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2-Ethoxy-3-pyridylboronic acid: a versatile reagent for the synthesis of highly-functionalised 3-aryl/heteroaryl-pyridines via Suzuki cross-coupling reactions

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Abstract—This paper describes the commercially-viable synthesis and isolation of 2-ethoxy-3-pyridylboronic acid on a ca. 70 g scale via a directed *ortho*-metalation reaction on readily-available 2-ethoxypyridine. A range of efficient cross-coupling reactions of 2-ethoxy-3-pyridylboronic acid with selected aryl/heteroaryl halides under palladium-catalysed Suzuki–Miyaura conditions yield novel 2-ethoxy-3-aryl/heteroaryl-pyridines in high yield (heteroaryl = pyridyl, pyrimidyl, pyrazyl). The X-ray crystal structure of 2-ethoxy-3-pyridylboronic acid reveals that the boronic acid group takes part in an intramolecular O–H···O bond with the adjacent ethoxy substituent, and an intermolecular O–H···N bond.

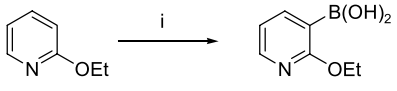
1. Introduction

Highly-functionalised pyridines, including aryl- and heteroaryl-substituted derivatives, are widespread in the pharmaceutical and agrochemical sectors.[1] They also have important applications as ligands for metal-coordination and supramolecular assemblies[2] and as fluorophores.[3] Efficient methodology for the synthesis of new derivatives, with broad functional group compatibility, is, therefore, of considerable current interest.[4] The use of catalytic cross-coupling protocols for preparing aryl-functionalised heterocycles is very topical,[5] and in this context heterocyclic boronic acids are emerging as important reagents for Suzuki-Miyaura reactions.[5c]

The syntheses of the parent (unsubstituted) pyridylboronic acids require precisely-controlled conditions and their purification is difficult (especially 2-pyridylboronic acid which readily deboronates).[6] This has restricted their use as routine reagents.[7] However, it has recently been shown that many halo- and dihalo-pyridylboronic acids (or their corresponding pinacol esters) are more stable,[8] although isolation is sometimes difficult due to partial solubility in water, and for some derivatives precise control of pH during workup is needed to avoid deboronation.[9] Cross-coupling reactions of bromopyridylboronic acids can suffer from competing self-coupling reactions[8a] or debromination.[8f]

2. Results and discussion

We now report that 2-ethoxy-3-pyridylboronic acid **2** is a versatile new reagent. The synthesis of **2** was readily achieved by a directed ortho-metalation reaction[10] of 2-ethoxypyridine **1** (LDA in THF at −50 °C) followed by addition of triisopropylborate and aqueous workup (Scheme 1) (70% yield on a 5 g scale). This procedure has been scaled-up to give ca. 70 g batches of analytically-pure **2** in 48% yield (see Section 4). In our hands, comparable scale-up reactions for many other pyridylboronic acid derivatives have proved to be practically far more difficult.



1 2

Scheme 1. Reagents and conditions: i LDA, THF, − 50 °C, triisopropylborate, H_2O.

Keywords: Boronic acid; Cross-coupling; Directed *ortho*-metalation; Pyridine.
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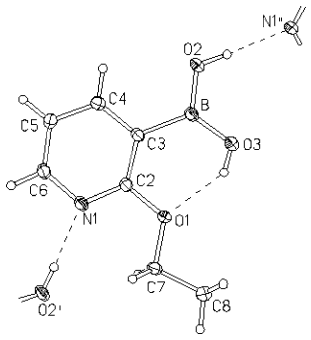
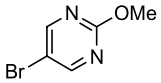
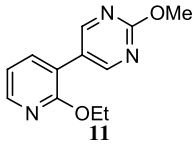
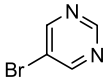
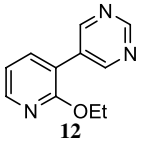
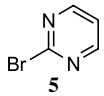
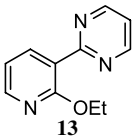
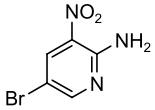
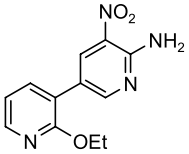
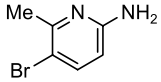
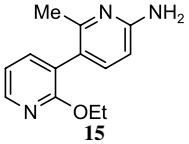
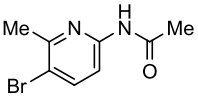
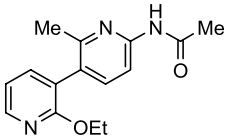
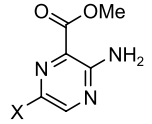
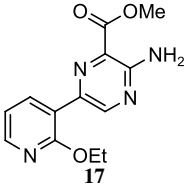
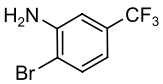
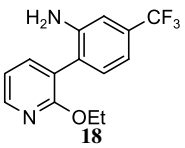


