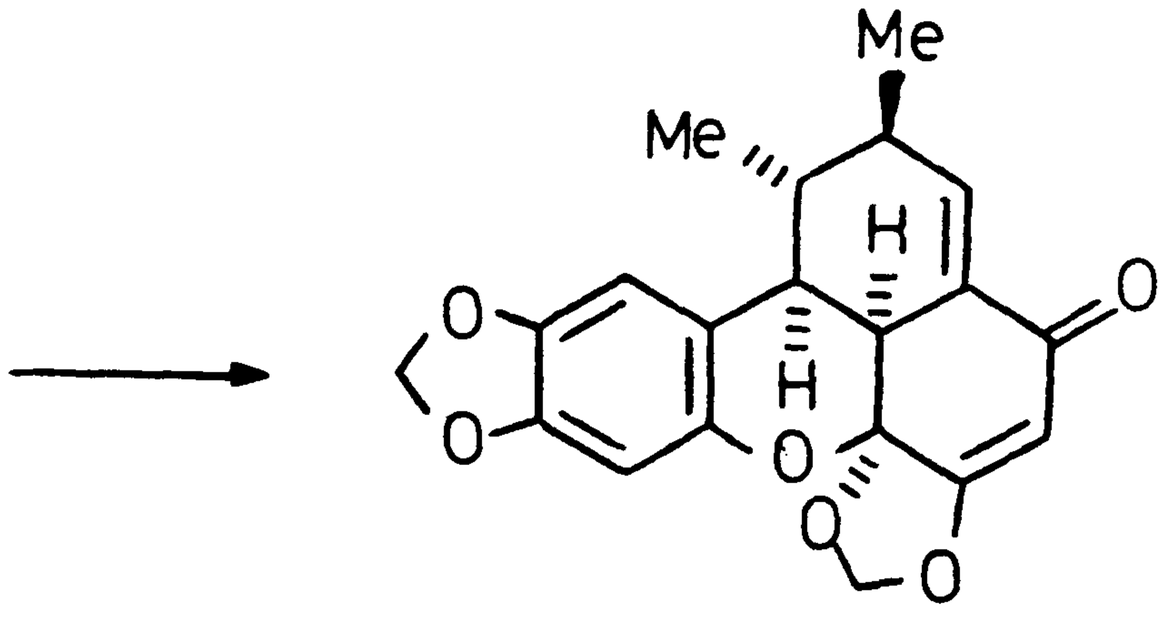

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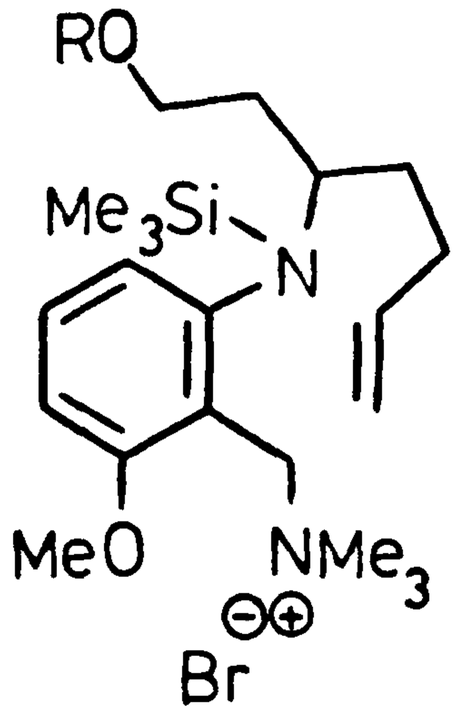

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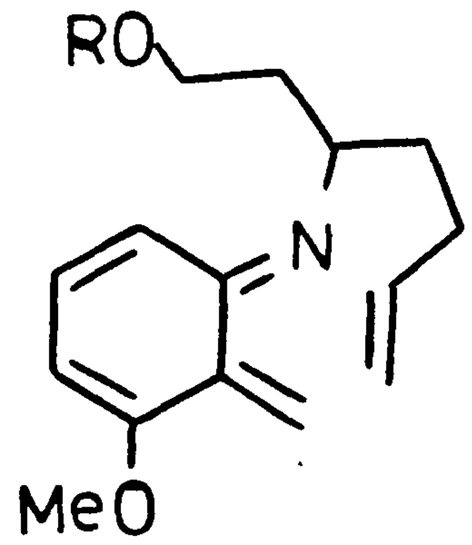
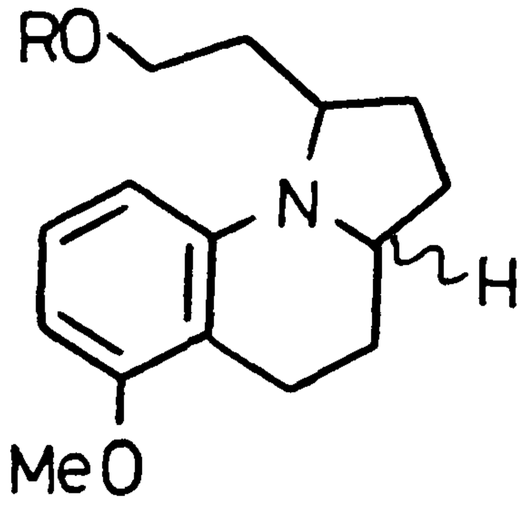
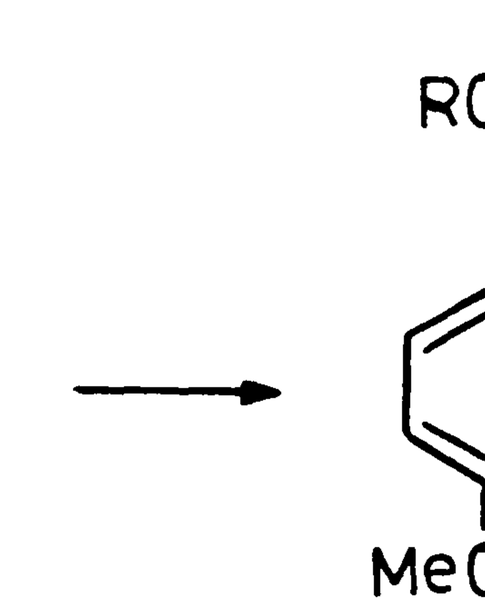


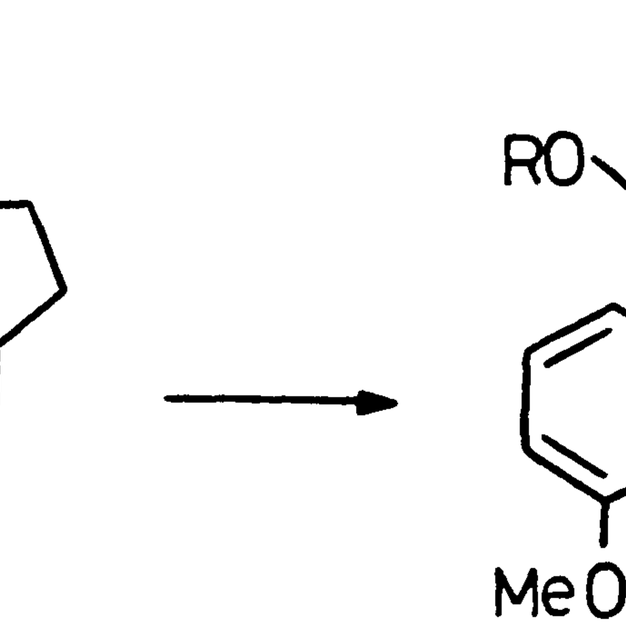
(371)



(372)

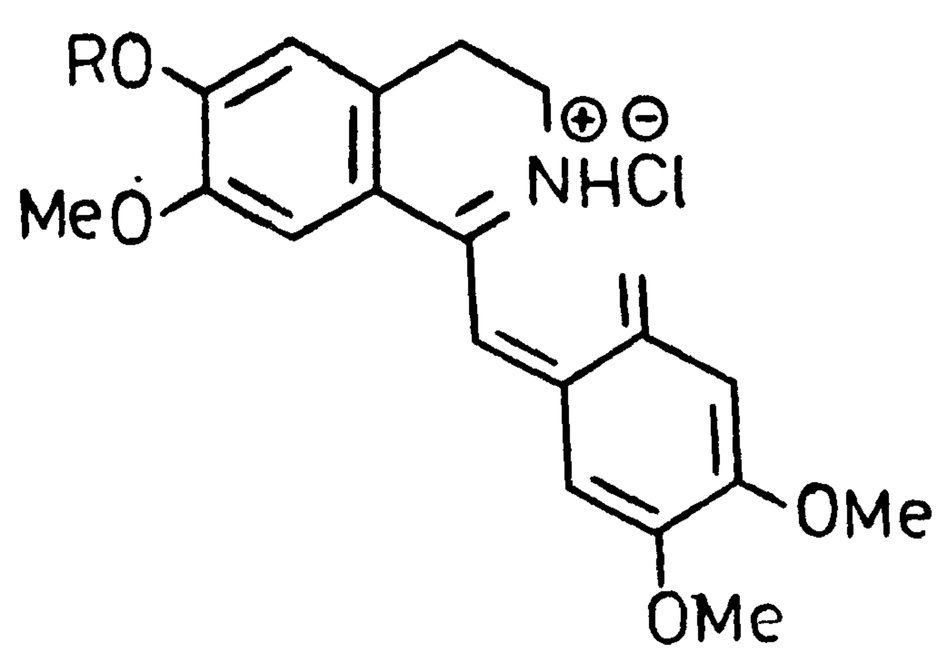
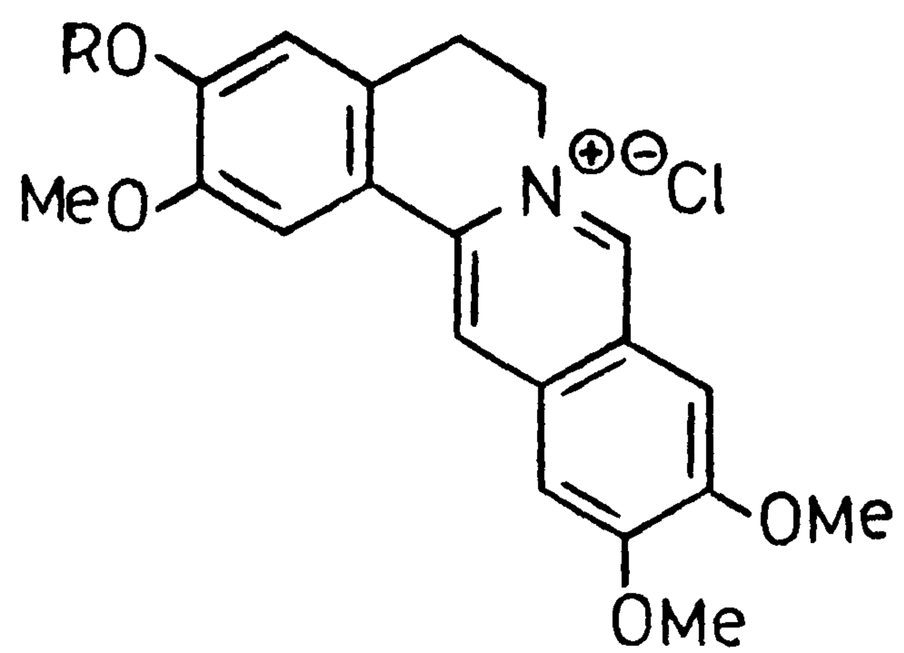
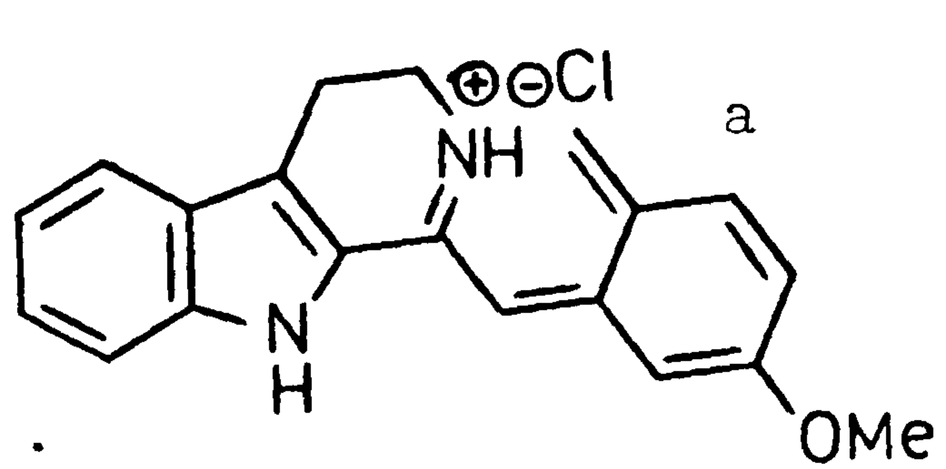
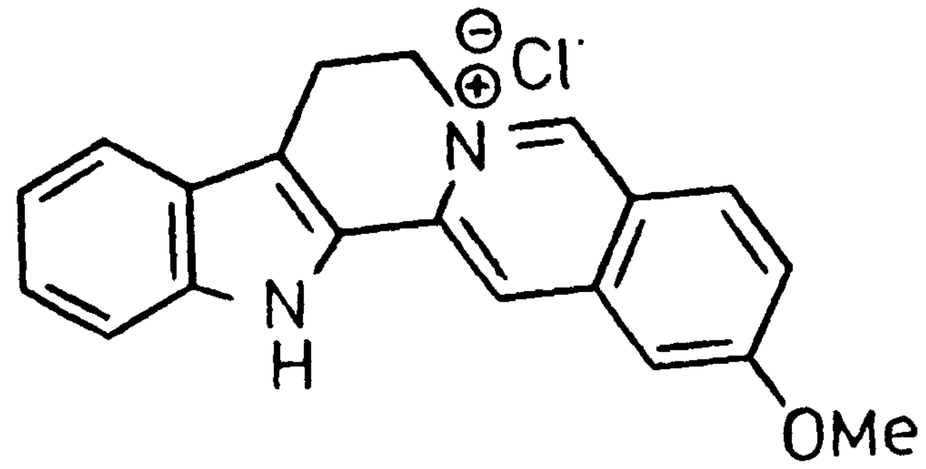


(373)

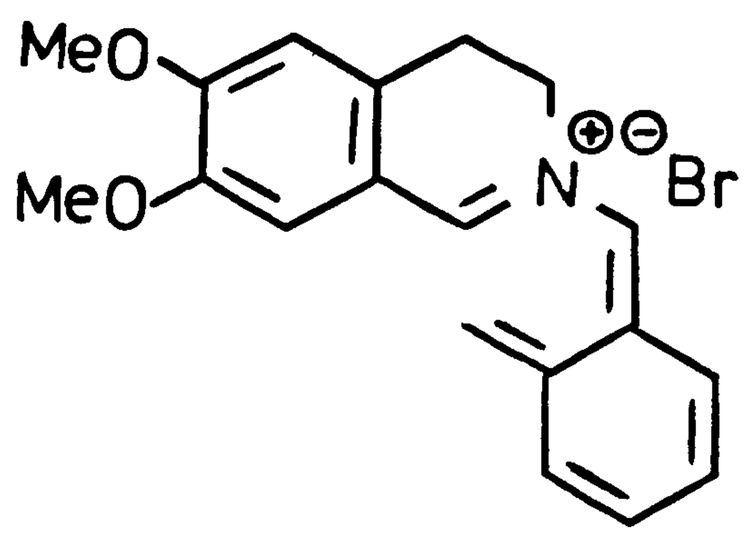


(374)

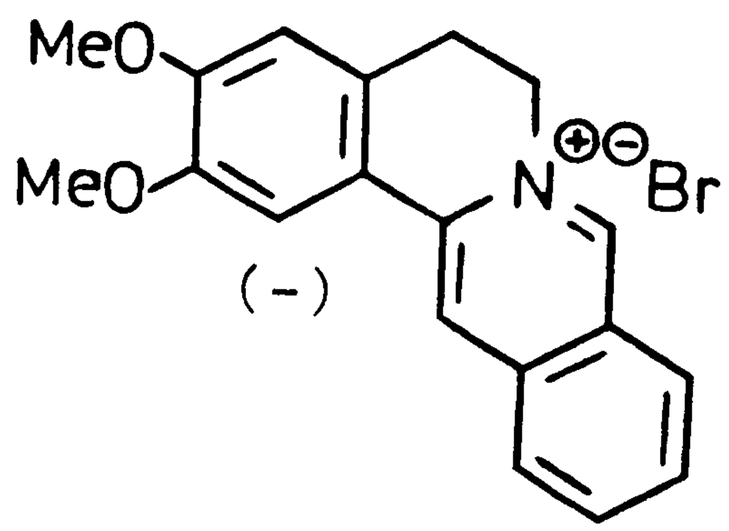
TABLE 5 o-QUINONOID INTERMEDIATES IN THE SYNTHESIS OF ALKALOIDS AND TERPENES

ENTRY	SUBSTRATE(S)	PRODUCT(S) AND YIELD(S) %	REFERENCES
			
	R		
1	Me[a]	(90)	185
2	$PhCH_2$[a]	(78)	186
3			188

4

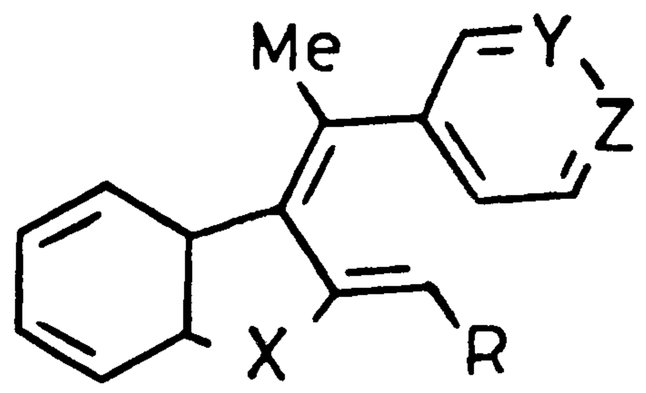


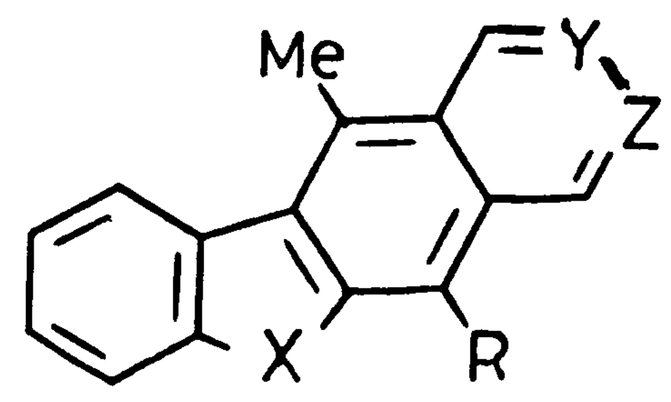
a



(-)

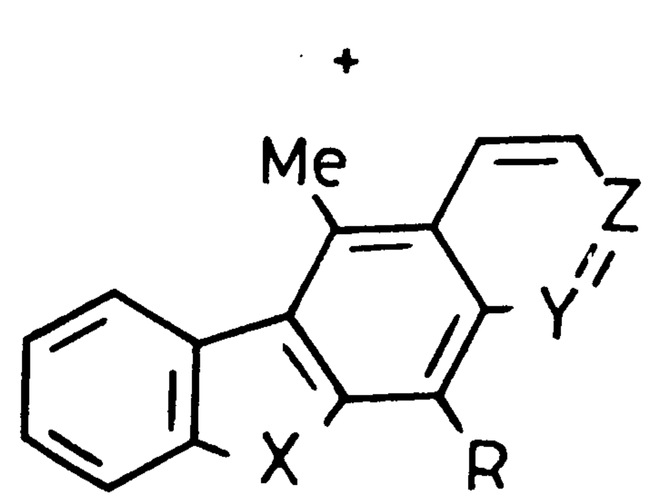
188





A

+



B

	R	X	Y	Z
5	Me	NH	N	CH
6	H	S	N	CH
7	Me	S	N	CH
8	H	S	CH	N
9	Me	S	CH	N

A	B
(-)	$(-)^y$
(11)	(12)
(18)	(18)
(29)	$(-)^y$
(27)	$(-)^y$

189

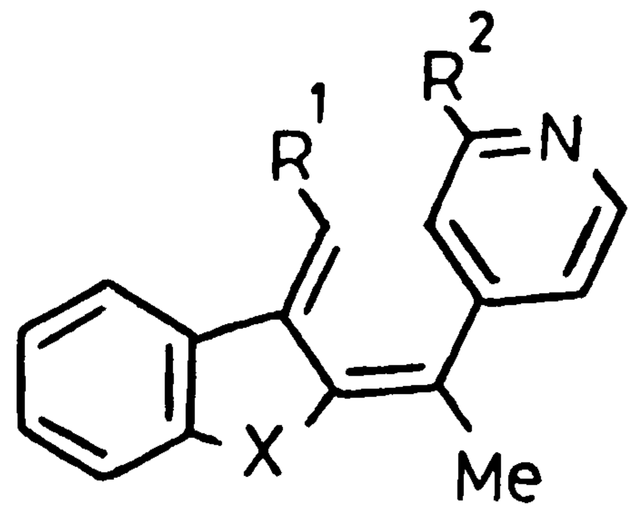
90

90

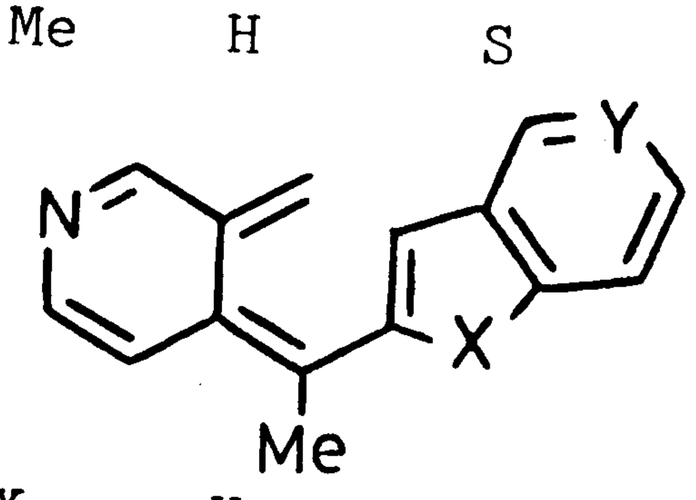
190

190

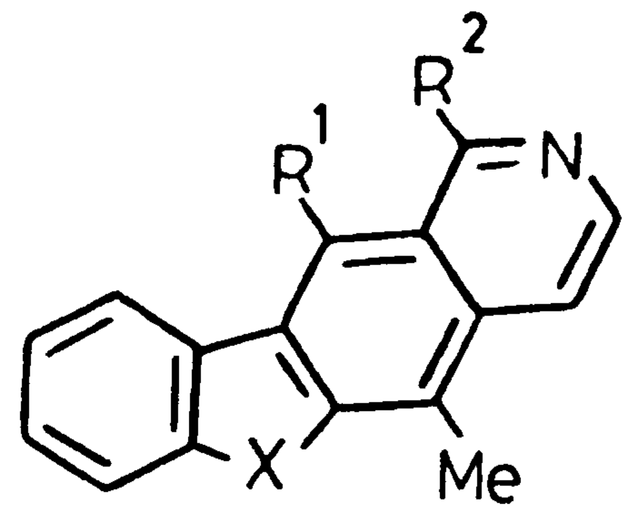
117



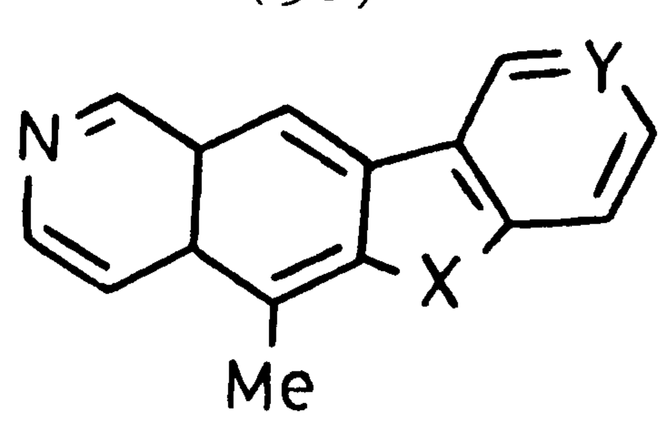
	R^1	R^2	X
10	H	Me	NH
11	Me	H	NH
12	Me	H	S



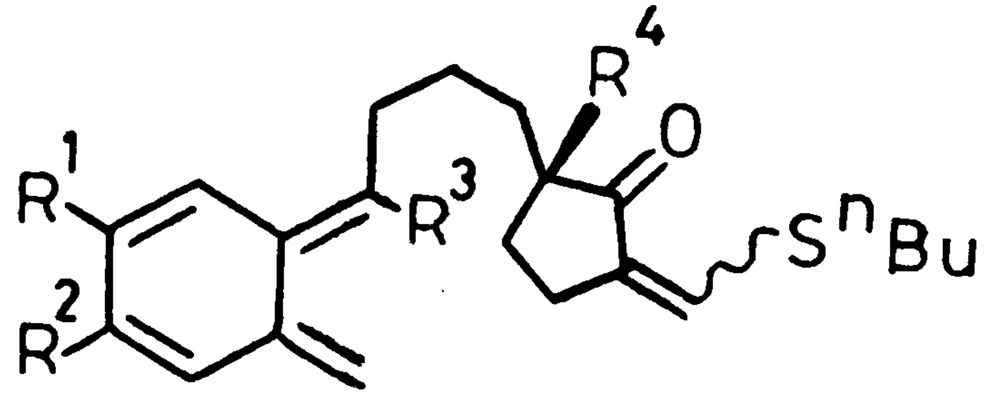
	X	Y
13	S	CH
14	O	CH
15	S	N

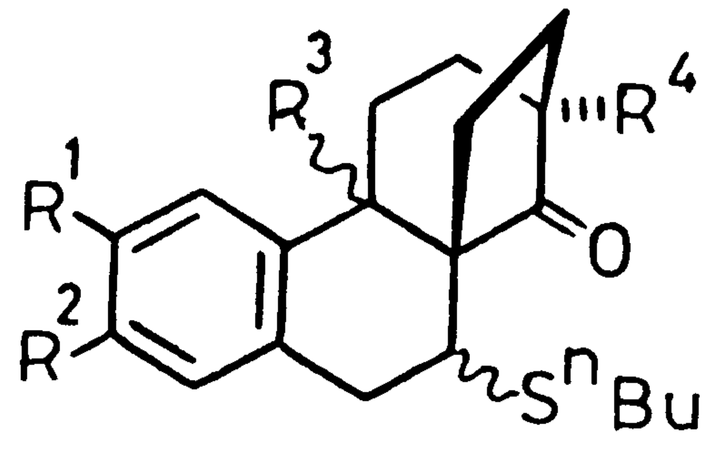


		$(-)^z$	191
		$(-)^z$	192
	(38)		190

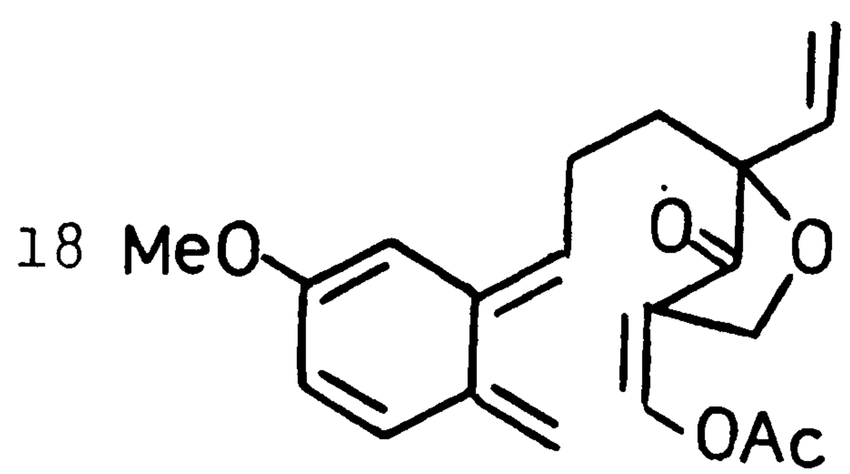


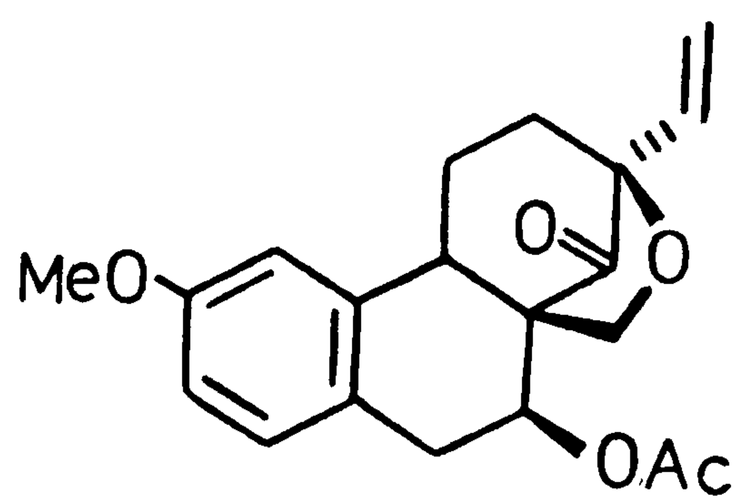
	(38)		190
	(45)		190
	(52)		190



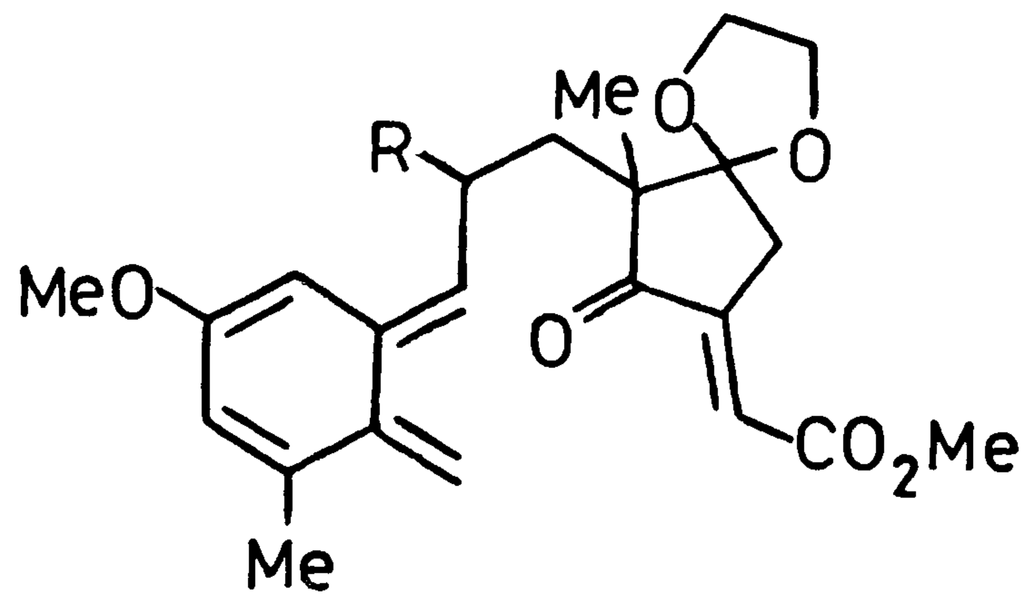


	R^1	R^2	R^3	R^4		
16	H	MeO	H	Me[a]	(78)[b]	199
17	MeO	H	H	Me[a]	(71)[b]	208

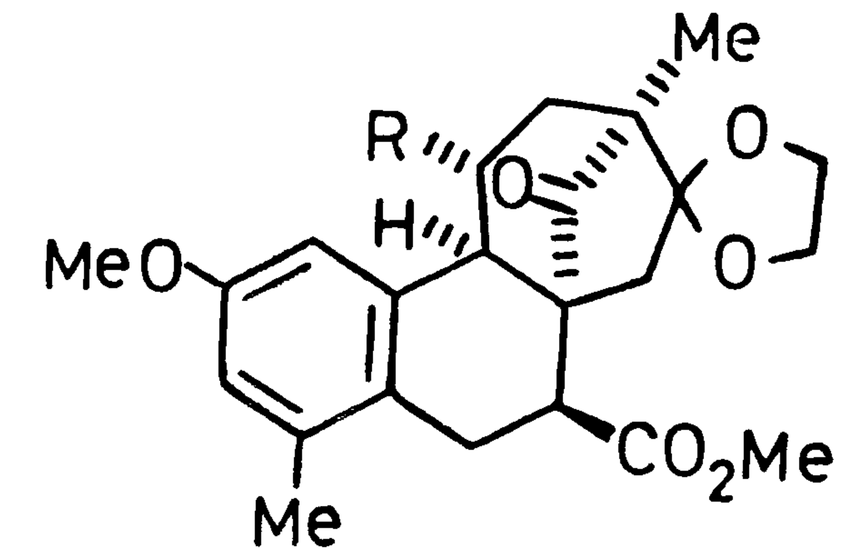
18  c

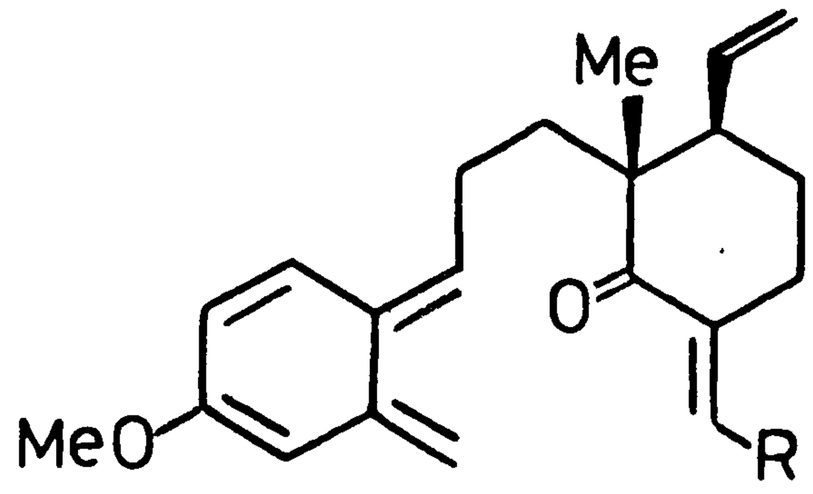


(74) 221

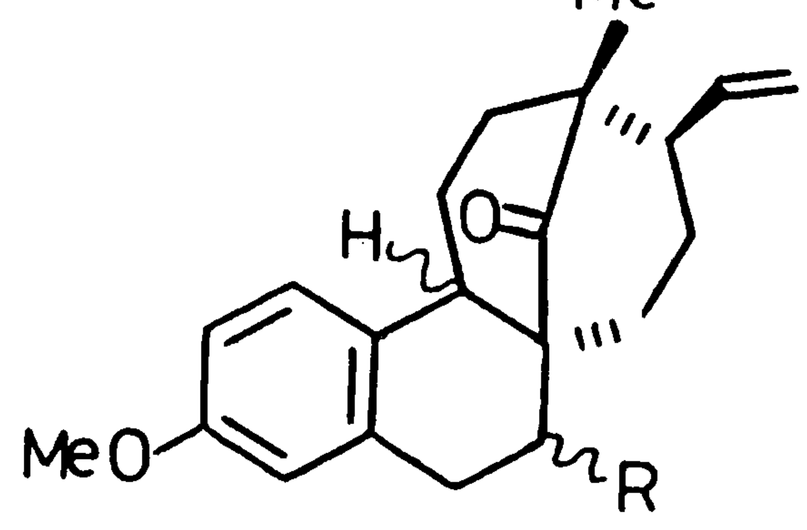


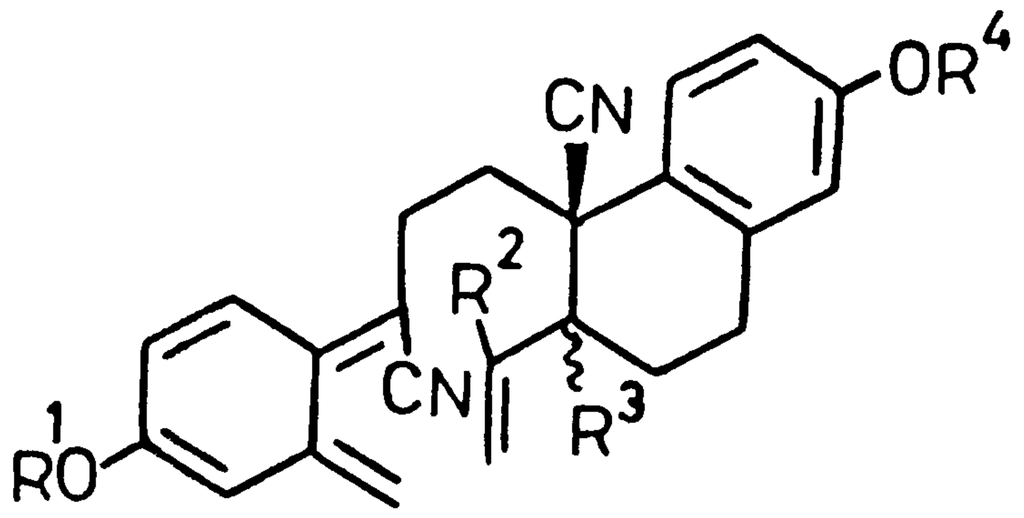
	R		
19	H[a]	(43)	200
20	$PhCH_2O$[a]	(41)	200

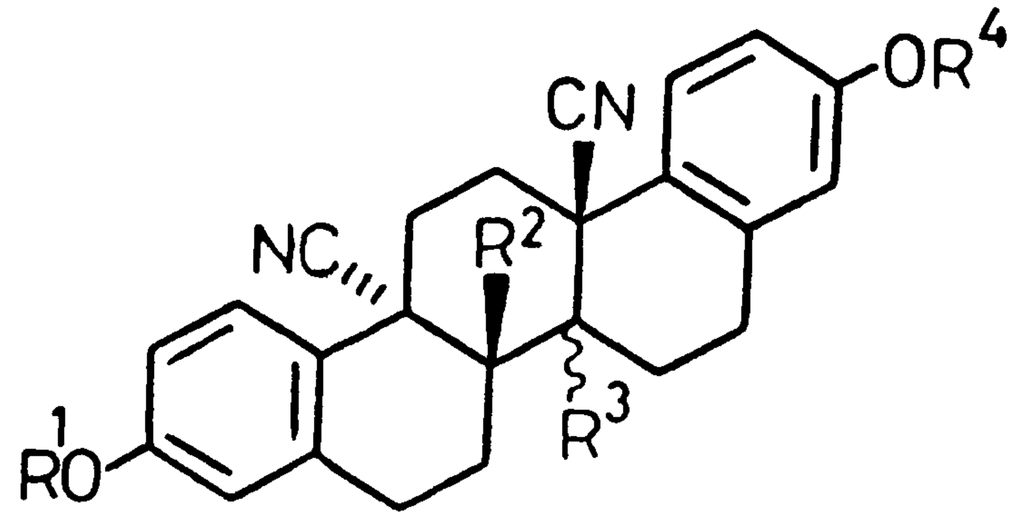




	R		
21	n_{BuS} [a]	(38)	179
22	Ph [a]	(17)	179

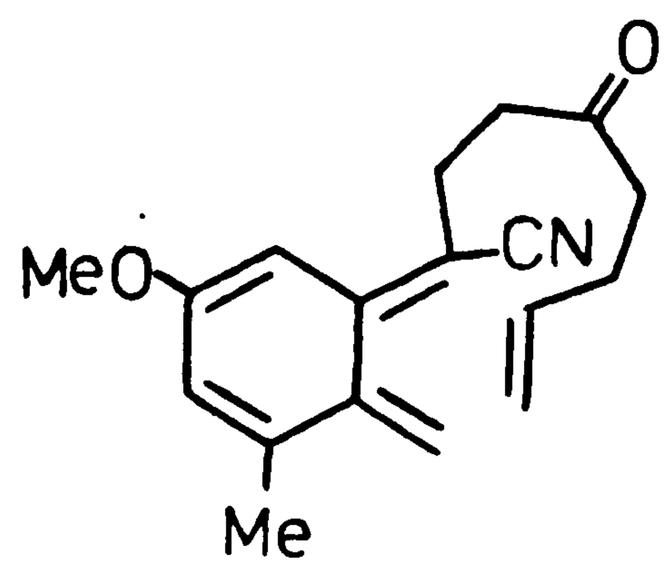




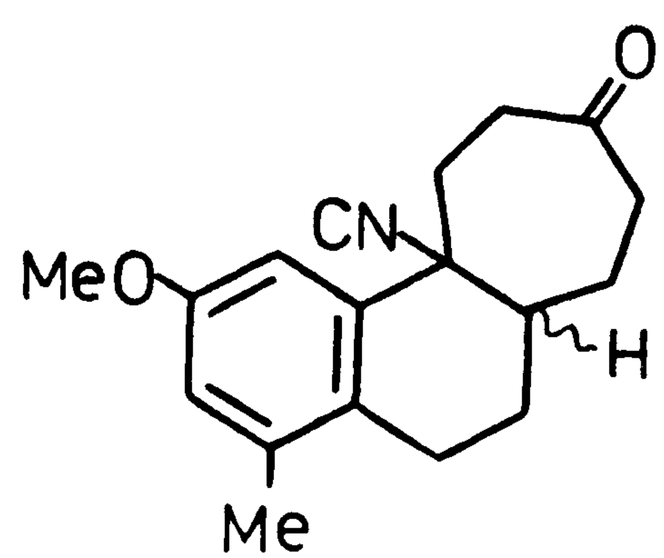


	R1	R2	R3	R4			
23	Me	Me	H	Et	a	(60)[c]	198
24	Et	Me	H	Me	a	(58)[c]	198
25	Me	H	Me	Et	a	(82)[d]	198

26

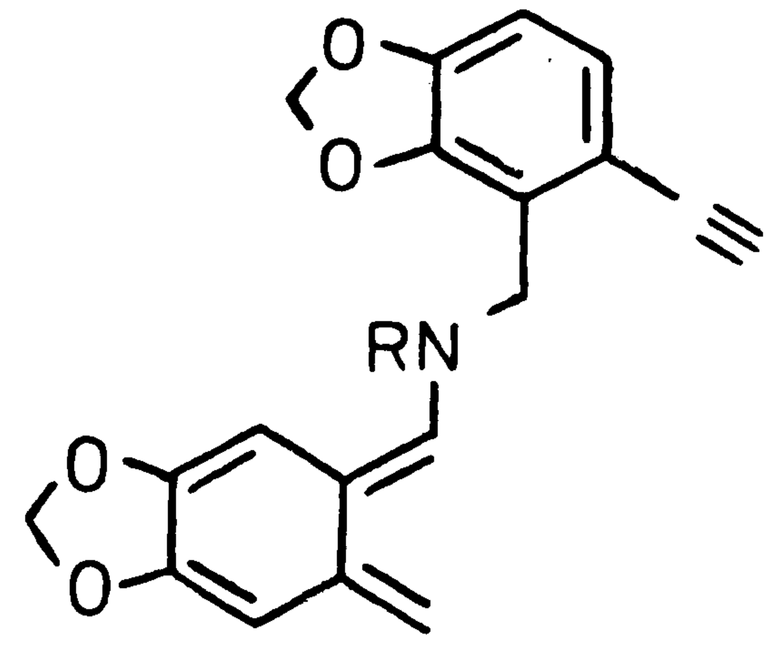


a

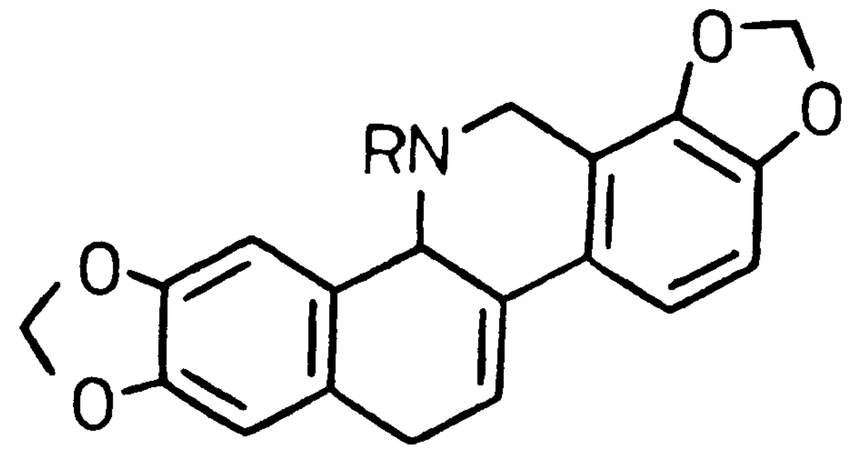


(55) 201

27



a

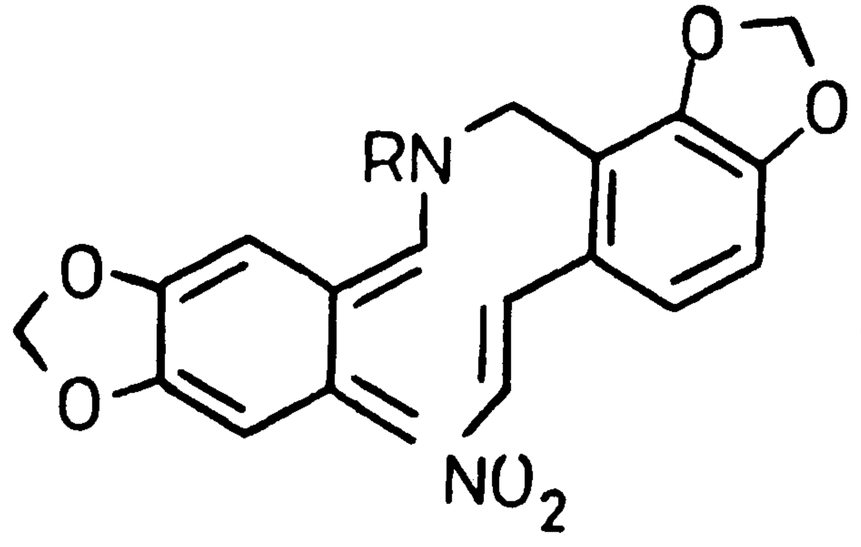


(73)

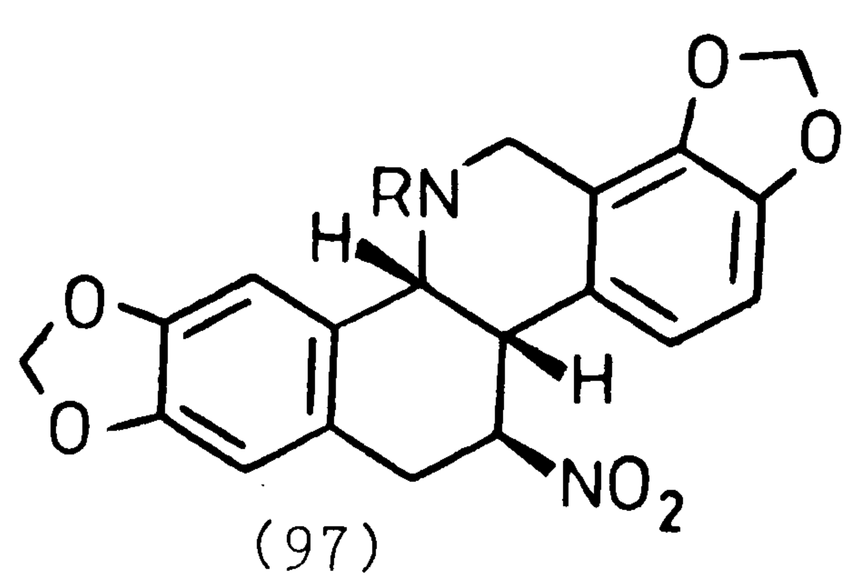
205

R = CO_2CH_2Ph

28



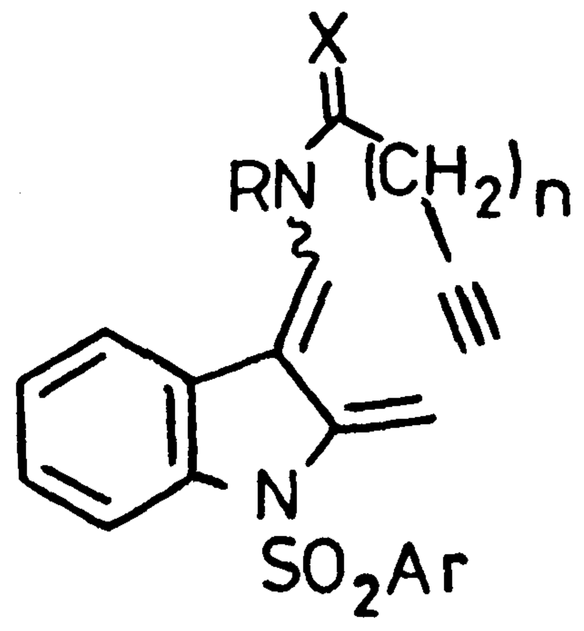
a

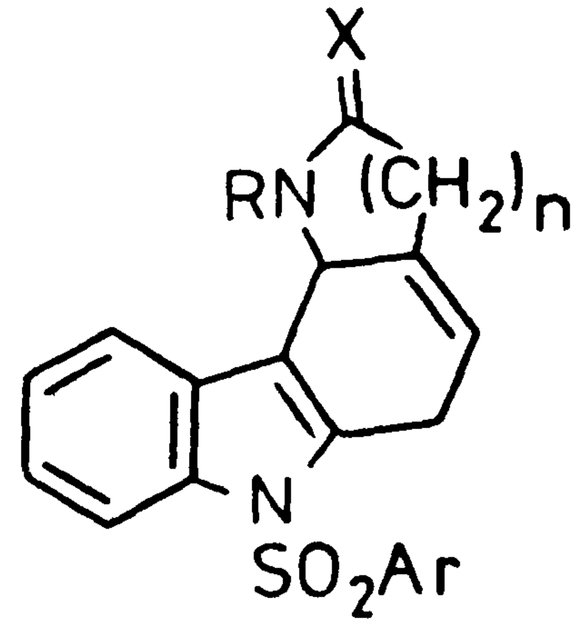


(97)

204

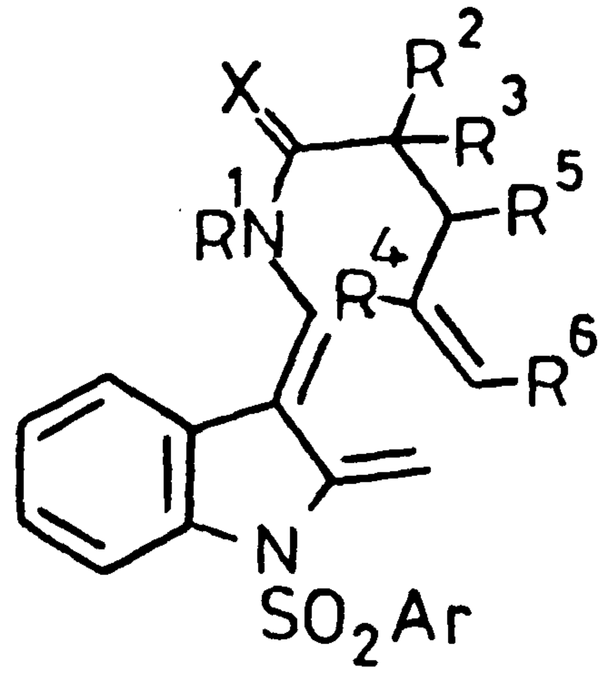
R = CO_2CH_2Ph



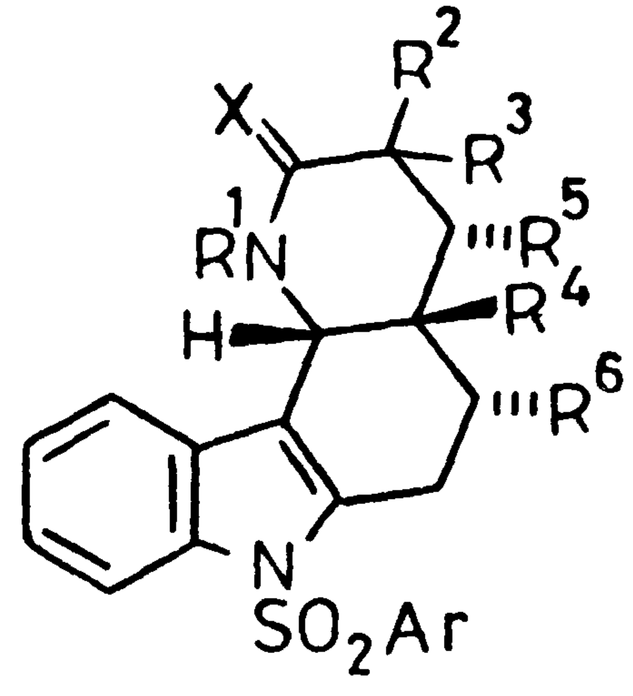


Ar = $SO_2C_6H_4CH_3$

	R	X	N		
29	MeO_2C	H_2	1[f]	(17)	209
30	$Cl(CH_2)_2O_2C$	H_2	1[f]	(>95)	209
31	$PhS(CH_2)_2$	O	2[f]	(31)	209



f, g

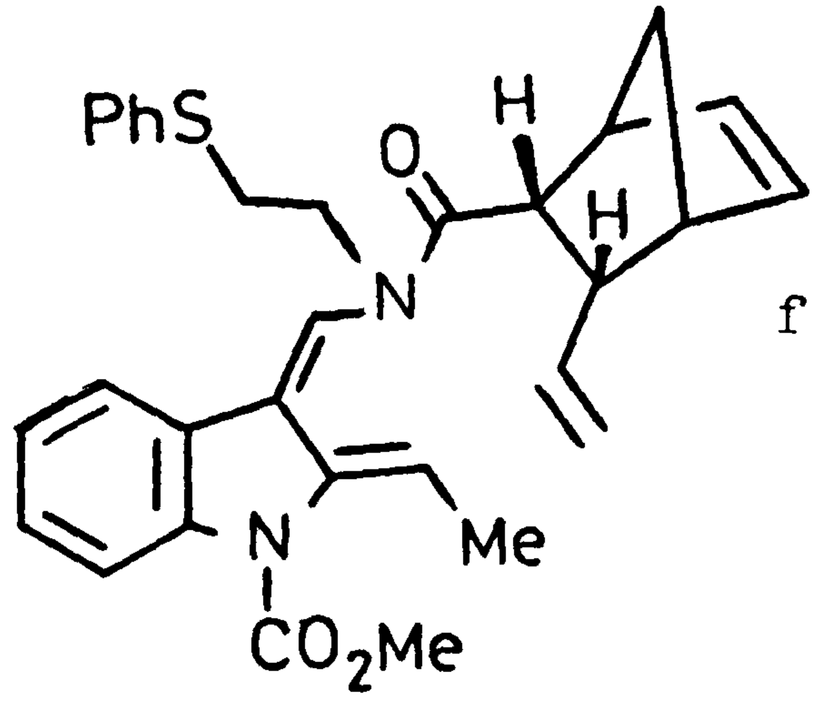


Ar = $SO_2C_6H_4CH_3$

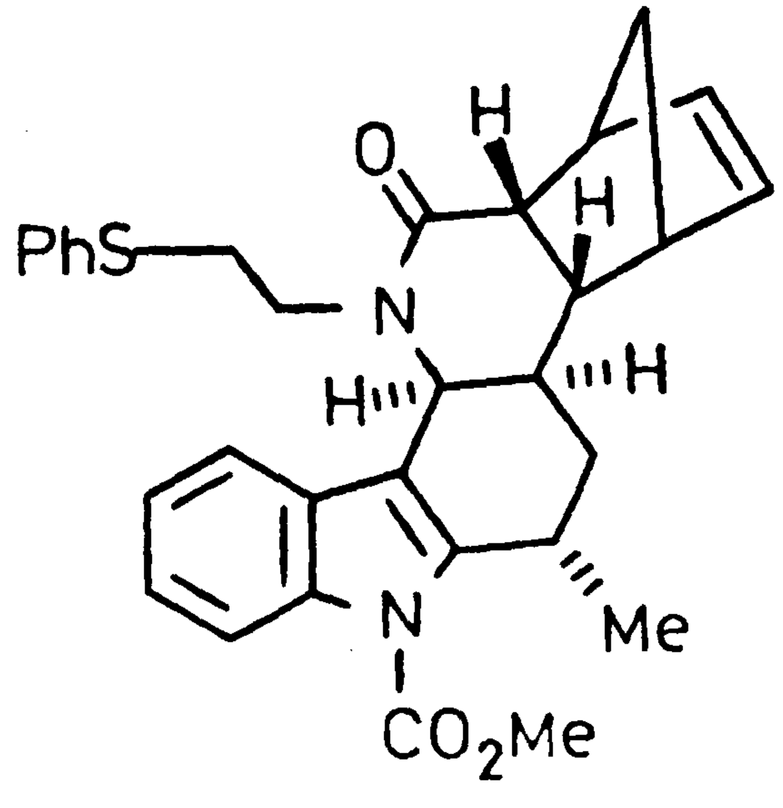
	R^1	R^2	R^3	R^4	R^5	R^6	X		
32	Me	H	H	H	H	H	O	(40)	210
33	MeCO	H	H	H	H	H	H_2	(64)	193
34	MeO_2C	H	H	H	H	H	H_2	(88)	193
35	EtO_2C	H	H	H	H	H	H_2	(43)	193
36	$MeO(CH_2)_2$	H	H	H	H	H	O	(55)	210
37	$Cl(CH_2)_2O_2C$	H	H	H	H	H	H_2	(92)	210
38	$Cl_3CCH_2O_2C$	H	H	H	H	H	H_2	(79)	210
39	CH_3O_2C	H	H	Et	H	H	H_2	(54)	210
40	$(CH_3O)_2CHCH_2$	H	H	H	H	H	O	(58)	210

41	$Cl(CH_2)_2O_2C$	H	H	Et	H	H	H_2	(70)	210
42	$Cl_3CCH_2O_2C$	H	H	Et	H	H	H_2	(46)	210
43	$CH_3O(CH_2)_2$	H	H	H	$-(CH_2)_3-$		O	(48)[h]	210
44	$(CH_3O)_2CHCH_2$	H	H	Et	H	H	O	(11)	210
45	$CH_3O(CH_2)_2$	H	H	H	$-(CH_2)_4-$		O	(31)[c]	210
46	$PhCH_2$	H	H	H	H	H	O	(56)	210
47	PhO_2C	H	H	H	H	H	H_2	(68)	193
48	$MeO(CH_2)_2$	$-(CH_2)_5-$		H	H	H	O	(38)	210
49	$PhS(CH_2)_2$	H	H	H	H	H	O	(60)	210
50	$PhSe(CH_2)_2$	H	H	H	H	H	O	(22)	210
51	$PhS(CH_2)_2$	H	H	Et	H	H	O	(33)	206,210

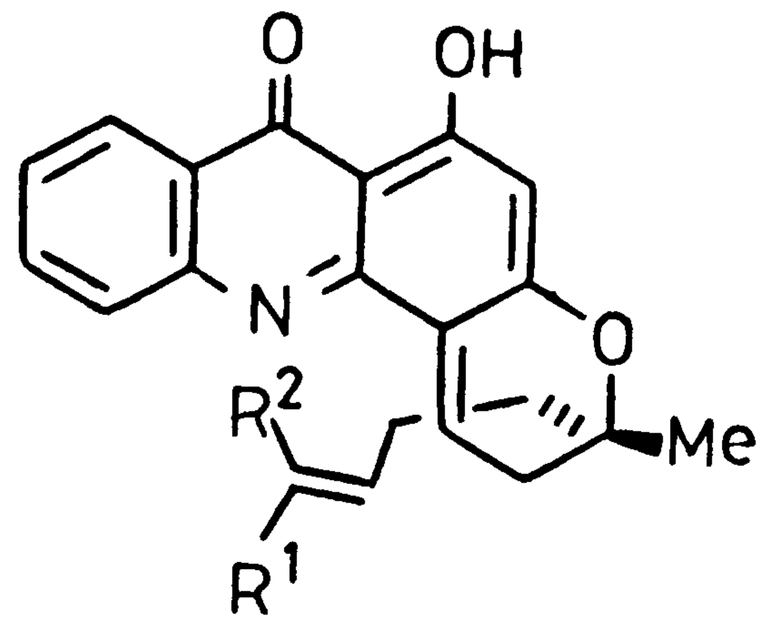
52

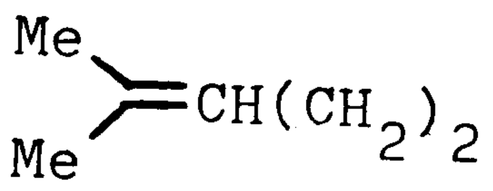


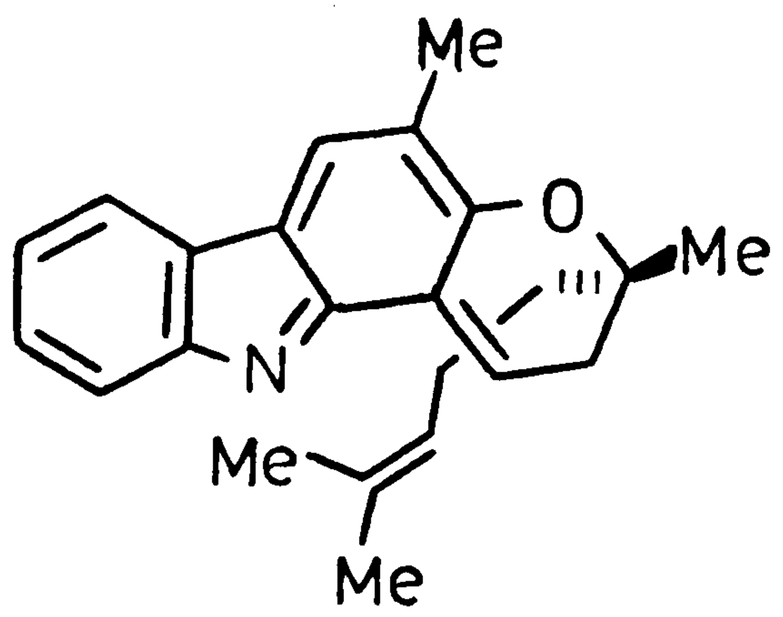
f



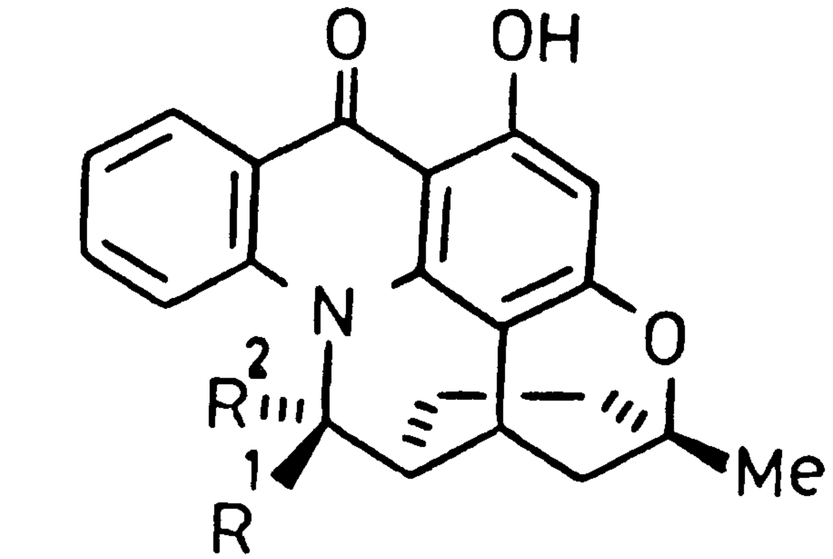
225



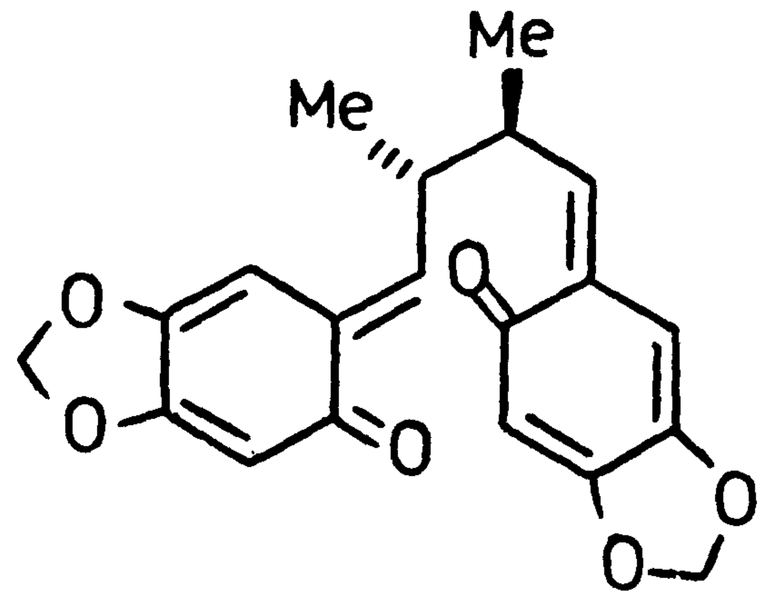
	R^1	R^2			
53	CH_3	CH_3		(30)	212
54		CH_3		(2.5)	212

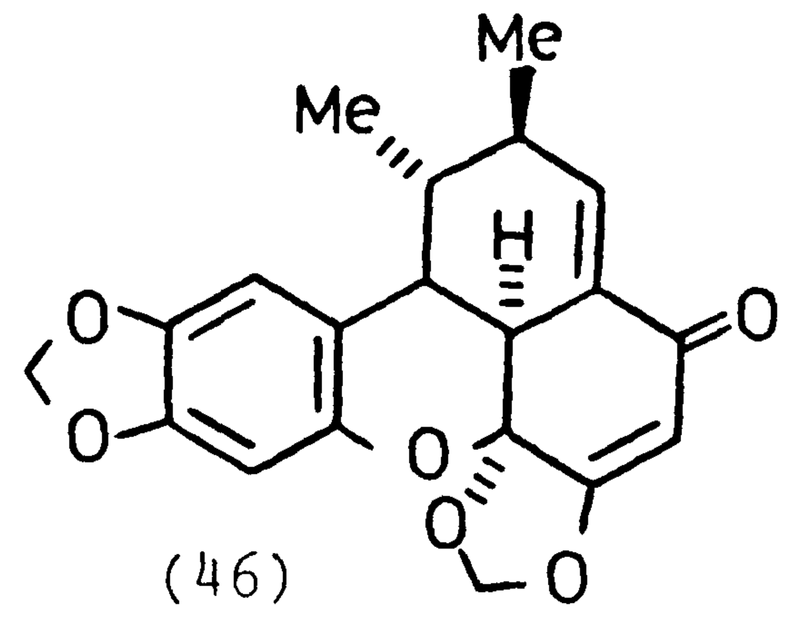


55 j

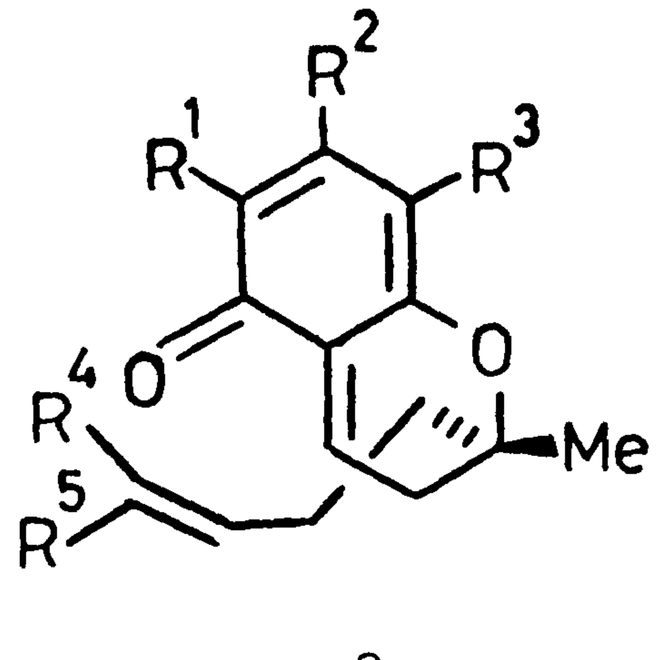


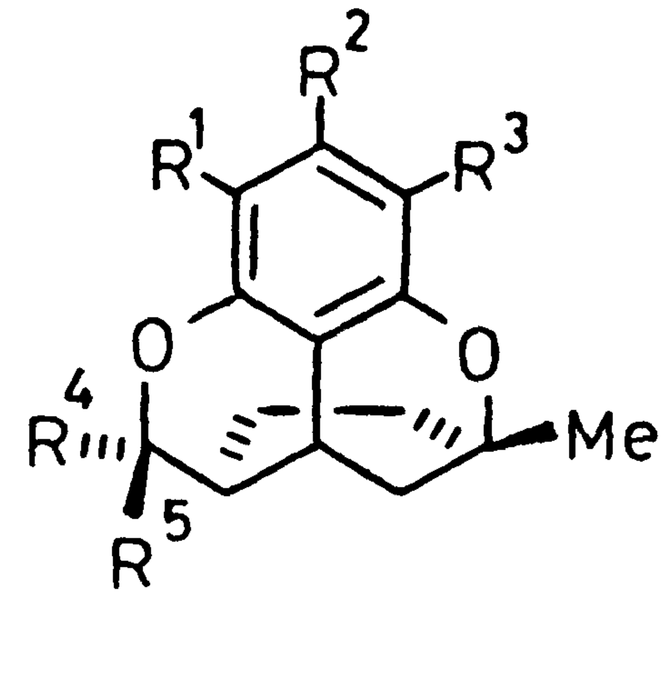
(3.5) 213

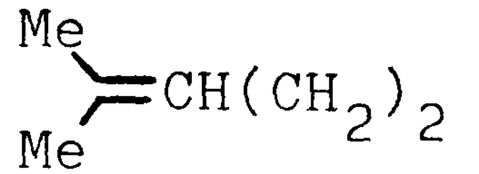


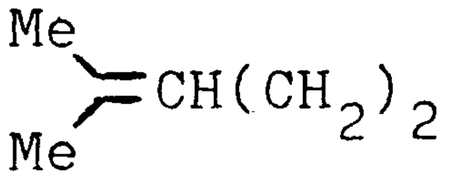
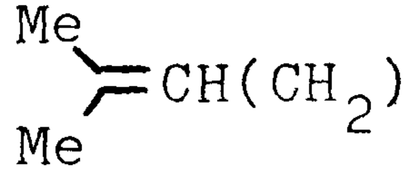
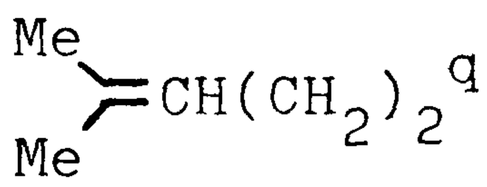
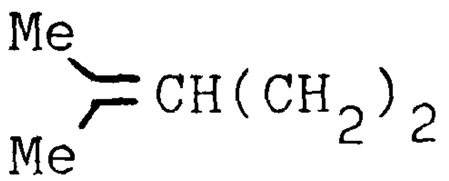
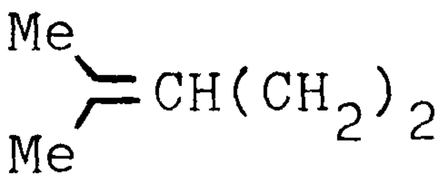
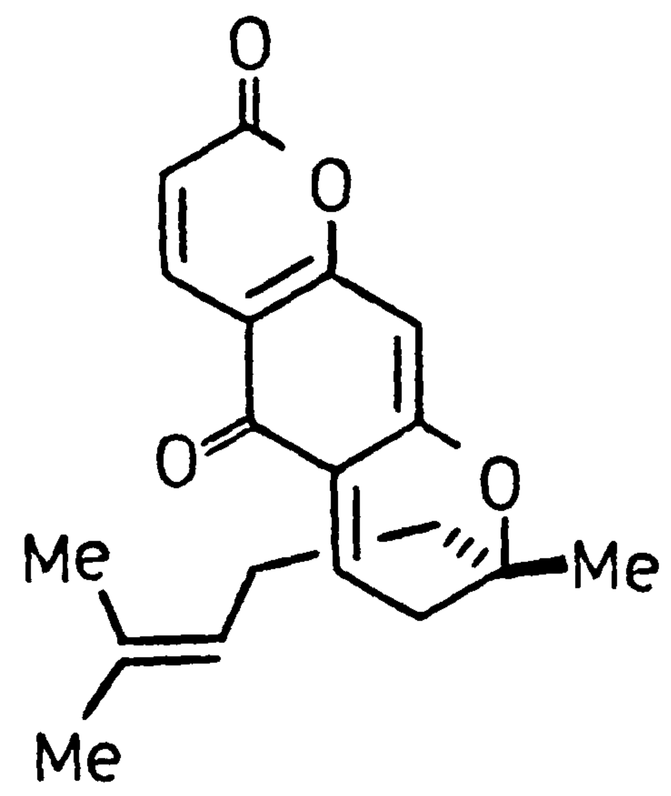
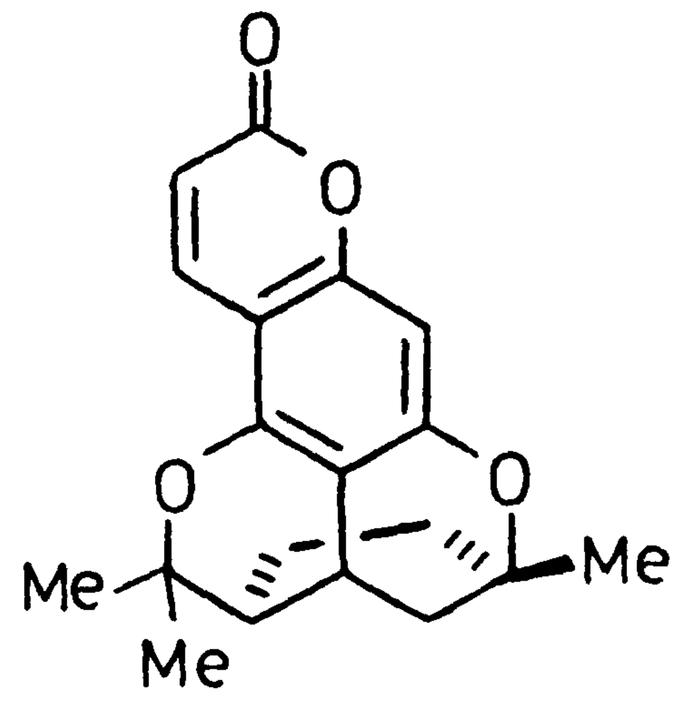


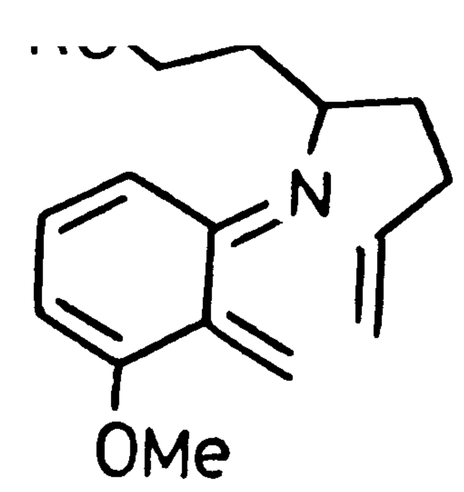
(46)



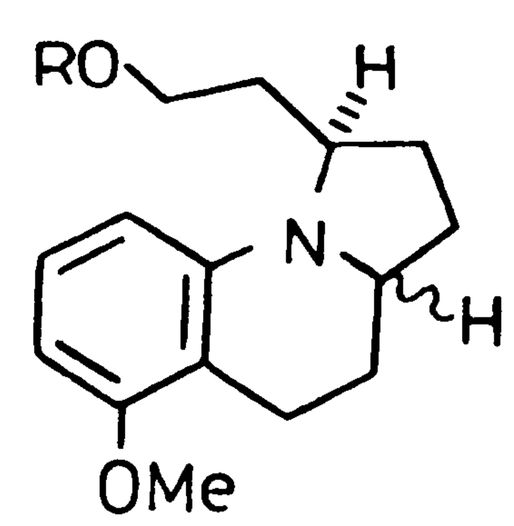


	R^1	R^2	R^3	R^4	R^5		
57	H	OH	H	Me	Me[k]	(40)	195,196,197
58	H	Me	H	Me	Me[l]	(-)	214
59	H	OH	OHC	Me	Me[m]	(10)	215,216
60	OHC	OH	H	Me	Me[m]	(59)	215,216
61	H	OH	CH_3O	Me	Me[m]	(8)	215,216
62	MeCO	OH	H	Me	Me[n]	(68)	215,217
63	H	OH	H	Me		(-)	211

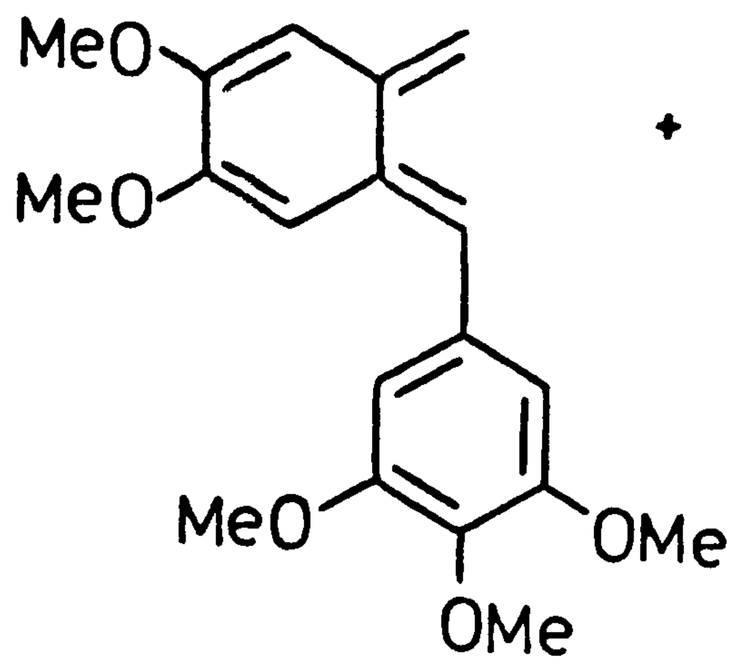
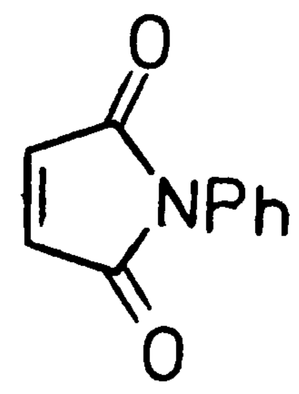
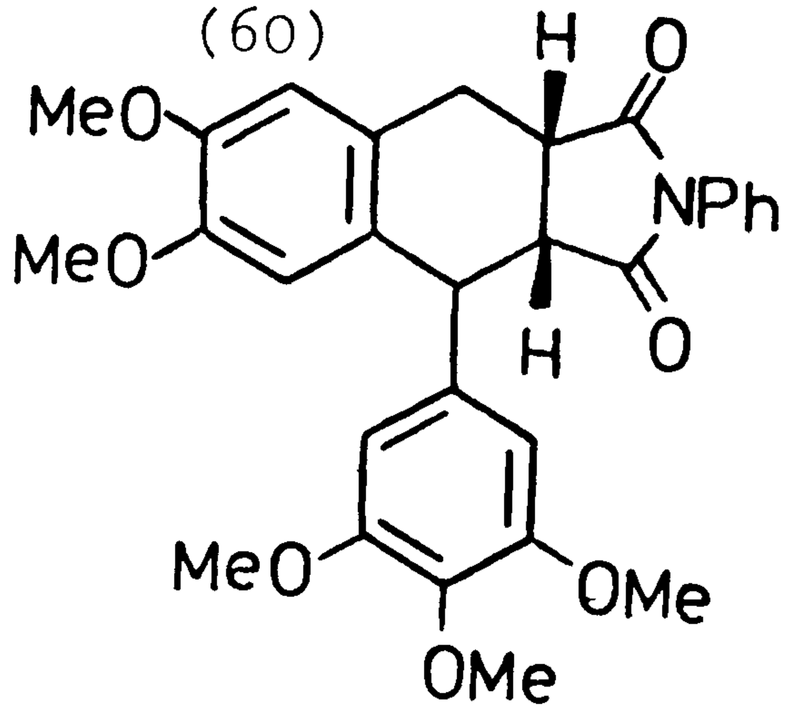
64	H	OH	H		Me[p]	(-)	211
65	H	OH	CHO	Me		(-)	194
66	OHC	OH	H	Me		(-)	194
67	H	OH	OHC		Me[r]	(-)	214
68	OHC	OH	H		Me[r]	(-)	218,219
69	H	$^{n}C_{5}H_{11}$	H	Me	Me[s]	(26)	220
70	PhCH-CHCO	OH	H	Me	Me[t]	(57)	185,106,202,203
71				u			195,196,202,203



v

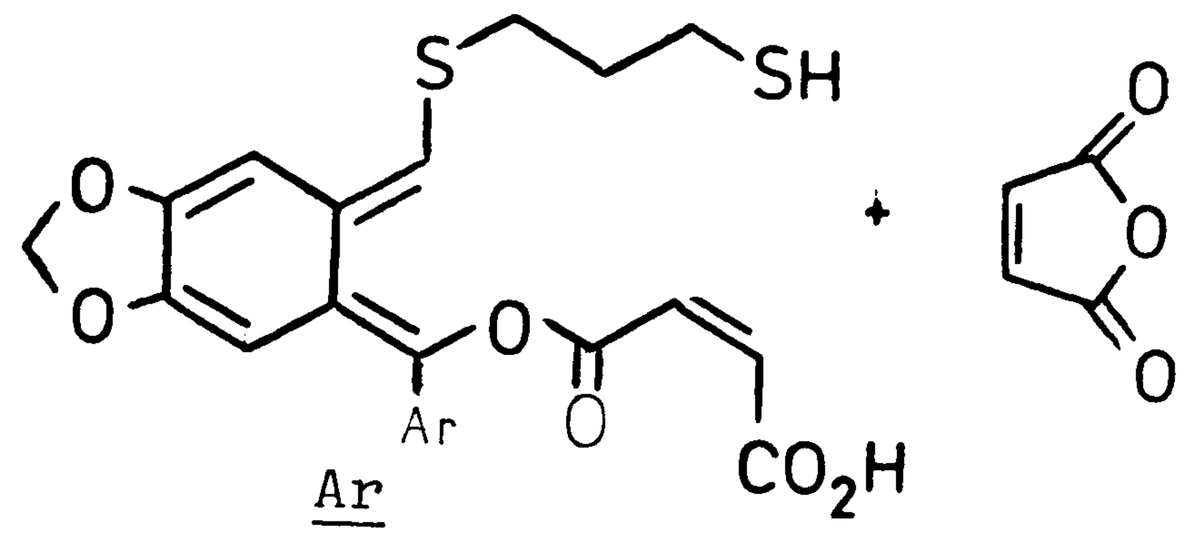


v

R		
72	$SiMe_3$	
73	THP	
74	 +  w	

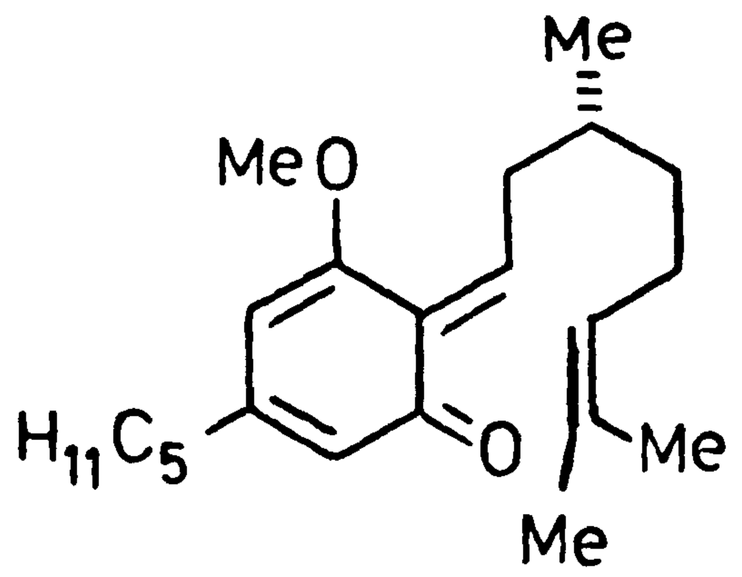
(71)

(60) 223

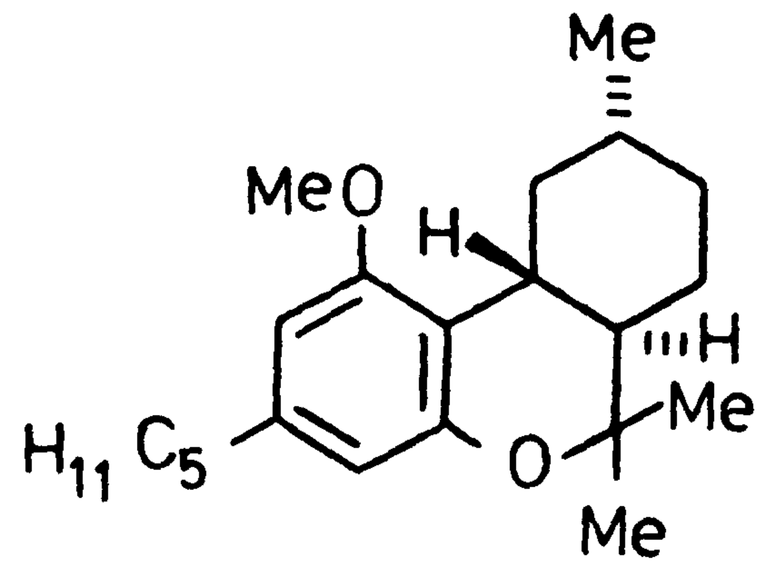


Ar		
75	3,4,5-(MeO)-C_6H_2	(38) 224
76	3,4-$(MeO)_2$-C_6H_3	(38) 224
77	3,4-(OCH_2O)-C_6H_3	(24) 224

78



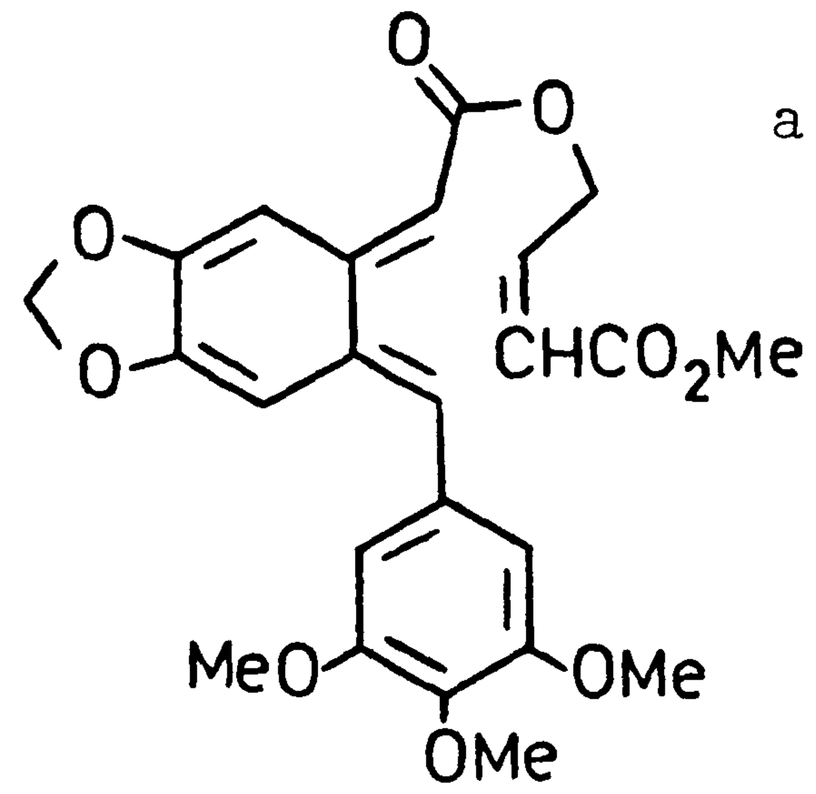
aa



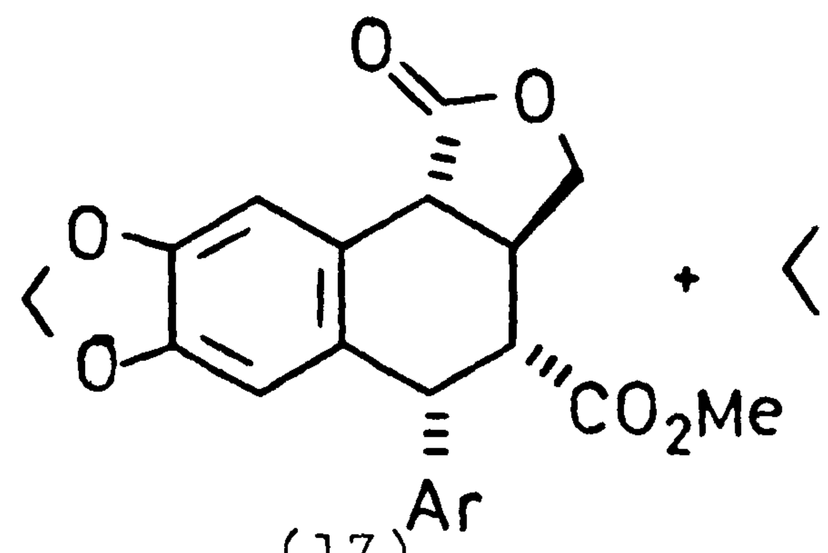
(90)

231

79

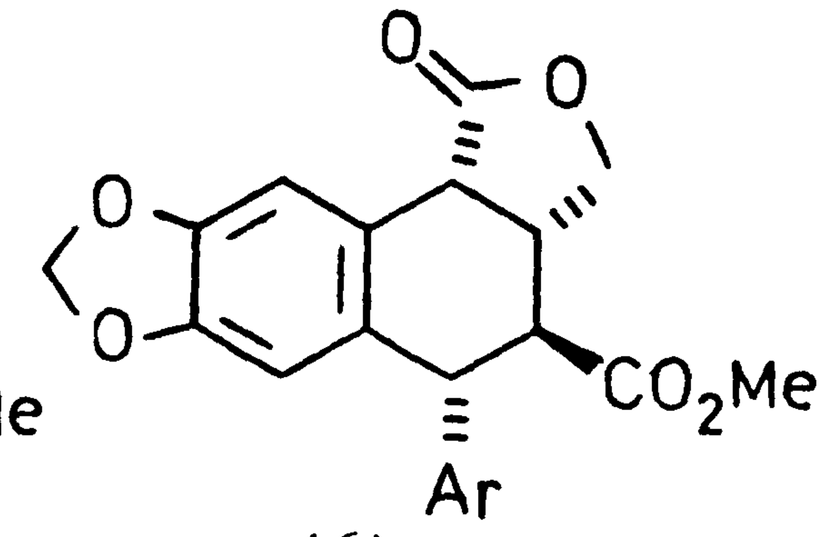


a



(17)

+



(6)

a. The substrate was generated from the benzocyclobutene.

b. The stereochemistry of the ^{n}BuS group was not reported.

c. R^3 is α.

d. The substrate and product were mixtures of R^3 α and β isomers.

e. The stereochemistry of the product was not specified, but appears to be cis, judged from the structure of a subsequent product.

f. The substrate was generated from a 2-methyl-1H-indole-3-methylenimine and a mixed anhydride or an acid chloride; see original work for details.

g. See original work for a discussion of possible transition states.

h. The stereochemical assignment was tentative.

i. R^5 is β.

j. The substrate was generated from mohanimbine.

k. The substrate was generated from phloroglucinol and citral.

l. The substrate was generated from orcinol and citral.

m. The substrate was generated from formylphloroglucinol and citral.

n. The substrate was generated from acetylphloroglucinol and citral.

o. The substrate was generated from phloroglucinol and (2E, 6E)-farnesal.

p. The substrate was generated from phloroglucinol and (2E, 6Z)-farnesal.

q. The substrate was generated from formylphloroglucinol and (2E, 6E)-farnesal.

