An Easy Access to Variously Substituted Thieno[2,3-*b*]pyrroles by Using Isothiocyanates

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Dedicated to Professor Jan Bergmann on the occasion of his 60th birthday

Abstract: Thieno[2,3-*b*]pyrroles **2** can easily be synthesised in two steps by using isothiocyanates and activated methylene compounds.

Key words: thieno[2,3-*b*]pyrrole, isothiocyanate, ketene-*N*,*S*-acetal, thiophene

Substituted thieno[2,3-*b*]thiophenes and their preparation methods are known since the 50's. One of the most recent synthetic pathways for their preparation is based on the cyclisation of ketene dithioacetals, obtained from carbon disulfide, in basic media.[1–4] We decided to extend this strategy to the formation of thieno[2,3-*b*]pyrroles, using an alkyl or aryl isothiocyanate, instead of carbon disulfide, under similar conditions. Our first attempt with phenyl isothiocyanate allowed us to isolate a 2-phenylaminothiophene by filtration when the reaction is quenched with water. Condensation with ethyl bromoacetate under harsher conditions led us to the expected thieno[2,3-*b*]pyrroles with good yields.

These first results, different from those reported by El-Shafei[1] and the lack of practical details and analytical data, prompted us to investigate this reaction.

We have shown that the preparation of thieno[2,3-*b*]pyrroles cannot be carried out in a one-pot procedure but our two-step pathway allows us to increase the diversity of the substituants on the thienopyrrole framework.

The first step is the condensation of activated methylene compounds with alkyl or aryl isothiocyanates in a basic medium, as has been already described for the preparation of a great number of heterocyclic compounds[5,6] especially thiophenes.[2,7] According to the results that we have recently reported in the field of thieno[2,3-*b*]thiophene[8], K_2CO_3 was used as the basic condensation promoter in order to obtain the intermediate ketene aminothioacetals. The addition of two or more equivalents of alkyl bromoacetate (or chloroacetonitrile) did not lead to the *N*,*S*-disubstituted ketene aminoacetals reported by El-Shafei[1] but only to the thiophenes **1** in moderate to good yields (Table 1).

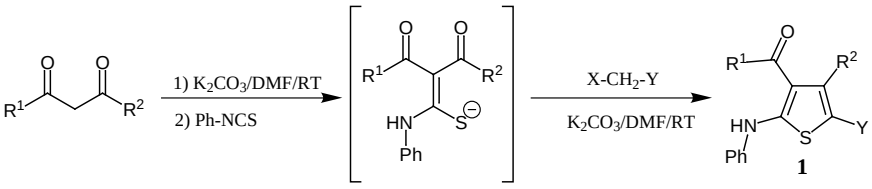
Condensation of the intermediate salt ketene *N*,*S*-acetal with the halide leads to the corresponding aminothioacetal which smoothly undergo a Dieckmann type cyclisation in basic medium at room temperature (Scheme 1).

This two-step method offers some advantages in comparison with those described in the literature generally based on cyclisation reactions of accurately substituted thiophenes[9] or pyrroles.[10]

By-products were not isolated from the resinous residue but the reaction products described by El-Shafei[1] should have been observed if formed, even if the basic media was not exactly the same (K_2CO_3/benzene under PTC conditions). Thiophenes **1** were easily removed from the crude reaction mixture by rapid hydrolysis in water followed by filtration.

With ethyl acetylacetate, only thiophene **1l** was formed by cyclisation of the ketone has been observed, which is in agreement with previous work on similar compounds.

Formation of the pyrrole-fused rings **2** and **3** was achieved by prolonged reflux of **1** in acetone for 4 to 5 days in the presence of 1.5 equivalents of an alkyl bromoacetate[10] (or chloroacetonitrile) (Scheme 2). All other attempts to obtain the corresponding thieno[2,3-*b*]pyrrole **2** and **3** failed, even the one described by El-Shafei[1] which was very surprising. Nevertheless, the yields of cyclisation (60 to



Scheme 1

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1437-2096,E;2001,0,11,1731,1734,ftx,en;G15001ST.pdf.

