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A facile synthesis of 2,3-disubstituted furo[2,3-*b*]pyridines

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ABSTRACT

In a three-step sequence starting from readily available starting materials, 2,3-carbon disubstituted furo[2,3-*b*]pyridines can be accessed in good yields and purity. Furo[2,3-*b*]pyridines bearing ester, amide and ketone groups at the 2-position can be prepared with a variety of aryl and alkyl groups at the 3-position.

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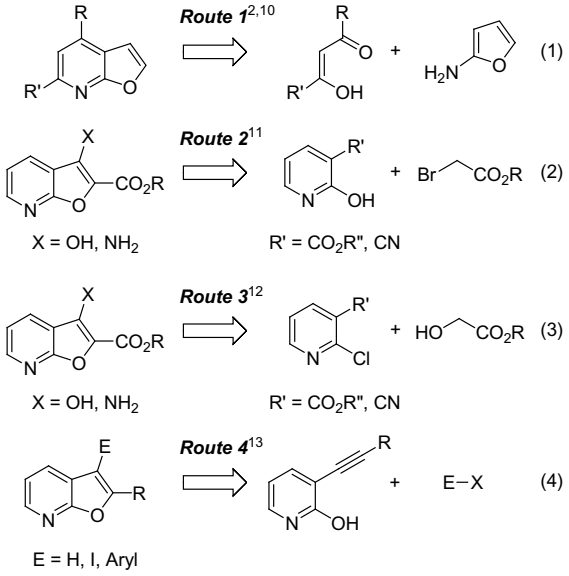
The frequent appearance of fused 5,6-ring systems in all classes of biologically active compounds attests to the important position these structures occupy in the development of new pharmaceutical agents. While some ring systems, such as indoles and pyrrolopyridines, are frequently employed as core scaffolds, others appear less frequently. One such ring system, the furo[2,3-*b*]pyridines, has received relatively little attention (Scheme 1). Furo[2,3-*b*]pyridines are rarely found in naturally occurring alkaloids.[1] However, this core structure has shown activity against HIV,[2] CNS disorders,[3] skin diseases[4] and hyperglycemia.[5] Furo[2,3-*b*]pyridines have also demonstrated some in vitro activity as tubulin polymerization,[6] Lck[7] and Akt[8] kinase inhibitors.

Despite the recent upsurge in interest regarding the medicinal chemistry of these compounds, relatively few general methods for their preparation have been reported.[9] Two general classes of disconnections have been reported in the literature (Scheme 1): annulation of a pyridine ring onto an appropriately functionalized furan (Route 1)[2,10] and annulation of a furan ring onto a functionalized pyridine (Routes 2–4).[11–13] Most of these routes are limited to the direct preparation of furo[2,3-*b*]pyridines with either unfunctionalized furan rings[2] or those bearing heteroatom substituents at the 3-position. Only the palladium-catalyzed cyclization of 3-alkynyl-2-hydroxypyridines (Route 4) has been demonstrated to provide access to 2,3-carbon disubstituted furo[2,3-*b*]pyridines,[13b,13c] a substitution pattern which is prevalent in many recent publications and patents describing the biological activity of these heterocyclic systems.[3,5,6] However, preparation of a target furo[2,3-*b*]pyridine by Route 4 typically requires the use of multiple palladium-catalyzed steps.

Considering this recent interest in 2,3-carbon disubstituted furo[2,3-*b*]pyridines, the development of methods which allow access to these biologically active compounds is an area of continuing research. In this Letter, we describe a protocol for preparation of a wide variety of 2,3-carbon disubstituted furo[2,3-*b*]pyridines **1** from readily accessible 2-fluoropyridines **2** and carboxylic acids **3** (Scheme 2). The method is based on Route 3 (Scheme 1) and begins with the acylation of a 2-fluoropyridine **4** with a Weinreb amide **5**, followed by a one-pot, base-induced displacement and cyclization. Following this method, compounds with an aryl or alkyl substituent at the 3-position and an ester, amide or ketone at the 2-position can be accessed.

Initial studies focused on the preparation of the ethyl ester containing furo[2,3-*b*]pyridine **12a** (Scheme 3). Acylation of 2-fluoropyridine **6** with the commercially available Weinreb amide **7a** was performed in THF at −78 °C with LDA. Using only 1 equiv of LDA and 1 equiv of 2-fluoropyridine in THF at −78 °C led to poor yields of the desired ketone **8a**. The mass balance of the reaction



Scheme 1. Syntheses of furo[2,3-*b*]pyridines.

