Developments in the Chemistry of Diazo-alkanes

By G. W. Cowell* and A. Ledwith
DONNAN LABORATORIES, UNIVERSITY OF LIVERPOOL

Diazo-alkanes (R_2CN_2) have been useful intermediates in organic chemistry for over forty years, and consequently many reactions of these molecules have been fully investigated.[1] It is now almost a decade since the last review[2] was completed, and in the meantime there has been a tremendous growth of interest in diazo-alkanes from both synthetic and theoretical (mechanistic) viewpoints.[3]

Diazomethane (1) is the simplest diazo-alkane and is best represented as a resonance hybrid comprising linear structures with opposing dipoles:

$$\underset{(1)}{CH_2{=}\overset{+}{N}{=}\overset{-}{N}} \longleftrightarrow \underset{(1b)}{\overset{+}{C}H_2{-}N{=}\overset{-}{N}} \longleftrightarrow \underset{(1c)}{\overset{-}{C}H_2{-}\overset{+}{N}{\equiv}N} \longleftrightarrow \underset{(1d)}{\overset{-}{C}H_2{-}N{=}\overset{+}{N}}$$

Under appropriate conditions, diazomethane will behave as an acid or a base, as an electrophile or a nucleophile, as a 1,3-dipole, or as a carbene source.

Much of the renewed activity in diazo-alkane chemistry derives from world-wide studies of the reactivity and structure of carbenes (R_2C:).[4,5] The latter are now recognised as the most common intermediates in photolysis and thermolysis of diazo-alkanes and were characterised during the early nineteen fifties, largely as a result of pioneering studies by Doering,[6] Skell,[7] Hertzberg,[8] and their collaborators. Other major developments in diazo-alkane chemistry include cycloaddition,[9] and catalysed alkylation, homologation, and polymerisation processes.[10]

Present Address: I.C.I. Mond Division, The Heath, Runcorn.

---

[1] R. Huisgen, *Angew. Chem.*, 1955, **67**, 439.
[2] H. Zollinger, 'Azo and Diazo Chemistry', Interscience, London, 1961.
[3] Brief surveys have appeared in two recent texts: P. A. S. Smith, 'Open Chain Nitrogen Compounds', Benjamin Inc., New York, 1966, vol. 2, p. 211; C. G. Overberger, J. P. Anselme, and J. G. Lombardino, 'Organic Compounds with Nitrogen–Nitrogen Bonds', Ronald Press, New York, 1966, p. 41.
[4] A. Ledwith, 'The Chemistry of Carbenes', R.I.C. Lecture Series Monographs, 1964, No. 5.
[5] W. Kirmse, 'Carbene Chemistry', Academic Press, London, 1964; J. Hine, 'Divalent Carbon', Ronald Press Co., New York, 1964.
[6] W. von E. Doering and A. K. Hoffman, *J. Amer. Chem. Soc.*, 1954, **76**, 6162; W. von E. Doering and L. H. Knox, *ibid.*, 1956, **78**, 4947.
[7] P. S. Skell and R. C. Woodworth, *J. Amer. Chem. Soc.*, 1956, **78**, 4496.
[8] G. Hertzberg and J. Shoosmith, *Nature*, 1959, **183**, 1801; G. Hertzberg, *Proc. Roy. Soc.*, 1961, *A*, **262**, 291.
[9] R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 565, 633.
[10] (*a*) C. E. H. Bawn and A. Ledwith, *Progr. Boron Chem.*, 1964, **1**, 345; (*b*) E. Müller, H. Kessler, and B. Zeeh, *Fortsch. Chem. Forsch.*, 1966, **7**, 128.

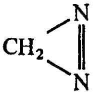
It is the purpose of this review article to survey major developments in diazo-alkane chemistry during the last fifteen years, exclusive of the chemistry of carbenes, which has already been discussed in a complementary review[4] and in several other recent surveys.[5,11,12] Familiarity with the general chemistry of diazo-alkanes will be assumed, and photolysis and thermolysis of diazo-alkanes will be considered only as they reflect on the properties of the diazo-alkane.

1 Structure and Stability of Diazo-alkanes

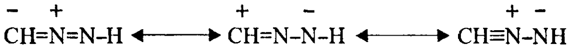
A linear, planar structure for diazomethane was established by electron diffraction[13] and microwave spectroscopic techniques,[14] and the dipole moment (1·4 D) and bond lengths ($>\mathrm{C}\overset{1.300}{\text{———}}\mathrm{N}\overset{1.139}{\text{———}}\mathrm{N}$) support the resonance hybrid formulation. Simple Hückel molecular orbital (HMO) calculations[15] indicate a resonance energy of 0·6 β and predict values for the bond lengths and dipole moment in close agreement with experiment.

A complete analysis[16] of the vibrational spectrum of gaseous and solid CH_2N_2 (and CD_2N_2) confirmed the linear, planar structure with sp^2 hybridised carbon, but indicated that there must be a non-planar structure (with sp^3 hybridised carbon) only a few kilocalories higher in energy than the equilibrium. It follows, therefore, that thermal reactions of diazomethane could involve a high-energy non-planar molecule, similar in structure to the low-lying electronically-excited states.

Two structural isomers of diazomethane are known, diazirine[17] (2) and isodiazomethane[18] (3).



(2)



$$\overset{-}{\mathrm{C}}\mathrm{H}{=}\overset{+}{\mathrm{N}}{=}\mathrm{N}\text{-}\mathrm{H} \longleftrightarrow \overset{+}{\mathrm{C}}\mathrm{H}{=}\mathrm{N}\text{-}\overset{-}{\mathrm{N}}\text{-}\mathrm{H} \longleftrightarrow \mathrm{CH}{\equiv}\overset{+}{\mathrm{N}}\text{-}\overset{-}{\mathrm{N}}\mathrm{H}$$

(3)

Diazirine (2) and its alkyl homologues are readily synthesised but are unreactive towards organic acids, whereas the corresponding diazo-alkanes react readily to form esters. Lower homologues are explosively unstable, as for the diazo-

---

[11] A. Ledwith, *Ann. Reports* (*B*), 1968, **65**, 143.

[12] D. Bethell, *Adv. Phys. Org. Chem.*, 1969, **7**, 153; A. M. Trozzolo, *Accounts Chem. Res.*, 1968, **1**, 329; G. L. Closs, *Topics Stereochem.*, 1968, **2**, 193.

[13] H. Boersch, *Monatsh.*, 1935, **65**, 331.

[14] A. P. Cox, L. F. Thomas, and J. Sheridan, *Nature*, 1958, **181**, 1000.

[15] A. J. Owen, *Tetrahedron*, 1961, **14**, 237.

[16] C. Bradley Moore and G. C. Pimentel, *J. Chem. Phys.*, 1964, **40**, 329, 340, 1529.

[17] E. Schmitz, *Angew. Chem., Internat. Edn.*, 1964, **3**, 333; E. Schmitz, *Adv. Heterocyclic Chem.*, 1964, **2**, 122; E. Schmitz, and R. Ohne, *Tetrahedron Letters*, 1961, 612; S. R. Paulsen, *Angew. Chem.*, 1960, **72**, 781.

[18] J. P. Anselme, *J. Chem. Educ.*, 1966, **43**, 596; E. Müller and D. Ludsteck, *Chem. Ber.*, 1954, **87**, 1887.

alkanes, and may be used as thermal and photochemical precursors to carbenes, but less conveniently. Isodiazomethane (3) is formed by reaction of diazomethane with organometallic reagents, particularly methyl-lithium, *via* the diazomethyl anion (4):

$$CH_2{=}\overset{+}{N}{=}\overset{-}{N} \underset{OH^-}{\overset{CH_3Li}{\rightleftharpoons}} [CH{-}N{=}N]^-Li^+ \underset{OH^-}{\overset{KH_2PO_4}{\rightleftharpoons}} H\overset{-}{C}{=}\overset{+}{N}{=}N{-}H$$

(4) (3)

Formation of isodiazomethane by acidic hydrolysis of (4) is apparently the result of a kinetically controlled reaction. Protonation occurs rapidly at the more nucleophilic nitrogen of (4) to give the thermodynamically less stable isomer.† Isodiazomethane is the parent of dipolar compounds known as nitrilimines (5).[3]

$$R^1{-}C{\equiv}\overset{+}{N}{-}\overset{-}{N}{-}R^2$$

(5)

Both diazirines and nitrilimines differ markedly from diazo-alkanes in their chemical and physical properties and will not be considered further. There is, however, considerable interest in the possibility of isomerisation of diazirines to diazo-alkanes before fragmentation in photolysis and thermolysis.[19]

Diazo-alkanes exhibit a strong asymmetric (> CNN) stretching mode in the i.r., centred between 4·7 and 4·9 μm, the exact position of the band is characteristic of the number of substituents rather than of their electronic character.[20] This asymmetric stretching mode also gives rise to a very strong first overtone centred around 2·4 μ, with molar extinction coefficients comparable to those for the corresponding visible absorption spectra.[21] For the lower diazo-alkanes in particular, the strong absorption in the near-i.r. provides a very convenient probe for monitoring concentration, without the risk of photochemical decomposition.

N.m.r. studies of diazo-alkanes[22,23] show that the proton attached to the diazo carbon atom is shielded (τ, 3·5—7) to an extent which depends markedly on the electronic nature of substituents. For example, electron-withdrawing

---

†Recent work has cast doubt on the accepted structure for isodiazomethane, suggesting $:C{=}N{-}NH_2$ as an alternative.[18a]

[18a] E. Müller, R. Beutler, and B. Zeeh, *Annalen*, 1968, **719**, 72.

[19] M. J. Amrich and J. A. Bell, *J. Amer. Chem. Soc.*, 1964, **86**, 292; H. M. Frey and I. D. R. Stevens, *J. Chem. Soc.*, 1962, 3865; C. G. Overberger and J. P. Anselme, *Tetrahedron Letters*, 1963, 1405.

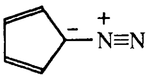
[20] P. Yates, B. Shapiro, N. Yoda, and J. Fugger, *J. Amer. Chem. Soc.*, 1957, **79**, 5756; A. Fottani, C. Pecille, and S. Ghersetti, *Tetrahedron*, 1960, **11**, 285; W. D. Hormann and E. Fahr, *Annalen*, 1963, **663**, 1; E. Fahr, *ibid.*, 1958, **617**, 11; E. Fahr, H. Aman, and A. Roedig, *ibid.*, 1964, **675**, 59.

[21] E. Fahr and K. H. Keil, *Annalen*, 1963, **663**, 4; A. Ledwith and E. C. Friedrich, unpublished results.

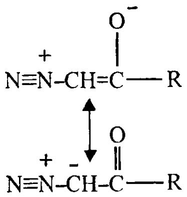
[22] A. Ledwith and E. C. Friedrich, *J. Chem. Soc.*, 1964, 504; D. F. Koster and A. Danti, *J. Chem. Phys.*, 1964, **41**, 582.

[23] F. Kaplan and G. K. Meloy, *J. Amer. Chem. Soc.*, 1966, **88**, 950.

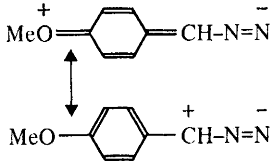
substituents favour a resonance structure having a formal carbanion ($>\overset{-}{C}\text{-}\overset{+}{N_2}$), whereas electron-releasing substituents favour a formal positive charge on carbon ($>\overset{+}{C}\text{-}\overset{-}{N_2}$). Diazocyclopentadiene (6), 9-diazofluorene, 3-diazopropene, and α-diazocarbonyl compounds (7) are in the former category, whereas diazoethane and *p*-methoxyphenyl diazomethane (8) are examples of the latter.



(6)

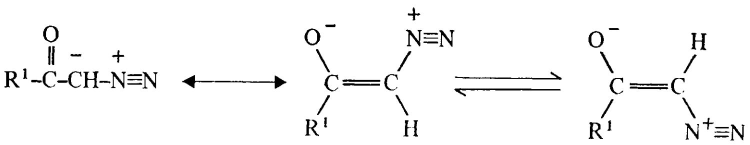


(7)



(8)

Resonance in α-diazo-carbonyl derivatives (7) causes restricted rotation around the C—C bond,[23,24] giving rise to *cis*- and *trans*-isomers (7a, b)



cis- *trans*-

(7) (7a) (7b)

For diazo-ketones (7) the barriers to rotation are in the range 15—18 kcal/mole, with the *cis*-form (7a) predominating. On the other hand, for diazoacetic esters (7, $R^1 = OR^2$), population of *cis*- and *trans*-forms is roughly the same, and the barriers to rotation are 9—12 kcal/mole. Because of the prevalence of *cis*-conformers in diazo-ketones, it was suggested[23] that the Wolff rearrangement,[25] proceeding *via* a concerted mechanism, could occur only from the *cis*-form (7a), in which the migrating group (R—) would be *trans* to the leaving group ($\text{—}\overset{+}{N}\equiv N$).

The thermal stability of diazo-alkanes depends markedly on the nature of substituents. Conjugating substituents increase stability irrespective of whether they are electron releasing or electron attracting. Diazomethane and diazo-

---

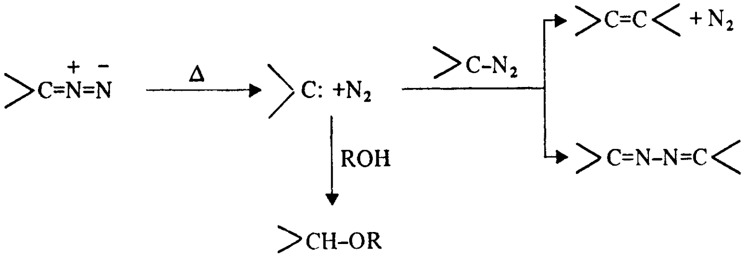
[24] C. Pecile, R. Fottani, and S. Ghersetti, *Tetrahedron*, 1964, **20**, 823.

[25] W. E. Bachman and W. S. Struve, *Org. Reactions*, 1942, **1**, 38; F. Weygand and H. J. Bestmann, *Angew. Chem.*, 1960, **72**, 535.

ethane are gases under normal atmospheric conditions, decomposing readily under the influence of rough surfaces. Dilute solutions in organic solvents are reasonably stable, but explosions are quite common when the pure materials are handled. Chlorodiazomethane[26] ($ClCH{=}N_2$) appears to be even less stable than diazomethane, decomposing to chlorocarbene at −20°. On the other hand, diazo-alkanes having carbonyl, aryl, nitrile, or other conjugating substituents are much more stable, and may be handled conveniently as pure liquids or solids.

Since the time of the last review,[1,2] the variety of substituents in diazo-alkanes has increased substantially. Particularly important is a wide range of fluorinated and perfluoro-diazo-alkanes, *e.g.* CF_3CHN_2,[27] $(CF_3)_2CN_2$,[28] $CF_3CO{\cdot}C(:N_2)CF_3$,[29] $MeC(:N_2)CF_3$,[30] and $PhC(:N_2)CF_3$.[31] Fluorinated substituents confer added stability to the diazo-compound, which may be conveniently generated by diazotisation of the appropriate fluorinated amine (see later). Diazo-alkanes having organotin,[32] mercury,[33] silver,[34] alkyl sulphide,[35] aryl and alkyl sulphone,[36] organophosphorus,[37] nitro-,[38] cyclopropyl-,[39] and cyano-[40] groups have also been synthesised.

Products from thermal decompositions of diazo-alkanes in aprotic media are usually mixtures of olefin and azine, formed by reaction of a carbene fragment with the starting diazo-alkane:



---

[26] G. L. Closs and J. J. Coyle, *J. Amer. Chem. Soc.*, 1962, **84**, 4350.

[27] R. Fields and R. N. Haszeldine, *J. Chem. Soc.*, 1964, 1881; B. L. Dyatkin and E. P. Mochalina, *Izvest. Akad. Nauk. SSSR, Ser. khim.*, 1964, 1225.

[28] D. M. Gale, W. J. Middleton, and C. G. Krespan, *J. Amer. Chem. Soc.*, 1966, **88**, 3617.

[29] B. L. Dyatkin, E. P. Mochalina, *Izvest. Akad. Nauk. SSSR, Ser. khim.*, 1965, 1035.

[30] R. A. Shepard and P. L. Sciaraffa, *J. Org. Chem.*, 1966, **31**, 964.

[31] R. A. Shepard and S. E. Wentworth, *J. Org. Chem.*, 1967, **32**, 3197.

[32] M. F. Lappert and J. Lorberth, *Chem. Comm.*, 1967, 836.

[33] A. N. Wright, K. A. W. Kramer, and G. Steel, *Nature*, 1963, **199**, 903; P. Yates and F. X. Garneau, *Tetrahedron Letters*, 1967, 71.

[34] U. Schöellkopf and N. Rieber, *Angew. Chem. Internat. Edn.*, 1967, **6**, 261.

[35] U. Schöellkopf and U. Wiskott, *Annalen*, 1966, **694**, 44.

[36] J. Diekmann, *J. Org. Chem.*, 1963, **28**, 2933; A. M. Leusen, R. J. Mulder, and J. Strating, *Rec. Trav. chim.*, 1967, **86**, 225.

[37] D. Seyferth, P. Hilbert, and R. S. Marmor, *J. Amer. Chem. Soc.*, 1967, **89**, 4811; L. Horner, H. Hoffman, H. Ertel, and G. Klahre, *Tetrahedron Letters*, 1961, 9; N. Kreutzkamp, E, Schmidt-Samoa, and A. K. Herberg, *Angew. Chem.*, 1965, **77**, 1138.

[38] U. Schöellkopf and P. Markush, *Tetrahedron Letters*, 1966, 6199.

[39] R. A. Moss and F. C. Shulman, *Chem. Comm.*, 1966, 372

[40] E. Ciganek, *J. Org. Chem.*, 1965, **30**, 4198.

In the presence of hydroxylic additives the intermediate carbene may be trapped to yield the corresponding ether or alcohol. Detailed kinetic studies of the decomposition of $PhCHN_2$[41] and Ph_2CN_2[42] have been made, and, in addition to the major reactions shown above, there is evidence for a minor process in which the appropriate aryl azine is formed directly by a bimolecular reaction of the aryl diazomethane, *e.g.*:

$$2\,Ar_2CN_2 \longrightarrow Ar_2C{=}N{-}N{=}CAr_2 + N_2$$

Although catalytic decomposition of diazomethane is ready even at the surface of glass vessels, a careful kinetic study of thermolysis in the gas phase established an activation energy of 34 kcal/mole.[43] This compares with an estimate of 43 kcal/mole for the bond dissociation energy of the C—N linkage, derived from electron impact data.[44] The latter studies also yielded a value of 9·03 ev for the ionisation potential of diazomethane and an estimate of 71 kcal/mole for ΔH_f^0. A reliable estimate of the heat of formation of diazomethane is necessary for interpretation of excess energy contributions to various (vapour phase) carbene reactions with olefins,[45] and there has been considerable uncertainty as to the true value.[43] However, independent calculations[46] of the thermochemistry of the reaction:

$$H_2 + CH_2N_2 \longrightarrow CH_4 + N_2$$

by use of self-consistent field (SCF) energies, yield values for ΔH^0 in very good agreement with experiment, taking ΔH_f^0 $(CH_2N_2) = 71$ kcal/mole.

Absorption spectra of diazo-alkanes are characterised by low intensity, low energy, transitions in the visible[47,48] and more intense absorption in the near and far-u.v.[49] Absorbance in the visible spectrum makes diazo-alkanes convenient substrates for the photochemical production of carbenes:

$$>C{=}\overset{+}{N}{=}\overset{-}{N} \xrightarrow[3000\,-\,6000\text{Å}]{h\nu} >C: + N_2$$

Diazo-alkanes which have conjugating substituents show broad unresolved bands in the visible spectrum, *e.g.* for Ph_2CN_2 in THF,[50] $\lambda_{max} = 529$ nm,

---

[41] D. Bethell and D. Whittaker, *J. Chem. Soc.* (*B*), 1966, 778.

