Synthesis of new functionalized thieno[2,3-*b*]pyridines

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Abstract

3-Aminothieno[2,3-b]pyridine-2-carboxamides react with chloroacetyl chloride to afford 3-(chloroacetylamino)thieno[2,3-b]pyridine-2-carboxamides. The latter upon treatment with sodium azide gave 3-(azidoacetylamino)thieno[2,3-b]pyridine-2-carboxamides. The reaction of 3-(chloroacetylamino)thieno[2,3-b]pyridine-2-carboxamides with sulfur and amines afforded new monothiooxamides.

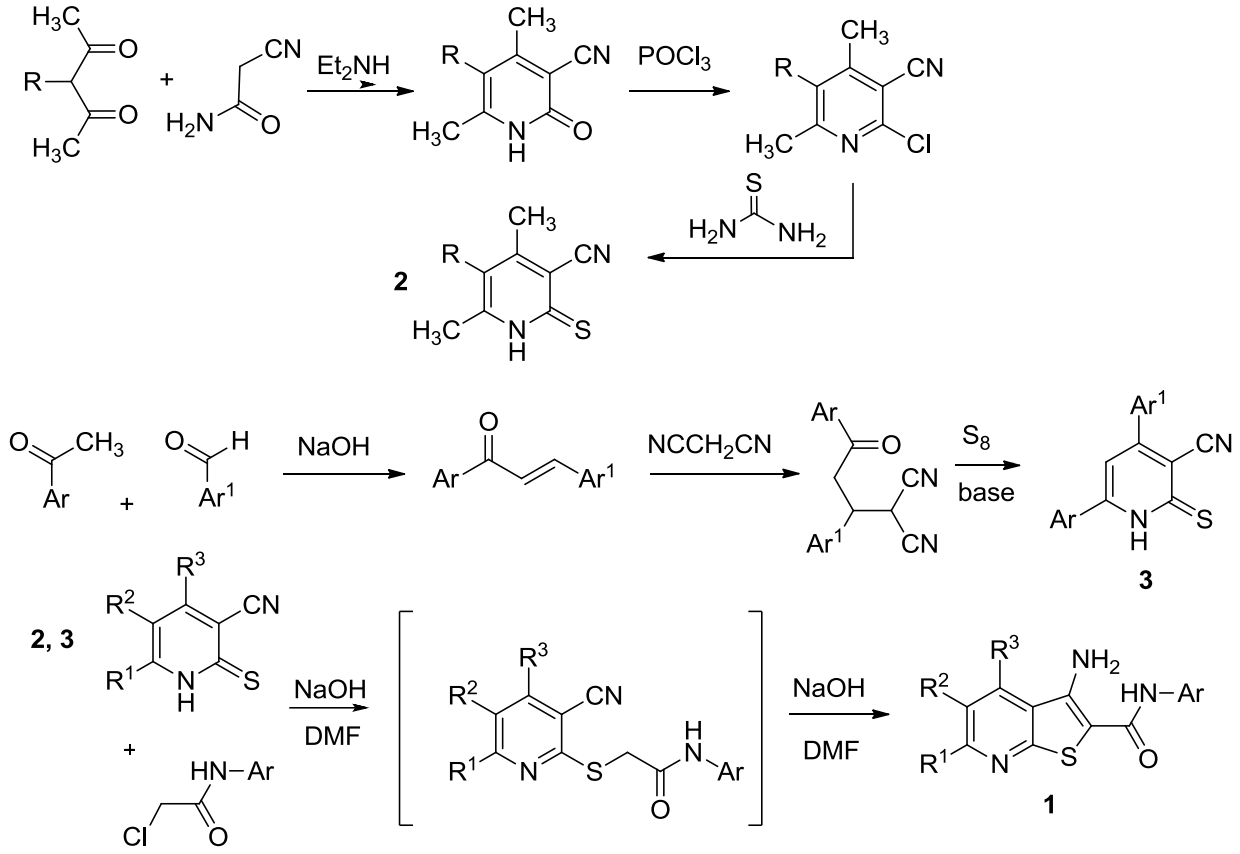
Keywords
thieno[2,3-b]pyridines, acylation, azides, monothiooxamides

Thienopyridines are important compounds because of their broad range of biological and pharmacological effects. Thieno[2,3-d]pyridines, for example, have been evaluated pharmacologically and used as potent and selective phosphodiesterase IV inhibitors, antipsychotics and anxiolytics, antiarrhythmics, antitumor agents, antibiotics, anti-inflammatory agents. Thus, the synthesis of thieno[2,3-b]pyridines as well as their ring condensed analogs is of interest.

