NUCLEOPHILIC SUBSTITUTION
OF HYDROGEN ATOMS IN THE
PYRIDAZINE SERIES*. (REVIEW)

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Information has been generalized on the nucleophilic substitution of hydrogen in monocyclic and condensed pyridazines, pyridazine N-oxides, and pyridazinium cations.

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The investigation of nucleophilic aromatic substitution has more than a century of history. Traditionally most attention has been paid to substitution of facile leaving groups, such as Hal, SO$_3$R, NO$_2$, etc. Reactions of this type ($S_N^{ipso}$) are in many cases the main method of functionalizing a heterocycle [1]. Nucleophilic substitution of hydrogen ($S_N^H$) is less widespread, primarily in view of the known instability of the hydride ion, which is formally a leaving group in these conversions. Meanwhile the $S_N^H$ methodology in principle enables simplification of the synthesis of many heterocyclic compounds, releasing them from the need first to introduce a nucleophile into the hetero ring.

The first examples of $S_N^H$ reactions, the amination and hydroxylation of heterocycles with sodium amide and solid anhydrous alkali respectively, were described by Chichibabin at the beginning of the twentieth century. They subsequently proved to have a large influence on the development of the chemistry of pyridine and other azines (see reviews [2-4]). However the need to use heterogeneous and extremely rigid conditions limited significantly the scope of the classical Chichibabin reaction. The most important achievement in this area remained the homogeneous oxidative amination of azines in the system KNH$_2$–NH$_3$–KMnO$_4$ proposed about 20 years ago by H. van der Plas (reviews [5, 6]). The use of potassium permanganate as an acceptor of hydride ion permitted working under exceptionally mild conditions and made possible the amination of substrates containing labile groups or simply groups unstable under the usual Chichibabin reaction conditions. It is curious that precisely this approach linked with the use of an external oxidizing agent in $S_N^H$-amination reactions was developed by Bergstrom [7, 8] in the thirties of the twentieth century, but the inorganic nitrates proposed by him as oxidizing agents were not very convenient.

In difference to other azines little attention has been paid to the investigation of nucleophilic substitution of hydrogen in pyridazines for a long time. The first communication on pyridazines is dated 1886 [9], the chemistry of this class of compounds began to be developed intensively in the seventies of the twentieth century. Interest in pyridazines was restricted probably due to the circumstance that their aromatic derivatives are not found in nature. The discovery of biological activity in a series of pyridazine derivatives stimulated the vigorous growth of investigations in this area (for a review of the pharmacology of pyridazines see [10, 11]). The

* Dedicated to Professor E. Ya. Lukevics on the occasion of his 65th birthday.
chemistry of pyridazine and its derivatives has been reviewed [12-20]. Some of the conversions discovered in recent years (such as the tandem SNH reaction), as it turned out, have no analogy in the azine series. In this case it seemed of interest to correlate all the existing information on reactions of the SNH type in monocyclic and condensed pyridazines.

In the present review conversions of neutral pyridazines and of activated systems based on them (pyridazine N-oxides and pyridazinium cations) are considered in order. Furthermore in the paper it emerged that certain SNH reactions proceed by a different mechanism, with the participation of not only anionic but also radical particles. Studies where only products of nucleophilic addition were isolated, but not of SNH substitution, are also cited, since the corresponding adducts, in principle, may readily be subjected to aromatization.

1. NUCLEOPHILIC SUBSTITUTION OF HYDROGEN ATOMS IN NEUTRAL PYRIDAZINES

In the pyridazine molecule each carbon atom is a subject to the action of two opposing forces, viz. the electron-withdrawing effect of the nitrogen atom in the ortho or para position conjugated with it and the weak electron-donating effect (due to the reorganization of the π-cloud) of the meta nitrogen atom. A characteristic feature of the π-electron distribution in pyridazine is the presence of a moderate positive π-charge on all the ring carbon atoms [21].

A characteristic of the disposition of the heteroatoms in the pyridazine molecule is that intermediates formed by the addition of nucleophiles to any of the carbon atoms are always stabilized by resonance. The energies of nucleophilic localization for C(4) and C(3) σ-complexes are comparable (2.35 and 2.36 β respectively). However in the majority of cases the C(4) atom in the pyridazine molecule undergoes nucleophilic attack.

1.1. Interaction with N-Nucleophiles

1.1.1. Oxidative amination. Pyridazine (1) undergoes oxidative amination on treatment with potassium amide in liquid ammonia in the presence of KMnO4 forming the 4-amino derivative 2 in 92% yield [22]. The reaction proceeds by the classical AdE mechanism. The intermediate dihydro adduct 3 was identified by low temperature NMR [23]. In the absence of potassium amide, i.e. under the action of ammonia itself, the reaction does not proceed, although in the case of other more π-deficient azines such reaction is possible.

\[
\begin{align*}
\text{N} & \quad \text{N} & \\
\text{H} & \quad \text{H} & \\
\text{H} & \quad \text{H} & \\
\text{N} & \quad \text{N} & \\
\text{N} & \quad \text{N} & \\
\end{align*}
\]

A mixture of 4-, 5-, and 6-amino derivatives is formed from 3-phenylpyridazine under analogous conditions in yields of 49, 18, and 5% respectively [22].