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A facile, scalable preparation of 4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carbonitriles

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ABSTRACT

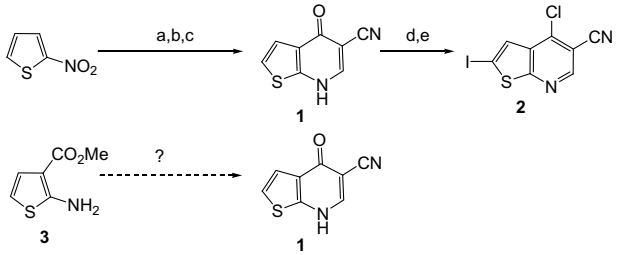
We report a new synthesis of thieno[2,3-*b*]pyridine-5-carbonitriles from 2-aminothiophene-3-carboxylate esters. The key step of the synthesis is a thermally promoted elimination/decarboxylation followed by nucleophilic cyclization to give 4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carbonitriles. The reactions proceed in good yield and generally require no chromatographic purification. These compounds are easily transformed in two steps to 4-chloro-2-iodothieno[2,3-*b*]pyridine-5-carbonitriles which are key intermediates in the synthesis of various kinase inhibitors.

1. Introduction

4-Oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carbonitriles such as **1** are important intermediates in the synthesis of thieno[2,3-*b*]-pyridine-5-carbonitrile kinase inhibitors.[1–3] Compound **1** can be transformed in two steps to **2**, a versatile intermediate whose unique structure allows for complementary addition of nucleophiles to the 2-position and to the 4-position of the thieno[2,3-*b*]-pyridine by palladium-catalyzed addition and S_NAr addition, respectively.

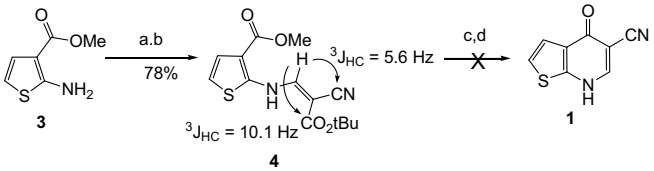
The previously reported synthesis of **2** began with tin-mediated reduction of 2-nitrothiophene followed by nucleophilic addition to ethyl ethoxymethylenecyanoacetate (EMCA) and electrophilic ring closure to gave **1**[4] (Scheme 1). Chlorination ($POCl_3$)[5] followed by nucleophilic iodination[1] gave the key intermediate **2** in 13% overall yield. In addition to the low yield, this sequence has several inherent drawbacks. First, the commercial 2-nitrothiophene is contaminated with small amounts (10–20%) of 3-nitrothiophene, creating purification issues through the sequence. Second, large amounts of toxic reagents such as tin and EMCA (a sensitizer) are required early in the reaction sequence. Finally, substituted 2-nitrothiophenes are not commercially available. This creates limitations on the SAR that may be readily explored at the 2 and 3 position of the thieno[2,3-*b*]pyridone.

With these issues in mind, we desired a route to compound **1** that would begin with 2-aminothiophene-3-carboxylate esters, such as **3**. Substituted 2-aminothiophene-3-carboxylate esters are widely available commercially and are easily synthesized by the classic Gewald reaction.[6,7] Therefore, such a synthetic method would presumably allow for a straightforward synthesis of substituted analogs of compound **1**.



Scheme 1. Reagents and conditions: (a) Sn, HCl; (b) EMCA, pyridine; (c) PhOPh, 255 °C; (d) $POCl_3$; (e) LDA then I_2, −78 °C.

Following literature precedent for a related anthranilic ester,[8] the aminothiophene **3** was treated with excess dimethylformamide dimethylacetal (DMF–DMA) at 100 °C overnight. Evaporation gave the dimethylamidine which was dissolved in *tert*-butanol and treated with *t*-butyl cyanoacetate (Scheme 2). Enamine **4** slowly crystallized out of the reaction solution over a period of 4 days in approximately 50% yield. Partial concentration of the mother liquor resulted in additional crystallization (over several days) to give a combined yield of 78%. Unexpectedly, the NMR analysis of **4** indicated the presence of only a single alkene isomer.