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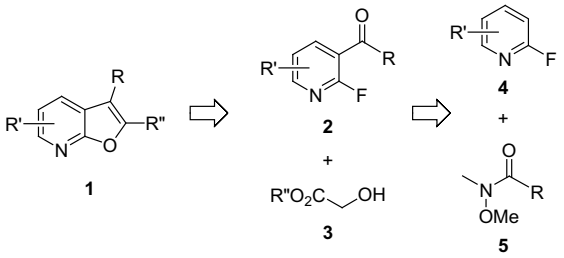


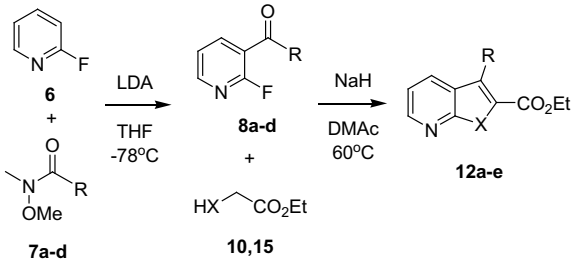
Scheme 2. Synthesis of 2,3-disubstituted furo[2,3-*b*]pyridines.

could be accounted for by the formation of amide **9a**.[14] Subsequent studies revealed that maintaining an internal temperature below −50 °C during the addition of the Weinreb amide and the use of a slight excess of 2-fluoropyridine (1.3 equiv) and LDA (1.3 equiv) gave a 51% yield of the desired ketone **8a** (Scheme 3, Eq. 1). Despite further attempts at optimization, the unproductive formation of **9a** could not be completely suppressed.

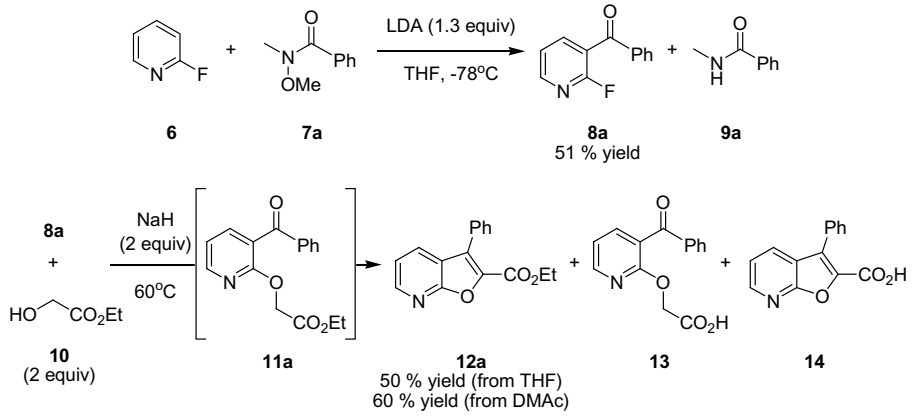
With ketone **8a** in hand, the formation of the furo[2,3-*b*]pyridine **12a** was investigated (Scheme 3, Eq. 2). Rather than isolating intermediate **11a** and subjecting it to a second cyclization step, we sought a one-pot synthesis of the furo[2,3-*b*]pyridine **12a**. Deprotonation of ethyl glycolate **10** (2 equiv) with sodium hydride (2 equiv) in THF followed by addition of the ketone **8a** and heating for 12 h at 60 °C gave the desired furo[2,3-*b*]pyridine **12a** in 50% yield after column chromatography. Under these conditions, the formation of **11a** was rapid, followed by slow cyclization to form **12a**. The mass balance of the reaction could be accounted for by the formation of the carboxylic acids **13** and **14**. These two compounds are derived from hydrolysis of **11a** and **12a**, respectively, under the reaction conditions, presumably by hydroxide released during the cyclization step. In an effort to increase the rate of the cyclization and possibly minimize this unproductive hydrolysis, examination of other solvents revealed that *N*,*N*′-dimethylacetamide (DMAc) was a far superior solvent when compared to THF. In this case, reaction was complete in 1 h at 60 °C, and the product could be isolated directly from the crude reaction mixture in 60% yield by addition of water and filtration. The formation of carboxylic acids **13** and **14** was still a competitive process, but these impurities were easily removed during the crystallization. Additional experiments were conducted in an effort to replace sodium hydride as the base for this transformation. Examination of a variety of inorganic bases, such as Cs_2CO_3 and NaO*t*-Bu, consistently led to a complex mixture of products and very little of the desired furo[2,3-*b*]pyridine **12a**. The use of Cs_2CO_3 in conjunction with catalytic sodium iodide in DMAc did lead to formation of the intermediate **11a** at room temperature; however, after heating to 60 °C, decomposition to unidentified products was observed. The use of amine bases, such as diisopropylethylamine (DIPEA) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), also led to complex mixtures of unidentified products.