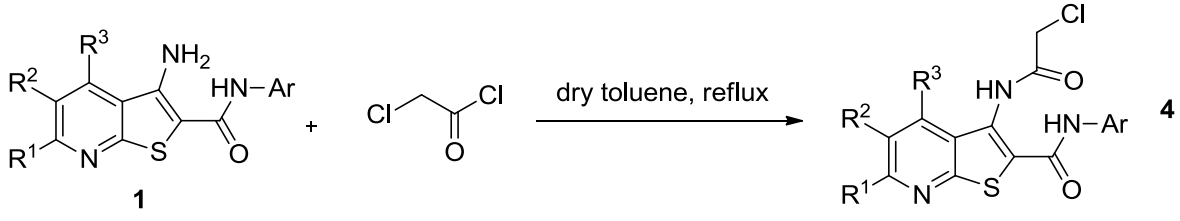
In the present paper we report the synthesis of certain new thienopyridines modified by acylation of 3-amino group. Starting 3-aminothieno[2,3-b]pyridine-2-carboxamides **1** were prepared by the known method [1] from 3-cyanopyridine-2(1H)-thiones **2** and 2-chloroacetanilides. First, we have prepared Guareschi-Thorpe 3-cyano-2-pyridones by reaction of 1,3-diketones with cyanoacetamide. The pyridones were converted to 2-chloronicotinonitriles by treatment with $POCl_3$ [1]. The prepared 2-chloronicotinonitriles were reacted with thiourea to give 3-cyanopyridine-

2(1H)-thiones **1** [2]. 4,6-Diaryl-3-cyanopyridine-2(1H)-thiones **3** were synthesized by reaction of malononitrile with chalcones, followed by the treatment of δ-keto dinitrile formed with sulphur in the presence of an amine (morpholine or diethylamine)[3].

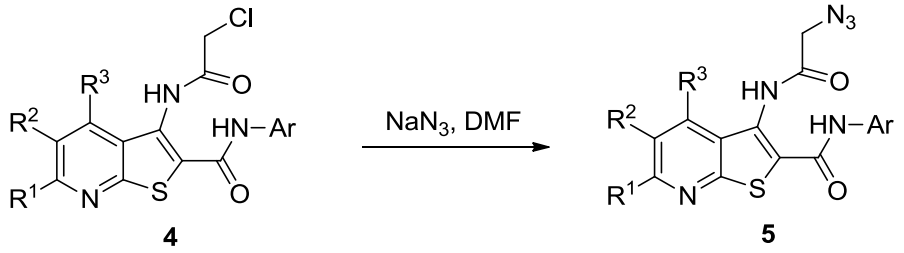
Starting 3-aminothieno[2,3-b]pyridine-2-carboxamides **1** were prepared in good yields by one-pot Thorpe–Ziegler cascade reaction of 3-cyanopyridine-2(1H)-thiones **2** and **3** with α-chloroacetanilides in boiling DMF in the presence of a strong base.



With 3-aminothieno[2,3-b]pyridine-2-carboxamides **1** in hands, we attempted to prepare 3-(chloroacetylamino) derivatives. We found that thienopyridines **1** easily react with chloroacetyl chloride in boiling dry toluene or benzene by known procedure [4] to give desired α-chloroacetamides **4** as white or pale yellow solids.

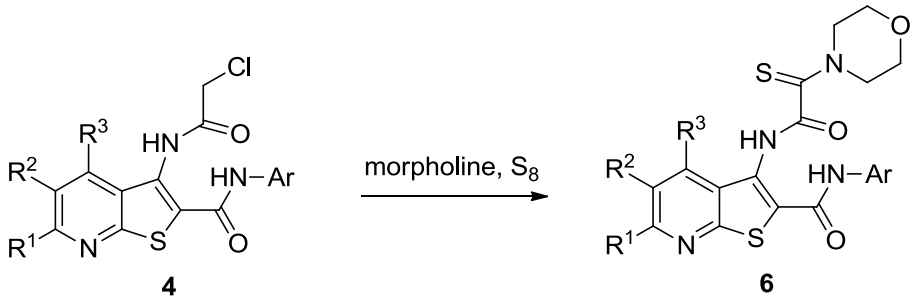


Compounds **4** were found to be useful reagents in the synthesis of functionalized thieno[2,3-b]pyridines. Thus, when compounds **4** were reacted with sodium azide in DMF, azidoacetamides **5** were isolated in yields ranged from moderate to very good. The studies on the reactivity of the prepared azides are currently underway. Azides **5** are white solids, quite stable at ambient temperature.



4 **5**

It is known that chloroacetamides react with sulphur and active amines to afford monothiooxamides [5, 6]. We found that the reaction of chloroacetamides **4** with morpholine and S_8 leads to the formation of thiomorpholides **6** in modest yields. The structure of products were confirmed by IR, NMR and LCMS data.



4 **6**

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