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Transesterification of trimethyl orthoacetate: an efficient protocol for the synthesis of 4-alkoxy-2-aminothiophene-3-carbonitriles

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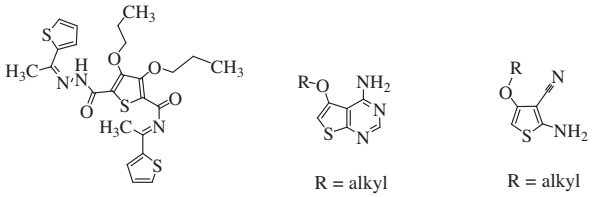
ABSTRACT

A facile one-pot method is reported for the synthesis of 4-alkoxy-2-aminothiophene-3-carbonitriles. Transesterification of trimethylorthoacetate technique allowed introducing alkoxy substituents into 2-aminothiophene ring system. Diverse alkoxy substituents could be introduced efficiently by using this methodology. Further the synthesis of some of new 4-alkylamino-2-aminothiophenes is also reported.

Multisubstituted 2-aminothiophenes are privileged structures, which attracted considerable attention in the design of several biologically active molecules.[1] Ample data have been accumulated highlighting their biological utility as synthons, that is, substituted 2-aminothiophenes and thieno[2,3-*d*]pyrimidines in the development of various interesting molecules. Some of them are known as kinase inhibitors, namely, receptor tyrosine kinase inhibitors (RTK1),[2] B-Raf kinase inhibitors,[3] ErbB-2 kinase inhibitors[4], and epidermal growth factor receptor (EGFR) kinase inhibitors.[5] One such substituted alkoxythiophene **1** (Fig. 1) is currently being explored for its anticonvulsant potency.[6] Further they are also explored for diverse industrial applications such as new conducting polymers[7] and in the preparations of dyes.[8]

In pursuance of our modeling studies based on structure-based drug design of new adenosine kinase inhibitors, 4-amino-5-alkoxythieno[2,3-*d*]pyrimidine **2** and its precursor 2-amino-4-alkoxythiophene **3** (Fig. 1) were identified as key intermediates. Hence we focused our attention to introduce diverse 4-alkoxy substituents into 2-aminothiophene ring system.

Alkoxythiophenes are usually synthesized by nucleophilic substitution of halothiophenes with an alkoxide,[9,10] or direct oxygenation of thiophenes or metallothiophenes with peroxides.[11–13] The presence of reactive functional groups, such as amines demand however pre-protection under such conditions.



1 2 3

Figure 1. Structures of alkoxythiophenes.

The versatility of the Gewald reaction (GR) to prepare 2-aminothiophenes with a high degree of functionality is well known.[14–22] When GR was employed to synthesize one of the desired 4-alkoxythiophene **6** (Scheme 1) by condensing a mixture of trimethylorthoacetate (**4**) and malononitrile in the presence of sulfur in ethanol using morpholine as base, in addition to the desired **6** in 25% yield, 2-amino-4-ethoxythiophene-3-carbonitrile (**8**, 10%) and 2-amino-4-morpholinothiophene-3-carbonitrile (**11**, 40%) were also isolated.

The formation of the products may be explained by two plausible ways: acrylonitrile **5** may undergo nucleophilic substitution reaction with ethanol/morpholine to give the intermediates **7** or **10** which were further converted to the respective thiophenes **8** or **11**. The other possibility could be transesterification of **4** resulting in triethylorthoacetate (**9**) which further underwent GR to give **8**. In order to delineate the formation of **7** a set of two different

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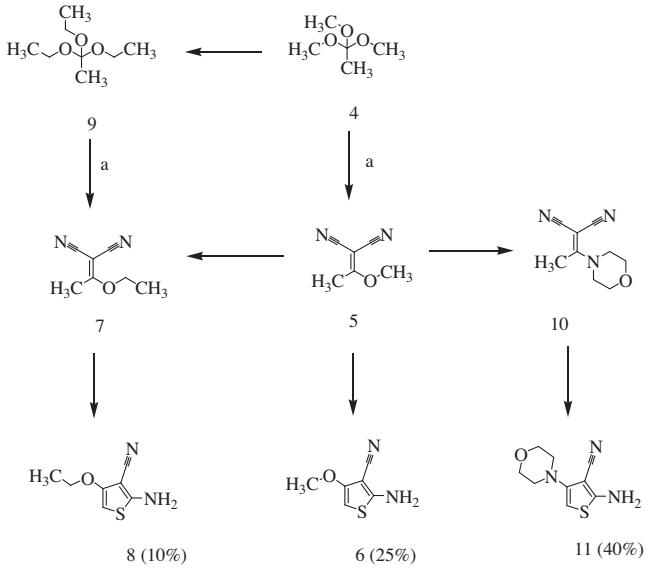


Scheme 1. Gewald reaction of trimethylorthoacetate; reagents and conditions: (a) (i) $CH_2(CN)_2$ (1 equiv), S_8 (1 equiv) morpholine (1.2 equiv), EtOH, 80 °C.