Using the optimal conditions, we examined the scope of the method (Table 1). Weinreb amides **7b**–**d** were easily prepared via amidation of the corresponding carboxylic acids with *N*-methyl-*N*-methoxyamine hydrochloride and carbonyl diimidazole (CDI) in good yields. In all cases examined, the acylation of 2-fluoropyridine **6** gave moderate yields, and the corresponding secondary amide of type **9** was also observed. The cyclization of the ketones to the furo[2,3-*b*]pyridines **12a–d** proceeded smoothly in all cases. With both electron-deficient and electron-rich aryl groups, the corresponding furo[2,3-*b*]pyridines could be obtained by direct crystallization (entries 2 + 3). Introduction of a 3-alkyl group was also possible, although lower yields of the desired furo[2,3-*b*]pyridine were obtained, even under optimal conditions (entry 4). Thieno[2,3-*b*]pyridines are another interesting class of biologically active compounds,[15] typically prepared in a manner analogous to

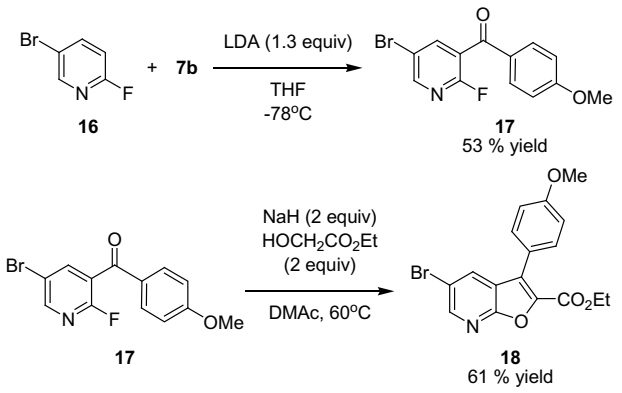
Table 1
Preparation of 3-substituted furo[2,3-*b*]pyridine esters



Entry	R	Yield (%) Step 1	X	Yield (%) Step 2
1	Ph (**7a**)	51 (**8a**)	O (**10**)	60 (**12a**)
2	*p*-$MeOC_6H_4$ (**7b**)	46 (**8b**)	O (**10**)	61 (**12b**)
3	*p*-$F_3CC_6H_4$ (**7c**)	54 (**8c**)	O (**10**)	55 (**12c**)
4	Me (**7d**)	34 (**8d**)	O (**10**)	38 (**12d**)
5	Ph (**7a**)	51 (**8a**)	S (**15**)	59 (**12e**)



Scheme 3. Synthesis of furo[2,3-*b*]pyridine **12a**.



Scheme 4. Preparation of furo[2,3-*b*]pyridine **18**.

Routes 1–3 shown in Scheme 1.[16] Under the conditions described above for the synthesis of the furo[2,3-*b*]pyridines, the related thieno[2,3-*b*]pyridine **12e** could be easily prepared in comparable yield after recrystallization from ethanol (entry 5). As in previous examples, the mass balance of the reaction could be accounted for by the formation of carboxylic acid by-products.

With the scope of the reaction with respect to the 3-position substituent defined, the possibility of installing additional substituents on the pyridine ring was briefly investigated. Starting with 5-bromo-2-fluoropyridine **16**, the trisubstituted furo[2,3-*b*]pyridine **18** could be prepared in a two-step sequence using the conditions described above (Scheme 4). The possibility of subsequent cross-coupling with the 5-bromo substituent offers many options for further elaboration of this heterocyclic core.

Having demonstrated the ability to access 2-carboxy furo[2,3-*b*]pyridines, we sought to extend the method to furo[2,3-*b*]pyridines containing amide and ketone substituents at the 2-position. In the case of furo[2,3-*b*]pyridine amides, the required α-hydroxy amides were easily prepared via opening of the 2,2-dimethyl-1,3-dioxolan-4-one **19** with the desired amine (Table 2).[17] Reaction of the resulting α-hydroxy amides **20a-c** with the ketone **8a** under the conditions described above led to the desired furo[2,3-*b*]pyridines **21a–c** in good yields. The products could easily be isolated directly from the crude reaction mixture by addition of water and filtration. In contrast to the formation of the furo[2,3-*b*]pyridine esters (Table 1), none of the corresponding carboxylic acids related to **13** and **14** were formed in these reactions, presumably since the amides **21a–c** are resistant to hydrolysis under the reaction conditions.

