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The synthesis of 5-alkoxy and 5-amino substituted thiophenes

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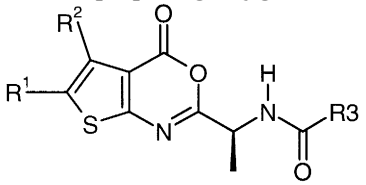
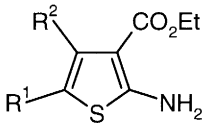
Abstract

5-Alkoxythiophenes have been prepared by an extension of the Gewald thiophene synthesis and a novel four component condensation reaction uncovered by which 5-aminothiophenes have been prepared.

The synthesis of highly substituted thiophenes has attracted a great deal of interest over the years due to their presence in natural products,[1] as novel conducting polymers[2] and as isosteric replacements for phenyl groups in medicinal chemistry.[3] Our interest in this class of compound was founded on their use as precursors to a series of novel serine protease inhibitors such as **1**.[3] Of particular interest was the preparation of analogues of **1** in which R^1 was an alkoxy substituent with a view to stabilising the oxazinone ring to hydrolytic cleavage. For this work we required intermediate **2** where R^1 was an alkoxy substituent. The synthesis of highly substituted thiophenes is restricted by the relative paucity of methods available to construct the ring bearing functionality in a controlled fashion. In particular, the introduction of alkoxy groups is very limited relying on substitution of halothiophenes with alkoxide[4,5] or oxygenation of metallothiophenes[6] or directly[7] and is generally low yielding. We therefore investigated a more versatile method for preparing oxygenated thiophenes.



1



2

The most convenient method for preparing thiophenes with a high degree of functionality as in **2** is by the Gewald method in which elemental sulfur is reacted with an activated acetonitrile and an aldehyde, ketone or 1,3-dicarbonyl compound in the presence of base (equimolar quantities of each).[8] However, there are no examples, to our knowledge, in which this methodology has been used to prepare 2-alkoxythiophenes, presumably due to the potential for mixtures of 4- and 5-regioisomers being formed

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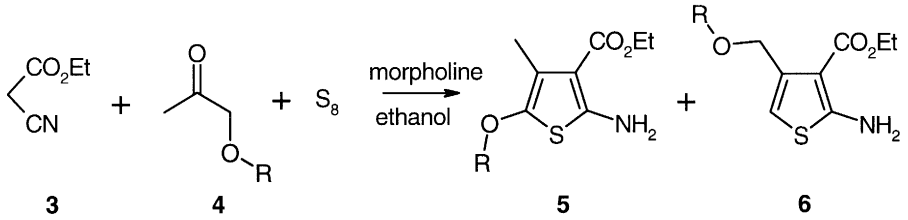
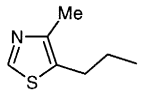
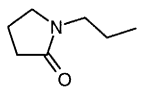
(Scheme 1).[9] We surmised that the presence of the heteroatom would render the methylene more acidic than the methyl group and would therefore direct the condensation reaction predominantly towards the 5-regioisomer. We tested this hypothesis with the reaction of methoxyacetone and ethyl cyanoacetate. The only product isolated from the reaction was 5-methoxythiophene **5a** (R=Me) in 61% yield (Table 1). Indeed when *tert*-butyl cyanoacetate was used in the same reaction the yield of **5a** (*tert*-butyl ester) was near quantitative. The reaction was found to be general for a range of alkoxymethylketones with yields from moderate to good (Table 1). Of particular note was the silyl derivative **5e** which could be desilylated[10] to the 5-hydroxythiophene **5f** which existed exclusively in the keto form.[5]



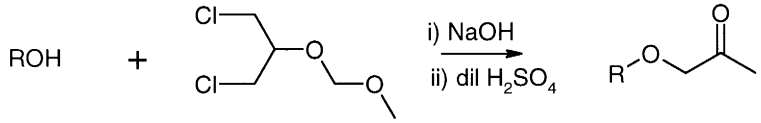
3 **4** **5** **6**

Scheme 1.

Table 1

5	R	%
a	Me-	61
b	C_5H_{11}-	63
c	$PhCH_2OCH_2CH_2$-	28
d	4-Cl-Ph-CH_2CH_2-	21
e	t-$BuMe_2Si$-	30
f	H-	37
g		32
h		49
i	$C_3H_7CH(SMe)CH_2CH_2$-	23

Non-trivial ketones **4** were readily prepared from the alcohol and chloroether **7** in a one-pot process using the method described by Okahara (Scheme 2).[11]

