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

U. R. GHATAK

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta 700 032, *India*

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 synthesis[1–8]. Diazomethyl ketones[8] 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 systems[9]. Although a relatively less explored reaction, the regio-selective intramolecular insertion of a metal-catalysed oxo-carbenoid into a carbon-hydrogen bond is also of great value[9] in the synthesis of complex carbocyclic systems as clearly evident from our own works[10–12] on the synthesis of the key intermediates for

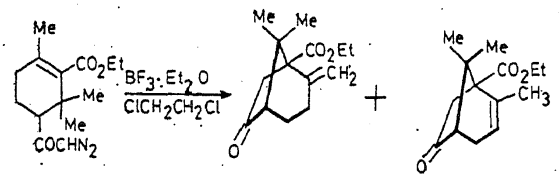
$$RCOCH=N_2 \xrightarrow{H^+} \underset{(A)}{RCOCH_2-\overset{+}{N}\equiv N} \xrightarrow{X^-} RCOCH_2X + N_2 \cdots \text{(eq. 1)}$$

$$RCOCH=N_2 \xrightarrow{h\nu \text{ or metal-catalyst } (\triangle)} \underset{(B)}{RCOCH:} + N_2 \cdots \text{(eq. 2)}$$

atisine, veatchine and gibberellins-A_{15} and the related systems. Similar intramolecular C–H insertion reaction of α-diazoamides have also been applied in the synthesis of nuclear analogues of the penicillin-cephalosporin antibiotics[13] 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 Schoental[16] 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 Newman[17].

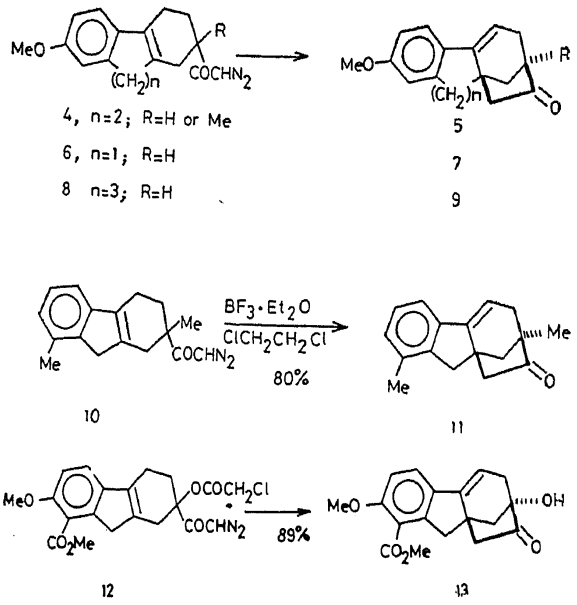
In the early nineteen-seventies, a new cyclopentanone annulation reaction of great synthetic potential was announced by several groups for the introduction of a bicyclo (3·2·1) octanone[18–20] or a bicyclo (2·2·1) hepatanone[21] moiety into a variety of systems by the acid-catalysed intramolecular electrophilic cyclisation of γ,δ-unsaturated α-diazomethyl ketones. This method was first applied[18] 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.



1 2 3

Chakrabortty *et al.*[20] and an Australian group[19] 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 ring[22–24] as well as in the alicyclic rings[25]. A simple and convenient synthesis of the B-homo-tetracyclic diterpene skeleton 9[26] 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.

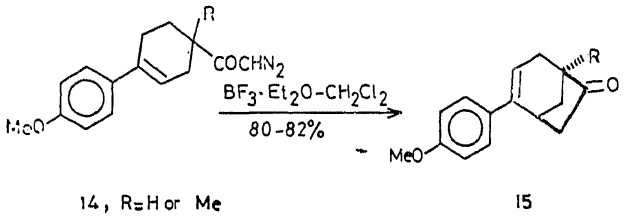
In an elegant total synthesis of gibberellins, Mander and his co-workers[28] have prepared the key tetracyclic intermediate 13 by cyclisation of the diazomethyl ketone (12).



