Tetrahedron Letters, Vol.27, No.8, pp 901-904, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

CARBENIC REACTIONS OF 4-DIAZO-4*H*-IMIDAZOLE WITH BENZENE DERIVATIVES

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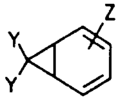
Abstract: The electrophilic behavior of 4H-imidazolylidene is greatly modified by coordinating groups in benzene derivatives undergoing substitution.

Carbenes (Y_2C:) react with benzenes (C_6H_5Z) to give (1) bicyclo[4.1.0]heptadienes (1) which may convert to other bicyclo[4.1.0]heptadienes (1'), cycloheptatrienes (2) and their rearrangement products and (2) substituted benzenes (3) by isomerization of 1 and/or 1' and/or by more direct processes.[1] Addition of carbenes to electron-donating benzenic substituents (I, Br, Cl, OCH_3 and CN) has also been reported to yield ylides (4) and/or products thereof.[1f,j,k] As yet, however, information is limited with respect to the directing effects of substituents, the reactivity patterns and the multiplicity factors in substitution of benzenes by carbenes. We now describe the behavior of benzene derivatives with 4*H*-imidazolylidene (5) generated photolytically and thermally from 4-diazo-4*H*-imidazole (6) prepared by diazotization of 4(5)-aminoimidazole dihydrochloride and neutralization of the resulting imidazole-4(5)-diazonium chloride.[2a] These studies (1) clarify the principles for *addition* of singlet carbenes to benzenes, (2) show that ring-opening of spironorcaradiene intermediates occur by highly-selective *dipolar* processes and (3) reveal remarkable *coordinative* and *ortho* directing influences of certain substituents in carbenic aromatic substitution.



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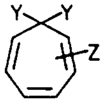

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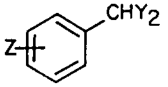

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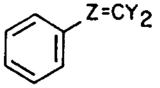

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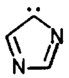

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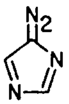

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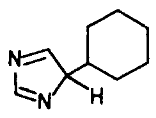
Irradiation (Hanovia 450-watt medium pressure Hg lamp in Pyrex, ~25°C) and thermolysis (78°C) of 6 in cyclohexane and in benzene yield 4(5)-cyclohexylimidazole (8) and 4(5)-phenylimidazole (9), respectively.[2b] Apparently 8 is formed by insertion of 5 into a C-H bond of cyclohexane to form 7 which then isomerizes. The photolytic and thermolytic molar reactivities of 5 with benzene compared to cyclohexane are 3.8:1.0 and 3.0:1.0, respectively. Also, 1,3,5-trimethylbenzene is substituted by 5 to give only 4(5)-(2,4,6-trimethylphenyl)imidazole (10). There is no isotope effect ($k_H/k_D = 1.00$) in competitive capture of 6 produced photolytically in mixtures of benzene and benzene-d_6. Thus 5 is an electrophilic carbene which attacks the *pi*-electrons in (1) benzene in preference to the C-H bonds in benzene or in cyclohexane and (2) 1,3,5-trimethylbenzene rather than C-H in its methyl groups. Triplet ESR signals are not observed for 5 upon irradiation of 6 in methanol, ethyl ether, chloroform or carbon tetrachloride at 78°K.[2c] These latter experiments, though not definitive, strongly indicate that 5 is a ground state singlet carbene and not a triplet which reacts with the matrices too rapidly for ESR detection.[2d,e]



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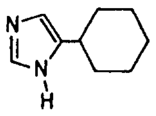

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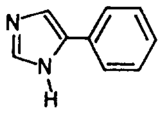

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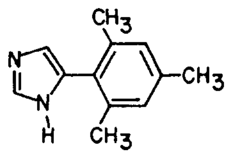

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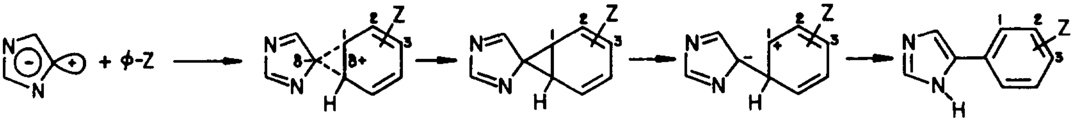
Photolyses and thermolyses of **6** (9.5×10^{-5} - 2.4×10^{-3}M) were then effected in substituted benzenes and in mixtures of benzene and individual monosubstituted benzenes to give 4(5)-*o*,*m* and *p*-(substituted-phenyl)imidazoles (**16a-c**, Table 1). Anisole and *t*-butylbenzene undergo major *ortho* (57-67%), minor *para* (20-29%) and no detectable *meta* substitution by **5**. Reactions of chlorobenzene result in *para* (71-80%) and *ortho* (1-11%) substitution. *Meta* (84-88%) along with 12-16% *ortho* attack occurs however with *α,α,α*-trifluorotoluene. In substitution of the above benzenes **5** is a highly selective *ortho* and *para* or a *meta* reactant. The competitive reactivities of the benzenes: anisole > *t*-butylbenzene > benzene > *α,α,α*-trifluorotoluene show that **5** is electron-demanding. The differences in the reactivities of the benzenes are small however and thus kinetically **5** is quite an indiscriminate electrophile.