[42] D. Bethell, D. Whittaker, and J. D. Callister, *J. Chem. Soc.* 1965, 2466; D. Bethell, A. R. Newall, G. Stevens, and D. Whittaker, *J. Chem. Soc.* (*B.*) 1969, 749; See also D. Bethell and R. D. Howard, *ibid.*, 1969, 745; H. Reimlinger, *Chem. Ber.*, 1964, **97**, 339, 3503; G. Murgulescu and T. Oncescu, *J. Chim. Phys.*, 1961, **58**, 508.

[43] D. W. Setser and B. S. Rabinovitch, *Canad. J. Chem.*, 1962, **40**, 1425.

[44] G. S. Paulett and R. Ettinger, *J. Chem. Phys.*, 1963, **39**, 825, 3534; G. S. Paulett and R. Ettinger, *ibid.*, 1964, **41**, 2557; J. A. Bell, *ibid.*, 1964, **41**, 2556.

[45] H. M. Frey, *Progr. Reaction Kinetics*, 1964, **2**, 131; J. A. Bell, *Progr. Phys. Org. Chem.*, 1964, **2**, 1.

[46] L. C. Snyder and H. Basch, *J. Amer. Chem. Soc.*, 1969, **91**, 2189.

[47] J. N. Bradley, G. W. Cowell, and A. Ledwith, *J. Chem. Soc.*, 1964, 353.

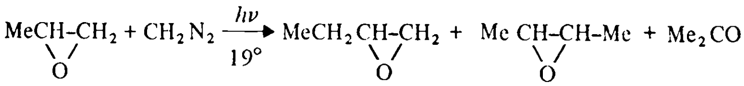
[48] D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 1937, 1551; R. K. Brinton and D. H. Volman, *J. Chem. Phys.*, 1951, **19**, 1394; F. W. Kirkbride and R. G. W. Norrish, *J. Chem. Soc.*, 1933, 119; G. Körtum. *Z. phys. Chem.*, 1941, **B**, **50**, 361.

[49] A. J. Merer, *Canad. J. Phys.* 1964, **42**, 1242.

[50] A. Ledwith and L. Phillips, *J. Chem. Soc.*, 1965 5969.

$\epsilon_{max} = 94$ l. mole^{-1} cm^{-1}. Diazomethane and the lower diazo-alkanes have visible spectra in the gas phase,[48] and in hexane solution,[47] which show considerable fine structure, *e.g.* for diazomethane in hexane[47] there are four maxima in the region 390—460 nm with ϵ_{max} in the range 6·0—10·0 l. mole^{-1} cm^{-1}. Formal assignment of the various transitions responsible for the fine structure has been attempted from both experimental observations[47,49] and theoretical calculations.[51] Although there is some disagreement as to the nature of the various excited states,[47,49,51] the fact that fine structure is apparent in solution[47] indicates that the upper electronic state is binding, and consequently may have an appreciable lifetime. It follows, therefore, that photolytic reactions of diazomethane in solution cannot be assumed to involve carbene without additional justification.

For example, photolysis of diazomethane in 1,2-epoxypropane (9) yielded the expected carbene-insertion products (10) and (11), with acetone as major product.[52]



$$\underset{\diagdown\,\text{O}\,\diagup}{\text{MeCH-CH}_2} + \text{CH}_2\text{N}_2 \xrightarrow[19^\circ]{h\nu} \text{MeCH}_2\underset{\diagdown\,\text{O}\,\diagup}{\text{CH-CH}_2} + \text{Me}\,\underset{\diagdown\,\text{O}\,\diagup}{\text{CH-CH}}\text{-Me} + \text{Me}_2\text{CO}$$

(9) (10) 4% (11) 12% 28%

Although diazomethane was the primary absorbing species it is clear that fragmentation to carbene was not the only photochemical process: apparently diazomethane photosensitises the isomerisation of 1,2-epoxypropane to acetone. Other examples of anomalous products resulting from photodecomposition of diazo-alkanes are the photosensitised autoxidation of cyclohexane to cyclohexanol and cyclohexanone in the presence of diazofluorene or diazodiphenylmethane,[53a] and the orbital-symmetry-forbidden (photo)cycloaddition of diazofluorene to norbornene and norbornadiene.[53b]

It must be emphasised, however, that the energy content of the visible light absorbed by diazo-alkanes[47] is in excess of the expected bond dissociation energy of the C—N linkage,[44] or the activation energy for thermal breakdown.[43] Consequently, in most cases, fragmentation to carbene and nitrogen will follow absorption of a photon at these wavelengths. For the lower diazo-alkanes quantum yields for photochemical fragmentation appear to be unity, but much lower quantum yields have been observed with diazo-alkanes possessing conjugating substituents.[54a]

---

[51] R. Hoffman, *Tetrahedron*, 1966, **22**, 539.

[52] J. N. Bradley and A. Ledwith, *J. Chem. Soc.* (*B*), 1967, 96.

[53] (*a*) G. A. Hamilton and J. R. Giacin, *J. Amer. Chem. Soc.*, 1966, **88**, 1584; (*b*) N. Filipescu and J. R. DeMember, *Tetrahedron*, 1968, **24**, 5181.

[54] (*a*) W. Kirmse and L. Horner, *Annalen*, 1959, **625**, 34; (*b*) W. Jugelt and F. Pragst, *Tetrahedron*, 1968, **24**, 5123; *Angew. Chem. Internat. Edn.*, 1968, **7**, 290; (*c*) P. D. Bartlett and T. G. Traylor, *J. Amer. Chem. Soc.*, 1962, **84**, 3408; (*d*) A. M. Reader, P. S. Bailey, and H. M. White, *J. Org. Chem.*, 1965, **30**, 784.

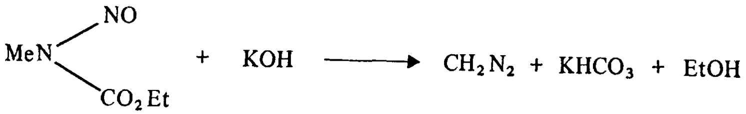
Simple cation-radicals are formed by reversible one-electron oxidation (platinum anode) of diphenyl diazomethane and several 4-substituted derivatives,[54b] *i.e.*:

$$\overset{-}{\mathrm{Ar_2C}}\text{—}\overset{+}{\mathrm{N}}\equiv\mathrm{N} \underset{+e}{\overset{-e}{\rightleftharpoons}} \mathrm{Ar_2C}\text{—}\overset{+}{\mathrm{N}}\equiv\mathrm{N}$$

For diphenyl diazomethane $E_{\frac{1}{2}} = +0{\cdot}95$ v (S.C.E.) and the initially formed cation-radical induces a chain reaction yielding tetraphenylethylene as the main product. Complete oxidation with molecular oxygen[54c] or ozone,[54d] yields benzophenones by complex reaction mechanisms.

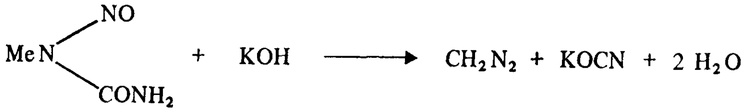
2 Synthesis of Diazo-alkanes

The classical methods for preparation of diazo-alkanes involve treatment of a nitroso-compound, of the general formula $\mathrm{RCH_2N(NO)X}$, with a suitable base to yield the diazo-alkane $\mathrm{RCHN_2}$. Thus, diazomethane is readily prepared by treating either *N*-nitroso-*N*-methylurethane[55] (12) or *N*-nitroso-*N*-methylurea[56] (13), with alkali.



$$\mathrm{MeN(NO)CO_2Et} + \mathrm{KOH} \longrightarrow \mathrm{CH_2N_2} + \mathrm{KHCO_3} + \mathrm{EtOH}$$

(12)



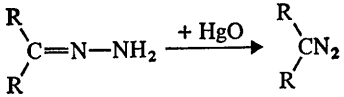
$$\mathrm{MeN(NO)CONH_2} + \mathrm{KOH} \longrightarrow \mathrm{CH_2N_2} + \mathrm{KOCN} + 2\,\mathrm{H_2O}$$

(13)

For the preparation of disubstituted diazo-alkanes the oxidation of a keto-hydrazone (14) is normally used.[57–63]

---

[55] A. P. N. Franchimont, *Rec. Trav. chim.*, 1890, **9**, 146.
[56] E. A. Werner, *J. Chem. Soc.*, 1919, 1093.
[57] T. Curtiss and H. Long, *J. prakt. Chem.*, 1891, **44**, 544; See also ref. 116.
[58] J. R. Dyer, R. B. Randall, jun., and H. M. Deutsch, *J. Org. Chem.*, 1964, **29**, 3423.
[59] A. C. Day, P. Raymond, R. M. Southam, and M. C. Whiting, *J. Chem. Soc.* (*C*), 1966, 467.
[60] G. M. Kaufman, J. A. Smith, G. C. von der Stouw, and H. Shechter, *J. Amer. Chem. Soc.*, 1965, **87**, 935.
[61] D. E. Applequist and H. Babad, *J. Org. Chem.*, 1962, **27**, 288.
[62] K. Nakagawa, H. Ondue, and K. Minami, *Chem. Comm.*, 1966, 736.
[63] D. H. R. Barton, R. E. O'Brien, and S. Sternhell, *J. Chem. Soc.*, 1962, 470.



(14)

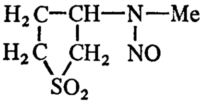
In the past ten years the efficiencies of the classical methods of preparation have been improved and several new intermediates for diazo-alkane preparation reported.

Rundel[64] has described a variation of the 'Forster Reaction'[65] for the preparation of diazomethane in 70—75% yields in which the sodium salt of formaldoxime is treated with chloramine.

$$CH_2{=}NONa + NH_2Cl \longrightarrow NaCl + CH_2N_2 + H_2O$$

In its original form the Forster reaction[65] involved reaction of an α-oximinoketone with chloramine to give a diazo-ketone. Meinwald *et al.*[66] have treated fluorenone oxime with chloramine to form diazofluorene, so that it now appears as if the presence of a carbonyl function is irrelevant to the formation of a diazo-compound. Thus with suitable choice of reaction conditions a new simple route to diazo-alkanes is available.

Two new stable, crystalline intermediates for the preparation of diazomethane, both easily made from readily available materials, have been reported. The first, *N*-nitro-3-(methylamino)sulpholane (15), formed by reaction of nitrous acid with 3-(methylamino)sulpholane, decomposes upon heating in aqueous base at 60° to give a 70% yield of diazomethane.[67] This intermediate has the advantage of being readily soluble in water, a property not shown by *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide, *p*-$CH_3C_6H_4SO_2N(NO)CH_3$, also a stable intermediate for the preparation of diazomethane.[68] The other new intermediate, *NN'*-dinitroso-*NN'*-dimethyloxamide $[C(O)N(NO)Me]_2$, prepared by nitrosation of the readily available *NN*-dimethyloxamide $(C(O)NHMe)_2$, undergoes decomposition in basic media to give diazomethane in high yields.[69] Higher



(15)

---

[64] W. Rundel, *Angew. Chem.*, 1962, **74**, 469.

[65] M. O. Forster, *J. Chem. Soc.*, 1915, **107**, 260.

[66] J. Meinwald, P. G. Gassman, and E. G. Miller, *J. Amer. Chem. Soc.*, 1959, **81**, 4751.

[67] V. Horak and M. Prochazka, *Czech.* 98007, 1959; V. Horak and M. Prochazka, *Chem. and Ind.*, 1961, 472.

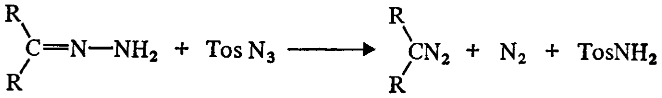
[68] T. J. De Boer and H. J. Backer, *Org. Synth.*, 1956, **36**, 16.

[69] H. K. Reimlinger, *Chem. Ber.*, 1961, **94**, 2547.

homologues $[C(O)N(NO)R]_2$ (R = Et, Pr, or Bu) are liquids, but gave relatively good yields of the corresponding diazo-alkanes.

For those cases where dry gaseous diazomethane is required, Dessaux and Durand[70] have described a low-temperature reaction system utilising the classical reaction of *N*-nitro-*N*-methylurea with potassium hydroxide.[56] [The hazards of working with gaseous diazo-alkanes should always be remembered and suitable precautions taken (see Zollinger[2]).]

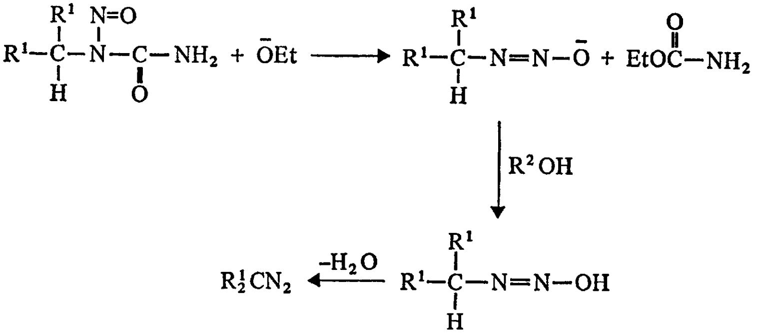
Toluene-*p*-sulphonyl azide[71] (16) in tetrahydrofuran converts hydrazones of benzophenone, 9-fluorenone, acetophenone, and benzil to the corresponding diazo-compounds. Reaction conditions in these cases are both mild and non-oxidising.



(16)

The mechanism of the formation of diazo-alkanes from nitroso-compounds has been investigated by several groups of workers.

In earlier work, Applequist and McGreer[72] had proposed that reaction of nitroso-ureas with base involved a displacement on the carbonyl groups:



More recently, Jones *et al.*[73] have shown that the lithium-ethoxide-induced conversion of several nitroso-ureas to diazo-alkanes proceeds instead by addition of ethoxide ion to the nitroso-group:

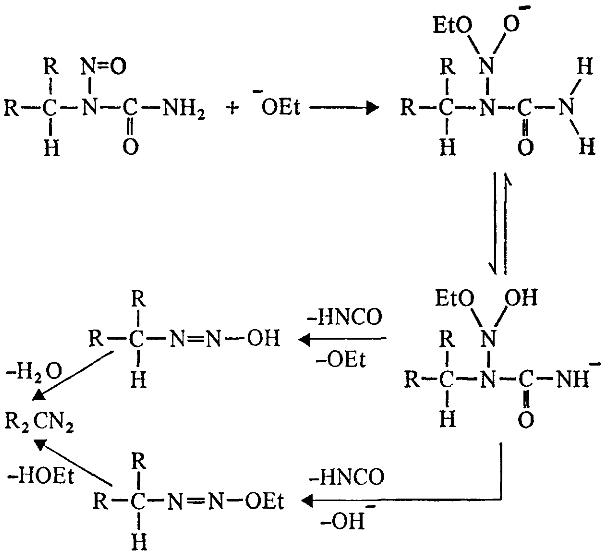
---

[70] O. Dessaux and M. Durand, *Bull. Soc. chim. France*, 1963, **1**, 41.

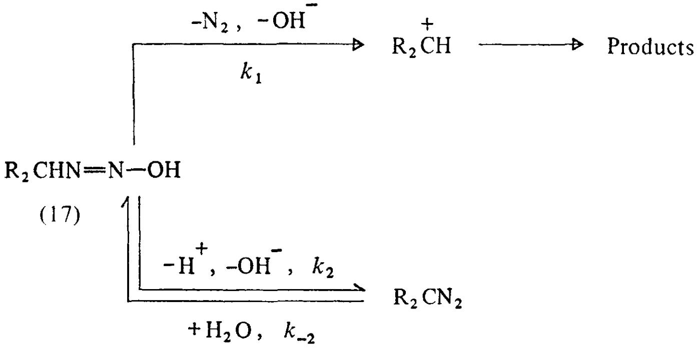
[71] W. Fischer and J. P. Anselme, *Tetrahedron Letters*, 1968, 877.

[72] D. E. Applequist and D. E. McGreer, *J. Amer. Chem. Soc.*, 1960, **82**, 1965.

[73] W. M. Jones, D. L. Muck, and T. K. Tonday, jun., *J. Amer. Chem. Soc.*, 1966, **88**, 68; W. M. Jones and D. L. Muck, *ibid.*, 1966, **88**, 3798.



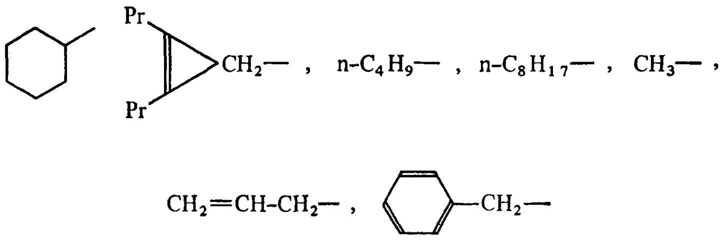
On the other hand, *N*-nitroso-*N*-alkylurethanes and *N*-nitroso-*N*-alkylamides appear to undergo competitive reaction at the nitroso nitrogen and the carbonyl carbon. The competitive processes are sensitive to the alkyl group, the group attached to the carbonyl carbon atom, the solvent, and the nature of the base. Both mechanisms have a common latter stage which has been investigated in detail by Moss.[74] Depending upon the nature of the alkyl group, formation of diazo-alkane or decomposition of the diazotic acid (17) to carbonium ion products occurs:



In order of decreasing product ratio k_1:k_2 (carbonium ion : diazo-alkane), the alkyl systems (R) studied could be placed in the sequence:

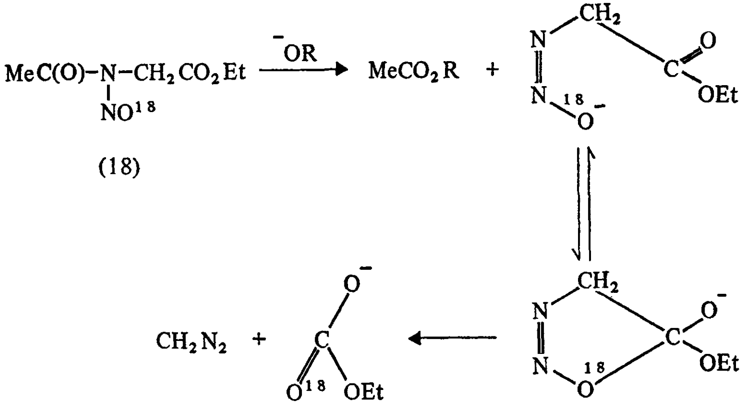
---

[74] R. A. Moss, *J. Org. Chem*, 1966, **31**, 1082; See also H. Hart and J. L. Brewbaker, *J. Amer. Chem. Soc.*, 1969, **91**, 716.



Thus, primary alkyl groups occupy a central position, while when R is secondary, *e.g.* cyclohexylidene, k_2 is reduced and k_1 increased by enhanced carbonium ion stability. Therefore $k_1 : k_2$ increases relative to that for primary R, so that no diazo-alkane formation is observed. When R is changed from primary alkyl to allyl or benzyl, k_2 is sufficiently enhanced so that $k_1 : k_2$ is too small to permit observation of solvolysis of the diazotic acid derivative.

