Review

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DIAZIRIDINES

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Introduction

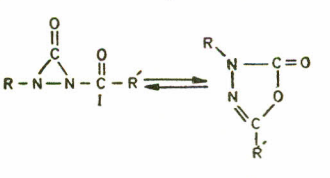
Diaziridines,[3,6] also referred to as isohydrazones,[1,4] have been the subject of investigation in the recent years as their chemistry is of interest to various chemists who specialize in the synthesis of unstable small heterocyclic compounds. They are also of interset to the chemists who like to study bonding in small cyclic molecules.

In the early days (~1910) diaziridines were believed to be formed by the addition of carbenes to diazo compounds. Thus the products of the reaction of ethyldiazoacetate and diazomethane with ethyl azodicarboxylate were assigned the diaziridine structure.[1] Following this the product of thermal reaction of diazofluorene with azodibenzolyl and ethylazodicarboxylate were also given the diaziridine structure. The structures of all these compounds have since then been revised in the light of new data becoming available. This field of the chemistry of diaziridines has since then developed quite a bit and lots of new members of this class of compounds have been synthesized, and new synthetic methods have been evolved.

In the early days the approach of the chemists to this class of compounds was quite understandable, since at that time the knowledge about carbenes was rather fresh and all kinds of new routes and reactions were being tried to test the potential of carbenes as a sound synthetic tool. Carbenes have been known to act as 1,1-dipoles.[6] And in this context it seemed reasonable to have expected their addition across the N=N double bond to form a 3-membered ring, as they were known to undergo such additions to C=C and C=N bonds. As a matter of fact the route still seems quite attractive in view of the ease, simplicity and resulting access to a large number of otherwise inaccessible compounds. But in the absence of a suitable carbene, or its precursor which will render such route feasible, this approach remains only of academic interest rather than having any practical utility.

Diaziridines are merely basic in character and form stable salts with oxalic acid. Members of this class of compounds which do not possess a free NH group dissolve with difficulty in strong acids. The diaziridines have a very characteristic feature of oxidizing the acid–iodide solution, liberating free iodine. This property has been used in diagnosing their existence. Fully N-substituted molecules, however, give this reaction only in the presence of a copper catalyst or on being heated. They offer a lot of scope for work to theoretical chemists in view of their peculiar nature of having two sp^3 hybridized nitrogen atoms and still conforming to the geometrical requirements of a 3-membered ring as regards the internal bond angles, and the charge density of the electronic cloud of free lone-pair of electrons on the N-atoms particularly their geometry and electronic interaction. These compounds serve as very good precursors to symmetrically substituted-hydrazines which otherwise are not accessible easily. Such hydrazines have a great demand in the rocket fuels. Diaziridines are also instrumental in yielding carbonylation of hydrazine derivatives,[2] and catalyze polymerization of HCHO on industrial scale. They are known to stabilize tri- and tetrachloroethylenes and other halogenated olefins. Diaziridinones, their carbonyl derivatives offer new routes to the preparation of substituted-carbazates and semicarbazides of special medicinal interest.

The diaziridinones which are even more strained, due to the presence of a sp^2 hybridized carbon in the ring, have also been synthesized and isolated. Surprisingly they are reasonably stable compounds, and can be isolated, particularly if the N-atoms bear electron donating substituents. Diaziridinones with one or both the N-atoms bearing electron withdrawing groups have so far evaded isolation. If one of the substituents on the N-atom is carbonyl or carbalkoxy moeity, then rearrangement to 1,3,4-oxadiazolinone is possible as they are isomeric.



