APPROACHES TO CYANOISOCYANIDE AND RELATED SYSTEMS

A thesis presented by

PHILIP CHOI

in partial fulfilment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

OF THE

UNIVERSITY OF LONDON

Hofmann Laboratory (1978-1979),
Whiffen Laboratory (1979-1981),
Chemistry Department,
Imperial College,
South Kensington,
London, SW7 2AY.

October, 1981.

For Ann Khim Ee

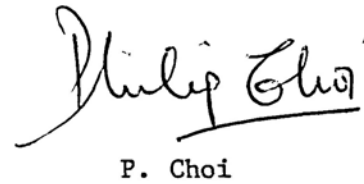
ACKNOWLEDGEMENTS

The work described in this thesis was carried out by the author at Imperial College of Science and Technology under the supervision of Professor C.W. Rees and Dr. E.H. Smith.

I thank Professor C.W. Rees and Dr. E.H. Smith for their advice, friendship, encouragement and enthusiastic interest throughout the course of this work. I also thank Mr. J. Bilton for prompt and excellent mass spectra service, Mrs B. Day for her good service at the chemical store, Mr. P. Sulsh for his technical assistance when this failed in the Whiffen Laboratory and Miss M. Shanahan for her diligent typing of this thesis.

I also thank my parents for their unfailing constant financial support and my wife, Ann Khim Ee, for her patience, support and understanding.

Finally, grateful acknowledgement is made to Dr. A.M. Roe and Smith, Kline and French Research Limited (Welwyn Garden City) for the award of a Research Studentship, 1978-1981.



P. Choi

The heights by great men reached and kept
Were not attained by sudden flight,
But they while their companions slept,
Were toiling upward in the night.

Henry Wadsworth Longfellow.

ABBREVIATIONS

The following abbreviations have been used throughout the text:

ir	:	infra-red
pmr	:	proton magnetic resonance
nmr	:	nuclear magnetic resonance
uv	:	ultra-violet
T.F.A.	:	trifluoroacetic acid
DMF	:	dimethylformamide
DMSO	:	dimethylsulphoxide
THF	:	tetrahydrofuran
DEAD	:	diethyl azodicarboxylate
DMA	:	9,10-dimethylanthracene
Cu(AcAc)	:	copper(II) penta-2,4-dione
F.V.P.	:	flash vacuum pyrolysis

ABSTRACT

The synthesis of cyanocarbonimidic dichloride was achieved and the product was found not to dimerise to 2,4-dichloro-6-dichloromethylimino-S-triazine as suggested in the literature. The synthesis of cyanoisocyanide was attempted using three different approaches, in which the cyanide function, the isocyanide function, and both functions were separately protected.

Three five-membered-ring heterocyclic azides have been synthesised. 3-Azido-5-phenyl-1,2,4-oxadiazole was prepared by heating the corresponding bromo compound with either lithium azide in dimethylformamide or potassium azide and 18-crown-6 in dimethylformamide. Heating 3-chloro- or 3-bromo-5-phenyl-1,2,4-oxadiazole with sodium azide in dimethylformamide provided N,N'-dimethyl-N" -(5-phenyl-1,2,4-oxadiazol-3-yl)formamidine in a novel reaction. The precise mechanism is not yet fully understood although 3-azido-5-phenyl-1,2,4-oxadiazole is probably the reactive intermediate. Decomposition of 3-azido-5-phenyl-1,2,4-oxadiazole under flash vacuum pyrolysis conditions provided unexpectedly benzoyl cyanide in high yield.

During the attempted synthesis of 3-azido-5-phenyl-1,2,4-thiadiazole by diazotisation of the corresponding amino compound and addition of sodium azide, benzonitrile was isolated presumably from the breakdown of the azide. This may represent a possible synthetic route to thionitrosyl cyanide.

3-Azido-4-phenyl-1,2,5-thiadiazole was prepared by diazotisation of the corresponding amino compound followed by the addition of sodium azide. Thermolysis of 3-azido-4-phenyl-1,2,5-thiadiazole in m- or p-xylene provided the Schiff bases, 3-(3'- or 4'-methylbenzyliden-amino)-4-phenyl-1,2,5-thiadiazole. These reactions represent the first observed intermolecular insertions of heterocyclic nitrenes into benzylic methyl groups with subsequent oxidation to the Schiff bases.

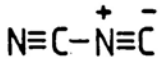
3-Azido-4-phenyl-1,2,5-oxadiazole was prepared by diazotisation of the corresponding amino compound and addition of sodium azide, but the decomposition of this azide remains to be investigated.

CONTENTS

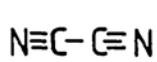
1.0. INTRODUCTION

1. INTRODUCTION

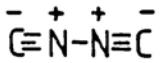
The synthetic target of the work described here is cyanoisocyanide (1). It has a molecular formula C_2N_2 and no synthesis or attempted synthesis has apparently been reported to date. There are three possible acyclic isomers on the C_2N_2 manifold, cyanoisocyanide (1), cyanogen (2), and diisocyanogen (3).



(1)

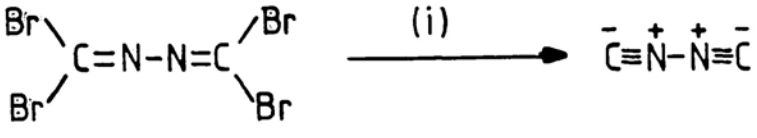


(2)



(3)

Cyanogen (2) is a colourless, flammable, extremely toxic gas (b.p. $-21^{\circ}C$; m.p. $-28^{\circ}C$) first prepared by Gay-Lussac in 1815 by thermal decomposition of silver cyanide.[1] The chemistry of cyanogen has been well reviewed by Brotherton and Lynn.[1] Diisocyanogen (3) was reported to have been synthesised by Thiele[2] in 1898 by the treatment of tetrabromo-N,N'-dimethylene hydrazine (4) with zinc or silver.



(4) (3)

(i) Zinc dust or silver

The reaction was repeated by Grundmann[3] in 1965 who claimed without experimental data that the hydrazine (4) cannot be reduced by metals to give the diisocyanogen (3) as reported by Thiele.

Theoretical calculations have been computed by Rzepa[4] on the three isomers. The heats of formation, ΔHf, of the three species are shown in Table I. The energies of the two unknown species relative

TABLE I.

C_2N_2	calc. ΔHf/Kcal mol^{-1}	obs. ΔHf/Kcal mol^{-1}
NCCN	65.9	73.8
NCNC	110.1	-
CNNC	168.6	-

to cyanogen in increasing order are thus 44.2 Kcal mol^{-1} (cyanoisocyanide) and 102.7 Kcal mol^{-1} (diisocyanogen).

Isocyanides undergoes thermal isomerisation to cyanides.[5,6] The corresponding rearrangement of cyanoisocyanide (1) to cyanogen (2) is calculated to require an activation energy of 65 Kcal mol^{-1}, although the figure may be as much as 40 Kcal mol^{-1} too high.

The theoretical calculations show that the target, cyanoisocyanide (1), is not as stable as cyanogen but is not the least stable of the three acyclic C_2N_2 isomers.

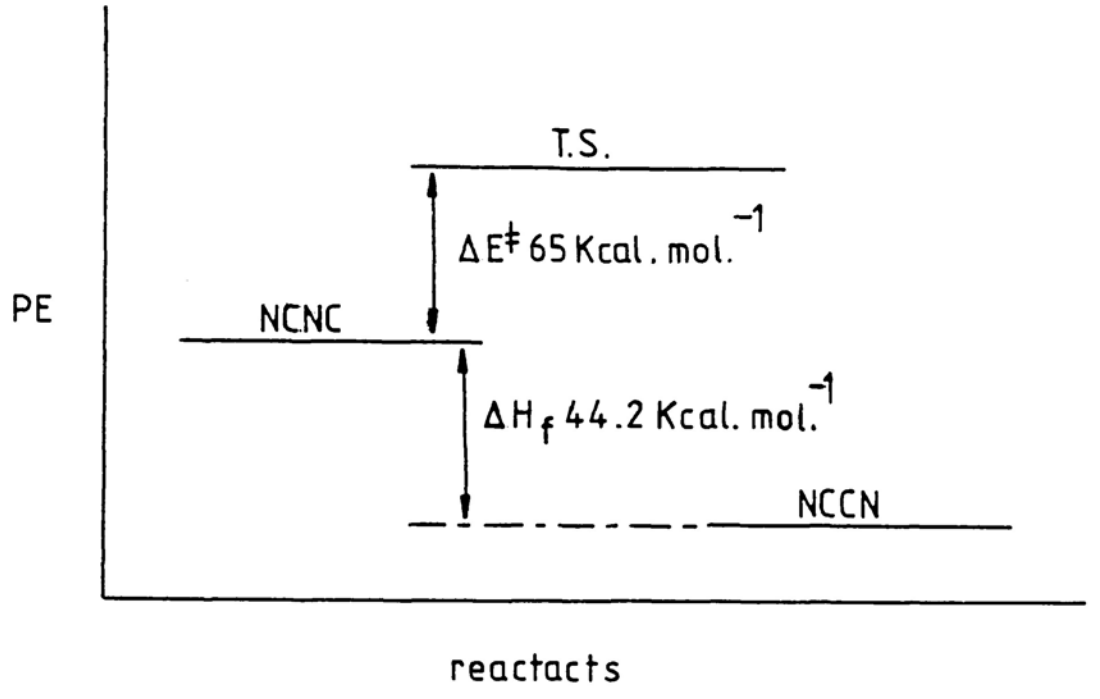
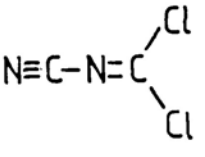


Fig. 1

Although cyanoisocyanide (1) has never been reported, Trompen[7] implicated its derivative, cyanocarbonimidic dichloride (5) as a reactive intermediate. Since the dichloride (5) could serve as a precursor to the target molecule (1), our initial work was concerned with attempts to substantiate the claim by Trompen and, if necessary, to find an alternative synthesis of dichloride (5). These syntheses and our attempts to prepare cyanoisocyanide (1) form the first two parts (2.0 and 3.0) of this Thesis.



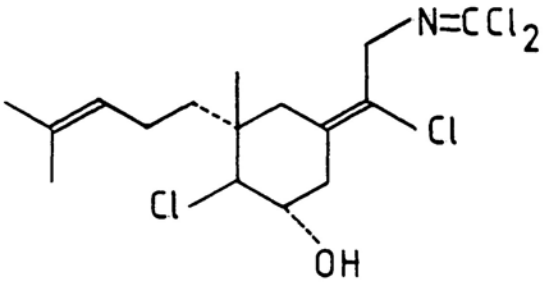
(5)

2.0. ATTEMPTED SYNTHESIS OF CYANOCARBONIMIDIC DICHLORIDE.

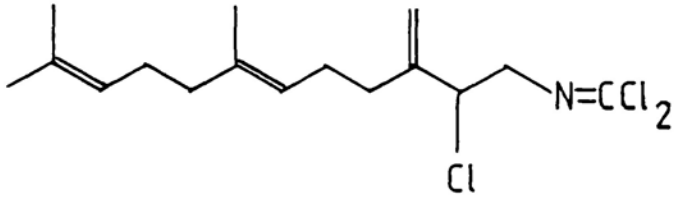
2.0. ATTEMPTED SYNTHESIS OF CYANOCARBONIMIDIC DICHLORIDE (5).

2.1. Introduction

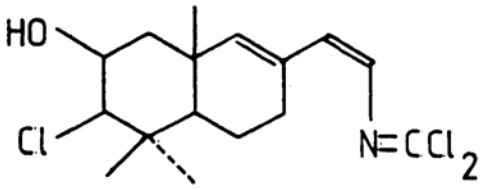
The synthesis and properties of a large number of carbonimidic dichlorides (isocyanide dichlorides) have been extensively studied.[8,9,10] Recently carbonimidic dichlorides (6-9) have been isolated from a natural source, the marine sponge Pseudaxinyssa pitys.[11] This is the first time that this functionality has been found in natural products.



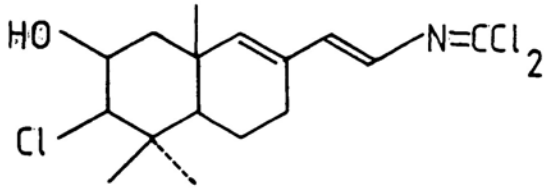
(6)



(7)

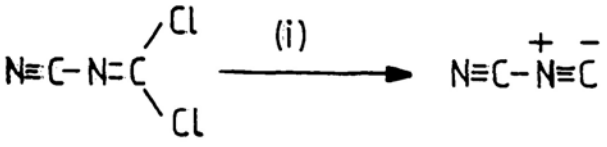


(8)



(9)

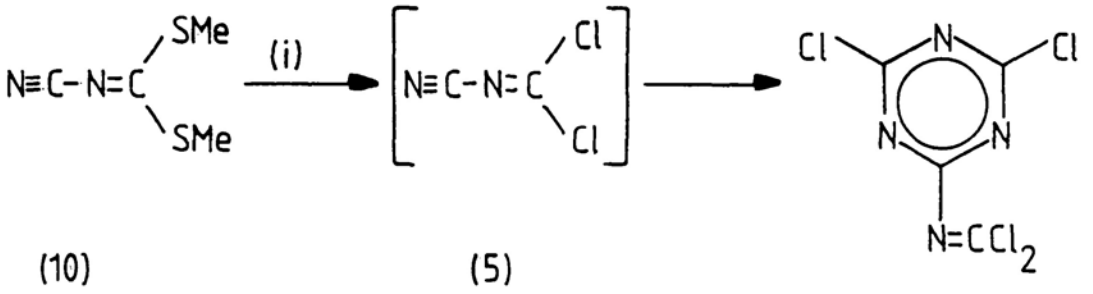
The carbonimidic dichloride that we are interested in is cyano-carbonimidic dichloride (5). Treatment of this dichloride with iodide anion should give the target compound, cyanoisocyanide (1). Thus, the dichloride (5) can serve as a precursor to isocyanide (1).



(5) (1)

(i) I^-

There has only been one reported attempt at the synthesis of the dichloride (5) by Trompen[7] from the low temperature (-15°C) chlorination of S,S'-dimethyldithiocarbonimidate (10) in anhydrous dichloromethane. The product from the chlorination was, however, not the desired dichloride (5) but 2,4-dichloro-6-dichloromethylimino-S-triazine (11) (65%). This was postulated as being formed by dimerisation of dichloride (5) even though the latter was not trapped or identified as an intermediate.

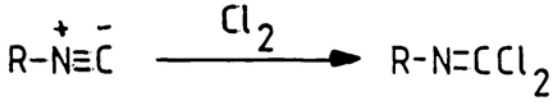


(10) (5) (11)

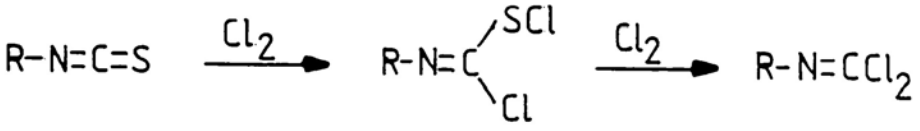
(i) Cl_2, CH_2Cl_2, -15°

General synthetic methods[8,9,10] for carbonimidic dichlorides which may be of use in the synthesis of dichloride (5) are as follows:

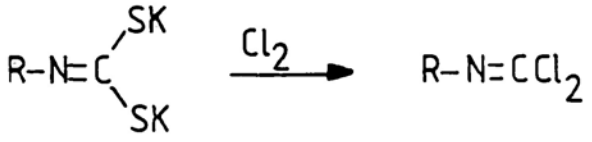
(a) Addition of halogen to isocyanides



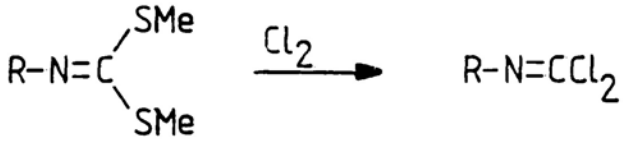
(b) halogenation of isothiocyanates



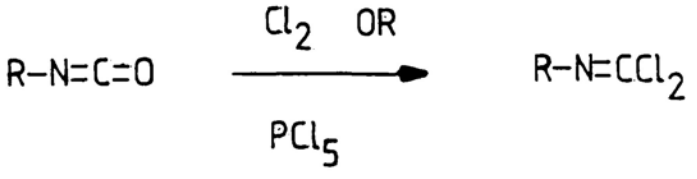
(c) halogenation of dithiocarbonimidate derivatives



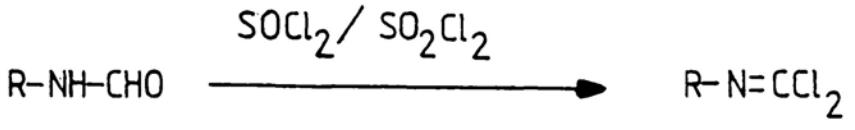
(c) halogenation of dithiocarbonimidate derivatives



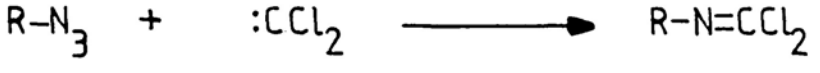
(d) halogenation of isocyanates



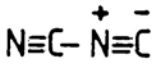
(e) halogenation of formimidoyl chlorides



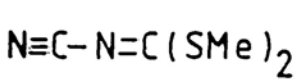
(f) from dichlorocarbene and nitrene precursors



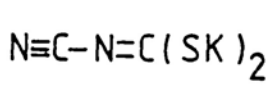
The list mentioned is not exhaustive but is relevant to the work described here. Thus, the required precursors to cyanocarbonimidic dichloride (5) would be S,S'-dimethylcyanodithiocarbonimidate (10), dipotassium cyanodithiocarbonimidate (12), cyanoisothiocyanate (13), cyanogen azide (14), N-cyano diphenyliminosulphurane (15), cyanoisocyanate (16) and N-formylcyanamide (17). The only unknown precursors are the target, cyanoisocyanide (1) and N-formylcyanmidė (17).



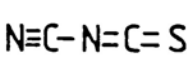
(1)



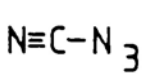
(10)



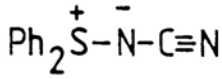
(12)



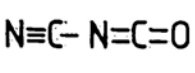
(13)



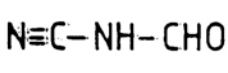
(14)



(15)

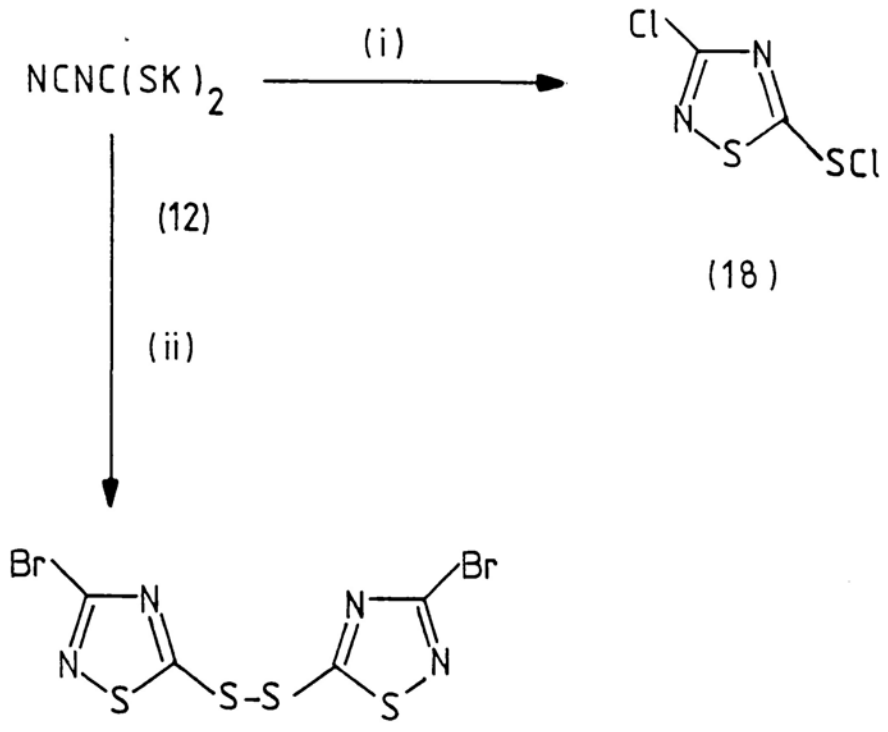


(16)



(17)

As described earlier, chlorination of compound (10) provided the dimeric species (11), and dichloride (5) was the proposed intermediate. Chlorination[12,13] of dipotassium cyanodithioimidocarbonimidate (12)[13] in dichloromethane at -40°C afforded 3-chloro-1,2,4-thiadiazol-5-yl sulphenyl chloride (18) (86%) and bromination[13] gave bis-(3-bromo-1,2,4-thiadiazol-5-yl)disulphide (19) (87%). Therefore, compound (12) does not appear to be a suitable precursor for the dichloride (5).

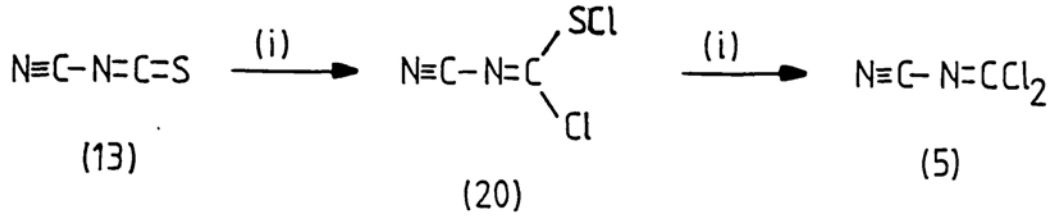


(18)

(19)

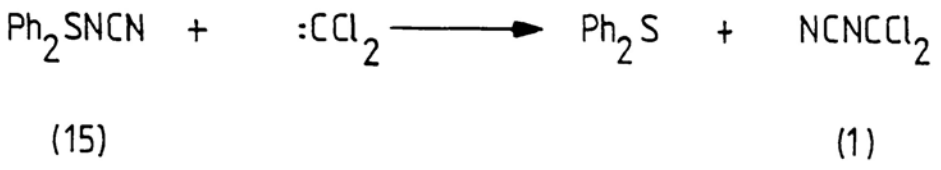
(i) $2\ Cl_2$, CH_2Cl_2, $-40°$, (ii) $3\ Br_2$, CH_2Cl_2, $-40°$

The most favoured precursor is the relatively stable cyanoisothiocyanate (13)[14] since most carbonimidic dichlorides are prepared by chlorination of the isothiocyanates,[8,9,10] (Scheme I).



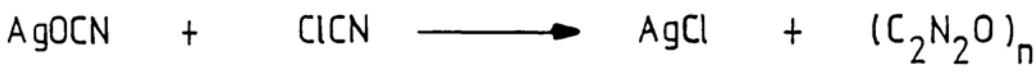
Scheme 1 (i) Cl_2

Cyanogen azide (14) is hazardous[15] and thus was undesirable as a starting compound. However, other nitrene sources should serve equally well and it was decided to investigate the reaction of N-cyano diphenyliminosulphurane (15)[16] and dichlorocarbene (Scheme 2).



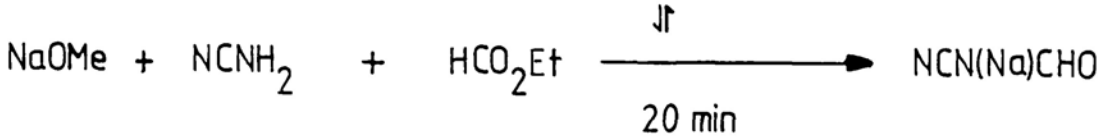
Scheme 2

Cyanoisocyanate (16)[17,18] was synthesised by Mayer[17] from silver cyanate and excess cyanogen chloride as the polymer $(C_2N_2O)_n$.



$(C_2N_2O)_n$ depolymerises by heating in vacuum above 140°C into C_2N_2O which is stable at room temperature for only a short time under low pressures and polymerises again already at pressures of a few Torr. Since polymerisation sets in in the liquid phase it is necessary to carry out reactions below the melting point (at best < -63°C). This makes cyanoisocyanate (16) an undesirable and an extremely difficult precursor for the synthesis of the dichloride (5).

N-formylcyanamide (17) is unknown but its sodium salt (17a) has recently been reported in a patent.[19]

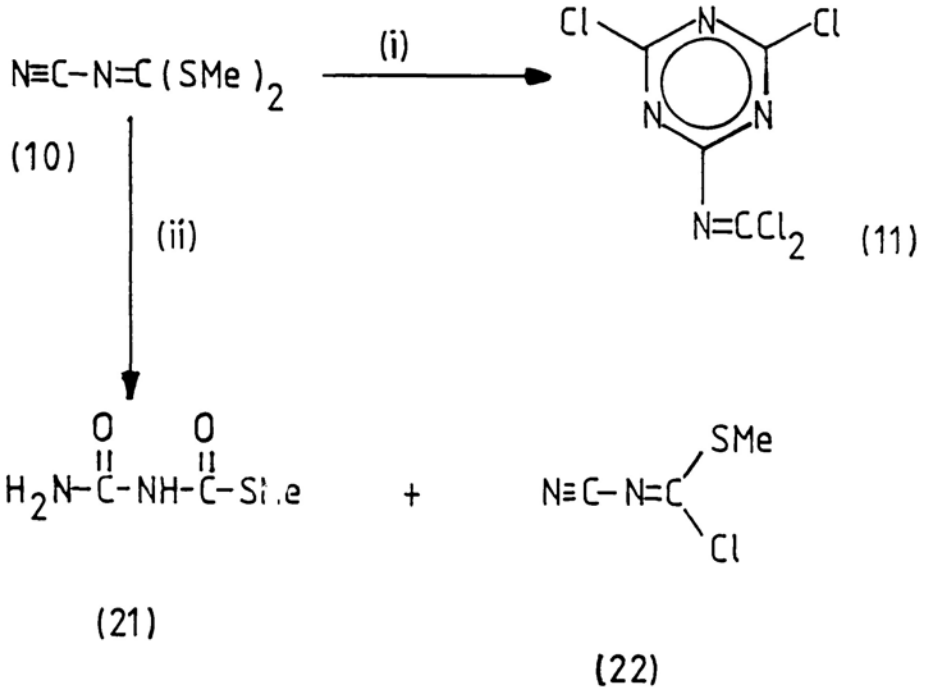


(17a)

Liberation of the free cyanamide (17) may not be easy.

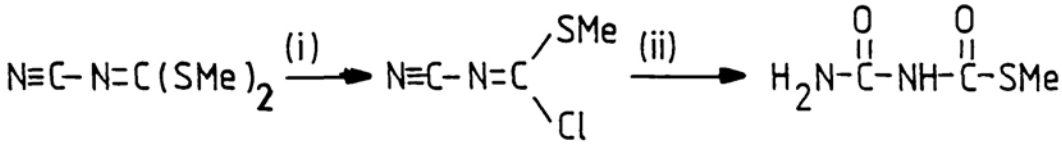
2.2. Discussion.

Our first synthetic approach to cyanocarbonimidic dichloride (5) was to repeat the chlorination of S,S'-dimethylcyanodithiocarbonimidate (10) at -15°C in anhydrous dichloromethane.[7] 2,4-Dichloro-6-dichloromethylimino-S-triazine (11) (65%) was indeed obtained as reported.[7] However, when the chlorination was repeated with wet dichloromethane and at temperatures varying from -78°C to -15°C, two different products were isolated with no triazine (11).



(i) Cl_2, anhydrous CH_2Cl_2, (ii) Cl_2, wet CH_2Cl_2, -78° to -15°

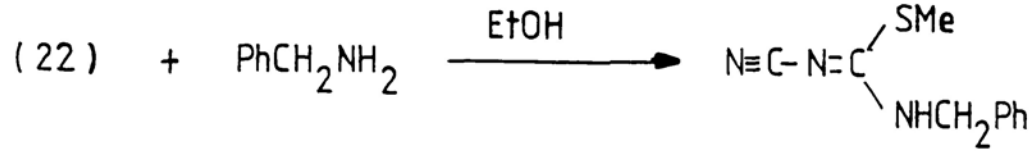
These two products were methylthioallophanate[20] (21) (50%) and N-cyanoimino-S-methylthiocarbonate chloride (22) (7%). The latter must have presumably hydrolysed to give the former product since hydrolysis of carbonimidate (10) in aqueous hydrochloric acid at 40°C provided the allophanate (21) (26%) as the only isolable product.[20]



(10) (22) (21)

(i) Cl_2, CH_2Cl_2, -78° to -15°, (ii) H_2O

The chloride (22) was not very stable, and to assist in its characterisation it was reacted with benzylamine to give N-benzyl-N'-cyano-S-methyl-isothiourea (23) (63%).



(23)

The product (23) was identical with an authentic sample prepared directly from carbonimidate (10) and benzylamine.[21]

Chlorination of (10) at room temperature or in anhydrous carbon tetrachloride under reflux provided polymeric material only. The dichloride (5) could not be isolated, nor observed by ir spectroscopy nor trapped with benzylamine to give N,N'-dibenzyl-N''-cyanoguanidine (24). An authentic sample of the latter compound (24) (44%) was synthesised by heating carbonimidate (10) with excess of benzylamine in ethanol over 24 h.

$$N{\equiv}C{-}N{=}C(SMe)_2 \quad + \quad PhCH_2NH_2 \xrightarrow[\Delta\ ,\ 24h]{EtOH} N{\equiv}C{-}N{=}C(NHCH_2Ph)_2$$

(10) (24)

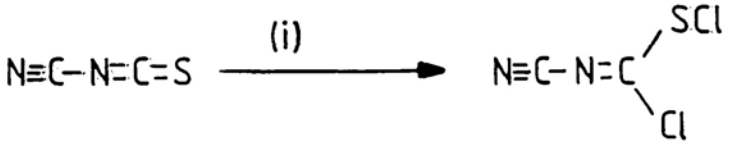
The second attempted synthetic route to the dichloride (5) was by chlorination of cyanoisothiocyanate (13). The latter, (13), was prepared from dipotassium cyanodithioimidocarbonimidate (12) and phosgene.[14] Dry chlorine gas was bubbled into a solution of cyanoisothiocyanate (13) in anhydrous dichloromethane at 0°C for 7.5 h to afford a solution of N-cyano-1-(chlorothio)formimidoyl chloride (20).

$$N{\equiv}C{-}N{=}C(SK)_2 \quad + \quad COCl_2 \xrightarrow[-COS]{(i),\ (ii)} N{\equiv}C{-}N{=}C{=}S \quad + \quad 2KCl$$

(12) (13)

(i) $COCl_2$ for 5h, CH_2Cl_2, (ii) reflux, CH_2Cl_2, 72h

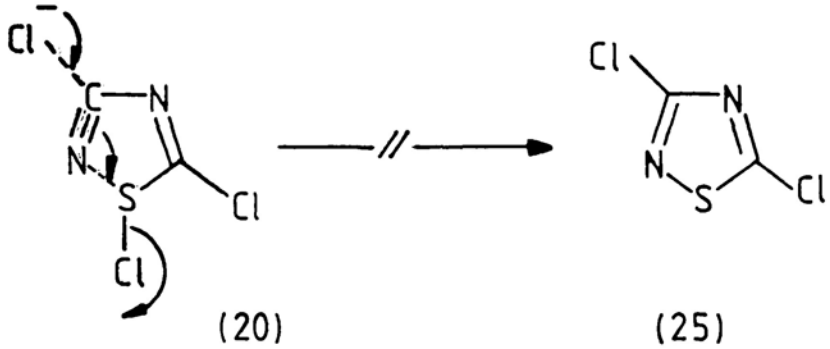
The chloride (20) was unstable and decomposed if neat; however, it was reasonably stable for up to two days if kept in anhydrous dichloromethane solution. The structure of N-cyano-1-(chlorothio)formimidoyl chloride (20) was assigned, from the ir spectrum, ν_{max} (CH_2Cl_2) 2220 (-CN), 1600 (C=N), 940 (C-Cl), 550 (S-Cl), and the mass spectrum which gave m/e 156, 154 (M^+, two chlorine pattern), 119 (M-Cl). (Chlorothio)-formimidoyl chlorides are well known intermediate products from chlorination of isothiocyanates.[8,9,10]



(13) (20)

(i) Cl_2 for 7·5h , 0° , CH_2Cl_2

Possible cyclisation of the formimidoyl chloride (20) to 3,5-dichloro-1,2,4-thiadiazole (25)[22] did not occur since the cyano stretching at 2220 cm^{-1} was present in the ir spectrum.



(20) (25)

Further chlorination of formimidoyl chloride (20) at room temperature afforded a mixture of starting material (20) and cyanocarbonimidic dichloride (5) after 13 h. The progress of the reaction was monitored by ir spectroscopy and the reaction did not proceed further even on reflux for another 16 h in dichloromethane. The ir evidence for the formation of the dichloride (5) was the decrease in the intensity of $\nu_{S-C\ell}$ at 550 cm^{-1} with an increase in intensity of a new absorption, $\nu_{C-C\ell}$ at 960 cm^{-1} and retention of the original $\nu_{C-C\ell}$ at 930 cm^{-1} during chlorination. Attempts to remove the starting material (20) by addition of raw linseed oil to the reaction mixture followed by distillation was not totally successful. It was hoped that the unsaturation in the raw linseed oil would trap the sulphenyl chloride by electrophilic addition. The mass spectrum showed that there were still traces of the starting material (20). The dichloride (5) was best stored in sealed vials as a solution in anhydrous dichloromethane at $0^{o}C$. Attempts to react the dichloride (5) with benzylamine gave a complex mixture on tlc, although one of the spots had the same Rf as an authentic sample of cyanoguanidine (24), the expected product. Isolation was not carried out because the scale was too small.

$$\underset{(5)}{NCNCCl_2} + PhCH_2NH_2 \longrightarrow \underset{(24)}{NCNC(NHCH_2Ph)_2}$$

Comparison of the cyano stretching frequencies in the ir spectra for analogous compounds, $NCNCR_1R_2$ (Table II) showed very little change.

TABLE II

R_1	R_2	ν_{CN}/cm^{-1}
$-NHCH_2Ph$	$-NHCH_2Ph$	2160 (Nujol)
$-NHCH_2Ph$	-SMe	2170 (Nujol)
-SMe	-SMe	2180 (Nujol)
-SCℓ	-Cℓ	2220 ($CH_2Cℓ_2$)
-Cℓ	-Cℓ	2220 ($CH_2Cℓ_2$)

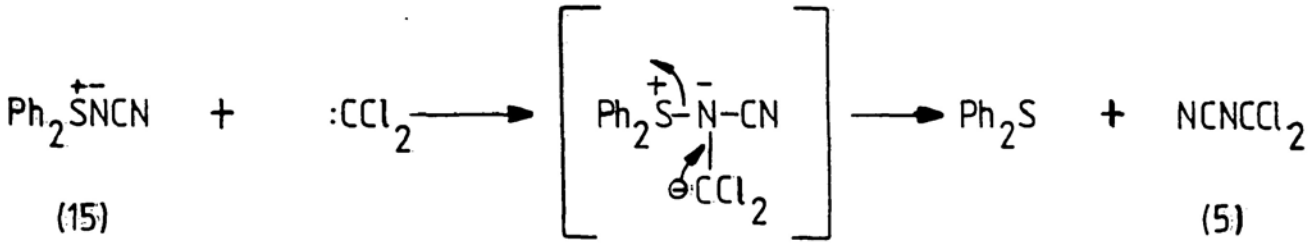
It can be concluded that the cyanoimino function was present in dichloride (5). The fragmentation pattern in the mass spectrum showed m/e 122, 119 (M^+, two chlorine pattern), 84 (M-35) and 156, 154 (M^+) 119 (M-35) for the dichloride (5) and the formimidoyl chloride (20) respectively, provided supporting evidence that the dichloride (5) was present in the distillate. The observed decrease in intensity of $\nu_{S-Cℓ}$ at 550 cm^{-1} and the appearance of a new $\nu_{C-Cℓ}$ at 960 cm^{-1} with increasing intensity besides the other $\nu_{C-Cℓ}$ at 930 cm^{-1} was further proof for the dichloride (5).

The ir spectrum of the dichloride (5) was different from that of the triazine (11). The obvious important difference was the presence of the cyano stretching ν_{CN} at 2220 cm^{-1} in the dichloride (5). If the

dichloride (5) was indeed the intermediate to triazine (11) at -15°C, some of the latter should have been isolated. The molecular ion, 246 (M^+), for the triazine (11) was not observed in the mass spectrum of the product from the chlorination of formimidoyl chloride (20). Therefore, the dichloride (5) is probably not the intermediate in the formation of the triazine as postulated by Trompen.[7]

Our third synthetic approach to the dichloride (5) was to react N-cyano-S-diphenyliminosulphurane (15)[16] with dichlorocarbene generated *in situ*. The former, (15), was prepared from diphenyl sulphide, monosodium cyanamide and t-butyl hypochlorite in anhydrous methanol at -60°C. The phase transfer catalysis (PTC) method for generation of dichlorocarbene from sodium hydroxide, chloroform and benzyltriethylammonium chloride as PTC catalyst was used. Diphenyl sulphide (trace) was the only product identified. It was thought that perhaps another method to generate the dichlorocarbene under anhydrous conditions would be desirable in order to avoid possible hydrolysis of the product. Iminosulphurane (15) was stirred with phenyl(trichloromethyl)mercury[23] in boiling anhydrous benzene under dry nitrogen. After 15 h reflux, phenylmercury chloride (74%) was filtered off. The filtrate contained a trace of diphenyl sulphide and unchanged iminosulphurane (15) by tlc. To this filtrate another equivalent of phenyl(trichloromethyl)mercury was added and the mixture was heated under reflux for another 18 h. On cooling, phenylmercury chloride (74%) was again filtered off. The ir spectrum of the filtrate showed diphenylsulphide only. On addition of benzylamine to the filtrate in an attempt to trap any dichloride

(5) present only unreacted benzylamine and diphenyl sulphide could be detected by ir and tlc. It is possible that the dichlorocarbene generated had reacted with the iminosulphurane (15), hence the formation of diphenyl sulphide. Perhaps the conditions used were too vigorous for the isolation of the dichloride (5).



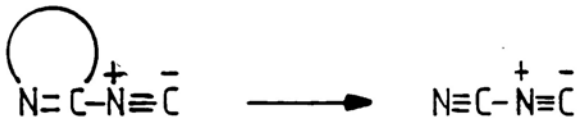
(15) (5)

3.0. ATTEMPTED SYNTHESIS OF CYANOISOCYANIDE

3.0. ATTEMPTED SYNTHESIS OF CYANOISOCYANIDE (1).

3.1. Introduction

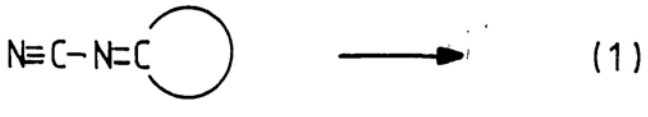
The synthesis of cyanoisocyanide (1) can be described retrosynthetically by three general approaches. The first approach (I), is to start with a precursor containing a free isocyano group and the cyano group 'masked' as part of a ring or as another group from which the cyano functionality can be generated easily.



(1)

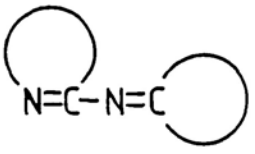
Approach (I)

The second approach, II, is the reverse of approach I, where now the isocyano group is 'masked' as part of a ring or as another group and the cyano group is present free in the precursor.



Approach (II)

The third approach, III, is to have both the cyano and isocyano group 'masked' separately.



(1)

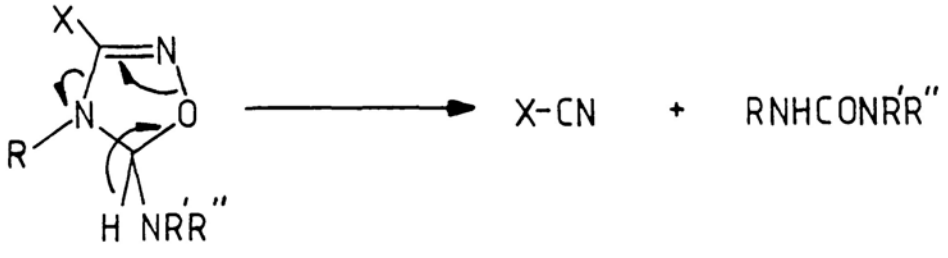
Approach (III)

3.2. Discussion

3.2.1. Approach I.

3.2.1.1. Fragmentation of 3-isocyano-5-morpholino-4-phenyl-1,2,4-oxadiazoline (28).

It has been shown recently that 1,2,4-oxadiazolines (26) in general break down under mild conditions* to give a cyanide and a urea.[24]

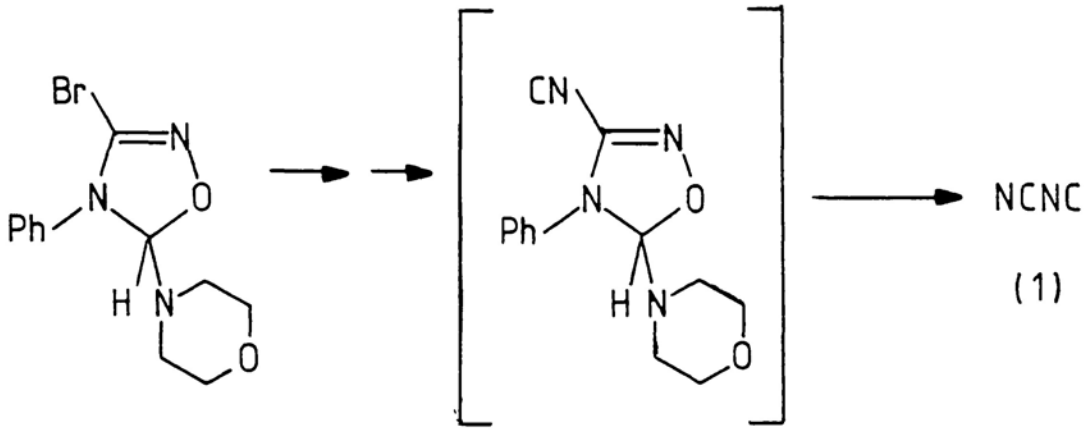


(26)

* Thermolysis in toluene solution or acid hydrolysis with T.F.A. or trityl tetrafluoroborate in dichloromethane.

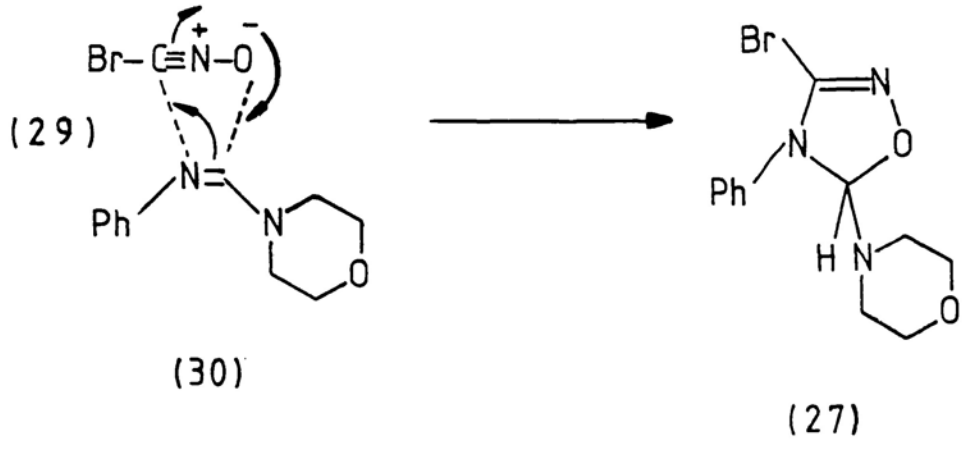
The cyanide generated in this way is 'masked' in the oxadiazoline (26). If X = -NC, cyanoisocyanide (1) could possibly be generated under relatively mild conditions. This route has the advantage that the cyano group is part of the oxadiazoline ring and cannot interact with reagents used to generate the isocyanide group, and the by-product, a substituted urea, is not likely to react with the product.

Initially the substituent, X, should preferably be a halogen which can be subsequently displaced by a variety of nucleophiles. Thus, 3-bromo-5-morpholino—4-phenyl-1,2,4-oxadiazoline (27) was chosen as the early precursor to the target (1)

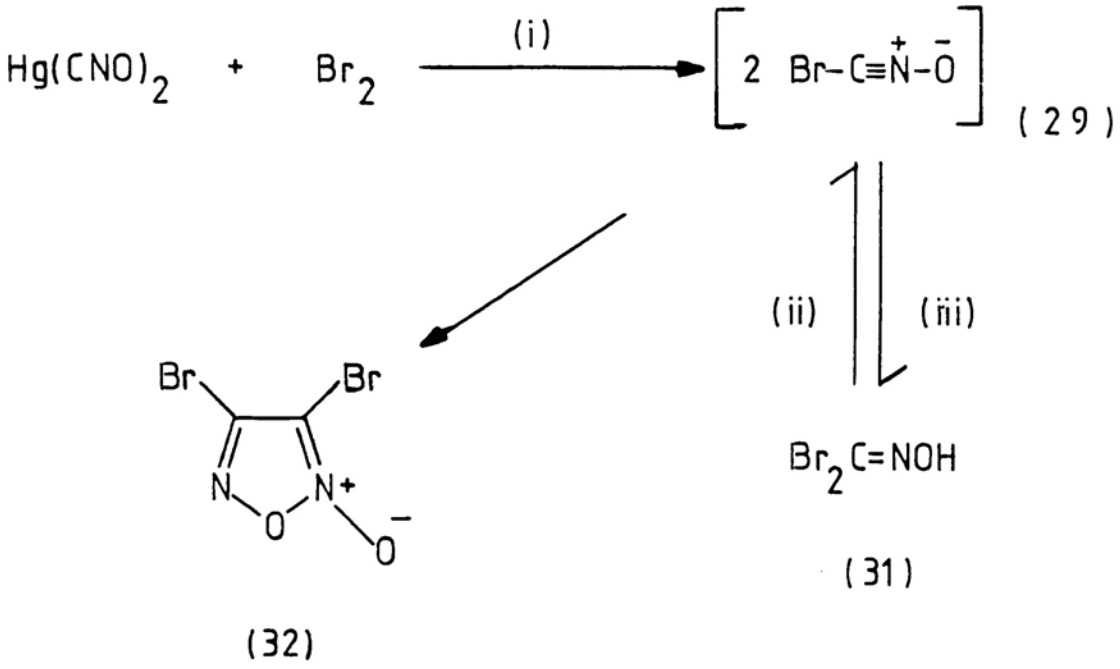


(27) (28)

Oxadiazoline (27) could presumably be synthesised by cycloaddition of bromoformonitrile oxide (29)[25] and the amidine, 4-(N-phenylformimidoyl)-morpholine (30).



Bromoformonitrile oxide (29) had to be generated in situ from dibromoformoxime (31). The latter was synthesised by bromination of mercury fulminate[25] in 1 M hydrobromic acid, and obtained as a (1:1) mixture of dibromofuroxan (32) and dibromoformoxime (31)[25] in 25-30% yield. At least 45-55% of the mercury fulminate is destroyed in this process by oxidation.[26] The crude product, assumed to contain an equal mixture of (31) and (32), by literature precedent,[26] was not distilled to prevent further decomposition of (31) to (32).



Scheme 3 (i) 1M HBr, $-HgCl_2$, (ii) -HBr (iii) +HBr

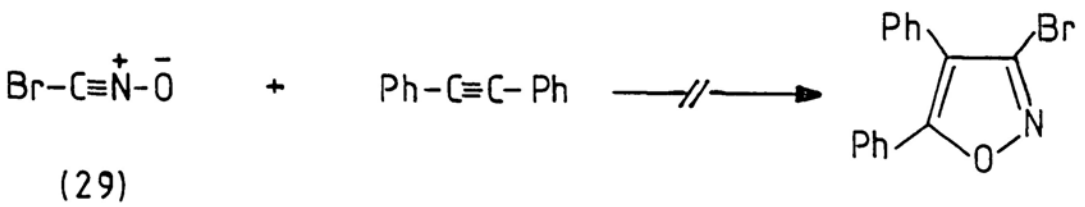
The first attempted cycloaddition of bromoformonitrile oxide (29), generated *in situ* with triethylamine and the crude dibromoformoxime (31), to the amidine (30) failed. An attempt to purify the crude product by column chromatography afforded *N*-formanilide (80%). The latter can be formed either from the breakdown of the oxadiazoline (27) formed or from acid hydrolysis of the amidine (30), if the latter had not reacted.

In order to determine the source of *N*-formanilide a blank reaction was carried out. Hydrolysis of the amidine (30), with silica gel in chloroform afforded *N*-formanilide (100%) at room temperature over 1 h.

No decomposition was observed when this reaction was repeated without the silica gel under identical conditions. The source of N-formanilide was probably therefore unreacted amidine (30), although hydrolysis of the oxadiazoline (27) cannot be ruled out.

A second attempt at the cycloaddition to form the oxadiazoline (27), using similar conditions to those above, afforded a brown oil. The oil contained a mixture of unreacted amidine (30),4-(N-phenylformimidoyl)-morpholine hydrobromide and furoxan (32) among other unidentified products from the ir, nmr, and mass spectrum. Attempts to purify the product by precipitation with solvents of varying dielectric constants afforded only the morpholine hydrobromide. No conclusive evidence could be obtained to show that the desired oxadiazoline (27) was present in the crude product.

Diphenylacetylene was chosen as an alternative dipolarophile to test formation of the bromoformonitrile oxide (29) because the product 3-bromo-4,5-diphenylisoxazole (33) should be stable. However, attempts to synthesise isoxazole (33) from bromoformonitrile oxide (29) and diphenyl-acetylene with triethylamine as the base failed. Triethylamine hydro-bromide and diphenylacetylene (quantitative recovery) were the only products isolated.



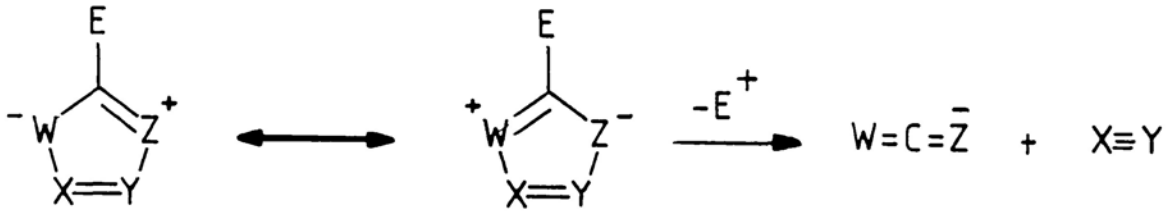
(29) (33)

This work suggests that either bromoformonitrile oxide was not generated or that it was formed but did not react. It has been reported[27] that chloroformonitrile oxide undergoes cycloaddition in certain cases but failed in others. This route in Approach I was therefore abandoned.

