IMIDAZOLE AND BENZIMIDAZOLE N-OXIDES (REVIEW)

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Information on the synthesis, properties, and chemical transformations of imidazole N-oxides that are aromatic in nature is correlated.

N-Oxides of five-membered aromatic nitrogen heterocycles — pyrazole, imidazole, 1,2,3- and 1,2,4-triazole, and tetrazole — have been investigated to a considerably lesser extent than N-oxides of azines. Furazan N-oxides (furoxans), exhaustive information regarding which has been presented in a two-volume monograph [1], constitute an exception. Individual problems in the chemistry of azole N-oxides have been dealt with in monographs by Ochiai [2] and Katritzky [3].

Reviews devoted to N-oxides of pyrazole [4] and 1,2,3-triazole [5] have been published only recently. A brief review on the chemistry of imidazole and benzimidazole N-oxides was published in 1970 [6], while a monograph by Volodarskii and coworkers, in which research on imidazoline N-oxides and imidazoline nitroxyl radicals was correlated, was published in 1988 [7]; problems in the chemistry of aromatic imidazole N-oxides are dealt with in passing.

In the present review we present information on the chemistry of imidazole and benzimidazole N-oxides that are aromatic in nature.

1. METHODS FOR OBTAINING IMIDAZOLE N-OXIDES

1.1. Oxidation of Imidazoles

In contrast to azine N-oxides, for which oxidation by peracids is the standard method of preparation [2, 3], the use of this method for azoles is very limited. The literature contains only individual examples of obtaining imidazole N-oxides (or the tautomeric N-hydroxyimidazoles) by oxidation. The preparation of 2,2'-diimidazolyl N,N'-dioxide (I) by oxidation of 2,2'-diimidazolyl with dilute hydrogen peroxide in an acidic medium was described in [8].

\[
\text{H}_2\text{O}_2 \rightarrow \text{H}_2\text{SO}_4
\]

However, the compound obtained does not give the reactions that are characteristic for N-oxides, which makes one doubt the correctness of structure I. In a later report [9] it is pointed out that the method in [8] is not reproducible. A patent report regarding the production of 1-hydroxyimidazole (II) in 2.5% yield in the oxidation of imidazole with perphthalic acid was recently published [10].
The available data on the production of imidazole N-oxides by direct oxidation are restricted to the indicated examples.

1.2. Cyclization of Derivatives of $\alpha$-Dicarbonyl Compounds

A general method for the synthesis of imidazoles III, which contain an N-oxide (N-hydroxy) group, is the cyclization of $\alpha$-hydroxyimino ketones with aldehydes and amines [6, 11-22]:

$$\begin{align*}
\text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{N}O + \text{R}^1'\text{CHO} + \text{R}^1\text{NH}_2 & \rightarrow \text{III} \\
\text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{N} + \text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{O} + \text{H}_2\text{O} & \rightarrow \text{IV}
\end{align*}$$

where 

$\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4 = \text{H, alkyl, aryl, } \alpha\text{-furyl, functional alkyl; }$

$\text{R}^1\text{R}^2 = \text{H, alkyl, aryl, acetyl, hydroximinomethyl, carbalkoxy}$

$\text{R}^3\text{R}^4 = \text{cycloalkyl, cycloalkenyl}$

When formaldehyde is used as the aldehyde component, the resulting 2-unsubstituted imidazole N-oxides III ($\text{R}^2 = \text{H}$) are unstable and undergo rapid rearrangement to 2-imidazolones IV, frequently during the cyclization process [21]:

$$\begin{align*}
\text{R}^1\text{R}^2\text{R}^3\text{R}^4\text{N}O + \text{HCOH} + \text{R}^1\text{NH}_2 & \rightarrow \text{IV}
\end{align*}$$

This rearrangement can be avoided by subjecting previously prepared azomethine derivatives (or hexahydrotriazines) to the reaction with $\alpha$-hydroxyimino ketones [18, 20]. A similar effect is achieved if a carboxy group is present in the alkyl(aryl)amino component [22].

The mechanism of the cyclization has not been investigated in detail. It is assumed [6, 15, 17] that the determining step in the synthesis is the $\alpha$-aminoalkylation of the hydroxyimino ketones with subsequent cyclization of $\text{C-(}\alpha\text{-acylalkyl)-N-(}\alpha\text{-aminoalkyl)}$ nitrones V to imidazoline N-oxides and dehydration of the latter to give imidazole N-oxides: