Tetrahedron Letters No. 49, pp 4697 - 4700. 0040-4039/79/1201-4697$02.00/0

SUBSTITUENT EFFECTS IN REACTIONS OF BENZENES WITH 5-TERT-BUTYL-3H-PYRAZOLYLIDENE

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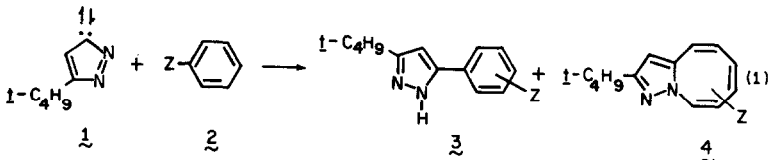
Summary: The effects of substituents on the conversions of benzenes by 5-tert-butyl-3H-pyrazolylidene to (substituted phenyl)pyrazoles and pyrazolo[1,5-a]azocines are described.

5-Tert-butyl-3H-pyrazolylidene (1), as derived from thermolysis of 3-tert-butyl-5-diazopyrazole,[1a] effects substitution and ring-expansion (Eq 1) of benzene (2c) to 3(5)-tert-butyl-5(3)-phenylpyrazole (3c, 85-90%) and 2-tert-butylpyrazolo[1,5-a]azocine (4c, 5-10%; a new heterocyclic system), respectively.[1b,c] We now report the effects of substituents on the types of reactions and the kinetic reactivities of 1 with various benzenes (2). It has been found that (1) electron-donors in 2 facilitate formation of (substituted phenyl)pyrazoles (3) whereas electron-withdrawing groups enhance ring-expansion to pyrazolo[1,5-a]azocines (4) and (2) 1 is an unusually unselective electrophile in its overall reactivities with 2, but o, m, and p-substitution of 2 by 1 is highly sensitive to substituent effects. These results provide significant insight into the mechanisms and the synthetic utility of substitution and ring-expansion reactions of 2 and 1 and portend that substituent effects will be important to the development of new ring-expansion reactions of 2 by various carbenes.

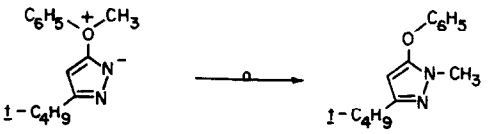


1 2 3 4

Z		Rel Reac.[2]	Yield (%)	o: m: p Ratio	Yield (%)
OCH_3	2a	(1.21)	3a (90)	1.3:0.0:1.0	4a (trace)
CH_3	b		b (92)	2.1:0.0:1.0	b (trace)
H	c	(1.00)	c (85-90)		c (5-10)
Cl	d	(0.72)	d (85)	1.9:0.0:1.0	d (9)
CN	e	(0.49)	e (84)	4.1:1.6:1.0	e (16)
NO_2	f		f (42)	tr:2.5:1.0	f (40)

Decompositions of 3-tert-butyl-5-diazopyrazole were effected in 2 at 65°C. Pyrazoles 3 were quantitatively methylated with methyl fluorosulfonate to 1-methyl-5-(substituted phenyl)-pyrazoles which were analyzed, separated (GC), and identified from their exact masses, IR and ^1H NMR spectra, and relative GC retention times. Pyrazoloazocines 4 were assigned from their mass and UV spectra, the absence of IR and ^1H NMR absorptions for N-H, and proper ^1H NMR absorbances for azacyclooctatriene and pyrazolo protons. The positions of the substituents in