By ^{18}O labelling Reimlinger *et al.*[75] have shown that formation of diazomethane from *N*-nitro-*N*-acetylglycine ethyl ester (18) follows a cyclic path:



Carboxylic acid chlorides and bromides, upon treatment with excess of diazomethane, can be converted, almost without exception and in good yields, into diazo-ketones:[76]

$$RCOCl + 2CH_2N_2 \longrightarrow RCOCHN_2 + MeCl + N_2$$

This constitutes the first stage of the Arndt–Eistert synthesis of homologous

---

[75] H. K. Reimlinger, L. Skattebol, and F. Billiou, *Chem. Ber.*, 1961, **94**, 2429.
[76] F. Arndt and J. Amende, *Chem. Ber.*, 1928, **61**, 1122.

carboxylic acids.[77] The last ten years has seen the development of two other methods of preparation of diazo-ketones which do not involve the use of diazomethane or its homologues.

In 1953 Doering and DePuy prepared diazocyclopentadiene (6) by the reaction of toluene-*p*-sulphonyl azide (16) with cyclopentadienyl-lithium.[78] The use of toluene-*p*-sulphonyl azide has now been widely applied in the conversion of compounds $R^1COCH_2R^2$ to diazo-ketones $R^1COCN_2R^2$.[79] An alkaline reaction medium is needed in all cases to get the best yields of diazo-compounds. Alternatively,[80] acyl bromides $RCOCH_2Br$ are treated with hydrazine to form the hydrazones, which are subsequently oxidised to diazo-ketones $RCOCHN_2$ by manganese dioxide. Diazo-ketones $RCOCN_2C_6H_5$ of the azibenzyl type were prepared analogously from desyl halides $RCOCH(C_6H_5)X$.

Certain aliphatic diazo-compounds may be prepared by diazotisation of the appropriate amine, provided that the amine possesses a strongly electron-withdrawing substituent on the α-carbon atom. Diazoacetic ester, the first aliphatic diazo-compound known,[81] was prepared in this manner by treatment of glycine ethyl ester hydrochloride with potassium nitrite:

$$HCl{\cdot}NH_2CH_2CO_2Et + KNO_2 \rightarrow N_2CHCO_2Et + KCl + 2H_2O$$

The trifluoromethyl group has an inductive effect similar to that of the ester group in aminoacetic ester, and preparations of 2,2,2-trifluorodiazoethane[27] and 2,2,3,3,4,4,4-heptafluorodiazo-n-butane,[27] and 1,1,1-trifluoro-2-diazopropane[30] by diazotisation of the corresponding amines have recently been reported. On the other hand, bis-trifluoromethyl diazomethane and bis-perfluoroethyl diazomethane are more conveniently prepared by oxidation of the corresponding hydrazones with lead tetra-acetate.[28] Both compounds show remarkable stability in the presence of acids. Diazotisation may be used similarly to prepare a range of diazocyclopentadienes[81a,b] which react as aryl diazonium salts rather than diazo-alkanes, on account of the aromatic character of cyclopentadienyl anion (*e.g.* 6).

3 Cycloaddition Reactions of Diazo-alkanes

Cycloadducts of diazo-alkanes have been known for a great many years[82] but it was not until the early 1960s that the classification 1,3-dipolar cycloaddition[83] became generally accepted. This followed a series of outstanding studies by

---

[77] F. Arndt and B. Eistert, *Chem. Ber.*, 1935, **68**, 200.

[78] W. von E. Doering and C. H. DePuy, *J. Amer. Chem. Soc.*, 1953, **75**, 5955.

[79] M. Regitz, *Tetrahedron Letters*, 1964, 1403; M. Regitz and G. Heck, *Chem. Ber.*, 1964, **97**, 1482; M. Rosenberger and P. Yates, *Tetrahedron Letters*, 1964, 2285; M. Regitz and A. Liedhegener, *Chem. Ber.*, 1966, **99**, 3128.

[80] S. Hauptmonn, M. Kluge, K. D. Seidig, and H. Wilde, *Angew. Chem.*, 1965, **4**, 688.

[81] T. Curtius, *Chem. Ber.*, 1883, **16**, 2230.

[81] (*a*) O. W. Webster, *J. Amer. Chem. Soc.*, 1966, **88**, 4055; (*b*) D. J. Cram and R. D. Partos, *ibid.*, 1963, **85**, 1273; P. L. Pauson and B. J. Williams, *J. Chem. Soc.*, 1961, 4153.

[82] L. I. Smith, *Chem. Rev.*, 1938, **23**, 193.

[83] R. Huisgen, *Proc. Chem. Soc.*, 1961, 357.

Huisgen and his collaborators[9,84,85] in which diazo-alkanes were shown to represent just one example of a wider class of 1,3-dipolar molecules abc which undergo 1,3-cycloadditions and are described by zwitterionic octet structures, *e.g.*:

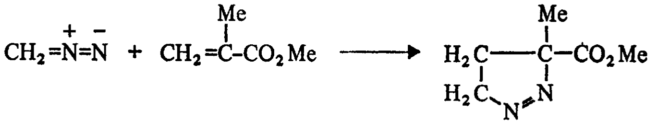
$$a\equiv\overset{+}{b}-\overset{-}{c} \longleftrightarrow a=\overset{+}{b}=\overset{-}{c} \quad (b = N)$$

$$a=\overset{+}{b}-\overset{-}{c} \longleftrightarrow \overset{-}{a}-\overset{+}{b}=c \quad (b = -NR, -O)$$

Specific classes of molecular 1,3-dipoles include diazo-alkanes ($R_2C=\overset{+}{N}=\overset{-}{N}$,), nitrile oxides ($Ar-C\equiv\overset{+}{N}-\overset{-}{O}$), azides ($Ar-N=\overset{+}{N}=\overset{-}{N}$), nitrones, ($Ar-CH=\overset{+}{N}(Me)-\overset{-}{O}$), and nitrile amines ($Ar-C\equiv\overset{+}{N}-\overset{-}{N}-Ar$).

1,3-Dipolar cycloadditions exhibit common mechanistic features:[9,84,85] they are not markedly influenced as to rate or stereochemistry by solvent polarity; they show low enthalpies of activation (5—15 kcal/mole) and large negative entropies of activation (−25 to −45 e.u.); they produce five-membered cyclic compounds in which the stereochemistry of the reacting olefin (dipolarophile) is maintained; reaction rates are markedly increased by conjugation of the reacting site in the dipolarophile but reduced by the steric effect of all types of substituent.

Study of cycloadditions has been stimulated enormously by current theories relating to conservation of orbital symmetry in concerted reactions.[11,86,87] Diazo-alkanes provide particularly useful substrates for kinetic studies of these processes with olefinic dipolarophiles. Thus diazomethane and methyl methacrylate[88] give a high yield of the Δ^1-pyrazoline (20) by what is now classified[89] as a 3 + 2 cycloaddition:



(20)

Reactivity of diazo-alkanes in cycloaddition is markedly reduced by conjugating substituents, but increased by alkyl groups: reactivity falls in the sequence[9,88]

---

[84] R. Huisgen, R. Grashey, and J. Sauer, in 'The Chemistry of Alkenes', ed. S. Patai, Interscience, London, 1964, p. 739

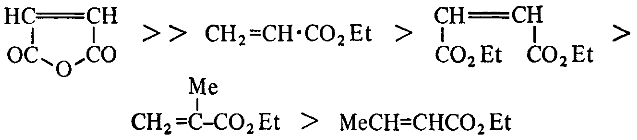
[85] R. Huisgen, *J. Org. Chem.*, 1968, **33**, 2291.

[86] R. Hoffman and R. B. Woodward, *Accounts Chem. Res.*, 1968, **1**, 17.

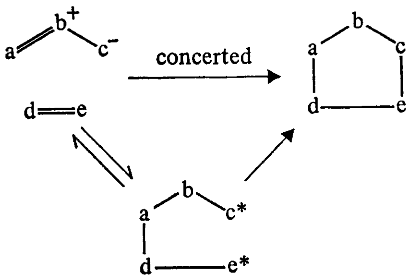
[87] S. I. Miller, *Adv. Phys. Org. Chem.*, 1968, **6**, 185; G. B. Gill, *Quart. Revs.*, 1968, **22**, 338.

[88] A. Ledwith and D. Parry, *J. Chem. Soc.* (*B*), 1966, 1408.

$MeCHN_2 > CH_2N_2 >> Ph_2CN_2 > N_2CHCO_2Et$, indicating dominance of electronic effects. On the other hand, ring strain or polarising influence of conjugating substituents strongly promotes dipolarophile reactivity and all types of substituent exert a retarding steric effect. For reactions with both CH_2N_2[88,90] and Ph_2CN_2,[91] dipolarophile activity falls in the sequence:



Apart from the obvious synthetic value of cycloadditions, there has been considerable interest in the reaction mechanism.[9,84,85,92,93] Basically the problem is to decide between a concerted or two-step mechanism, *i.e.*:

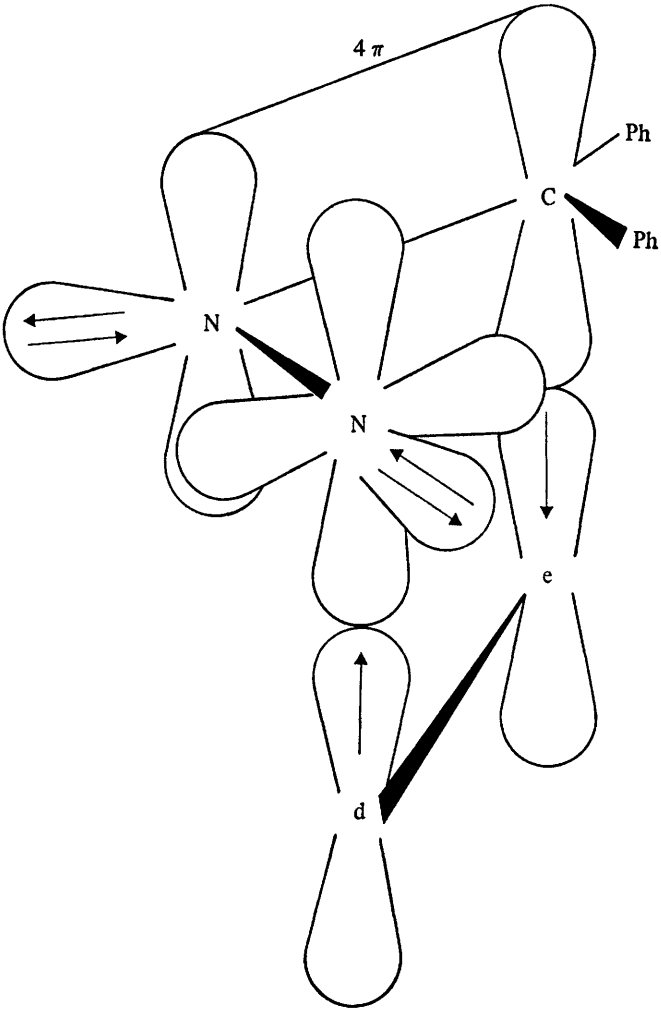


A two-step mechanism involving polar intermediates had seemed unlikely because of the lack of any clearly defined dependence of reaction rate on solvent polarity.[9] However, Firestone[92] has recently argued cogently in favour of a two-step mechanism involving biradical intermediates.

Some years ago Huisgen[9] proposed that 3 + 2 cycloadditions of diazo-alkanes occurred *via* a concerted process involving a cyclic transition state oriented in two planes, *e.g.* (21) for diphenyl diazomethane.

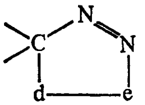
---

[89] R. Huisgen, *Angew. Chem. Internat. Edn.*, 1968, **7**, 321.
[90] A. Ledwith and Yang Shih-Lin, *J. Chem. Soc.* (*B*), 1967, 83.
[91] R. Huisgen, H. Stangl, H. J. Sturm, and H. Wagenhofer, *Angew. Chem.*, 1961, **73**, 170.
[92] R. A. Firestone, *J. Org. Chem.*, 1968, **33**, 2285.
[93] O. E. Polansky and P. Schuster, *Tetrahedron Letters*, 1964, 2019.



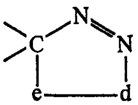
(21)

Woodward–Hoffmann rules for conservation of orbital symmetry[86] now supply the theoretical basis and, taken with most of the experimental work,[85] provide overwhelming support for Huisgen's earlier predictions.[11] It must be noted, however, that the nature of orientation [*i.e.* whether (a) or (b)].



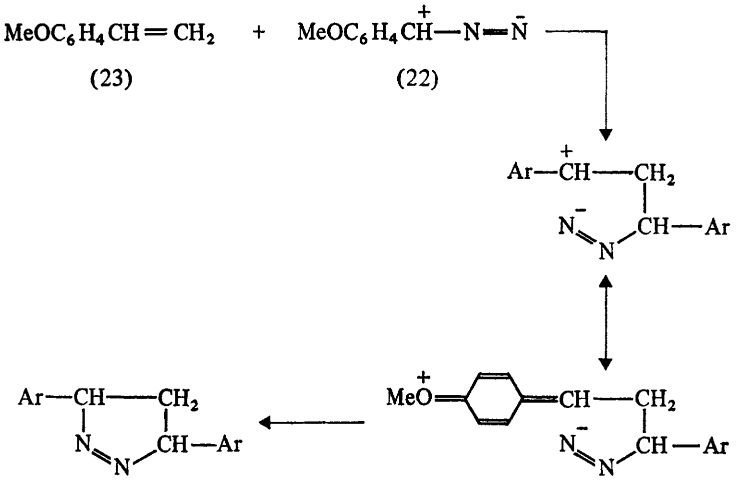
(a)

or



(b)

is not adequately predicted by either concerted or biradical mechanisms. The only significant evidence for a two-step cycloaddition of a diazo-alkane, proceeding *via* polar intermediates, was obtained from reactions of *p*-methoxyphenyl diazomethane (22) with *p*-methoxystyrene (23). *cis*- and *trans*-3,5-bis(*p*-anisyl)-1-pyrazolines (24) were formed in roughly equal amounts.[94]



(23) (22)

cis- and trans- (24)

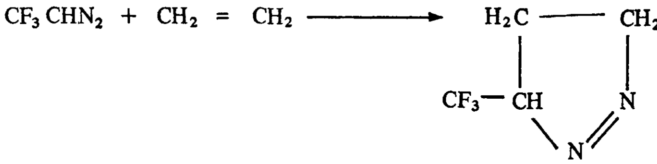
(25)

Formation of a *cis*-disubstituted pyrazoline is without precedent in the reactions of aryl diazo-alkanes with styrenes. The conclusion must be that stabilisation of a dipolar intermediate (25) by the *p*-methoxy group permits rotation around the original styrene C=C bond, to give roughly equal amounts of *cis*- and *trans*-pyrazolines on collapse of the dipolar species.

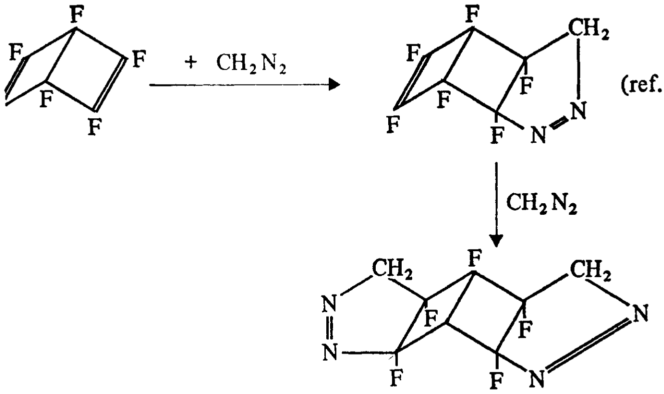
A few recent examples showing the wide synthetic value of 3 + 2 cycloadditions of diazo-alkanes are indicated below:

---

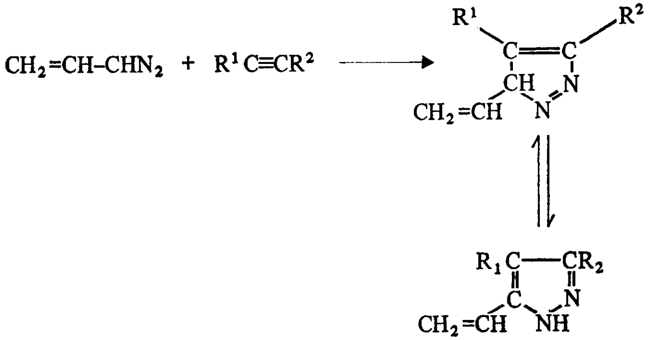
[94] C. G. Overberger, N. Weinshenker, and J. P. Anselme, *J. Amer. Chem. Soc.*, 1965, **87**, 4119.



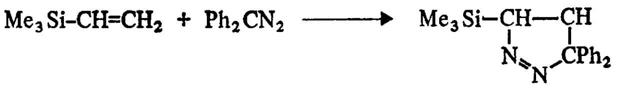
(ref. 95)



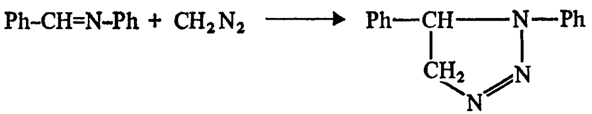
(ref. 96)



(ref. 97)



(ref. 98)



(ref. 99)

---

[95] J. H. Atherton and R. Fields, *J. Chem. Soc.* (*C*), 1968, 1507.

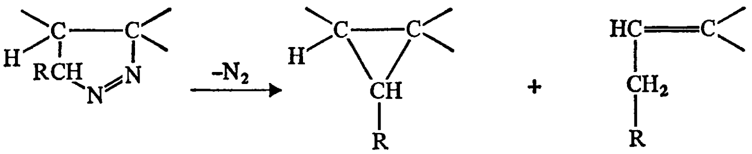
[96] M. G. Barlow, R. N. Hazseldine, and W. D. Morton, *Chem. Comm.*, 1969, 931.

[97] G. Manecke and H. U. Schenck, *Tetrahedron Letters*, 1968, 2061; See also I. Tabushi, K. Takagi, M. Okano, and R. Oda, *Tetrahedron*, 1967, **23**, 2621.

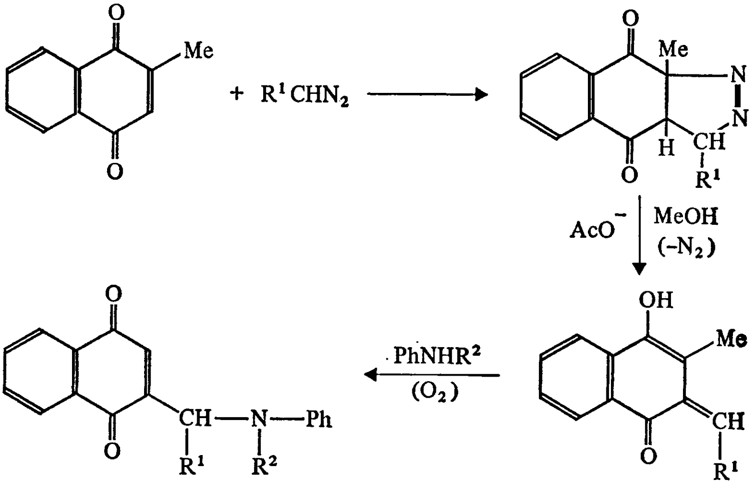
[98] I. A. D'Yakonov, I. B. Repinskaya, and G. V. Golodnikov, *Zhur. org. Khim.*, 1966, **2**, 2256.

[99] P. K. Kadaba, *Tetrahedron*, 1966, **22**, 2453.

