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A new and facile synthesis of methyl 3-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylate

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ABSTRACT

A four-step synthesis of methyl 3-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylate from commercially available starting materials is presented.

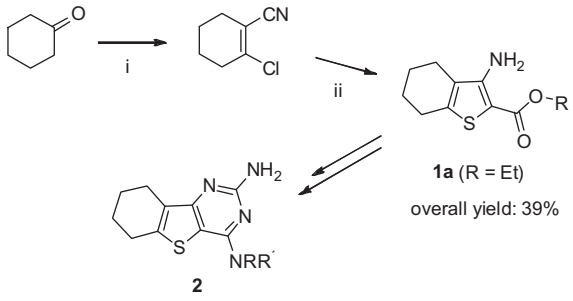
Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylate (**1a**), its 3-carboxylate regioisomer and derivatives were recently found to be important intermediates in the synthesis of pharmaceutically active compounds. Their structural framework can be found in products with antimicrobial, antimycobacterial, anti-inflamatory[1–3] and antitumor properties.[4] Especially interesting are those molecules with a fused pyrimidine ring as they can be considered as potential nucleic acid antimetabolites. Thus, compound **1a** is a key intermediate in the synthesis of modulators **2** of histamine H4 receptors (Scheme 1). They are used for the treatment of disease states, disorders and conditions mediated by the receptor connected with allergy-related diseases.[5]

The recent patented synthesis[5] of compound **1a** is based on a two-step protocol starting from cyclohexanone. Column chromatography had to be used to obtain the final product **1a** in 39% overall yield (Scheme 1).

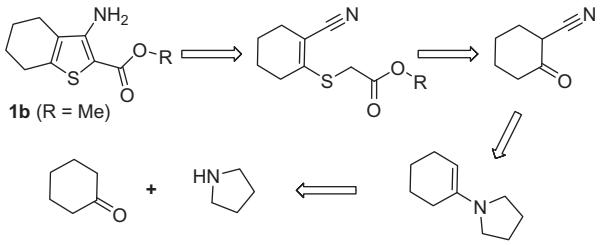
We report herein a new approach to the title compound, the methyl homologue **1b**. The retrosynthetic analysis is shown in Scheme 2.

Our synthesis began with the reaction of cyclohexanone and pyrrolidine in benzene (or toluene) leading to enamine **3**. Compound **3** reacted smoothly with cyanogen chloride using a modification of Kuehne's protocol[6] to give either 2-pyrrolidinylcyclohexene carbonitrile (**5**) or 2-oxo-cyclohexane carbonitrile (**4**) depending on the work-up procedure (Scheme 3). Contrary to Kuehne's procedure we used toluene as the solvent instead of the more toxic 1,4-dioxane. The best results were obtained when a toluene solution of enamine **3** was added to a carefully cooled toluene solution of cyanogen chloride. If target compound **4** was to be isolated directly, an aqueous hydrochloric acid work-up had to be used.[6,7] Ketone **4** was obtained in 78% yield (see Supplementary data for details).

At first, reactions of compound **5** with ethyl 2-sulfanylacetate (**6**) were tested keeping in mind the synthesis of the target molecule **9** (Scheme 3). However, enamine **5** was found to be an unsuitable substrate for the intended incorporation of acetate **6** into the structure. Under acidic conditions, only starting material was recovered, or rapid decomposition of compound **5** into ketone **4** was observed when the reaction mixture contained even a trace amount of water. Basic conditions resulted in the same negative results, and additionally, slow transformation of acetate **6** into its disulfide oxidation product was observed.



Scheme 1. Reagents and conditions: (i) DMF, $POCl_3$, $NH_2OH{\cdot}HCl$, 40 °C; (ii) ethyl 2-sulfanylacetate, K_2CO_3, EtOH/THF, 90 °C, 24 h, column chromatography.



Scheme 2. Retrosynthetic analysis of **1b**.

