INVESTIGATION OF THE ALKYLLATION OF NITROAZOLES WITH α-HALOKETONES BY 13C, 15N, and 14N NMR

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General methods have been worked out for the alkylation of nitroazoles with bromoacetone, bromoacetophenone, and diazoacetone in homogeneous media and by phase-transfer catalysis. The structures of the N-acetonylazoles were established by 13C, 15N, and 14N high-resolution NMR spectroscopy.

Nitroazoles with a carbonyl function in the substituents provide convenient synthons for the synthesis of polycyclic compounds having biological activity [1-3]. These structures are most simply obtained by alkylating nitro-NH-azoles with α-haloketones.

Such reactions have previously been examined in only a few cases [4-6], and there have been no literature reports of the use of high-resolution NMR spectroscopy (especially 15N) which is essential for the correct assignment of the positions of the substituents in the heterocycle.

Most of the N-acetonylazoles obtained were prepared by alkylating the anions of the appropriate azoles with bromoacetone in aqueous acetone. As will be seen from Table 1, the reaction is undergone by azoles which differ wisely in the basicity of the anions, their NH-acidity values ranging over some ten orders of magnitude. The conditions required for the reaction to proceed depend on the pKₐ value of the heterocycle (scheme 1, Table 1).

*Deceased.


Azoles with pKₐ values of 3-6 (tetrazole, 5-methyltetrazole, 3-nitro-1,2,4-triazole, 4-nitro-1,2,3-triazole, 4,5- and 2,4-dinitroimidazole) are alkylated by bromoacetone in high yield in a homogeneous acetone-water medium over 24 h at 20°C. With the more basic 4-nitroimidazole and 4-nitropyrazole anions (pKₐ = 9.3 and 9.7), the reaction proceeds with evolution of heat, and is complete within a few hours.

In the case of the highly basic imidazole and pyrazole anions (pKₐ = 14.5 and 14.2), which decompose α-halocarbonyl compounds, the required ketones can only be obtained by quaternization via hydrobromides (1) and (7) followed by treatment with base:

\[
\begin{align*}
\text{HN} & \quad \text{N} + \quad \text{BrCH₂COCH₃} \quad \text{HN} \quad \text{N} \quad \text{BrCH₂COCH₃} \\
\text{Br} & \quad \text{Br} \\
(1) & \quad (7)
\end{align*}
\]

The weakly nucleophilic anions of fully nitrated and bicyclic azoles (nitrotetrazole, dinitro-1,2,4- and 1,2,3-triazoles, bicyclic nitro-1,2,4- and 1,2,3-triazoles, and bitetrazolyl) are alkylated in acceptable yields only at 60-70°C.

This method, however, fails even in strongly polar solvents (DMF and DMSO) to give ketones derived from 2,4,5-trinitroimidazole and bis(4,5-dinitroimidazol-2-yl), since in the final structures (5) and (6) the nitro groups are extremely readily replaced by the nucleophilic reagents present in the reaction mixture (Br⁻ and H₂O).

In such cases, alkylation requires the use of diazoacetone. As a result of the high NH-acidity of the nitroazoles, the diazoacetone is readily protonated, and reacts rapidly with the heterocyclic anion:

\[
\begin{align*}
\text{N} & \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \\
\text{O₂N} & \quad \text{O₂N} \quad \text{O₂N} \quad \text{O₂N} \\
(5) & \quad \text{O₂N} \quad \text{O₂N} \quad \text{O₂N} \\
\end{align*}
\]

Efficient methods for the alkylation of weakly nucleophilic nitroazoles by α-bromo-ketones involving phase-transfer catalysis have been developed by us (for the use of phase-transfer catalysis for the alkylation of azoles, see [8]). The phase transfer catalyst used