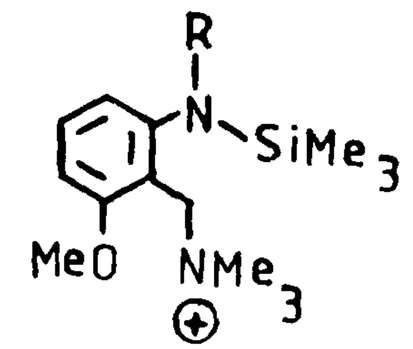
r. The substrate was generated from formylphloroglucinol and (2E,6Z)-farnesal.

s. The substrate was generated by reaction of olivetol with citral.

t. The substrate was generated from pinocembrin and citral.

u. The substrate was generated from 5,7-dihydroxycoumarin and citral.

v. The substrate was generated by flouride induced 1,4-elimination of

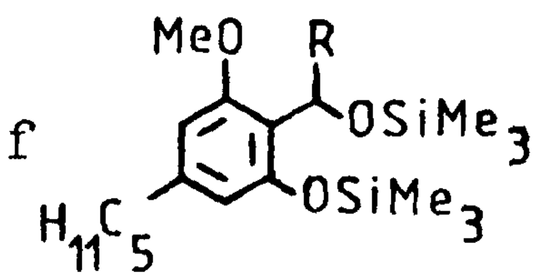


w. See original work for precursors.

x. Generated by thermal dehydration of the corresponding o-alkyl alcohols.

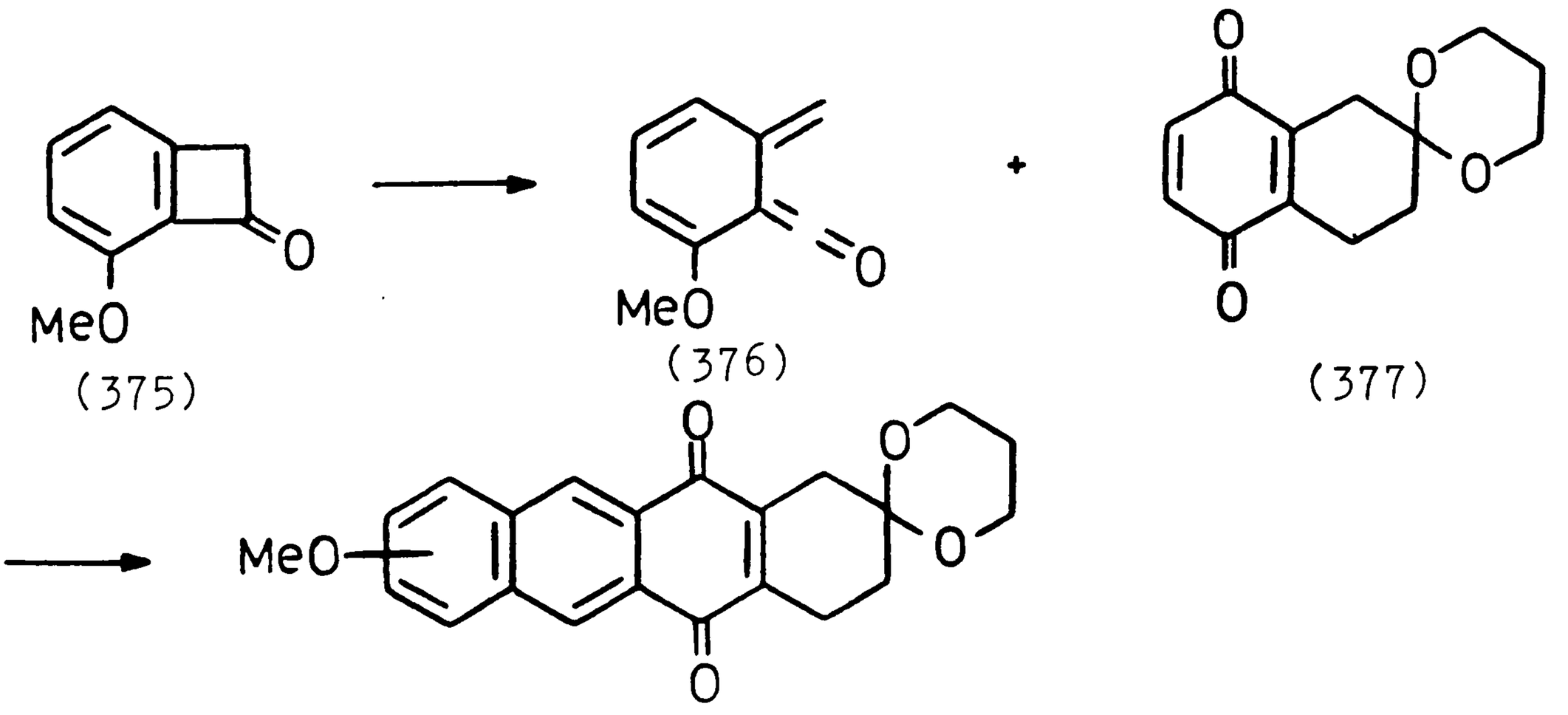
y. The ratio of isomers was not stated.

z. The product yield was not stated.

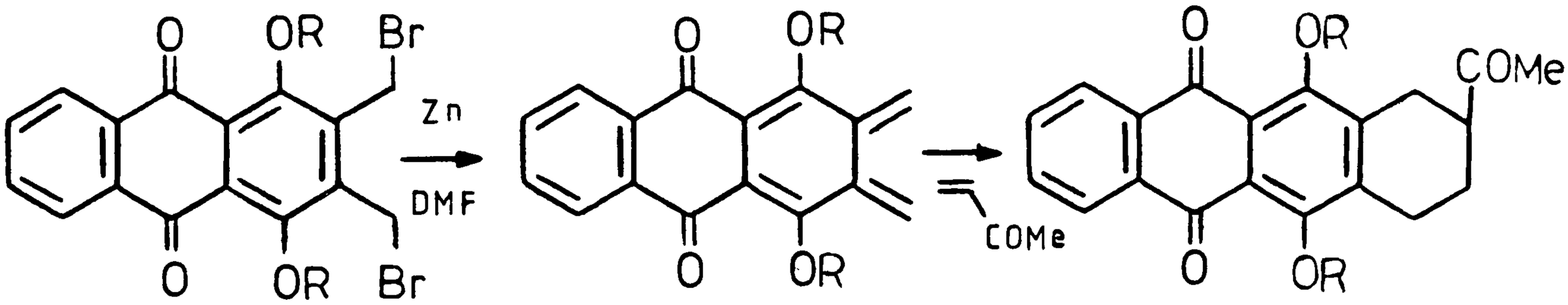
aa. The substrate was generated by fluoride-anion induced desilylation of 

(c) THE TOTAL SYNTHESIS OF ANTHRACYCLINONES

The synthesis of anthracycline antibiotics has recently aroused considerable interest because of their potent activity against experimental tumours and human cancers.[226] As can be seen from Table 6, a number of groups have constructed the basic framework of anthracyclinones utilizing various intermolecular cycloadditions of o-xylylenes. The main advantage of this approach is that it allows rapid construction of the required framework from simple, readily available starting materials. However, because we are dealing with intermolecular cycloadditions, non-symmetrically substituted dienes or dienophiles can produce isomeric mixtures in the cycloadducts. For example, in entries 1 - 6, various o-xylylenes (generated by thermal ring opening of the corresponding benzocyclobutenes) are coupled with fused quinones to yield the corresponding quinone adducts. Similarly, ketene (376) generated from ring opening of ketone (375) reacts with quinone (377) to give the two possible regioisomers (378) (entry 7), after dehydration of the initial cycloadduct.[229]

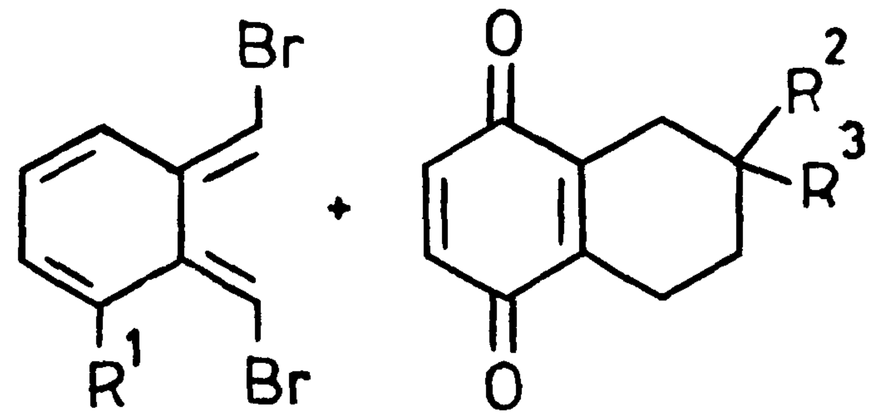
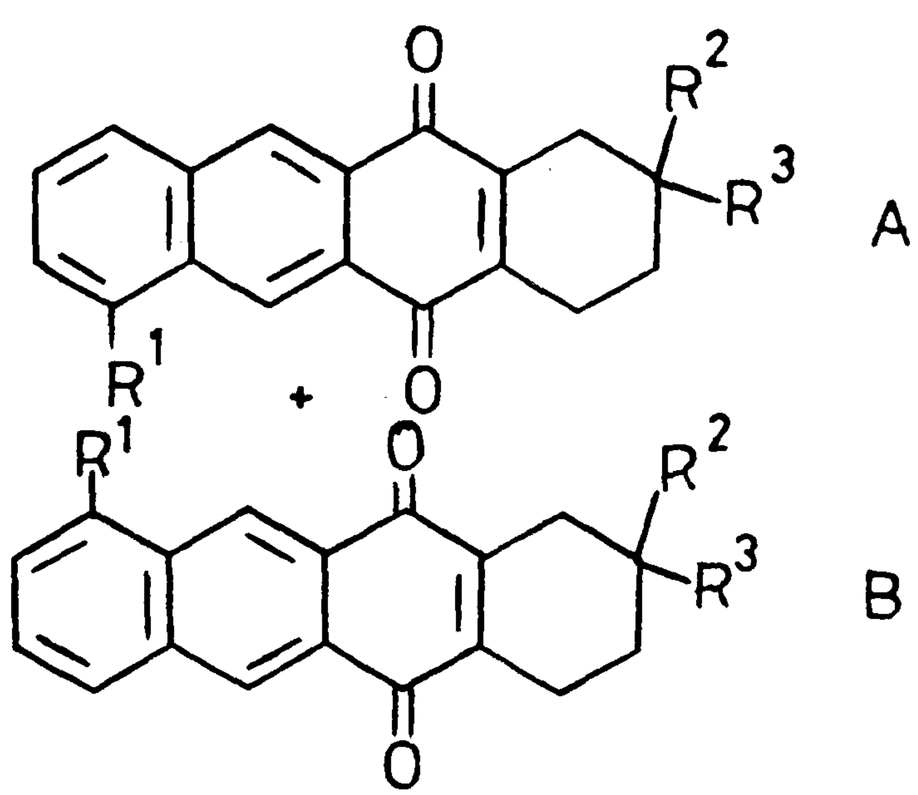
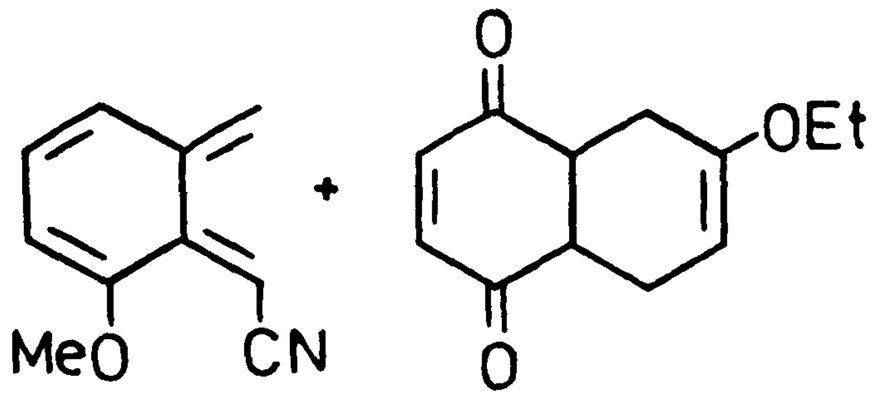
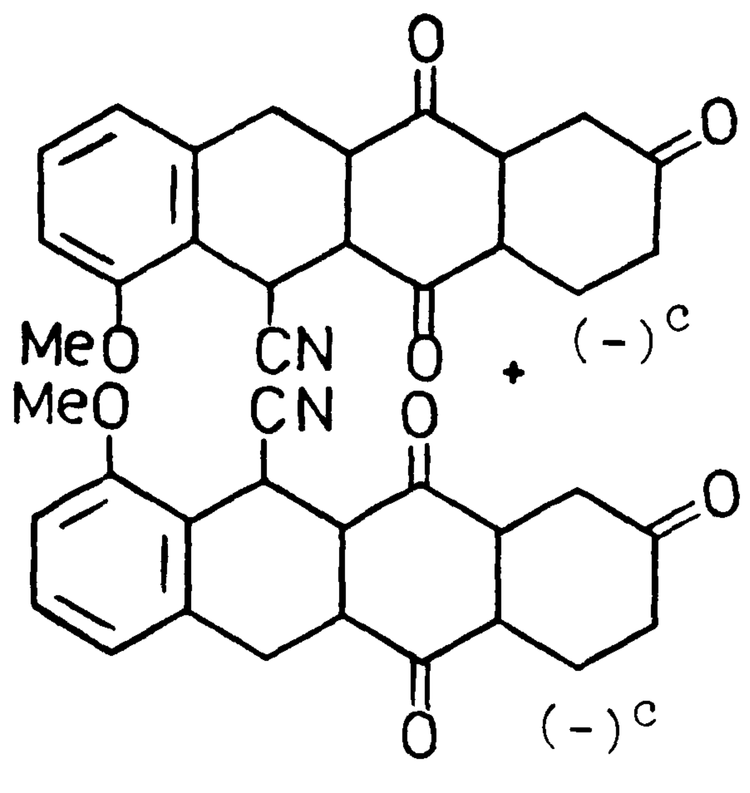


A different strategy is shown in entries 8 and 9. Generation of tricyclic o-xylylenes (380) from debromination of (379) in the presence of methyl vinyl ketone produces moderate to good yields of the adducts (381).[230]

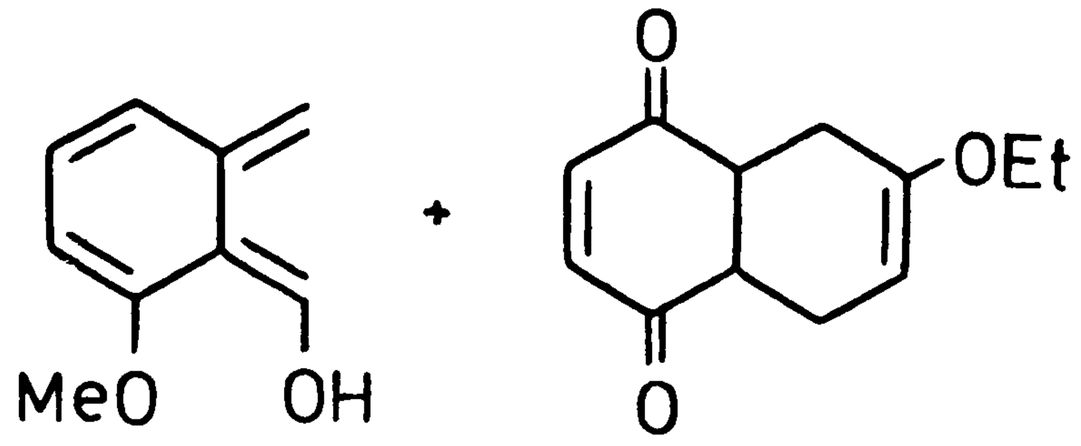


(379), R = Me, H (380) (381)

TABLE 6 o-Xylylenes in the synthesis of anthracylinones.

ENTRY	SUBSTRATE			PRODUCT(S) AND YIELD(S) %		REFERENCES
						
	R^1	R^2	R^3	A	B	
1	H		[a]	(94)		227
2	H	H	H[a]	(72)		228
3	H	COMe	OH[a]	(33)		228
4	Ome	COMe	OH[a]	(-)	(-)[c]	228
			[a]			229

6



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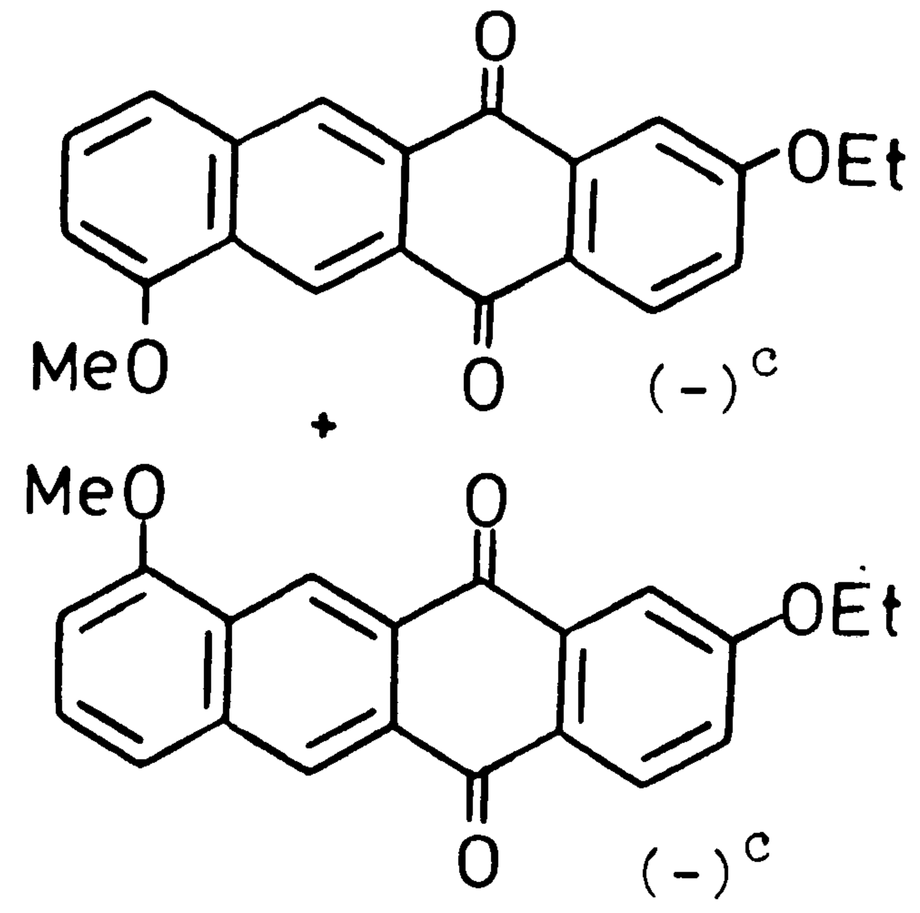
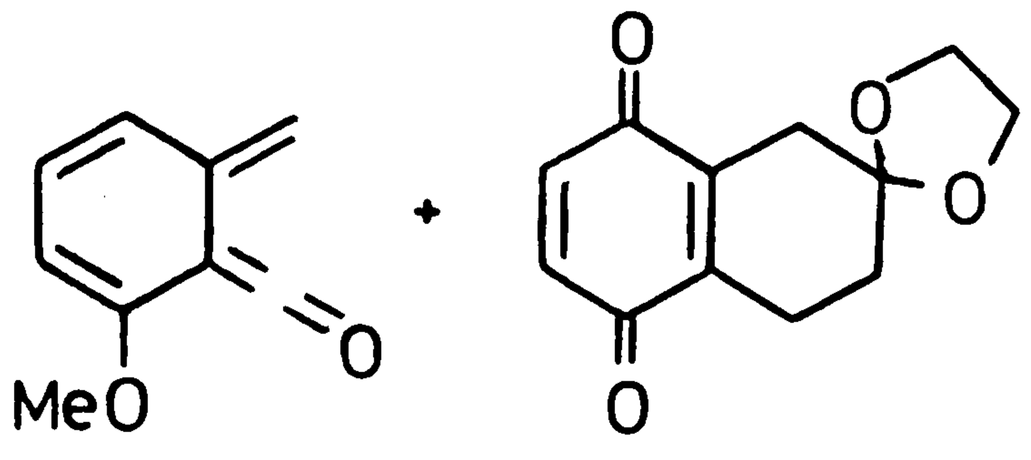
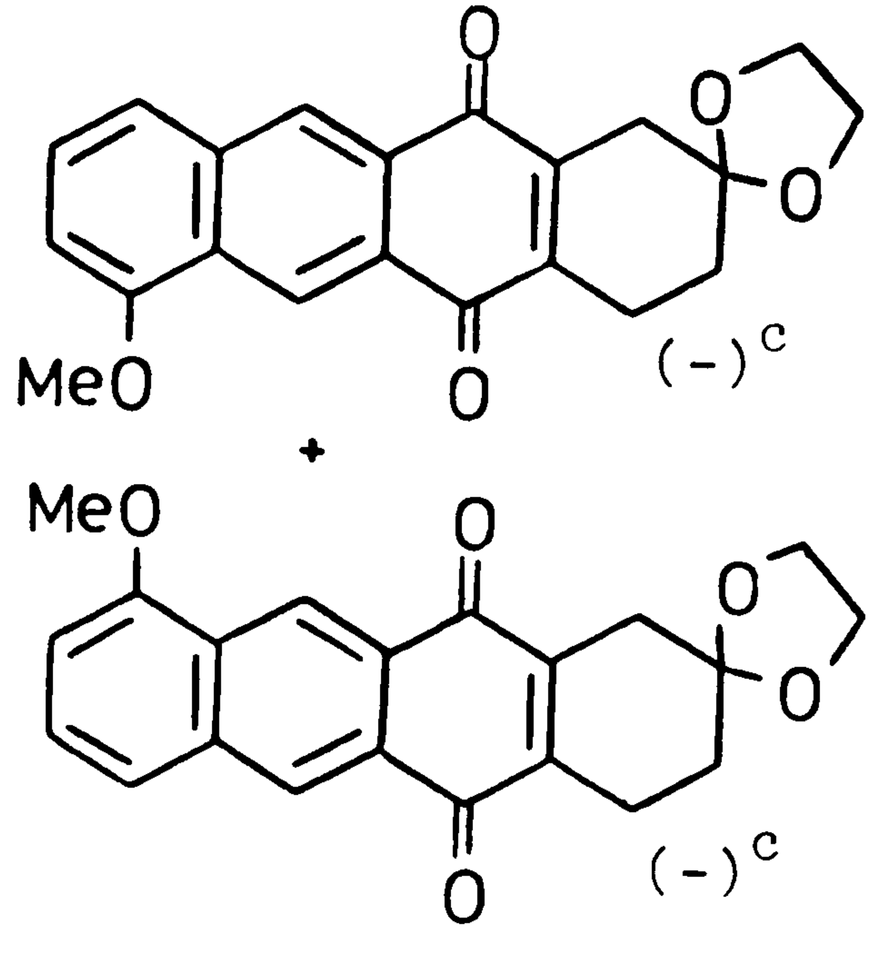


229

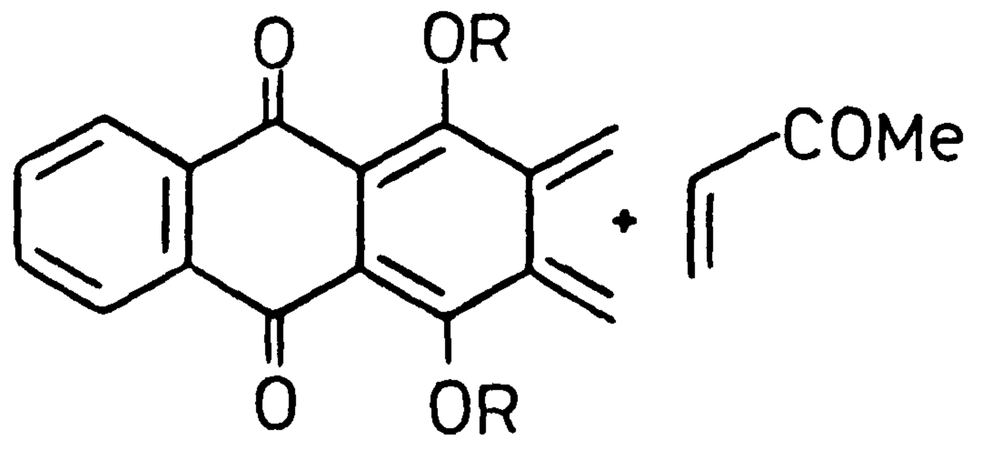
7



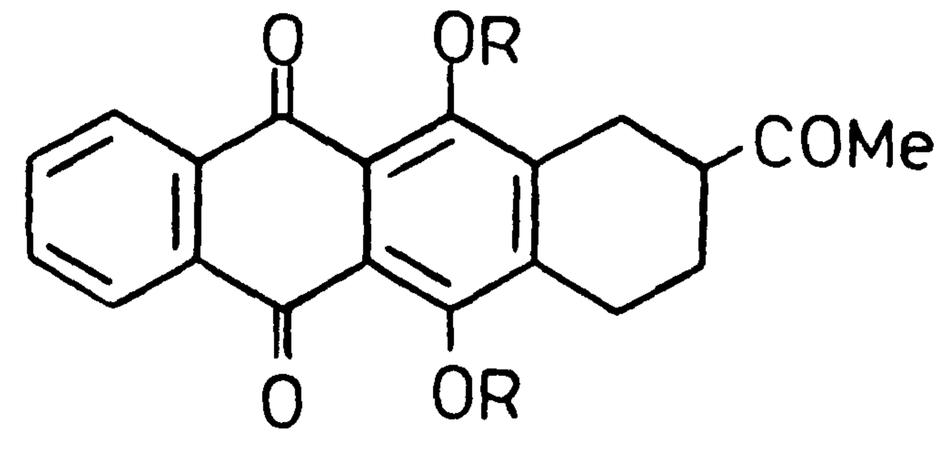
a



229



b



	R		
8	Me	(28)	230
9	H	(52)	230

a. The substrate was generated from the benzocyclobutene.

b. The substrate was generated by dehalogenation of the bis(bromomethyl) derivative.

c. The product yield was not stated.

RESULTS AND DISCUSSION

2. THE GENERATION AND CHEMISTRY OF o-AZAXYLYLENES

BENZAZETIDINES AS PRECURSORS TO o-AZAXYLYLENES

2.1 INTRODUCTION

Benzocyclobutenes have become established as extremely useful intermediates in organic synthesis because of the ease with which they may be functionalised, and their ready conversion to transient o-xylylenes.

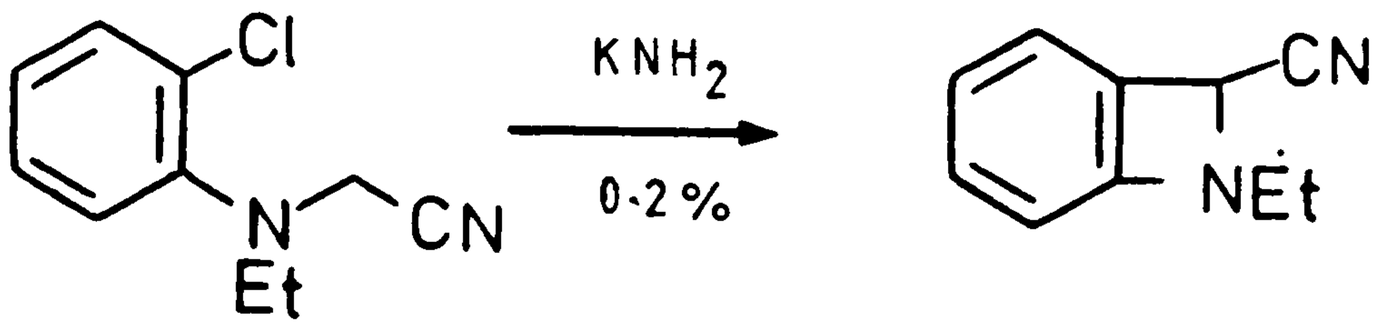
In contrast, benzazetidines despite their potential in the synthesis of polycyclic natural products, are virtually unknown. They are the ideal precursors to o-azaxylylenes as they can be used to generate these systems both in solution and in the gas phase. As was discussed previously in the Introduction, a good way of forming benzocyclobutenes is ring closure of o-xylylenes but this seems to be limited to those systems generated in the gas phase.

In solution, other reactions such as dimerization, tend to occur in preference to ring closure. There are only two reports of ring closure of o-azaxylylenes to benzazetidines (see page 86 for a brief discussion). In all other cases it has proved to be entirely unsuccessful. However, a number of different approaches have been used to produce a limited number of these elusive heterocycles and these are outlined briefly below.

2.2 FORMATION OF BENZAZETIDINES BY BASE INDUCED ARYNE CYCLIZATION

Jaquès and Wallase[233] have reported that treatment of

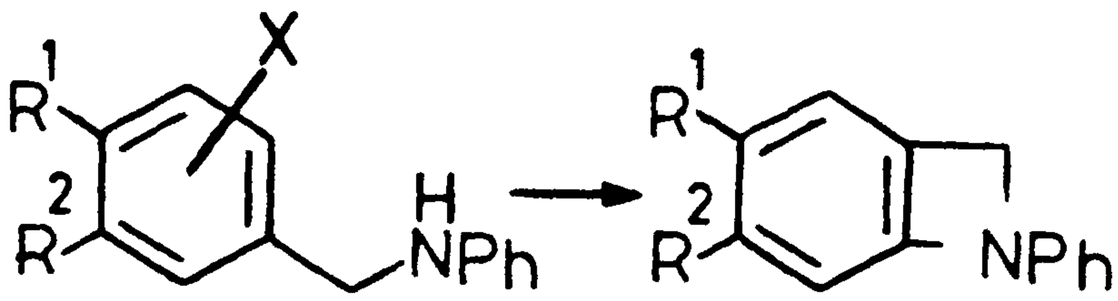
amine (382) with potassium amide gave a trace of a product which was tentatively assigned the structure (383). The low yield of benzazetidine (383) was thought to be due to nucleophilic attack and ring opening by potassium amide but no attempts to avoid this by using a more hindered base such as LDA or LTMP were reported.



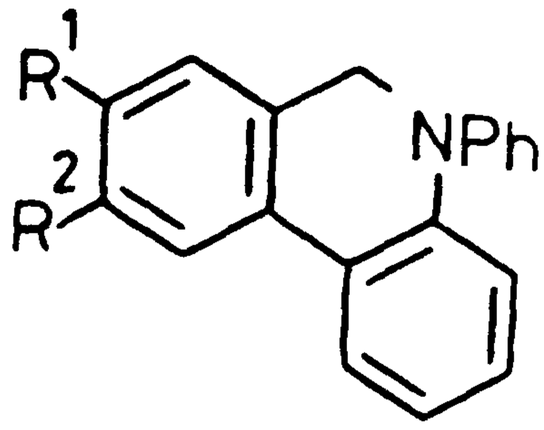
(382) (383)

Interestingly, an analogous reaction gives the cyanobenzocyclobutene in 70% yield[11] (reaction (a), Scheme 2, page 9). It has also been reported[234] that treatment of (384) with potassium amide gave a low yield of benzazetidine (385) together with dihydrophenanthridine (386). However, it was found that at least one alkoxy group is necessary in either the four or five position for formation of the benzazetidine as shown by the exclusive formation of phenanthridine (386, $R^1 = R^2 = H$), from unsubstituted precursor (389).

This reaction was later investigated by Manley[235] who attempted to block the formation of phenanthridine by introducing methyl groups at the ortho positions of the phenyl ring. The reaction afforded the amine (391, 5%) together with an oil which was tentatively assigned the benzazetidine structure (392, 8%).



(385)



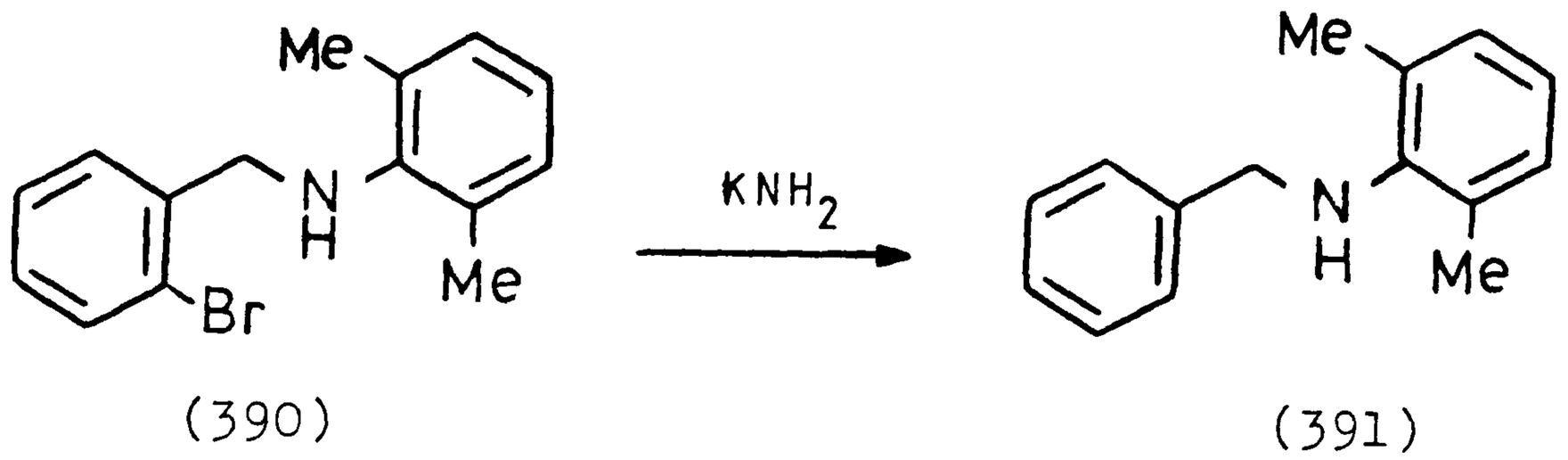
(386)

(384) X = 2-Cl, R^1 = H, R^2 = OMe

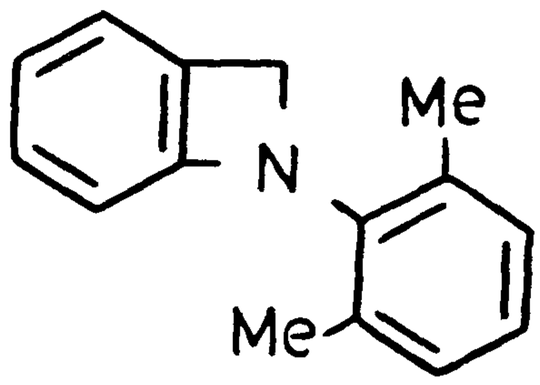
(387) X = 3-Br, R^1 = OMe, R^2 = OMe

(388) X = 3-Br, R^1, R^2 = O-CH_2-O

(389) X = 3-Br, R^1 = R^2 = H



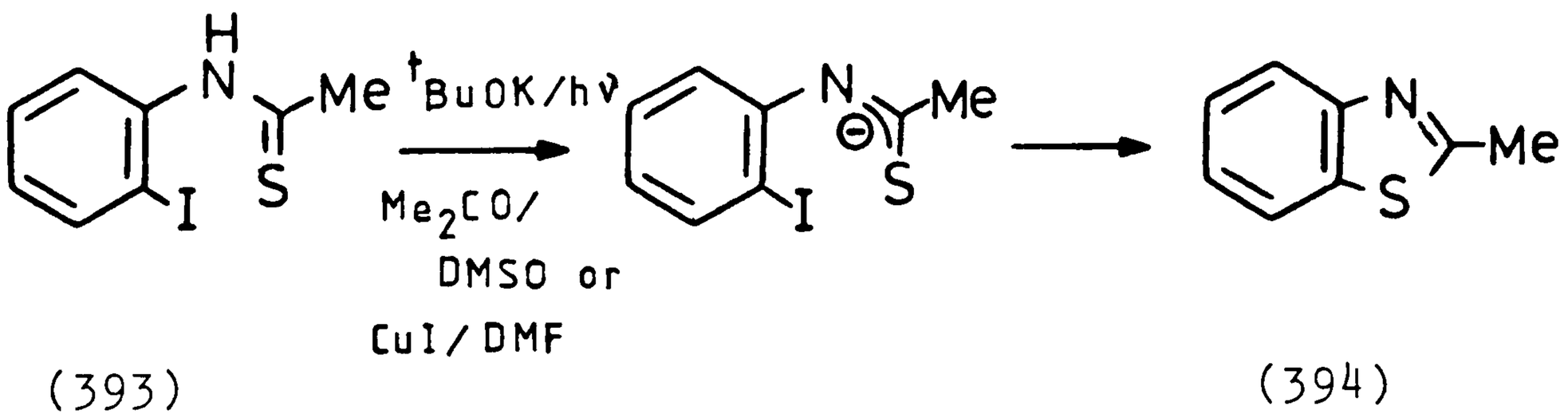
(390) (391)



(392)

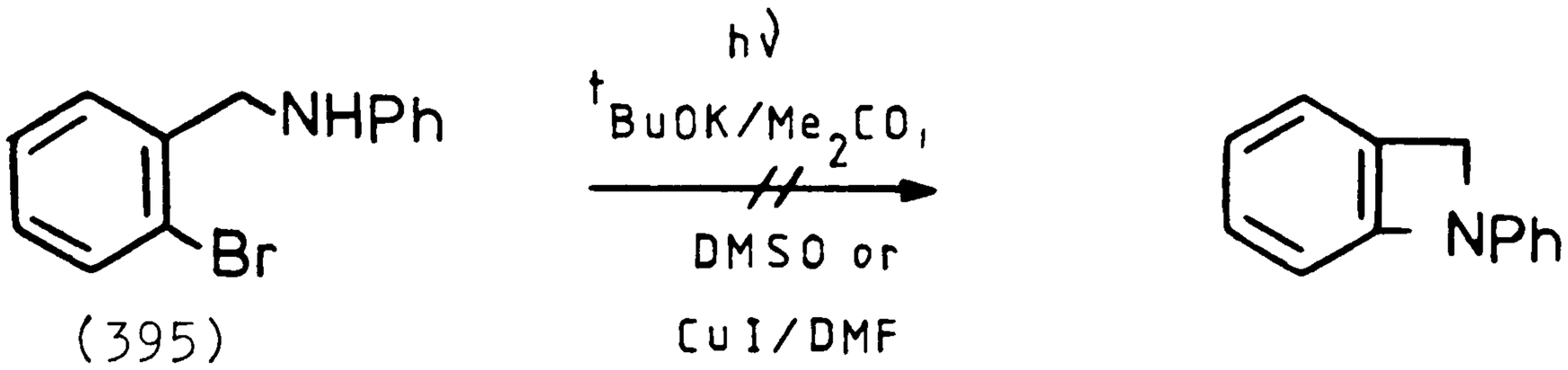
Bowman[236] has reported that the o-halothioamides (393) can be cyclized to benzothiazoles (394) in high yield by treatment with base under free-radical initiation conditions (a reaction likely to involve an $S_{RN}1$ mechanism). For example, irradiation of a solution of (393), together with potassium tert-butoxide and acetone, whose enolate is known to promote $S_{RN}1$ reactions,[237] in DMSO gave (394) in quantitative yield. It was also found that treatment of (393) with base in the presence of copper (I) iodide as the free radical initiator gives (394) in 70% yield.

It was hoped that this anion-entrainment method may prove successful for the cyclization of o-halobenzylamines to form the smaller benzazetidine ring.

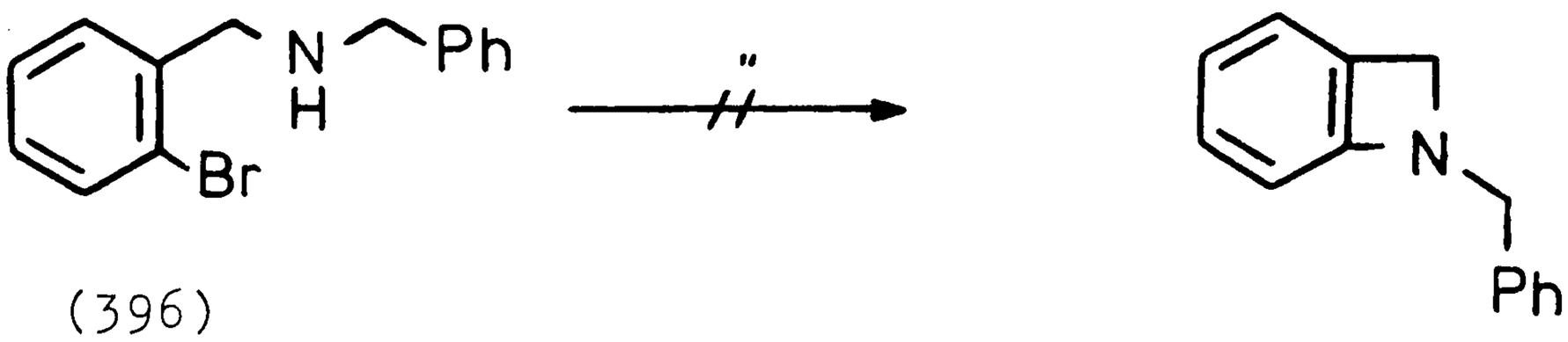


(393) (394)

However, treatment of the N-phenylbenzylamine (395) and the dibenzylamine (396) under both types of anion-entrainment conditions mentioned above gave only starting material despite prolonged reaction times.



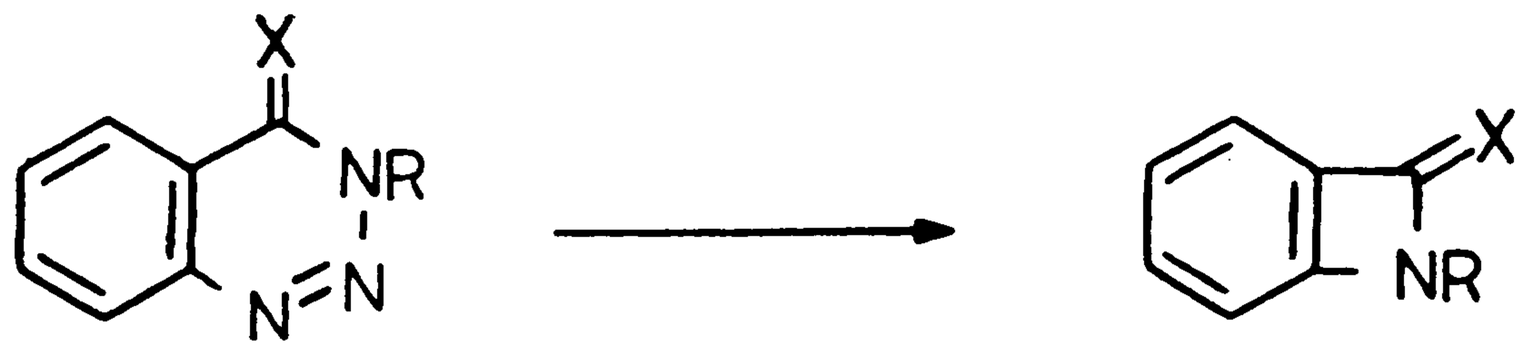
(395)



(396)

2.3 FROM FRAGMENTATION OF DIHYDROBENZOTRIAZINES

The most successful approach to benzazetidines is fragmentation of 3,4-dihydro-1,2,3-benzotriazines. This method was used for the formation of the first reported benzazetidine (95) in 50% yield by the photochemical elimination of nitrogen from benzotriazine (397).[95] A similar approach was used for the generation of benzazetidinone (399).[238] Noyce[239] has also investigated the potential of 1,2,3-benzotriazines and has found that other functionalized benzotriazines are, at best, extremely inefficient for the formation of benzazetidines.



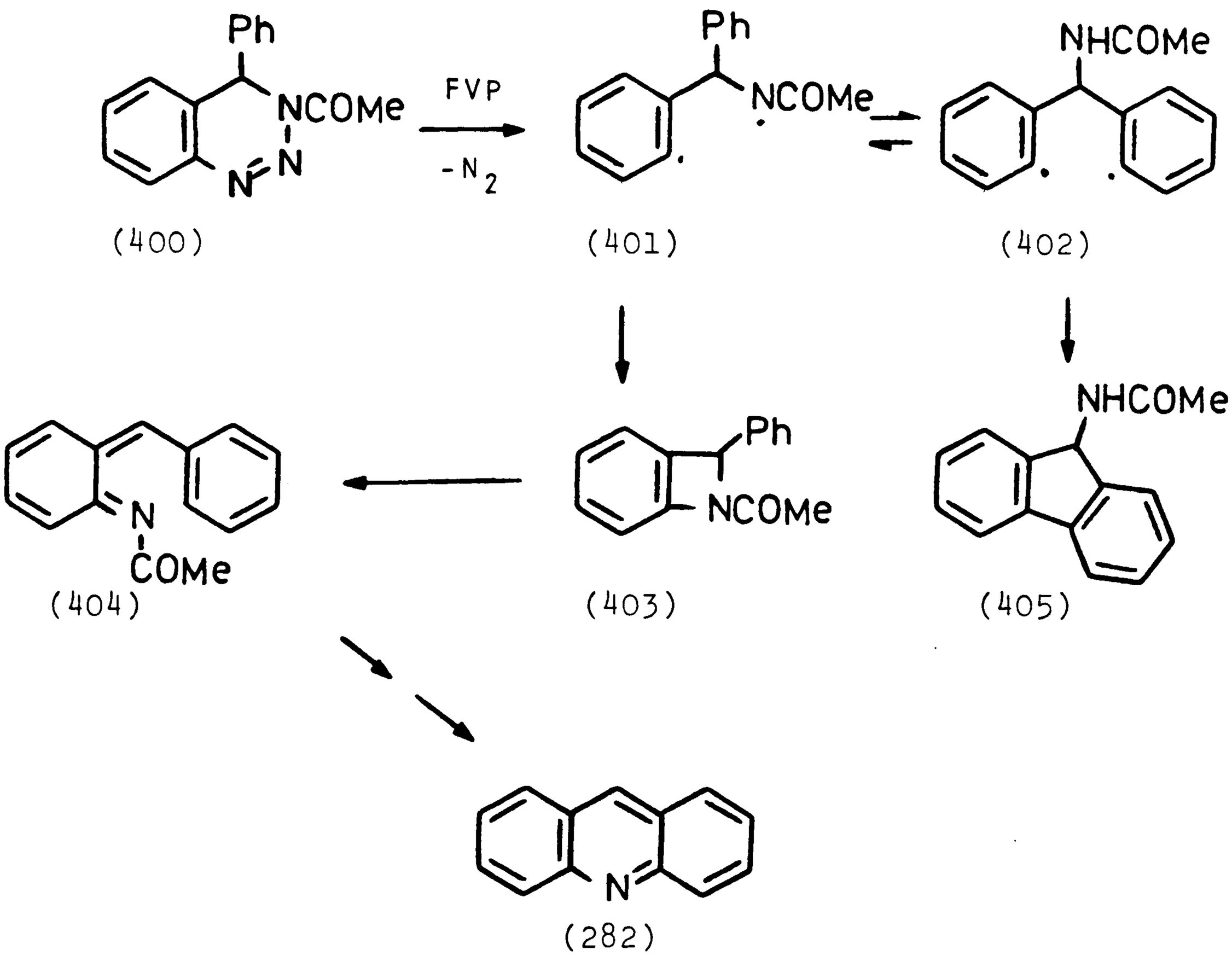
(397) X = H_2, R = Ph

(398) X = O, R = adamantyl

(95) X = H_2, R = Ph

(399) X = O, R = adamantyl

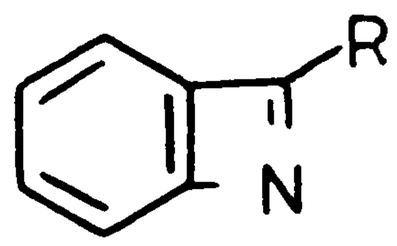
For example, FVP of N-acyl triazine (400) gives acridine (282) and acetamidofluorene (405) in 18% and 10% yields respectively. The formation of acridine most reasonably occurs via ring closure of diradical (401) formed from loss of nitrogen from the triazine to give N-acetylbenzazetidine (403) which ring opens to o-azaxylylene (404). This then undergoes electrocyclization with dehydrogenation of the initial dihydro-species to give acridine. The fluorene derivative (405) is probably derived from cyclization of diradical (402) via the phenyl ring.



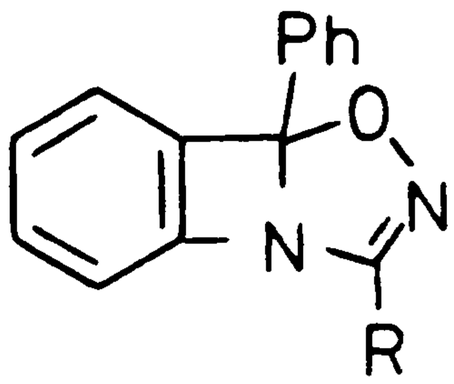
In contrast to the photolysis of N-phenylbenzotriazine reported by Burgess,[95] photolysis of (400) did not give any benzazetidine derived products.[239] Therefore, although 1,2,3-benzotriazines can give rise to isolable benzazetidines the difficulty in the synthesis of these compounds coupled with their inefficiency as benzazetidine precursors led us to abandon this approach.

2.4 FROM BENZAZETES

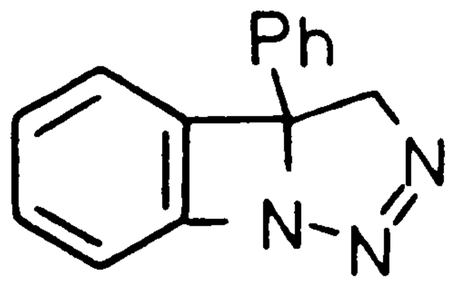
The benzazete system (406) is a potential precursor to benzazetidines by functionalization of the imine double bond. Indeed, the initial cycloadducts from reaction with dienes and 1,3-dipoles are all benzazetidines, but only those from nitrile oxides (407),[240] diazomethane (408),[241] and diphenylisobenzofuran (409)[242] are isolable although these too decompose on heating or attempted chromatography. However attempts to produce benzazetidines by reaction of benzazetes with either nucleophiles[239] or reducing agents[243] failed. The instability of these adducts coupled with the relative inaccessability of benzazetes severely limits this approach to benzazetidines and again we did not pursue this route further.



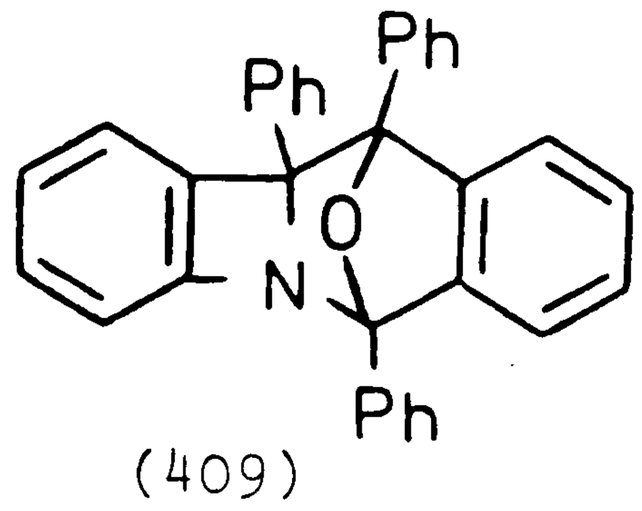
(406)



(407)



(408)



(409)

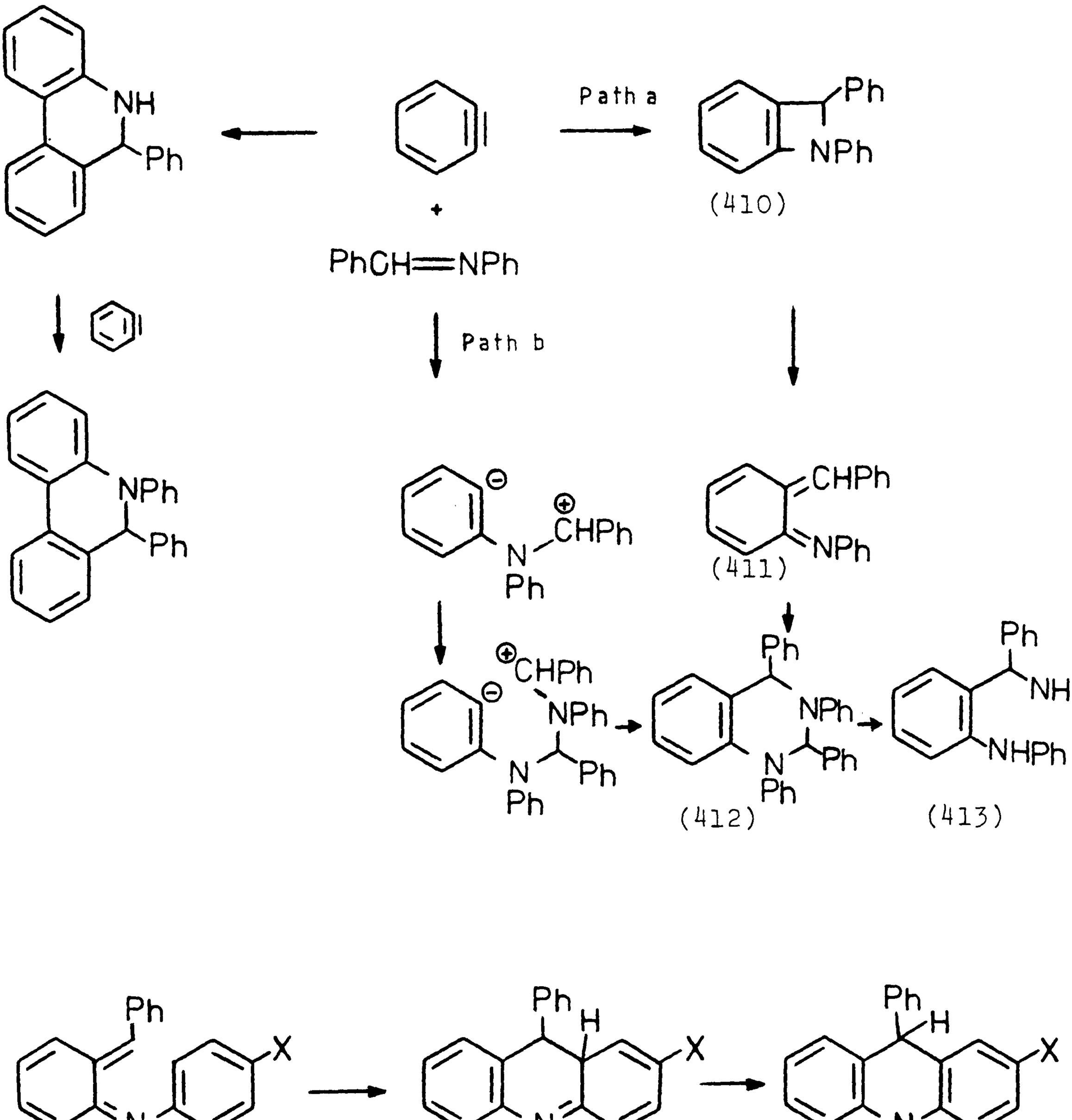
2.5 BY [2+2] REACTION OF BENZYNE WITH IMINES

One obvious approach to benzazetidines is by [2+2] cycloaddition of benzyne to imines, but so far only one claim for this reaction has appeared. Thus in 1975 Nakayama[244] and his co-workers isolated N- α-(o-anilinophenyl)benzyl aniline (413) from the thermal decomposition of benzenediazonium carboxylate in the presence of N-benzylideneaniline. This was interpreted in terms of [2+2] addition to give diphenylbenzazetidine (410) which underwent spontaneous ring opening to o-azaxylylene (411) and trapping with more N-benzylideneaniline to give the tetrahydroquinazoline derivative (412). This suffered hydrolysis to the observed diamine during chromatographic work-up (path a). Whilst this explanation is plausible, isolation of the diamine (413) does not constitute unambiguous evidence for the intervention of a benzazetidine since the

proposed tetrahydroquinazoline could also, reasonably, arise by a stepwise, [2+2+2] addition of the imine to benzyne (path b). Furthermore, it has been observed in these laboratories,[157] and by others,[64] that both N and C-phenyl substituted azaxylylenes can undergo electro-cyclization reactions to give dihydroacridines, and acridines. This led us to expect that the claimed intermediate (411) might also undergo electrocyclization to give dihydroacridine derivatives.

Therefore, it was decided to reinvestigate[245] this reaction with a view to establishing firm evidence for the intermediacy of benzazetidines and with the ultimate objective of finding conditions which would permit their isolation.

Decomposition of benzenediazonium carboxylate in boiling dichloroethane in the presence of benzylidineaniline gave a complex mixture which on chromatography on alumina gave, in addition to the diamine (413) and diphenyl-dihydrophenanthridine reported by Nakayama, 5,10-diphenyl-dihydroacridine (417, X = H), (5%). This last product can be explained by electrocyclization involving the N-phenyl group in the azaxylylene (411, X = H), followed by H-tautomerism and phenylation with benzyne. This mechanism for formation of the acridine rather than interception of the azaxylylene with benzyne, was confirmed by the isolation of 2-chloro-5,10-diphenyldihydroacridine (417, X = Cl), (1%), and 2-chloro-10-phenylacridine (416, X = Cl), (3%) in the similar reaction of N-benzylidine-4-


NH
Ph
Path a
Ph
NPh
(410)
PhCH=NPh
Path b
NPh
Ph
CHPh
N
Ph
CHPh
NPh
(411)
Ph
NPh
N
Ph
(412)
Ph
NHPh
NHPh
(413)
X
N
(411)
Ph
H
(414)
(415)
H
Ph
(416)
(417)

SCHEME 7

chloroaniline with benzyne. These arise from the intermediate dihydroacridine (415, X = Cl) by phenylation and dehydrogenation respectively; 2-chloro-5,6-dihydro-5,6-diphenylphenanthridine (9%) was also isolated from this reaction.

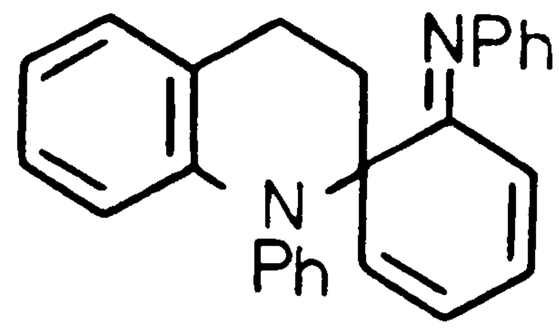
In the formation of dihydroacridines via azaxylylenes (411), electrocyclization clearly involves the N-phenyl rather than the C-phenyl substituent as shown by the exclusive formation of chloroacridine (416), indicating that this more readily adopts the required Z-configuration as only this configuration allows electrocyclization to acridines. As mentioned earlier (page 88), N, and C-phenyl azaxylylenes, when generated flash pyrolytically, electrocyclize to give high yields of acridines.[64,157] However, when the benzazetidine (95) is heated in solution (up to 200°C) only azaxylylene dimer (169) is obtained and no dihydroacridine is formed.[246] Presumably, in solution there is insufficient thermal energy to give enough Z-azaxylylene (96a) to allow electrocyclization to compete with dimerization. The Z-azaxylylene is postulated to be a higher energy configuration than the E-form due to steric interaction between the substituent and the azaxylylene system. In the gas phase at high temperatures, dimerization is suppressed and ample energy is available for E - Z isomerization (96a $\rightleftharpoons$ 96b). In these benzyne additions, conversion of the initial diarylbenzazetidines (410) into dihydroacridines in solution at 80°C indicates that a conjugating (or see below, electron releasing)

group on carbon facilitates the E - Z configurational changes required to convert the sterically more favoured E-azaxylylene into the Z-isomer.

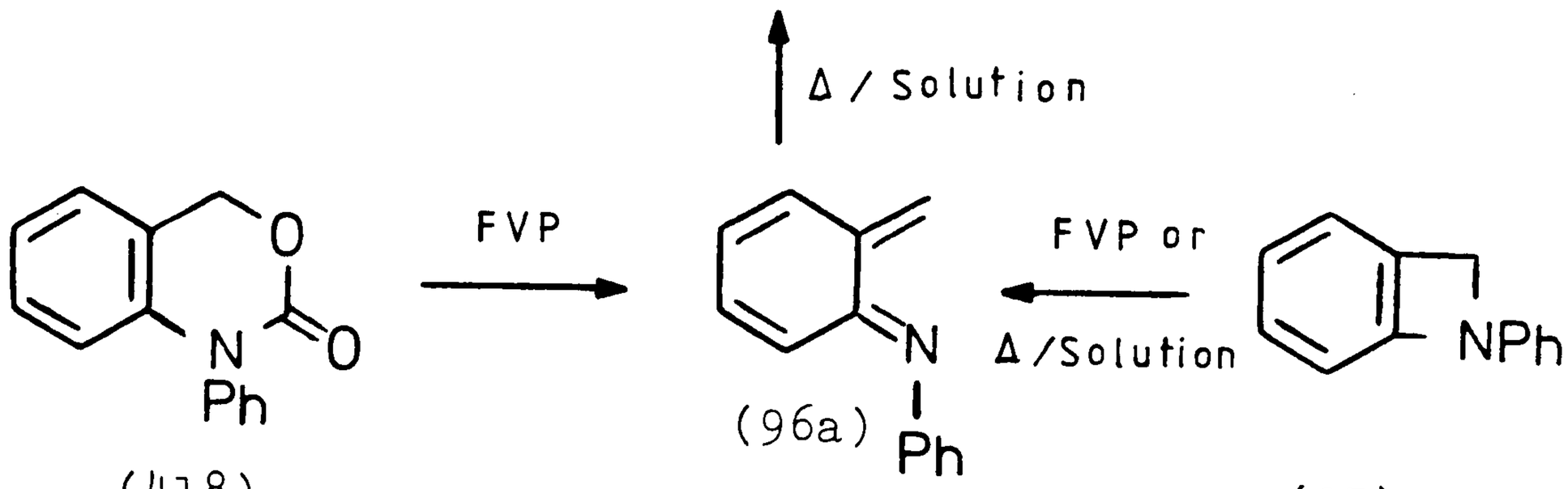
Generation of benzyne in the presence of N-benzylidene-ethylamine (419) gave N,N-diphenylethylamine in 13% yield as the only characterisable product, there being no evidence for formation of a benzazetidine. Because traces of water are inevitably present in the generation of benzyne from the diazonium carboxylate, this amine possibly arises by phenylation of ethylamine produced by hydrolysis of the imine. Alternatively, N-phenylation of the imine would give an immonium cation which would be especially susceptible to hydrolysis leading to phenyl-ethylamine which could then undergo further phenylation.

These encouraging preliminary results prompted us to investigate the reaction of benzyne with the amidine (420) in anticipation of a more efficient addition with this relatively electron-rich imine. Generation of benzyne from benzenediazonium carboxylate in boiling 1,2-dichloro-ethane in the presence of (420) gave N-phenylanthranaldehyde (421) in 8% yield and acridine (282) in 17% yield after chromatography.

The formation of acridine clearly provides further evidence for a [2+2] addition to give benzazetidine (423) which, because of the vigorous conditions used for benzyne generation, undergoes spontaneous ring opening to a transient azaxylylene (422) followed by electrocyclization and aromatization of the resulting dimethylaminodihydroacridine.



(169)

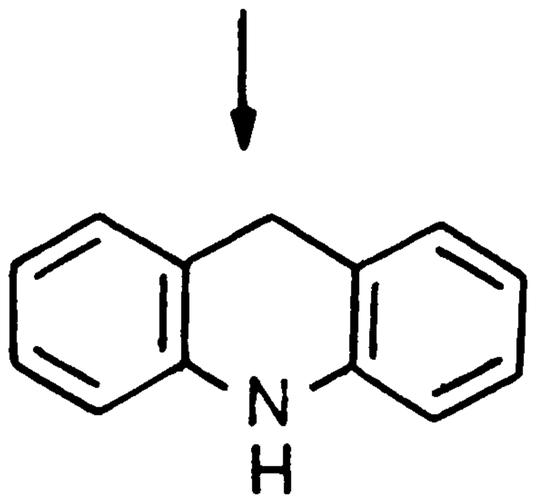


(418)

(96a)

(95)

(96a)

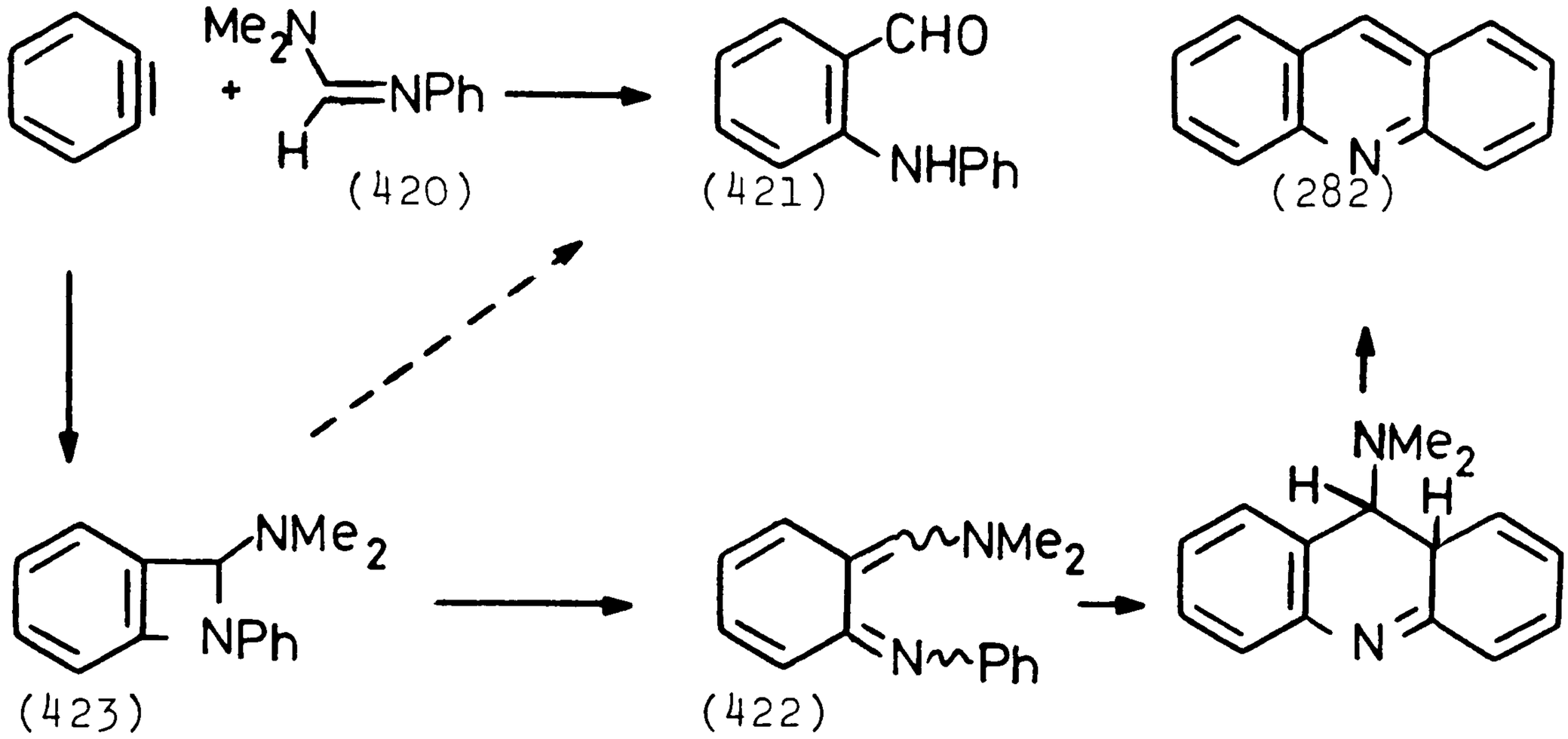


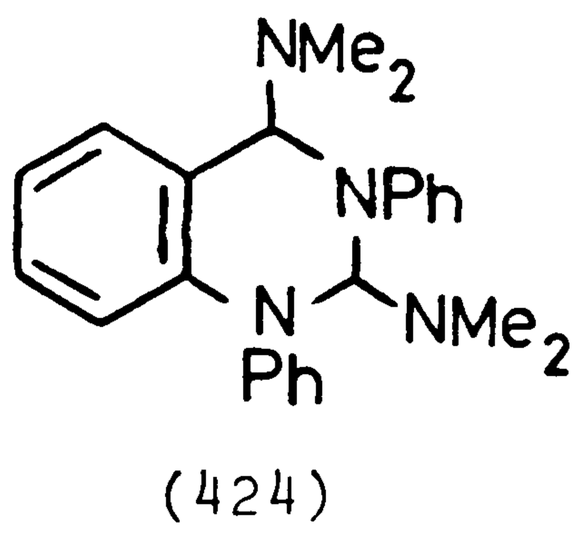
(281)

(419)

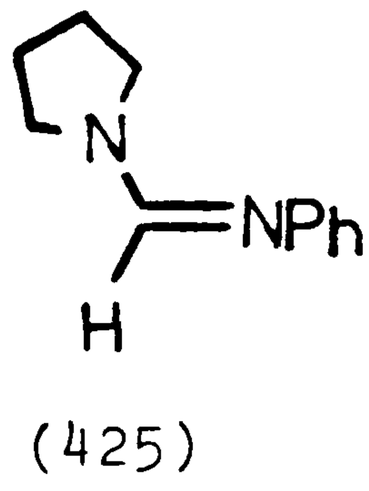
The amino-aldehyde (421) could have arisen by hydrolysis of the tetrahydroquinazoline (424) which in turn could be formed by addition of azaxylylene (422) to amidine or by [2+2+2] addition of amidine to benzyne. When the generation of benzyne was carried out at 55°C, the ratio of amino aldehyde (421) (16%) to acridine (282) (10%) was increased possibly suggesting that at this lower

temperature, more benzazetidine survives to suffer ultimate hydrolysis to the amino aldehyde on work-up. Acridine (282) (15%) and amino aldehyde (421) (6%) were similarly obtained from the amidine (425). The imidate (426) also gave acridine in 3% yield.

