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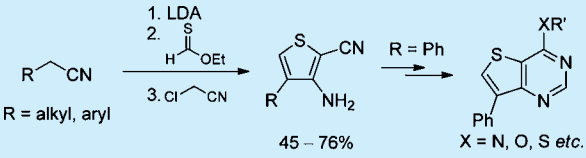
One-Pot Synthesis of 4-Substituted 3-Amino-2-cyanothiophenes Involving *O*-Ethyl Thioformate

Haiming Zhang,*,† Mark S. Bednarz, Ngiap-Kie Lim, Gonzalo Hernandez, and Wenxue Wu*

Chemical Development, Lexicon Pharmaceuticals, Inc., 350 Carter Road, Princeton, New Jersey 08540, United States

Supporting Information

ABSTRACT: An efficient one-pot synthesis of 4-substituted 3-amino-2-cyanothiophenes is described. Treatment of 2-alkyl or aryl substituted acetonitrile sequentially with 2.1 equiv of LDA, 1.1 equiv of *O*-ethyl thioformate, and 1.2 equiv of 2-chloroacetonitrile afforded the thiophenes in moderate to good yields. The thiophene core can be readily incorporated into more elaborate pharmaceutically relevant structures as demonstrated by converting 3-amino-2-cyano-4-phenylthiophene (**1g**) to various functionalized thieno[3,2-*d*]pyrimidines in only two steps.



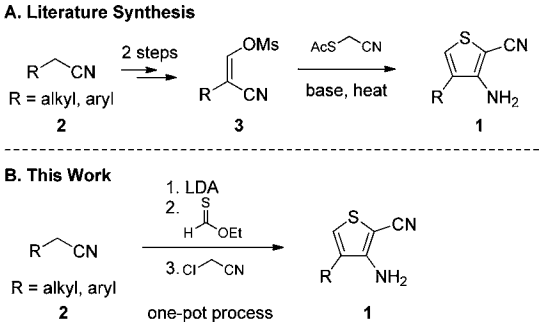
The utilities of substituted 2- or 3-aminothiophenes have been demonstrated in an array of applications in pharmaceuticals, dyes, and agrochemicals.[1] The synthesis of 2-aminothiophenes can be accomplished by well-established Gewald reactions[2] involving multicomponent condensation of a ketone, an activated nitrile, and elemental sulfur.[1a,c] Alternatively, 2-aminothiophene can be accessed via a stepwise approach employing a Knoevenagel condensation,[3] followed by a base-promoted sulfuration and cyclization.[1a,c] In contrast, the synthesis of 3-aminothiophenes is rather challenging and underdeveloped.[1b,c] The synthetic routes to 3-aminothiophenes primarily involve the modified Fiesselmann thiophene synthesis,[1d,e,4a] the Gommper reaction,[1f] and reaction of β-halogenated or oxygenated acrylonitriles with mercaptans containing an activated methylene group.[4b−e]

Our recent project needs required us to develop an efficient synthesis of 4-substituted 3-amino-2-cyanothiophenes (**1**). Literature searches showed that the only available synthesis of 4-substituted 3-amino-2-cyanothiophenes (**1**) involved the generation of a vinyl mesylate intermediate **3** from nitrile **2**, followed by treatment with *S*-acetylmercaptoacetonitrile in the presence of a base and heat to complete the cyclization (Scheme 1A).[5] This chemistry, however, suffers from a very limited scope, the use of an expensive reagent *S*-acetylmercaptoacetonitrile, and the requirement of a multistep synthesis. Therefore, a more practical and efficient synthesis was highly desirable.

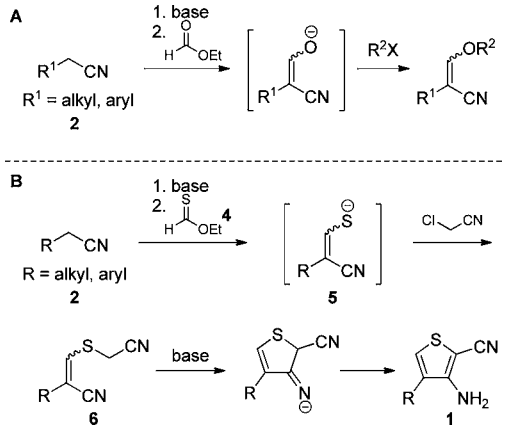
Herein, we wish to report a one-pot synthesis of 4-substituted 3-amino-2-cyanothiophenes (**1**) from 2-alkyl or aryl substituted acetonitrile (**2**) by sequential treatment with LDA, *O*-ethyl thioformate,[6] and 2-chloroacetonitrile (Scheme 1B).

