Organic Process Research & Development **2007**, *11*, 899–902

A Scaleable Synthesis of Methyl 3-Amino-5-(4-fluorobenzyl)-2-pyridinecarboxylate

Eric E. Boros,* Svetlana A. Burova, Greg A. Erickson, Brian A. Johns, Cecilia S. Koble, Noriyuki Kurose,† Matthew J. Sharp, Elie A. Tabet, James B. Thompson, and Matthew A. Toczko

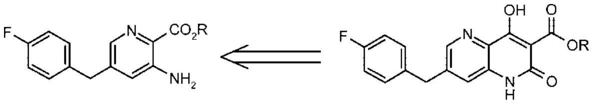
GlaxoSmithKline Research & Development, Five Moore Drive, Research Triangle Park, North Carolina 27709, U.S.A.

Abstract:

A scaleable synthesis of methyl 3-amino-5-(4-fluorobenzyl)-2-pyridinecarboxylate (1b), starting from 5-bromo-2-methoxypyridine (8) and 4-fluorobenzaldehyde (9), is described. Key steps in the process include lithium–bromine exchange of 8, addition of the resulting lithiate to aldehyde 9, regioselective nitration of pyridone 12, and Pd-catalyzed alkoxycarbonylation of bromopyridine 15b. Overall yield of the five-stage synthesis was 23%; intermediates 10, 12, 13, 15b, and final product 1b·HCl were isolated as filterable solids. Compounds 1a,b are important intermediates in the synthesis of 7-benzylnaphthyridinones (e.g., 2) and related HIV-1 integrase inhibitors.

Introduction

Alkyl 3-amino-5-(4-fluorobenzyl)-2-pyridinecarboxylates **1** are useful intermediates in the synthesis of 7-benzyl-4-hydroxy-1,5-naphthyridin-2(1*H*)-ones (e.g., **2**) and related HIV-1 integrase inhibitors[1–3] (eq 1). The original synthesis of **1a**[2] (Scheme 1, practical for medicinal chemistry purposes, posed several feasibility issues with large-scale applications. These concerns included the moderate instability of aldehyde intermediate **3** (prepared in 2 steps from 1-fluoro-4-iodobenzene) and the formation of unwanted regioisomer **7b** from ring opening of pyridine carboxylic anhydride **6** with ethanol (ratio **7a**:**7b** ≈ 7:3). Moreover, Curtius rearrangement of **7a**,**b** with diphenylphosphoryl azide (DPPA) and TEA, although uneventful on a multigram scale, generates potentially dangerous acyl azide intermediates.[4] For these reasons, an alternate route to **7a**,**b** was developed (Scheme 2) for kilogram-scale applications.



1a: R = Et
1b: R = Me

2

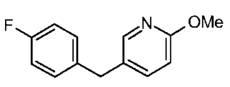
(1)

Results and Discussion

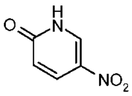
Efficient placement of the fluorobenzyl group in **1** was a desirable feature of any new synthesis, and commercially available 5-bromo-2-methoxypyridine (**8**)[5] appeared well-suited for this purpose. We assumed that metal–halogen exchange of **8** and trapping of the resulting organometallic species with benzyl acceptor synthons would yield the desired 5-benzylpyridine structure. In addition, the C-2 oxygen of **8** might direct nitration to the 3-pyridyl position and later be converted to a leaving group suitable for alkoxycarbonylation chemistry. Along these lines, we worked towards a more development-friendly synthesis of **7a**,**b** starting from pyridine **8**.

Lithium-bromine exchange of **8** was initially explored with *n*-BuLi in THF at −78 °C; reaction of the resulting 5-lithio species with 4-fluorobenzaldehyde afforded the desired alcohol **10** in good yield. When this reaction was examined at higher temperatures (−20 °C) in THF, the 5-lithio species was unstable and reacted with the bromobutane generated during the reaction. However, when the reaction was performed in *tert*-butyl methyl ether (TBME), the 5-lithiopyridine was stable below −18 °C (reaction maintained between −32 and −18 °C), and upon addition of 4-fluorobenzaldehye, clean conversion to **10** was observed; the product was crystallized from 2,2,4-trimethylpentane/TBME following workup and was isolated in 74% yield.