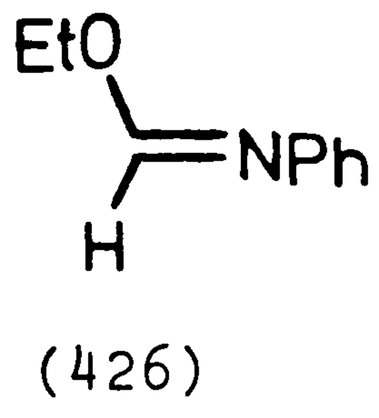




(424)



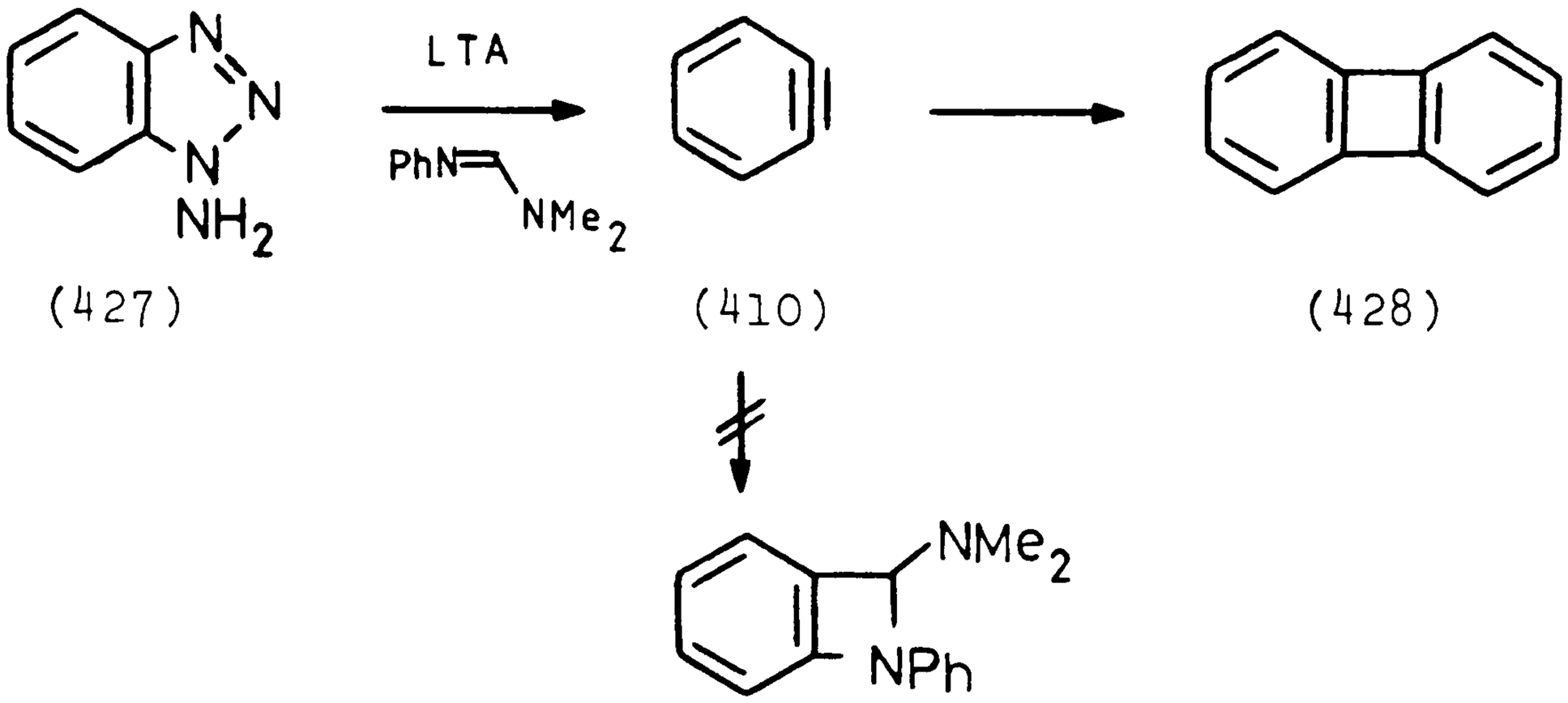
(425)



(426)

Although these experiments establish that [2+2] addition of benzyne to imines does occur, no benzazetidines can be isolated and the maximum combined yield of benzazetidine-derived products (ca. 30%) indicates that the reaction is inefficient. We, therefore, decided to investigate both the generation of benzyne at lower temperatures, and the generation of more reactive, substituted benzynes in the presence of amidine to see if the efficiency of the reaction could be further increased. Campbell and Rees[247] have described a mild method of generating benzyne from the oxidation of the readily available 1-aminobenzotriazoles with lead tetra-acetate. Oxidation of 1-aminobenzotriazole (427) in the presence of N,N-dimethyl-N'-phenylformamidine in dichloromethane at room temperature gave a dark brown oil from which biphenylene (428) was obtained in 23% yield as the only characterizable product. Repeating this reaction at -78° again produced a dark brown oil, but which failed to yield any identifiable products. Control experiments established that there is no reaction between 1-amino-benzotriazole and the amidine nor is there reaction between the above amidine and lead tetra-acetate under the reaction conditions.

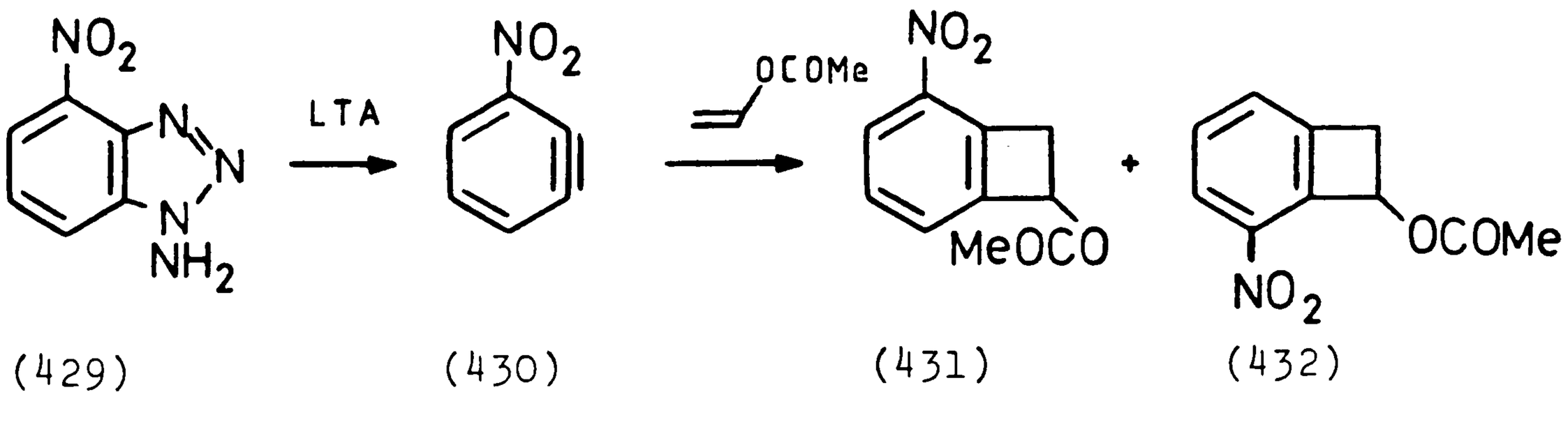
It therefore seems that at room temperature or lower, the [2+2] reaction of benzyne with the amidine is now so inefficient, that it cannot compete with the dimerization of benzyne to biphenylene.



(427) (410) (428)

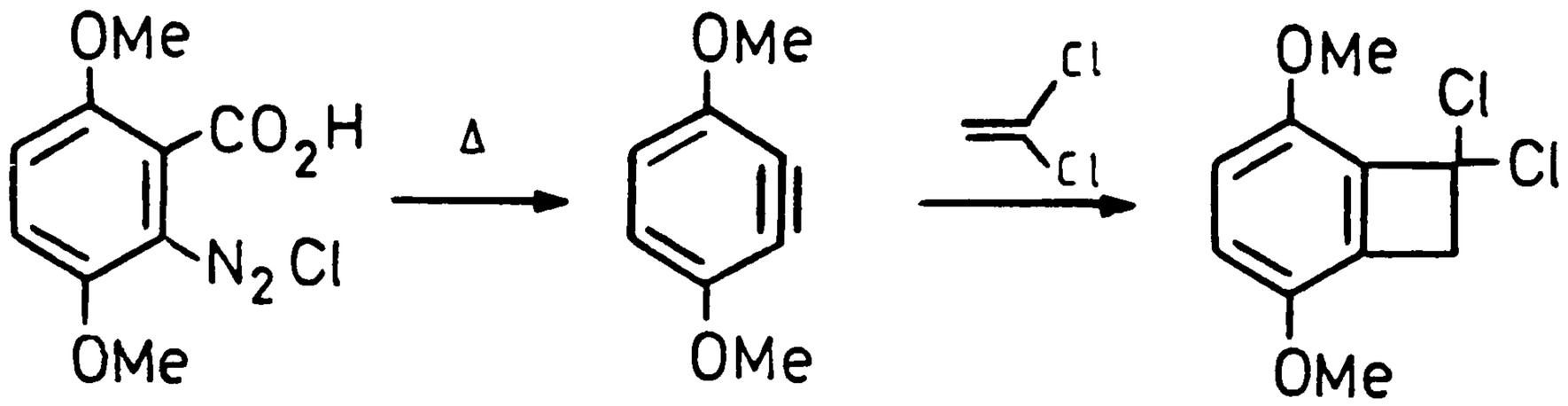
(423)

Atkins[248] has investigated the reactivity of a series of substituted benzynes towards olefins and has found 3-nitrobenzyne (430) exhibits the highest degree of reactivity towards unsaturated bonds. For example, when generated from oxidation of 1-amino-4-nitrobenzotriazole (429), 3-nitrobenzyne in the presence of vinyl acetate, produced a mixture of the benzocyclobutenes (431) and (432) in 51% yield with (431) being the dominant isomer.



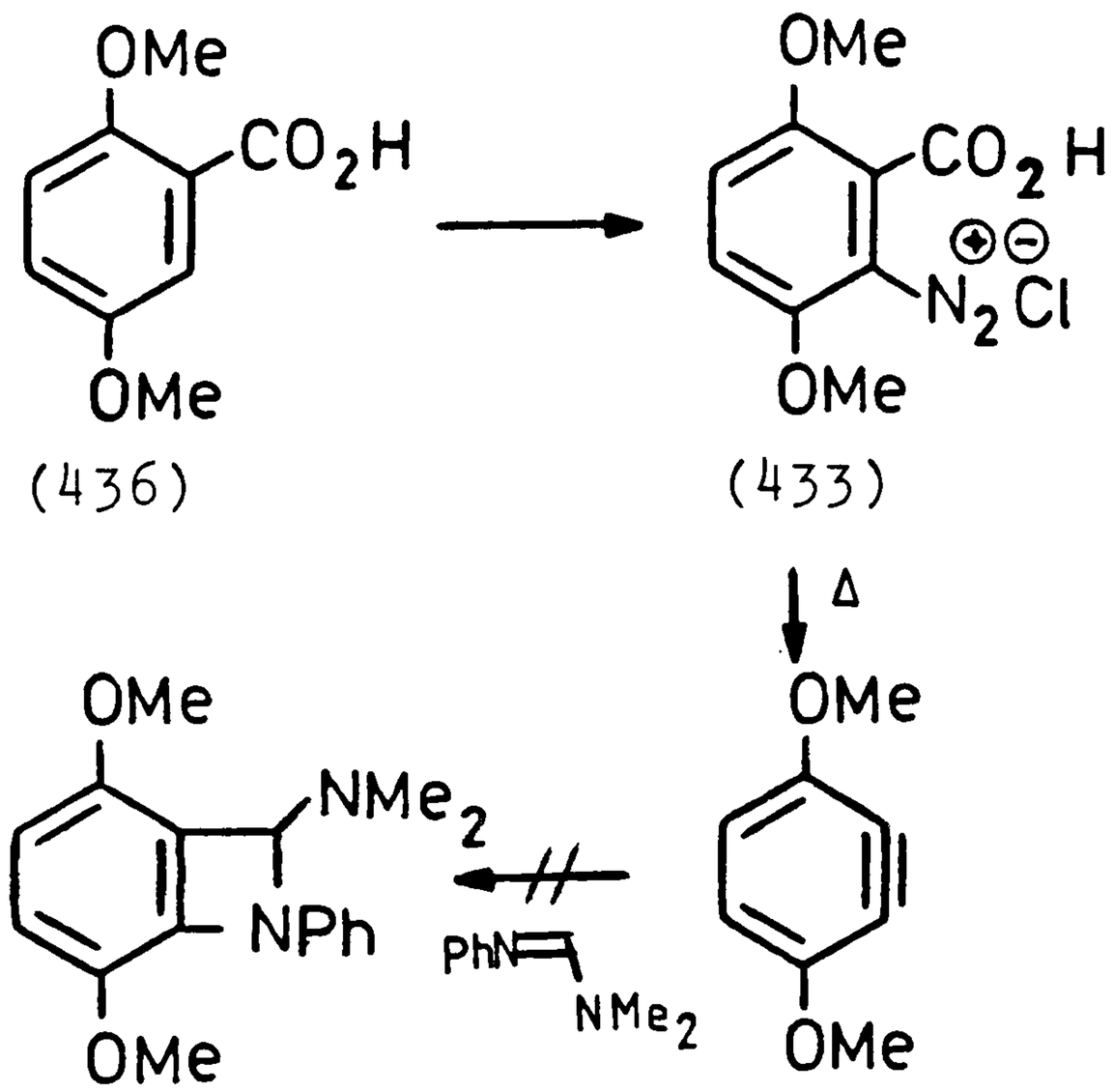
(429) (430) (431) (432)

It was therefore hoped that in generating this very electron-deficient species in the presence of an electron rich imine at low temperatures, an efficient [2+2] reaction would occur to form the corresponding benzazetidine which may then be isolated. Benzotriazole was nitrated with a mixture of concentrated nitric and sulphuric acids at $0^{o}C$ to give 4-nitrobenzotriazole in good yield.[248] This was then aminated using hydroxylamine-O-sulphonic acid[249] to give a 1:1 mixture of 1-amino-4-nitro, and 1-amino-7-nitrobenzo triazoles as judged by the comparison of the ^{1}H n.m.r. spectrum of this mixture with that of authentic samples.[248] The addition of lead tetra-acetate to a solution containing the isomeric mixture of benzotriazoles and the amidine in dichloromethane at $-78^{o}C$ resulted in vigorous effervescence and a dark brown oil was obtained after work-up. However, thin layer chromatographic analysis revealed this to be an extremely complex mixture, and chromatography on alumina gave recovered amidine (14%) as the only characterizable product, and no benzatidines ortheir derived products. Recently, Wallace and co-workers[250] reported that decomposition of diazonium carboxylate (433) in the presence of 1,1-dichloroethene gave benzocyclobutene (435) in 80% yield. It was hoped that the remarkable efficiency with which benzyne (434) adds to olefins would also apply in its addition to amidines.



(433) (434) (435)

The benzyne precursor (433) was prepared by the literature procedure[251] in three steps from 3,6-dimethoxybenzoic acid (436). Disappointingly, however, decomposition of hydrochloride (433) in boiling 1,2-dichloroethane in the presence of the amidine gave a complex mixture. Chromatography on silica gave recovered amidine (64%) as the only characterizable product.



(436) (433) (437)

In conclusion, there is good evidence that benzazetidines are indeed the initial adducts from benzyne [2+2] cycloadditions to imines. However, under the conditions where addition takes place, it was not possible to isolate them, but products which could only have been derived from the subsequent reactions of these initial benzazetidines were obtained.

It therefore seems that [2+2] cycloaddition reactions of benzynes to imines are generally not a useful synthetic route to benzazetidines, or the valence tautomeric o-azaxylylenes.

2.6 FUNCTIONALIZATION OF FUSED AZETIDINES

All of the methods described previously for the preparation of benzazetidines have depended on the formation of the four-membered ring onto an already existing benzene nucleus. However, it was felt that the alternative approach of formation of an aromatic ring onto a preformed azetidine ring might merit investigation (Figure 3).

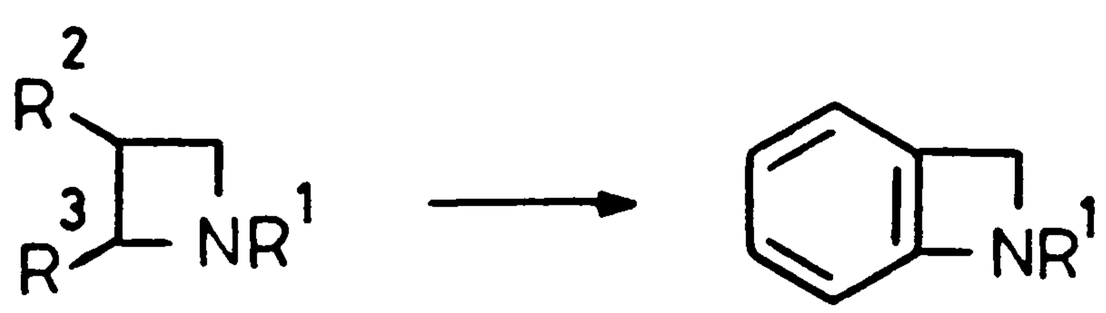
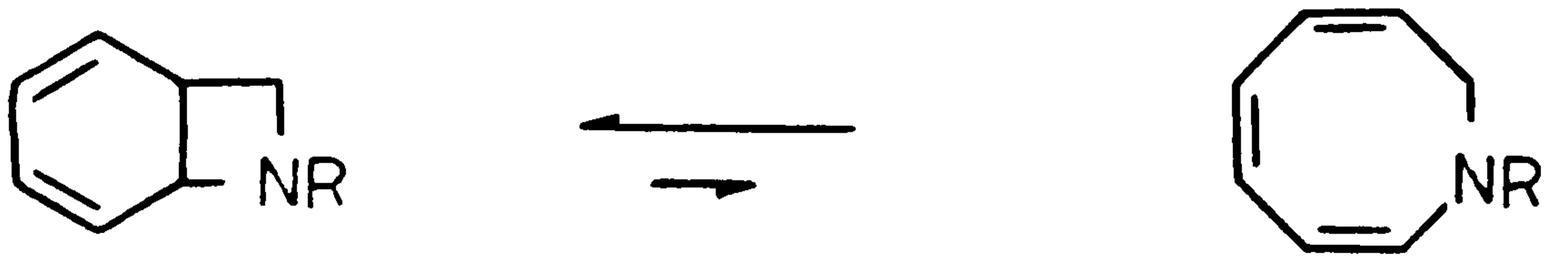


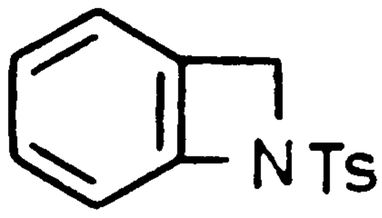
FIGURE 3

In fact, Paquette[252] appears to have come close to achieving this objective whilst studying the 1-aza-2,4,6-

cyclooctatriene (438)/7-azabicyclo[4.2.0]octadiene (439) valence tautomeric equilibrium.



(438) (439)

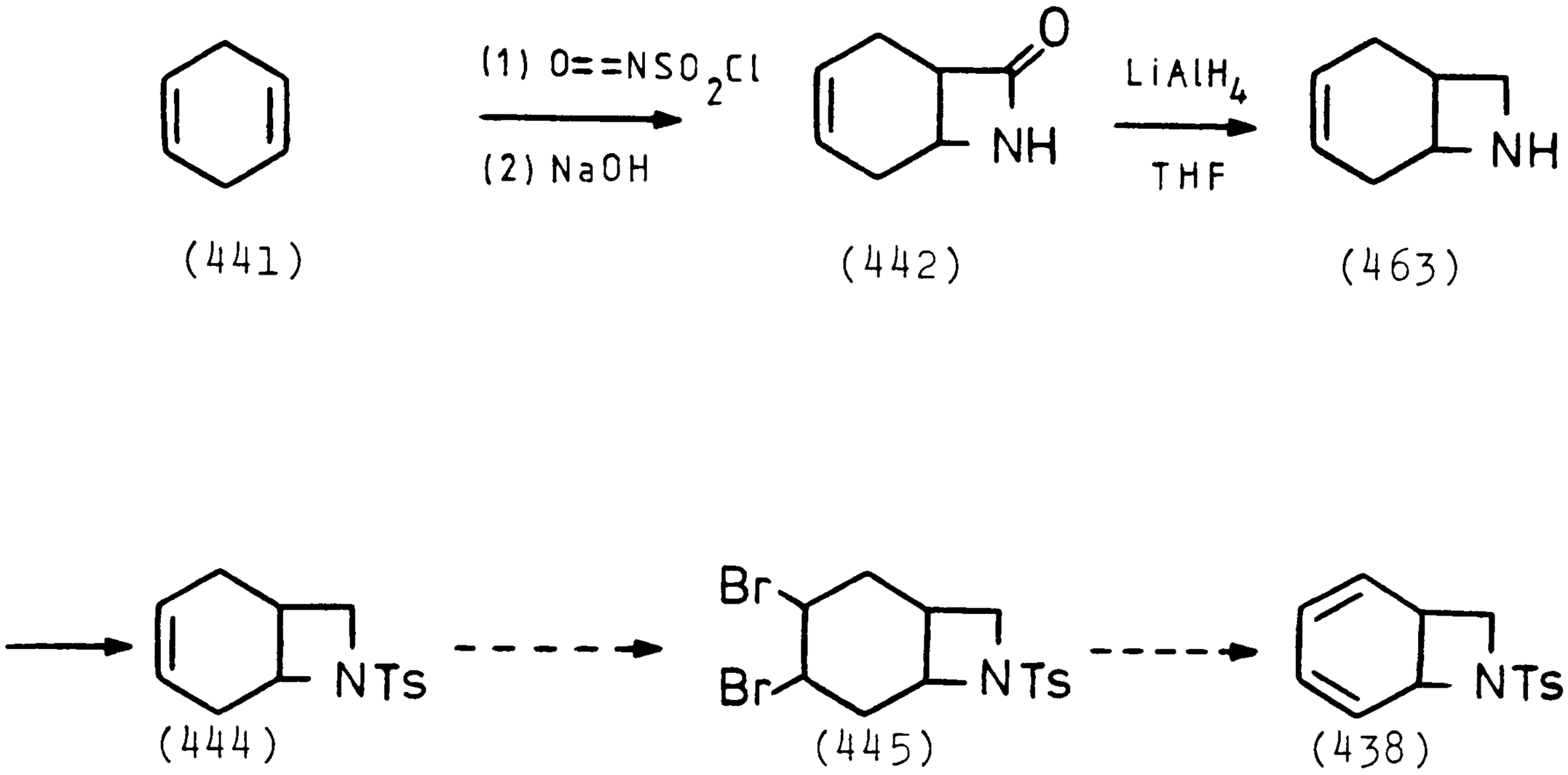


(440)

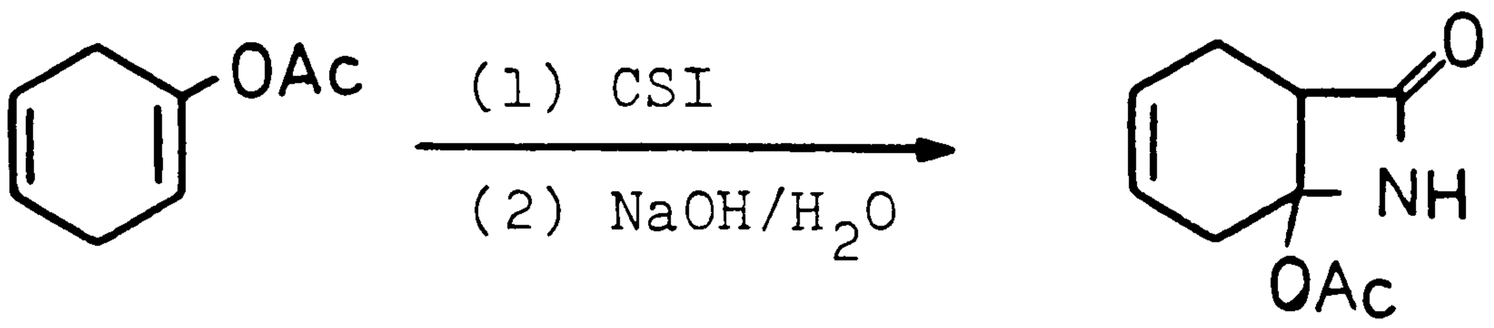
He reported that at temperatures below 100°C in the absence of air, azetidine (438, R = Ts) is a stable crystalline solid. Thus it should be possible to dehydrogenate (438) to give N-tosylbenzazetidine (440).

The attempted synthesis of azetidine (438) follows the previously described route.[252] Reaction of 1,4-cyclohexadiene (441) with chlorosulphonylisocyanate in benzene at 74°C followed by hydrolysis of the initially formed N-chlorosulphonyl lactam gave azetidinone (442) in moderate yield after distillation. Reduction of this lactam with lithium aluminium hydride in THF gave azetidine (463). Reaction of (463) with TsCl in aqueous sodium hydroxide gave sulphonamide (444) in 20% yield. However, because of the low yield of this step, insufficient material was at hand to make dibromide (445) and thus azetidine (438).

In fact, certain cyclic monoenes have been converted in high yield to fully aromatised products using activated manganese dioxide.[253] An attempt was, therefore, made



to dehydrogenate (444) directly to benzazetidine (440). However, even prolonged treatment of tosylate (438) with activated manganese dioxide led to complete recovery of starting materials. This route may, however, be worth reinvestigating as it should be possible to perform the reaction sequence on a large scale and, therefore, allow a variety of methods for dehydrogenation of azetidine (438) to be attempted. Vinyl esters are known to react with CSI to give good yields of the corresponding β-lactams.[254] Therefore a possible variation would be the reaction of CSI with vinyl ester (446) to give lactam (447). This now places a leaving group at one of the bridgehead carbons and thus opens up the possibility of introducing unsaturation at this position by elimination of acetic acid.



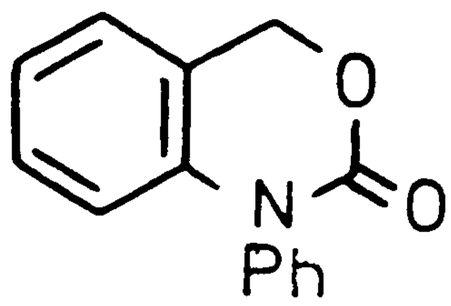
(446) (447)

3. THE FLASH VACUUM PYROLYTIC GENERATION OF o-AZAXYLYLENES

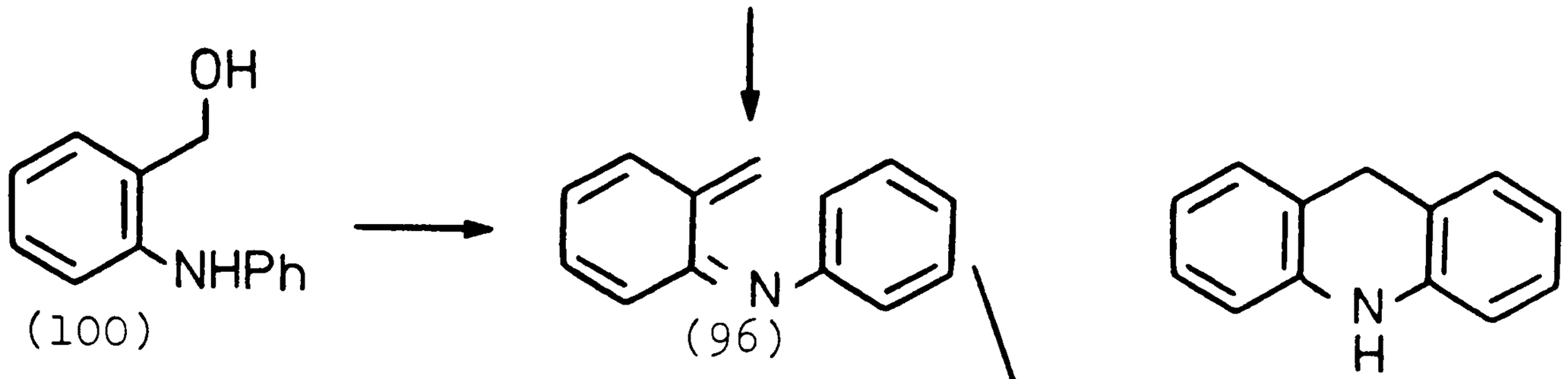
INTRODUCTION

Early work in these laboratories by Glasbey[243] and Davies[255] had established flash vacuum pyrolysis as a powerful technique for the efficient generation of o-azaxylylenes from simple, readily available precursors. Thus flash vacuum pyrolysis of N-phenyl-2-aminobenzyl alcohol (100) results in the formation of acridine (282) and dihydroacridine (281) in good yield, presumably by dehydration to give azaxylylene (96) which undergoes electrocyclization to give the observed products (see also page 88). Similarly, pyrolysis of the C-phenyl amino alcohol (448) gives a good yield of acridine,again presumably by electrocyclization of the C-substituted o-azaxylylene (449).

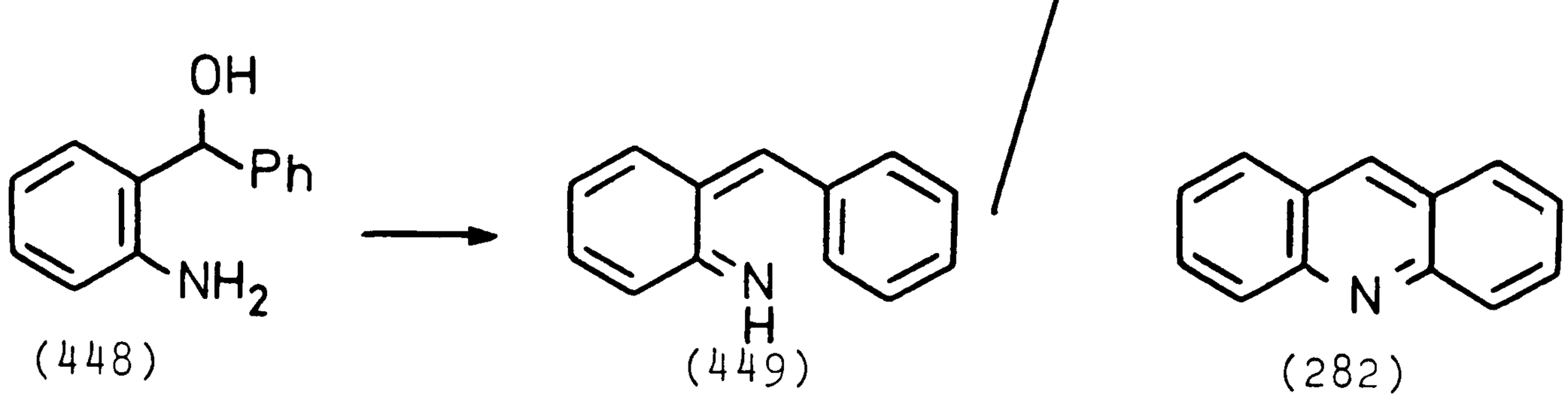
The same workers also found that azaxylylenes can also be generated by the flash vacuum pyrolytic elimination of CO_2 from dihydrobenzoxazinones which are easily obtained from reaction of the corresponding amino alcohols with phosgene. For example, FVP of N-phenyl-



(448a)



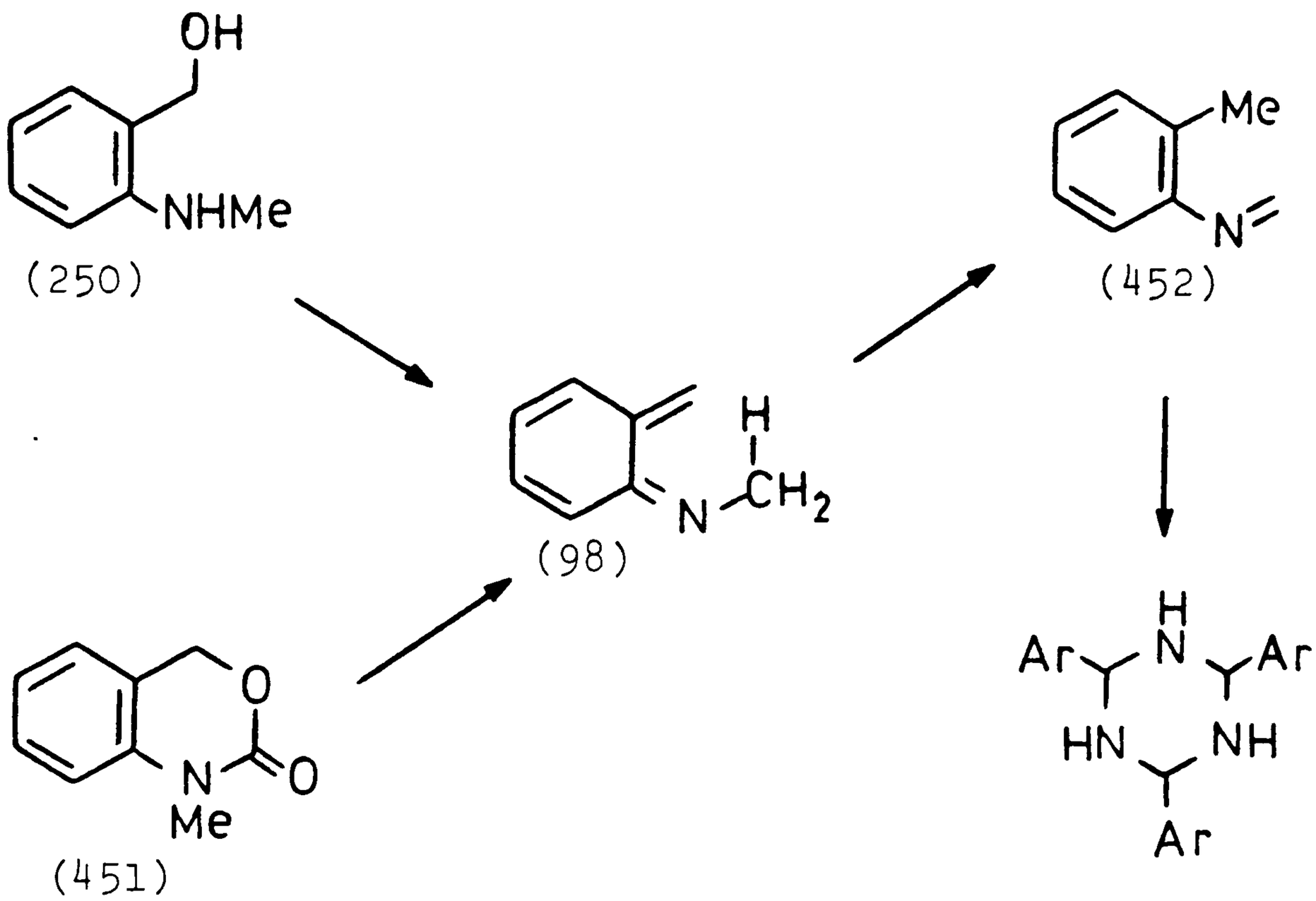
(100) (96) (281)



(448) (449) (282)

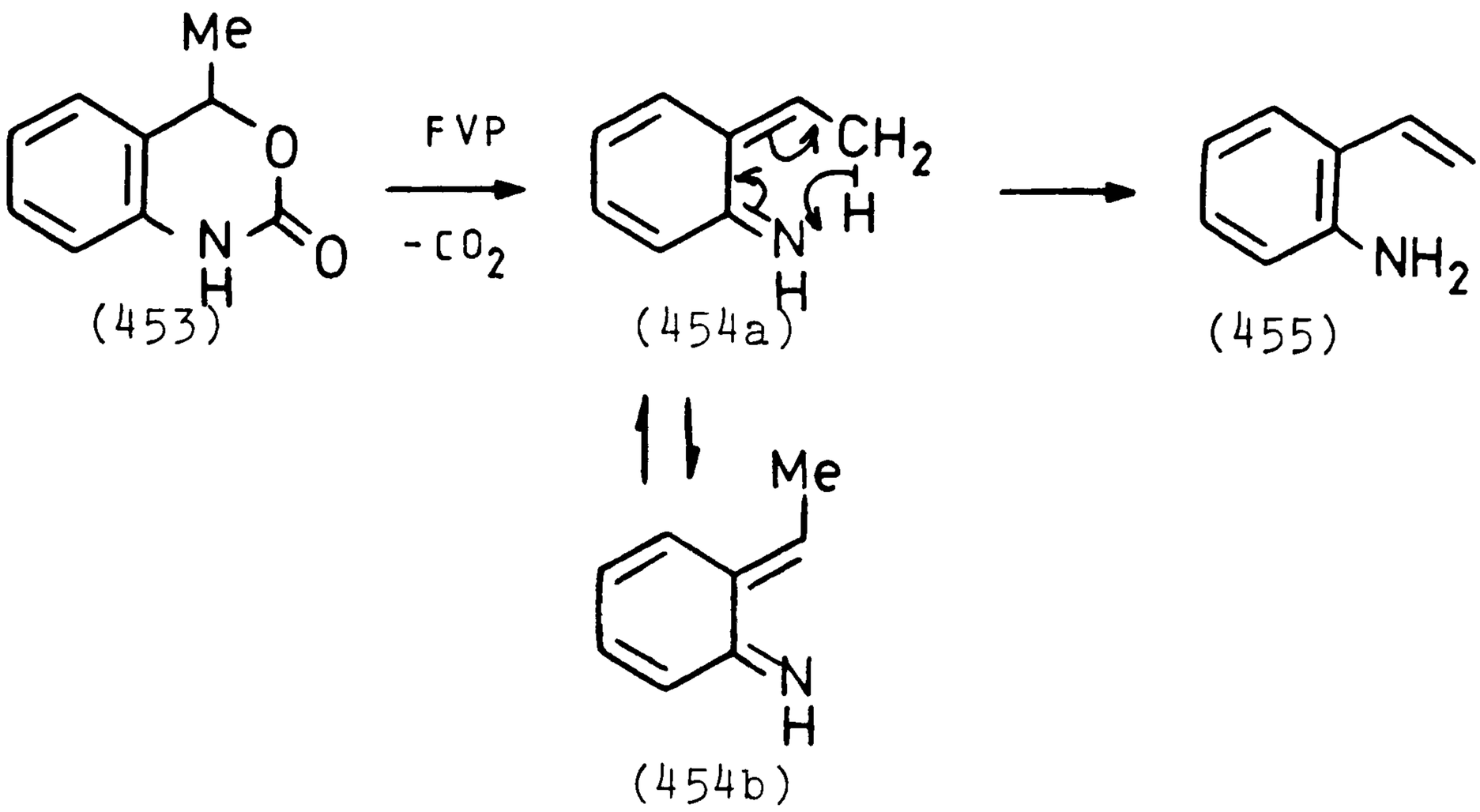
benzoxazinone (448a) gives a near quantitative yield of acridine (282) and pyrolysis of N-methyl amino alcohol (250) or N-methyl benzoxazinone (451) gave the o-tolyl imine (452). The latter is formed by 1,5-hydrogen shift, in the N-methylazaxylylene and was isolated as its trimer.

Similar pyrolysis of the C-methylbenzoxazinone (453) gives 2-aminostyrene (455) again, presumably by 1,5-hydrogen shift in the intermediate C-methyl azaxylylene (454).



However, it was noted in the Introduction (page 41) that the generation of N-methyl azaxylylene in solution (by fluoride ion induced desilylation) gave only spiro dimer and no hydrogen shift products were reported.[65] It seems, therefore, that azaxylylenes react differently in the gas phase and in solution. For a 1,5-hydrogen shift (or indeed an electrocyclization) reaction to occur, the azaxylylene must adopt the higher energy Z-configuration which is only viable under flash vacuum pyrolytic conditions. Also, at the low pressures involved in flash vacuum pyrolysis, dimerization is suppressed.

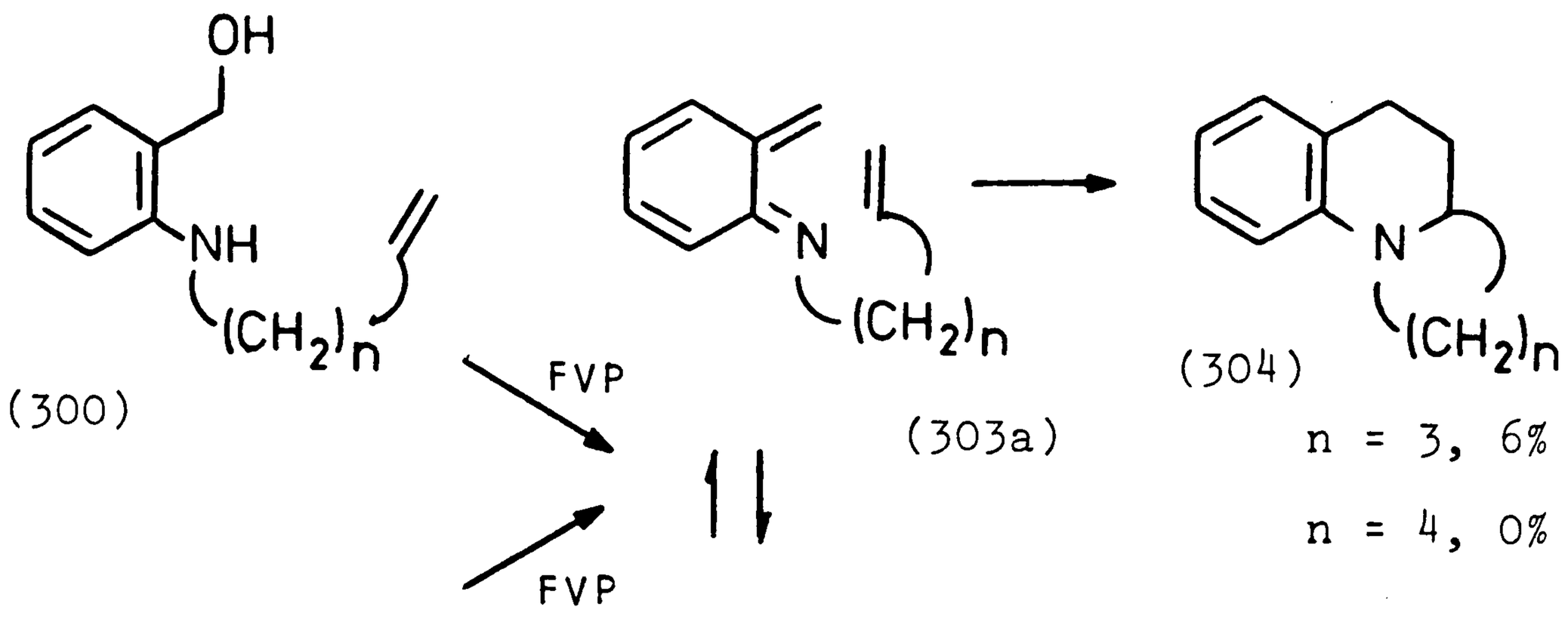
Later work by Noyce[239,157] showed that azaxylylenes (303) generated from either the amino alcohols (300) or dihydrobenzoxazines (301) underwent intramolecular



(453) (454a) (455)

(454b)

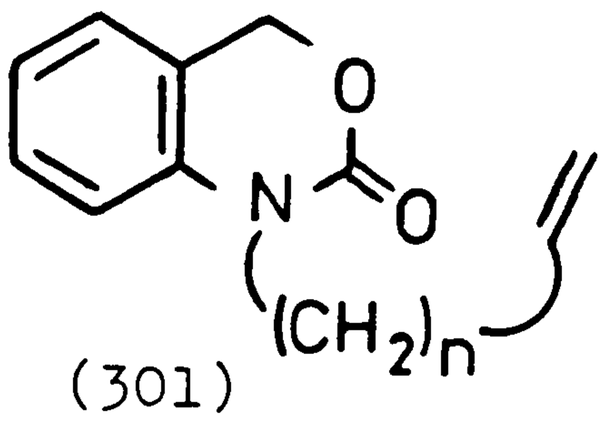
Diels-Alder cycloaddition to give tricycles (304) when the chain connecting diene to dienophile is attached to nitrogen. However, the major reaction involved is a competing 1,5-hydrogen shift in the intermediate Z-azaxylylenes (303b) which leads to the corresponding imines (456).



(300) (303a) (304)

n = 3, 6%

n = 4, 0%



(301)

(303b) (456)

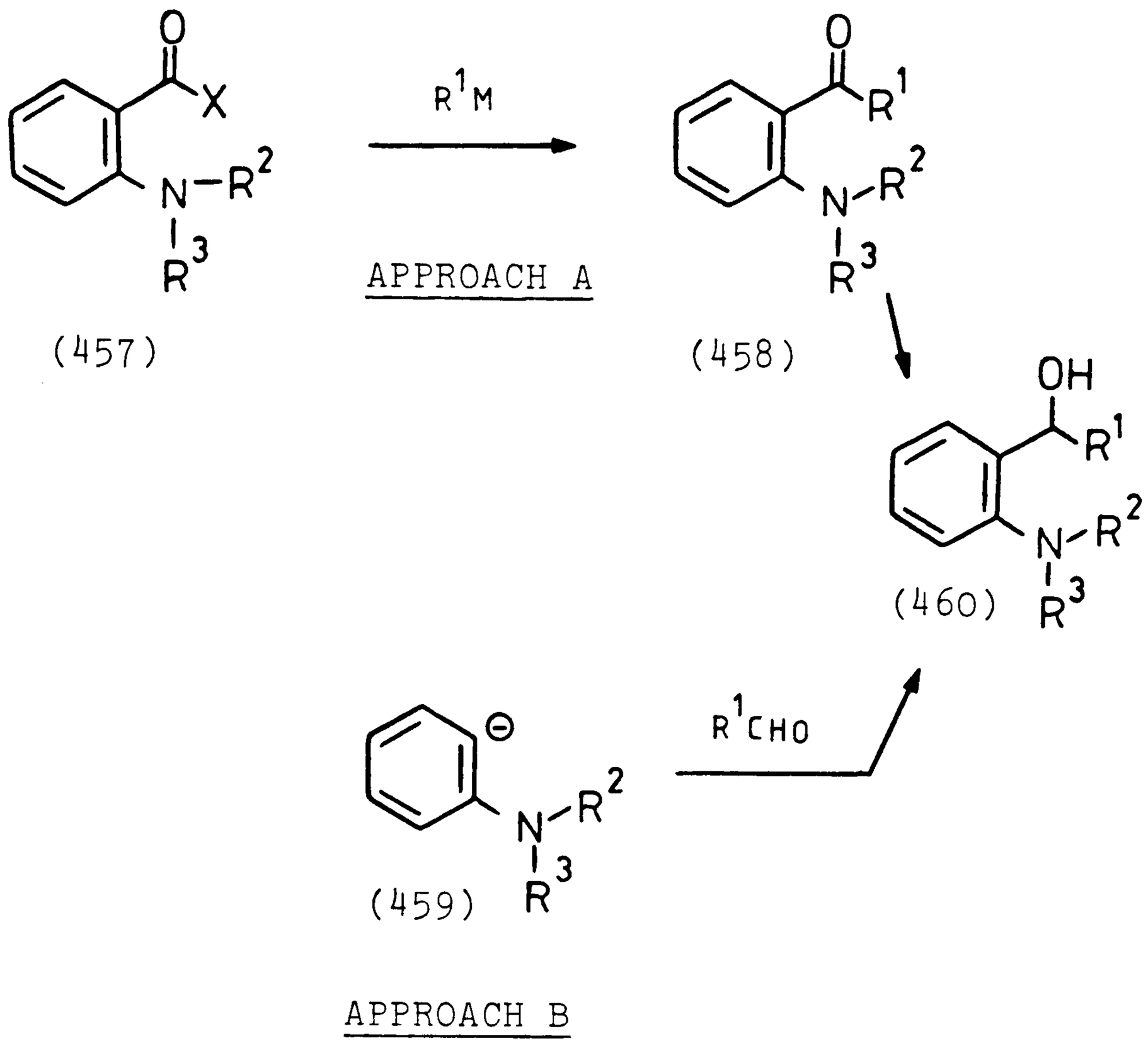
n = 2, 29%

n = 3, 60%

However it was also discovered that solid supports such as alumina or silica in the hot zone of the pyrolysis apparatus, lowered the temperature required for formation of the azaxylylene from either the o-amino alcohols or dihydrobenzoxazinones by approximately 400°C. This was found to be particularly useful in the pyrolysis of (300) and (301) as under these lower temperature conditions there was a relatively greater population of the E-azaxylylene (303a) thus resulting in much improved yields of the Diels-Alder cycloadducts (304).[256]

4. ROUTES TO C-SUBSTITUTED o-AZAXYLYLENES

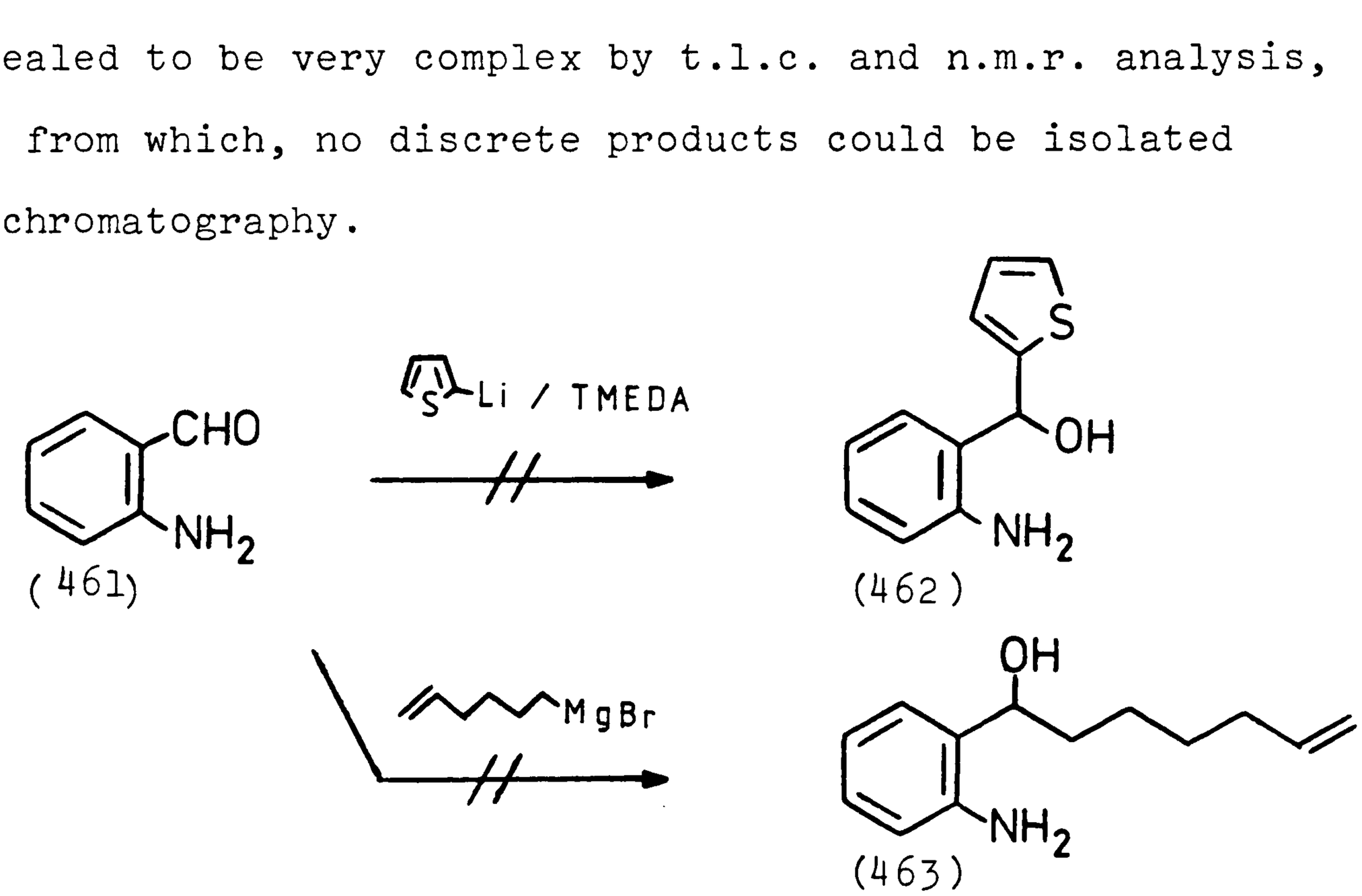
Since virtually all the previously mentioned preliminary work on azaxylylenes was concerned with the nitrogen substituted derivatives, we undertook a systematic study of the carbon substituted analogues. We envisaged two possible approaches to the formation of the required amino alcohol (and thus benzoxazinone) precursors. The first, approach A, was attack of nucleophiles on an o-amino carbonyl compound of type (457). If X was a leaving group, then this should give the corresponding o-amino ketones (458) which should then be easily reduced to the required o-amino alcohols (460). In principle, the generality of this route would only be limited by the availability of the nucleophile RM. A second method, approach B, would be by reaction of an o-aminophenyl carbanion equivalent (459) with an aldehyde which would lead to the required o-aminobenzyl alcohol (460) directly



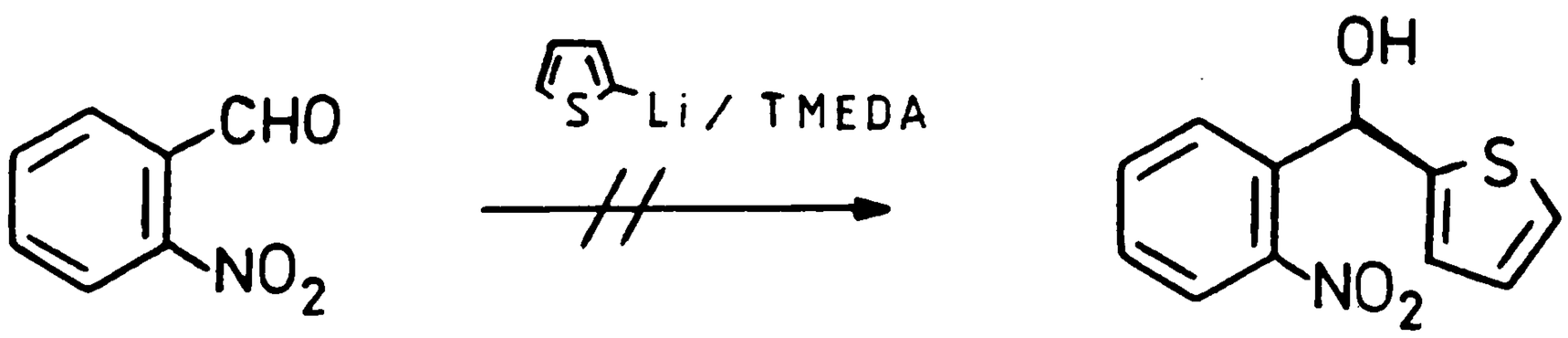
SCHEME 7

(Scheme 7). We chose to test the feasibility of these approaches by attempting to make the known thienyl alcohol (462)[257] as a precursor to a thiophene-substituted azaxylylene and hence the thiophene-fused quinoline (see later). However, approach A proved to be inefficient and difficult to use in practice. The obvious precursor is 2-aminobenzaldehyde (461). However, treatment of an ethereal solution of (461) with a three-fold excess of 2-lithiothiophene[258] generated as its complex with tetramethylethylenediamine (TMEDA) gave a complex mixture from which no discrete products could be obtained on chromatography. This failure may be due to

the likely formation of an amino anion which is ortho to the aldehyde group and will tend to reduce the reactivity of the aldehyde. Not surprisingly, treatment of 2-aminobenzaldehyde with an excess of hex-5-enyl-1-magnesium iodide did not give any of the required alcohol (463). The precursor to the Grignard reagent, 1-iodo-hex-5-ene, was prepared in four steps from tetrahydropyranyl-2-methanol.[259] In an attempt to overcome this problem, the 2-lithiothiophene/TMEDA complex was added to a solution of 2-nitrobenzaldehyde (464) at room temperature. However, after aqueous work-up, only a dark brown oil was obtained which was revealed to be very complex by t.l.c. and n.m.r. analysis, and from which, no discrete products could be isolated by chromatography.



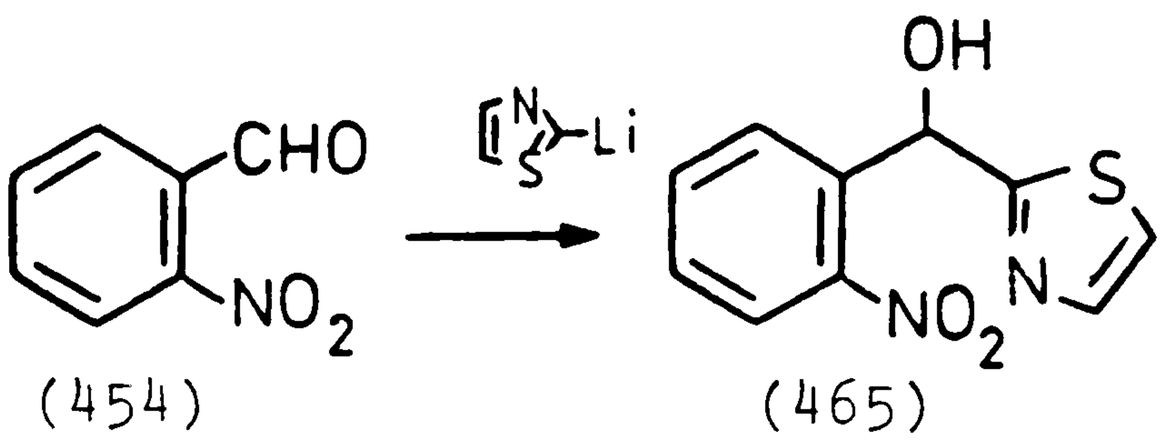
(461) (462) (463)



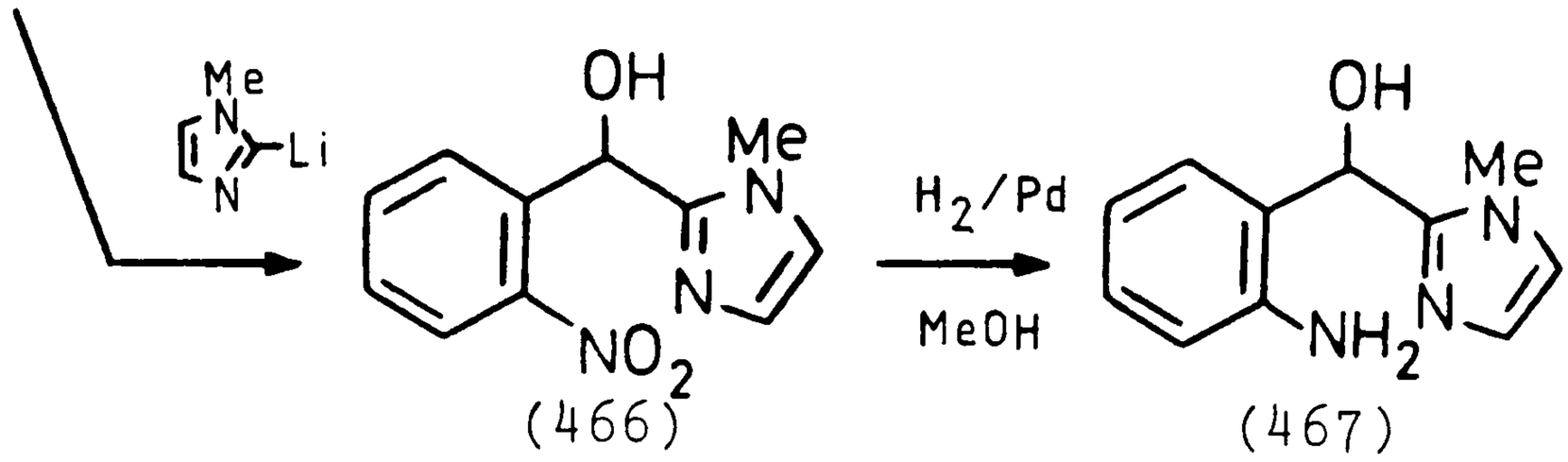
(464)

This failure of 2-lithiothiophen to undergo clean reaction with 2-nitrobenzaldehyde may be due to attack on the nitro group by the nucleophile at this temperature. However, repeating this reaction at -78°C followed by immediate aqueous work-up gave no new products, probably due to the low reactivity of the 2-lithio-thiophene complex at lower temperatures.

However, Kalish[260] has reported that treatment of (464) with 2-lithiothiazole at -78°C gave alcohol (465) in good yield. It was decided to use this approach to prepare the structurally similar imidazolyl alcohol (466) and thus amino alcohol (467) by reduction. Treatment of 2-nitrobenzaldehyde in ether at -78°C with an equivalent of N-methyl-2-lithioimidazole[261] gave alcohol (466) in 35% yield. Catalytic hydrogenation using 10% palladium on charcoal in ethanol at room temperature produced amino alcohol (467) in 76% yield. This compound proved difficult to recrystallize and could not be produced in a sufficiently pure form to allow a satisfactory elemental analysis to be obtained. However, the ^{1}H n.m.r. spectrum was in complete support of the assigned structure showing in particular the hydrogen α to the alcohol group as a singlet at δ 5.86 ppm, and the amine and alcohol protons as a broad singlet between δ 5.10 and δ 4.40 ppm. In addition, the accurate mass of 203.1057 was in close agreement with the required value of 203.1059.



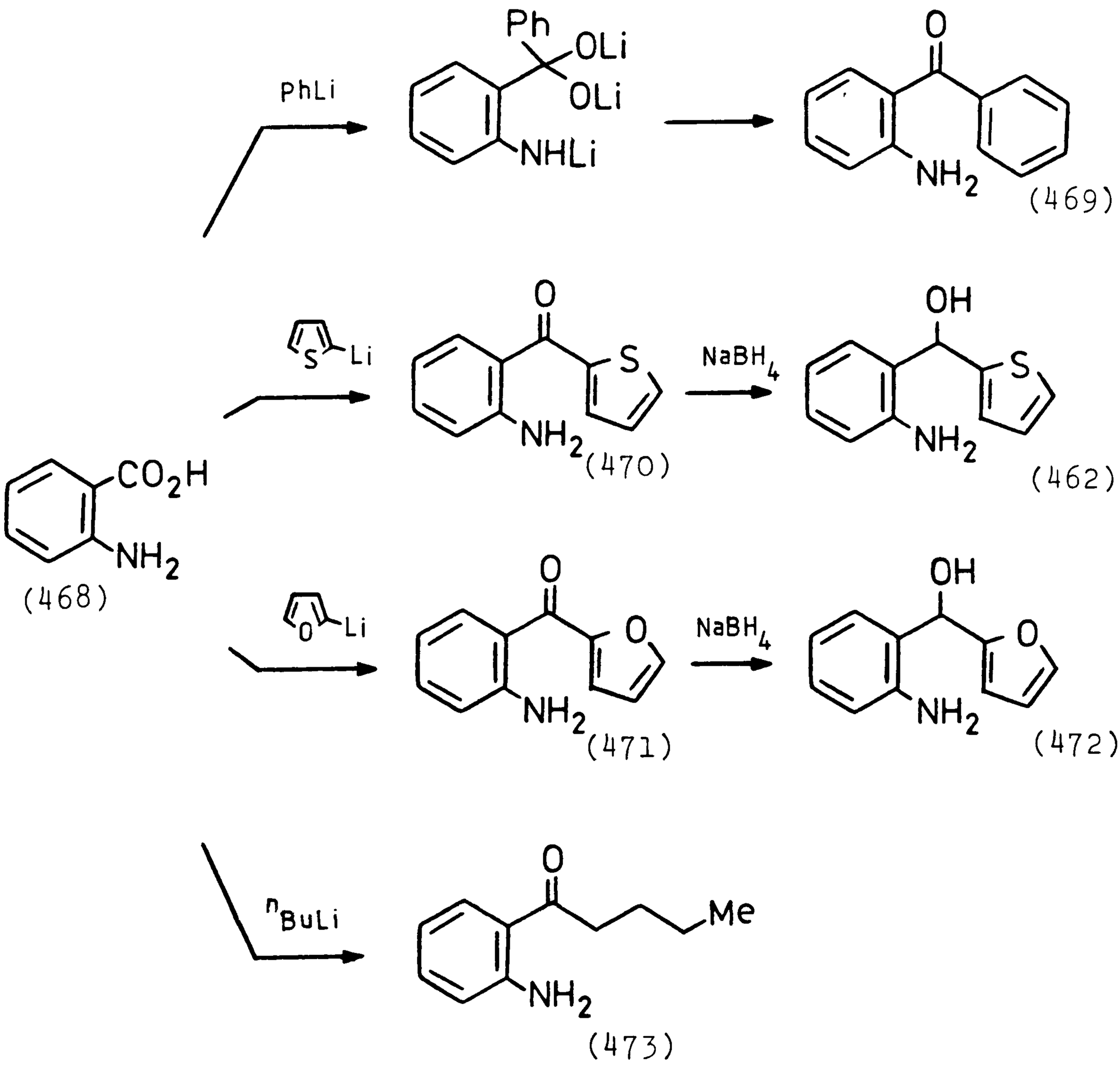
(454) (465)



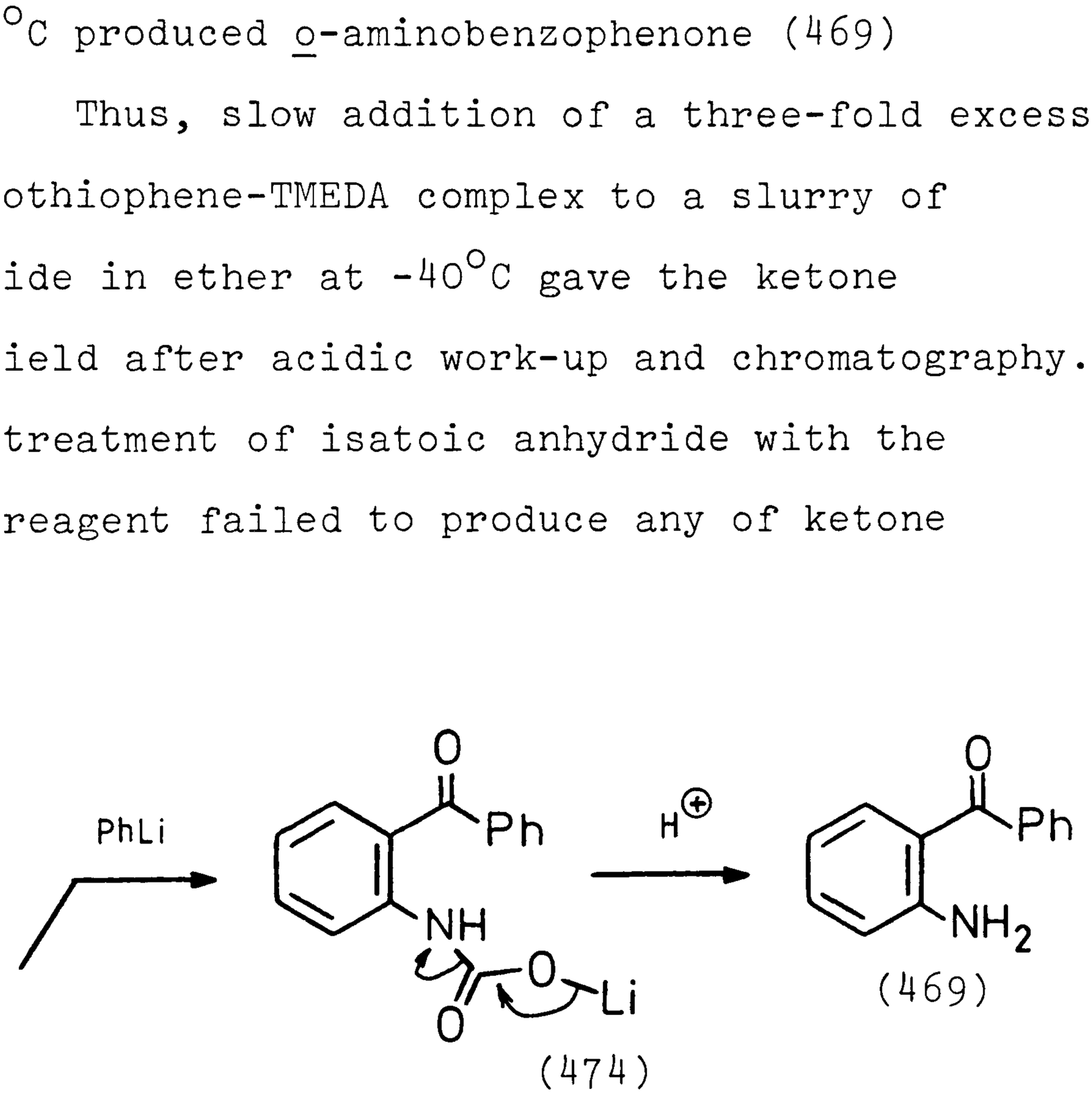
(466) (467)

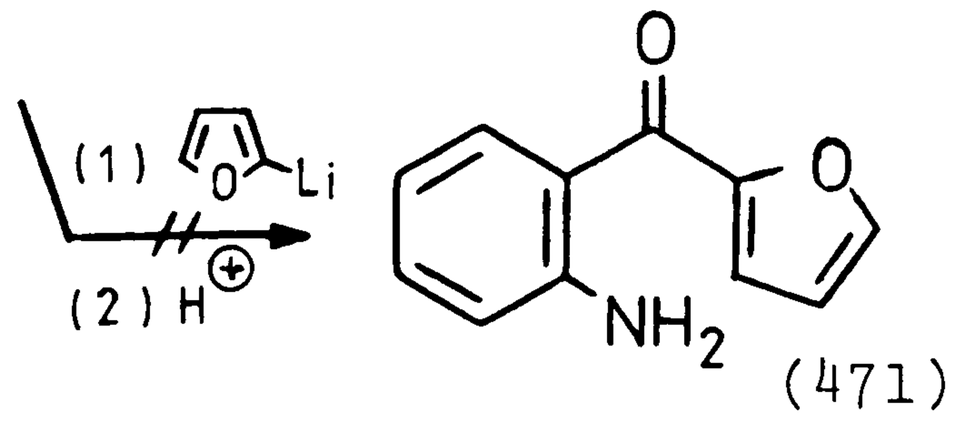
Adger[262] has found that 2-aminobenzophenone (469) can be obtained in high yield from treatment of anthranilic acid (468) with a four-fold excess of phenyl lithium at room temperature. Thus treatment of a solution of anthranilic acid in ether with a four-fold excess of 2-lithiothiophene at room temperature produced the thienyl ketone (470) in 25% yield. Reduction of ketone (470) with sodium borohydride in methanol at room temperature gave alcohol (462) in quantitative yield. Similarly, treatment of anthranilic acid (468) with a four-fold excess of the 2-lithiofuran-TMEDA complex[258] at room temperature gave the furanoyl ketone (471) in 47% yield. Reduction of this ketone with sodium borohydride gave the corresponding alcohol (472) in high yield. This alcohol proved to be a rather unstable system and prolonged storage, even at

-78°C, resulted in its decomposition to a brown oil which was seen to be a complex mixture of components by t.l.c. analysis. However, functionalization of anthranilic acid seems to be of limited use for the preparation of alkenyl-substituted amino alcohols as implied by the inefficient reaction with n-butyllithium which gave the n-butyl ketone (473) in only 6% yield.



Alternatively, isatoic anhydride (109) is known to behave as a masked form of anthranilic acid with nucleophiles, and undergoes attack at C-4 to give the corresponding o-amino ketones after decarboxylation of the initial salt (474).[263] For example, Akatsu[264] has found that treatment of isatoic anhydride with phenyl lithium at -40°C produced o-aminobenzophenone (469) in good yield. Thus, slow addition of a three-fold excess of the 2-lithiothiophene-TMEDA complex to a slurry of isatoic anhydride in ether at -40°C gave the ketone (470) in 22% yield after acidic work-up and chromatography. Surprisingly, treatment of isatoic anhydride with the 2-lithiofuran reagent failed to produce any of ketone (471).





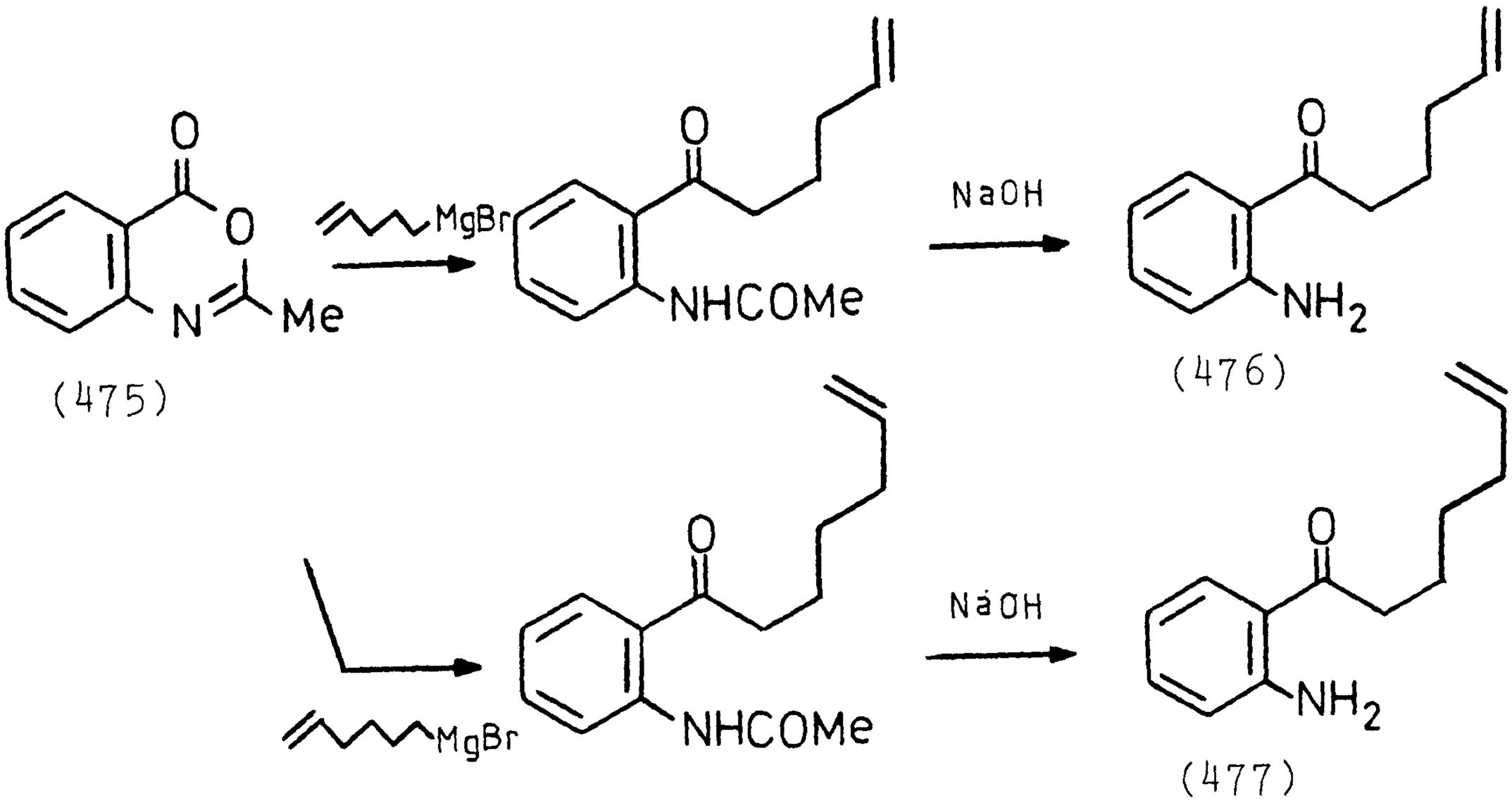
Alkyl ketones can be obtained in moderate yield from the reaction of Grignard reagents with 3,1-benzoxazin-4-one (475).[265] This route was applied successfully to the synthesis of the pentenyl amino ketone (476) using pent-4-enyl-1-magnesium iodide giving (476) in 23% yield. The precursor to the Grignard reagent, 1-iodopent-4-ene (481) was prepared in four steps from tetrahydrofurfuryl alcohol (478)[266] by conversion into the chloride (479) with thionyl chloride, ring opening with metallic sodium to give alcohol (480) followed by conversion into the tosylate with tosyl chloride. Treatment of this tosylate with sodium iodide gave iodide (481). Similarly, the hexenyl amino ketone (477) was prepared by reaction of an equivalent of hex-5-enyl-1-magnesium iodide with the 1,4-benzoxazinone (475), in 20% yield.

Reduction of these ketones with an excess of sodium borohydride in methanol gave the required amino alcohols (482) and (463) in high yields.

These in turn were converted into the corresponding 1,4-dihydro-3,1-benzoxazin-2-ones (483) and (484) in 79% and 58% yields respectively, by treatment with phosgene in dichloromethane at $0^{o}C$ in the presence of triethylamine.

However, because of the general inefficiency of approach A, our attention was focused on approach B.

Muchowski and Venuti[267] reported that N-tert-butoxy-carbonyl aniline (485) undergoes directed ortho-lithiation with two equivalents of tert-butyl lithium at $-78^{o}C$ to yield the yellow dianion (486). This dianion was then



(475)

(476)

(477)

(478)

(479)

(480)

(481)

(476) n = 3

(477) n = 4

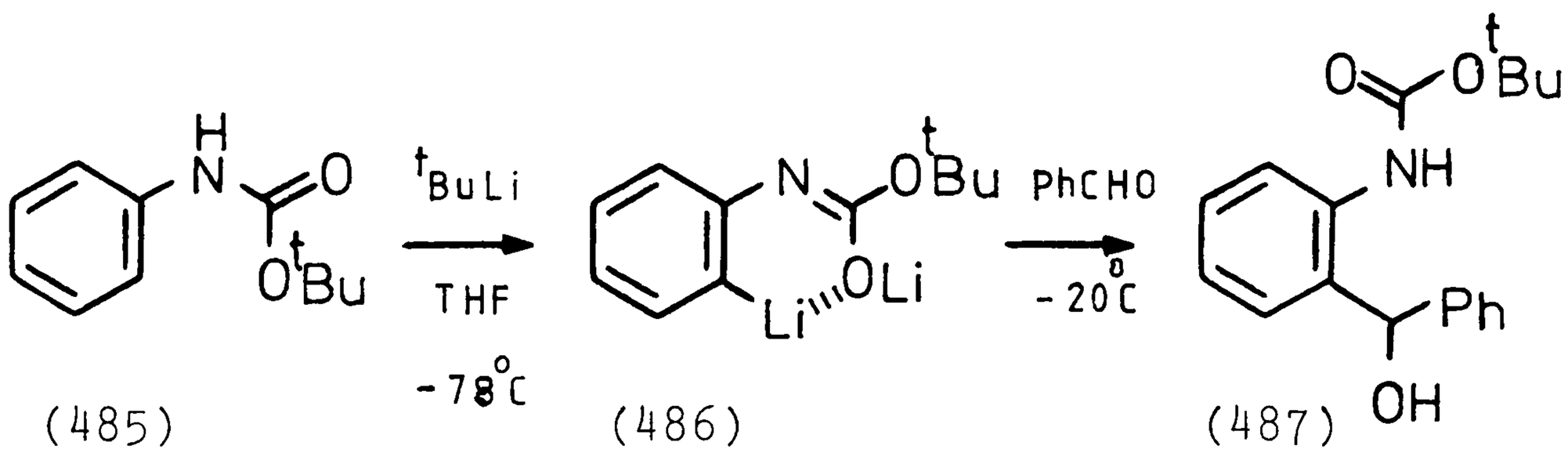
(482) n = 3

(463) n = 4

(483) n = 3

(484) n = 4

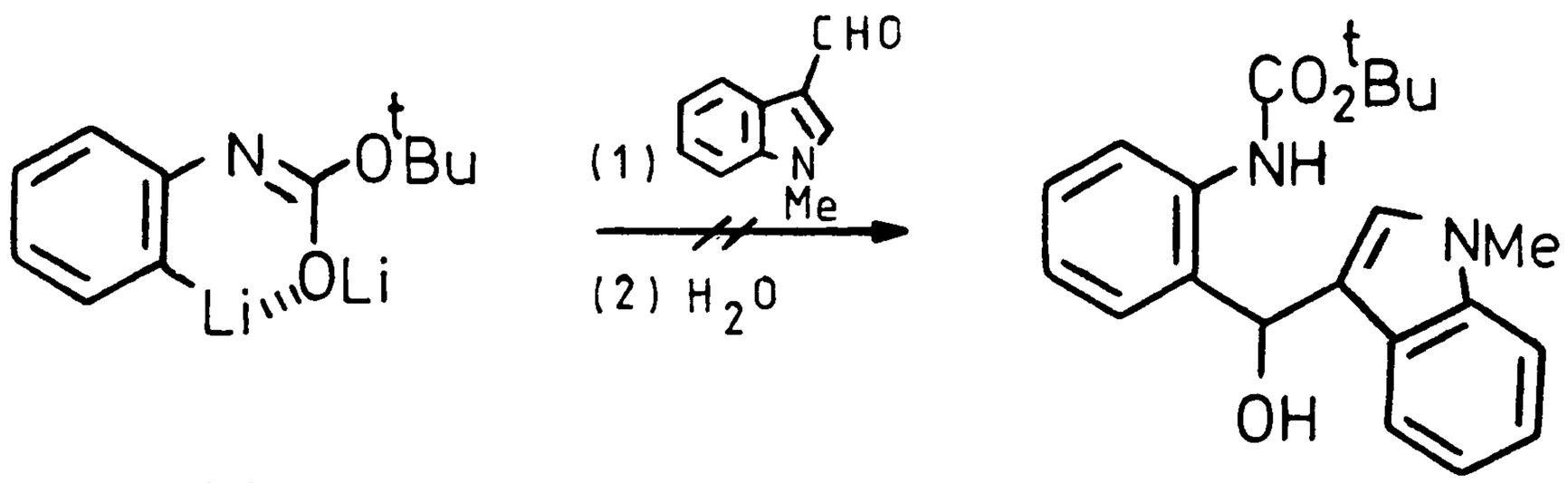
allowed to react with a variety of electrophiles to give the corresponding ortho-substituted urethanes in reasonable yields. It was decided to explore the generality of this approach for the synthesis of o-azaxylylene precursors since these urethanes can be deprotected in high yield with aqueous acid to yield the corresponding amines.[267] Indeed,it was found that treatment of N-tert-butoxycarbonyl aniline (485), which was prepared in quantitative yield by reaction of aniline with di-tert-butyl dicarbonate, with two equivalents of tert-butyl lithium at -78°C in THF under argon, followed by treatment with benzaldehyde gave the corresponding alcohol (487) in 57%.



