

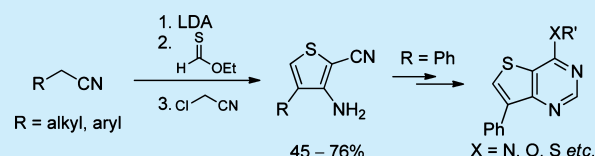
One-Pot Synthesis of 4-Substituted 3-Amino-2-cyanothiophenes Involving *O*-Ethyl Thioformate

Haiming Zhang,^{*,†} Mark S. Bednarz, Ngai-Kie Lim, Gonzalo Hernandez, and Wenxue Wu^{*}

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

S 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 reactions² 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 Fiessemann thiophene synthesis,^{1d,e,4a} the Gompper reaction,^{1f} and reaction of β -halogenated or oxygenated acrylonitriles with mercaptans containing an activated methylene group.^{4b-e}

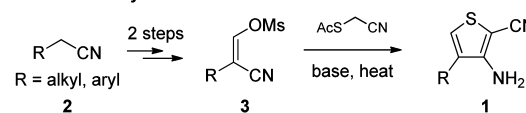
Our recent project needs required us to develop an efficient synthesis of 4-substituted 3-amino-2-cyanothiophenes (**1**). Literature searches showed that the only available synthesis of 4-substituted 3-amino-2-cyanothiophenes (**1**) involved the generation of a vinyl mesylate intermediate **3** from 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).

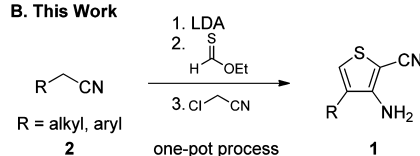
It has been reported in the literature that treatment of substituted acetonitriles with a strong base and then ethyl formate generates a vinyl oxide species which can be readily quenched with an electrophile to produce oxygenated acrylonitriles (Scheme 2A).^{5,7} We envisioned that substituting ethyl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

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

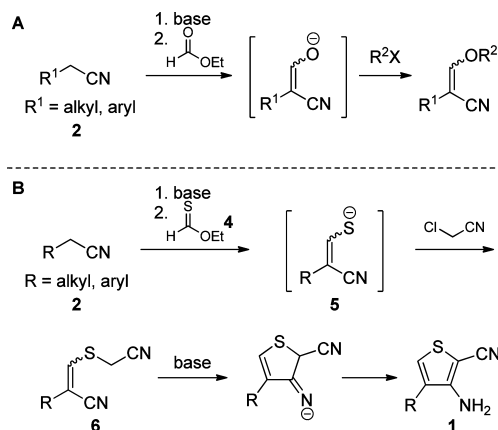
A. Literature Synthesis



B. This Work



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



Received: March 25, 2014

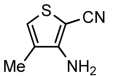
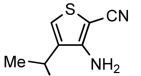
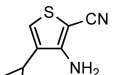
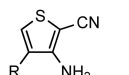
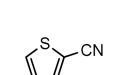
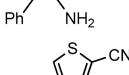
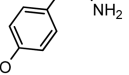
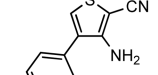
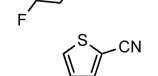
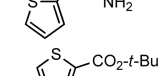
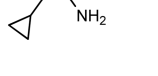
Published: April 18, 2014

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 $-40\text{ }^{\circ}\text{C}$ 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

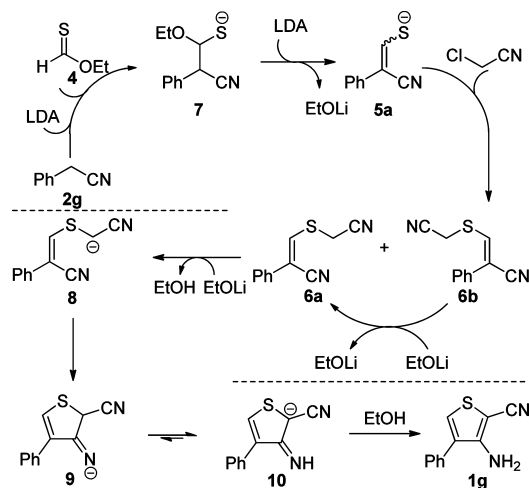
entry	nitrile R =	thiophene	yield (%)
1	Me		63 ^b
2	<i>i</i> -Pr		45 ^b
3	<i>c</i> -Pr		63 ^b
4	CF ₃		0
5	CN		0
6	H		0
7	Ph		70
8	4-MeOC ₆ H ₄		73
9	4-FC ₆ H ₄		76
10	2-thiophenyl		74 ^b
11	<i>c</i> -Pr		65 ^c

^aAll reactions were carried out at 1.00 g scale of the nitrile except for **2a** (0.50 g). ^bThe yield is based on the isolated HCl salt. ^c1.2 equiv of *tert*-butyl 2-chloroacetate was employed.