The synthetic value of 3 + 2 cycloadditions is the greater because in most cases the pyrazoline products are thermally and photochemically unstable,[1,2,100,101] permitting convenient generation of cyclopropanes or alkylated olefins:



The 3 + 2 cycloadducts of diazomethane and diazoethane with 2-methyl naphthaquinone (26) are activated sufficiently to undergo base-catalysed decomposition, providing a novel synthetic route to the highly reactive quinone methides (27).[102] Trapping of (27) by reaction with primary or secondary aromatic amines in air, gives rise to the intensely coloured adducts (28).[103]



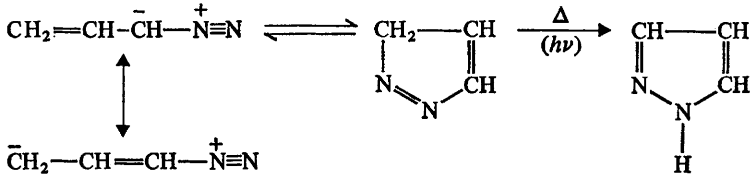
(28)

(27)

The intense colours of (28) are due to charge-transfer transitions involving orbital overlap in the non-conjugated donor (amine) and acceptor (quinone) parts of the molecule, and represent the most striking examples of this type of intramolecular interaction so far reported.[104]

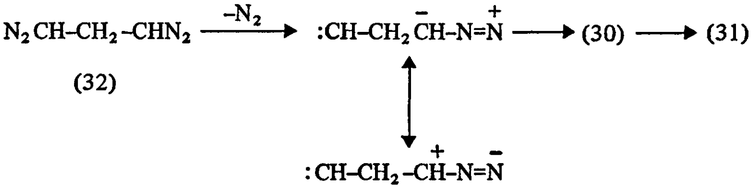
[100] T. U. Van Auken and K. L. Rinehart, *J. Amer. Chem. Soc.*, 1962, **84**, 3736.
[101] J. Hamelin and R. Carrie, *Bull. Soc. chim. France*, 1968, 2162, 3000.
[102] F. M. Dean, L. E. Houghton, and R. B. Morton, *J. Chem. Soc.* (*C*), 1967, 1980.
[103] F. M. Dean, L. E. Houghton, and R. B. Morton, *J. Chem. Soc.* (*C*), 1968, 2065.
[104] R. Carruthers, F. M. Dean, L. E. Houghton, and A. Ledwith, *Chem. Comm.*, 1967, 1206.

Alkenyl diazo-compounds may be used to form pyrazolines by reaction with dipolarophiles in the normal manner,[97] but also undergo a slower intramolecular cycloaddition yielding pryazoles.[105,106] For 3-diazopropene (29) it was shown[106] that the initial adduct was a pyrazolenine (30) which underwent thermal and photochemical prototropy to give pyrazole (31).



(29) (30) (31)

The reaction has been extended[107] to a series of aryl and alkyl substituted homologues of (29) giving good yields of the corresponding pyrazoles, and from the very small rate-enhancing effect of 4-substituents in Ar—CH=CH—CH=N_2 ($\rho = -0{\cdot}40$), the reaction was confirmed as an intramolecular concerted process. Interestingly, formation of pyrazole (31) from 1,3-bisdiazopropane (32) does not involve prior formation of 3-diazopropene (29), but probably occurs *via* the diazocarbene intermediate[108] (33)



(33)

4 Reactions of Diazo-alkanes with Free Radicals

Free radical processes are fairly common in reactions of carbenes[4,5,11] but there are comparatively few reported examples of the reactions of diazo-alkanes with free radicals.[54b,109–114] Most of these have been discussed in earlier reviews

---

[105] D. W. Adamson and J. W. Kenner, *J. Chem. Soc.*, 1935, 286; C. D. Hurd and S. C. Lui, *J. Amer. Chem. Soc.*, 1935, **57**, 2656.

[106] A. Ledwith and D. Parry, *J. Chem. Soc.* (*B*), 1967, 41 [for a related interconversion of diazoalkene and pyrazolenine see A. C. Day and M. C. Whiting, *J. Chem. Soc.* (*C*), 1966, 1719].

[107] J. L. Brewbaker, and H. Hart, *J. Amer. Chem. Soc.*, 1969, **91**, 711.

[108] H. Hart and J. L. Brewbaker, *J. Amer. Chem. Soc.*, 1969, **91**, 706.

[109] W. Schlenk and C. Bornhardt, *Annalen*, 1912, **394**, 183.

[110] D. B. Denney and M. F. Newman, *J. Amer. Chem. Soc.*, 1967, **89**, 4692.

[111] W. H. Urry, J. R. Eiszner, and J. W. Wilt, *J. Amer. Chem. Soc.*, 1957, **79**, 918.

[112] W. J. Middleton, D. M. Gale, and C. G. Krespan, *J. Amer. Chem. Soc.*, 1968, **90**, 6813.

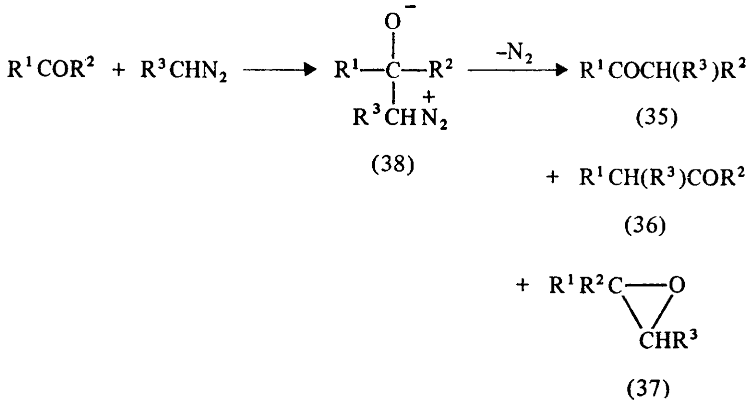
[113] E. Müller, A. Moosmayer, and A. Rieker, *Z. Naturforsch.*, 1963, **18b**, 982.

[114] E. Müller, R. Renner, and A. Rieker, *Tetrahedron Letters*, 1968, 891.

and will not be considered here. It should be noted, however, that for all reactions of diazomethane with free radicals, rearrangement or radical recombination is the preferred course. There is no evidence for a chain process leading to polymethylene, involving initiation by a known free radical. This point will become more relevant during discussion of polymerisation of diazo-alkanes (see later).

5 Reactions of Diazo-alkanes with Carbonyl Compounds

Diazo-alkanes react thermally with aldehydes and ketones to give mixtures of homologous carbonyl compounds (35), (36) and epoxides (37),[115–117] *e.g.*



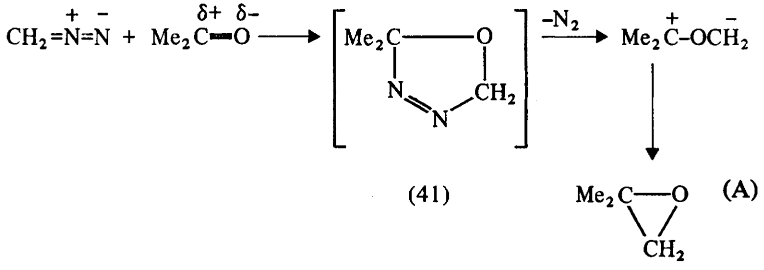
(38) (35) (36) (37)

Epoxide formation is favoured by electron-withdrawing substituents in the carbonyl compound, *e.g.* chloral[118] (CCl_3CHO), and the reactions are catalysed by protic agents, particularly alcohols. Alcohols also control the nature of reaction products: reactions of aldehydes with diazomethane in dry ether give predominantly methyl ketones, whereas increasing homologation of the aldehyde occurs as alcohols are added to the solvent. Most of the synthetic and mechanistic work was carried out before 1960 and has been extensively reviewed.[1,2,115–117]

Recently, the long established view that both epoxide and homologous carbonyl compound arise from a common intermediate (38) (by ring closure or Wagner–Meerwein rearrangement respectively) has been questioned. From a detailed kinetic and product analysis of the dark reaction between diazomethane and acetone, catalysed by n-butanol, it was concluded[119] that two reactions occur simultaneously: one leads to formation of 12-epoxypropane (39) and the other gives a mixture of (39) and ethyl methyl ketone (40). It was suggested that the two competing processes are derived directly from the two important resonance structures for diazomethane, *i.e.*

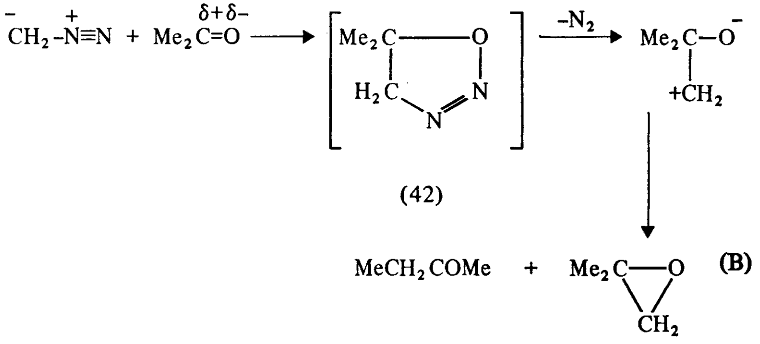
---

[115] C. D. Gutsche and D. Redmore, 'Carbocyclic Ring Expansion Reactions', Academic Press, New York, 1968, p. 81.
[116] C. D. Gutsche, *Org. Reactions*, 1954, **8**, 364.
[117] N. C. Hancox, *Roy. Australian Chem. Inst. J. and Proc.*, 1949, **16**, 282.
[118] R. E. Bowman, A. Campbell, and W. R. N. Williamson, *J. Chem. Soc.*, 1964, 3846.
[119] J. N. Bradley, G. W. Cowell, and A. Ledwith, *J. Chem. Soc.*, 1964, 4334.



(41)

(39)



(42)

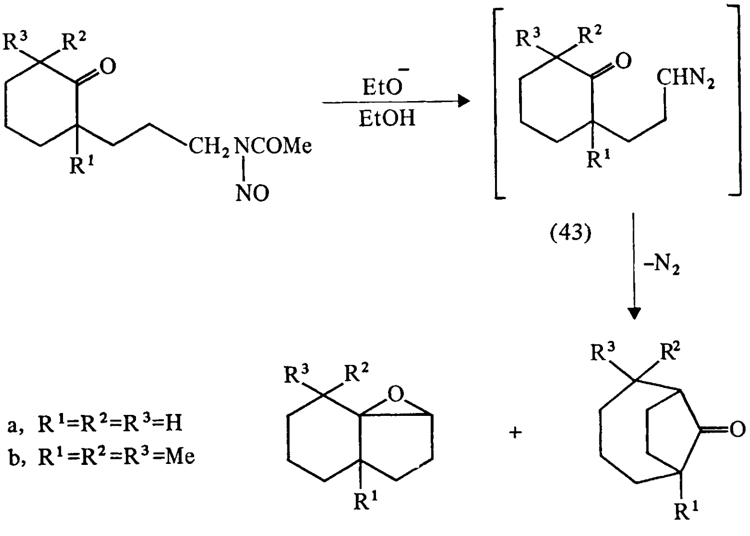
(40) (39)

In acetone solvent, reaction (B) was of a higher kinetic order in n-butanol than reaction (A) and the product was mainly homologous ketone. Consistent with these observations, hydrogen bonding between alcohol promoter and carbonyl oxygen of acetone would be expected to favour process (B), and to minimise epoxide formation. More powerful co-ordination of the carbonyl oxygen function with Lewis Acids completely eliminates epoxide formation[10] (see below).

Although it is commonly assumed that reactions of carbonyl compounds with diazo-alkanes involve nucleophilic attack by the latter, characterisation of a mechanistic dichotomy raises the possibility that primary (unstable) intermediates (41) and (42) might be formed by competing 3 + 2 cycloadditions. If this idea was based solely on the kinetic analysis of the n-butanol–diazomethane–acetone reaction (*i.e.* purely a solvent effect) it should properly be regarded as entirely speculative. However, independent work[120] leads to essentially the same conclusions from a consideration of substituent effects in quite different substrates. Intramolecular reactions of the diazocarbonyl derivatives (43) yield mixtures of bicyclic ketone (44) and epoxide (45), in a ratio which depends markedly on substituents. From (43a) bicyclic ketone (44a) is the major product, the yield of epoxide increasing with increasing substitution by methyl

[120] C. D. Gutsche and J. E. Bowers, *J. Org. Chem.*, 1967, **32**, 1203; See also C. D. Gutsche and C. T. Chang, *J. Amer. Chem. Soc.*, 1962, **84**, 2263.

groups, so that for (43b) the product is almost exclusively epoxide (45b). Two distinct processes are shown to be involved, similar to reactions (A) and (B) with mode of addition of the diazo unit controlled by conformational effects of the cyclohexanone system.[120]*



(43)

a, $R^1=R^2=R^3=H$
b, $R^1=R^2=R^3=Me$

(45)

(44)

Of much greater synthetic value is the homologation of ketones, catalysed by Lewis Acids.[10] This type of reaction was discovered independently by several groups of workers but has been developed largely by Müller and his collaborators.[10b]

House, Grubbs, and Gannon[121] found that reactions between diazomethane and acyclic ketones in ether were strongly promoted by addition of one mole equivalent of boron trifluoride. Compared with alcohol-catalysed systems, reaction times are much shorter (minutes rather than hours or days), yields are higher, and, most important, formation of epoxide does not occur. Cyclic ketones gave ring homologation, and for unsymmetrical acyclic derivatives migratory aptitudes fell in the order: Ph—~ $Me_2C=CH$— > Me— > Pr— >

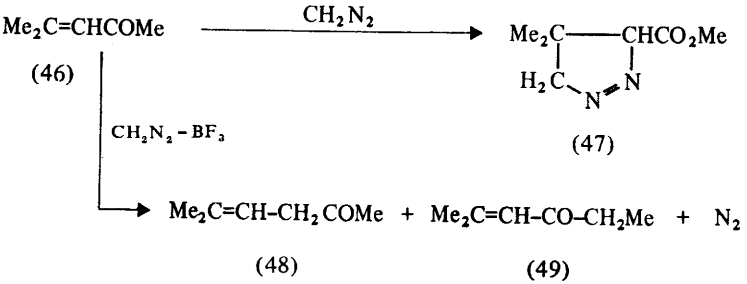
---

* Since this survey was completed the stereochemistry and mechanisms of related ring expansion of cyclopropanones[120a,b] and steroidal ketones[120c] by diazo-alkanes have recently been discussed in detail.

[120] (*a*) N. J. Turro and R. B. Gagosian, *Chem. Comm.*, 1969, 949; (*b*) J. A. Marshall and J. J. Partridge, *J. Org. Chem.*, 1968, **33**, 4090; (*c*) J. B. Jones and P. Price, *Chem. Comm.*, 1969, 1478.

[121] H. O. House, E. J. Grubbs, and W. F. Gannon, *J. Amer. Chem. Soc.*, 1960, **82**, 4099.

Pr^i— ~ $PhCH_2$— ~ Bu^t—, closely similar to that found for pinacol rearrangement during deamination of corresponding 1,1-disubstituted-2-aminoethanols. 1,2-Unsaturated ketones which normally react with diazomethane to give pyrazoline derivatives (47), gave only homologous ketones (48, 49), in good yield, *e.g.* for mesityl oxide (46) in ether at 0°:



Similarly, Johnston, Neeman, Birkeland, and Fedoruk[122] showed that certain steroid ketones yielded ring homologised products when treated with diazomethane in methylene chloride in the presence of catalytic amounts of fluoroboric acid.

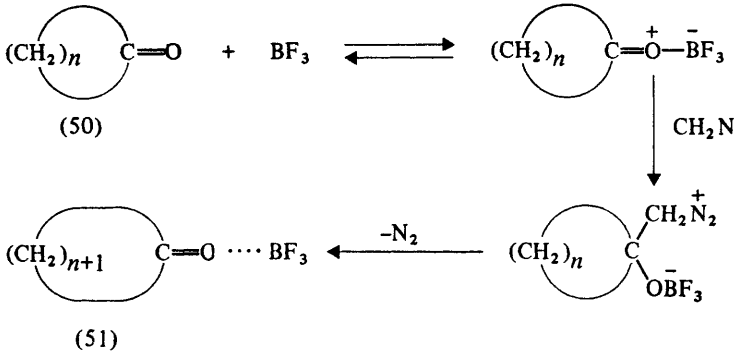
Müller and his collaborators[123] studied related homologation reactions of cyclic ketones (50). Using catalytic amounts of boron trifluoride in ether, all the cyclic ketones from cyclohexanone to cyclotetradecanone were successfully homologised to the next highest ring ketone in good yield, with an approximately 2:1 molar excess of diazomethane. The yield of homologous ketone (51) falls as the ring size increases, and in addition there is a marked tendency for more than one methylene group to enter the ring, especially with the larger ring ketones, increasing the ring size by two or three carbon atoms *via* repetitive reaction on the successive homologues.

Whilst many Friedel–Crafts halides, such as boron trifluoride, aluminium chloride, zinc chloride, titanium tetrachloride, *etc.*, could be used as catalysts for the homologation of cyclic ketones with diazomethane, other boron compounds, *e.g.* boron trichloride, boron tribromide, trialkylboranes, and trialkyl borates, were completely ineffective and served only to convert the diazomethane into polymethylene. Since the catalytic efficiency of the various halides parallels their effect on the u.v. absorption spectra of the ketones, the following mechanism is indicated:

---

[122] W. S. Johnson, M. Neeman, S. P. Birkeland, and N. A. Fedoruk, *J. Amer. Chem. Soc.*, 1962, **84**, 989; W. S. Johnson, M. Neeman, and S. P. Birkeland, *Tetrahedron Letters*, 1960, No. 5, 1.

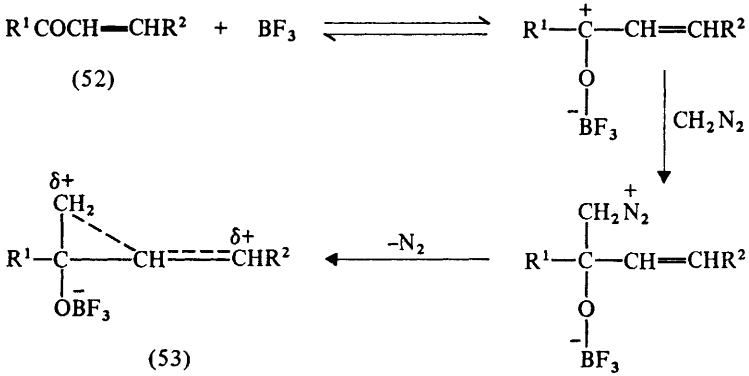
[123] E. Müller, B. Zeeh, and R. Meischkeil, *Annalen*, 1964, **677**, 47; E. Müller and M. Bauer, *ibid.*, 1962, **654**, 92; E. Müller, M. Bauer, and W. Rundel, *Z. Naturforsch.*, 1960, **15b**, 268; E. Müller, M. Bauer, and W. Rundel, *Tetrahedron Letters*, 1960, No. 13, 30; E. Müller and R. Heischkeil, *ibid.*, 1964, **2809**.