Figure 1. X-ray structure of **2**, showing thermal ellipsoids (50% probability) and hydrogen bonds. Symmetry transformations: (i) x+½, ½–y, z–½; (ii) x–½, ½–y, z+½.

Compound **2** has the following attractive features: (i) it is shelf-stable at room temperature (no observable decomposition after 9 months' storage); (ii) 2-ethoxypyridine is cheap and readily-available from commercial suppliers; (iii) the hydrophobic ethoxy substituent ensures good solubility of **2** in organic solvents which makes extraction from the aqueous phase easier than for most other pyridylboronic acid derivatives we have studied; (iv) in the cross-coupled products the 2-ethoxy group leads to sterically-induced twisting of the biaryl system (*peri*-interactions) and hence increased solubility, which assists chromatographic separation from any minor byproducts.

The X-ray crystal structure[11] of **2** shows a nearly planar conformation of the molecule, stabilised by an

Table 1. **1**+R−X $\xrightarrow{i}$ **11–18**

Entry	Boronic acid	R–X	Product	Isolated yield (%)
1	**2**	 **3**	 **11**	82
2	**2**	 **4**	 **12**	90
3	**2**	 **5**	 **13**	89
4	**2**	 **6**	 **14**	74
5	**2**	 **7**	 **15**	75
6	**2**	 **8**	 **16**	78
7	**2**	 **9** **a** X=Br, **b** X=Cl	 **17**	90 (from **9a**) 62 (from **9b**)
8	**2**	 **10**	 **18**	71

Reagents and conditions: $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, Na_2CO_3 (1 M), reflux, 24 h; for **9a**, 20 °C, 16 h; for **9b**, 60 °C, 15 min.

intramolecular O–H···O hydrogen bond (Fig. 1), while the other hydroxyl group forms an intermolecular O–H···N bond linking the molecules into an infinite chain. This structure is unusual as arylboronic acids (like carboxylic acids) typically form H-bonded dimers in crystals;[8a,12] this does not occur with compound **2**.

Suzuki cross-coupling reactions of **2** were carried out with a range of aryl/heteroaryl halides **3**–**10** under standard conditions [$Pd(PPh_3)_2Cl_2$, dioxane, reflux] to yield products **11**–**18**, respectively. The results are collated in Table 1. There are some important features of these results. (i) The reactions are high-yielding with a variety of halogenated coupling partners (viz. pyridyl, pyrimidyl, pyrazyl and phenyl derivatives). (ii) The reaction is versatile with respect to functional group tolerance (viz. nitro, amine, amide, ester and trifluoromethyl) thereby allowing access to highly-functionalised 2-ethoxy-3-aryl/heteroaryl-pyridine derivatives, which are attractive drug and agrochemical candidates. (iii) The high-yielding reactions in the presence of a primary amine substituent (entries 4, 5 and 7) are notable:[8a,13] protection of the amino group is sometimes necessary for Suzuki reactions.[14]

Substrates **3**–**8** and **10** gave the optimised yield of products after 24 h at reflux, as judged by tlc and ^{1}H NMR monitoring of the reaction mixture. Reagent **9a** is a notable exception. A high yield of product **17** (78%) was obtained after only 15 min reflux; the yield decreased after 2 h and 8 h to 40 and 12%, respectively; 24 h reflux gave an intractable green product. Indeed, the reaction of **2** with **9a** at 20 °C for 16 h gave **17** in 90% yield. The chloro analogue **9b** was also very reactive: 62% yield of **17** was obtained after only 15 min reaction at 60 °C. Refluxing analytically-pure compound **17** in dioxane in the presence of $Pd(PPh_3)_2Cl_2$ led to the decomposition of **17** to yield an insoluble green solid which accounts for the reduced isolated yield of **17** after longer reaction times. The reasons for the increased reactivity of **9a** and **9b**, compared to **3**–**8** and **10** are not clear at present.

