

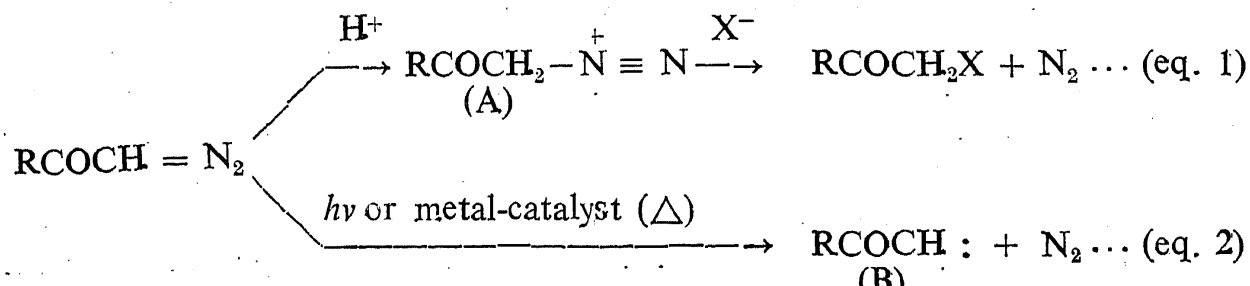
ACID-CATALYSED INTRAMOLECULAR C-ALKYLATION AND ALKYLATION-REARRANGEMENTS THROUGH UNSATURATED DIAZOMETHYL KETONES. A NEW VERSATILE APPROACH TO THE SYNTHESIS OF COMPLEX CARBOCYCLIC SYSTEMS

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THE pronounced stability of molecular nitrogen and its ready elimination from the diazo-compounds have rendered these as a source of numerous reactive intermediates in organic synthesis¹⁻⁸. Diazomethyl ketones⁸ represent a class of such compounds which may lead to a wide variety of products arising either through the reaction of nucleophiles with the protonated diazocarbonyl function, *e.g.*, diazonium or oxo-carbonium ion intermediates (A) (eq. 1), or by the loss of nitrogen resulting in an oxo-carbene or oxo-carbenoid species (B) (eq. 2).

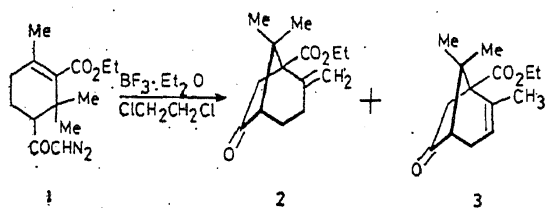
Intramolecular carbon-carbon bond formation of a metal-catalysed oxo-carbenoid with an appropriately situated olefinic bond or an aromatic double bond has been thoroughly investigated and is of great synthetic value for complex carbocyclic systems⁹. Although a relatively less explored reaction, the regioselective intramolecular insertion of a metal-catalysed oxo-carbenoid into a carbon-hydrogen bond is also of great value⁹ in the synthesis of complex carbocyclic systems as clearly evident from our own works¹⁰⁻¹² on the synthesis of the key intermediates for



atisane, veatchine and gibberellins-A₁₅ and the related systems. Similar intramolecular C-H insertion reaction of α -diazomides have also been applied in the synthesis of nuclear analogues of the penicillin-cephalosporin antibiotics¹³ and other highly rigid polycyclic compounds^{9,14,15}.

An important aspect of diazocarbonyl chemistry, that was observed more than thirty years ago by Cook and Schoental¹⁶ but remained unexplored, is the acid-catalysed intramolecular carbon-carbon bond forming process through an aromatic carbon nucleophile. An analogous cyclisation reaction leading to a tricyclic steroid intermediate was also reported by Newman¹⁷.

