

A Convenient Procedure for the Formation of 2-Substituted Thiazolopyridines

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Summary. 2-Substituted thiazolo[4,5-*b*]pyridines and thiazolo[5,4-*c*]pyridines are prepared in reasonable yields by a procedure involving reaction of a mixture of *ortho*-amino (diisopropylthiocarbamato) pyridine, carboxylic acid, and phosphorus oxychloride. The procedure provides a more convenient route than methods involving prior formation and isolation of the acid amide and cyclisation to give the desired product. The procedure is proven to be general for a wide range of substituents.

Keywords. Thiazolopyridines; Carboxylic acids; Phosphorus oxychloride; Amino (diisopropylthiocarbamato) pyridines; Cyclisation.

Introduction

Derivatives of thiazolopyridine have been reported to exhibit various biological activities including analgesic, antipyretic, anti-inflammatory, and antifungal effects [1–4]. Therefore, the synthesis of such heterocyclic ring systems is attractive. In the last few years a number of methods has been developed for the synthesis of thiazolopyridines [5–11]. As part of our own interests [12], recently, we have developed a novel approach to various heterocyclic compounds [13]. In the present work we report a convenient procedure for the synthesis of 2-substituted thiazolo[4,5-*b*]pyridines (**1**) and 2-substituted thiazolo[5,4-*c*]pyridines (**2**).

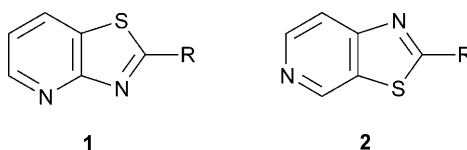


Fig. 1. Compounds **1** and **2**

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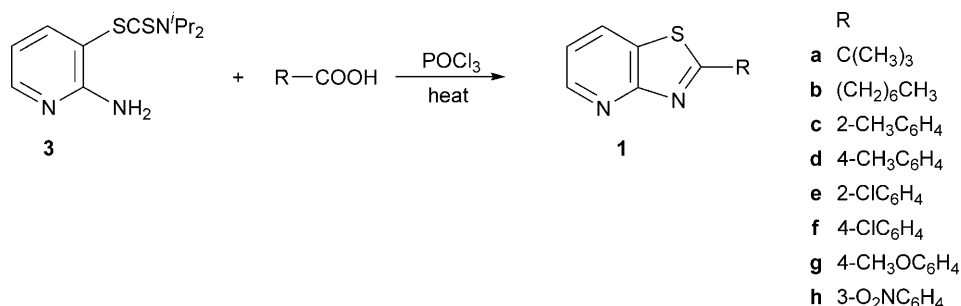
Results and Discussion

Synthesis of **1** and **2** usually involves treatment of *ortho*-aminochloropyridines with a thioester in alkaline medium, followed by acid treatment [6]. However, this method has not been widely applied and no simple 2-substituted thiazolopyridines have been prepared. Moreover, it involves three steps and usually gives moderate yields which considerably limits its scope. An attractive alternative approach involves treatment of *ortho*-amino (diisopropylthiocarbamate) pyridine with acid chloride in the presence of base to produce the corresponding acid amide, followed by acid treatment to afford 2-substituted thiazolopyridines [10, 11]. This method has been widely applied and usually gives excellent yields. Whilst such a method can be quite efficient and convenient, it suffers from the poor availability and stability of appropriately substituted acid chlorides. Moreover, it involves an extra step to prepare the acid chloride. This prompted us to investigate a novel approach in which *ortho*-amino (diisopropylthiocarbamate) pyridine (**3**) or (**4**) and the carboxylic acid were treated *in-situ* with phosphorus oxychloride.

2-Amino-3-(diisopropylthiocarbamate) pyridine (**3**) and 4-amino-3-(diisopropylthiocarbamate) pyridine (**4**) were prepared according to literature procedures [10, 11]. Thus, mixture of **3** and 2,2-dimethylpropionic acid in phosphorus oxychloride was heated under reflux and after work-up 2-*tert*-butylthiazolo[4,5-*b*]pyridine (**1a**) was isolated. A series of experiments was conducted in which the reaction conditions were varied in an attempt to improve the yield of the desired product. It was found that the optimum yield was obtained when the reaction mixture of **3** (1.0 molar equivalents), carboxylic acid (1.2 molar equivalents), and phosphorus oxychloride (5 cm³) was refluxed for 4 h. The procedure is proven to be general for a wide variety of carboxylic acids (pivalic, octanoic, 2-toluic, 4-toluic, 2-chlorobenzoic, 4-chlorobenzoic, 4-anisic, and 3-nitrobenzoic acid) to produce **1** (Scheme 1) in 58–70% yields.

The structures of compounds **1** were confirmed by ¹H NMR, ¹³C NMR, mass spectra, and high resolution mass spectral data and found to be identical with those published already [10, 11, 14].

In the same way as described for **3**, **4** was reacted with carboxylic acid (acetic, propanoic, benzoic, 2-toluic, 4-toluic, 2-chlorobenzoic, and 3-bromobenzoic acid) in phosphorus oxychloride. Indeed, various 2-substituted thiazolo[5,4-*c*]pyridines (**2**) (Scheme 2) were obtained in reasonable yields (54–71%).



Scheme 1