(485) (486) (487)

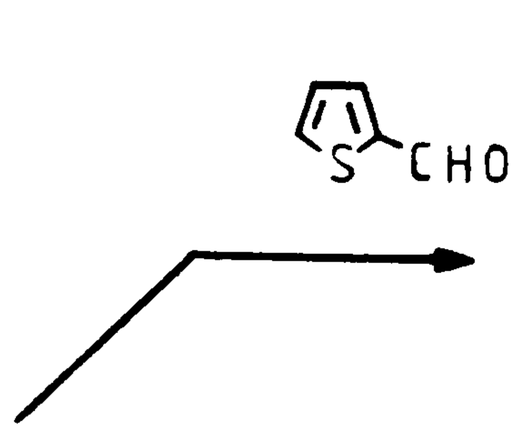
Initial attempts to extend this approach by quenching the dianion with thiophene-2-carboxaldehyde were rather disappointing giving the thiophen-substituted urethane (489) in only 10% yield. This low yield of (489) may be

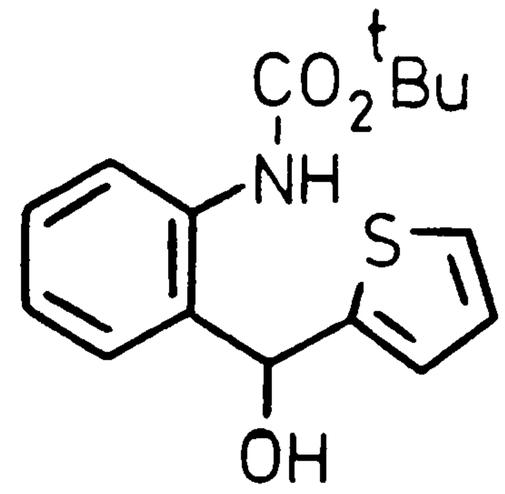
due to competing hydrogen-lithium exchange of thiophene-2-carboxaldehyde in the five-position by the dianion. It was also found that treatment of this dianion with an equivalent of N-methylindole-3-carboxaldehyde gave no trace of the required indolyl-substituted urethane (488). The failure of this reaction may again be due to competing lithiation at the two-position of the indole.



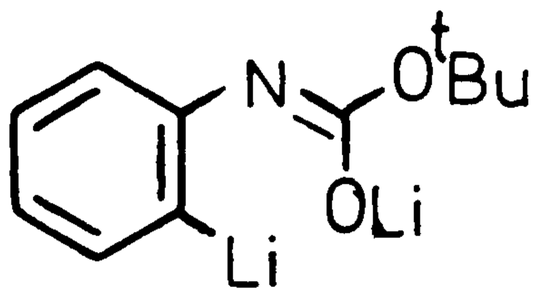
(486) (488)

Treatment of the dianion with hex-5-enal, made from the oxidation of the corresponding alcohol with pyridinium chlorochromate,[268] gave the alcohol (490) in a more encouraging yield of 57% after chromatography. Similarly, reaction of the dianion with hept-6-enal, prepared by reaction of hex-5-enyl-1-magnesium iodide with triethyl orthoformate followed by hydrolysis of the resulting acetal,[269] produced the hexenyl alcohol (491) in 31% yield. It should be noted that both of these urethanes were viscous oils, which made purification by distillation extremely difficult.

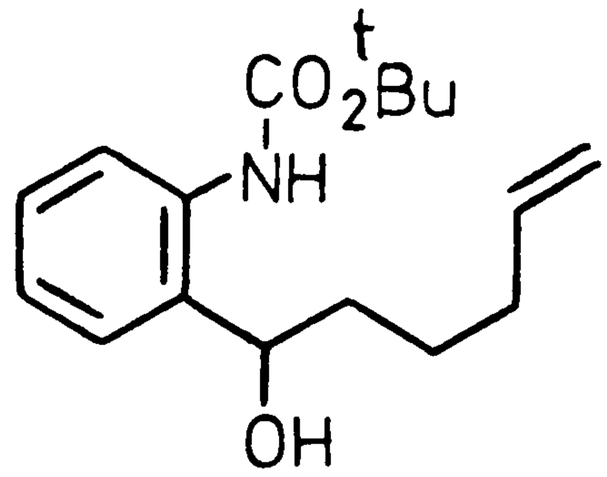




(489)



(486)



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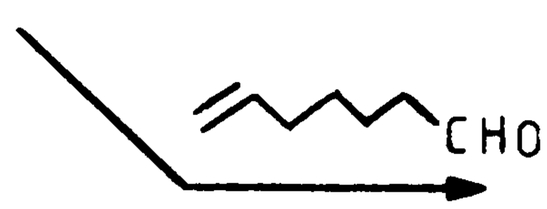
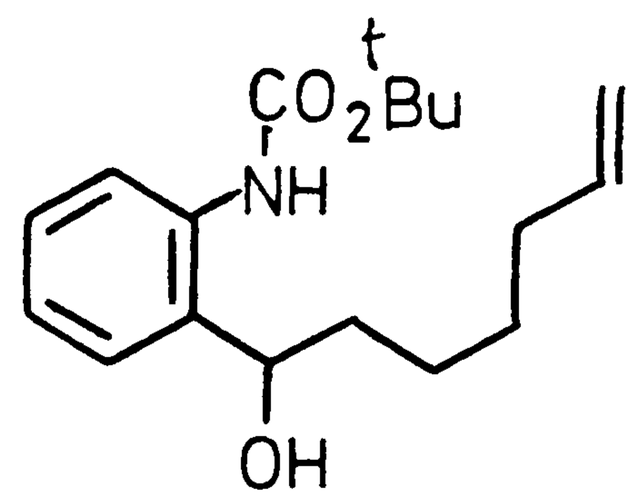




(491)

Several more examples of this approach are detailed in Chapter 6 on heteroaromatic-based o-azaxylylenes (page 196).

5. THE GENERATION AND CHEMISTRY OF CARBON-SUBSTITUTED AZAXYLYLENES

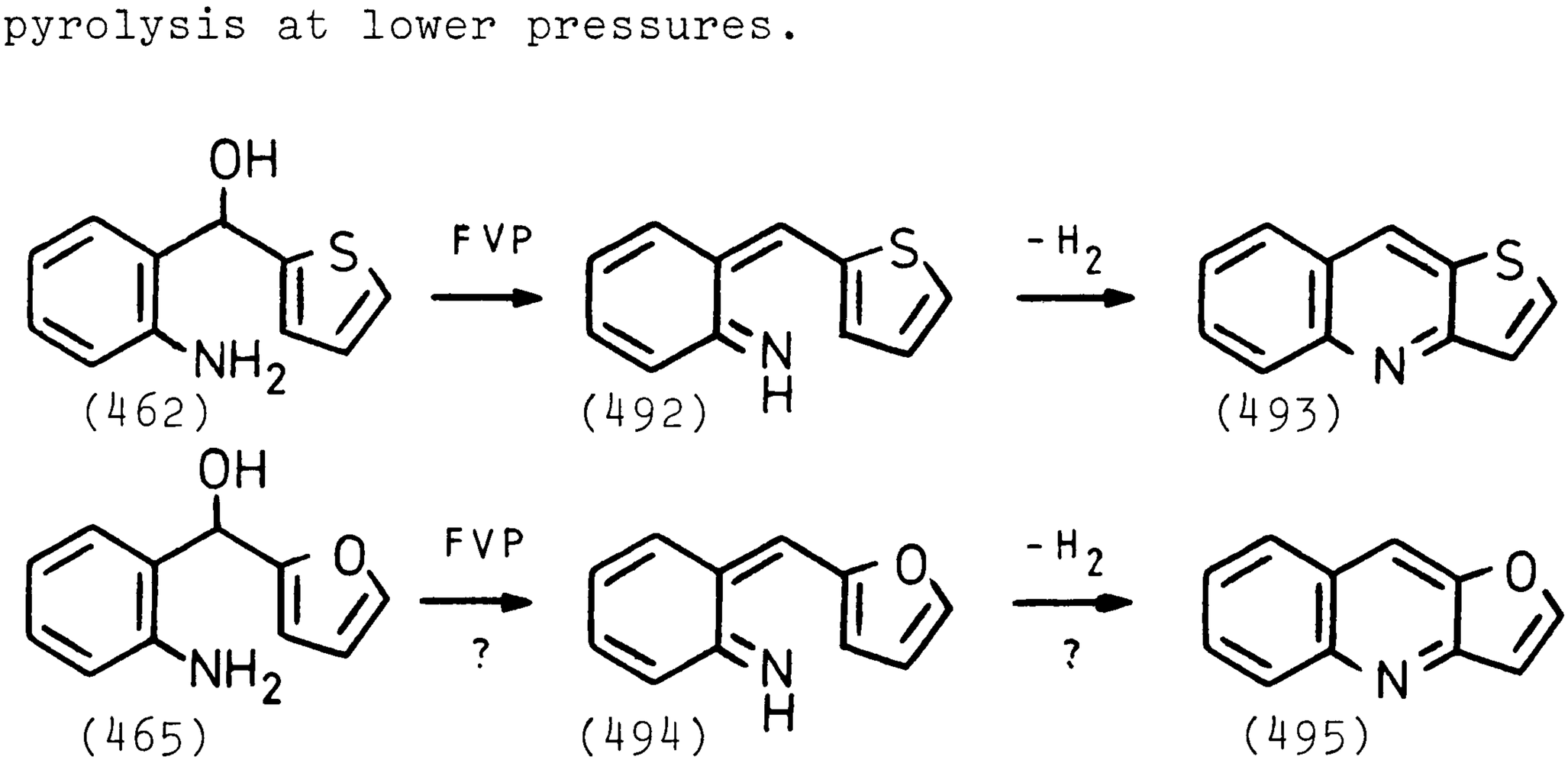
5.1 FROM AMINO ALCOHOL PRECURSORS

Pyrolysis of thienyl amino alcohol (462) at 750°C/ 10^{-2} torr using the procedure described on page 247 produced a pale yellow pyrolysate at -78°C which changed colour to dark green upon warming to room temperature. Chromatography followed by recrystallization gave the known thieno[3,2-b]quinoline (493)[270] in 22% yield, thus demonstrating that electrocyclization reactions also occur with heterocyclic rings. The physical properties of this

system were in close agreement with those reported in the literature.[270] The ^{1}H n.m.r. spectrum consisted of a singlet at δ 8.57 corresponding to the C-5 proton, and two doublets each integrating for one proton at δ 8.17 and δ 7.58 ppm respectively. The remainder of the spectrum contained a multiplet between δ 7.91 and δ 7.79 integrating for two hydrogens, and two triplets each due to a single proton at δ 7.70 and δ 7.49 ppm. The ^{13}C off-resonance n.m.r. spectrum consisted of four singlets at δ 157.31, 146.78, 130.81 and 124.84 and six of the seven doublets could be seen at δ 134.30, 129.45, 128.99, 127.15, 125.46 and 124.56 ppm. The mass spectrum gave a clear molecular ion peak at m/z 185 which is consistent with the molecular formula for the assigned structure. However, formation of this product in only 22% yield compared to the almost quantitative recovery of acridine from the similar pyrolysis of the phenyl-substituted amino alcohol (448) was disappointing. The presence of silica or alumina in the hot zone of the pyrolysis apparatus can signifciantly lower the temperatures required for azaxylylene generation. Accordingly, pyrolysis of alcohol (462) at $450^{\circ}C/10^{-2}$ torr over alumina gave thienoquinioline (493) in 92% yield after recrystallization.

In view of the behaviour of the thiophene-substituted azaxylylene, it was anticipated that similar pyrolysis of the furanoyl alcohol (465) would produce the furan-fused quinoline (495) again by electrocyclization of the

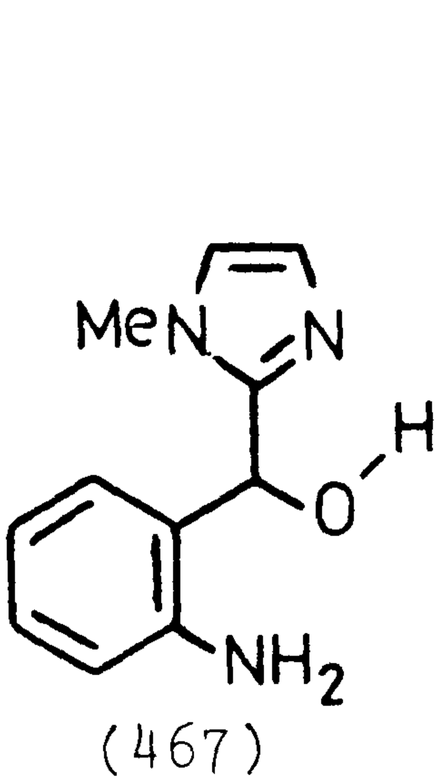
azaxylylene (494). Disappointingly, however, pyrolysis of this system at 750°C/10^{-2} torr or at 450°C/10^{-2} torr over alumina only produced a brown viscous oil which was revealed to be a complex mixture by t.l.c., and n.m.r. analysis, and from which no discrete components could be isolated by chromatography. Significantly, it was noticed that during pyrolysis, the substrate (465) suffered extensive decomposition, and after five hours, there remained a large amount of an intractable tar in the pyrolysis flask. It is likely, therefore, that the failure of these pyrolyses to produce any cyclised products is due to the fragile nature of the amino alcohol, and it is anticipated that more success may be obtained by pyrolysis at lower pressures.



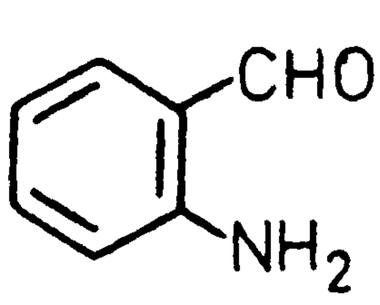
Pyrolysis of the imidazolyl alcohol (467) at 750°C/10^{-2} torr produced a pale brown pyrolysate at -78°C which turned red/orange on warming to room temperature. Immediate inspection of this crude pyrolysate by n.m.r. indicated that it consisted almost exclusively of equal amounts of N-methyl imidazole and 2-aminobenzaldehyde with

no trace of tricycle (498) resulting from electrocyclization of intermediate azaxylylene (497). Pyrolysis at 450°C/ 10^{-2} torr over alumina similarly gave N-methylimidazole and 2-aminobenzaldehyde. This result is analogous to that found by Glasbey[243] for the pyrolysis of alcohol (499) which gave equal amounts of 2-aminobenzaldehyde and thiazole. This reaction was rationalized by a 1,2-elimination of the stabilized thiazolyl carbene (500) which would rearrange to thiazole, leaving the amino-aldehyde as the remaining fragment. Later Noyce[239] provided further evidence for this 1,2-elimination by observing the formation of benzaldehyde and thiazole from pyrolysis of the alcohol (501). Thus, similar 1,2-elimination of the imidazolyl-stabilized carbene (496) would account for the observed products from pyrolysis of (467) and may well preclude the formation of azaxylylenes with five-membered ring heterocyclic substituents having hetero-atoms in the 2,5-positions.

Our attention was then turned to the exploration of the intramolecular Diels-Alder reactions of carbon-substituted o-azaxylylenes. However, with the alkenyl amino alcohols 1,2-elimination to yield the corresponding amino styrenes may well occur in preference to the desired 1,4-elimination. Indeed, pyrolysis of the pentenyl amino alcohol (482) at 750°C/10^{-2} torr gave only a complex mixture of products by g.c. analysis with extensive olefinic activity revealed to be present by n.m.r. analysis. This is consistent with the presence of



(467)



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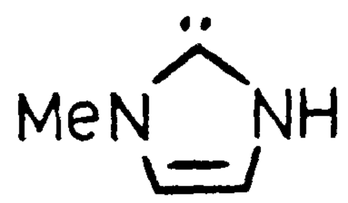
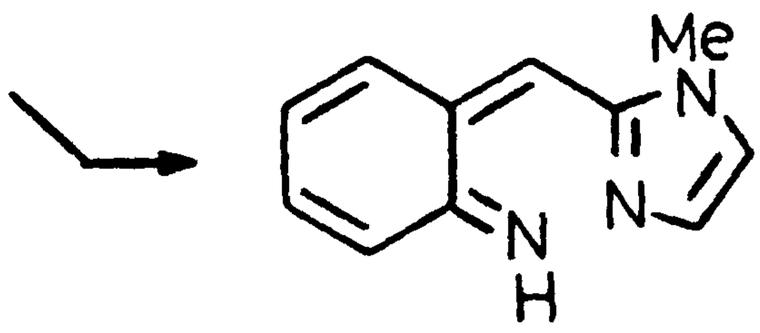
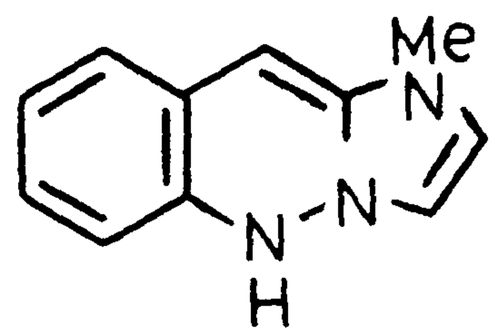


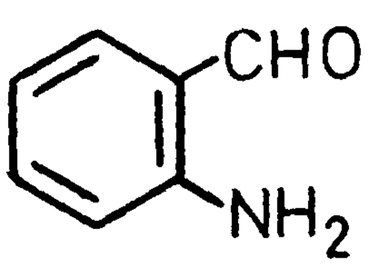
(496)



(497)



(498)



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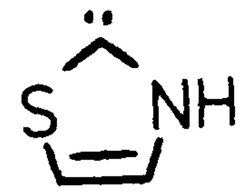

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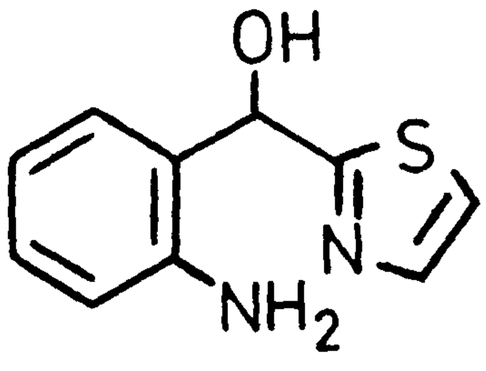
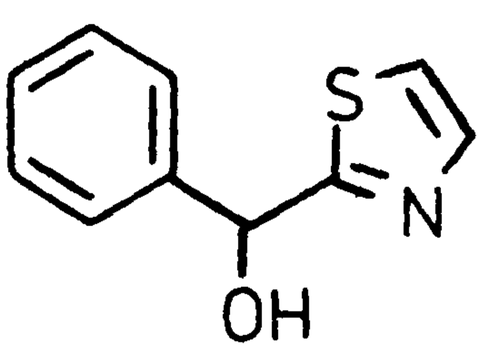
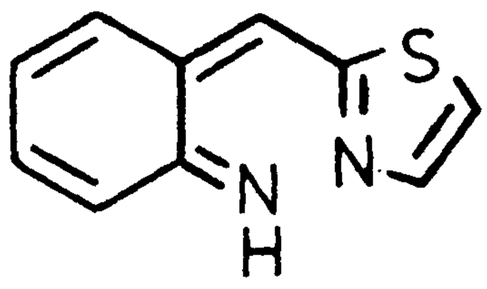
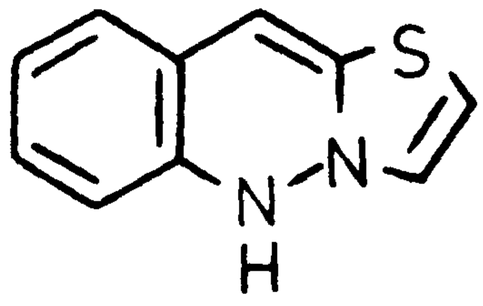


(499)



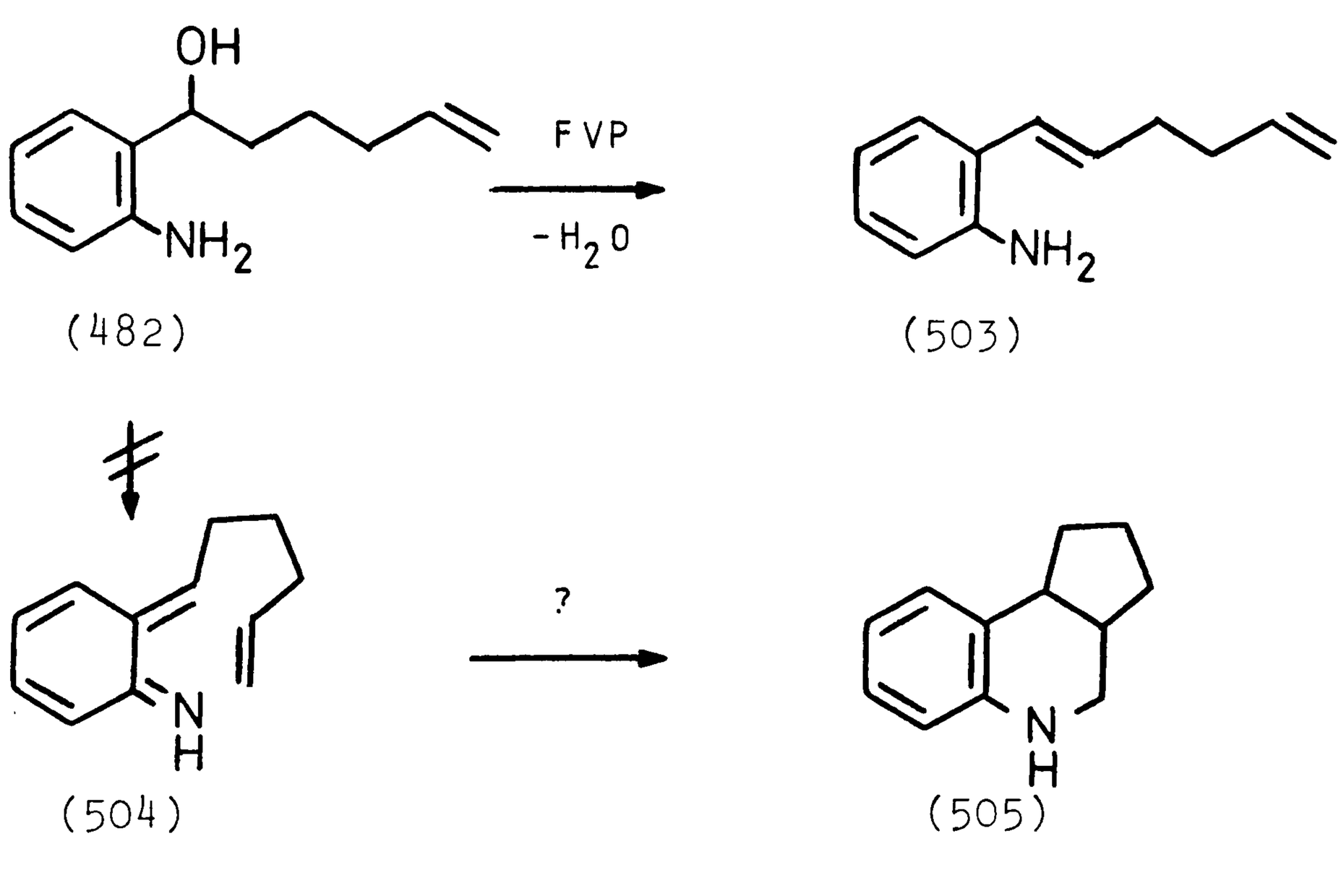
(501)

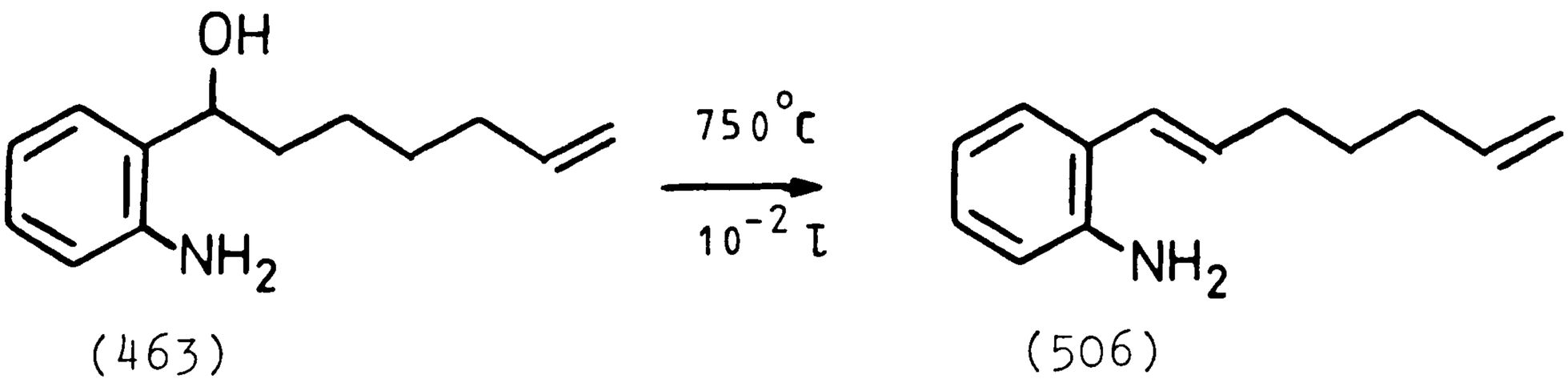




(502)

amino styrene (503) formed by 1,2-dehydration of alcohol (482). Under these conditions of high temperature, dehydrogenation or double bond migration might also be expected to occur thus producing this complex mixture of products. Pyrolysis of this system at $480^{o}C/10^{-2}$ torr over alumina similarly gave a complex reaction mixture. Pyrolysis of the hexenyl analogue (463) at $750^{o}C/10^{-2}$ torr also gave a complex reaction mixture which was shown by n.m.r. analysis to contain extensive aliphatic unsaturation and attempted chromatography gave no discrete, identifiable products.



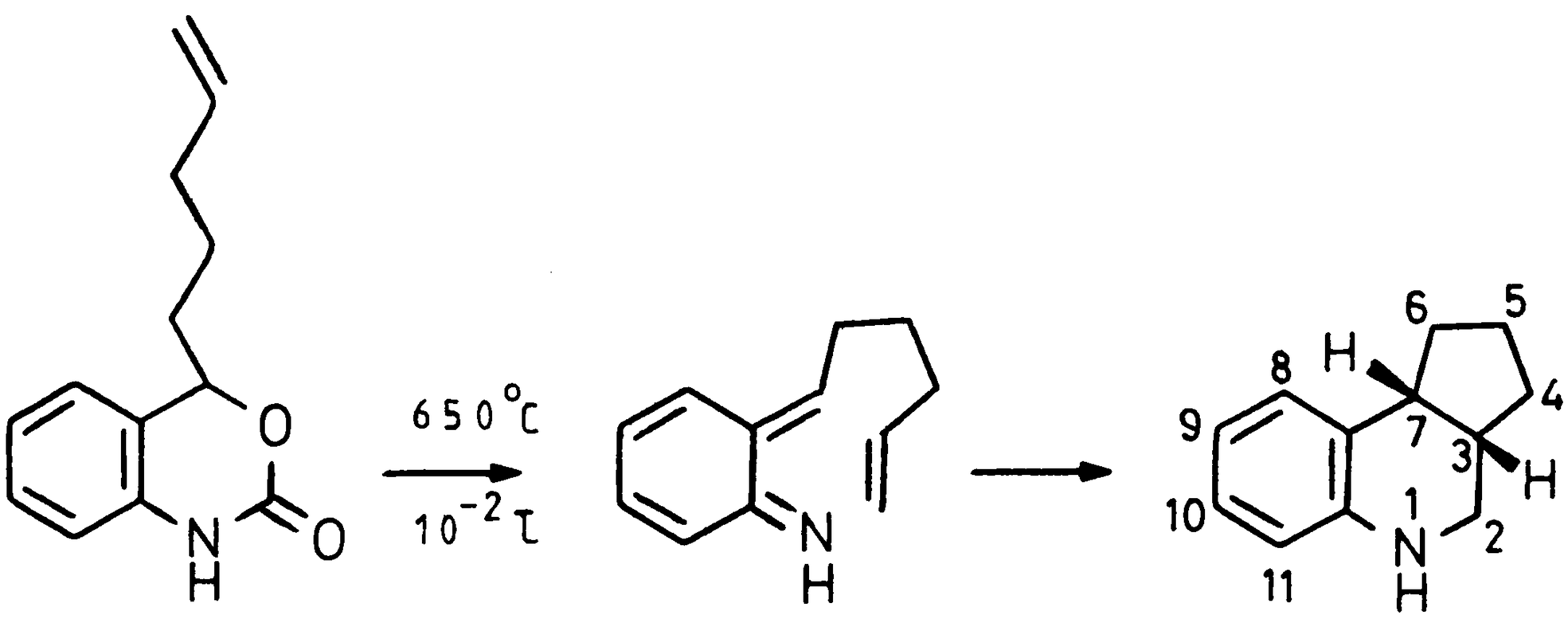


5.2 FROM DIHYDROBENZOXAZINONES

The dihydrobenzoxazinones corresponding to these alcohols do not suffer from the possibility of 1,2-dehydration and therefore are more likely to fragment to yield the desired o-azaxylylenes.

Flash vacuum pyrolysis of the 4-pentenylbenzoxazinone (483) at 650°C/10^{-2} torr produced a pale yellow pyrolysate at -78°C, which changed to a pink colour on warming to room temperature. Chromatography of the resulting pale pink solid on silica gave a colourless oil which solidified on standing. Recrystallization from dichloromethane/hexane gave the tricyclic adduct (505) in 51% yield as colourless needles. The melting point for this compound was identical to that reported for the tentatively assigned cis-isomer.[271] Inspection of the ^{1}H n.m.r. which indicated that this product was a single isomer, revealed the presence of four aromatic protons, two of which appear as a multiplet between δ 6.95 and 7.06 ppm and the remaining two as a triplet at δ 6.64 and a doublet at δ 6.51 ppm. Since there are two asymmetric centres in this molecule with a total of six adjacent protons the remainder of the spectrum was complex. However, with the aid of homo-nuclear decoupling experiments, some assignment was possible. One of the two protons on C-2 gave a multiplet between δ 4.42 and 4.65 ppm due to coupling with its geminal proton, and the C-3 proton, (which overlaps with the broad N-H peak and therefore integrated for two hydrogens) and the other gave a triplet

at δ 4.23. The C-7 bridgehead proton was assigned to the multiplet between δ 3.40 and 3.60 ppm. The C-3 bridgehead proton was assigned to the multiplet between δ 2.65 and 2.71 ppm. However, decoupling experiments could not simplify either of these signals sufficiently to allow the measurement of the C-3 - C-7 coupling between the bridgehead protons, and so the assignment of the stereochemistry of this compound as cis remains tentative. The formation of a cis-fused cycloadduct is consistent with reaction of an intermediate E-azaxylylene (504) in the endo transition state (see page 64 of Introduction).

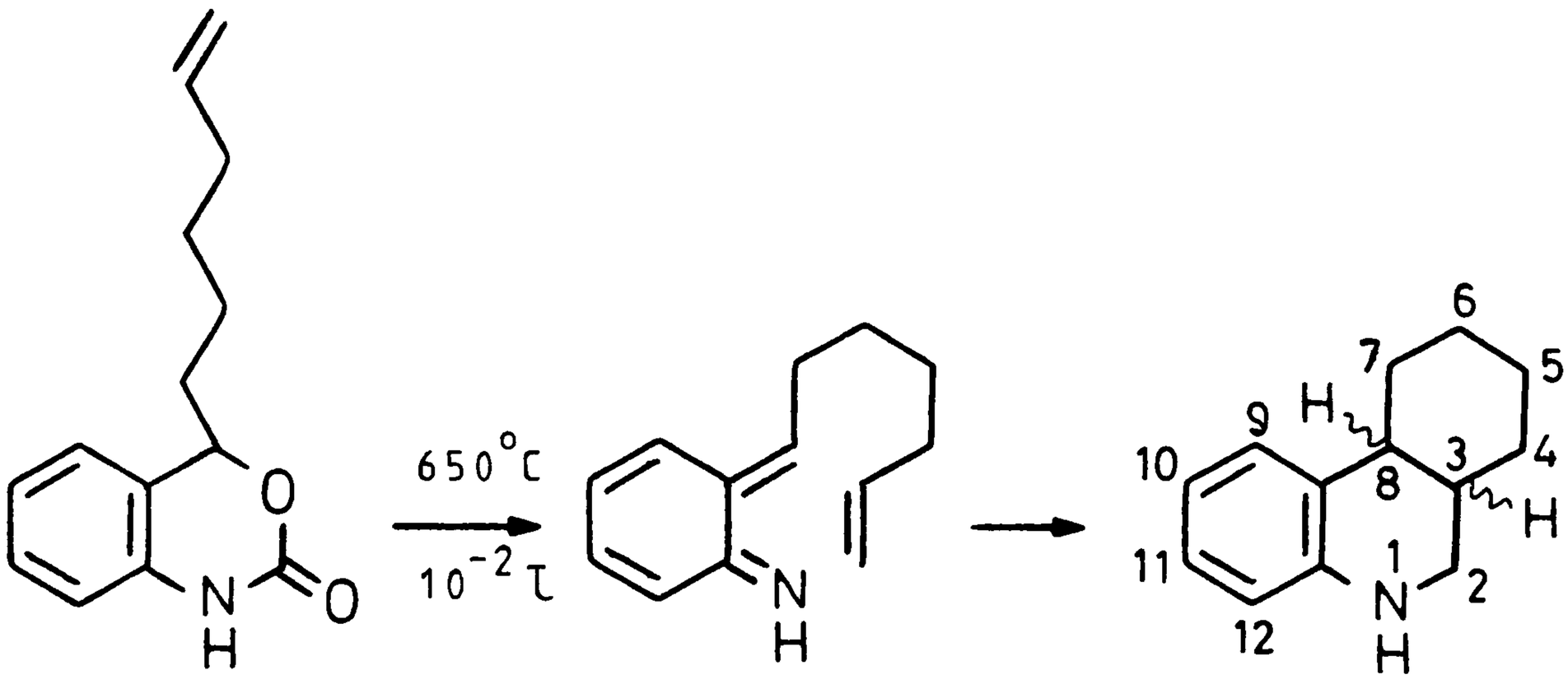


(483) (504) (505)

The ^{13}C n.m.r. spectrum was in total agreement with the proposed tricyclic structure and all twelve carbons were visible in the noise-decoupled spectrum. The off-resonance spectrum revealed these to consist of two singlets at δ 143.86 and 125.78 ppm corresponding to the two quaternary carbons in the molecule. The four remaining aromatic carbons appeared as doublets at δ 126.85, 126.00,

116.29 and 112.64 ppm. The C-2 carbon appeared as a triplet at δ 47.90. The C-7 and C-3 bridgehead carbons could be assigned to the doublets at δ 45.04 and 41.37 ppm. The remaining aliphatic carbons at C-4, C-5 and C-6 appeared as triplets at δ 28.26, 28.00 and 23.29 ppm. Finally, the mass spectrum of adduct (505) gave a clearly defined molecular ion peak at m/z 173 which further supports the proposed structure. Similar pyrolysis of the hexenyl substituted benzoxazinone (484) at 650°C/ 10^{-2} torr again produced a pale yellow pyrolysate at -78°C. Chromatography on silica gave the intramolecular Diels-Alder adduct (508) in 49% yield. Analysis by n.m.r. revealed this to be a 3:1 mixture of diastereoisomers, in which the major isomer was tentatively assigned the cis stereochemistry, due to the similarity of the aliphatic region to the previously discussed spectrum obtained from cycloadduct (505). The melting point of this isomeric mixture, which was a colourless solid, was the same as that reported for the cis-isomer.[272] Attempts to separate this mixture by repeated elution p.t.l.c. or attempted partial recrystallization failed. However, in the ^{1}H n.m.r. spectrum all the main features of each isomer could be clearly observed. In particular, the C-2 protons of the major isomer appear as a doublet of doublets at δ 3.19 ppm and a triplet at δ 3.01 ppm. The same two protons on the minor isomer appeared at δ 3.39 ppm and 3.12 ppm respectively. Further assignment of the higher field signals proved to be extremely difficult

due to the complex nature of the spectrum in this region. The ^{13}C n.m.r. of the isomeric mixture was, however, more informative, as all thirteen carbons for each isomer could be clearly observed, each isomer having two singlets, four aromatic doublets, two aliphatic doublets and five triplets. The mass spectrum gave a single clearly defined molecular ion peak at m/z 187, in complete agreement with the assigned tricyclic structure.



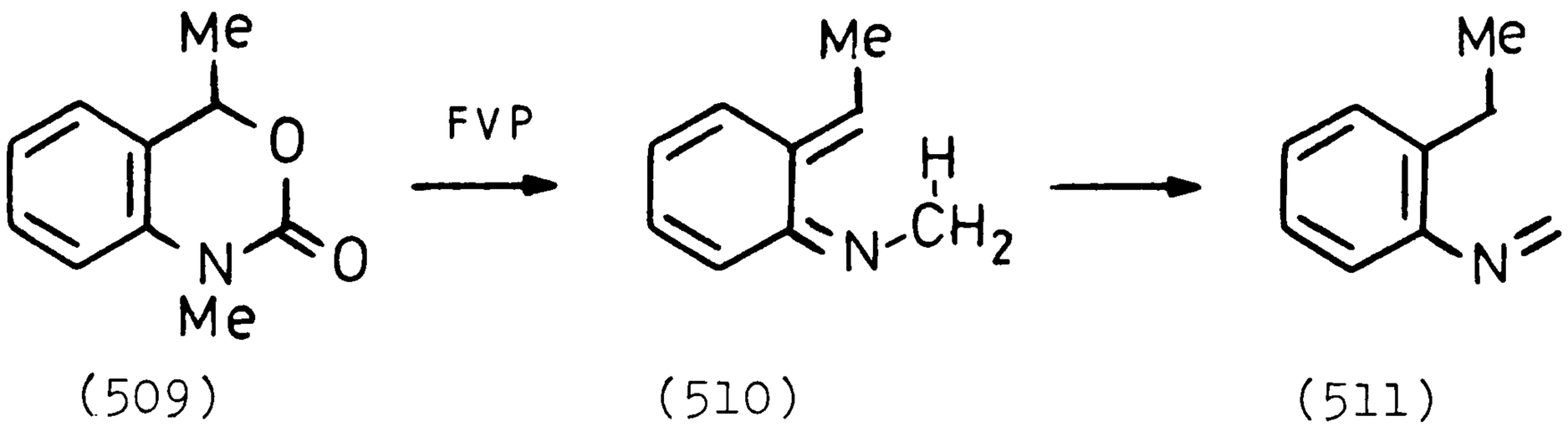
(484) (507) (508)

Cis:Trans

3:1

Presumably, the transition state for formation of tricycle (508) is less strained than that for formation of (505) and thus with a more flexible transition state, azaxylylene (507) can cyclize *via* either the *endo* or *exo* transition states to give both *cis* and *trans* fused products.

The efficiency with which azaxylylenes (504) and (507) cyclize to give the cycloadducts (505) and (508) is worthy of comment. As was stated earlier, Noyce[239] found that similar pyrolysis of the corresponding N-substituted systems gave only a low yield (6%) of the lower tricyclic homologue (304, n = 3) and none of the higher homologue (304, n = 4). However, from earlier work by Glasbey[243] it seems that substituents on the nitrogen of the azaxylylene can more easily locate themselves in the "inside" (Z) configuration than the same substituents on carbon due to inversion of the nitrogen which may occur through an sp hybridized atomic centre. Thus generation of dimethyl azaxylylene (510) from dihydrobenzoxazinone(509) gives the imine (511) by hydrogen shift from the N-methyl substituent. Thus for the N-substituted alkenyl azaxylylenes, hydrogen shift will be easier than for the corresponding carbon substituted systems due to the N-substituted azaxylylenes being more able to adopt the Z-configuration.

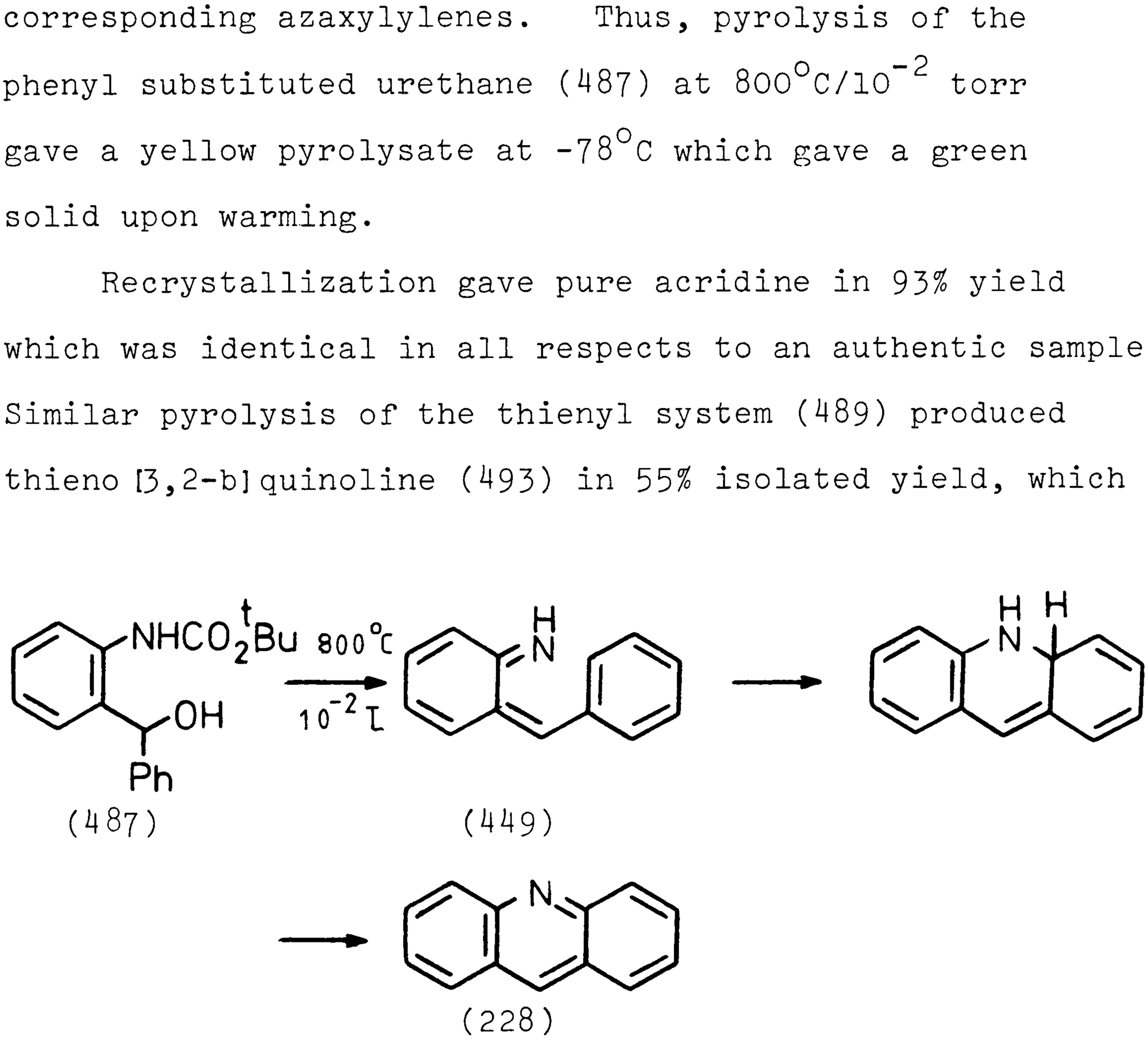


(509) (510) (511)

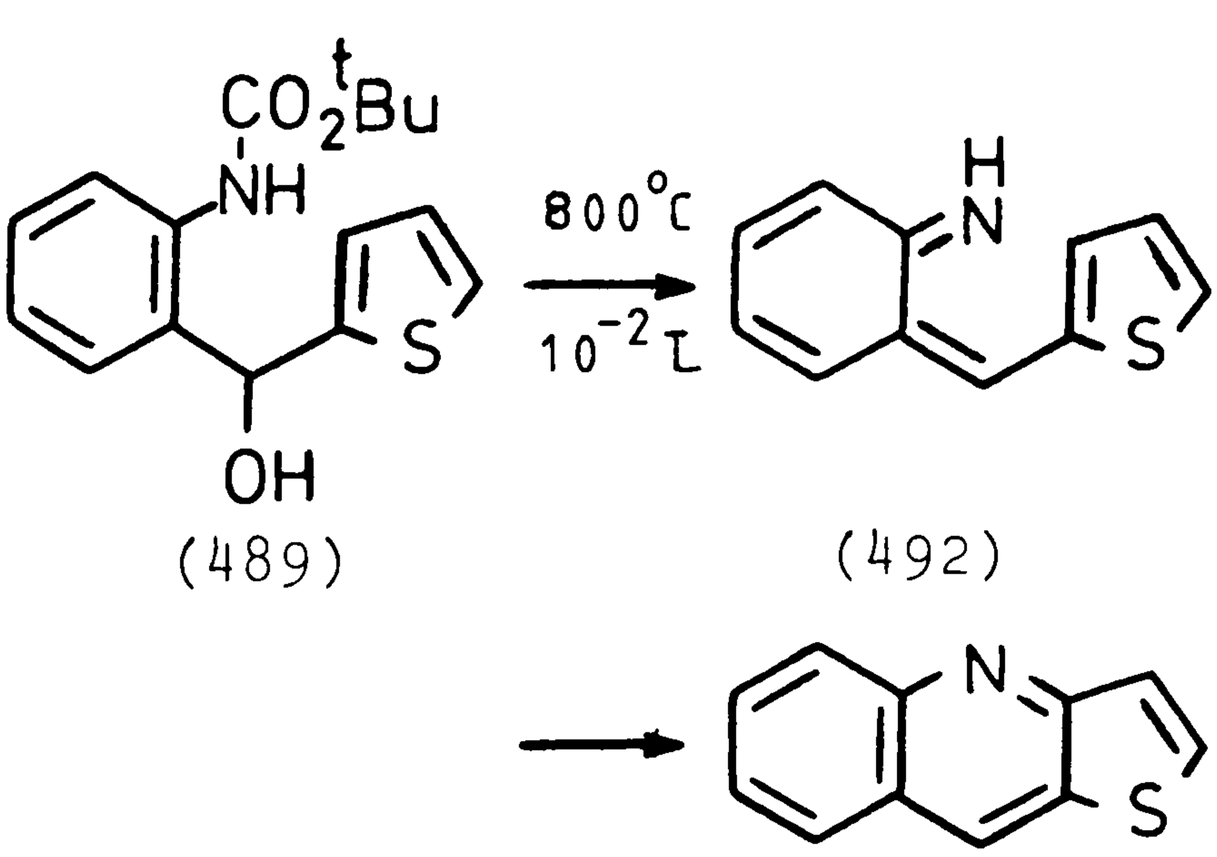
5.3 FROM 2-N-tert-(BUTOXYCARBONYL)AMINOBENZYL ALCOHOLS

It was found that deprotection of the urethanes prepared as described in Chapter 4 (page 171) to the corresponding amino alcohols was entirely unnecessary as direct pyrolysis of these urethanes at an ideal temperature of 800°C appears to generate efficiently the corresponding azaxylylenes. Thus, pyrolysis of the phenyl substituted urethane (487) at 800°C/10^{-2} torr gave a yellow pyrolysate at -78°C which gave a green solid upon warming.

Recrystallization gave pure acridine in 93% yield which was identical in all respects to an authentic sample. Similar pyrolysis of the thienyl system (489) produced thieno[3,2-b]quinoline (493) in 55% isolated yield, which



(487) (449) (228)

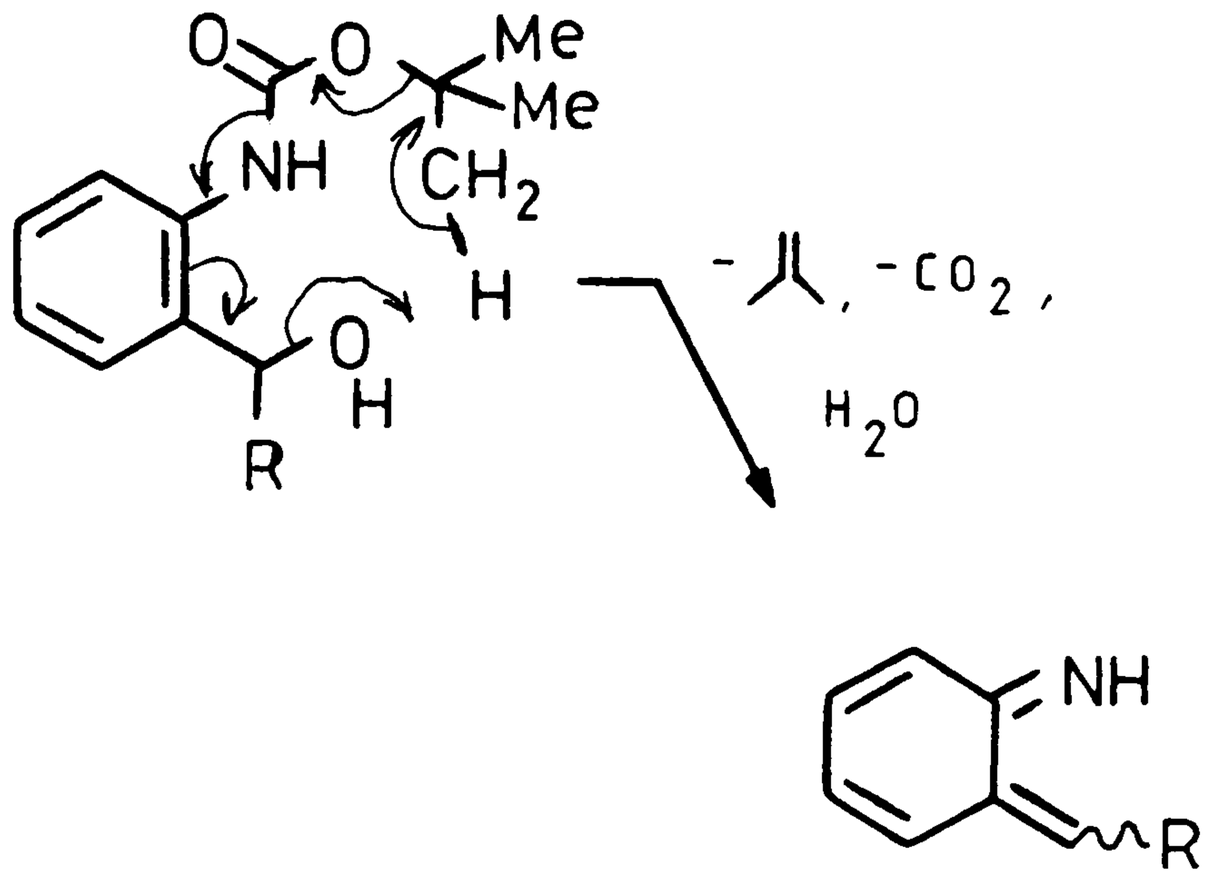


(489) (492)

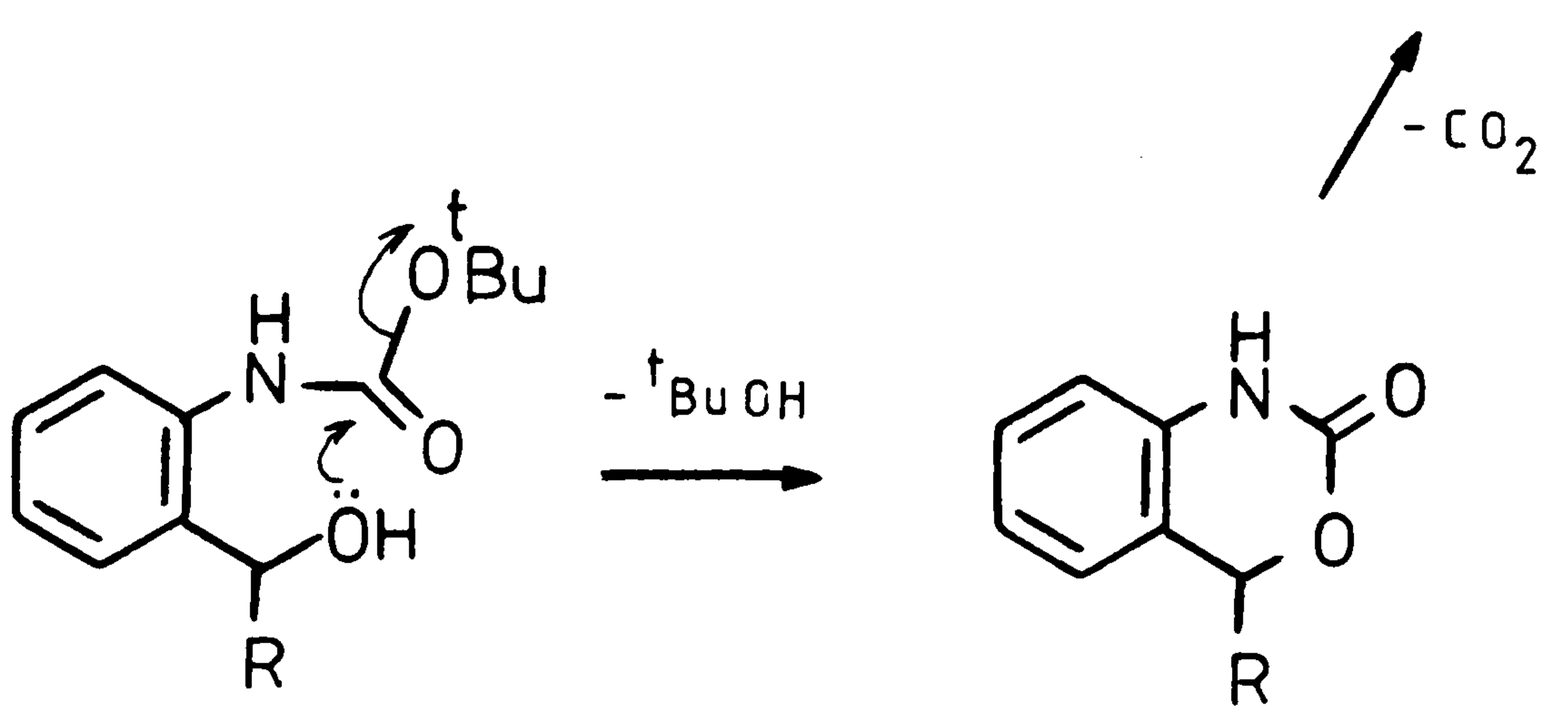
was identical to a sample produced from pyrolysis of the free amino alcohol (462) described previously.

Two reasonable mechanisms can be proposed for this fragmentation. The first involves loss of isobutene, CO_2, and water, possibly in concert, to give the azaxylylene directly (path a). The second and perhaps more likely mechanism, involves intramolecular displacement of tert-butanol from attack of the hydroxyl on the urethane moiety to give an intermediate dihydrobenzoxazinone which under the conditions of flash vacuum pyrolysis undergoes retro Diels-Alder reaction to yield the azaxylylene (path b).

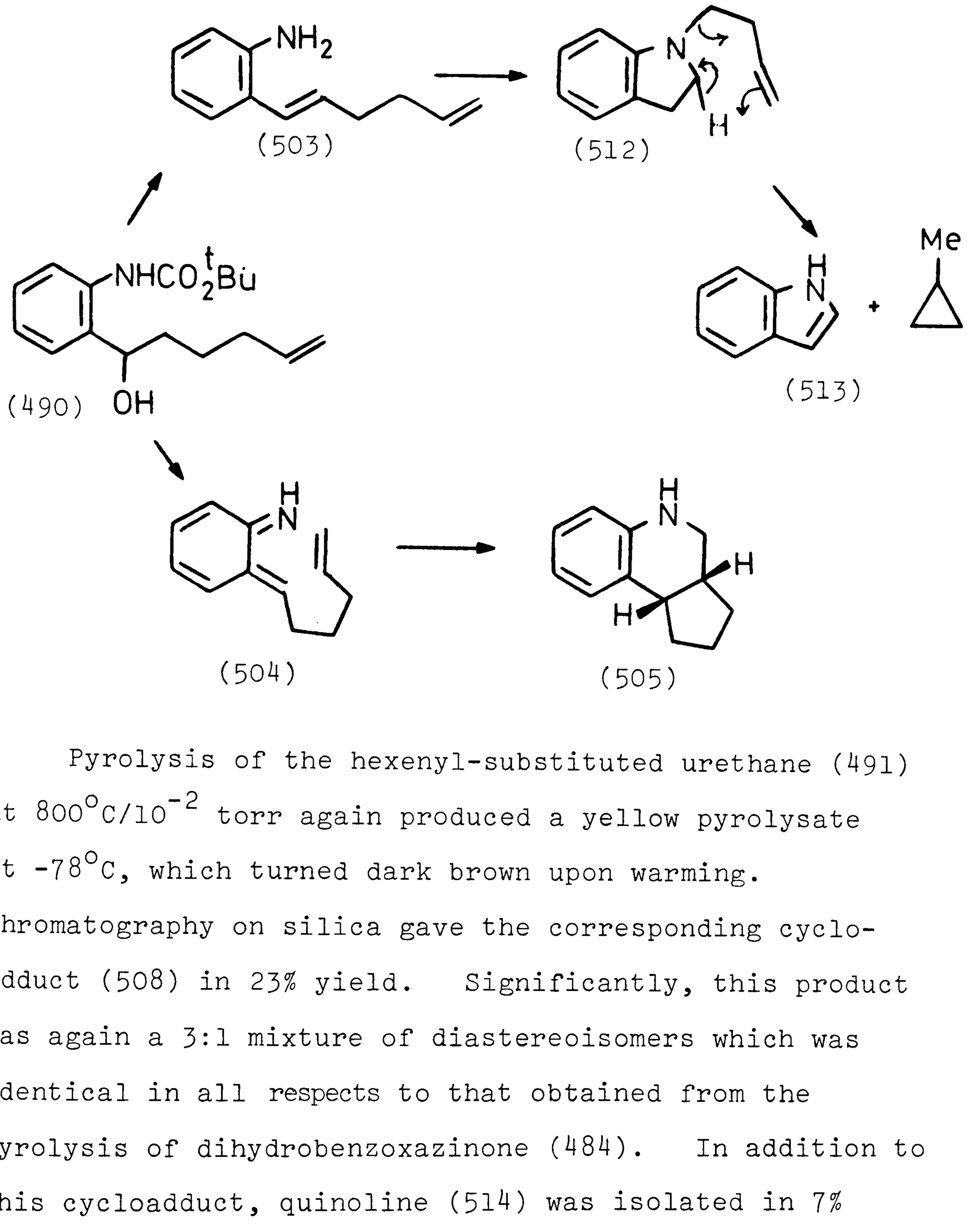
Path a



Path b

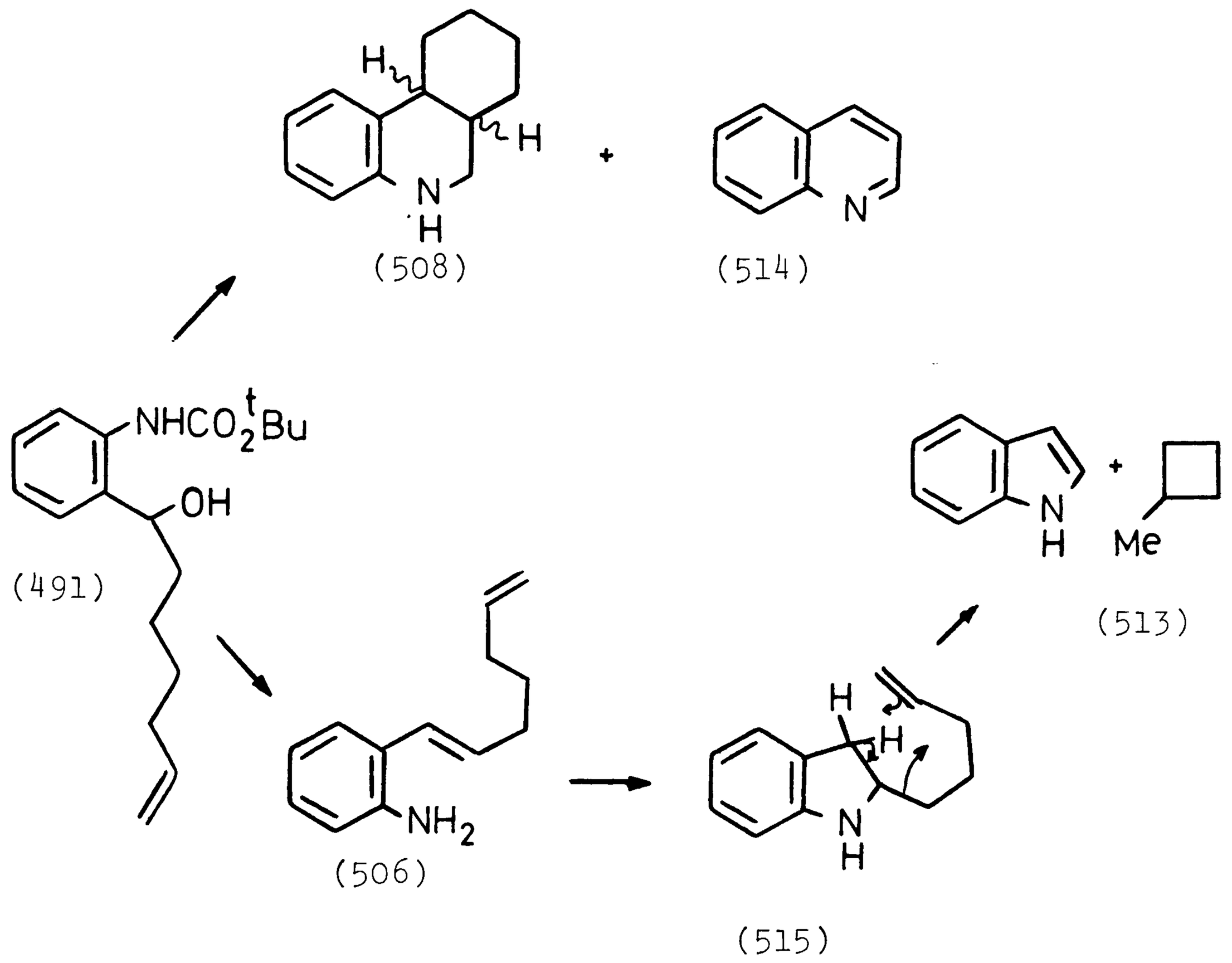


Pyrolysis of the pentenyl substituted urethane (490) at $800^{\circ}C/10^{-2}$ torr gave a deep yellow pyrolysate at $-78^{\circ}C$ which turned dark red on warming to room temperature. Chromatography of the resulting dark red oil gave the tricyclic cycloadduct (505) in 21% yield. This was again a single diastereoisomer as revealed by ^{1}H and ^{13}C n.m.r. and was identical in all respects to the same product obtained from pyrolysis of the pentenyl benzoxazinone (483) described earlier. However, in addition to this product, indole (513) was isolated in 15% yield and was identified by comparison with an authentic sample. The presence of this product together with the cycloadduct (505) was also confirmed by analysis of the crude pyrolysate using g.c./m.s. which showed components with molecular ions at m/z 173 for the cycloadduct, and m/z 117 for indole. The formation of indole (513) from the pyrolysis of urethane (490) was unexpected and difficult to explain. However, one possible mechanism would involve the initial formation of the amino styrene (503) from either 1,5-hydrogen shift in azaxylylene (504), or 1,2-dehydration of alcohol (490) followed by loss of the urethane group. Under the conditions of flash vacuum pyrolysis this could then cyclize to give indoline (512). In order for this system to lose the alkenyl chain, we must either postulate direct homolytic cleavage or a homo-ene reaction with elimination of methyl cyclopropane. This latter product was not detected by g.c./m.s., possibly due to loss on work-up.

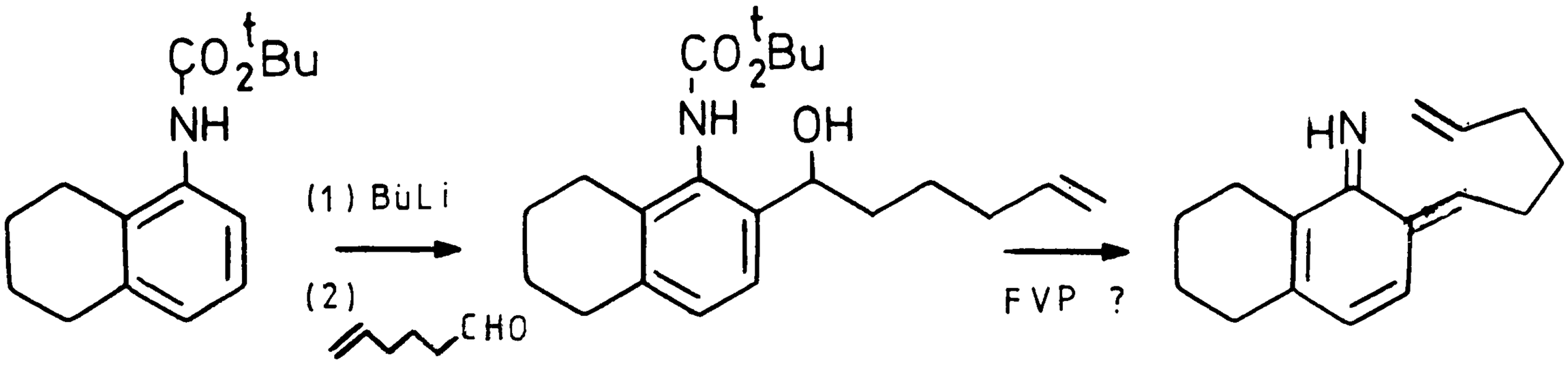


Pyrolysis of the hexenyl-substituted urethane (491) at $800^{\circ}C/10^{-2}$ torr again produced a yellow pyrolysate at $-78^{\circ}C$, which turned dark brown upon warming. Chromatography on silica gave the corresponding cyclo-adduct (508) in 23% yield. Significantly, this product was again a 3:1 mixture of diastereoisomers which was identical in all respects to that obtained from the pyrolysis of dihydrobenzoxazinone (484). In addition to this cycloadduct, quinoline (514) was isolated in 7% yield. The origin of quinoline from the pyrolysis of (491) is not clear, but fragmentation of the cycloadduct (508) under these high temperatures cannot be ruled out. In addition, indole (513) (8%) was also obtained from chromatography of the reaction mixture. Thus, indole formation in these pyrolyses appears to be general and an

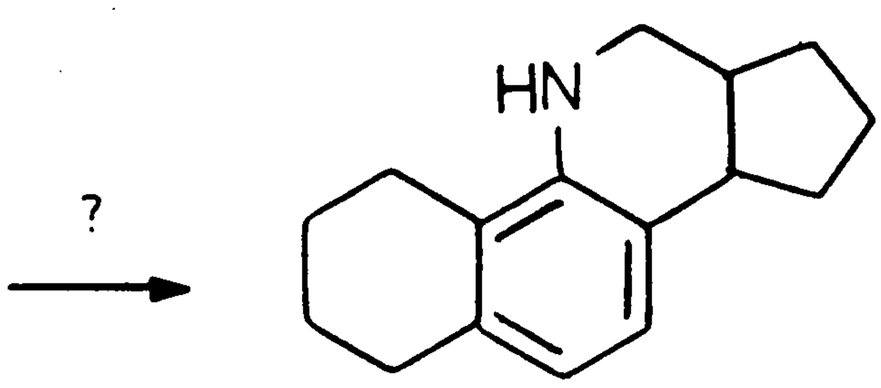
analogous reaction to that proposed for the pentenyl derivative can be considered.



In an attempt to use this approach to produce the B-ring aromatic steroid (518), the urethane (516) (made in high yield from treatment of 1-aminotetralin with di-tert-butyldicarbonate) was heated with two equivalents of tert-butyllithium to give a yellow solution. However, addition of an equivalent of hex-5-enal followed by aqueous work-up gave only recovered starting materials and none of alcohol (517). Repeated attempts failed to alter the outcome of this reaction.



(516) (517)



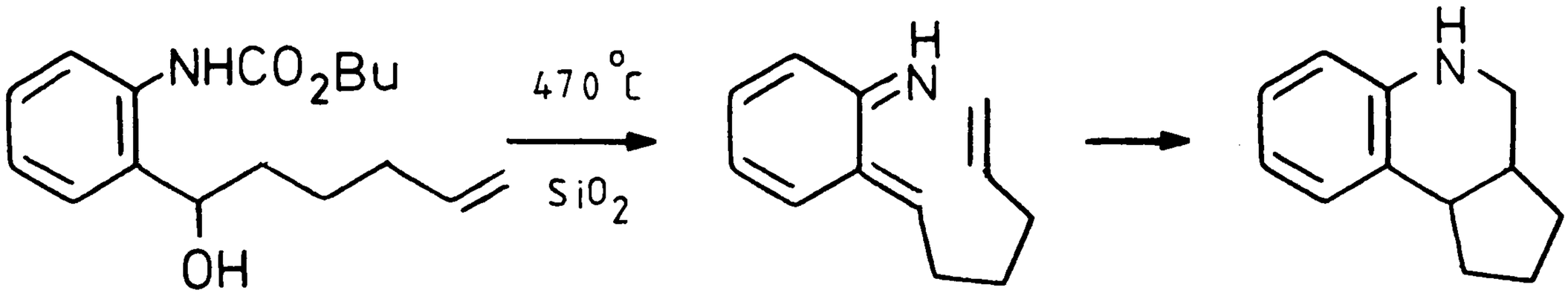
(518)

In addition, quenching the reaction mixture with deuterated methanol resulted in no incorporation of deuterium into urethane (516), indicating no anion formation was taking place. An explanation for the lack of reactivity of (516) to tert-butyllithium is yet to be found.

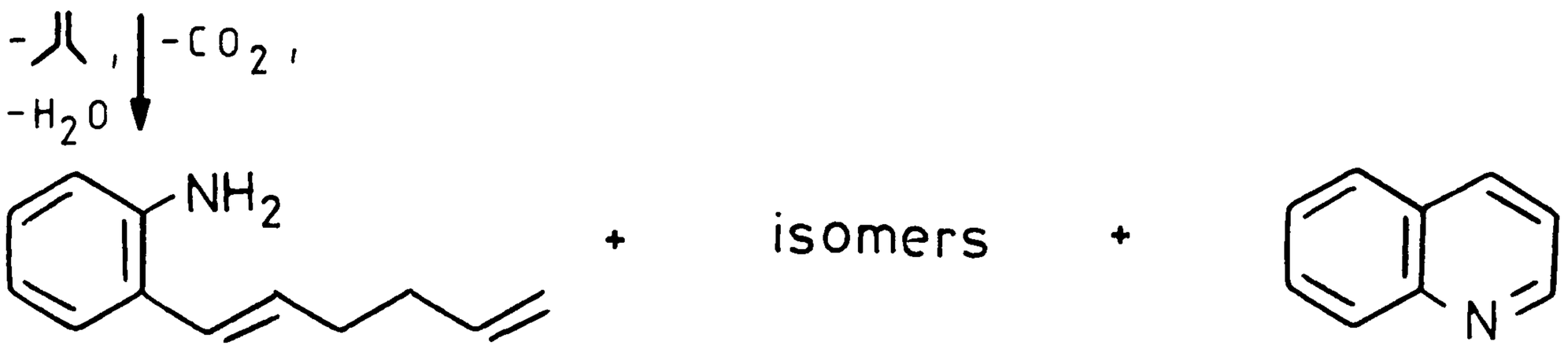
Pyrolysis of azaxylylene precursors over solid supports can have marked effects on product distributions.[256] Thus we were hopeful that pyrolysis of the alkenyl-substituted urethanes at lower temperatures over solids would increase the yields of cycloadducts obtained. Pyrolysis of the pentenyl system (490) at $470^{\circ}C/10^{-2}$ torr over silica produced a yellow pyrolysate at $-78^{\circ}C$ which turned dark green on warming to room temperature. Chromatography on silica gave the cycloadduct (505) but

in only 6% yield. Also obtained was a brown liquid which was shown to consist of at least five major components on g.c. analysis, all of which had very similar retention times, together with a number of minor products. The ^{1}H n.m.r. of this mixture was complex and revealed the presence of extensive aliphatic unsaturation in the mixture. Analysis of this mixture by g.c./m.s. revealed that almost all of these major components gave molecular ion peaks at m/z 173, and gave very similar fragmentation patterns. In addition, a minor component gave a spectrum very similar to that of quinoline (m/z 129) as found by computer aided comparison of the spectrum of this component with that of an authentic sample. The major components of this mixture would seem to correspond to various isomers of the amino styrene (503) formed from either direct 1,2-elimination and loss of the urethane protecting group from (490) or by 1,5-hydrogen shift in the azaxylylene (504). Thermal isomerization of the double bonds in (503) would account for the range of similar products in this mixture. The origin of the quinoline is harder to explain although again, fragmentation of the cycloadduct (505) cannot be discounted.

Pyrolysis of the alcohol (490) at $480^{\circ}C/10^{-2}$ torr over alumina again produced a yellow pyrolysate at $-78^{\circ}C$ which became a brown oil upon warming to room temperature. Chromatography on silica gave carbazole (519) in 35% yield as the only isolable product. This material was identified by its complete comparison (m.p., m.m.p.,

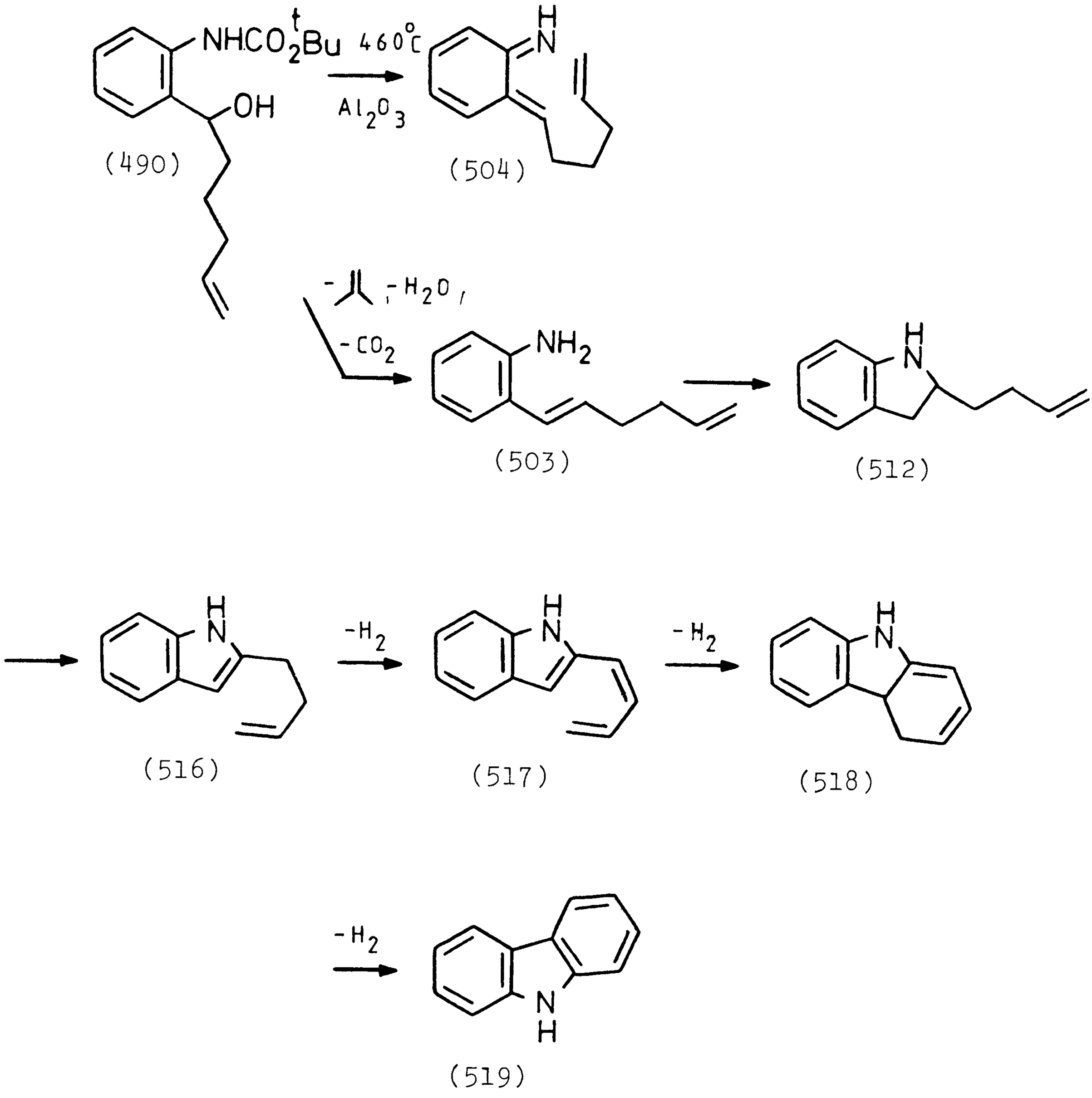


(490) (504) (505)



(503) (514)

n.m.r., i.r., g.c.) to an authentic sample. The presence of this product in the crude pyrolysate was confirmed by analysis using g.c./m.s. which in addition suggested the presence of a small amount of quinoline (m/z 129) although this was not isolated. The formation of carbazole from this pyrolysis was unexpected but can be rationalised by considering the reaction to proceed by formation of the amino styrene (503) either by 1,5-hydrogen shift in the azaxylylene (504) or 1,2-dehydration of the alcohol (490). Cyclization of this amino styrene under the conditions of pyrolysis gives indoline (512) which could dehydrogenate to give the indole (516). Further dehydrogenation of the chain then gives diene (517) which is set up to undergo a Cope-rearrangement to give dihydrocarbazole (518).



Final dehydrogenation of (518) gives carbazole (519).

The enhanced ability of alumina as a dehydrogenating agent compared to that of silica in flash vacuum pyrolysis was noted by Noyce.[239] This may explain why pyrolysis of this alcohol over silica seems to produce mainly amino styrenes whereas pyrolysis of the same system over alumina allows further reactions to occur by dehydrogenation.

The following points have emerged from the reactions of carbon substituted azaxylylenes discussed so far. Once generated, carbon substituted azaxylylenes appear to undergo the same types of reactions as the nitrogen analogues, regardless of the precursor used. Specifically, they can undergo intramolecular Diels-Alder cycloadditions, electrocyclization reactions and possibly 1,5-hydrogen shifts. However, in certain instances, the precursor of choice appears to depend on the particular product required from reaction of the o-azaxylylene. For the products of electrocyclization of o-azaxylylenes, o-aminobenzyl alcohols, o-N-tert-(butoxycarbonyl)aminobenzyl alcohols and, 1,4-dihydro-3,1-benzoxazin-2-ones appear equally suitable precursors with the urethanes offering the advantage of generality and ease of synthesis.

For intramolecular Diels-Alder cycloadditions, the dihydrobenzoxazinones are clearly the most efficient precursors as 1,2-dehydration is precluded.

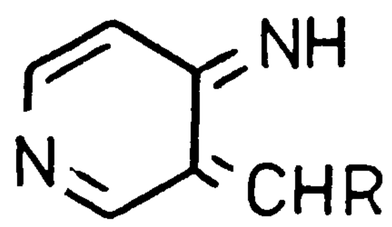
The urethanes are less efficient in producing the Diels-Alder adducts, but again they have the advantage of ease of preparation. The amino alcohols themselves are essentially useless for obtaining intramolecular Diels-Alder cycloadducts from o-azaxylylenes.

From preliminary studies, it appears that the presence of silica or alumina in the hot zone during FVP is only useful when it is necessary to lower the temperature needed to generate a carbon-substituted azaxylylene which is required to undergo electrocyclization. With the alkenyl substituted

urethanes, silica and alumina appear to promote 1,2-dehydration and particularly in the case of alumina, the products from this dehydration can undergo further reaction.