II

R′, alkyl or alkoxy; R, alkyl (or aryl)

Such diaziridinones, contrary to the expectation, are not formed via 1,1-diplar addition of a carbonyl- or alkoxycarbonyl-nitrenes to isocyanates. Even if they are formed they perhaps, undergo a fast

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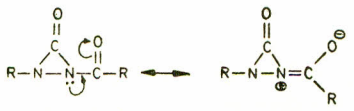
rearrangement to thermodynamically more stable five-membered oxadiazolinone ring.[7,8] Instability of such derivatives may be ascribed to the fact that the charge density in the amide functions is greater on the O-atoms making it more basic then nitrogen.[3,4] Due to this the contribution of the resonance form (Ib) to the resonance hybrid will be quite significant. Consequently it will destabilize the ring, as the quaternary N-atom will further increase the strain of the



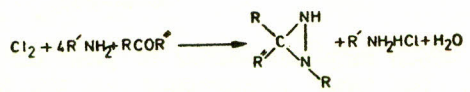
I(a) I(b)

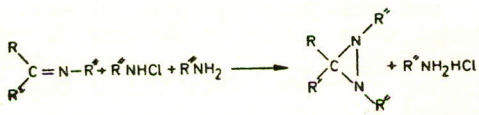
ring and weaken its bond with the carbonyl carbon, since the carbonyl carbon already has a partial positive charge on it, due to the greater electronegativity of oxygen atom. This state of affairs will increase the potential energy of the incipient diaziridinone ring.

Preparation

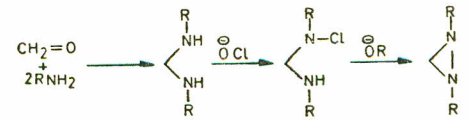
Generally these compounds are obtained[3] by the reaction of NH_3 with a carbonyl compound in the presence of gaseous chlorine. It has since then been developed to evolve a general method of their synthesis on a large scale. Both aldehydes and ketones can be used with equal facility. Excess NH_3 or amine is used to absorb the HCl produced in the reaction. Other HCl traps such as Et_3N etc. have also been used. various modifications have been developed to suit the conditions desired for a particular compound. Thus, chloramine which acts virtually in the same way as a mixture of NH_3 and Cl_2 has also been used. Mono N-substituted derivatives are produced when chloramine is reacted with an aldimine or a ketimine in the presence of the amine from which latter derivatives are derived. One can also use hydroxylamine-*o*-sulphonic acid in place of chloramine. Sulphonoxy derivatives of hydroxylamine have also been used in some cases.[5] Nitrobenzene used to extract the diaziridines gives higher yields than usual techniques.[17]

As a simple corollary to the above stated method alkylchloramines or a mixture of alkylamine and chlorine gives a symmetrically substituted-diaziridine derivative. Different substituents may be put on the N-atoms by using an aldimine or ketimine derived from an amine different from substituent on chloramine, e.g.



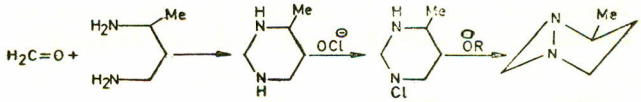


The reaction of formaldehyde and a primary amine leads to a 1,3-diamino derivative which on treatment with hypochlorite ion leads to a mono-N-chloro derivative, which eliminates HCl by reaction with alkoxide, resulting in ring closure to a diaziridine ring.

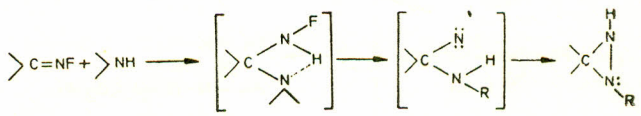


III

The reaction has fairly general application, being successful with primary as well as secondary alkyl groups.[11]



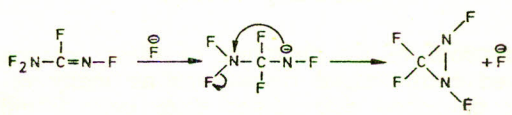
A nitrene is invoked in the formation of a diaziridine[11] by the reaction of a 1°or 2°-amine with N-fluoroimines as shown below.