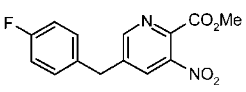
The original conversion of alcohol **10** to benzylpyridine **11** was achieved by silane-hydride transfer[6] with TFA/triethylsilane in refluxing 1,2-dichloroethane; O-demethylation of **11** in refluxing HBr/acetic acid then afforded pyridone **12**. Since both reduction[7] of electron-deficient benzylic alcohols and O-demethylation[8] of 2-methoxypyridines are known to occur in the presence of large excesses of TMSI, we decided to combine conditions for in situ TMSI formation (TMSCl/NaI)[7] with silane hydride transfer conditions (TFA/triethylsilane)[6] in an attempt to "telescope" conversion of **10** to **12**. Remarkably, when **10** was subjected to these conditions at 70 °C in acetonitrile, clean conversion to **12** occurred in excellent yield (Scheme 2).



11



14



16

---

* To whom correspondence should be addressed. Fax: 919-315-0430. E-mail: eric e. boros@gsk.com.

† Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka, Japan.

(1) For a recent review of HIV integrase inhibitors, see: Pommier, Y.; Johnson, A. A.; Marchand, C. *Nat. Rev. Drug Discovery* **2005**, *4*, 236–248.

(2) Johns, B. A.; Boros, E. E.; Kawasuji, T.; Koble, C. S.; Kurose, N.; Murai, H.; Sherrill, R. G.; Weatherhead, J. G. *Chem. Abstr.* **2005**, *143*, 248371 (WO 05077050, August 25, 2005) .

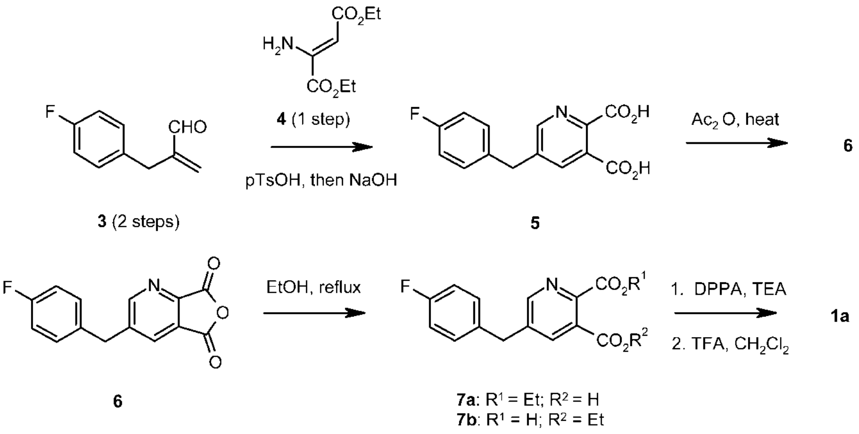
(3) Murai, H.; Endo, T.; Kurose, N.; Taishi, T.; Yoshida, H. *Chem. Abstr.* **2004**, *140*, 287278 (WO 04024693, March 25, 2004) .

(4) Curtius rearrangements have the capacity to be performed on limited scale, if necessary, under carefully controlled conditions; acyl azide intermediates are explosive hazards and their isolation should be avoided, see: am Ende, D. J.; DeVries, K. M.; Clifford, P. J.; Brenek, S. J. *Org. Process Res. Dev.* **1998**, *2*, 382–392.

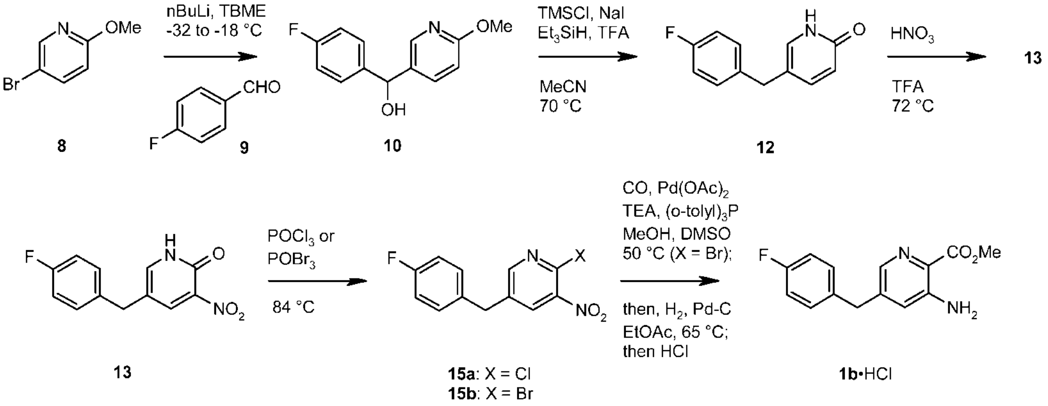
(5) Starting materials and selected reagents (sources and approximate cost): compd **8** ($825.00/kg; Synthon Chemicals); compd **9** ($60.00/kg; ABCR); phosphorous oxybromide was purchased from Lancaster Synthesis ($2.31/g).