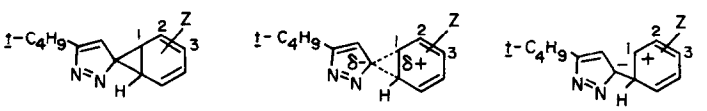
the azocine moieties of 4 cannot yet be designated (X-ray study of 4e and 4f will be initiated). The relative reactivities of 2 were determined upon generation of 1 (1 equiv) in mixtures (200 equiv) of 2c and a substituted benzene (2), methylation of the pyrazoles (3), and molar comparison of the 3-tert-butyl-1-methyl-5-phenylpyrazole with the total 3-tert-butyl-1-methyl-5-(substituted phenyl)pyrazoles formed. Anisole (2a), along with o- and p-substitution, undergoes O-methyl cleavage to give 3-tert-butyl-1-methyl-5-phenoxypyrazole (6)



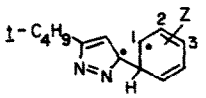
5 6 (2)

Pyrazolylidene 1 behaves as an energetic singlet electrophile. Thus electron donation by substituents accelerate substitution of 2 by 1 in the order OCH_3 > H > Cl > CN, the usual behavior of benzenes with cationic reactants.[3] The electrophilicity of 1 is also revealed by O-CH_3 cleavage of 2a to give 6. Further, 1 does not abstract hydrogen from 2a, 2b, cyclohexane,[1] or ethyl ether[1] as is expected for a triplet. Although the differences in the overall reactivities of 1 with 2 are small, there is great selectivity in the ability of a group to direct the positions of substitution into 2. When the substituents are hyperconjugative or resonance electron-donors such as CH_3, OCH_3, and Cl, only o-(68, 55, and 66%, respectively) and p-(32, 43, and 34%, respectively) (substituted phenyl)pyrazoles (3) are formed. With CN, a strong electron-withdrawing group, m-substitution (24%)[4] occurs along with o-(61%) and p-(15%)-substitution. The NO_2 group directs m-(71%) and p-(29%) to give 3f (40%); of further importance is that 2f also undergoes major ring expansion to form pyrazoloazocine 4f (40%).

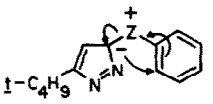
The electrophilic reactivity insensitivity but yet positional discrimination in substitutions of 2 are rationalizable on the basis of (1) rate controlling, exothermic additions of 1 to 2 to give isomeric spiropyrazolonorcaradienes (7a-c) via transition states (8a-c) having limited dipolar character[5] and (2) rapid collapse of 7a-c to dipolar (9a-c)[5] or diradical (10a-c) intermediates by processes expressing significant substituent effects and then hydrogen migration to give the isomers of 3. Additional processes involving coordination of 1 with



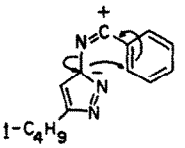
7a; Z at C-1 8a 9a; Z at C-1
b; Z at C-2 b b; Z at C-2
c; Z at C-3 c c; Z at C-3



10 a ; Z at C-1
b ; Z at C-2
c ; Z at C-3



11 a ; Z = OCH_3
b ; Z = Cl



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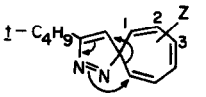
an electron pair in a substituent in 2 and directed nucleophilic attack as in 11a,b and 12 may be operational.

Dipolar ring rupture of 7a-c (Z = OCH_3, CH_3, and Cl) to 9a and 9c (not 9b) in which the vacant benzenium orbital effectively conjugates with the electron-donor substituent allows the observed selectivity in substitution of 2a,b and d and the absence of m-products. Thus such 7a and 7b will give 9a and then (o-substituted phenyl)pyrazoles; likewise, 7c converts to 9c and thence (p-substituted phenyl)pyrazoles. On the basis that there is no real selectivity in formation of 7a-c from 2b (Z = CH_3) and 2d (Z = Cl) and an expected steric effect of the methoxy group in 2a (Z = OCH_3) in generation of 7a, the o:p substitution ratios of 2a, b and d are understandable. As an effect compensating usual steric hindrance, ortho attack on 2a (Z = OCH_3) and 2d (Z = Cl) may be ehhanced by ylidic coordination as in 11a-b leading to 9a (or 7a).