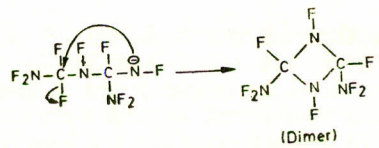


a Nitrene

Side reactions accompany the reaction of N-fluoroimines of α-ketoperfluoronitrile on account of the pseudohalogen character of C≡N. In spite of this, however, the yield of diaziridine is pretty good.

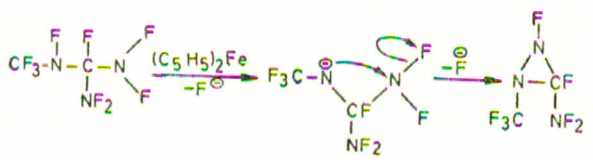
Perfluoroformamidines' conversion to diaziridines[18] is catalyzed by metal fluorides and the diaziridine formation is accompanied by dimerization of the starting material. RbF, KF and CsF are used as catalysts, the latter, however, needs careful handling, since explosions have been reported in some cases. The formation of the dimer is a competitive reaction and one should be able to control its formation by avoiding the presence of excess of amidine in the reaction vessel at any time. This may be achieved by carefully adding small quantities of amidine to the catalyst and continuously removing the diaziridine formed:





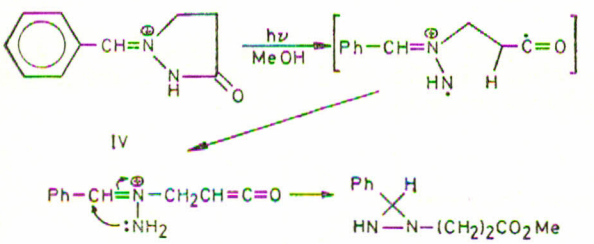
(Dimer)

Dicyclopentadienyliron[19] and dicumenechromium also act as a catalyst at R. T. to effect cyclization of 1,1-bis-(difluoroamino)perfluorazapropane.



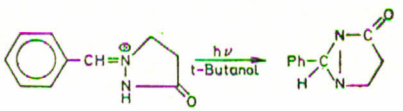
Thus tetrafluoroformamidine, pentafluoroguanidine and tris-(difluoroamino)fluoromethane give 3-membered heterocycles with two nitrogen atoms as the principal isolable products by this method. The product identification is chiefly based on IR and F^{19} NMR spectral data.

Diaziridines may also be prepared[25] by photochemical treatment of betains derived from pyrazolidone and aldehyde. Thus 1-(2-carbomethoxyethyl)-3-phenyl diaziridine is obtained by photolysis in methanol of 1-benzylidene-3-pyrazolidone betain (IV).



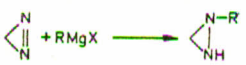
IV

Irradiation of IV in t-butanol gives 6-phenyl-1, 5-diazabicyclo(3.1.0)-hexane-2-one.



IV

Diaziridines have also been obtained by the reaction of Grignard reagent with diazirene.[11] This method is only of academic interest in view of the difficult accessibility of diazirine itself.



R, Ph CH_2—; *t*-butyl

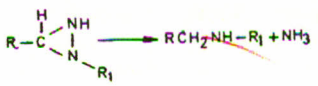
The proof of the structure of these compounds involved controversial discussions as many of the earlier described diaziridines were later found to have a different structure, having an oxadiazolin ring system.

To resolve the controversy Schmitz[12] did some painstaking work and established by his valuable contribution that the nitrogen atoms in the ring of the compounds synthesized by him were completely equivalent. In a bid to confirm the identity of the nitrogen atoms in the ring of N-methyl pentamethylene diaziridine derived from various routes discussed above, he obtained N^{15}-labelled pentamethylene diaziridine. On subsequent degradation it gave a mixture of cyclohexylamine-HCl and ammonium chloride both having N^{15}-label. This indicates the equivalence of 2 N-atoms in the parent ring wherein either N-atom of the diaziridine may be attacked by cyclohexylmagnesium bromide following statistical distribution and giving uniform scrambling of the label.