3.2.1.2. Base-induced fragmentation of 2-isocyano-1,3,4-thiadiazole (35).

Recently, Olofson[28,29] had shown that base-induced fragmentation of five-membered heterocycles provided some inaccessible cyanamides. From his work, there are two general fragmentations formalised as equations A and B.

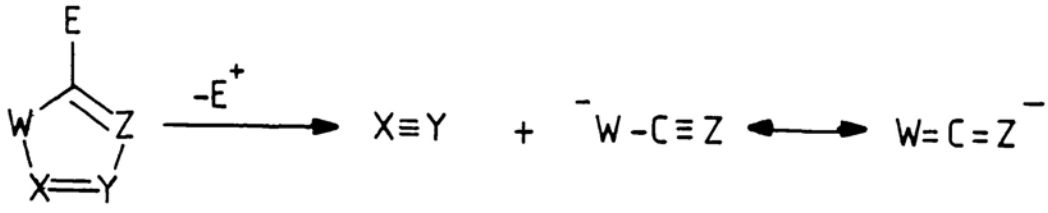
Equation A



W,Z = O, S, NR

X,Y = N, CR

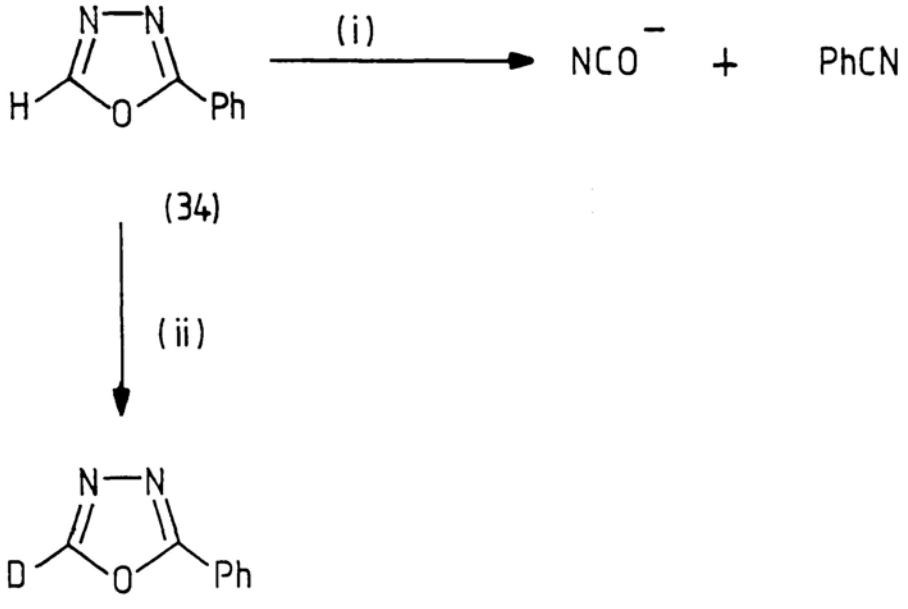
Equation B



W = O, S, NR

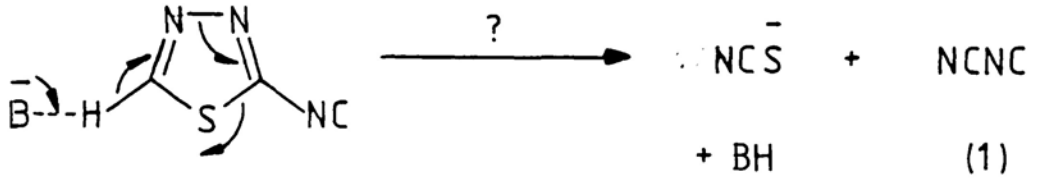
X, Y, Z = N, CR

An example of Olofson's fragmentation occurs when 2-phenyl-1,3,4-oxadiazole (34) is treated with the " H^+arpoon" base, lithium 2,2,6,6-tetramethylpiperidide (LiTMP).[30,31]



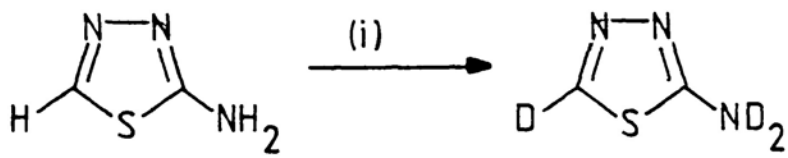
Scheme 4 (i) LiTMP (ii) 0·4M piperidine, MeOD, $t_{1/2}$ 19 min

Thus, in principle we could use base induced fragmentation of 2-isocyano-1,3,4-thiadiazole (35) to provide the target, cyanoisocyanide (1).



(35)

It is assumed that the thiocyanate ion generated will form a salt with the base and will not interact with the desired product (1). It was established by Olofson[29] that the proton on the heterocyclic ring of oxadiazole (34) could be exchanged with deuterium under mild conditions ($t_{\frac{1}{2}}$: 19 min at 31°C in 0.4 M piperidine/MeOD). In our heterocyclic system, 2-amino-1,3,4-thiadiazole (36), under identical conditions exchanged the proton in the 5-position with a half-life ($t_{\frac{1}{2}}$) of 3 h 35 min. This established that this proton can be removed easily.

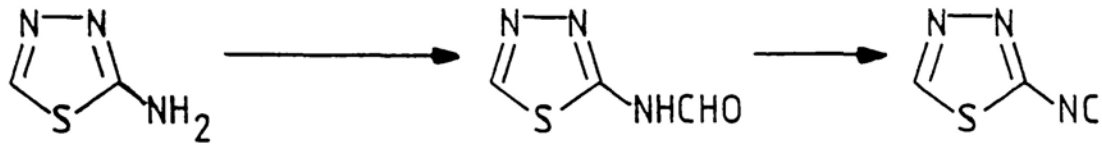


(36) (36a)

(i) 0·4M piperidine / MeOD

The deuterium exchange experiment did not show that the thiadiazole ring in (36) could be fragmented with piperidine. Attempted fragmentation by triethylamine or piperidine of the thiadiazole (36) at room temperature in diethyl ether afforded quantitative recovery of starting material (36). Thus, a much stronger base (pka > 11.1), e.g., LiTMP will be required to fragment the thiadiazole rings (35) and (36).

2-Isocyano-1,3,4-thiadiazole (35) is an unknown isocyanide and can be envisaged to be synthesised by formylation of the amine (36)[32] followed by dehydration of the resultant 2-formamido-1,3,4-thiadiazole (37).



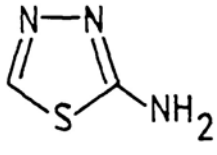
(36) (37) (35)

The first step was formylation of the amine (36). Acetoformic anhydride[33,34] in pyridine gave the acetylated product.[35] No formylated product was obtained even though two different procedures[32,33] for the preparation of acetoformic anhydride were used. Formylation failed with methyl formate in boiling ethanol for 24 h and sodium methoxide/DMF mixture[36] gave only poor yields (< 10%) of the product (37). The best method for formylation of the amine (36) was found to be by azeotroping the amine (36) under reflux with 90-100% formic acid for 48 h in benzene. Periodical addition of formic acid to the reaction mixture was essential to ensure complete reaction.

Dehydration of 2-formamido-1,3,4-thiadiazole (37) was first attempted with phosgene and triethylamine.[5] This method failed to provide the desired product (35), and gave diethylcarbamoyl chloride as the only product isolated. This is the product of the reaction of phosgene with

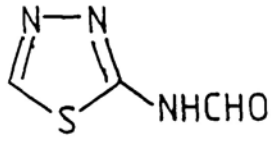
triethylamine.[37] The next method of dehydration was to use p-toluene sulphonyl chloride and anhydrous pyridine. This method is recommended as a method for dehydration of formamides to isocyanides on a small scale.[5]

Dehydration of formamide (37) with p-toluene sulphonyl chloride and pyridine for 6 h at room temperature provided the unexpected product (38) (21%) with no isocyanide (35). An ir spectrum of the crude product showed no bands in the isocyanide region.



λ_{max}(MeOH) 215(767), 256(1414)

(36)



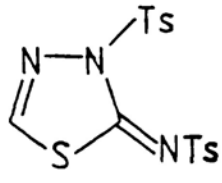
λ_{max}(MeOH) 208(826), 252(1860)

(37)

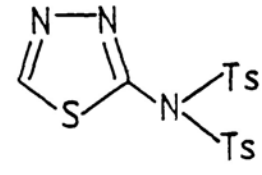
?

(38) λ_{max}(MeOH) 242(6139), 274(5745)

On comparison of the uv (methanol) of the two thiadiazoles (36) and (37) with the unexpected product (38), it could be seen that the chromophore of (38) was different from that of the amine (36) or the formamide (37). The pmr spectrum showed that there were two p-toluene sulphonyl groups with the two methyl groups in different environment. The pmr spectrum of pyridinium tosylate, a by-product in the reaction, was different from the product (38). The mass spectrum gave a mass ion of 410 (protonated in the mass spectrum) and the elemental analysis showed a molecular formula of $C_{16}H_{15}N_3O_4S_3$. From the spectral evidence, the two possible structures are (38a) or (38b).



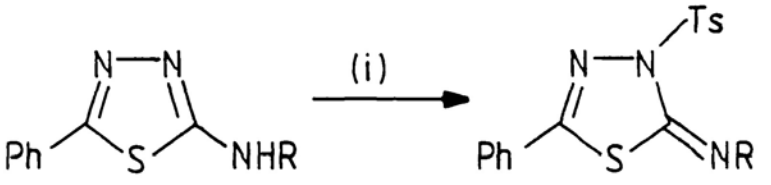
(38a)



(38b)

The fact that the two methyls in the pmr spectrum are in different environments suggests the structure (38a). However, if free rotation about the C-N bond between the heterocyclic ring (38b) and the ditosyl groups is restricted, the methyl groups will also appear in different environments. The uv spectra also supported structure (38a) since its

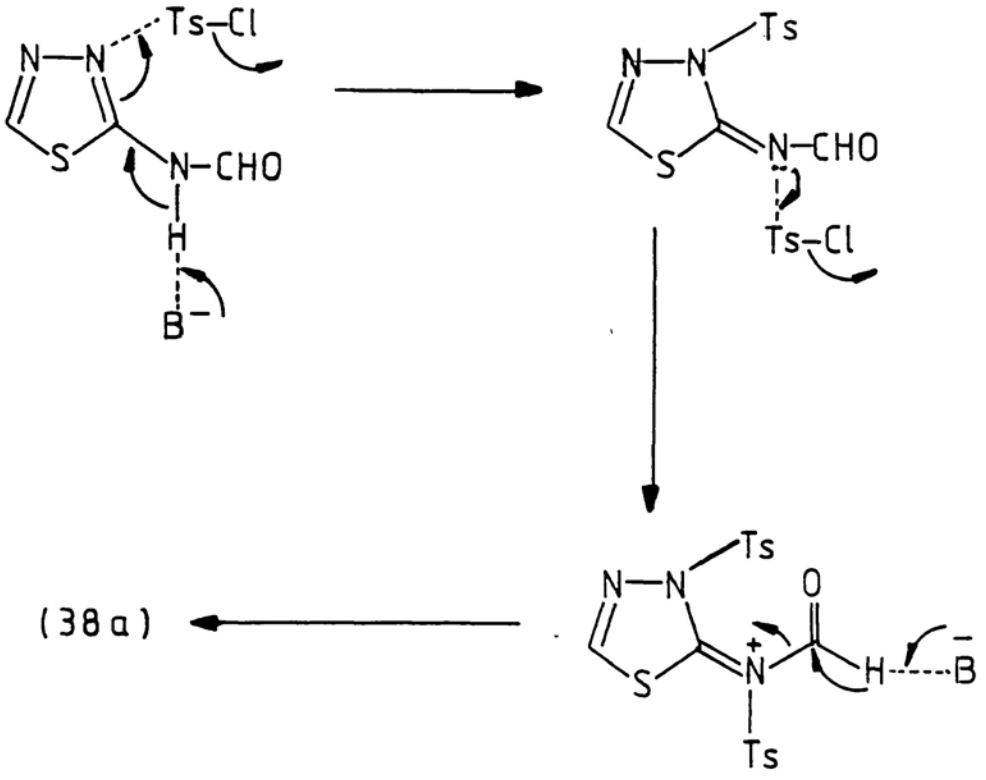
absorption pattern was different from both thiadiazoles (36) and (37). This could be explained by the presence of an exocyclic double bond in (38a). If the product had structure (38b), the uv spectrum would be expected to be similar to (36) and (37). p-Toluene sulphonic acid absorbs at 220 nm (MeOH). In a literature precedent,[38] tosylation of 2-monosubstituted amino-1,3,4-thiadiazoles (39) occurred in the presence of triethylamine on the nitrogen in the 3-position of the ring to give Δ^2-1,3,-4-thiadiazoline (40).



(39) (40)

(i) TsCl , Et_3N , C_6H_6 , 12h , Δ

Therefore, the structure of the unexpected product (38) from all spectral evidence and literature precedent is probably 2-tosylimino-3-tosyl-Δ^4-1,3,4-thiadiazoline (38b). The proposed mechanism for its formation is shown in Scheme 5.



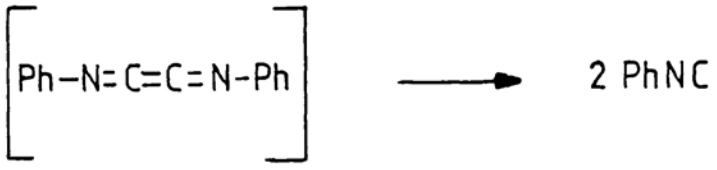
Scheme 5

This approach to the synthesis of cyanoisocyanide (1) was thus abandoned since the precursor (35) could not be synthesised.

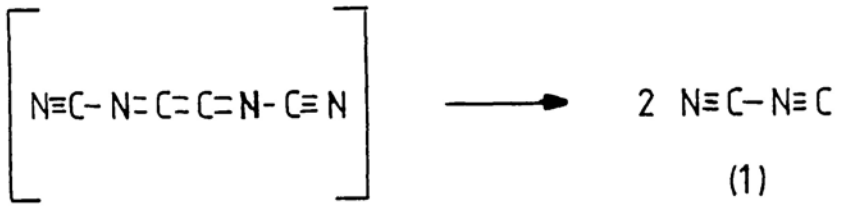
3.2.2. Approach II.

3.2.2.1. Synthesis of 1,4-dicyano- and 1-phenyl-4-cyano-1,4-diazabuta-1,2,3-triene (42) and (48).

It is known[39] that attempted formation of 1,4-diphenyl-1,4-diazabuta-1,2,3-triene (41) generates two moles of phenyl isocyanide. By analogy, 1,4-dicyano-1,4-diazabuta-1,2,3-triene (42) could generate two moles of cyanoisocyanide (1), and so we attempted to synthesise the novel compound (42).



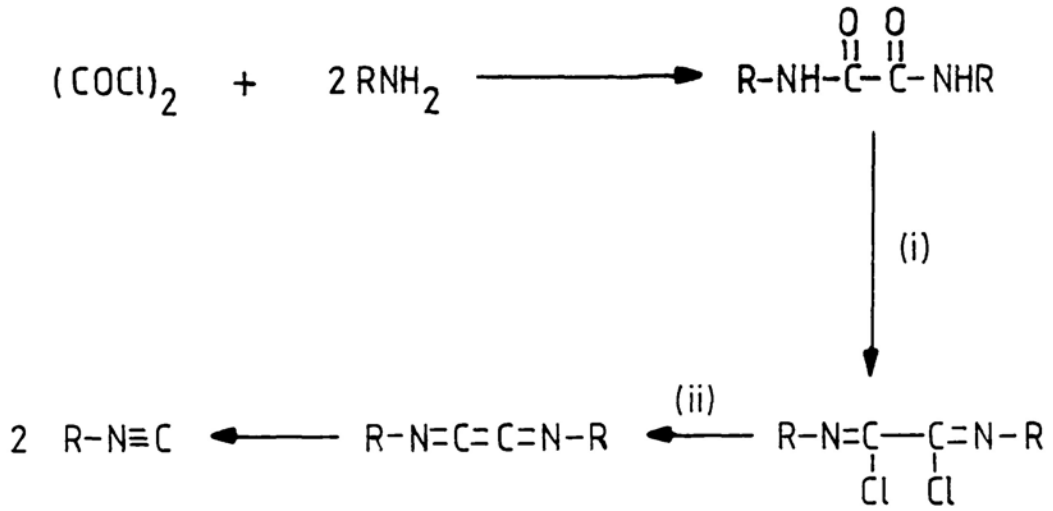
(41)



(1)

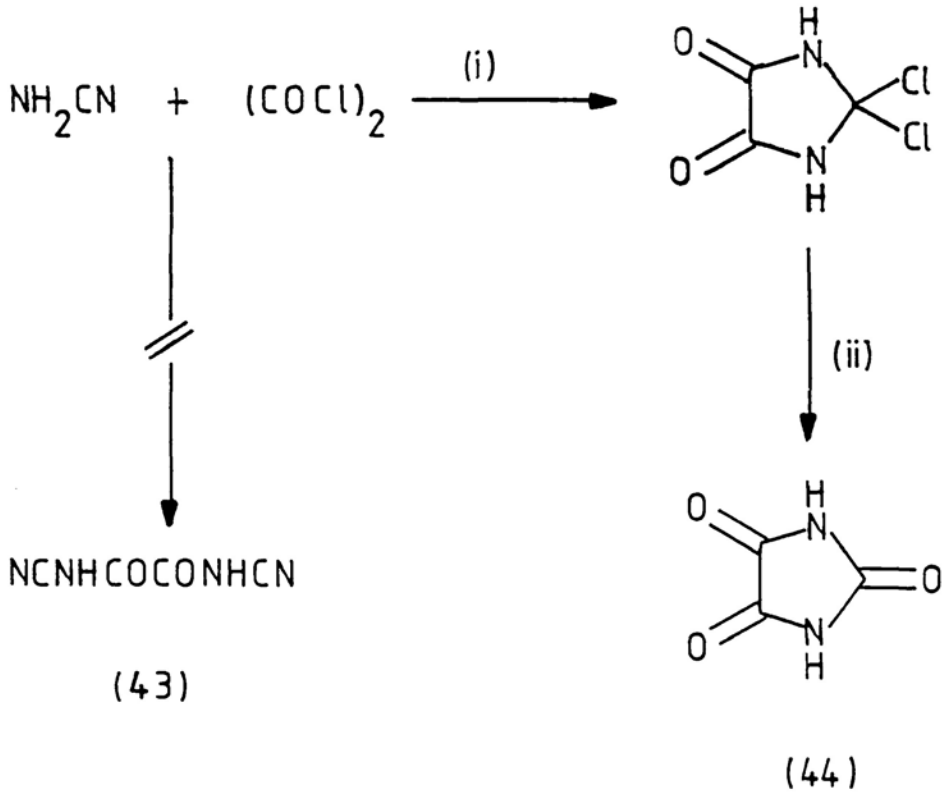
(42)

The first synthetic route to precursor (42) followed closely the existing method[40] for triene (41) as shown in Scheme 6 (R=Ph).



Scheme 6 R = Ph (i) PCl_5 (ii) Zn

If R is -CN, i.e., the amine is cyanamide, precursor (42) can hopefully also be synthesised in this way. However, the reaction of oxalyl chloride and cyanamide (R=CN) in Scheme 6 is known not to give the desired product, N,N'-dicyanooxamide (43) but parabamic acid (44).[41]



(i) dioxan, 20° (ii) moist air

This reaction was repeated and found to give the same results even if an ethereal solution of oxalyl chloride was added to an excess of cyanamide in anhydrous diethyl ether. Thus an alternative method for the first step of Scheme 6 (R=CN) was required.

The first attempt was to use monosodium cyanamide instead of cyanamide. The former was known to react cleanly with acyl chlorides to give the sodium salt of the acyl cyanamide.[42,43] When the reaction

$$2\ RCOCl + 4\ NaNHCN \xrightarrow{Et_2O} 2\ RCON(Na)CN + 2\ NH_2CN + 2\ NaCl$$

was repeated with oxalyl chloride and monosodium cyanamide in anhydrous diethylether, the presumed disodium salt (45) was filtered off and washed with anhydrous diethyl ether to remove any cyanamide formed during the reaction. Attempts to liberate sodium-free amide (43) by

$$(COCl)_2 + 4NaNHCN \xrightarrow{Et_2O\ ,\ \Delta} NCN(Na)COCON(Na)CN + 2\ NH_2CN$$

(45)

Gerlich's method,[43] viz. formation of the disilver salt (46) with silver nitrate followed by acidification with hydrogen sulphide, failed.

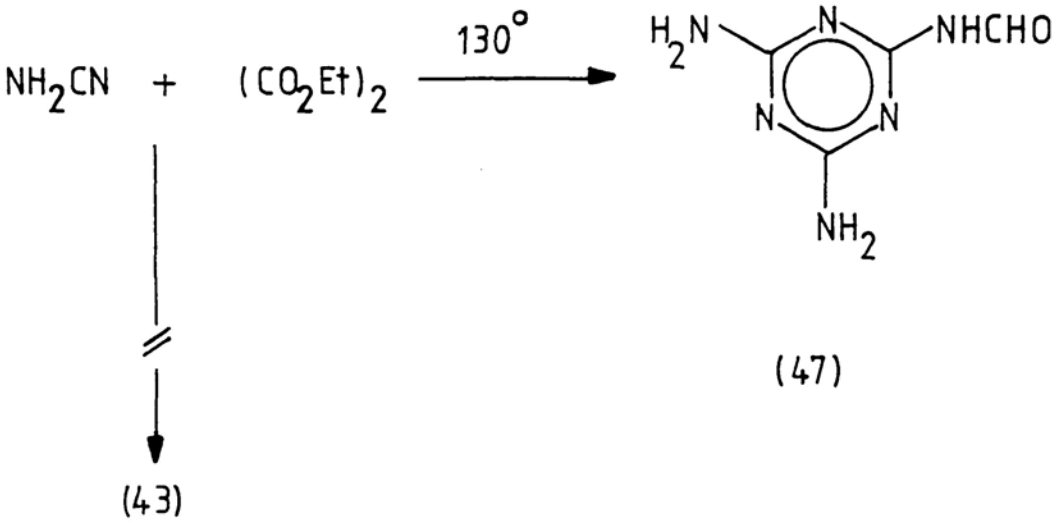
Although this method had proved satisfactory for acetyl cyanamide,[42,43] it failed to afford oxamide (43) in this case. Since this reaction is

(45) (46)

(i) $AgNO_3$, (ii) H_2S

heterogenous it is possible that formation of the disodium salt (45) had not occurred so that the filtered solid would have been only unreacted sodium cyanamide.

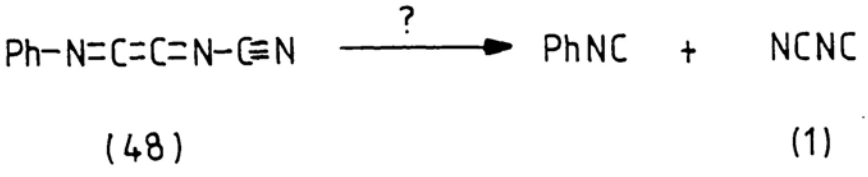
An attempt to synthesise oxamide (43) by stirring cyanamide and diethyl oxalate in ethanol at room temperature for 76 h gave no reaction. It is known that on heating at 130°C a complex reaction results in which a possible product is formylmelamine (47).[44]



(47)

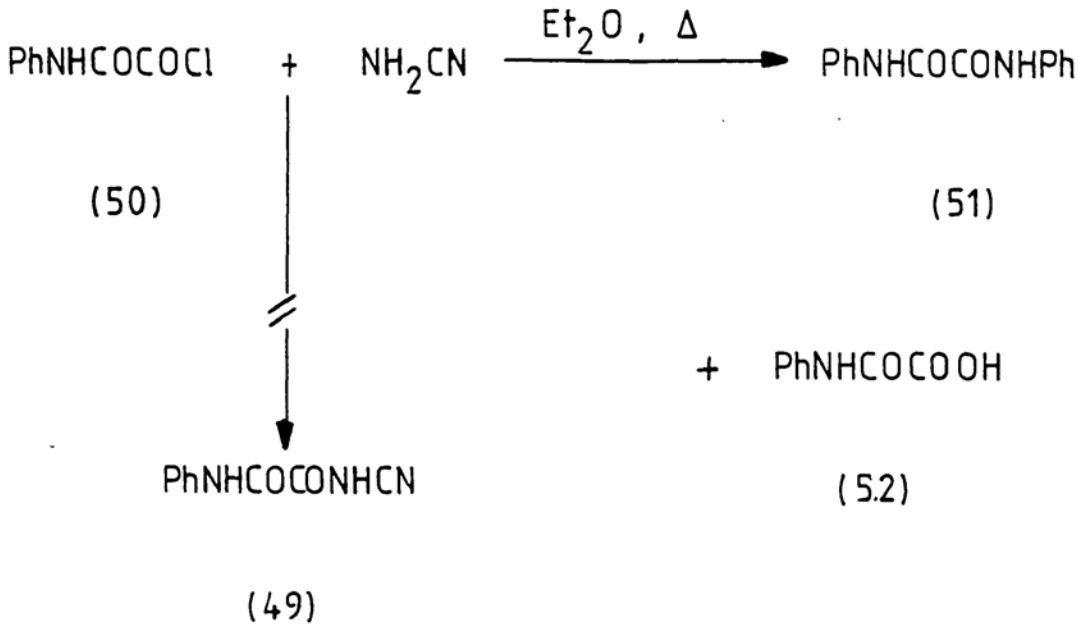
An attempted synthesis of the oxamide (43) by stirring oxamide with cyanogen bromide in anhydrous diethyl ether for 6 h at room temperature also failed. Oxamide was recovered quantitatively.

Since the synthesis of precursor (42) proved to be unsuccessful by known methods, it was felt that replacement of one of the terminal cyano groups by a phenyl group would be more successful. Thus, the intermediates should be more stable, more soluble in organic solvents and should be readily detected because of the presence of the phenyl group. The new precursor to the target (1) would be 1-phenyl-4-cyano-1,4-diazabuta-1,2,3-triene (48) which would give one equivalent of phenyl isocyanide and one equivalent of cyano isocyanide (1). The detection of the former in the final step would be indicative of success even if cyanoisocyanide (1) proved too unstable to isolate.

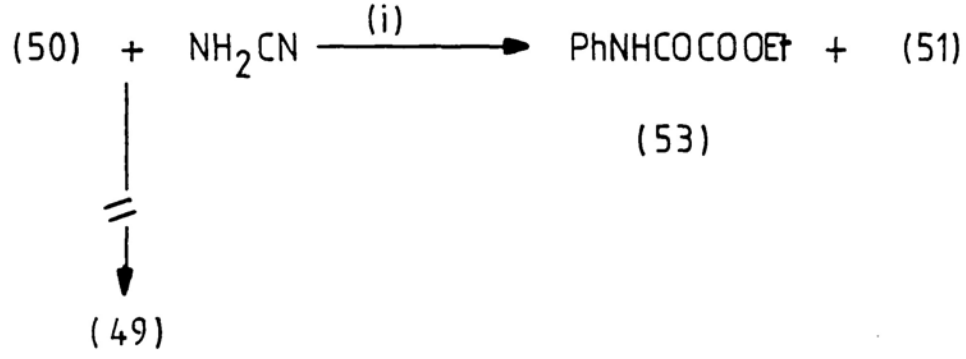


(48) (1)

The first step (Scheme 6) was to synthesise the unknown N-phenyl-N'-cyanooxamide (49). The initial attempt to synthesise oxamide (49) from oxanilic acid choride (50)[45] and cyanamide afforded two products but not the expected product (49). These two products were oxanilide (51) (15%) and oxanilic acid (52) (56%).



If chloroform was used as the solvent for the above reaction, oxanilic acid ether ester (53) (63%) and oxanilide (51) (8%) were obtained but again no oxamide (49).



(i) $NaHCO_3$, $CHCl_3$

The ester (53) was presumably formed from the 1% ethanol used to stabilise chloroform.

Reaction of the ester (53) with cyanamide in the presence of sodium ethoxide as base in absolute ethanol afforded after 15 min at room temperature a high melting solid (m.p. > 300°C) with no nitrile stretching in the ir spectrum.

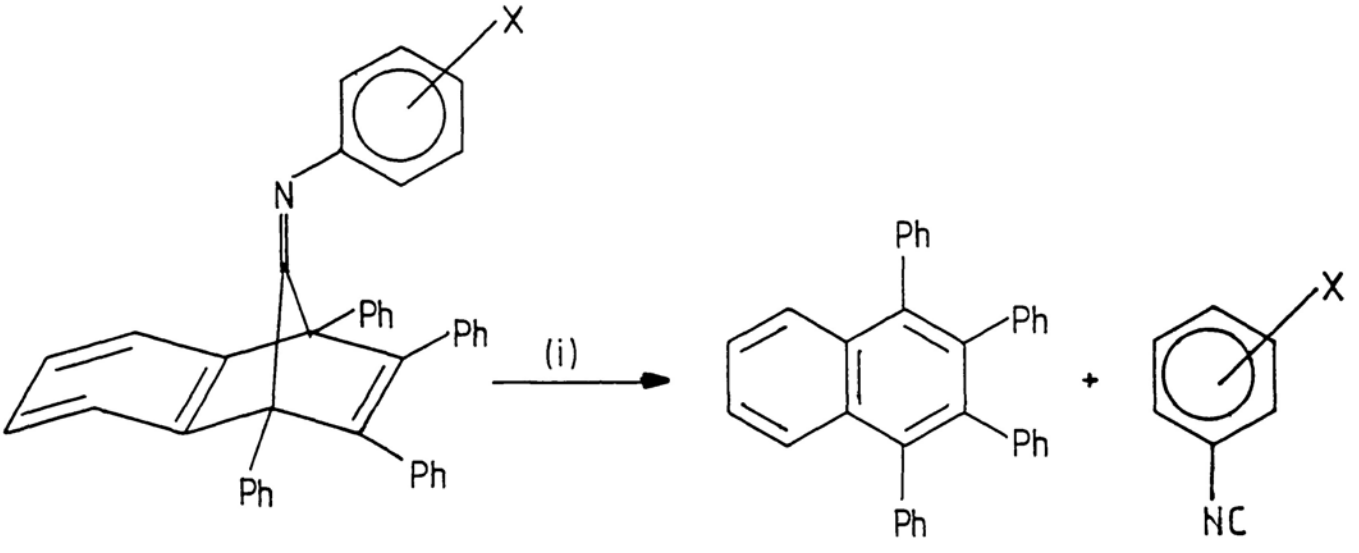
Since cyanamide did not give the desired product, monosodium cyanamide was used in the reaction with oxanilic acid chloride (50).

$$(50) + 2\,NaNHCN \xrightarrow{Et_2O} \underset{(54)}{PhNHCOCON(Na)CN} + NH_2CN + NaCl$$

A solid, presumed to be the monosodium salt (54) was obtained as before. Since Gerlich's method[43] for liberation of the amide failed in previous attempts, a new and different method according to Brigl[46] using tartaric acid was tried. Unfortunately, this method failed too, to give the 'free' cyanamide (49). This approach from 1,4-diaza-buta-1,2,3-trienes was therefore abandoned.

3.2.2.2. Extrusion from 7-cyanoimino-1,2,3,4,5-pentaphenylbicyclo[2.2.1]-hept-2-ene (58a).

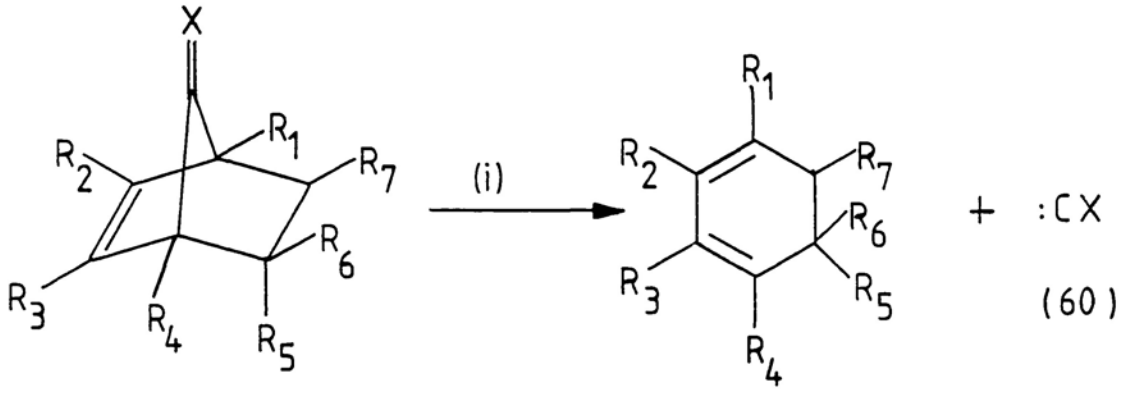
A new method for the synthesis of isocyanides by the decomposition of 9-(substituted phenylimino)-1,4-dihydro-1,2,3,4-tetraphenyl-1,4-methanonaphthalenes (55) was reported by Atkinson and Harger.[47] The thermolysis of (55) in toluene at 120°C resulted in elimination of aryl isocyanides (56) and the other very stable product, 1,2,3,4-tetraphenyl-naphthalene (57).



(55) (57) (56)

(i) 120°, toluene X=H, p-OMe, p-Me, p-Cl, p-CO_2Et, o-Me

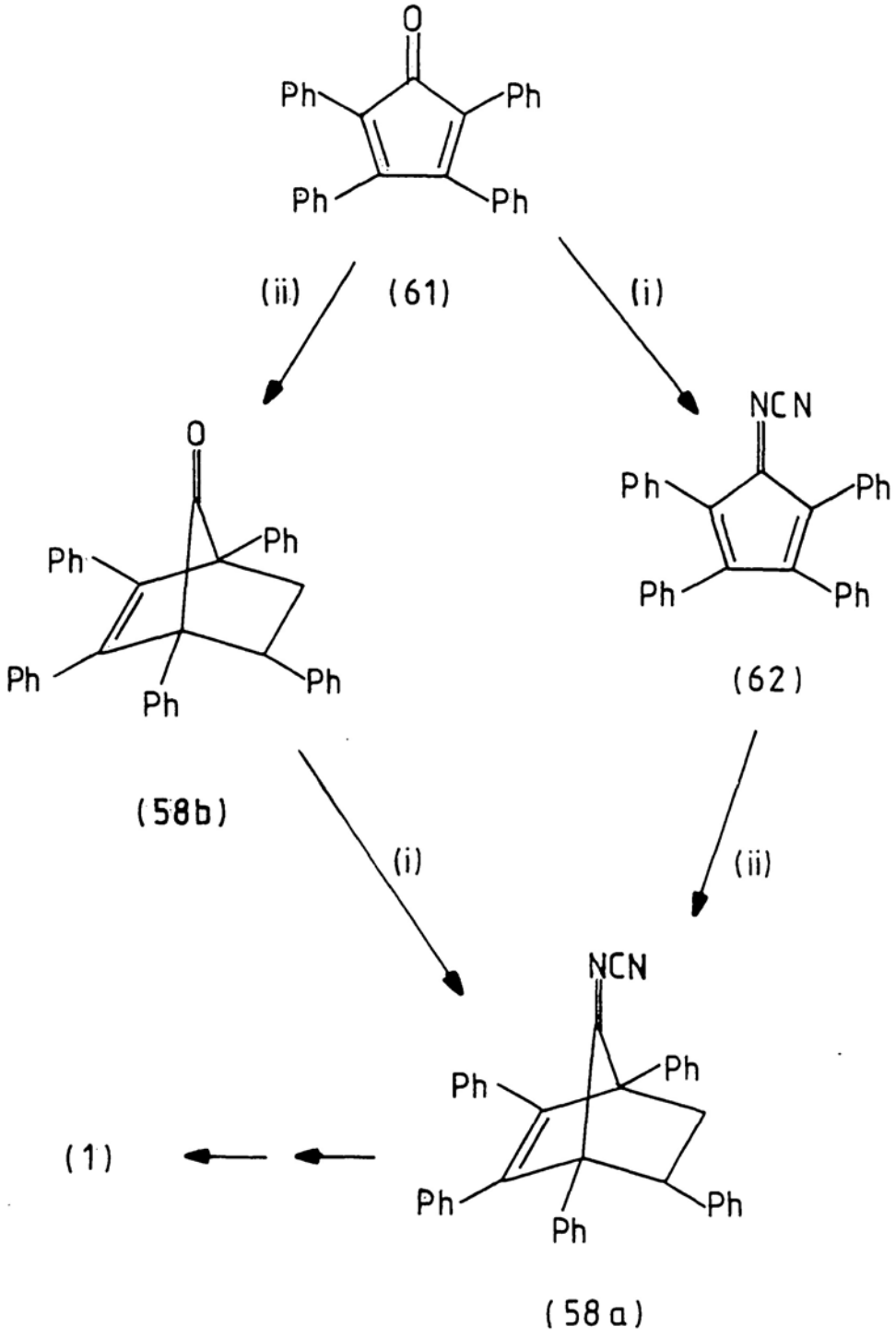
This suggests another possible approach to the synthesis of cyano-isocyanide (1) by dehydrogenation and/or thermolysis of a suitable precursor (58) giving an inert by-product, a pentasubstituted dihydro benzene or benzene (59), and the target (60) (1; X = NCN). The decomposition at high temperatures of bicyclo-[2.2.1.]-hepten-7-ones (58b; X = O, R_6, R_7 = H) is well known for the extrusion of carbon monoxide.[48]



(58) (59)

(i) Δ, $R_6 = R_7 = H$ or $R_6 = R_7 = \pi$ bond

The proposed scheme for the synthesis of precursor (58a, X = NCN) by two routes, A and B, is outlined in Scheme 7.



Scheme 7 (i) NH_2CN (ii) styrene

The first route, A, was the condensation of tetracyclone[49] (61) with cyanamide followed by the Diels Alder reaction with styrene to give the precursor (58a).[50] The second route, B, is the reverse in this sequence.

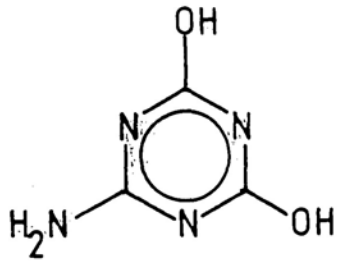
The attempted condensation of tetracyclone with cyanamide in Route A failed using the following conditions.

(a) concentrated sulphuric acid (catalytic amount) in dioxan under reflux for 1 h.

(b) concentrated sulphuric acid (catalytic amount) in benzene azotrope for 3 h.

(c) glacial acetic acid (catalytic amount) in dioxan under reflux for 24 h.

Tetracyclone was recovered quantitatively in all the above conditions. Concentrated sulphuric acid was found to be the wrong choice of acid although it was successfully used by Sonntag[51] for other condensation reactions with tetracyclone. Cyanamide reacts with concentrated sulphuric acid to give ammelide (63).[52]



(63)

Even if ammelide (63) was the amine present for condensation instead of cyanamide, no Schiff base was obtained since the tetracyclone (61) was recovered quantitatively in each of the three different conditions.

There was no reaction even when glacial acetic acid was used. This acid does not react with, but stabilises cyanamide.[52] Route A in Scheme 7 was therefore abandoned.

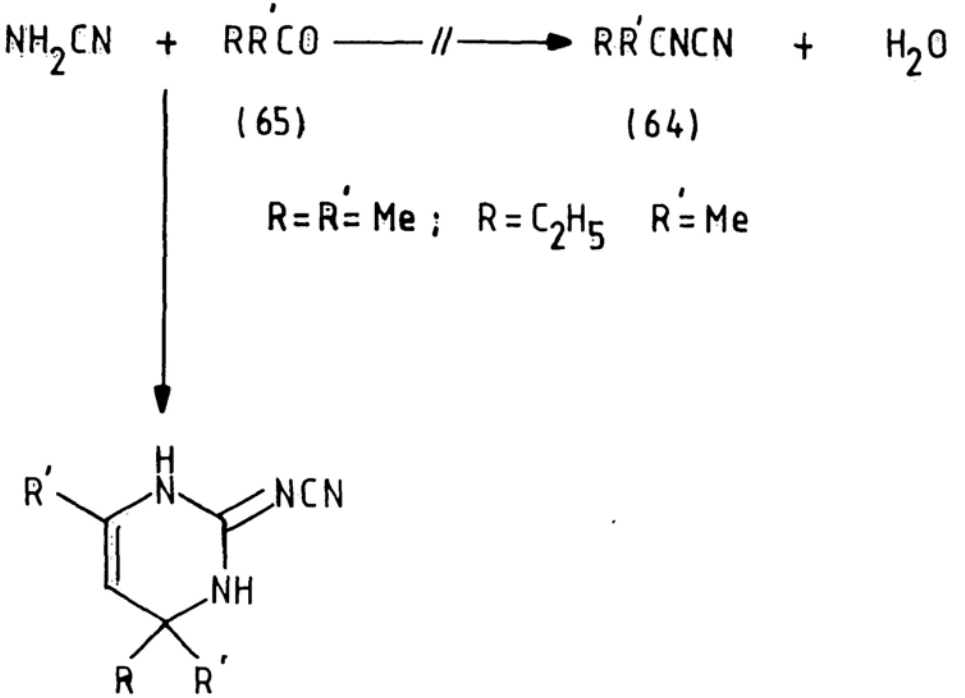
The second route, B, was attempted with the advantage that the adduct (58b) was a known compound and had a normal ketone carbonyl reactive towards nucleophiles. Tetracyclone (61) has a positively charged oxygen in the carbonyl and its reactivity is altered from 'true' carbonyl groups. 1,2,3,4,5-Pentaphenylbicyclo[2.2.1.]-2-hepten-7-one (58b)[50] was synthesised easily from tetracyclone and styrene in anhydrous benzene under reflux for 24 h. The following conditions for condensation of (58b) with cyanamide were attempted but all failed.

(a) in dichloromethane under reflux for 72 h

(b) in dioxan under reflux with a catalytic amount of glacial acetic acid and magnesium sulphate for 24 h

(c) in dioxan under reflux with a catalytic amount of PTSA for 24 h.

The ketone was recovered quantitatively in all three conditions. The failure of both these routes, A and B, was the condensation. Cyanamide was probably the wrong choice of amine for the condensation. The amino group is much more acidic than normal amines due to the electron withdrawing cyano group. When cyanamide reacts with aldehydes, particularly lower aldehydes, the addition compounds formed will polymerise readily to give resinous products.[53] The earlier reported reaction of cyanamide with ketones to give alkylidene cyanamides (64)[54,55] was showed to be incorrect. A later paper[56] suggested that the correct structure for the product of the reaction of ketones (65) with cyanamide to be 2-cyano-1,2,3,4-tetrahydropyrimidines (66).

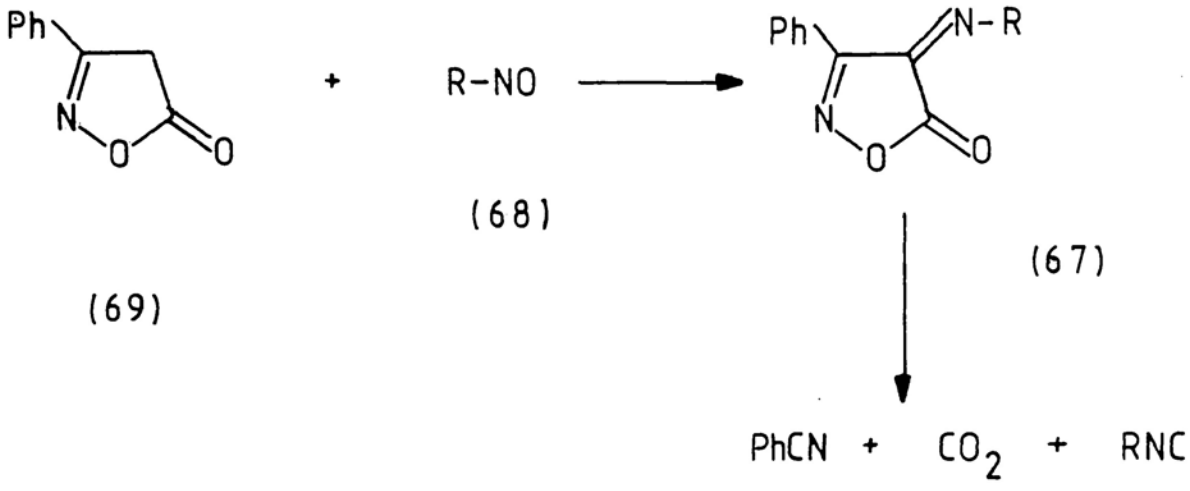


(66)

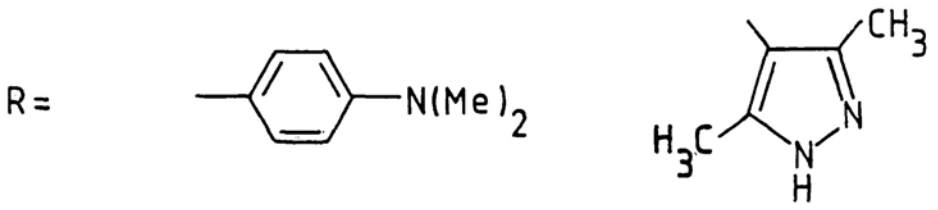
R=R'=Me ; R=C_2H_5 , R'=Me

3.2.2.3. Fragmentation of 3-phenyl-4-cyanoimino-isoxazol-5-(4-H)-one (70).

Wentrup[57] had recently reported a new synthetic method for the preparation of aryl and heteroaryl isocyanides. 3-Phenyl-4-(substituted imino)isoxazol-5(4H)-ones (67), easily obtained by condensation of a nitroso compound (68) with 3-phenylisoxazol-5(4H)-one (69),[58] decompose at between 90° to 110°C with the formation of benzonitrile, carbon dioxide and an isocyanide.

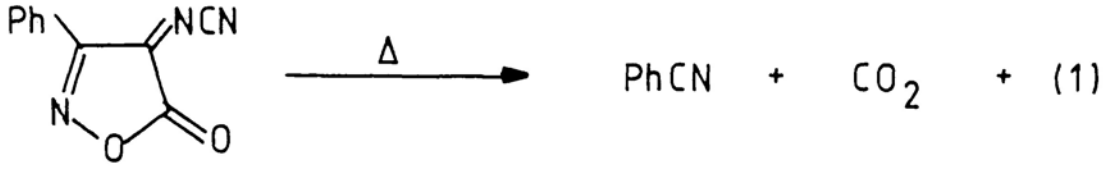


Isocyanides (e.g., 67a, 67b) were obtained in near quantitative yields.



(67a) (67b)

By analogy, with R = CN (70), our target compound (1) could be synthesised in the same way, with the very inert benzonitrile and carbon dioxide as by-products.



(70)

The required precursor, 3-phenyl-4-cyanoimino-isoxazol-5(4H)-one (70), is unknown. One proposed route to this precursor (70) was from 3-phenyl-4-oximino-isoxazol-5(4H)-one (71)[59] which can be easily prepared by nitrosation of the parent (69). It was hoped that nucleophilic attack

by cyanamide on the 4-position of the oxazol-4(4H)-one (71) to displace hydroxylamine would take place. Reactions of the oxime (71) with cyanamide or monosodium cyanamide failed to afford the precursor (70) but gave either polymeric material or a complex mixture without any identified products under the following conditions.

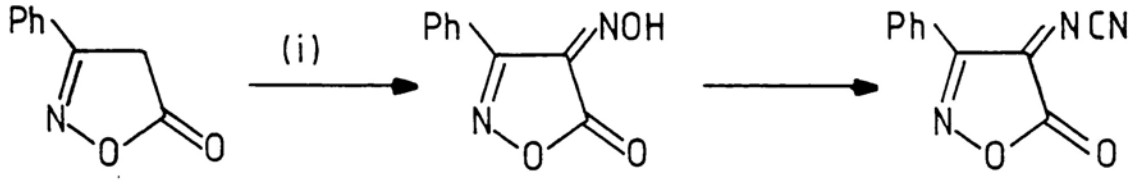
(a) with cyanamide (1 eqv.) under reflux in THF for 48h.

(b) with excess cyanamide under reflux in THF for 15 h.

(c) with cyanamide (1 eqv.) and PTSA (catalytic amount) under reflux in THF for 48 h.

(d) with monosodium cyanamide (1 eqv.) under reflux in THF for 48 h.

(e) with monosodium cyanamide (1 eqv.) and PTSA (catalytic amount) under reflux in THF for 48 h.