3. Conclusions

We have described an efficient synthesis of 2-ethoxy-3-pyridylboronic acid **2** which serves as a versatile compound for the preparation of functionalised aryl/heteroaryl-pyridine libraries. Reagent **2** offers significant practical advantages over other pyridylboronic acid derivatives we have studied in this context: notably, ease of synthesis and purification, efficient scale-up to 70 g batches, shelf-stability at 20 °C, and high-yielding cross-coupling reactions. Compound **2** is, therefore, highly recommended as a new reagent in pyridine chemistry.

4. Experimental

4.1. General

General details of equipment and techniques used are the same as those we have reported previously.[8a] All synthetic reagents were used as supplied. Solvents were dried and distilled using standard procedures.

4.1.1. 2-Ethoxy-3-pyridylboronic acid (2). Procedure A. To a solution of diisopropylamine (5.9 mL, 41.69 mmol) in anhydrous THF (50 mL) at −10 °C, n-BuLi (2.5 M in hexane, 17.4 mL, 43.59 mmol) was added dropwise. The reaction was stirred for 0.5 h at −10 °C then cooled to −50 °C. 2-Ethoxypyridine **1** (4.5 mL, 37.9 mmol) in anhydrous THF (10 mL) was added dropwise. The reaction was stirred for 1 h at −50 °C then triisopropylborate (10.5 mL, 45.5 mmol) was added slowly. The reaction mixture was stirred at −50 °C for another 1 h, then allowed to warm to −10 °C and quenched with water (50 mL). The reaction was left at room temperature with stirring overnight. The organic solvent was evaporated in vacuo and the remaining aqueous layer, pH 10, was filtered. The filtrate was washed with diethyl ether (2×50 mL). The aqueous layer was then acidified to pH 4 (with 48% HBr) to give **2** as a white solid (4.4 g, 70%), mp 103.0–103.8 °C; υ_{max}(KBr) 3200, 2992, 2912, 1585, 1439 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.16 (1H, dd, J=2.0, 4.8 Hz), 7.87 (1H, dd, J=2.0, 6.8 Hz), 7.83 (2H, s), 6.94 (1H, dd, J=4.8, 7.2 Hz), 4.33 (2H, q, J=6.8 Hz), 1.31 (3H, t, J=6.8 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.0, 148.4, 144.8, 116.9, 115.7 (br C-B), 61.2, 14.5; MS (EI) *m/z* 166.9 (M^+, 100%). Anal. Calcd. for $C_7H_{10}BNO_3$: C, 50.35; H, 6.04; N, 8.39. Found: C, 50.32; H, 5.92; N, 8.34%.

Procedure B. Following procedure A, diisopropylamine (96.7 g, 0.96 mol) in anhydrous THF (500 mL), n-BuLi (2.5 M in hexane, 400 mL, 1.00 mol), 2-ethoxypyridine **1** (107 g, 0.87 mol) and triisopropylborate (196 g, 1.04 mol) were used. After quenching with water the reaction was left at room temperature with stirring overnight. The organic layer was discarded and the aqueous layer, pH 10, was then filtered. The filtrate was washed with diethyl ether (200 mL) until no starting material was detected in the ether washings by tlc. The aqueous layer was then acidified to pH 7 (with 48% HBr) to give **2** as an analytically-pure off-white solid (69.7 g, 48%) spectroscopically identical with the sample from Procedure A.