Reactions and Properties

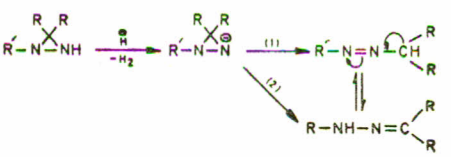
Diaziridines are generally liquids of fairly high consistency. They are fairly stable to heat. On strong heating or shock explosion may occur, therefore, they should be carefully handled. Even under mild acidic conditions on heating they are hydrolyzed, but fairly strong alkalies have no effect, and the ring remains intact.

Oxidation of the acidic KI solution and salt formation with oxalic acid is considered a characteristic feature and diagnostic property of these compounds. The reaction with isocyanic acid esters also falls in the same category, and all these reactions have generally been used in the identification and characterization of these compounds. They themselves undergo oxidation and offer a convenient access to diazirines[15] by the action of oxidizing agents such as Ag_2O, mercuric oxide, alkaline potassium permanganate and acid dichromate solutions. Reducing agents such as $LiAlH_4$ or NaH which are a potential source of nucleophilic anion which generally attack polarized multiple bonds at the more positive atom of the available reaction site, do not attack diaziridines without a free NH. In the presence of the latter, ring opening occurs to give ammonia and an amine. This seems to be a case of simple nucleophilic displacement on the N-atom bearing the

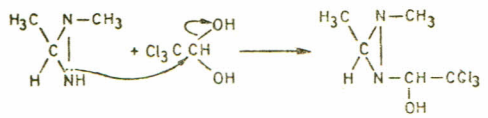


least number of substituents. Attack on the tertiary carbon or N being precluded on steric grounds, simply following the rules of nucleophilic attack. Metal hydrides usually abstract a proton from active-hydrogen compounds such as alcohols or amines. Such H-abstraction reactions which may lead to ring opening as shown below to give azo derivatives have so far not been encountered.

Such ring opening may occur to give the azo compound directly, or a hydrazone may initially be



formed which may tautomerize to yield the azo-product. The latter phenomenon, i.e. the tautomerization of hydrazones to azo compounds is well-known,[13] and takes place rapidly in solution. Free NH group, when present in the ring, is reactive enough to displace groups which have reasonably good leaving character. Thus OH is displaced[21] from chloral hydrate :

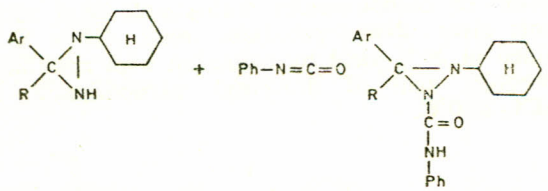


This nucleophilic property is also utilized in the synthesis of 1-(2,4-dinitrophenyl)- and 1-(2,4,6-trinitrophenyl) diaziridine derivatives by displacement of F anion from the aromatic ring of an appropriate fluorobenzene.[20] The nitro groups serve to stablize the negative charge in the incipient transition state of the SN reaction.

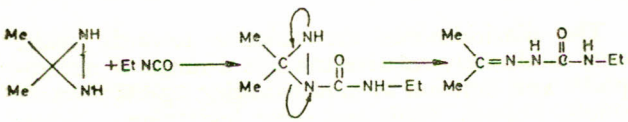
Diaziridines also undergo ring cleavage on polarographic reduction by dropping mercury electrode method in a two-step process[14] to imines and amines respectively.