(69) (71) (70)

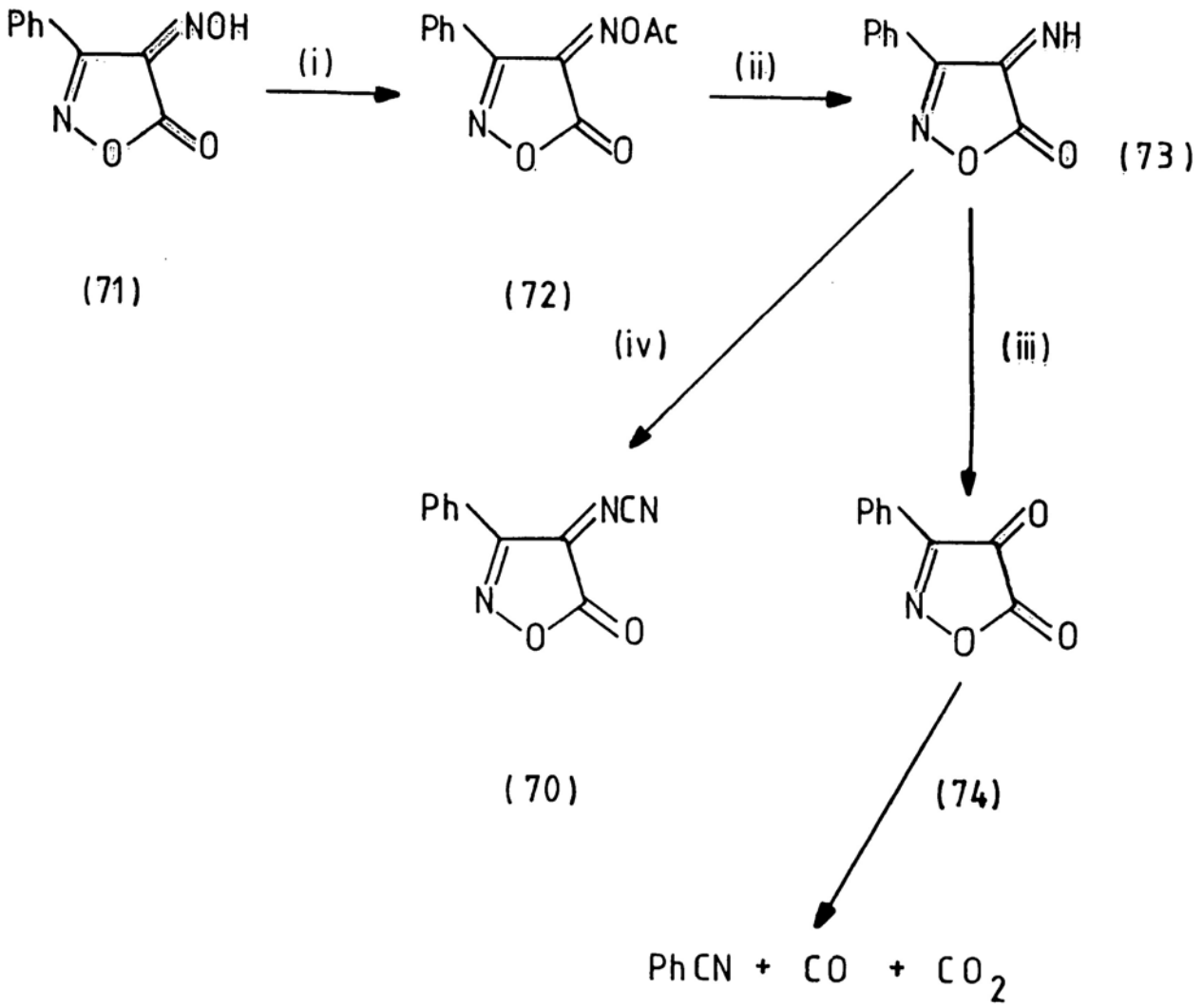
Scheme 8 (i) HNO_2

3-Phenyl-4-*O*-acetyloximino-isoxazol-5(4*H*)-one (72) was synthesised from the oxime (71) with acetic anhydride. It is known that treatment of *O*-acetyloximes with chromium(II) acetate in anhydrous THF[60] can cause fission of the weak N-O bond to give an imine. The latter, if obtained, on treatment with cyanogen bromide could afford the desired precursor (70) by a von Braun type of reaction. However, there is another N-O bond in the heterocyclic ring, so that fission of one or both of the N-O bonds may occur. A further problem in this route is that the desired imine (73) may be hydrolysed to give the ketone (74). In this case, Wentrup has shown that 3-phenyl-isoxazol-4,5-dione (74) breaks down very easily to benzonitrile, carbon monoxide and carbon dioxide. However, this latter problem may be overcome provided the conditions remain anhydrous.

The reaction of the *O*-acetyloxime (72) with chromium(II) acetate[60] and attempted reaction with cyanogen bromide on the imine (73) generated, failed to give the required precursor (70). The products isolated from the reaction were benzonitrile (1%), possibly from dione (74), and other unidentified products. Timms and Wildsmith[61] had used aqueous titanium(III) chloride successfully on oximes (*e.g.*, erythromycin oxime and methyl mesityl ketoxime) to give the imines and the latter were stable enough to be isolated. They also claimed that this method is better than the chromium(II) acetate method because

(a) the reaction proceeds readily with oximes themselves and thus prior acetylation is not necessary,

(b) the reaction is usually carried out at room temperature and is complete in 1 h,



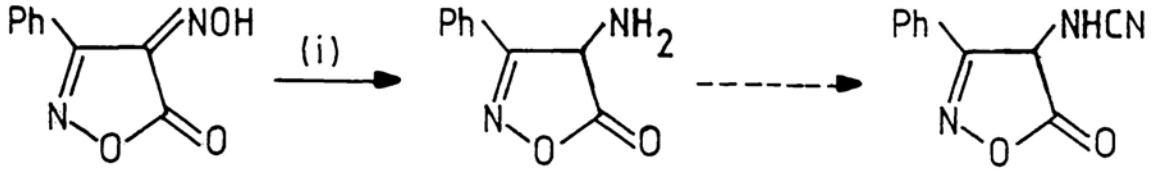
Scheme 9 (i) Ac_2O (ii) $Cr(OAc)_2$ (iii) H_2O (iv) BrCN

(c) the reaction is successful in cases where the chromium(II) acetate method fails,

(d) commercially available $TiCl_3$ solution may be used and the reaction can be followed by the loss of the dark colour of Ti^{3+} complexes.

However, treatment of our oxime (71) with aqueous $TiCl_3$ gave a very complex mixture with no loss of the dark colour of the Ti^{3+} complex. This route to the precursor (70) from the oxime (71) was therefore abandoned.

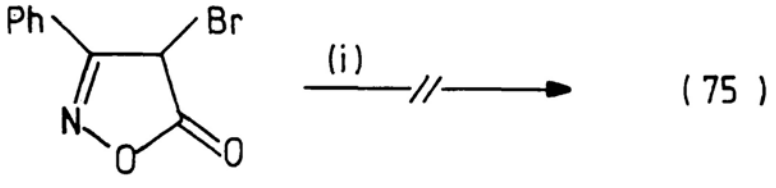
Since the easy oxidation of a cyanoamino functionality to a cyano-imino one can be envisaged it was decided to synthesise 3-phenyl-4-cyanoamino-isoxazol-5(4H)-one (75). The first attempt to (75) was via the 3-phenyl-4-amino-isoxazol-5(4H)-one (76) by cyanation, but reduction[62] of the oxime (71) to the amine (76) with tin and hydrochloric acid always gave a complex mixture.



(71) (76) (75)

(i) Sn / HCl

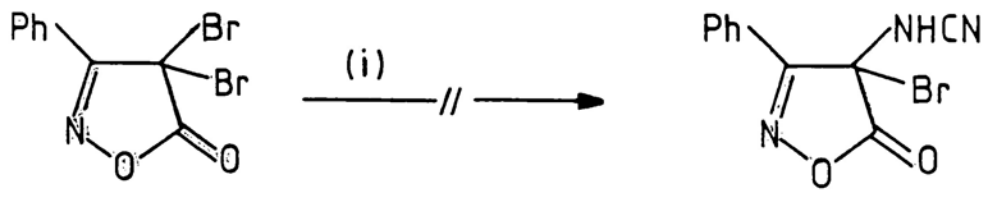
Alternatively, displacement of halide in the 4-position of the isoxazol-5(4H)-one ring by cyanamide or its derivatives might lead to the formation of 4-cyanoamino (75). Bromination[63,64] of (69) provided 3-phenyl-4-bromo- or 4,4-dibromo-isoxazol-5(4H)-one, (77) and (78) respectively, depending on the amount of bromine used. Reaction of 4-bromo (77) with either cyanamide or monosodium cyanamide in THF under reflux for 96 h gave a complex mixture including a trace of benzonitrile (detected by tlc).



(77)

(i) NH_2CN, THF, Δ, 96h

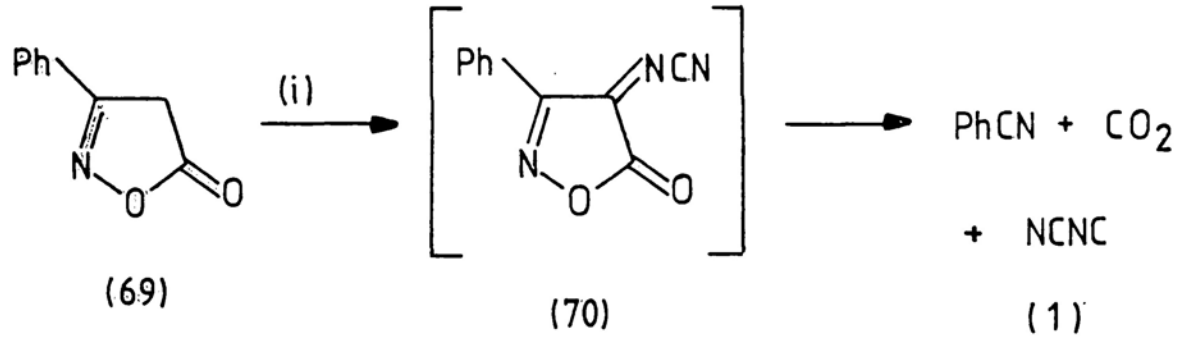
Attempted synthesis of 3-phenyl-4-bromo-4-cyanoamino-isoxazol-5(4H)-one (79), another possible precursor, to (70), from dibromide (78) with cyanamide in THF under reflux for 96 h also gave a complex mixture.



(78) (79)

(i) NH_2CN , THF , Δ , 96h

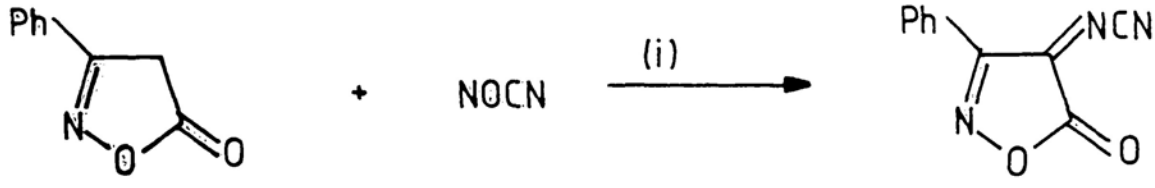
Recently Kemp[65] had reported a new method for generating cyanonitrene from cyanamide and iodosobenzene diacetate in dichloromethane or diethyl ether. It was hoped that the cyanonitrene would insert into the acidic protons in the 4-position of isoxazol-5(4H)-one (69). Attempted reaction of (69) with cyanamide and iodosobenzene diacetate in anhydrous dichloromethane at 30°C for 0.5 h gave benzonitrile (62.5%). This indicated that the heterocyclic ring had fragmented under these reaction conditions. A possible explanation for this was competitive oxidation of (69) to the dione (74) which had decomposed. This seems unlikely since Kemp[65] did not obtain DMSO or triphenylphosphine oxide when dimethylsulphide or triphenylphosphine was treated with cyanonitrene



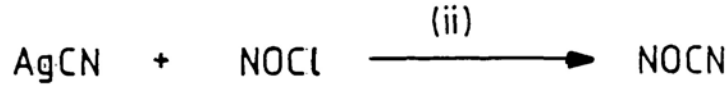
(i) NH_2CN , (PhIOAc)(OAc) , CH_2Cl_2 , 30° , 0·5h

generated under these conditions. A blank experiment carried out under identical conditons without cyanamide failed to provide benzonitrile. Tlc and ir spectrum of the reaction mixture showed starting materials only. This suggests very strongly that the precursor (70) was formed but it was unstable under these reaction conditions and fragmented to give benzonitrile.

Since all the synthetic routes to the precursor (70) starting from 4-mono or disubstituted isoxazol-5(4H)-one had failed, it was decided that the original Wentrup route using the condensation of isoxazol-5(4H)-one (69) with a nitrosyl compound should be investigated. In our case, the required nitrosyl compound is nitrosyl cyanide[65,66,67] a highly reactive blue-green gas at -25° generated from silver cyanide and nitrosyl cyanide.



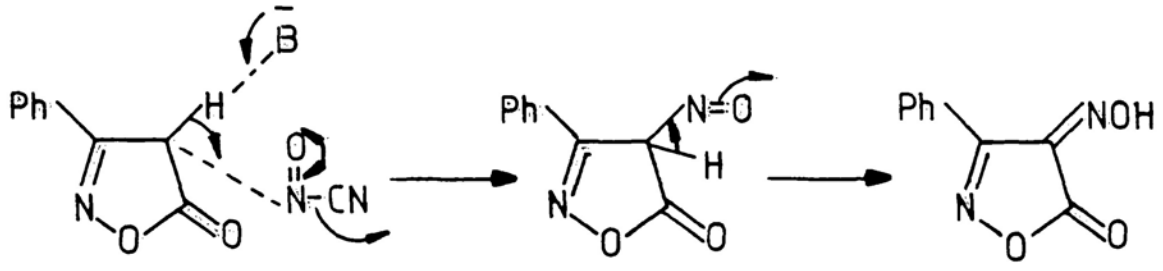
(69) (70)



(i) base (ii) -78° to -25°, $CHCl_3$

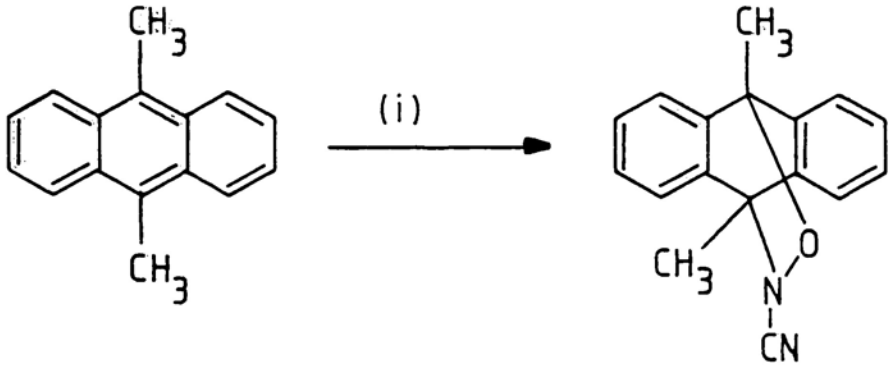
There is of course, the possibility that the condensation with nitrosyl cyanide may not give the desired products (70) but the oxime (71) instead by elimination of hydrogen cyanide rather than water.

Attempted condensation of heterocycle (69) with nitrosyl cyanide generated *in situ* failed to provide the product (70) but gave a complex mixture on five occasions. The generation of nitrosyl cyanide *in situ*[67,68] from silver cyanide and nitrosyl chloride seemed unsatisfactory since it is known that impurities such as nitrosyl chloride, hydrogen cyanide,



(69) (71)

water and considerable amounts of cyanogen chloride, nitric oxide and nitrogen dioxide are always present,[64,69] and these can lead to formation of troublesome by-products. Kirby[69] stated that purification on a small scale for spectroscopic studies can be carried out readily by vacuum line techniques. However, this is inconvenient for preparative work and may be hazardous. Kirby had observed rapid decomposition of impure nitrosyl cyanide in the condensed state and explosions may occur, expecially on bulb-to-bulb distillation. An alternative method of generating nitrosyl cyanide was devised by Kirby.[69,70] Treatment of 9,10-dimethylanthracene (DMA) with the impure gas gave the expected [$\pi_4 + \pi_2$] adduct (80). This adduct (80) was readily chromatographed and recrystallised. Samples have been stored at room temperature for extended periods without decomposition. However, the reversal of the



(80)

(i) NOCN

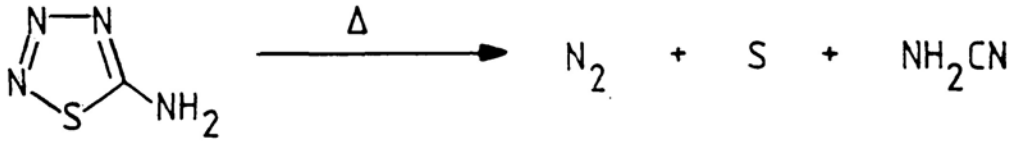
Diels-Alder reaction with the regeneration of DMA was achieved in refluxing benzene (80°) and the rapid and quantitative transfer of nitrosyl cyanide on to a number of diene substrates were observed.[68]

Attempts to repeat the Diels-Alder reaction using DMA and nitrosyl cyanide generated <u>in situ</u> consistently gave a very complex mixture (> 15 spots on tlc) and it was impossible to isolate the adduct (80).

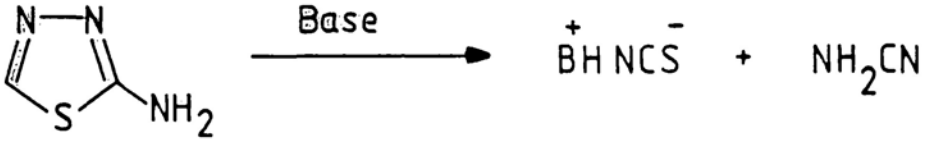
3.2.3. Approach III.

3.2.3.1. Extrusion/fragmentation in 1,2,3,4,5-pentaphenyl bicyclo[2.2.1]-hept-2-ene-7-one (58c) anils.

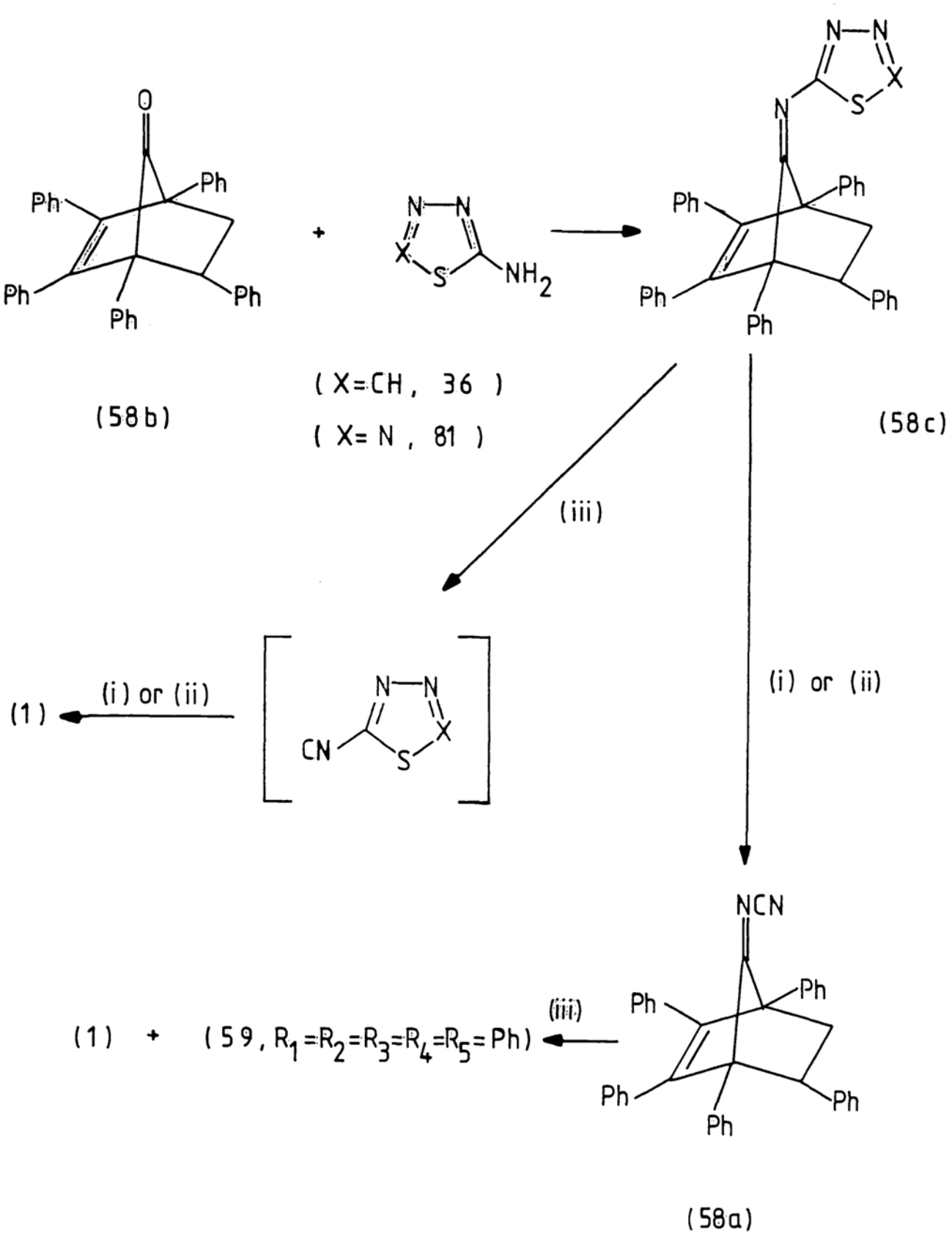
Since the two routes A and B to synthesise the precursor (58a) in Approach II failed, mainly because of the special reactivity of cyanamide, it was decided to use a heterocycle containing the cyanamide fragment as a 'masked' cyanamide. Thus cyanamide could be released by thermal decomposition of 5-amino-1,2,3,4-thiatriazole (81)[71,72,73] or by base-induced fragmentation of 2-amino-1,3,4-thiadiazole (36).[28,29]



(81)



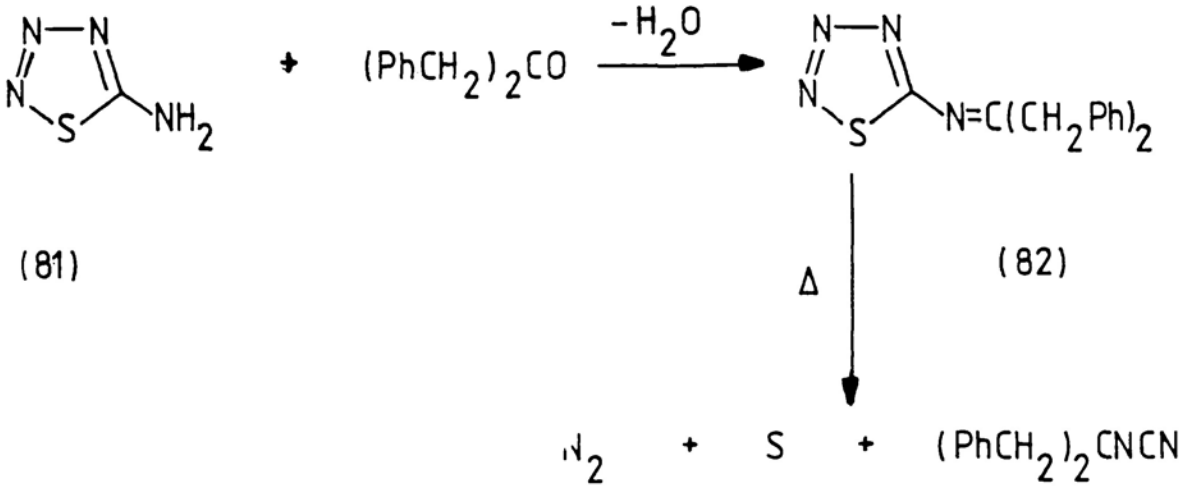
(36)



(i) Δ, (X = N) (ii) base, (X = CH) (iii) Δ

Although condensation reactions of the amine (81) with aldehydes or ketones are unknown, this amine (81) should be more nucleophilic than cyanamide. The other amine (36) is known to react with aldehydes[74,75] but not with ketones. The general scheme to the synthesis of the target (1) is represented over.

1,3-Diphenylacetone was chosen as a model ketone for trial condensation with both amines (36) and (81) to obtain optimum conditions. Attempted condensations of 1,3-diphenyl acetone with amine (81) failed to give the desired Schiff base (82) under the conditions listed below.



(a) with titanium(IV) chloride (1.5 eqv.) in THF at 60° for 12 h[76]

(b) stirred over potassium hydroxide pellets in THF overnight[77]

(c) shaken with ground activated molecular sieves (5A) in cyclohexane at room temperature for 24 h[78]

(d) shaken with ground activated molecular sieves (5A) in THF for 18 h[78]

(e) azeotroped in benzene with a catalytic amount of PTSA for 4 h

(f) under reflux in THF over dry magnesium sulphate for 24 h

(g) in anhydrous pyridine at 45° over dry magnesium sulphate for 24 h.

1,3-Diphenyl acetone was recovered almost quantitatively in all seven cases. Sulphur was obtained in methods (a) to (f) and cyanamide from method (g), probably from fragmented amine (81). This suggested that the amine (81) was too unstable for formation of the Schiff base (82).

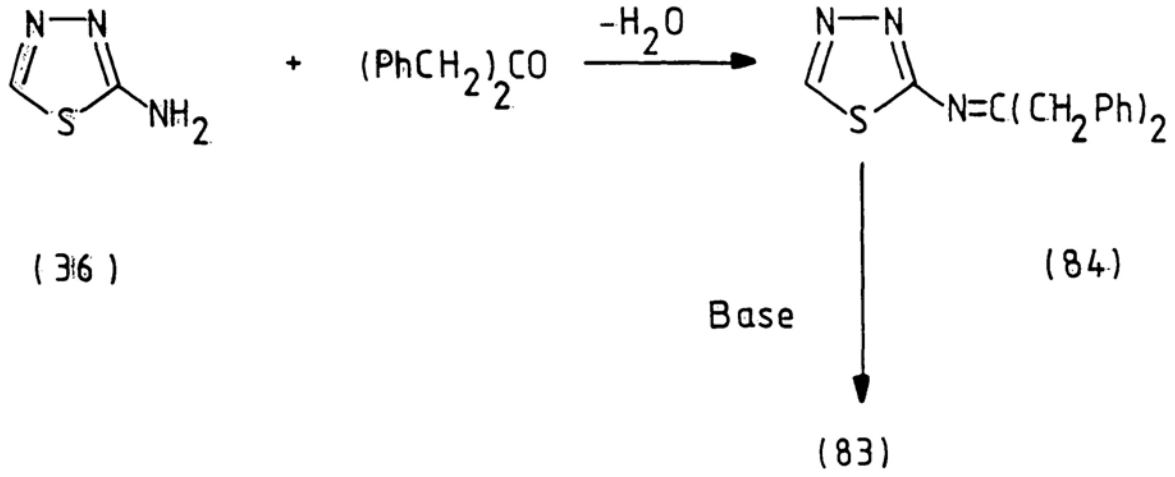
This led to the attempted condensation of 1,3-diphenyl acetone with the amine (36). The following reaction conditions were used but failed to provide the Schiff base (84).

(a) with titanium(IV) chloride (1.5 eqv.) in benzene[76]

(b) under reflux in pyridine over dry magnesium sulphate for 48 h

(c) azeotroped in benzene with a catalytic amount of PTSA for 18 h

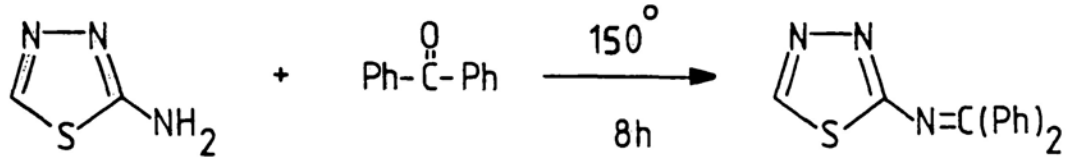
(d) with triphenylphosphine and DEAD under reflux in THF for 48 h[79,80]



(36) (84) (83)

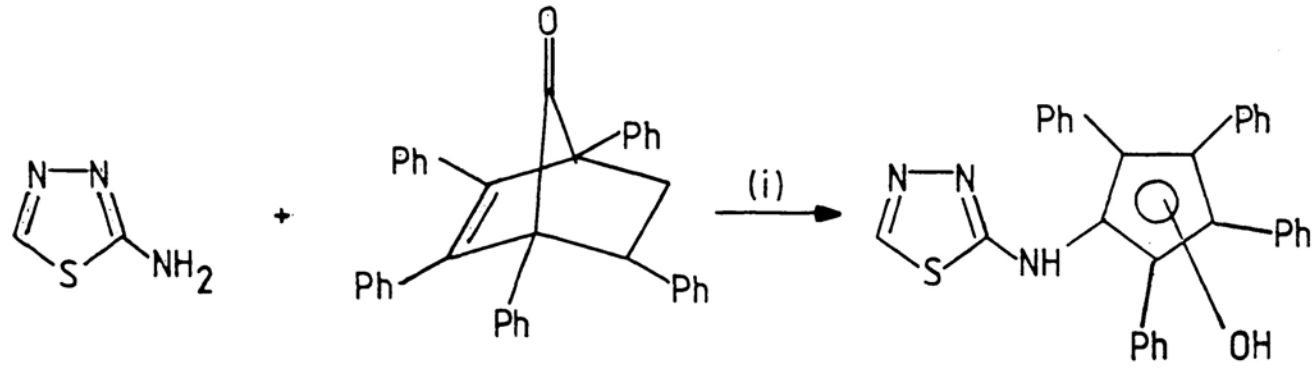
In all cases a complex mixture was formed from which only 1,3-diphenyl acetone was recovered in near quantitative amounts.

Since all the above methods for the condensation failed, amine (36) and benzophenone were heated at 150° for 18 h. A product, formed in very low yield (4%), was identified as the Schiff base (85) from ir, pmr and mass spectral evidence. The other compounds isolated were a yellow unidentified solid (2%) and unreacted benzophenone (50%). The remaining residue in the reaction mixture was polymeric material.



(36) (85)

Since the model systems failed to provide any information on the conditions for condensation, the last attempt was to carry out the condensation of the actual ketone (58b) with amine (36) using the titanium(IV) chloride method.[76] Three attempts at this condensation consistently gave a complex mixture.



(36) (58b) (86)

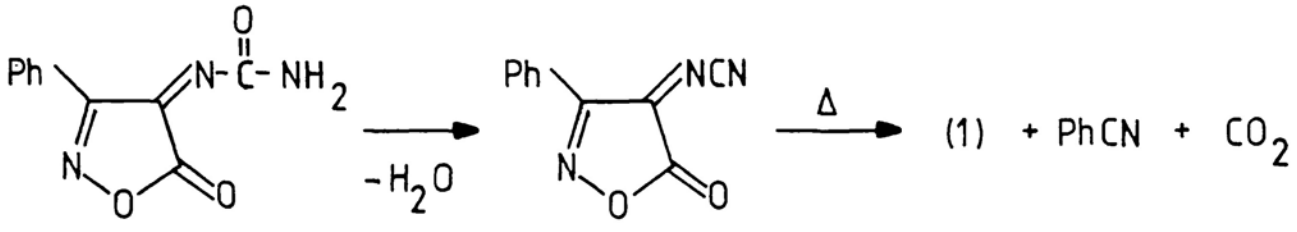
(i) $TiCl_4$, C_6H_6

In the last attempt, two solids and a yellow oil were isolated. The yellow oil and one of the solids were unidentified. The structure (86) was proposed for the other yellow solid (18%) on the basis of the ir spectrum where there was an NH at 3540 cm^{-1} and a hydrogen bonded OH at

3250 cm^{-1} (broad). The pmr spectrum showed aromatic protons only (δ 7.75) as a multiplet. The other protons on the thiadiazole ring, NH and OH groups could not be observed probably overshadowed by the twenty aromatic protons. The mass spectrum showed a molecular ion (M^+) at 486. The position of the hydroxyl group in (86) is uncertain. No further reactions were carried out on this compound and this route was abandoned.

3.2.3.2. Fragmentation/dehydration of 3-phenyl-4-carbamoylimino-isoxazol-5(4H)-one (87).

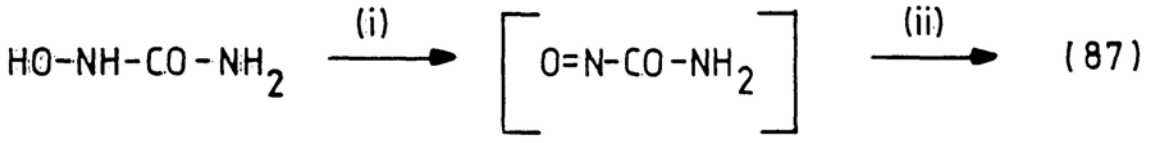
A modification of the Wentrup-nitrosyl cyanide route[57] would be to 'mask' the cyano group as an amide. Thus, dehydration of 3-phenyl-4-carbamoylimino-isoxazol-5(4H)-one (87) may lead to the precursor (70) sought earlier.



(87) (70)

The amide (87) could be envisaged to come from oxidation of hydroxyurea (88) to the unknown, perhaps unstable, C-nitrosoformamide (89) followed

by condensation of the latter with isoxazol-5(4H)-one (69) to afford the desired product (87).

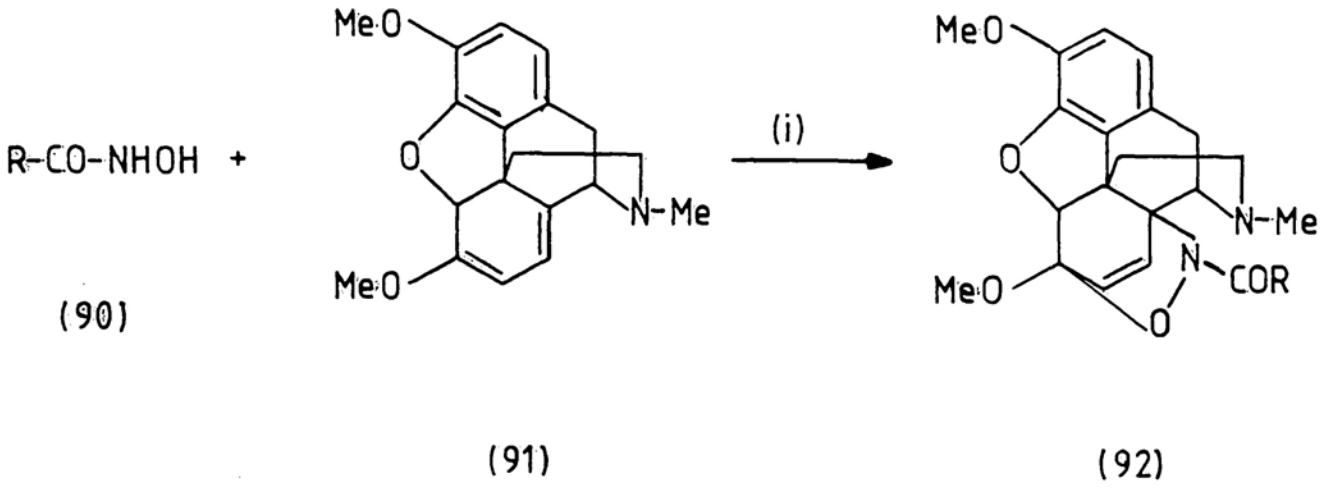


(88) (89)

(i) $Et_4\overset{+}{N}I\overset{-}{O}_4$ (ii) (70), base

Hydroxyurea (88)[81] can be easily prepared in high yield from urethane and hydroxylamine hydrochloride in aqueous sodium hydroxide. Kirby[69] had shown that addition of benzo- or aceto-hydroxamic acid (90) (R = Ph and Me respectively) at 0° to a solution of thebaine (91) and tetraethylammonium periodate gave the corresponding adduct (92) in high yield. This tetraethylammonium periodiate was used to oxidise hydroxyurea (88).

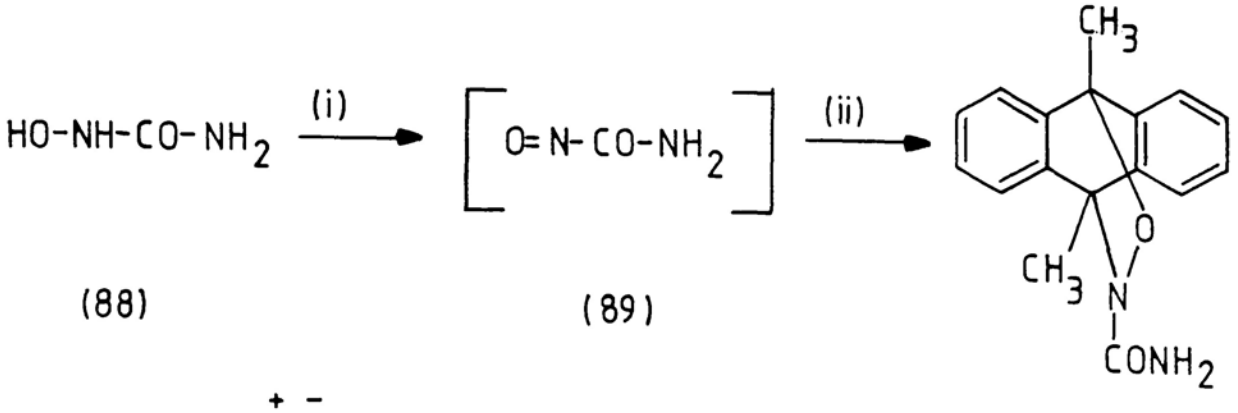
Treatment of hydroxyurea (88) with tetraethylammonium periodate[82] followed by condensation with isoxazol-5(4H)-one (69) using Wentrup's method[57] gave a very complex mixture. It was therefore decided to use DMA



(i) $Et_4\overset{+}{N}I\overset{-}{O_4}$

to trap C-nitrosoformamide (89), if generated, to give the corresponding adduct (92) since thebaine (91) was not available.

Attempts to obtain the adduct (93) failed and DMA was recovered almost quantitatively. This route was abandoned. It is not certain whether the nitroso compound (89) was generated or whether the adduct was too unstable to be isolated.



(88) (89)

(i) $Et_4\overset{+}{N}I\overset{-}{O_4}$ (ii) DMA

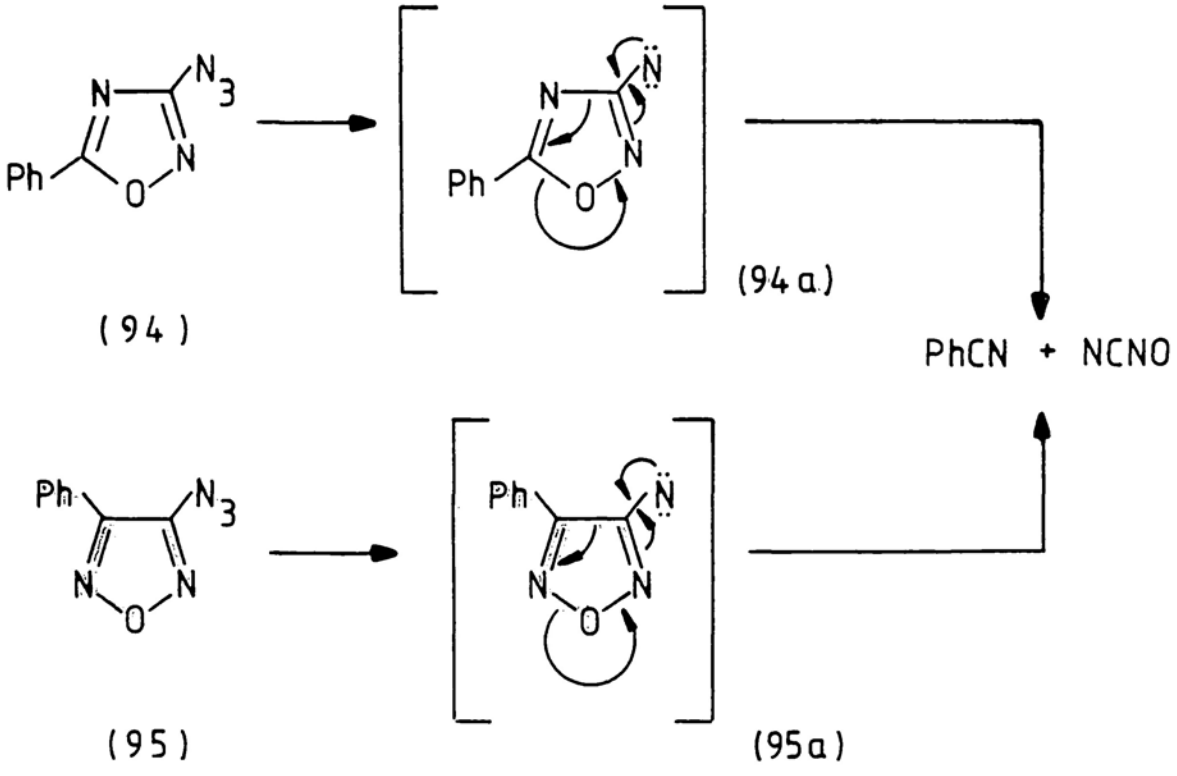
(93)

4.0. SYNTHESIS AND REACTIONS OF SOME FIVE-MEMBERED-RING HETEROCYCLIC AZIDES

4.0. SYNTHESIS AND REACTIONS OF SOME FIVE-MEMBERED-RING HETEROCYCLIC AZIDES.

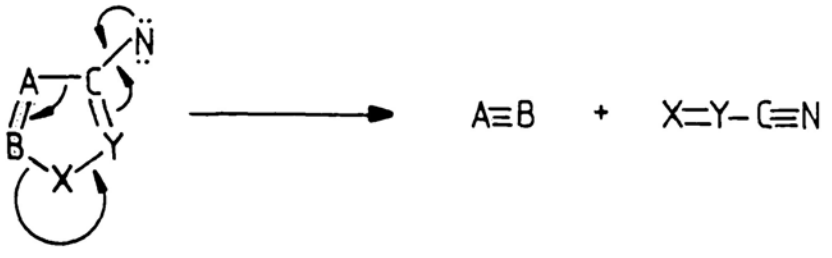
4.1. Introduction.

Since the synthesis of nitrosyl cyanide by Kirby's method[70] proved to be extremely difficult and other approaches to the precursor, 3-phenyl-4-cyanimino-isoxazol-5(4H)-one (70) were not successful, it was decided to attempt generation of nitrosyl cyanide by fragmentation of heterocyclic azides such as 3-azido-5-phenyl-1,2,4-oxadiazole (94) or 3-azido-4-phenyl-1,2,5-oxadiazole (95). Both of these azides were unknown compounds.



Previous work[86] on five-membered-ring heterocycles had shown that in general when a nitrene was generated in the β-position (equation A) fragmentation of the ring occurred whereas generation in the α-position (equation B) led to ring opened products. The positions A, B and Y in the ring can be N or CH and X can be O, S, or NH.

Equation A

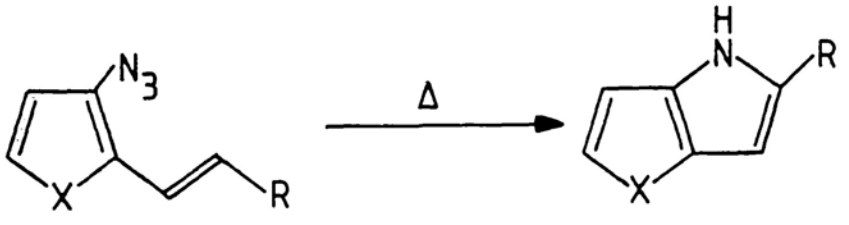


Equation B

The ring cleavage reactions of five-membered-ring heterocyclic nitrenes in general were well reviewed up to 1973 by Pearson.[86] The following

brief review covers the literature on the reactions of nitrenes derived from five-membered-ring heterocyclic azides from 1973 to early 1981.

There have been very few cleavage reactions involving five-membered-ring heterocyclic azides reported since 1973. Gronowitz and co-workers[88-90] have been extensively studying the synthetic utility of heterocyclic azides. 3-Azido-2-vinyl derivatives of furan (96a), thiophen (96b) and selenophen (96c) were decomposed in xylene at 120-130° to give [3,2-b] fused pyrrole systems (97a-c) in 54-90% yield.[88] No fragmentation was observed.

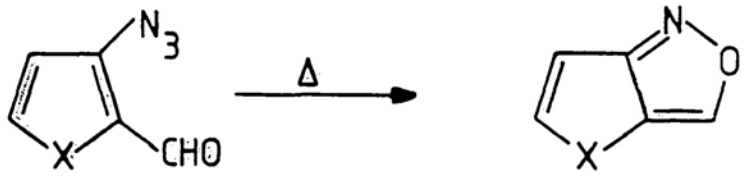


(96) a: X = O
b: X = S
c: X = Se

(97)

R = $COCH_3$, $COCH_2NO_2$

A similar approach was adopted for the synthesis of the isoxazole-fused systems (98a-c) starting from 3-azido-2-formyl-furan (99a), -thiophen (99b) and selenophen (99c). These azides (99a-c) were decomposed by heating in xylene until no more asymmetric azide stretching was observed in the ir spectrum of the reaction mixture.[89]

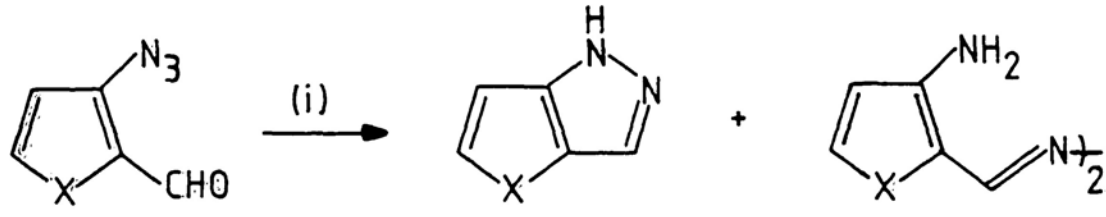


(99) a: X=O
b: X=S
c: X=Se

(98) a: X=O
b: X=S
c: X=Se

This gave furo[3,2-c]isoxazole (98a) (3%), thieno[3,2-c]isoxazole (98b) (22%) and selenolo[3,2-c]isoxazole (98c) (40%).[89] The reactions were accompanied by the formation of a large amount of resinous materials. Efforts to increase the yields by working at higher dilution were not successful.