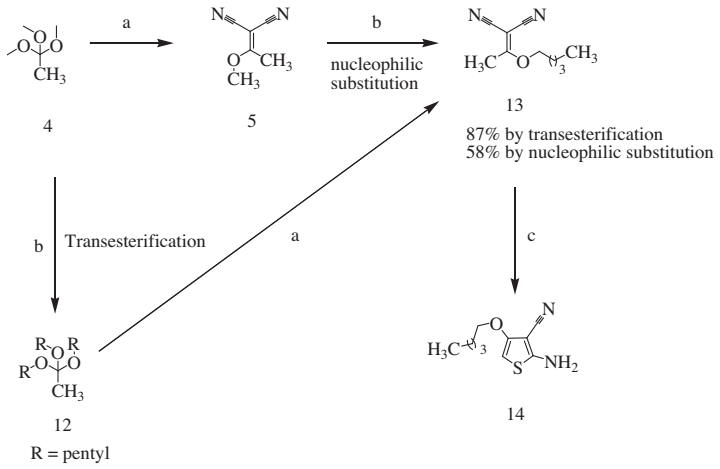
reactions were conducted (Scheme 2). In one set acrylonitrile **5** was heated to 80 °C in *n*-pentanol, and in the other *n*-pentyl orthoacetate (**12**) (synthesized by transesterification of trimethylorthoacetate) was reacted with malononitrile. Interestingly both methods gave identical acrylonitrile intermediate **13** which could be isolated and characterized by spectroscopic studies. Under GR conditions **13** was further converted into 2-amino-4-pentyloxythiophene-3-carbonitrile **14** smoothly in 81% yield.

To explore and further exploit transesterification protocol in the present synthetic study, a detailed investigation was taken up. According to the literature no such attempts were made for the synthesis of functionalized thiophenes. Further it was also observed that the purity profile and yield of **13** was noticeably high by transesterification methodology (87%) as compared to nucleophilic substitution (58%). These observations prompted us to explore this strategy to introduce a variety of alkoxy groups into the 2-aminothiophene ring system. Thus 'higher' orthoacetate esters were synthesized following a transesterification procedure described by Alexander et al.[23] and others.[24] Trimethyl orthoacetate (**4**) was reacted with different alcohols (3 equiv) followed by Knoevenagel condensation of 'higher' orthoacetate esters with malononitrile to give the new acrylonitrile intermediates **15a–o** (Scheme 3).

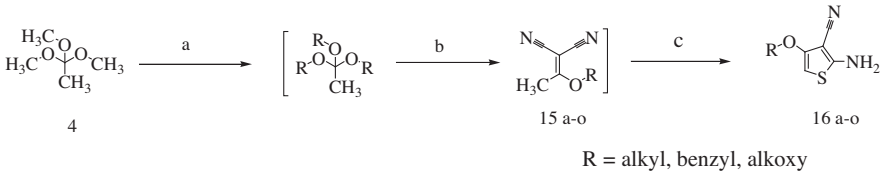
To generate the desired 4-alkoxythiophenes in high yields we further attempted to optimize the reaction conditions. In order to identify the ideal base for the synthesis of the desired product **6** different inorganic (Table 1, entry 1–6) and organic bases (entry 7–10) were exploited. A perusal of the results presented in Table 1 indicates that aqueous reaction conditions coupled with inorganic bases could be the best bet for completion of the reaction (entry 10). However, in addition to $NaHCO_3$, triethylamine was also found to be superior by giving higher yields (67%). The reaction was also investigated at 3 different temperatures (entry 3–6). At room temperature (35 °C), reaction rate was slow and moderate yield was obtained. At a high temperature (80 °C), although the reaction was spontaneous with the addition of base, the yield was low. This may be due to the decomposition of the product. Highest yield of the product was obtained at 60 °C. In the optimized procedure, 1 equiv of triethylamine or aqueous $NaHCO_3$ is added for 15 min to a stirring mixture of sulfur and ylidene **5** in THF at 60 °C.