(50)

(51)

Homologation of acyclic ketones presumably involves a similar mechanism, and for $\alpha\beta$-unsaturated ketones (52) a non-classical homoallylic cation (53) would ensure homologation on the ethylenic side of the carbonyl group, *i.e.*



(52)

(53)

Homologation reactions of cyclic ketones have been extended to include diazoethane: whereas 60—80% yields of the next higher α-methyl-substituted ring ketone can be obtained from diazoethane using aluminium chloride as catalyst, boron trifluoride and other boron compounds are inactive.[124]

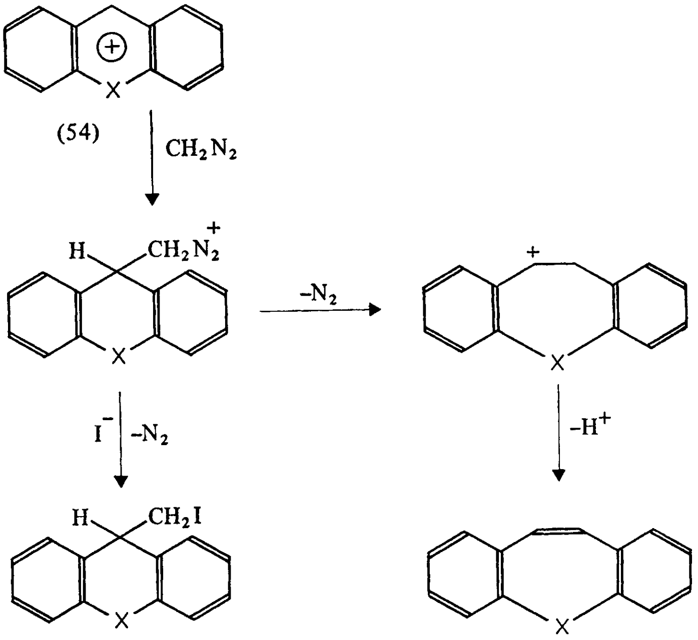
6 Reactions of Diazo-alkanes with Carbonium Ions

Certain stable organic cations may be conveniently homologised by reaction with diazomethane. Other diazo-alkanes react but give either lower yields or

---

[124] E. Müller, M. Bauer, and W. Rundel, *Tetrahedron Letters*, 1961, 136.

complex mixtures of products. The best example is the conversion of xanthylium perchlorate (54, X = O) into dibenzo[*b*, *f*]oxepine[125] (55, X = O), in 60% yield:

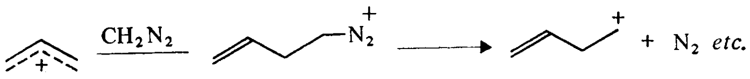


(54)

(56)

(55)

Similar conversion was effected with the corresponding thio-compound (54, X = S) but *N*-methyl acridinium iodide (54, X = —NCH_3) gave mainly the iodomethyl homologue[125] (56, X = —NCH_3), reflecting increased nucleophilicity of I^- over ClO_4^-. In theory, homoallylic cations could be generated by reaction of a suitable allylic carbonium ion with diazomethane, *i.e.*

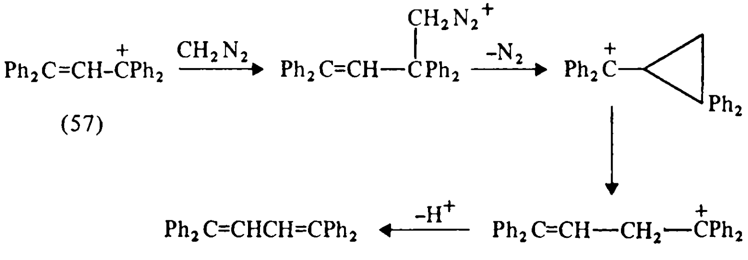


but there is only one reported example[126] involving the transformation of (57) into 1,1,4,4-tetraphenylbutadiene (58):

---

[125] H. W. Whitlock, *Tetrahedron Letters*, 1961, 593.

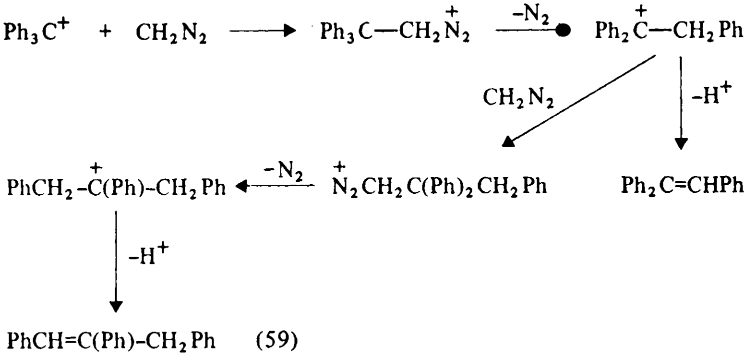
[126] H. W. Whitlock and M. R. Pesce, *Tetrahedron Letters*, 1964, 743.



(57)

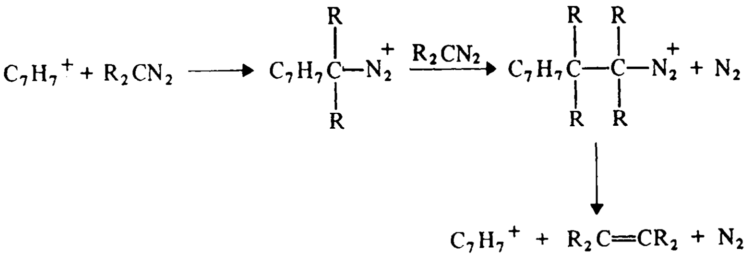
(58)

Triphenylmethyl cation reacts smoothly with diazomethane[127] forming triphenylethylene and 1,2,3-triphenylpropene, (59) by phenyl migration in the homologised intermediates:



(59)

Tropylium ion reacts vigorously with diazomethane and diphenyl diazomethane causing (catalytic) formation of ethylene and tetraphenylethylene respectively.[128] Yields of olefin are quantitative, and presumably result from the well-known[129] fragmentation of 2-cycloheptatrienylethyl cations:



$$C_7H_7^+ + R_2CN_2 \longrightarrow C_7H_7CR_2\overset{+}{N_2} \xrightarrow{R_2CN_2} C_7H_7CR_2{-}CR_2{-}\overset{+}{N_2} + N_2 \longrightarrow C_7H_7^+ + R_2C{=}CR_2 + N_2$$

---

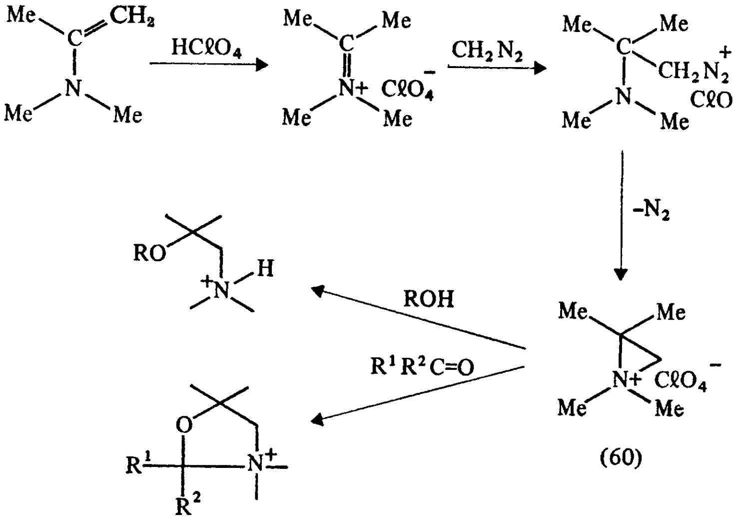
[127] H. W. Whitlock, *J. Amer. Chem. Soc.*, 1962, **84**, 2807.

[128] A. Ledwith and A. C. White, unpublished results.

[129] K. Conrow, *J. Amer. Chem. Soc.*, 1959, **81**, 5461.

Diphenyl diazomethane forms tetraphenylethylene by a similar process involving triphenylmethyl cation.[127]

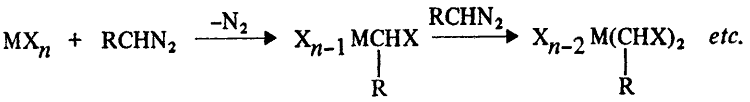
A related reaction of synthetic value is the formation of aziridinium salts (60) by reactions of diazomethane with protonated enamines,[130] *e.g.*



(60)

7 Diazo-alkanes in the Formation of Organometallic Compounds

The reaction between diazo-alkanes and metal halides is a particularly useful synthetic route to carbon-functional organometallic compounds,[131] *e.g.*:



$$MX_n + RCHN_2 \xrightarrow{-N_2} X_{n-1}M\underset{\displaystyle R}{\underset{|}{C}}HX \xrightarrow{RCHN_2} X_{n-2}M(\underset{\displaystyle R}{\underset{|}{C}}HX)_2 \quad etc.$$

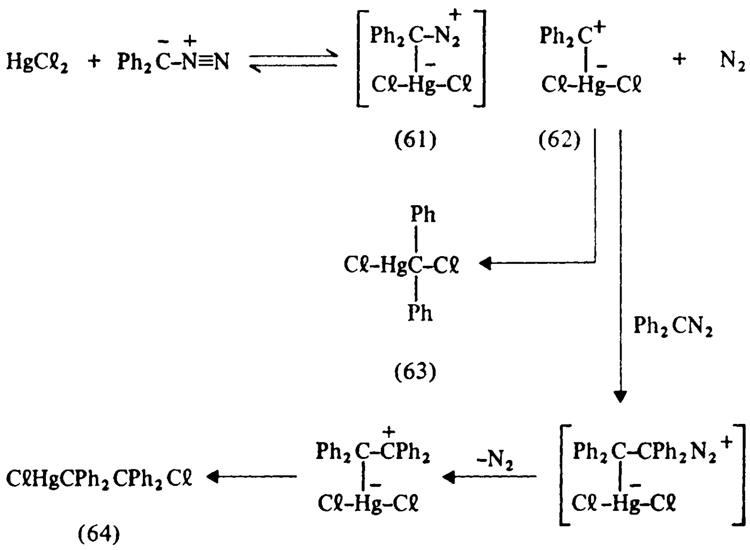
Metal halides are the most common reagents and good yields of halogenoalkyl derivative are obtained, especially for the elements forming covalent bonds with carbon.

A detailed kinetic study[50] of the reaction between diphenyl diazomethane and mercury(II) chloride in tetrahydrofuran established that polar intermediates were involved, as suggested initially by Huisgen.[1] However, whereas diazomethane reacts with mercury(II) chloride to give ultimately $Hg(CH_2Cl)_2$, the corresponding reaction with diphenyl diazomethane involves the following steps:

---

[130] N. J. Leonard, J. V. Paukstelis, and L. E. Brady, *J. Org. Chem.*, 1964, **29**, 3383; N. J. Leonard and K. Jann, *J. Amer. Chem. Soc.*, 1962, **84**, 4806; N. J. Leonard and K. Jann, *ibid.*, 1960, **82**, 6418.

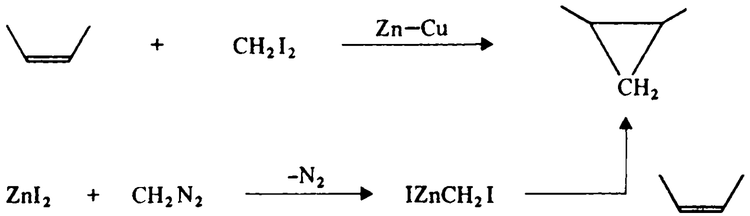
[131] D. Seyferth, *Chem. Rev.*, 1955, **55**, 1155.



A quantitative yield of products (63) or (64) was obtained according to the initial molar ratio diazo-compound:$HgCl_2$, and both organometallics were rapidly hydrolysed by small amounts of water to give benzophenone and benzpinacolone respectively, *e.g.*

$$ClHgC(Ph)_2Cl + H_2O \longrightarrow Hg^0 + Ph_2C{=}O + 2HCl$$

Corresponding reactions of diphenyl diazomethane with zinc chloride and zinc bromide are similar[132,133] but the dipolar intermediates corresponding to (61) and (62) react also with diazo-compound to give benzophenone azine. Reactions of diazo-alkanes with zinc iodide[134a,b] are of special importance because the initial product is thought to be related to the Simmons–Smith cyclopropane synthesis,[135] as exemplified:



---

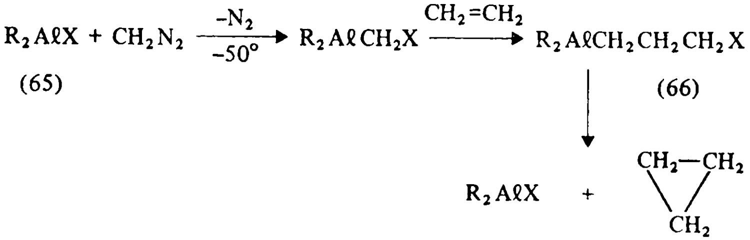
[132] D. Bethell and K. C. Brown, *Chem. Comm.*, 1967, 1266.

[133] D. E. Applequist and H. Babad, *J. Org. Chem.*, 1962, **27**, 288.

[134] (*a*) G. Wittig and K. Schwarzenbach, *Angew. Chem.*, 1959, **71**, 652; *Annalen*, 1961, **650**, 1; G. Wittig and F. Wingler, *ibid.*, 1962, **656**, 18; (*b*) S. H. Goh, L. E. Closs, and G. L. Closs, *J. Org. Chem.*, 1969, **34**, 25.

[135] H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, 1959, **81**, 4256; E. P. Blanchard, and H. E. Simmons, *ibid.*, 1964, **86**, 1337; H. E. Simmons, E. P. Blanchard, and R. D. Smith, *ibid.*, 1964, **86**, 133.

Cyclopropane formation also occurs when diazomethane reacts with olefins in the presence of dialkylaluminium halides (65), but in this case the intermediate γ-halogenopropyl organometallic (66) may be isolated at low temperatures, and shown to generate cyclopropane:[136]



In contrast, trialkylaluminium derivatives (65, X = alkyl), or dialkylaluminium hydrides (65, X = H) yield stable homologous products, except in the presence of strong donor molecules (*e.g.* tetrahydrofuran), when polymethylene is the sole product. The latter is formed exclusively, under all conditions, when dialkylaluminium fluoride or alkoxide derivatives are used[137] (*i.e.* 65, X = —F, —OR^2). Organoboron compounds react with diazo-alkanes in a manner very similar to that of the corresponding aluminium derivatives. Starting materials are more readily accessible and the reactions are of synthetic value and pertinent to the mechanism of polymerisation of diazo-alkanes (discussed separately).

Some years ago, the gas-phase reaction between diazomethane and boron trifluoride was shown to give F_2BCH_2F, providing the first example of methylenation of a boron compound.[138] Many boron compounds were known to catalyse polymerisation of diazomethane in solution and consequently the methylenation reaction was proposed[139] as the propagation step for boron-catalysed polymerisations. In particular, it was suggested[139] that alkyl boron derivatives would undergo homologation, *i.e.*

$$R\text{—}B< \xrightarrow[-N_2]{CH_2N_2} RCH_2B< \xrightarrow[-N_2]{CH_2N_2} RCH_2CH_2B< \qquad \textit{etc.}$$

Davies and his co-workers[140] substantiated this suggestion and synthesised previously unavailable neopentyl boron compounds by treating the corresponding t-butyl derivative with diazomethane. In addition, n-butyl boronic anhydride was shown to react with diazomethane forming a mixture of organoboron compounds, which after oxidation and hydrolysis, produced all the

---

[136] H. Hoberg, *Annalen*, 1962, **656**, 1; H. Hoberg, *Angew. Chem.*, 1961, **73**, 114.

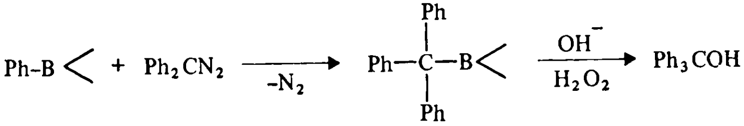
[137] H. Hoberg, *Annalen*, 1966, **695**, 1; H. Hoberg, *Angew. Chem., Internat. Edn.*, 1965, **4**, 1088.

[138] J. Goubeau and K. H. Rohwedder, *Annalen*, 1957, **604**, 168.

[139] C. E. H. Bawn, A. Ledwith, and P. Matthies, *J. Polymer Sci.*, 1959, **34**, 93.

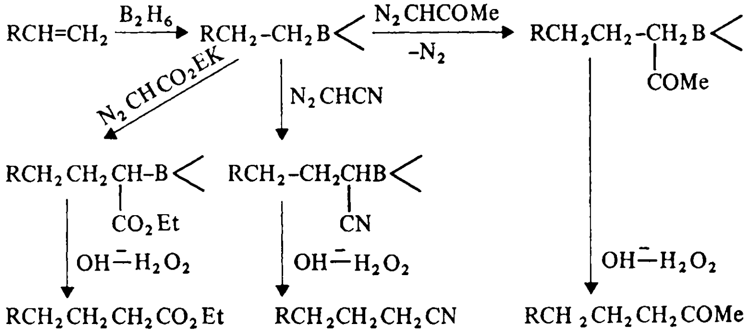
[140] A. G. Davies, D. G. Hare, O. R. Khan, and J. Sikora, *J. Chem. Soc.*, 1963, 4461; *Proc. Chem. Soc.*, 1961, 172.

normal alcohols up to C_8. Similarly, triphenylborane reacts with diphenyl diazomethane to give triphenylmethanol as a major product:[141]



$$\mathrm{Ph{-}B}\!< + \mathrm{Ph_2CN_2} \xrightarrow[-\mathrm{N_2}]{} \mathrm{Ph{-}\overset{Ph}{\underset{Ph}{C}}{-}B}\!< \xrightarrow[\mathrm{H_2O_2}]{\mathrm{OH^-}} \mathrm{Ph_3COH}$$

Very recently the alkylenation of organoboron compounds has been extended to provide a useful synthetic route to ketones, esters, and nitriles.[142,143] Alkyl boron compounds are readily available as *in situ* intermediates following hydroboronation of alkenes.[144] Immediate reaction with diazo-ketones,[142] diazoacetic ester,[143] or cyanodiazomethane[143] gives, after alkaline oxidation, very good yields of alkylated products, as indicated:



Most workers assume that alkylenation of aluminium,[137] boron,[138,139,140] silicon,[145,146] and tin[147] compounds involves primary co-ordination of diazo-alkane carbon with a vacant *p*-orbital in the Lewis Acid, as illustrated above for reaction of diphenyl diazomethane with mercury(II) chloride;[50] ramifications are discussed below in connection with polymerisation.

8 Polymerisation of Diazo-alkanes Catalysed by Boron Compounds

As outlined above, many inorganic compounds react with diazo-alkanes to form organometallic derivatives. Compounds of boron,[139,140] aluminium,[137] and silicon[145] may be active catalysts for polymerisations or may be alkylenated according to solvent and substituents on the metal. Boron compounds have been most widely used for the former purpose and there is every reason for

---

[141] J. E. Lettler and B. G. Ramsey, *Proc. Chem. Soc.*, 1961, 117.

[142] J. Hooz and S. Lincke, *J. Amer. Chem. Soc.*, 1968, **90**, 5936; J. Hooz and D. M. Gunn, *Chem. Comm.*, 1969, 139; *J. Amer. Chem. Soc.*, 1969, **91**, 6195.

[143] J. Hooz and S. Lincke, *J. Amer. Chem. Soc.*, 1968, **90**, 6891.

[144] H. C. Brown, 'Hydroboronation', Benjamin Inc., New York, 1962.

[145] R. A. Shaw, *J. Chem. Soc.*, 1957, 2831.