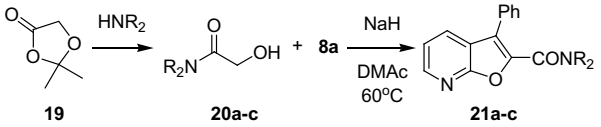
Applying this protocol to the synthesis of 2-keto furo[2,3-*b*]pyridines proved more challenging. Under the conditions described above (NaH, DMAc, 60 °C for 1 h), none of the desired ketone (**22**) could be obtained in the addition of α-hydroxy acetophenone to **8a**. A high throughput screen of bases and solvents was undertaken at 50 μmol scale in a 96-well plate in an attempt to rapidly improve the reaction using only minimal amounts of material. It was found that the use of KOAc, K_3PO_4, $NaHCO_3$, Cs_2CO_3, K_2CO_3, KF, Na_2CO_3 and CsF in either THF or DMAc led to either no conversion or decomposition. On the other hand, the use of NaOH, KOH, NaO*t*-Bu and NaO*t*-Bu in DMAc did lead to partial conversion to the ketone **22**. However, upon scaling up these conditions, complex reaction mixtures were obtained and the desired furo[2,3-*b*]pyridine ketone **22** could only be isolated after column chromatography in low yields (<20% yield). Careful examination of the crude reaction mixture revealed that α-hydroxy acetophenone was not stable under the strongly basic conditions required for the displacement and cyclization. Therefore, an alternative approach to 2-keto furo[2,3-*b*]pyridines was envisioned. The displacement of heteroaromatic morpholine amides with lithium reagents has been demonstrated in the literature[18], and it was thought that this strategy could be extended to the preparation of 2-keto furo[2,3-*b*]pyridines. The high yielding preparation of 2-amido furo[2,3-*b*]pyridine **21b** could serve as an access point to a wide variety of 2-keto furo[2,3-*b*]pyridines. In the case of **21b**, reaction with either PhLi or MeLi at −78 °C gave excellent yields of the desired ketones **22** and **23** without the formation of any observable impurities (Scheme 5). A similarly high yield of **23** could be obtained by treating **21b** with MeMgBr at 0 °C followed by warming to room temperature.

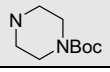
In conclusion, we have developed a straightforward and versatile method for the preparation of 2,3-disubstituted furo[2,3-*b*]pyridines. Starting from readily available and inexpensive materials, the ester, amide and ketone containing furo[2,3-*b*]pyridines could all be prepared rapidly using robust chemistry that did not require complex transition metal catalysts or chromatographic purification. This class of compound is known to possess interesting biological activities, and we feel that this method will further facilitate exploration of this increasingly important pharmacophore.

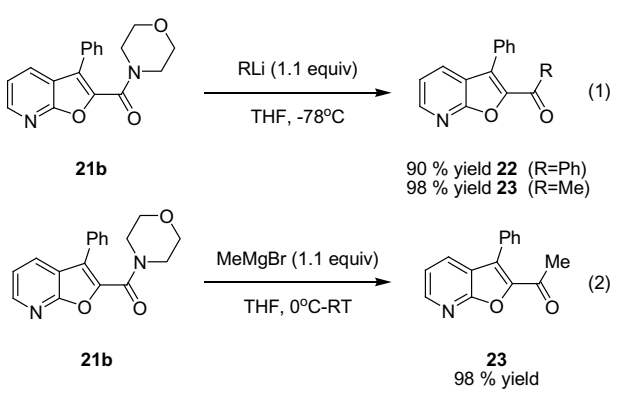
Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.125.

Table 2
Preparation of 3-substituted furo[2,3-*b*]pyridine amides



Entry	NR_2	Yield (%) Step 1	Yield (%) Step 2
1	NEt_2	– (**20a**)[17]	75 (**21a**)
2		88 (**20b**)	70 (**21b**)
3		89 (**20c**)	86 (**21c**)



Scheme 5. Preparation of 3-substituted furo[2,3-*b*]pyridine ketones.

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