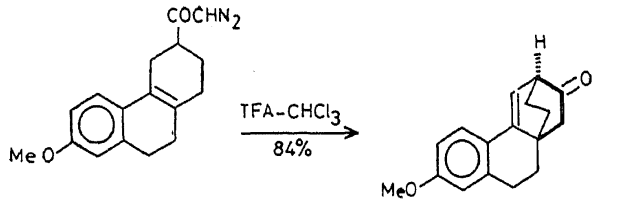
The intramolecular cyclisation was also extended[29] for the synthesis of some important intermediates 15 for B-seco-gibberellins through the diazomethyl ketones (14). Similar reaction has also been used by Mander[30] for the synthesis of norhelminthosporin analogues. The acid catalysed cyclisation of the diazoketone (16) leads to the tetracyclic intermediate 17[31], 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 evidenced[32] 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 regiospecific cyclisation of 21 to 22.

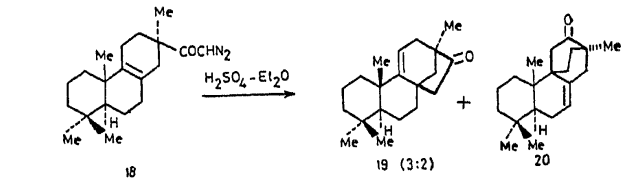
Similar lack of regioselectivity in the carbon-carbon bond formation has been observed in some relatively simple substituted monocyclic γ,δ-unsaturated diazomethyl ketones in this laboratory[33].



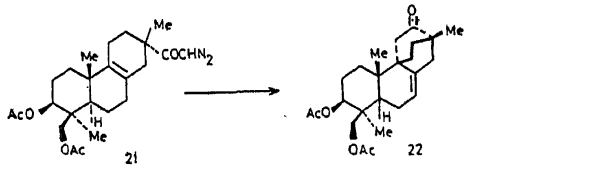
14, R=H or Me 15



16 17

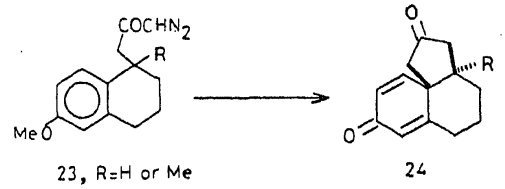


18 19 (3:2) 20

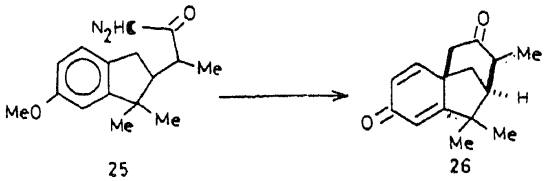


21 22

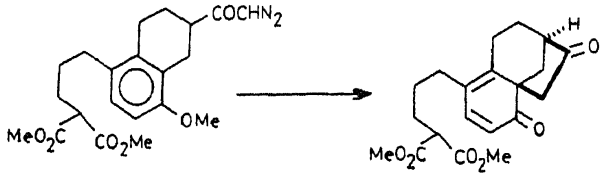
The elegant studies of Mander[34] have elaborated the aryl participations in protonated diazomethyl carbonyl alkylation as a viable method for bridged- and spiro-ring annulations. Spiroannulation reactions have been extended by Bhattacharyya and Sen[35] for the synthesis of a spirocyclobutanone and a few spirocyclopentanones. Ring annulation by aryl participation has been successfully utilised by Dutta[36] and Mukherjee[37] and their co-workers in these laboratories, for preparation of the spiro- and the bridged-ketones 24[36], 26[37] and a number of related compounds[38] as key intermediates towards sester- and sesquiterpene total synthesis. An efficient synthesis[39] of the key tricyclic ketone 28 for C_{19}-gibberellins has been achieved by diazo-ketone alkylation route.