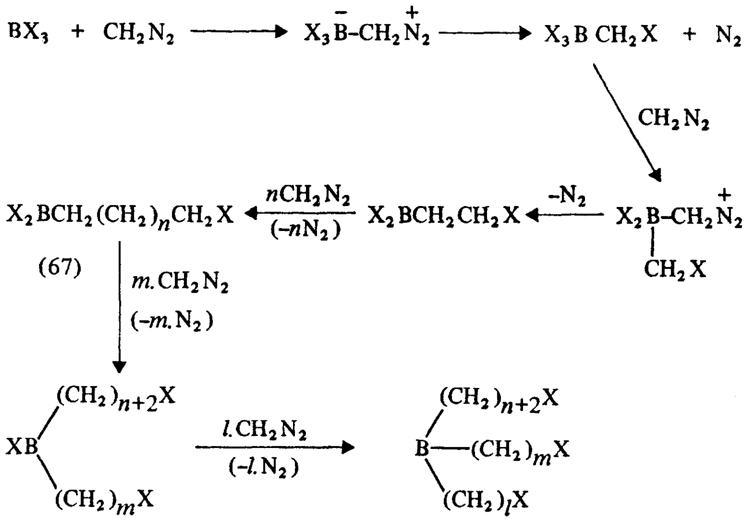
[146] K. A. W. Kramer and A. N. Wright, *J. Chem. Soc.*, 1963, 3604; *Chem. Ber.*, 1963, **96**, 1877.

[147] M. Lesbre and R. Buisson, *Bull. Soc. chim. France*, 1957, 1204.

assuming that mechanisms of reactions involving the other elements would be closely related.

Polyalkylidenes $[-(\underset{R}{CH})_n-]$ are synthesised almost exclusively by catalysed polymerisation of the appropriate diazo-alkane.[148] The linear homopolymers of diazomethane and copolymers with other diazo-alkanes provide excellent models[149] for commercially important linear and branched polyethylenes, and for anticipated (but not yet realised) homopolymers of 1,2-disubstituted ethylenes. Polyethylidene[150] $[-(\underset{Me}{CH})_n-]$ and polybenzylidene[151] $[-(\underset{Ph}{CH})_n-]$ are particularly interesting in this respect (*c.f.* the non-homopolymerisability of *cis*- and *trans*-but-2-ene and stilbenes).

Boron halides, boron alkyls, and boric esters have been used as catalysts, but boron trifluoride and trialkyl borates give best yields.[152,153] The various mechanisms proposed for polymerisation of diazo-alkanes, catalysed by boron compounds, have been reviewed,[139,10a] but recent work[140] makes it probable that more than one process must be operative, depending on the nature of the catalyst. Successive methylenation is an obvious possibility, *e.g.*



(68) (69)

---

[148] C. E. H. Bawn and A. Ledwith, 'Encyclopedia of Polymer Science and Technology', Wiley, Interscience, New York, 1969, **10**, 337.

[149] M. J. Richardson, P. J. Flory, and J. B. Jackson, *Polymer*, 1963, **4**, 221.

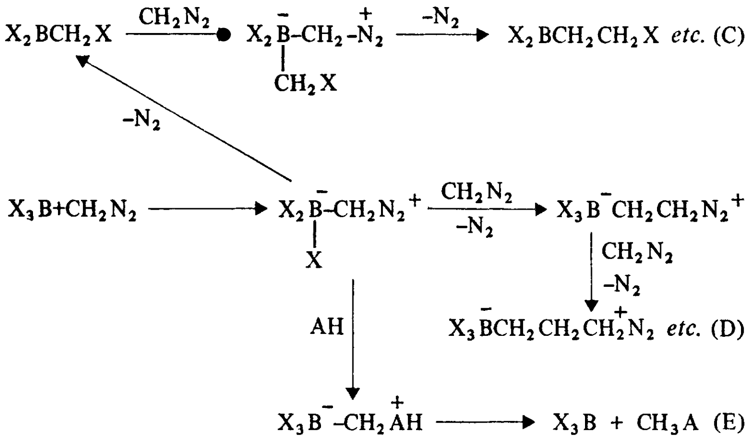
[150] G. D. Buckley, L. H. Cross, and N. H. Ray, *J. Chem. Soc.*, 1950, 2714.

[151] C. E. H. Bawn, A. Ledwith, and P. Matthies, *J. Polymer Sci.*, 1958, **33**, 21.

[152] S. W. Kantor and R. C. Osthoff, *J. Amer. Chem. Soc.*, 1953, **75**, 931.

[153] G. D. Buckley and N. H. Ray, *J. Chem. Soc.*, 1952, 3701.

Polyalkylenated boron[140] and aluminium[137] compounds have been characterised, supporting such a scheme, but for reactions with silicon tetrachloride the products are either polymethylene or mixtures of mono- bis-, tris-, and tetrakis-chloromethyl silicon derivatives.[145] Further confirmation of the polymethylenation mechanism was obtained by polymerisation of diazomethane with triphenylborane.[141] Treatment of the polymer with alkaline hydrogen peroxide gave benzyl alcohol and polymethylene containing a monosubstituted benzene ring, compelling evidence for the formation of molecules such as (67—69, X = Ph—). Similar results were obtained with tris α-naphthyl boron as catalyst.[141,154] Clearly, the repetitive methylenation mechanism is appropriate in some circumstances. By such a reaction the average molecular weight of polyalkylidene chains would be given by the ratio $3(RCHN_2):BX_3$, but for catalysis by excess quantities of BF_3,[155] BR_3,[140] or B_2H_6,[156] diazomethane is completely polymerised to high molecular weight products, with only partial utilisation of the catalyst. Further, Davies and his co-workers have shown[140] that polymerisation of diazomethane may be intercepted by addition of a nucleophilic reagent AH (*e.g.* amine, water, or alcohol), forming CH_3A. It was suggested,[140] therefore, that three reactions (C,D,E) may occur simultaneously, *i.e.*



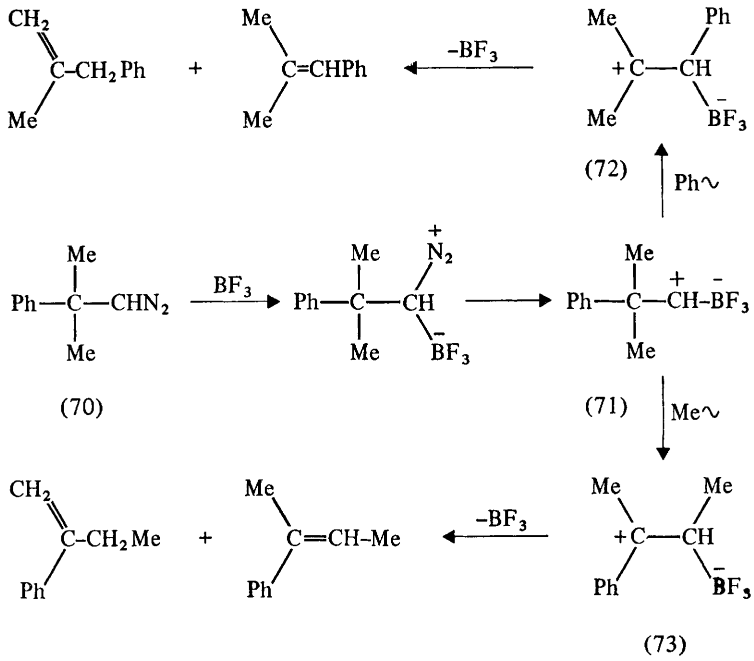
Polymerisation of diazomethane is a very rapid reaction, and consequently detailed kinetic investigation is experimentally difficult. Nevertheless, Davies *et al.*[140] suggest that reaction (D) is the dominant polymerisation mechanism under most reaction conditions, although minor variations to allow propagation by ion-pairs such as $X_2BCH_2(CH_2)_nCH_2N_2^+\ BX_4^-$ could not be excluded. Concurrent methylenation of added nucleophilic reagents is readily explained

---

[154] M. G. Krakovyak, E. V. Anufrieva, and S. S. Skorokhodov, *Vysokomol. Soedineniya*, 1966, **8**, 1681.
[155] A. Ledwith, Ph.D. Thesis, Liverpool, 1957.
[156] G. H. Dorion, S. E. Polchlopek, and E. H. Sheers, *Angew. Chem.*, 1964, **76**, 495.

by a mechanism such as (E), although it is now evident that this is a special case of a useful alkylation reaction for which alternative mechanisms have been proposed (see later).

A related study[157] is significant in discussion of boron trifluoride catalysed polymerisation of diazo-alkanes. Decomposition of 2-phenyl-2-methyl diazopropane (70), catalysed by protic and Lewis Acids, yields a mixture of alkene products consequent on methyl or phenyl migration:[157]



In strictly anhydrous conditions, boron trifluoride gave a product composition different from that given by protic acids but consistent with indiscriminate phenyl or methyl migration. Other Lewis Acids gave product mixtures in between the boron trifluoride–protic acid extremes, and addition of small amounts of water or alcohols to the boron trifluoride system produced a mixture identical with that from protic acids. The latter react with diazo-alkanes to give products arising from the corresponding diazonium and carbonium ions (see later section). It must be concluded, therefore, that boron trifluoride catalysed decomposition does not involve the corresponding carbonium ion. Formation of a boron trifluoride–carbene adduct (71) was suggested, and its demonstrated rearrangement to (72) or (73), involving charge separation, helps to overcome

---

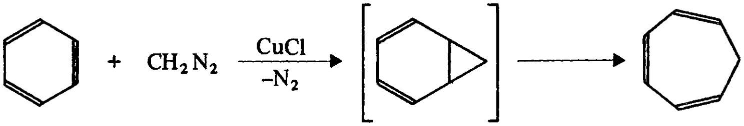
[157] H. Philip, M. K. Lowery, and J. Havel, *Tetrahedron Letters*, 1967, 5049.

previous objections[139] to long standing[152] polymerisation mechanisms such as (D) above. Polar intermediates have long been assumed for polymerisation of diazo-alkanes largely because of the very high rates of reaction and the ineffectiveness of conventional radical traps.[139] Similar criteria have been used to support the assumption that polar intermediates were dominant in reactions of oxygen with organoboron compounds,[158,159] but very recent work demonstrates rather that free radical intermediates are important.[160] Free radical reactions of boron compounds now appear to be much more general[161] than had been supposed, and it is at least a possibility that boron-catalysed polymerisation of diazomethane might involve some kind of boron–complexed radical species.

9 Reactions of Diazo-alkanes Catalysed by Copper Salts

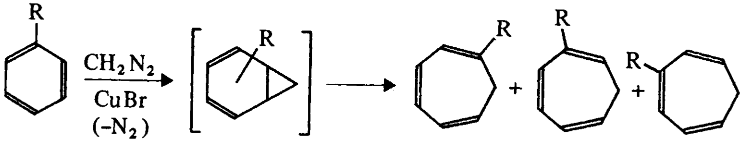
Catalysis by copper metal, cuprous, and cupric salts is frequently utilised to facilitate reactions of diazo-alkanes, including polymerisation[150,162,163] and (apparent) formation of carbenes.[4,5] Interest in the latter possibility has been widespread, although the most comprehensive study is that of E. Müller and his collaborators.[10b] Cupric salts are immediately reduced by diazomethane, and consequently cuprous compounds are the most convenient catalysts. Presumably copper metal functions *via* surface impurities.

Benzene reacts readily with diazomethane[164] in the presence of cuprous halides to form cycloheptatriene (74) in high yield:



(74)

The reaction is general for aromatic systems, substituted benzenes giving a mixture of the corresponding substituted cycloheptatrienes,[10b] *i.e.*

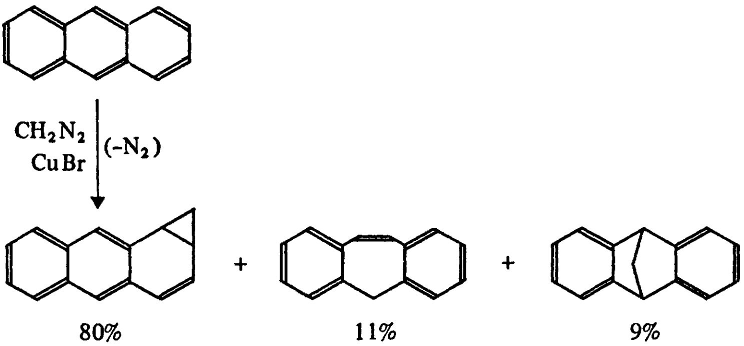


R = alkyl, halogen or alkoxy

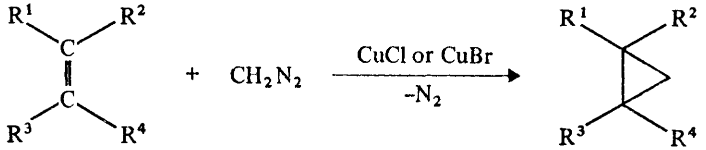
---

[158] A. G. Davies, 'Organic Peroxides', Butterworths, London, 1961.
[159] A. G. Davies, *Progr. Boron Chem.*, 1964, **1**, 265.
[160] A. G. Davies and B. P. Roberts, *J. Chem. Soc.* (*B*), 1969, 311; 1967, 17.
[161] A. G. Davies and B. P. Roberts, *Chem. Comm.*, 1969, 699; K. U. Ingold, *Chem. Comm.*, 1969, 911; P. G. Allies and P. B. Brindley, *Chem. and Ind.*, 1967, 319; 1968, 1439.
[162] C. E. H. Bawn and T. B. Rhodes, *Trans. Faraday Soc.*, 1954, **50**, 934.
[163] J. Feltzin, A. J. Restaino, and R. B. Mesrobian, *J. Amer. Chem. Soc.*, 1955, **77**, 206.
[164] E. Müller and H. Fricke, *Annalen*, 1963, **661**, 38; E. Müller, H. Kessler, H. Fricke, and W. Kiedaisch, *ibid.*, 1964, **675**, 63.

Condensed aromatics also give mixtures of products,[165] *e.g.* for anthracene;[166]



Related reactions of cyclic and acyclic olefins produce cyclopropanes (75) in good yield:[134,167–170]



(75)

A survey of the scope of copper-catalysed homologations has been published[10b] and in all cases the products resemble those expected from reaction of carbene (CH_2:) with the same substrate. Particularly important is the reaction of diazomethane with allylic compounds, studied by Kirmse and his collaborators.[171a–c] Thus *cis*- and *trans*-isomers of (76) react to give the corresponding cyclopropanes with complete retention of configuration,[171a] *i.e.*

---

[165] W. E., von Doering and M. S. Goldstein, *Tetrahedron*, 1959, **5**, 53; E. Müller, H. Fricke, and H. Kessler *Tetrahedron Letters*, 1964, 1525; E. Müller, H. Kessler, and H. Suhr, *ibid.*, 1965, 423; C. R. Ganellin, *ibid.*, 1964, 2919.

[166] E. Müller and H. Kessler, *Annalen*, 1966, **692**, 58.

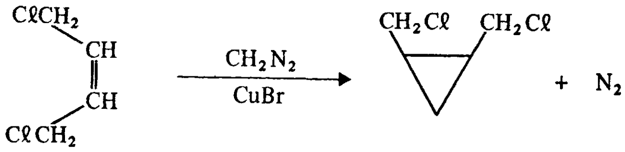
[167] M. F. Dull and P. G. Abend, *J. Amer. Chem. Soc.*, 1959, **81**, 2588.

[168] W. R. Roth and J. König, *Annalen*, 1965, **688**, 28.

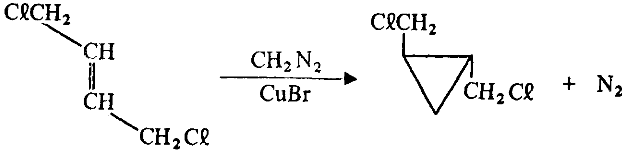
[169] E. Müller, H. Fricke, and W. Rundel, *Z. Naturforsch*, 1960, **15b**, 753; E. Müller and H. Kessler, *Tetrahedron Letters*, 1968, 3037.

[170] W. Roth, *Annalen*, 1964, **671**, 10.

[171] (*a*) W. Kirmse and M. Kapps, *Angew. Chem. Internat. Edn.*, 1965, **4**, 691; (*b*) W. Kirmse, M. Kapps, and R. B. Hager, *Chem. Ber.*, 1966, **99**, 2855; (*c*) W. Kirmse and M. Kapps, *ibid.*, 1968, **101**, 994; W. Kirmse and H. Arold, *ibid.*, 1968, **101**, 1008.

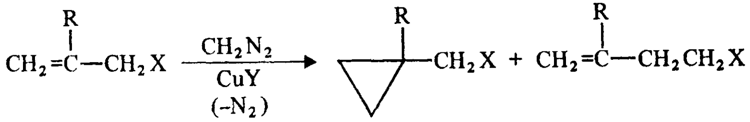


(76)



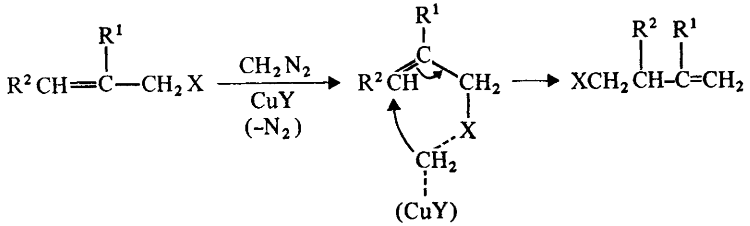
(76)

Simple allyl halides (77) give mixtures of cyclopropane (78) and 4-halogenobut-1-enes (79), depending on the nature of R, X, and the solvent, *i.e.*



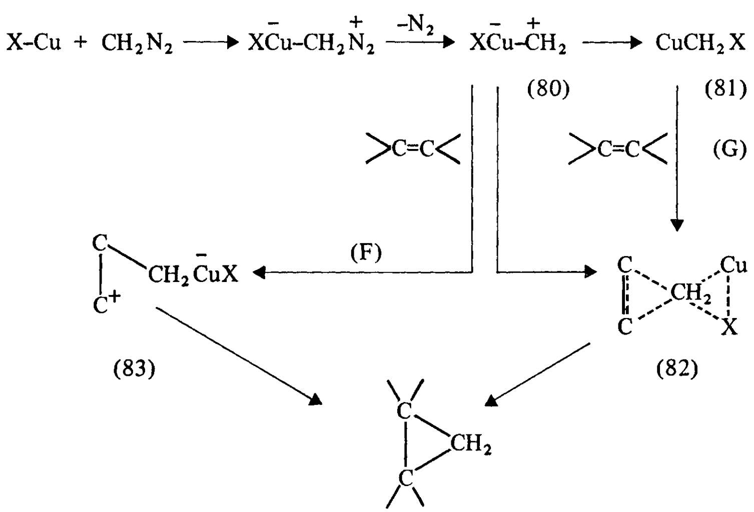
(77) (78) (79)

Cyclopropanes (78) are the main product when X = Cl but 4-halogenobut-1-enes (79) predominate when X = Br. By means of deuterium labelling in methyl derivatives it was demonstrated that formation of (79) involves a complete allylic rearrangement, *e.g.*

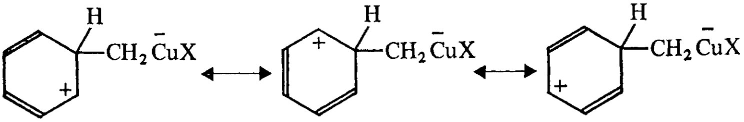


In contrast, the corresponding reaction of carbene, produced by photolysis of diazomethane, gives the 4-halogenobut-1-ene derivative by direct insertion of CH_2 into the C—Cl bond.[171] Furthermore, copper-catalysed reactions of diazo-alkanes are normally free of products resulting from insertion of carbenes into C—H bonds, so typical of free carbene processes.[4,5]

Free carbenes, therefore, do not play a role in copper-catalysed reactions of diazo-alkanes, and two possible reaction paths (F and G) are indicated below,[10b]



Reaction (F) would be anticipated for reactions with aromatic molecules because of resonance stabilisation of the dipolar intermediates (83), *e.g.*



By analogy with intermediates in the Simmons–Smith cyclopropane synthesis,[135] copper-catalysed reactions of diazomethane with olefins probably involve intermediates such as (82) formed *via* either reaction (F) or (G).