The synthetic utility of these azides (99a-c)[90] was further illustrated by Gronowitz by synthesising unsubstituted furo- (100a), thieno- (100b) and selenolopyrazoles (100c). 3-Azido-2-formylthiophen (99b) was treated with hydrazine hydrate in boiling ethanol containing a small amount of acetic acid to give the thieno[3,2-c]pyrazole (100b) (10%) and the azine of 3-amino-2-formylthiophen (51%) (101). The yield of pyrazole (100b) could not be increased by altering the reaction conditions. When 3-azido-2-formylselenophen (99c) was treated in the manner described



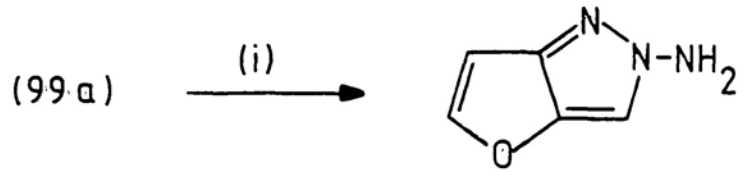
(99) b: X=S
c: X=Se

(100) b: X=S
c: X=Se

(101) b: X=S
c: X=Se

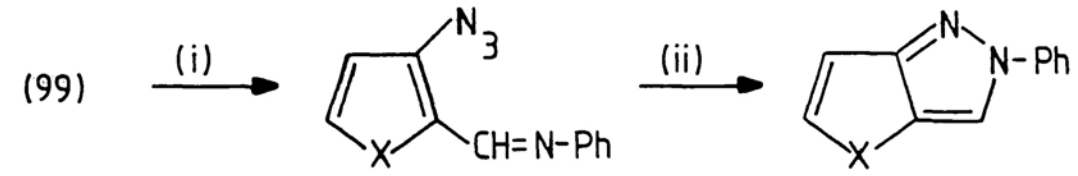
(i) $NH_2NH_2.H_2O$, EtOH, H^+

above selenolo[3,2-c]pyrazole (100c) was obtained in 10% yield with no azine (101) in the crude reaction product. No unsubstituted furopyrazole (100a) was obtained when 3-azido-2-formylfuran (99a) was subjected to the reaction with hydrazine hydrate. In this case, the crude product consisted mainly of 2-amino-furo[3,2-c]pyrazole (102) in very low yield (not specified). When 3-azido-2-formylfuran (99a), -thiophen (99b) and selenophen (99c) were treated with aniline in slightly acidic ethanol, the corresponding imines (103a-c) were formed in 49-96% yield. These azido compounds, (103a-c), which contained the necessary azomethine linkage, were decomposed by heating in 1,2-dichlorobenzene at 130-140° until the evolution of nitrogen gas had ceased. This gave 2-phenyl-substituted furo-, thieno- and selenolo[3,2,c]pyrazoles (104a), (104b) and (104c) respectively in 58-66% yield.[90]



(102)

(i) $NH_2NH_2.H_2O$, EtOH , H^+



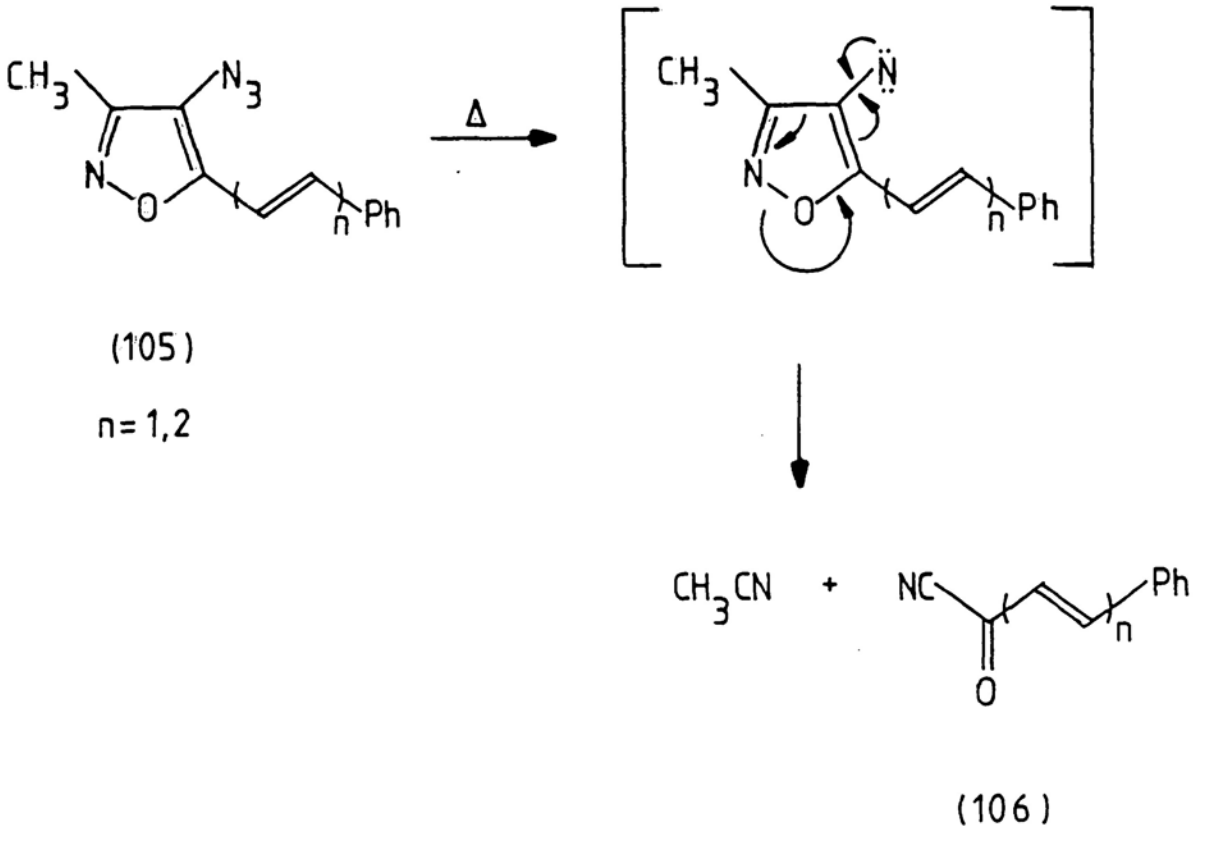
a: X= O
b: X= S
c: X=Se

(103) a: X= O
b: X=S
c: X=Se

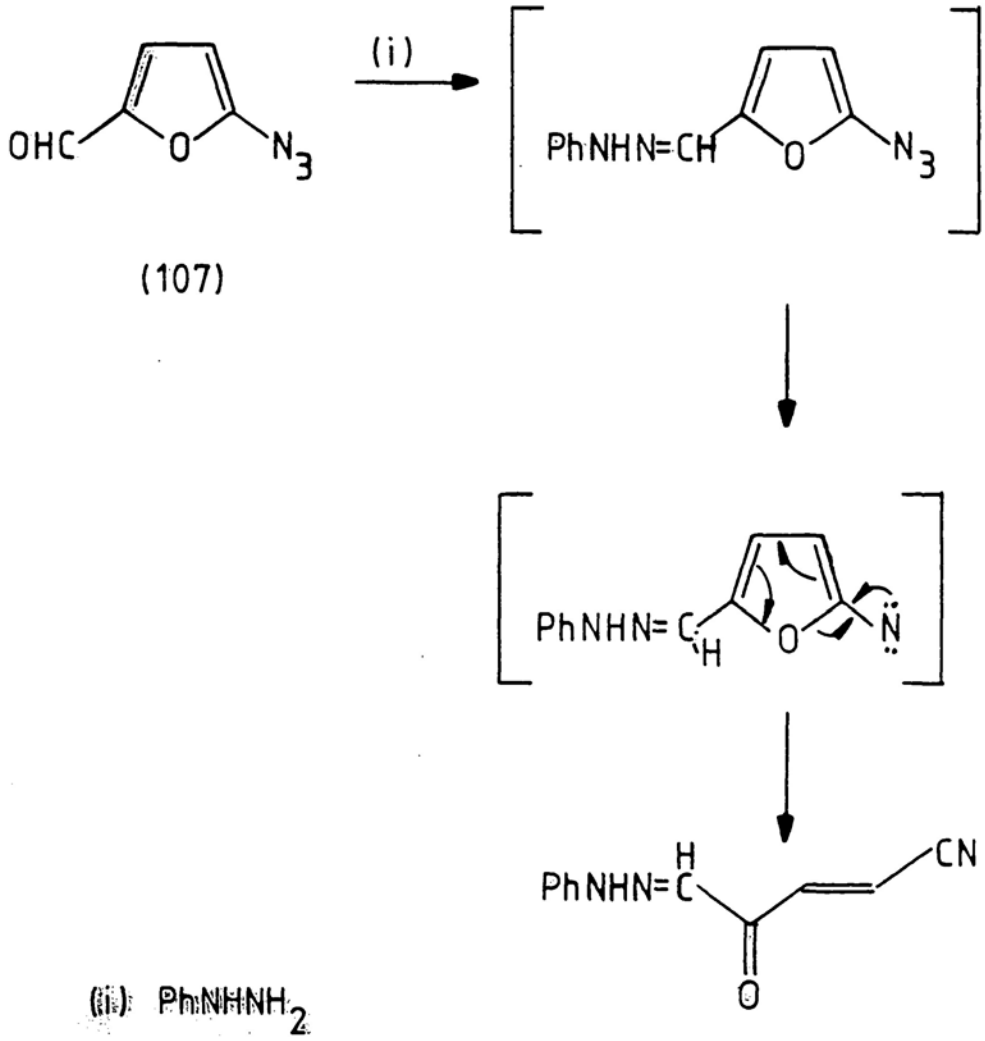
(104) a: X=O
b: X= S
c: X= Se

(i) $PhNH_2$, EtOH , H^+ (ii) 1,2-dichlorobenzene , Δ

Recently thermolysis of the 4-azido-3-methylisoxazole (105) (n = 1) in decalin over 1 h provided the fragmentation product, cinnamoyl cyanide (106) (n = 1) (90%).[91]



This result is in agreement with the general observation that when the azide is in the β-position (equation A) fragmentation occurs. An example of the ring opening reaction (equation B) can be seen in the reaction of 2-azido-5-formylfuran (107) with phenyl hydrazine followed by the decomposition of the azide to give a nitrile (108).[90]

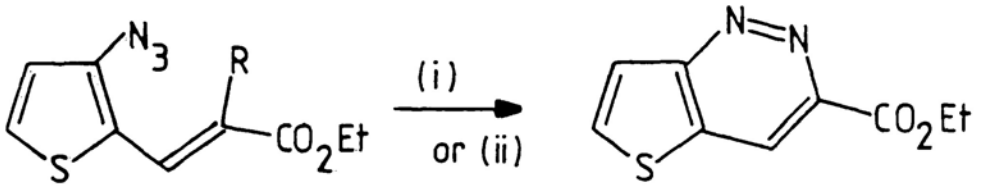


(107)

(108)

(i) $PhNHNH_2$

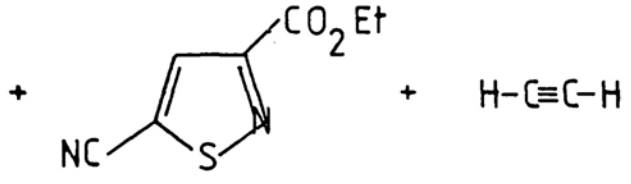
Rees and co-workers[93] recently showed that thermolysis of the 3-azido-2-vinyl derivative of thiophen (109a) in toluene or xylene provided ethylthio[3,2-c]pyridazine-3-carboxylate (110), ethyl-5-cyanoisothiazole-3-carboxylate (111) and acetylene.



(110)

(109) a: R = N_3

b: R = CO_2Et

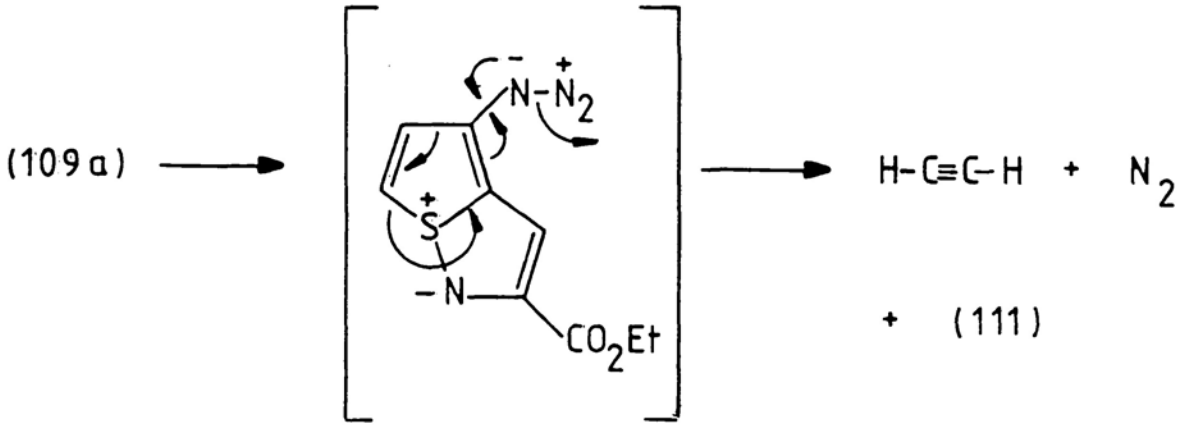


(111)

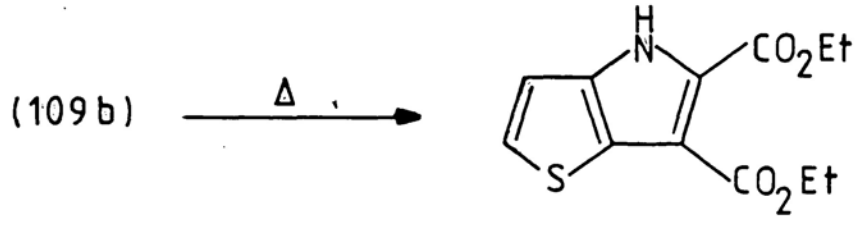
Table III. Results of decomposition of (109a).

Conditions	Time	Solvent	(110)	(111)	Acetylene
(i)	0.5h	toluene	17%	19%	15%
(ii)	0.5h	xylene	26%	27%	21%

The suggested mechanism for formation of (111) involves initial decomposition of the vinyl azide to give a vinyl nitrene, presumably in equilibrium with the azirine, and coordination of the nitrene to the thiophen sulphur, thereby weakening the ring. Loss of acetylene and isothiazole (111) may then occur simultaneously.

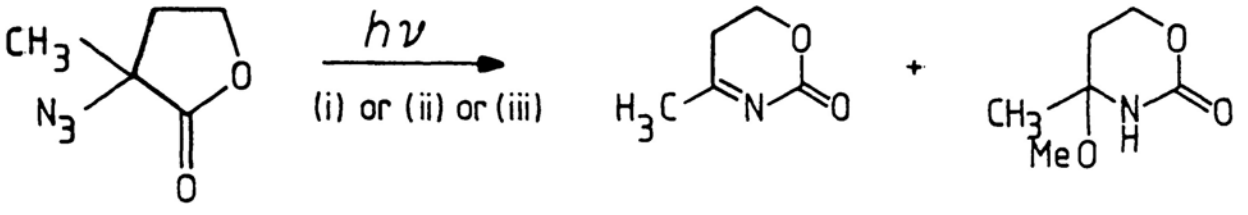


No acetylene was observed when the 3-azido-2-vinyl derivative of thiophen (109b) was decomposed in toluene but only diethyl thieno[3,2-b]pyrrole-5,6-dicarboxylate (112) (76%).[93]



(112)

Examples of photolytic decomposition of five-membered-ring heterocyclic azides are also rare in the literature from 1973. Recently, Court *et al.*[94] photolysed the α-azidolactone (113) in methanol using a Hanovia 100W lamp and Vycor filter for 7 h at -25° to give a mixture of 4-methyl-5,6-dihydro-1,3-oxazin-2-one (114) and 4-methoxy-4-methyl-tetrahydro-1,3-oxazine-2-one (115) in the ratio 2.5:1.0. Variation of the photolytic conditions gave different product ratios (Table IV).

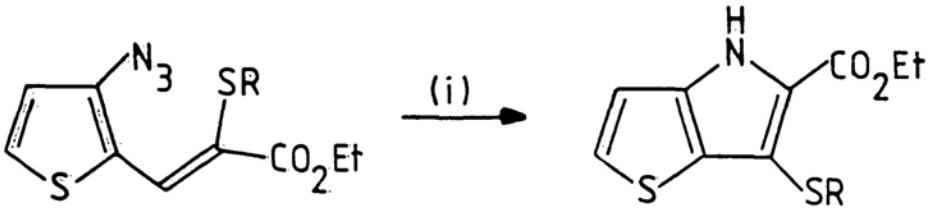


(113) (114) (115)

Table IV

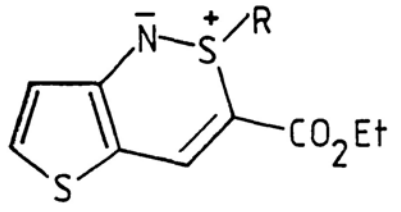
Conditions	Temp/°C	Solvent	Time	(114):(115)
(i)	-25	MeOH	7h	2.5:1.0
(ii)	-25	MeOH	10h	1.5:1.0
(iii)	-25	CH_2Cl_2	7h	only (114) detected

Photolysis of the 3-azido-2-vinyl thiophene (116a,b) in acetonitrile over 0.5 h provided 6-phenyl- or 6-methyl-thio-4H-thieno[3,2-b]pyrrole (117a,b) and the cyclic sulphimide (118a,b).[95]



(116) a: R = Ph
b: R = Me

(117) a: R = Ph (41%)
b: R = Me (52%)



(i) $h\nu$ 350 nm, MeCN, 0·5 h

(118) a: R = Ph (56%)
b: R = Me (40%)

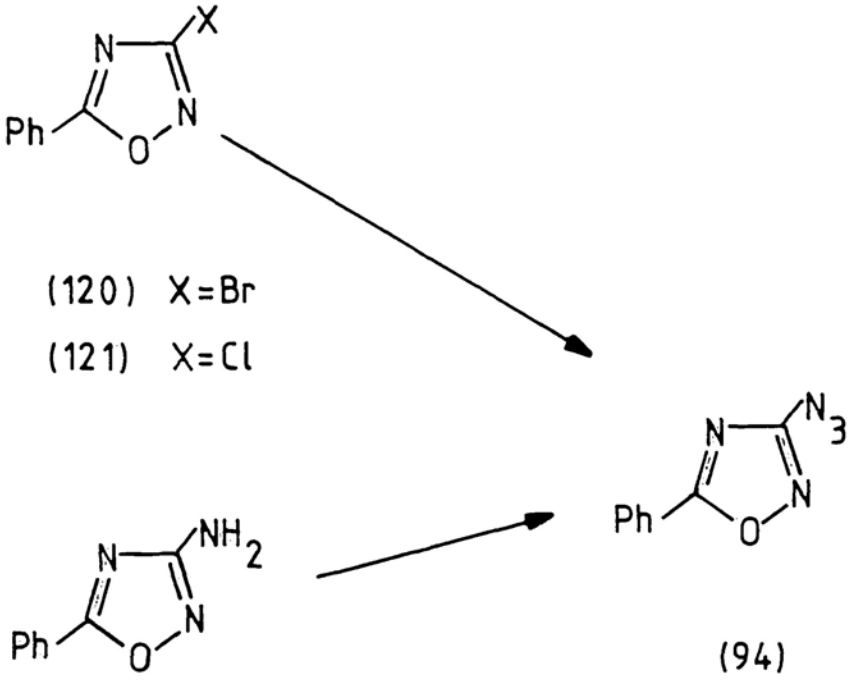
From the above review covering the literature from 1973, it can be seen that photolytic decomposition of five-membered-ring heterocyclic azides gave no ring fragmentation and the two examples of thermal decomposition led to ring opening, one of which was a fragmentation.

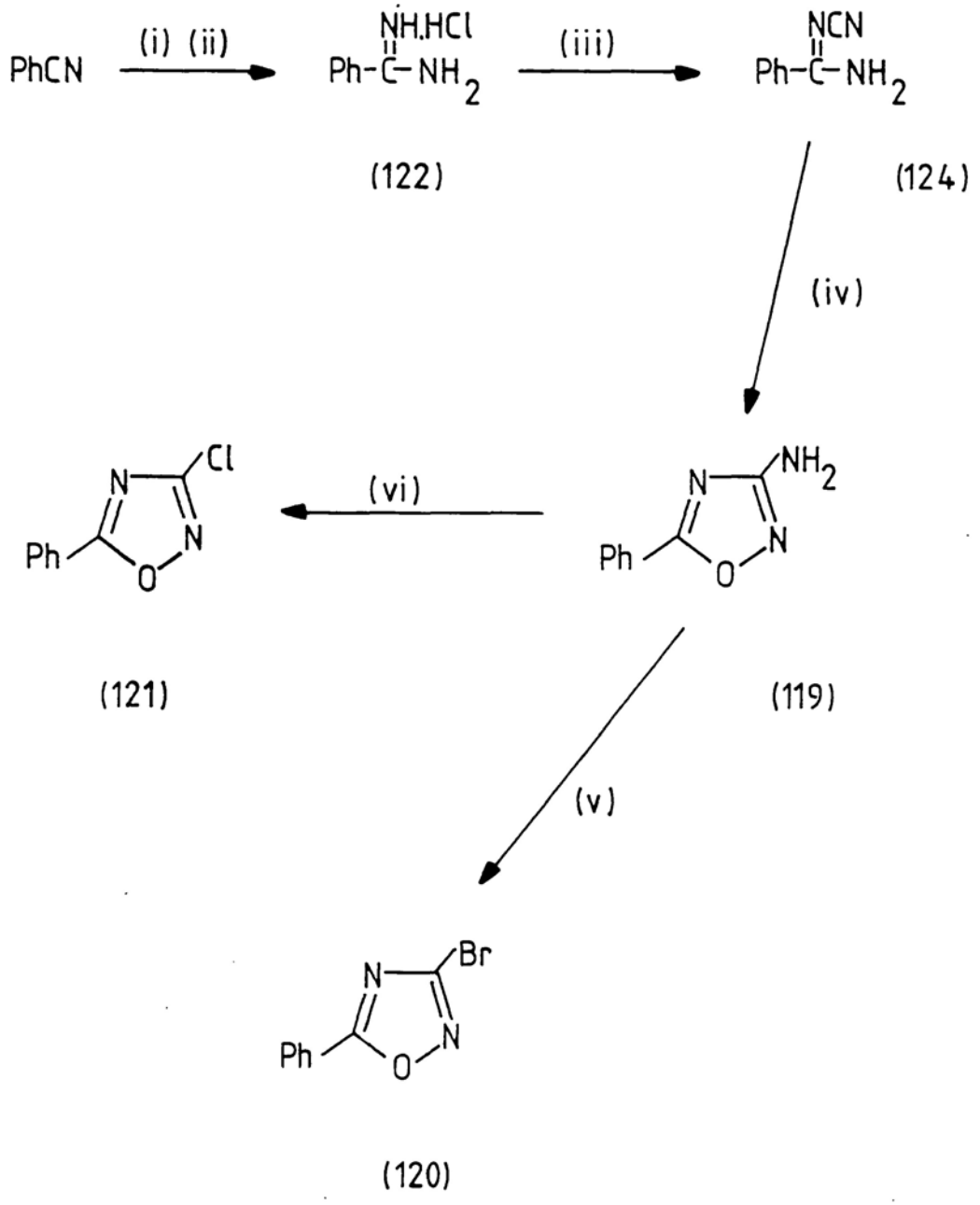
4.2. Synthesis and reactions of 3-azido-5-phenyl-1,2,4-oxadiazole (94) and 3-azido-4-phenyl-1,2,5-oxadiazole (95).

4.2.1. 3-Azido-5-phenyl-1,2,4-oxadiazole (94).

4.2.1.1. Synthesis.

The unknown 3-azido-5-phenyl-1,2,4-oxadiazole (94) was one of the two heterocyclic azides required in order to study possible fragmentation to give nitrosyl cyanide. The latter was required for condensation with 3-phenyl-isoxazol-5-(4H)-one (69) as described in Approach II (3.2.2.3). Three known precursors to the heterocyclic azide (94) may be considered namely, 3-amino-5-phenyl-1,2,4-oxadiazole (119) and 3-bromo- or 3-chloro-5-phenyl-1,2,4-oxadiazole, (120) and (121) respectively.





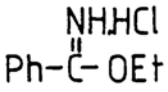
Scheme 10 (i) EtOH, HCl gas (ii) NH_3 in EtOH (iii) NaNHCN, H_2O

(iv) $NH_2OH.HCl$, EtOH, pyridine (v) $NaNO_2$, 0°, HBr

(vi) $NaNO_2$, 0°, HCl

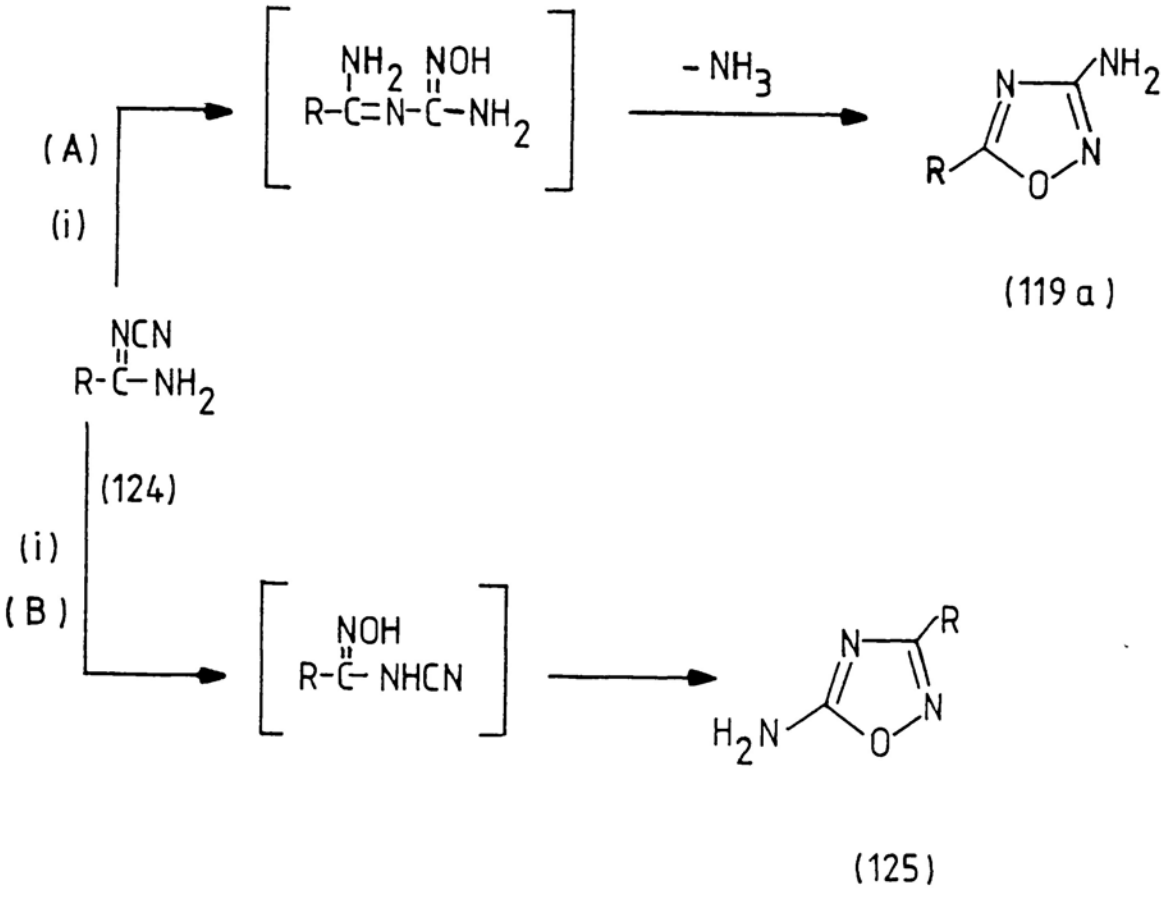
Nucleophilic displacement of a halogen by azide ion and diazotisation of an amine followed by addition of an inorganic azide, usually sodium azide, are well known and common methods for the synthesis of azides.[96]

The three precursors (119), (120) and (121) were prepared according to the literature as shown in Scheme (10). Benzamidine hydrochloride dihydrate (122) (95%)[97] was easily prepared by bubbling a steady stream of dry hydrogen chloride into an ethanolic solution of benzonitrile to give the imido ethyl ether hydrochloride (123) and by treatment of the



(123)

latter with an ethanolic solution of ammonia. N-Cyanobenzamidine (124) (70%) was obtained by stirring an aqueous solution of benzamidine hydrochloride (122) with monosodium cyanamide.[98] N-Cyanobenzamidine (124) was heated under reflux with hydroxylamine hydrochloride in ethanol and pyridine for 0.5 h to provide the amine (119) (31%).[99] This reaction had been investigated by Eloy[99] since there are two possible pathways, A and B, which may result in two isomeric 1,2,4-oxadiazoles (119a) and (125).



Scheme 11 (i) NH_2OH

When R is aliphatic, pathway B is preferred and when R is aromatic, pathway A is preferred (Scheme 11). The chloride (121) (65%) and the bromide (120) (65%) were obtained by diazotisation of the amine (119) in concentrated hydrochloric and hydrobromic acid respectively.[100]

The first attempted synthesis of azide (94) by diazotisation of the amine (119) followed by addition of sodium azide under varying reaction conditions failed.[49,58,101] The crude reaction product was consistently a mixture including starting material but no azide (94). Thus, the other two precursors, the chloro compound (121) and the bromo compound (120) were used. The usual conditions for the synthesis of azides from halides, as shown below, were employed but without success.

(a) chloride (121) and sodium azide in anhydrous DMF at 50° for 48 h,

(b) chloride (121) and sodium azide in DMSO on the steam bath for 0.5 h,

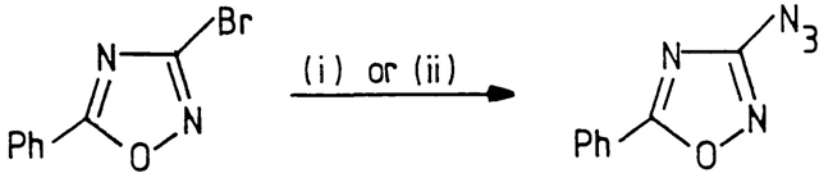
(c) bromide (120) and tetrabutylammonium azide[103] in anhydrous acetonitrile heated under reflux for 24 h,

(d) bromide (120) and lithium azide in methanol heated under reflux for 48 h,

(e) bromide (120) and sodium azide in dichloromethane/water with tetrabutylammonium iodide and/or bromide as the PTC catalyst over 24 h.

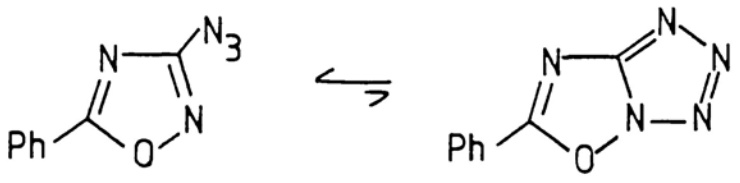
The starting materials were recovered quantitatively in all the five attempts. The azide (94) (50%) was finally synthesised by heating the bromide (120) either with lithium azide in anhydrous DMF at 90° for 45 h or with potassium azide, 18-crown-6 in anhydrous DMF at 90° for 72 h.

It is known that azide-tetrazole tautomerism[96] exists but the ir spectrum of the azide (94) in chloroform and in the solid state both showed a very strong azide stretching at 2140 cm^{-1}. This suggested that for this azide (94) the equilibrium lies in favour of the azide form both as a solid and in solution.



(120) (94)

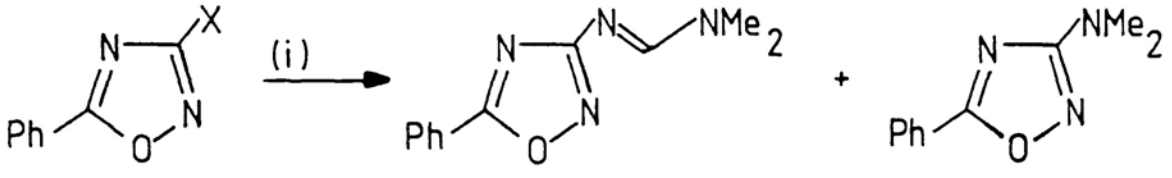
(i) LiN_3 , DMF , 90° , 45h (ii) KN_3 , 18-crown-6 , DMF , 90° , 72h



(94) (94b)

4.2.1.2. Novel Reactions of 3-halogeno-5-phenyl-1,2,4-oxadiazoles (120 and 121) with sodium azide and DMF.

One of the reactions carried out in the attempted synthesis of 3-azido-5-phenyl-1,2,4-oxadiazole (94) involved heating 3-chloro-5-phenyl-1,2,4-oxadiazole (121) with sodium azide in anhydrous DMF at 120-130°. After heating for 30 h, two products, N,N',-dimethyl-N" - (5-phenyl-1,2,4-oxadiazol-3-yl)formamidine (126) (26%) and 3-dimethylamino-5-phenyl-1,2,4-oxadiazole (127) (8%) were obtained with no azide (94). When the reaction was repeated with 3-bromo-5-phenyl-1,2,4-oxadiazole (120) under identical conditions, the reaction was complete in 3 h to give the same products as had been obtained with the chloro compound (121) but in higher yields, 34% of (126) and 39% of (127), and again with no azide (94). The bromo compound (120) reacted very much



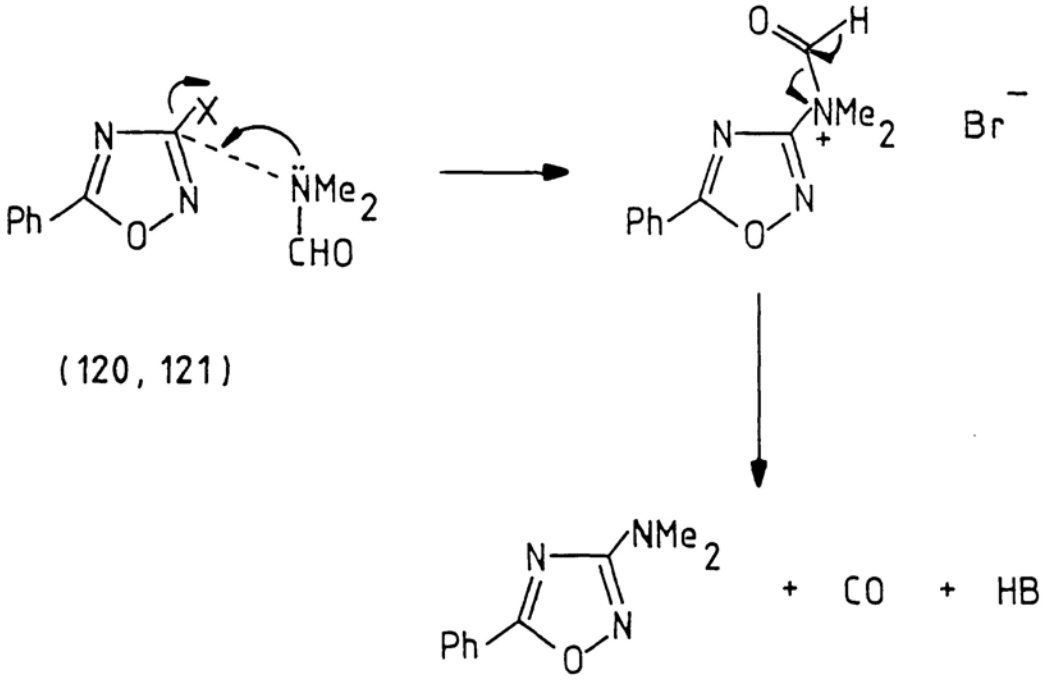
(120) X=Br (126) (127)

(121) X = Cl

(i) NaN_3 , DMF , 120-130°

faster than the chloro compound (121) as expected. The starting chloride (121) was present (by tlc) even after 30 h whereas the bromo compound (120) had been completely used up after 3 h. The formation of the dimethylamino compound (127) could be explained by N,N-dimethylammination of the chloro (121) or bromo (120) compounds by DMF under these reaction conditions. Such aminations by DMF are known in the literature with, for example, 1-chloroanthraquinone[104,105] and 1-chloro-4-nitrobenzene.[106,107] Two possible mechanisms for this process can be envisaged.

The first mechanism involves the nucleophilic displacement of the halogen by DMF, followed subsequently by neutralisation of the charge on the nitrogen with loss of carbon monoxide to give the dimethylamino compound (127) as the product.



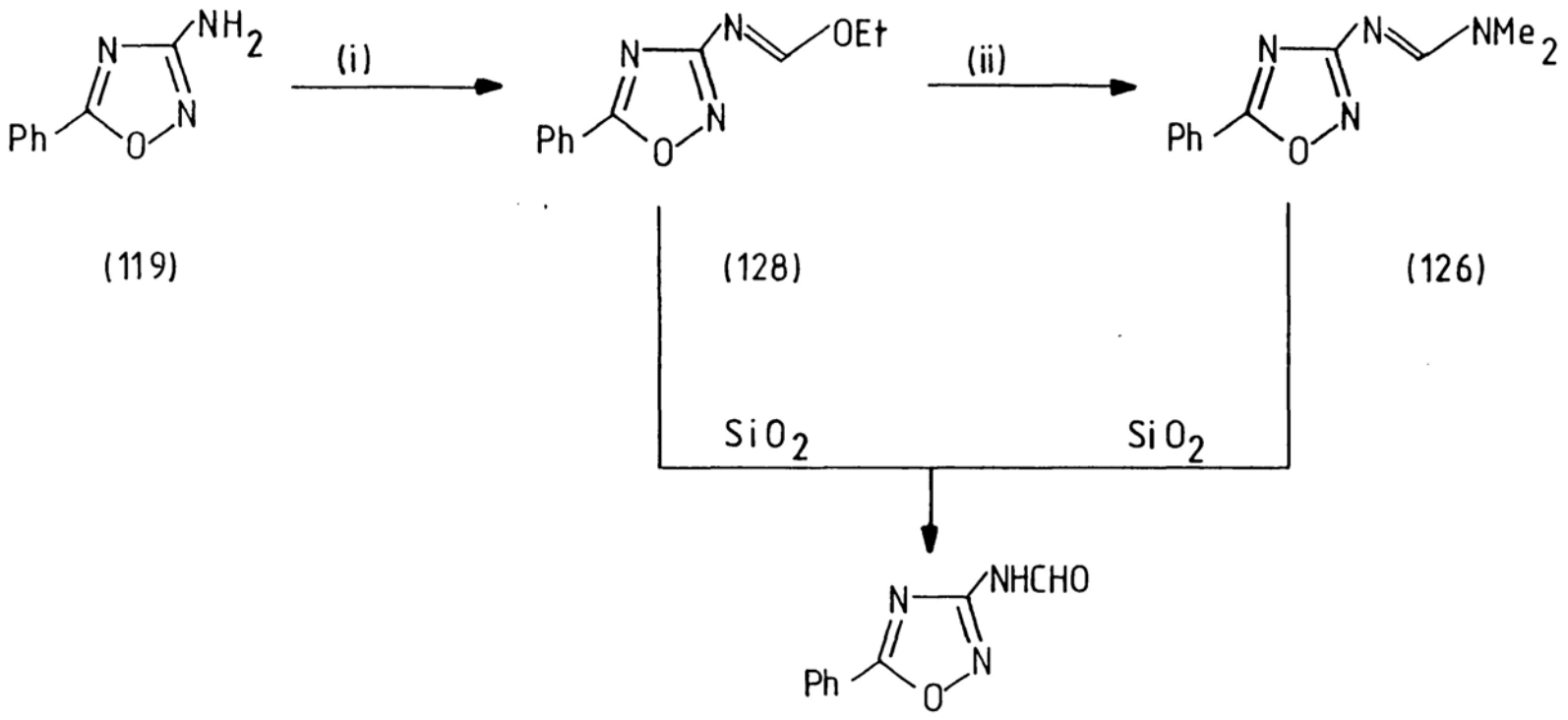
(120, 121)

(127)

The second mechanism for the formation of dimethylamino compound (127) could be a break down of DMF into dimethylamine and carbon monoxide[108] on heating and displacement of the halogen by the amine. An authentic sample of the previously unknown 3-dimethylamino-5-phenyl-1,2,4-oxadiazole (127) (83%) was synthesised by heating the bromo compound (120) with dimethylamine (33% w/w) in ethanol for 27 h. The product obtained from the DMF reaction had identical m.p., ir, pmr and mass spectral properties to those of the authentic sample.

In order to prove conclusively the structure of the amidine (126) an independent synthesis was carried out. There are two possible ways to synthesise the amidine (126) from the amine (119). The first method involves the direct reaction of the amine (119) with dimethylformamide dimethyl acetal. The alternative method is to react 3-ethoxy-formylimino-5-phenyl-1,2,4-oxadiazole (128), a known compound obtained from the amine (119) and triethyl orthoformate,[109] with dimethylamine. It was decided to use the second method since the independent synthetic route thereby totally excludes DMF or its derivatives.

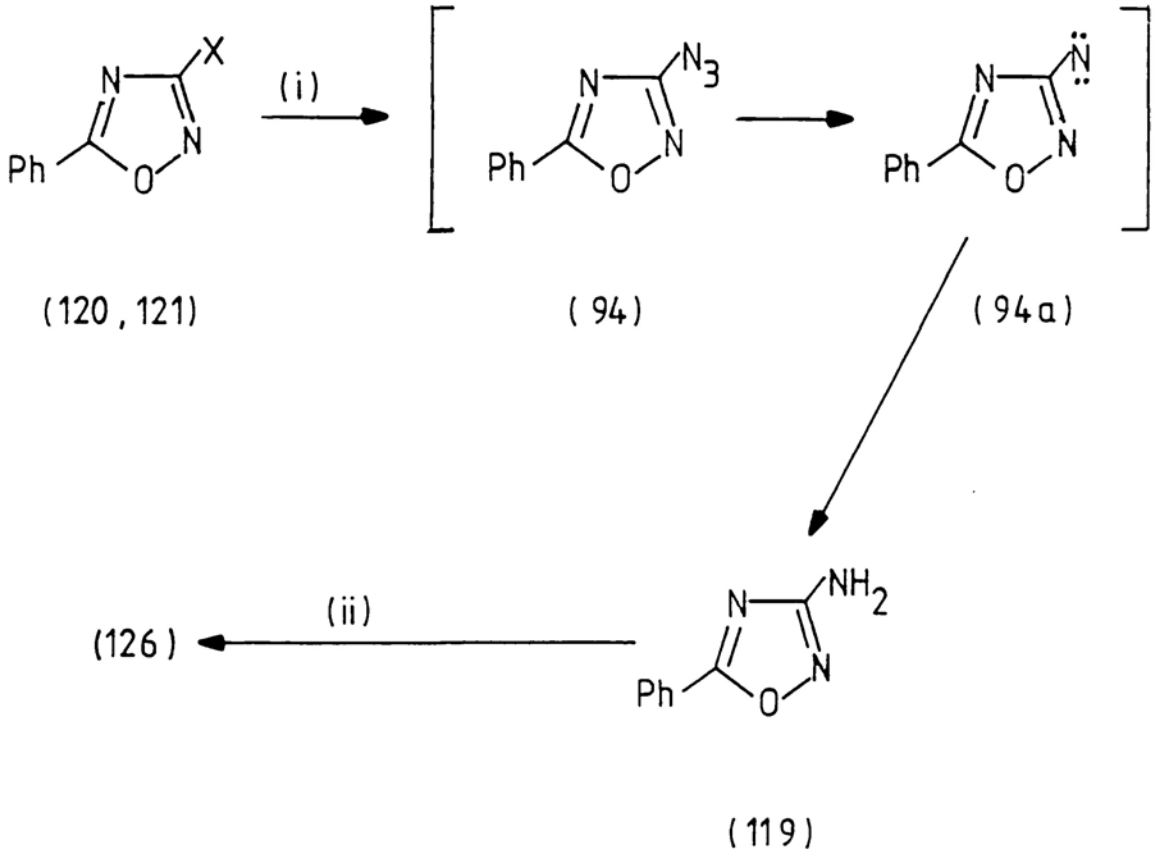
Ruccia had synthesised the precursor (128) to the amidine (126) by heating the amine (119) with triethylorthoformate at 150° for 3 h.[109] It was found that prolonged heating, for 8 h, was required to obtain the same yield (74%). The amidine (126) was obtained in 91% yield by stirring the ethoxy-formylimino compound (128) with dimethylamine (33% w/w) in ethanol for 48 h at room temperature. Chromatography had to be avoided for both compounds, (126) and (128), since they decomposed by acid hydrolysis to give 3-formamido-5-phenyl-1,2,4-oxadiazole (129). The amidine (126) obtained from the chloro or bromo compound (121) or (120) with sodium azide in DMF had identical m.p. and ir, pmr and mass spectral properties to those of the authentic sample prepared by the independent synthesis.



(i) $CH(OEt)_3$, 150°, 8h (ii) Me_2NH , EtOH , 48h , room temperature

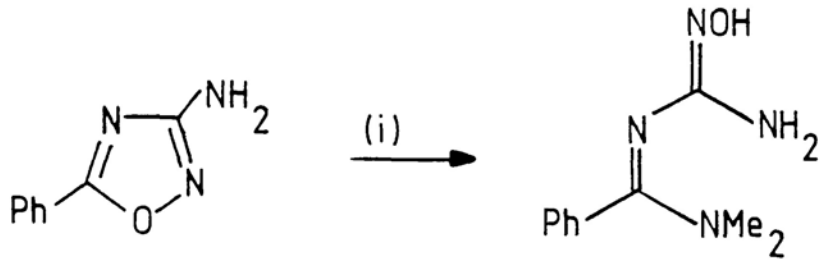
There are a number of possible mechanisms for the formation of the amidine (126). One of these, mechanism A, involves the formation of the azide (94) from either of the starting materials (120) or (121). The azide (94) then decomposes to give a nitrene (with the loss of nitrogen) and the nitrene abstracts hydrogens from the solvent to give 3-amino-5-phenyl-1,2,4-oxadiazole (119). The amine (119) could then react with DMF under these reaction conditions to give the amidine (126).

Mechanism A



(i) NaN_3, DMF (ii) DMF

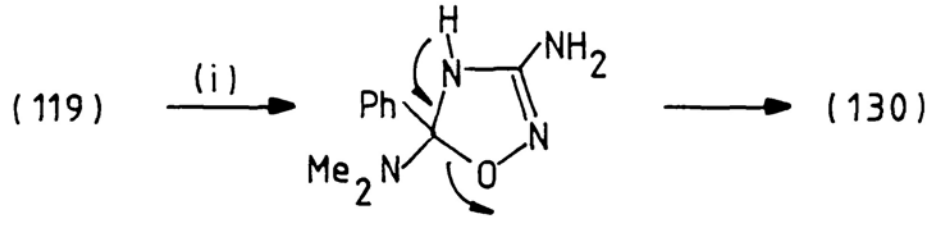
A blank reaction was carried out by heating the amine (119) in anhydrous DMF at 140° (no reaction takes place below this temperature) for 3 h. The product from this blank was not the amidine (126) but an oil identified tentatively as 2-methyl-3-phenyl-2,4,6-triazahex-3-en-5-one oxime (130) (76%) from its ir, pmr and mass spectra.



(119) (130)

(i) DMF, 140°, 3h

The mechanism for the formation of this oxime (130) probably involves the attack of dimethylamine, from the decomposed DMF, on to the 5-position of the oxadiazole ring, followed by ring opening to give the product (130).



(i) Me_2NH

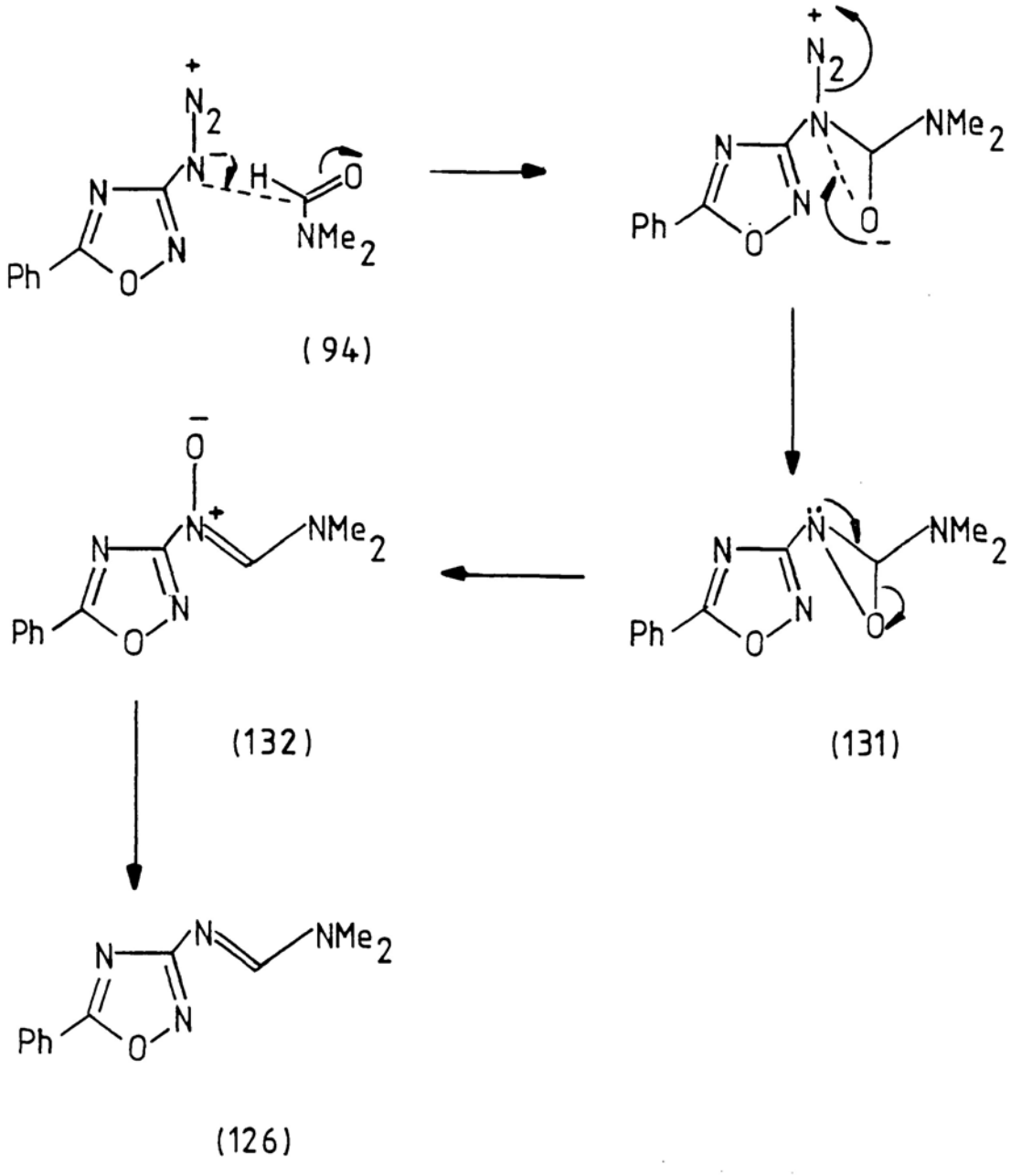
The second mechanism, B, proposed for the formation of the amidine (126) is, again, the displacement of halogen (121) or (120) by sodium azide to give the azide (94) followed by nucleophilic attack on the carbonyl of DMF, elimination of nitrogen, rearrangement of the resultant oxaziridine (131) and deoxygenation of (132) to the amidine.*

Alternatively, a third mechanism, C, may be postulated where, instead of the azide (94) as in mechanism, B, a nitrene from the azide adds to DMF to give oxaziridine (131) in one or two steps.* The remaining steps in this mechanism proceed as in mechanism B. Thermal deoxygenation of N-oxides as postulated in mechanisms B and C is not unreasonable under these reaction conditions. Rees et al. have reported an intramolecular interaction of an azide with amides in the thermal decomposition of the

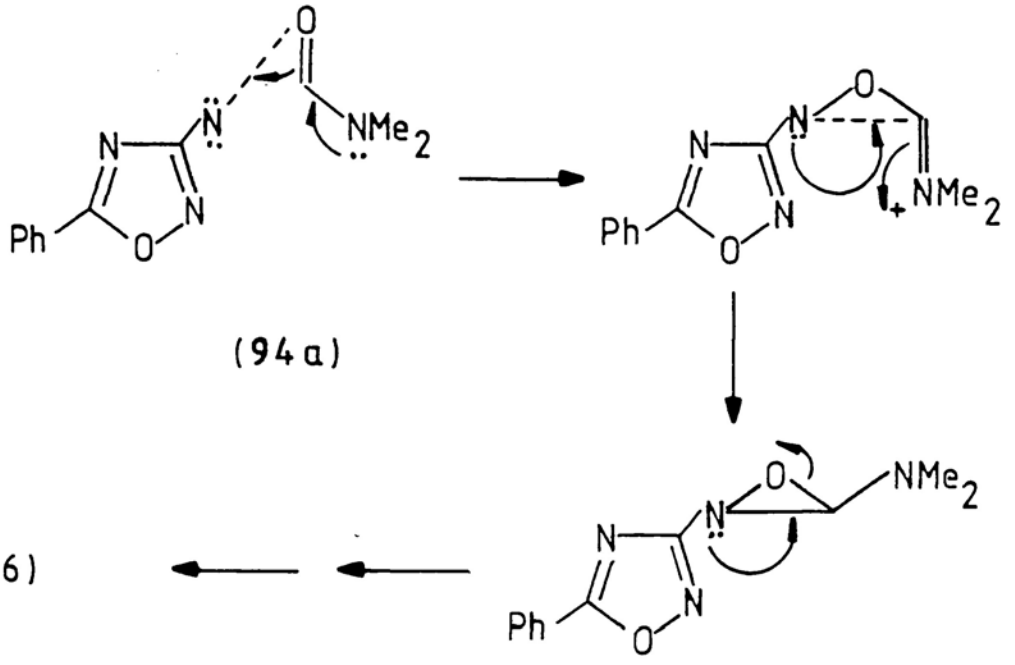
---

* See Appendix 6.0.