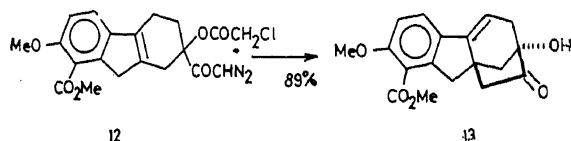
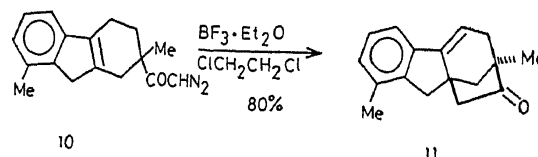
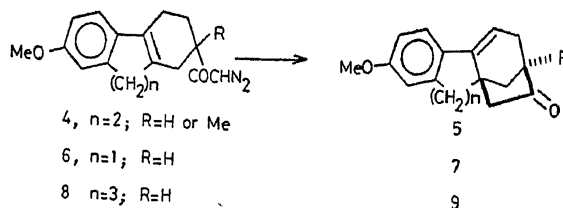
In the early nineteen-seventies, a new cyclopentanone annulation reaction of great synthetic potential was announced by several groups for the introduction of a bicyclo(3·2·1) octanone¹⁸⁻²⁰ or a bicyclo(2·2·1) heptanone²¹ moiety into a variety of systems by the acid-catalysed intramolecular electrophilic cyclisation of γ,δ -unsaturated α -diazomethyl ketones. This method was first applied¹⁸ to construct the complex skeleton of the sesquiterpene, α -patchoulane in a single step transformation of 1 to a double bond isomers 2 and 3.



Chakraborty *et al.*²⁰ and an Australian group¹⁹ also independently reported the facile acid-catalysed cyclisations of the γ,δ -unsaturated tricyclic diazomethyl ketones (4 and 6) to the respective tetracyclic ketones (5 and 7), key intermediates for plant-growth hormones gibberellins and related compounds, incorporating the bicyclo(3·2·1)octanone moiety. This reaction was further extended to a large number of substrates leading to tetracyclic systems incorporating substituents in the aromatic ring²²⁻²⁴ as well as in the alicyclic rings²⁵. A simple and convenient synthesis

of the B-homo-tetracyclic diterpene skeleton 9²⁶ and *dl*-gibberone (11)²⁷, a degradation product of gibberellic acid, were also achieved by acid catalysed cyclisations of the respective diazomethyl ketones 8 and 10.

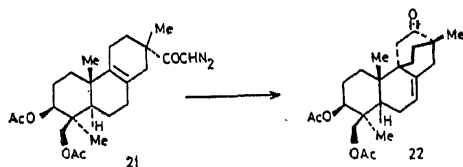
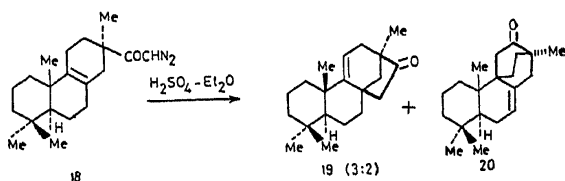
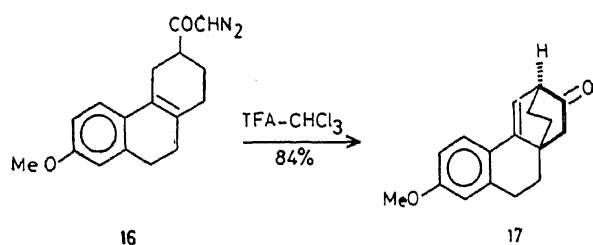
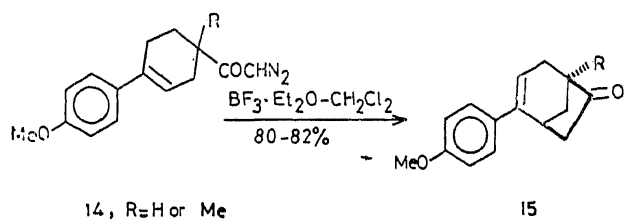
In an elegant total synthesis of gibberellins, Mander and his co-workers²⁸ have prepared the key tetracyclic intermediate 13 by cyclisation of the diazomethyl ketone (12).