6. THE GENERATION AND CHEMISTRY OF HETEROAROMATIC-BASED o-AZAXYLYLENES

All of the o-azaxylylenes mentioned so far have been based entirely on the benzene ring as the aromatic nucleus of the system. Having developed a satisfactory route to carbon substituted o-azaxylylenes, it was decided to turn our attention to using this methodology to produce the first examples of o-azaxylylenes based on heteroaromatic ring systems and to explore their chemistry.[273] Initially, it was decided to attempt the generation of the pyridine-4,5-azaxylylene system (520) since construction of the urethane precursor would start from the readily available 4-amino pyridine.



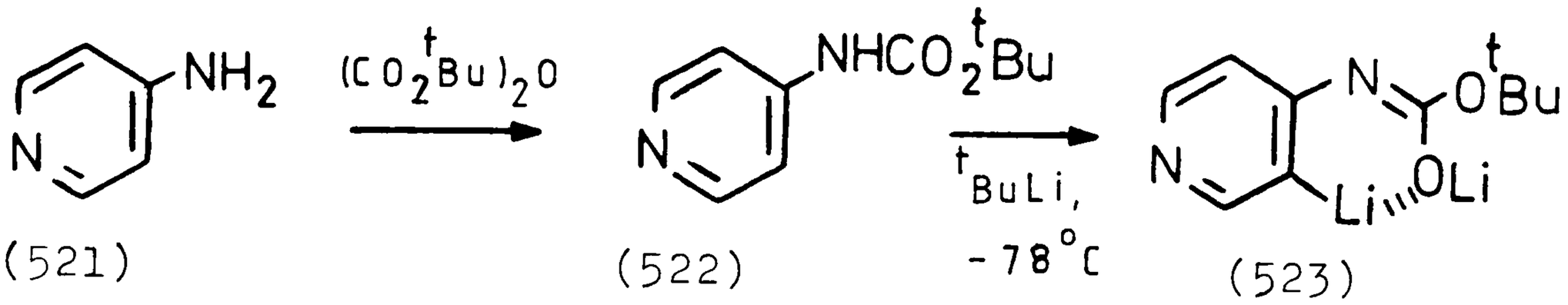
(520)

Our planned strategy was to construct the precursor to this system by directed o-lithiation of the tert-butoxycarbonyl urethane of 4-aminopyridine, followed by reaction with an aldehyde to give the required tert-butoxycarbonyl urethane-alcohols. The reaction of

4-amino pyridine (521) with di-tert-butyl dicarbonate in refluxing THF under nitrogen gave a near quantitative yield of the 4-N-tert-butoxycarbonylamino pyridine (522). Treatment of this urethane with the two-fold excess of tert-butyl lithium in anhydrous THF under argon at -78°C gave a yellow/orange solution presumably of the dianion (523). Treatment of this solution with an equivalent of benzaldehyde gave the phenyl-substituted urethane (524) in 63% yield after recrystallization.

As before, deprotection of this urethane to the amino alcohol was unnecessary as direct pyrolysis of this system at 800°C/10^{-2} torr gave a pale yellow pyrolysate at -78°C which afforded a pale yellow solid on warming to room temperature. Recrystallization gave the known naphthyridine (526) in 80% yield. Presumably, flash vacuum pyrolytic fragmentation of the urethane (524) produces pyridine-4,5-azaxylylene (525) which undergoes electrocyclization to give (526) after dehydrogenation of the initial dihydro species.

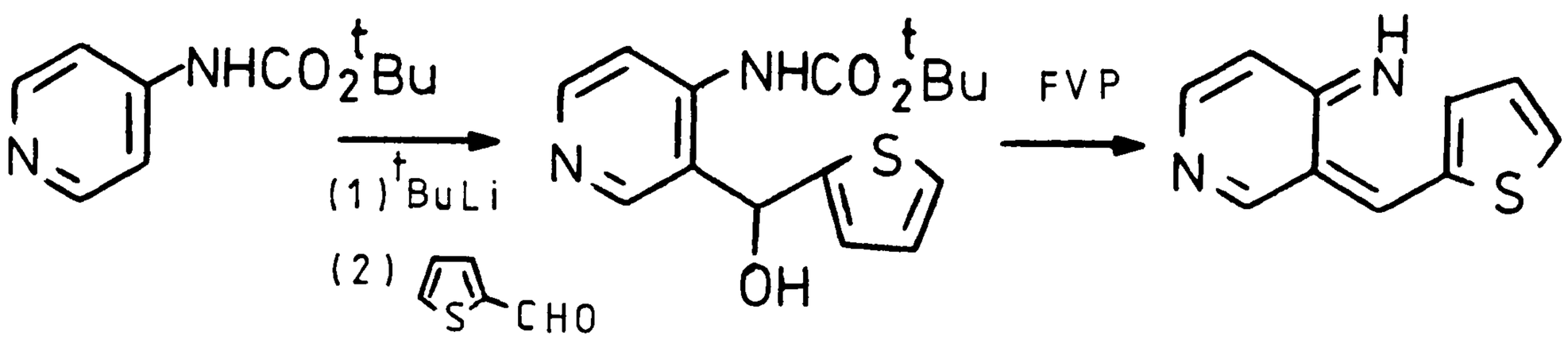
The physical properties of naphthyridine (526) were in full agreement with those reported.[274] The ^{1}H n.m.r. spectrum was similarly in agreement with the assigned structure and showed two singlets at δ 9.45 and 8.85 corresponding to the C-6 and C-5 protons respectively. The rest of the spectrum consisted of four doublets at δ 8.69, 8.20, 8.20, 8.03 and 7.98 ppm, corresponding to the protons at C-3, C-2, C-10 and C-7 respectively. Finally, the signals due to the C-8 and C-9 protons appear



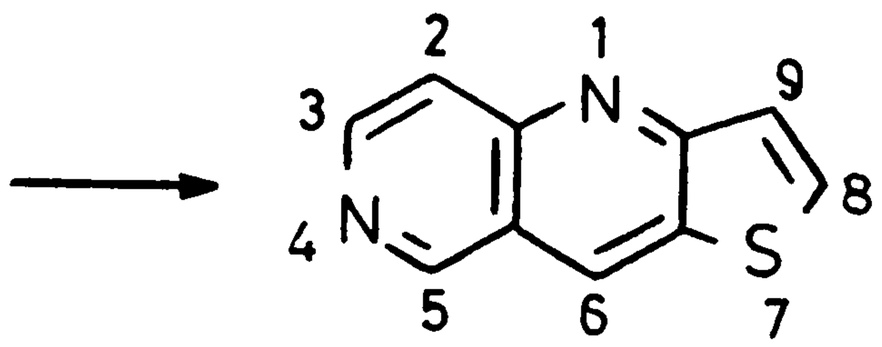
as triplets at δ 7.86 and 7.57 ppm. In the proton noise decoupled ^{13}C n.m.r. spectrum, the signals due to all twelve carbons could clearly be seen. The off-resonance spectrum consisted of four singlets due to the four quaternary carbons in the molecule, and the remainder appeared as eight doublets. Finally, the mass spectrum gave a molecular ion at m/z 180 which agrees with the proposed formula of $C_{12}H_8N_2$.

In view of the success of this approach, we decided to demonstrate its generality by placing different substituents on the pyridine-azaxylylene precursor. Reaction of the dianion (523) with thiophene-2-carboxaldehyde followed by aqueous work-up gave the thiophene substituted urethane (527) in 71% yield after recrystallization.

Flash vacuum pyrolysis of (527) at 800°C/10^{-2} torr similarly gave a yellow pyrolysate at -78°C which produced a dark green oil. Chromatography on silica gave a brown solid which was recrystallized to give the thieno-naphthyridine (529) in 68% yield.



(522) (527) (528)



(529)

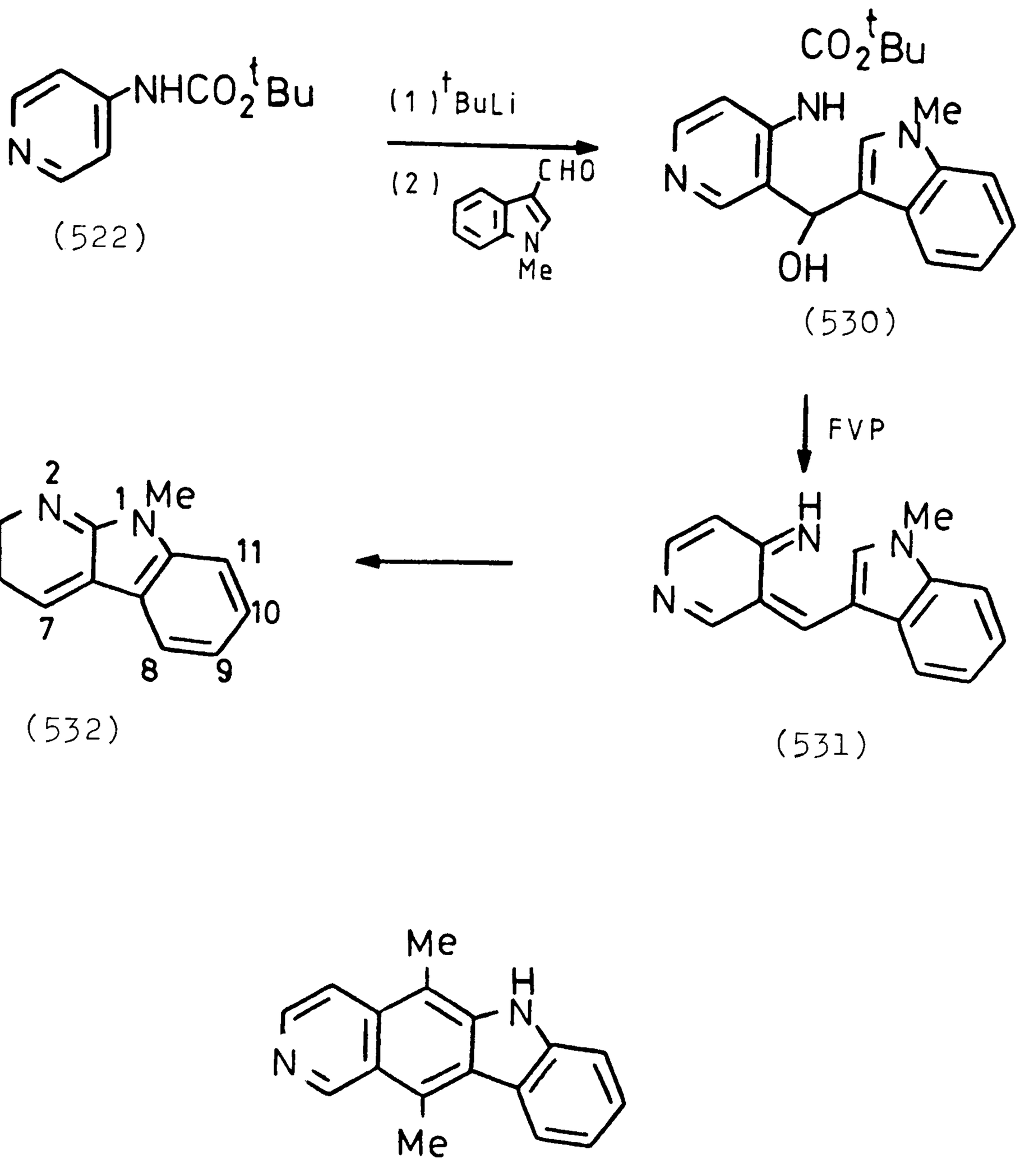
The ^{1}H n.m.r. spectrum of thienonaphthyridine (529) consisted of two singlets at δ 9.41 and 8.85 corresponding to protons at C-6 and C-5 respectively, the rest of the spectrum consisted of four doublets at δ 8.76, 8.16, 8.01 and 7.70 ppm corresponding to protons at C-3, C-2, C-8, and C-9 respectively. The mass spectrum showed a molecular

ion at m/z 186 with an accurate mass of 186.0275 which is in complete agreement with the assigned structure. Finally, the elemental analytical data further supports the proposed structure.

Reaction of the pyridine dianion (523) with the commercially available N-methylindole-3-carboxaldehyde followed by aqueous work-up gave the indolyl urethane (530) but in a disappointing yield of 10% after chromatography on silica and recrystallization from dichloromethane/hexane. This low yield was not entirely surprising, since attempted reaction of the aniline derived di-lithiated urethane (486) with this aldehyde did not produce any of the desired indolyl urethane (488) (page 174). Pyrolysis of (530) gave a yellow pyrolysate at -78°C which changed to dark brown on warming to room temperature. Chromatography on alumina produced a pale brown oil which solidified on standing. Recrystallization gave the indole-fused system (532) but in only 13.5% yield. The assignment of the structure (532) to this product was essentially based on ^{1}H n.m.r. and mass spectral data. The proton spectrum consisted of two singlets at δ 9.35 and 8.91 ppm, each integrating for one proton and were assigned to the protons at C-7 and C-6 respectively. The three doublets which would be expected for the protons at C-4, C-3 and C-11 could be seen at δ 8.66, 8.20 and 7.86 ppm respectively, each of which integrate for one proton.

The signal due to the C-10 proton appeared as a triplet at δ 7.31 ppm. The remaining signals for the C-8 and C-9 protons which should appear as a doublet and a triplet were observed as a multiplet between δ 8.32 and 8.21 ppm, which integrated for two protons. Finally, the protons on the methyl at N-1 were observed as a singlet at δ 3.94 ppm. The mass spectrum of this product gave a molecular ion peak at m/z 233 which had an accurate mass of 233.0940 which is in close agreement to that required for the proposed molecular formula. Unfortunately, there was insufficient material to obtain an elemental analysis on this compound. However, despite the low yields encountered for the preparation of this product, we feel that its formation provides an illustration of the potential of these gas-phase electrocyclization reactions of o-azaxylylenes. Indole (532) is in fact an aza-analogue of the alkaloid ellipticene (533) which has been shown to have potent antitumour activity.[275]

To complete our studies on the pyridine-4,5-azaxylylene system, we decided to test the feasibility of trapping this species in an intramolecular Diels-Alder reaction. The synthesis of the precursor proceeded straightforwardly by reaction of the lithium dianion with an equivalent of hex-5-enal to give alcohol (534) in 37% yield after chromatography on silica. Pyrolysis of this system using the usual conditions gave a pale yellow pyrolysate. Recrystallization gave the cycloadduct (536) in 64% yield. As with previous cycloadducts, the evidence for

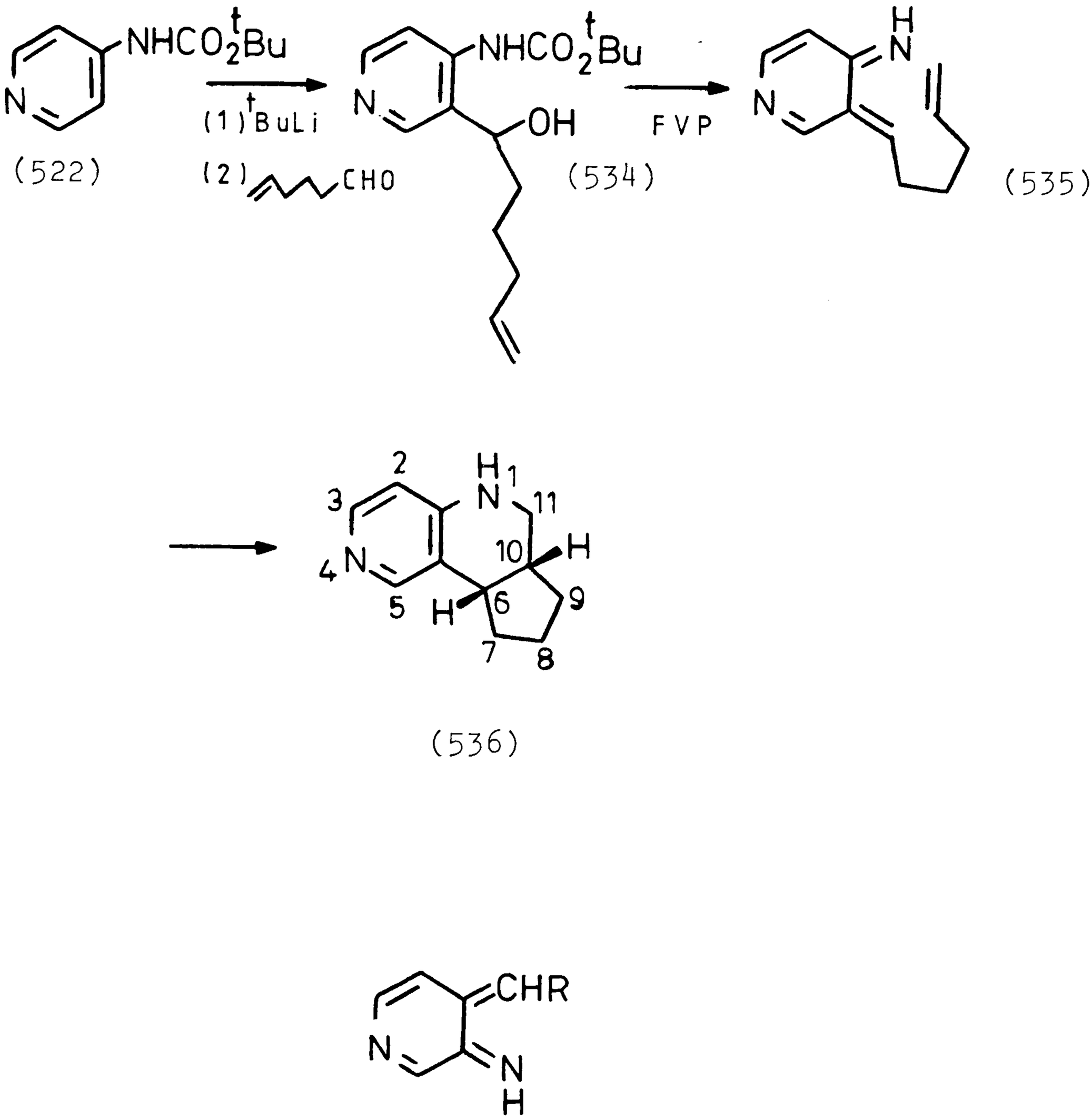


the structure of this compound ultimately rests on the ^{1}H n.m.r. in which the aromatic hydrogens could be seen as a doublet for C-3 at δ 7.90, a singlet for C-5 at δ 7.84, and a doublet for C-2 at δ 6.33 ppm. The two protons at C-11 as with previous tricyclic adducts, are prochiral and therefore appear separately as a doublet of doublets at δ 3.58 ppm, and a triplet at δ 3.19 ppm. As with previous examples, further assignment of the spectrum, which consisted of a series of multiplets integrating for

eight protons, was hindered by its complexity. However, using homonuclear decoupling techniques, it was possible to assign the signals due to the bridgehead protons at C-6 and C-10 to the multiplets between δ 2.45 and 2.25 ppm, and 1.80 and 1.45 respectively. Unfortunately, these multiplets could not be further simplified using decoupling techniques to allow measurement of the C-6, C-10 coupling constant which would reveal the stereochemistry of the ring junction. However, the aliphatic region of the spectrum was extremely similar to that of the tricyclic adduct (505) obtained previously, and thus the stereochemistry of this adduct is tentatively assigned as cis. The ^{13}C n.m.r. spectrum fully supported the proposed tricyclic structure and all carbons except for the quaternary carbons could be clearly observed, the off-resonance noise decoupled spectrum showing three aromatic doublets, two aliphatic doublets and four aliphatic triplets. The molecular ion in the mass spectrum at m/z 174 and its accurate mass of 174.1766 are in full agreement with the molecular formula of $C_{11}H_{14}N_2$ as is the elemental analysis.

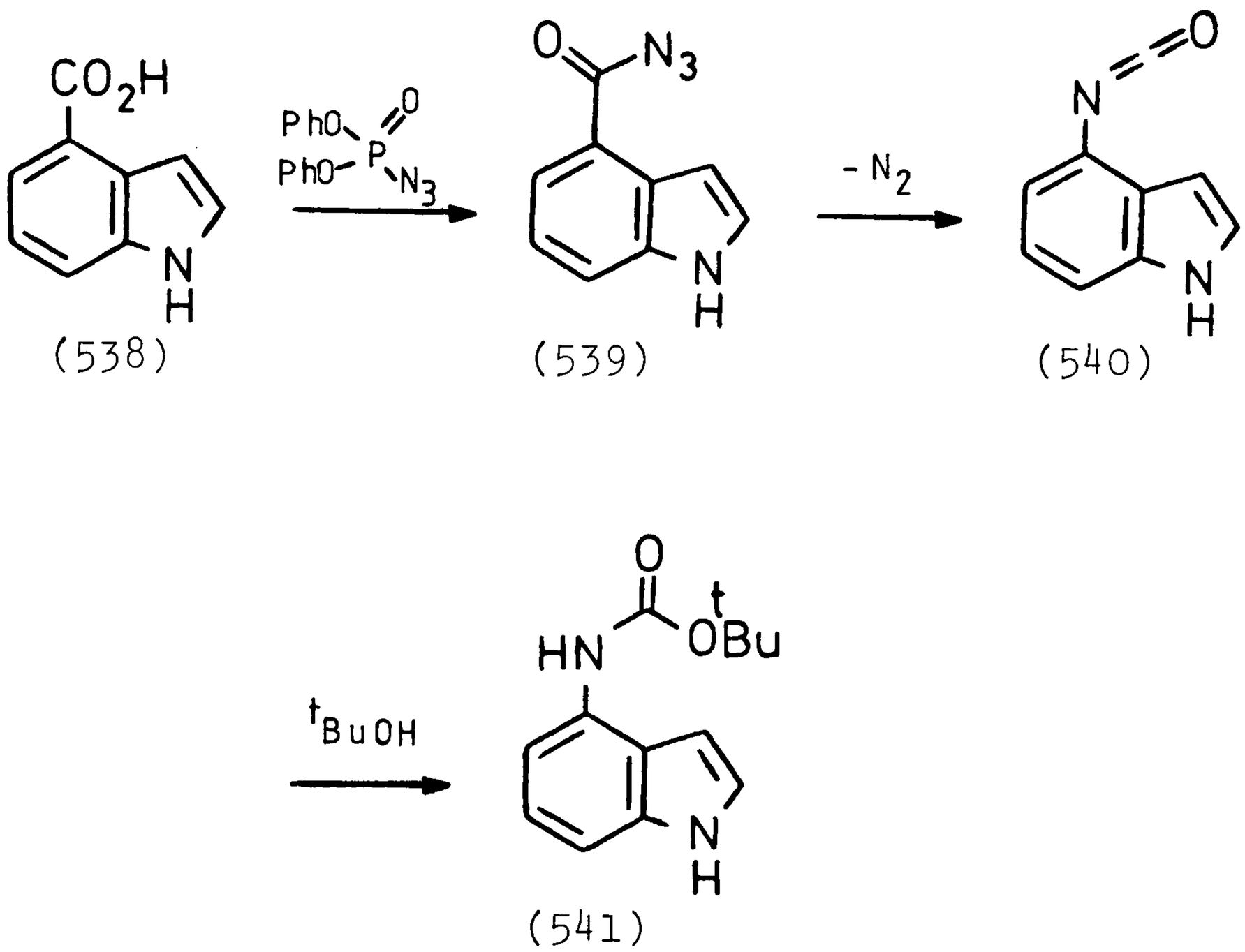
Encouraged by the efficient cycloadditions of this azaxylylene, it was decided to extend our studies to other pyridine based o-azaxylylene systems.

For the generation of the pyridine-3,4-azaxylylene system (537), a similar approach to that used previously was envisaged, starting from 3-N-tert-butoxycarbonylamino-pyridine, followed by lithation and quenching with a suitable aldehyde.



However, the synthesis of the urethane (543) proved to be problematical. All attempts to form (543) by reaction of 3-amino pyridine with di-tert-butyl dicarbonate in refluxing THF or dichloromethane gave only an amorphous, polymeric brown solid. The presence of a catalytic amount of 4-N,N-dimethylaminopyridine or an equivalent of triethylamine

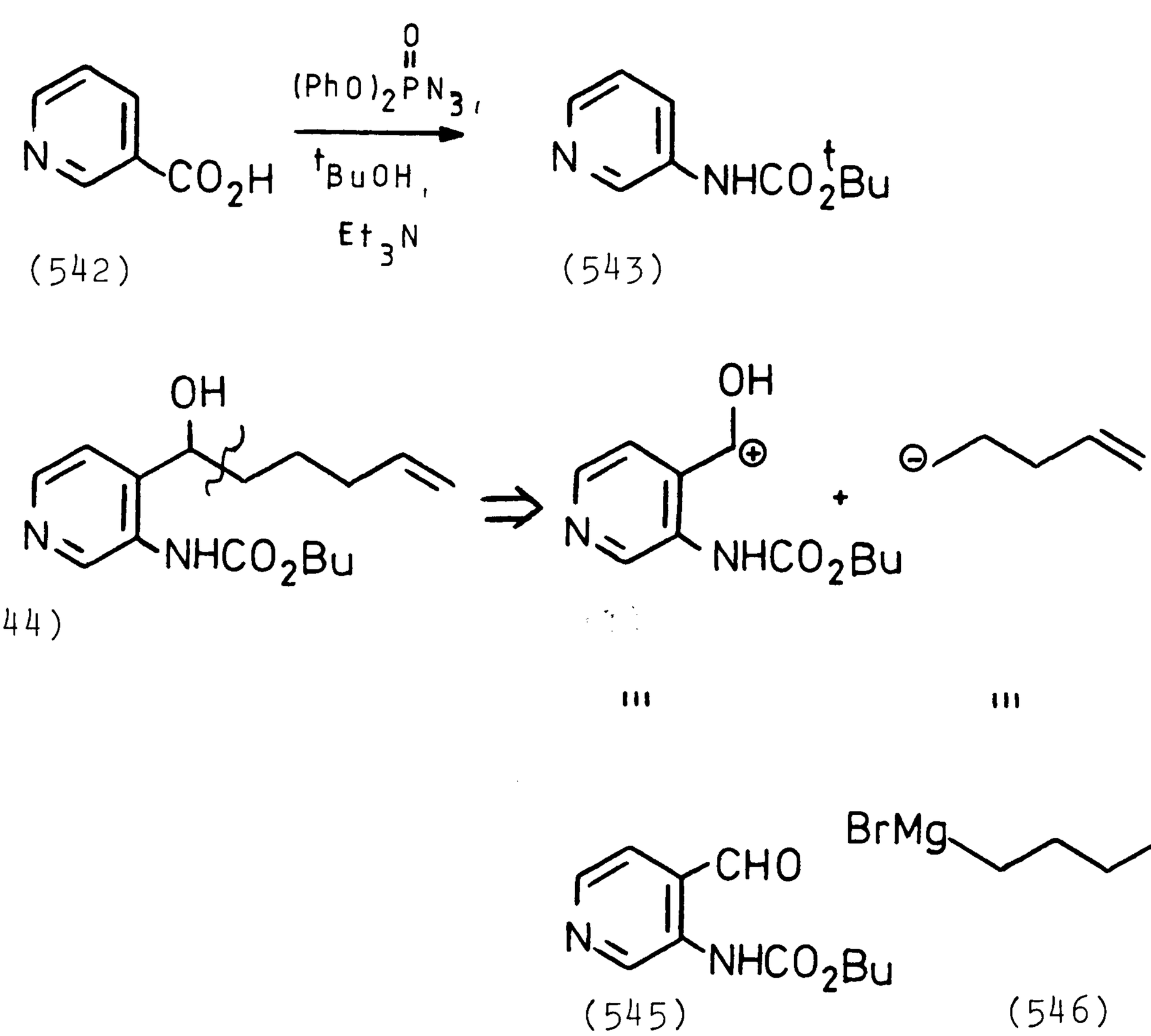
did not significantly alter the course of the reaction. However, Shioiri[276] has found that a good way of making the indole based urethane (541) is by treatment of indole-4-carboxylic acid (538) with diphenylphosphoryl azide in tert-butanol in the presence of triethylamine. This essentially involves formation of an intermediate acyl azide (539), and Curtius rearrangement to give isocyanate (540) which is trapped in situ with tert-butanol to provide the urethane (541).



(538) (539) (540) (541)

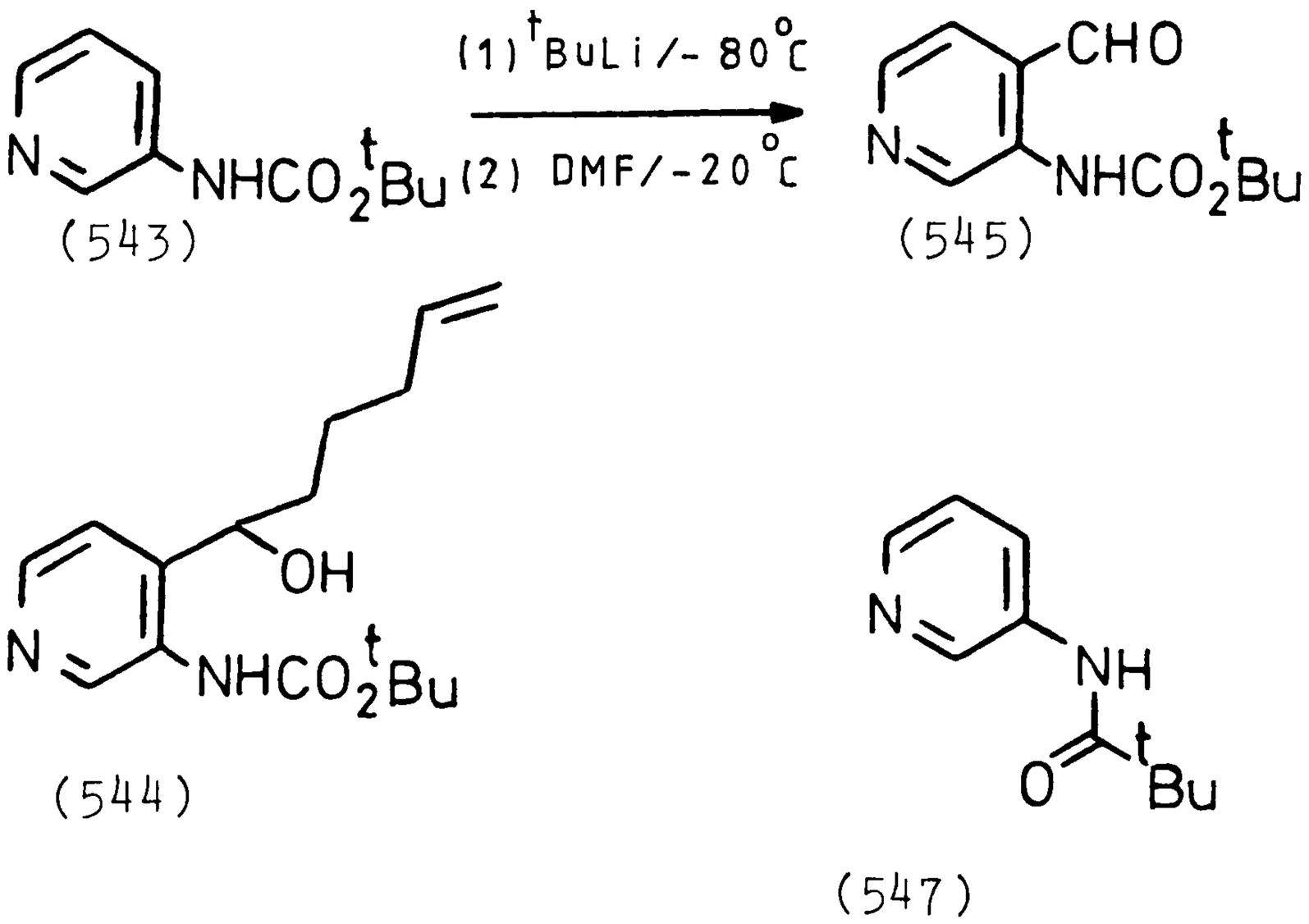
Thus, heating a solution of nicotinic acid (542) under reflux with an equivalent of diphenylphosphoryl azide in anhydrous tert-butanol under argon gave the

desired pyridine urethane (543) in 77% yield. It then only remained to achieve directed o-lithiation of (543) and quenching with a long-chain aldehyde as before to obtain the required azaxylylene precursor (544). However, this approach to (544) is perhaps not the most convenient, as although hex-5-enal is available, its synthesis is rather tedious and it was, therefore, desirable to modify this route. Retrosynthetic disconnection of the target molecule (544) as shown in Scheme 8 gives the aldehyde (545) and Grignard reagent (546) as the required components.

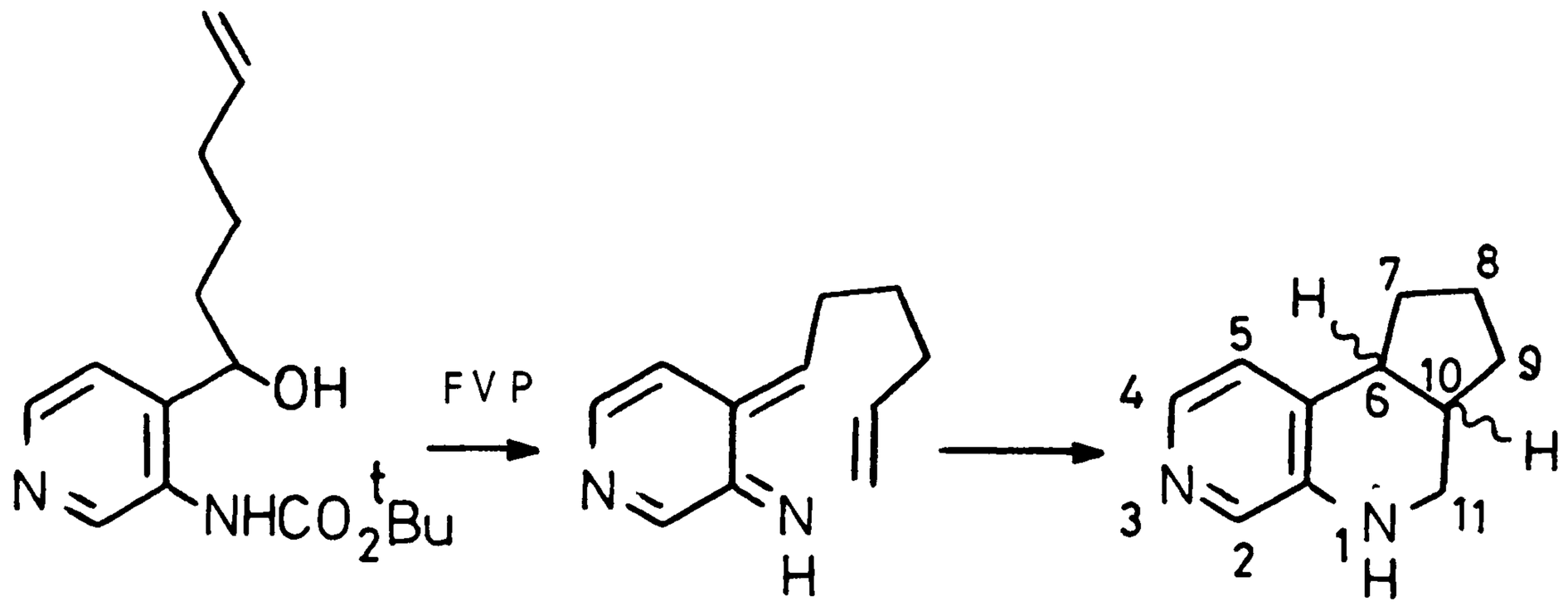


SCHEME 8

Treatment of urethane (543) with two equivalents of tert-butyllithium at -78°C followed by the addition of anhydrous DMF was straightforward and gave the aldehyde (545) in 81% yield. Inspection of the ^1H n.m.r. spectrum of aldehyde (545) clearly revealed the exclusive formation of the 4-formyl derivative and the total absence of any 2-formylated material. There is some literature precedent for this behaviour as the similar 4-pivaloyl pyridine system (547) also undergoes exclusive lithiation at the 4-position.[277] Treatment of aldehyde (545) with 3.5 equivalents of pent-5-enyl-1-magnesium bromide (prepared from the commercially available 5-bromohexene) produced the desired alcohol (544) in 88% yield. Like other alkenyl-urethane systems, this compound was an extremely viscous glass-like oil which could not be induced to solidify and which suffered partial decomposition on attempted distillation so that an elemental analysis was not obtained. However, all the spectroscopic data obtained for this compound were in full agreement with the proposed structure.



Pyrolysis of urethane (544) at 800°C/10^{-2} torr produced a yellow pyrolysate at -78°C which gave a brown tacky solid upon warming to room temperature. This was shown to be a mixture of two products with very similar R_f values on t.l.c. However, purification by p.t.l.c. on silica using repeated elutions did allow some degree of separation of these components and they were identified as the cis- and trans-diastereoisomers of the intramolecular Diels-Alder cycloadducts (549) from pyridine-3,4-azaxylylene (548).



(544) (548) (549)

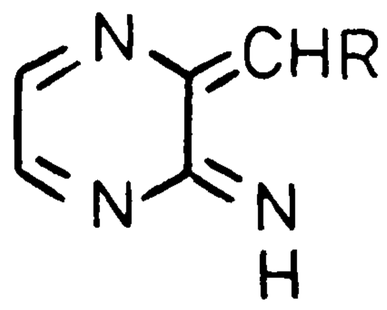
The faster running isomer was obtained as a colourless oil and the ^1H n.m.r. spectrum revealed the expected di-substituted pyridine pattern consisting of a singlet at δ 7.94 ppm corresponding to the C-2 proton, and two doublets at δ 7.89 and 6.97 ppm corresponding to the

C-4 and C-5 protons respectively. In accord with the spectral data from previous cycloadducts, the two protons at C-11 could be observed as a doublet of doublets at δ 3.20 and a triplet at δ 2.81 ppm. However, in between these, there was a multiplet between δ 3.05 and 2.91 ppm, integrating for one proton which was tentatively assigned to the C-6 bridgehead. The remainder of the spectrum consisted of a set of overlapping multiplets between δ 2.46 and 1.40 which integrated for seven hydrogens, corresponding to the C-7, C-8 and C-9 methylenes, and the C-10 bridgehead proton.

The slower running isomer was a colourless, crystalline solid, whose ^{1}H n.m.r. contained the same type of 2,3-disubstituted pyridine pattern, namely, a singlet at δ 7.84 (C-2), and a pair of doublets at δ 7.81 (C-4), and δ 6.93 (C-5). The peak patterns in the aliphatic region of the spectrum appeared more familiar than those of the faster running isomer, and closely resembled the spectra of the previously mentioned pyridine-4,5-azaxylylene derived cycloadduct (536) which had been tentatively assigned cis-stereochemistry. This region of the spectrum contained a doublet of doublets at δ 3.61 ppm and a triplet at δ 3.19 ppm corresponding to the protons at C-11 in this isomer. The rest of the spectrum consisted of a set of overlapping doublets corresponding to the eight protons at C-7, C-8 and C-9. The rest of the cycloadduct obtained from chromatography was a pure mixture of slower and faster running isomers

in the ratio 4:1 as determined by ^{1}H n.m.r. Thus, the cycloadduct (549) was obtained as a 1:1 mixture of cis and trans-isomers. Because of the close similarity of the spectrum obtained from the slower running isomer to the tentatively assigned cis cycloadducts obtained from the cycloadditions of other azaxylylenes, it is tempting to assign the stereochemistry of this isomer as cis with the faster running isomer therefore being trans, but as with previous assignments, this must remain tentative.

Having investigated the chemistry of pyridine-based systems, we turned our attention to the generation of a pyrazine-2,3-azaxylylene (550) since a variety of starting materials were available for construction of the azaxylylene precursor.



(550)

Following the now familiar route, we envisaged the starting material to be 2-aminopyrazine (553). However, as was found with the 3-aminopyridine case, all attempts to convert this compound to the corresponding urethane by refluxing with di-tert-butyldicarbonate produced only an amorphous, polymeric solid. We therefore turned to the carboxylic acid (551) as precursor to this

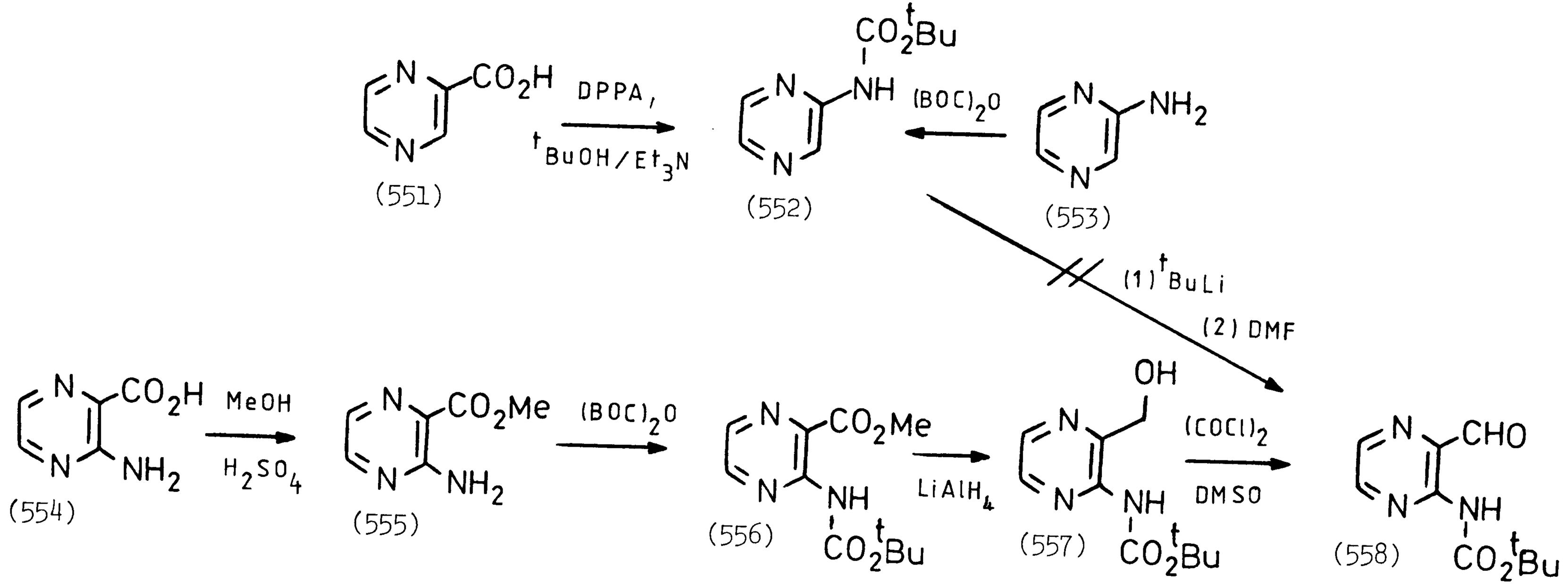
urethane which was then obtained in 96% yield. Treatment of urethane (552) with tert-butyllithium in the usual way produced a yellow solution thought at first to be the required dianion. However, quenching with DMF produced a complex reaction mixture from which no characterizable products could be obtained. Therefore, we decided to attempt to prepare the required precursor (559) using a 2,3-disubstituted pyrazine. Thus, treatment of 2-aminopyrazine-3-carboxylic acid (554) with sulphuric acid in methanol using the literature procedure[278] gave the corresponding amino ester (555) in 54% yield after recrystallization from water. Heating this ester under reflux with an excess of di-tert-butyldicarbonate in the presence of 4-(dimethylamino)pyridine gave the N-tert-butoxycarbonyl amino ester (556) in 48% yield. Reduction of (556) with an excess of lithium aluminium hydride in THF gave the corresponding alcohol (557) in 58% yield as a colourless oil. It was necessary to use this compound immediately after preparation due to its tendency to decompose even when stored at low temperature. Swern oxidation[279] using oxalyl chloride and DMSO gave aldehyde (558) in 71% yield. This aldehyde could not be obtained in a sufficiently pure state to allow complete characterization and was used directly. Treatment of aldehyde (558) with an excess of pent-5-enyl-1-magnesium bromide gave the required alcohol (559) in 78% yield after chromatography. As was found with pyrazine alcohol (557), this system tended to decompose on storage and was

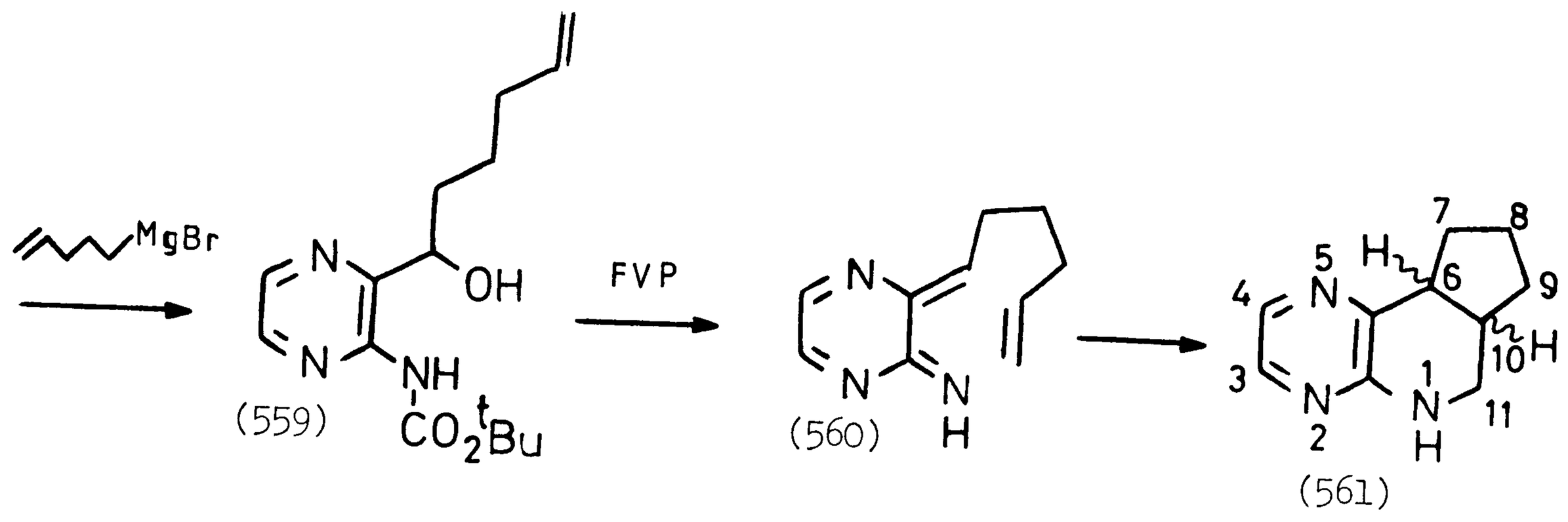
used soon after preparation. Pyrolysis of (559) at $800^{o}C/10^{-2}$ torr produced a bright yellow pyrolysate at $-78^{o}C$, which gave a brown solid upon warming to room temperature. Chromatography on silica gave the intramolecular cycloadduct (561) from azaxylylene (560) in 67% yield. The ^{1}H n.m.r. spectrum of this product revealed it to be a mixture of diastereoisomers in the ratio 2:1. If we assume that the stereochemical assignment of the previously mentioned cycloadducts are correct, then comparison of this spectrum with those previously obtained suggest that the major isomer has the cis-configuration, but again this must remain tentative. The ^{1}H n.m.r. spectrum consisted of a multiplet between δ 7.83 and 7.84, which integrated for three protons due to two from the major isomer and two from the minor isomer which because of the isomer ratio, contribute a single proton to the overall aromatic integral.

The aliphatic region consisted of a multiplet between δ 3.69 and 3.59 ppm, which integrated for one proton and was assigned to one of the C-11 protons on the major isomer. Also present was a multiplet between δ 3.39 and 3.25 ppm, integrating at $1\frac{1}{2}$ protons on the major isomer and a C-11 proton on the minor isomer. The multiplet between δ 3.22 and 3.11 ppm integrating for $\frac{1}{2}$ proton was assigned to the C-6 bridgehead proton on the minor (tentatively assigned trans) isomer. The triplet at δ 3.04 integrating for $\frac{1}{2}$ proton was assigned to the remaining C-11 proton on the minor isomer. The

remainder of the spectrum consisted of a series of closely overlapping multiplets between δ 2.68 and 1.20 ppm, integrating for approximately 11½ protons which is consistent with the remaining protons at C-6, C-7, C-8, C-9 and C-10 on the major isomer, and C-7, C-8, C-9 and C-10 on the minor isomer. The mass spectrum of this mixture gave a molecular ion at m/z 175 and an accurate mass of 175.1099 which is in full agreement with the proposed molecular formula. Because of difficulties encountered in recrystallization of this isomeric mixture, a satisfactory elemental analysis could not be obtained.

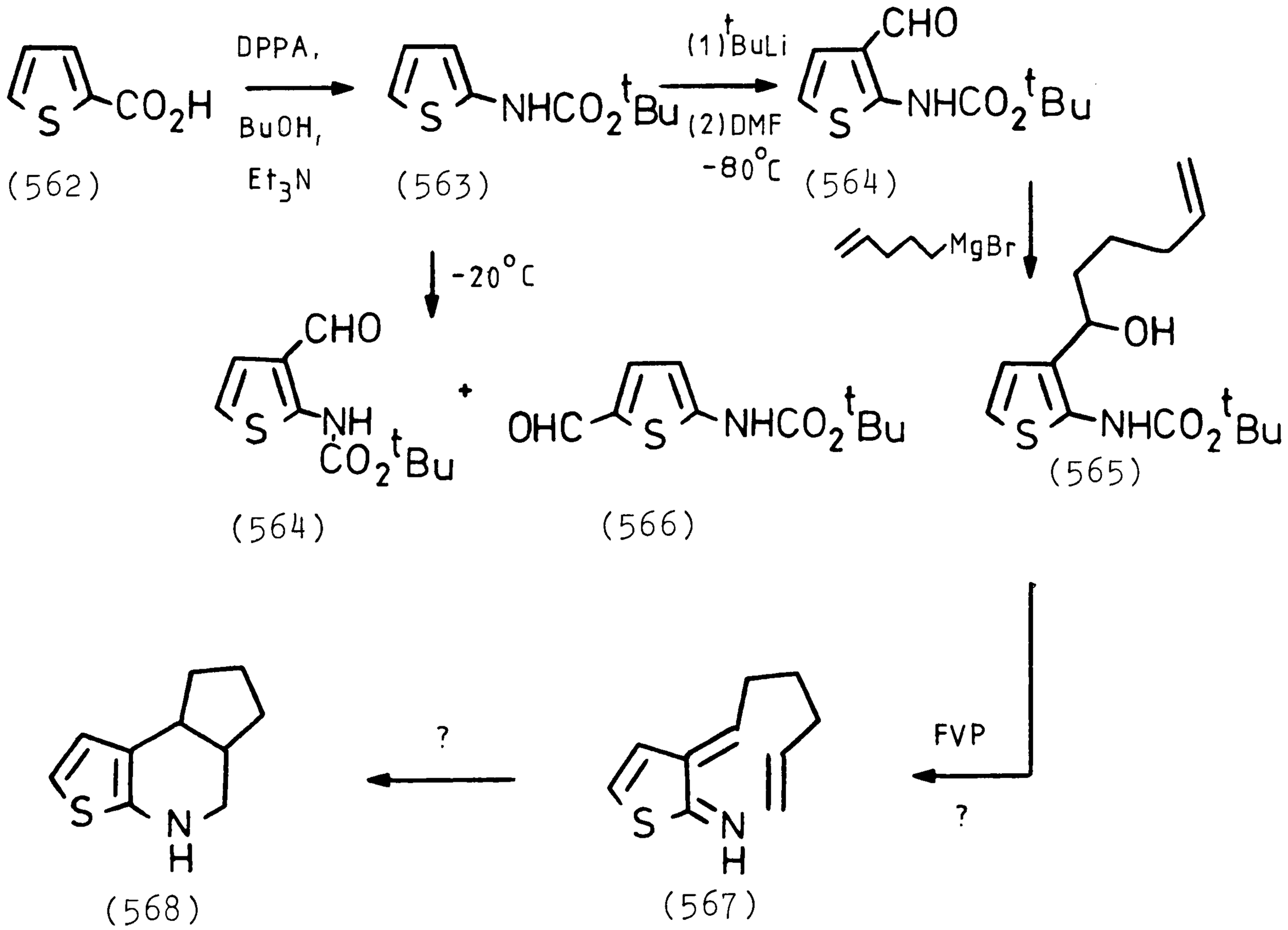
In view of the success in generating these heterocyclic derived o-azaxylylenes we then turned our attention to the five-membered ring analogues, in particular to the generation of thiophene-2,3- and 3,2-based o-azaxylylenes. For the 2,3-substituted system the required starting material appeared to be 2-N-tert-butoxycarbonylamino thiophene (563). Since simple amino thiophenes are extremely unstable molecules, the route to this system from 2-aminothiophene was not attempted. Treatment of thiophene-2-carboxylic acid (562) with DPPA in refluxing tert-butanol gave the required urethane (563) in 68% yield. Directed o-lithiation with tert-butyllithium followed by addition of DMF to the yellow dianion at -78°C gave the aldehyde (564) in 33% yield. Addition of DMF to the dianion at a higher temperature (-20°C) gave a 4:1 mixture of 3- and 5-formylated products as revealed by the n.m.r. spectrum. Addition of an excess of


DPPA,
^{t}BuOH/Et$_3$N
(BOC)$_2$O
(1) ^{t}BuLi
(2) DMF
MeOH
H$_2$SO$_4$
(BOC)$_2$O
LiAlH$_4$
(COCl)$_2$
DMSO
(551)
(552)
(553)
(554)
(555)
(556)
(557)
(558)


MgBr
FVP
(559)
(560)
(561)

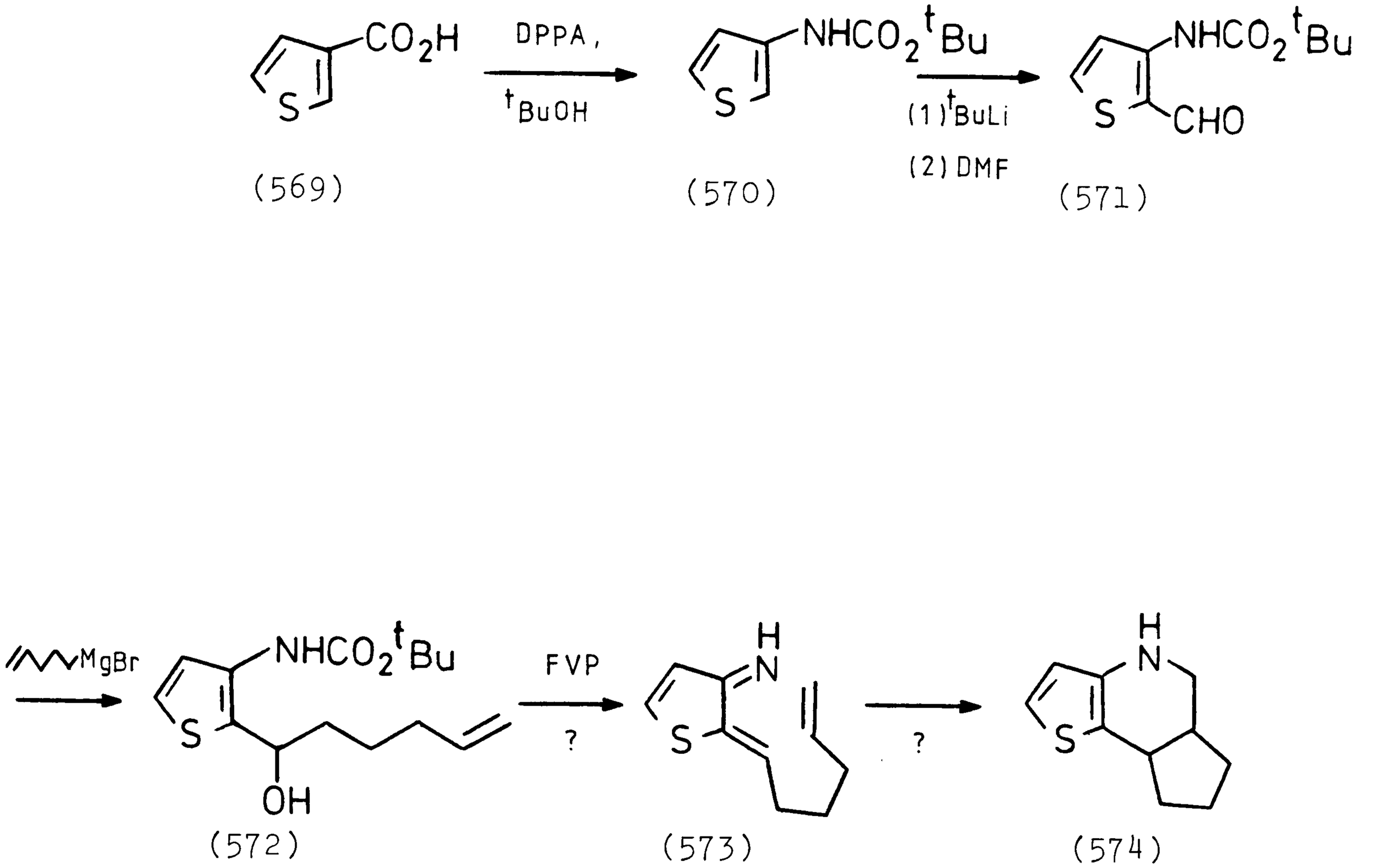
pent-5-enyl-1-magnesium bromide to aldehyde (564) gave the required alcohol (565) in 90% yield after chromatography. Disappointingly, FVP of this alcohol at $800^{\circ}C/10^{-2}$ torr gave an extremely complex mixture from which no discrete products could be obtained by chromatography. The urethane (565) slowly decomposed on sublimation and at the end of the pyrolysis there was a black intractable tar present in the sublimation flask.

Despite this failure to obtain any product from intramolecular Diels-Alder cycloaddition of thiophene-2,3-azaxylylene (567), we decided to study the isomeric thiophene-3,2-system.

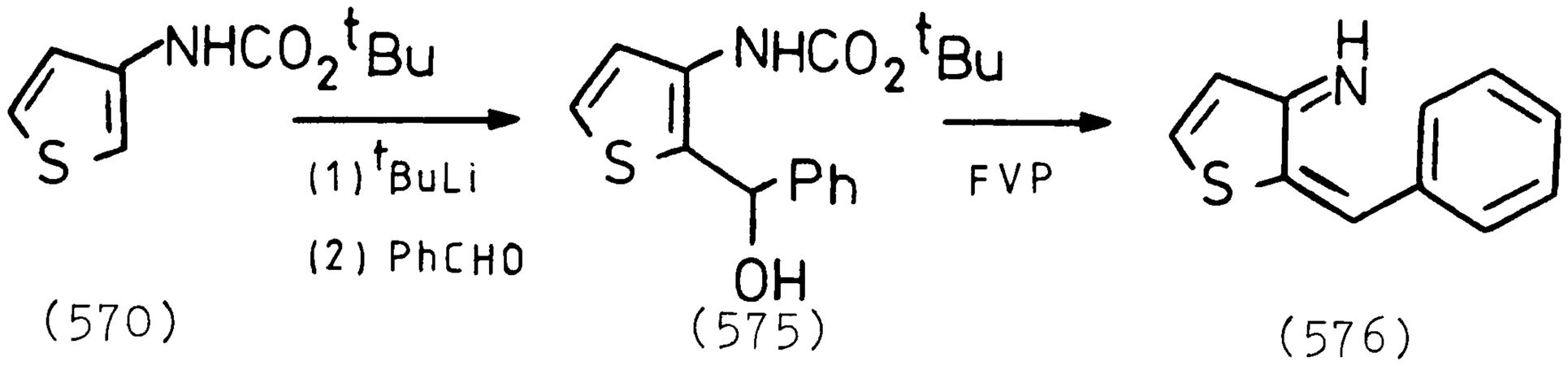


Conversion of thiophene-3-carboxylic acid (569) into the 3-substituted urethane (570) proceeded efficiently in 60% yield. Directed o-lithiation in the 2-position with tert-butyllithium followed by addition of DMF gave the 2-formylated urethane (571) in 57% yield. Addition of pent-5-enyl-1-magnesium bromide in the usual way gave alcohol (572) in 90% yield. Although this product proved to have increased thermal stability compared to the isomeric system (565), pyrolysis at $800^{o}C/10^{-2}$ torr again gave a dark oil which gave no indication of the presence of cycloadduct (574) from Diels-Alder trapping of thiophene-3,2-azaxylylene (573) and was extremely complex as indicated by t.l.c. and n.m.r. spectral analysis. However, in retrospect, the failure to produce any cyclo-adducts from the pyrolysis of these thiophene systems is not too surprising since these adducts are themselves just alkyl-substituted amino thiophenes and therefore like the parent systems, would be expected to be unstable. It may be possible to isolate these tricycles as their N-acyl derivatives by addition of an acylating agent to the crude pyrolysate.

However, although intramolecular Diels-Alder trapping of thiophene azaxylylenes to produce stable adducts looks unlikely, we reasoned that there would be a better chance of trapping a system of this sort in an electrocyclization reaction. Treatment of urethane (570) with tert-butyl lithium followed by quenching the resulting dianion with benzaldehyde gave alcohol (575) in 71% yield after



recrystallization. Pyrolysis of this alcohol at 800°C/ 10^{-2} torr produced thieno[3,2-b]quinoline (493) in 65% yield after chromatography. This thienoquinoline was identical in all respects with that obtained previously from pyrolysis of the amine (462) and urethane (489) respectively.



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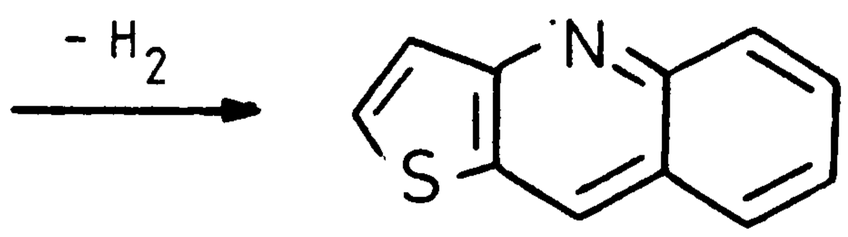
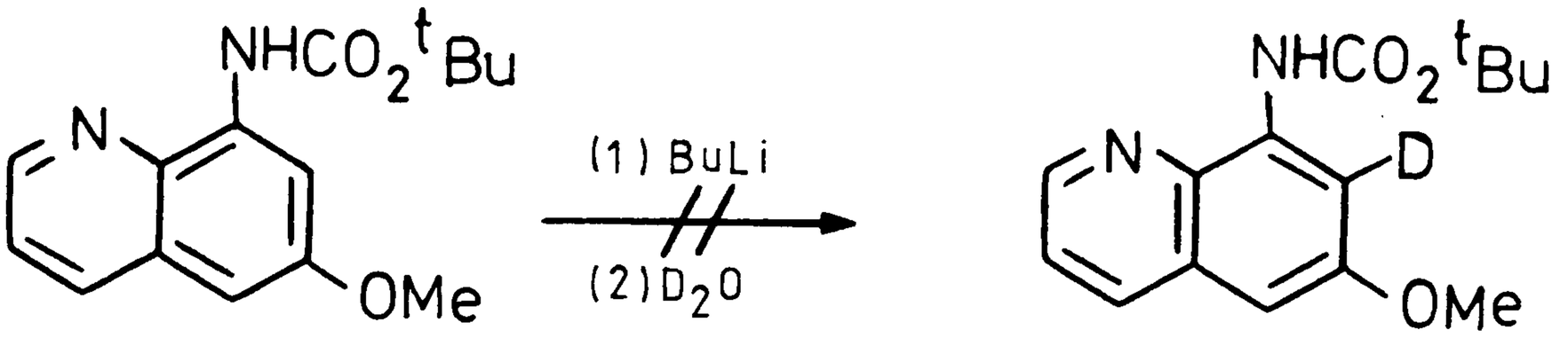


(493)

The attempted synthesis of quinoline and benzofuran based o-azaxylylene precursors failed. Thus attempted lithiation of methoxyquinoline-based urethane (577) with tert-butyllithium and quenching with D_2O did not give any evidence for o-lithiation, probably due to the steric crowding and the powerful chelating effect of the quinoline nitrogen which may prevent the urethane moiety from adopting the appropriate conformation for directed o-lithiation. Also, attempted lithiation of benzofuran based urethane (579) (produced in 85% yield from benzofuran-2-carboxylic acid by the Curtius rearrangement procedure) with two equivalants of tert-butyllithium followed by quenching with DMF produced a complex reaction mixture.

In summary, it is clear that heteroaromatic based o-azaxylylenes, like their benzene based analogues can undergo extremely efficient electrocyclization reactions



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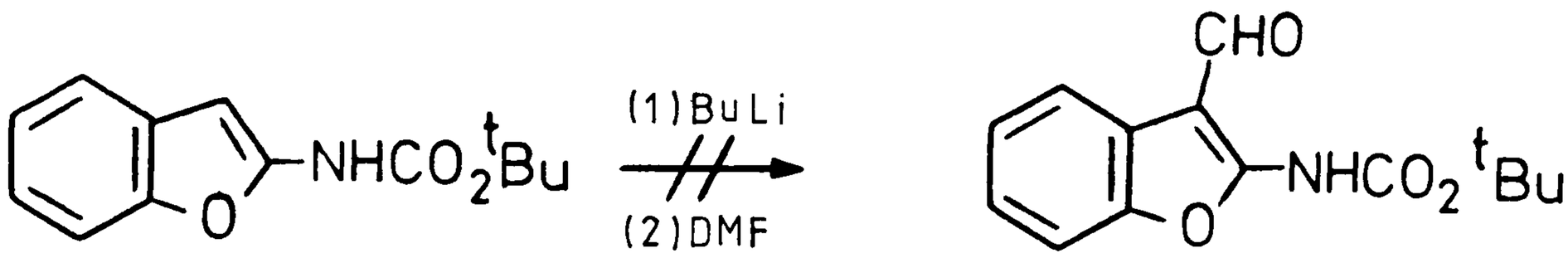
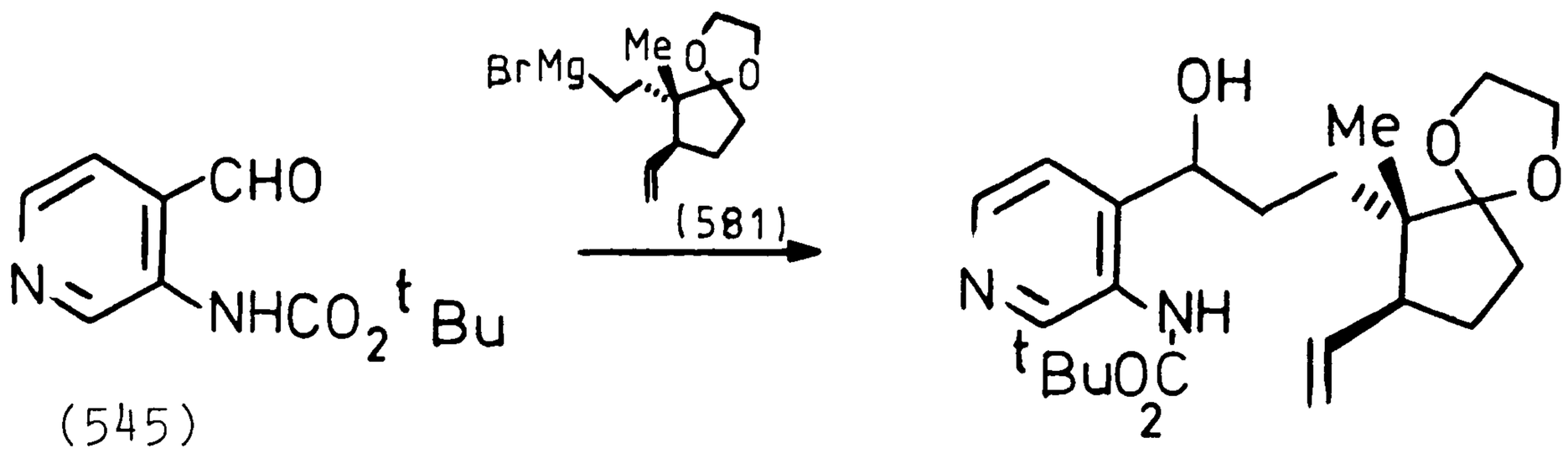


(579) (580)

and provide a rapid entry into linear poly-fused aromatic heterocycles. In addition, it appears that intramolecular Diels-Alder trapping is efficient where the products are stable. Using this urethane-based approach to these systems, it should be possible to build rapidly the necessary precursors for use of these azaxylylenes for the synthesis of natural products and products of potential therapeutic value. For example, coupling of aldehyde (545) with the Grignard reagent (581), (the bromide of which is available by a high yielding procedure from 2-methyl cyclohexenone)[280] would give alcohol (582). Pyrolysis of this system should give the diazaestrone (584) by intramolecular trapping of azaxylylene (583) followed by deprotection.



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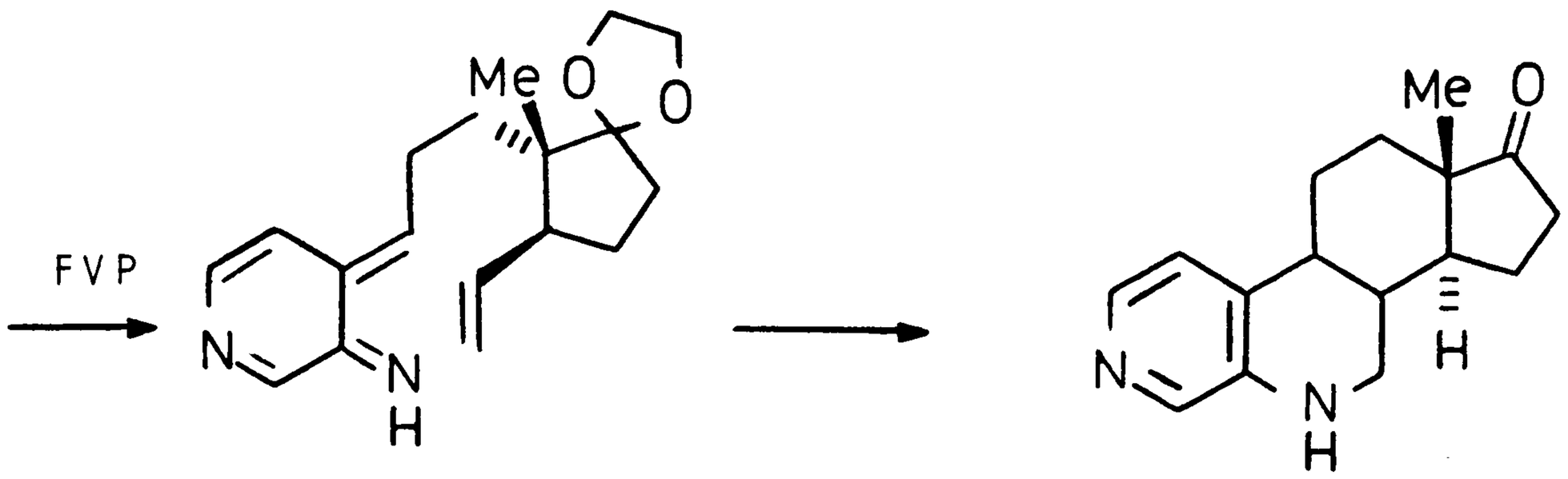


(583)

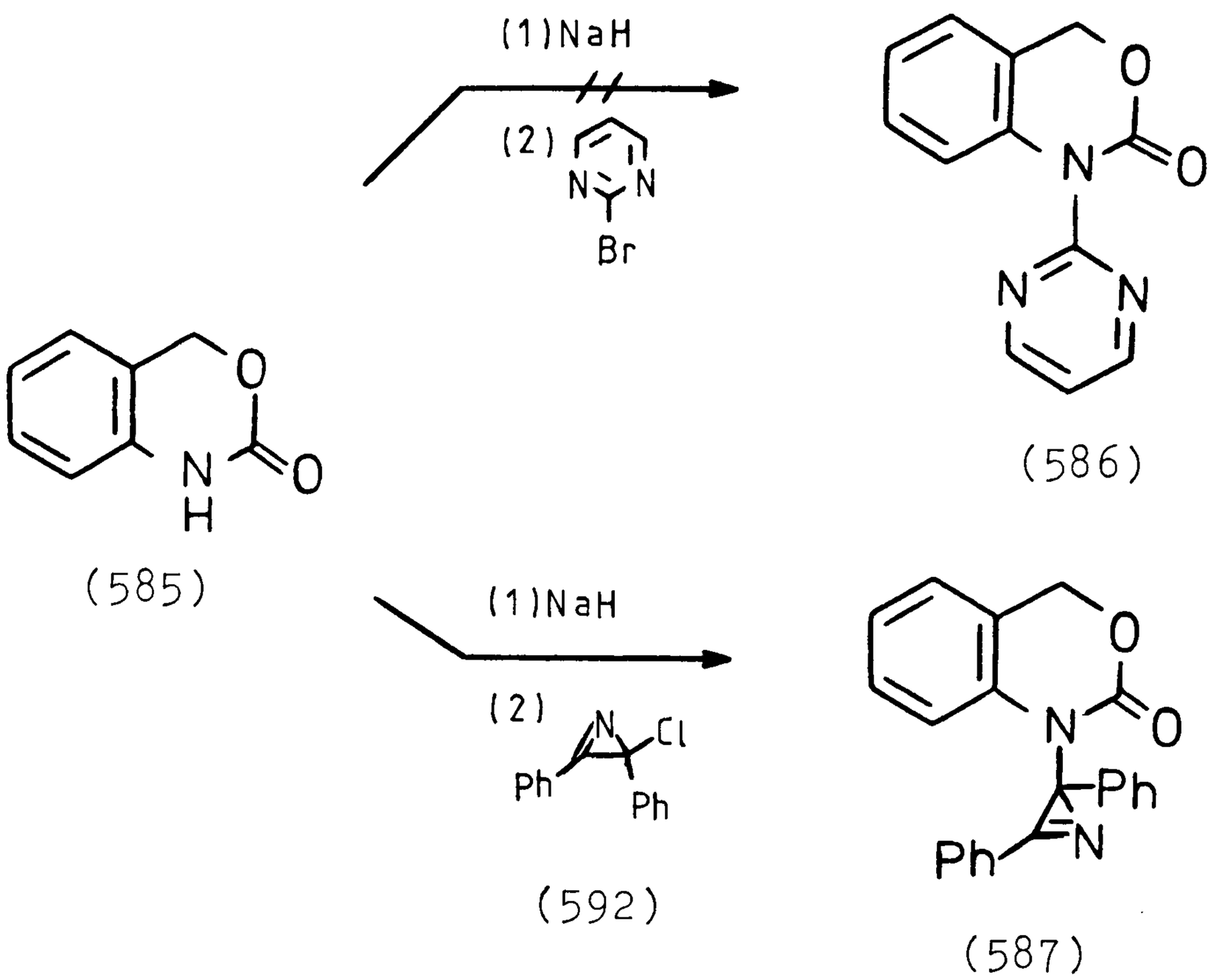
(584)

7. THE FLASH VACUUM PYROLYTIC BEHAVIOUR OF N-AZIRINYL-1,3-DIHYDROBENZOXAZINONES, o-ALKYL IMIDOYL CHLORIDES, AND o-ALKYL AMIDINES

We have seen that azaxylylenes containing heterocyclic ring systems attached to carbon can undergo efficient electrocyclization to give aromatic polyfused heterocycles and that we have efficient methods for the synthesis of the precursors to these systems. However, from Chapter 1 , we saw that the N-phenyl system is capable of undergoing efficient electrocyclization and thus we would expect equal efficiency for electrocyclization of other aromatic rings on the nitrogen atom. However, it has proved extremely difficult to place suitable ring systems on the nitrogen atom of the azaxylylene precursors.

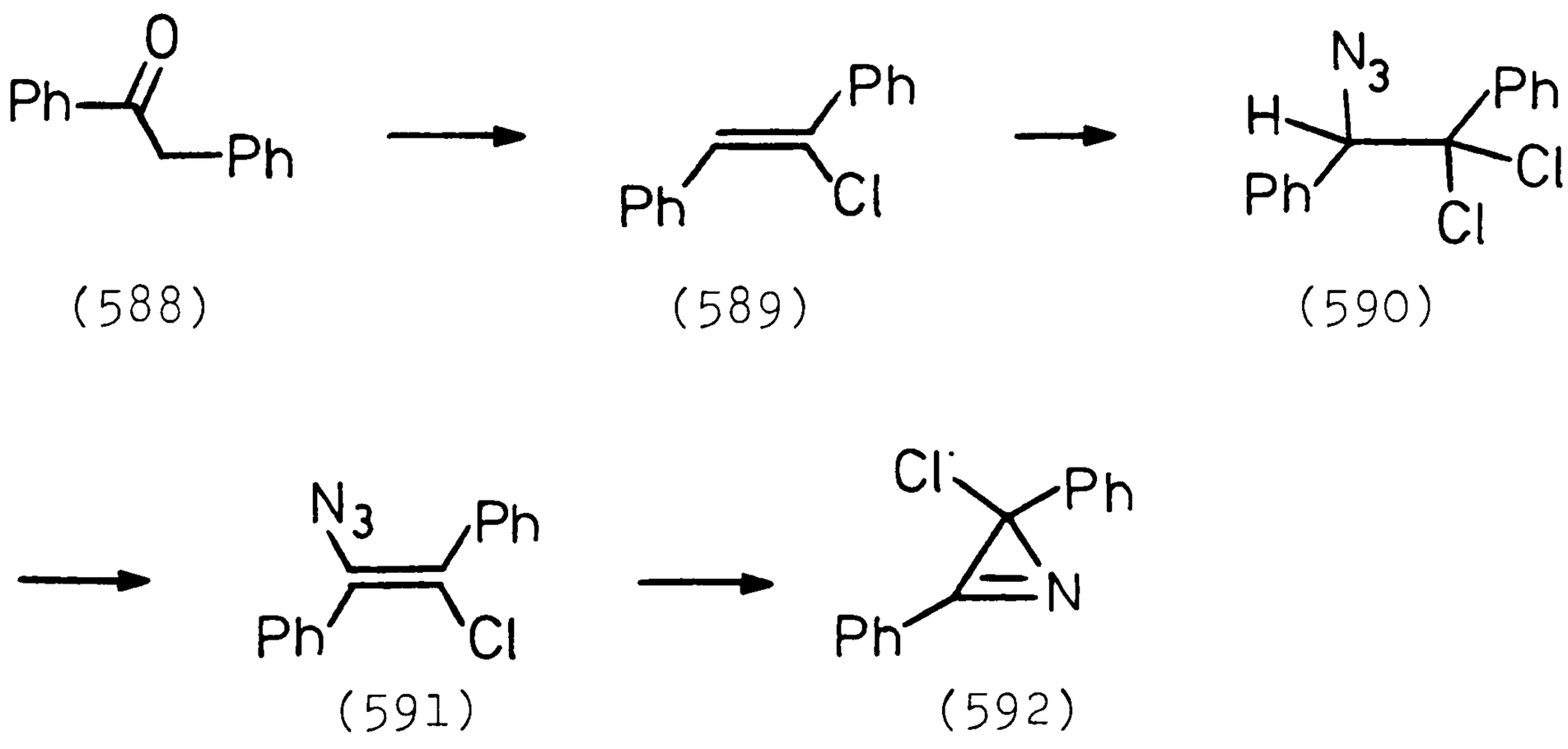
For example, attempted formation of the pyrimidine substituted benzoxazinone system (586) by displacement of the 2-pyrimidyl bromine with the sodium salt of the parent benzoxazinone (585) gave only recovered starting materials.[239] The low nucleophilicity of this anion also prevents reaction with other activated heterocycles. However, the ability of the chloroazirine system (592) to undergo rapid attack by nucleophiles resulting in the displacement of the chlorine atom has been noted by Gallagher.[281] We were, therefore, hopeful that even with the weakly nucleophilic anion of (585), chloroazirine (592) would suffer nucleophilic attack to give the N-azirinyl system (587). Indeed, heating a solution of the sodium salt of (585) (made from treatment of benzoxazinone (585) with sodium hydride) under reflux with an equivalent of the chlorozirine (592) in THF under nitrogen overnight afforded the benzoxazinone (587) in 74% yield. All spectroscopic and physical data were in full agreement with the assigned structure (587), in particular the i.r. spectrum revealing the presence of a broad absorption between 1670 and 1770 cm^{-1} corresponding to the carbonyl of the oxazinone together with the C=N of the azirine. The carbon at the point of attachment of the azirine ring to the oxazinone nitrogen could clearly be seen as a singlet in the ^{13}C off-resonance n.m.r. spectrum at δ 51.42 ppm.