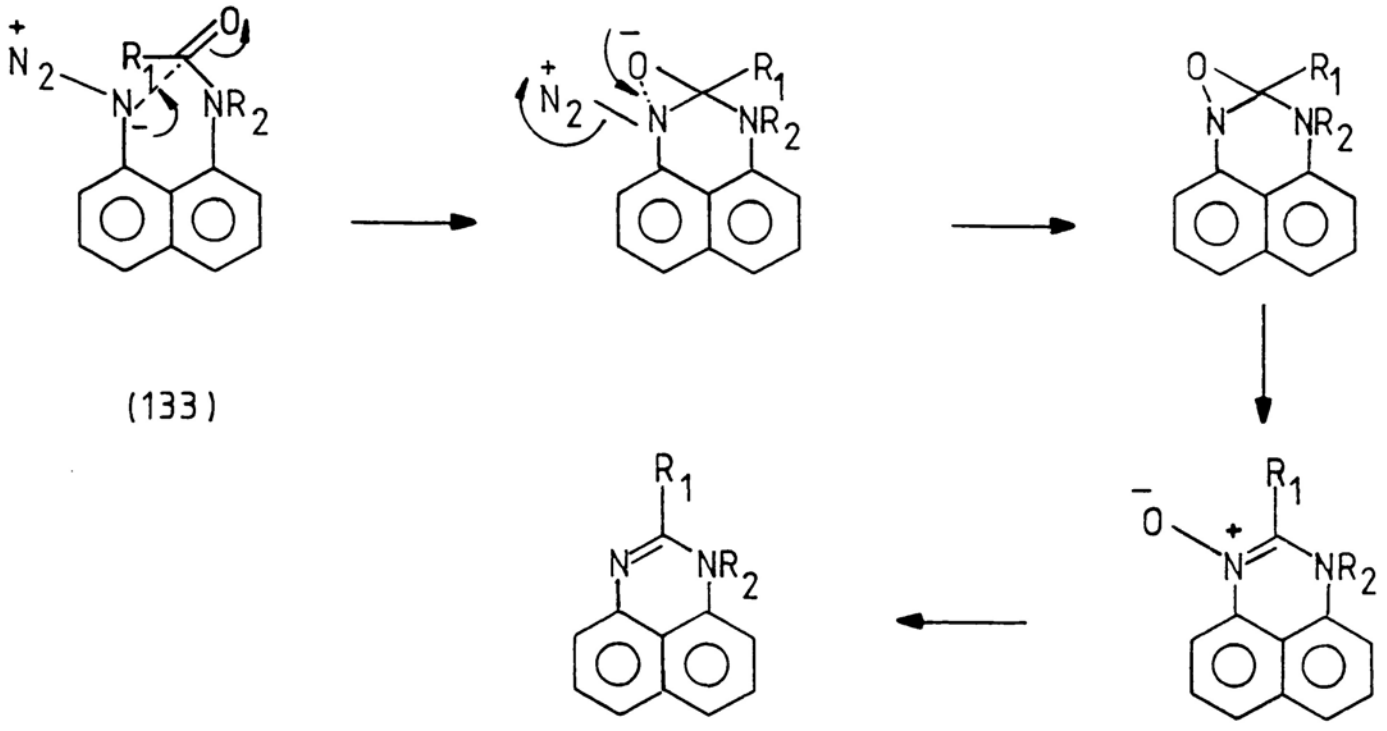
Mechanism B



Mechanism C



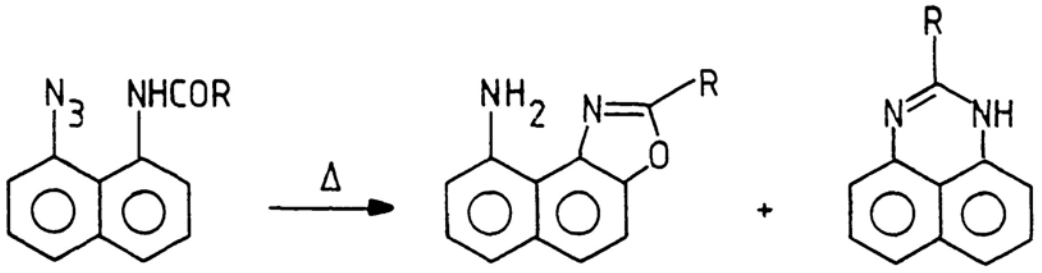
1-amino-8-azido-naphthalene derivatives (133) which gave rise to oxazoles (134) and perimidines (135).[110] The former were thought to arise via an intramolecular acid-catalysed reaction (amide N-H), and the latter via a concerted reaction of an azide and a carbonyl group. The mechanism proposed for the formation of perimidines (135) (Scheme 12) is similar to mechanisms B and C.



(133)

(135)

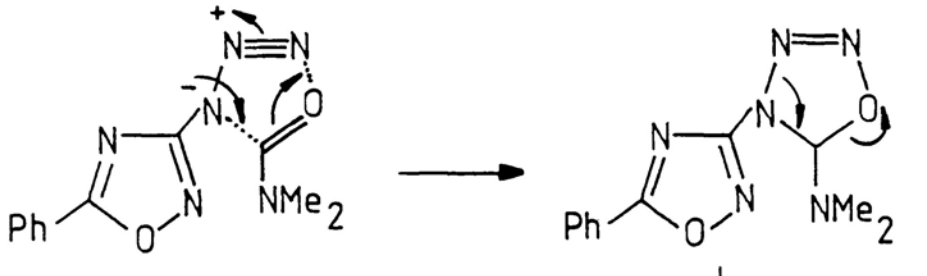
Scheme 12



(133) (134) (135)

The fourth possible mechanism, D, involves the cycloaddition of the azide (94) to the carbonyl group of DMF, with the loss of nitrous oxide from the adduct (136) to give the amidine (126).*

Mechanism D



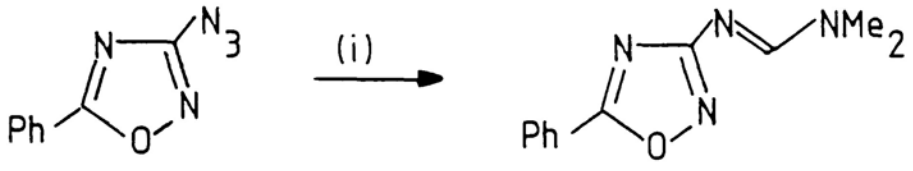
(94) (136)

(126) + N_2O

* See Appendix 6.0

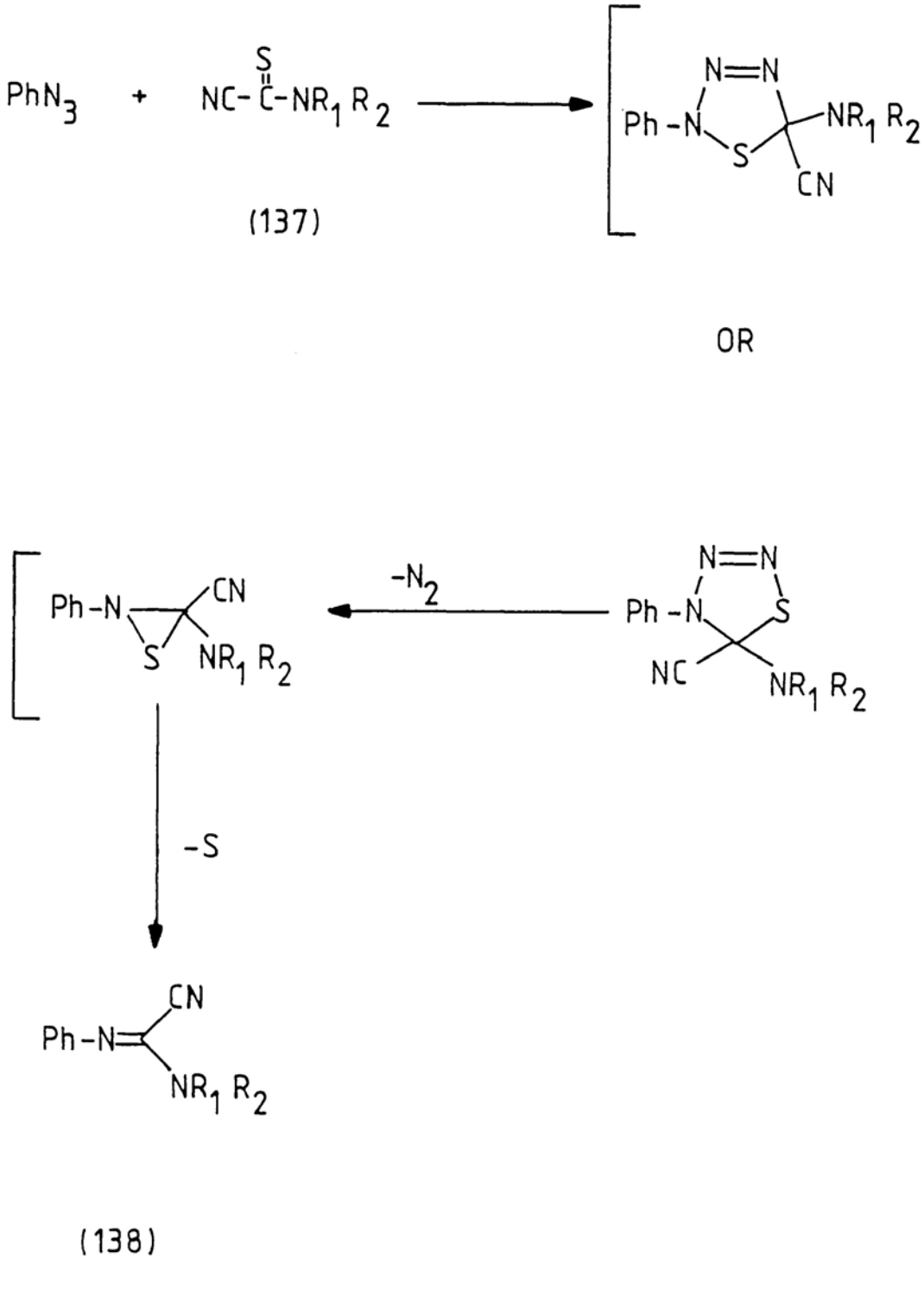
Cycloadditions of azides with carbonyl groups of amides are unknown. The closest analogy to mechanism D is the reported reaction of phenyl azide with monosubstituted cyanothioformamides (137) to give cyanoformamidines (138) at 100° over 12-18 h.[111] The mechanism proposed for the formation of the cyanoformamidines involves the cycloaddition of phenyl azide to the thiocarbonyl group as shown in Scheme (13).

The proposed intermediate in all the mechanisms A,B,C, and D is the azide (94). A blank experiment carried out by decomposing the azide in anhydrous DMF with one equivalent of dry sodium bromide at 140° for 31 h provided the amidine (126) (47%). This blank showed that postulated mechanisms involving interaction of the azide (94) with DMF are reasonable.



(94) (126)

(i) NaBr , DMF , 140° , 31h



(138)

Scheme 13

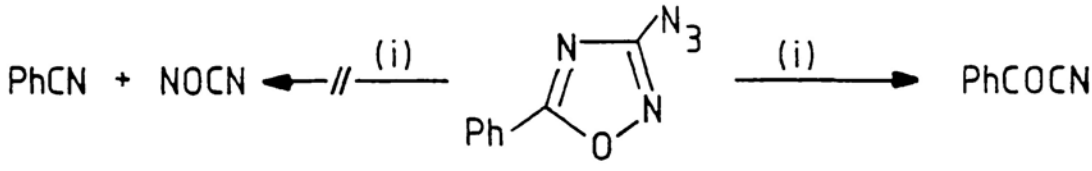
The role of sodium bromide in the thermolysis is not exactly understood but its absence reduces the yield of the amidine (126) to about 10%. The rate and yield of the reaction was not increased if the thermolysis of the azide (94) was carried out with excess sodium azide in DMF.

Although the mechanism of the reaction is not clear, this discovery is the first demonstrated example of the intermolecular reaction of an azide with the carbonyl group of an amide and represents a new route to amidines.

4.2.1.3. Decomposition of 3-azido-5-phenyl-1,2,4-oxadiazole (94).

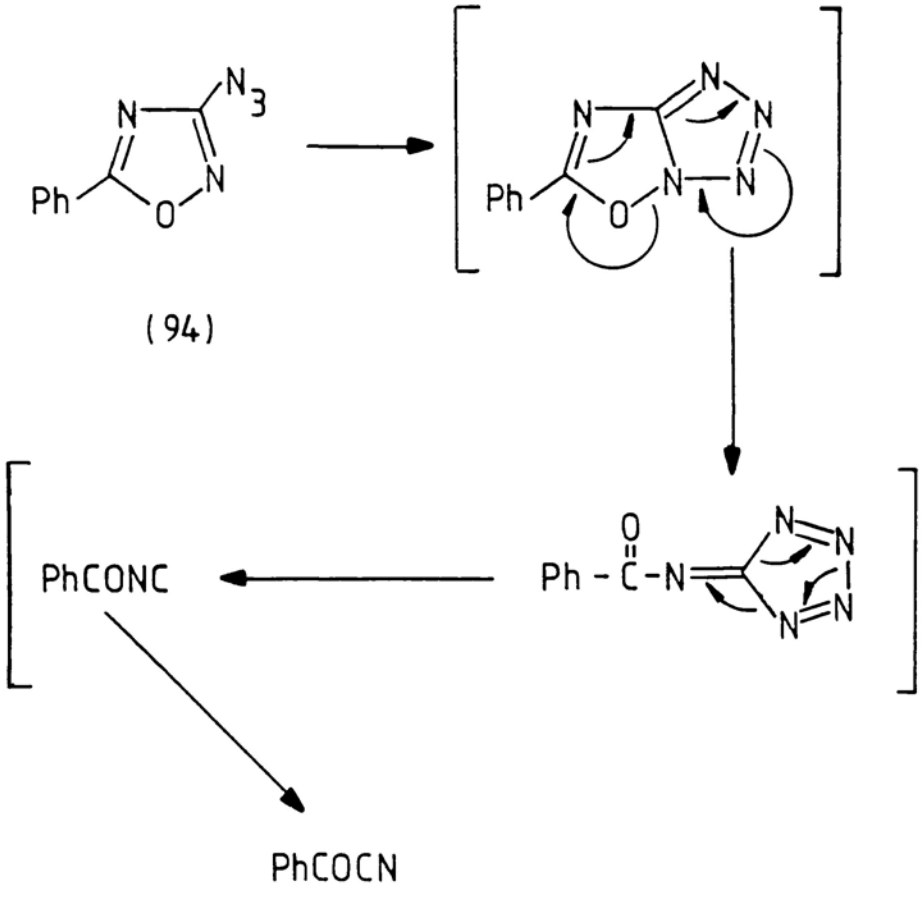
4.2.1.3.1. Flash Vacuum Pyrolysis (F.V.P.).

When the azide (94) was decomposed by F.V.P. at 500° to 550° and 7.5×10^{-2} Torr, the crude product isolated from the cold finger (-78°) showed a nitrile stretching band in the ir spectrum at 2200 cm^{-1} but also a carbonyl stretching band at 1680 cm^{-1}. After distillation, the oil (70%) was identified as benzoyl cyanide, presumably formed by the loss of two molecules of nitrogen. In order to prove conclusively the structure of the product, an authentic sample of benzoyl cyanide was prepared from benzoyl chloride and sodium cyanide in dichloromethane/water using tetrabutylammonium bromide as the phase transfer catalyst.[113] The m.p., ir, pmr and mass spectra of the authentic sample of benzoyl cyanide were identical to those of the benzoyl cyanide from the F.V.P. experiment. A proposed mechanism for the formation of benzoyl cyanide in this novel rearrangement is shown over.



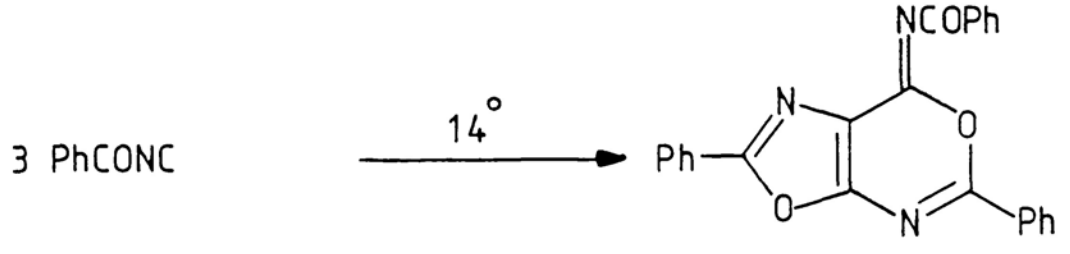
(94)

(i) 500 - 550 °, 7·5 x 10^{-2} torr



PhCOCN

The first step is the formation of the tetrazole. The weakest bond, N-O, in the resultant oxadiazolo-tetrazole breaks to form the benzoylimino-tetrazole, which being unstable under the F.V.P. conditions, rapidly loses two moles of nitrogen to give benzoyl isocyanide. Oxidative cleavage of arylidene-5-hydrazino-tetrazoles is known to produce isonitrile dihalides with the loss of two moles of nitrogen.[148-151] The mechanism of this conversion is postulated to involve a 5-imino-tetrazole analogous to (94c).[148] Benzoyl isocyanide is known to give the trimer (139) at temperatures above 14°[112] but this trimer (139) was not observed in the crude reaction product by ir spectroscopy.



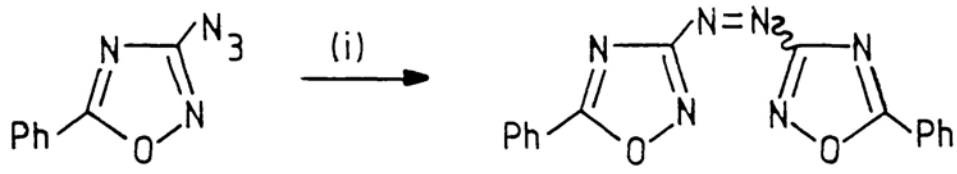
(139)

The last step of the mechanism is the isomerisation of benzoyl isocyanide to the more stable benzoyl cyanide. Isomerisation of heterocyclic isocyanides to heterocyclic cyanides was recently observed at ca. 500° under F.V.P. conditions by Wentrup.[57] Such isomerisations are well known to occur at temperatures above 400°.[6,57]

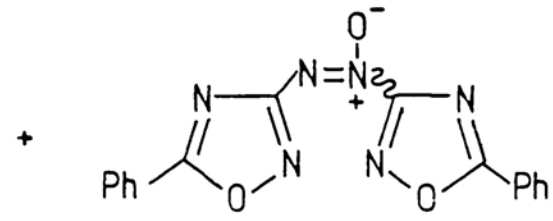
4.2.1.3.2. Photolysis.

In the course of our study on the fragmentation of the azide (94) the latter was photolysed at 254 nm in degassed anhydrous acetonitrile. Tlc indicated that the reaction was complete in 1 h. On evaporation of the solvent an orange residue was obtained. When chloroform was added to this residue an insoluble yellow solid precipitated out. Tlc indicated that the insoluble yellow solid was a mixture of two compounds and that the filtrate after removal of this solid was also a complex mixture. One component in the yellow solid was shown to be azo-3,3'-bis-(5-phenyl-1,2,4-oxadiazole) (140) (8%). The other minor component in the mixture was shown to be azoxy-3,3'-bis-(5-phenyl-1,2,4-oxadiazole) (141) (2%). This azoxy compound (141) was identified mainly by mass spectra evidence since there was very little difference between the ir and pmr of the azo (140) and the azoxy compound (141). The filtrate, on work up, provided recovered azide (94) (6%), another crop of the azo compound (140) (2%) and polymeric material (12%). Benzonitrile could not be detected (tlc) or isolated on work up. There is a possibility that benzonitrile could have reacted with one of the species formed in solution during photolysis since the major product was polymeric material.

The formation of the azo compound (140) was most likely a result of reaction of the nitrene intermediate formed during the photolysis with another molecule of azide, followed by loss of nitrogen. This process is one of the pathways in which nitrenes are known to react.[87,96] The azoxy compound (141) could be formed by cycloaddition of the azide with oxygen, presumably singlet oxygen being formed in the photolysis, followed by the loss of nitrous oxide to give 3-nitroso-5-phenyl-1,2,4-

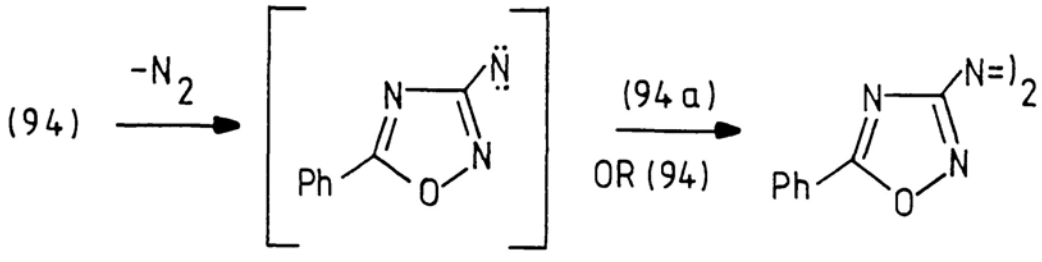


(94) (140)



(141)

(i) $h\nu$, 254nm, MeCN, N_2, 1h



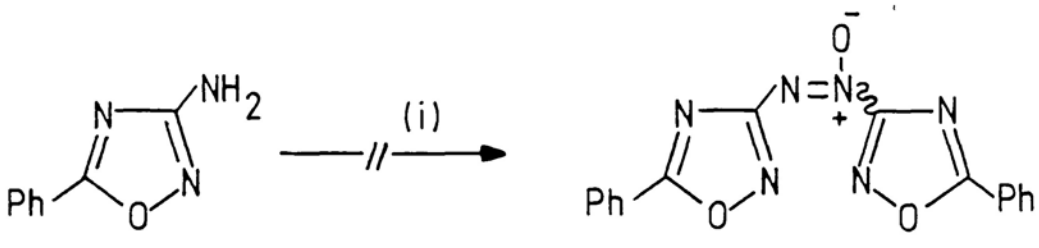
(94) (94a) (140)

oxadiazole (142). The latter could react with the heterocyclic nitrene or the heterocyclic azide to give the azoxy compound (141). The other possible pathway could be reaction of singlet oxygen with the azo compound formed under the photolytic conditions.

The source of oxygen could be either from the supposedly oxygen-free nitrogen gas bubbling through the solution during photolysis or the intake of air while taking aliquots for tlc every 5 min over 1 h. The reaction of aryl azides with singlet oxygen resulting in the formation of azoxy compounds has been thoroughly investigated by Abramovitch.[114]

Since both the azo (140) and the azoxy compounds (141) were unknown, it was decided that authentic samples of each should be synthesised for comparison with the products from photolysis.

The attempted synthesis of the azoxy compound (141) by oxidation of the amine (119) with peracetic acid in glacial acetic acid failed.[102,115] Thus it was decided to synthesise the azo compound (140) first, followed



(119) (141)

(i) CH_3CO_3H , CH_3CO_2H

by further oxidation to the azoxy compound (141). Oxidation of the amine (119) to the azo compound (140) failed when the following oxidising agents were used:

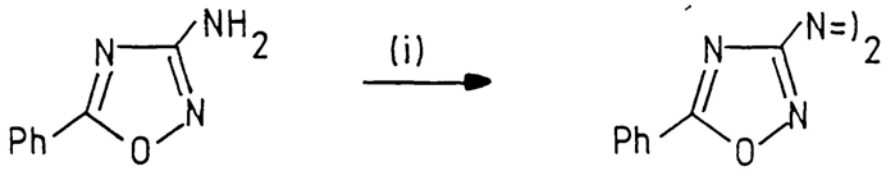
(a) lead tetraacetate[102]

(b) sodium perborate in boric acid and acetic acid[117]

(c) iodosobenzene diacetate

(d) tetraethylammonium periodiate

However, when the amine (119) was stirred in excess sodium hypochlorite[102] as solvent for 2 h at room temperature, the azo compound (140) was obtained in 76% yield. This oxidising agent usually gives low yields (less than 30% in most cases).[102] Commercial bleach can also be used but the reaction is not as clean, possibly due to additives.

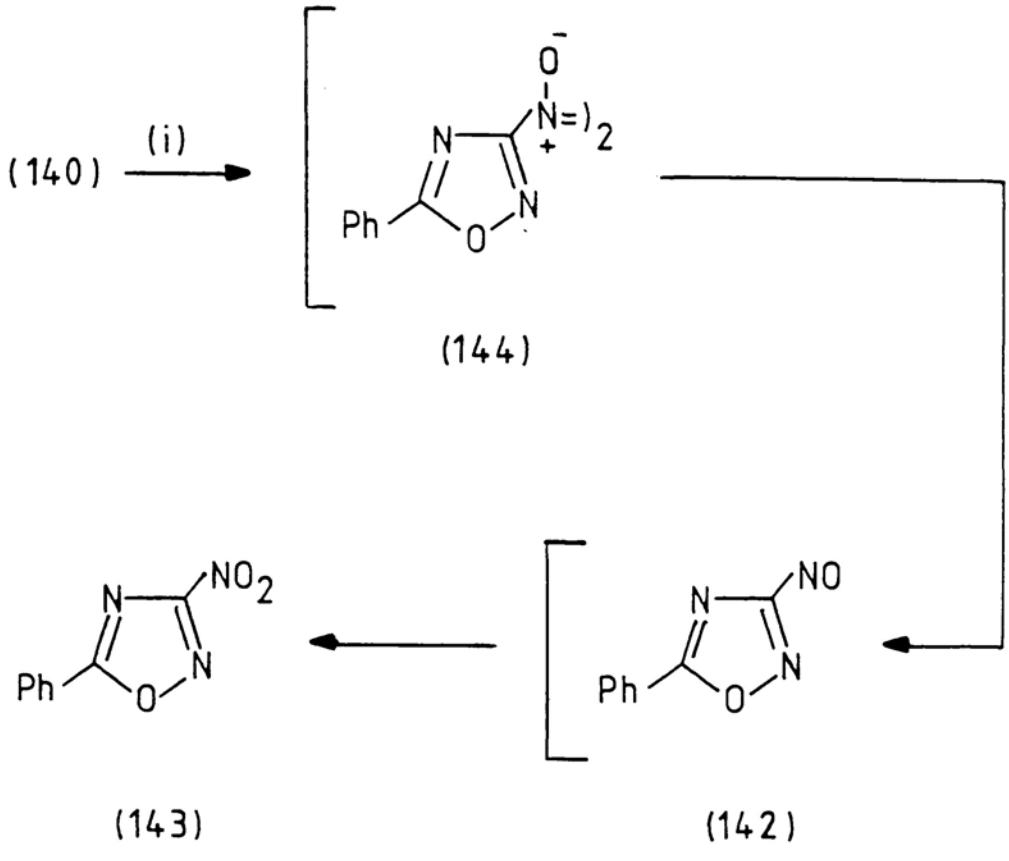


(119) (140)

(i) NaOCl, 2h, room temperature

Oxidation of the azo compound (140) using MCPBA in anhydrous dichloromethane at room temperature failed to provide the azoxy compound (141).[118] When the azo compound (140) was heated in hydrogen peroxide

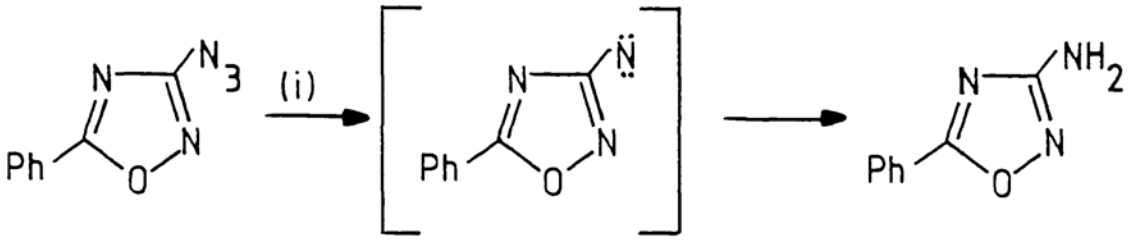
(30%) and glacial acetic acid[102] at 80°-90° for 36 h the starting material was recovered unchanged (> 90%) by filtration after cooling the reaction mixture to room temperature. Neutralisation of the filtrate with sodium carbonate to pH 7, extraction of the aqueous solution with dichloromethane and on work up provided the previously unknown 3-nitro-5-phenyl-1,2,4-oxadiazole (143) (8%), identified by its ir and mass spectra.



(i) H_2O_2 (30%), CH_3CO_2H, 80-90°, 36h

The formation of the nitro compound (143) was probably a result of the over-oxidation of the azo compound (140) to give the nitroso dimer (144) followed by cleavage of the N-N bond to give the highly unstable 3-nitroso-5-phenyl-1,2,4-oxadiazole (142). The latter (142) would be immediately oxidised to give the more stable nitro compound (143) as the product.[116]

When the azide (94) was photolysed at 254 nm in anhydrous THF over 15 min the amine (119) (22%) was the only product isolated from a complex mixture of unidentified products. When the amine (119) was photolysed under identical conditions over 2 h, no reaction was observed and the starting material was recovered quantitatively. Thus, we could safely suggest that no further decomposition of the amine (119) could be possible in 15 min under these photolytic conditions. The formation of this amine can be explained by hydrogen abstraction from the solvent by the nitrene, the latter formed from the azide (94) on decomposition.



(94) (94a) (119)

(i) $h\nu$, 254nm, THF, N_2, 15min

4.2.1.3.3. Thermolysis.

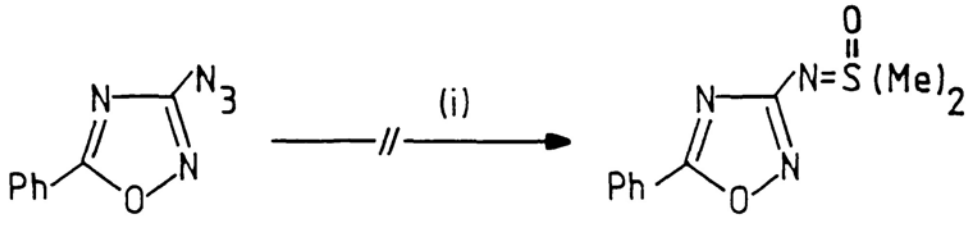
Fragmentation of azide (94) by thermal decomposition in solution failed under the following conditions:

(a) heating under reflux in anhydrous bromobenzene for 21 h gave a complex mixture and tlc showed azide (94) to be present as the major component,

(b) heating under reflux in anhydrous toluene and xylene for 2 h and 2.5 h respectively led to quantitative recovery of the azide (94),

(c) heating under reflux in anhydrous decalin failed to give any identifiable products or recovered starting material, and only base line material was observed on tlc.

An attempt to trap the possible intermediate, the nitrene (94a), by thermal decomposition of the azide (94) in DMSO in the presence of copper(II) penta-2,4-dione at 180° for 0.5 h failed to provide the sulphoximide (145), starting material or any identified products. Benzonitrile was not present in the crude reaction mixture by tlc.



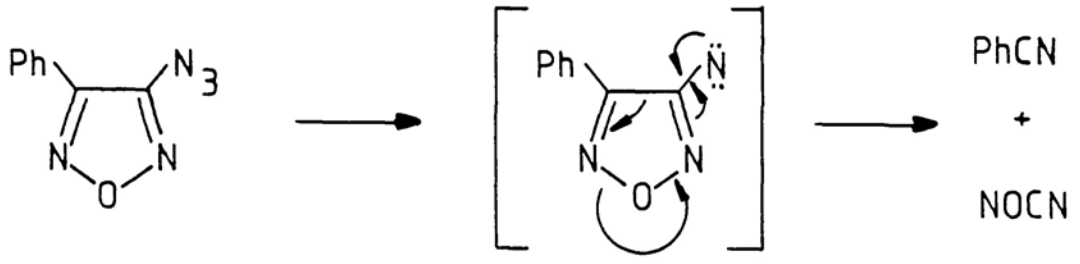
(94) (145)

(i) DMSO, $Cu(AcAc)_2$, 180°, 0·5h

4.2.2. 3-Azido-4-phenyl-1,2,5-oxadiazole (95).

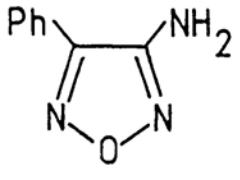
4.2.2.1. Synthesis

3-Azido-4-phenyl-1,2,5-oxadiazole (95) was chosen for synthesis since it is a possible alternative precursor for generation of nitrosyl cyanide by fragmentation. It would also provide a comparison with 3-azido-5-phenyl-1,2,4-oxadiazole (94).

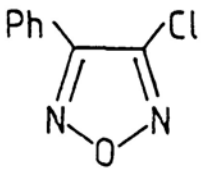


(95) (95a)

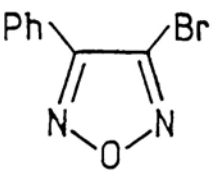
The usual precursors for the synthesis of the azide (95) are 3-amino-, 3-chloro- or 3-bromo-4-phenyl-1,2,5-oxadiazole, (146), (147) and (148) respectively. Although the amine (146) is known,[119] the 3-halogeno derivatives of this oxadiazole are not known.



(146)

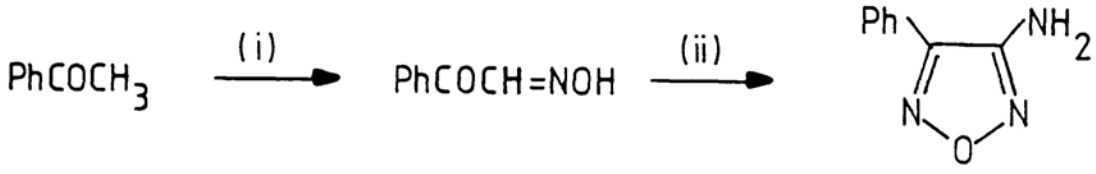


(147)



(148)

The amine (146) can be synthesised in two steps very easily from acetophenone. Treatment of acetophenone with amyl nitrite and sodium ethoxide at room temperature for 48 h provided ω-oximino-acetophenone (149) (50%).[120] The amine (145) (31%) was obtained by heating (149) under reflux with hydroxylamine hydrochloride and potassium hydroxide in water for 8 h.[119]



(149)

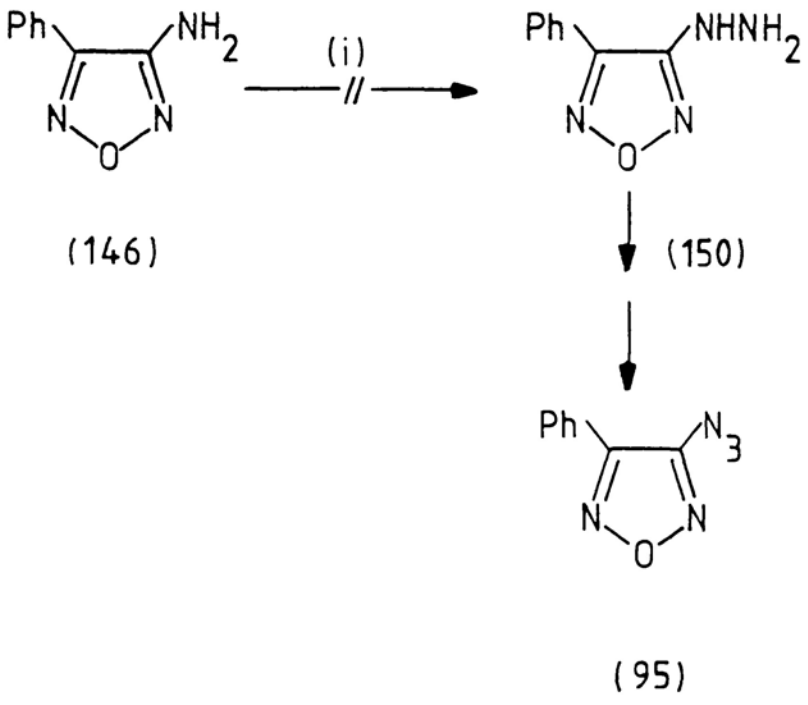
(146)

(i) EtONa, $C_5H_{11}NO$, EtOH (ii) $NH_2OH.HCl$, KOH, H_2O, Δ 8h

Although the yield is not high, this method nevertheless presents a short and simple route to the amine (146) from readily available and simple starting materials.

The attempted synthesis of the azide (95) by diazotisation of the amine (146) in 2 M hydrochloric acid at 0°C followed by the addition of sodium azide provided the azide (95) in very low yield (2%) after recrystallisation. An increase in acid strength or variation in the temperature above 5° resulted in complex mixtures. The starting material (146) was usually recovered in substantial amounts (30-50%).

An alternative route[122] to the azide (95) would be by diazotisation of the corresponding 3-hydrazino-4-phenyl-1,2,5-oxadiazole (150). Treatment of amine (146) and hydroxylamine-O-sulphonic acid with potassium hydroxide at 180° for 1 h failed to give the hydrazine (150). A quantitative recovery of the amine (146) was obtained from this attempted amination.

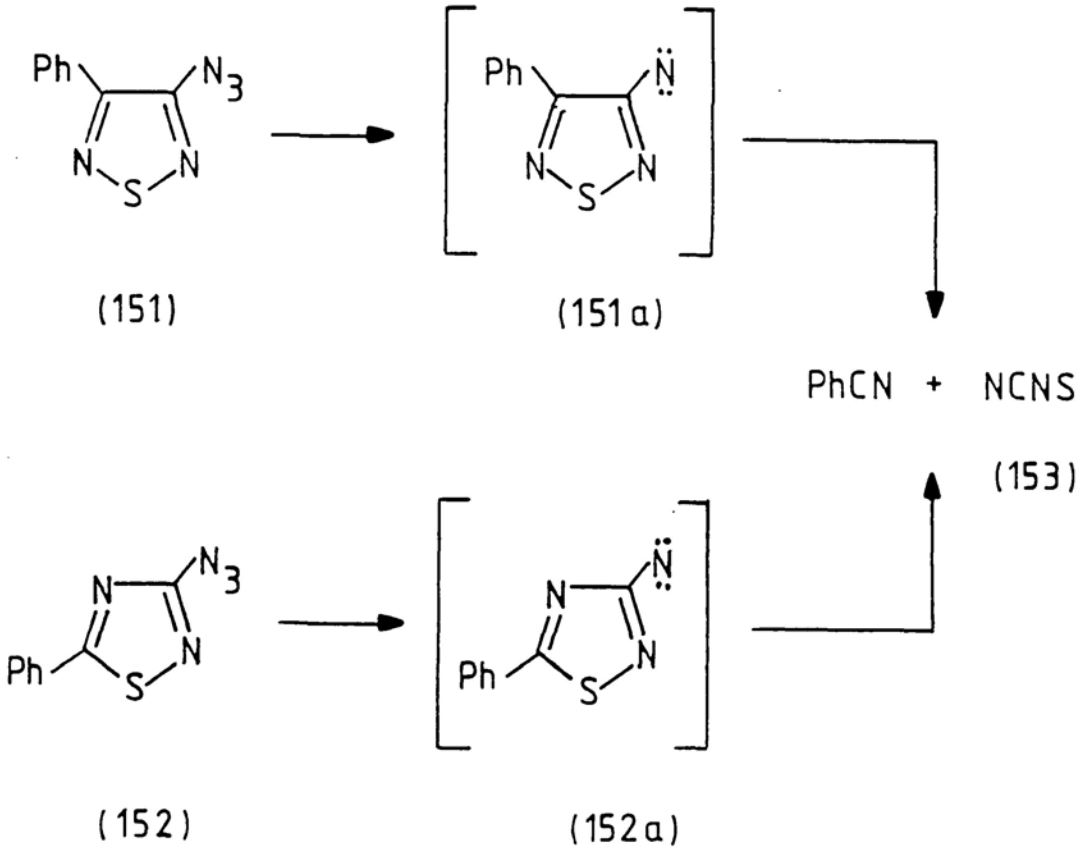


(i) H_2NSO_3H , KOH

4.3. Synthesis and Reactions of 3-azido-4-phenyl-1,2,5-thiadiazole (151) and 3-azido-5-phenyl-1,2,4-thiadiazole (152).

4.3.1. Introduction.

Following the interesting, initial results from 3-azido-5-phenyl-1,2,4-oxadiazole (94), it was decided to study the chemistry of two other heterocyclic azides which would provide thio-analogues of the oxadiazole system, i.e., 3-azido-4-phenyl-1,2,5-thiadiazole (151) and 3-azido-5-phenyl-1,2,4-thiadiazole (152). It can be envisaged that fragmentation of these two azides, (151) and (152) might provide a new species, thionitrosyl cyanide (153), and the inert benzonitrile.



The presence of benzonitrile in the reaction mixture resulting from the decomposition of these azides (151) and (152), would provide an indication of the formation of the possibly highly reactive, unknown species (153).

The synthesis and decomposition reactions of the azide (151) will be discussed first, followed by those of azide (152).

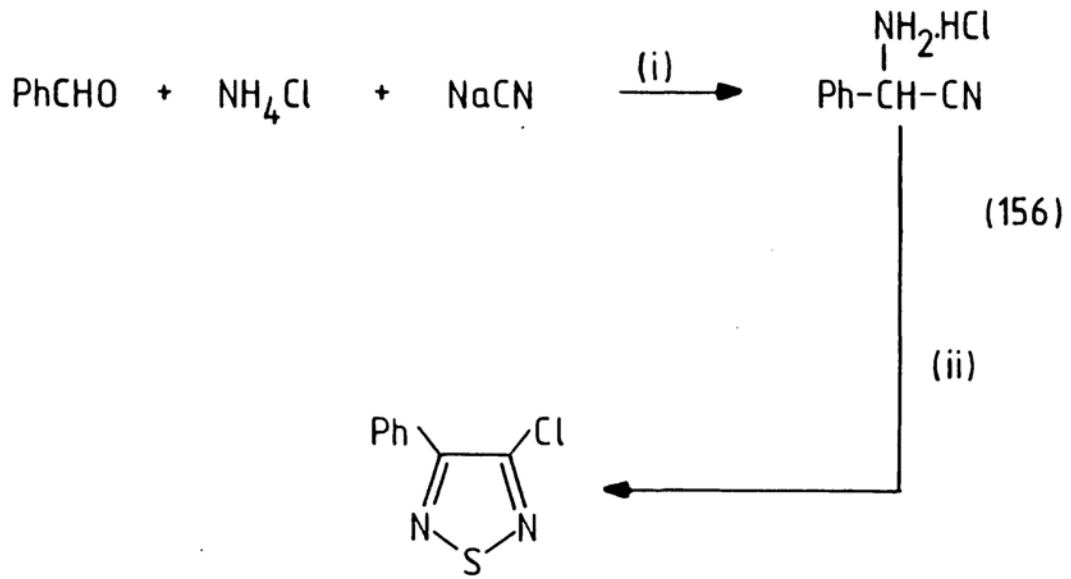
4.3.2. 3-Azido-4-phenyl-1,2,5-thiadiazole (151).

4.3.2.1. Synthesis.

The two known precursors of 3-azido-4-phenyl-1,2,5-thiadiazole (151) are 3-chloro- and 3-amino-4-phenyl-1,2,5-thiadiazole (154) and (155) respectively. Both precursors have been synthesised by entirely different routes. Interconversion of the chloro (154) and the amino (155) compounds is unknown.

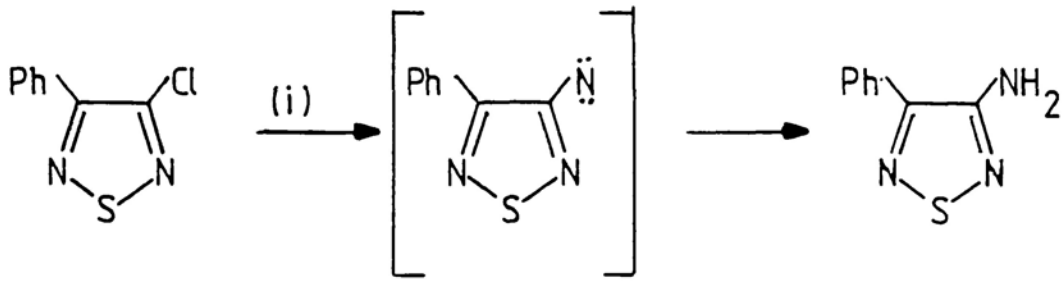
The chloro compound (154) (52%)[123] can be synthesised from 2-phenylglycinonitrile hydrochloride (156)[124] by treatment with sulphur monochloride in DMF at room temperature for 16 h. The hydrochloride (156) (15%) was prepared by using a modified procedure from benzaldehyde, sodium cyanide and ammonium chloride.[49]

Attempts to synthesise the azide (151) by heating the chloro compound (154) with potassium azide and 18-crown-6 in anhydrous DMF at 140° for 6.5 h gave a complex mixture. The only product isolated was the amine (155) (22%). The ir spectrum showed that azide (151) was not among the six unidentified products.



(154)

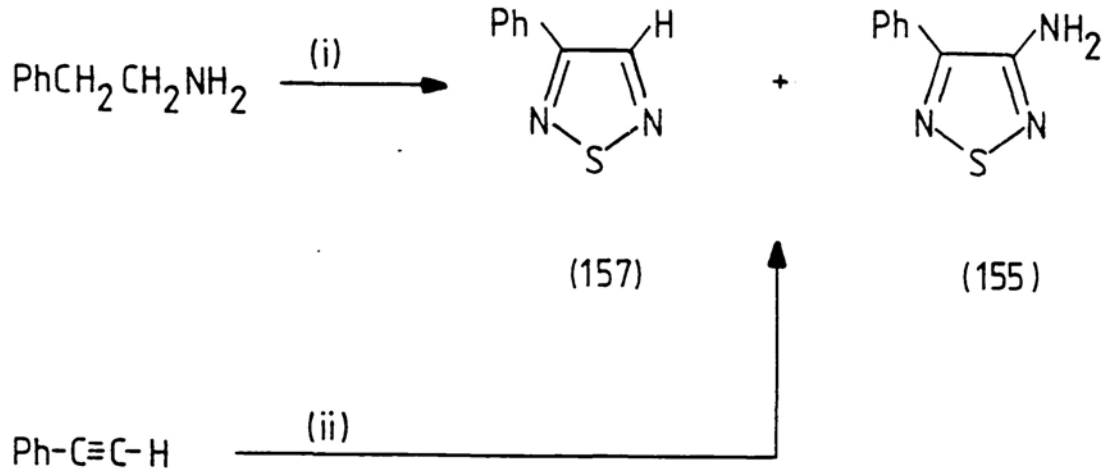
(i) MeOH, HCl (ii) S_2Cl_2, DMF, 16h, room temperature



(154) (151a) (155)

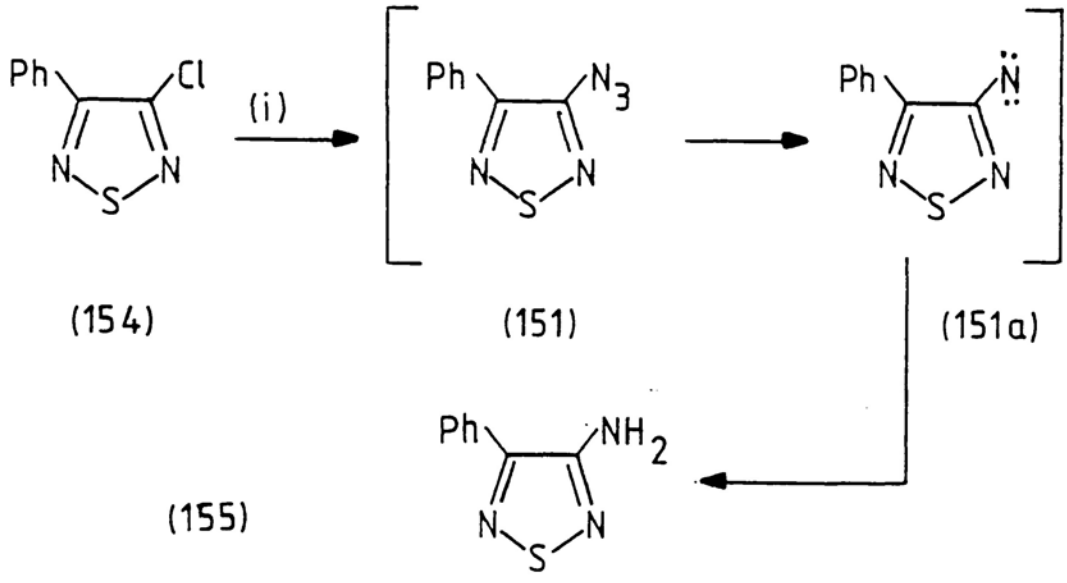
(i) KN_3 , 18-crown-6 , DMF, 140°, 6·5 h

The production of the amine (155) suggested strongly that the azide (151) had indeed been formed. There is no other more likely way in which a C-N bond can be formed with cleavage of the C-Cl bond of the thiadiazole except than by nucleophilic displacement of the chloride by the 'naked' azide ion in the aprotic solvent. The azide (151) presumably decomposed with the loss of nitrogen under these reaction conditions to the nitrene intermediate (151a) which underwent hydrogen abstraction to give the amine (155). This method of preparation of the amine (155) provides a useful alternative to two



(i) S_4N_4 , xylene , Δ , 6h (ii) S_4N_4 , toluene , Δ , 6h

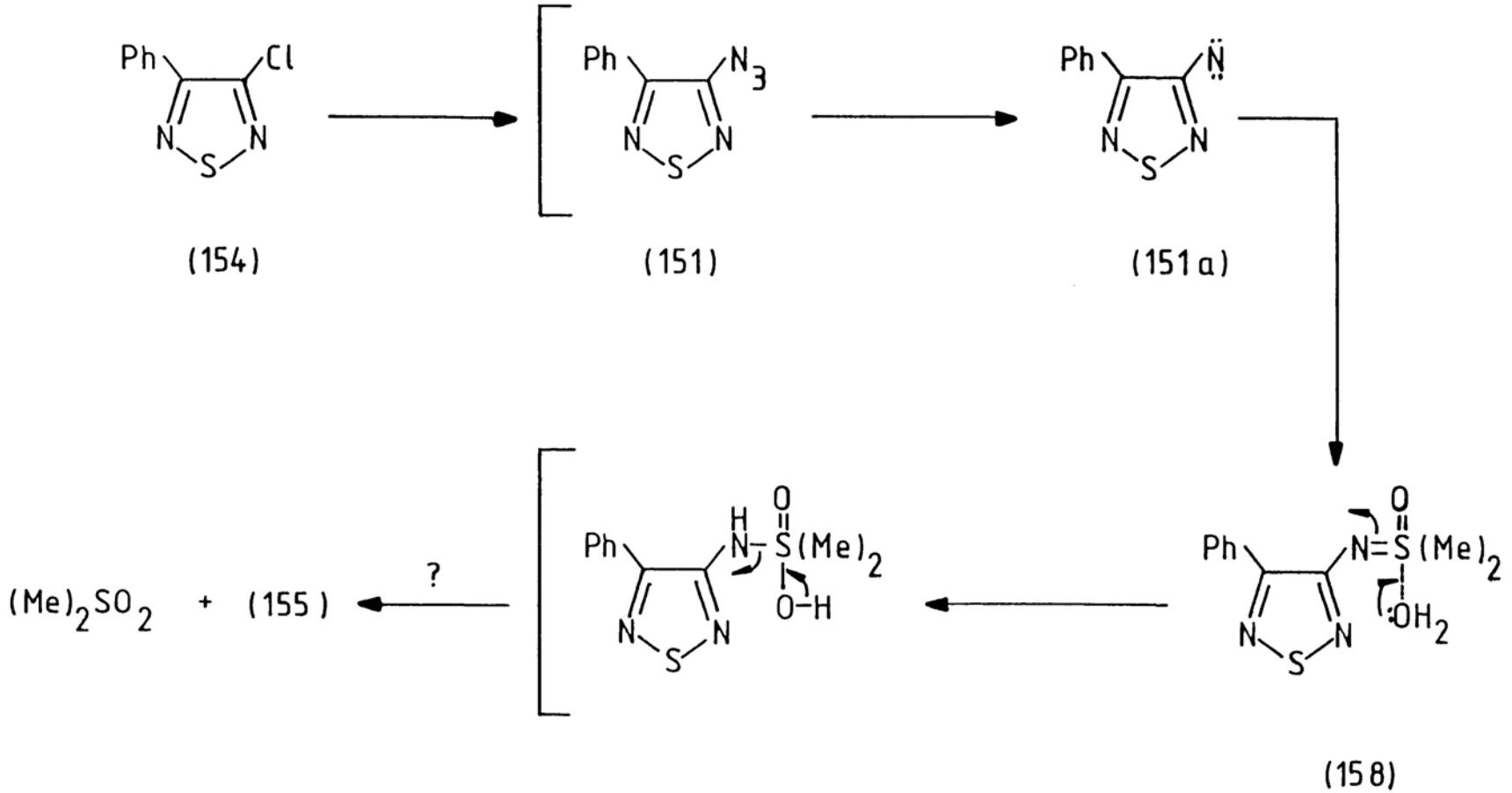
known literature methods.[125,126] The amine (155) was reported to have been synthesised from 2-phenethylamine[125] or phenylacetylene[126] on heating under reflux with tetrasulphur tetranitride in xylene and toluene for 6 h. The reported yield of the amine (155) varied from 5% to a maximum of 15% compared to 22% obtained from the chloro compound (154) by the method described above. We found that reactions with tetrasulphur tetranitride constantly gave complex mixtures of at least 15 spots on tlc. These reactions either proceeded extremely slowly or not at all if the temperature was lowered to that of boiling benzene. Attempts to alter the azide displacement reactions conditions to favour azide formation by heating the chloro compound (154) with sodium azide in aqueous DMSO (DMSO: water, 5:1) at 125° for 6 h provided an improved yield of the amine (155) (50%). Neither the azide (151) nor the sulphoximide (158) were



(i) NaN_3 , DMSO:water(5:1), 125°, 6h

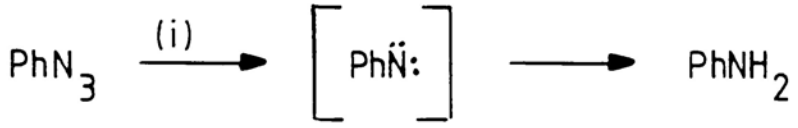
isolated. This reaction was very clean compared to the three methods mentioned above and it was routinely used for preparing the amine (155).