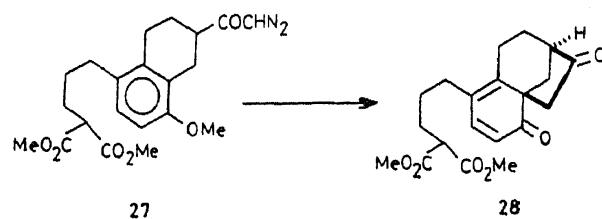
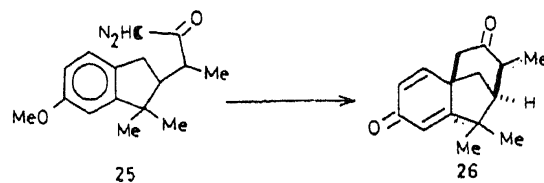
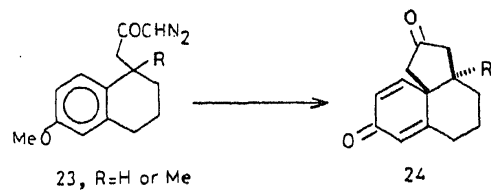
The intramolecular cyclisation was also extended²⁹ for the synthesis of some important intermediates 15 for B-*seco*-gibberellins through the diazomethyl ketones (14). Similar reaction has also been used by Mander³⁰ for the synthesis of norhelminthosporin analogues. The acid catalysed cyclisation of the diazomethyl ketone (16) leads to the tetracyclic intermediate 17³¹, incorporating the basic bicyclo(2·2·2)-octanone skeletal structure of atisane diterpenoids.

In each of the above examples, acid-catalysed cyclisation reaction of the γ,δ -unsaturated diazomethyl ketones produced essentially a single annulated product arising from the electronic stabilisation of the intermediate cations. The absence of such a stabilisation factor may lead to regioisomeric products as evidenced³² in the cyclisation of 18 to 19 and 20 in a 3 : 2 ratio. The steric environment also seems to be important as it reflects in the regioselective cyclisation of 21 to 22.

Similar lack of regioselectivity in the carbon-carbon bond formation has been observed in some relatively simple substituted monocyclic γ, δ -unsaturated diazomethyl ketones in this laboratory³³.



The elegant studies of Mander³⁴ have elaborated the aryl participations in protonated diazomethyl carbonyl alkylation as a viable method for bridged- and spiro-ring annulations. Spiroannulation reactions have been extended by Bhattacharyya and Sen³⁵ for the synthesis of a spirocyclobutanone and a few spirocyclopentanones. Ring annulation by aryl participation has been successfully utilised by Dutta³⁶ and Mukherjee³⁷ and their co-workers in these laboratories, for preparation of the spiro- and the bridged-ketones 24³⁶, 26³⁷ and a number of related compounds³⁸ as key intermediates towards sester- and sesquiterpene total synthesis. An efficient synthesis³⁹ of the key tricyclic ketone 28 for C_{19} -gibberellins has been achieved by diazo-ketone alkylation route.

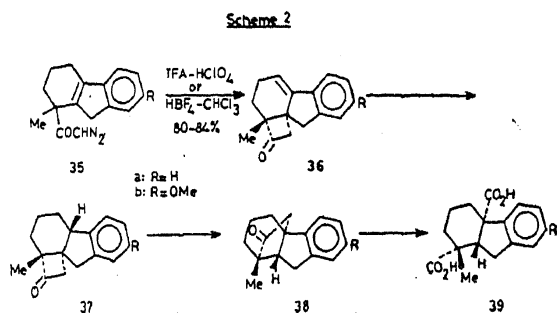
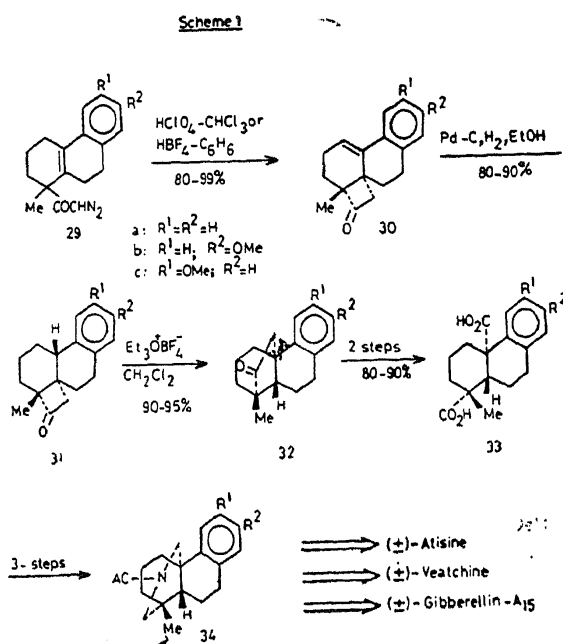


These reactions probably proceed^{9,21,34} via initial protonation (*cf.* eq. (1) (Bronstead-acid catalysis) or complexing (Lewis-acid catalysis) of the diazocarbonyl functionality, followed by displacement of nitrogen from the resultant diazonium species by π -bond or aryl participation.