It has been reported in the literature that treatment of substituted acetonitriles with a strong base and then ethyl formate generates a vinyl oxide species which can be readily quenched with an electrophile to produce oxygenated acrylonitriles (Scheme 2A).[5,7] We envisioned that substituting ethyl formate with *O*-ethyl thioformate (**4**) should produce a

Scheme 1. Synthesis of 4-Substituted 3-Amino-2-cyanothiophenes 1



Scheme 2. Proposed Synthesis of 1 Using *O*-Ethyl Thioformate



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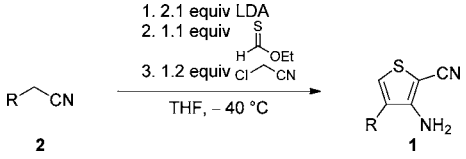
vinyl thiolate intermediate **5**, which should react with 2-chloroacetonitrile to give intermediate **6**. In the presence of a base, compound **6** should cyclize to furnish the desired 4-substituted 3-amino-2-cyanothiophenes (**1**) (Scheme 2B).

It is noteworthy that *O*-ethyl thioformate (**4**) has been used to generate thioformamides which are synthetically useful intermediates for the synthesis of various heterocycles,[8] thioamides,[9] iminyl sulfides,[10] enamines,[11] and amines.[12] However, it was only recently, as reported by Borths, that the preparation of *O*-ethyl thioformate became readily achievable at a large scale and in high yield.[6a]

To our great delight, when 2-alkyl or aryl substituted acetonitriles (**2**) were sequentially treated at −40 °C with LDA (2.1 equiv), *O*-ethyl thioformate (**4**, 1.1 equiv), and 2-chloroacetonitrile (1.2 equiv), the desired thiophene product **1** was indeed produced (Table 1).[13]

Table 1. One-Pot Synthesis of 3-Amino-2-cyanothiophenes 1[a]



2 1

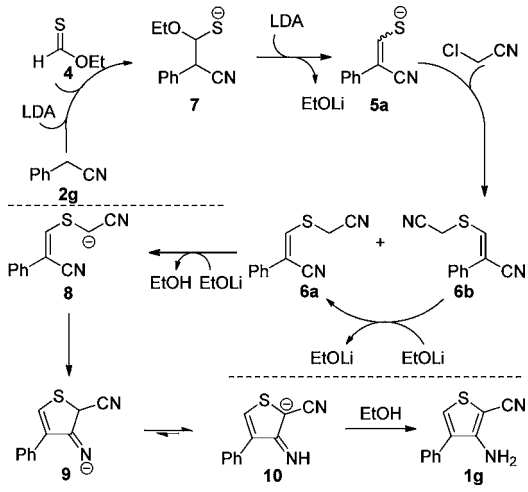
entry	nitrile R =		thiophene		yield (%)
1	Me	**2a**		**1a**	63[b]
2	*i*-Pr	**2b**		**1b**	45[b]
3	*c*-Pr	**2c**		**1c**	63[b]
4	CF_3	**2d**		**1d**	0
5	CN	**2e**		**1e**	0
6	H	**2f**		**1f**	0
7	Ph	**2g**		**1g**	70
8	4-$MeOC_6H_4$	**2h**		**1h**	73
9	4-FC_6H_4	**2i**		**1i**	76
10	2-thiophenyl	**2j**		**1j**	74[b]
11	*c*-Pr	**2c**		**1k**	65[c]

[a]All reactions were carried out at 1.00 g scale of the nitrile except for **2a** (0.50 g). [b]The yield is based on the isolated HCl salt. [c]1.2 equiv of *tert*-butyl 2-chloroacetate was employed.