A copper–carbene complex, first suggested by Yates[172] to explain copper-catalysed reactions of diazoacetic ester with olefins, has recently been confirmed[173] by detailed kinetic studies of similar reactions, with the further conclusion that cyclopropane formation involves a copper–carbene–olefin complex such as (82). It is perhaps worth recalling that a methylcarbene–platinum complex was originally proposed[174] as a structure for the platinum(II)–ethylene adduct (Zeise's salt), and recently stable transition metal–carbene complexes have been characterised.[175] Diazo-alkanes may also form a stable complex with transition metals, *via* the nitrogen atoms, in favourable circumstances.[176]

Synthesis of unstable copper(I) alkyls (81) was first suggested[177] to explain copper-catalysed polymerisation of diazo-alkanes. The latter has been known for many years[150] and represents perhaps the most convenient method for

[172] P. Yates, *J. Amer. Chem. Soc.*, 1952, **74**, 5376.

[173] W. R. Moser, *J. Amer. Chem. Soc.*, 1969, **91**, 1135, 1141.

[174] J. Chatt, *Research*, 1951, **4**, 180.

[175] E. O. Fischer and A. Riedel, *Chem. Ber.*, 1968, **101**, 151; O. S. Mills and A. D. Redhouse, *J. Chem. Soc.* (*A*), 1968, 642.

[176] P. E. Baikie and O. S. Mills, *Chem. Comm.*, 1967, 1228; M. M. Bagga, P. E. Baikie, O. S. Mills, and P. L. Pauson, *ibid.*, 1967, 1106.

[177] C. E. H. Bawn, A. Ledwith, and J. A. Whittleston, *Angew. Chem.*, 1960, **72**, 115.

producing homopolymers of alkyl-substituted diazomethanes, although polymethylene may also be obtained in this way.[162,163] A significant conclusion emerging from the results of several groups of workers[10b,177] is that for reactions of diazomethane, copper salts active for formation of cyclopropanes (*e.g.* CuCl, CuBr) are poorly effective as catalysts for polymethylene formation. Conversely copper salts of organic acids (*e.g.* copper(II) stearate) which are particularly useful for polymerisation, are almost completely inactive in cyclopropane formation. Although copper(II) salts are used for convenience in polymerisation of diazo-alkanes, the corresponding copper(I) salts constitute the active catalysts.[177] The precise mechanism for polymerisation is even less clear than for catalysis by boron compounds, but analogous possibilities exist, *e.g.* repetitive insertion growth of a copper(I) alkyl (81), or a rapidly growing cationic chain from (80) (*cf.* reactions C, D). Protic additives have lesser effects on the copper-catalysed polymerisations, which argues against a propagating ionic species. Indeed, for the polymerisation of diazoethane in tetrahydrofuran, catalysed by CuI–amine adducts,[178] the polymer yield and molecular weight are unaffected by massive amounts of water. It seems likely, therefore, that copper-catalysed polymerisation of diazo-alkanes involves a propagating 'free radical' suitably stabilised as a copper(I) complex, *e.g.* $(RCH_2CH_2\cdot)CuX$ (solvent)$_x$.

Many other transition-metal compounds have been used to polymerise diazo-alkanes,[155,178] the most successful (and enigmatic) being nickelocene.[179] Metallic gold surfaces and colloidal gold[180,181] have the added advantage of inducing formation of stereoregular[182] polyethylidene; mechanisms for these reactions are not known but it is probable that they involve intermediates similar to those discussed above for catalysis by copper compounds.

10 Reactions of Diazo-alkanes with Protic Acids

The basic character of diazo-alkanes derives mainly from the resonance structure $R_2\overset{-}{C}\text{—}\overset{+}{N}{\equiv}N$. Thus with a protic acid HB, reaction occurs primarily at the nucleophilic carbon atom yielding an alkyl diazonium salt which rapidly decomposes to give the corresponding highly reactive carbonium ion:

$$\begin{tikzcd}
R_2C{=}N_2 \arrow[r, "H^+\bar{B}"] & R_2CHN_2{}^+\bar{B} \arrow[r, "-N_2"] & R_2CH^+\bar{B} \arrow[dl, "Nu^-"'] \arrow[d] \arrow[dr, "HB^1"] & \\
 & R_2CHNu & R_2CHB & R_2CHB^1 + H^+
\end{tikzcd}$$

---

[178] C. E. H. Bawn and A. Ledwith, *Chem. and Ind.*, 1957, 1180; A. Ledwith and A. C. White, unpublished results.

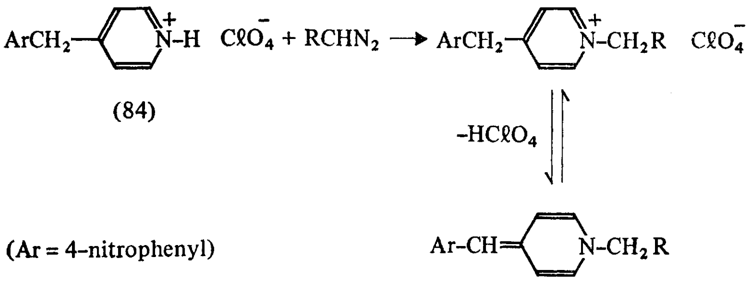
[179] H. Werner and J. H. Richards, *J. Amer. Chem. Soc.*, 1968, **90**, 4976.

[180] A. G. Nasini and L. Trossarelli, *J. Polymer Sci., Part C Polymer Symposia*, 1965, **3**, 378; A. G. Nasini, L. Trossarelli, and G. Saini, *Makromol. Chem.*, 1961, **44-46**, 550; A. G. Nasini, G. Saini, L. Trossarelli, and E. Campi, *J. Polymer Sci.*, 1960, **48**, 435; G. Saini and A. G. Nasini, *Atti. Accad. Sci. Torino*, 1955-56, **90**, 586.

[181] A. Ledwith, *Chem. and Ind.*, 1956, 1310.

[182] C. E. H. Bawn and A. Ledwith, *Quart. Rev.*, 1962, **26**, 363.

Reactivity of a series of diazo-alkanes towards a particular acid depends upon the nature of the groups (R) and their effect upon the basic character of the α-carbon of the diazo-alkane. Thus, substituting aryl groups for the hydrogen atoms in diazomethane decreases reactivity, as will carbonyl and alkoxycarbonyl groups. Nevertheless, rapid and quantitative esterification of organic acids by diazo-alkanes is a very common reaction, and is frequently used for estimation of the latter. A recent variation of the reaction of diazo-alkanes with strong acids provides a convenient spectrophotometric procedure for assay purposes.[183] The diazo-alkane is allowed to react with the pyridinium perchlorate (84) to give a quantitative yield of a quinonoid dye (85), absorbing in the region 5190—5880 Å:



(84)

(85)

(Ar = 4-nitrophenyl)

More generally, pyridines, quinolines, and isoquinolines are readily converted into corresponding *N*-methyl quaternary salts by reaction with diazomethane in the presence of fluoroboric acid.[184]

Deamination of aliphatic primary amines[185] and protonation of the corresponding diazo-alkanes[1,2,185] have long been known to give rise to very similar reaction products, presumably *via* the common diazonium ion. Very recently, Friedman and his co-workers[186] have made an elegant study of the fate of the isobutyl cation (88) formed both by deamination of 2-methyl 1-propylamine, (86) and by acid-catalysed decomposition of 2-methyl-1-diazopropane (87) in common solvent systems. Isobutyl cation (88) gives mainly hydrocarbon products (89—93) after formation from either (86) or (87):

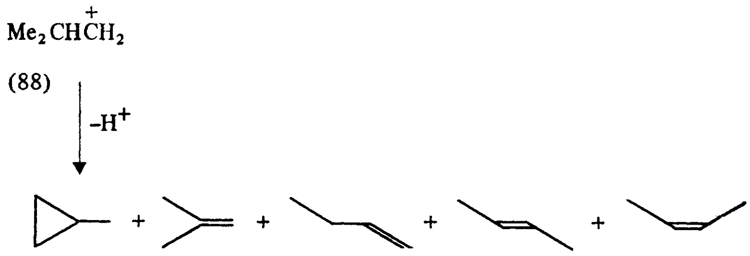
---

[183] R. Preussemann, H. Hengy, H. Druckrey, *Annalen*, 1965, **684**, 57.

[184] R. Daniels and C. G. Kormenoy, *J. Org. Chem.*, 1962, **27**, 1860.

[185] J. H. Ridd, *Quart. Rev.*, 1961, **15**, 418.

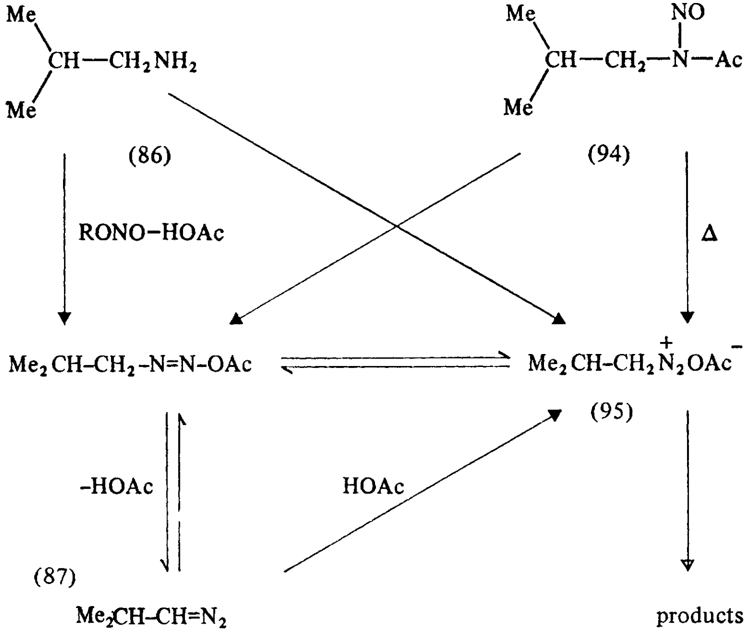
[186] L. Friedman and J. H. Baylen, *J. Amer. Chem. Soc.*, 1969, **91**, 1790; L. Friedman, A. T. Jurewicz, and J. H. Bayless, *ibid.*, 1969, **91**, 1795; L. Friedman and A. T. Jurewicz, *ibid.*, 1969, **91**, 1800, 1803, 1808.



(88)

(89) (90) (91) (92) (93)

When the diazo precursor (94) was thermally decomposed in the presence of stoicheiometric quantities of HOAc and DOAc in aprotic solvents, the product composition was identical with that from reaction of (86) and its —ND_2 analogue with octyl or amyl nitrites. By careful analysis of the deuterium content of the hydrocarbon products from these and related reactions, it was shown that if the alkyl group is primary, diazo-alkanes are intermediates in thermal decomposition of nitrosoamides in poorly solvating media. The extent of diazo-alkane formation diminishes with an increase in solvating power of the medium, so that in protic media such as aqueous acetic acid there is no evidence for its intermediacy at all. Under all the conditions of reaction, products arise from the diazonium species, formed either by protonation of the intermediate diazo-alkane or directly from precursor nitrosoamine or nitrosoamide, *i.e.*

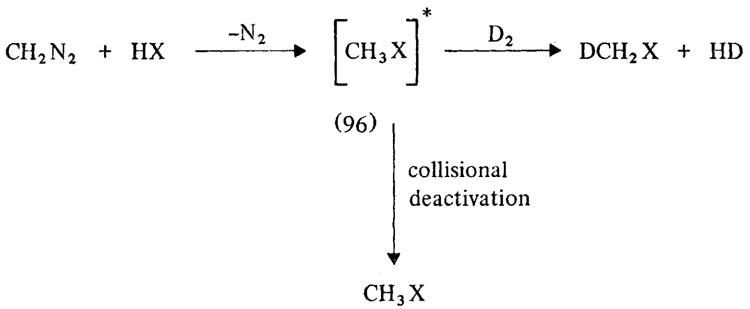


(86) (94) (95) (87)

Product composition varies with solvent, reflecting probable solvation characteristics of the diazonium ion pairs (95), and related reactions of s-alkylamine derivatives proceed without formation of the appropriate diazo-alkane, probably because of the very short lifetime of secondary diazonium ions.[186]

There is only limited evidence[186a] regarding lifetimes of s-alkyl diazonium ions ($R_2CHN_2^+$), but it is well known that substitution in the opposite sense, *i.e.* with electron-withdrawing groups, enhances the lifetime of the diazonium unit. Stable alkyl diazonium ions are formed when there are strongly electron withdrawing and conjugating substituents.[187] The simplest alkyl diazonium ion to be characterised is 2,2,2-trifluoroethyl diazonium ion[188] ($CF_3CH_2N_2^+$), formed by dissolving CF_3CHN_2 in FSO_3H at $-60°$ (half life *ca.* 1 hr).

A most interesting application of the reactivity of diazo-alkanes towards protic acids is the formation of 'hot' methyl halides (96) by gas phase reactions of diazomethane with hydrogen chloride, hydrogen bromide, and hydrogen iodide.



$$\begin{tikzcd} CH_2N_2 + HX \arrow[r, "-N_2"] & {[CH_3X]^*} \arrow[r, "D_2"] \arrow[d, "\text{collisional deactivation}"] & DCH_2X + HD \\ & CH_3X & \end{tikzcd}$$

(96)

The reactions are homogeneous, quantitative, extremely rapid, and involve polar transition states, although it is not clear whether these should be linear or cyclic.[189] Overall, the reactions are exothermic by approximately ΔH_f^0 for diazomethane, and consequently the methyl halide is generated in a high-energy vibrationally-excited state, reflected in deuterium exchange between nascent $[CH_3X]^*$ and D_2 or CD_4 diluents. Experiments of this type are important as test reactions for theories of unimolecular decomposition and energy transfer between vibrational and translational states.

One of the most important reactions of diazomethane (methylation) depends on its ability to react with a weakly acidic hydrogen atom in enols, lactams, thiolactams, *etc.*[1,2,117] The reaction is especially useful for sensitive compounds because of high yields and simplicity of reaction products, facilitating work-up procedures. If tautomeric or potentially tautomeric compounds (97) are treated with diazomethane, two reactive centres are available and the methylated

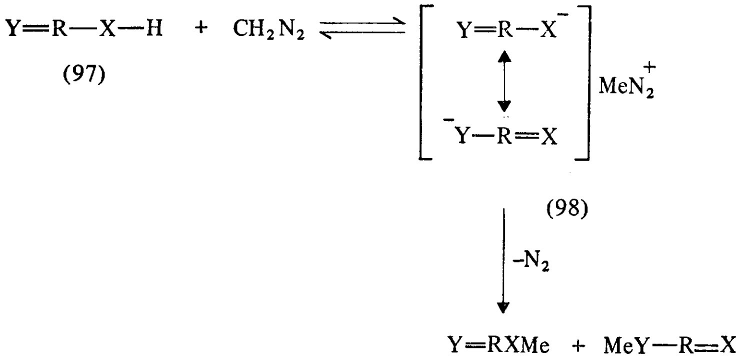
[186] (*a*) H. Maskill, R. M. Southam and M. C. Whiting, *Chem. Comm.*, 1965, 496.

[187] K. Bott, *Angew. Chem. Internat. Edn.*, 1964, **3**, 804, *Tetrahedron*, 1966, **22**, 1251; H. Reimlinger, *Angew. Chem. Internat. Edn.*, 1963, **2**, 482.

[188] J. R. Mohrig and K. Keegstra, *J. Amer. Chem. Soc.*, 1967, **89**, 5492.

[189] S. H. Bauer, D. Marshall, and T. Baer, *J. Amer. Chem. Soc.*, 1965, **87**, 5514; J. C. Hassler and D. W. Setser, *ibid.*, 1965, **87**, 3793.

products are frequently different from those which are obtained by other methods, *e.g.*



Collapse of the methyl diazonium ion-pair (98) gives kinetically controlled products, rather than the thermodynamically more stable methyl derivatives obtained with other methylating agents. There are many examples[117] of pronounced solvent effects on product composition from reactions of diazomethane with tautomeric systems and there has been much discussion of relative Brönsted acidity, and of electrostatic factors in controlling product distribution.[190,191]

From present-day knowledge of polar intermediates it would appear that the mechanism and product distributions are a consequence of solvation and dissociation equilibria of ion-pairs,[192] together with relative nucleophilicities and steric effects of ambident anions.[193] However, more detailed kinetic work is needed for a complete understanding of these factors in controlling methylation. Two recent studies are pertinent.

Hammond and Williams[194] reinvestigated the reactions between diazomethane and acetylacetone in diethyl ether. In agreement with results of earlier workers, the main product was shown to be the enol ether (99). However, there was a small but significant yield of 3-methyl acetylacetone (100), suggesting involvement of the symmetrical ion pair (101) as common intermediate.

Addition of toluene-*p*-sulphonic acid to diazomethane in ether caused rapid formation of methyl toluene-*p*-sulphonate and polymethylene, but in the presence of acetylacetone concomitant alkylation occurred yielding (99) and (100). Formation of higher alkyl ethers was not observed, even when polymethylene was formed,[194] and hence the ion-pairs (101) must be of the 'intimate' or 'contact' type.[192]

---

[190] F. Arndt, B. Eistert, R. Gompper, and W. Walter, *Chem. Ber.*, 1961, **94**, 2125.

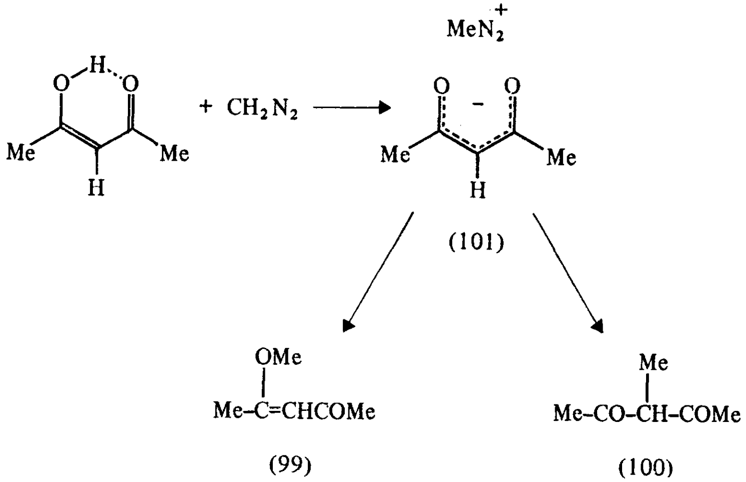
[191] R. Gompper, *Adv. Heterocyclic Chem.*, 1964, **2**, 245.

[192] S. Winstein, B. Appel, R. Baker, and A. Diaz, *Chem. Soc. Special Publ.*, No. 19, 1965, p. 109; M. Szwarc, *Accounts Chem. Res.*, 1969, **2**, 87.

[193] J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, 1966, **84**, 16; N. Kornblum, *Trans. N.Y. Acad. Sci.*, 1966, **29**, 1.

[194] G. S. Hammond and R. M. Williams, *J. Org. Chem.*, 1962, **27**, 3775.

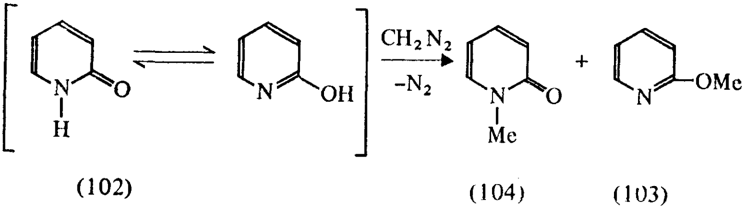
Kornblum and Coffey[195] made a thorough reinvestigation of the alkylation of 2-pyridone (102) with diazomethane. Contrary to the widely accepted view that this reaction yields exclusively oxygen methylation (103), it has now been shown that nitrogen methylation (104) predominates in the solvent systems MeOH–Et_2O and CH_2Cl_2–Et_2O.