Addition Reactions

NCO. They undergo a simple addition to isocyanates,[22] which is used to characterize and diagnose the existence of a diaziridine ring. Thus 1-cyclohexyl-3-aryldiaziridine adds to PhNCO :



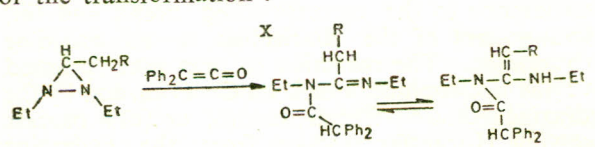
Reactions of 3,3-dimethyldiaziridine with EtNCO goes one step further due to the presence of an



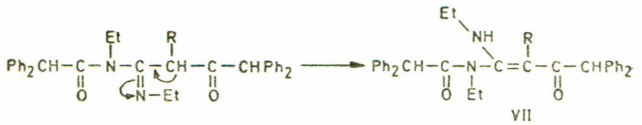
VI

active hydrogen in the adduct, resulting in the ring opening and isomerization to hydrazone.

Ketenes.[23] 1,2,3-Triethyldiazirine and its 1, diethyl-3-methyl analogue undergo addition to diphenylke tene to give an open chain 1:2 adduct (VII). The structure of the product has been proved by its acid hydrolysis to *N*-ethyldiphenylacetamide and 1,1-diphenylbutan-2-one. This reaction is in contrast with the similar reaction of oxaziridines, and displays a different participation of *C*-alkyl group. The formation of the final product involves overall migration of three hydrogen atoms, the one on the ring, and the two from the α-methylene of the *C*-alkyl group. There is no parallel found for this reaction in other 3-membered heterocyclic ring systems, and no mechanism has been proposed. In our opinion following sequence involving an enamine type of intermediate seems a logical explanation for the transformation :

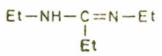


VIII



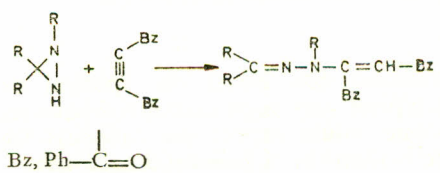
VII

One might also envisage prior ring opening of the diaziridine ring to VIIIa in a sequence leading to the final product.



VIIIa

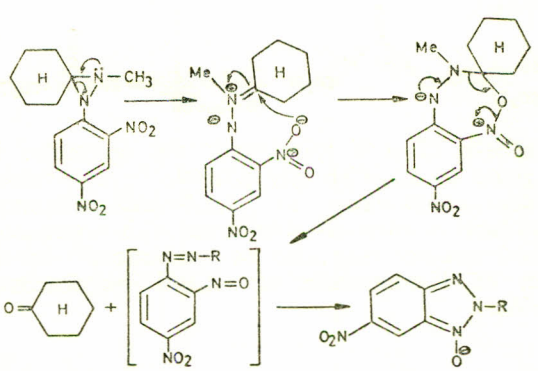
Acetylenes. Diaziridines undergo nucleophilic addition[26] to acetylenes in the following fashion :



Various substituted diaziridinzs and acetylenes may be used in this reaction widening its scope.

Rearrangement

The 1-(2,4-dinitrophenyl) and 1-(2,4,6-trinitro-2, 3-dialkyl) diaziridines, on being refluxed in toluene, rearrange to benzotriazole-1-oxides.[20] An *ortho*-nitrosoazo intermediate IX is proposed for this type of rearrangement, following the analogy of *ortho*-nitroazo compounds, conversion of which on treatment with reducing agents such as sodium bisulphite, sodium sulphide, and hydrazine to benzotriazole-1-oxides is known.[27]

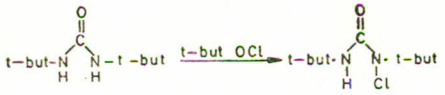


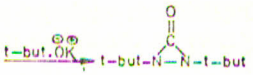
IX

The 3,3-dialkyl derivatives on similar thermal treatment give hydrazones. This departure from the above stated route is probably due to the availability of an active H-atom, making an alternate pathway more feasible.

