Synthesis of Pyridine Derivatives by Reactions of α,β-Unsaturated Nitriles with 2-Oxo-cycloalkano Carbothioic Acid Anilides

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Summary. The tandem Michael addition-cyclization of 2-oxo-cycloalkane carbothioic acid anilides 1 – 3 to benzylidenemalononitrile 4 yielded spiroannulated pyridines 5 – 7. Reaction of acrylonitrile with 2 and 3 gave 2,2-disubstituted Michael adducts 14, 15, whereas with 1 led to 2,2,5-tri(2-cyanoethyl)cyclopentanone 11.

Keywords. 2-Oxo-cycloalkano carbothioic acid anilides; 3-Pyridine-spiro-2'-cycloalkanone; α,β- Unsaturated nitriles.

Introduction

The synthesis and chemistry of polyfunctionalized pyridines have attracted considerable attention of many laboratories as they were found to be valuable precursors in the approach to a wide branch of natural products [1, 2] and due to their biological activity [3].

We have previously published [4, 5] the synthesis of enammonitriles of fused cycloalkenopyridines, which involved the reaction of enamines of cyclic β-keto acid anilides with malononitrile. Another highly efficient synthetic route to polyfunctionalized pyridines [6], which has been developed by us, consists in tandem Michael addition cyclization of benzoylthioacetanilides to aryldienemalononitriles or ethyl 2-cyanocinnamates.

In this study the reactions of 2-oxo-cycloalkano carbothioic acid anilides containing five-(1), six-(2) and seven-(3) membered rings with benzylidenemalononitrile 4 and acrylonitrile 10 are reported.
Results and Discussion

The reaction of the appropriate thioanilides 1–3 with benzylidenemalononitrile 4, carried out in the boiling acetonitrile solution in the presence of piperidine as a catalyst, gave yellow coloured products 5–7 in moderate to good yields (Table 1, Scheme 1).

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\begin{align*}
\text{1-3} & \quad \text{4} \\
\rightarrow & \quad \text{A} \\
\rightarrow & \quad \text{5-7 (a-e)} \\
1.5 & \quad n=0 \\
2.6 & \quad n=1 \\
3.7 & \quad n=2
\end{align*}
\]

According to the reference reports [7, 8] as well as our experiences [6] the Michael addition of 1–3 to 4 is assumed to be the first step of these reactions. There are three acidic centers in each molecule of 1–3, which are able to participate in an addition to 4. The strongest acidity reveals the hydrogen atom attached to C-1, due to the influence of the neighboring carbonyl and thiocarbamyl groups. Thus the Michael addition of 1–3 to 4 leads to formation of adducts A as the intermediates (Scheme 1). The further ring closure of these intermediates is dependent on the presence of a compatible functionality at the proper position within the molecules and on the reaction condition. In the investigated reactions the intermediate adducts A were not isolated, since after their formation, they immediately underwent intramolecular cyclization resulting in compounds 5–7.

In order to confirm the assumption that the intermediate Michael adducts were formed exclusively by nucleophilic attack of carboanion at C-1 of thioanilides 1–3 on 4, we carried out the analogous reaction of 4 with 1-oxo-indano-2-carbothioic acid anilide 8 [9]. Compound 8 contains only one acidic hydrogen atom at carbon C-2. The reaction of 4 with 8 performed under the same conditions gave yellow coloured product 9 (Scheme 2). Its IR spectrum was similar to those of compounds 5–7 (Table 1). It displayed a strong stretching absorption at 1706 cm\(^{-1}\) (CO), 2186 cm\(^{-1}\) (CN), and three bands at 3320–3480 cm\(^{-1}\) (NH\(_2\)). The most valuable for structure elucidation was the \(^1\)H-NMR spectrum of 9. It revealed the multiplet of 14 aromatic protons at \(\delta = 7.2–7.7\) ppm, two singlets at \(\delta = 4.4\) ppm and \(\delta = 3.8\) ppm of two protons of NH\(_2\), and one proton at C-4 of the pyridine ring.