23, R=H or Me 24



25 26



27 28

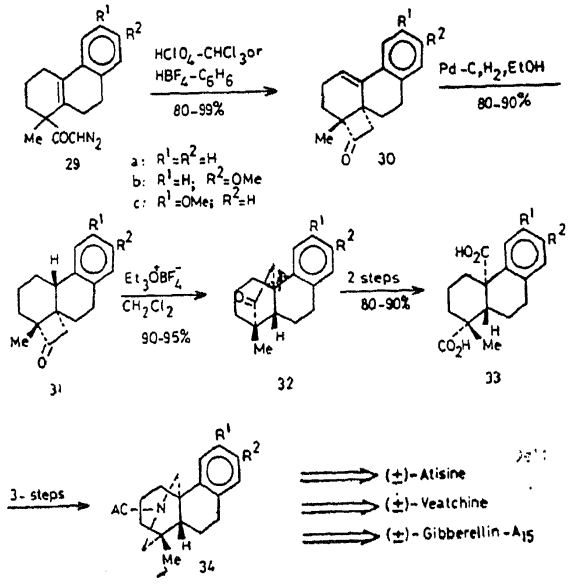
These reactions probably proceed[9,21,34] *via* initial protonation (*cf.* eq. (1) (Bronsted-acid catalysis) or complexing (Lewis-acid catalysis) of the diazocarbonyl functionality, followed by displacement of nitrogen from the resultant diazonium species by π-bond or aryl participation.

In 1974 we introduced[40] 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 rearrangement[41] 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}.

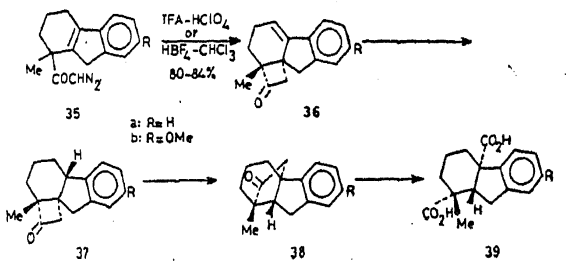
The β,γ-unsaturated α-diazomethyl ketones (35) incorporating a tetrahydrofluorene moiety, also produced the respective styrenoid cyclobutanones (36)[46] which were transformed through a similar sequence of reactions[43]

to the potential hydrofluorene intermediates 39 towards C_{20}-gibberellins (Scheme 2).

Scheme 1



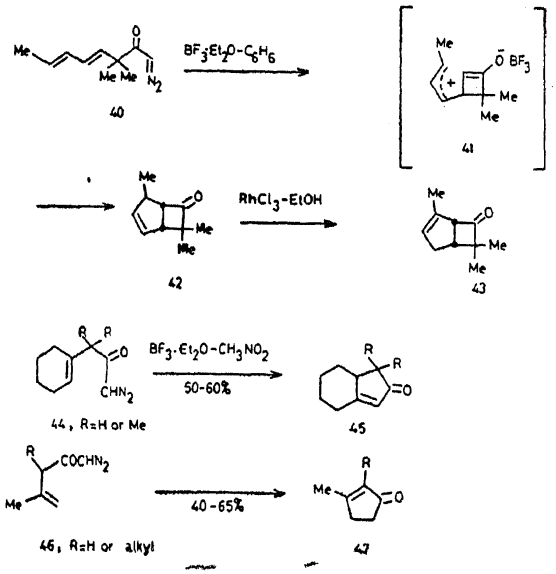
Scheme 2



Pellicciari and co-workers[44] have utilised our cyclobutanone annulation route for the preparation of two 4, 4-dimethyl-D-nor-steroids. Hudlicky and Kutchan[45] 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 developed[46] 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 reaction[47] and its extension[48] in a series of papers.

