**Tetrahedron Letters No. 40, pp 4113 - 4116, 1972. Pergamon Press. Printed in Great Britain.**

# HOMOLYTIC AROMATIC SUBSTITUTION:
# A SIMPLE ROUTE TO THE ALDEHYDES OF HETEROAROMATIC BASES

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**(Received in UK 24 August 1972; accepted for publication 4 September 1972)**

In spite of Taylor's and Martin's opinion, who very recently relegated the homolytic heteroaromatic substitution in the "plethora" of "severely limited in scope methods" for the direct introduction of functional groups in heterocyclic systems,[1] we believe that synthetic and theoretical aspects of this type of reaction may be instead a very new and interesting chapter of the chemistry of heterocyclic compounds.

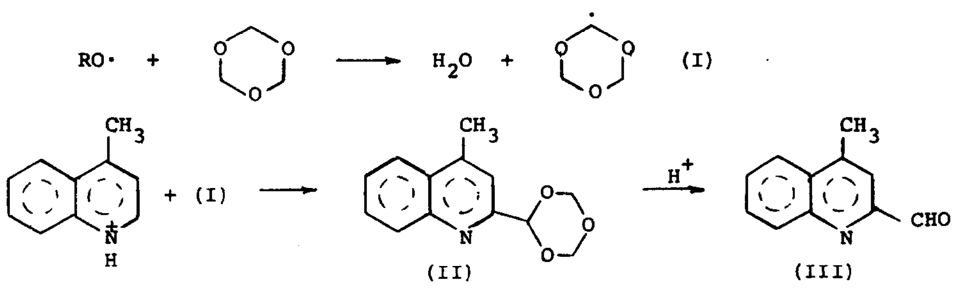
In fact, alkylation,[2] acylation,[3] amidation[4] and α-amidoalkylation,[5] α-oxyalkylation by alcohols and ethers[6] have been recently carried out by us, under very mild conditions and high yields, by direct introduction of corresponding free C-radicals in protonated heteroaromatic bases.

The complete selectivity in α- and γ-positions with respect to the heteroatom was discussed before,[2] as the nature of the transition state[2] and the rearomatization of the unstable reaction-intermediate.[7]

We were not able to realize the direct introduction of formyl group by our usual techniques, successfully employed for several other substituents, including acyl groups. The present paper reports a simple two-steps route to the aldehydes of heteroaromatic bases: the first step is the introduction of the trioxanyl radical in the aromatic substrates, with subsequent hydrolysis of the cyclic acetalic to the formyl group. (Scheme I).

SCHEME I

$$Fe^{++} + ROOH \longrightarrow Fe^{+++} + OH^{-} + RO\cdot \quad (R = H, t\text{-but})$$



Standard operating conditions are clearly illustrated by the following example: 30% hydrogen peroxide and a saturated solution of $FeSO_4 \cdot 7H_2O$ (0·03 mole each) were separately and simultaneously added with efficient stirring and cooling to a solution of 4-methyl-quinoline (0·02 mole) and trioxane (0·1 mole) in 3% aqueous sulfuric acid (0·03 mole). Temperature 5°. The pH was subsequently adjusted to 5-6 with a saturated $Na_2CO_3$ solution and the reaction mixture was exaustively extracted with ether or chloroform. After evaporation under vacuum of the organic solvent and the excess trioxane, the oily residue was chromatographed ($SiO_2$ column, eluent hexane/ethyl acetate 5:1) yielding unchanged 4-methyl-quinoline (48%) and 2-trioxanyl-4-methyl-quinoline (II, 32%), m.p. 100°(ligroine). The structure was assigned by spectroscopic techniques; ir: C-O-C stretching at 1180 $cm^{-1}$; nmr: ppm (δ) 2·7, s, 3H, $CH_3$; 5·4, s, 4H, 2 $-OCH_2O-$; 6·1, s, 1H, $ArC\underline{H}-O-$; 7·5-8·3, m, 5H, aromatic protons. Mass spectrum: $M^+$ at $m/e$ 231; other peaks at $m/e$ 171, 157, 143, 115, 89. (Found: C, 67·60; H, 5·48; N, 6·19. $C_{13}H_{13}NO_3$ requires C, 67·52; H, 5·67; N, 6·19%).