Scheme 2. Reagents and conditions: (a) DMF–DMA, 100 °C; (b) *t*-Bu-cyanoacetate, *t*-BuOH; (c) TfOH; (d) DBU.

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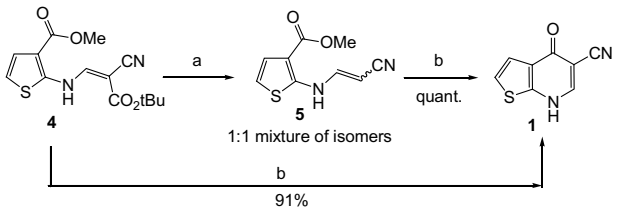


Scheme 3. Reagents and conditions: (a) PhOPh or $C_6H_4Cl_2$, 180 °C; (b) PhOPh, 255 °C, 2 h.

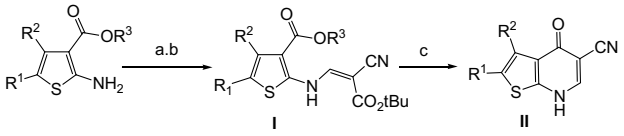
^1H–^{13}C HSQMBC experiments indicated that the J_{CCCH} between the olefinic proton and the carbonyl carbon was significantly greater than the J_{CCCH} between the olefinic proton and the nitrile carbon. This strongly suggests that the obtained isomer is the shown (*Z*) isomer. The previous work on related quinolones had shown that triflic acid-promoted removal of the *t*-butyl group followed by basification with DBU would give the desired thieno[2,3-*b*]pyridone **1**.[8] While the triflic acid-promoted dealkylation proceeded as expected, numerous byproducts were observed following DBU treatment and only a trace of **1** was obtained.

Alternatively, compound **4** could be heated in dichlorobenzene or diphenyl ether to 180 °C to affect the thermal elimination of the *t*-butyl and concomitant decarboxylation to give enamine **5** as a mixture of regiomers (Scheme 3). Once again, literature precedent for the synthesis of quinolones suggested that the ring closure to form **1** should be trivial. Analogous quinolone ring closures have been performed under basic conditions.[9,10] However, both base (DBU, LDA, NaOH, NaOMe) and acid (HOAc, TsOH) failed to affect the cyclization of **5**. Only starting material or polymerized material was obtained. Interestingly however, refluxing **5** in diphenyl ether promoted a nearly quantitative conversion to the desired thieno[2,3-*b*]pyridone **1** (Scheme 3). To the best of our knowledge, thermal ring closure of enamines onto esters to form pyridone-containing scaffolds is unprecedented in the literature.[†]

Given that both the decarboxylation and ring closure reactions are promoted thermally, we attempted to perform these two reactions in a single operation. To our satisfaction, we found that slowly adding **4** to refluxing diphenyl ether followed by heating at reflux for approximately 2 h then cooling the reaction and pouring into hexanes gave a 91% isolated yield of thieno[2,3-*b*]pyridone **1**. Extending the reaction beyond 2 h resulted in gradually decreased yields due to thermal decomposition of the desired product. In spite of the high temperature, this reaction was easily scalable and was conducted successfully up to a 0.5 mol scale. (*CAUTION*: On a large scale, compound **4** must be added to the refluxing diphenyl ether in portions over a 30 min period due to the vigorous release of 1 M equiv each of CO_2, isobutylene, and methanol gas during the cyclization.)