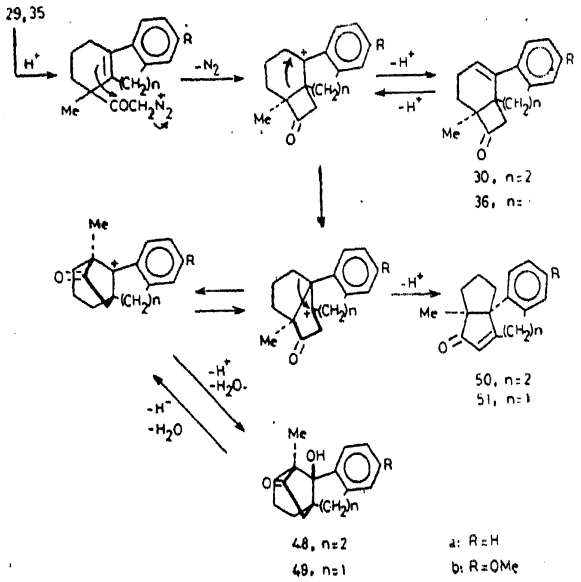
After considerable experimentation, we have now discovered[49] that it is not the structure



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 29*a*, *b* and 35*a*, *b* but that the choice of the acid catalyst and solvent is also critical. For example, the reactions of the diazo-ketones (29*a*, *b*) and (35*a*, *b*) in weakly polar solvents, such as benzene, $CHCl_3$ or CH_2Cl_2 in the presence of strong protic acids namely, aq. $HClO_4$ (70%), aq. HBF_4 (48%), CF_3COOH or H_2SO_4 (98%) gave the respective unsaturated cyclobutanones (30*a*, *b*) and (36*a*, *b*) in good to excellent yields. In contrast, when the diazoketones (29*a*) and (35*a*,*b*) were subjected to cyclisations[49,50] with aq. HBF_4 (48%) or $BF_3 \cdot Et_2O$ in strongly polar solvent nitromethane, the respective rearranged bridged hydroxy-ketones (48*a*) and (49*a*,*b*) were the predominating products (*ca* 90%) (Scheme 3). Specifically, the methoxy-diazomethyl ketone (29*b*) showed a sharp difference in the nature of the products with respect to the *de*-methoxy analogue (29*a*), giving rise to the cyclobutanone (30*b*), as the major product even with HBF_4 in CH_3NO_2. However, the hydroxy-cyclopentanone (48*b*) was obtained in 79% yield by reaction of (29*b*) with H_2SO_4 in CH_3NO_2. The hydroxy-cyclopentanones (48*a*, *b*) underwent facile rearrangement[49,50] with *p*-TsOH or iodine in boiling benzene to afford the respective rearranged cyclopentenones (50*a*, *b*). In contrast, the hydrofluorene analogues (49*a*, *b*) under similar conditions did not

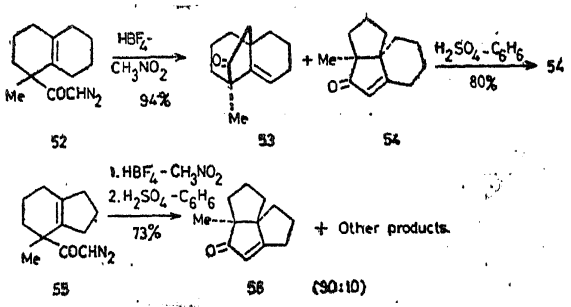
produce the rearranged cyclopentenones (51*a*, *b*). These compounds however, have been obtained in excellent yields[51] by direct cyclisations of the diazo-ketones (35*a*, *b*) with *p*-TsOH in boiling benzene. The mechanistic pathways for the formation of different products from the diazomethyl ketones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

Scheme 3



The alkylation-rearrangement reaction has also been extended[51] 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 previously[53] 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 difficulty accessible carbocylic 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.