10.1021/op7001326 CCC: $37.00

Scheme 1



Scheme 2



Regioselective nitration of pyridone **12** was a critical step in the synthesis of **1**. Although 2-pyridones are easily nitrated,[9] there was some concern that the fluorophenyl ring of **12** might undergo competing nitration.[10] Although both sulfuric acid and TFA were examined as solvents for nitration of **12**, TFA gave a considerably cleaner product. Nitration of **12** was accomplished with 90% HNO_3 in TFA (2.7 vol) at 72 °C and was relatively selective (70–80%) for the 3-pyridyl position. Little or no nitration of the fluorophenyl ring was observed. After dilution of the reaction mixture with water, the product **13** crystallized from the reaction mixture and was isolated in 61% yield. The major byproduct of this reaction was the 5-nitro-2-pyridone **14** (20–30%), a result of apparent *ipso*-nitration[11] and debenzylation of **12**. Byproduct **14** was completely removed in the aqueous filtrate.

We next explored conversion of **13** to "activated" pyridines **15a**,**b** suitable for carbonylation chemistry. Treatment of pyridone **13** with neat $POCl_3$ at 112 °C easily afforded 2-chloropyridine **15a**. Unfortunately, the rate of CO insertion of **15a** was sluggish; therefore, rather than optimizing CO insertion of the chloropyridine, we opted to investigate reaction with the corresponding 2-bromopyridine **15b**.

Bromination of **13** was initially performed with $POBr_3$[5] in toluene; however, significant solubility problems were encountered with this solvent. By changing the solvent to 1,2-dichloroethane we were able to obtain efficient bromination of **13** with $POBr_3$ at 84 °C; this procedure provided 2-bromopyridine **15b** in 74% yield.

Various conditions were examined for CO insertion[12] of **15b**; the most effective ones included methanol as solvent or co-solvent. Efficient methyl ester formation was achieved with $Pd(OAc)_2$, (*o*-tolyl)$_3$P, and TEA in MeOH/DMSO at 50 °C under an atmosphere of carbon monoxide. Following workup, an EtOAc solution of **16** was carried directly to the final reduction step without isolation.

Remarkably, hydrogenation of the nitro group in **16** was one of the more difficult reactions to optimize. Although this reaction

---

(6) (a) For reductions of substituted benzhydrol derivatives with TFA/triethylsilane, see: Waterlot, C.; Hasiak, B.; Couturier, D.; Rigo, B. *Tetrahedron* **2001**, *57*, 4889–4901. (b) Barda, D. A.; Wang, Z-Q.; Britton, T. C.; Henry, S. S.; Jagdmann, G. E.; Coleman, D. S.; Johnson, M. P.; Andis, S. L.; Schoepp, D. D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3099–3102.

(7) Moderately electron-deficient benzyl alcohols may be reduced with TMSI generated in situ; see: Cain, G. A.; Holler, E. R. *Chem. Commun.* **2001**, 1168–1169.

(8) For O-demethylation of heteroaromatic methyl ethers with TMSI, see: McBriar, M. D.; Guzik, H.; Shapiro, S.; Xu, R.; Paruchova, J.; Clader, J. W.; O'Neill, K.; Hawes, B.; Sorota, S.; Margulis, M.; Tucker, K.; Weston, D. J.; Cox, K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4262–4265.

(9) For nitration of 2-pyridones in sulfuric acid, see: Burton, A. G.; Halls, P. J.; Katritzky, A. R. *Tetrahedron Lett.* **1971**, *12*, 2211–2212.

(10) Aromatic nitration of ethyl 4-fluorophenylacetate in sulfuric acid is reported; see: Kuse, M.; Doi, I.; Kondo, N.; Kageyama, Y.; Isobe, M. *Tetrahedron* **2005**, *61*, 5754–5762.

(11) Tashiro, M.; Yamato, T.; Fukata, G.; Fukuda, Y. *J. Org. Chem.* **1981**, *46*, 2376–2379.