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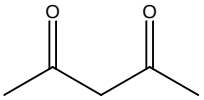
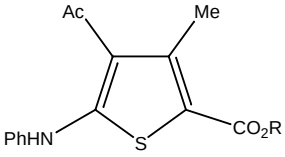
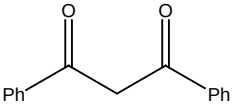
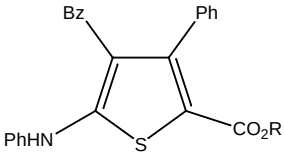
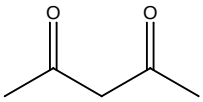
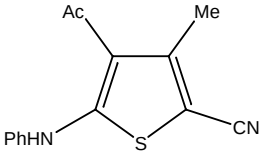
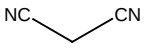
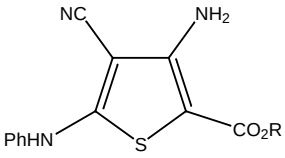
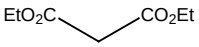
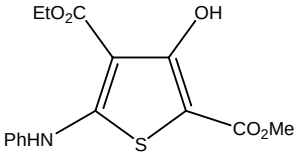
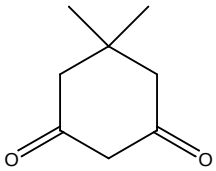
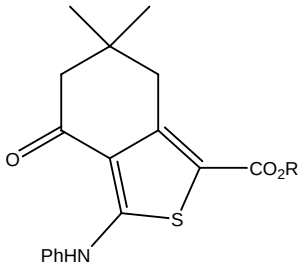
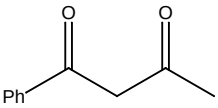
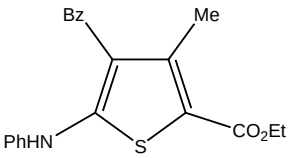
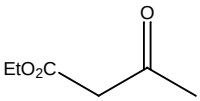
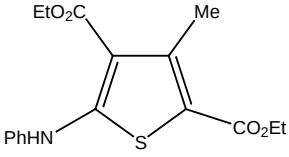
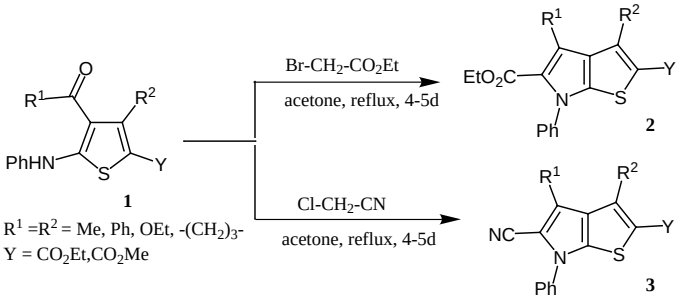
Table 1 Synthesis of Thiophenes **2** from Compounds **1**

Entry	Compound 1	Product 2	Yield (%)
a **b**			40 (R=Me) 47 (R=Et)
c **d**			65 (R=Me) 71 (R=Et)
e			34
f **g**			10 (R=Me) 19 (R=Et)
h			34
i **j**			43 (R=Me) 50 (R=Et)
k			42
l			46

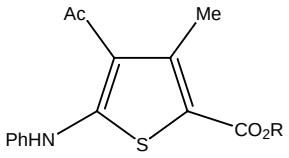
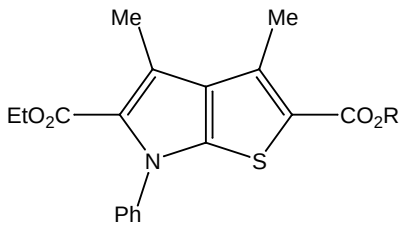
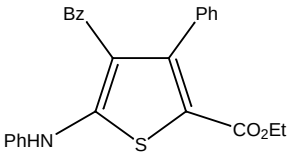
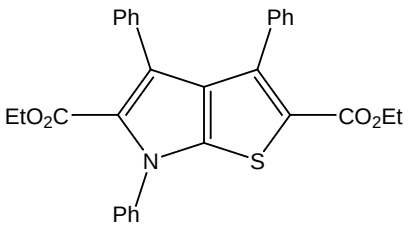
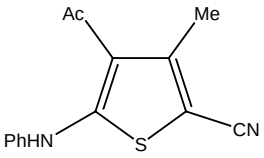
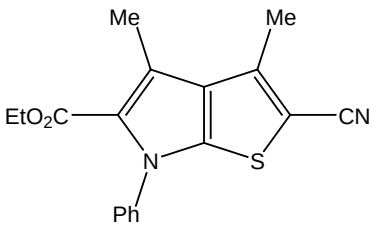
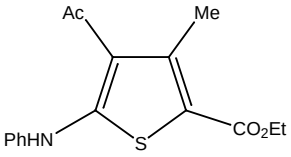
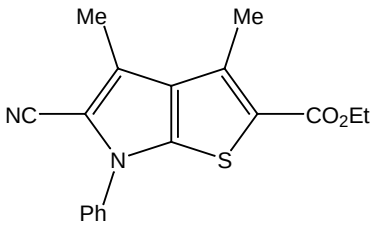
85%) were in accordance with the literature.[10] Although this strategy has already been described, our modifications offer some advantages. Formation of the thiophene and pyrrole rings are independent and can be extended to a large number of symmetrical and unsymmetrical activated methylene substrates even though only one example of thienopyrrole has been described by El-Shafei.[1]

The influence of the substituents of the isothiocyanate on its behaviour during the condensation under basic conditions has been investigated in a last step. Phenyl isothio-