Chloro-azirine (592) was prepared by the procedure described by Gallagher[281] and involved treatment of



(585) (586) (592) (587)

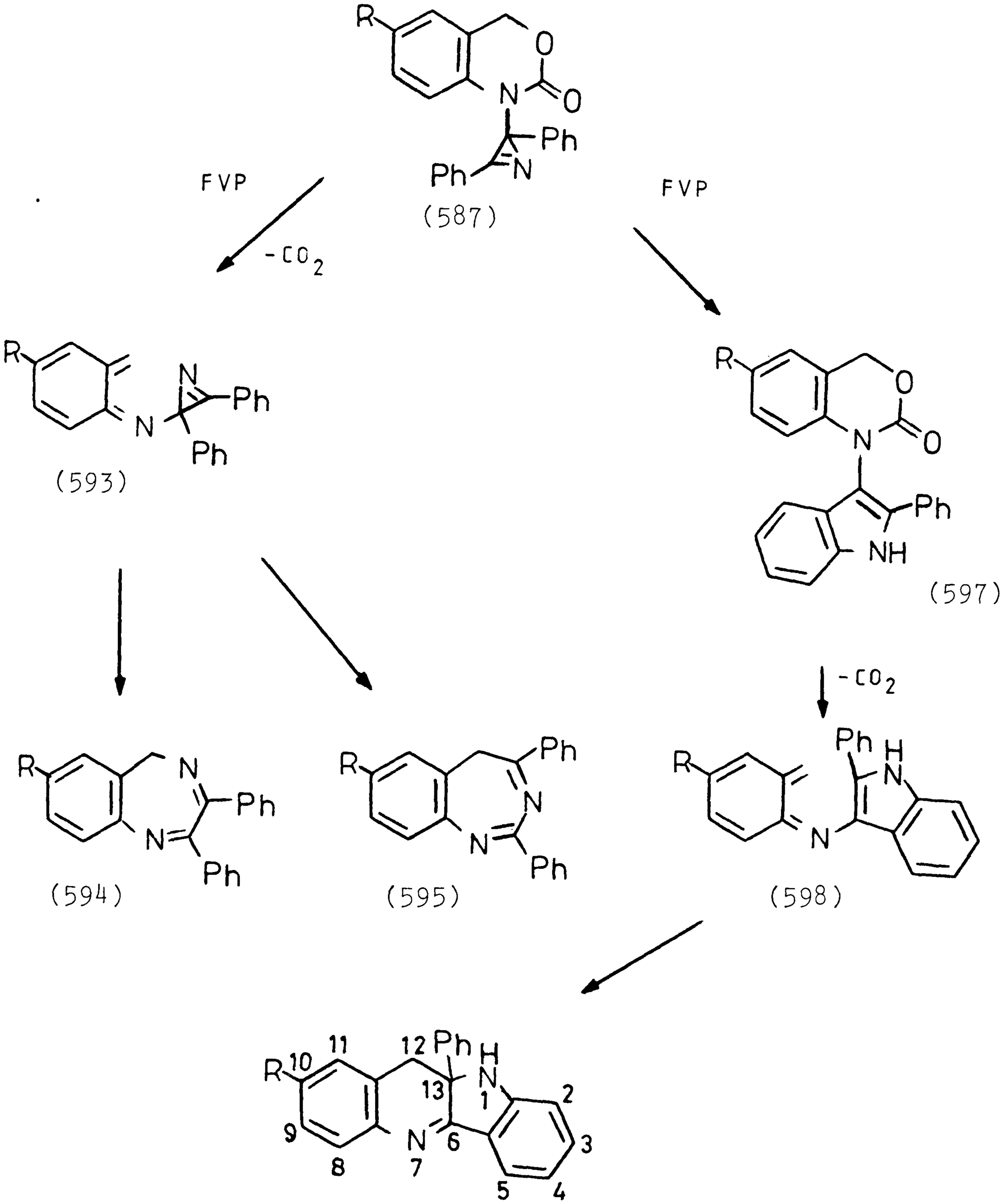
deoxybenzoin (588) with PCl_5 to give vinyl chloride (589), conversion into dichloroazide (590) with chlorine azide, and elimination of HCl with potassium tert-butoxide to give vinyl azide (591). Heating this system in hexane under reflux gave a quantitative yield of the chloroazirine (592).



(588) (589) (590) (591) (592)

Pathway A

Pathway B



(596)

SCHEME 9

We envisaged two possible modes of reaction upon flash vacuum pyrolysis of benzoxazinone (587). Pathway A would involve initial loss of CO_2 in a retro Diels-Alder reaction to produce N-azirinyl azaxylylene (593). One might then observe electrocyclization of the azirine ring with the azaxylylene system to give either the 1,3- or 1,4-benzodiazepines (594) and (595) depending on which of the single bonds in the azirine migrates. However, Isomura[282] has found that 3-phenyl azirines can be converted to indoles upon pyrolysis. The reaction can be rationalized as involving ring opening of the azirine to yield a transient vinyl nitrene which inserts into the adjacent phenyl ring to give indole after hydrogen migration. Therefore, alternatively pathway B would involve initial rearrangement of the azirine ring in (587) to yield indole-substituted benzoxazinone (597). If this now loses CO_2 in the retro Diels-Alder reaction this would produce N-indolylazaxylylene (598) which we would expect to electrocyclize to give the quindoline (596).

In the event[283] FVP of dihydrobenzoxazinone (587, R = H), at $650^{\circ}C/10^{-2}$ torr produced a pale yellow pyrolysate at $-196^{\circ}C$ which gave a brown tacky solid upon warming to room temperature. Purification by p.t.l.c. on silica gave 2-phenylindole (30%) identified by comparison with an authentic sample, and the dihydro-quindoline (596, R = H) in 25% yield. The isolation of quindoline (596) supports the reaction sequence outlined in pathway B (Scheme 9), and although limited

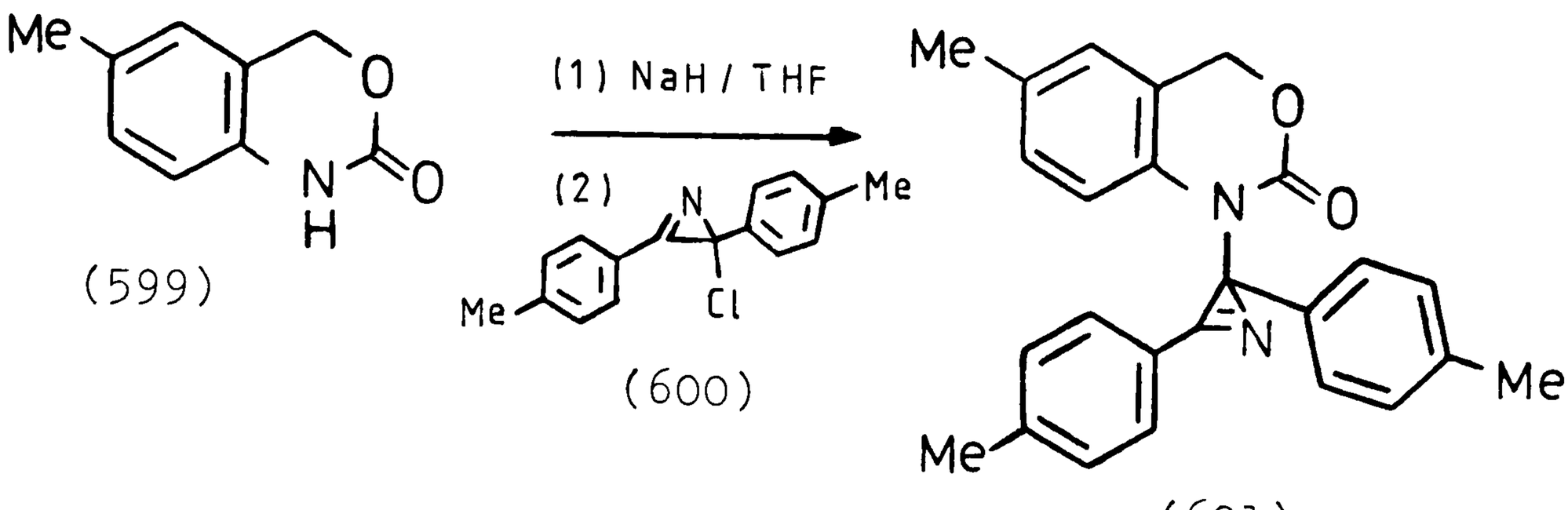
in application, it has shown that the electrocyclization reactions of azaxylylenes substituted with heterocycles on nitrogen are indeed feasible. The assignment of this structure to product (596) was completely supported by analysis of the spectral data. In particular, the i.r. spectrum showed an NH stretch at 3110 cm^{-1} and a C=N stretch at 1612 cm^{-1}. The ^{1}H n.m.r. possessed a total of thirteen aromatic hydrogens which included a low field doublet at δ 7.95 and a high field doublet at 6.79 ppm. At higher field, an AB quartet was present due to the magnetic non-equivalence of the hydrogens on C-12 due to their close proximity to the assymetric centre at C-13.

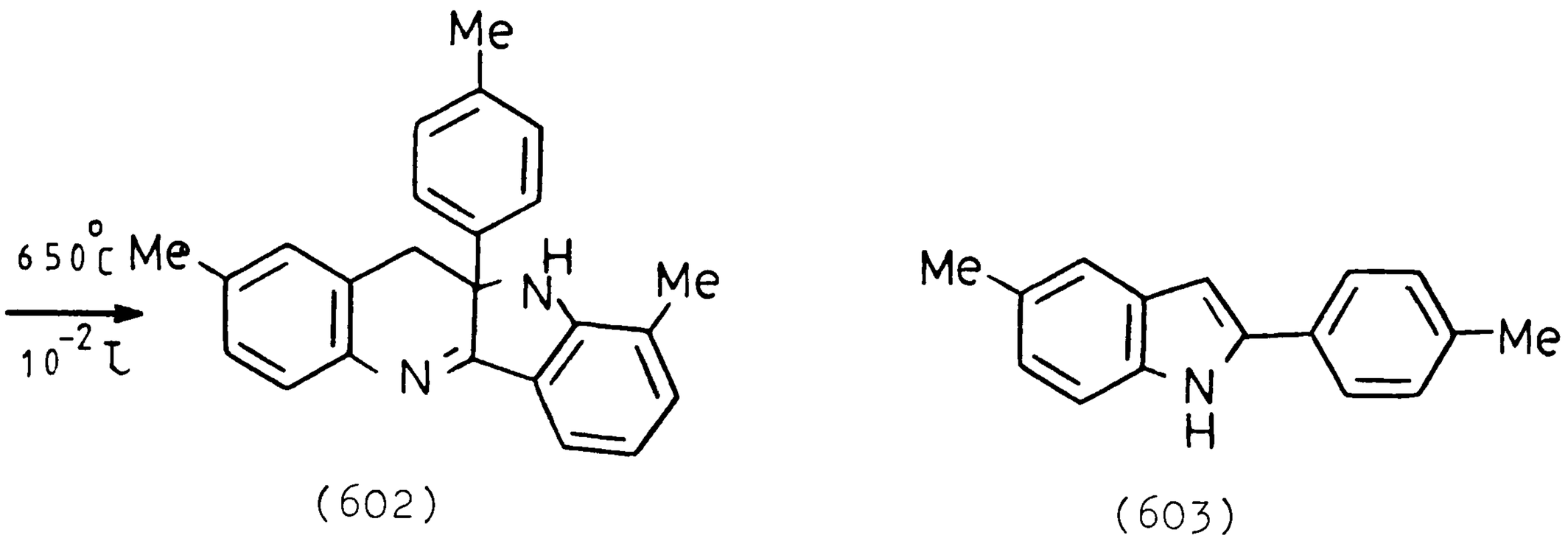
The ^{13}C n.m.r. spectrum showed a total of six low field singlets in the off-resonance spectrum which are due to the five aromatic quaternary carbons plus the imine carbon at C-6. The quaternary carbon at C-13 could be clearly seen as a singlet at δ 63.57 ppm. All eleven doublets due to the remaining aromatic carbons could be seen occupying the region between δ 134.11 and 112.25 ppm. Finally, the expected triplet due to the carbon at C-12 was present at δ 37.68 ppm. The molecular ion at m/z 296 and its accurate mass of 296.1306 fully supports the molecular formular of $C_{21}H_{16}N_2$ as does the elemental analysis.

The origin of 2-phenylindole in this reaction was not at first clear, although it was suspected that it may be due to the initial cleavage of the azirine ring from the

rest of the molecule followed by rearrangement of the azirine ring to yield 2-phenylindole. However, pyrolysis of the methyl substituted benzoxazinone system (587, R = Me) made in an analogous way to that described for (587, R = H) in 82% yield), gave the methyl-substituted quindoline (596, R = Me) in 11% yield and 5-methyl-2-phenylindole in 30% yield. The isolation of 5-methyl-2-phenylindole shows that the mechanism for its formation must involve the benzene ring in the dihydrobenzoxazinone and rules out fragmentation of the system as suggested above.

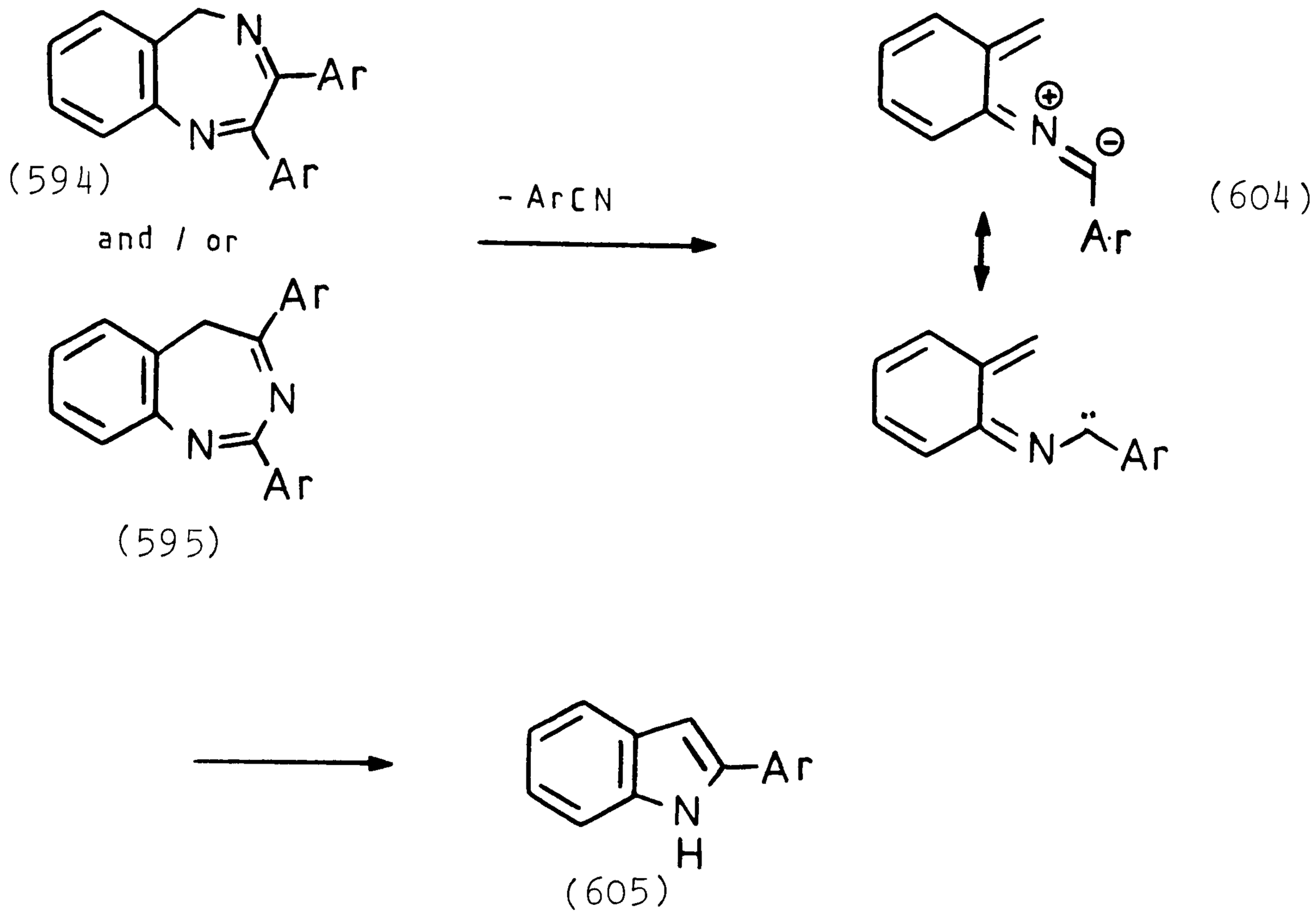
The benzoxazinone (601) was prepared in 93% yield by reaction of 6-methylbenzoxazinone (599) with 2,3-bis-(4-methylphenyl)-2-chloroazirine (600) (prepared in six steps from p-tolunitrile by the procedure described by Gallagher).[281] Pyrolysis of this benzoxazinone at $650^{o}C/10^{-5}$ torr using a mercury diffusion pump gave indole (603) in only 2% yield, and the dihydroquindoline (602) in 1.3% isolated yield. The very low yields encountered in the pyrolysis are probably due to extensive decomposition of oxazinone (601) during pyrolysis as even at the low pressures used, it proved to be a very involatile compound and required heating for prolonged periods of time to obtain a satisfactory amount of pyrolysate. The physical and spectral data for 5-methyl-2-phenylindole [284] and indole (603)[285] were in good agreement with those reported in the literature and the spectral data for quindolines (597, R = Me) and (602) was in full support of their proposed structures.





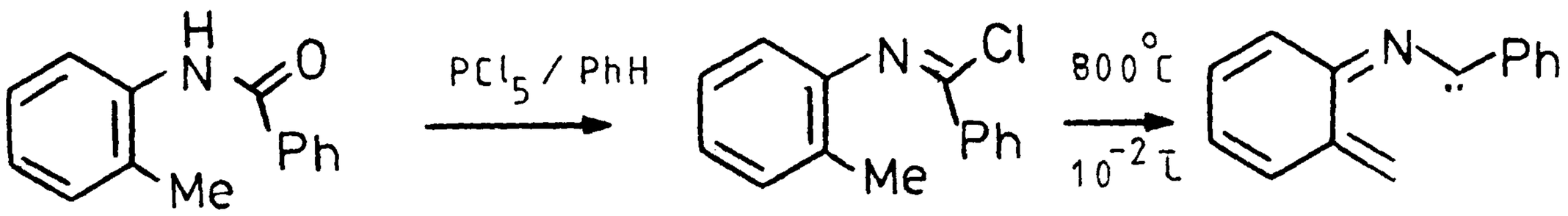
A possible mechanism for formation of these 2-aryl indoles would be loss of ArCN from either of the benzodiazepines (594) and (595) during pyrolysis to yield the methylene nitrile ylide intermediate (604) which could then ring close to give the 2-aryl indole (60) after hydrogen migration (Scheme 10).

One would predict this loss of nitrile to be a stepwise process, as a concerted process would necessarily involve the formation of an 8-π-anti-aromatic transition state. Recently, both the 5H-2,3-diphenyl and 2,3-dimethyl-1,4-benzodiazepines have been prepared in these laboratories[286] and these are indeed converted to 2-phenyl and 2-methyl indoles in high yield upon flash vacuum pyrolysis, thus

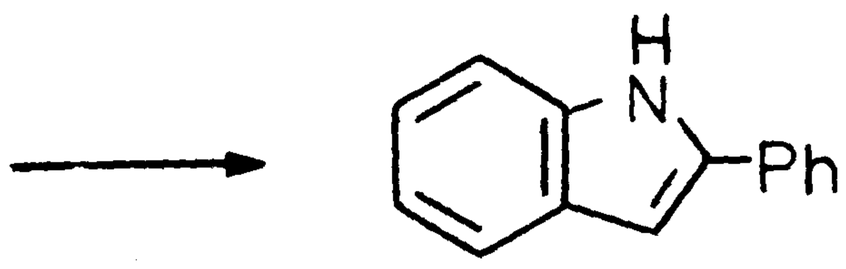


SCHEME 10

showing that the 5H-1,4-benzodiazepines (594) are indeed feasible intermediates, although the direct conversion of the azirinyl azaxylylene (593) to the methylene nitrile ylide (604) and hence indole (605) is also possible. The generation of the proposed nitrile ylide intermediate (604) (which can also be regarded as an azadienyl carbene) by an alternative route would provide further evidence as to its intermediacy in the previously described pyrolyses. Indeed, pyrolysis of o-methyl imidolyl chloride (607), made in high yield from treatment of o-tolylbenzanilide (606) with PCl_5 in benzene, at $800^{o}C/10^{-2}$ torr gave 2-phenyl indole in 76% yield. In this case, 1,5-elimination of HCl would lead to the same intermediate (604). Not



(606) (607) (604)



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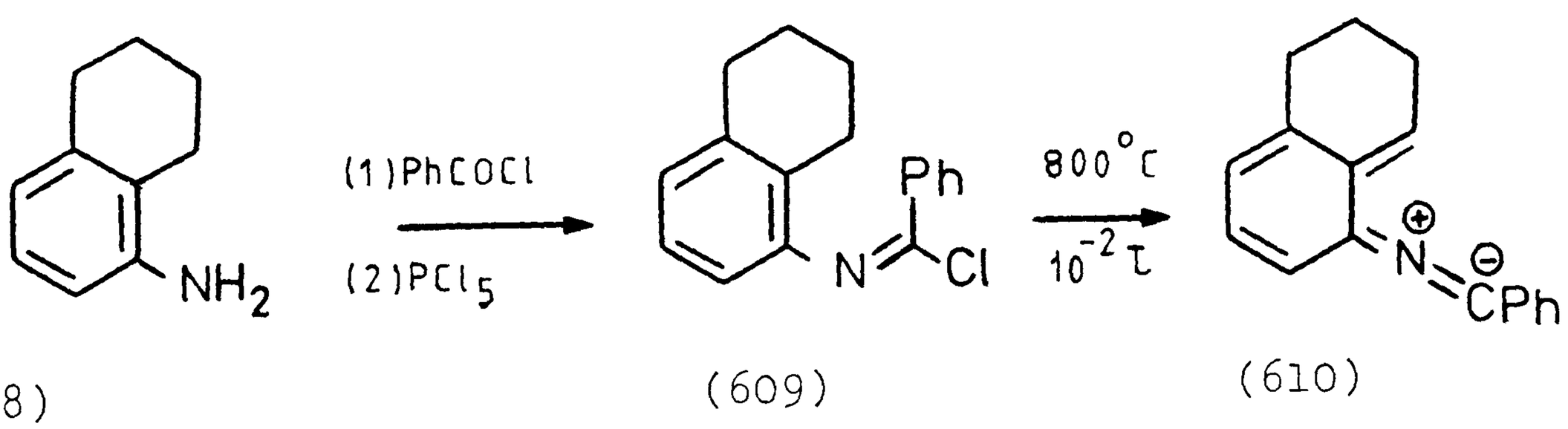

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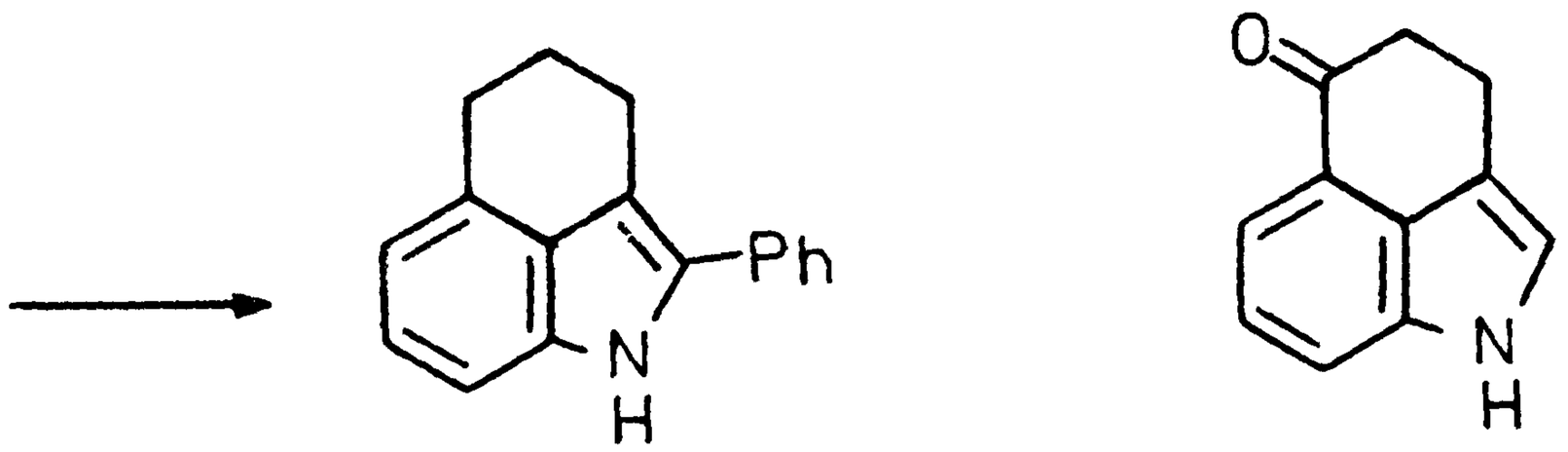
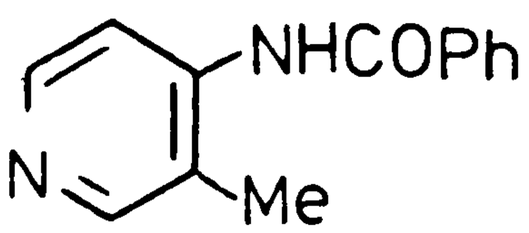


(611) (612)

only did this provide further support for the proposed mechanism of formation of these indoles from the N-azirinyl benzoxazinones, but it also provides a new route to 2-aryl indoles, from o-alkyl anilines. Pyrolysis of imidoyl chloride (609), made from 1-amino-tetralin (608) by benzoylation and treatment with PCl_5 respectively, gave the fused indole (611), in 74% yield, presumably by ring closure of the intermediate azaxylylene-dipole (610). This indole has also been reported[287] from treatment of benzoylamide of (608) with LDA in a reaction which is essentially a variation of the Madelung indole synthesis, although the yield was a more modest 41%. Indole (611) possesses the skeletal framework of the indolyl ketone (612) (Uhle's ketone) which is a useful precursor to various indole based alkaloids.[288]

Subsequent work in these laboratories[289] has further demonstrated the generality of this reaction sequence by the conversion of pyridine amide (613) and thiophene substituted amide (615) into indoles (614) and (616) respectively.

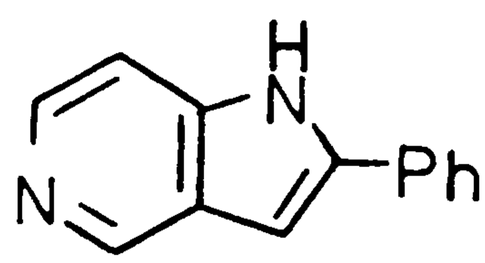
To extend this method to the synthesis of 2-alkyl indoles (619) would require pyrolysis of the corresponding alkyl imidoyl chlorides (617), in which there is the possibility of 1,2-elimination of HCl to yield ketene-imine (618).



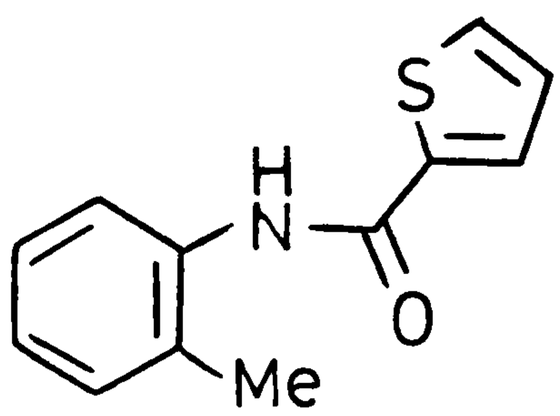
(613)

(1) PCl_5

(2) FVP

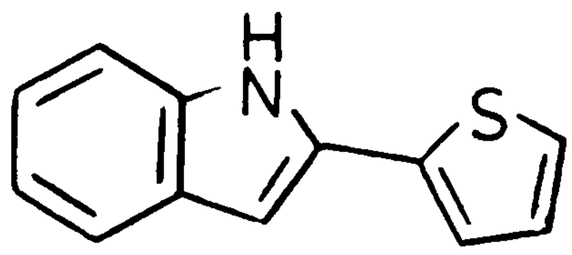


(614)

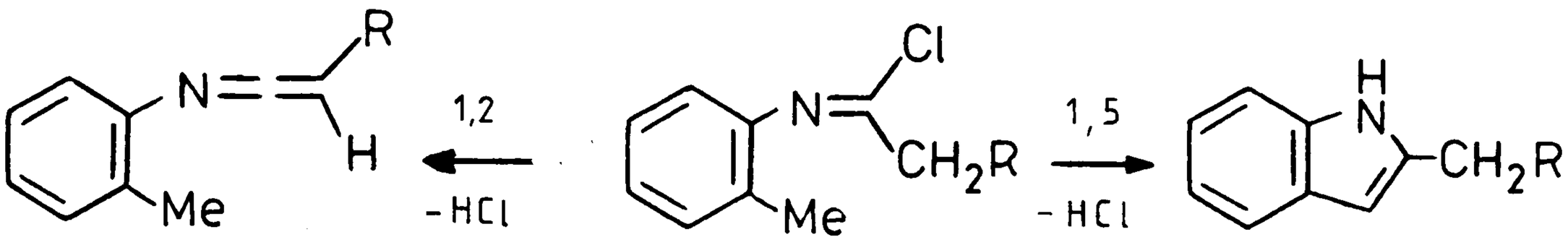


(615)

"



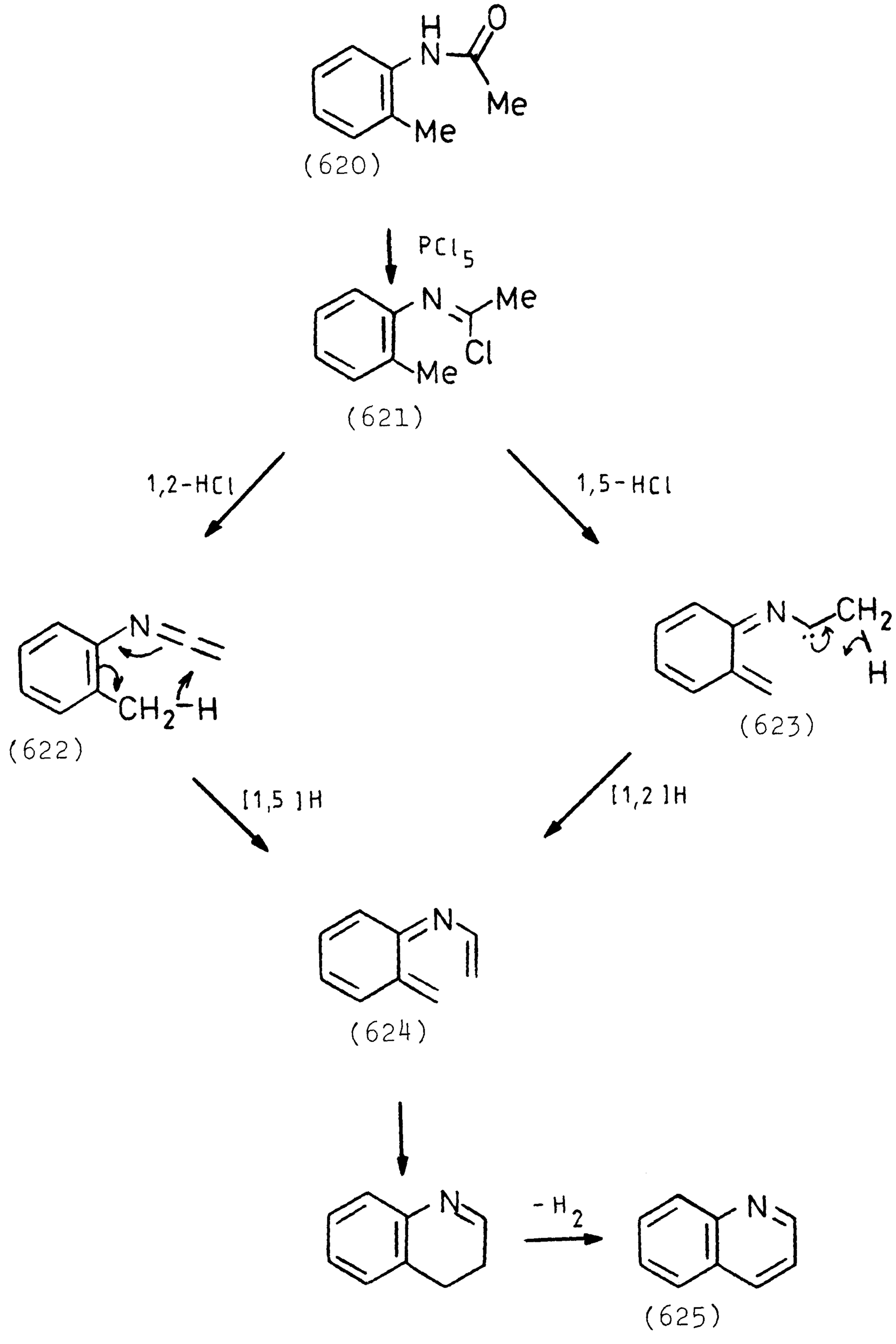
(616)

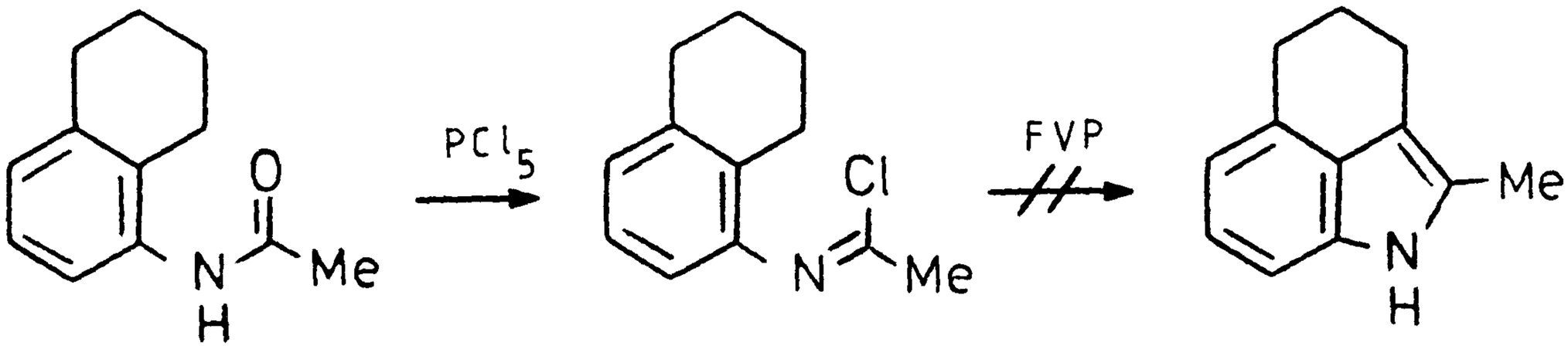


(618) (617) (619)

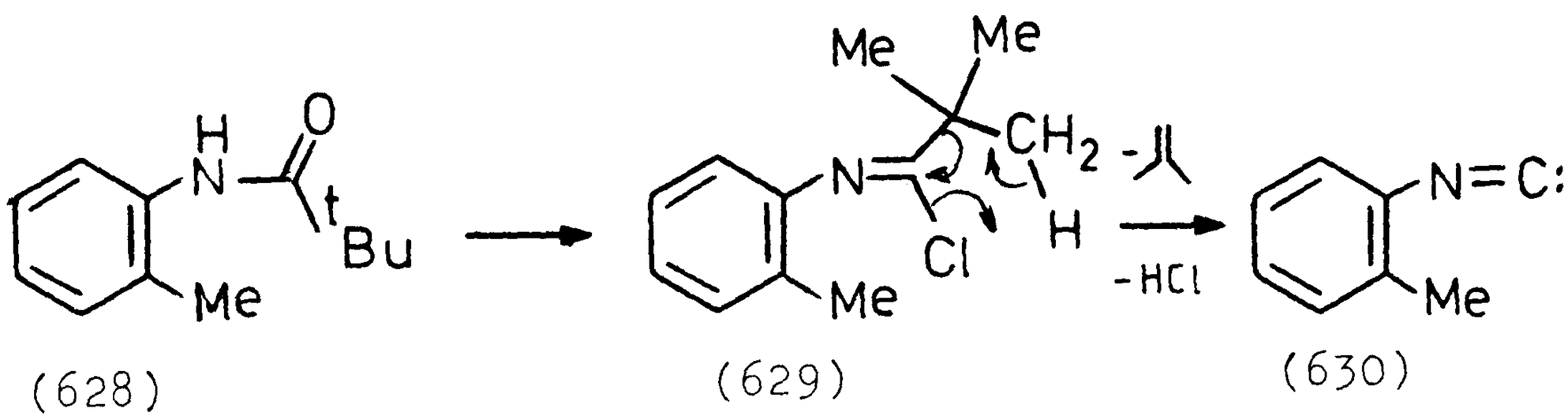
Indeed, pyrolysis of the crude imidoyl chloride (621) obtained by treatment of acetamide (620) with PCl_5 in acid-free chloroform produced a complex mixture. However, chromatography on silica yielded quinoline (625) in 15% yield. The formation of this product can be rationalized as involving a 1,5-elimination of HCl to yield ylide (623) followed by a 1,2-hydrogen shift from the

methyl group to give the N-vinyl azaxylylene (624). Electrocyclization and dehydrogenation gives (625). Alternatively, (625) could be formed by a 1,2-elimination of HCl from imidoyl chloride (621) followed by a 1,5-hydrogen shift from the o-methyl group in the resulting imine (622) to yield the N-vinyl azaxylylene (624) and thus quinoline (625) (see later). Pyrolysis of imidoyl chloride (627) made from acetamide (626) gave a complex mixture, from which no characterizable products could be obtained. Pyrolysis of the amides of these imidoyl chlorides even at very high temperatures gave complete recovery of starting materials. Surprisingly, pyrolysis of the tert-butyl imidoyl chloride (628) in which the possibility of 1,2-elimination is excluded gives the expected 2-tert-butyl indole (632) in 20% yield together with o-tolunitrile (633) in 68% yield.[289] A possible explanation for formation of nitrile (633) is α-elimination involving loss of isobutene and HCl to give isocyanide (630) which rearranges under the pyrolysis conditions[290] to give the observed product.

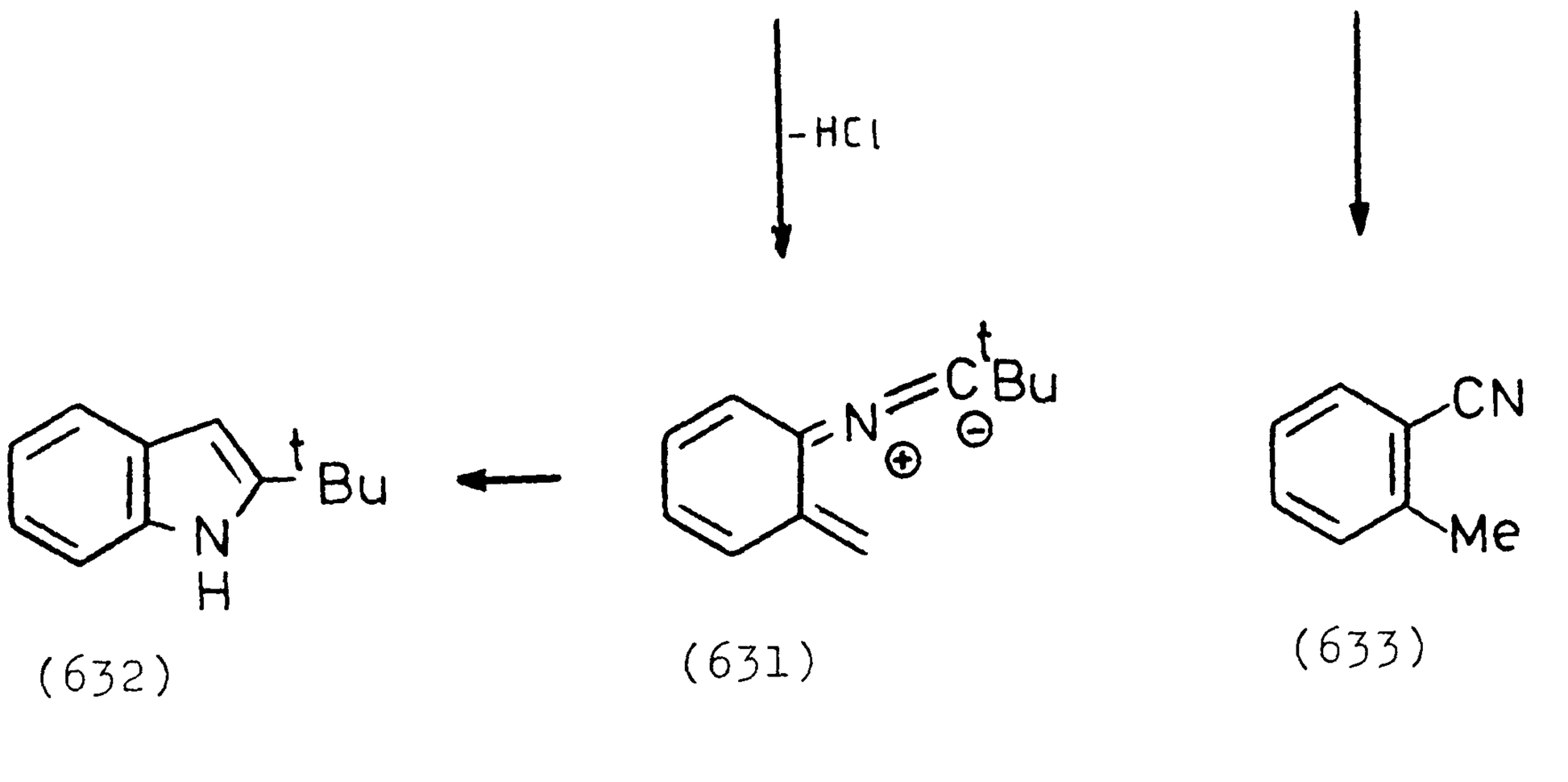

H
N
O
Me
Me
(620)
PCl5
N
Me
Me
Cl
(621)
1,2-HCl
1,5-HCl
N
CH2
H
(622)
N
CH2
H
(623)
[1,5]H
[1,2]H
N
(624)
N
N
-H2
N
(625)



(626) (627)

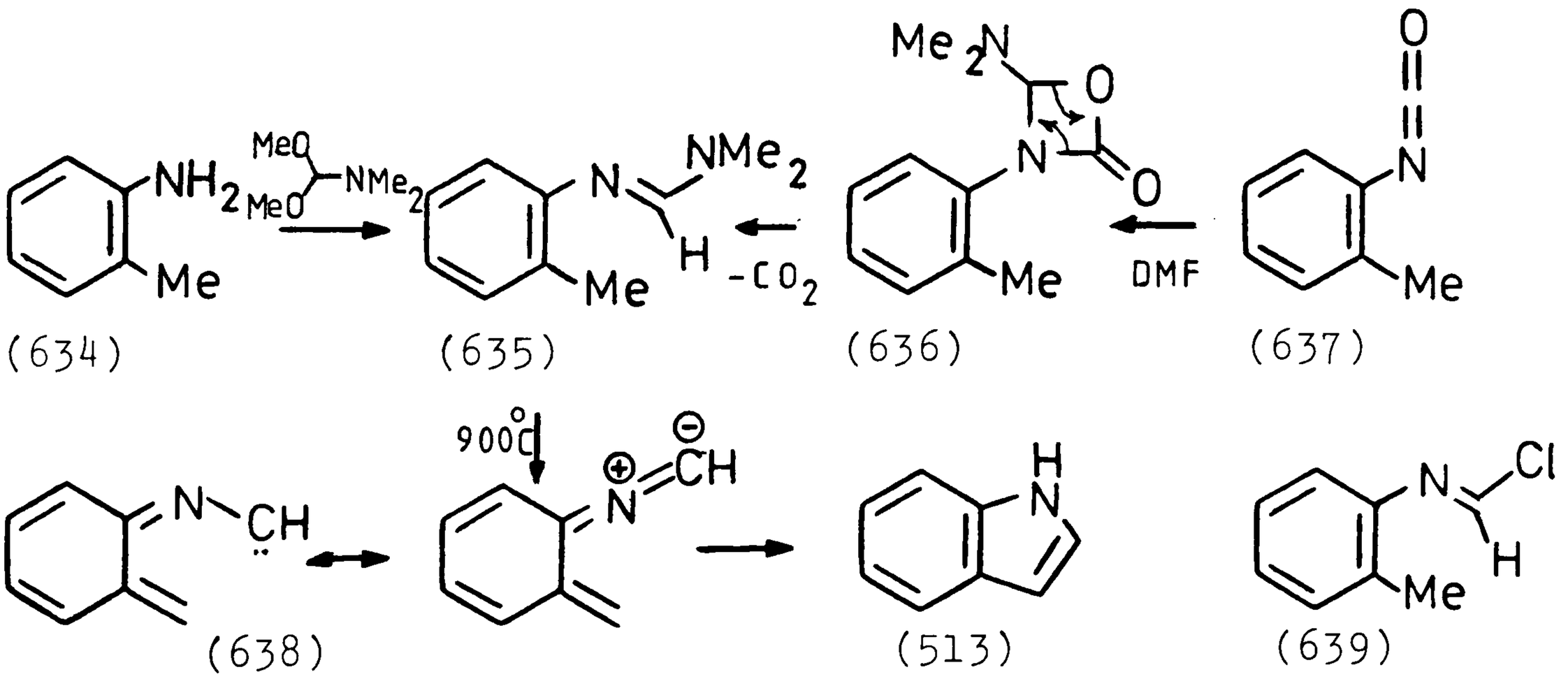


(628) (629) (630)



(632) (631) (633)

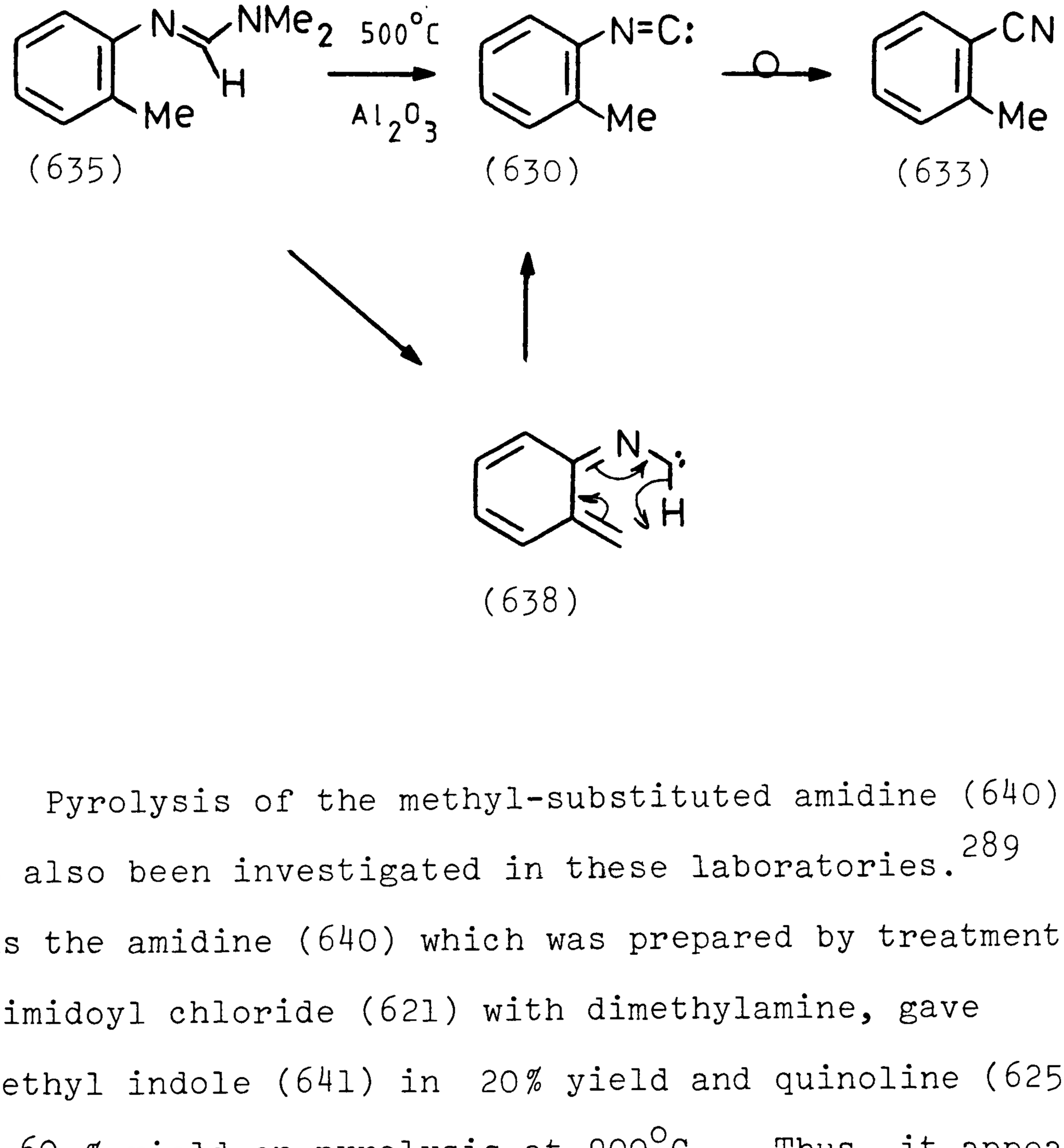
Attention was then turned to the synthesis of unsubstituted indoles. However, the route from unsubstituted imidoyl chlorides (639) looked unattractive due to the inaccessability of these systems. We therefore considered 1,5-elimination of dimethylamine from the formamidine (635). This amidine can be readily prepared in high yield by treatment of o-tolyl isocyanate (637) with DMF in a reaction which can be formally regarded as involving [2+2] addition followed by loss of CO_2 from the adduct (636), or by treatment of o-toludine (634) with DMF-dimethyl acetal.[291] Pyrolysis of amidine (635) at 900°C using an oven packed with small silica glass tubes to increase the contact time, produced indole (513) in 51% yield, after chromatography. We can postulate that this occurs by loss of dimethylamine from amidine (635) followed by ring closure as before. Clearly, the elimination of dimethylamine is less favourable than that of HCl as shown by the more vigorous conditions required for elimination.



(634) (635) (636) (637)

(638) (513) (639)

In an attempt to lower the thermal input required for this reaction, this pyrolysis was repeated at 500°C over alumina and gave o-tolunitrile (633) in 72% yield after chromatography on silica. It seems that alumina promotes an α-elimination reaction involving loss of dimethyl-amine to give isocyanide (630) which rearranges to nitrile (633), although a 1,5 -hydrogen shift in the ylide (638) cannot be discounted.

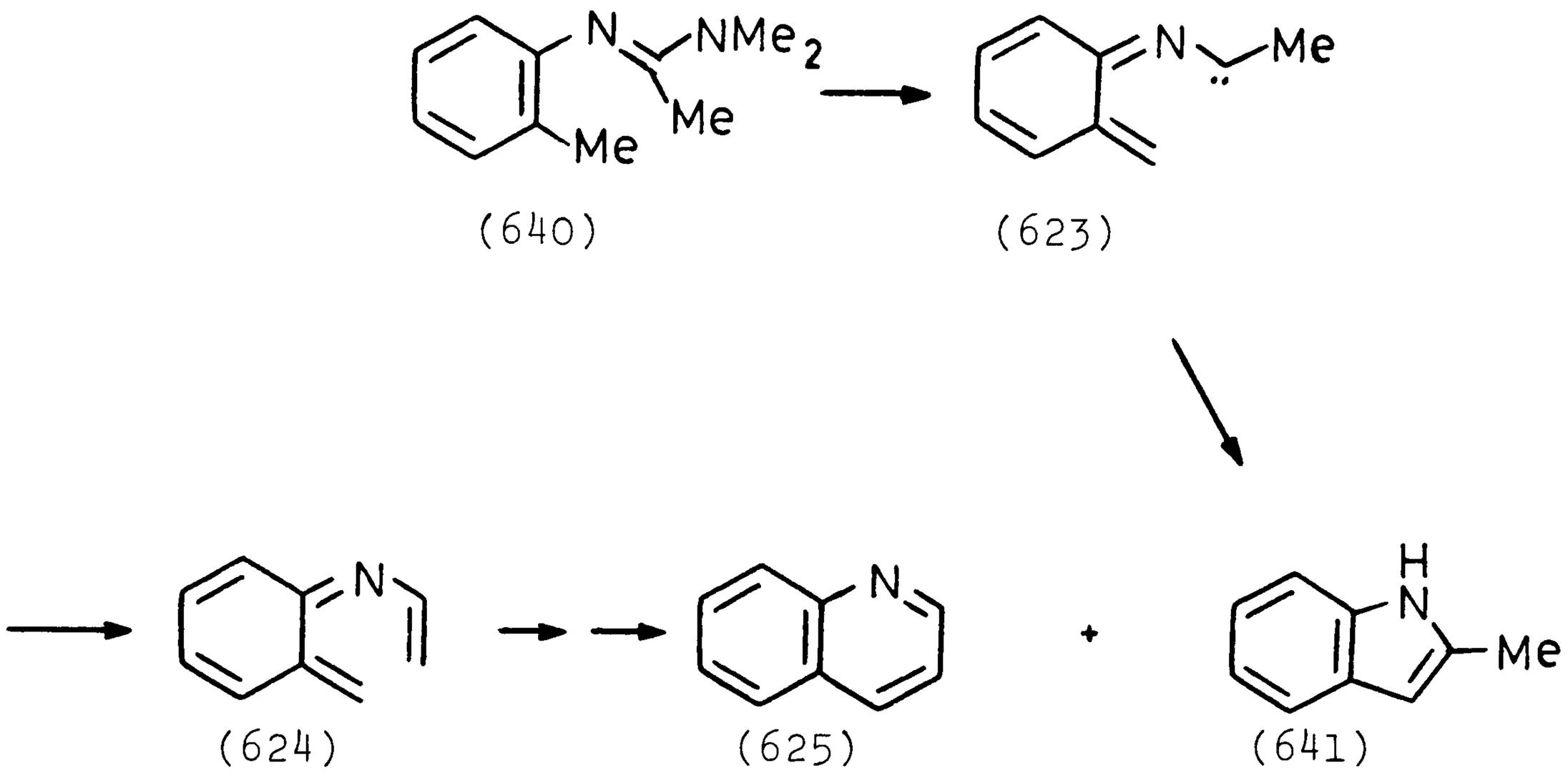


(635) (630) (633)

(638)

Pyrolysis of the methyl-substituted amidine (640) has also been investigated in these laboratories.[289] Thus the amidine (640) which was prepared by treatment of imidoyl chloride (621) with dimethylamine, gave 2-methyl indole (641) in 20% yield and quinoline (625) in 60 % yield on pyrolysis at 900°C. Thus, it appears that amidine (640) loses dimethylamine efficiently to give

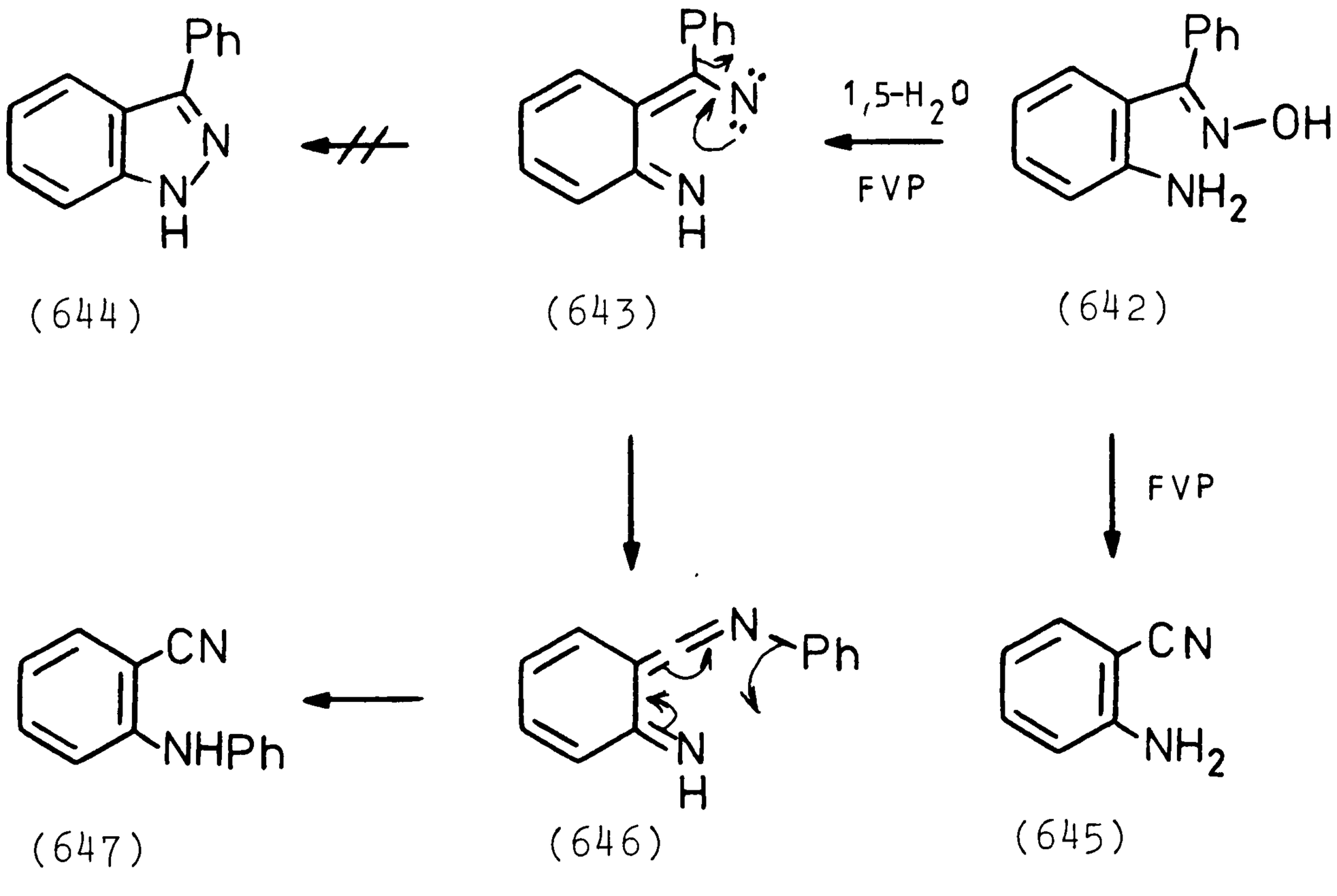
methylene nitrile ylide (623) which cyclizes to indole (641), or undergoes hydrogen shift to yield the N-vinyl azaxylylene (624) and thus quinoline (625).



(640) (623) (624) (625) (641)

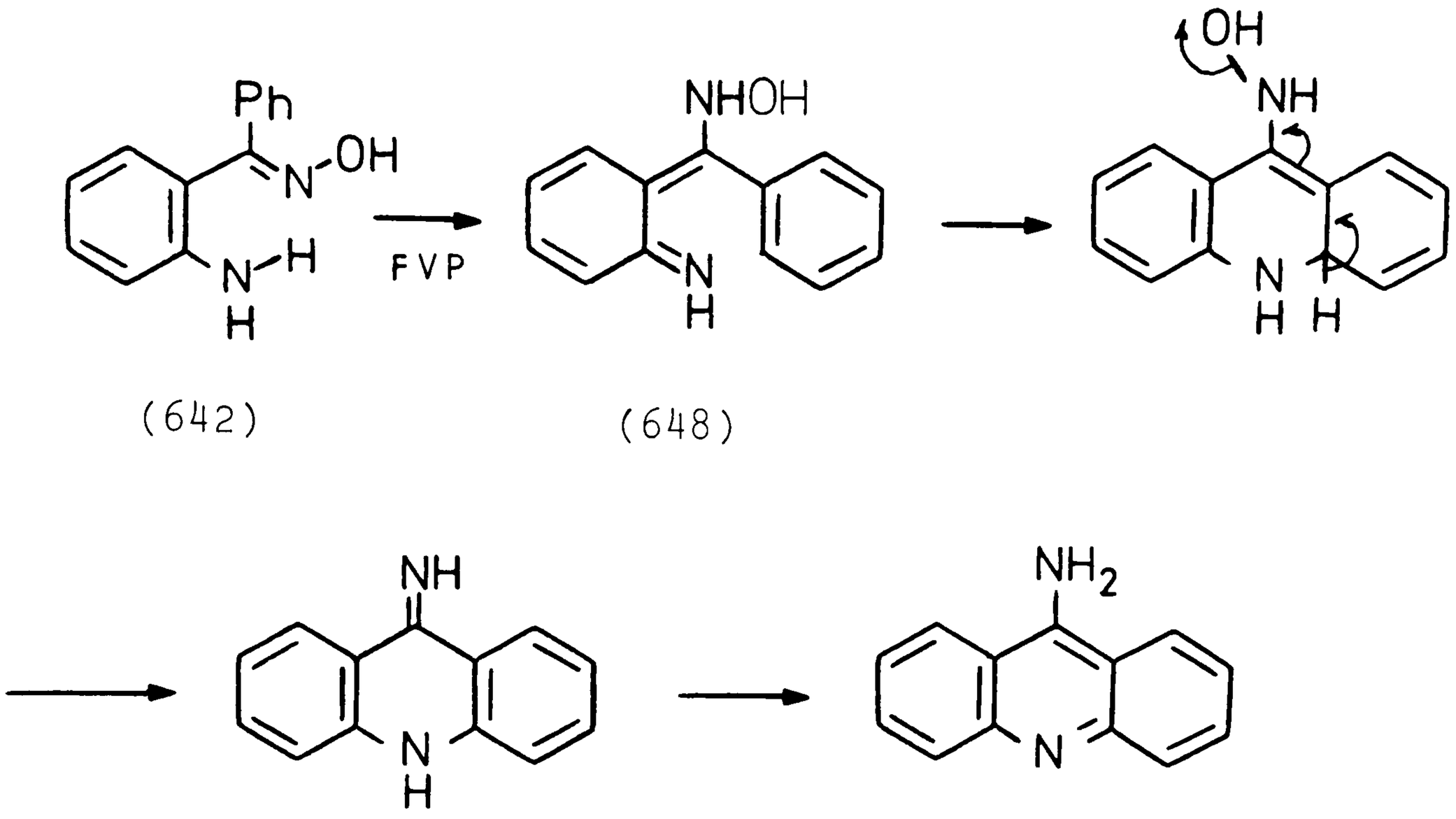
A brief attempt was made to extend this 1,5-elimination approach to other ylide intermediates. However, pyrolysis of o-aminobenzophenone oxime (642) at $800^{\circ}C/10^{-2}$ torr did not produce indazole (644) which would result from 1,5-dehydration and ring closure of intermediate nitrene (643). Instead, anthranilonitrile (645) (20%), N-phenylanthranilonitrile (647) (6%) and 9-aminoacridine (649) (6%) were isolated after chromatography on silica. The formation of anthranilonitrile (645) is difficult to explain, but at these high temperatures loss of the phenyl

substituent as a phenyl radical is a possibility. This may also explain the formation of N-phenylanthranilonitrile (647) by transfer of a phenyl radical onto the amine moiety. Alternatively, we could envisage a 1,2-shift of the phenyl substituent in nitrene (643) to give the intermediate imine (646). A 1,5-phenyl shift onto the azaxylylene nitrogen would then yield the required nitrile. Very similar quinonoid systems have been shown to undergo this type of shift.[289]



The formation of the acridine (649) can be explained by considering the reaction occurring via an initial 1,5-hydrogen shift to yield azaxylylene (648) followed by

electrocyclization and loss of water to yield acridine (649) after tautomerization.

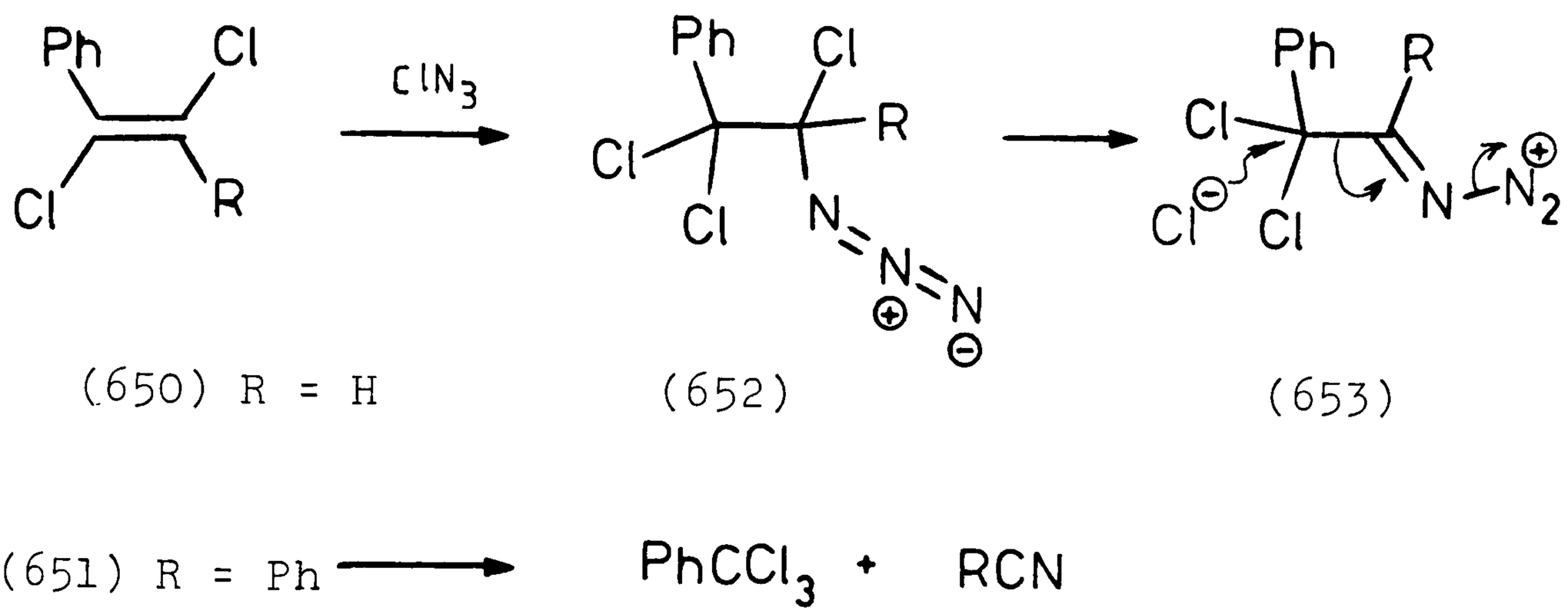


(642) (648) (649)

8. THE FRAGMENTATION OF α-CHLOROAZIDES.

During the synthesis of the chloroazirines used for the construction of the N-azirinyldihydrobenzoxazinones described in Chapter 7 (page 220) it was decided to investigate the reported instability of α-chloroazides. Previously, Crabb[292] had found that treatment of 1,2-dichlorostyrene (650) with chlorine azide did not give the expected trichloroazide (652), but an almost quantitative yield of α,α,α-trichlorotoluene. It was suggested that α-chloroazide (652) is unstable and expulsion of chloride anion yields the cation (653) which loses nitrogen with cleavage of the central carbon-carbon bond and formation of $PhCCl_3$ and HCN. In order to establish that the second product of the

fragmentation is a nitrile, we treated α,β-dichlorostilbene (651) with chlorine azide. Analysis of the products by g.c. revealed that α,α,α-trichlorotoluene and benzonitrile were formed in equimolar amounts although in only moderate yield (15 - 20%). In addition, dichlorostilbene (651) (40 - 50%) was recovered by chromatography of the crude reaction mixture on silica. These results support the mechanism shown in Scheme 11.

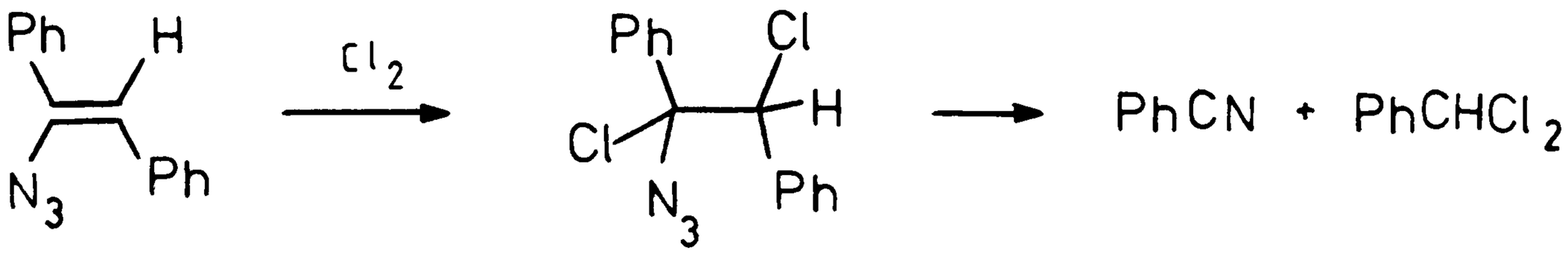


(650) R = H (652) (653)

(651) R = Ph ⟶ $PhCCl_3$ + RCN

SCHEME 11

Additional evidence for the instability of α-chloroazides was obtained from treatment of vinyl azide (654) (made by addition of ClN_3 to stilbene followed by elimination of HCl with KO^t-Bu) with Cl_2. Inspection of the crude reaction mixture by g.c. revealed benzonitrile and α,α-dichlorotoluene as the only detectable products which were again formed in equimolar amounts.[293]



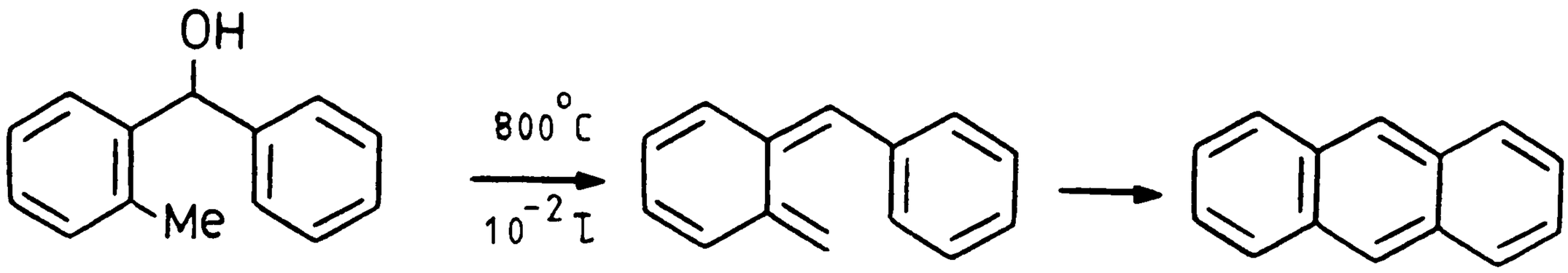
(654) (655)

9. THE FLASH VACUUM PYROLYTIC GENERATION OF o-XYLYLENES

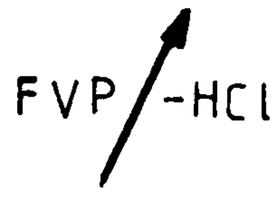
In spite of the vast amount of work carried out with o-xylylenes, there are surprisngly few reports of electrocyclization reactions. We were, therefore interested to see if aryl substituted o-xylylenes produced by flash vacuum pyrolysis underwent electrocyclization.

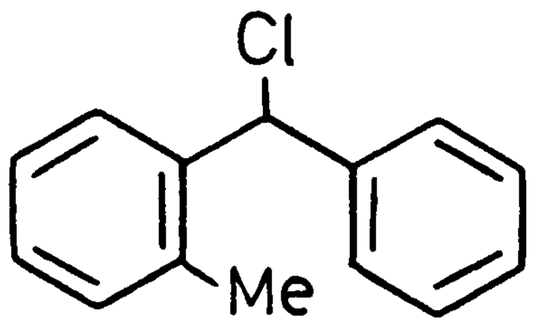
Flash vacuum pyrolysis of alcohol (656) which was prepared in high yield from reaction of benzaldehyde with o-tolyl magnesium bromide by the literature procedure,[294] produced anthracene (218) in 28% yield. It has subsequently been found[295] that the yields of cyclized products could be greatly increased by pyrolysis of the corresponding chloride (658). It has been reported that similar pyrolysis of dichloride (216) again produced anthracene in good yield.[29]

Pyrolysis of thiophene substituted alcohol (659), made in high yield from addition of 2-lithiothiophene to o-tolylcarboxaldehyde, produced naphthothiophene (661) in 5% yield after chromatography on silica. The physical and spectral properties of this product were in

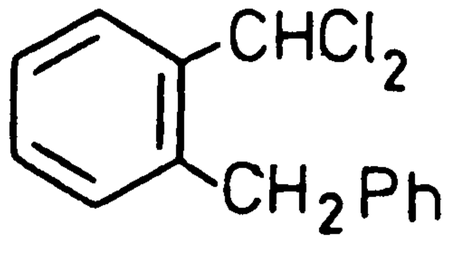


(656) (657) (218)





(658)

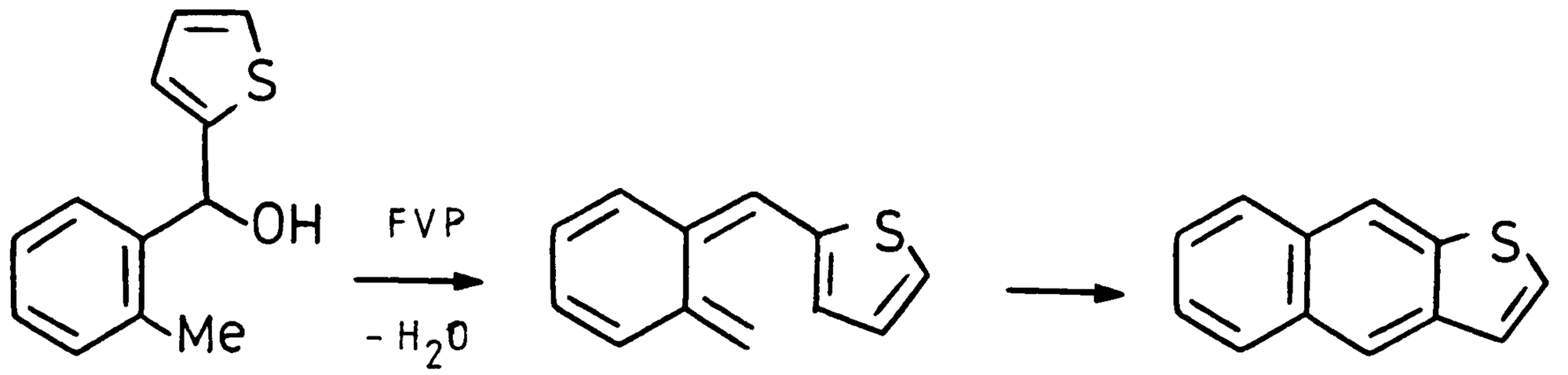


(216)

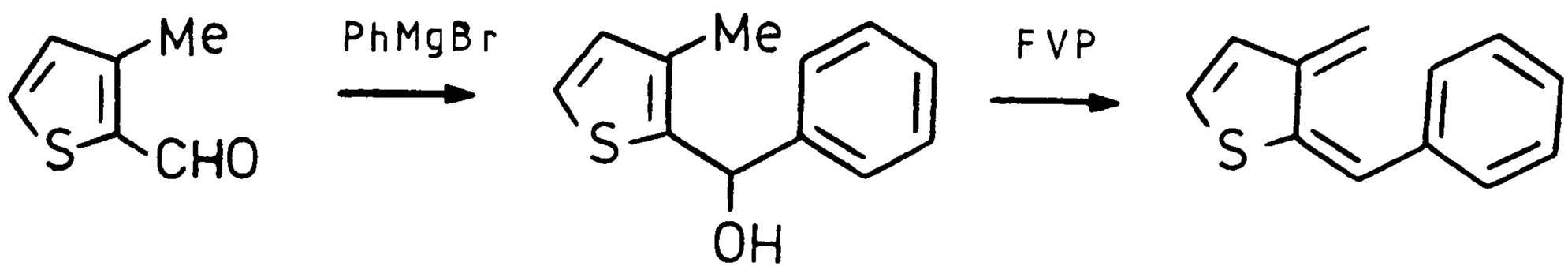
close agreement to those reported in the literature.[296] Presumably, product (661) originates from loss of water from alcohol (659) to give o-xylylene (660) followed by electrocylization with the thiophene ring. The yield of this product could be increased to 20% by pyrolysis at 450°C over alumina.

Finally, we were able to extend this approach to the generation of the thiophene-2,3-xylylene system (664). The precursor (663) was readily prepared by treatment of 3-methylthiophene-2-carboxaldehyde (662) with phenyl magnesium bromide in 86% yield after chromatography. Pyrolysis of (663) at 450°C over alumina gave naphthothiophene (661) in 21% yield which was identical in all respects to that obtained previously. Pyrolysis

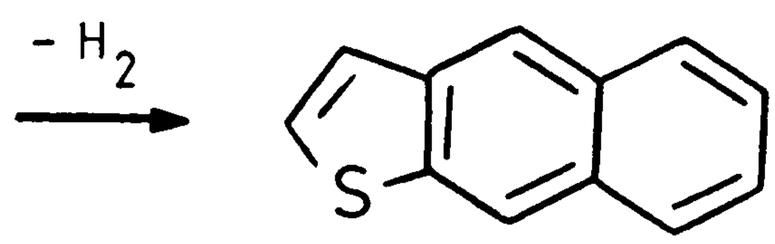
of this alcohol at 900°C in the absence of alumina gave this product in 12% yield.



(659) (660) (661)



(662) (663) (664)



(661)

Attempts to form the corresponding chlorides from these alcohols by a variety of methods results in the formation of intractable tars.

Despite the moderate yields of cyclized products obtained from the electrocyclization reactions of o-xylylenes, they do allow the rapid production of polyfused aromatic compounds from very simple, readily available precursors.

EXPERIMENTAL

10 INSTRUMENTATION AND EXPERIMENTAL TECHNIQUES

(a) Infra-red (i.r.) spectra were recorded in the range 4000- 600 cm^{-1} using Pye Unicam SP1025 and SP298 infra red spectrometers. Spectra of solid samples were taken as nujol mulls or as solutions. Sodium chloride plates were used in both cases. Spectra of liquids were taken as thin films between sodium chloride plates or as solutions.

(b) ^{1}H Nuclear magnetic resonance (n.m.r.) spectra were recorded on JEOL PMX60 (60 MHz), Perkin Elmer R34 (220 MHz), and Bruker WM250 (250 MHz) instruments. Solvents are indicated in the text, and tetramethylsilane was used as an internal reference. Spectra were recorded on the δ scale and signals are quoted in the form; chemical shift [number of protons, multiplicity, exch. (if applicable, meaning the signal was removed by the addition of D_2O)], measured in p.p.m. ^{13}C Nuclear magnetic resonance spectra were recorded on Varian XLFT 100 and Brucker WM250 spectrometers. Solvents are indicated in the text and tetramethylsilane was used as an internal reference. Spectra were recorded on the δ scale and signals are quoted in the form; chemical shift (multiplicity as seen in the ^{13}C off-resonance spectrum), measured in p.p.m.

(c) Routine mass spectra were recorded at 70 eV on an A.E.I. MS12 spectrometer and the samples were introduced using a direct insertion probe. In the text the molecular

ion ($\underline{M}^+$) is given followed by peaks corresponding to major fragment losses.

(d) Gas/liquid chromatography (g.c.) was performed using a capillary column with OV351 type packing and a DANI 3800 chromatograph with Hewlett-Packard 3390A digital integrator. Peaks were identified by comparison with authentic samples and by peak enhancement with authentic samples.

(e) Gas chromatography/mass spectrometry (g.c./m.s.) was performed using a VG 7070E mass spectrometer coupled to a capillary column with type OV351 packing.

(f) Melting points (m.p.) and mixed melting points (m.m.p.) were determined on a Kofler hot stage apparatus and are uncorrected.

(g) Thin layer chromatography (t.l.c.) was performed using Merck type 5554 and 818133 pre-coated silica plates and Merck type 5550 pre-coated alumina plates, and was used extensively as a qualitative guide to the composition of reaction mixtures and for assessing the purity of compounds.

(h) Preparative thin layer chromatography (p.t.l.c.) was performed using Merck type 5717 pre-coated 20 x 20 cm silica plates, and on 20 x 20 cm glass plates coated with Merck PF154 type alumina.

(i) Column chromatography (medium pressure) was carried out using silica gel type 9385 (Merck), Whatman S.O.T.L.C., or 15111 (Merck), or aluminium oxide without binder (for thin layer chromatography, B.D.H.).

(j) Unless otherwise stated, petroleum refers to petroleum spirit, b.p. range 60 - 80°C. This was distilled for use as eluant in column chromatography. Solvents were purified and, where necessary, dried by standard techniques. Hexane (for the preparation of chloroazirines) was distilled from lithium aluminium hydride before use. Ether and tetrahydrofuran for use in organolithium and organomagnesium reactions were distilled from the benzophenone radical anion under nitrogen before use.

(k) FLASH VACUUM PYROLYSIS (F.V.P.)

The majority of pyrolyses were conducted in the apparatus shown in Figure 4 . Pyrolytic experiments involving catalytic surfaces were carried out in the horizontal apparatus, Figure 5 .