Of interest then is that 2e (Z = CN) substitutes m- more extensively than p- but by far the dominant process is o-substitution.[6] Formation of 3e (m-CN) over 3e (p-CN) may be rationalized on the basis of electronic control in dipolar collapse of 7c (Z = CN) to 9b rather than 9c and of 7b (Z = CN) to 9b over 9a.[7] To give 3e (o-CN) as the principal product, however, by such processes, 7a (Z = CN) must be the major intermediate or else there are o-directing processes to 9a (Z = CN) based on coordination as in 12. As a mechanistic alternative, cyanonorcaradienes 7a-c (Z = CN) may collapse to diradicals 10a-c from which hydrogen migrations yield 3e. Although homolysis of 7c (Z = CN) will favor 10c over 10b because of advantageous radical stabilization by CN, formation of 3e (m-CN) may be greater than 3d (p-CN) because 7b (Z = CN) gives 10b along with 10a. Hydrogen rearrangement in 10a as derived from 7a (Z = CN major) and from 7b (Z = CN) will yield 3e (o-CN).

A result of particular present note is that electron-withdrawing substituents increase the conversions of 2 to 4 whereas electron-donating groups augment formation of 3.[8] For 4 to be formed, 7a-c apparently isomerize to spiropyrazolocycloheptatrienes 13 which rearrange (1,5-sigmatropic) by attack on the cycloheptatriene moiety by nitrogen of the pyrazole nucleus. Electron-withdrawing groups (Z) will retard heterolytic collapse of 7 to 9. Electron-attracting substituents may also enhance ring-opening of 7 to 13 and/or facilitate rearrangement of 13 in which the pyrazolyl system is the electron-donor. For more complete definition of the relationships between 7a-c and 13, location of the substituents and determination of the isomeric distributions of 4 are necessary.



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Further study of reactions of carbenes with substituted benzenes is in progress. Major attention is to be given to synthesis of new heterocyclic analogs of 4 by reactions of 2 with various heterocyclic carbenes.

Acknowledgement. This research was supported by the National Institutes of Health CA 11185 and the State of Ohio.

References and Notes

1. (a) Prepared by diazotization of 3(5)-amino-5(3)-tert-butylpyrazole in fluoboric acid and neutralization with sodium carbonate. (b) W. L. Magee, Ph.D. dissertation, The Ohio State University, Columbus, Ohio, 1974. (c) W. L. Magee and H. Shechter, J. Am. Chem. Soc., 99, 633 (1977).
2. The relative reactivities for 2d and 2e are corrected for the differences in their substitutable hydrogens (5) as compared with that of 2c (6).
3. (a) C. K. Ingold and M. S. Smith, J. Chem. Soc., 905 (1938). (b) M. L. Bird and C. K. Ingold, ibid., 918 (1938).
4. Possibly low because of formation of 4e.
5. M. J. S. Dewar and K. Narayanaswami, J. Am. Chem. Soc., 86, 2422 (1964) interpret the carbenic substitution reactions of various benzenes with benzene-1,4-diazooxides to involve spironorcaradienes which isomerize by dipolar processes.
6. Benzonitrile undergoes o-(45%) and p-(38.5%) rather than m-(16.5%) substitution by 3,5-dichloro-4-ketocyclohexadienylidene.[5] Although the mechanisms of these processes were not discussed,[5] it may be that the intermediate spironorcaradienes cleave homolytically and/or else the CN group enhances o-substitution by coordination.
7. The mechanisms of reactions of 1 and 2f will be clearer upon establishing the structure of 4f.
8. It has recently been observed by Dr. S. Kakodkar of this laboratory that 3-diazo-5-phenylpyrazole thermolyzes in benzene to give 3,5-diphenylpyrazole ($C_{15}H_{12}N_2$) along with an unidentified product, $C_{30}H_{24}N_4$. The structure of the dimeric product is under investigation.

(Received in USA 2 March 1979)