Diaziridinones. Much attention has been given to aziridinones and diaziridinones since the first synthesis of an α-lactam.[30] Such carbonyl deri-

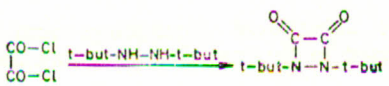
vatives of diaziridines, a new 3-membered ring heterocycle, have since then been synthesized. The first member of this class of compounds was reported by Greene[24] in 1964. He was able to obtain 1,2-di-*t*-butyl diaziridinone (X), by the ring closure of 1-chloro-1,3-di-*t*-butyl urea. The method has since then been found to be generally applicable to such ureas in which the groups are tertiary alkyl. The





X

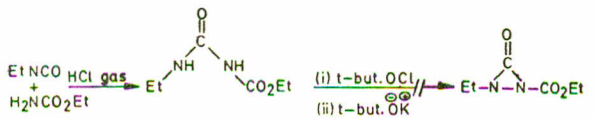
characterization was based on spectral evidence, having a typical very high carbonyl frequency in the IR. As one would expect the carbonyl frequency is higher[35] than in 1,2-diazetidinediones.



C=O, 1813 cm^{-1}

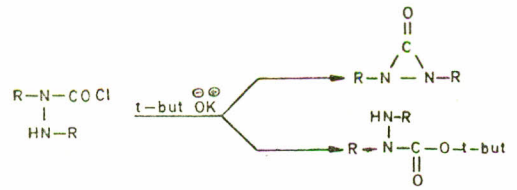
From the spectral data it is also known that the substituents on the N-atoms have *trans* orientation.[16]

A noticeable feature of these compounds is that only compounds with bulky alkyl groups which have electron donating property (hyperconjungation), undergo such type of ring closure. Attempts to make such compounds with electron withdrawing substituents failed to materialize.[28]



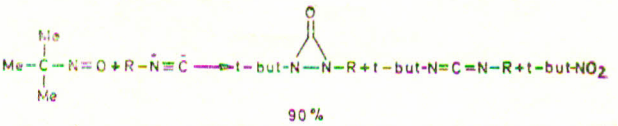
Synthesis of such compounds was attempted by this route to establish any possible interconversion of these compounds to 1,3,4-oxadiazolinones,[8] the adducts of carboalkoxynitrenes with isocyanates.

Diaziridinones may also be synthesized[16] by the action of K-t-butoxide on 2,3-di-t-butylcarbazyl chloride.



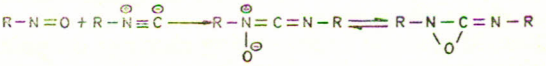
R, t-butyl A substituted carbazate

Thermal condensation of alkylisocyanide with nitrosoalkane (1 : 1 neat) affords diaziridones in good yields.[37] The simplicity of the operation of this reaction is an added advantage, and offers a convenient source to a number of diaziridones with varying substituents.



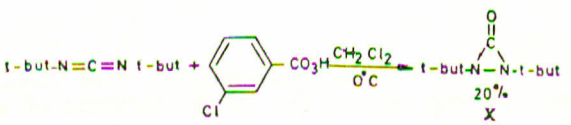
R, t-but., isopropyl, methyl, sec-butyl and cyclohexyl

A carbodiimide N-oxide intermediate is proposed to give the diaziridinone via an oxaziridinimine.



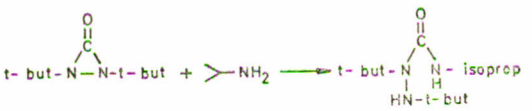
The yields of diaziridinones are dependent on the nature of the alkyl group used in the isocyanide, and follow the pattern tertiary > secondary > primary. Increasing concentration of nitrosoalkane favours the formation of the carbodiimide, while increase in temperature increases the yield of diaziridinones.

They are also obtained[29] by peracid oxidation of a carbodiimide bearing bulky alkyl substituents. Reaction of carbodiimides with simple alkyl substituents gives diacyl peroxides only. Thus X is obtained in 20% yield by oxidation with *m*-chloroperbenzoic acid of di-t-butyl carbodiimide in CH_2Cl_2 at 0°C.