In 1974 we introduced⁴⁰ a highly efficient new synthesis of angularly fused cyclobutanones by the acid-catalysed intramolecular C-alkylation of β, γ -unsaturated α -diazomethyl ketones. The readily available styrenoid cyclobutanones such 30 from the respective diazomethyl ketones (29), have been further transformed to the corresponding bridged-cyclopentanones (32) by a remarkable stereospecific rearrangement⁴¹ of the stereoselectively hydrogenated cyclobutanones (31) and finally to the bridged-acylamines (34), through the respective dicarboxylic acids (33) as presented in Scheme 1. This sequence represents a highly efficient formal stereospecific total synthesis^{42,43} of *dl*-atisine, *dl*-veatchine and gibberellin- A_{15} .

The β, γ -unsaturated α -diazomethyl ketones (35) incorporating a tetrahydrofluorene moiety, also produced the respective styrenoid cyclobutanones (36)⁴⁶ which were transformed through a similar sequence of reactions⁴³

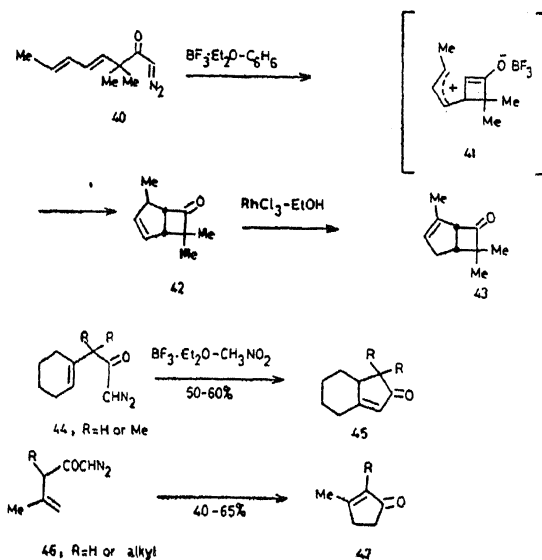
to the potential hydrofluorene intermediates 39 towards C₂₀-gibberellins (Scheme 2).



Pellicciari and co-workers⁴⁴ have utilised our cyclobutanone annulation route for the preparation of two 4,4-dimethyl-D-norsteroids. Hudlicky and Kutchan⁴⁵ have also applied this method on the diazomethyl ketone (40) to the respective cyclobutanone (42) and finally to filifolone (43).

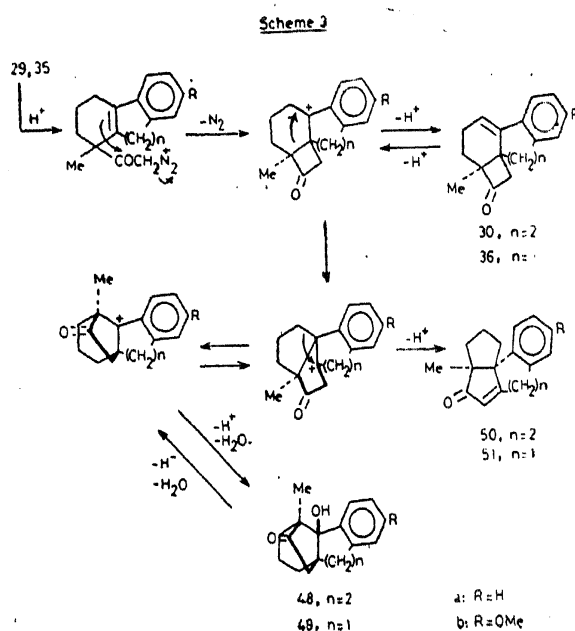
Following our preliminary communication of the aforementioned cyclobutanone annulation, Smith developed⁴⁶ the acid-catalysed alkylation method to a few relatively flexible β, γ -unsaturated α -diazomethyl ketones, for examples 44 and 46 leading to the corresponding cyclopentenones 45 and 47 as sole products. This group has just reported their extensive studies on the related cyclopentenone annulation reaction⁴⁷ and its extension⁴⁸ in a series of papers.

