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An efficient synthetic route towards novel thienobenzothiazoles, thienobenzothiazepines, and thienobenzothiazines

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ABSTRACT

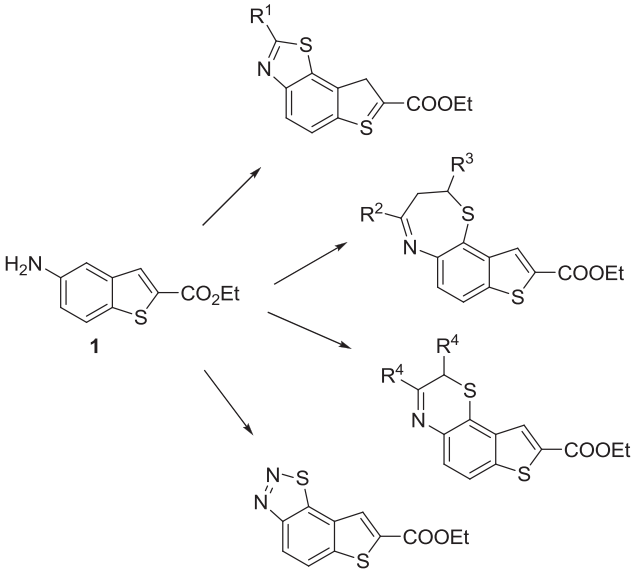
Efficient methods for the synthesis of novel nitrogen- and sulfur-containing heterocycles, annulated in the 4,5-position of benzothiophene, are described. Applying the Herz reaction, 3*H*-thienobenzodithiazole 2-oxide was prepared. This compound served as *o*-aminothiophenol precursor in the synthesis of a variety of thienobenzothiazoles, thienobenzothiazepines, thienobenzothiazines, and thienothiadiazole.

1. Introduction

Sulfur-containing heterocyclic ring systems, such as benzothiazoles, benzothiazepines, and benzothiazines, have shown a great potential in pharmaceutical research and serve as versatile scaffolds in experimental drug design.[1–4] These heterocycles are generally synthesized via condensation of an *o*-aminothiophenol with substituted aromatic aldehydes, acid chlorides, acetophenones, α,β-unsaturated ketones or substituted α-bromoacetophenones.

Our general point of interest goes to the synthesis of 4,5-annulated benzothiophenes with *N*-containing heterocycles, thus providing easy strategies towards the synthesis of novel benzothiophene fused structures. Therefore, we use the 5-aminobenzothio phene scaffold as starting material. In our preceding work we described the synthesis of ethyl 5-aminobenzothiophene-2-carboxy late (**1**),[5] the latter conveniently prepared by the condensation of 2-chloro-4-nitrobenzaldehyde with ethyl-2-mercaptoacetate, followed by reduction of the nitro group.

In this manuscript, we wish to report the synthesis of novel thienobenzothiazoles, thienobenzothiazepines, thienobenzothiazines, and thienobenzothiadiazole in moderate to high yields, all based on our 5-aminobenzothiophene scaffold **1** (Scheme 1). It was therefore necessary to introduce an extra sulfur atom into the 4-position of this 5-aminobenzothiophene **1**, in order to obtain an *o*-aminothiophenol derivative.



Scheme 1. Synthesis of novel thienobenzothiazoles, thienobenzothiazepines, thienobenzothiazines, and thienobenzothiadiazole.

One of the most commonly used pathways for the synthesis of *o*-aminothiophenol derivatives takes place via the synthesis of a 2-aminobenzothiazole. This 2-aminobenzothiazole is easily formed by reaction of the corresponding aniline with potassium

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thiocyanate (or ammonium thiocyanate), followed by the oxidative cyclization of the formed thiourea with bromine.[6,7] The next step involves the hydrolytic cleavage of the formed benzothiazole, to yield the expected 2-aminothiophenol. However, the necessity of hydroxide base under refluxing conditions forms an obstacle, as the benzothiophene ester function, present in the starting material **1**, will be hydrolyzed too.

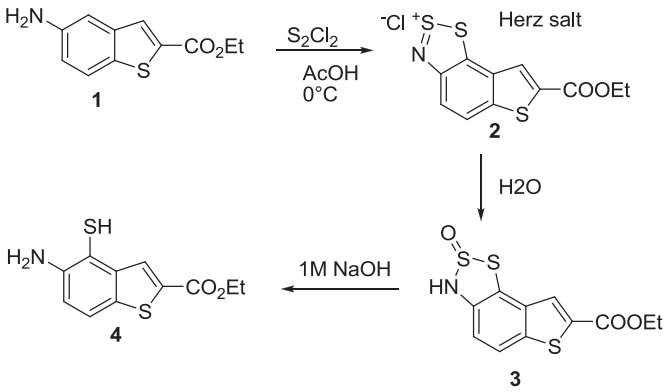
Another pathway towards our 2-aminothiophenol precursor is the Herz reaction.[8,9] This reaction involves the condensation of a primary aniline with sulfur monochloride to give the corresponding, benzodithiazolium chloride (Herz salt). Since the discovery of Herz salts, a number of reports have appeared using this method.[10–16] This method was found very popular for the synthesis of substituted *o*-aminothiophenols, as the salt can be easily hydrolyzed with sodium hydroxide. In his review, W.K. Warburton[11] described this Herz reaction and the subsequent hydrolysis of the condensation product towards *o*-aminothiophenols. Of course, 2-aminothiophenols readily undergo oxidation, forming the more stable and in this case synthetically less useful disulfides. On the other hand, the Herz salt can readily be hydrolyzed in water to give the fairly stable 3*H*-benzodithiazole 2-oxide derivative. This was reported by Herz,[9] Warburton,[11] Blomquist et al.,[12] Huestis et al.,[13] and Belica et al.[14]

We thus report herein the synthesis of a 5-amino-4-mercapto benzothiophene precursor, being the corresponding 3*H*-thienobenzodithiazole 2-oxide **3**, using the Herz reaction, and optimized methods for the synthesis of five-, six-, and seven-membered heterocyclic rings, starting from this benzodithiazole 2-oxide precursor.