Under the above optimized reaction conditions, using triethylamine as base GR of the acrylonitriles **15a–o** (Scheme 3) provided respective 4-alkoxy-2-aminothiophene-3-carbonitriles smoothly (**16a–o**, Table 2). The results shown in Table 2 illustrate the versatility of the reaction. The nature of alcohol was found to exhibit a decisive bearing on the yield of the reaction. Transesterification reactions proceeded smoothly with primary alcohols; as is evident from high yields of 4-alkoxythiophenes (**16a–i**). Secondary alcohols, aryl alcohols, and alkoxyethanols underwent sluggish interchange reactions, leading to moderate to low yields of 4-alkoxythiophenes (**16j–l**, **n**, and **o**) respectively. Whereas with tertiary alcohol (**16 m**) no exchange occurred as no methanol was formed during the reaction. Conversely, reaction of trimethyl orthoacetate and malononitrile in *tert*-butanol resulted in 2-amino-4-methoxythiophene as the only product suggesting that the reaction is not proceeding either by transesterification process or by nucleophilic substitution. The mechanistic pathway of alkoxythiophene formation could be explained in similar lines as that of GR (Supplementary data-2). The compounds (**16a–o**) summarized in Table 2 were synthesized according to the procedure illustrated under the preparation of 2-amino-4-pentyloxythiophene-3-carbonitrile (**16e**).[25]

It is noteworthy that, acrylonitrile **5** undergoes nucleophilic substitution reaction with secondary amines, such as morpholine

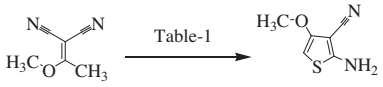


Scheme 2. Synthesis of 4-pentyloxy-2-aminothiophene **14** and precursor **13** by transesterification of trimethylorthoacetate; reagents and conditions: (a) $CH_2(CN)_2$, 60 °C, 3 h; (b) *n*-pentanol, 24 h, 80 °C; (c) S_8, triethylamine, 60 °C, 15 min.



Scheme 3. Synthesis of 4-alkoxy-2-aminothiophenes (**16a–o**); reagents and conditions: (a) R-OH (3 equiv), 24 h, 80 °C; (b) $CH_2(CN)_2$, 60 °C, 3 h; (c) S_8, triethylamine (1 equiv), 60 °C, 15 min.

Table 1
Yield of 2-amino-4-methoxythiophene-3-carbonitrile with different bases



Entry	Base (1 equiv)	Solvent	Temp (°C)	Time	Yield (%)
1	NaOH (aqueous)	THF	60	30 min	31[c]
2	$NaHCO_3$	THF	60	4 h	21[a]
3	$NaHCO_3$[b] (aqueous)	THF	35	3 h	36[a]
4	$NaHCO_3$[b] (aqueous)	THF	60	15 min	53[c]
5	[b]$NaHCO_3$ (aqueous)	THF	80	15 min	22[c]
6	$NaHCO_3$[b] (aqueous)	EtOAC	60	45 min	38[a]
7	Pyridine	Pyridine	35	4 h	32[c]
8	Diethylamine	EtOH	35	1	15[a]
9	Triethylamine	THF	35	2 h	54[a]
10	Triethylamine	THF	60	15 min	67[c]

[a] Conversion into **6** by GC.
[b] 7.3% Aqueous $NaHCO_3$.
[c] Isolated yields.

and piperidine to give the new intermediates **17a–c**. The GR of **17a–c** provided 4-alkylamino-2-aminothiophene-3-carbonitriles **18a–c** in moderate to good yields (Scheme 4). Although the limited results available using a few amines indicate a good scope of this methodology to synthesize 4-alkylamino-2-aminothiophenes, a more generalized extension of this methodology for the synthesis of other analogues like 4-aryl/heteroarylamino-2-aminothiophenes needs further investigation.

In conclusion, a facile method was developed by expanding the application and scope of transesterification protocol for the synthesis of 2-amino-4-alkoxythiophenes. The utility of the method lies in its suitability to introduce diverse alkoxy substituents into 2-aminothiophene ring system by GR. Besides being a one-pot synthetic protocol, it distinctly adds enough advantage in pursuit of higher yields. Further studies on nucleophilic substitution of **5** by different arylamines, heterocyclic amines, and thiols could have potential in combinatorial chemistry for generating diverse library of 4-alkoxy/alkylamino-2-aminothiophenes.

