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A NEW SELECTIVE TYPE OF AROMATIC SUBSTITUTION: HOMOLYTIC AMIDATION

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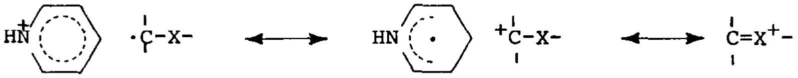
The prevalent nucleophilic character of the alkyl radicals[1] readily permits the homolytic alkylation of protonated heteroaromatic bases[2], due to the contribution of polar forms in the transition state:

The oxygen atom of ethers and alcohols as well as the nitrogen of amides and amines, attached to the carbon radical, increase the final nucleophilic character of reactive species through their contribution to the stabilization of the cation R^+ and make still easier the homolytic alkylation:



X = O or NR

Likewise, the acyl radicals show a clear nucleophilic character due to the stability of the corresponding acyl ions, and permit the selective acylation of protonated heteroaromatic systems[3].

We now wish to report a new selective type of homolytic aromatic substitution, in which the reacting radical is the carbamoyl $\cdot CONH_2$ radical, formed by hydrogen abstraction from formamide by the action of hydroxy or alkoxy radicals. A quite different reaction, chain free radical addition of formamide to olefins through carbamoyl radical, has already been reported[4].

The synthetic interest in heteroaromatic series is clearly illustrated by the following example: to a solution of 13 g (0.1 mole) of quinoxaline and 5.5 ml (0.1 mole) of concentrated sulphuric acid in 100 ml of formamide, 15 ml (0.15 mole) of 34% hydrogen peroxide and 41.7 g of finely powdered ferrous sulphate ($FeSO_4 \cdot 7H_2O$) (0.15 mole) were separately and simultaneously added, during 15 minutes with efficient stirring and cooling. Temperature 10-15°. The excess formamide was distilled off and the residue was extracted with chloroform. On evaporating off the solvent, 14.2 g (82%) of 2-quinoxalyl carboxamide were obtained, m.p. 200°, which was characterized by comparison with an authentic sample.

On making alkaline the residue, left after the chloroform extraction, 2 g of quinoxaline were recovered. The yield based on the total quinoxaline converted in the reaction was 97%.

This reaction is very general for the heteroaromatic bases. The following compounds have been so far successfully experimented with using this new reaction (in parenthesis the positions of attack are shown): pyridine (2, 4), 4-ethylpyridine (2), isonicotinamide (2), quinoline (2, 4), 4-methylquinoline (2), isoquinoline (1), 2-methylquinoline (4), pyrazine (2), benzothiazole (2), benzimidazole (2). Yields higher than 80%, based on converted heteroaromatic base, were obtained in all cases.

Analogous results were obtained using, in place of redox system, the homolytic decomposition of di-t-butyl-peroxide.

A competitive reaction between quinoline and naphthalene in homogeneous medium, using the t-butyl-hydroperoxide as a component of the redox system, resulted in the amidation of the quinoline only.

On the basis of the reactivity and orientation, also the carbamoyl $\cdot CONH_2$ radical therefore shows clear nucleophilic character. From this point of view, the protonation of the heteroaromatic base plays a very important role in determining the high reactivity towards the nucleophilic radical. This permits in a speedy new way, and with high selectivity, the formation of useful compounds such as the amides of heteroaromatic bases.

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