**Tetrahedron Letters No. 20, pp 1731 - 1732, 1976. Pergamon Press. Printed in Great Britain.**

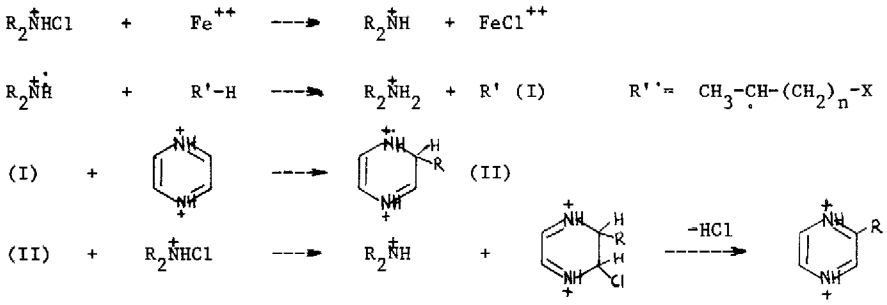
# A NEW GENERAL METHOD FOR SELECTIVE HOMOLYTIC ALKYLATION OF HETEROAROMATIC BASES

T. Caronna, A. Citterio★, T. Crolla and F Minisci

Istituto di Chimica del Politecnico, Piazza L. da Vinci 32, 20133 Milano ITALY

**(Received in UK 22 March 1976; accepted for publication 5 April 1976)**

In recent years two general free-radical processes have shown great synthetic potentialities. i) The selective ω-1 halogenation(1) by protonated N-haloamines of alkyl derivatives, $CH_3-(CH_2)_nX$ where **X** is an electron-withdrawing group halogen, OH, OCOR, OR, COOR, CN, $\overset{+}{N}R_3$ etc., (n= 3-9). ii) The selective substitution of protonated heteroaromatic bases by nucleophilic carbon centered free-radical(2). We now report a new general method for alkylation of heteroaromatic bases which arises by the combination of the two above mentioned processes. It is based on the fact that the reaction rates(3) of the alkyl radicals with many protonated heteroaromatic bases are very high ($K \geqslant 10^5 M^{-1} sec.^{-1}$). We suggest that the chain mechanism of the Scheme is responsible for the very clean substitution reaction on the heteroaromatic bases·



SCHEME

The oxidation of the radical adduct II by $Fe^{+++}$ is considered less important in conc $H_2SO_4$, owing to the very low solubility of the ferric salt in the reaction mixture. However the reaction also takes place with lower conversion in the absence of the iron salt, by thermal initiation.

The Table shows same results including also those with cycloexane for which there is no problem of selectivity. Dimethyl, diisopropyl, diisobuthyl-N-chloroamines were successfully used. By using dimethyl-N-chloroamine; in addition to the main substitution products due to the ω-1 radi-

TABLE

| Heteroaromatic base | Alkyl radical I X | n | N-chloroamine | Isomers(%) | Base converted | Yield(%)* |
|---|---|---|---|---|---|---|
| Quinoxaline(conc. $H_2SO_4$) | $OCH_3$ | 4 | diisobuthyl | 2(31), 6(69) | 50 | 98 |
| Quinoxaline " | COOMe | 3 | " | 2(36), 6(64) | 65 | 94 |
| Quinoxaline " | COOH | 3 | " | 2(35), 6(65) | 42 | 97 |
| Quinoxaline " | Cl | 4 | " | 2(42), 6(58) | 40 | 90 |
| Quinoxaline " | $NH_2$ | 3 | dimethyl | 2(33), 6(67) | 55 | 90 |
| Quinoline (50% $H_2SO_4$) | $OCH_3$ | 4 | diisobuthyl | 2(48), 4(52) | 15 | 98 |
| Pyrazine (conc $H_2SO_4$) | $NH_2$ | 4 | diisopropyl | 2(100) | 40 | 85 |
| Quinoxaline(conc $H_2SO_4$) | cycloexyl | | dimethyl | 2(45), 6(55) | 40 | 100 |
| Quinoxaline( 50% $H_2SO_4$) | " | | " | 2(98), 6(2) | 35 | 100 |
| Pyrazine (conc. $H_2SO_4$) | " | | " | 2(100) | 45 | 100 |
| 4-4'Bipyridile " | " | | " | 2(95), 2,2'(5) | 50 | 95 |

* based on converted base

cal, indicated in the Table, small amounts(< 10%) of products due to the isomer radicals $CH_2\text{-}(CH_2)_{2n+}$ and $CH_3\text{-}CH_2\text{-}\underset{\cdot}{C}H\text{-}(CH_2)_{n-1}X$ are also formed(4), with diisopropyl and diisobuthyl-N-chloroamine these isomers are less than 2% The heavier amines are more easily recovered and recycled making the following synthesis pratically effective

$$R'\text{-}H \quad + \quad ArH_2^{+} \quad + \quad Cl_2 \quad \dashrightarrow \quad R'\text{-}ArH^{+} \quad + \quad 2\ HCl$$

Quinoxaline in conc $H_2SO_4$ gives rise to the substitution products in position 2 and 6 while only the position 2 is attacked in 50% $H_2SO_4$, confirming the results obtained in δ-aminoalkylation and explained on the ground of mono and diprotonation of the base(5) Preliminary results indicate a yet larger variety of alkylating agent and heteroaromatic base can be used, making the method extremely versatile

## REFERENCES

1) F.Minisci, Synthesis 1(1973), N.C.Deno "Methods in Free-Radical Chemistry"Ed. Huyser 143(1972)
2) F Minisci and O Porta "Advances in Heterocyclic Chemistry" vol. 16, p 123(1974).
F Minisci "Topics in Current Chemistry" vol. 62 in the press.
3) Unpublished results of this laboratory.
4) R Bernardi, R.Galli and F.Minisci, J. Chem. Soc. B, 324(1968).
5) A.Citterio, M.Ghirardini and F Minisci, Tetrahedron Letters 3, 203(1976)