Table 2
Yields of 4-alkoxy-2-amino-thiophene-3-carbonitriles

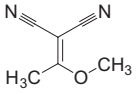
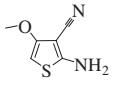
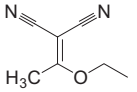
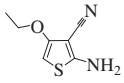
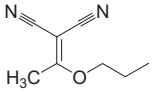
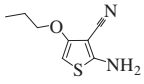
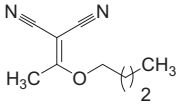
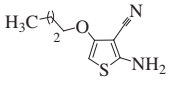
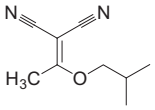
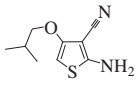
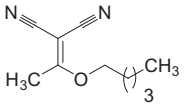
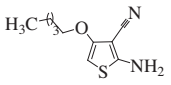
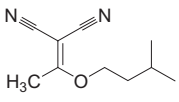
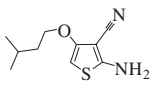
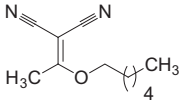
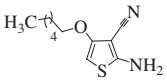
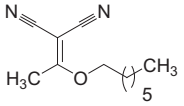
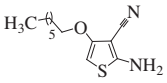
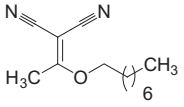
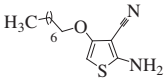
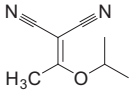
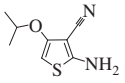
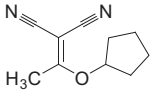
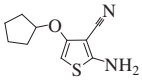
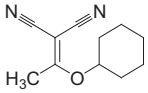
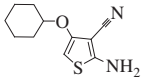
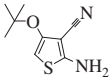
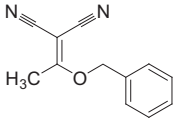
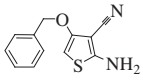
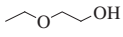
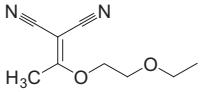
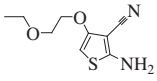
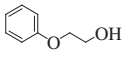
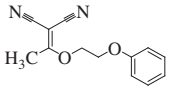
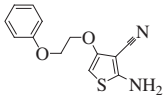
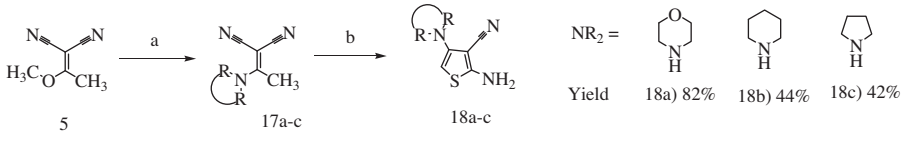
Compd No.[b]	Alcohol/Orthoester (R-OH)/$CH_3(OR)_3$	Acrylonitrile **15a–o**	4-Alkoxythiophene **16a–o**	Yield (%)	mp (°C)
7	$(OCH_3)_3C–CH_3$			74	193–194
16a	$(OC_2H_5)_3C–CH_3$			84	131–132
16b[a]	$CH_3–CH_2–CH_2–OH$			67	220–221
16c	$CH_3–(CH_2)_2–CH_2–OH$			76	84–85
16d	$(CH_3)_2CH–CH_2–OH$			55	103–104
16e	$CH_3–(CH_2)_3–CH_2–OH$			81	76–78
16f	$(CH_3)_2CH–CH_2–CH_2–OH$			61	190–191

Table 2 (*continued*)

Compd No.[b]	Alcohol/Orthoester (R-OH)/$CH_3(OR)_3$	Acrylonitrile **15a–o**	4-Alkoxythiophene **16a–o**	Yield (%)	mp (°C)
16g	CH_3–$(CH_2)_4$–CH_2–OH			72	124
16h	CH_3–$(CH_2)_5$–CH_2–OH			69	119–120
16i	CH_3–$(CH_2)_6$–CH_2–OH			76	82–83
16j[a]	$(CH_3)_2$CH–OH			48	178
16k				26	100–102
16l				28	98
16m	$(CH_3)_3$–CH–OH	—		NR	—
16n				32	112
16o				32	93–95
16p				48	124–125

[a] 5 equiv of alcohol was used, mp = melting point.
[b] Compound no, NR = no reaction.



Scheme 4. Synthesis of 4-alkylamino-2-aminothiophene-3-carbonitriles; reagents and conditions: (a) HNR_2 (1.5 equiv); (b) S_8 (1 equiv), triethylamine (1 equiv), THF, 60 °C, 4 h.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.090.

References and notes

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25. *A general protocol of the reaction is as follows:* While continuously distilling methanol from the reaction, a mixture of trimethyl orthoacetate (10.5 mL, 100 mmol) and *n*-amyl alcohol (31.5 mL, 300 mmol) was heated to 80 °C for 24 h. Reaction mixture was cooled to room temperature; malononitrile (6.6 g, 100 mmol) was added and further heated to 60 °C for 2–3 h. Excess amyl alcohol in the reaction mixture was removed under vacuum. After addition of sulfur (3.2 g, 100 mmol) and THF (50 mL) to the crude mixture, 1 equiv of triethylamine (13 mL, 100 mmol) is added for 15 min and reaction continued for additional 15–20 min at 60 °C. After completion of the reaction, solvent was removed under vacuum, diluted with water, and the aqueous layer was extracted twice with ethyl acetate. Organic layers were combined, dried over Na_2SO_4, and concentrated under vacuum. The product obtained was purified by column chromatography (20% ethylacetate in hexane).