1. Kirmse, W., *Angew. Chem. Int. Ed. Engl.*, 1976, **15**, 251.
2. Meier, H. and Zeller, K. P., *Ibid.*, 1975, **32**, 32.
3. Wulfman, D. S., Linstrumelle, G. and Cooper, C. F., In *The Chemistry of Diazonium and Diazo Groups*, (ed.) S. Patai, Wiley, New York, 1978, **2**, Ch. 18, p. 821.
4. Jones, M. Jr. and Moss, R. A., *Carbenes*, Wiley, New York, 1973.
5. Bethell, D., *Organic Reactive Intermediates*, (ed.) McManus, S. P., Academic Press, London, 1973, p. 61.
6. Kirmse, W., *Carbene Chemistry*, Academic Press, New York, 1971.
7. Dave, V. and Warnhoff, E. W., *Org. React.*, 1970, **18**, 217.
8. Weygand, F. and Bestmann, H. J. In *Newer Methods of Preparative Organic Chemistry*, (ed.) W. Foerst, Academic Press, New York, 1964, **3**, 451.
9. For a comprehensive recent review see, Burke, S. D. and Grieco, P. A., *Org. React.*, 1979, **26**, 361.
10. Ghatak, U. R. and Chakrabarty, S., *J. Am. Chem. Soc.*, 1972, **94**, 4756.
11. — and —, *J. Org. Chem.*, 1976, **41**, 1089.
12. Chakrabarty, S., Ray, J. K., Mukherjee, D. and Ghatak, U. R., *Syn. Comm.*, 1975, **5**, 275.
13. Brunwin, D. M., Lowe, G. and Parker, J., *J. Chem. Soc.* (*C*), 1971, p. 3756; Brunwin, D. M. and Lowe, G., *J. Chem. Soc. Chem. Commun.*, 1972, p. 589; Golding, B. T. and Hall, D. R., *Ibid.*, 1973, p. 293.