Having successfully worked out conditions for the conversion of methyl 2-aminothiophene-3-carboxylate (**3**) to pyridone **1**, we set about exploring the utilization of 4-substituted and 5-substituted 2-aminothiophene-3-carboxylate esters. We found that numerous substituted 2-aminothiophene-3-carboxylates were able to be successfully transformed in three steps to the desired 4-oxo-4,7-dihydrothieno[2,3-*b*]pyridines (**IIa**–**m**) (Table 1). The isolated yields of the intermediate cyanoacrylate esters **I** were generally modest (23–73%). In all but two examples, compound **I** crystallized out of the reaction solution over a period of several days. This dependence upon the crystallinity and poor solubility of **Ia**–**m** may account for some of the lower yields obtained in this reaction. In almost all cases, intermediate **I** was obtained as a single regiomer presumed to be of the (*Z*) configuration based on the NMR studies of compound **4**. The second step of the sequence, the thermal-promoted cyclization to form **II**, proceeded with generally high yield (64–99% isolated yield).

Table 1
Reagents: (a) DMF–DMA, 100 °C, 2 h; (b) *t*-Bu-cyanoacetate, *t*-BuOH, 2–8 days; (c) PhOPh, 255 °C, 2 h

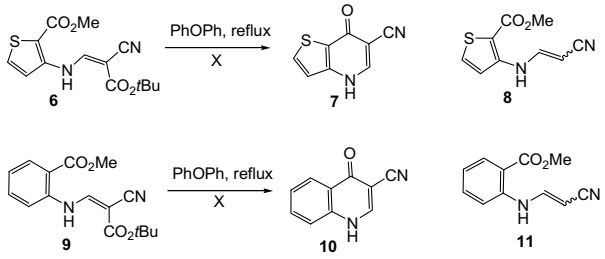


R^1	R^2	R^3	Yield I[a] (%)	Yield II (%)
H	H	Me	**4**, 78	**1**, 91
H	Me	Et	**Ia**, 64	**IIa**, 85
H	*i*-Pr	Et	**Ib**, 73	**IIb**, 78
Me	H	Me	**Ic**, 53	**IIc**, 86
Et	H	Et	**Id**, 33	**IId**, 88
Ph	H	Et	**Ie**, 53	**IIe**, 90
Bn	H	Me	**If**, 70	**IIf**, 79
Me	Me	Me	**Ig**, 69	**IIg**, 91
H	4-F–Ph	Et	**Ih**, 23	**IIh**, 87
Me	4-F–Ph	Me	**Ii**, 76	**IIi**, 64
H	4-Cl–Ph	Et	**Ij**, 70	**IIj**, 72
H	4-Br–Ph	Et	**Ik**, 41	**IIk**, 77
H	4-OMe–Ph	Me	**Il**, 32[b]	**III**, 99
H	2-Furyl	Et	**Im**, 55[b]	**IIm**, 77

[a] Yield over two steps.
[b] Chromatography was required to isolate compound **I** cleanly.

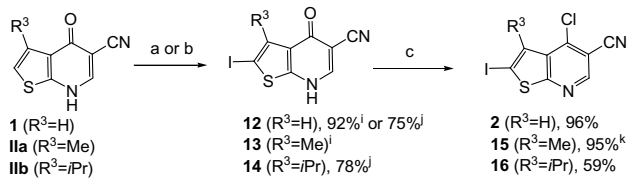
Surprisingly, two substrates closely related to **4** failed to undergo the cyclization reaction (Scheme 4). The 3-aminothiophene-2-carboxylate **6** failed to cyclize to compound **7**. Likewise, anthranilate **9** failed to undergo ring closure to form **10**. In both cases, the major product resulted from loss of the *t*-butyl ester resulting in **8** and **11**, respectively. The reason for this unexpected result remains unclear.

Having developed a suitable method for the transformation of 2-aminothiophene-3-carboxylates into the desired 4-oxo-4,7-dihydrothieno[2,3-*b*]pyridines, we next turned our attention to the synthesis of 4-chloro-2-iodothieno[2,3-*b*]pyridine-5-carbonitriles (**2**). The previous synthetic methodology (Scheme 1) employed $POCl_3$ in order to form 4-chlorothieno[2,3-*b*]pyridine-5-carbonitrile. This compound proved to be resistant to electrophilic iodination, and therefore was deprotonated with LDA at low temperatures and quenched with iodine. We reasoned that



Scheme 4.