The formation of the amino compound (155) from the chloro compound (154) in both cases, i.e., with potassium azide, 18-crown-6 in DMF at 140° for 6.5 h and with sodium azide in aqueous DMSO at 125° for 6 h probably occurred through hydrogen abstraction by nitrene intermediate (151a), the latter coming from the decomposition of the azide (151). However, it was rather surprising to observe the production of the amine (155) in the latter case rather than the formation of the sulphoximide (158) since DMSO is usually an extremely good nitrene trap.[87, 96, 127] A possible explanation for the formation of the amine (155) in this case could be hydrolysis of the sulphoximide (158), if this is formed under the vigorous reaction conditions with the elimination of water soluble dimethyl sulphone. The hydrolysis has yet to be tested since sulphoximides


Ph
Cl
N
S
N
(154)
Ph
N3
(151)
Ph
N
(151a)
Ph
O
N=S(Me)2
OH2
(158)
Ph
H
N
O
S(Me)2
O–H
?
(Me)2SO2 + (155)

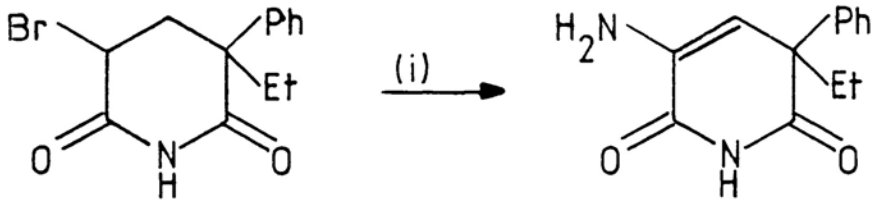
are usually stable compounds.[127] An explanation for the formation of the amine (155) invoking hydrogen abstraction from water by a nitrene is very unlikely since the species generated ($^{\cdot}OH$ or ^{+}OH) in the process would be extremely reactive. Hydrogen abstraction from DMSO by nitrenes is also unknown and unlikely since DMSO usually traps nitrenes very efficiently as sulphoximides.

The formation of the amine (155) by hydrogen abstraction of the nitrene generated when DMF was used seemed reasonable. The formation of an amidine corresponding to that of 1,2,4-oxadiazole azide was not observed with azide (151). When phenyl azide was heated under reflux in anhydrous DMF for 24 h a complex mixture was obtained and aniline (4%) was the only product identified. The formation of the aniline must be by hydrogen abstraction of the nitrene generated by the loss of nitrogen from phenyl azide.



(i) DMF, Δ, 24h

There are two recent reports of similar reactions involving the formation of primary amines from the corresponding chloro- or bromo compounds by using sodium azide in DMSO. The first report was the conversion of the bromo compound (159) to the amino compound (160).[128]



(159) (160)

(i) NaN_3 , aq. DMSO

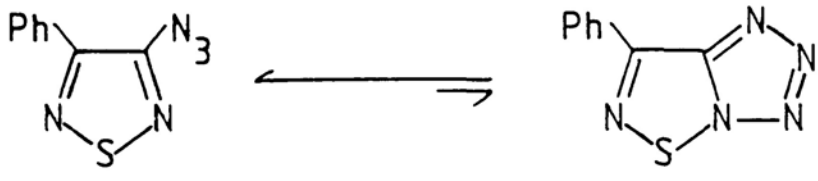
The mechanism for the formation of the amine was claimed to be a nitrene insertion into a C-H bond. This compares with the presumed intermolecular hydrogen abstraction in our case. The second report[129] was the conversion of the aryl-halogeno derivatives shown in Table V to the corresponding primary arylamines.

Table V.

Substrate	temp/°C	time/h	Yield of $ArNH_2$/%
p-chloronitrobenzene	140	2.5	60
m-chloronitrobenzene	170	20	40
p-chloroacetophenone	170	16-18	30
4-chlorobenzofurazan	140	14-15	35

The direct procedure for this synthesis of primary aromatic amines seems to be of synthetic interest and far shorter than other routes which start from the corresponding halogen compound. Thus, the best route to the amino compound (155) is from heating the chloro compound (154) with sodium azide in aqueous DMSO as described earlier.

Diazotisation of the amine (155) in 2 M hydrochloric acid at -10° followed by the addition of the solution of the diazonium salt over 0.5 h to a solution of excess sodium azide in water and dichloromethane at -10° provided the azide (151) (50%). Any variation of these reaction conditions or of the procedure results in a complex mixture. Azido-tetrazole tautomerism was not observed with this azide since the azide stretching band at 2120 cm^{-1} was still very strong in solution (chloroform).

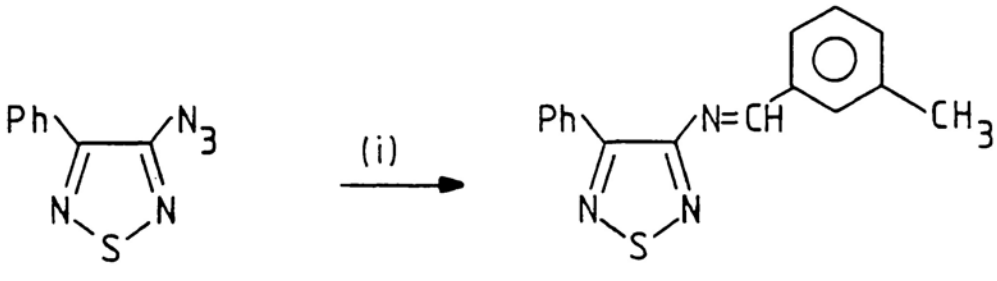


(151) (151a)

4.3.2.2. Decomposition.

4.3.2.2.1. Thermolysis.

An attempted fragmentation of 3-azido-4-phenyl-1,2,5-thiadiazole (151) by thermal decomposition was carried out to see if thionitrosyl cyanide (153) could be generated. When the azide (151) was heated under reflux in anhydrous toluene for 10 h, tlc indicated that the reaction mixture contained mainly the starting material. However, on heating the azide (151) under reflux in anhydrous m-xylene for 14 h an unexpected product, 3-(3'-methylbenzylidenamino)-4-phenyl-1,2,5-thiadiazole (161) (52%, based on azide consumed) was obtained together with recovered starting material (151) (27%). The structure of the Schiff base (161) was elucidated from its mass spectrum and pmr spectrum. As additional evidence, an authentic sample of this Schiff base (161) (75%) was synthesised by condensation of 3-amino-4-phenyl-1,2,5-thiadiazole (155) with m-tolualdehyde. The m.p. and ir, pmr, and mass spectra of the Schiff base obtained from thermolysis were identical to those of the authentic sample.



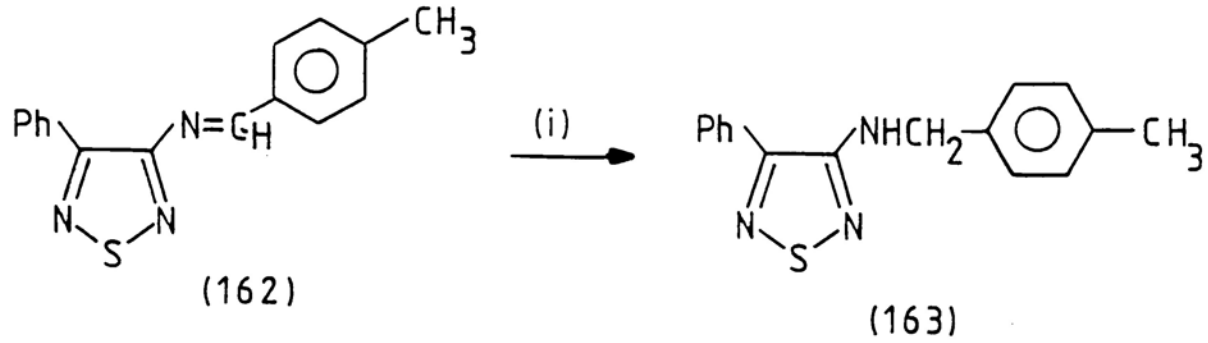
(151) (161)

(i) m-xylene , Δ , 14h

When the thermolysis of the azide (151) was carried out by heating under reflux in anhydrous p-xylene for 16 h the corresponding 3-(4'-methylbenzilidenamino)-4-phenyl-1,2,5-thiadiazole (162) (65%, based on the azide consumed) was obtained together with some recovered starting material (151) (25%). An authentic sample of this Schiff base (162) (75%) was prepared by condensation of the amine (155) with p-tolualdehyde and had identical m.p., ir, pmr, mass spectra to those of the product from the azide thermolysis.

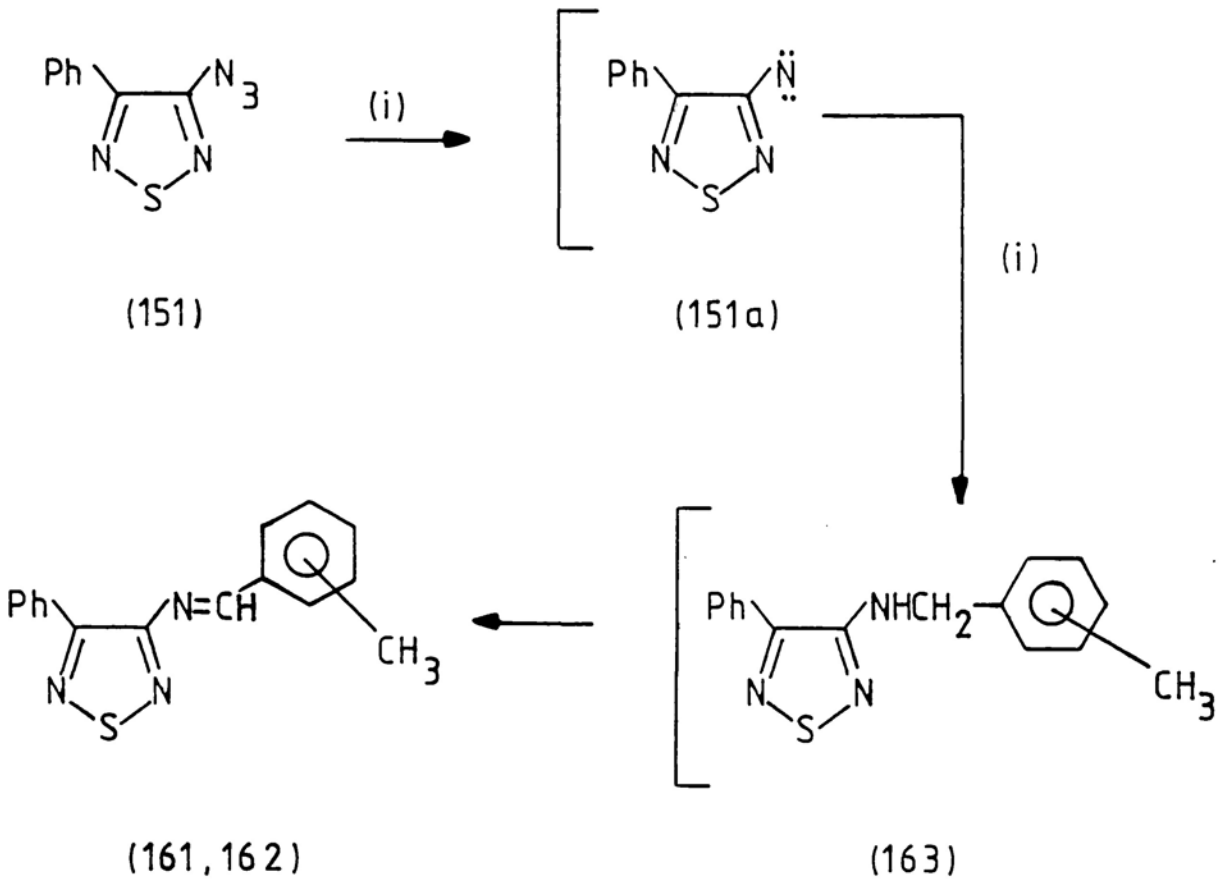
These Schiff bases, (161) and (162) were presumably formed by nitrene insertion into one of the methyl groups of the xylene, followed by hydrogen abstraction from the resultant amine (163) by air oxidation or by a second nitrene molecule.

This explanation for the formation of the Schiff bases (161) and (162) seems reasonable since oxidation occurs at a reactive benzylic position. In order to test this hypothesis an authentic sample of the proposed and previously unknown intermediate, 3-(4'-methylbenzylamino)-4-phenyl-1,2,5-thiadiazole (163) was required. Attempts to synthesise this amine (163) from the chloro compound (154) by heating with benzylamine at 145^{o} for 6.5 h gave a complex mixture. When 3-amino-4-phenyl-1,2,5-thiadiazole (155) was heated under reflux in anhydrous toluene with benzyl chloride and potassium carbonate, no reaction occurred after 14.5 h. The amine (163) (93%) was finally synthesised by sodium borohydride reduction of the Schiff base (162) in anhydrous methanol.



(162) (163)

(i) $NaBH_4$, MeOH, Δ

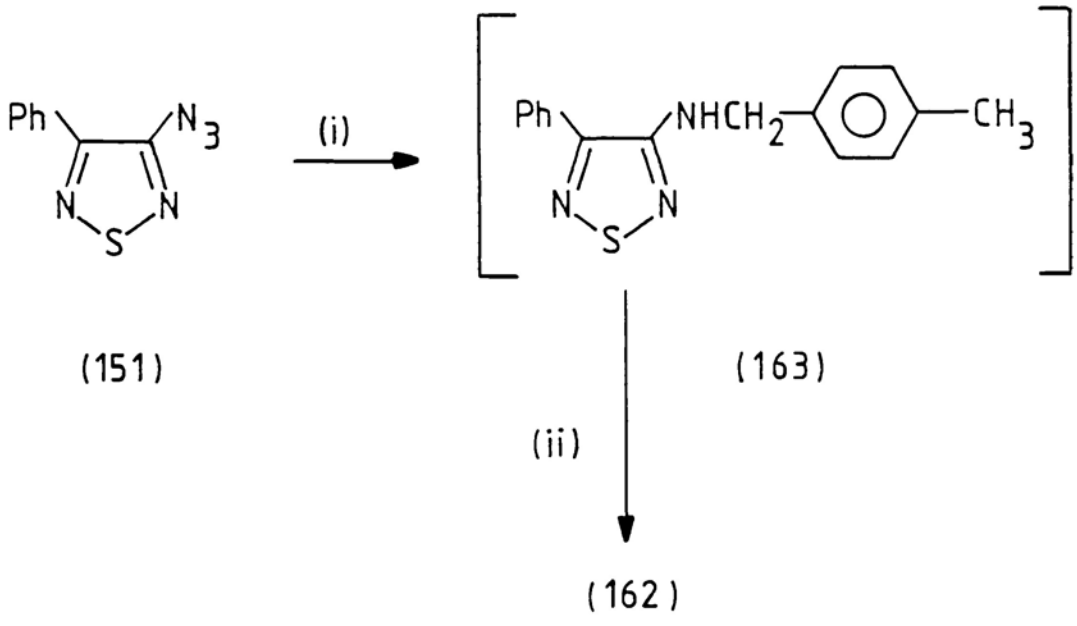


(151) (151a) (163) (161, 162)

(i) m- or p-xylene

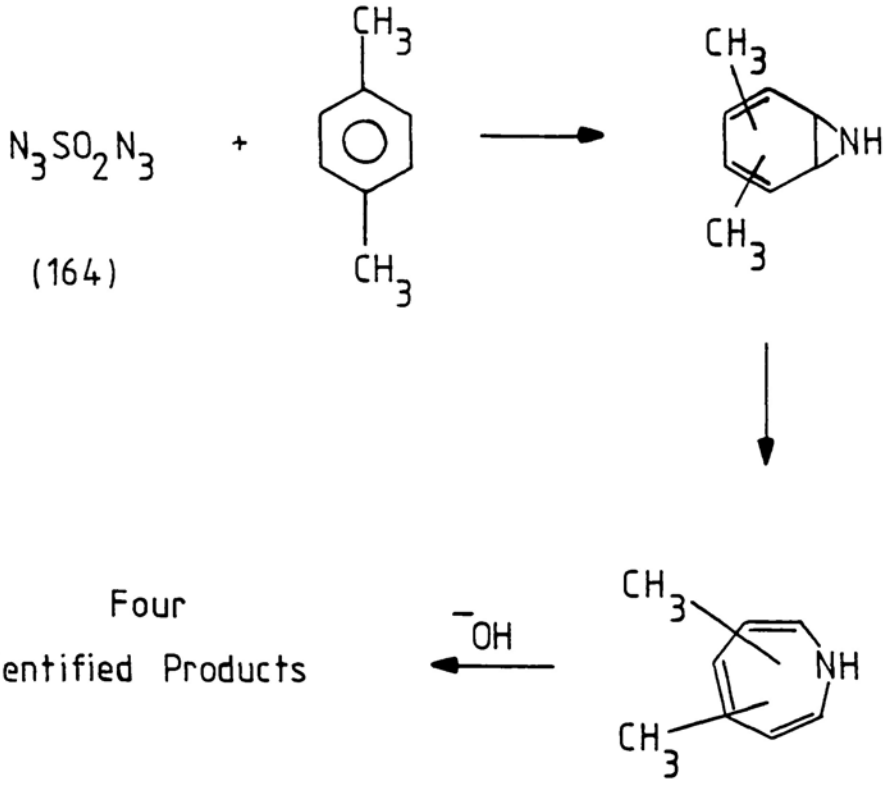
Having synthesised the proposed intermediate (163), a blank experiment was carried out by heating this amine (163) in anhydrous p-xylene under reflux in air for 18 h. A quantitative recovery of the amine (163) was obtained on work up and no Schiff base (162) was present in the reaction mixture by ir and tlc. This strongly suggested that benzylic oxidation by air of the amine (163) did not take place.

The other explanation for the formation of the Schiff bases, (161) and (162), by hydrogen abstraction by the heterocyclic nitrene from the intermediate (163) also seemed to be reasonable. If the reaction did occur by this mechanism, the primary amine (155) will be a by-product of this reaction. However, the presence of this amine (155) could not be inferred by tlc since the Schiff bases, (161) and (162), were hydrolysed extremely easily on silica gel, and did themselves show a spot for the amine (155).

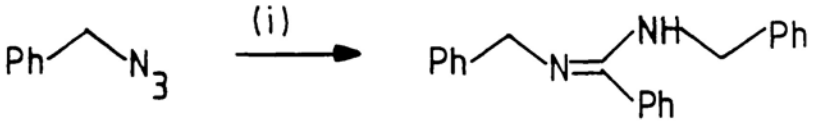


(i) p-xylene (ii) (151a)

Intermolecular insertion of a nitrene into one of the methyl groups of xylene is not known to date. Thermolysis of various azides in xylene (ortho or para) resulted either in no insertion at all or insertion of the nitrene into a ring C-H of the xylene leaving the two methyl groups intact.[87,96] The first reported thermolysis of an azide in xylene was carried out by Curtius in 1915 when he heated bis(sulphonylazide) (164) with p-xylene and obtained four unidentified products of molecular formula, $C_8H_{11}N$, C_8H_9N, C_8H_9N (m.p. 112°) and C_8H_9N (m.p. 85°) after alkaline hydrolysis.[130]



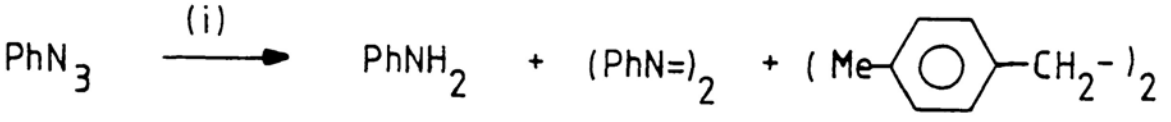
Seven years later Curtius reported that on thermolysis of benzyl azide (165) in xylène, N,N'-dibenzylbenzamidine (166) was obtained.[131]



(165) (166)

(i) Δ , xylene

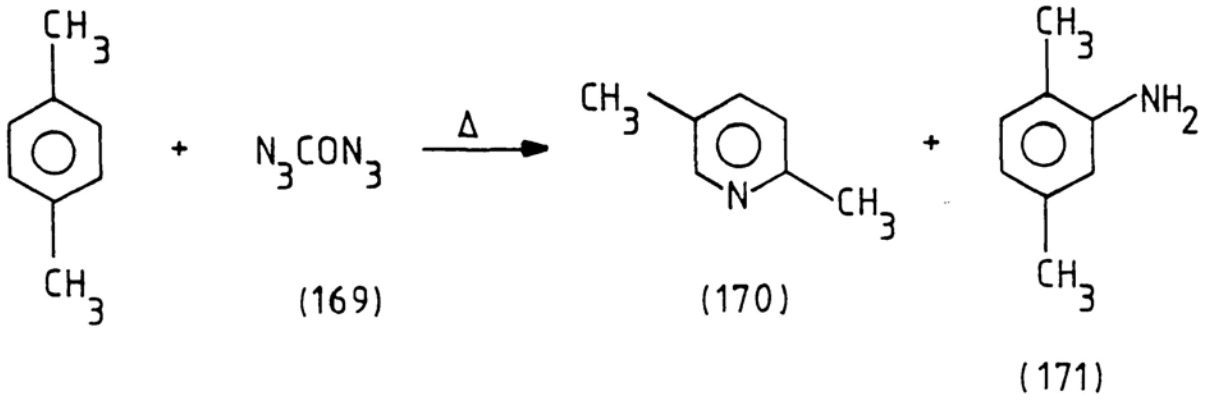
The mechanism was not given by the author but reaction of the benzyl azide (165) with xylene was ruled out. Two years later, Bertho[132] described the thermolysis of phenyl azide in p-xylene under pressure at 150-160° for 7-8 h to give aniline (85%) and small amounts of azobenzene (dimerisation product) (167) and p,p'-ditolylethane (168). The latter was presumably formed from the dimerisation of the two p-xylene radicals after hydrogen abstraction by the nitrene.



(167) (168)

(i) Δ , p-xylene

Thermolysis of bis(carbonyl azide) (169) with p-xylene was reported in 1926 by Curtius and the insertion products were 2,5-lutidine (170) and p-xylidine (171) produced in small amounts, with " Humuskörper" , a brown amorphous substance of undetermined composition being the major product of the reaction.[133]



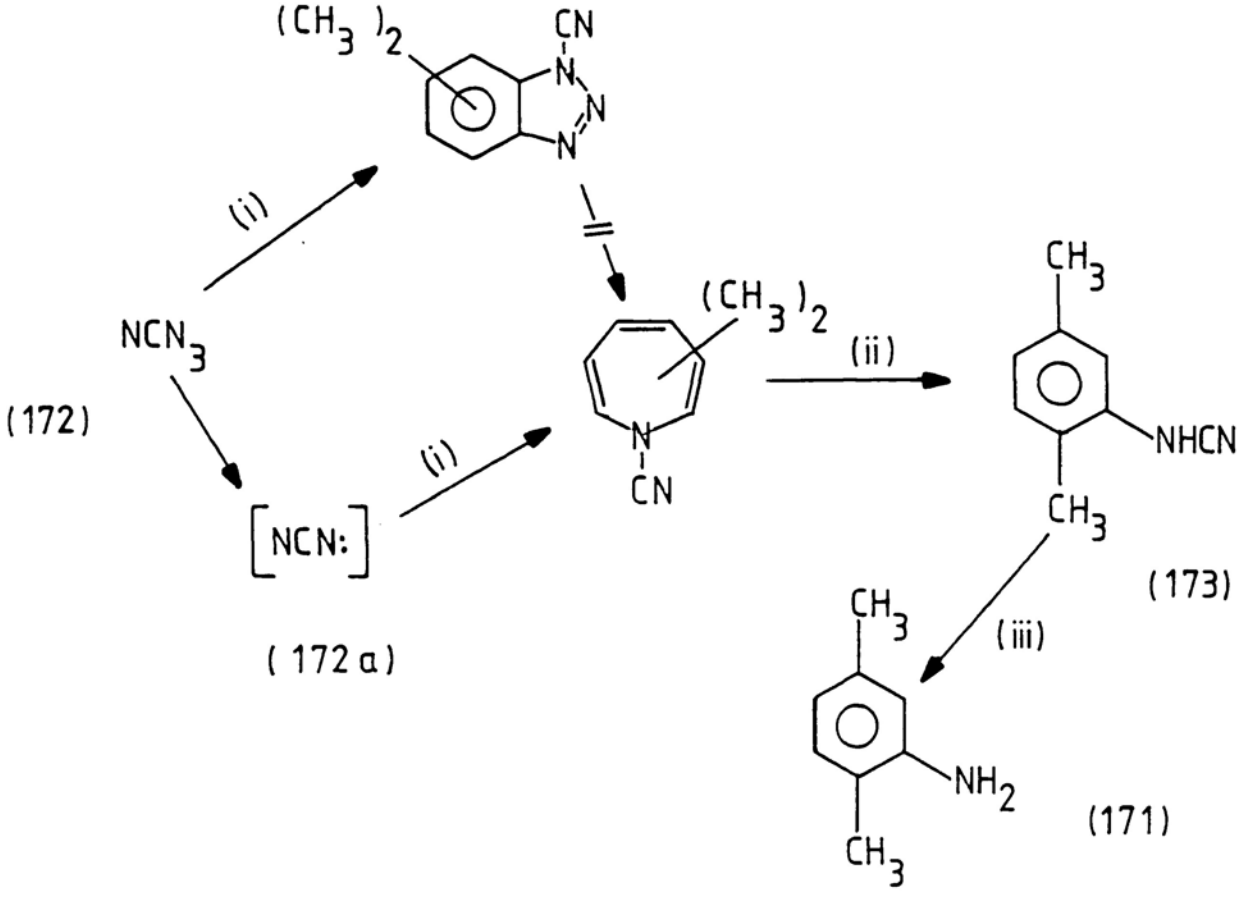
(169) (170) (171)

Thermolysis of cyanogen azide (172) in p-xylene to give p-xylidine (171) on acid hydrolysis of the cyanamide (173) was reported by Marsh in 1965 (Scheme 14).[134] A list of insertion products derived from reactions of arylsulphonyl azides with o- and p-xylene is shown in Table VI.[135-140] In all the cases where insertion of the nitrene into the xylene took place, both the methyl groups were still present in the products.

This brief summary of intermolecular insertions into xylene by a variety of nitrenes showed that preferential insertion into the ring C-H bond occurred. In general, the order of insertions by nitrenes into aliphatic and aryl C-H bonds are in the order $CH > CH_2 > CH_3$.[87,96]

Table VI

Solvent	RSO_2N_3, R =	Insertion Product	Yield/%	Reference
o-xylene	p-$CH_3CONHC_6H_4$	$RSO_2NHC_6H_4$-3,4-$(Me)_2$	25	139
p-xylene	$PhCH_2$	$RSO_2NHC_6H_3$-2,5-$(Me)_2$	-	135
p-xylene	Ph	$RSO_2NHC_6H_3$-2,5-$(Me)_2$	67	136
p-xylene	p-$CH_3C_6H_4$	$RSO_2NHC_6H_3$-2,5-$(Me)_2$	53 (crude)	138
p-xylene	p-$C\ell C_6H_4$	$RSO_2NHC_6H_3$-2,5-$(Me)_2$	51 (crude)	139
p-xylene	o-IC_6H_4	$RSO_2NHC_6H_3$-2,5-$(Me)_2$	Trace	136
p-xylene	o-$NO_2C_6H_4$	$RSO_2NHC_6H_3$-2,5-$(Me)_2$	33	136
p-xylene	p-$CH_3CONHC_6H_4$	$RSO_2NHC_6H_3$-2,5-$(Me)_2$	50	137
p-xylene	2-$C_{10}H_7$	$RSO_2NHC_6H_3$-2,5-$(Me)_2$	12	140

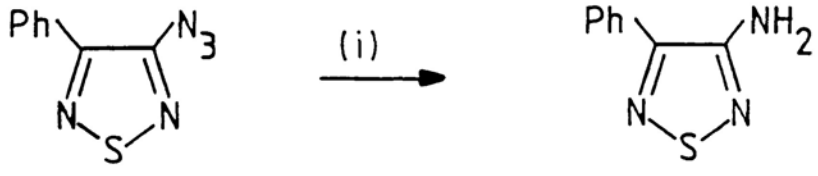


Scheme 14 (i) p-xylene (ii) H^+ (iii) Δ , H_3O^+

From this discussion, we can see that the reaction discovered in the course of this work is a unique example of intermolecular nitrene insertion into one of the methyl groups of m- and p-xylene, proceeding in moderately good yields, though the mechanistic details still need to be unravelled.

4.3.2.2.2. Photolysis.

Attempts to fragment the azide (151) by photolysis at 300 nm in anhydrous, degassed, acetonitrile over 15 min provided a complex mixture of five different compounds by tlc (dichloromethane: petroleum ether; 1:1). The only products isolated were 3-amino-4-phenyl-1,2,5-thiadiazole (155) (26%) and an unidentified yellow solid (14.8%), the latter being the major component among the four other products which could not be identified.



(151) (155)

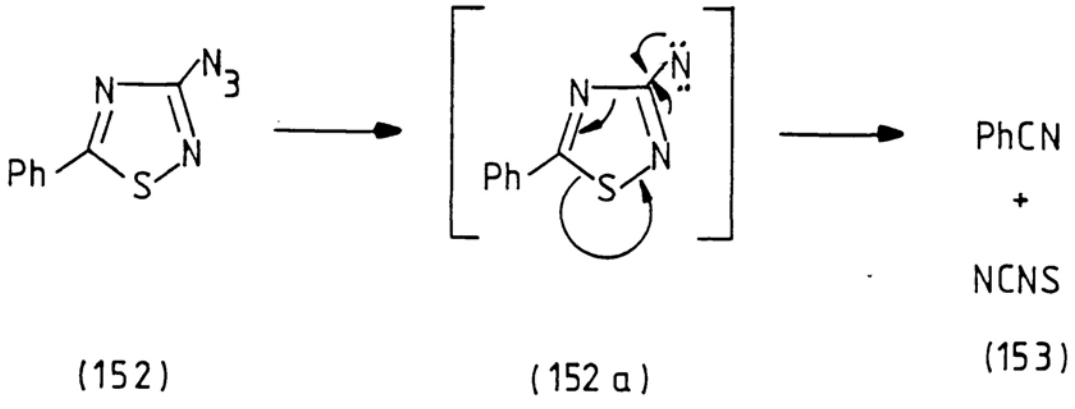
(i) $h\nu$ 300nm , MeCN , N_2 , 15 min

When the azide (151) was photolysed at 254 nm in anhydrous, degassed acetonitrile in the presence of DMSO (50:1) for 0.5 h in an attempt to trap the nitrene, a complex mixture of at least five spots was observed on tlc. The sulphoximide (158) could not be identified in any of fractions after chromatography and no benzonitrile could be detected in the crude reaction mixture.

4.3.3. 3-Azido-5-phenyl-1,2,4-thiadiazole (154).

4.3.3.1. Synthesis and decomposition

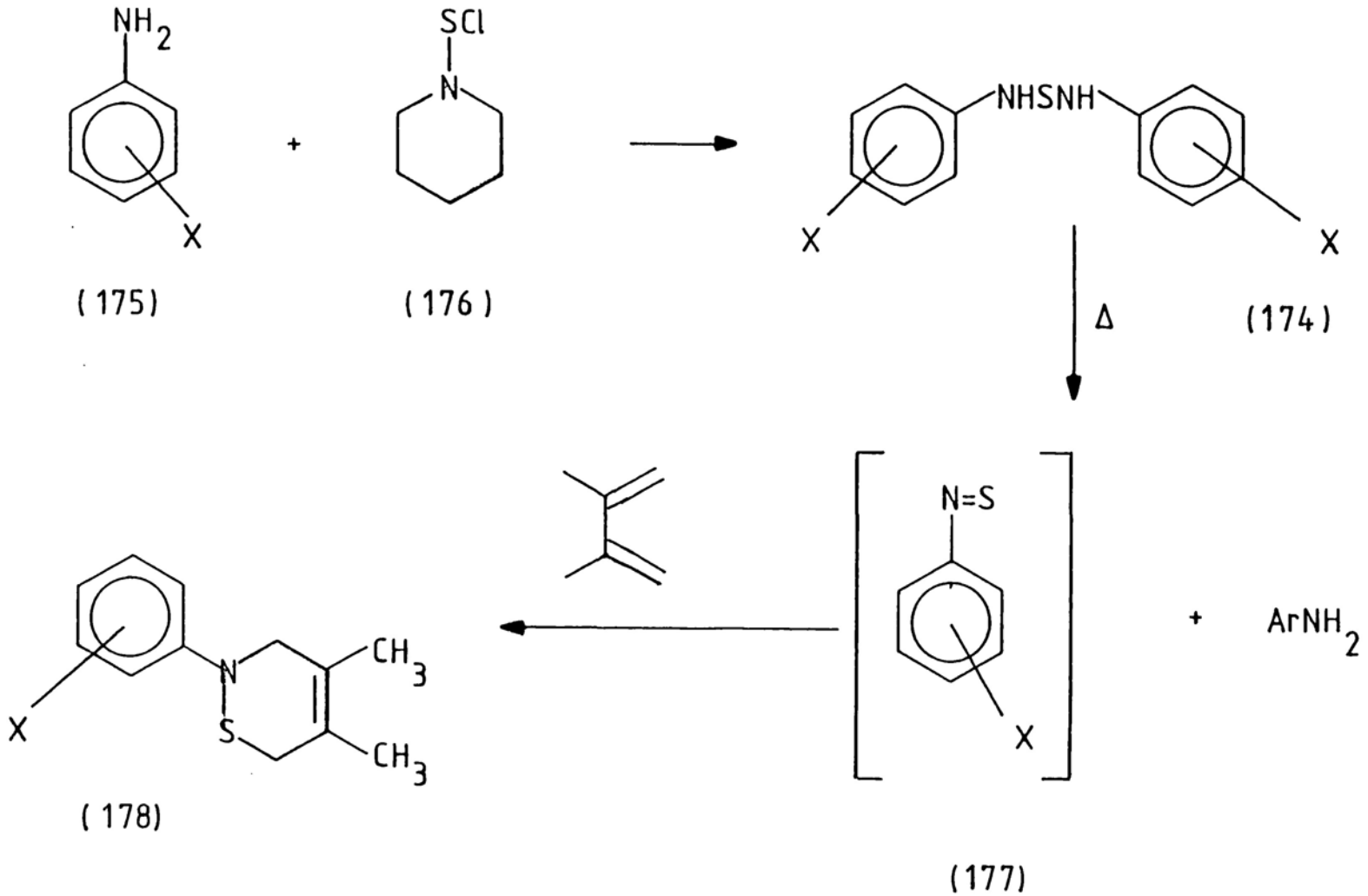
This azide, 3-azido-5-phenyl-1,2,4-thiadiazole (152) represents an alternative source of the unknown thionitrosyl cyanide if the corresponding nitrene undergoes fragmentation of the heterocyclic ring as in equation A, the nitrene being in the β-position (see 4.1).



(152) (152 a) (153)

Thionitrosyl compounds, R-N=S, are rare, but have been reported as reactive intermediates in the decomposition of N,N'-thiodianilines (174). The latter were prepared from substituted anilines (175) and piperidine-1-sulphenyl chloride (176) in anhydrous diethyl ether at -20°. The intermediate N-thioanilines (177), were trapped with dimethylbutadiene to give the adducts, 2-aryl-3,6-dihydro-4,5-dimethyl-1,2-thiazines (178),[141] (Scheme 15).

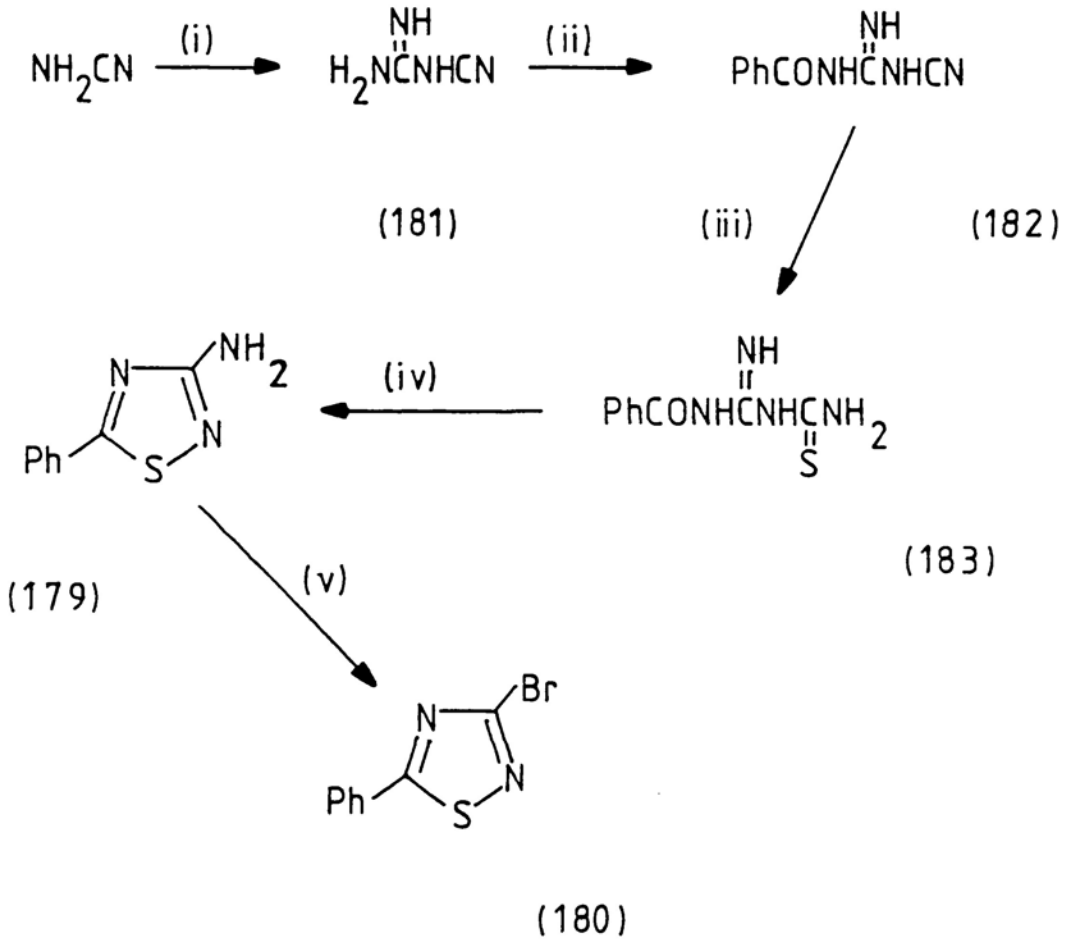
The two possible precursors to the required azide (152) viz., 3-amino- and 3-bromo-5-phenyl-1,2,4-thiadiazole, (179) and (180)



(175) (176) (174) (177) (178)

Scheme 15 X = H, Cl, Br, NO_2

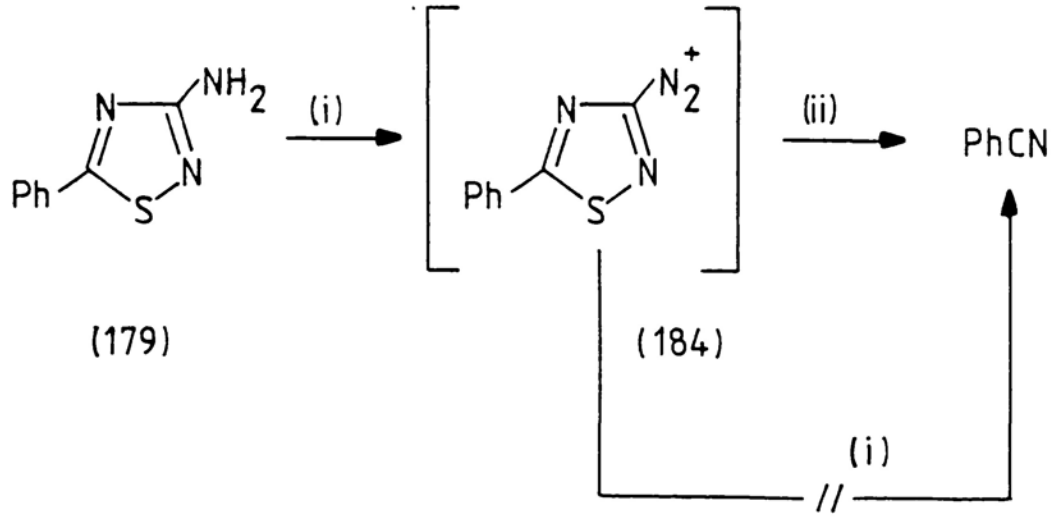
respectively, are known compounds. The bromo compound (180) (22%) can be synthesised by diazotisation of the amino compound (179) at 0^{o} in concentrated hydrobromic acid.[142] The synthesis of the amino compound (179) starting from cyanamide or dicyanamide is shown in Scheme (16).



Scheme 16 (i) aqueous NH_3 (ii) PhCOCl (iii) H_2S , EtOH (iv) H_2O_2 , EtOH (v) $NaNO_2$, Cu , HBr

Dicyanamide (181) was readily synthesised in quantitative yield by dimerisation of cyanamide in aqueous ammonia.[143] Benzoylation of the dicyanamide (181) in the presence of potassium hydroxide in acetone at 10° provided N-benzoyldicyanamide (182) (90%).[144] The latter was not isolated but was reacted immediately with a saturated ethanolic solution of hydrogen sulphide to give N-(benzoylamido)thiourea (183) (50%)[144] as yellow crystals after two recrystallisations from ethanol. On heating the thiourea (183) in hydrogen peroxide (6%) and ethanol under reflux until the yellow colour of the solution was completely discharged, the amino compound (179) was obtained in 80% yield.[145]

It was decided to attempt initial synthesis of the azide (152) from the amine (179). The first attempt by diazotisation of the amine (179) in 6 M hydrochloric acid at 0°, followed by the addition of sodium azide did not give the azide (152) but gave benzonitrile (18%) instead.



(i) $NaNO_2$, 0° (ii) NaN_3, H_2O, CH_2Cl_2, 0°

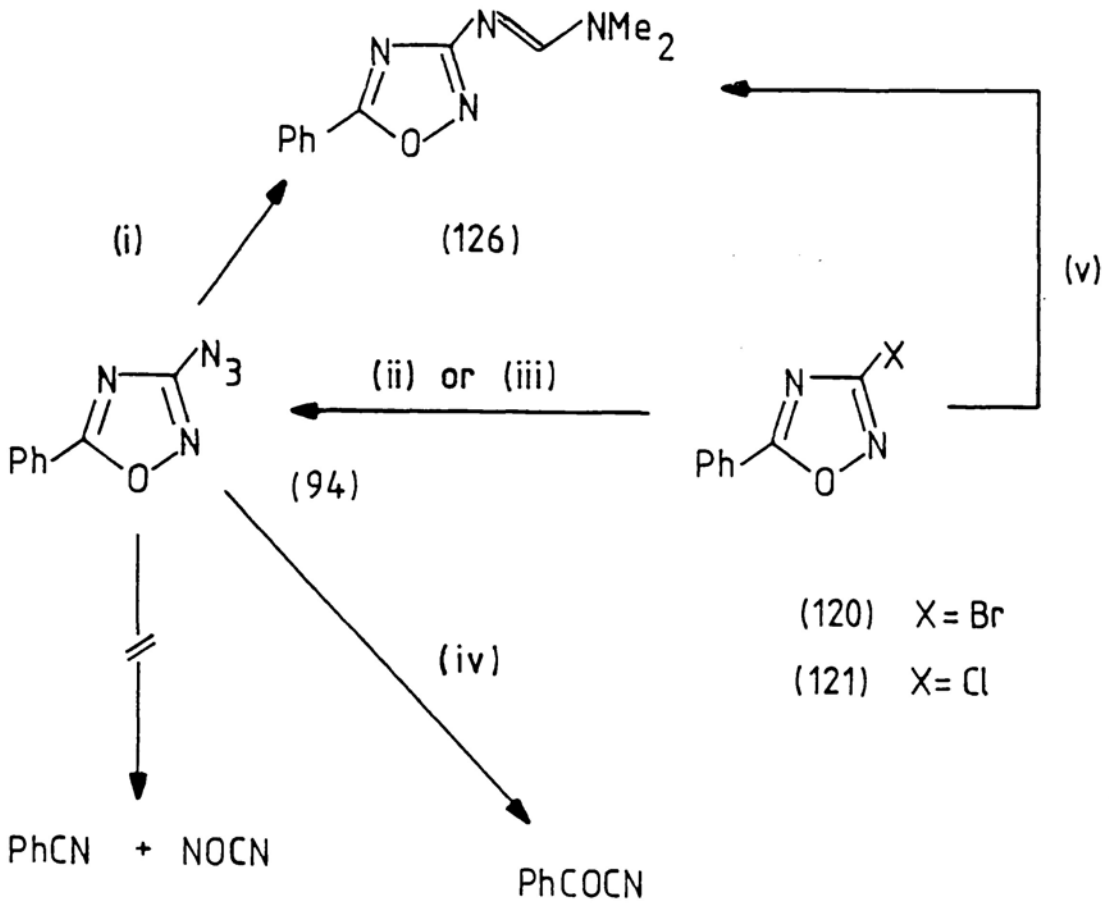
Benzonitrile could have been obtained from either the breakdown of the diazonium salt (184) in some unknown fashion or of the azide (152) once formed. A blank experiment showed that benzonitrile was not present after diazotisation of the amine (179). Tlc showed base-line material only. Benzonitrile (R_f 0.85) was obtained only on addition of sodium azide when rapid evolution of gas occurred. This observation strongly suggested that the azide (152) was formed but was too unstable under these reaction conditions and fragmented to give benzonitrile. The other fragment could well have been thionitrosyl cyanide (153) but it was probably too reactive and unstable to be isolated under these reaction conditions. This could present a synthetic method to generate this new highly reactive and unstable species (153) if sufficiently mild conditions could be found for its isolation or trapping.

Georgeler and Mertens[146] claimed that the diazonium salt (184) was relatively unstable. This could have accounted for the low yield of the benzonitrile obtained. Benzonitrile was not detected when they diazotised the amine (179). This substantiated the blank experiment and the supposition that the benzonitrile was a fragmentation product of the azide (152). The synthesis of the azide (152) from the bromo compound (180) was not attempted since this azide appeared to be too unstable to survive the vigorous conditions which may have been required. It is just possible, however, that the rapid decomposition of azide (152) is acid catalysed and the azide (152) is thermally fairly stable.

4.4. Concluding remarks to 4.0.

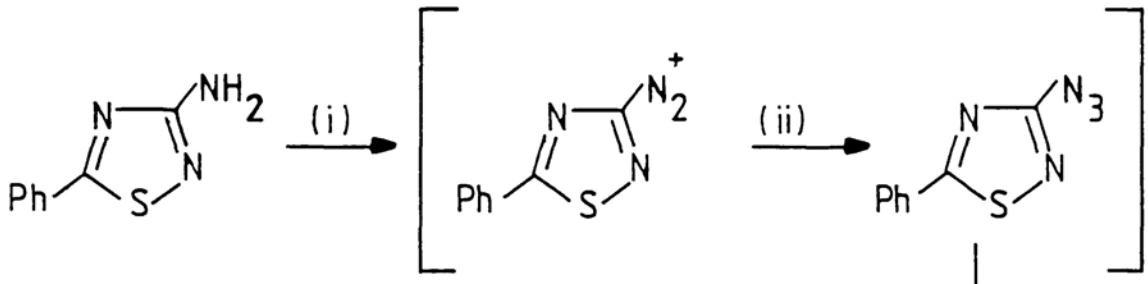
The study of the decomposition reactions of five-membered-ring heterocyclic azides provided some very interesting and novel reactions. Although 3-azido-5-phenyl-1,2,4-oxadiazole (94) did not provide nitrosyl cyanide on decomposition as expected nevertheless the F.V.P. of this azide (94) gave the unexpected benzoyl cyanide in high yield and its thermolysis in DMF provided N,N'-dimethyl-N" -(5-phenyl-1,2,4-oxadiazol-3-yl)formamidine (126) in moderate yields. This new and novel reaction was first observed in the attempted synthesis of azide (94) from the corresponding 3-bromo and chloro-5-phenyl-1,2,4-oxadiazole (120 and 121) with sodium azide in DMF. Subsequently, the azide (94) was postulated and proved to be the intermediate in the reaction. It is unfortunate that the corresponding 3-azido-4-phenyl-1,2,5-oxadiazole (95) could not be synthesised in substantial amounts for decomposition reactions. Comparison of these two oxadiazole azides, (94) and (95) will be interesting.