Table 1. Percentage Compositions of the 4(5)-*o*,*m* and *p*-(Substituted-phenyl)imidazoles (**16a-c**) from Photolyses and Thermolyses of **6** in Substituted Benzenes; Relative Photolytic and Thermal Molar Reactivities of the Indicated Substituted Benzene Compared to Benzene.

16a-c	hν,%			Δ;%			Rel. React.[a]	Rel. React.
	o	*m*	*p*	*o*	*m*	*p*	hν	Δ
OCH_3[b]	57	-	28	67[d]	-	20	4.6	1.9
$C(CH_3)_3$[c]	61	-	29	61[d]	-	27	1.5	1.1
Cl[b]	>1	-	80	11[d]	-	71	-	-
H	-	-	-	-	-	-	1.0	1.0
CF_3	16	84	-	12[d]	88	-	0.6	0.4
CN	49	51	-	45[e]	55	-	0.2	0.4
NO_2	61	27	11	68[e]	32	-	0.7	0.8

[a] Determined from photolyses or thermolyses of **6** in dilute solutions of equimolar substituted benzenes and benzene. [b] Products other than **16a-c** were identified in these experiments. [c] A third product (10%) assigned by ^{1}H NMR as 4(5)-(2-methyl-2-phenylpropyl)imidazole was detected by gc. [d] Conducted at 100°C. [e] Effected at reflux temperature.

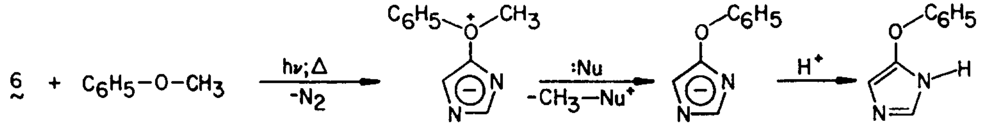
The reactivity behavior and the highly directed electrophilic substitution patterns in the above experiments are interpretable (Eq 1) by (1) low activation energy, rate-determining exothermic additions of singlet **5** in its p^2 state (**11**)[2d] to benzenes (**12**) via transition states **13a-c** which resemble the reactants and thus have minor dipolar character, (2) formation of isomeric imidazolospironorcaradienes **14a-c**, (3) relatively rapid conversion of **14a-c** to dipolar intermediates **15a-c** in which substituent effects control ring-opening and (4) hydrogen rearrangement to yield isomeric 4(5)-(substituted-phenyl)imidazoles (**16a-c**).[2f] For **5** to effect *ortho* substitution of anisole and *t*-butylbenzene, the controlling factors to **13a** and/or **13b** are electronic rather than steric[2g] and intermediates of type **14a** and/or **14b**[2g] have to be



11 12 13a; Z at C-1 14a 15a 16a
b; Z at C-2 b b b
c; Z at C-3 c c c

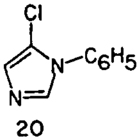
major. Norcaradienes 14b and/or possibly 14c however would predominate in the reactions of 5 with α,α,α-trifluorotoluene to give the observed high-order *meta*-substitution.

Substituents having non-bonded electron pairs on atoms attached to phenyl groups also react with 5. Thus, along with its photolytic and thermal conversions to 16a and 16c ($Z = OCH_3$), anisole is cleaved to 4(5)-phenoxyimidazole (19; 14 and 13%). Formation of 19 clearly illustrates attack on oxygen of anisole, presumably via ylide 17. Although the fate of the methyl group in 17 is unknown, production of 19 is explained by (1) methylation of nucleophiles such as 6, anisole and/or 16a and 16c ($Z = OCH_3$) and then protonation of 18 (Eq 2).



17 18 19 (2)

A further aspect of the behavior of benzenes having substituents with non-bonded electron pairs is revealed in the reactions of 6 with chlorobenzene to yield 5-chloro-1-phenylimidazole (20, >3%) and 4(5)-chloroimidazole (21, 15%) along with 4(5)-(*o*- and p-chlorophenyl)-imidazoles (16; Z_1 and Z_3 = Cl).[2h] Products 20 and 21 imply addition of 5 to chlorobenzene to give ylide 22 which (1) isomerizes to 20[2j] and (2) collapses homolytically with chlorine transfer, to give 23 and phenyl radicals. Subsequent hydrogen abstraction by 23 yields 21.