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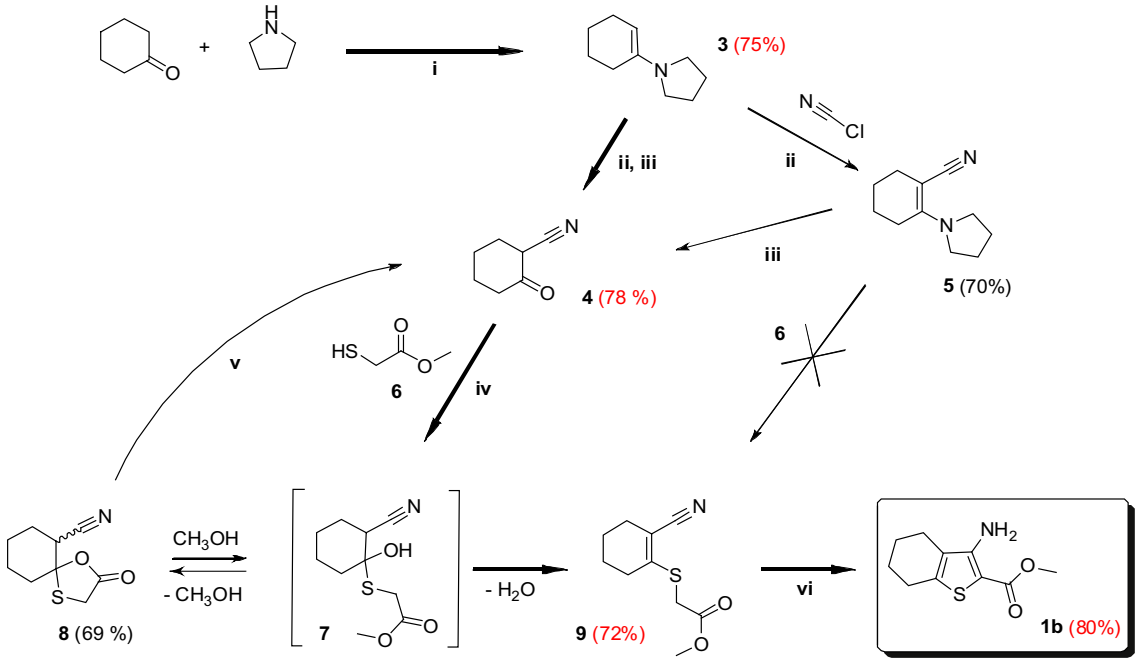

Scheme 3. Reagents and conditions: (i) *p*-toluenesulfonic acid, benzene, reflux; (ii) Et_3N, toluene, 4 °C, then rt for 18 h; (iii) 10% HCl, H_2O, rt; (iv) HCl (g), Et_2O, molecular sieves (5 Å), MeOH, rt; (v) base, MeOH, rt; or *p*-toluenesulfonic acid, EtOH, rt; (vi) *t*-BuOK, THF, reflux.

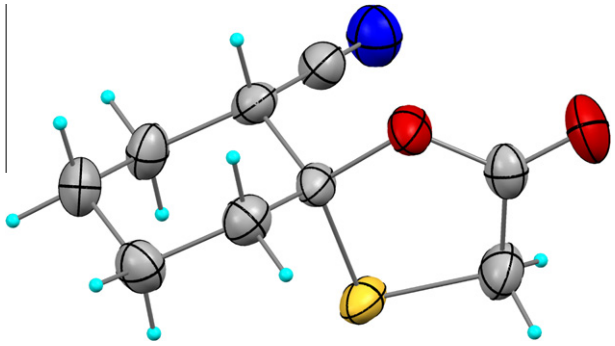

Figure 1. ORTEP representation[9] of compound **8** (major diastereomer).

Thus, we tested the analogous treatment of ketone **4** with sulfanylacetate **6** according to a procedure carried out on similar structures.[8] To our surprise, we were only able to obtain a mixture of diastereomeric lactones **8** in the ratio 2:1 (Scheme 3). The major diastereomer was isolated by fractional crystallization from methanol. The stereochemistry was determined by X-ray analysis[9] (Fig. 1). Most attempts to transform lactones **8** into compound **9** by ring-opening resulted in recovery of ketone **4** (Scheme 3). However, passing anhydrous hydrogen chloride through a methanolic solution of lactones **8** finally yielded the desired product **9**.

On this basis we developed a new reaction protocol for the reaction of ketone **4** with acetate **6**. Both reactants were mixed in diethyl ether and gaseous HCl was bubbled through the reaction mixture for a few minutes. It was shown that at the moment when compound **4** was consumed, the reaction mixture contained, beside lactone **8** (85%), a small amount of product **9** (15%, monitored by GC–MS). Subsequently, methanol and an additional portion of gaseous HCl were added. The reaction was stopped when complete conversion of lactones **8** into product **9** was registered by GC–MS. During this transformation, intermediate **7** was also detected. However, its isolation was not attempted. Comparable results were obtained when the reaction was performed under solvent-free conditions with an excess of compound **6** (8 equiv).

In the final step, base-promoted cyclization of compound **9** was realized (Scheme 3). The reaction was accomplished either at room temperature in 24 h or in 15–30 min in boiling THF. The target molecule **1b** was obtained in pure form without any other purification necessary (see Supplementary data for analytical data).

In conclusion, we have developed a new means of access to methyl 3-amino-4,5,6,7-tetrahydrobenzo[*b*]-thiophene-2-carboxylate (**1b**) as an important intermediate in the synthesis of histamine H4 receptor modulators. Our synthesis consists of four steps leading to compound **1b** in 34% overall yield without any column chromatography required. The method is based on simple and industrially accessible chemicals with yields comparable to those obtained by other research groups.

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Supplementary data

Supplementary data (experimental procedures) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.076.

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9. Carbon (grey), oxygen (red), nitrogen (blue) and sulfur (yellow) atoms are drawn as principal ellipses (70% probability level); hydrogen atoms are drawn as fixed-size spheres (cyan). Crystallographic data for compound **8** (CCDC deposition number 795007) have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.