The sulphur analogues, 3-azido-4-phenyl-1,2,5-thiadiazole (151) and 3-azido-5-phenyl-1,2,4-thiadiazole (152), also provided some very interesting decomposition reactions. 3-Azido-5-phenyl-1,2,4-thiadiazole was believed to be very unstable even at 0-5^{o} since benzonitrile, a fragmentation product, was obtained during its synthesis by diazotisation of the corresponding amine (179). This reaction provided a possible synthetic route to a new and highly reactive species, thionitrosyl cyanide (153) and was the only azide that fragmented as expected for



(i) NaBr, DMF (ii) LiN_3, DMF, 90° (iii) KN_3, 18-crown-6, DMF, 90°
(iv) 500-550°, 7.5×10^{-2} torr (v) NaN_3, DMF, 120-130°

β-substituted heterocyclic azides. The decomposition product of azide (151) in m or p-xylene provided 3(3'- or 4'-methylbenzylidenamino)-4-phenyl-1,2,5-thiadiazole (161 or 162) in moderately good yields. These reactions are the first observed intermolecular insertions of heterocyclic nitrenes (151a or 152a) into one of the methyl groups of xylene with subsequent hydrogen abstraction by the excess nitrene to provide the Schiff bases (161 or 162).

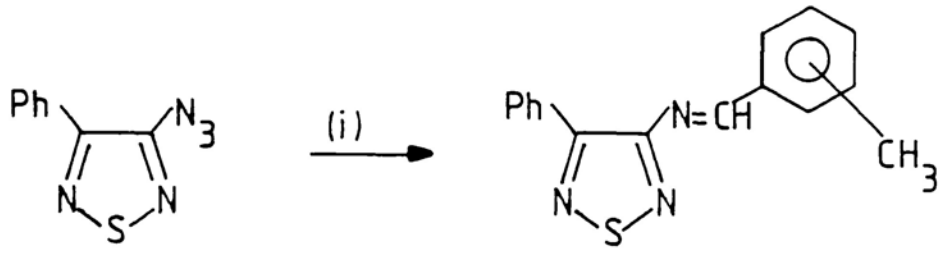


(179) (152)

PhCN + N_2 + NCNS

(153)

(i) HNO_2, 0-5° (ii) NaN_3



(151) (161, 162)

(i) m- or p-xylene

All three azides (94), (95) and (151) remained mainly in the azido form both in the solid state or in solution and cyclisation to the tetrazole form was not observed. It is interesting to note that azide (94) was not decomposed in boiling xylene but the sulphur analogue decomposed at 0-5°. Comparison of the stability and reactivity of these four azides (94, 95, 151 and 152) will be interesting but a very much better synthetic route to azide (95) will be required to provide the 'missing link' in this study.

EXPERIMENTAL

5.0. EXPERIMENTAL

Spectra.

Infra-red spectra (ir) were recorded in the range 200-4000 cm^{-1} and/or 600-4000 cm^{-1} using Perkin-Elmer 257 and 298 spectrophotometers and calibrated against polystyrene. Spectra of solids were taken as Nujol mulls or potassium bromide disc and liquids as thin films between sodium chloride plates or in solution cells with the appropriate solvents. All values quoted are medium to strong stretching bands in the spectra.

Ultra-violet and visible spectra (uv) were recorded in the range 200-700 nm using a Pye Unicam SP 800 or SP 1800 ultraviolet spectrophotometer using cells of 1 cm path length. Solvents used are indicated in the experimental data.

Proton nuclear magnetic resonance spectra (pmr) were recorded using Varian T60 (60 MHz), EM 360 A (60 MHz), Perkin-Elmer R 32 (90 MHz), or Bruker WM 250 (250 MHz) instruments, with tetramethylsilane as internal standard and reference. Signals are quoted as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m), or broad (br). Solvents are indicated in the experimental data.

Low and high resolution mass spectra were recorded on A.E.I. MS 12 and VG Micromass 7070 B instruments. Spectra were recorded at 70 or 12 eV using a direct insertion probe or septum inlet.

Melting points.

Melting points were carried out on a Kofler Hot Stage apparatus and are uncorrected.

Solvents.

Petroleum ether b.p. 40-60°, 60-80°, 80-100° were distilled before used. Petroleum ether in the experimental referred to 60-80° b.p. range. Dichloromethane was distilled prior to use and dried by refluxing over phosphorus pentoxide. Acetonitrile, dimethylformamide, and dimethyl sulphoxide were dried over calcium hydride and distilled directly into the reaction vessel. Pyridine, triethylamine and piperidine were dried over potassium hydroxide. Hydrocarbon and diethyl ether were dried by standing over sodium wire. Tetrahydrofuran and dioxan were dried over sodium wire and benzophenone and distilled directly into the reaction vessel under dry nitrogen. Carbon tetrachloride was dried over calcium chloride and distilled before use. Ethyl acetate and bromobenzene were distilled before use. Ethanol in chloroform was removed by passing through a column of basic Alumina (Brockmann Grade I) when necessary. Acetone, ethanol and methanol were used as supplied commercially in AR grade.

Chromatography.

Column chromatography was carried out on silica gel H Art. 7736 (Merck) or neutral alumina 'H' (Laporte Industries Ltd.) under pump pressure or nitrogen at 7 p.s.i. Thin layer chromatography (tlc) were used extensively as an analytical technique for following the progress of reactions and assessing the purity of compounds. Silica gel GF_{254} (Merck) on 20 x 5 cm plates and commercial tlc plates Art. 5554 (Merck) were also used. All commercial tlc plates were developed once in the appropriate solvents before use.

Preparative layer chromatography (plc) was carried out on 20 x 5, 20 x 20, or 20 x 40 cm glass plates coated with a layer of silica gel GF_{254} (Merck) or Alumina 60 PF_{254} (Type E) (Merck). All plates were observed under ultraviolet light (254 nm) or in an iodine tank.

Photolysis.

Photochemical reactions were carried out using a Rayonet photochemical reactor of lamps 253.7 or 300 nm wavelength. The solvent used was degassed with dry nitrogen or argon. Nitrogen was bubbled into the reaction mixture throughout photolysis.

Drying agents.

Anhydrous sodium sulphate or magnesium sulphate were used extensively for drying solutions in organic solvents.

EXPERIMENTAL TO 2.0.

S,S'-Dimethylcyanodithiocarbonimidate (10) m.p. 52-53° (lit.[7] 53-54°).

Chlorination of S,S'-dimethylcyanodithiocarbonimidate (10).

S,S'-Dimethylcyanodithiocarbonimidate (19 g, 0.13 mol) was dissolved in dichloromethane (75 cm^3) and treated with chlorine (21 g, 0.3 mol) at -15° over 1 h. The reaction mixture was allowed to warm up to 0° and stirred for another 2 h. The excess chlorine in the reaction mixture was removed by bubbling nitrogen through the solution for 1 h at room temperature. The solvent was evaporated under reduced pressure to give a yellow oil. This yellow oil on standing at room temperature provided a white solid, (8.7 g, 50%), m.p., 210-212° (sublimed at 125°/4 mmHg) (methylthiollophanate, lit.[20] 205°); ν_{max} (nujol) 3380, 3350, 3320 (NH and NH_2), 1690 (C=O), 1670 (C=O), 1170, 1090, 1045, 970, 950, 890, 790, 740, 720, 625; δ (CF_3CO_2H), 2.5 (s, 3H, SMe); m/e, 134 (M^+), 87 (base), 48, 44, 28. After filtering, the filtrate was chromatographed on silica gel with petroleum ether: ethyl acetate (3:1) to provide an unstable white crystalline solid, N-cyanoimino-S-methylthiocarbonate chloride, (1.3 g, 7%), m.p. 34-36°, ν_{max} (nujol) 2210 (-CN), 1580 (C=N) 960, 725; δ ($CDC\ell_3$) 2.7 (s, 3H, SMe); m/e 136, 134 (M^+, one chlorine pattern), 99 (M-Cℓ, base), 73, 18 (Found: C, 25.65; H, 2.10; N, 19.82; Cℓ, 26.45; S, 24.53. $C_3H_3N_2SC\ell$ requires C, 26.73; H, 2.40; N, 20.78; Cℓ, 26.30; S, 23.78%). Due to the instability of this product, better analysis figures could not be obtained.

Reaction of N-cyanoimino-S-methylthiocarbonate chloride (22) with benzylamine.

N-Cyano-S-methylthiocarbonate chloride (100 mg, 0.7 mmol) and benzylamine (160 mg, 1.48 mmol) were stirred in ethanol (20 cm^3) at room temperature for 0.5 h. The white solid which precipitated on standing at 2° overnight was filtered, dried (96 mg, 63%), m.p. 158-159° (N-benzyl-N'-cyano-S-methylthiourea, lit.[21] 157-158°), ν_{max} (nujol) 3290 (NH), 2170 (-CN), 1550, 1520, 1465, 1380, 1290, 965, 700; δ ($CDC\ell_3$) 7.5-7.1 (m, 5H), 4.5 (d, 2H), 2.5 (s, 3H); m/e 205 (M^+), 190, 158, 116, 106, 91 (base), 65, 48, 47, 32, 28.

N-Benzyl-N'-cyano-S-methylthiourea (23) m.p. 157-158° (lit.[21] 157-158°).

N,N'-Dibenzyl-N''-cyanoguanidine (24).

N-Benzyl-N'-cyano-S-methylthiourea was prepared *in situ* by treating S,S'-dimethyl-N-cyanodithiocarbonimidate (2 g, 13.7 mmol) with benzylamine (1.5 cm^3, 13.9 mmol) in ethanol (40 cm^3). Excess benzylamine (5 cm^3, 46.6 mmol) was added to the reaction mixture when tlc (petroleum ether: ethyl acetate (1:2)) indicated the absence of the starting material. The reaction mixture was heated under reflux for 32 h (Rf of the product and N-benzyl-N'-cyano-S-methylthiourea was identical). The solvent was removed under reduced pressure to provide the product (1.6 g, 44%), m.p. 140-141° (ethanol), ν_{max} (nujol) 3410, 3290 (NH), 2160 (-CN), 1580, 1500, 1425, 1365, 1355, 1275, 1260, 1075, 1030, 970, 810, 730, 700, 670; δ ($CDC\ell_3$) 7.2 (s, 10H, Ph), 5.8 (s, br, 2H, NH), 4.3 (d, 4H, CH_2); m/e, 264 (M^+), 106, 91 (base), 28 (Found: C, 72.77; H, 6.13; N, 21.35. $C_{16}H_{16}N_4$ requires C, 72.73; H, 6.10; N, 21.21%).

Dipotassium N-cyanodithiocarbonimidate (12) m.p. 218-219° (lit.[12] 215°).

Cyanoisothiocyanate (13)[14] ν_{max} ($CH_2C\ell_2$) 2240 (-CN), 1970 (br, -NCS).

N-Cyano-1-(chlorothio)formimidoyl chloride (20).

To cyanoisothiocyanate in anhydrous dichloromethane (100 cm^3), prepared according to the literature from dipotassium N-cyanodithiocarbonimidate (19.4 g, 0.1 mol), was added freshly distilled anhydrous dichloromethane (100 cm^3). Dry chlorine was bubbled through the reaction mixture at 0° for 7.5 h. The excess chlorine was removed by bubbling dry nitrogen through the solution for 1 h at room temperature. The volume of the solvent was reduced from ca. 200 cm^3 to 20 cm^3 on a rotary evaporator at room temperature. The product showed ν_{max} ($CH_2C\ell_2$) 2220 (-CN), 1600 (C=N), 940 (C-Cℓ), 550 (-SCℓ); m/e, 156, 154 (M^+, two chlorine pattern), 119 (M-Cℓ), 117, 103, 88, 87, 86, 84, 83 ($CH_2C\ell_2$), 51, 49, 48, 47, 42, 41, 35. It was unstable neat but would be stored for two days in anhydrous dichloromethane at 0°.

Cyanocarbonimidic dichloride (5).

A solution of N-cyano-1-(chlorothio)formimidoyl chloride in anhydrous dichloromethane (100 cm^3) was chlorinated at room temperature for 12.5 h. The progress of the chlorination was monitored by taking aliquots every hour for examination by ir spectroscopy where the $\nu_{SC\ell}$ (550 cm^{-1}) intensity decreased as the new $\nu_{C-C\ell}$ (960 cm^{-1}) increased in intensity. The intensity of $\nu_{SC\ell}$ (550 cm^{-1}) and $\nu_{C-C\ell}$ (960 cm^{-1}) remained constant after 12.5 h of chlorination at room temperature and even during chlorination

in dichloromethane under reflux for another 15.5 h. The reaction mixture was cooled to room temperature and the excess chlorine was removed by bubbling dry nitrogen through the solution for 1 h at room temperature. Raw linseed oil (1 cm^3) was added to the product mixture. Distillation at 20^o/1 mmHg into a liquid nitrogen trap provided a colourless solution of the product which showed ν_{max} ($CH_2C\ell_2$) 2210 (-CN), 1600 (C=N), 960 (C-Cℓ), 930 (C-Cℓ); m/e 156, 154, 122 (M^+), 119, 117, 84, 51, 49, 48, 28. The ratio of the peak heights at 122:124:154:156 was 8.8:4.0:1.5:1.0 in the product and 1.0:1.0:2.2:1.6 in the starting material.

Excess benzylamine (0.3 cm^3, 2.7 mmol) was added to a solution of the product in anhydrous dichloromethane (0.5 cm^3) and the mixture was stirred for 5 min at room temperature. Tlc (chloroform) showed a mixture but repeated development on the same plate showed that one of the spots had the same Rf as the authentic N,N'-dibenzyl-N" -cyanoguanidine after each development.

N-Cyanodiphenyliminosulphurane (15) m.p. 59-60° (lit.[16] 60-62.5°).

Phenyl(trichloromethyl)mercury m.p. 117-118° (lit.[23] 115-116°).

Reaction of N-cyanodiphenyliminosulphurane (15) with dichlorocarbene.

A. Generation of dichlorocarbene by base treatment of chloroform.

To a solution of N-cyanodiphenyliminosulphurane (2.3 g, 10 mmol) in chloroform (10 cm^3) was added benzyltriethyl ammonium chloride (20 mg, 0.1 mmol) at 0-5°. A freshly prepared solution of sodium hydroxide (1.6 g,

40 mmol) in water (2.5 cm^3) was cooled to 5° before adding to the reaction mixture. The reaction was monitored by tlc (ethyl acetate). The starting material was still present after stirring at 0-5° for 192 h. A white solid (1.0 g) m.p. > 270° was filtered off and the filtrate was extracted with chloroform. Diphenyl sulphide (trace) was the only product by tlc.

B. Generation of dichlorocarbene from phenyl(trichloromethyl)mercury.

N-Cyanodiphenyliminosulphurane (0.2 g, 0.88 mmol) was added to phenyl-(trichloromethyl)mercury (0.4 g, 0.88 mmol) in anhydrous benzene (25 cm^3). The mixture was refluxed for 15 h. On cooling, phenyl mercuric chloride, m.p. 247-250° (lit.[83] 248-250°) (0.2 g, 74%), was filtered off and the ir spectrum of the filtrate showed a mixture of the starting material, ν_{max} (C_6H_6) 2260 (-CN), and diphenyl sulphide, ν_{max} (C_6H_6) 1620, 1580, 1030. Another equivalent of phenyl(trichloromethyl)mercury (0.4 g, 0.88 mmol) was added to the filtrate and the mixture was refluxed for another 18 h. Phenyl mercuric chloride, m.p. 247-250° (0.2 g, 74%), was filtered off on cooling. Tlc (carbon tetrachloride) indicated diphenyl sulphide was the main product in the filtrate; no starting material could be detected. Excess benzylamine (1.5 cm^3, 13.9 mmol) was added to the reaction mixture to trap any cyanocarbonimidic dichloride present. Tlc (carbon tetrachloride) failed to show a spot whose Rf corresponded to that of an authentic sample of N,N'-dibenzyl-N" -cyanoguanidine. The ir spectrum of the mixture showed only diphenyl sulphide (trace), ν_{max} (film) 3090, 3080, 1920, 1820, 1780, 1580, 1480, 1025, 735, and benzylamine, ν_{max} (film) 3380, 3300, 2920, 2860, 1610, 1500, 1455, 700, 680.

EXPERIMENTAL TO 3.0.

4-(N-Phenylformimidoyl)morpholine (30) was a gift from Dr. D.G. McCarthy.

Mercury fulminate[25] was prepared according to the literature using mercury (5 g), concentrated nitric acid (60 g) and absolute alcohol (55 g).

Dibromoformoxime (31)[25]

1 M Hydrobromic acid (48 cm^3) and bromine (3.2 cm^3) were used for bromination of the mercury fulminate prepared above. The product was not distilled but was used directly assuming a 1:1 mixture of dibromofuroxan (32) and dibromoformoxime (31) on the basis of the literature.[25]

Attempted synthesis of 3-bromo-5-morpholino-4-phenyl-1,2,4-oxadiazoline (27).

A. A solution of the dibromoformoxime mixture (ca. 0.5 g, 2.5 mmol) in anhydrous diethyl ether (30 cm^3) was added dropwise over 0.5 h to a solution of 4-(N-phenylformimidoyl)morpholine (0.94 g, 5.0 mmol) in anhydrous diethyl ether (30 cm^3) maintained at 0^oC. The mixture was allowed to stir for another 0.5 h at 0^oC before it was warmed up to room temperature and stirred for another 19 h. A white solid (possibly a hydrobromide salt) was filtered off and the filtrate was evaporated to dryness to give a yellow oil (1 g). Chromatography on silica gel with dichloromethane provided N-formanilide (0.24 g, 80%), m.p. 46-48° (lit.[85] 46.5-47.5°), ν_{max} (nujol) 3360, 3300, 3120 (NH), 1675 (C=O), 1620 (C-N), 1600 (Ph), 1545, 1490, 1440, 1400, 1310, 1250, 750 (Ph), 680 (Ph), 650; δ ($CDCl_3$) 8.7 (s, 1H), 8.25 (s, 1H), 7.75 (m, 5H); m/e, 121 (M^+), 93 (base), 92, 66, 65.

B. A solution of the crude dibromoformoxime mixture (ca. 1.0 g, 5 mmol) in anhydrous diethyl ether (50 cm^3) was added dropwise over 15 min to an ice-cooled solution of 4-(N-phenylformimidoyl)morpholine (0.94 g, 5 mmol) in anhydrous diethyl ether (50 cm^3). When the addition was complete, the mixture was allowed to warm up to room temperature over 2 h with stirring. A white solid (0.3 g) was filtered off and the filtrate was evaporated to dryness to give a brown oil (0.8 g), ν_{max} (film) 3400 (br), 1665, 1590, 1490, 1110, 1065, 1030, 860, 720, 700, 660; δ ($CDCl_3$) 9.1 (s), 8.3 (s), 7.1-7.7 (m), 5.3 (s), 3.0-4.3 (m), 2.8 (m), 1.3 (t); m/e, 273, 271 (one bromine pattern), 233, 231, 229 (two bromine pattern), 205, 203, 201 (two bromine pattern), 121, 103 (base), 84, 75, 47.

Silica gel-promoted hydrolysis of 4-(N-phenylformimidoyl)morpholine (30).

4-(N-Phenylformimidoyl)morpholine (0.1 g, 0.5 mmol) and silica gel (5 g) were stirred in dichloromethane at room temperature for 1 h. The silica gel was filtered off and the filtrate was evaporated to dryness to give N-formanilide, m.p. 46-48° (64 mg, 100%). N-Formanilide was not obtained if silica gel was absent.

Attempted synthesis of 3-bromo-4,5-diphenylisoxazole (33).

A solution of the crude dibromoformoxime mixture (ca. 2.0 g, 0.2 mmol) in anhydrous diethyl ether (20 cm^3) was added dropwise over 0.5 h to an ice-cooled mixture of diphenylacetylene (0.73 g, 4.1 mmol) and dry triethylamine (0.6 cm^3, 4.1 mmol) in anhydrous diethyl ether (20 cm^3). After the addition was complete, the reaction mixture was

allowed to warm up to room temperature and stirred for another 2 h. The triethylamine hydrobromide (0.25 g) was filtered off, and the filtrate was evaporated to dryness to give a solid (1.65 g). Tlc (petroleum ether) indicated the presence of diphenylacetylene only. More triethylamine hydrobromide (0.3 g) was obtained by dissolving the residue from the filtrate in dichloromethane and adding petroleum ether. The total amount of triethylamine hydrobromide obtained was 0.55 g, m.p. 251-254° dec. (lit.[85] 248°), δ ($CDC\ell_3$) 3.2 (q, 2H), 1.5 (t, 3H). The remaining filtrate was evaporated and the residue was chromatographed on silica gel (10 g) with dichloromethane to give crude diphenylacetylene (1.05 g), m.p. 50-55° (lit.[85] 59-61°); ν_{max} ($CHC\ell_3$) 3000-3060 (br), 2220 (-C≡C-), 1600 (Ph), 1490, 1440; δ ($CDC\ell_3$) 7.4 (m); m/e 234, 232, 230, 204, 180, 179, 177, 153, 152, 151, 103, 89, 76, 75.

2-Amino-1,3,4-thiadiazole (36) m.p. 196-197° (lit.[32] 195-198°)

Formylation of 2-amino-1,3,4-thiadiazole (36) with acetoformic anhydride.

2-Amino-1,3,4-thiadiazole (0.5 g, 5 mmol) was dissolved in anhydrous pyridine (20 cm^3) and the solution was cooled to 0°. The acetoformic anhydride (8 cm^3) was added dropwise over 8 min with stirring. The reaction mixture was allowed to stir at 0-10° for 1 h and to warm up to room temperature overnight. The white solid which had precipitated was filtered off and, on evaporation, the filtrate provided a second crop of the white solid (total yield 0.48 g, 68%), m.p. 277-279°

(2-acetoamino-1,3,4-thiadiazole lit.[35] 275-277°), ν_{max} (nujol) 3150 (NH), 1690 (C=O), 1560, 1310, 1270, 1250, 1210, 1150, 960, 790, 720, 660; δ (DMSO-d^6) 9.0 (s, 1H), 2.1 (s, 3H, CH_3-); m/e, 143 (M^+), 115, 101 (base).

2-Formamido-1,3,4-thiadiazole (37).

2-Amino-1,3,4-thiadiazole (2.1 g, 20.7 mmol) and 90-100% formic acid (2 cm^3, 41.4 mmol) were azeotroped with benzene (50 cm^3) for 48h. Formic acid was added periodically until there was no further increase in the volume of water collected. Hot filtration gave the product as a white solid (1.55 g, 58%), m.p. 225-229° (ethanol); ν_{max} (nujol) 3150 (NH), 1675 (C=O), 1550, 1310, 1140, 1030, 845, 820, 720, 680; δ (DMSO-d^6) 10.4 (br, s, 1H exch. D_2O), 9.0 (s, 1H), 8.0 (s, 1H); λ_{max} (MeOH) 208 (826), 252 (1860); m/e, 129 (M^+), 101 (base), 74, 60, 45; (Found: C, 27.94; H, 2.29; N, 32.55; S, 24.39. $C_3H_3N_3OS$ requires C, 27.86; H, 2.33; N, 32.48; S, 24.78%).

Deuteration of 2-amino-1,3,4-thiadiazole (36).

A sample of 2-amino-1,3,4-thiadiazole (10 mg, 0.1 mmol) was dissolved in piperidine (0.1 cm^3, 1 mmol) and deuterated methanol (1.0 cm^3) with tetramethylsilane as the internal standard. The pmr spectrum was taken at intervals of 5-15 min. The height of the peak at δ 8.4 (s, 1H, C5 of the ring) decreases to one half of its original height after 3 h 35 min at 30°.

(h) height/ cm at δ 8.4	log $(h_o - h_t)$/ cm	(t) time/ min
3.3	0.52	0
3.3	0.52	10
3.0	0.47	15
3.0	0.47	20
3.0	0.47	25
2.8	0.45	38
2.8	0.45	50
2.7	0.43	60
2.6	0.41	75
2.4	0.38	90

h_o and h_t are heights of peaks at δ 8.4 when the time is zero and (t) respectively.

correlation coefficient (r) = 0.96

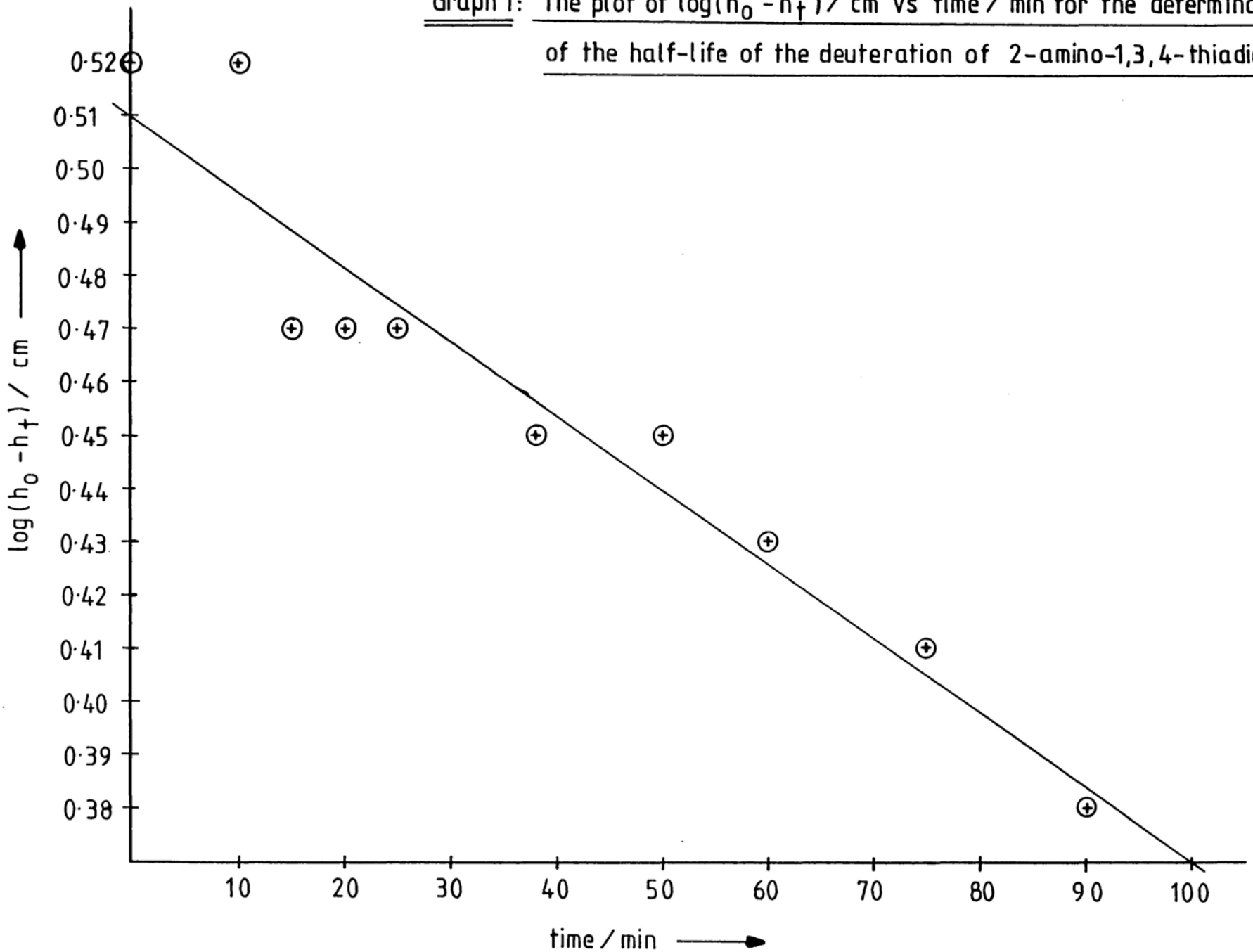
slope = $\frac{kr}{2.303}$ where kr is the rate constant

$\therefore$ The half life, $t_{\frac{1}{2}} = \frac{0.693}{kr} = \frac{0.693}{2.303 \times \text{slope}}$

$$t_{\frac{1}{2}} = \frac{0.693}{2.303 \times 1.4 \times 10^{-3}}$$

$$t_{\frac{1}{2}} = \underline{\underline{215 \text{ min or } 3 \text{ h } 35 \text{ min}}}$$

Graph 1: The plot of $\log(h_0 - h_t)$ / cm vs time / min for the determination of the half-life of the deuteration of 2-amino-1,3,4-thiadiazole (36)



Attempted synthesis of 2-isocyano-1,3,4-thiadiazole (35).

A. Phosgene/triethylamine method.

2-Formamido-1,3,4-thiadiazole (0.2 g, 1.5 mmol), ground to a fine powder, dried and freed from formic acid, was suspended in anhydrous dichloromethane (50 cm^3). Anhydrous triethylamine (0.5 cm^3, 3.6 mmol) was charged into the vessel and dry phosgene was bubbled into the mixture for 1 h. The excess phosgene in the mixture was removed by bubbling dry nitrogen through for 2 h at room temperature. Dry ammonia gas was bubbled in slowly (caution) and immediate precipitation of ammonium chloride was observed. The solid was filtered off and ammonia gas was bubbled through the filtrate. This process was repeated until no further precipitation occurred. On evaporation, the filtrate gave a yellow oil containing a white solid. The oil was extracted with dichloromethane and the extract was dried. The drying agent was removed and the extract was evaporated to dryness to give diethyl carbamoyl chloride (1.8 g), ν_{max} (film) 2970, 1730 (C=O), 1445, 1400, 1380, 1245, 1200, 1100, 835 (C-Cℓ); δ ($CDCℓ_3$) 3.6-3.1 (q, 4H), 1.3-1.0 (t, 6H); m/e, 137, 135 (M^+, one chlorine pattern), 122, 121, 100 (base), 92, 86, 84, 72, 56, 49, 44, 29.

B. p-Toluenesulphonyl chloride/pyridine method.

A mixture of 2-formamido-1,3,4-thiadiazole (0.3 g, 2.3 mmol), powdered, dried and freed from formic acid, and p-toluenesulphonyl chloride (0.61 g, 3.2 mmol), recrystallised and dried, in freshly distilled anhydrous pyridine (6 cm^3) was stirred at room temperature for 6 h. A white crystalline solid began to precipitate from the green

solution after 4 h. The reaction mixture was cooled in ice/water for 10 min before pouring into ice/water (ca. 100 cm^3). An immediate white coloration was observed. The aqueous mixture was extracted with diethyl ether (2 x 50 cm^3). The ethereal extract was washed with distilled water (2 x 50 cm^3) dried, filtered and evaporated to near-dryness to afford a white solid, 2-tosylimino-3-tosyl-Δ^4-1,3,4-thiadiazoline, (0.2 g, 21%), m.p. 133-135° (chloroform-cyclohexane), ν_{max} (nujol) 1595, 1535, 1500, 1310, 1300, 1190, 1180, 1150, 890, 810, 780, 720, 680, 660; ν_{max} ($CHC\ell_3$) 1600 (Ph), 1560, 1400, 1315, 1150, 1115, 1080, 905, 875; δ ($CDC\ell_3$) 8.3 (s, 1H), 7-8 (m, 8H), 2.3 (d, 6H, CH_3-); λ_{max} (MeOH) 242 (6139), 274 (5745); m/e, 410 (M^+ protonated in the mass spectrum), 345, 281, 190, 155, 139, 132, 105, 91 (base), 65, 45. (Found: C, 46.80; H, 3.68; N, 10.25. $C_{16}H_{15}N_3O_4S_3$ requires C, 46.94; H, 3.66; N, 10.26%).

Reaction of oxalyl chloride with monosodium cyanamide.

A solution of oxalyl chloride (5 cm^3, 58.7 mmol) in anhydrous diethyl ether (25 cm^3) was added in one go to a boiling mixture of dried monosodium cyanamide (15.0 g, 0.23 mol) in anhydrous diethyl ether (150 cm^3) and the suspension was stirred at 50° (bath temperature) for 5 h. The reaction was cooled to room temperature when the mixture turned from pale yellow to white. The white solid was filtered off and washed with anhydrous diethyl ether. The ir spectrum of the filtrate showed mainly unreacted oxalyl chloride, ν_{max} (Et_2O) 3550, 1850-1800 (br, C=O), 740 (br, C-Cℓ). Silver nitrate (10 g, 58.7 mmol) was added slowly to the filtered solid dissolved in distilled water (150 cm^3) and the mixture was stirred slowly for 2 h at room temperature. The reaction

flask was protected from light with aluminium foil. The yellow solid which precipitated was filtered and dried in vacuo in the dark and charged into a 500 cm^3 round-bottom flask containing anhydrous diethyl ether (200 cm^3). A steady stream of hydrogen sulphide was bubbled into the suspension (protected from light) for 12 h for complete precipitation of silver sulphide. The excess hydrogen sulphide can be seen by the colour change in an aqueous iron(III) chloride trap placed after the reaction vessel. The solid was filtered and the ethereal filtrate was dried. On evaporation the ethereal solution gave a solid (0.2 g), m.p. 35° (cyanamide m.p. 45-46°); ν_{max} (nujol) 3330 (NH_2), 2260 (-CN), 1640, 1585.

Oxanilic acid chloride (50) m.p. 82-83° (lit.[45] 82-5°).

Reaction of oxanilic acid chloride (50) with cyanamide.

A. A solution of oxanilic acid chloride (0.5 g, 2.73 mmol) in anhydrous diethyl ether (25 cm^3) was added dropwise over 5 min to a stirred solution of cyanamide (0.11 g, 2.73 mmol) in anhydrous diethyl ether (10 cm^3). The mixture was heated to reflux on a steam bath for 0.5 h after the addition, and stirred for 1 h at room temperature after reflux. A yellow solid was filtered off, (0.1 g, 15%), m.p. 250-254° (oxanilide, lit.[85] 254°), ν_{max} (nujol) 3350 (NH), 1780 (C=O), 1715, 1690 (C=O), 1660, 1440; m/e, 240 (M^+), 190 (base), 120, 119, 103, 77, 76. The filtrate was evaporated to dryness to give a white solid which turned yellow on exposure to air, (0.25 g, 56%), m.p. 150° (oxanilic acid, lit.[85] 148-150°), ν_{max} (nujol) 3350 (NH), 3100 (br, OH), 1780 (C=O), 1660 (C=O), 1600, 720; m/e, 165 (M^+), 120 (base), 92, 91, 77.

B. To a solution of oxanilic acid chloride (0.5 g, 2.73 mmol) in AR chloroform (25 cm^3), sodium bicarbonate (0.1 g) and cyanamide (0.11 g, 2.73 mmol) were added and the mixture was stirred at room temperature overnight. The inorganic solid was filtered off and the filtrate was evaporated to give a solid. Addition of anhydrous ether (25 cm^3) left an insoluble solid, m.p. 250-255° (oxanilide, lit.[85] 254°) (0.05 g, 8%). After removal of this solid, the filtrate was evaporated to dryness and the residue was chromatographed on silica gel (20 g) with dichloromethane to give a white solid (0.33 g, 62%), m.p. 58-60° (oxanilic acid ethyl ester, lit.[85] 66-67°), ν_{max} (nujol), 3340 (NH), 1725 (C=O), 1710 (C=O), 1600 (Ph), 1550, 1290, 1235, 1170, 1160, 770 (Ph), 730 (Ph); δ ($CDCl_3$) 8.7 (br, s, 1H, NH), 7.0-7.5 (m, 5H, Ph), 4.2 (q, 2H, $-CH_2-$), 1.3 (t, 3H, CH_3-); m/e, 193 (M^+) 120 (base), 93, 92, 77.

Reaction of oxanilic acid chloride (50) with monosodium cyanamide.

A solution of oxanilic acid chloride (1.0 g, 5.46 mmol) in anhydrous diethyl ether (50 cm^3) was stirred with monosodium cyanamide (0.7 g, 10.9 mmol) at room temperature overnight. The solid (0.8 g) was filtered off, washed with anhydrous diethyl ether to remove excess cyanamide and dried. A portion of the solid (0.65 g) was dissolved in distilled water (15 cm^3) and the solution was covered with diethyl ether (150 cm^3). Tartaric acid (45 g) in distilled water (50 cm^3) was added portionwise over 5 min and the mixture was stirred vigorously. The top ethereal layer was decanted and the aqueous layer extracted four times with

diethyl ether. The combined ethereal extracts were dried over calcium chloride. Filtration and evaporation of the solvent gave a purple solid (0.1 g), m.p. 155-160° (d-tartaric acid lit.[85] 171-174°); ν_{max} (nujol) 3400, 3300, 3000 (br, OH), 1730 (C=O), 1315, 1250, 1220, 1185, 1125, 1080, 990, 935, 870, 825, 790, 730, 660.

3-Phenylisoxazol-5(4H)-one (69) m.p. 151-153° (lit.[58] 151-152°).

3-Phenyl-4-oximino-isoxazol-5(4H)-one (71) m.p. 130-131° (lit.[59] 130°).

3-Phenyl-4-O-acetyloximino-isoxazol-5(4H)-one (72).

3-Phenyl-4-oximino-isoxazol-5(4H)-one (0.2 g, 1.05 mmol) was dissolved in acetic ~~acid~~ anhydride (20 cm^3) at room temperature and left to stand for 10 min. Excess ice was charged into the beaker containing the reaction mixture and the aqueous suspension was basified (litmus) with sodium carbonate solution (30% w/v). The mixture was stirred until all the ice had melted and the yellow oil had solidified to give the product as a yellow solid which was filtered and dried in vacuo, (0.24 g, 98%), m.p. 156-157°; ν_{max} (nujol) 1810 (C=O), 1800 (C=O), 1620 (C=N), 1600 (Ph), 1580, 1530, 1510, 1400, 1175, 1155, 1125, 1101, 1000, 990, 940, 880, 770, 650; δ ($CDCl_3$) 7-8 (m, 5H, Ph), 2.5 (s, 3H, CH_3-); m/e, 232 (M^+), 205, 190, 119, 103, 43 (base). (Found: C, 57.14; H, 3.50; N, 12.07. $C_{11}H_8N_2O_4$ requires C, 56.89; H, 3.45; N, 12.07%).

Attempted synthesis of 3-phenyl-4-cyanoimino-isoxazol-5-(4H)-one (70).

A. From 3-phenyl-4-O-acetyloximino-isoxazol-5(4H)-one (72) with chromium(II) acetate and cyanogen bromide.

To a solution of 3-phenyl-4-O-acetyloximino-isoxazol-5(4H)-one (1.85 g, 7.96 mmol) in anhydrous tetrahydrofuran (100 cm^3) was added anhydrous sodium acetate (10 g), followed quickly by chromium(II) acetate (7.8 g, 39.8 mmol). The reaction mixture was allowed to stir at room temperature for 22 h. The chromium(III) acetate was filtered off. Cyanogen bromide (0.84 g, 7.96 mmol) was added to the filtrate and the mixture was stirred at room temperature for another 23 h. The solvent was evaporated to give a dark brown oil (2 g) which on tlc (dichloromethane) showed five spots. Chromatography on plc (20 x 40 cm) (silica gel) with dichloromethane provided benzonitrile (8 mg, 1%) the ir spectrum of which was identical to that of an authentic sample.

B. From 3-phenylisoxazol-5(4H)-one (69) and 'cyanonitrene'.

3-Phenylisoxazol-5(4H)-one (2.0 g, 12.4 mmol) and cyanamide (1.0 g, 23.8 mmol) were dissolved in anhydrous dichloromethane (50 cm^3). Iodosobenzene diacetate (7.68 g, 23.8 mmol) was added portionwise over 10 min to the reaction mixture at 30° which was allowed to stir for another 20 min. The solid was filtered off and the filtrate was evaporated to dryness to give a residue which was chromatographed on silica gel (20 g) with chloroform. The only identified product isolated besides iodobenzene was benzonitrile (0.8 g, 62.5%) the ir spectrum of which was identical to that of an authentic sample.

Blank experiment

3-Phenylisoxazol-5(4H)-one (0.5 g, 3.0 mmol) and iodosobenzene diacetate (1.92 g, 5.96 mmol) were dissolved in anhydrous dichloromethane (25 cm^3) and the mixture was stirred at 30° for 1 h. On work up only the starting materials were present with no trace of benzonitrile by tlc (dichloromethane) and ir spectroscopy.

C. By condensation of 3-phenylisoxazol-5(4H)-one (69) with nitrosyl cyanide.

Dry silver cyanide (2.66 g, 0.02 mol) was suspended in AR chloroform (30 cm^3) and nitrosyl chloride was bubbled through the solution at -78° for 5 min. The temperature was raised to -30° and, after 3 min stirring at this temperature, a solution of 3-phenyl-isoxazol-5(4H)-one (0.8 g, 5 mmol) in AR chloroform (30 cm^3) was added dropwise over 10 min followed by a few drops of piperidine. The reaction mixture was allowed to warm up to -20° for 0.5 h and finally to room temperature. Tlc (ethyl acetate) indicated the presence of mainly the starting material.

Condensation of 2-amino-1,3,4-thiadiazole (36) with benzophenone.

2-Amino-1,3,4-thiadiazole (150 mg, 1.5 mmol) and benzophenone (200 mg, 1 mmol) were heated at 150° for 18 h. The reaction mixture was cooled and treated with chloroform (30 cm^3). The supernatant was decanted from the polymeric material and was evaporated to dryness. The residue from the supernatant was chromatographed on silica gel with chloroform to give unreacted benzophenone (100 mg, 50%), an unidentified yellow

solid (15 mg, 2%), m.p. > 300°; ν_{max} ($CHC\ell_3$) 3400, 2920, 1600, 1590, 1570, 1450, 1320, 1140, 1100; δ ($CDC\ell_3$) 7.5-7.8 (m); m/e, 430 (M^+), 297 (base), 165, 77 and a colourless solid (15 mg, 4%), m.p. 190-195°; ν_{max} ($CHC\ell_3$) 2980, 1610 (C=N), 1600 (Ph), 1575, 1450, 1320, 1290, 1140, 1110; δ ($CDC\ell_3$) 8.8 (s, 1H), 7.5 (m, 10H, 2Ph); m/e, 265 (M^+), 182, 120, 105, 84 (base), 82, 77. The polymeric material obtained was insoluble both in water and all organic solvents.

Tetraphenylcyclopentadienone (tetracyclone) (61) m.p. 217-220° (lit.[49] 217-220°).

1,2,3,4,5-Pentaphenylbicyclo[2.2.1]-hept-2-ene-7-one (58b).

Styrene (1.14 cm^3, 0.01 mol) was added dropwise to a solution of tetracyclone (3.84 g, 0.01 mol) in anhydrous benzene (50 cm^3) and the reaction mixture was heated under reflux for 24 h. Tlc (petroleum ether: chloroform (1:1)) showed only tetracyclone. The reaction mixture was evaporated to dryness and the residue was treated with methanol (25 cm^3). The product precipitated out immediately as colourless crystals (3.0 g, 61%), m.p. 188-190° (lit.[48] 191°).

Condensation of 2-amino-1,3,4-thiadiazole (36) and 1,2,3,4,5-pentaphenylbicyclo[2.2.1]hept-2-ene-7-one (58b) using the titanium(IV) chloride method.

A solution of titanium tetrachloride (1.0 cm^3) in anhydrous benzene (20 cm^3) was added over 20 min to a solution of 2-amino-1,3,4-thiadiazole (0.2 g, 1.98 mmol) and 1,2,3,4,5-pentaphenylbicyclo[2.2.1]hept-2-ene-7-one

(0.27 g, 0.66 mmol) in anhydrous benzene (20 cm^3) at 0^o under dry nitrogen. When the addition was complete, the reaction mixture was allowed to warm up to room temperature and was stirred overnight. The mixture was filtered, the filtrate was evaporated to dryness and the residue was chromatographed on silica gel with dichloromethane: petroleum ether (1:1). A yellow solid was obtained (62 mg, 18%), m.p. 281-286° (dec); ν_{max} ($CHC\ell_3$) 3450, 3250 (br), 3000 (OH and NH), 1625 (C=N), 1600 (Ph), 1490, 1450, 1360, 1300, 1140, 1105; δ ($CDC\ell_3$) 7.75 (m); m/e, 486 (M^+), 409, 391, 331, 302, 205, 105, 87, 77. Two other unidentified minor products, obtained from subsequent fractions, were a yellow oil (0.02 g), ν_{max} ($CHC\ell_3$) 1700, 1650, 1600, 1490, 1460, 1150, 1100; δ ($CDC\ell_3$) 7.0-7.5 (m) and a yellow solid (0.02 g), m.p. > 300°, ν_{max} ($CHC\ell_3$) 1710, 1650, 1600, 1490, 1290, 1150, 1100; δ ($CDC\ell_3$) 7.75 (m).

Hydroxyurea (88) 138-140° (lit.[81] 137-141°).

Tetraethylammonium periodate m.p. 175-177° (lit.[82] 176-177°).

Attempted synthesis of 3-phenyl-4-carbamoylimino-isoxazol-5(4H)-one (87).

Hydroxyurea (0.5 g, 6.6 mmol) was added over 30 sec to a stirred, cooled (0°) mixture of 3-phenylisoxazol-5(4H)-one (0.46 g, 2.8 mmol) in distilled ethyl acetate (40 cm^3) and tetraethylammonium periodate (1.33 g, 4.2 mmol) in aqueous acetic acid-sodium acetate buffer (pH 7)

($75\ cm^3$) and piperidine (10 drops). The reaction mixture was stirred at room temperature for 1 h. The solid was filtered off, the aqueous layer was separated and the organic layer was washed with saturated sodium sulphite solution to remove excess iodine. The organic layer was dried, filtered and evaporated to dryness (no heat) to give a red oil (0.25 g) which was a complex mixture by tlc (diethyl ether).

9,10-Bis-(chloromethyl)-anthracene m.p. 258-259° (lit.[84] 258-260°).

9,10-Dimethylanthracene m.p. 182-184° (lit.[85] 182-184°).

Attempted trapping of C-nitrosoformamidine (89) with 9,10-dimethylanthracene.

Hydroxyurea (0.1 g, 1.3 mmol) was added to a stirred mixture of 9,10-dimethylanthracene (0.12 g, 0.57 mmol) in anhydrous dichloromethane ($30\ cm^3$) and tetraethylammonium periodate (0.27 g, 0.8 mmol) in aqueous acetic acid-sodium acetate buffer (pH 7) at 0°. The reaction was stirred for 4 h at room temperature. The organic layer was separated, dried, filtered and evaporated to dryness. The residue was chromatographed on silica gel (22 g) with dichloromethane: petroleum ether (4:1) to give mainly dimethylanthracene (0.1 g, 83% recovery) and a mixture of unidentified products.

EXPERIMENTAL TO 4.0.

Benzamidine hydrochloride (122) m.p. 70-72° (lit.[97] 70-73°).

N-Cyanobenzamidine (124) m.p. 140-142° (lit.[98] 141-142°).

3-Amino-5-phenyl-1,2,4-oxadiazole (119) m.p. 160-161° (lit.[99] 156-160°).

3-Chloro-5-phenyl-1,2,4-oxadiazole (121) m.p. 35-37° (lit.[100] 35°).

3-Bromo-5-phenyl-1,2,4-oxadiazole (120) m.p. 50-51° (lit.[100] 51°).

Lithium azide m.p. 208-209° (lit.[147] 208.5-209°).

3-Azido-5-phenyl-1,2,4-oxadiazole (94).

A. Lithium azide/DMF method.

3-Bromo-5-phenyl-1,2,4-oxadiazole (0.1 g, 0.4 mmol) and dry lithium azide (0.2 g, 4 mmol) were dissolved in distilled anhydrous DMF (20 cm^3). The mixture was heated at 90° for 45 h protected from atmospheric moisture. The reaction was followed by ir spectroscopy. When the reaction was judged to be complete, the mixture was cooled, treated with dichloromethane (100 cm^3) and washed twice (2 x 100 cm^3) with brine (1%). The aqueous layer was extracted once with dichloromethane (100 cm^3). The combined organic solutions were dried. The drying agent was removed by filtration and the filtrate was evaporated to dryness to give a residue which on plc (Aluminium oxide) (petroleum ether) provided the azide as a white crystalline solid (0.04 g, 50%), m.p. 66-68° (ethanol-water), R_f 0.45.

B. Potassium azide and 18-crown-6/DMF method.

3-Bromo-5-phenyl-1,2,4-oxadiazole (2.1 g, 0.01 mmol), potassium azide (2.0 g, 0.02 mol) and 18-crown-6 (0.1 g) were dissolved in distilled anhydrous DMF (70 cm^3) and heated at 90° for 72 h. The reaction mixture was protected from atmospheric moisture and the progress of the reaction was followed by ir spectroscopy. The mixture was cooled, diluted with dichloromethane (100 cm^3) and the resultant suspension washed twice with brine (1%) (2 x 100 cm^3). The aqueous layer was extracted once with dichloromethane (100 cm^3). The combined organic solutions were dried, the drying agent was filtered off and the filtrate evaporated to dryness. The residue was chromatographed on silica gel H (15 g) with petroleum ether. The starting material, R_f 0.78, eluted first followed very closely by the product, R_f 0.57, as a white crystalline solid, (0.9 g, 51%) m.p. 66-68° (ethanol-water); ν_{max} ($CHC\ell_3$) 2140 (N_3), 1610, 1560, 1500, 1450, 1380; ν_{max} (KBr) 2140 (N_3), 1600 (Ph), 1545, 1500, 1445, 1380, 1270, 1200, 910, 780, 730, 685; δ ($CDC\ell_3$) 7.3-8.0 (m); m/e 187 (M^+, base), 129, 77; λ_{max} (EtOH) 210 (18,868), 240 (21,698), 258 sh (20,755); (Found: C, 51.11; H, 2.65; N, 37.43. $C_8H_5N_3O$ requires C, 51.33; H, 2.67; N, 37.13%).

Reaction of 3-chloro-5-phenyl-1,2,4-oxadiazole (121) with sodium azide in DMF.