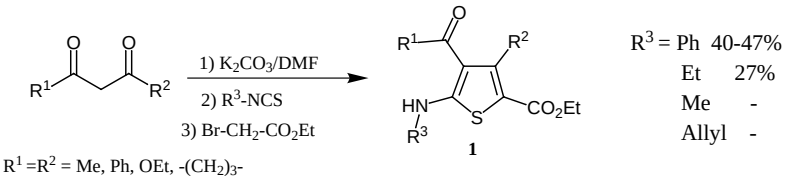
Scheme 2

Table 2 Synthesis of Thienopyrroles **2** and **3** from Thiophenes **1**

Entry	Compound	Product	Yield (%)
2a **2b**			71(R=Me) 73(R=Et)
2d			61
2e			65
3b			85

cyanate has been almost exclusively used for related studies and this choice could be explained by the availability of this compound, but above all it appeared to be the best candidate for this reaction (Scheme 3). The replacement of phenyl isothiocyanate by other commercially available ones decreases dramatically the yields of thiophene **1**.

Our second goal was to obtain a *N*-substituted thieno[2,3-*b*]pyrrole **2** that could be deprotected in an additional step. Until now, all our attempts were unsuccessful using benzyl, methyl, carbethoxy or *p*-methoxyphenyl isothiocyanates, which can actually be a limitation of this synthetic way.



Scheme 3

In summary, we have shown that facile formation of diversily substituted thieno[2,3-*b*]pyrrole **2** or **3** can be carried out in two steps using phenyl isothiocyanate and K_2CO_3/DMF as the condensation promoter. The described method is easy and can be applied to a large number of activated methylene compounds.

References and Notes

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(11) Typical procedure for the preparation of thiophenes **1**: A 100 mL three-necked round-bottom flask equipped with magnetic stirrer, condenser and septum was charged with a solution of 1,3-diketone (10.0 mmol, 1 equiv) in DMF (30 mL). Dried K_2CO_3 (10.0 mmol, 1 equiv), was added and the mixture was stirred for 1 h at r.t. The isothiocyanate (10.0 mmol, 1 equiv) was then added dropwise and the mixture was stirred 2 h at r.t. The alkyl bromoacetate (or chloroacetonitrile) (10.0 mmol, 1 equiv) was added and dried K_2CO_3 (10.0 mmol, 1 equiv). The reaction was quenched with 100 mL of H_2O after having stirred 4 h at r.t. The crude product precipitated and was purified by filtration followed by crystallisation in EtOH.
4-Acetyl-3-methyl-5-phenylamino-thiophene-2-carboxylic Acid Ethyl Ester(**1b**): **mp** : 125 °C. **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.34 (t, 3 H, *J* = 7.1 Hz), 2.58 (s, 3 H), 2.82 (s, 3 H), 4.28 (q, 2 H, *J* = 7.1 Hz), 7.35–7.42 (m, 5 HAr), 12.1 (s, 1 H). **^{13}C NMR** (62.5 MHz, $CDCl_3$): δ 14.3 (CH_3), 16.5 (CH_3), 31.3 (CH_3), 60.5 (CH_2), 108.9 (CAr), 119.2 (Car), 120.5 (CHAr), 124.7 (2 CHAr), 129.5 (2 CHAr), 139.6 (CAr), 145.8 (CAr), 162.7 (CAr), 163.4 (CO_2), 195.7 (CO).
(12) Typical procedure for the preparation of thieno[2,3-*b*]pyrroles **2**: Alkyl bromoacetate (or chloroaceto nitrile) (15.0 mmol, 1.5 equiv) was added to a stirred solution of thiophene **1** (10.0 mmol, 1 equiv) in 30 mL of dry acetone and dried K_2CO_3 (10.0 mmol, 1 equiv). The reaction mixture was heated at reflux for 5 days before quenching in 100 mL of water. The crude product precipitated and was purified by filtration followed by recrystallisation in EtOH.
3,4-Dimethyl-6-phenyl-6*H*-thieno[2,3-*b*]pyrrole-2,5-dicarboxylic Acid Diethyl Ester(**2b**): **mp** : 127 °C. **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.08 (t, 3 H, *J* = 7.2 Hz), 1.33 (t, 3 H, *J* = 7.2 Hz), 2.71 (s, 3 H), 2.83 (s, 3 H), 4.14 (q, 2 H, *J* = 7.2 Hz), 4.16 (q, 2 H, *J* = 7.2 Hz), 7.30–7.34 (m, 5 Har). **^{13}C NMR** (62.5 MHz, $CDCl_3$): δ 11.7 (CH_3), 13.8 (CH_3), 14.3 (CH_3), 14.5 (CH_3), 60.1 (CH_2), 60.5 (CH_2), 120.3 (CAr), 124.8 (CAr), 125.0 (CAr), 126.1 (CHAr), 127.5 (2 CHAr), 128.9 (2 CHAr), 130.7 (CAr), 139.7 (CAr), 139.9 (CAr), 143.5 (CAr), 161.1 (CO_2), 163.1 (CO_2).