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A Practical Synthesis of the 5-Chloromethyl-furo[2,3-b]pyridine Pharmacophore

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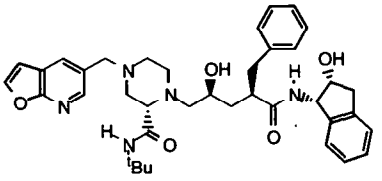
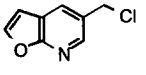
Abstract: Synthesis of the furopyridine **2** was accomplished in 52% overall yield from 6-hydroxynicotinic acid (**3**). The synthesis is highlighted by a Heck coupling of **5** with ethylene followed by an NCS mediated oxidative cyclization and elimination sequence.

Despite the recent emergence of the 5-substituted furo[2,3-b]pyridine moiety as a useful pharmacophore, methodology for preparation of this interesting heterocyclic ring system remains severely limited.[1] However, since the recent discovery of L-754,394 (**1**) as a potent and bioavailable inhibitor of the HIV-Protease enzyme, intense efforts in these laboratories have been directed towards the development of efficient, viable pathways to suitably functionalized furopyridine derivatives, e.g. the 5-chloromethyl-furo[2,3-b]pyridine (**2**).[2,3] In this report, we wish to describe a convenient and scaleable 7-step synthesis of **2** (52% overall yield) from commercially available 6-hydroxynicotinic acid (**3**). The synthesis is highlighted by a palladium catalyzed vinylation of the readily available iodopyridone **4** followed by an oxidative cyclization/elimination sequence to yield the 5-carboethoxy-furo[2,3-b]pyridine (**12**).

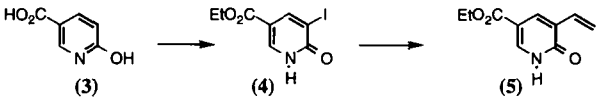


L-754,394 (1)

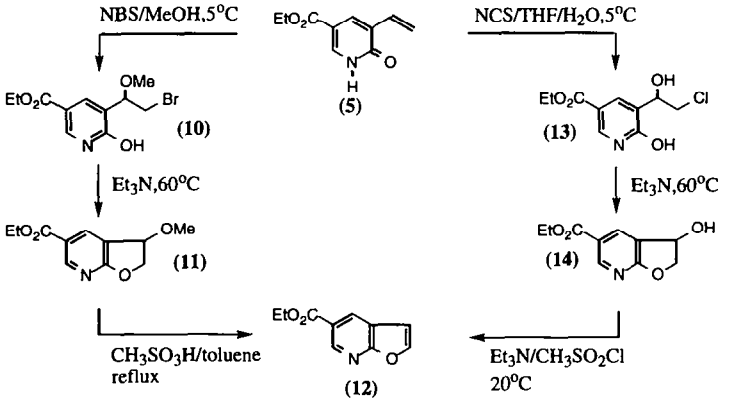


(2)

3-Iodopyridone **4** (prepared in two steps from commercially available 6-hydroxynicotinic acid (**3**), 95% overall) could be readily converted to vinylpyridone **5** by coupling with vinyltributyltin and tetrakis-triphenylphosphine Pd(0) in the presence of triethylamine at 80°C.[4] Similarly, treatment of **4** with vinylboronate reagents[5] also led to the desired vinylpyridone **5**. However, due to both the toxicity and high cost of the above reagents, more cost efficient and scaleable alternative vinylation methods were investigated for the preparation of **5**. Heck coupling between **4** and ethylene with 1 mol% $Pd(OAc)_2$, 2 mol% triphenylphosphine and triethylamine in acetonitrile at 100-150 psi at 100°C provided the desired vinylpyridone **5** in 80% yield.[6,7]



Initial attempts to directly cyclize the vinylpyridone **5** using NBS in THF led to a complex mixture of products consisting primarily of oligomeric species.[8] In order to avoid the apparent oligomerization problem, the cyclization of vinyl pyridone **5** was carried out in a stepwise fashion. First, oxidation with NBS in methanol gave the bromomethoxy compound **10**, which was then treated, *in situ* , with triethylamine to form the methoxy-dihydro-furopyridine **11** in 90% yield. Conversion of **11** to 5-carboethoxy-furo[2,3-b]pyridine (**12**) was then readily effected by treatment with methanesulfonic acid (cat.) in toluene at reflux (80%, 72% overall from **5**). Alternatively, oxidation of **5** with NCS in THF/water generated chlorohydrin **13**, which was directly cyclized to hydroxy-furopyridine **14** by the addition of triethylamine in 85% yield. Subsequent treatment of **14** with methanesulfonyl chloride and triethylamine spontaneously resulted in elimination of the hydroxyl functionality to produce **12** in 95% yield (81 % from **5**). Finally, reduction of the carboethoxy group of **12** with diisobutylaluminum hydride followed by chlorination of the resulting alcohol with thionyl chloride provided the title compound **2** in excellent yield (85% from **12**).[9]



In conclusion, we have demonstrated a highly efficient process that allows rapid access to the versatile pharmaceutically important 5-carboethoxy-furo[2,3-b]pyridine (**12**) moiety in 5 steps from commercially available 6-hydroxy nicotinic acid (**3**). The synthesis of **12** proceeds in 62% overall yield. The carboethoxy moiety of **12** was also readily processed to the more electrophillic 5-chloromethyl-furo[2,3-b]pyridine (**2**) analog (85%, 52% overall from **3**) as required for conversion to the HIV-protease inhibitor candidate L-754,394 (**1**).[10]

Acknowledgment

We wish to thank R. Reamer for proton and carbon-13 NMR analysis of the dimer **6,** as well as adducts **8** and **9**, and Messrs. T. Houck and C. Bazaral for performing high pressure reactions.