14. Ghatak, U. R., Ray, J. K. and Chakrabarty, S., *J. Chem. Soc. Perkin Trans.* 1, 1976, p. 1975.
15. Ōsawa, E., Engler, E. M., Godleski, S. A., Inamoto, Y., Kent, G. J., Kausch, M. and Schleyer, P. V. R., *J. Org. Chem.*, 1980, **45**, 984, and other papers in this series.
16. Cook, J. W. and Schoental, R., *J. Chem. Soc.*, 1945, p. 288.
17. Newman, M. S., Eglinton, G. and Grotta, H. M., *J. Am. Chem. Soc.*, 1953, **75**, 349.
18. Erman, W. F. and Stone, L. C., *J. Am. Chem. Soc.*, 1971, **93**, 2821; *J. Agric. Food Chem.*, 1971, **19**, 1093.
19. Beames, D. J., Klose, T. R. and Mander, L. N., *Chem. Commun.*, 1971, p. 773; Klose, T. R. and Mander, L. N., *Aust. J. Chem.*, 1974, **27**, 1287; Beames, D. J., Mander, L. N. and Turner, J. V., *Ibid.*, 1974, **27**, 1977.
20. Chakrabortty, P. N., Dasgupta, R., Dasgupta, S. K., Ghosh, S. R. and Ghatak, U. R., *Tetrahedron*, 1972, **28**, 4653.
21. Malherbe, R., Tam, N. T. T. and Dahn, H., *Helv. Chim. Acta*, 1972, **55**, 245; Malherbe, R. and Dahn, H., *Ibid.*, 1977, **60**, 2539.
22. Ghatak, U. R., Chakraborti, P. C., Ranu, B. C., and Sanyal, B., *J. Chem. Soc. Chem. Commun.*, 1973, p. 548.
23. — and Roy, S. C., *J. Chem. Research (S)*, 1981, p. 5; *J. Chem. Research (M)*, 1981, p. 159.
24. Ranu, B. C., Sarkar, M. and Ghatak, U. R., *J. Chem. Soc. Perkin Trans.* 1, in press.
25. Ghatak, U. R., Chakrabarty, S. and Rudra, K., *Ibid.*, 1974, p. 1957.
26. — and Ray, J. K., *Ibid.*, 1977, p. 518.
27. — and Chakraborti, P. C., *J. Org. Chem.*, 1979, **44**, 4562.
28. Hook, J. M., Mander, L. N. and Urech, R., *J. Am. Chem. Soc.*, 1980, **102**, 6628.
29. Ghatak, U. R., Alam, S. K., Chakraborti, P. C. and Ranu, B. C., *J. Chem. Soc. Perkin Trans.* 1, 1976, p. 1669.
30. Mander, L. N., Turner, J. V., and Coombe, B. G., *Aust. J. Chem.*, 1974, **27**, 1985; Cossey, A. L., Mander, L. N. and Turner, J. V., *Ibid.*, 1980, **33**, 2061.
31. Roy, S. C., Sarkar, M. and Ghatak, U. R., *Indian J. Chem. Sec. B*, 1980, **19**, 305.
32. Ceccherelli, P., Tingoli, M., Curini, M. and Pellicciari, R., *Tetrahedron Lett.*, 1978, p. 4959.
33. Saha, B. and Chakraborti, A. K., Unpublished results.
34. Beames, D. J. and Mander, L. N., *Aust. J. Chem.*, 1974, **27**, 1257; Beames, D. J., Klose, T. R., and Mander, L. N., *Ibid.*, 1974, **27**, 1269; Johnson, D. W. and Mander, L. N., *Ibid.*, 1974, **27**, 1277; Blair, I. A., Ellis, A., Johnson, D. W. and Mander, L. N., *Ibid.*, 1978, **31**, 405; Lombardo, L., Mander, L. N. and Turner, J. V., *J. Am. Chem. Soc.*, 1980, **102**, 6626.
35. Bhattacharya, K. K. and Sen, P. K., *Syn. Comm.*, 1979, **9**, 77; *Experientia*, 1979, **35**, 1543.
36. Sanyal, U., Ghoshal, P. K. and Dutta, P. C., *Tetrahedron Lett.*, 1978, p. 2187.
37. Mukherjee, D., Personal communication.
38. Basu, B., Maity, S. K. and Mukherjee, D., *Syn. Comm*, 1981, in press.
39. Mander, L. N. and Pyne, S. G., *J. Am. Chem. Soc.*, 1979, **101**, 3374.
40. Ghatak, U. R. and Sanyal, B., *J. Chem. Soc. Chem. Commun.*, 1974, p. 876.
41. —, — and Ghosh, S., *J. Am. Chem. Soc.*, 1976, **98**, 3721.
42. —, Alam, S. K. and Ray, J. K., *J. Org. Chem.*, 1978, **43**, 4598.
43. —, Ghosh, S. and Sanyal, B., *J. Chem. Soc. Perkin Trans.* 1, 1980, p. 2881.
44. Ceccherelli, P., Curini, M., Tingoli, M. and Pellicciari, *Ibid.*, 1980, p. 1924.
45. Hudlicky, T. and Kutchan, T., *Tetrahedron Lett.* 1980, **21**, 691.
46. Smith, III, A. B., *J. Chem. Soc. Chem. Commun.*, 1975, p. 274; Smith III, A. B., Branca, S. J. and Toder, B. H., *Tetrahedron Lett.*, 1975, p. 4225; Smith, III, A. B. and Dieter, R. K., *J. Org. Chem.*, 1977, **42**, 396.
47. Smith, III, A. B., Toder, B. H., Branca, S. J., and Dieter, R. K., *J. Am. Chem. Soc.*, 1981, **103**, 1996.
48. — and Dieter, R. K., *Ibid.*, 1981, **103**, 2009, 2017.
49. Ghatak, U. R., Sanyal, B., Satyanarayana, G. O. S. V. and Ghosh, S., *J. Chem. Soc. Perkin Trans.* 1, 1981, p. 1203.
50. Satyanarayana, G. O. S. V., Unpublished results.
51. —, Kanjilal, P. R. and Ghatak, U. R., *J. Chem. Soc. Chem. Commun.*, 1981, 746.
52. Kanjilal, P. R., Unpublishd results.
53. Takano, S., Shishido, K., Sato, M., Yuta, K. and Ogasawara, *J. Chem. Soc. Chem. Commun.*, 1978, p. 943.