As shown in Table 1, simple alkyl-substituted acetonitriles produced moderate to good yields of the desired thiophenes (entries 1−3). The yield of the isopropyl substituted thiophene **1b** was relatively low, presumably due to the extra steric hindrance that the isopropyl group introduced. Acetonitriles substituted with an electron-withdrawing group, for example 3,3,3-trifluoropropanenitrile (**2d**) and malonitrile (**2e**), as well as simple acetonitrile (**2f**), unfortunately, did not afford any desired thiophene products (entries 4−6). Instead, formation of dark-colored gummy residues was observed in each of these three reactions, which indicates possible polymerization of intermediates **5** due to either their electron-deficient nature (for **2d** and **2e**) or the lack of steric hindrance (for **2f**). 2-Aryl substituted acetonitriles, on the other hand, underwent the thiophene formation smoothly, generating the desired products in good yields. For example, benzyl cyanide (**2g**) readily afforded the desired 3-amino-2-cyano-4-phenylthiophene (**1g**) in 70% yield (entry 7). 2-Aryl acetonitrile with either an electron-donating group (4-MeO, **2h**) or an electron-withdrawing group (4-F, **2i**), as well as a heterocycle (2-thiophenyl) substituted acetonitrile (**2j**), also uneventfully produced the desired thiophene products in 73−76% yields (entries 8−10). Gratifyingly, *tert*-butyl 2-chloroacetate reacts similarly to chloroacetonitrile to give the desired thiophene ester **1k** in good yield (65%) (entry 11). Thus, we believe this chemistry could be readily extended and provide an alternative to the synthesis of a wide spectrum of 4-subsituted 3-aminothiophene-2-carboxylates.[4b−e]

We propose that the mechanism for this process, illustrated using benzyl cyanide (**2g**) as a representative example, involves the deprotonation of nitrile **2g**, followed by a Claisen-like nucleophilic addition of the resulting anion to *O*-ethyl thioformate (**4**) to generate thiolate **7** when 1 equiv of LDA was employed. The second equivalent of LDA then promotes an elimination reaction of thiolate **7** to afford an ethoxide and thiolate **5a**. Upon treatment with 2-chloroacetonitrile, thiolate **5a** is readily converted to a mixture of isomeric vinyl thiolates (**6a** and **6b**). An ethoxide anion promotes not only the isomerization of *E*-thiolate **6b** to *Z*-thiolate **6a** but also the facile cyclization of *Z*-thiolate **6a** to the cyclized intermediate **9**, which quickly undergoes tautomerization to form the desired thiophene **1g** (Scheme 3).

Scheme 3. Proposed Mechanism



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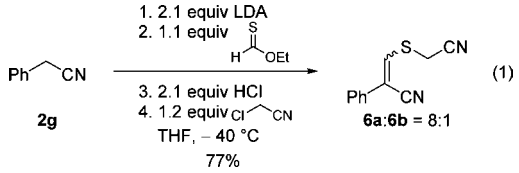
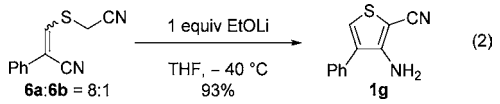
Under our reaction conditions, we were unable to observe the formation of intermediates **6a** and **6b**, presumably because the isomerization of **6b** to **6a** and the cyclization of **6a** to thiophene **1g** are too rapid to monitor on the experimental time scale. To confirm the formation of thiolates **6a** and **6b**, benzyl cyanide (**2g**) was treated with 2.1 equiv of LDA and 1.1 equiv of *O*-ethyl thioformate (**4**) to generate intermediate **5a**, which was neutralized with 2.1 equiv of HCl in dioxane. 2-Chloroacetonitrile was then charged into the reaction mixture. Gratifyingly, we were able to isolate an 8:1 mixture (by ^{1}H NMR) of thiolates **6a**:**6b** in 77% yield (eq 1). The mixture was



then treated with 1 equiv of EtOLi (prepared from *n*-BuLi and EtOH) at −40 °C to afford thiophene **1g** in 93% yield (eq 2).



The reaction kinetics clearly showed that, in the presence of 1 equiv of base EtOLi, the conversion of *Z*-isomer **6a** to thiophene **1g** is essentially instantaneous (<5 min) while the transformation of *E*-isomer **6b** to **6a**/**1g** is somewhat slower (ca. 1% remaining at 30 min based on HPLC analysis, Figure 1) at −40 °C.