2. Results and discussion

Conforming these literature procedures, we synthesized the corresponding Herz salt **2** by reaction of the starting compound 5-aminobenzothiophene **1** with S_2Cl_2 in acetic acid. This Herz compound **2** was readily hydrolyzed in water to give the 3*H*-thienobenzodithiazole 2-oxide **3** (Scheme 2). We have also tried to hydrolyze compound **3**, by treatment with a 1 M sodium hydroxide solution (Scheme 2).[11] Although the smell of sulfide was readily observed, we were not able to isolate the desired 5-amino-4-mercaptobenzothiophene derivative **4**, due to the quick oxidation of the free thiophenol function to disulfides. Moreover, ^{1}H NMR analysis also indicated hydrolysis of the ester function, as the specific signals (a quartet at 4.45 ppm and a triplet at 1.45 ppm) were no longer present in the ^{1}H NMR spectrum.

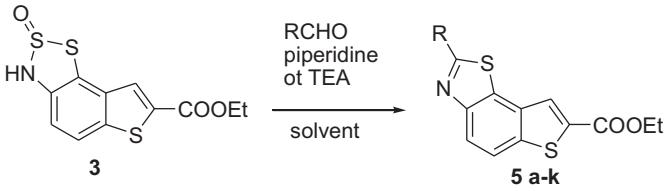
It is worth noting that brief heating of this dithiazole-oxide **3** causes decomposition, which is observed by the presence of sulfur dioxide.[15] In order to purify the compound, we generally followed



Scheme 2. Synthesis of 3*H*-thienobenzodithiazole 2-oxide **3**.

literature procedures. The crude reaction product needed to be dissolved in a large amount of methanol (about 150 mL per gram of product), followed by precipitation of the product on addition of water.[13,15] In larger scale reactions (more than 10 g of product), the workup of compound **3** seemed to become problematic. The exothermic reaction, upon mixing both liquids, was difficult to control and led to a drastic decrease of the yield with about 50%. Moreover, this purification method turned out to be less efficient on large scale, as the compound still contained impurities, which was indicated by ^{1}H NMR spectral analysis. We finally found that simply washing the compound **3** with toluene removed these impurities. Using this optimized procedure, we were able to synthesize **3** in an overall yield of 78%.

The synthesized 3*H*-thienobenzodithiazole 2-oxide **3** serves as a more stable and convenient alternative for the corresponding oxidation-sensitive *o*-aminothiophenol, as we have noticed before. Sawhney et al.[16] have reported that 3*H*-benzodithiazole 2-oxide can be reacted with benzaldehyde to afford 2-phenylbenzothia zole. We applied this reaction procedure, using benzaldehyde and triethylamine as base, at room temperature and in refluxing ethanol (Scheme 3 and Table 1, entry 1–2). In both cases we obtained the expected 2-phenylthienobenzothiazole **5a** in low to fair yields (27% and 44% resp.).



Scheme 3. Thienobenzothiazole synthesis from **3** and aromatic aldehydes.

Table 1
Optimization of thienobenzothiazole synthesis (R=phenyl)

Entry	Benzaldehyde	Solvent	Temperature	Yield **5a** [%][b]
1	1.2 equiv	EtOH[a]	25 °C	27
2	1.2 equiv	EtOH[a]	Reflux	44
3	1.2 equiv	DMSO	25 °C+120 °C	48
4	2.2 equiv	DMSO	25 °C+120 °C	77

[a] Et_3N is used as base.
[b] Yields refer to isolated products.

The mechanism of the general benzothiazole synthesis starting from 2-aminothiophenol is described in literature to go via formation of a benzothiazoline intermediate,[17] which is then oxidized to the benzothiazole. We therefore used DMSO as solvent (Table 1, entry 3). After completion of the reaction at room temperature, as indicated by TLC, we increased the reaction temperature to 120 °C and observed the formation of the final benzothiazole **5a**. We assume that the solvent DMSO acts as oxidant, because of the strong odor of dimethylsulfide, which was observed after reaction. Besides the oxidation by DMSO, it is also possible that part of the aldehyde present in the reaction is used as oxidant or hydride acceptor. In support of this the yield strikingly increased (77%) on adding more benzaldehyde to the reaction mixture (Table 1, entry 4).

We next explored this benzothiazole synthesis using a variety of aldehydes to establish optimized reaction conditions, being an excess of aldehyde in DMSO with piperidine as base (Scheme 3 & Table 2). We obtained moderate to good yields (39–77%). No specific influence from the electronic effects of the substituents was observed, except in one case, **5e** (Table 2, entry 5). Thus, an electron-donating substituent, such as the dimethylamino group, has a negative effect on the reaction, by making the aldehyde and the imine