The diaziridinones are reactive towards acids, only moderately reactive towards a range of nucleophiles and function as mild oxidizing agents towards thiols, phenols, enols and some hydrazines. Aqueous HCl effects ring opening and decarboxylation to hydrazines.

With nucleophiles such as t-butoxide, $\overline{O}H$, MeO^- and MeOH ring opening to alkyl carbazates takes place. With isopropylamine ring opening to substituted semicarbazide and with hydrazine ring opening and conversion to carbohydrazide XI is observed.



X XI

The reaction with nucleophiles semicarbazide is slow. With hydrazines, diaziridinones undergo following reactions :

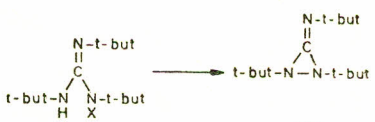
(i) nucleophilic attack at the C=O carbon, (ii) oxidation of the hydrazine and reduction of diaziridinone to the corresponding ureas, and (iii) rearrangement of the diaziridine to an aziridine carboxamide. The reduction to urea may proceed via : (a) nucleophilic attack on C=O carbon by the hydrazine (addition–fragmentation), or (b) a process involving H-transfer reaction from the hydrazine to the diaziridinone.

From the crossover experiments it is found that all azo compound (obtained by oxidation of hydrazine) comes from hydrazo reactant. This evidence goes against the first probability, i.e. addition fragmentation reaction, as virtually no crossover takes place. It is established beyond doubt that the reaction is not thermal by the fact that the diaziridinone is stable in refluxing benzene for a long time. The rate of the reaction and competition between isomerization of diaziridinone and its reduction, is dependent on the substituents on the hydrazine.

The H-transfer necessary for the conversion of diaziridinone to urea may be accomplished via a charge transfer complex between the diaziridinone and hydrazine, or the NH bond of hydrazine may play some role. The evidence is against the first possibility. It seems that initial H-transfer to N involves intramolecular abstraction by oxygen and/or H-tautomerizations prior to ring closure. So far this is the easiest explanation for this transformation. Trivalent P-compounds such as triphenyl phosphine cause deoxygenation of di-t-butyl diaziridinone to carbodiimide in 49% yield. With triethylphosphite $(EtO_3)P$ the yield of carbodiimide is 90% and t-butyl isocyanate is also obtained as one of the products.

Diaziridine Immines.[31,38] Such species have been proposed as intermediate[33] only, in the reaction of carbodiimides with phenyl (bromodichloromethyl) mercury.

Reasonable evidence for the existence of these compounds is, however, found in case of di-t-butyldiaziridine imine (XIV) which has been isolated in 80–85% yield from 2 moles of *N-N′-N″*-tri-t-butyl guanidine (XII), and one mole of t-butyl hypochlorite in CCl_4 or n-pentane.



XIV

X, H; X, Cl

The *N*-chloroguanidine (XIII) is assumed to be an intermediate undergoing an intramolecular SN reaction under the influence of a strong base. The imine is less stable than the corresponding C=O compound. Whereas the latter survives for 2 hr at 175°C, the imine decomposes within 1 hr at 150°C giving 2-2′-azoisobutane and t-butyl isocyanide.

Diaziridine imines are of interest as possible intermediate in the rearrangement of *N*-haloguanidine to semicarbazide derivatives.