3-Chloro-5-phenyl-1,2,4-oxadiazole (0.13 g, 0.72 mmol) and sodium azide (0.05 g, 0.72 mmol) were stirred at 120-130° in distilled anhydrous DMF (20 cm^3) for 30 h. The reaction mixture was cooled and charged into distilled water (100 cm^3) and the aqueous mixture was extracted with

dichloromethane (3 x 50 cm^3). The organic extract was dried, the drying agent was filtered off and the filtrate evaporated to dryness to give a residue which was chromatographed on silica gel H (12 g) with chloroform. The starting material (trace) was eluted first, R_f 0.85, followed by 3-dimethylamino-5-phenyl-1,2,4-oxadiazole, (0.01g, 8%), R_f 0.56, m.p. 40-42° (ethanol-water); ν_{max} 1600, 1565, 1400; δ ($CDC\ell_3$) 7.5-8.0 (m, 5H, Ph), 3.1 (s, 6H, NMe_2); m/e 189 (M^+), 165, 147, 105, 93, 86, 77; and N,N'-dimethyl-N''-(5-phenyl-1,2,4-oxadiazol-3-yl) formamidine, (0.04 g, 26%), m.p. 113-115° (ethanol-water), ν_{max} ($CHC\ell_3$) 1635 (C=N), 1610,1590,1565, 1530, 1450, 1410, 1360, 1115; δ ($CDC\ell_3$), 8.5 (s, 1H, CH), 7.5-8.4 (m, 5H, Ph), 3.2 (s, 6H, NMe_2); m/e 216 (M^+), 161, 139, 105, 104 (base), 83, 77.

Reaction of 3-bromo-5-phenyl-1,2,4-oxadiazole (120) with sodium azide in DMF.

3-Bromo-5-phenyl-1,2,4-oxadiazole (0.02 g, 0.13 mmol) and sodium azide (0.02 g, 0.13 mmol) were stirred in distilled anhydrous DMF (7 cm^3) at 120-130° for 3 h. The reaction mixture was worked up as for the reaction of the corresponding 3-chloro derivative. 3-Dimethylamino-5-phenyl-1,2,4-oxadiazole (0.01 g, 39%) and N,N'-dimethyl-N" -(5-phenyl-1,2,4-oxadiazol-3-yl)formamidine (0.01 g, 34%) were obtained. The m.p., ir, pmr and mass spectra of these two compounds were identical to the corresponding ones obtained previously.

3-Dimethylamino-5-phenyl-1,2,4-oxadiazole (127).

3-Bromo-5-phenyl-1,2,4-oxadiazole (0.1 g, 0.44 mmol) was dissolved in absolute alcohol (20 cm^3) and a solution of dimethylamine in ethanol (33% w/w, 1 cm^3, 0.25 g, 5.5 mmol) was added dropwise over 30 sec. The reaction mixture was heated under reflux for 27 h protected from atmospheric moisture. The mixture was cooled, treated with charcoal and filtered. The filtrate was evaporated to dryness to give the product as a white solid (0.07 g, 83%), m.p. 40-42° (ethanol-water); ν_{max} ($CHC\ell_3$), 1600, 1565, 1400; δ ($CDC\ell_3$) 7.5-8.0 (m, 5H, Ph), 3.1 (s, 6H, NMe_2); m/e 189 (M^+, base), 165, 147, 105, 93, 86, 77 (Found: C, 63.36; H, 5.94; N, 22.03. $C_{10}H_{11}N_3O$ requires C, 63.49; H, 5.82; N, 22.00%).

3-Ethoxyformylimino-5-phenyl-1,2,4-oxadiazole (128) m.p. 96-98° (lit.[109] 95-98°) was prepared (62%) by the literature method but with the reaction time extended from 3 h to 8 h.

N,N'-Dimethyl-N" -(5-phenyl-1,2,4-oxadiazol-3-yl)formamidine (126).

3-Ethoxyformylimino-5-phenyl-1,2,4-oxadiazole (0.22 g, 1.0 mmol) was dissolved in hot absolute alcohol (20 cm^3) and a solution of dimethylamine in ethanol (33% w/w, 0.5 cm^3, 1.1 mmol) was added by means of a syringe. The mixture was protected from atmospheric moisture and left to stir at room temperature for 48 h. The white solid which had precipitated was filtered off and the filtrate was evaporated to dryness to give the product as a yellow crystalline solid, (0.2 g, 81%), m.p. 113.5-114.5° (ligroin); ν_{max} ($CHC\ell_3$) 1635 (C=N), 1610, 1590, 1580, 1565, 1530, 1450,

1410, 1360, 1115; δ ($CDC\ell_3$), 8.5 (s, 1H, C-H), 7.5-8.4 (m, 5H, Ph), 3.2 (s, 6H, NMe_2); m/e 216 (M^+), 161, 139, 105, 104 (base), 83, 77; (Found: C, 61.48; H, 5.62; N, 25.82. $C_{11}H_{12}N_4O$ requires C, 61.11; H, 5.55; N, 25.92%).

3-Formamido-5-phenyl-1,2,4-oxadiazole (129) obtained as a white crystalline solid from (126) or (128) on chromatography on silica gel H, m.p. 125-127°, (dichloromethane-petroleum ether); ν_{max} ($CHC\ell_3$), 3400, 3200-3000 (NH), 1720 (C=O), 1610, 1600 (Ph), 1580, 1560, 1470, 1450, 1400, 1330, 1305, 1110; δ ($CDC\ell_3$), 9.4 (s, br, 2H, NH, CHO), 8.4-7.6 (m, 5H, Ph); m/e, 189 (M^+), 161, 104 (base), 77), (Found: C, 57.05; H, 3.73; N, 22.14. $C_9H_7N_3O_2$ requires C, 57.14; H, 3.70; N, 22.22%).

Thermolysis of 3-amino-5-phenyl-1,2,4-oxadiazole (119) in DMF.

A solution of 3-amino-5-phenyl-1,2,4-oxadiazole (0.2 g, 1.2 mmol) in distilled, anhydrous DMF (10 cm^3) was heated at 140° for 3 h protected from atmospheric moisture (below this temperature no reaction was observed and the amine recovered quantitatively). The reaction mixture was cooled, treated with dichloromethane (100 cm^3) and the mixture was back washed twice with brine (1%) (2 x 100 cm^3). The organic solution was dried, the drying agent was filtered off and the filtrate evaporated to dryness to give an oil. Chromatography on silica gel H (25 g) with diethyl ether gave an oil tentatively identified as 2-methyl-3-phenyl-2,4,6-triazahex-3-en-5-one oxime (0.19 g, 76%), ν_{max} ($CHC\ell_3$) 3520, 3440, 3400, 3340, 3260, 2950 (NH_2, NOH), 1610 (Ph),1570, 1450, 1430, 1380, 1360, 1330,

1300, 900; ν_{max} (film) 3430, 3210, 3060, 2990, 2960, 2860, 2820, 2780 (NH_2, NOH), 1610-1540 (br), 1450, 1430, 1400, 1300, 1240, 1215, 1165, 1090, 1065, 1025, 1010, 900, 860, 815, 750, 710, 690, 660; δ ($CDCl_3$) 8.7 (s, br, 1H, -NOH), 8.2-7.2 (m, 5H, Ph), 2.2 (s, 6H, NMe_2); m/e, 206 (M^+, protonated in the mass spectrum), 162, 122, 105 (base), 77.

Thermolysis of 3-azido-5-phenyl-1,2,4-oxadiazole (94) in DMF.

A solution of 3-azido-5-phenyl-1,2,4-oxadiazole (50 mg, 0.26 mmol) and anhydrous sodium bromide (20 mg, 0.26 mmol) in distilled anhydrous DMF (10 cm^3) was heated at 130-140^o for 31 h. The mixture was treated with dichloromethane (100 cm^3) and brine (1%) (2 x 100 cm^3). The organic layer was separated and dried, the drying agent was filtered off and the filtrate was evaporated to dryness. The residue was chromatographed on silica gel H (13 g) with chloroform to give N,N'-dimethyl-N" -(5-phenyl-1,2,4-oxadiazole-3-yl)formamidine as a white crystalline solid, (26.7 mg, 47%), the m.p., ir, and pmr spectra of which were identical to those of the authentic sample.

Flash Vacuum Pyrolysis of 3-azido-5-phenyl-1,2,4-oxadiazole (94).

3-Azido-5-phenyl-1,2,4-oxadiazole (50 mg, 0.26 mmol) was dissolved in anhydrous dichloromethane (100 cm^3) in a 50 cm^3 round bottom flask and the solvent was evaporated to dryness under reduced pressure to provide a film of the azide around the inner surface of the flask. The cold finger of the FVP apparatus was filled with dry ice/acetone and a constant flow of nitrogen was introduced to stop atmospheric

moisture condensing on to the cold finger while the pyrolysis oven was heated to 500-550°. When the temperature was reached and stabilised, the flask containing the starting material was connected to the FVP apparatus, the nitrogen was turned off and the system evacuated to 7.5×10^{-2} Torr. The flask containing the starting material was heated to 85° in a small oven for 10 min. The product was collected on the cold finger. The pyrolysis oven was switched off, and allowed to cool to ca. 50° before turning off the vacuum. Nitrogen was introduced to equalise the pressure in the apparatus. The product was collected from the cold finger by rinsing the latter with dichloromethane (20 cm^3). On evaporation to dryness, an oil with a strong smell of benzonitrile was obtained. On distillation, benzoyl cyanide was obtained as a white crystalline solid (25 mg, 70%), m.p. 30° (lit.[113] 30-31°), ν_{max} ($CHC\ell_3$) 2200 (CN), 1680 (C=O), 1600 (Ph), 1580, 1450, 1315, 980; δ ($CDC\ell_3$) 7.3-8.0 (m, Ph); m/e 131 (M^+), 122, 105 (base), 77.

Benzoyl cyanide m.p. 30° (lit.[113] 30-31°), ν_{max} ($CHC\ell_3$), 2200 (CN), 1680 (C=O), 1600 (Ph, 1580, 1450, 1315, 980; δ ($CDC\ell_3$) 7.3-8.0 (m, Ph); m/e 131 (M^+), 122, 105 (base), 77.

Photolysis of 3-azido-5-phenyl-1,2,4-oxadiazole (94).

A. In acetonitrile.

3-Azido-5-phenyl-1,2,4-oxadiazole (250 mg, 1.3 mmol) was dissolved in freshly distilled anhydrous acetonitrile (100 cm^3) in a 44 x 2.5 cm quartz tube. The solution was degassed with nitrogen for 20 min before being photolysed at 254 nm for 1 h with nitrogen bubbling through during photolysis. The reaction was monitored by taking aliquots every 5 min

for tlc (dichloromethane: petroleum ether, 1:1) on silica gel. On evaporation of the solvent to dryness, the residue on tlc (dichloromethane: petroleum ether) (neutral alumina) showed two major components at R_f 0.6 and 0.4 with minor components at R_f 0.9. Addition of AR chloroform to this residue provided a yellow solid (25 mg) which was filtered off. The filtrate on tlc (dichloromethane: petroleum ether, 1:1) (neutral alumina) showed a complex mixture with components at R_f 0.98, 0.95, 0.9, 0.6, 0.4 and base line material. The yellow solid, a mixture, was chromatographed on silica gel H (22 g) with dichloromethane: petroleum ether (1:1). The first component (R_f 0.37) was azo-3,3'-bis-(-5-phenyl-1,2,4-oxadiazole) (20 mg, 8%), m.p. 290-291°, ν_{max} ($CH_2C\ell_2$), 1610, 1565, 1475, 1360; m/e, 318 (M^+, base), 257, 248, 173, 145, 129, 106, 105, 103, 77, and the second component (R_f 0.25) was azoxy-3,3'-bis-(-5-phenyl-1,2,4-oxadiazole) (5 mg, 2%) as a white solid, m.p. > 300°, ν_{max} ($CH_2C\ell_2$), 1610, 1560, 1485 (br), 1390, 1360; m/e, 334 (M^+), 318, 234, 173, 145, 129, 105 (base), 77; λ_{max} (EtOH) 212 (1670), 260 (2388).

Polymeric material (30 mg, 12%) precipitated on addition of dichloromethane (10 cm^3) followed by petroleum ether (20 cm^3) to the residue from the filtrate after evaporation of the chloroform. This was filtered off and the filtrate was evaporated to dryness. The residue was chromatographed on silica gel H (30 g) with dichloromethane: petroleum ether (1:1) to give the recovered azide, R_f 0.9, (7 mg, 3%) and more azo compound, R_f 0.36, (5 mg, 2%).

B. In THF.

A solution of 3-azido-5-phenyl-1,2,4-oxadiazole (50 mg) in freshly distilled anhydrous THF (100 cm^3) in a 44 x 2.5 cm quartz tube was degassed with nitrogen for 20 min. The mixture was photolysed at 254 nm for 15 min following the reaction by tlc (dichloromethane: petroleum ether, 1:1). The solvent was removed and the residue was chromatographed on plc (neutral alumina) with diethyl ether. 3-Amino-5-phenyl-1,2,4-oxadiazole (R_f 0.8) (8 mg, 19%) (by ir) was the only identified product isolated.

Azo-3,3'-bis(-5-phenyl-1,2,4-oxadiazole) (140).

Aqueous sodium hypochlorite solution (50 cm^3) was added to 3-amino-5-phenyl-1,2,4-oxadiazole (200 mg, 1.24 mmol) and the mixture was stirred for 2 h at room temperature. The yellow solution containing a fine suspension of solid was treated with brine (10%) and the solid was filtered off and washed thoroughly with water. The yellow solid was chromatographed on silica gel H (10 g) with dichloromethane to give the bright yellow crystalline product (150 mg, 75%), m.p. 290-291°; ν_{max} (nujol) 1610, 1565, 1490, 1470, 1365, 1270, 1150, 1065, 940, 840, 760, 740, 720, 700, 680; ν_{max} ($CH_2C\ell_2$) 1610, 1565, 1475, 1360; λ_{max} ($CH_2C\ell_2$) 235 sh (17,515), 265 (37,579), 294 sh (6369); m/e, 318 (M^+, base), 257, 248, 173, 145, 129, 106, 105, 103, 77; (Found: C, 60.72; H, 3.29; N, 26.01. $C_{16}H_{10}N_6O_2$ requires C, 60.38; H, 3.14; N, 26.41%).

Oxidation of azo-3,3'-bis-(-5-phenyl-1,2,4-oxadiazole) (140).

Glacial acetic acid (20 cm^3) and hydrogen peroxide (30%) (20 cm^3) were added to azo-3,3'-bis-(-5-phenyl-1,2,4-oxadiazole) (50 mg, 0.15 mmol). The mixture was heated at 80-90° for 36 h behind a safety screen. The yellow solid (45 mg, 90%) was filtered off on cooling and shown to be starting material by ir and tlc. The filtrate was brought carefully to pH 7 with saturated sodium carbonate solution and the resultant solution was extracted twice with dichloromethane (2 x 50 cm^3) and the organic extracts were backwashed twice with distilled water (2 x 50 cm^3). The organic extracts were dried, the drying agent filtered off and the filtrate was evaporated to dryness. The residue was chromatographed (plc) (silica gel) with dichloromethane: petroleum ether (1:1) (developed twice) to provide a white solid, 3-nitro-5-phenyl-1,2,4-oxadiazole, R_f 0.55, (4.2 mg, 8%), m.p. 82-85°; ν_{max} 1610 (Ph), 1570, 1560 (NO_2), 1500, 1470, 1390, 1300, 1290 (NO_2); m/e, 191 (M^+), 149, 145, 115, 105 (base), 77, 51; λ_{max} (EtOH) 210 (7449), 252 (10, 218).

ω-Oximinoacetophenone (149) m.p. 126-128° (lit.[120] 126-127°).

3-Amino-4-phenyl-1,2,5-oxadiazole (146) m.p. 98-99° (lit.[119] 98°).

3-Azido-4-phenyl-1,2,5-oxadiazole (95).

3-Amino-4-phenyl-1,2,5-oxadiazole (400 mg, 2.5 mmol) was dissolved in 6 M hydrochloric acid (50 cm^3) on a steam bath and any insoluble solid was filtered off. The filtrate was cooled to -10° and a solution of

sodium nitrite (500 mg, 7.2 mmol) in distilled water (3 cm^3) was added dropwise maintaining the temperature below -5^o. After 20 min, a solution of sodium azide (1.0 g, 15.4 mmol) in distilled water (5 cm^3) was added over 5 min at a temperature maintained below 2^o. The mixture was allowed to warm up to room temperature over 1 h and the aqueous solution was extracted with dichloromethane. The organic extract was dried, the drying agent was filtered off and the filtrate was evaporated to dryness. The residue was chromatographed on silica gel H (27 g) with dichloromethane to give the product, (10 mg, 2%), m.p. 43-45° (ethanol-water); ν_{max} ($CHC\ell_3$) 2140 (N_3), 1580, 1550, 1510, 1460, 1380, 1310, 1290, 990, 880; m/e, 187 (M^+, base), 129, 103, 77.

2-Phenylglycinonitrile hydrochloride (156).

To sodium cyanide (10 g, 0.2 mol) in distilled water (40 cm^3) was added ammonium chloride (11 g). A solution of freshly distilled benzaldehyde (20 cm^3, 0.2 mol) in methanol (40 cm^3) was added and the mixture was shaken vigorously for 5 min and then left to stand at room temperature, with occasional shaking, for 2.5 h. To the light yellow mixture, distilled water (100 cm^3) was added and the mixture was extracted twice with toluene (2 x 50 cm^3) and the combined extracts were dried. After removal of the drying agent, dry hydrogen chloride was passed into the filtrate until precipitation of the yellow solid stopped. Dry nitrogen was bubbled into the solution for ca. 15 min to remove excess hydrogen chloride. The yellow solid was filtered, washed with anhydrous diethyl ether (200 cm^3) and dried in vacuo overnight to provide 2-phenylglycinonitrile hydrochloride (5 g, 15%), m.p. 164-166° (lit.[124] 164-165°).

3-Chloro-4-phenyl-1,2,5-thiadiazole (154) b.p. 120°/1 mmHg (lit.[123] 110°/1 mmHg).

3-Amino-4-phenyl-1,2,5-thiadiazole (155).

A. Potassium azide and 18-crown-6 in DMF.

A solution of 3-chloro-4-phenyl-1,2,5-thiadiazole (1.0 g, 5.1 mmol), potassium azide (1.0 g, 12.3 mmol) and 18-crown-6 (0.5 g, 1.9 mmol) in anhydrous DMF (3 cm^3) was heated at 140° for 6.5 h. On cooling, the mixture was treated with brine (10%) (500 cm^3) and the aqueous solution was extracted twice with dichloromethane (2 x 100 cm^3). The combined organic extracts were backwashed with distilled water twice (2 x 100 cm^3). The extract was dried, the drying agent filtered off and the filtrate was evaporated to dryness to give an oil (0.6 g) which on tlc (dichloromethane: petroleum ether, 1:1) showed six spots and baseline material. Chromatography on silica gel H (35 g) with dichloromethane: petroleum ether (1:1) gave 3-amino-4-phenyl-1,2,5-thiadiazole (R_f 0.4) (0.2 g, 22%), m.p. 100-102° (lit.[125] 101-102°) as the only identified product.

B. Sodium azide in aqueous DMSO.

A solution of 3-chloro-4-phenyl-1,2,5-thiadiazole (5.0 g, 25.4 mmol) and sodium azide (5.0 g, 77 mmol) in aqueous DMSO (DMSO: water, 5:1) (60 cm^3) was heated at 125° for 6.5 h. On cooling the mixture was treated with brine (10%) (500 cm^3) and the aqueous solution was extracted twice with dichloromethane (2 x 100 cm^3). The extracts were backwashed with distilled water (2 x 100 cm^3), dried, the drying agent was filtered off and the filtrated was evaporated to dryness. The residue was

chromatographed on alumina H (150 g) with dichloromethane. The first component eluted was an unidentified product with some starting material, R_f 0.98, followed by 3-amino-4-phenyl-1,2,5-thiadiazole, R_f 0.45, (2.2 g, 50%), m.p. 100-102° (lit.[125] 101-102°), ir spectrum identical to that of an authentic sample.

C. Benzyl cyanide, tetrasulphur tetranitride in toluene.

A mixture of benzyl cyanide (2.5 g, 21 mmol) and tetrasulphur tetranitride (1 g, 5 mmol) in anhydrous toluene (12 cm^3) was heated under reflux for 5.5 h under nitrogen. The solvent was removed after cooling and the residue, a complex mixture (> 15 spots) by tlc, was chromatographed on alumina H (150 g) with dichloromethane to provide 3-amino-4-phenyl-1,2,5-thiadiazole (100 mg, 3%), m.p. and ir spectrum identical to those of an authentic sample.

Thermolysis of phenyl azide in DMF.

A solution of phenyl azide (1 cm^3, 0.01 mol) in anhydrous DMF (6 cm^3) was heated under reflux for 23 h. The mixture was treated with brine (2 x 100 cm^3) (2%) and the aqueous solution was extracted twice with dichloromethane (2 x 100 cm^3). The extract was dried, the drying agent filtered off and the filtrate was evaporated to dryness. The residue was chromatographed on silica gel H (25 g) with dichloromethane. The only identified product was aniline (31 mg, 4%), ir spectrum identical to that of an authentic sample.

3-Azido-4-phenyl-1,2,5-thiadiazole (151).

3-Amino-4-phenyl-1,2,5-thiadiazole (60 mg, 0.33 mmol) was dissolved in 2 M hydrochloric acid (20 cm^3) and the solution was cooled to -10^o. A solution of sodium nitrite (500 mg, 7.2 mmol) in distilled water (5 cm^3) was added dropwise maintaining the temperature below -8^o. The mixture was allowed to stir for 15 min before diazotisation was complete. A solution of sodium azide (1.0 g, 15.4 mmol) and sodium acetate (30 g) in the minimum amount of water (20 cm^3) was added dropwise at -8^o. The mixture was extracted immediately with dichloromethane (100 cm^3), the extracts were dried and the drying agent was filtered off. The filtrate was evaporated to dryness and the residue was chromatographed on silica gel H (15 g) with dichloromethane: petroleum ether (1:1) to provide the product, R_f 0.8, (31 mg, 50%), m.p. 60-65° (ethanol-water), ν_{max} (nujol) 2120 (N_3), 1410, 1365, 1260, 1145, 895, 860, 775, 720, 690; ν_{max} ($CHC\ell_3$), 2120 (N_3), 1600 (Ph), 1470, 1405, 1260, 890; m/e 203 (M^+), 175, 129, 103 (base), 77, 76, 72; λ_{max} (EtOH) 210 (1975), 218 (1700), 259 (2200), 300 (1775).

Thermolysis of 3-azido-4-phenyl-1,2,5-thiadiazole (151).

A. In m-xylene.

A solution of 3-azido-4-phenyl-1,2,5-thiadiazole (20 mg, 0.098 mmol) in anhydrous m-xylene (15 cm^3) was heated under reflux for 14 h excluding atmospheric moisture. After cooling, the reaction mixture was evaporated to dryness and the residue was chromatographed on silica gel H (15 g) with dichloromethane to give the recovered starting material, R_f 0.75,

(9.2 mg, 27.5%) and 3-(3'-methylbenzlidenamino)-4-phenyl-1,2,5-thiadiazole R_f 0.58, (10.5 mg, 52.5%) as a red oil; ν_{max} ($CHC\ell_3$) 1620 (C=N), 1600 (Ph), 1580, 1480, 1460, 1435, 1405, 1340, 1290, 1265 (br), 1117, 1115, 985, 890; δ ($CDC\ell_3$) 9.1 (s, 1H, CH), 8.4-7.1 (m, 9H, Ph, C_6H_4-), 2.4 (s, 3H, CH_3), m/e 279 (M^+), 188, 177 (base), 134.5, 104, 91, 74.

B. In p-xylene.

A solution of 3-azido-4-phenyl-1,2,5-thiadiazole (20 mg, 0.098 mmol) in anhydrous p-xylene (15 cm^3) was heated under reflux for 16 h excluding atmospheric moisture. The solvent was removed and the residue was chromatographed on silica gel H (10 g) with dichloromethane to give the recovered starting material, R_f 0.69, (5 mg, 25%) and 3-(4'-methylbenzylidenamino)-4-phenyl-1,2,5-thiadiazole, R_f 0.28, (13 mg, 65%), m.p. 80-85°, ν_{max} ($CH_2C\ell_2$), 1610 (C=N), 1600 (Ph), 1560, 1430, 1340, 1160, δ ($CC\ell_4$) 9.0 (s, 1H, CH), 8.3-7.1 (m, 9H, Ph, C_6H_4), 2.4 (s, 3H, CH_3); m/e, 279 (M^+), 278, 188 (base), 175, 103, 105, 77.

Authentic Samples.

A. General procedure.

A mixture of 3-amino-4-phenyl-1,2,5-thiadiazole (0.1 g, 0.56 mmol), the appropriate aldehyde (1 equiv.) and a catalytic amount of PTSA were azeotroped in anhydrous benzene (25 cm^3) for 16 h. The solvent was removed and the residue was chromatographed quickly on silica gel (10 g) with dichloromethane. The Schiff base eluted first, followed by the aldehyde and the amine.

B. 3-(3'-Methylbenzylidenamino)-4-phenyl-1,2,5-thiadiazole (161), as a red oil, R_f 0.6, (0.15 g, 75%), ν_{max} ($CHC\ell_3$) 1620 (C=N), 1600 (Ph), 1580, 1475, 1430, 1340, 1150, 980, 885; δ ($CDC\ell_3$) 9.1 (s, 1H, CH), 8.4-7.1 (m, 9H, Ph, C_6H_4-), 2.4 (s, 3H, CH_3), m/e, 279 (M^+), 188, 177 (base), 134.5, 104, 91, 74; λ_{max} (EtOH) 214 (14,508), 237 (11,160), 300 (15,903); (Found: m/e 279.0830. $C_{16}H_{13}N_3S$ requires 279.0830). Accurate analysis figures could not be obtained because the product was unstable.

C. 3-(4'-Methylbenzylidenamino)-4-phenyl-1,2,5-thiadiazole (162), as a yellow crystalline solid, R_f 0.46, (0.15 g, 75%), m.p. 80-85°; ν_{max} ($CHC\ell_3$) 1610 (C=N), 1600 (Ph), 1560, 1430, 1340, 1160; δ ($CC\ell_4$) 9.0 (s, 1H, CH), 8.3-7.1 (m, 9H, Ph, C_6H_4-), 2.4 (s, 3H, CH_3); λ_{max} (EtOH) 230 (36,270), 290 (44,640), 340 sh (29,016); m/e, 279 (M^+), 278 (base), 188, 175; (Found: C, 68.88; H, 4.79; N, 15.02; S, 10.42. $C_{16}H_{13}N_3S$ requires C, 68.82; H, 4.66; N, 15.05; S, 10.46%).

3-(4'-Methylbenzylamino)-4-phenyl-1,2,5-thiadiazole (163).

3-(4'-Methylbenzylidenamino)-4-phenyl-1,2,5-thiadiazole (30 mg, 0.11 mmol) was dissolved in anhydrous distilled methanol (10 cm^3) and sodium borohydride (0.1 g) was added over 30 sec at room temperature. The mixture was heated under reflux, protected from atmospheric moisture for 50 min. Additional sodium borohydride (2 x 0.05 g) was added during this period. The mixture was evaporated to near dryness, distilled water (20 cm^3) was added and the precipitated product was filtered off as white crystalline solid (28 mg, 93%), m.p. 87-89°; ν_{max} ($CHC\ell_3$), 3420,

(NH), 3000 (br), 1600 (Ph), 1575, 1535, 1505 (br), 1305; δ ($CDC\ell_3$) 7.8-7.0 (m, 9H, Ph, C_6H_4), 5.1 (br, s, 1H, NH), 4.5 (d, 2H, CH_2), 2.2 (s, 3H, CH_3); m/e, 281 (M^+), 120, 105 (base), 32, 28; λ_{max} (EtOH), 216 (17,574), 240 (15,114), 326 (13,356); (Found: C, 68.06; H, 5.46; N, 14.79. $C_{16}H_{15}N_3S$ requires C, 68.32; H, 5.34; N, 14.94%).

Photolysis of 3-azido-4-phenyl-1,2,5-thiadiazole (151).

3-Azido-4-phenyl-1,2,5-thiadiazole (54 mg, 0.25 mmol) was dissolved in anhydrous freshly distilled acetonitrile (100 cm^3) and the solution was deoxygenated for 20 min. The solution was photolysed at 300 nm for 15 min with nitrogen bubbling through the mixture during photolysis. The reaction was followed by tlc (dichloromethane: petroleum ether, 1:1) of aliquots taken every 5 min. An unidentified yellow solid (2.5 mg, 4.6%) was filtered off after 15 min and the filtrate was evaporated to dryness. Plc (silica gel) with dichloromethane: petroleum ether (1:1) of the residue provided 3-amino-4-phenyl-1,2,5-thiadiazole (14 mg, 26%), R_f 0.08, ir spectrum identical to that of an authentic sample, and an unidentified yellow solid, R_f 0.6, (8 mg, 14.8%), m.p. 105-110°, ν_{max} ($CHC\ell_3$) 2210, 1720 (br), 1590, 1460, 1440, 1370, 1310, 1270, 1005; δ ($CDC\ell_3$) 8.0 (m, 2H), 7.6-7.5 (m, 3H); m/e 290, 289, 220, 205, 196, 182, 171, 156, 155 (base), 141, 57, 55, 43, 41.

Dicyanamide (181) m.p. 205-208° (lit.[143] 208-209°).

N-(Benzoylamido)thiourea (183) m.p. 168-170 (lit.[144] 170-171°).

3-Azido-5-phenyl-1,2,4-thiadiazole (152).

3-Amino-5-phenyl-1,2,4-thiadiazole (100 mg, 0.56 mmol) was dissolved in 6 M hydrochloric acid (25 cm^3) at room temperature. The mixture was cooled to 0-5° in an ice/water bath. A solution of sodium nitrite (500 mg, 7.25 mmol) in distilled water (2 cm^3) was added dropwise, maintaining the temperature below 5°. The reaction mixture was allowed to stir for another 3 min before the addition of a solution of sodium azide (1.0 g, 15.38 mmol) in distilled water (4 cm^3) maintaining the temperature below 5°. The mixture was stirred for another 15 min at this temperature before it was allowed to warm up to room temperature over 1 h. The product was extracted from the aqueous solution with dichloromethane (50 cm^3) the extracts were dried, the drying agent was filtered off and the filtrate was evaporated to dryness. Chromatography on silica gel H (15 g) with diethyl ether provided benzonitrile, R_f 0.99, (11 mg, 18%), ir identical to that of an authentic sample, as the only identified product.

Diazotisation of 3-amino-5-phenyl-1,2,4-thiadiazole (179).

The diazotisation of 3-amino-5-phenyl-1,2,4-thiadiazole (100 mg, 0.56 mmol) was carried out under identical conditions to those used above. On extraction of the aqueous mixture with dichloromethane (50 cm^3), the organic layer showed on tlc (dichloromethane) baseline material only and no trace of benzonitrile. When sodium azide (0.5 g, 7.7 mmol) was added to the aqueous solution of diazotised amine at 0-5°, immediate evolution of gas was observed. On work up as described before, benzonitrile was detected on tlc (dichloromethane) at R_f 0.7.

6.0. APPENDIX

6.0. APPENDIX.

6.1. High resolution mass spectrometric (HRMS) determination of gaseous components in the novel reaction (4.2.1.2.).

There are two possible gaseous components which may be extruded from the reaction of 3-halogeno-5-phenyl-1,2,4-oxadiazole (120, 121) with sodium azide in DMF, namely, oxygen, as suggested in mechanisms B, C, and nitrous oxide, as in mechanism D. Current chemical methods for the detection of oxygen extruded from a reaction are not satisfactory since an oxygen-free system required before and during the reaction is very difficult to achieve. Nitrous oxide is a very unreactive gas and its only known complex is with $[Ru(NH_3)_5(H_2O)]^{2+}$. However, this method is not suitable for our purpose because the complex $[Ru(NH_3)_5N_2O]^{2+}$ decomposes rapidly. Thus, HRMS was chosen as the tool for the detection of oxygen or nitrous oxide. The absence of a peak m/e 44.0011 (N_2O) and the presence of a peak enhancement at m/e 28.00615 (N_2) suggested that nitrous oxide is not a product of this reaction for which mechanism D can be ruled out.

6.2. 3-Bromo-5-phenyl-1,2,4-oxadiazole (0.5 g, 2.2 mmol) and sodium azide (0.3 g, 4.6 mmol) were dissolved in anhydrous DMF (8 cm^3) in a 25 cm^3 round-bottomed flask (F_1). This flask (F_1) was connected to a gas cell (C_1) which was in turn connected to an oil pump. There was a tap (T_1) between the flask (F_1) and gas cell (C_1) and a tap (T_2)

between C_1 and the pump. The system was evacuated for 10 min with the reaction mixture in F_1 cooled (-78^{o}) to prevent loss of DMF. T_1 was closed while T_2 remained opened. Flask (F_1) was lowered slowly into a preheated Woods metal bath (130^{o}). The reaction mixture which boiled vigorously initially for 15 min, was heated for 3 h with stirring. The flask was cooled down to room temperature after removal from the Woods metal bath, T_2 was closed, T_1 was opened to allow the gases into the gas cell (C_1). The gas cell (C_1) was disconnected with T_1 and T_2 closed. HRMS of the gases in C_1 showed no trace of nitrous oxide (44.0011), with carbon dioxide (43.9898) as reference; there was a peak enhancement for nitrogen (28.00615).

6.3. Reaction of azo-3,3'-bis(5-phenyl-1,2,4-oxadiazole)(140) with singlet oxygen.

In section 4.2.1.3.2., photolysis of 3-azido-5-phenyl-1,2,4-oxadiazole (94) provided azoxy-3,3'-bis(5-phenyl-1,2,4-oxadiazole) (141) (2%). Two reaction mechanisms were postulated for the formation of the azoxy compound (141). One mechanism is thought to be the cycloaddition of the azide (94) with singlet oxygen and the other the reaction of singlet oxygen with the azo compound (140) to give the azoxy compound (141). To test the latter mechanism, the azo compound (140) was photolysed in a quartz tube in anhydrous acetonitrile at 254 nm under a constant stream of oxygen for 20 min. On work up, a quantitative recovery of the azo compound was obtained and no azoxy compound (141) could be seen on tlc. This ruled out the latter mechanism and supports the mechanism involving cycloaddition of the azide (94) with singlet oxygen. There is precedent for this from Abramovitch's work.[114]

6.4. Azo-3,3'-bis(-5-phenyl-1,2,4-oxadiazole (20 mg, 0.06 mmol) was dissolved in freshly distilled anhydrous acetonitrile (100 cm^3). The solution was photolysed in a quartz tube for 20 min at 254 nm with oxygen bubbling through the solution. The solvent was evaporated to give a quantitative recovery of the starting material. Tlc (dichloromethane) indicated only the starting material R_f 0.45 and no azoxy-3,3'-bis(-5-phenyl-1,2,4-oxadiazole).

7.0. REFERENCES

7.0. REFERENCES.

1. T.K. Brotherton, J.W. Lynn, Chem. Rev., 1959, 59, 841.
2. T. Thiele, Ann. Chem., 1898, 303, 68.
3. G. Grundman, personal communication in I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, K. Offerman, Angew. Chem. Int. Ed. Engl., 1965, 4, 472.
4. H. Rzepa, personal communication.
5. I. Ugi, 'Isonitrile Chemistry', Academic Press, N.Y., 1971.
6. Z. Rappoport (Ed.), 'The Chemistry of the Cyano Group', John Wiley, N.Y., 1970.
7. W.P. Trompen, J. Geevers, J. Th. Hackmann, Rev. Trav. Chim., 1971, 90, 463.
8. E. Kühle, B. Anders, G. Zumach, Angew. Chem. Int. Ed. Engl., 1967, 6, 649.
9. E. Kühle, B. Anders, E. Klauke, H. Tarnow, G. Zumach, ibid., 1969, 8, 20.
10. H. Ulrich, R. Richter, 'The Chemistry of Cyanate, Isocyanate and Thioisocyanate Group', S. Patai (Ed.), John Wiley, N.Y., 1977, p. 969.
11. S.J. Wratten, D.J. Faulkner, J. Am. Chem. Soc., 1977, 99, 7367; idem, Tetrahedron Lett., 1978, 1391, 1395.
12. L.S. Wittenbrook, G.L. Smith, R.J. Timmons, J. Org. Chem., 1973, 38, 465.
13. W.A. Thaler, J.R. McDivitt, ibid., 1971, 36, 14.
14. R. Neidlein, H.G. Reuter, Arch.Pharmaz., 1975, 308, 189.
15. F.D. Marsh, M.E. Hermes, J. Am. Chem. Soc., 1964, 86, 4506.
16. D. Swern, I. Ikeda, G.F. Whitfield, Tetrahedron Lett., 1972, 2635.
17. E. Mayer, Monatsh. Chemie, 1970, 101, 834.
18. W. Gottardi, ibid., 1971, 102, 264.
19. S. Weiss, Ger. Patent, 2,757,586 (1979).
20. A.I. Ui'yanova, N.I. Rudneva, N.P. Lyalyakina, N.I. Shevtov-Shilovski, Zh. Obshch. Khim., 1975, 45, 1193.

21. J.S. Davidson, Chem. Ind. (London), 1965, 48, 1977.

22. A.E. Barnett, P. Piotis, B. Tittle, J. Inorg. Nuclear Chem., 1976, 38, 1575.

23. M. Fedorynski, M. Makosza, J. Organometallic Chem., 1973, 51, 89.

24. D.C. McCarthy, personal communication.

25. P. Kurtz, 'Houben-Weyl', 1952, 8, 355.

26. Ch. Grundmann, P. Grünanger, 'The Nitrile Oxide', Springer-Verlag, Berlin, 1971.

27. J.E. Baldwin, C. Hoskins, L. Kruse, J. Chem. Soc., Chem. Commun., 1976, 795.

28. R.A. Olofson, J.P. Pepe, Tetrahedron Lett., 1979, 3129.

29. R.A. Olofson, K.D. Lotts, ibid., 1979, 3131.

30. R.A. Olofson, C.M. Dougherty, J. Am. Chem. Soc., 1973, 95, 581.

31. R.A. Olofson, K.D. Lotts, G.N. Barber, Tetrahedron Lett., 1976, 3381, 3779.

32. R.F. Lauer, G. Zenchoff, J. Heterocyclic Chem., 1976, 13, 291.

33. V.C. Mehlenbacher, 'Organic Analyses', 1953, 1, 37.

34. W. Stevens, A. van Es., Rev. Trav. Chem., 1964, 83, 1287, 1294.

35. M. Kanaoka, J. Pharm. Soc. Japan, 1955, 75, 1149 (Chem. Abstr., 1956, 50, 5647).

36. G.R. Pettit, E.G. Thomas, J. Org. Chem., 1959, 24, 895.

37. F. Klages, G. Lukasczyk, Chem. Ber., 1963, 96, 2066.

38. G.L. abbe, G. Verhelst, L. Huybrechts, S. Toppet, J. Heterocyclic Chem., 1977, 14, 515.

39. R. Storr, personal communication.

40. 'Rodd's Chemistry of Carbon Compounds', Elsevier Publishing Company, Amsterdam, 1954, Vol. III, p. 206.

41. G. Zinner, R. Vollrath, Chem. Ber., 1970, 103, 2006.

42. W. Buddeus, J. Prakt. Chem., 1890, 42, 82.

43. G. Gerlich, ibid., 1876, 13, 270.

44. E. Mulder, Chem. Ber., 1874, 7, 1631.

45. I.G. Farbenind, U.K. Patent, 282,891 (1926).

46. P. Brigl, Chem. Ber., 1912, 45, 1557.

47. R.S. Atkinson, M.J.P. Harger, J. Chem. Soc., Perkin I, 1974, 2619.

48. M.A. Ogliaruso, M.G. Romanelli, E.I. Becker, Chem. Rev., 1965, 65, 261.

49. 'Vogel's Textbook of Practical Organic Chemistry', Longman, London, 4th Ed., 1978, p. 858.

50. C.F.H. Allen, J.A. VanAllan, J. Am. Chem. Soc., 1943, 65, 1384.

51. N.O.V. Sonntag, S. Linder, E.I. Becker, P.E. Spoerri, ibid., 1953, 75, 2283.

52. V. Migrchichian (Ed.), 'The Chemistry of Organic Cyanogen Compounds', Reinhold Publishing Corporation, N.Y., 1974, p. 116.

53. 'Cyanamide', American Cyanamide Company, 1966.

54. N.A. Gol'dberg, V.G. Golov, Khim. Nauka i Prom., 1959, 4, 138 (Chem. Abstr., 1959, 53, 16953g).

55. B.I. Sukhorukov, A.I. Finkel'shtein, Optika i Spektroskopiya, 1959, 9, 46 (Chem. Abstr., 1960, 54, 23816i).

56. V.G. Golov, V.G. Vodop'yanov, Yu. I. Mushkin, J. Org. Chem. USSR, 1971, 7, 2186.

57. C. Wentrup, U. Stutz, H-J. Wollweber, Angew. Chem. Int. Ed. Engl., 1978, 17, 688.

58. A.O. Fitton, R.K. Smalley, 'Practical Heterocyclic Chemistry', Academic Press, London, 1968.

59. S. Dutt, I.N.D. Dass, Proc. Indian Acad. Sci., 1939, 10A, 55.

60. E.J. Corey, J.E. Richman, J. Am. Chem. Soc., 1970, 92, 5276.

61. G.H. Timms, E. Wildsmith, Tetrahedron Lett., 1971, 195.

62. W. Pelz, L. Burgardt, O. Wahl, U.S. Patent, 2,895,825 (1959).

63. T. Posner, Chem. Ber., 1906, 39, 3521.

64. A. Meyer, Ann. Chim., 1914, 1, 315.

65. J.E.G. Kemp, D. Ellis, M.D. Closier, Tetrahedron Lett., 1979, 3781.

66. E.A. Dorko, L. Buelow, J. Chem. .Phy., 1975, 62, 1869.

67. R. Dickinson, G.W. Kirby, J.G. Sweeny, J.K. Tyler, J. Chem. Soc. Faraday II, 1978, 74, 1393; idem., J. Chem. Soc., Chem. Commun., 1973, 241.

68. P. Horsewood, G.W. Kirby, J. Chem. Soc., Chem. Commun., 1971, 1139.

69. G.W. Kirby, Chem. Soc. Rev., 1977, 6, 1.

70. P. Horsewood, G.W. Kirby, R.P. Sharma, J.G. Sweeny, J. Chem. Soc., Perkin I, 1981, 6, 1802.

71. M. Freund, A. Schander, Chem. Ber., 1896, 29, 2500.

72. F.L. Scott, A. Koczarski, J. Reilly, Nature, 1952, 170, 922.

73. E. Lieber, C.N. Pillai, J. Org. Chem., 1957, 22, 1054.

74. A. Gursoy, H. Amal, Istanbul Univ. Eszacilik Fak. Mecmuasi, 1967, 3, 148 (Chem. Abstr., 1968, 69, 105113w).

75. M. Ohta, H. Oya, A. Mifune, J. Pharm. Soc. Japan, 1953, 73, 852 (Chem. Abstr., 1954, 48, 10006).

76. W.A. White, H. Weingarten, J. Org. Chem., 1967, 32, 213.

77. K.N. Campbell, B.K. Campbell, A.H. Sommers, J. Am. Chem. Soc., 1944, 66, 82.

78. D.P. Roelofsen, H. Van Bekkum, Rev. Trav. Chem., 1972, 91, 605.

79. J.T. Carlock, M.P. Mack, Tetrahedron Lett., 1978, 5153.

80. H. Loibner, E. Zbiral, Ann. Chem., 1978, 78.

81. R. Deghenghi, Org. Syn., 1960, 40, 60.

82. A.K. Qureshi, B. Sklarz, J. Chem. Soc. (C), 1966, 412.

83. 'The Merck Index', Merck and Co. Inc., N.J., 9th Ed., 1979.

84. M.W. Miller, R.W. Amidon, P.O. Tawney, J. Am. Chem. Soc., 1955, 77, 2845.

85. 'Dictionary of Organic Compounds', Eyre and Spottiswode Publishers Ltd., London, 1965.

86. D.P.J. Pearson, Ph.D. Thesis, University of Liverpool, 1975.

87. P.A.S. Smith, 'Nitrenes', Ed., W. Lwowski, Interscience, N.Y., 1970.

88. S. Gronowitz, C. Westerlund, A-B. Hörnfeldt, Acta Chem. Scand., 1976, B30, 391.

89. idem., Chemica Scripta, 1976, 10, 165.

90. idem., ibid., 1977, 12, 1

91. G. Kumar, K. Rajagopalan, S. Swaminathan, K.K. Balasubramanian, Tetrahedron Lett., 1979, 4685.

92. F. Povanzance, J. Kovac, D. Hasek, Coll. Czech. Chem. Comm., 1980, 45, 150.

93. C.J. Moody, C.W. Rees, S.C. Tsoi, J. Chem. Soc., Chem. Commun., 1981, 550.

94. W.A. Court, O.E. Edwards, C. Greico, W. Rank, T. Sano, Can. J. Chem., 1975, 53, 463.

95. S.C. Tsoi, personal communication.

96. 'Chemistry of the Azido Group', Ed. S. Patai, Interscience, N.Y., 1971,

97. A.W. Dox, Org. Syn., 1941, Coll. Vol. I, 5.

98. K.R. Huffman, F.C. Schaefer, J. Org. Chem., 1963, 28, 1812.

99. F. Eloy, A. Deryekere, Bull. Soc. Chim. Belges, 1969, 78, 41.

100. F. Eloy, A. Deryekere, A. van Overstraeten, ibid., 1969, 78, 47.

101. P.A.S. Smith, B.B. Brown, J. Am. Chem. Soc., 1951, 73, 2438.

102. S.R. Sandler, W. Karo, 'Organic Functional Group Preparations', Vol. II, Academic Press, London, 1971.

103. A. Brändström, B. Lamm, I. Palmertz, Acta Chem. Scand., 1974, B28, 699.

104. W.M. Lord, A.T. Peters, J. Chem. Soc. (C), 1968, 783.

105. Idem., Chem. and Ind. (London), 1973, 227.

106. M. Wakae, K. Hamano, Bull. Chem. Soc. Japan, 1963, 36, 230.

107. D.S. Doerha, H.L. Sharma, J. Indian Chem. Soc., 1963, 40, 819, 973.

108. D.D. Perrin, W.L.F. Armarego, D.R. Perrin, 'Purification of Laboratory Chemicals', Pergamon Press, London, 1966.

109. R. Ruccia, N. Vivona, G. Cusmano, J. Heterocyclic Chem., 1971, 8, 137.

110. S. Bradbury, C.W. Rees, R.C. Storr, J. Chem. Soc., Perkin I, 1972, 72.

111. K. Friedrich, M. Zamkanei, Chem. Ber., 1979, 112, 1873.

112. G. Höfle, B. Lange, Angew. Chem. Int. Ed. Engl., 1977, 16, 262.

113. K.E. Koenig, W.P. Weber, Tetrahedron Lett., 1974, 2275.

114. R.A. Abramovitch, S.R. Challand, J. Chem. Soc., Chem. Commun., 1972, 964.

115. S. Patai (Ed.), 'The Chemistry of the Hydrazo, Azo and Azoxy Groups', John Wily, London, 1975.

116. 'The Chemistry of the Nitro and Nitroso Groups', H. Feuer (Ed.), Interscience, London, 1969.

117. P. Santurri, F. Robbins, R. Stubbings, Org. Syn., 1973, Coll. Vol. V, 341.

118. A.H. Beckett, G.R. Jones, R.T. Coutts, Tetrahedron, 1976, 32, 1267.

119. F. Angelico, S. Cusmano, Gazz. Chim. Ital., 1936, 66, 3.

120. L.C. Claisen, O. Manasse, Chem. Ber., 1887, 20, 2194.

121. S. Cusamo, T. Tiberio, Gazz. Chim., Ital., 1951, 81, 106.

122. R.O. Lindsay, C.F.H. Allen, Org. Syn., 1955, Coll. Vol. III, 710.

123. L.M. Weinstock, P. Davis, B. Handelsmann, R. Tull, J. Org. Chem., 1967, 32, 2823.

124. W.D. Wensink and Ch. Granacher, Chem. Ber., 1919, 52, 232.

125. V. Bertini, A. de Munno, Gazz. Chim. Ital., 1971, 101, 259.

126. S. Mataka, K. Takahashi, Y. Yamada, M. Tashiro, J. Heterocyclic Chem., 1979, 16, 1009.

127. P.D. Kennewell, J.B. Taylor, Chem. Soc. Rev., 1975, 4, 189; 1980, 9, 477.

128. H.Y. Aboul-Enein, A.I. Iado, E.A. Lotfi, Acta Pharm. Suec., 1980, 17, 143 (Chem. Abstr., 1981, 94, 47088r)

129. F. Babudri, L. DiNunno, S. Florio, Chem. Ind. (Milan), 1980, 62, 755.

130. T. Curtius, Z. Angew. Chem., 1915, 28, 5.

131. T. Curtius, G. Ehrhart, Chem. Ber., 1922, 55, 1559.

132. A. Bertho, Chem. Ber., 1924, 57, 1138.

133. T. Curtius, A. Bertho, Chem. Ber., 1926, 59, 565.

134. F.D. Marsh, H.E. Simmons, J. Am. Chem. Soc., 1965, 87, 3529.

135. R.A. Abramovitch, C.I. Azogu, I.T. McMaster, J. Am. Chem. Soc., 1969, 91, 1219.

136. J.E. Leffler, Y. Tsuno, J. Org. Chem., 1963, 28, 902.

137. R.J.W. Cremlyn, J. Chem. Soc., 1965, 1132.

138. T. Curtius, G. Kraemer, J. Prakt. Chem., 1930, 125, 323.

139. T. Curtius, K. Vorbach, ibid., 1930, 125, 340.

140. T. Curtius, H. Bottler, W. Raudenbusch, ibid., 1930, 125, 380.

141. P. Tavs, Angew. Chem. Int. Ed. Engl., 1966, 5, 1048.

142. F. Kurzer, S.A. Taylor, J. Chem. Soc., 1960, 3234.

143. L.A. Pinck, Inorganic Synthesis, 1950, 3, 43.

144. P. Adams, D.W. Kaiser, D.E. Nagy, G.A. Peters, R.L. Sperry, T.T. Thurston, J. Org. Chem., 1952, 17, 1162.

145. F. Kurzer, J. Chem. Soc., 1956, 4524.

146. J. Goerdeler, P. Mertens, Chem. Ber., 1970, 103, 1805.

147. N. H-Bang, Acta. Chem. Scand., 1957, 11, 581.

148. F.L. Scott, J. Donovan, J.K. O'Halloran, Tetrahedron Lett., 1970, 4079.

149. F.L. Scott, D.A. Cronin, Chem. and Ind. (London), 1964, 1757.

150. F.L. Scott, J.A. Cronin, J. Donovan, Tetrahedron Lett., 1969, 4615.

151. H. Behringer, M. Matner, ibid., 1966, 1663.