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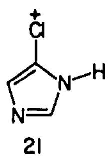

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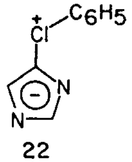

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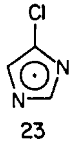

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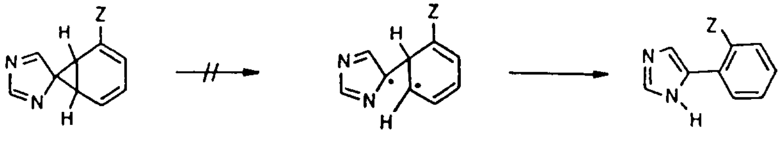
Of greatest present interest is that in the reactions of 6 with benzonitrile (bp 188°C) and nitrobenzene (bp 210°C), either photolytically or at reflux, (1) the cyano and the nitro groups are powerfully *ortho* directing, (2) *meta* substitutions far outweigh that at the *para* positions and (3) the reactivities of the highly electronegatively-substituted benzenes are less than for benzene (Table 1). Even more spectacular is that the distributions in *ortho*, *meta* and *para* substitutions of benzonitrile (52% yield) and nitrobenzene (72% yield) at 100°C are 97:2:0.3 and 92:8:0, respectively. It is thus noted that, if the mechanism of reaction of 5 with α,α,α-trifluorotoluene (Eq 1) is the same as that with benzonitrile and nitrobenzene, spironorcaradienes 24 (Z = CN and NO_2) would be *major* intermediates.[2j] For 26 (Z = CN and NO_2) to be formed however as the principal products from 24, the rearrangement reactions would



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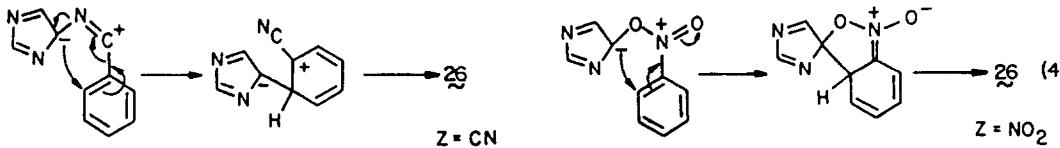

27 28 29 30 (4)

have to occur by highly-specific diradical processes (Eq 3).[2j] Because such mechanism changes seem unlikely, it is proposed that the enhanced ortho substitution reactions of benzonitrile and nitrobenzene arise from coordination of 5 (or 6 with collapse to 5 or modifications thereof) with the cyano and the nitro groups and reorganization perhaps as illustrated in Eq 4. Whatever be the details of such processes, complexation of electrophilic carbenes or their diazo precursors with electron-donor substituents is important in aromatic substitution.

Acknowledgment: This research was supported by the National Institutes of Health.

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2. (a) Extraction (CH_2Cl_2), drying (Na_2SO_4) and vacuum removal of solvent gives 6, a sensitive product, to which various solvents were added. (b) All new products have proper analyses and spectral (IR, ^1H NMR and MS) properties. (c) We thank Dr. M. Platz for his help in these experiments. (d) Calculations by T. J. Amick indicate that azolylidenes with nitrogen in the 2-position are stabilized as singlets. (e) At 78°K cyclopentadienylidene is a long-lived triplet ("for hours") in hexachlorobutadiene; E. Wasserman, L. Barash, A. M. Trozzolo, R. W. Murray and W. A. Slager, J. Am. Chem. Soc., 86, 2304 (1964). (f) Argument against rate-controlling addition of triplet and/or diradical singlet 5 to benzenes (Table 1) is that the distributions of the isomeric products, the relative reactivities and the partial rate factors do not correlate with those for substitution of the benzenes by phenyl, substituted phenyl and other free radicals. See D. I. Davies, D. H. Hey and B. Summers, J. Chem. Soc. C, 2681 (1971) and D. H. Hey, Adv. Free Radical Chem., 2, 47 (1967). (g) Because of their spiro structures 13a-b and 14a-b are not highly encumbered by Z. Also 14a-c may be formed as (E) and (Z) isomers. (h) Further products are as yet unassigned. (i) Formally, isomerization of 22 to 20 is a Stevens-like rearrangement; A. R. Lepley and A. G. Giumanini, Mech. Mol. Migr., 3, 297 (1971). (j) Homolytic phenylation of α,α,α-trifluorotoluene results in 20% ortho, 40% meta and 40% para substitution and with a relative reactivity compared to benzene of 0.99:1 (F_o = 0.59; F_m = 1.2; F_p = 2.4); C. S. Rondestvedt, Jr. and H. S. Blanchard, J. Org. Chem., 21, 229 (1956).

(Received in USA 24 June 1986)