References

1. E. Chinoporos, Chem. Rev., **63**, 248 (1963).
2. K. Doerschner, Arch. Pharm., **306**, 35 (1973).
3. Abendroth and Henrich, Angew. Chem., **71**, 283 (1959).
4. Bergwerasverband, Belgian Patent 652,812 Dec. 31, 1964.
5. Y. Zeifmaw, V. Abduganir, E. G. Rokhlin, Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk., 2737 (1972) ; Chem. Abstr., **78**, 97752t.
6. H. W. Wanzlick, Angew. Chem. Intern. Ed. Engl., **1**, 75 (1962).
7. S. M. A. Hai, Pakistan J. Sc. Ind. Res., **15**, 258 (1972).
8. S. M. A. Hai and W. Lwowski, J. Org. Chem., **38**, 2442 (1973).
9. A. A. Dudinskaya, L. I. Khamelnitski, I. D. Petrova, E. B. Baryshnikova and S. S. Nonikov., Tetrahedron, **27**, 4053 (1971).
10. B. L. Dyatkin, K. N. Makanov and I. L. Knunyants, *ibid*, **51** (1971).
11. R. Ohme, E. Schmitz and P. Dolge, Chem. Ber., **99**, 2104 (1966).
12. E. Schmitz, R. Ohme and R. D. Schmidt, *ibid.*, **95**, 2716 (1962).
13. Rod O'connor, J. Org. Chem., **26**, 4375 (1961).
14. Yu. P. Kitaev and G. K. Budnikov, Coll. Czech. Chem. Commun., **30**, 4178 (1965); Chem. Abstr., **64**, 6467g.
15. E. Schmitz, C. Horigunal, C. Grundemann, Chem. Ber., **100**, 2093 (1967).
16. F. D. Greene, J.C. Stowell and W.R. Bergmark, J. Org. Chem., **34**, 2254 (1969).
17. Solvay et Cie, Belg. Patent 715,868,02 (1968).
18. W.C. Firth Jr., J. Org. Chem., **33**, 3489 (1968).
19. R. A. Mitsch, *ibid.*, **33**, 1847 (1968).
20. H. W. Heine, P. G. Williard and T. R. Hoye, *ibid.*, **37**, 2980 (1972).
21. A. A. D. Kaya, A. E. Bova, L. I. Khmelnitski, S. S. Novikov, Izv. Akad. Nauk. SSSR, 1523 (1971) ; Chem. Abstr., **75**, 98473c.
22. A. Nalieya, Y. Tamura, T. Kodema and Y. Iwakura, J. Org. Chem., **38**, 3758 (1973).
23. M. Komatso, Y. Oshiro and T. Agawa, Tetrahedron Letters, 3999 (1972).
24. F. D. Greene and J. C. Stowell, J. Am. Chem. Soc., **86**, 3569 (1964).
25. M. Schulz and G. West, J. Prakt. Chem., **312**, 161 (1970); Chem. Abstr., **73**, 3827t.
26. H. W. Heine, T. R. Hoye, P. G. Williard and R. C. Hoye, J. Org. Chem., **38**, 2984 (1973).
27. R. Grashey, Angew. Chem. Intern. Ed. Engl., **1**, 158 (1962).
28. S. M. A. Hai and W. Lwowski, unpublished results, Yale University, 1965.
29. F. D. Greene, W. R. Bergmark and J. F. Pazos, J. Org. Chem., **35**, 2813 (1970).
30. H. E. Baumgarten, R. L. Zey and U. Krolls, J. Am. Chem. Soc., **83**, 4469 (1961).
31. H. Quast and E. Schmitt, Angew. Chem. Intern. Ed. Engl., **8**, 448 (1969).
32. F. D. Greene, W. R. Bergmark and J. G. Pacifici, J. Org. Chem., **34**, 2263 (1969).

33. D. Seyferth and R. Damrauer, Tetrahedron Letters, 189 (1966).
34. Fraenkel and E. Niemann, Proc. Natl. Acad. Sci., U. S., **44**, 688 (1958).
35. J. C. Stowell, J. Org. Chem., **32**, 2360 (1967).
36. E. Schmitz, *Dreiringe Mit Zwei Heteroatomen, Oxoaziridine, Diaziridine, Cyclische Diazoverbindungen*, Monograph in Organic Chemistry (Springer Verlag, Berlin, 1967), vol. IX.
37. F. D. Greene and Jose F. Pazos, J. Org. Chem., **34**, 2269 (1969).
38. H. Quast, E. Schmitt, Chem. Ber., **103**, 1234 (1970).