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HOMOLYTIC δ-AMINOALKYLATION OF PROTONATED QUINOXALINE BY N-CHLOROAMINE

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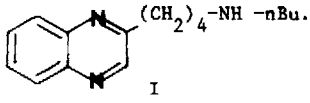
Protonated N-chloroamines are readily available sources of aminium radical-cations ($R_2NH^{\cdot+}$) which are very versatile reacting species: in fact they react in different ways with alkanes, alkenes, alkynes and aromatics, involving potentially many types of organic compounds and showing in all cases an exceptional sensitivity to polar effects[1]. One of the oldest reactions of protonated N-chloroalkylamines of wide synthetic interest is the Hofmann-Löffler-Freytag rearrangement[2], a free radical chain characterized by propagation steps of eqs. 1 and 2:

$$\underset{(a)}{R\text{-}\overset{+}{N}H\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_3^{\cdot}} \longrightarrow \underset{(b)}{R\text{-}\overset{+}{N}H_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2^{\cdot}} \qquad -1$$

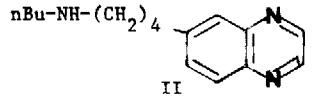
$$(b) + R\text{-}\overset{+}{N}HCl\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_3 \longrightarrow R\text{-}\overset{+}{N}H_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2Cl + (a) \qquad -2$$

We now report a new example of homolytic aromatic substitution based on the H.L.F. rearrangement of N-chloroalkylamines catalyzed by ferrous ions. When a solution of N-chlorodi-n-butyl-amine in conc. sulfuric acid is added to a mixture of ferrous sulfate and quinoxaline in 50% sulfuric acid at room temperature, the compound 2-(4-n-butylamino-butyl)quinoxaline (I) is obtained as the only product of the attack on quinoxaline ring. The yield based on quinoxaline is almost quantitative, while that based on N-chloroamine is 60%. When also the mixture of quinoxaline and ferrous salt is in conc. sulfuric acid, the same reaction gives rise to two isomers : I (60%) and 6-(4-n-butylamino-butyl)quinoxaline (II) (40%) in high yield based on

both reagents (70%). The compound I and II were separated by column chromatography and identified

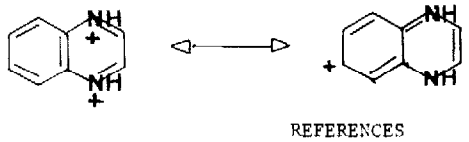


I



II

by analytical and spectroscopical data (IR, NMR, MS spectra). Moreover, preliminary results indicate that the reaction is of general application with N-chloroalkylamines carrying a hydrogen atom on δ carbon of the alkyl chain and with several heteroaromatic bases (phenazine, diazines, quinoline). The reaction has synthetic interest owing to the easy availability of the radical source, the simple experimental conditions, the good yields, the high selectivity and the lack of any alternative one-step synthetic route to the same products. The alkyl radical (b) has a clear-cut nucleophilic character in spite of the presence of a protonated amino group in δ position. The aromatic attack of the radical (b) successfully competes with the very fast process of chlorine atom transfer[3] (eq. 2). In conc. sulfuric acid the position 6 of the quinoxaline is as reactive as the position 2. Since the orientation in the substitution of protonated heteroaromatic bases by nucleophilic radicals is mainly determined by polar factors[4,5], we explain this quite unusual behavior by protonation of quinoxaline III and by a large contribution of the resonance forme IV with the highest charge separation.

(III)  (IV) etc.

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