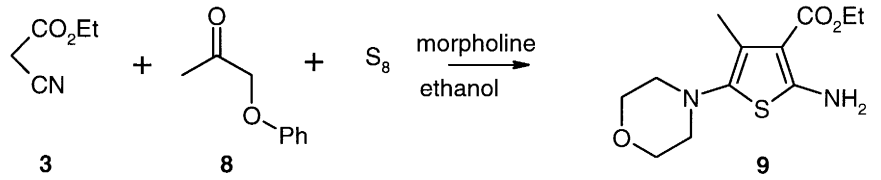


7 **4**

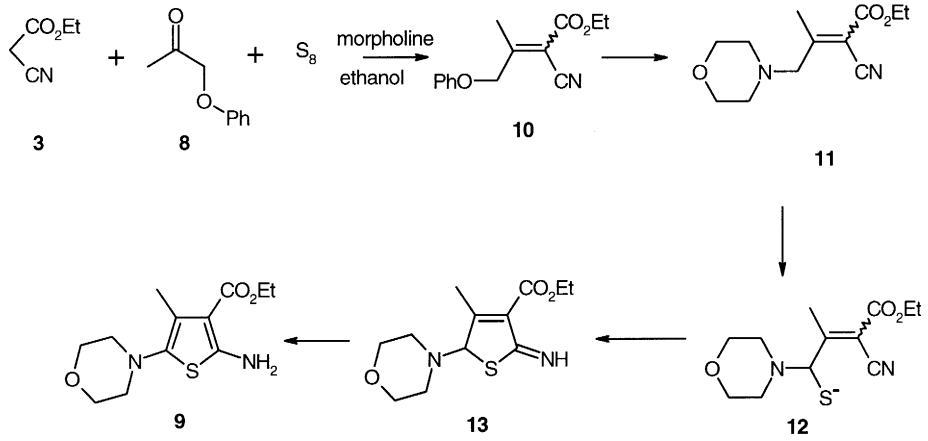
Scheme 2.

Attempts to introduce a 5-aryloxy substituent into the thiophene ring led to the discovery of an unexpected transformation. Reaction of phenoxyacetone **8** with ethyl cyanoacetate and sulfur in the presence of morpholine as described above, resulted not in the 5-phenoxythiophene but in 5-morpholinothiophene **9** in 21% yield (Scheme 3). Clearly the morpholine displaces the phenoxy group but it is not apparent at what stage in the reaction sequence this occurs. It is known that the initial condensation product (e.g. **10**) can react further with sulfur and morpholine to provide the thiophene[9,12] suggesting that displacement occurs after this stage but before insertion of sulfur. We speculate that the reaction proceeds as shown

in Scheme 4 but further studies are required to delineate the exact mechanism. In any event the reaction constitutes a novel four component condensation reaction.



Scheme 3.



Scheme 4.

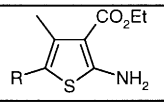
The morpholine can be replaced by a variety of cyclic secondary amines all of which provided the 5-aminothiophene as the sole thiophene product in modest yields (Table 2). A variety of functional groups are tolerated under these mild reaction conditions as demonstrated in Table 2. When the amine was replaced by pyrrolidine or homopiperidine the condensation failed, as it did if an acyclic secondary amine was used. The requirement for a cyclic six-membered ring secondary amine is difficult to rationalise but may be related to the stability of the intermediate **12** and whether it cyclises or eliminates the amine to give a thioaldehyde which would be unstable under the reaction conditions.

In conclusion, we have extended the Gewald synthesis of thiophenes to the preparation of a variety of 5-alkoxythiophenes and provided a convenient method for the preparation of 5-hydroxythiophenes. A novel four component condensation reaction in which 5-aminothiophenes are formed has also been disclosed which could have potential in combinatorial chemistry for the preparation of diverse libraries.[13]

*Preparation of **5a***: To ethyl cyanoacetate (26.6 mmol) in 6 ml ethanol was added methoxyacetone (26.6 mmol) followed by powdered sulfur (26.6 mmol) and morpholine (3.5 ml). The solution was stirred for 18 h, concentrated and chromatographed over silica (CH_2Cl_2/5% diethyl ether) to yield 61% of **5a** (mp 61–63°C). ^{1}H NMR ($CDCl_3$): 5.86 (br, 2H); 4.26 (q, J=7 Hz, 2H); 3.73 (s, 3H); 2.13 (s, 3H); 1.33 (t, J=7 Hz, 3H). ^{13}C NMR ($CDCl_3$): 166.2, 155.4, 142.7, 118.1, 103.3, 63.5, 59.5, 14.4, 12.5.

*Preparation of **9***: To phenoxyacetone (13.3 mmol) in 4 ml ethanol was added ethyl cyanoacetate (13.3 mmol) followed by sulfur (13.3 mmol) and morpholine (1.5 ml). The solution was stirred for 18 h, concentrated and chromatographed over silica (CH_2Cl_2/5% diethyl ether) to yield 21% of **9** (mp 137°C). ^{1}H NMR ($CDCl_3$): 6.0 (br, 2H); 4.26 (q, J=7 Hz, 2H); 3.78 (br t, J=5 Hz, 4H); 2.75 (br t, J=5 Hz, 4H); 2.22 (s,3H); 1.34 (t, J=7 Hz, 3H). ^{13}C NMR ($CDCl_3$): 166.4, 159.4, 134.9, 127.0, 104.2, 67.1, 59.5, 54.6, 14.5, 14.3.

Table 2

	R	Yield / %
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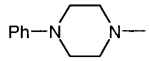
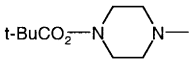
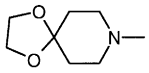
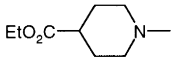
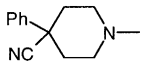
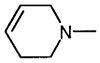
b	thiomorpholine	30
c		27
d		21
e		21
f		30
h		19
i (*tert*-butyl ester)		39

Acknowledgements

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