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SELECTIVE FREE-RADICAL PHENYLATIONS: NITROGEN-HETEROAROMATIC COMPOUNDS IN ACIDIC MEDIA

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R. D. Brown (1) has shown that molecular-orbital calculations of localization energies satisfactorily reproduce the observed partial rate factors for substitution of pyridine by phenyl radicals. Similar calculations for the pyridinium ion (2) suggest greatly enhanced reactivity at the 2-position as compared with pyridine, but no direct evidence is available.

Indirect support for the suggested reactivity of pyridinium ion is supplied by our recent report (3) that high proportions (greater than 85 % of the phenylation products) of 2-phenylpyridine are obtained from thermal decomposition of benzenediazonium tetrafluoroborate in concentrated solution in pyridine. We attributed the unusual orientation to phenyl-radical attack on the species $C_5H_5\overset{+}{N}$-N:N-Ph, which we regarded as analogous to pyridinium ion.

The present communication summarizes the preliminary results of a study of the free-radical phenylations of several nitrogen-heteroaromatic compounds in acetic acid, where proton transfer to give ion-pairs will be

complete except for very weak bases (cf. (4)).

The various heteroaromatic compounds (0.07 mole) in acetic acid (0.25 mole) at 118° were allowed to react with the phenyl radicals provided by added benzoyl peroxide (0.004 mole). The proportions of isomeric phenylation products formed were determined by gas-liquid chromatographic analysis of the reaction mixtures, after removal of acetic and benzoic acids. Table 1 reproduces a selection of the results, together with those of control phenylations carried out at 118° using an excess of the appropriate heteroaromatic compound as solvent. The control results agree well with previous work (pyridine (5), 1-methyldiazoles (6), and thiazole (7)).

TABLE 1

Phenylations in Acetic Acid

Substrate	Isomeric Phenylation Products (%)	
	In Acetic Acid	In Excess of Heteroaromatic
Pyridine	2-: 79-82 3- + 4-: 18-21	2: 61-63 3- + 4-: 37-39
1-Methyl-imidazole	2-: 100	2-: 60 5-: 40
1-Methyl-pyrazole	5-: 60 3-: 40	5-: 95 3- + 4-: 5
Thiazole	2-: 84 4- + 5-: 16	2-: 49 4- + 5-: 51

With each of these compounds, the proportion of substitution at positions adjacent to the pyridine-type nitrogen increases markedly in acetic acid. The changes in orientation are accompanied by changes in total reactivity,

demonstrated by competition experiments with nitrobenzene. Equimolar mixtures of nitrobenzene and heteroaromatic compound (0.07 mole) in acetic acid (0.25 mole) at 118° were phenylated using benzoyl peroxide. Table 2 summarizes the results, together with those of control phenylations performed in the absence of acetic acid. The proportions of the isomeric nitrobiphenyls in the reaction mixtures were 57 ± 2% 2-, 43 ± 2% (3- + 4-)-isomers (typical of free-radical phenylation), and were not affected by the presence of acetic acid. Again, the results from the control experiments are in good agreement with previous work.

TABLE 2

Competition between Heteroaromatics (A) and Nitrobenzene (B)

(A)	Reactivity in Phenylation (benzene = 1, nitrobenzene = 2.94)	
	(A) + (B) + acetic acid	(A) + (B) only
Pyridine	1.61	0.97
1-Methylpyrazole	1.41	0.57
Thiazole	1.53	0.53

It is apparent that the partial rate factors at positions adjacent to pyridine-type nitrogens are increased in acetic acid, in excellent qualitative agreement with Brown's molecular-orbital calculations for pyridinium ion. The calculations exaggerate the effect of protonation, since the localization energy of -2.28β at the 2-position of the pyridinium ion would suggest a partial rate factor of *ca.* 100 (1) (the observed value is 4); it seems likely that the

accompanying acetate counter-ion decreases the pi-electron polarization considerably (for evidence supporting this suggestion, see ref. (8)).

The results cited seem general for nitrogen-heteroaromatic compounds, since we find similar effects of protonation on orientation and/or reactivity in the phenylations of benzothiazole, isoquinoline, 1-methylbenzimidazole, pyrazine, pyrimidine, quinoline, and quinoxaline.

Further, although the stoichiometry of the reactions in acetic acid has not been explored fully, the yields of phenylation products are comparable to those found when a simple excess of heteroaromatic compound is used as reaction medium. Thus, phenylations of pyridine in acetic acid by benzoyl peroxide afford 0.36-0.40 mole of phenylation products per mole of peroxide, as compared with 0.58 mole per mole for similar phenylation of the free base (9), while phenylations of thiazole in acetic acid afford 0.30-0.35 mole of phenylation products per mole of peroxide, as compared with 0.08 mole per mole for phenylation of the free base (7). It is evident that the acetic acid competes rather ineffectively for the liberated phenyl radicals (cf. 10, 11).

In view of their high positional selectivity, the reactions in acetic acid offer simple one-step routes to specific phenyl-substituted heteroaromatic compounds, and promise to be of synthetic value.

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