(12) For examples of Pd-catalyzed methoxycarbonylation of 2-bromopyridine derivatives, see: Ducharme, Y.; Friesen, R. W.; Blouin, M.; Cote, B.; Dube, D.; Ethier, D.; Frenette, R.; Laliberte, F.; Mancini, J. A.; Masson, P.; Styhler, A.; Young, R. N.; Girard, Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1923–1926.

proceeded cleanly at atmospheric pressure, the rate was slow and significant buildup of hydroxylamine intermediate was observed. For example, hydrogenation of **16** in aqueous HCl–MeOH with Pd on carbon catalyst required 9 days for complete reaction. Moreover, after 2 days, the product mixture consisted of 3% desired amine **1b** and 97% of the corresponding hydroxylamine intermediate. Interestingly, we discovered that by adding a small amount of iron powder to the reaction mixture, hydrogen uptake was enhanced to the point where little or no hydroxylamine intermediate was observed.[13,14] Acceptable hydrogenation rates were achieved with Pd on carbon catalyst and addition of catalytic quantities of iron powder (Pd:Fe = 40:1) in EtOAc at 65 °C. Under these conditions, hydrogenation was complete in 8 h, and product **1b** was isolated as a hydrochloride salt in 77% yield (from **15b**).

In summary, a scaleable synthesis of **1b** was developed starting from pyridine **8** and aldehyde **9**. A 0.523 kg batch of **1b**·HCl was prepared in 5 stages and 23% overall yield. Compounds **1a**,**b** are important intermediates in the synthesis of 7-benzylnaphthyridinones (e.g., **2**) and related HIV-1 integrase inhibitors.

Experimental Section

(4-Fluorophenyl)[6-(methyloxy)-3-pyridinyl]methanol (10). A 20-L jacketed glass laboratory reactor (graduated volume = 20 L; quench volume ca. 30 L) equipped with mechanical stirrer and reflux condenser was charged with **8** (1.25 kg, 6.64 mol, 1 equiv) and TBME (12 L). The solution was cooled to −32 °C. A solution of 2.5 M *n*-BuLi in hexanes (2.7 L, 6.64 mol, 1 equiv) was added over 30 min while maintaining the temperature below −18 °C. The mixture was stirred for 60 min at −32 °C. 4-Fluorobenzaldehyde (**9**) (0.64 L, 6.04 mol, 0.91 equiv) was then added to the lithiate over 30 min while maintaining the temperature below −23 °C. After stirring for 30 min, the batch was warmed to 0 °C and quenched with 1 M HCl (8.6 L). The phases were separated and the aqueous layer was extracted twice with TBME (8.6 and 3.4 L). All combined organic phases were washed with water (2 L), distilled to a final volume of 9 L, and then diluted with 2,2,4-trimethylpentane (12 L). Distillation was continued to a final volume of 12.5 L at which point the batch was cooled to ambient temperature and then to −10 °C. The resulting precipitate was collected by filtration, washed with 2,2,4-trimethylpentane, and dried to afford **10** as a light tan solid (1.05 kg, 74% yield): ^{1}H NMR ($CDCl_3$, δ) 3.91 (s, 3H), 5.80 (s, 1H), 6.70 (d, 1H, J = 8.6 Hz), 7.02 (dd, 2H, J_{HF} = 8.7 Hz, J_{HH} = 8.7 Hz), 7.33 (dd, 2H, J_{HF} = 5.5, J_{HH} = 8.6 Hz), 7.51 (dd, 1H, J = 2.5 and 8.6 Hz), 8.12 (d, 1H, J = 2.5 Hz); AP$^+$ MS 234 (M + H$^+$, 100); hydroxylic proton not observed.