References and notes

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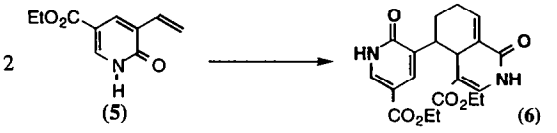
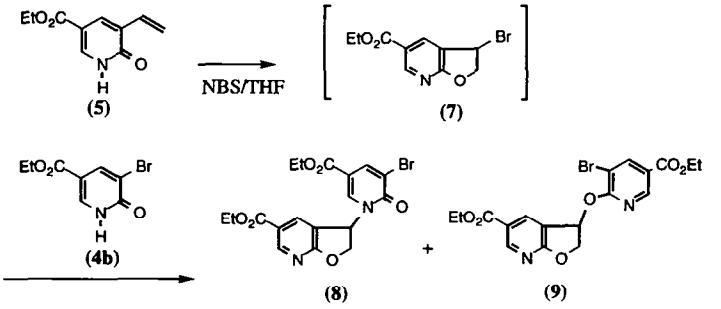
7. It is noteworthy that the yield of the Heck reaction was highly concentration dependent. The reaction proceeded in 80% yield at 0.1M of **4** in acetonitrile; however, attempts to improve productivity by increasing the reaction concentration led to loss in yield. Stability studies at 0.5 M showed that vinyl pyridone **5** readily dimerized under the reaction conditions giving rise to the Diels Alder adduct **6**, which was likewise unstable leading to an uncharacterizeable, highly insoluble solid on further heating.



8. Interestingly, performing the cyclization reaction with a 1:1 mixture of bromopyridone **4b** and the vinylpyridone **5** in anhydrous THF with NBS led cleanly to the dimeric N- and O-alkylation

products **8** and **9.** This result is readily explained by a bromonium ion induced cyclization followed by capture of the intermediate bromofuropyridine **7** by N- or O-alkylation of the bromopyridone **4b**.



9. All the reported compounds, including **2**, **4**, **5**, **10**, **11**, **12**, **13** and **14**, showed good spectral matches for the corresponding structures and elemental analysis results within 0.3%.

10. The complex piperazine component of **1** was obtained as described for the closely related HIV-Protease inhibitor L-735,524. See Askin, D.; Eng, K.; Rossen, K.; Purick, R.M.; Wells, K.M.; Volante, R.P.; Reider, P.J.,*Tetrahedron Lett.* **1994**, *35*, 673.

11. **4**; ^{1}H NMR ($CDCl_3$) δ 11.82 (1H, broad, NH), 8.65 (1H, d, H_6, J = 2.3 Hz), 8.33 (1H, d, H_4, J = 2.3 Hz), 4.34 (2H, q, CH_2, J = 7.1 Hz), 1.37 (3H, t, CH_3); ^{13}C NMR ($CDCl_3$) 162.92, 162.88, 149.95, 139.78, 112.92, 90.15, 61.54, 14.33; mp = 168-168.5°C; Anal. Calcd for $C_8H_8NO_3I$: C, 32.79; H, 2.75; N, 4.78; I, 43.30. Found: C, 32.58; H, 2.63; N, 4.71; I, 43.52. **5**; ^{1}H NMR ($CDCl_3$) δ 11.54 (1H, broad, NH), 8.18 (1H, d, H_6, J = 2.3 Hz), 8.10 (1H, d, H_4, J = 2.3 Hz), 6.80 (1H, dd, $H_{1'}$, J = 11.3 and 16.7 Hz), 6.16 (1H, dd, $1H_{2'}$, J = 1.1 and 16.7 Hz), 5.45 (1H, dd, $1H_{2'}$, J = 1.1 and 11.3 Hz), 4.34 (2H, q, CH_2, J = 7.1 Hz), 1.37 (3H, t, CH_3); ^{13}C NMR ($CDCl_3$) 164.41, 164.28, 137.97, 136.26, 130.63, 127.60, 118.12, 111.41, 61.18, 14.36; softening at 125°C, decomposed at 220°C; Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.96; H, 5.69; N, 7.13. **14**; ^{1}H NMR ($CDCl_3$) δ 8.69 (1H, d, H_6, J = 2.0 Hz), 8.30 (1H, d, H_4, J = 2.0 Hz), 5.46 (1H, m, $H_{1'}$), 4.73 (1H, dd, $1CH_2$, J = 7.1 and 10.8 Hz), 4.57 (1H, dd, $1CH_2$, J = 3.2 and 10.8 Hz), 4.34 (2H, q, CH_2, J = 7.1 Hz), 4.22 (1H, broad, OH), 1.37 (3H, t, CH_3); ^{13}C NMR ($CDCl_3$) 170.81, 165.13, 152.19, 136.62, 121.83, 120.65, 78.69, 69.29, 61.38, 14.29; mp = 109.5-110°C; Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.55; H, 5.21; N, 6.71. **12**; ^{1}H NMR ($CDCl_3$) δ 8.96 (1H, d, J = 2.1 Hz), 8.53 (1H, d, J = 2.1 Hz), 7.73 (1H, d, J = 2.4 Hz), 6.82 (1H, d, J = 2.4 Hz), 4.38 (2H, q, CH_2, J = 7.2 Hz), 1.37 (3H, t, CH_3); ^{13}C NMR ($CDCl_3$) 165.45, 163.93, 146.53, 146.15, 132.06, 122.67, 118.94, 106.48, 61.36, 14.30; mp = 72-73°C; Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.78; H, 4.67; N, 7.41.

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