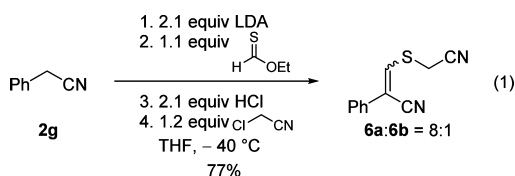
As shown in Table 1, simple alkyl-substituted acetonitriles produced moderate to good yields of the desired thiophenes (entries 1–3). The yield of the isopropyl substituted thiophene **1b** was relatively low, presumably due to the extra steric hindrance that the isopropyl group introduced. Acetonitriles 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-substituted 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).

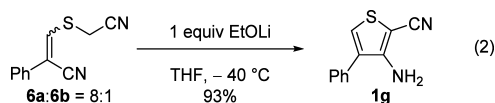
Scheme 3. Proposed Mechanism



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 ^1H 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 $-40\text{ }^\circ\text{C}$ 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 ($<5\text{ min}$) 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 $-40\text{ }^\circ\text{C}$.

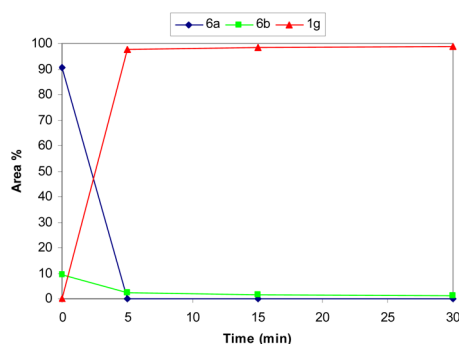
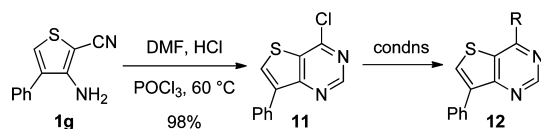


Figure 1. EtOLi promoted thiophene **1g** formation from **6a/6b**.

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 $\text{S}_\text{N}\text{Ar}$ reactions to afford the desired substituted thieno[3,2-*d*]pyrimidines¹⁵ in excellent yields (Table 2, entries 1–3). It can also undergo palladium-catalyzed Suzuki–Miyaura¹⁶ or

Scheme 4. Synthetic Utility of Thiophene **1g**



Sonogashira¹⁷ reactions to generate the desired coupling products in moderate yields (Table 2, entries 4–5).

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

entry	reactant	condn	product	yield (%)
1		A		94
2		B		90
3		C		93
4		D		52
5		E		51 ^b

^aAll reactions were performed using 0.50 mmol of **11**. Conditions: (A) 4.0 equiv of morpholine in THF at $20\text{ }^\circ\text{C}$. (B) 1.2 equiv of *p*-cresol, 2.0 equiv of K_2CO_3 in THF/DMF at $60\text{ }^\circ\text{C}$. (C) 1.2 equiv of *n*-C₁₂H₂₅SH, 2.0 equiv of K_2CO_3 in MeOH at $20\text{ }^\circ\text{C}$. (D) 10 mol % Pd(OAc)₂, 20 mol % PPh₃, 2.5 equiv of *c*-PrB(OH)₂, 3.0 equiv of K_2CO_3 in PhMe/H₂O (4:1) at $90\text{ }^\circ\text{C}$. (E) 2 mol % PdCl₂(PPh₃)₂, 4 mol % CuI, 2.4 equiv of PhC≡CH in Et₃N at $80\text{ }^\circ\text{C}$. ^b38% 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 ^1H and ^{13}C NMR of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ 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.

■ ACKNOWLEDGMENTS

The authors would like to thank Mr. Leonard Hargiss for collecting HRMS data as well as Drs. Matt Zhao and Lauren Sirois (all from Lexicon Pharmaceuticals) for proofreading the manuscript.

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