5-[(4-Fluorophenyl)methyl]-2(1*H*)-pyridinone (12). A 20-L jacketed glass laboratory reactor equipped with mechanical stirrer, caustic scrubber, and reflux condenser was charged with **10** (0.92 kg, 3.94 mol, 1 equiv), CH_3CN (9.2 L), NaI (2.37 kg, 15.8 mol, 4 equiv), and triethylsilane (945 mL, 5.92 mol, 1.5 equiv). Trifluoroacetic acid (477 mL, 6.19 mol, 1.57 equiv) was added at a rate that maintained the temperature below 30 °C; TMSCl (2.5 L, 19.7 mol, 5 equiv) was added, and the batch was heated at 70 °C for 3 h. Upon cooling to 55 °C, a solution of 0.8 M Na_2SO_3 (4.6 L) was added, and the mixture was distilled to a final volume of 12 L. A solution of 0.15 M Na_2SO_3 (4.6 L) was added, and the mixture was stirred at room temperature overnight. A solution of 1.4 M K_2CO_3 solution (6 L) was added, and the mixture was cooled to 0 °C. The resulting solid was collected by filtration and washed with water and TBME. The filter cake was dried to afford **12** as a tan solid (749 g, 93% yield): ^{1}H NMR (DMSO-d_6, δ) 3.62 (s, 2H), 6.24 (d, 1H, J = 9.3 Hz), 7.08 (dd, 2H, J_{HF} = 9 Hz, J_{HH} = 9 Hz), 7.26–7.19 (m, 4H), 11.39 (br s, 1H); ES$^+$ MS 204 (M + H$^+$, 100); mp 145–147 °C. Anal. Calcd for $C_{12}H_{10}FNO\cdot(0.1\ H_2O)$: C, 70.30; H, 5.01; N, 6.83. Found: C, 70.24; H, 4.91; N, 6.78.

5-[(4-Fluorophenyl)methyl]-3-nitro-2(1*H*)-pyridinone (13). A 20-L jacketed glass laboratory reactor equipped with mechanical stirrer, Na_2SO_3 scrubber (to remove NO_x gases), and reflux condenser was charged with TFA (4 L), **12** (1.484 kg, 7.30 mol, 1 equiv) and 90% HNO_3 (618 mL, 14.6 mol, 2 equiv). The batch was heated at 72 °C for 1.5 h and then cooled to 24 °C. Water (14.8 L) was added, and the mixture was stirred for 2 h. The mixture was filtered, and the filter cake was washed with water and dried to afford **13** as a yellow-orange solid (1.11 kg, 61% yield): ^{1}H NMR (DMSO-d_6, δ) 3.76 (s, 2H), 7.11 (dd, 2H, J_{HF} = 8.6 Hz, J_{HH} = 8.6 Hz), 7.30 (dd, 2H, J_{HF} = 5.7 Hz, J_{HH} = 8.6 Hz), 7.80 (d, 1H, J = 2.4 Hz), 8.31 (d, 1H, J = 2.4 Hz), 12.76 (br s, 1H); ES$^+$ MS 249 (M + H$^+$, 100); mp 265–266 °C (dec). Anal. Calcd for $C_{12}H_9FN_2O_3\cdot(0.1\ H_2O)$: C, 57.65; H, 3.71; N, 11.20. Found: C, 57.63; H, 3.59; N, 11.15.

2-Bromo-5-[(4-fluorophenyl)methyl]-3-nitropyridine (15b). A 20-L jacketed glass laboratory reactor equipped with mechanical stirrer, caustic scrubber, and reflux condenser was charged with **13** (931 g, 3.75 mol, 1 equiv) and 1,2-dichloroethane (5.6 L). A solution of $POBr_3$ (1.18 kg, 4.13 mol, 1.1 equiv) in 1,2-dichloroethane (2.9 L) was added, and the mixture was heated at 84 °C for 3 h. Additional $POBr_3$ (96 g, 0.33 mol, 0.088 equiv) was added, and heating was continued for 2 h at which point the mixture was cooled to ambient temperature and then to 2 °C. A solution of 2 M NaOH (10.2 L) was added over 30 min, maintaining the temperature below 20 °C. The organic phase was separated, filtered through celite, and washed with water (3 L). The organic layer was separated and distilled to a final volume of 3.9 L at which point it was cooled to 56 °C and diluted with 2,2,4-trimethylpentane (10 L). The mixture was heated to 80 °C and then cooled slowly to −15 °C. The resulting solids were collected by filtration, and the filter cake was washed with 2,2,4-trimethylpentane. Further drying of the filter cake provided **15b** as a sand-like solid (843 g, 72% yield): ^{1}H NMR (DMSO-d_6, δ) 4.05 (s, 2H), 7.12 (dd, 2H, J_{HF} = 8.7 Hz, J_{HH} = 8.7 Hz), 7.33 (dd, 2H, J_{HF} = 5.6 Hz, J_{HH} = 8.7 Hz), 8.37 (d, 1H, J = 2 Hz), 8.62 (d, 1H, J = 2 Hz); ES$^+$ MS 313 (M + H$^+$, 100), 311 (M + H$^+$, 100); mp 80–82 °C. Anal. Calcd for $C_{12}H_8BrFN_2O_2$: C, 46.33; H, 2.59; N, 9.00; Br, 25.68. Found: C, 46.38; H, 2.53; N, 8.86; Br, 25.52.