With diazomethane the product ratio *N*-alkylate:O-alkylate was 1·7, whereas with diazoethane the value was 0·36, indicating that the oxygen end of the 2-pyridone anion was less sterically hindered, and hence more readily attacked by ethyl diazonium ion.

In recent years a substantial effort has been devoted to elucidation of the kinetics and mechanism of acid-catalysed reactions of more stable diazo-alkanes, particularly diphenyl diazomethane and diazoacetic ester, in both protic and aprotic media. The topic has been extensively reviewed by More O'Ferrall[196] and will therefore be treated only briefly.

Pioneering studies by Roberts and his collaborators[197] in the early nineteen fifties had established that decomposition of diphenyl diazomethane catalysed by strong acids involved rate-determining proton transfer to the α carbon atom.



---

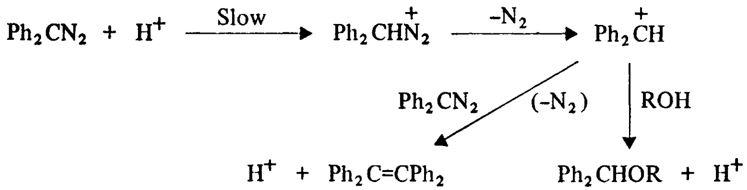
[195] N. Kornblum and G. P. Coffey, *J. Org. Chem.*, 1966, **31**, 3447.

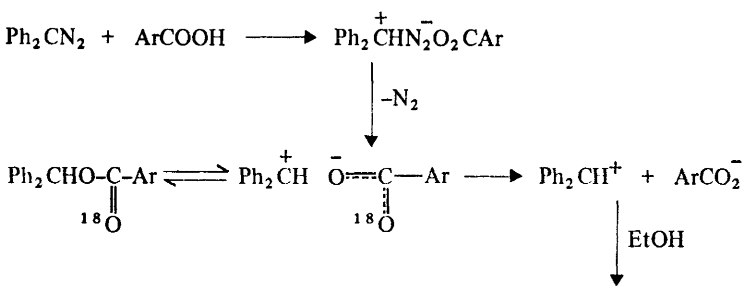
[196] R. A. More O'Ferrall, *Adv. Phys. Org. Chem.*, 1967, **5**, 331.

[197] J. D. Roberts and W. Watanabe, *J. Amer. Chem. Soc.*, 1950, **72**, 4869; J. D. Roberts, W. Watanabe, and R. E. McMahon, *ibid.*, 1951, **73**, 760, 2521; J. D. Roberts and C. M. Regan, *ibid.*, 1952, **74**, 3695.

Subsequent loss of nitrogen yields benzhydryl cation, which reacts with the diazo precursor to give tetraphenylethylene, or with protic solvent (ROH) to give benzhydrol or benzhydryl ethers.

Essentially similar steps were observed for catalysis by weak acids, except that a major product was the benzhydryl ester of the weak acid. Significantly, however, salts of the weak acid had no effect on the product ratio ester : ether. Later work showed that this product ratio was also insensitive to changes in reaction temperature,[198] and moderate changes in the reactivity of the catalysing acid.[199] These experimental observations, which imply that the ester is not formed from dissociated anions of the acid and that the product-partitioning occurs *via* steps of low activation energy, may be rationalised in terms of competing ion-pair return and reaction.[198,199] Direct proof of the intervention of ion-pairs was obtained by Diaz and Winstein[200] from the reaction of diphenyl diazomethane with ^{18}O-labelled *p*-nitrobenzoic acid in ethanol. Competition between ion-pair return, dissociation, and ethanolysis of ^{18}O-labelled benzhydryl *p*-nitrobenzoate had previously been established by Goering and Levy[201] by comparison of rates of ^{18}O-scrambling and acid production. Using similar techniques, Diaz and Winstein[200] showed that, within probable experimental error, the same ion-pair (or spectrum of ion-pairs) was involved in decomposition of the diazo-compound:





(Ar– = *p*-nitrophenyl

---

[198] K. Bowden, A. Buckley, N. B. Chapman, and J. Shorter, *J. Chem. Soc.*, 1964, 3380.

[199] R. A. More O'Ferrall, Wo Kong Kwok, and S. I. Miller, *J. Amer. Chem. Soc.*, 1964, **86**, 5553.

[200] A. F. Diaz and S. Winstein, *J. Amer. Chem. Soc.*, 1966, **88**, 1318.

[201] H. L. Goering and J. F. Levy, *J. Amer. Chem. Soc.*, 1962, **84**, 3853.

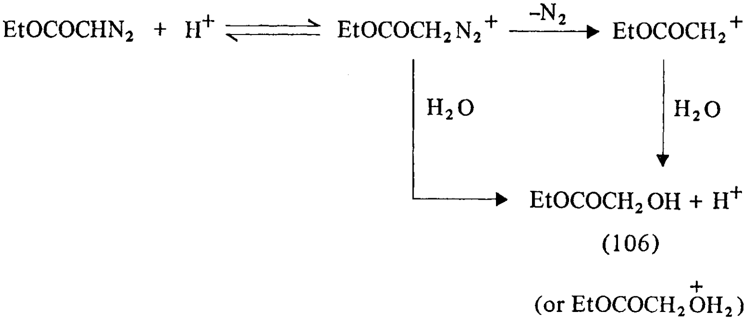
This work also confirms the previous assumption that nitrogen evolution from a secondary diazonium benzoate ion-pair is very much faster than its dissociation.

General acid catalysis, *via* rate-determining proton transfer, is now widely accepted as the primary step in acid-catalysed decomposition of diaryl diazomethanes in protic solvents,[196] and the reactions have found extensive use in studies of polar and steric effects, with particular reference to linear free energy relationships.[202] For aprotic solvents, reaction characteristics are generally similar,[199,203–206] with occasional complications arising when the ester formed is itself solvolytically unstable. For example, the reaction between diphenyl diazomethane and toluene-*p*-sulphonic acid in ether solvents gives quantitative yields of the highly reactive benzhydryl toluene-*p*-sulphonate (105),

$$\mathrm{Ph_2CN_2 + HOTos \longrightarrow \underset{(105)}{Ph_2CHOTos} + N_2}$$

and constitutes the most convenient synthetic route to this reactive material.[207] The same ester is formed in acetonitrile solvent but the increased ionising and dissociating power of this solvent drastically shortens its half life.[203] Consequently, kinetic studies of the toluene-*p*-sulphonic acid-catalysed decomposition of diphenyl diazomethane in acetonitrile[203] are complicated by rate-limiting ionisation of the rapidly formed ester (105).

In contrast to the diaryl diazomethanes, reactions of diazoacetic ester (N_2CHCO_2Et) involve specific acid catalysis,[208] with pre-equilibrium proton transfer between acid and diazoester forming ethyl glycollate (106) in water and the corresponding ethyl ether in ethanol.



$$\begin{tikzcd}
\mathrm{EtOCOCHN_2 + H^+} \arrow[r, shift left] & \mathrm{EtOCOCH_2N_2^+} \arrow[l, shift left] \arrow[r, "-N_2"] \arrow[dr, "H_2O"'] & \mathrm{EtOCOCH_2^+} \arrow[d, "H_2O"] \\
 & & \mathrm{\underset{(106)}{EtOCOCH_2OH + H^+}} \\
 & & \mathrm{(or\ EtOCOCH_2\overset{+}{O}H_2)}
\end{tikzcd}$$

Evidence for specific acid catalysis includes solvent kinetic isotope effect $D_2O/H_2O = 2{\cdot}9$ at 25°, and the fact that deuterium exchange of the alpha

---

[202] A. Buckley, N. B. Chapman, and J. Shorter, *J. Chem. Soc.* (*B*), 1968, 195; A. Buckley, N. B. Chapman, M. R. J. Dack, J. Shorter, and H. M. Wall, *ibid.*, 1968, 631; N. B. Chapman, J. R. Lee, and J. Shorter, *ibid.*, 1969, 769; see also ref. 54b.

[203] D. Bethell and J. D. Callister, *J. Chem. Soc.*, 1963, 3801, 3808.

[204] D. Bethell and R. D. Howard, *J. Chem. Soc.* (*B*), 1968, 430; *Chem. Comm.*, 1966, 94.

[205] N. B. Chapman, A. Eshaw, J. Shorter, and K. J. Toye, *Tetrahedron Letters*, 1968, 1049.

[206] F. Klages, K. Bott, P. Hegenberg, and H. A. Jung, *Chem. Ber.*, 1965, **98**, 3765.

[207] A. Ledwith and D. J. Morris, *J. Chem. Soc.*, 1964, 508.

[208] R. P. Bell, 'Acid Base Catalysis', Oxford Univ. Press, London, 1941, p. 100; J. D. Roberts, C. M. Reagen, and I. Allen, *J. Amer. Chem. Soc.*, 1952, **74**, 3679.

hydrogen atom is more rapid than the overall rate of hydrolysis.[209] Again, in contrast to the reactions of diphenyl diazomethane, addition of other nucleophiles (*e.g.* chloride ion) permits trapping of the reaction intermediate, and it is clear from the kinetic data that loss of nitrogen from the diazonium ion requires assistance from solvent or added nucleophile[210] (S_N2 process). Similar effects have been observed in acid-catalysed decomposition of α-diazo-ketones[211] and α-diazo-sulphones.[212]

It should be observed that diazomethane and the lower diazo-alkanes undergo acid and base catalysed deuterium exchange with D_2O more rapidly than esterification or decomposition.[213]

11 Lewis-acid-catalysed Alkylation of Alcohols and Amines

Normally the —OH and —NH groups in alcohols and amines are not sufficiently acidic to react with diazo-alkanes. The reactions may, however, be catalysed by Lewis Acids such as aluminium alkoxides, boron trifluoride, aluminium chloride, and by fluoroboric acid,[10] *e.g.*

$$R^2OH + R^1CHN_2 \xrightarrow{BF_3} R^2OCH_2R^1 + N_2 .$$

For alkylation of alcohols the most effective catalysts are boron trifluoride[214–217] and fluoroboric acid[218] in ether and methylene chloride solvents respectively. A wide range of primary, secondary, and tertiary alcohols have been converted into corresponding alkyl ethers in this way; yields are good for methylation with diazomethane but are seldom higher than 50% for higher diazo-alkanes.[10] For catalysis by fluoroboric acid in methylene chloride,[218] relative rates of methylation (isomeric butanols) were in the order primary:secondary:tertiary = 2·2 : 1·3 : 1·0, whereas for boron trifluoride in ether[216] (isomeric pentanols) the corresponding reactivities were 1·7 : 1·55 : 1, indicating great similarities in the two processes and low selectivity by the reagents.

Primary and secondary amines are alkylated in a similar manner,[217] except that in this case catalysis by fluoroboric acid corresponds with the use of preformed amine salt (107) as the reactant:

---

[209] P. Gross, H. Steiner, and F. Krauss, *Trans. Faraday Soc.*, 1938, **34**, 351.

[210] W. J. Albery and R. P. Bell, *Trans. Faraday Soc.*, 1961, **57**, 1942; W. J. Albery, J. E. C. Hutchins, R. M. Hyde, and R. H. Johnson, *J. Chem. Soc.* (*B*), 1968, 219.

[211] J. B. F. N. Engberts, N. F. Bosch, and B. Zwanenburg, *Rec. Trav. chim.*, 1966, **85**, 1068; H. E. Baumgarten and C. H. Anderson, *J. Amer. Chem. Soc.*, 1961, **83**, 399; H. Dahn and H. Gold, *Helv. Chim. Acta*, 1963, **46**, 983; H. Dahn, A. Donzel, A. Merbach, and H. Gold, *ibid.*, 1963, **46**, 994; D. M. Jordan, *Diss. Abs.*, 1966, **26**, 3633; S. Aziz and J. G. Tillett, *Tetrahedron Letters*, 1968, 2321; *J. Chem. Soc.* (*B*), 1968, 1302.

[212] B. Zwanenburg and J. B. F. N. Ehgberts, *Rec. Trav. chim.*, 1965, **84**, 165; *Tetrahedron*, 1968, **24**, 1737.

[213] K. J. van der Merwe, P. S. Steyn, and S. H. Eggers, *Tetrahedron Letters*, 1964, 3923; W. Kirmse and H. A. Rinkler, *Annalen*, 1967, **707**, 57; A. Bhati, *J. Chem. Soc.*, 1963, 729.

[214] E. Müller, M. Bauer, and W. Rundel, *Z. Naturforsch*, 1959, **14b**, 209.

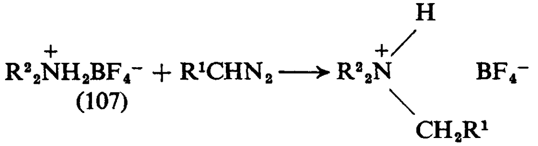
[215] E. Müller and W. Rundel, *Angew. Chem.*, 1958, **70**, 105.

[216] E. Müller, R. Meischkeil, and M. Bauer, *Annalen*, 1964, **677**, 55.

[217] E. Müller, W. Rundel, and H. Huber-Emden, *Angew. Chem.*, 1957, **69**, 614; E. Müller and H. Huber-Emden, *Annalen*, 1961, **649**, 70; E. Müller, H. Huber-Emden, and W. Rundel, *ibid.*, 1959, **623**, 34.

[218] M. Neeman, M. C. Caserio, J. D. Roberts, and W. S. Johnson, *Tetrahedron*, 1959, **6**, 36; *J. Amer. Chem. Soc.*, 1958, **80**, 2584.

$$R^2NH_2 + R^1CHN_2 \xrightarrow{BF_3} R^2NH{-}CH_2R^1 + N_2$$

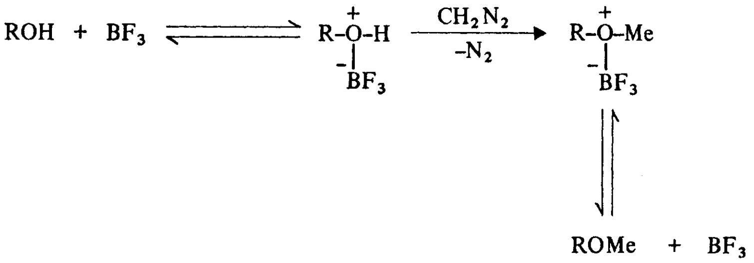


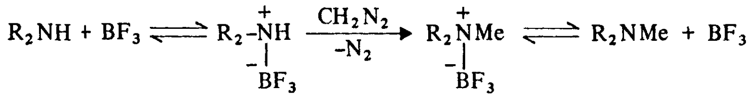
$$\underset{(107)}{R^2_2\overset{+}{N}H_2BF_4^-} + R^1CHN_2 \longrightarrow R^2_2\overset{+}{N}(H)(CH_2R^1) \quad BF_4^-$$

Several mechanisms have been proposed, and it may be that distinct processes operate according to the particular catalyst. Fluoroboric acid would logically be expected to function by primary protonation of the diazo-alkane, yielding the corresponding diazonium ion (108), as discussed in the previous section, *i.e.*

$$HBF_4 + CH_2N_2 \longrightarrow \underset{(108)}{CH_3N_2{}^+BF_4{}^-} \xrightarrow[-N_2]{ROH} ROCH_3 + HBF_4$$

Müller and his collaborators[216,217] have made extensive use of alkylations catalysed by boron trifluoride and suggest that the reaction mechanism is similar to that originally proposed by Meerwein and Hintz[219] for catalysis by aluminium alkoxides, *viz*:





A third possibility[140] has already been discussed (reaction E, p. 151) in connection with the mechanism of boron trifluoride catalysed polymerisation of diazo-alkanes. Irrespective of the precise reaction mechanism for alkylation, it is bound to have a bearing on the related boron trifluoride catalysed polymerisations (and homologation of ketones), and in fact low yields of alkylated products invariably imply significant, concurrent polymerisation of the diazo-alkane.

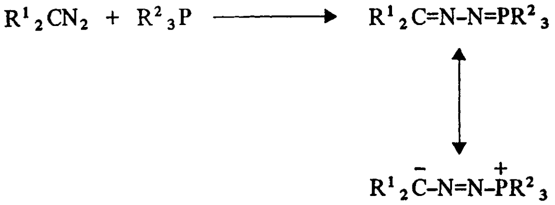
12 Reactions of Diazo-alkanes with Phosphines

It has been known for many years[220] that diazo-alkanes react with phosphines forming phosphazines (109):

---

[219] H. Meerwein and G. Hintz, *Annalen*, 1930, **484**, 1.

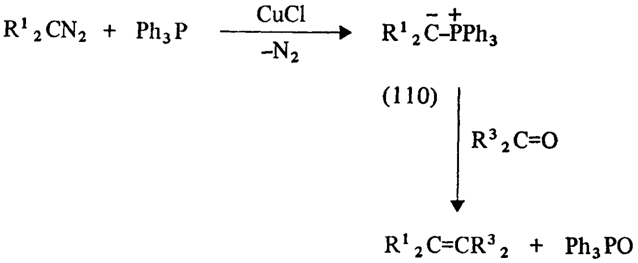
[220] H. Staudinger and J. Meyer, *Helv. Chim. Acta.*, 1919, **2**, 619, 635; H. Staudinger and G. Luscher, *ibid.*, 1922, **5**, 75.



$$R^1{}_2CN_2 + R^2{}_3P \longrightarrow R^1{}_2C{=}N{-}N{=}PR^2{}_3 \longleftrightarrow R^1{}_2\overset{-}{C}{-}N{=}N{-}\overset{+}{P}R^2{}_3$$

(109)

However, in the presence of copper(I) chloride similar reactions with Ph_3P lead to corresponding phosphorus ylides (110), and the process may be used as a one-step synthesis of olefins from ketones,[221] *i.e.*



$$R^1{}_2CN_2 + Ph_3P \xrightarrow[-N_2]{CuCl} R^1{}_2\overset{-}{C}{-}\overset{+}{P}Ph_3 \xrightarrow{R^3{}_2C{=}O} R^1{}_2C{=}CR^3{}_2 + Ph_3PO$$

(110)

Product olefins were obtained in *ca.* 30% yields, the remaining diazo-alkane forming phosphazine.

13 Health Hazards in Use of Diazo-alkanes

The explosive nature of pure samples of diazo-alkanes has already been referred to, and is widely recognised. Pharmacological effects have also been noted in previous surveys.[2,62,116] In recent years, however, there has been a growing recognition that diazomethane and its nitrosourethane precursor are active carcinogenic materials.[222] It appears that carcinoma of the lungs and stomach may result from inhalation of the vapours of the lower diazo-alkanes and their volatile precursors. Whilst there is yet no published evidence for carcinogenic activity in the wider range of diazo-alkane precursors, or in the more stable diazo-alkanes, it may be that this results from lack of experimentation rather than lack of activity.[223]

The authors thank Dr. D. Bethell for many helpful suggestions and discussions.

---

[221] G. Wittig and M. Schlosser, *Tetrahedron*, 1962, **18**, 1023.

[222] H. Marquardt, F. K. Zimmermann, and R. Schwaier, *Naturwiss*, 1963, **50**, 625; R. Schoental and P. W. Magee, *Brit. J. Cancer*, 1962, **16**, 92; I. J. Mizrahi and P. Emmelot, *Cancer Res.*, 1962, **22**, 339; R. Schoental, *Nature*, 1961, **192**, 670; 1960, **188**, 420; R. Schoental, *Acta. Unio. Intern. Contra Cancrum*, 1963, **19**, 680.

[223] C. E. Searle, *Chem. in Britain*, 1970, **6**, 5.