[†] A similar reaction was reported in which a 2,2-disubstituted enamine closes onto a carboxylic acid to form a pyridone. However, the reaction proceeds via decarboxylation of the aryl carboxylic acid followed by an electrophilic addition to the thiophene by one of the esters attached to the enamine. See Ref. 11. Also, a similar microwave-promoted reaction was described recently. However few experimental details were provided. See Ref. 12.



Scheme 5. Reagents and conditions: (a) I_2, $(CF_3CO_2)_2PhI$, $CHCl_3$; (b) ICl, MeOH; (c) $POCl_3$, DMF (cat). [i] using I_2 method; [j] using ICl method; [k] yield over two steps.

the intermediate thieno[2,3-*b*]pyridone **1** may be more electron rich in nature, and therefore more susceptible to electrophilic attack. Gratifyingly, compound **1** was iodinated at the 2-position to give **12** in 92% yield (using I_2/$(CF_3CO_2)_2PhI$ or 75% (using iodine monochloride). Compound **12** was readily chlorinated with $POCl_3$ to give **2** in 96% yield (Scheme 5). The overall 5-step yield from commercial material **3** was 62%. Two other analogs (**IIa** and **IIb**) were subjected to the same conditions and transformed to the 3-methyl and 3-isopropyl analogs of **2**, namely **15** and **16**, in good yield.

In conclusion, we developed a 5-step route for the synthesis of 4-chloro-2-iodothieno[2,3-*b*]pyridine-5-carbonitrile (**2**) and related analogs. The yield of the overall sequence is 62% and thus represents a significant advance over the previously reported 6-step route, which provided a 13% yield. No chromatographic purification is necessary and the reactions have been performed up to a 0.5 mol scale. The synthesis begins with readily available 2-aminothiophene-3-carboxylate esters which allows for the facile incorporation of substituents at the C-2 and C-3 positions of the thieno[2,3-*b*]pyridone. An alternative iodination protocol was developed which negates the need for the previously reported low temperature lithiation. This sequence has enabled synthesis-substituted thieno[2,3-*b*]pyridine-5-carbonitrile kinase inhibitors that were not readily accessible with existing methodology.

2. Experimental details

2.1. General procedure for the synthesis of intermediates I

The 2-aminothiophene-3-carboxylate ester is treated with DMF–DMA (4 equiv) and heated to 100 °C overnight. The resulting solution is cooled and concentrated under vacuum. The crude residue is dissolved in *t*-butanol (0.5–1 M) and treated with *t*-butyl cyanoacetate (1.5 equiv). After stirring for an extended period (2–8 days), the resulting precipitate is collected by filtration and washed with *t*-butanol until the washings run nearly clear. Further product can often be obtained by concentrating the mother liquor and allowing the reaction to stand for a few additional days.

2.2. General procedure for the thermal cyclization of I to form II

The *t*-butyl acrylate obtained above is slowly added in portions to refluxing diphenyl ether (~0.5 M). Nitrogen is gently blown over the top of the refluxing solvent during the course of the reaction. After heating at reflux for approximately 2 h, the reaction solution is cooled and poured over excess hexanes. The product (a brown precipitate) is filtered and washed extensively with hexanes in order to remove residual solvent. *CAUTION*: The starting material must be added to the refluxing diphenyl ether in portions over a 30 min period due to the vigorous gas evolution during the cyclization.

2.3. General procedure for the iodination and chlorination of II

The thieno[2,3-*b*]pyridone **II** is stirred as a suspension in $CHCl_3$ (.05 M) and treated sequentially with [bis(trifluoroacetoxy)-iodo]benzene (1.5 equiv) and iodine (1.5 equiv). After stirring at rt for 24 h, the mixture is concentrated to approximately ½ volume and the resulting solid is filtered and washed with hexanes. The solid thus obtained is treated with $POCl_3$ (~10 equiv) and DMF (cat). After heating to 70 °C overnight, the reaction is carefully quenched over ice and the resulting product is filtered and washed with water.

Acknowledgments

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