4.2. General procedure for the cross-coupling reactions

The boronic acid **2** (1.0 equiv) the arylhalide (0.9 equiv) and $Pd(PPh_3)_2Cl_2$ (ca. 5 mol%) were sequentially added to degassed 1,4-dioxane (10 mL) and the mixture was stirred at 20 °C for 30 min. Degassed aqueous Na_2CO_3 solution (1 M, 3.0 equiv.) was added and the reaction mixture was heated under argon at reflux (typically for 24 h; entry **7** is the only exception). The solvent was removed in vacuo then ethyl acetate was added and the organic layer was washed with brine, separated, and dried over $MgSO_4$. The mixture was purified by chromatography on a silica gel column. On some occasions an additional recrystallisation was necessary. Other products isolated were small amounts of the 'self-coupled' boronic acid, i.e. 2,2′-diethoxy-[3,3′]bipyridine, which was usually the first material to elute, and unreacted arylhalide.

4.2.1. 5-(2-Ethoxy-3-pyridyl)-2-methoxypyrimidine (11). Boronic acid **2** (284 mg, 1.7 mmol), 5-bromo-2-methoxypyrimidine **3** (260 mg, 1.4 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reaction time 24 h; eluent EtOAc:hexane (1:2 v/v), gave **11**

as a white solid (260 mg, 82%) mp 70.9–71.6 °C; υ_{max}(KBr) 3054, 2988, 2952, 1568, 1546, 1450 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.79 (2H, s), 8.17 (1H, dd, J= 1.6, 4.8 Hz), 7.82 (1H, dd, J=1.6, 7.2 Hz), 7.06 (1H, dd, J= 4.8, 7.2 Hz), 4.42 (2H, q, J=7.2 Hz), 3.98 (3H, s), 1.34 (3H, t, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.70, 160.42, 158.80, 146.80, 137.38, 124.10, 117.69, 116.91, 96.11, 61.99, 54.82, 14.57; MS (EI) *m/z* 231.1 (M^+, 100%). Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.42; H, 5.74; N, 17.93%.

4.2.2. 5-(2-Ethoxy-3-pyridyl)pyrimidine (12). Boronic acid **2** (284 mg, 1.7 mmol), 5-bromopyrimidine **4** (239 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reaction time 24 h; eluent EtOAc:hexane (1:1 v/v), gave **12** as a white solid (271 mg, 90%) mp 119.0–119.8 °C; υ_{max}(KBr) 2992, 2966, 2908, 1579, 1555, 1439 cm^{-1};^1H NMR (400 MHz, acetone-d_6) δ 9.10 (1H, s), 9.01 (2H, s), 8.23 (1H, dd, J= 1.6, 4.8 Hz), 7.89 (1H, dd, J=1.6, 8.0 Hz), 7.11 (1H, dd, J= 5.2, 7.6 Hz), 4.43 (2H, q, J=7.2 Hz), 1.34 (3H, t, J= 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 157.3, 156.4, 147.7, 138.0, 130.6, 117.5, 117.0, 96.2, 62.2, 14.6; MS (EI) *m/z* 201.1 (M^+, 100%). Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.46; H, 5.51; N, 20.63%.

4.2.3. 2-(2-Ethoxy-3-pyridyl)pyrimidine (13). Boronic acid **2** (284 mg, 1.7 mmol), 2-bromopyrimidine **5** (239 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reaction time 24 h; eluent EtOAc:hexane (1:2 v/v), gave **13** as a colourless viscous oil (268 mg, 89%); υ_{max}(KBr) 2977, 1571, 1445, 1415 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.68 (2H, d, J=4.8 Hz), 8.11 (1H, d, J=4.8 Hz), 7.94 (1H, d, J= 7.3 Hz), 7.03 (1H, t, J=4.8 Hz), 6.83 (1H, dd, J=5.1, 7.2 Hz), 4.37 (2H, q, J=7.0 Hz), 1.23 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 161.1, 156.8 (2C), 148.0, 140.1, 122.3, 118.7, 116.3, 62.0, 14.2; HRMS (EI) calcd for $C_{11}H_{11}N_3O$ (M^+) 201.09121, found 201.09133.