(p) PYROLYSIS AT PRESSURES OF 10^{-2} - 10^{-3} TORR

The apparatus in Figure 4 or 5 was connected to a broad sweep vacuum pump capable of maintaining a pressure of less than 0.01 torr and the silica tube was pre-heated to the required temperature by surrounding it with a clindrical oven (the temperature of the oven was measured by a thermocouple capable of reading up to 1000° inserted between the oven and the silica tube). The material to be

pyrolysed was dissolved in dichloromethane or ether and the solvent removed in vacuo so as to deposit the material as a thin coating on the walls of a 50 ml B19 round bottomed flask. This large area facilitated sublimation. The flask was then fitted onto the end of the silica tube and the system was evacuated, the pressure being monitored using an Edwards type PRM10 Pressure head and a type 1105 digital monitoring system, and the cold finger was cooled usually to -78°C or occasionally to -196°C. Solids were sublimed into the hot zone by heating in an oil bath or in a Kugelrohr oven so that pyrolysis proceeded at the rate of 0.1g hr^{-1}. Liquids were distilled (in the presence of a magnetic agitator) into the hot zone using an oil bath.

When the pyrolysis was complete the vacuum pump was isolated and dry nitrogen or argon was introduced through a tap in the pumping arm. The round bottomed flask and oven were removed and replaced with a drying tube while nitrogen or argon was passed through the apparatus. When the oven tube had cooled, the coolant in the cold finger was removed and the pyrolysate allowed to warm to room temperature under the inert atmosphere. The pyrolsate was removed from the cold finger by addition of a suitable solvent (usually dichloromethane). The operation of the horizontal apparatus was essentially the same, except that the pyrolysates were washed off the cold finger with a solvent introduced through the B10 joint.

(m) PYROLYSES CONDUCTED AT PRESSURES BELOW 10^{-3} TORR

This technique was used for material which decomposed under normal conditions of sublimation or distillation. The same apparatus and procedure were used as above, except that a double stage mercury diffusion pump was connected to the existing vacuum pump enabling the pressure to be reduced to ca. 10^{-5} torr.

(n) PREPARATION OF CATALYTIC SUPPORTS

The silica and alumina supports were prepared by coating three 5 cm x 8 mm o.d. silica glass tubes internally with t.l.c., grade alumina and silica (coated in the same way as glass p.t.l.c. plates) and then stacked together in the centre of the horizontal hot tube (Figure 5).

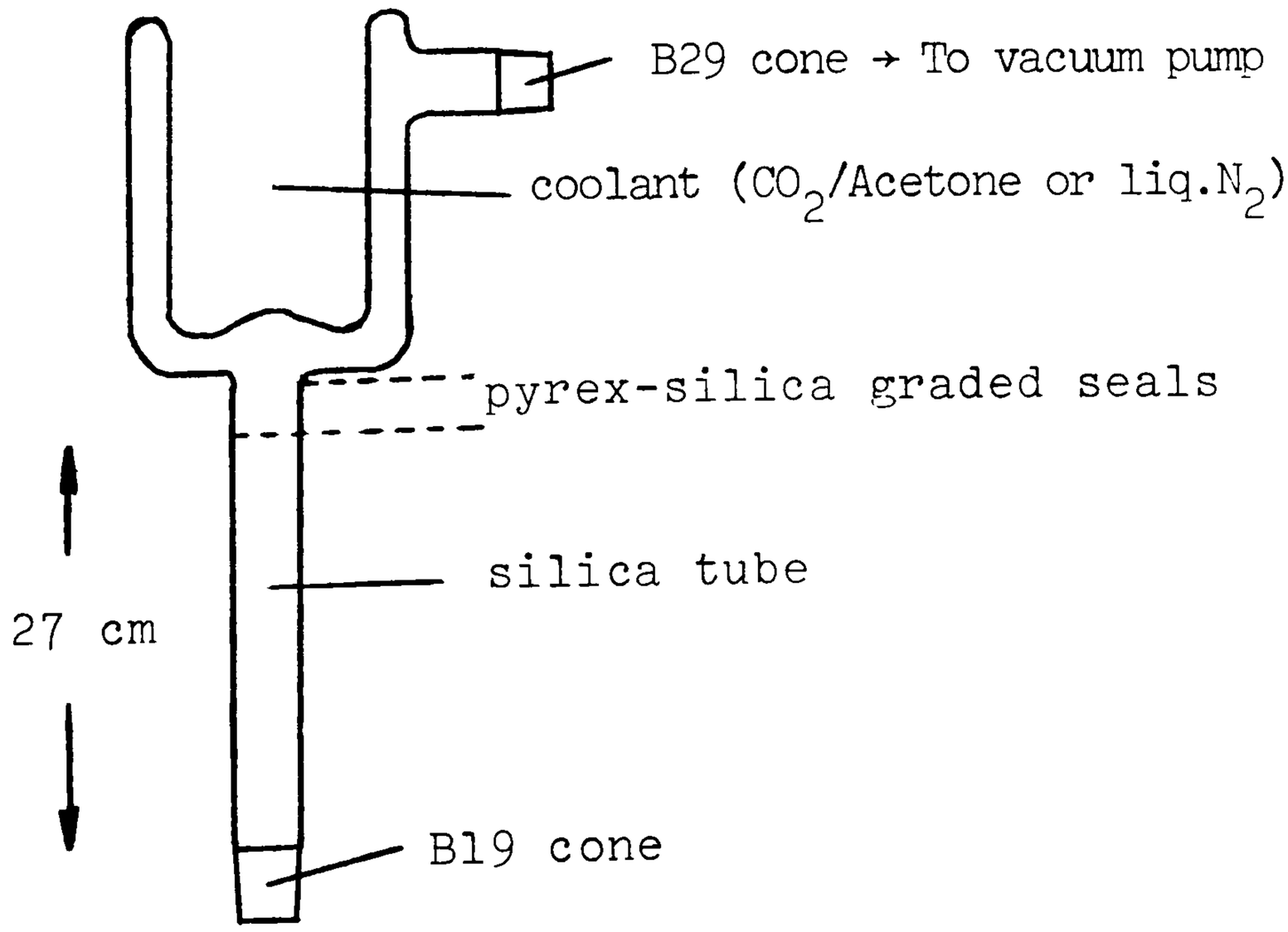


FIGURE 4 "Vertical" Pyrolysis apparatus.

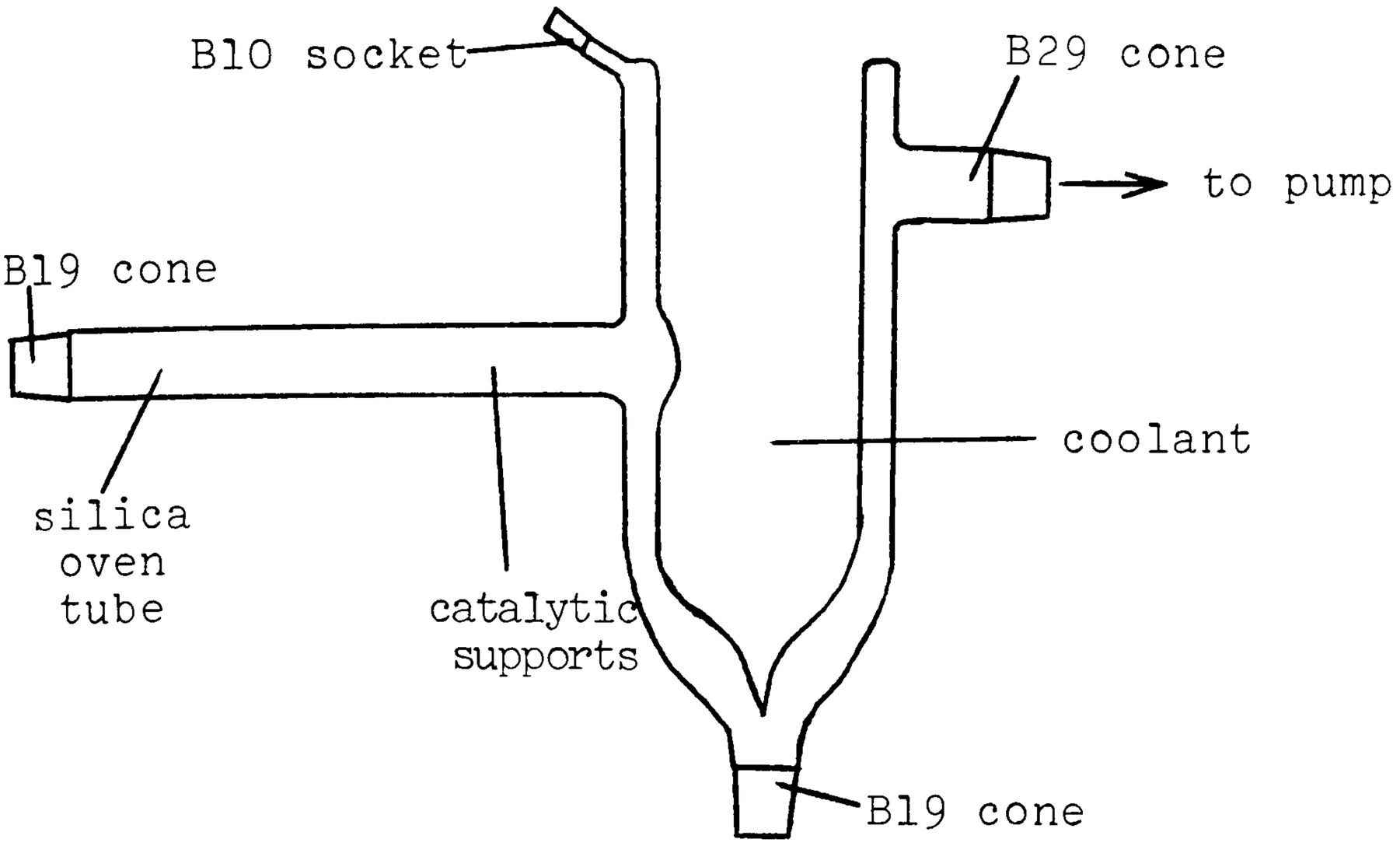


FIGURE 5 "Horizontal" pyrolysis appartus.

11. ATTEMPTED FORMATION OF BENZAZETIDINES FROM RING CLOSURE OF o-BROMOBENZYLAMINES

11.1 PREPARATION OF o-BROMOBENZYLAMINES

(a) N-PHENYL-2-BROMOBENZENETHANIMINE was prepared from condensation of 2-bromobenzaldehyde and aniline[235] for which; $\nu_{max.}$ 3070, 2925, 1620 (C = N), 1585, 1488, 1028, 965, 695 cm^{-1}. This crude product was used directly.

(b) N-PHENYL-2-BROMOBENZENEMETHANAMINE (395) was prepared by reduction of N-phenyl-2-bromobenzenemethanimine with sodium borohydride as described by Manley,[235] and had b.p. 100°/0.05 torr, (lit.,[297] b.p., 184 - 9°C/7.0 torr); $\nu_{max.}$ 3430 (NH), 3060, 2930, 1602, 1500, 1328, 1270, 1028, 755, 695 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.55 (1H, d, J = 8.2 Hz), 7.46 (1H, d, J = 7.6 Hz), 7.27 - 7.04 (4H, m), 6.70 (1H, t,

J = 7.6 Hz), 6.59 (2H, d, J = 8.2 Hz), and 4.38 (2H, s); m/z 263 and 261 (M^+), 182, 180, 169, 171, 106, and 77.

(c) N-BENZYL-2-BROMOBENZENEMETHANIMINE was prepared from condensation of 2-bromobenzaldehyde with benzylamine as described by Mori[298] and gave the crude imine as a pale yellow oil; $\nu_{max.}$ 3070, 2930, 1618 (C = N), 1588, 1488, 1028 and 766 cm^{-1}. This crude product was used directly.

(d) N-BENZYL-2-BROMOBENZENEMETHANAMINE (396) was prepared by reduction of N-benzyl-2-bromobenzenemethanimine with sodium borohydride as described by Mori.[298] The crude product was purified by chromatography on silica to give the title compound which was used without further purification; $\nu_{max.}$ 3430 (NH), 3060, 2922, 1599, 1502, 1270, 1270, 760 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.47 (1H, d, J = 9.9 Hz), 7.36 - 7.13 (7H, m), 7.02 (1H, t, J = 8.8 Hz), 3.81 (2H, s), 3.72 (2H, s).

11.2 ATTEMPTED RING CLOSURE OF o-BROMOBENZYLAMINES

(a) BY COPPER CATALYSIS

A solution of amine (395) (0.55g, 2.1 mmol) in anhydrous DMF (10 ml) was added to a stirred solution containing anhydrous copper (I) bromide (0.1g) and potassium tert-butoxide (0.5g, 4.5 mmol) in anhydrous DMF. This solution was stirred for six hours at room temperature and then heated under reflux overnight. After filtering and

pouring into water (30 ml), the mixture was extracted with ether (2 x 25 ml), dried ($MgSO_4$), and the solvents evaporated in vacuo to give the starting amine (395) (95%). Similar treatment of (396) gave no new products.

(b) BY PHOTOLYSIS

Amine (395) (0.55g, 2.1 mmol) was dissolved in anhydrous DMSO (10 ml) and potassium tert-butoxide (4.3g) was added in small portions followed by acetone (1g). The resulting dark brown solution was irradiated using a high pressure mercury immersion lamp set in a pyrex tube for 24 hours. However, aqueous work-up led to the complete recovery of starting materials. Similar irradiation of amine (396) again led to complete recovery of starting materials.

12. ATTEMPTED PREPARATION OF BENZAZETIDINES BY REACTION OF BENZYNE WITH IMINES AND AMIDINES

12.1 PREPARATION OF IMINES AND AMIDINES

Benzylidine aniline[299] (m.p. 51 - 2°C), benzylidine-4-chloroaniline[300] (b.p. 60 - 1°C), benzylidine ethylamine (419),[301] (b.p. 52 - 3°C/4.5 torr), ethyl-N-phenyl-formimidate (426)[302] (b.p. 87 - 89°C), N-phenyliminomethyl-pyrrolidine (425)[303] (b.p. 153°C), and N,N-dimethyl-N'-phenylformamidine (420)[304] (b.p. 107 - 8°C/2.0 torr) were prepared according to literature procedures.

12.2 GENERAL PROCEDURE FOR REACTION OF BENZYNE WITH IMINES

Benzenediazonium-carboxylate prepared fron anthranilic acid[305] (10 mmol) was added slowly to a boiling solution of the imine (5 mmol) in dichloroethane (100 ml) in an open beaker. The mixture was heated for 5 min., cooled, and filtered. The resulting brown solution was concentrated and the residue subjected to chromatography on alumina. The separated components were further purified by p.t.l.c.

(a) BENZYLIDINE ANILINE gave; 5,10-diphenyl-5,10-dihydroacridine (417, X = H) (5%), m.p. 172 - 3°C, (lit.,[306] m.p. 175°C), 5,6-diphenyl-5,6-dihydrophenanthridine (6%), m.p. 139 - 140°C, (lit.,[244] m.p. 138 - 140°C) and N-(o-anilinobenzhydryl)aniline (413) (16%), m.p. 134 - 5°C, (lit.,[307] m.p. 134 - 5°C).

(b) BENZYLIDINE-4-CHLOROANILINE gave; 2-chloro-5,10-diphenyl-5,10-dihydroacridine (417, X = Cl) (3%), m.p. 149 - 150°C, (lit.,[306] m.p. 150 - 151.5°C) and 2-chloro-5,6-diphenyl-5,6-dihydrophenanthridine (9%), m.p. 134 - 135°C from light petroleum; δ($CDCl_3$, 220 MHz), 5.88 (1H, s), 6.92 - 7.43 (15H, m), 7.62 - 7.78 (2H, m); m/z 369, 367 (M^+), 292, 290, 254, 177, 152, 69; Found: C, 81.30%; H, 4.95%; N, 3.70%. $C_{25}H_{18}NCl$ requires C, 81.60%; H, 4.90%; N, 3.81%.

(c) BENZYLIDINE ETHYLAMINE (419) gave N,N-diphenyl-ethylamine (13%) as a colourless oil, b.p. 78°C/1 torr (lit.,[307] b.p. 149.5 - 150°C/10 torr).

(d) ETHYL-N-PHENYLFORMIMIDATE (426) gave acridine (282) (3%), m.p. 110 - 111°C, (lit.,[308] m.p. 111°C).

(e) N-PHENYLIMINOMETHYL PYRROLIDINE (425) gave acridine (15%), m.p., 110 - 111°C and 2-N-phenylaminobenzaldehyde (421) (8%), m.p., 71 - 72°C, (lit.,[309] m.p. 72.5°C). Further elution also gave diphenylamine (2%).

(f) N,N-DIMETHYL-N'-PHENYLFORMAMIDINE (420) gave 2,N-phenylaminobenzaldehyde (8%) and acridine (17%).

(g) OXIDATION OF 1-AMINOBENZOTRIAZOLE (427) IN THE PRESENCE OF N ,N-DIMETHYL-N'-PHENYLFORMAMIDINE (420).

1-Aminobenzotriazole (427), (0.8g, 6 mmol) which was prepared by the method of Atkin,[248] was dissolved in anhydrous dichloromethane (50 ml) together with amidine (420) (0.9g, 6 mmol) and to this stirred solution , lead tetra-acetate (4g, 9 mmol) in anhydrous dichloromethane (10 ml) was added dropwise over 5 min. After the initial vigorous reaction, the solution was stirred for 5 min., and glycerol (0.5 ml) was added. The resulting precipitate consisting of lead (II) salts was filtered-off and the solvent removed in vacuo giving 1.6g of a dark brown oil. Chromatography on silica and elution with petroleum afforded biphenylene

(428) (0.2g, 23%), m.p. 109 - 110°C, (lit.,[310] m.p. 110°C). Further elution with 20% ether-petroleum gave only trace amounts of unidentifiable material. Repeating this reaction at -78°C gave no identifiable products. Treatment of a solution of the amidine (420) (0.9g, 6 mmol) with lead tetra-acetate (4g, 9 mmol) in dichloromethane (50 ml) and stirring for 2 hours gave the recovered amidine (0.9g, 100%). In addition, stirring a solution of amidine (420) and 1-aminobenzotrazole (427) in dichloro-methane at room temperature for 2 hours gave complete recovery of starting materials.

(h) ATTEMPTED REACTION OF 3-NITROBENZYNE WITH AMIDINE (420).

(i) 4-NITROBENZOTRIAZOLE

Benzotriazole (10g, 83 mmol) was nitrated with a mixture of concentrated sulphuric and fuming nitric acids according to the procedure described by Atkin[248] and the title compound, (9.3g, 68%) was obtained as light yellow needles, m.p. 234 - 5°C from ethanol, (lit.,[248] m.p. 234 - 5°C).

(ii) 1-AMINO-4- AND 7-NITROBENZOTRIAZOLES

4-Nitrobenzotriazole (8g, 48 mmol) was aminated using hydroxylamine-O-sulphonic acid[311] (30g) according to the procedure of Atkin[248] to give a mixture of 1-amino-4- and 7-nitrobenzotriazoles as a yellow solid (0.25g, 3%), m.p. 120 - 126°C (lit.,[248] m.p. 121 - 123°C); $\nu_{max.}$ 3391 and 3318 (NH_2), 1648, 1628, 1530, 1348, 1005 cm^{-1};

δ ($CDCl_3$, 220 MHz), 8.28 (1H, d, J = 8.8 Hz), 8.09 (1H, d, J = 8.8 Hz), 7.67 (1H, t, J = 8.8 Hz), 6.14 - 5.50 (2H, br.s.,); m/z 179 (M^+), 144, 150, 122, 105, 92, 78.

(iii) OXIDATION OF 1-AMINO-4- AND 7-NITROBENZOTRIAZOLES IN THE PRESENCE OF AMIDINE (420).

The isomeric mixture of benzotriazoles (0.25g, 2 mmol) was dissolved in anhydrous dichloromethane (15 ml) together with amidine (420) (0.21g, 2 mmol) and cooled to -78°C. To this rapidly stirred solution was added lead tetra-acetate (1.4g, 2 mmol) in anhydrous dichloromethane (10 ml), over 5 min. After the initial vigorous reaction, the resulting dark brown solution was stirred for 1.5 hours and allowed to attain room temperature. The inorganic salts were removed by filtration and evaporation of the solvents in vacuo gave 1.4g of a dark brown oil which was revealed to be a complex mixture on examination by t.l.c. Chromatography on silica and elution with 50% ether-petroleum gave recovered amidine (420) (0.03g) as the only identifiable material.

(i) ATTEMPTED REACTION OF 3,6-DIMETHOXYBENZYNE WITH AMIDINE (420).

(i) 2-NITRO-3,6-DIMETHOXYBENZOIC ACID

Nitration of 2,5-dimethoxybenzoic acid (436) using the procedure of Banerjee[312] gave the title compound as pale yellow needles, m.p., 194 - 6°C, from water, (lit.,[312] m.p. 194°C); $\nu_{max.}$ 2400 - 3300 (broad OH, CH), 1745 (C = O), 1580, 1550, 1470, 1065, 815 and 720 cm^{-1}; δ ($CDCl_2$, 220 MHz),

7.92 (1H, s), 7.53 (1H, s), 4.11 (3H, s), 4.00 (3H, s); m/z 227 (M^+), 183, 179, 151, 137, 123, 79, 77.

(ii) 2-AMINO-3,6-DIMETHOXYBENZOIC ACID

Reduction of 2-nitro-3,6-dimethoxybenzoic acid with sodium dithionite according to the procedure of Banerjee[312] gave the title compound, m.p. 98 - 100°C, (lit.,[312] m.p. 97°C); $\nu_{max.}$ 3520 and 3378 (NH_2), 3330 - 3120 (broad OH), 1710 (C = O), 1629, 1455, 1382 and 1115 cm^{-1}; δ ($CDCl_2$, 220 MHz), 6.73 (1H, d, J = 11.0 Hz), 6.90 - 6.40 (2H, br.s.,), 6.10 (1H, d, J = 11.0 Hz), 3.95 (3H, s), and 3.83 (3H, s); m/z, 197 (M^+), 182, 179, 164, 150, 137 and 136.

(iii) 3,6-DIMETHOXYBENZENE-1-DIAZONIUM-2-CARBOXYLATE HYDROCHLORIDE (433).

2-Amino-3,6-dimethoxybenzoic acid (0.42g, 2 mmol), was dissolved in absolute ethanol (10 ml) in a 50 ml beaker. The stirred solution was cooled to 0°C and concentrated hydrochloric acid (0.2 ml) was added followed by cold (0°C) iso-amyl nitrite (0.5 ml, 4 mmol). The resulting dark brown solution was stirred for 10 min., and ether (10 ml) was added and stirring continued for an additional 5 min. The yellow crystals of hydrochloride (433) were collected by suction filtration using a plastic Buchner funnel and washed with cold ether (25 ml). This material was used immediately after preparation.

(iv) GENERATION OF 3,6-DIMETHOXYBENZYNE IN THE PRESENCE OF AMIDINE (420).

Hydrochloride (433) (0.44g, 2 mmol) together with propylene oxide (0.2 ml), and amidine (420) (2.2g, 15 mmol) were dissolved in 1,2-dichloroethane (10 ml). This solution was then heated under reflux under an atmosphere of nitrogen overnight. The solvents were removed *in vacuo*, and the resulting dark brown oil subjected to chromatography on silica, which gave recovered amidine (1.4g) as the only characterizable material.

13. ATTEMPTED FORMATION OF BENZAZETIDINES FROM FORMATION OF THE AROMATIC RING

(a) N-TOSYL-7-AZABICYCLO [4.2.0] OCT-3-ENE (444).

Treatment of 7-azabicyclo [4.2.0] oct-3-ene (462) (prepared in two steps from 1,4-cyclohexadiene)[313] with toluene-4-sulphonyl chloride in 30% aqueous sodium hydroxide solution according to the method of Paquette[252] gave an off-white solid. Recrystallization from hexane afforded the title compound as colourless needles (20.2%); m.p. 100 - 103°, (lit.,[252] m.p. 100 - 101°C); $\nu_{max.}$ 2860, 1605, 1510, 1342, 1510 and 955 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.72 (2H, d, J = 8.8 Hz), 7.33 (2H, d, J = 8.8 Hz), 5.93 (2H, d, J = 4.4 Hz), 4.31 - 4.19 (1H, m), 3.74 (1H, t, J = 8.8 Hz), 3.32 (1H, dd, J = 4.4 Hz, 8.8 Hz), 2.55 - 2.34 (2H, m), 2.40 (3H, s), 2.05 - 1.88 (3H, m); m/z 263 (M^+), 185, 156 and 119.

(b) ATTEMPTED FORMATION OF N-TOSYLBENZAZETIDINE (440).

Tosylate (444) (0.11g, 1 mmol) and activated manganese dioxide (0.55g, 10 mmol) were stirred together in refluxing benzene in a Dean-Stark apparatus for 68 hours. The mixture was then filtered and the solvent removed *in vacuo* to give the starting tosylate (444) (0.11g, 100%).

14. THE FLASH VACUUM PYROLTIC GENERATION OF O-AZAXYLYLENES

14.1 PREPARATION OF 2-AMINOBENZENEMETHANOLS

(a) α-(2-AMINOPHENYL)THIOPHENE-2-METHANOL (462)

(i) ATTEMPTED PREPARATION FROM O-AMINOBENZALDEHYDE (461)

A solution of 2-lithiophene (7.5 mmol) (generated as a complex with tetramethylethylenediamine (TMEDA) by the method of Chadwick)[258] in anhydrous ether (30 ml) was added slowly to a solution of 2-aminobenzaldehyde (0.3g, 2.5 mmol) in anhydrous ether at room temperature under nitrogen. After stirring for one hour, the resulting dark brown solution was poured into water (50 ml) and the organic phase separated and dried ($MgSO_4$). Removal of the solvents *in vacuo* gave a dark brown viscous oil which was shown to be a complex mixture by t.l.c., and n.m.r., analysis, and from which no discrete products could be identified on chromatography.

(ii) ATTEMPTED PREPARATION FROM O-NITROBENZALDEHYDE

A solution of 2-lithiothiophene/TMEDA complex (7.5 mmol) in anhydrous ether (30 ml) was cooled to $0^{o}C$ and added to a cooled ($0^{o}C$), stirred solution of 2-nitrobenzaldehyde (1.13g,

7.5 mmol) in anhydrous ether (20 ml) under nitrogen. The resulting dark brown solution was stirred for 0.5 hours at 0°C and four hours at room temperature. After pouring into water (50 ml), the organic phase was separated and dried ($MgSO_4$) and the solvents evaporated under reduced pressure to give a dark brown viscous oil which was revealed to be extremely complex by t.l.c., and n.m.r., analysis. Isolation of the components in this mixture was not attempted.

(iii) FROM REDUCTION OF 2-AMINOPHENYL-2-THIENYL KETONE (470)

(iiia) PREPARATION OF (470) FROM ANTHANILIC ACID

A solution of 2-lithiothiophene/TMEDA complex (60 mmol) in anhydrous ether (60 ml) was added to a stirred solution of anthranilic acid (2g, 15 mmol) in anhydrous ether (25 ml) under nitrogen at room temperature. After stirring for four hours, the reaction mixture was poured into water (100 ml) and the ethereal layer separated. The aqueous phase was extracted with ether (2 x 50 ml) and the combined ether extracts dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a yellow oil. Chromatography on silica and elution with 50% ether-petroleum gave the thienyl ketone (470) (0.77g, 25%). A small aliquot was further purified by bulb-to-bulb distillation which had the following spectral characteristics; b.p. 62 - 4°C/ 0.05 torr, (lit.,[314] 188 - 9°C); $\nu_{max.}$ 3982 and 3370 (NH_2), 1620 (C = O), 1586, 1415, 1300, 1255, 1163, 758 and722 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.80 (1H, d, J = 8.8 Hz),

7.70 - 7.50 (2H, m), 7.32 (1H, t, J = 8.8 Hz), 7.14 (1H, t, J = 4.4 Hz), 6.83 - 6.67 (2H, m), 6.20 - 5.60 (2H, br.s., exch.); m/z 203 (M^+), 202, 170, 120, 119, 111 and 92.

(iiib) PREPARATION OF (470) FROM ISATOIC ANHYDRIDE

A solution of 2-lithiothiophene/TMEDA complex (26 mmol) in anhydrous ether (60 ml) was cooled to -40°C and added to a cooled (-40°C) mixture containing isatoic anhydride (2.0g, 12 mmol) in anhydrous ether under nitrogen over 0.5 hours. The resulting red solution was stirred at -40°C for 4.5 hours and after warming to room temperature, poured into water (250 ml). Dilute hydrochloric acid (70 ml , 0.1M) was then added which resulted in effervescence and the colour of the solution changed from red to bright yellow. The ethereal layer was separated and the aqueous phase extracted with ether (50 ml). The combined ether extracts were dried ($MgSO_4$) and the solvent removed in vacuo to yield a yellow oil. Chromatography on silica and elution with 50% ether-petroleum gave ketone (470) (0.52g, 22%) which was identical in all respects to that obtained from anthranilic acid.

REDUCTION OF KETONE (470)

To a stirred solution of thienyl ketone (470) (0.44g, 2.2 mmol) in methanol (50 ml) was added sodium borohydride (0.5g, 13 mmol) in small portions over 15 minutes. The yellow colour of the solution was discharged after 30 min.,

and the solution was stirred for a further hour and then poured into water (100 ml) and extracted with dichloromethane (3 x 75 ml). The combined extracts were dried ($MgSO_4$) and the solvents removed in vacuo to give a white solid. Recrystallization from chloroform-petroleum gave alcohol (462) (6.44g, 98%) as colourless needles, m.p. 80 - 82°C, (lit.,[257] no m.p. given); $\nu_{max.}$ 3340 and 3170 (NH_2), 3200 - 2900 (broad OH), 1585, 1568, 1005, 990, 735, 675 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.25 (1H, d, J = 4.4 Hz), 7.20 - 7.05 (2H, m), 6.05 (1H, t, J = 4.4 Hz), 6.92 - 6.62 (3H, m), 3.95 - 3.25 (2H, br.s., exch.); m/z 205 (M^+), 187, 186, 120, 93 and 77.

(b) α-(2-AMINOPHENYL)FURAN-2-METHANOL (472)

(i) FROM REDUCTION OF 2-AMINOPHENYL-2-FURANYL KETONE (471). ATTEMPTED PREPARATION OF (471) FROM ISOTOIC ANHYDRIDE (109)

A solution of 2-lithiofuran/TMEDA complex (26 mmol) (prepared by the method of Chadwick)[258] in anhydrous ether (30 ml) was cooled to -40°C and added to a cooled (-40°C), stirred mixture containing isatoic anhydride (2.0g, 12 mmol) in anhydrous ether (30 ml) under nitrogen. After proceeding as described for addition of 2-lithiothiophene to isatoic anhydride, aqueous work-up produced a red oil. However this was shown to be a complex mixture by t.l.c., from which no discrete products could be isolated upon chromatography.

PREPARATION OF (471) FROM ANTHRANILIC ACID

A solution of 2-lithiofuran/TMEDA complex (30 mmol) in anhydrous ether (25 ml) was added to a stirred solution of anthranilic acid (1g, 7.5 mmol) in anhydrous ether (20 ml) under nitrogen at room temperature. After proceeding exactly as described for reaction of anthranilic acid with 2-lithiothiophene, furanoyl ketone (471) was obtained as a bright yellow oil (0.66g, 47%) and was used directly; $\nu_{max.}$ 3465 and 3350 (NH_2), 2950, 1615 (C = O), 1580, 1460, 1255, 1160, and 752 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.89 (1H, d, J = 8.8 Hz), 7.64 (1H, d, J = 3.0 Hz), 7.26 (1H, t, J = 8.8 Hz), 7.11 (1H, d, J = 4.4 Hz), 6.76 (2H, m), 6.53 (1H, t, J = 3.0 Hz), 6.20 - 5.70 (2H, br.s., exch.); m/z 187 (M^+), 186, 181, 169, 131 and 119.

REDUCTION OF KETONE (471)

Ketone (471) (0.13g, 0.7 mmol) was dissolved in methanol (30 ml) and treated with sodium borohydride (0.13g, 3.4 mmol) portionwise with stirring over 10 minutes. After 0.5 hours the yellow colour was completely discharged, and the solution was stirred for a further hour and poured into water. After extraction with dichloromethane (2 x 25 ml) and after drying ($MgSO_4$), the extracts were evaporated under reduced pressure to give a pale yellow oil which slowly solidified. Recrystallization from chloroform-hexane gave alcohol (472) as colourless needles (0.11g, 83%), m.p. 54 - 56°C), (lit.,[315] m.p., 64 - 5°C); $\nu_{max.}$ 3000 - 3550 (broad OH, NH_2), 2950, 1612, 1580, 1495, 1458, 1010 and

750 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.32 (1H, d, J = 3.0 Hz), 7.05 (1H, t, J = 8.8 Hz), 6.96 (1H, d, J = 8.8 Hz), 6.67 (1H, t, J = 8.8 Hz), 6.55 (1H, d, J = 8.8 Hz), 6.25 (1H, t, J = 3.0 Hz), 6.10 (1H, d, J = 3.0 Hz), 5.65 (1H, s), 4.10 - 3.70 (3H, br.s., exch.); m/z 189 (M^+), 171, 170, 143, 117, 77 and 65. This product was observed to decompose upon storage and was used soon after preparation.

(c) α-(2-Aminophenyl)-N-METHYLIMIDAZOLE-2-METHANOL (467)

(i) α-(2-NITROPHENYL)-N-METHYLIMIDAZOLE-2-METHANOL (466)

To a cooled (-78°C), stirred solution of 2-lithio-N-methylimidazole (83 mmol) (prepared by the method of Roe[261]) in anhydrous ether (100 ml) under nitrogen was added a solution of 2-nitrobenzaldehyde (10g, 66 mmol) in anhydrous THF (30 ml) dropwise over 1.5 hours. The resulting grey-brown suspension was stirred for a further 1.5 hours at -78°C and after warming to room temperature was poured into water (50 ml). A solution of 10%, aqueous hydrochloric acid (100 ml) was then added and the aqueous layer was separated and the pH adjusted to between 7 - 8 by the addition of saturated sodium hydrogen carbonate solution. This mixture was extracted with dichloromethane (4 x 150 ml) and the combined extracts dried ($MgSO_4$) and the solvents removed in vacuo to give a yellow/orange solid. Chromatography on silica and elution with ethyl acetate gave a yellow solid which was recystallized from ethyl acetate - hexane to give (466) (5.9g, 38%) as colourless needles, m.p. 172 - 174°C; $\nu_{max.}$ 2600 - 3300

(broad OH), 1516, 1342, 1038, and 742 cm^{-1}; δ DMSO-d_6, 250 MHz), 8.00 (2H, d, J = 8.6 Hz), 7.82 (1H, t, J = 8.7 Hz), 7.57 (1H, t, J = 8.7 Hz), 6.61 (1H, s), 6.45 (1H, d, J = 6.8 Hz), 6.38 (1H, d, J = 6.8 Hz), 3.77 (3H, s); δ ^{13}C (DMSO-d_6), 147.34 (s), 147.05 (s), 137.67 (s), 133.05 (d), 128.49 (d), 127.90 (d), 125.60 (d), 123.86 (d), 121.63 (d), 63.16 (d), 32.31 (q); m/z (CI, isobutene), 234 (M^+ + 1), 170; Found: C, 56.49%; H, 4.65%; N, 18.35%. $C_{11}H_{11}N_3O_3$ requires C, 56.65%; H, 4.75%; N, 18.02%.

(ii) α-(2-AMINOPHENYL)-2-N-METHYLIMIDAZOLE-2-METHANOL (467)

Alcohol (466) (1.0g, 4.3 mmol) was dissolved in methanol (100 ml) and 10% palladium on charcoal (0.01g) added. The stirred mixture was hydrogenated at room temperature until 2.88 ml of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate was evaporated to give a white solid. Recrystallization from chloroform-hexane gave α-(2-aminophenyl)-2-N-methyl-imidazole-2-methanol (0.66g, 76%) as a colourless, microcrystalline solid, m.p. 125 - 7°C; $\nu_{max.}$ 2600 - 3500 (broad NH_2, OH, CH), 1605, 1485, 1452, 1274, 1025 and 740 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.06 (1H, t, J = 6.8 Hz), 6.95 (1H, d, J = 8.8 Hz), 6.82 - 6.57 (4H, m), 5.86 (1H, s), 5.10 - 4.40 (3H, br.s., exch.), 3.42 (3H, s); m/z 203 (M^+), 185, 119, 91 and 77; accurate mass, Found: 203.1057. $C_{11}H_{13}N_3O$ requires 203.1059. Despite repeated attempts, a satisfactory elemental analysis could not be obtained.

(d) 1-(2-AMINOPHENYL)HEX-5-EN-1-OL (482)

(i) PENT-4-ENYL TOSYLATE

Toluene-4-sulphonyl chloride (15.0g, 78 mmol) was added portionwise to a cooled ($0^{o}C$), stirred solution of pent-4-en-1-ol[266] (5.0g, 58 mmol) in dry pyridine (75 ml) so that the temperature of the reaction mixture remained below $3^{o}C$. The mixture was stored in a refrigerator for three days, then poured into ice water (200 ml) and the organic phase was extracted into dichloromethane. This solution was washed with dilute hydrochloric acid, followed by water, separated, dried ($MgSO_4$) and evaporated under reduced pressure. The resulting crude red oil of pent-4-enyl tosylate (8.8g, 64%) was useddirectly.

(ii) PENT-4-ENYL IODIDE (481)

A mixture of the crude pent-4-enyl tosylate (8.0g, 33 mmol) in a saturated solution of sodium iodide in "analar" acetone (50 ml) was stirred for three days at room temperature. The resulting precipitate was filtered off, washed with acetone and the filtrate evaporated under reduced pressure to give a semi-solid. This was dissolved in water (100 ml) and the organic phase was extracted into dichloromethane, separated and washed with aqueous sodium thiosulphate. After a further separation, the organic phase was dried over calcium sulphate, filtered and the solvent removed under reduced pressure to give a colourless oil. Distillation afforded

pent-4-enyl iodide (3.5g, 53%) as a colourless oil, b.p. 145°C (lit.,[316] b.p., 150°C).

(iii) 1-(2-AMINOPHENYL)HEX-5-EN-1-ONE (476)

A solution of pent-4-enyl-1-magnesium iodide (prepared from pent-4-enyl iodide) (30 mmol) in anhydrous ether (20 ml) was added to a cooled (8°C), stirred solution of 2-methyl-1,3-benzoxazin-4-one (4.83g, 30 mmol) (prepared by the method of Campbell [265]) in ahydrous benzene (30 ml) under nitrogen over 2 hours. The resulting yellow suspension was allowed to warm to room temperature and stirred overnight. After pouring into water, the aqueous layer was extracted with ether (3 x 50 ml), and the combined extracts dried ($MgSO_4$) and the solvents removed under reduced pressure to give a light brown oil which solidified on standing. This was then placed in a mixture of ethanol (75 ml), water (50 ml) and sodium hydroxide (15g) and this mixture was then heated under reflux for 2 hours. After cooling, the mixture was extracted with dichloromethane (2 x 70 ml) dried ($MgSO_4$), and the solvents removed under reduced pressure to give a dark yellow oil. Chromatography on silica and elution with dichloromethane gave a yellow oil. Bulb-to-bulb distillation gave ketone (476) as a pale yellow oil (1.3g, 23%), b.p. 124°C/0.05 torr; $\nu_{max.}$ 3460 and 3325 (NH_2), 3055, 2815, 1680 (C = O), 1100, 855 and 690 cm^{-1}; δ ($CDCl_3$, 250 MHz); 7.70 (1H, d, J = 8.8 Hz), 7.21 (1H, t, J 2 8.8 Hz), 6.66 - 6.55 (2H, m), 6.42 - 6.10 (2H, br.s.,

exch.), 5.94 - 5.70 (1H, m), 5.10 - 4.90 (2H, m), 2.90 (2H, t, J 2 8.7 Hz), 2.12 (2H, q, J = 8.7 Hz), 1.88 - 1.70 (2H, m); m/z 189 (M^+), 135, 120, 92 and 65; accurate mass, Found: 189.1147. $C_{12}H_{15}NO$ requires 189.1153, Found: C, 76.61%; H, 8.37%; N, 7.50%. $C_{12}H_{15}NO$ requires C, 76.15%; H, 7.99%; N, 7.40%.

(iv) 1-(2-AMINOPHENYL)HEX-5-EN-1-OL (482)

The ketone (476) (0.64g, 3.4 mmol) was dissolved in methanol (100 ml) and sodium borohydride (0.5g, 14 mmol) was added in small portions with stirring over 10 minutes. After 0.5 hours, all colour in the solution had been discharged and after stirring for a further 0.5 hours, the reaction mixture was poured into water (150 ml) and extracted with dichloromethane (3 x 100 ml). The combined organic extracts were dried ($MgSO_4$) and the solvents removed under reduced pressure to give a colourless solid. This was dissolved in the minimum of hot dichloromethane (ca. 3 ml) and hexane was added until the solution was slightly turbid. After storing in a refrigerator overnight the title compound was obtained as colourless cubes (0.63g, 94%), m.p. 39 - 41°C; $\nu_{max.}$ 3150 - 3600 (broad NH_2, OH), 2922, 2850, 1612, 1588, 1500, 905 and 745 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.19 - 6.95 (2H, m), 6.67 (1H, t, J = 8.8 Hz), 6.57 (1H, d, J = 8.8 Hz), 5.90 - 5.68 (1H, m), 5.80 - 4.88 (2H, m), 4.53 (1H, t, J = 6.5 Hz), 4.30 - 3.40 (3H, br.s., exch.), 2.05 (2H, q, J = 6.5 Hz), 1.91 - 1.58 (2H, m), 1.63 - 1.20 (2H, m); m/z 191 (M^+),

173, 132, 122, 94 and 77; accurate mass, found: 191.1304 $C_{12}H_{17}NO$, 191.1304; Found: C, 75.21%; H, 9.17%; N, 7.22%. $C_{12}H_{17}NO$ requires, C, 73.35%; H, 8.96%; N, 7.32%.

(e) 1-(2-AMINOPHENYL)HEPT-6-EN-1-OL (463)

(i) ATTEMPTED PREPARATION FROM 2-AMINOBENZALDEHYDE

A solution of hex-5-enyl-1-magnesium iodide (7.5 mmol) (the hexenyl iodide was prepared from hex-5-en-1-ol[259]) in anhydrous ether (20 ml) was added to a solution of 2-aminobenzaldehyde (0.3g, 2.5 mmol) in anhydrous ether (30 ml) over 10 minutes. After stirring for one hour, t.l.c., examination of this reaction revealed it to be an extremely complex mixture and purification was not attempted.

(ii) 1-(2-AMINOPHENYL)HEPT-6-EN-1-ONE (477)

A sample of alcohol (463) from reduction of the corresponding ketone (prepared by an analogous procedure to that described for ketone (476)) was kindly supplied by Dr. R.D.Bowen and had the following spectral characteristics; $\nu_{max.}$ 3550 - 3200 (broad NH_2, OH), 2960, 1615, 940 and 780 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.03 - 6.89 (2H, m), 6.66 - 6.49 (2H, m), 5.92 - 5.60 (1H, m), 5.00 - 4.80 (2H, m), 4.52 (1H, t, J 2 6.5 Hz), 3.63 - 3.45 (2H, br.s., exch.), 2.06 - 1.87 (2H, m), 1.84 - 1.56 (2H, m), 1.54 - 1.10 (4H, m).

(f) 1-(2-AMINOPHENYL)PENTAN-1-ONE[317] (473)

A solution of n-butyllithium (30 mmol) in hexane (18.25 ml) was added to a stirred solution of anthranilic acid (1g, 7.3 mmol) in anhydrous ether (50 ml) at room temperature under nitrogen and stirred for one hour. The reaction mixture was then poured into water (50 ml) and the organic phase separated, dried ($MgSO_4$) and the solvents removed in vacuo to yield a brown oil. Chromatography on alumina with elution with 50% dichloromethane-petroleum gave ketone (473) (0.08g, 6%) as a pale yellow oil; $\nu_{max.}$ 3470 and 3350 (NH_2), 2940, 1644 (C = O), 1612, 1578, 1556, 1450, 1158 and 748 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.74 (1H, d), 7.24 (1H, t), 6.71 - 6.57 (2H, m), 6.45 - 6.06 (2H, br.s., exch.), 2.91 (2H, t), 1.78 - 1.60 (2H, m), 1.46 - 1.29 (2H, m), 0.93 (3H, **t); m/z 177 (M^+)**, 135, 120, 92 and 64.

14.2 PREPARATION OF 1,4-DIHYDRO-3,1-BENZOXAZIN-2-ONES

(a) 4-(PENT-4-ENYL)-1,4-DIHYDRO-3,1-BENZOXAZIN-2-ONE (483)

A solution of phosgene (0.3g, 58 mmol) in anhydrous dichloromethane (10 ml) was added over 0.75 hours to a cooled ($0^{\circ}C$), stirred solution of alcohol (482) (0.65g, 0.3 mmol) and anhydrous triethylamine (2 ml) in anhydrous dichloromethane (50 ml) under nitrogen. After warming to room temperature, the reaction mixture was stirred for 18 hours and then poured into water (100 ml). The organic phase was separated and dried ($MgSO_4$) and evaporated under reduced pressure to give a light brown oil. Chromatography on silica and elution with 10%

ethyl acetate - dichloromethane gave benzoxazinone (483) as a viscous, colourless oil. A small aliquot was further purified by bulb-to-bulb distillation, b.p., 140°C/0.01 torr; $\nu_{max.}$ 3230 (NH), 2920, 1710 (C = O), 1632 (C = C), 1595, 1030, 900 and 745 cm^{-1}; δ ($CDCl_3$, 220 MHz), 9.80 (1H, s), 7.30 - 6.80 (4H, m), 5.90 - 5.60 (4H, m); m/z 217 (M^+), 174, 163, 148, 132, and 117; accurate mass, found: 217.1206. $C_{13}H_{15}NO_2$ requires 217.1316; Found: C, 71.37%; H, 7.16%; N, 6.46%. $C_{13}H_{15}NO_2$ requires C, 71.86%; H, 6.96%; N, 6.45%.

(b) 4-(HEX-5-ENYL)-1,4-DIHYDRO-3,1-BENZOXAZIN-2-ONE (484)

Benzoxazinone (484) was prepared in an analogous manner to that described for the pentenyl benzoxazinone (483), using the hexenyl alcohol (463) (0.73g, 3.5 mmol), triethylamine (2 ml), and phosgene (0.35g, 3.5 mmol). Chromatography on silica and elution with 10% ethyl acetate - dichloromethane gave (484) (0.47g, 58%) as a colourless oil. A small aliquot was further purified by bulb-to-bulb distillation, b.p. 147°C/0.01 torr; $\nu_{max.}$ 3250 (NH), 2930, 1720 (C = O), 1645 (C = C), 1487, 1390 and 915 cm^{-1}; δ ($CDCl_3$, 220 MHz), 9.80 (1H, s), 7.31 - 6.80 (4H, m), 5.90 - 5.60 (1H, m), 5.39 (1H, t, J = 6.8 Hz), 5.06 - 4.87 (2H, m), 2.13 - 1.80 (4H, m), 1.70 - 1.30 (4H, m); m/z 231 (M^+), 174, 132, 118 and 106; accurate mass found: 231.1258 $C_{14}H_{17}NO_2$ requires 231.1259; Found: C, 72.74%; H, 7.64%; N, 5.76%. $C_{14}H_{17}NO_2$ requires C, 72.70%; H, 7.41%; N, 6.06%.

14.3 PREPARATION OF N-tert-BUTOXYCARBONYLURETHANES

(a) N-tert-BUTOXYCARBONYLANILINE (485)

This compound was prepared according to the procedure of Muchowski and Venuti[267] by heating a solution of aniline (2.33g, 25 mmol) and di-tert-butyl dicarbonate (6.0g, 27.5 mmol) in anhydrous THF (25 ml) under reflux for 2 hours. After removal of the solvent under reduced pressure the resulting white solid was dissolved in ethyl acetate (75 ml) and washed successively with 1M citric acid solution (30 ml) and saturated salt solution (30 ml). After drying the organic phase over anhydrous magnesium sulphate, the solvent was removed in vacuo to give a white solid. Recrystallization from hexane gave urethane (485) (4.52g, 100%) as colourless needles, m.p. 136 - 7°C, (lit.,[267], m.p. 137°C); $\nu_{max.}$ 3322 (NH), 2930, 1690 (C = O), 1602, 1532, 1444, 1152 and 749 cm^{-1}; δ ($CDCl_3$, 250 MHz), 7.20 - 7.40 (4H, m), j.02 (1H, t, J = 6.4 Hz), 6.63 - 6.52 (1H, br.s.), 1.51 (9H, s); m/z 193 (M^+), 137, 93 and 77.

(b) 2-LITHIO-N-tert-BUTOXYCARBONYLANILINE (486)

For the following experiments, a solution of 2-lithio-N-(tert-butoxycarbonyl)aniline was prepared by adding tert-butyllithium (2.4 equiv.) to a cooled (-78°C) stirred solution of N-tert-butoxy carbonyl aniline in anhydrous THF under argon. After addition, the resulting bright yellow solution was stirred for a further 15 minutes at -78°C, followed by stirring for 2.5 hours at -20°C, after which time the dianion was ready for use.

(c) α-(2-N-tert-BUTOXYCARBONYL AM I NOPHENYL)BENZENE-METHANOL (487

A solution of benzaldehyde (1.32g, 12.5 mmol) in anhydrous THF (25 ml) was added over ten minutes to a cooled (-20°C), stirred solution of dianion (486) in anhydrous THF (25 ml) under argon. The reaction mixture was then stirred for 2.5 hours at -20°C and allowed to warm to room temperature. It was then poured onto water (50 ml) and extracted with ether (3 x 20 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure to give a viscous, yellow oil, which solidified upon standing. Recrystallization from dichloromethane - hexane gave alcohol (487) (1.69g, 57%) as colourless needles, m.p. 140 - 142°C, (lit.,[267] m.p. 141 - 2°C); $\nu_{max.}$ 3200 - 3600 (broad, NH, OH), 2978, 1726 (C = O), 1715, 1602, 1590, 1518, 1160, 750 and 695 cm^{-1}; δ ($CDCl_3$, 220 MHz), 8.58 (1H, s, exch.), 8.16 (1H, d, J = 6.8 Hz), 7.98 (1H, t, J = 7.0 Hz), 7.84 (1H, d, J = 7.0 Hz), 7.40 - 7.24 (6H, m), 5.77 (1H, s), 1.44 (9H, s); m/z 299 (M^+), 243, 208, 180, 137, 105, 93, 77 and 57.

(d) α-(2-N-tert-BUTOXYCARBONYLAMINOPHENYL)THIOPHENE-2-METHANOL (489)

This compound was prepared in an analogous way to that described for alcohol (487) using thiophene-2-carboxaldehyde in place of benzaldehyde. The resulting dark brown oil was chromatographed on silica and elution with 5% ethyl acetate - dichloromethane gave alcohol (489) as a very pale yellow viscous liquid (0.3g, 10%). A small aliquot

had b.p. 142°/0.01 torr; $\nu_{max.}$ 3150 - 3600 (broad NH,OH), 1700 (C = O), 1480, 1510, 1150, 744 and 688 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.76 (1H, d, J = 8.8 Hz), 7.70 (1H, s), 7.30 - 6.70 (6H, m), 5.96 (1H, s), 3.83 (1H, s, exch.), 1.38 (4H, s); m/z 305 (M^+), 249, 231, 205, 186, 120 and 69; accurate mass, found: 305.1079. $C_{16}H_{19}N_2O_3S$ requires 305.1044; Found: C, 62.66%; H, 6.23%. $C_{16}H_{19}N_2O_3S$ requires C, 62.94%; H, 6.27%.

(e) 1- 2-N-(tert-BUTOXYCARBONYL)AMINOPHENYL HEX-5-EN-1-OL (490)

(i) HEX-5-ENAL

A solution of hex-5-en-1-ol (6g, 60 mmol) in anhydrous dichloromethane (10 ml) was added to a stirred mixture of pyridinium chlorochromate (19.4g, 90 mmol) in anhydrous dichloromethane (100 ml) in one portion. The resulting black gum was stirred for 3 hours at room temperature and anhydrous ether (100 ml) was then added and the supernatant solution decanted off the black gum. The residue was thoroughly extracted with anhydrous ether and the combined extracts were passed through a bed of florisil (40g). Removal of the solvents by distillation followed by distillation of the resulting dark brown liquid through a short Vigreux column gave hex-5-enal (2.7g, 46%) as a colourless liquid, b.p. 130 - 5°C, (lit.,[318] b.p. 118 - 20°C); $\nu_{max.}$ 3085,2950, 2860, 2725, 1730 (C = O), 1642 (C = C), 996 and 916 cm^{-1}; δ ($CDCl_3$, 220 MHz), 9.66 (1H, s), 5.81 - 5.58 (1H, m), 5.02 - 4.86 (2H, m), 2.35 (2H, t, J = 7.0 Hz), 2.02 (2H, q, J = 7.0 Hz), 1.73 - 1.55 (2H, m); m/z 98 (M^+), 96, 55, 41 and 39.

(ii) 1-[2-N-(tert-BUTOXYCARBONYL)AMINOPHENYL]HEX-5-EN-1-OL

A solution of hex-5-enal (1.23g, 12.5 mmol) in anhydrous THF (10 ml) was added to a cooled (-20°C), stirred solution of lithium dianion (486) (10 mmol) in ahydrous THF (25 ml) over ten minutes. After stirring at -20°C for a further 2.5 hours the reaction mixture was poured into water (50 ml) and extracted with ether (3 x 20 ml). The combined ether extracts were dried ($MgSO_4$), and the solvents removed under reduced pressure to give a bright yellow oil. Chromatography on silica and elution with 15% ethyl acetate - petroleum gave (490) (1.65g, 57%) as a pale yellow viscous oil, b.p. 142°C/0.01 torr; $\nu_{max.}$ 3200 - 3650 (broad OH, NH), 2940, 1708 (C = O), 1642 (C = C), 1522, 1450, 1163 and 754 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.95 (1H, s), 7.73 (1H, d, J 2 8.7 Hz), 7.08 (1H, t, J = 8.7 Hz), 6.93 - 6.82 (2H, m), 6.72 - 5.51 (1H, m), 4.90 - 4.73 (2H, m), 4.49 (1H, t, J = 6.6 Hz), 2.98 - 2.84 (1H, br.s.), 1.89 (2H, q, J 2 6.6 Hz), 1.79 - 1.50 (2H, m), 1.33 (9H, s), 1.28 - 1.00 (3H, m); m/z 291 (M^+), 235, 191, 173, 148, 132, 122 and 81; Found: C, 70.25%; H, 8.68%; N, 4.65%. $C_{17}H_{25}NO_3$ requires C, 70.15%; H, 8.65%; N, 4.80%.

(f) 1-(2-N-tert-BUTOXYCARBONYLAMINOPHENYL)HEPT-6-EN-1-OL (491)

(i) HEPT-6-ENAL

This was prepared by the method of Le Bel[269] and had the following characteristics, b.p. 89 - 92°C, (lit.,[269] b.p. 88 - 90°); $\nu_{max.}$ 3058, 2915, 2850, 2200, 1720

(C = O), 1632 (C = C), 1400, 988 and 905 cm^{-1}; δ ($CDCl_3$, 250 MHz), 9.75 (1H, s), 5.69 - 5.90 (1H, m), 4.90 - 5.08 (2H, m), 2.44 (2H, t, J = 6.9 Hz), 2.05 (2H, q, (J = 6.9 Hz), 1.63 - 1.59 (2H, m), 1.54 - 1.35 (2H, m).

(ii) 1-(2-N-tert-BUTOXYCARBONYLAMINOPHENYL)HEPT-6-EN-1-OL (491)

Addition of hept-6-enal (1.2g, 10.7 mmol) to a solution of the dianion (486) (9.8 mmol) in anhydrous THF (25 ml) at -20°C as described for (490), gave a yellow oil after the usual work-up. Chromatography on silica and elution with dichloromethane gave alcohol (491) (0.93g, 31%) as a very pale yellow oil. Attempted purification by bulb-to-bulb distillation resulted in partial decomposition. However, a small aliquot had b.p. 146°C/0.01 torr; $\nu_{max.}$ 3150 - 3600 (broad NH, OH), 3055, 2910, 1702 (C = O), 1632 (C = C), 1354; δ ($CDCl_3$, 220 MHz), 8.08 (1H, s), 7.88 (1H, d, J = 8.8 Hz), 7.19 (1H, d, J = 8.8 Hz), 7.16 - 6.86 (2H, m), 5.86 - 5.61 (1H, m), 5.46 - 5.16 (1H, br.s.), 5.02 - 4.81 (2H, m), 4.62 (1H, t, J = 6.6 Hz), 2.06 - 1.62 (4H, m), 1.46 (9H, s), 1.42 - 1.00 (4H, m); m/z 305 (M^+), 249, 166, 148, 122, 57; accurate mass, found: 305.1989. $C_{18}H_{27}NO_3$ requires 305.1991. Because of the difficulties encountered with the distillation of this material, it could not be purified sufficiently for complete characterization.

(g) ATTEMPTED PREPARATION OF α-(2-N-tert-BUTOXYCARBONYL-AMINOPHENYL)-N-METHYLINDOLE-3-METHANOL (488)

A solution of N-methylindole-3-carboxaldehyde (1.99g, 12.5 mmol) in ahydrous THF (10 ml) was added to a cooled (-20°C), stirred solution of dianion (486) (10 mmol) in anhydrous THF (25 ml) over ten minutes, and the resulting solution stirred at -20°C for a further 2.5 hours. After employing the work-up procedure described previously, a yellow, mobile liquid was obtained which was shown to be a complex mixture upon examination by t.l.c., and n.m.r. Chromatography on silica afforded only dark red oils which proceeded to darken rapidly upon isolation to give black intractable tars.

(h) α-[6-(N-tert-BUTOXYCARBONYLAMINO)-3-PYRIDYL]BENZENE-METHANOL (524)

(i) 4-N-(tert-BUTOXYCARBONYLAMINO)PYRIDINE (522)

A solution of 4-aminopyridine (2.5g, 25 mmol) and di-tert-butyl dicarbonate (6.0g, 27.5 mmol) in anhydrous THF (25 ml) was heated under reflux for 2 hours under argon. After cooling, the solvent was evaporated under pressure to give a white solid. This was then dissolved in ethyl acetate (50 ml) and washed with water (2 x 25 ml). After separating and drying of the organic phase, the solvent was removed under reduced pressure to give a white solid which was recrystallized from dichloro-methane-hexane to give urethane (522) as colourless needles, (4.7g, 97%), m.p. 139 - 140°C; $\nu_{max.}$ 3170 (NH), 2940,

1734 (C = O), 1612, 1530, 1160, 1002, 822 and 760 cm^{-1}; τ ($CDCl_3$, 220 MHz), 2.42 (2H, d, J = 5.0 Hz), 2.12 (1H, s), 3.39 (2H, d, J 2 5.0 Hz), 9.47 (9H, s); m/z 194 (M^+), 193, 138, 137, 121, 77; Found: C, 61.77%; H, 7.38%; N, 14.45%. $C_{10}H_{14}N_2O_2$ requires C, 61.83%; H, 7.27%; N, 14.42%.

(ii) LITHIATION OF URETHANE (522)

A solution of tert-butyllithium (2.4 equiv.) was added dropwise to a cooled (-78°C), stirred solution of urethane (522) in anhydrous THF under argon over ten minutes. It was observed that addition of the first equivalent resulted in the formation of a white suspension with further addition producing a bright yellow solution. After stirring for a further 15 minutes at -78°C the reaction mixture was then stirred at -20°C for 2.5 hours after which time it was ready for use.

(iii) α-[6-(N-tert-BUTOXYCARBONYLAMINO)3-PYRIDYL]-BENZENEMETHANOL (524)

A solution of benzaldehyde (0.5g, 5 mmol) in anhydrous THF (10 ml) was added over ten minutes to a stirred solution of 4-N-tert-butoxycarbonylaminopyridine (523) (5 mmol) in anhydrous THF (30 ml) under argon. After addition, the reaction mixture was stirred for a further 2.5 hours at -20°C and 18 hours at room temperature. After pouring into water (50 ml) and extracting with ether (2 x 50 ml), the organic phase was dried ($MgSO_4$) and

the solvents removed under reduced pressure to yield a pale yellow oil, which solidified on standing. Recrystallization from hexane gave alcohol (524) (0.95g, 63%) as colourless needles, m.p. 176 - 178°C; $\nu_{max.}$ 3270 (NH), 2750 - 3250 (broad OH), 1720 (C = O), 1560, 1145, 1012, 825 and 720 cm^{-1}; δ ($CDCl_3$, 250 MHz), 8.24 - 8.29 (2H, m), 7.99 - 8.08 (2H, m), 7.37 - 7.25 (4H, m); m/z 300 (M^+), 199, 244, 226, 182, 181 and 77; Found: C, 68.01%; H, 6.80%; N, 9.52%. $C_{17}H_{20}N_2O_3$ requires C, 67.98%; H, 6.71%; N, 9.33%.

(i) α-[6-(N-tert-BUTOXYCARBONYLAMINO)-3-PYRIDYL]THIOPHENE-2-METHANOL (527)

A solution of thiophene-2-carboxaldehyde (1.4g, 12 mmol) in anhydrous THF (10 ml) was added to a cooled (-20°C) solution of 3-lithio-4-(N-tert-butoxycarbonylamino)pyridine (10 mmol) in THF (30 ml) under argon. After stirring for a further 2.5 hours at -20°C, the reaction mixture was poured into water (50 ml) and extracted with ether 2 x 50 ml. The combined extracts were dried ($MgSO_4$) and the solvents removed under reduced pressure to give a tacky orange solid. Recrystallization from 5% aqueous ethanol afforded alcohol (527) as colourless needles, (2.2g, 71%), m.p. 141 - 142°C; $\nu_{max.}$ 3285 (NH), 3200 - 2750 (broad OH), 1724 (C = O), 1587, 1145, 1015 and 842 cm^{-1}; δ ($CDCl_3$, 220 MHz), 8.33 (1H, d, J = 6.7 Hz), 8.16 (1H, s), 8.12 (1H, d, J = 6.7 Hz), 7.30 (1H, d, J = 6.6 Hz), 7.00 - 6.90 (1H, m), 6.84 (1H, d, J = 4.3 Hz), 6.06 (1H, s), 4.00 - 3.75 (1H, br.s.), 1.46 (9H, s); m/z 306 (M^+), 305,

250, 249, 232, 188, 186, 147, 121, 194; Found: C, 58.73%; H, 5.95%; N, 8.95%. $C_{15}H_{18}N_2O_3S$ requires C, 58.81%; H, 5.92%; N, 9.15%.

(j) <u>α-[6-(N-tert-BUTOXYCARBONYLAMINO)-3-PYRIDYL]-N-METHYLINDOLE-3-METHANOL</u> (530)

A solution of <u>N</u>-methylindole-3-carboxaldehyde (2.0g, 12.5 mmol) in anhydrous THF (10 ml) was added to a solution of 3-lithio-4-(<u>N</u>-<u>tert</u>-butoxycarbonylamino)-pyridine (10 mmol) in anhydrous THF (30 ml) at -20°C using the same procedure as described for the preparation of alcohols (524) and (527). After the usual work-up, the resulting dark red viscous oil was subjected to chromatography on silica and elution with 50% ethyl acetate-petroleum gave a light orange, tacky solid which was recrystallized from dichloromethane-hexane to give alcohol (530) (0.35g, 10%) as colourless needles, which became dark red upon storage, m.p. 157 - 9°C ; $\nu_{max.}$ 3000 - 4000 (broad OH, NH), 1725 (C = O), 1575, 1500, 1235, 1155, 1048 and 732 cm^{-1}; δ ($CDCl_3$, 220 MHz), 9.05 (1H, s, exch.), 8.19 (1H, d, J = 6.4 Hz), 8.06 (1H, s), 7.50 (1H, d, J = 8.8 Hz), 7.31 (1H, d, J = 6.6 Hz), 7.27 - 7.12 (2H, m), 7.01 (1H, t, J = 8.8 Hz), 6.80 (1H, s), 6.12 (1H, s), 7.60 (3H, s), 1.44 (9H, s); <u>m/z</u> 353 ($\underline{M}^+$), 335, 297, 279, 262, 235, 233, 219, 194, 132, 111, 97 and 83; accurate mass, Found: 353.1748. $C_{20}H_{23}N_3O_3$ requires 353.1739. Unfortunately a satisfactory elemental analysis could not be obtained for this compound.

(k) 1-[6-N-(tert-BUTOXYCARBONYL)AMINO-3-PYRIDYL]HEX-5-EN-1-OL (534)

A solution of hex-5-enal (0.44g, 4.5 mmol in anhydrous THF (10 ml) was added to a solution of 3-lithio-4-(N'-tert-butoxycarbonylamino)pyridine (3.6 mmol) in anhydrous THF (30 ml) at -20°C using the procedure described previously. After the usual work-up, the resulting yellow oil was chromatographed on silica and elution with ethyl acetate gave alcohol (534) (0.39g, 37%) as a very pale yellow viscous oil. A small aliquot was further purified by bulb-to-bulb distillation, b.p. 148°C/0.01 torr; $\nu_{max.}$ 3000 - 3500 (broad NH, OH), 2960, 2920, 1732 (C = O), 1633 (C = C), 1580, 1500, 1145, 904 and 725 cm^{-1}; δ ($CDCl_3$, 220 MHz), 9.03 (1H, s), 8.02 (2H, s), 7.60 (1H, s), 5.76 - 5.54 (1H, m), 4.95 - 4.77 (2H, m), 4.48 (1H, t, J = 6.5 Hz), 1.43 (2H, q, J = 6.5 Hz), 1.85 - 1.45 (2H, m), 1.38 (9H, s), 1.30 - 1.05 (2H, m); m/z 292 (M^+), 264, 208, 175, 149; accurate mass, found: 292.1791. $C_{16}H_{24}N_2O_3$ requires 292.1787; Found: C, 65.49%; H, 8.34%: N, 9.39%. $C_{16}H_{24}N_2O_3$ requires C, 65.72%; H, 8.27%; N, 9.58%.

(l) 1-[2-N-(tert-BUTOXYCARBONYL)AMINO-4-PYRIDYL]HEX-5-EN-1-OL (544)

(i) 3-N-(tert-BUTOXYCARBONYL)AMINOPYRIDINE (543)

(ia) ATTEMPTED PREPARATION FROM 3-AMINOPYRIDINE

A solution of 3-aminopyridine (2.5g, 25 mmol) and di-tert-butyl dicarbonate (6.0g, 27.5 mmol), in anhydrous THF (25 ml) was heated under reflux for 2 hours under nitrogen.

After cooling, the solvent was evaporated under reduced pressure to give a brown amorphous solid. This was shown to be an extremely complex mixture by t.l.c., and n.m.r., analysis, and separation of the compounds in the mixture was not attempted.

(ib) PREPARATION FROM NICOTINIC ACID

Nicotinic acid (7.55g, 61 mmol) was dissolved in anhydrous tert-butanol (270 ml) together with diphenyl-phosphoryl azide (DPPA), (15g, 55 mmol), and anhydrous triethylamine (10 ml) and this stirred solution was heated under reflux for 20 hours under argon. After cooling, the resulting pale brown solution was evaporated under reduced pressure to give a pale brown oil. This was then dissolved in dichloromethane (60 ml) and washed with water (100 ml). The organic phase was separated, and dried ($MgSO_4$) and the solvents removed under reduced pressure to yield a pale brown tacky solid. Chromatography on silica and elution with chloroform gave a white solid. Recrystallization from dichloromethane-hexane gave urethane (543) as colourless cubes, (9.1g, 77%), m.p. 119 - 121°C; $\nu_{max.}$ 3160 (NH), 2915, 1714 (C = O), 1598, 1350, 1017, 818 and 748 cm^{-1}; δ ($CDCl_3$, 250 MHz), 8.50 (1H, d, J = 5.0 Hz), 8.28 (1H, d, J = 5.5 Hz), 8.40 (1H, d, J = 7.5 Hz), 7.45 (1H, s), 7.26 (1H, dd, J = 5.0, 7.5 Hz), 1.52 (9H, s); m/z 194 (M^+), 138, 121, 94 and 78; Found: C, 61.90%; H, 7.35%; N, 14.49%. $C_{10}H_{14}N_2O_2$ requires C, 61.84%; H, 7.27%; N, 14.42%.

(ii) 3-(N-tert-BUTOXYCARBONYLAMINO)PYRIDINE-4-CARBOXALDEHYDE (545)

A solution of tert-butyllithium (48 mmol) in hexane (27 ml) was added dropwise to a cooled (-78°C), stirred solution of urethane (543) (3.88g, 20 mmol) in anhydrous THF (40 ml) under argon over ten minutes. The resulting bright yellow solution was stirred at -78°C for a further 15 minutes and then stirred at -20°C for 2.5 hours. A solution of anhydrous DMF (3 ml) in anhydrous THF (5 ml) was added dropwise over 10 minutes and this solution then stirred at -20°C for 4 hours, followed by 12 hours at room temperature. The reaction mixture was then poured into water (50 ml) and extracted with ether (2 x 25 ml). After separating, the organic phase was dried ($MgSO_4$) and the solvents removed under reduced pressure to give a yellow-orange oil. Chromatography on silica and elution with 5% ethanol-chloroform gave a yellow oil. Purification by bulb-to-bulb distillation gave the aldehyde (545) (3.6g, 81%) as a pale yellow oil, b.p. 122°C/0.01 torr; $\nu_{max.}$ 3330, 2990, 1740, 1690, 1570, 1520, 1430 and 1160 cm^{-1}; δ ($CDCl_3$, 250 MHz), 10.10 (1H, s), 9.90 (1H, s), 9.84 (1H, s), 8.53 (1H, d, J = 4.9 Hz), 7.51 (1H, d, J = 4.9 Hz), 1.56 (9H, s); m/z 222 (M^+), 221, 166, 165, 149; accurate mass: found 222.1009. $C_{11}H_{14}N_2O_3$ requires 222.1004; Found: C, 59.58%; H, 6.34%; N, 12.50%. $C_{11}H_{14}N_2O_3$ requires C, 59.45%; H, 6.35%; N, 12.60%.

(iii) 1-[2-N-(tert-BUTOXYCARBONYLAMINO)-4-PYRIDYL]-HEX-5-EN-1-OL (544)

A solution of pent-4-enyl-1-magnesium bromide (46 mmol) in anhydrous THF (10 ml) was added dropwise to a cooled ($0^{o}C$), stirred solution of aldehyde (545) (3.0g, 14 mmol) in anhydrous THF (40 ml) under argon over 10 minutes. The resulting orange solution was allowed to attain room temperature and stirred overnight. The reaction mixture was then poured into saturated ammonium chloride solution (50 ml) and extracted with ether (2 x 30 ml). The combined ether extracts were dried ($MgSO_4$), and evaporated under reduced pressure to give a yellow oil. Chromatography on silica and elution with 10% ethanol-chloroform gave the alcohol (544) as a colourless glass (3.6g, 88%). This material could not be induced to crystallize and attempts at large scale distillation resulted in its partial decomposition. However, for a small aliquot, b.p. $148^{o}C/0.01$ torr; $\nu_{max.}$ 3500 - 3100 (broad NH, OH), 2940, 1725 (C = O), 1648 (C = C), 1578, 1155 and 915 cm^{-1}; δ ($CDCl_3$, 250 MHz), 9.04 (1H, s), 8.42 (1H, s), 7.96 (1H, d, J = 5.1 Hz), 6.96 (1H, d, J = 5.1 Hz), 6.20 - 5.85 (1H, br.s.), 5.87 - 5.68 (1H, m), 5.08 - 4.90 (2H, m), 4.70 (1H, t, J = 7.5 Hz), 2.07 (2H, q, J = 7.5 Hz), 1.95 - 1.60 (2H, m), 1.52 (9H, s), 1.47 - 1.16 (2H, m); m/z 292 (M^+), 236, 218, 149, 123, 94 and 57; accurate mass, found: 292.1789. $C_{16}H_{24}N_2O_3$ requires 292.1787. A satisfactory elemental analysis could not be obtained for this compound.

(m) 1-[3-N-(tert-BUTOXYCARBONYLAMINO)-2-PYRAZINYL]HEX-5-EN-1-OL (559)

(i) 2-N-tert-BUTOXYCARBONYLAMINOPYRAZINE (552)

(ia) ATTEMPTED PREPARATION FROM 2-AMINOPYRAZINE

A solution of 2-aminopyrazine (2.4g, 25 mmol) and di-tert-butyl dicarbonate (6.0g, 27.5 mmol) in anhydrous THF (25 ml) was heated under reflux for 2 hours. After the usual work-up procedure, a brown, amorphous solid was obtained which was extremely complex on t.l.c., and n.m.r., analysis, and separation of the components by chromatography was not attempted.

(ib) PREPARATION FROM PYRAZINE-2-CARBOXYLIC ACID (551)

A solution of pyrazine-2-carboxylic acid (7.56g, 61 mmol), anhydrous triethylamine (10 ml) and DPPA (15g, 55 mmol) in anhydrous tert-butanol (270 ml)was heated under reflux for 20 hours under argon. After removal of the solvent under reduced pressure, the resulting brown oil was dissolved in dichloromethane (100 ml) and washed with water. After drying ($MgSO_4$), the solvent was evaporated under reduced pressure to give a tacky white solid. Chromatography on silica and elution with 10% ethanol-chloroform gave a white solid. Recrystallization from dichloromethane-hexane gave urethane (552) (11.5g, 96%) as colourless needles (11.5g, 96%); m.p. 115 - 116.5°C; $\nu_{max.}$ 3200 (NH), 2900, 1728 (C = O), 1416, 1245, 1155, 1078, 850 and 780 cm^{-1}; δ ($CDCl_3$, 250 MHz), 9.40 (1H, s), 9.34 (1H, s), 8.30 (2H, s), 1.59 (9H, s); m/z 185 (M^+),

140, 139, 122, 121, 95 and 79; Found: C, 55.38%; H, 6.74%; N, 21.59%. $C_9H_{13}N_3O_2$ requires C, 55.37%; H, 6.71%; N, 21.52%.

(ii) ATTEMPTED o-LITHIATION OF URETHANE (552)

Treatment of a stirred solution of urethane (552) (1.95g, 10 mmol) in anhydrous THF (25 ml) at -78°C under argon with a solution of tert-butyllithium (24 mmol), produced a yellow-orange solution which after 15 minutes at -78°C was stirred for 2 hours at -20°C. A solution of anhydrous DMF (3 ml) in anhydrous THF (5 ml) was then added and after stirring for a further 2 hours at -20°C, the reaction mixture was allowed to attain room temperature. Aqueous work-up afforded a dark brown viscous oil which was extremely complex by t.l.c., and n.m.r., analysis. No characterizable products could be isolated upon chromatography on silica.

(iii) METHYL-2-AMINOPYRAZINE-3-CARBOXYLATE (555)

A cooled (0°C) solution of 2-aminopyrazine-3-carboxylic acid (5.5g, 40 mmol) in methanol (28 ml) was treated with concentrated sulphuric acid (28 ml) over 10 minutes, allowed to warm to room temperature, and stirred for 48 hours. The reaction mixture was then poured into water (70 ml) and made alkaline by the addition of sodium hydrogen carbonate (18g), and the precipitated yellow solid removed by filtration. Recrystallization from water, gave the ester (555), m.p. 172 - 4°C, (lit.,[278] m.p. 172°C); $\nu_{max.}$ 3450 and 3260

(NH_2), 3190, 3150, 2920, 2850 and 1693 (C = O), 1612, 1205, 1128 and 902 cm^{-1}; δ ($CDCl_3$, 250 MHz), 8.22 (1H, d, J = 2.0 Hz), 8.01 (1H, d, J = 2.0 Hz), 7.00 - 6.00 (2H, br.s., exch.), 4.00 (3H, s); m/z 153 (M^+), 152, 122, 94 and 67.

(iv) METHYL-2-(N-tert-BUTOXYCARBONYLAMINO)PYRAZINE-2-CARBOXYLATE (556)

A solution of (555) (5g, 32.7 mmol) together with anhydrous triethylamine (6.6g, 65.4 mmol) and di-tert-butyl dicarbonate (14.2g, 65.4 mmol) and 4,-N,N-dimethylamino-pyridine (0.05g) in anhydrous THF (75 ml) was heated under reflux for 48 hours under argon. After cooling, the solvent was removed under reduced pressure to give a brown oil. This was dissolved in dichloromethane, washed with water (100 ml) and the organic phase separated, dried ($MgSO_4$) and the solvents removed under reduced pressure to give a pale brown tacky solid. Chromatography on silica and elution with 50% chloroform-petroleum gave a white solid which was recystallized from dichloromethane-hexane to give urethane (556) (3.3g, 48%) as colourless cubes, m.p. 127 - 9°C; $\nu_{max.}$ 3000 - 2800 (broad NH, CH), 1760 - 1830 (broad C = O), 1720, 1388, 1128, 854, 830 and 782 cm^{-1}; δ ($CDCl_3$, 250 MHz), 8.69 (1H, s), 8.68 (1H, s), 7.30 (1H, s), 4.00 (3H, s), 1.40 (9H, s); m/z 253 (M^+), 194, 180, 153, 148, 138, 123, 95, 69, 57; accurate mass, found: 253.1059. $C_{11}H_{15}N_3O_4$ requires 253.1062.

Despite repeated attempts a satisfactory elemental analysis could not be obtained for this compound.

(v) 2-(N-tert-BUTOXYCARBONYLAMINO)PYRAZINE-3-METHANOL (557)

A solution of lithium aluminium hydride (40 mmol) in anhydrous THF (50 ml) was added dropwise to a cooled ($0^{o}C$), stirred solution of urethane (556) (10g, 40 mmol) in anhydrous THF (20 ml) under argon over 0.5 hours. A saturated aqueous solution of ammonium chloride was then added dropwise with occasional cooling of the reaction flask by immersion in ice. The resulting mixture was extracted with ether (3 x 50 ml) and the combined extracts were dried ($MgSO_4$) and the solvents evaporated under reduced pressure to give an orange oil. Chromatography on silica and elution with 5% ethanol-chloroform gave alcohol (557) as a colourless oil (5.2g, 58%). Prolonged storage or attempted distillation of this material resulted in its decomposition, b.p. $105^{o}C$/ 0.05 torr (decomp.); $\nu_{max.}$ 3100 - 3500 (broad NH, OH), 2970, 1705 (C = O), 1580, 1515, 1370, 1200 and 820 cm^{-1}; δ ($CDCl_3$, 250 MHz), 8.30 (1H, d, J = 4.8 Hz), 8.25 (1H, d, J = 4.8 Hz), 8.03 (1H, s), 4.80 (2H, s), 1.52 (9H, s). This compound was used directly in the next stage.

(vi) 2-(N-tert-BUTOXYCARBONYLAMINO)PYRAZINE-3-CARBOXALDEHYDE (558)

A solution of anhydrous DMSO (0.055g, 0.7 mmol) in anhydrous dichloromethane (10 ml) was added to a cooled

(-50°C), stirred solution of oxalyl chloride (0.03 ml, 0.044 mmol) in anhydrous dichloromethane (20 ml) and this solution was stirred for 10 minutes under nitrogen at -50°C. A solution of alcohol (557) (0.07g, 0.3 mmol) in anhydrous dichloromethane (10 ml) was then added dropwise over 3 minutes. The resulting dark brown solution was stirred for one hour at -50°C and then allowed to warm to room temperature. Triethylamine (5 ml) was then added and the reaction mixture poured into water (20 ml). The organic phase was separated, dried ($MgSO_4$), and evaporated under reduced pressure to give a brown oil. Chromatography on silica and elution with chloroform afforded (558) (0.048g, 71.5%) as a pale yellow liquid; $\nu_{max.}$ 3300 (NH), 2975, 1755 (C = O), 1685, 1580, 1500, 1368, 1223, 1145 and 675; δ ($CDCl_3$, 250 MHz), 10.12 (1H, s), 10.09 (1H, s, exch.), 8.62 (1H, d, J = 4.6 Hz), 8.42 (1H, d, J = 4.6 Hz), 1.58 (9H, s); m/z 223 (M^+), 194, 100, 169 and 57; accurate mass, Found: 223.0967. $C_{10}H_{13}N_3O_3$ requires 223.0957. This compound was used directly in the next stage.

(vii) 1-[3-(N-tert-BUTOXYCARBONYLAMINO)-2-PYRAZINYL]-HEX-5-EN-1-OL (559)

A solution of pent-4-enyl-1-magnesium bromide (6 mmol) in anhydrous THF (20 ml) was added to a cooled (0°C), stirred solution of aldehyde (558) (0.3g, 1.34 mmol) in anhydrous THF (25 ml). Using the procedure and work-up

described previously, a pale brown oil was obtained. Chromatography on silica and elution with 10% ethanol-chloroform gave the alcohol (559) (0.31g, 78%) as a colourless oil. A small portion was further purified by bulb-to-bulb distillation, b.p. 120°C/0.01 torr; $\nu_{max.}$ 3600 - 3150 (broad NH, OH), 2978, 2924, 2880, 1725 (C = O), 1690 (C = C), 1590, 1305 and 913 cm^{-1}; δ ($CDCl_3$, 220 MHz), 8.46 (1H, s), 8.26 (1H, d, J = 4.3 Hz), 8.13 (1H, d, J = 4.3 Hz), 5.88 - 5.69 (1H, m), 5.05 - 4.92 (2H, m), 4.88 (1H, t, J = 7.5 Hz), 2.10 (2H, q, J = 7.5 Hz), 1.92 - 1.75 (2H, m), 1.68 - 1.33 (11H, m). This alcohol was observed to rapidly decompose upon storage even at low temperatures, and could not be fully characterized.