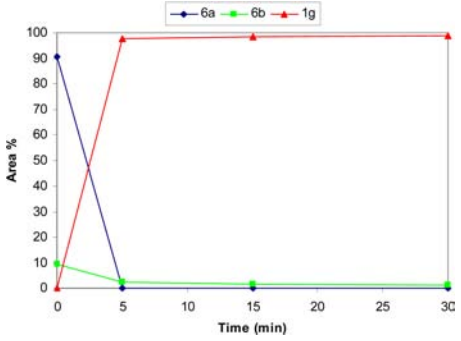


Figure 1. EtOLi promoted thiophene **1g** formation from **6a**/**6b**.

To demonstrate the synthetic utility of 4-substituted 3-amino-2-cyanothiophenes (**1**), thiophene **1g** was smoothly converted to 4-chloro[3,2-*d*]thienopyrimidine **11** in 98% yield under Vilsmeier−Haack conditions (Scheme 4).[14] Compound **11** then can react with nitrogen, oxygen, or sulfur nucleophiles via S_NAr reactions to afford the desired substituted thieno[3,2-*d*]pyrimidines[15] in excellent yields (Table 2, entries 1−3). It can also undergo palladium-catalyzed Suzuki−Miyaura[16] or Sonogashira[17] reactions to generate the desired coupling products in moderate yields (Table 2, entries 4−5).

Scheme 4. Synthetic Utility of Thiophene 1g

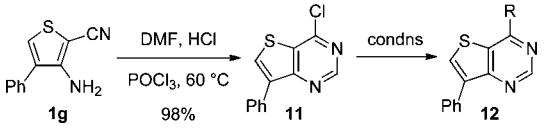
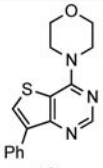
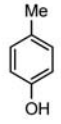
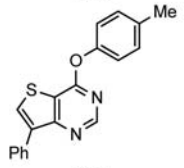
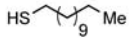
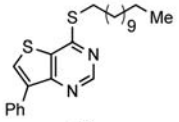
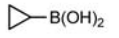
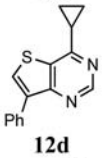
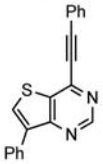


Table 2. Functionalization of Thieno[3,2-*d*]pyrimidine 11[a]

entry	reactant	condn	product	yield (%)
1		A	 **12a**	94
2		B	 **12b**	90
3		C	 **12c**	93
4		D	 **12d**	52
5		E	 **12e**	51[b]

[a]All reactions were performed using 0.50 mmol of **11**. Conditions: (A) 4.0 equiv of morpholine in THF at 20 °C. (B) 1.2 equiv of *p*-cresol, 2.0 equiv of K_2CO_3 in THF/DMF at 60 °C. (C) 1.2 equiv of *n*-$C_{12}H_{23}SH$, 2.0 equiv of K_2CO_3 in MeOH at 20 °C. (D) 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, 2.5 equiv of *c*-$PrB(OH)_2$, 3.0 equiv of K_2CO_3 in PhMe/H_2O (4:1) at 90 °C. (E) 2 mol % $PdCl_2(PPh_3)_2$, 4 mol % CuI, 2.4 equiv of PhC≡CH in Et_3N at 80 °C. [b]38% of **11** was recovered.

In conclusion, we have developed an efficient one-pot synthesis of 4-substituted 3-amino-2-cyanothiophenes in moderate to good yields by treating 2-alkyl or aryl substituted acetonitrile with LDA, followed by *O*-ethyl thioformate and then 2-chloroacetonitrile. The synthetic utility of the resulting thiophenes was demonstrated by converting 3-amino-2-cyano-4-phenylthiophene (**1g**) to the corresponding 4-chlorothieno-[3,2-*d*]pyrimidine **11** which then undergoes nucleophilic aromatic substitution with amine, phenol, or thiol nucleophiles or palladium-catalyzed cross-coupling reactions to generate structurally diverse thieno[3,2-*d*]pyrimidines in moderate to excellent yields.

■ ASSOCIATED CONTENT

Supporting Information

General experimental information, copies of ^{1}H and ^{13}C NMR of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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AUTHOR INFORMATION

Corresponding Authors

*E-mail: zhang.haiming@gene.com.
*E-mail: wwu@lexpharma.com.

Present Address

†Small Molecule Process Chemistry, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080.

Notes

The authors declare no competing financial interest.

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