After considerable experimentation, we have now discovered⁴⁹ that it is not the structure



of the substrate alone which controls the nature of the products in the acid-catalysed reactions of the β, γ -unsaturated diazo-ketones such as 29a, b and 35a, b but that the choice of the acid catalyst and solvent is also critical. For example, the reactions of the diazo-ketones (29a, b) and (35a, b) in weakly polar solvents, such as benzene, CHCl₃ or CH₂Cl₂ in the presence of strong protic acids namely, aq. HClO₄ (70%), aq. HBF₄ (48%), CF₃COOH or H₂SO₄ (98%) gave the respective unsaturated cyclobutanones (30a, b) and (36a, b) in good to excellent yields. In contrast, when the diazo-ketones (29a) and (35a, b) were subjected to cyclisations^{49,50} with aq. HBF₄ (48%) or BF₃ · Et₂O in strongly polar solvent nitromethane, the respective rearranged bridged hydroxy-ketones (48a) and (49a, b) were the predominating products (ca 90%) (Scheme 3). Specifically, the methoxy-diazomethyl ketone (29b) showed a sharp difference in the nature of the products with respect to the *de*-methoxy analogue (29a), giving rise to the cyclobutanone (30b), as the major product even with HBF₄ in CH₃NO₂. However, the hydroxy-cyclopentanone (48b) was obtained in 79% yield by reaction of (29b) with H₂SO₄ in CH₃NO₂. The hydroxy-cyclopentanones (48a, b) underwent facile rearrangement^{49,50} with *p*-TsOH or iodine in boiling benzene to afford the respective rearranged cyclopentenones (50a, b). In contrast, the hydrofluorene analogues (49a, b) under similar conditions did not

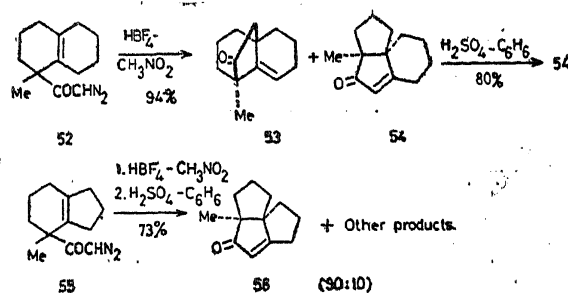
produce the rearranged cyclopentenones (51a, b). These compounds however, have been obtained in excellent yields⁵¹ by direct cyclisations of the diazo-ketones (35a, b) with *p*-TsOH in boiling benzene. The mechanistic pathways for the formation of different products from the diazomethyl ketones (29a, b) and (35a, b) have been rationalised as depicted in Scheme 3.



The alkylation-rearrangement reaction has also been extended⁵¹ to the bicyclic diazo-ketone (52) leading to the bridged-ketone (53) and the rearranged cyclopentenone (54) in excellent yields. This mixture undergoes facile acid-catalysed rearrangement to 54. The lower homologous diazomethyl ketone (55)⁵² undergoes cyclisation-rearrangement to afford the angularly fused cyclopentenone (56) along with other minor products. This sequence appears extremely attractive for the synthesis of complex polycyclopentanoid sesqui- and sesterterpenes. A similar alkylation-rearrangement of a diazomethyl ketone has been exploited previously⁵³ for the synthesis of an intermediate towards aspidosperma alkaloids.

It is clear from the present account that acid-catalysed intramolecular C-alkylation and alkylation-rearrangement reactions of unsaturated diazomethyl ketones have great potentiality in organic synthesis both as general methods and as strategies designed to reach

complex natural products bearing difficultly accessible carbocyclic systems with multiple centres of chirality.



I am indebted to my colleagues, whose names are listed in the references, for participation in the above studies performed by our group. It is mostly their hard works, clear understanding and experimental skills that have proven decisive both in the formulation of the projects and their executions in the laboratory to a successful conclusion.

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