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An improved method for the synthesis of aminothiophenes precursors of thieno[2,3-*b*]pyrrole

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Abstract—Thiophenes **2** can easily be synthesized in two steps by using phenyl isothiocyanate and activated methylene compounds.

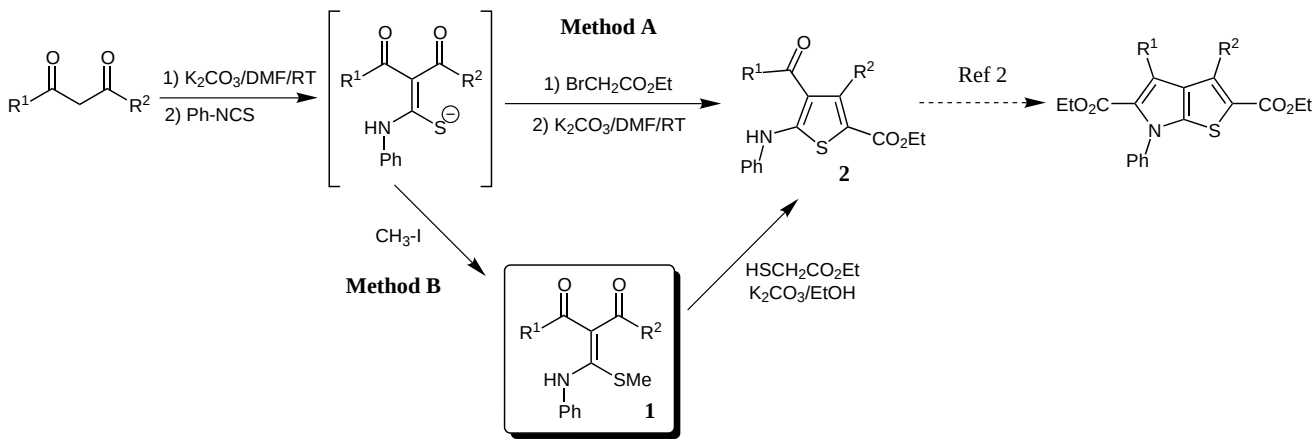
Ketene dithioacetals are key intermediates for the preparation of a large number of heterocyclic structures[1]. Various nucleophiles (amines, hydrazines, organometallic reagents,…) can displace one of the methylthio group and cyclisation of the intermediate can generally occur during the same stage.

We described recently[2] a one-pot procedure to obtain thiophenes in moderate to good yields, by reacting 1,3-diketones or equivalents with isothiocyanates (generally phenyl isothiocyanate) in a basic medium (K_2CO_3/DMF), followed by a condensation with bromacetate or chloracetonitrile and a Dieckmann-type cyclisation in the same step.

A similar strategy had already been used[3] but the formation of thieno[2,3-*b*]pyrrole from the obtained thiophenes **2** was poorly related.

In order to improve the yields described in our previous work and to extend this method to starting compounds that failed to give the expected thiophenes **2**, we decided to isolate ketene phenylamino methylthio acetals **1**. These compounds were easily obtained in yields around 90% in all cases following the same conditions[2] using methyl iodide (Scheme 1).

We therefore, investigated in a second step the ability of thioglycolate to react with compounds **1** what is well



Scheme 1.

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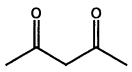
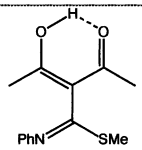
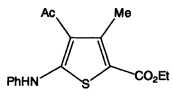
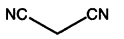
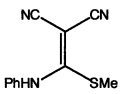
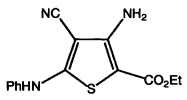
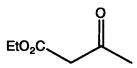
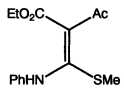
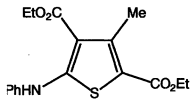
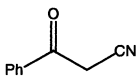
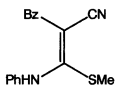
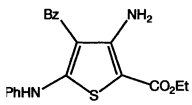
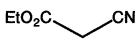
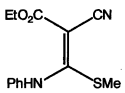
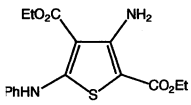
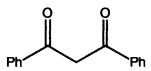
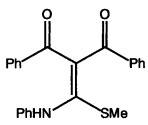
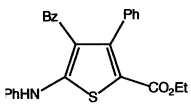
Table 1. Comparison of the two methods for the preparation of thiophenes **2**

Entry	Starting Compound	Product 1	Yield (%)	Product 2	Yield (%)	
					Method A	Method B
a			**96**		**47**	**79**
b			**91**		**19**	**64**
c		 Mixture of two isomers	**97**		**46**	**62**
d			**80**		-	**32**
e			**87**		-	**28**
f			**58**		**65**	**21**

known for other various nucleophiles[1] like amines, hydrazines or organometallics reagents but surprisingly never used for thiols. To the best of our knowledge, the displacement of the thiomethyl group of a ketene dithioacetal or aminothioacetal using a thiol is just described in one case in the literature[4] even though our initial results indicated that this was the way of choice for the preparation of thiophenes **2**. Similarly to what we described for our one-step method, we have not been able to isolate the new ketene aminothioacetals formed and cyclization occurred under our experimental conditions to furnish thiophenes **2** in moderate to good yields (Table 1).

Although two steps are required for the preparation of the thiophene ring the yields for the two steps, in the cases we reported here, have been increased by a factor of 2–3.

On the other hand, thiophenes **2d–e** could be obtained by this way in moderate yields when our one-step method completely failed. We must note that in some cases, our previous one-step method remains attractive for the preparation of thiophenes **2** (see **2f**).

In summary, this two-step method is an accurate complement to the one we described earlier and should be used each time the one-step pathway does not allow to obtain thiophenes **2** in reasonable yields.

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Zhou, Z.; Sharp, C.; Maguire, D.; Grasberger, B.; Desjarlais, R. L.; Spurlino, J. *Bioorg. Med. Chem. Lett* **2001**, *11*, 915; (b) Tominaga, Y.; Luo, J.-K.; Castle, R. N. *J. Heterocyclic Chem.* **1994**, *31*, 771.

3-(Methylsulfanyl-phenylamino-methylene)-pentane-2,4-dione **1a**: Mp: 72°C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.12 (s, 6H), 2.50 (s, 3H), 6.70 (d, 2Har, $J=7.3$ Hz), 7.04 (d, 1Har, $J=7.3$ Hz), 7.26 (dd, 2Har, $J=7.3$ Hz), 15.04 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 14.3, 23.8, 111.6, 118.9, 120.1, 123.9, 128.8, 149.6, 164.9, 190.3.

4-Acetyl-3-methyl-5-phenylaminothiophene-2-carboxylic acid ethyl ester **2a**:Mp: 125°C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.34 (t, 3H, $J=7.1$ Hz), 2.58 (s, 3H), 2.82 (s, 3H), 4.28 (q, 2H, $J=7.1$ Hz), 7.35–7.42 (m, 5Har), 12.1 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 14.3, 16.5, 31.3, 60.5, 108.9, 119.2, 120.5, 124.7, 129.5, 139.6, 145.8, 162.7, 163.4, 195.7.