By refluxing in 2N hydrochloric acid for 60-90 minutes, (II) gave the corresponding aldehyde (III) in 93% yield. M.p. 77° (ligroine). Ir: strong band at 1700 $cm^{-1}$ for the C=O group; nmr: 2·75 ppm, s, 3H, $CH_3$; 7·6-8·4, m, 5H, aromatic protons; 9·55, s, 1H, $C\underline{H}O$. Mass spectrum: $M^+$ at $m/e$ 171; other peaks at 143, 128, 115, 89. (Found: C, 77·19; H, 5·45; N, 8·05. $C_{11}H_9NO$ requires C, 77·17; H, 5·30; N, 8·18%).

In Table I results obtained with various substrates are reported. The reaction may be carried out in one step only, by adding excess sulfuric acid to the reaction mixture after the end of addition of peroxide, and heating at 100° for 1-2 hours. The overall yield of aldehyde was practically unchanged (28%).

TABLE I

| SUBSTRATUM | PRODUCT | M.p. | Yield % | ALDEHYDE | | |
|---|---|---|---|---|---|---|
| | | | | M.p. °C | Yield[†] | Yield[††] |
| 2-Me-quinoline | 4-trioxanyl-2--Me-quinoline | 162 | 24 | 84-85 | 92 | 21 |
| 4-Me-quinoline | 2-trioxanyl-4--Me-quinoline | 100 | 32 | 77 | 93 | 28 |
| Benzothiazole | 2-trioxanyl-benzothiazole | 143-44 | 26 | 75-76 | 88 | 22 |
| Quinoxaline | 2-trioxanyl-quinoxaline | 143-45 | 18 | 110 | 95 | 17 |

[†] By the hydrolysis of pure trioxanyl-derivatives.

[††] Overall yields, without the isolation of the trioxanyl-derivatives.

From Table I it appears that yields are not satisfactory in the homolytic step of the reaction, although the yields calculated on the converted substratum were generally about 80%. We think, however, that this method may be synthetically interesting for the following reasons: (*i*) the formyl group allows further various syntheses and give a good stability to the heterocyclic molecule and a better resistence to oxidation than corresponding $CH_2OH$ group, another starting-point for pharmaceutical syntheses; (*ii*) actually, general methods to obtain formyl--derivatives of heteroaromatic bases are not known, except the oxidation of preexisting methyl group with selenium dioxide: this method requires however the availability of suitable methyl-derivatives and cannot be utilized, for instance, to obtain methyl-formyl-derivatives such as compound (III).

In Table II yields of trioxanyl-derivatives obtained by varying experimental conditions are reported. We believe that an oxidation process of the trioxanyl radical to the corresponding carbenium ion may be the main competitive reaction to the homolytic substitution. An attempt to generate trioxanyl radicals by photochemical methods[8] gave no useful results.

TABLE II

| RUN | SUBSTRATUM (1 mole) | REDOX SYSTEM | | | | Yields % |
|---|---|---|---|---|---|---|
| | | Peroxide | (mole) | Metal ion | (mole) | |
| 1 | Benzothiazole | $H_2O_2$ | (1·0) | Fe$^{++}$ | (1·0) | 10 |
| 2 | " | " | (1·2) | " | (1·2) | 18 |
| 3 | " | " | (1·5) | " | (1·5) | 26 |
| 4 | " | " | (2·0) | " | (2·0) | 20 |
| 5 | 2-Me-quinoline | " | (1·1) | " | (1·1) | 18 |
| 6 | " | " | (1·5) | " | (1·5) | 24 |
| 7 | " | " | (2·0) | " | (2·0) | 20 |
| 8 | " | " | (3·0) | " | (3·0) | 17 |
| 9 | " | " | (1·5) | " | trace | 3 |
| 10 | " | " | (1·5) | " | (0·2) | 12 |
| 11 | " | " | (1·5) | " | (0·6) | 19 |
| 12 | " | " | (1·5) | " | (1·0) | 21 |
| 13 | " | t-butOOH | (1·5) | " | (1·5) | 18 |
| 14 | " | $H_2O_2$ | (1·5) | Ti$^{+++}$ | (1·5) | 10 |
| 15 | " | $S_2O_8^{--}$ | (1·5) | Ag$^{+}$ | trace | 8 |

Note: Temperature was always kept at 5° except for the run 15 (75°).

*Acknowledgments.* The author is indebted to C.N.R. for its financial support and to Professor F. Minisci for his interest.

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[8] Hanovia 1 liter Photochemical Reactor, equipped with U.V.S. 500 medium pressure lamp.