(n) 1-[2-N-tert-(BUTOXYCARBONYL)AMINO-3-THIENYL]HEX-5-EN-1-OL (565)

(i) 2-N-tert-BUTOXYCARBONYLAMINOTHIOPHENE (563)

Thiophene-2-carboxylic acid (3.9g, 31 mmol) was dissolved in anhydrous tert-butanol (135 ml) together with anhydrous triethylamine (5 ml) and DPPA (8.56g, 31 mmol) and this solution was then heated at reflux for 20 hours under argon. The previously described work-up procedure gave a brown oil.

Chromatography on silica and elution with chloroform gave a white solid which was recrystallized from hexane to give the urethane (563) (2.5g, 68%), m.p. 149 - 150°C, (lit.,[319] m.p. 100 - 101°C); $\nu_{max.}$ 3312 (NH), 1683 (C = O), 1290 and 685 cm^{-1}; δ ($CDCl_3$, 250 MHz), 7.05 - 6.90 (1H, br.s.,

6.76 - 6.84 (2H, m), 6.52 (1H, m), 1.50 (9H, s).

(ii) 2-(N-tert-BUTOXYCARBONYLAMINO)THIOPHEN-3-CARBOXALDEHYDE (564).

A solution of tert-butyllithium (45 mmol) in hexane (31 ml) was added to a cooled (-78°C), stirred solution of urethane (563) (3.6g, 18 mmol) in anhydrous THF (50 ml) under argon over 10 minutes. The resulting bright yellow solution was stirred for a further 15 minutes at -78°C and then for 2 hours at -20°C. After cooling the reaction mixture to -78°C, a solution of DMF (5 ml) in anhydrous THF (5 ml) was then added dropwise over 10 minutes and this solution was then stirred for a further 5 hours at -78°C. After warming to room temperature, the resulting orange solution was poured into water (100 ml) and extracted with ether (2 x 75 ml). The separated ether extracts were combined and dried ($MgSO_4$), and the solvents removed under reduced pressure to give a pale yellow oil. Chromatography on silica and elution with chloroform gave the title compound (1.34g, 33%) as a pale yellow oil; $\nu_{max.}$ 3285 (NH), 2980, 1728 (C = O), 1705, 1540, 1370, 1160 and 668 cm^{-1}; δ ($CDCl_3$, 250 MHz), 10.54 (1H, s), 9.80 (1H, s), 7.12 (1H, d, J = 5.9 Hz), 6.70 (1H, d, J = 5.9 Hz), 1.55 (9H, s). This compound was used directly without further purification.

(iii) 1-(2-N-tert-BUTOXYCARBONYLAMINO-3-THIENYL)HEX-5-1-OL (565).

A solution of pent-4-enyl-1-magnesium bromide (15 mmol) in anhydrous THF (20 ml) was added dropwise to a cooled ($0^{o}C$), stirred solution of aldehyde (564) (1.0g, 4.4 mmol) in anhydrous THF (30 ml) under argon over 10 minutes. The resulting orange solution was stirred at room temperature overnight and after pouring into saturated aqueous ammonium chloride solution, and extracting with ether (2 x 30 ml), the combined extracts were dried ($MgSO_4$) and the solvents evaporated under reduced pressure to give a yellow oil. Chromatography on silica and elution with chloroform gave alcohol (565) (1.12g, 85%) as a colourless, viscous oil. Distillation of this compound resulted in its partial decomposition and a sample of sufficient purity could not be obtained for elemental analysis. However, for a small portion, b.p. 150^{o}/0.01 torr (decomp.); $\nu_{max.}$ 3200 - 3550 (broad OH, NH), 2975, 2930, 1700 (C = O), 1570 (C = C), 1175, 910 and 735 cm^{-1}; δ ($CDCl_3$, 250 MHz), 8.12 (1H, s), 6.75 (1H, d, J = 5.6 Hz), 6.65 (1H, d, J = 6.5 Hz), 5.90 - 5.70 (1H, m), 5.08 - 4.90 (2H, m), 4.77 (1H, t, J = 7.1 Hz), 2.73 (1H, s), 2.09 (2H, q, J = 7.1 Hz), 1.88 - 1.70 (2H, m), 1.50 (9H, s), 1.45 - 1.35 (2H, m); m/z 297 (M^+), 279, 241, 223, 182, 138 and 57; accurate mass, Found: 297.1391. $C_{15}H_{23}NO_3S$ requires 297.1399. A satisfactory elemental analysis could not be obtained for this alcohol.

(o) 1-(3-N-tert-BUTOXYCARBONYLAMINO-2-THIENYL)HEX-5-EN-1-OL (572)

(i) 3-N-tert-BUTOXYCARBONYLAMINOTHIOPHENE (570)

This was prepared in an analogous way to that described for urethane (563), from thiophen-3-carboxylic acid (3.9g, 31 mmol), anhydrous triethylamine (5 ml), DPPA (8.56g, 31 mmol) and tert-butanol (135 ml). The usual work-up procedure produced a brown oil which was purified by chromatography on silica and elution with chloroform to give a white solid. Recrystallization from hexane gave the urethane (570) (3.72g, 60%) as colourless needles, m.p. 137 - 9°C; $\nu_{max.}$ 3315 (NH), 2920), 1686(C = O), 1368, 1289, 1155 and 770 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.25 (2H, m), 6.88 (1H, d, J = 6.1 Hz), 6.8 - 6.65 (1H, br.s., exch.), 1.48 (9H, s); m/z 199 (M^+), 143, 99 and 57; Found: C, 54.39%; H, 6.62%; N, 7.06%. $C_9H_{13}NO_2S$ requires: C, 54.25%; H, 6.58%; N, 7.03%.

(ii) 3-N-tert-BUTOXYCARBONYLAMINOTHIOPHEN-2-CARBOXALDEHYDE (571).

A solution of tert-butyllithium (24 mmol) in hexane (17 ml) was added dropwise to a cooled (-78°C), stirred solution of urethane (570) (1.99g, 10 mmol) in anhydrous THF (25 ml) under argon over 10 minutes. The resulting bright yellow solution was stirred for a further 15 minutes at -78°C, and 2.5 hours at -20°C. The reaction mixture was then cooled to -78°C and a solution of DMF (3 ml) in anhydrous THF (3 ml) was added dropwise over 10 minutes.

The resulting pale yellow solution was stirred for 2 hours at -78°C and 5 hours at room temperature. After pouring onto water (50 ml) and extracting with ether (2 x 25 ml) the combined extracts were dried ($MgSO_4$), and evaporated under reduced pressure to give a yellow oil. Chromatography on silica and elution with chloroform gave a pale yellow oil. Purification by bulb-to-bulb distillation gave the aldehyde (571) as a pale yellow oil (1.3g, 57%), b.p. 150°C/0.05 torr; $\nu_{max.}$ 3328 (NH), 2980, 1735 (C = O), 1640, 1565, 1440, 1380, 1235, 1165 and 860 cm^{-1}; δ ($CDCl_3$, 250 MHz), 9.80 (1H, s), 9.66 (1H, s), 7.92 (1H, d, J = 5.8 Hz), 7.69 (1H, d, J = 5.8 Hz), 1.53 (9H, s); m/z 227 (M^+), 171, 154, 127 and 99; accurate mass, found: 227.0611. $C_{10}H_{13}NO_3S$ requires 227.0616; Found: C, 53.39%; H, 5.74%; N, 6.06%. $C_{10}H_{13}NO_3S$ requires C, 52.86%; H, 5.77%; N, 6.17%.

(iii) 1-(3-N-tert-BUTOXYCARBONYLAMINO-2-THIENYL)HEX-5-EN-1-OL (572).

A solution of pent-4-enyl-1-magnesium bromide (9.3 mmol) in anhydrous THF (15 ml) was added dropwise to a cooled (0°C), stirred solution of aldehyde (571) (0.6g, 3 mmol) in anhydrous THF (25 ml) under argon over 10 minutes. The resulting pale orange solution was stirred for 18 hours at room temperature after which time it was poured into saturated aqueous ammonium chloride solution and this then extracted with ether (2 x 25 ml) and the combined extracts dried ($MgSO_4$) and the solvents evaporated

under reduced pressure to give a pale yellow oil. Chromatography on silica and elution with chloroform produced a colourless oil which solidified on standing to give a white solid. Recrystallization from dichloromethane-hexane gave the alcohol (572) (0.8g, 90%) as a colourless microcrystalline solid, m.p. 64 - 5°C; $\nu_{max.}$ 3550 - 3200 (broad NH, OH), 2970, 2925, 1725, 1695 (C = O), 1640 (C = C), 1590, 1165 and 910 cm^{-1}; δ ($CDCl_3$, 250 MHz), 7.22 (1H, d, J = 5.3 Hz), 7.15 - 7.05 (2H, m), 5.90 - 5.70 (1H, m), 5.10 - 4.90 (2H, m), 4.80 (1H, t, J = 7.0 Hz), 3.48 (1H, s, exch.), 2.09 (2H, q, J = 7.0 Hz), 1.94 - 1.74 (2H, m), 1.64 - 1.36 (11H, m); m/z 297 (M^+), 241, 180, 172, 144, 128, 100 and 57; accurate mass, found: 297.1385. $C_{15}H_{23}NO_3S$ requires 297.1399; Found: C, 60.39%; H, 7.67%; N, 4.66%. $C_{15}H_{23}NO_3S$ requires C, 60.59%; H, 7.80%; N, 4.71%.

(p) α-(2-N-tert-BUTOXYCARBONYLAMINO-3-THIENYL)-BENZENEMETHANOL (575)

A solution of benzaldehyde (1.27g, 12 mmol) in anhydrous THF (10 ml) was added to a cooled (-78°C), stirred solution of 2-lithio-N-tert-butoxycarbonylaminothiphene (1.99g, 10 mmol) under argon over 10 minutes. The resulting pale yellow solution was stirred at -78°C for 2 hours and after warming to room temperature, was poured into water (50 ml) and extracted with ether (2 x 30 ml). The combined ether extracts were dried ($MgSO_4$) and the solvents removed under reduced pressure

to give a yellow tacky solid. Chromatography on silica and elution with chloroform gave a white solid which was recrystallized from dichloromethane-hexane to give the alcohol (575) (2.16g, 71%) as colourless needles, m.p. 136 - 8°C; $\nu_{max.}$ 3600 - 3200 (broad NH, OH), 2992, 1708 (C = O), 1585, 1252, 1165 and 708 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.46 - 7.22 (6H, m), 7.09 (1H, d, J = 6.6 Hz), 7.04 - 6.90 (1H, br.s.,), 5.96 (1H, s), 1.40 (9H, s); m/z 305 (M^+), 249, 231, 214, 204, 188, 186, 105, 77, 69, and 57; Found: C, 62.72%; H, 6.31%; N, 4.58% $C_{16}H_{19}NO_3S$ requires C, 62.94%; H, 6.27%; N, 4.59%.

14.4 MISCELLANEOUS PREPARATIONS

(a) 1-N-tert-BUTOXYCARBONYLAMINO-5,6,7,8-TETRAHYDRO-NAPHTHALENE (516)

This urethane was prepared from 1-amino-5,6,7,8-tetrahydronaphthalene (4g, 27 mmol), and di-tert-butyl dicarbonate (6.5g, 29.7 mmol) in anhydrous THF (50 ml) as described for tert-butoxycarbonylaniline (485). The usual work-up gave a pale pink solid which was recrystallized from ethanol-water to give the title compound (6.7g, 100%) as colourless needles, m.p. 69 - 70°C; $\nu_{max.}$ 3290 (NH), 2930, 1820, 1705, 1590, 1525, 1453, 1366, 1245, 1160 and 775 cm^{-1}; δ ($CDCl_3$, 250 MHz), 7.60 (1H, d, J = 11.0 Hz), 7.08 (1H, t, J = 11.0 Hz), 6.79 (1H, d, J = 10.9 Hz), 6.28 (1H, s), 2.72 (2H, t, J = 7.5 Hz), 2.51 (2H, t, J = 7.5 Hz), 1.65 - 1.86 (4H, m), 1.51 (9H, s); m/z 247 (M^+), 191, 173, 166, 147 and 119; Found: C, 72.69%; H, 8.32%; N, 5.92%. $C_{15}H_{21}NO_2$ requires C, 72.84%; H, 8.56%; N, 5.66%.

(b) ATTEMPTED LITHIATION OF 1-N-tert-BUTOXYCARBONYL-AMINO-5,6,7,8-TETRAHYDRONAPHTHALENE (516).

A solution of tert-butyllithium (24 mmol) in hexane (17 ml) was added dropwise to a cooled (-78°C), stirred solution of urethane (516) (2.47g, 10 mmol) in anhydrous THF (25 ml) under argon over 10 minutes. The resulting bright yellow solution was stirred for 15 minutes at -78°C and then for 2.5 hours at -20°C. A solution of hex-5-enal (1.23g, 12.5 mmol) in anhydrous THF (10 ml) was then added dropwise over 10 minutes and the resulting pale yellow solution stirred for 2.5 hours at -20°C. After warming to room temperature, the reaction mixture was extracted with ether (2 x 20 ml) and the combined ether extracts dried ($MgSO_4$) and evaporated under reduced pressure to give a tacky white solid. Chromatography on silica gave complete recovery of starting meterials. Addition of hex-5-enal to the yellow solution at -78°C also gave starting material. In addition, quenching the yellow solution with deuterated methanol at -20°C gave no incorporation of deuterium into the products as revealed by n.m.r. analysis.

(c) 6-METHOXY-8-(N-tert-BUTOXYCARBONYLAMINO)QUINOLINE (578)

This urethane was prepared by the method as previously described for N-tert-butoxycarbonylaniline (485) from 8-amino-6-methoxyquinoline (4.35g, 25 mmol) and di-tert-butyldicarbonate (6.0g, 27 mmol) in anhydrous THF (25 ml), to give a dark brown oil. Chromatography on silica and elution with 15% ethyl acetate - petroleum gave a white

solid. Recrystallization from dichloromethane - hexane gave urethane (578) (5.2g, 76%) as colourless cubes, m.p. 81 - 82°C; $\nu_{max.}$ 3350 (NH), 2980, 1808, 1750, 1720, 1630, 1370, 1212, 1070 and 845 cm^{-1}; δ ($CDCl_3$, 220 MHz), 9.86 (1H, s), 8.57 (1H, dd, J = 2.0, 5.0 Hz), 8.13 (1H, d, J = 2.0 Hz), 7.92 (1H, d, J = 8.8 Hz), 7.29 (1H, dd, J = 5.0, 8.8 Hz), 6.63 (1H, d, J = 2.0 Hz), 3.84 (3H, s), 1.51 (9H, s); m/z 274 (M^+), 200, 174, 145, 129, 102 and 57; Found: C, 65.39%; H, 6.45%; N, 10.33%. $C_{15}H_{18}N_2O_3$ requires C, 65.67%; H, 6.61%; N, 10.21%.

(d) ATTEMPTED o-LITHIATION OF URETHANE (578)

Treatment of a cooled (-78°C), stirred solution of urethane (578) (0.1g, 0.38 mmol) in anhydrous THF (10 ml) under argon with a solution of tert-butyllithium (0.94 mmol) in pentane (5 ml) produced a bright yellow solution which after stirring for a further 15 minutes at -78°C was stirred for 2.5 hours at -20°C. Deuterated methanol (d_4, 99%) (1 ml) was then added and the resulting colourless solution stirred at -20°C for 2 hours. After warming to room temperature, this solution was partitioned between water and ether and the organic phase separated, dried ($MgSO_4$), and the solvents removed under reduced pressure to give a white solid which was revealed to be totally non-deuterated starting material by inspection using n.m.r. It was also found that the addition of deuterated methanol at -80°C did not lead to the deuteration of urethane (578).

(e) 2-N-tert-BUTOXYCARBONYLAMINOBENZOFURAN (580)

This was prepared from benzofuran-2-carboxylic acid (9.9g, 61 mmol), anhydrous triethylamine (10 ml), DPPA (16.8g, 61 mmol), in anhydrous tert-butanol (270 ml) using the method previously described for 2-N-tert-butoxycarbonyl-aminothiophene. Chromatography of the resulting pale yellow solid on silica and elution with chloroform gave a pale yellow solid which was recrystallized from hexane to give the urethane (580) (12g, 85%) as colourless needles, m.p. 80 - 81°C; $\nu_{max.}$ 3320 (NH), 1710 (C = O, 1610, 1247, 1160 and 785 cm^{-1}; δ ($CDCl_3$, 250 MHz), 7.44 (1H, dd, J = 2.0, 10.0 Hz), 7.32 (1H, d, J = 10.0 Hz, 7.27 - 7.10 (2H, m), 7.06 (1H, s), 6.44 (1H, s), 1.54 (9H, s); m/z 233 (M^+), 177, 133, 82, 69 and 57; Found: C, 66.93%; H, 6.48%; N, 6.01%. $C_{13}H_{15}NO_3$ requires C, 66.59%; H, 6.54%; N, 5.78%.

(d) ATTEMPTED LITHIATION OF URETHANE (580)

Treatment of a solution of urethane (580) with an equivalent of tert-butyllithium as previous described for the lithiation of 2-N-tert-butoxycarbonylaminothiophene (563) gave a bright yellow solution. However, the addition of anhydrous DMF followed by the usual work-up gave complete recovery of starting materials.

14.5 THE FLASH VACUUM PYROLYSIS OF 2-AMINOBENZENE METHANOLS

(a) α-(2-AMINOPHENYL)THIOPHENE-2-METHANOL (462)

Pyrolysis of this amino alcohol (0.16g, 0.77 mmol) at $450^{\circ}C/10^{-2}$ torr over alumina (using the apparatus described on page 250) over 4 hours with a sublimation temperature of $142^{\circ}C$ gave a pale yellow pyrolysate at $-78^{\circ}C$. After warming to room temperature, the pyrolysate was removed with dichloromethane and the solvent removed under reduced pressure to give a white tacky solid. Purification by p.t.l.c. on silica and elution with 50% ether-petroleum gave a solid which was recrystallized from dichloromethane-hexane to give thieno[3.2-b]quinoline (493) (0.13g, 92%) as colourless plates, m.p. 108 - $110^{\circ}C$ (lit.,[270] m.p. $113^{\circ}C$); $\nu_{max.}$ 2950, 1628, 1593, 1369, 1312 and 903 cm^{-1}; δ ($CDCl_3$, 220 MHz), 8.57 (1H, s), 8.17 (1H, d, J = 8.8 Hz), 7.91 - 7.79 (2H, m), 7.70 (1H, t, J = 8.5 Hz), 7.58 (1H, d, J = 8.8 Hz), 7.49 (1H, t, J = 8.8 Hz); ^{13}C δ ($CDCl_3$), 157.31 (s), 146.78 (s), 134.30 (d), 130.81 (s), 129.45 (d), 128.99 (d), 127.15 (d), 125.46 (d), 124.84 (s), 124.56 (d); m/z 185 (M^+), 154, 117, and 77. Pyrolysis of this alcohol at $750^{\circ}C/10^{-2}$ torr in the absence of alumina produced thienoquinoline (493) in 22% yield.

(b) α-(2-AMINOPHENYL)FURAN-2-METHANOL (465)

Pyrolysis of this alcohol (0.36g, 1.9 mmol) at $450^{\circ}C/10^{-2}$ torr over alumina for 5 hours with a sublimation temperature of $85^{\circ}C$ produced a very pale yellow pyrolysate

at -78°C. During this time, the substrate was observed to darken to a black tar. After warming to room temperature, the pyrolysate was removed using dichloromethane, and the solvent evaporated under reduced pressure to give a brown oil (0.038g). This was shown to be a complex mixture by t.l.c., and n.m.r. analysis and no discrete, characterizable products could be obtained upon chromatography on silica. Pyrolysis at 800°C/10^{-2} torr again produced a complex mixture of uncharacterizable products.

(c) α-(2-AMINOPHENYL)-N-METHYLIMIDAZOLE-2-METHANOL (467)

Pyrolysis of this alcohol (0.25g, 1.2 mmol) at 750°C/10^{-2} torr over 4.5 hours with a sublima tion temperature of 150°C produced a yellow pyrolysate at -78°C. After warming to room temperature, the pyrolysate was removed with dichloromethane and the solvent evaporated under reduced pressure to yield a yellow, tacky solid. This was revealed to consist exclusively of an equal mixture of N-methylimidazole and 2-aminobenzaldehyde by n.m.r. comparison with a mixture of equal amounts of the authentic materials. Pyrolysis of alcohol (467) at 450°C/10^{-2} torr over alumina did not significantly alter the product distribution.

(d) 1-(2-AMINOPHENYL)HEX-5-EN-1-OL (482)

Pyrolysis of this alcohol (0.22g, 1.1 mmol) at 750°C/10^{-2} torr over 3 hours with a sublimation temperature of 152°C produced a pale yellow pyrolysate at -78°C. After

warming to room temperature, the pyrolysate was removed using dichloromethane and evaporation of the solvent under reduced pressure gave a dark brown oil which was revealed to be an extremely complex mixture by t.l.c. and g.c. analysis. The n.m.r. spectrum of this mixture indicated the presence of extensive aliphatic unsaturation. Separation of the components in this mixture was not attempted.

(e) 1-(2-AMINOPHENYL)HEPT-6-EN-1-OL (463)

Pyrolysis of (463) (0.12g, 0.59 mmol) at 800°C/10^{-2} torr over 3 hours with a sublimation temperature of 160°C produced a dark yellow pyrolysate at -196°C. After warming to room temperature, the pyrolysate was removed with dichloromethane, and evaporation of the solvent under reduced pressure gave a dark brown oil. This was shown to be a complex mixture by t.l.c. and n.m.r. analysis and again substantial aliphatic unsaturation was apparent. No discrete, characterizable products were obtained upon chromatography on silica. Pyrolysis of alcohol (463) at 480°C/10^{-2} torr over alumina produced a similar complex mixture.

14.6 FLASH VACUUM PYROLYSIS OF 1,4-DIHYDROBENZOXAZINONES

(a) 4-(PENT-4-ENYL)-1,4-DIHYDRO-3,1-BENZOXAZIN-2-ONE (483)

Pyrolysis of this benzoxazinone (0.29g, 1.3 mmol) at 650°C/10^{-2} torr over 3 hours with a sublimation temperature of 132°C produced a pale yellow pyrolysate at -78°C. This changed colour to pale pink upon warming to room

temperature. Removal of the pyrolysate with dichloromethane and evaporation of the solvent under reduced pressure gave a pale pink solid. Chromatography on silica and elution with dichloromethane gave a white solid. Recrystallization from dichloromethane-hexane gave amine (505) as colourless needles (0.15g, 51%). m.p. 38 - 41°C, (lit.,[271] m.p. for tentatively assigned cis-isomer, 38 - 41°C); $\nu_{max.}$ 3460 (NH), 1615, 1472, 1372, 1310 and 1295 cm^{-1}; δ ($CDCl_3$, 250 MHz), 6.95 - 7.06 (2H, m), 6.64 (1H, t, J = 8.4 Hz), 6.51 (1H, d, J = 11.0 Hz), 4.42 - 4.65 (2H, m), 4.23 (1H, t, J = 12.0 Hz), 3.40 - 3.60 (1H, m), 3.22 - 3.38 (1H, m), 2.88 - 3.05 (3H, m), 2.71 - 2.85 (1H, m), 2.48 - 2.65 (1H, m), 2.21 - 2.39 (1H, m); ^{13}C δ ($CDCl_3$), 143.86 (s), 126.85 (d), 126.00 (d), 125.78 (s), 116.29 (d), 112.64 (d), 47.90 (t), 45.04 (d), 41.37 (d), 28.26 (t), 28.00 (t), 23.29 (t); m/z 173 (M^+), 144, 130, 117 and 77.

(b) 4-(HEX-5-ENYL)-1,4-DIHYDRO-3,1-BENZOXAZIN-2-ONE (484)

Pyrolysis of this benzoxazinone (0.31g, 1.4 mmol) at 650°C/10^{-2} torr over 3 hours with a sublimation temperature of 140°C produced a pale yellow pyrolysate at -78°C which changed colour to pale pink on warming to room temperature. The pyrolysate was removed with dichloromethane and evaporation of the solvent under reduced pressure gave a pale pink tacky solid. Chromatography on silica and elution with dichloromethane gave the amine (508) (0.13g, 49%) as a white solid, m.p. 42 - 44°C (lit.,[272] m.p. for cis-isomer, 42 - 44°C). This was revealed to be a 3:1 mixture of isomers

by ^{1}H and ^{13}C n.m.r. analysis; $\nu_{max.}$ 3390 (NH), 2930, 2860, 1610, 1495, 1297 and 750 cm^{-1}; δ ($CDCl_3$, 250 MHz), 7.12 (1H, d, J = 8.9 Hz), 7.01 - 6.91 (1.6H, m), 6.67 - 6.57 (1.3H, m), 6.49 - 6.43 (1.3H, m), 3.80 - 3.48 (1.3H, br.s.,), 3.39 (0.3H, dd, J = 10.0, 15.1 Hz), 3.19 (1H, dd, J = 12.5, 8.0 Hz), 3.12 (0.3H, dd, J = 7.5, 15.0 Hz), 3.01 (1H, t, J = 12.5 Hz), 2.74 - 2.85 (0.3H, m), 2.50 - 0.99 (13.8H, m); ^{13}C δ ($CDCl_3$), (* indicates peak due to the minor isomer), 144.20 (s), 143.77 (s)*, 128.68 (s), 127.42 (s)*, 126.79 (d), 126.68 (d)*, 125.53 (d), 124.98 (d)*, 116.88 (d)*, 116.75 (d), 114.02 (d)*, 113.83 (d), 48.18 (t), 43.19 (t)*, 40.91 (d), 37.61 (d), 32.27 (d)*, 31.40 (d)*, 25.77 (t), 24.94 (t)*, 22.76 (t)*; m/z 187 (M^+), 186, 144, 130, 106 and 77.

14.7 FLASH VACUUM PYROLYSIS OF N-tert-BUTOXYCARBONYLAMINO-BENZYL ALCOHOLS

(a) α-(2-N-tert-BUTOXYCARBONYLAMINOPHENYL)BENZENE-METHANOL (487)

Pyrolysis of this alcohol (0.31g, 1 mmol) at 800°C/ 10^{-2} torr over 3 hours with a sublimation temperature of 66°C produced a yellow pyrolysate at -78°C which turned pale green upon warming to room temperature. This was removed using dichloromethane and the solvent was evaporated under reduced pressure to give a green solid. Recrystallization from chloroform-hexane gave acridine (0.18g, 93%), as colourless needles, which were identical in all respects to an authentic sample.

(b) α-(2-N-tert-BUTOXYCARBONYLAMINOPHENYL)THIOPHEN-2-METHANOL (489)

Pyrolysis of alcohol (489) (0.25g, 0.8 mmol) at 800°C/10^{-2} torr over 3 hours with a sublimation temperature of 142°C produced a bright yellow pyrolysate at -78°C. After warming to room temperature the pyrolysate was removed with dichloromethane and evaporation of the solvent under reduced pressure gave a tacky brown solid. Purification by p.t.l.c. on silica and elution with 50% ether - petroleum gave thieno[3,2-b]quinoline (493) (0.082g, 55%) which was identical in all respects to that obtained from the pyrolysis of alcohol (462) (page 300).

(c) 1-[2-N-(tert-BUTOXYCARBONYL)AMINOPHENYL]HEX-5-EN-1-OL (490)

(i) IN THE ABSENCE OF SOLID CATALYSTS

Pyrolysis of (490) (0.4g, 1.4 mmol) at 800°C/10^{-2} torr over 3 hours with a sublimation temperature of 143°C produced a bright yellow pyrolysate at -78°C which changed colour to dark red upon warming to room temperature. The pyrolysate was removed using dichloromethane, and the solvent evaporated under reduced pressure to give a dark red oil (0.19g). Purification by p.t.l.c. on silica and elution with dichloromethane gave indole (0.026g, 15%) as a pale brown solid, spectroscopically identical (n.m.r., i.r., m.s.) to an authentic sample. Further elution gave amine (505) (0.05g, 21%) which was identical in all respects to that obtained from pyrolysis of benzoxazinone (483) (page 302). The presence of both these products

was confirmed by analysis of the crude pyrolysate by g.c. and g.c./m.s.

(ii) OVER SILICA

Pyrolysis of (490) (0.29g, 1 mmol) at 470°C/10^{-2} torr over silica produced a yellow pyrolysate at -78°C, which turned dark green on warming to room temperature. The pyrolysate was removed using dichloromethane and the solvent evaporated under reduced pressure to give a dark green oil (0.19g). Purification by p.t.l.c. on silica gave amine (505) (0.018g, 6.2%) as a white solid which was identical in all respects to that obtained from pyrolysis of this alcohol in the absence of solid catalysts. Further elution gave a light brown mobile liquid (0.05g) which was shown to consist of at least five major components by g.c. analysis. Analysis of this mixture by g.c./m.s. revealed that almost all of these compounds had a molecular mass of 173 and gave very similar fragmentation patterns. In addition, a trace of quinoline ($\underline{M}^+$ 129) was indicated to be present. Analysis of this mixture by n.m.r. revaled the presence of extensive aliphatic unsaturation.

(iii) OVER ALUMINA

Pyrolysis of this alcohol (0.27g, 0.43 mmol) at 480°C/10^{-2} torr over alumina gave a yellow pyrolysate at -78°C which changed colour to brown upon warming to room temperature. The pyrolysate was removed with dichloromethane

and the solvent evaporated under reduced pressure to give a brown oil. Purification by p.t.l.c., and elution with 70% dichloromethane - petroleum gave carbazole (0.035g, 35%) which was identical in all respects (m.p., m.m.p., n.m.r., and m.s.,) to an authentic sample.

(d) 1-(2-N-tert-BUTOXYCARBONYLAMINOPHENYL)HEPT-6-EN-1-OL (491)

Pyrolysis of this urethane (0.52g, 1.7 mmol) at 800°C/ 10^{-2} torr over 3 hours with a sublimation temperature of 146°C produced a pale yellow pyrolysate at -78°C which changed colour to dark brown on warming to room temperature. The pyrolysate was removed with dichloromethane and evaporation of the solvent under reduced pressure gave a dark brown oil (0.23g). Purification by p.t.l.c., on silica and elution with 15% ethylacetate - petroleum gave amine (508) (0.072g, 23%) or 30% based on the amount of pyrolysate obtained. This product was obtained as a 3:1 mixture of diastereoisomers and was identical in all respects to that obtained from pyrolysis of 4-(hex-5-enyl)-1,4-dihydro-3,1-benzoxazin-2-one (484) (page 303). Further elution gave indole (0.016g, 8%) and quinoline (0.016g, 7%). Both of these products were spectroscopically identical (n.m.r., i.r., m.s.,) to authentic samples.

(e) α-[2-(N-tert-BUTOXCYARBONYLAMINO)-4-PYRIDYL]BENZENE METHANOL (524)

Pyrolysis of this urethane (0.45g, 1.57 mmol) at 800°C/ 10^{-2} torr over 3 hours with a sublimation temperature of 154°C

gave a pale yellow pyrolysate at -78°C. After warming to room temperature, removal of the pyrolysate with dichloromethane and evaporation under reduced pressure gave a pale yellow solid. Recrystallization from water gave the naphthyridine (526) (0.22g, 80%) as buff prisms, m.p. 143 - 5°C, (lit.,[274] m.p. 138 - 9°C); $\nu_{max.}$ 1618, 1155, 905 and 748 cm^{-1}; δ ($CDCl_3$, 250 MHz), 9.45 (1H, s), 8.85 (1H, s), 8.69 (1H, d, J = 8.7 Hz), 8.20 (1H, d, J = 11.0 Hz), 8.03 (1H, d, J = 11.0 Hz), 7.98 (1H, d, J = 11.0 Hz), 7.86 (1H, t, J = 11.0 Hz), 7.57 (1H, t, J = 8.7 Hz); ^{13}C δ ($CDCl_3$), 170.01 (s), 154.80 (d), 151.50 (s), 149.34 (s), 145.23 (d), 141.43 (s), 137.26 (d), 132.46 (d), 129.12 (d), 128.75 (d), 126.35 (d), 121.24 (d); m/z 180 (M^+), 154 and 153.

(f) α-[2-N-(tert-BUTOXYCARBONYL)AMINO-4-PYRIDYL]THIOPHENE-2-METHANOL (527)

Pyrolysis of this urethane (0.23g, 0.75 mmol) at 800°C/10^{-2} torr over 3 hours with a sublimation temperature of 154°C produced a pale yellow pyrolysate at -78°C. After warming to room temperature, the pyrolysate was removed using dichloromethane and evaporation of the solvent under reduced pressure gave a dark green oil (0.18g). Purification by p.t.l.c., and elution with 50% ether-ethyl acetate gave a brown solid which was recrystallized from dichloromethane - hexane to give thienonaphthyridine (529) (0.095g, 68%) as buff needles, m.p. 170 - 2°C; $\nu_{max.}$ 1612, 1550, 1318 and 922 cm^{-1}; δ ($CDCl_3$, 250 MHz), 9.41 (1H, s), 8.85

(1H, s), 8.76 (1H, d, J = 8.8 Hz), 8.16 (1H, d, J = 8.8 Hz), 8.01 (1H, d, J = 8.8 Hz), 7.70 (1H, d, J = 8.8 Hz); m/z 186 (M^+), 169, 159, 151, 131 and 119 ; accurate mass found: 186.0275. $C_{10}H_6N_2S$ requires 186.0273; Found: C, 64.28%; H, 3.39%. $C_{10}H_6N_2S$ requires C, 64.49%; H, 3.25%.

(g) α-[2-N-(tert-BUTOXYCARBONYL)AMINO-4-PYRIDYL]-N-METHYLINDOLE-3-METHANOL (530)

Pyrolysis of urethane (530) (0.36g, 1 mmol) at 800°C/ 10^{-2} torr over 3 hours with a sublimation temperature of 180°C produced a yellow pyrolysate at -78°C which changed to dark brown on warming to room temperature. Removal of the pyrolysate with methanol and evaporation of the solvent under reduced pressure gave a brown oil. Purification by p.t.l.c., on alumina and elution with ethyl acetate gave indolonaphthyridine (532) as a pale brown oil which slowly solidified on standing. Recrystallization from chloroform - hexane gave pure (532) as colourless needles (0.032g, 13.5%), m.p. 294 - 6°C; $\nu_{max.}$ 1612, 1455, 1328, 998 and 903 cm^{-1}; δ (methanol -d_4, 250 MHz), 9.35 (1H, s), 8.91 (1H, s), 8.66 (1H, d, J = 6.1 Hz), 8.20 (1H, d, J = 7.4 Hz), 7.86 (1H, d, J = 6.0 Hz), 7.62 - 7.50 (2H, m), 7.31 (1H, t, J = 7.4 Hz), 3.94 (3H, s); m/z 233 (M^+), 231, 219, 181, 169, 151, 131, 119 and 100; accurate mass found: 233.0940. $C_{15}H_{11}N_3$ requires 233.0953. Unfortunately, there was insufficient material for full characterization.

(h) 1-[2-(N-tert-BUTOXYCARBONYLAMINO)-3-PYRIDYL]HEX-5-EN-1-OL (534)

Pyrolysis of this urethane (0.25g, 0.85 mmol) at 800°C/ 10^{-2} torr over 3 hours with a sublimation temperature of 148°C produced a pale yellow pyrolysate at -78°C. After warming to room temperature, the pyrolysate was removed using dichloromethane and evaporation of the solvent under reduced pressure gave a pale yellow solid. Recrystallization from dichloromethane - hexane gave amine (536) (0.094g, 64%) as colourless cubes, m.p. 235 - 7°C; $\nu_{max.}$ 3260 (NH), 1613, 1372, 1325, 1079, 1050 and 822 cm^{-1}; δ (methanol - d_4), 7.90 (1H, d, J = 5.7 Hz), 7.84 (1H, s), 6.33 (1H, d, J = 5.7 Hz), 3.58 (1H, dd, J = 7.5, 15.0 Hz), 3.19 (1H, t, J = 12.5 Hz), 2.45 - 2.25 (2H, m), 2.06 - 1.90 (3H, m), 1.80 - 1.45 (2H, m), 1.36 - 1.19 (1H, m); ^{13}C δ (methanol-d_4, 250 MHz), 146.87 (d), 145.00 (d), 106.99 (d), 47.13 (t), 42.39 (d), 40.56 (d), 27.57 (t), 27.08 (t), 23.11 (t); m/z 174 (M^+), 173, 145, 131 and 69; accurate mass, found: 174.1766. $C_{11}H_{14}N_2$ requires 174.1157; Found: C, 75.61%; H, 8.04%; N, 15.85%. $C_{11}H_{14}N_2$ requires C, 75.82%; H, 8.10%; N, 16.08%.

(i) 1-[2-(N-tert-BUTOXYCARBONYLAMINO)-4-PYRIDYL]HEX-5-EN-1-OL (544)

Pyrolysis of this urethane (0.3g, 0.83 mmol) at 800°C/ 10^{-2} torr over 3 hours with a sublimation temperature of 148°C, produced a yellow pyrolysate at -78°C. After warming to room temperature, the pyrolysate was removed

using dichloromethane and the solvent evaporated under reduced pressure to give a tacky brown solid, which was shown to consist of two components with very similar R_f values by t.l.c. analysis. Chromatography on silica and elution with 10% ethanol - chloroform gave a tacky white solid. Purification by p.t.l.c. on silica and elution with chloroform allowed partial separation of these components after repeated elutions and gave:

(a) The less polar isomer of tricycle (549) as a yellow oil (0.047g) which was one single isomer by n.m.r. analysis; $\nu_{max.}$ 3120 (NH), 2800, 1530, 1493, 1425, 1215 and 745 cm^{-1}; δ ($CDCl_3$, 250 MHz), 7.94 (1H, s), 7.89 (1H, d, J = 4.9 Hz), 6.97 (1H, d, J 2 4.9 Hz), 4.15 - 3.80 (1H, br.s., exch.), 3.20 (1H, dd, J = 5.0, 12.5 Hz), 3.05 - 2.91 (1H, m), 2.81 (1H, t, J = 12.5 Hz), 2.46 - 1.20 (7H, m); 174 ($\underline{M}^+$), 173, 159, 145, 131 and 119; accurate mass, found: 174.1151. $C_{11}H_{14}N_2$ requires 174.1157.

(b) The slower running isomer as a pale white solid. Recrystallization from dichloromethane - hexane gave the second diastereoisomer of tricycle (549) (0.02g) as buff prisms, m.p. 103 - 5°C; $\nu_{max.}$ 3144 (NH), 2840, 1533, 1214 and 750 cm^{-1}; δ (methanol - d_4, 250 MHz), 7.84 (1H, s), 7.81 (1H, d, J = 4.7 Hz), 6.93 (1H, d, J = 4.7 Hz), 4.20 - 3.90 (1H, br.s., exch.), 3.61 (1H, dd, J = 5.0, 12.5 Hz), 3.19 (1H, t, J =

10.0 Hz), 2.49 - 1.18 (8H, m); m/z 174 (M^+), 173, 159, 145 and 119; accurate mass, found 174.1156. $C_{11}H_{14}N_2$ requires 174.1157. Unfortunately, there was insufficient sample to allow full characterization.

(c) A mixture of the two diastereoisomers (0.07g) as a pale white tacky solid revealed by n.m.r. analysis to be a pure mixture of the isomers from (a) and (b) in the ratio of 3:1.

total yield from (a), (b) and (c), 0.137g, 77%.

(j) 1-[3-N(tert-BUTOXYCARBONYL)AMINO-2-PYRAZINYL]HEX-5-EN-1-OL (559)

Pyrolysis of this urethane (0.25g, 0.85 mmol) at 800°C/10^{-2} torr over 3 hours with a sublimation temperature of 130°C produced a bright yellow pyrolysate at -78°C. After warming to room temperature, the pyrolysate was removed using dichloromethane and the solvent evaporated to give a brown tacky solid. Chromatography on silica and elution with 10% ethanol - chloroform gave tricycle (561) (0.099g, 67%) as a white solid which was shown to be a 2:1 mixture of isomers by n.m.r. analysis. All attempts to separate this mixture by chromatography or partial recrystallization failed, m.p. 112 - 117°C ; $\nu_{max.}$ 3440 (NH), 1565, 1450, 1370, 1154 and 914 cm^{-1}; δ (methanol - d_4, 250 MHz), 7.83 - 7.64 (3H, m), 5.24 (1H, br.s., exch.), 5.10 (0.5H, br.s., exch.), 3.69 - 3.59 (1H, m), 3.39 - 3.25 (1.5H, m), 3.22 - 3.11 (0.5H, m), 3.04 (0.5H, t, J = 12.4 Hz), 2.68 - 1.20

(11.5H, m); m/z 175 (M^+), 174, 146, 132, 121, 199 and 69; accurate mass, found: 175.1099. $C_{10}H_{13}N_3$ requires 175.1109. Unfortunately, this isomeric mixture could not be purified sufficiently for complete characterization.

(k) α-[2-N-(tert-BUTOXYCARBONYL)AMINO-3-THIENYL]BENZENE-METHANOL (575)

Pyrolysis of this urethane (0.37g, 1.2 mmol) at 800°C/ 10^{-2} torr over 3 hours with a sublimation temperature of 70°C produced a yellow pyrolysate at -78°C which turned dark green on warming to room temperature. In addition, a black intractable tar (0.1g) was observed in the pyrolysis flask. The pyrolysate was removed with dichloromethane and the solvent evaporated under reduced pressure to give a dark green oil. Purification by p.t.l.c. on silica and elution with 5% ether - hexane gave thieno-[3,2-b]quinoline (493) (0.14g, 65%) as a colourless solid which was identical in all respects to that obtained from pyrolysis of alcohol (462) (page 300).

(l) 1-(2-N-tert-BUTOXYCARBONYLAMINO-3-THIENYL)HEX-5-EN-1-OL (565)

Pyrolysis of this urethane (0.3g, 1.1 mmol) at 800°C/ 10^{-2} torr over 3 hours with a sublimation temperature of 150°C produced a yellow pyrolysate at -78°C, which turned dark brown on warming to room temperature. There was also extensive decomposition of the substrate in the sublimation flask, with an intractable tar (0.099g)

remaining after 3 hours. Removal of the pyrolysate with dichloromethane and evaporation of the solvent under reduced pressure gave a dark brown intractable tar from which no identifiable products could be isolated by chromatography. Pyrolysis of alcohol (565) at 650°C/ 10^{-2} torr did not significantly alter the product distribution.

(m) 1-(3-N-tert-BUTOXYCARBONYLAMINO-2-THIENYL)HEX-5-EN-1-OL (572)

Pyrolysis of this alcohol (0.38g, 1.3 mmol) at 800°C/ 10^{-2} torr over 3 hours with a sublimation temperature of 140°C produced a yellow-orange pyrolysate at -78°C which turned dark brown on warming to room temperature. The pyrolysate was removed with dichloromethane and evaporation of the solvent gave a dark brown oil (0.28g). Analysis by t.l.c., and n.m.r., revealed this to be an extremely complex mixture from which no identifiable compounds could be isolated.

15. THE FLASH VACUUM PYROLYTIC BEHAVIOUR OF N-AZIRINYL-DIHYDROBENZOXAZINONES, o-ALKYLIMIDOYL CHLORIDES AND o-ALKYL AMIDINES.

15.1 PREPARATION OF N-AZIRINYLDIHYDROBENZOXAZINONES

(a) N-(2,3-DIPHENYLAZIRIN-3-YL)-1,4-DIHYDRO-3,1-BENZOXAZIN-2-ONE (587, R = H).

(i) 2-CHLORO-2,3-DIPHENYLAZIRINE (592)

1-Azido-1,2-diphenyl-2-choroethene (591) (1.0g, 4 mmol), prepared from deoxybenzoin as described by Gallagher,[281] was heated under reflux for 4 hours in anhydrous hexane (800 ml) under nitrogen. After cooling, the solvent was removed *in vacuo* to give a yellow oil. Purification by bulb-to-bulb distillation gave the title compound (592) (0.81g, 91%), b.p. 108°C/0.03 torr (lit.,[281] b.p. 75°C/0.01 torr); $\nu_{max.}$ 3075, 2950, 1738 (C = N), 1600, 1496, 1450, 1228, 1120, 822, 766 and 694 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.96 (2H, d, J = 8.5 Hz), 7.72 - 7.29 (8H, m); *m/z* 229 and 277 (M^+), 192, 178 and 106.

(ii) N-(2,3-DIPHENYLAZIRIN-3-YL)-1,4-DIHYDRO-3,1-BENZOXAZIN-2-ONE (587, R = H).

1,3-Dihydro-3,1-benzoxazin-2-one (585) was prepared by reaction of 2-aminobenzyl alcohol with phosgene by the method of Davies.[255] Sodium hydride (0.1g of a 50% dispersion in oil) was added in small portions over 5 minutes to a solution of benzoxazinone (585) (0.33g, 2 mmol) in anhydrous THF (20 ml) under an atmosphere of nitrogen. After stirring for 3 hours at room temperature, a solution

of 2-chloro-2,3-diphenylazirine (592) (0.5g, 2 mmol) in anhydrous THF (10 ml) was added dropwise over ten minutes. The resulting pale yellow solution was heated under reflux overnight. After cooling, the suspension was filtered through Celite and the filtrate evaporated in vacuo to give a tacky yellow solid. Chromatography on silica and elution with 50% ether-petroleum gave dihydrobenzoxazinone (587, R = H) (0.37g, 74%) as colourless needles from ethanol, m.p. 172 - 173°C; $\nu_{max.}$ 3070, 2950, 1670 - 1770 (broad, C = N and C = O), 1608, 1502, 1467, 1398, 1310, 1265, 1215, 745 and 698 cm^{-1}; δ ($CDCl_3$, 220 MHz), 8.24 (2H, d, J = 9.0 Hz), 7.65 - 7.00 (12H, m), 5.20 (2H, s); ^{13}C δ ($CDCl_3$), 164.66 (s), 152.73 (s), 138.12 (s), 135.28 (s), 133.66 (d), 131.04 (d), 128.96 (d), 128.79 (d), 128.53 (d), 127.38 (d), 125.40 (d), 124.00 (d), 123.42 (d), 121.68 (s), 120.20 (s), 116.10 (d), 67.69 (t), 51.42 (s); m/z 340 (M^+), 295, 193, 103 and 89; Found: C, 77.62%, H, 4.75%, N, 8.26%. $C_{22}H_{16}N_2O_2$ requires C, 77.63%; H, 4.74%; N, 8.23%.

(b) 6-METHYL-N-(2,3-DIPHENYLAZIRIN-3-YL)-1,4-DIHYDRO-3,1-BENZOXAZIN-2-ONE (587, R = CH_3)

(i) 2-AMINO-5-METHYLBENZENEMETHANOL

This alcohol was prepared by the reduction of 2-amino-5-methylbenzoic acid (15.1g, 0.1 mmol) with lithium aluminium hydride (10g) according to the literature procedure.[320] After aqueous work-up recrystallization of the crude pale brown solid from benzene gave the title compound, (10.1g,

74%) as colourless needles, m.p. 122 - 3°, (lit.,[320] m.p. 121 - 3°C); $\nu_{max.}$ 3395 and 3310 (NH_2), 3000 - 3300 (broad OH), 1640, 1512, 1465, 1275, 1020 and 820 cm^{-1}; δ ($CDCl_3$, 220 MHz), 6.93 (1H, d, J = 10.9 Hz), 6.85 (1H, s), 4.60 (1H, d, J = 10.9 Hz), 6.57 (2H, s), 7.30 - 6.90 (2H, br.s., exch.), 8.20 (3H, s); m/z, 137 (M^+), 119, 118, 91 and 77.

(ii) 6-METHYL-1,4-DIHYDRO-3,1-BENZOXAZIN-2-ONE (599)

A solution of phosgene (5.78g, 58 mmol) in anhydrous dichloromethane (100 ml) was added to a cooled (0°C), stirred solution of 2-amino-5-methylbenzenemethanol (8g, 58 mmol) and anhydrous triethylamine (20 ml) in anhydrous dichloromethane (230 ml) over 0.75 hours. The mixture was then stirred overnight at room temperature and then poured into water (200 ml). The organic layer was separated and dried ($MgSO_4$) and the solvent removed *in vacuo* to give a light brown solid. Recrystallization from dichloromethane - petroleum gave the title compound (8.5g, 82%) as colourless needles, m.p. 142 - 3°C; $\nu_{max.}$ 3000 - 3250 (broad OH), 1650 - 1780 (broad C = O), 1042, and 810 cm^{-1}; δ ($CDCl_3$, 220 MHz), 9.44 (1H, s), 7.04 (1H, d, J = 11.0 Hz), 6.92 - 6.83 (2H, m), 5.26 (2H, s), 2.27 (3H, s); m/z 163 (M^+), 119, 118, 92, 91 and 77; accurate mass, Found: 163.0655. $C_9H_9NO_2$ requires 163.0633. A satisfactory elemental analysis could not be obtained for this compound.

(c) 6-METHYL-N-(2,3-DIPHENYLAZIRIN-3-YL)1,4-DIHYDRO-3,1-BENZOXAZIN-2-ONE (587, R = CH_3)

The sodium salt of dihydrobenzoxazinone (599) was prepared from (599) (0.72g, 4.1 mmol), and sodium hydride (0.22g, of a 50% dispersion in oil) in anhydrous THF (40ml), (see 15.1(a)). To a suspension of this salt was added dropwise a solution of 2-chloro-2,3-diphenylazirine (1.0g, 4.4 mmol) in anhydrous THF (10 ml) over 10 minutes, and this mixture was heated under reflux overnight. After cooling, the solution was filtered through Celite and the solvent removed in vacuo to give a pale yellow, tacky solid. Recrystallization from ethanol gave (587, R = CH_3) (1.43g, 93%) as pale yellow needles, m.p. 138 - 139°; $\nu_{max.}$ 3050, 3020, 2910, 2850, 1720 (C = O, C = N), 1495, 1440, 1373, 1300, 1215 and 686 cm^{-1}; δ ($CDCl_3$, 220 MHz), 8.24 (2H, d, J = 10.8 Hz), 7.58 - 6.97 (10H, m), 6.86 (1H, s), 5.10 (2H, s), 2.23 (3H, s); m/z, 354 (M^+), 310, 192 and 105; Found: C, 77.61%; H, 5.16%; N, 7.74%. $C_{23}H_{18}N_2O_2$ requires C, 77.95%; H, 5.12%; N, 7.91%.

(d) 6-METHYL-N-(2,3-bis(4-METHYLPHENYL)AZIRIN-3-YL)-1,4-DIHYDRO-3,1-BENZOXAZIN-2-ONE (601).

(i) 3-CHLORO-2,3-bis(4-METHYLPHENYL)-1-AZIRINE (600)

This was prepared in four steps from 4,4'-dimethyl-deoxybenzoin by the procedure of Gallagher[281] and had the following spectral characteristics; $\nu_{max.}$ 3015, 2910, 2850, 1625 (C = N), 1598, 1505, 1812 and 768 cm^{-1};

δ ($CDCl_3$, 220 MHz), 7.84 (2H, d, J = 11.0 Hz), 7.44 - 7.26 (4H, m), 7.14 (2H, d, J = 10.9 Hz), 2.44 (3H, s), 2.34 (3H, s).

(ii) 6-METHYL-N-(2,3-bis(4-METHYLPHENYL)AZIRIN-3-YL)-1,4-DIHYDRO-3,1-BENZOXAZIN-2-ONE (601)

This compound was prepared as described in Section 15.1(a)(ii) from benzoxazinone (585) (1.4g, 8.6 mmol), sodium hydride (0.42g, of a 50% dispersion in oil) and azirine (600) (2.2g, 8.6 mmol) in anhydrous THF (120 ml). Chromatography of the crude yellow tacky solid on silica and elution with 50% ether-petroleum gave benzoxazinone (601) as colourless cubes (2.4g, 73%) from ethanol, m.p. 154 - 6°C; $\nu_{max.}$ 2910, 1718, 1705 (C = N), 1595, 1080, 865 and 802 cm^{-1}; δ ($CDCl_3$, 250 MHz), 8.15 (2H, d, J = 8.0 Hz), 7.40 (1H, d, J = 12.5 Hz), 7.30 (2H, d, J = 12.5 Hz), 7.12 - 6.95 (5H, m), 6.86 (1H, s), 5.11 (2H, s), 2.36 (3H, s), 2.24 (3H, s), 1.40 (3H, s); m/z 383 (M^+), 221, 119 and 69; accurate mass, Found: 382.1650. $C_{25}H_{22}N_2O_2$ requires 382.1649. Found: C, 78.16%; H, 5.83%; N, 7.25%. $C_{25}H_{22}N_2O_2$ requires C, 78.51%; H, 5.80%; N, 7.25%.

15.2 PREPARATION OF o-TOLYLBENZAMIDES

(a) o-TOLYLBENZANILIDE (606) was prepared by the literature procedure[321] from o-toluidine and benzoyl chloride and had m.p. 144 - 145° (lit.,[321] m.p. 144°C).

(b) 1-N-BENZOYLAMINO-5,6,7,8-TETRAHYDRONAPHTHALENE

A mixture of benzoyl chloride (8.5g, 7 ml, 60 mmol), 1-amino-5,6,7,8-tetrahydronaphthalene (8.2g, 56 mmol) and 10% aqueous sodium hydroxide solution (45 ml) was shaken thoroughly in a stoppered flask, and the resulting white solid was removed by filtration and recrystallized from ethanol to give the title compound as colourless needles (10.1g, 72%), m.p. 154 - 156°C (lit.,[322] m.p. 154°C); δ ($CDCl_3$, 250 MHz), 7.86 (2H, d, J = 10.0 Hz), 7.75 (1H, d, J = 10.0 Hz), 7.58 - 7.39 (3H, m), 7.14 (1H, t, J = 10.0 Hz), 6.93 (1H, d, J = 10.0 Hz), 2.77 (2H, t, J=7.5 Hz), 2.65 (2H, t, J = 7.5 Hz), 1.91 - 1.66 (4H, m)

(c) 1-N-ACETAMIDO-5,6,7,8-TETRAHYDRONAPHTHALENE (626)

This was prepared from 1-amino-5,6,7,8-tetrahydronaphthalene and acetic acid using the literature procedure,[323] which gave amide (626) as colourless needles, m.p. 156 - 158°C from ethanol, (lit.,[323] m.p. 156 - 157°C); $\nu_{max.}$ 3285 (NH), 2420, 1705 (C = O), 1540 and 770 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.60 (1H, d, J = 10.0 Hz), 7.12 (1H, t, J = 10.0 Hz), 6.95 (1H, d, J = 10.0 Hz), 2.79 (2H, t, J = 7.5 Hz), 2.62 (2H, t, J = 7.5 Hz), 2.20 (3H, s), 1.98 - 1.70 (4H, m); accurate mass Found: 189.1154. $C_{12}H_{15}NO$ requires 189.1154; m/z 189 (M^+), 162, 147, 146, 119, 113 and 82.

(d) 2-METHYLBENZACETAMIDE (620)

This was prepared according to the literature procedure[324] in 68% yield from o-toluidine and acetic anhydride and had m.p. 112 - 114°C (lit.,[324] m.p. 110°C).

15.3 PREPARATION OF o-TOLYLBENZIMIDOYL CHLORIDES

(a) GENERAL PROCEDURE

A suspension of the amide and phosphorus pentachloride (1.1 equiv.) was heated under reflux in anhydrous benzene for 10 - 15 hours under nitrogen. After cooling, all volatile material was removed in vacuo to give the crude imidoyl chloride as a yellow oil, which was used directly without further purification.

(i) N-(2-METHYLPHENYL)BENZIMIDOYL CHLORIDE (607) was prepared in 87%; $\nu_{max.}$ 3060, 1650 (C = N), 1593, 1575, 1165, 890 and 762 cm^{-1}; δ ($CDCl_3$, 220 MHz), 8.18 (2H, d, J = 11.0 Hz), 7.55 - 7.35 (3H, m), 7.20 (2H, t, J = 11.0 Hz), 7.07 (1H, t, J = 11.0 Hz), 6.85 (1H, d, J = 11.0 Hz), 2.15 (3H, s).

(ii) N-(5,6,7,8-TETRAHYDRO-1-NAPHTHYL)BENZIMIDOYL-CHLORIDE (609).

This was prepared in 90% yield and was used directly.

(iii) N-(2-METHYLPHENYL)ACETIMIDOYL CHLORIDE (621)

The imidoyl chloride was prepared as described in the general procedure except that the solvent was acid-free chloroform, and the time of refluxing was 0.5 hours. Removal of all volatile materials *in vacuo* gave (621) as a pale pink liquid which was used directly.

(iv) N-(5,6,7,8-TETRAHYDRO-1-NAPHTHYL)ACETIMIDOYL CHLORIDE (627) was prepared as described for imidoyl chloride (627), and this crude material used directly.

15.4 PREPARATION OF N,N-DIMETHYL-N'-(2-METHYLPHENYL)-FORMAMIDINE (635)

(a) *o*-Tolyl isocyanate (3.0g, 22.5 mmol) was heated at reflux in anhydrous DMF for 4 hours. After cooling, the majority of unreacted DMF was removed *in vacuo* and the remaining pale brown liquid purified by bulb-to-bulb distillation to give amidine (635) (2.5g, 70%) as a very pale yellow liquid, b.p. 110°/0.03 torr (lit.,[291] no b.p. given); $\nu_{max.}$ 2920, 1645 (C = O), 1360, 1995 and 760 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.30 (1H, s), 7.10 - 6.98 (2H, m), 6.85 (1H, t, J = 10.6 Hz), 6.67 (1H, t, J = 10.8 Hz), 2.87 (6H, s), 2.21 (3H, s).

(b) *o*-Toluidine (6g, 56 mmol) and dimethylformamide dimethyl acetal (5.9g, 56 mmol) was heated under reflux in methanol for 4 hours. After cooling to room temperature, evaporation *in vacuo* gave a pale yellow oil. Bulb-to-bulb

distillation gave amidine (635) as a colourless liquid (7.7g, 85%) which was identical in all respects to that obtained above.

15.5 FLASH VACUUM PYROLYSIS OF N-AZIRINYLBENZOXAZINONES

(a) N-(2,3-DIPHENYLAZIRIN-3-YL)-1,4-DIHYDRO-3,1-BENZOXAZIN-2-ONE (587, R = H).

Pyrolysis of benzoxazinone (587, R = H), (0.25g, 74 mmol) at 650°C/10^{-2} torr over 8 hours with a sublimation temperature of 120°C gave a pale yellow pyrolysate at -196°C. The pyrolysate was removed at room temperature with dichloromethane and evaporated *in vacuo* to give 0.14g of a tacky brown solid. Purification by p.t.l.c. on silica and elution with 60% ether - hexane gave 2-phenylindole (0.043g, 30%), m.p., 162 - 4°C(lit.,[292] m.p. 171 - 5°C) with spectral properties identical to those of an authentic sample. Further elution gave 13-phenyl-12,13-dihydroindolo[3.2-b]quinoline (596, R = H) (0.052g, 25%), m.p. 194 - 5°C from dichloromethane - hexane; $\nu_{max.}$ 3110 (NH), 2900, 1612 (C = N), 1588, 1563, 1318, 1308, 1140, 752 and 684 cm^{-1}; δ ($CDCl_3$, 250 MHz), 7.95 (1H, d, J = 7.5 Hz), 6.93 - 7.43 (1H, m), 6.79 (1H, d, J = 8.0 Hz), 3.53 (1H, d, J = 15.5 Hz), 3.33 (1H, d, J = 15.5 Hz); m/z 296 (M^+), 295, 219; accurate mass, Found: 296.1306. $C_{21}H_{16}N_2$ requires 296.1314. Found: C, 84.84%; H, 5.60%; N, 9.52%. $C_{21}H_{16}N_2$ requires C, 85.11%; H, 5.44%; N, 9.45%; ^{13}C δ (CD_2Cl_2), 171.84 (s), 156.54 (s), 145.35 (s),

134.75 (s), 134.11 (d), 128.74 (d), 128.55 (s), 128.04 (d), 127.97 (d), 127.32 (s), 126.22 (d), 126.02 (d), 125.29 (d), 123.66 (d), 123.51 (d), 120.40 (d), 112.25 (d), 63.57 (s), 37.68 (t).

(b) 6-METHYL-N-(2,3-DIPHENYLAZIRIN-3-YL)-1,4-DIHYDRO-3,1-BENZOXAZIN-2-ONE (587, R = CH_3).

Pyrolysis of this benzoxazinone (0.31g, 0.88 mmol) at 650°C/5 x 10^{-6} torr over 6 hours with a sublimation temperature of 150°C gave a yellow pyrolysate at -196°C. After warming to room temperature, the pyrolysate was removed with dichloromethane and the solvent evaporated *in vacuo* to yield a brown oil. Purification by p.t.l.c. on silica and elution with 50% ether - hexane gave 5-methyl-2-phenylindole (0.055g, 30%), m.p. 131 - 4°C (lit.,[284] m.p. 132°C); $\nu_{max.}$ 3410 (NH), 2920, 1600, 1300, 802, 757, 742 and 686 cm^{-1}; δ ($CDCl_3$, 220 MHz), 8.24 (1H, s), 7.68 - 7.28 (7H, m), 7.02 (1H, d, J = 11.0 Hz), 6.74 (1H, s), 2.44 (3H, s); *m/z* 207 (M^+), 206, 179, 178, 105 and 77. Further elution gave 10-methyl-13-phenyl-12,13-dihydroindolo[3,2-b]quinoline (596, R = CH_3) (0.03g, 11%), m.p. 184 - 5°C from dichloromethane - hexane; $\nu_{max.}$ 1639, 1621, 1608, 1522 and 1325 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.95 (2H, d, J = 11.1 Hz), 7.66 - 6.92 (9H, m), 6.87 (1H, s), 6.77 (1H, d, J = 11.0 Hz), 4.52 (1H, s, exch.), 3.47 (1H, d, J 2 15.4 Hz), 3.30 (1H, d, J = 15.4 Hz), 2.25 (3H, s); *m/z* 310 (M^+), 309, 169, 119 and 69; ^{13}C δ (CD_2Cl_2), 170.83 (s),

156.43 (s), 143.10 (s), 139.84 (s), 136.14 (s), 134.01 (d), 130.02 (s), 128.78 (d), 128.58 (d), 128.25 (d), 127.90 (d), 125.77 (d), 125.28 (d), 123.63 (d), 123.24 (s), 120.38 (d), 112.19 (d), 63.71 (s), 37.71 (t) and 21.14 (q); accurate mass, Found: 310.1470. $C_{22}H_{18}N_2$ requires 310.1470. Unfortunately there was insufficient sample to allow a satisfactory elemental analysis to be obtained for this compound.

(c) 6-METHYL-N-(2,3-bis(4-METHYLPHENYL)AZIRIN-3-YL)-1,4-DIHYDRO-3,1-BENZOXAZIN-2-ONE (601)

This benzoxazinone (1.7g, 4.5 mmol) was pyrolysed at $650^{\circ}C/10^{-4}$ torr using a sublimation temperature of $190^{\circ}C$ for 6 hours. After this time, a black gum was present in the sublimation flask, and an orange pyrolysate was present on the cold finger at $-196^{\circ}C$. After warming to room temperature, the pyrolysate was removed using dichloromethane and the solvent evaporated to give 1.2g of a dark brown oil. Purification by p.t.l.c. on alumina and elution with dichloromethane gave 5-methyl-2-(4-methylphenyl)indole (603) (0.02g, 2%), m.p. 153 - $5^{\circ}C$ (lit.,[285] m.p. $142^{\circ}C$); $\nu_{max.}$ 1315, 825 and 798 cm^{-1}; δ ($CDCl_3$, 220 MHz), 8.28 - 8.12 (1H, br.s.,), 7.53 (2H, d, J = 10.8 Hz), 7.39 (1H, s), 7.30 - 7.15 (3H, m), 6.99 (1H, d, J = 11.0 Hz), 6.68 (1H, s), 2.39 (3H, s), 2.33 (3H, s); m/z 221 (M^+), 204, 110, 94 and 83; accurate mass, Found: 221.1203. $C_{16}H_{15}N$ requires 221.1204. Further elution gave 10-Methyl-13-(4-methylphenyl)-12,13-dihydroindolo[3,2-b]quinoline (602),

(0.022g, 1.3%), m.p. 95 - 98°C; $\nu_{max.}$ 2925, 1650, 1626 and 1340 cm^{-1}; δ ($CDCl_3$, 250 MHz), 7.10 - 7.17 (3H, m), 7.01 - 7.99 (4H, m), 6.95 (1H, s), 6.89 (1H, d, J = 12.4 Hz), 6.68 (1H, s), 5.30 - 5.60 (1H, br.s.,), 3.64 (1H, d, J = 15.1 Hz), 3.29 (1H, d, J = 15.1 Hz), 2.39 (3H, s), 2.28 (3H, s), 2.22 (3H, s); m/z 338 (M^+), 337, 323, 247, 221, 151, 113, 97 and 83; accurate mass, Found: 338.1052. $C_{24}H_{22}N_2$ requires 338.1183.

15.6 FLASH VACUUM PYROLYSIS OF o-ALKYLIMIDOYL CHLORIDES

(a) N-(2-METHYLPHENYL)BENZIMIDOYL CHLORIDE (607)

Pyrolysis of (607) (0.4g, 1.7 mmol) at 800°C/10^{-2} torr over 3 hours with a sublimation temperature of 70°C produced a yellow/brown pyrolysate at -78°C. After warming to room temperature, the pyrolysate was removed using dichloromethane followed by evaporation of the solvent to give a light brown tacky solid. Chromatography on silica and elution with 50% ether - petroleum gave 2-phenylindole (605) (0.249g, 76%), identical by t.l.c., and n.m.r., to an authentic sample.

(b) N-(5,6,7,8-TETRAHYDRO-1-NAPHTHYL)BENZIMIDOYL CHLORIDE (609).

Pyrolysis of (609) (0.3g, 1.2 mmol) at 800°C/10^{-2} torr over 3 hours with a sublimation temperature of 80°C produced a yellow/brown pyrolysate at -78°C. After warming to room temperature, the pyrolysate was removed with dichloromethane and the solvent evaporated *in vacuo*

to give a pale yellow solid. Chromatography on silica and elution with 50% chloroform - petroleum gave a white solid. Recrystallization from dichloromethane - hexane gave, 2-phenyl-1,3,4,5-tetrahydrobenz[c,d]indole (0.21g, 74%) as colourless needles, m.p. 118 - 119.5°C, (lit.,[287] m.p. 118 - 120°C); $\nu_{max.}$ 3360 (NH), 2928, 1602, 1448, 1248, 765 and 698 cm^{-1}; δ ($CDCl_3$, 250 MHz), 7.93 (1H, s), 7.57 (2H, d, J = 5.6 Hz), 7.43 (2H, t, J = 7.5 Hz), 7.29 (1H, t, J = 7.2 Hz), 7.19 - 7.06 (2H, m), 6.84 (1H, d, J = 5.1 Hz), 3.05 (2H, t, J = 5.0 Hz), 2.95 (2H, t, J = 5.0 Hz), 2.16 - 2.02 (2H, m); m/z 233 (M^+), 232, 205, 156, 127, 109 and 77; accurate mass, Found: 233.1189. $C_{16}H_{15}N$ requires 233.1205.

(c) N-(2-METHYLPHENYL)ACETIMIDOYL CHLORIDE (621).

Pyrolysis of (621) (0.3g, 2 mmol) at 800°C/10^{-2} torr over 3 hours with a sublimation temperature maintained at 50°C produced a yellow/brown pyrolysate at -78°C. After warming to room temperature, the pyrolysate was removed with dichloromethane and evaporation of the solvent *in vacuo* gave a dark brown oil. Immediate analysis by n.m.r. revealed this to contain substantial low-field aromatic activity. Purification using p.t.l.c. on silica and elution with dichloromethane, gave quinoline (625) (0.015g, 6%), identical by t.l.c., n.m.r., and i.r., to an authentic sample.

(d) N-(5,6,7,8-TETRAHYDRO-1-NAPHTHYL)ACETIMIDOYL CHLORIDE (627)

Pyrolysis of (627) (0.32g, 1.7 mmol) at 800°C/10^{-2} torr over 3 hours with a sublimation temperature of 62°C produced a yellow/brown pyrolysate at -78°C. Removal of the pyrolysate with dichloromethane at room temperature followed by evaporation of the solvent *in vacuo* gave a brown oil, which exhibited similar n.m.r. characteristics to the pyrolysate obtained from (621). However, t.l.c. examination revealed this to be a complex mixture and no identifiable products could be obtained on chromatography.

(e) PYROLYSIS OF AMIDINE (635)

(i) IN THE ABSENCE OF SOLID CATALYSTS

Pyrolysis of amidine (635) (0.3g, 1.85 mmol) over 3 hours at 900°C/10^{-2} torr using the apparatus shown in Figure 5 ,(with the silica tube of the apparatus packed with nine smaller tubes to increase the contact time), and a sublimation temperature of 82°C, produced a very pale yellow pyrolysate at -78°C which changed to dark red on warming to room temperature. The pyrolysate was removed with dichloromethane and evaporation *in vacuo* gave a dark red oil. Purification by p.t.l.c. on alumina and elution with dichloromethane gave indole (513) (0.11g, 51%) which was identical in all respects to an authentic sample.

(ii) OVER ALUMINA

Pyrolysis of the amidine (0.3g, 1.85 mmol) at 500°C/ 10^{-2} torr over alumina over 3 hours with a sublimation temperature of 82°C produced a colourless pyrolysate at -78°C which after warming to room temperature was removed using dichloromethane. Evaporation *in vacuo* gave a light red oil. Chromatography on silica and elution with dichloromethane gave *o*-tolunitrile (0.16g, 72.3%) which was identical by t.l.c., n.m.r., and i.r., to an authentic sample.

(iii) OVER SILICA

Pyrolysis of (635) at 500°C/10^{-2} torr over silica produced a pale red liquid which was shown by n.m.r. to consist of a mixture of starting amidine and *o*-tolunitrile in the ratio 4:1.

15.8 MISCELLANEOUS PYROLYSES

(a) 2-AMINOBENZOPHENONE OXIME (642)

2-Aminobenzophenone oxime was prepared by the method of Noyce.[239] Pyrolysis of (642) (0.27g, 1.2 mmol) at 800°C/10^{-2} torr over 3 hours with a sublimation temperature of 122°C produced a yellow/brown pyrolysate at -78°C. This was removed with dichloromethane after warming to room temperature. Evaporation of the solvent *in vacuo* gave a dark brown oil. Purification by p.t.l.c. on silica with dichloromethane as eluant gave anthranilonitrile (0.05g, 20%), which was identical by t.l.c., n.m.r., and i.r., to an authentic sample. Further elution gave *N*-phenyl-

anthranilonitrile (0.015g, 6%), identical by t.l.c., i.r., and n.m.r., to an authentic sample. Elution with 50% ethyl acetate - dichloromethane gave 9-aminoacridine (0.015g, 6%), m.p. 238 - 240°C, (lit.,[325] m.p. 233°C); δ ($CDCl_3$, 250 MHz), 8.30 (1H, d, J = 8.7 Hz), 7.86 - 7.73 (2H, m), 7.42 (1H, t, J = 9.0 Hz).

16. FRAGMENTATION OF 1,2-DICHLOROALKENES BY CHLORINE AZIDE, AND OF AZIDOVINYL CHLORIDES BY CHLORINE

(a) trans-1,2-DICHLOROSTILBENE (651)

Diphenylacetylene (1.8g, 10 mmol) was added to a suspension of anhydrous copper(II) chloride (53.6g, 0.4 mmol) and anhydrous lithium chloride (16.8g, 0.4 mmol) in anhydrous acetonitrile (100 ml). This mixture was then refluxed for 24 hours. After cooling, the precipitated copper(I) salts were filtered off, and the filtrate added to water. The resulting solid was filtered off, dried, and recrystallized from ethanol to give trans-dichlorostilbene (651) (0.74g, 30%), m.p. 144 - 5°C, (lit.,[326] m.p. 144 - 5°C); $\nu_{max.}$ 2940, 862, 735 and 694 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.60 - 7.52 (2H, m), 7.43 - 7.26 (3H, m); m/z, 251 and 249 (M^+), 214, 178, 180 and 77.

(b) threo-1-AZIDO-2-IODO-1,2-DIPHENYLETHANE

This compound was prepared according to the method of Fowler[326] from addition of iodine azide to cis-stilbene and had the following characteristics, m.p. 88 - 9°C (from ethanol), lit.,[326] m.p. 89 - 90°C); $\nu_{max.}$ 2950,

2095 (N_3), 1255, 1138 and 653 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.21 - 7.47 (10H, m), 5.22 (1H, d, J = 11.0 Hz), 5.08 (1H, d, J = 11.0 Hz); m/z (no visible M^+), 217, 180, 179, 128, 127 and 70.

(c) trans-1-AZIDOSTILBENE (654)

To a solution of threo-1-azido-2-iodo-1,2-diphenyl ethane (1.7g, 4.8 mmol) in anhydrous ether (25 ml) at 0°C was added potassium tert-butoxide (0.7g) in portions over 10 minutes. The resulting suspension (which was kept in the dark) was stirred for 20 hours. This was then washed with water (100 ml) followed by 5% aqueous sodium thiosulphate solution (75 ml) and water (100 ml). After drying ($MgSO_4$) the solvents were removed in vacuo to give a bright yellow solid. Recrystallization from pentane afforded the title compound (0.55g, 52%) as yellow cubes, m.p. 41 - 3°c (lit.,[327] m.p. 44 - 6°c); $\nu_{max.}$ 2960, 2115 (N_3), 1628 (C = C), 1250, 870, 770 and 703 cm^{-1}.

(d) ADDITION OF CHLORINE AZIDE TO trans-1,2-DICHLORO STILBENE

To a solution of trans-1,2-dichlorostilbene (0.41g, 1.65 mmol) in anhydrous dichloromethane (5 ml) was added a solution of chlorine azide (1.9 mmol) in anhydrous dichloromethane (15 ml) at -10°C. (Chlorine azide solution was prepared by the method described by Gallagher[281].) After stirring overnight, ethyl benzoate (0.221g, 1.65 mmol) was added as internal standard. After washing with

water (10 ml), followed by 5% aqueous sodium thiosulphate solution (10 ml), and water (10 ml), the organic extracts were dried ($MgSO_4$) and directly analysed by g.c., which revealed the presence of equimolar quantities (15 - 20% yield) of benzonitrile and α,α,α-trichlorostilbene. This was also confirmed by analysis of the crude reaction mixture by g.c./m.s.

(e) ADDITION OF CHLORINE TO AZIDOSTILBENE (654)

To a solution of azidostilbene (654) (0.37g, 2.0 mmol) in anhydrous dichloromethane (25 ml) at -10°C was added a solution of chlorine (0.15g, 2.0 mmol) in dichloromethane (10 ml). After stirring overnight, the mixture was analysed directly by g.c., and found to contain equimolar quantities of α,α-dichlorotoluene and benzonitrile (each in 20% yield).

17. THE FLASH VACUUM PYROLYTIC GENERATION OF o-XYLYLENES

17.1 PREPARATION OF o-XYLYLENE PRECURSORS

(a) α-(2-METHYLPHENYL)BENZENE METHANOL (656)

This was prepared by the method of Staum[294] in 40% yield, m.p. 88 - 89°C (lit.,[294] 92°C).

(b) α-(2-METHYLPHENYL)THIOPHENE-2-METHANOL (659)

A solution of 2-lithiothiophene/TMEDA complex (24 mmol) in anhydrous ether (45 ml) was added to a solution of 2-methylbenzaldehyde (2.63g, 22 mmol) in anhydrous THF

(15 ml) under nitrogen. After stirring for 3 hours at room temperature, the reaction mixture was poured into water (50 ml) and extracted with ether (2 x 30 ml). The combined ether extracts were dried ($MgSO_4$) and the solvents removed in vacuo to give a colourless, viscous oil which solidified on standing. Recrystallization from 5% aqueous ethanol gave alcohol (659) (3.0g, 67%) as colourless needles, m.p. 40 - 41°C; $\nu_{max.}$ 3200 - 3600 (broad OH), 2930, 1608, 1460, 1380, 1230, 1010, 743 and 700 cm^{-1}; δ ($CDCl_3$, 220 MHz), 7.57 (1H, dd, J = 3.1, 10.0 Hz), 7.30 - 6.74 (6H, m), 6.12 (1H, s), 2.52 (1H, s, exch.), 2.19 (3H, s); m/z 204 (M^+), 187, 186, 119 and 91; accurate mass, Found: 204.0593. $C_{12}H_{12}OS$ requires 204.0609; Found: C, 70.79%; H, 5.94. $C_{12}H_{12}OS$ requires C, 70.57; H, 5.92.

(c) ATTEMPTED CHLORINATION OF α-(2-METHYLPHENYL)THIOPHENE-2-METHANOL (659)

All attempts at the chlorination of alcohol (659) using dry HCl gas in benzene, thionyl chloride in pyridine and triphenyl phosphine in carbon tetrachloride resulted in the formation of intractable tars.

(d) α-(3-METHYL-2-THIENYL)BENZENE METHANOL (663)

To a stirred solution of 3-methyl-thiophene-2-carboxaldehyde (5.7g, 45 mmol) in anhydrous ether (30 ml) was added a solution of phenyl magnesium bromide (35 ml of a 2M solution in ether) under nitrogen at such a rate as

to allow the ether to reflux gently (ca. 20 minutes). After addition was complete the resulting white suspension was stirred for 18 hours at room temperature and was then poured onto saturated ammonium chloride solution (60 ml). The organic phase was decanted off from the aqueous layer, which was thoroughly washed with ether (2 x 50 ml). The combined ether extracts were dried ($MgSO_4$) and the solvent removed to give alcohol (663) (7.9g, 86%). A small aliquot was purified by bulb-to-bulb distillation for which, b.p. 110°C/0.02 torr; $\nu_{max.}$ 3150 - 3600 (broad OH), 3040, 3010, 2905, 2845, 1483, 1440, 1040 and 690 cm^{-1}; δ ($CDCl_3$, 250 MHz), 7.45 - 7.10 (5H, m), 6.98 (1H, d, J = 6.0 Hz), 6.68 (1H, d, J = 6.0 Hz), 5.83 (1H, s), 3.69 - 3.22 (1H, br.s., exch.), 2.05 (3H, s); m/z 204 (M^+), 203, 188, 187, 173 and 105; Found: C, 70.51%; H, 6.19%. $C_{12}H_{12}OS$ requires C, 70.57%; H, 5.92%.

17.2 FLASH VACUUM PYROLYTIC GENERATION OF o-XYLYLENES

(a) α-(2-METHYLPHENYL)BENZENE METHANOL (656)

Pyrolysis of (656) (0.3g, 1.5 mmol) at 800°C/10^{-2} torr over 3 hours, with a sublimation temperature of 69°C, produced a pale yellow pyrolysate at -78°C. After warming to room temperature the pyrolysate was removed using dichloromethane to give a brown oil after evaporation of the solvent. Chromatography on silica with petroleum as eluent gave a white solid which was recrystallized from ethanol to give anthracene (218) as colourless plates (0.076g, 28%), m.p. 215 - 216°C, m.m.p. 214 - 216°,

(lit.,[328] m.p. 216°C), identical by t.l.c., and n.m.r., to an authentic sample.

(b) <u>α-(2-METHYLPHENYL)THIOPHENE-2-METHANOL</u> (659)

Pyrolysis of alcohol (659) (0.28g, 1.4 mmol) at 480°C/10^{-2} torr over alumina during 3 hours with a sublimation temperature of 83°C gave a colourless pyrolysate at -78°C. After warming to room temperature, the pyrolysate was removed with dichloromethane and the solvent evaporated <u>in vacuo</u> to give a pale yellow, tacky solid. Recrystallization from ethanol - benzene gave naphthothiophene (661) as colourless plates (0.046g, 20%), m.p. 189 - 190°C, (lit.,[296] m.p. 192 - 3°C); $\nu_{max.}$ 1603, 1310, 898 and 870 cm^{-1}; δ ($CDCl_3$, 250 MHz), 8.36 (1H, s), 8.30 (1H, s), 7.87 - 7.99 (2H, m), 7.52 - 7.37 (4H, m); <u>m/z</u> 184 (<u>M^+</u>), 151, 138, 92 and 79. Pyrolysis of alcohol (659) at 900°C/10^{-2} torr in the absence of alumina gave naphthothiophene (661) in 5% yield.

(c) <u>α-(3-METHYL-2-THIENYL)BENZENE METHANOL</u> (663)

Pyrolysis of (663) (0.24g, 1.2 mmol) at 450°C/10^{-2} torr over alumina during 3 hours with a sublimation temperature of 142°C produced a pale yellow pyrolysate at -78°C. After warming to room temperature the pyrolysate was removed with dichloromethane and the solvent evaporated at reduced pressure to give a brown oil. Purification by p.t.l.c. on alumina with 5% benzene - petroleum as eluant gave naphthothiophene (661) (0.045g, 20%), identical to that obtained from pyrolysis of alcohol (659).

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