---

(13) Metal salts (including iron) have potential to eliminate hydroxylamine accumulation during aromatic nitro group reductions; see: Baumeister, P.; Blaser, H. U.; Studer, M. *Catal. Lett.* **1997**, *49*, 219–222.

(14) Catalytic amounts of iron in the presence of noble metal catalysts are known to facilitate selective hydrogenation of polynitroaromatic compounds; see: Theodoridis, G.; Manfredi, M. C.; Krebs, J. D. *Tetrahedron Lett.* **1990**, *31*, 6141–6144.

Methyl 3-Amino-5-[(4-fluorophenyl)methyl]-2-pyridinecarboxylate Hydrochloride (1b). A 20-L jacketed glass laboratory reactor equipped with mechanical stirrer, reflux condenser, and Büchi gas flow apparatus (bpc 1202) was charged with **15b** (708 g, 2.28 mol, 1 equiv), 2:1 MeOH/DMSO (7.1 L), $Pd(OAc)_2$ (25.5 g, 0.11 mol, 4.8 mol%), tri-*o*-tolylphosphine (34.6 g, 0.11 mol, 4.8 mol%), and TEA (952 mL, 6.8 mol). The Büchi press-flow apparatus was attached to a carbon monoxide cylinder and the reaction vessel was evacuated and purged three times with carbon monoxide. The batch was heated at 50 °C for 18 h under carbon monoxide atmosphere until gas uptake ceased. Upon cooling to rt, the vessel was evacuated and purged with nitrogen. The mixture was vacuum distilled (0.8 bar) until the batch reached 56 °C at which point it was allowed to cool to rt. The mixture was diluted with EtOAc (7.1 L) and the organic phase was washed three times with water (3.5 L each). The aqueous washes were removed and the remaining EtOAc layer containing **16** was charged with a mixture of 10% Pd on carbon (242 g, 50% wet Degussa E101 NE/W) and iron powder (6 g). A hydrogen cylinder was attached to the Büchi press-flow apparatus and the reaction vessel was evacuated and purged with hydrogen. The reaction mixture was stirred for 8 h at 65 °C under hydrogen atmosphere until gas uptake ceased. The reaction vessel was evacuated and flushed with nitrogen. The hot reaction mixture was filtered through celite and the filtrate was treated with a solution of 10% HCl (5.3 L). Most of the EtOAc was removed by distillation (50 °C; 150–200 mmHg). The aqueous HCl mixture was diluted with toluene (1.5 L), cooled to 2 °C and stirred for 1 h. Filtration of the resulting solids and washing with EtOAc afforded **1b**·HCl (523 g, 77% yield) as a beige solid: ^{1}H NMR (HCl salt, DMSO-d_6, δ) 3.86 (s, 3H), 4.01 (s, 2H), 6.90 (br, 3H), 7.15 (dd, 2H, $J_{HF} = 8.6$ Hz, $J_{HH} = 8.6$ Hz), 7.29 (dd, 2H, $J_{HF} = 5.6$ Hz, $J_{HH} = 8.6$ Hz), 7.44 (s, 1H), 7.95 (s, 1H). An analytical sample of **1b** was obtained by crystallization of the free amine from EtOAc: ^{1}H NMR (free amine, $CDCl_3$, δ) 3.89 (s, 2H), 3.95 (s, 3H), 5.67 (br s, 2H), 6.71 (d, 1H, $J \approx 1.5$ Hz), 6.98 (dd, 2H, $J_{HF} = 8.6$ Hz, $J_{HH} = 8.6$ Hz), 7.12 (dd, 2H, $J_{HF} = 5.4$ Hz, $J_{HH} = 8.6$ Hz), 7.94 (d, 1H, $J \approx 1.5$ Hz); ES$^+$ MS: 261 ($M + H^+$, 100); mp 156–158 °C. Anal. Calcd for $C_{14}H_{13}FN_2O_2$: C, 64.61; H, 5.03; N, 10.76. Found: C, 64.36; H, 5.04; N, 10.72.

Acknowledgment

This work was conducted as part of a research collaboration between GlaxoSmithKline and Shionogi & Co., Ltd.

Received for review June 13, 2007.

OP7001326