4.2.4. 2′-Ethoxy-5-nitro-[3,3′]bipyridinyl-6-ylamine (14). Boronic acid **2** (284 mg, 1.7 mmol), 5-bromo-2-amino-3-nitropyridine **6** (327 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reaction time 24 h; eluent EtOAc, gave **14** as a yellow solid (289 mg, 74%) mp 193.0–193.9 °C; υ_{max}(KBr) 3470, 3275, 3121, 2984, 1654, 1561, 1351 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.67 (1H, d, J=2.0 Hz), 8.63 (1H, d, J=2.0 Hz), 8.15 (1H, dd, J=2.0 Hz, J=4.8 Hz), 8.03 (2H, br s, NH_2), 7.90 (1H, dd, J=2.0, 4.8 Hz), 7.07 (1H, dd, J=4.8, 7.6 Hz), 4.37 (2H, q, J=7.2 Hz), 1.31 (3H, t, J= 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.7, 156.0, 152.7, 146.0, 137.9, 134.2, 126.2, 120.5, 118.7, 117.4, 61.5, 14.3; MS (EI) *m/z* 260.0 (M^+, 100%). Anal. Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.38; H, 4.65; N, 21.53. Found: C, 55.12; H, 4.58; N, 21.36%.

4.2.5. 2′-Ethoxy-5-methyl-[3,3′]bipyridinyl-6-ylamine (15). Boronic acid **2** (284 mg, 1.7 mmol), 6-amino-3-bromo-2-methylpyridine **7** (281 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reaction time 24 h; eluent EtOAc, gave **15** as a crystalline solid (258 mg, 75%) mp 138.6–139.0 °C; υ_{max}(KBr) 3466, 3299, 3151, 2975, 1639 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.10 (1H, dd, J=2.0, 4.8 Hz), 7.47 (1H, dd, J=2.0, 7.2 Hz), 7.12 (1H, d, J=8.4 Hz), 6.99 (1H, dd, J=4.8, 7.2 Hz), 6.30 (1H, d, J=8.4 Hz), 5.88 (2H, br s, NH_2), 4.29 (2H, q, J=7.2 Hz), 2.05 (3H, s), 1.22 (3H, t, J= 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.2, 158.5, 153.6, 145.3, 139.6, 139.0, 123.3, 119.0, 116.8, 104.9, 60.9, 22.3, 14.5; MS (EI) *m/z* 229.1 (M^+, 100%). Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.23. Found: C, 67.85; H, 6.54; N, 17.96%.

4.2.6. N-(2′-Ethoxy-2-methyl-[3,3′]bipyridinyl-6-yl)-acetamide (16). Boronic acid **2** (284 mg, 1.7 mmol), N-(5-bromo-6-methyl-pyridin-2-yl)-acetamide **8**[15] (334 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reaction time 24 h; eluent EtOAc, gave **16** as a crystalline solid (317 mg, 78%) mp 147.7–148.6 °C; υ_{max}(KBr) 3241, 3042, 2981, 1669, 1577, 1533 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.50 (1H, br s, NH), 8.17 (1H, dd, J=2.0, 4.8 Hz), 7.94 (1H, d, J= 8.4 Hz), 7.57 (1H, dd, J=2.0, 7.2 Hz), 7.51 (1H, d, J= 8.4 Hz), 7.04 (1H, dd, J=4.8, 7.2 Hz), 4.31 (2H, q, J= 7.2 Hz), 2.20 (3H, s), 2.08 (3H, s), 1.20 (3H, t, J=7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.2, 160.0, 154.3, 150.7, 146.3, 139.7, 139.6, 126.7, 122.0, 116.9, 110.4, 61.1, 23.3, 22.1, 14.4; MS (EI) *m/z* 271.0 (M^+, 100%). Anal. Calcd. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.18; H, 6.25; N, 15.31%.

4.2.7. Methyl 2-amino-5-(2-ethoxy-3-pyridyl)-3-pyrazinoate (17). Boronic acid **2** (284 mg, 1.7 mmol), 3-amino-6-bromopyrazine-2-carboxylic acid methyl ester **9a**[16] (345 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reaction time 16 h at 20 °C; eluent EtOAc, gave **17** as a yellow solid (440 mg, 90%) mp 156.6–157.0 °C; υ_{max}(KBr) 3447, 3264, 3146, 2979, 1693, 1618 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.89 (1H, s), 8.17 (1H, dd, J=2.0, 4.8 Hz), 8.12 (1H, dd, J=2.0, 7.6 Hz), 7.46 (2H, br s, NH_2), 7.11 (1H, dd, J=4.8, 7.6 Hz), 4.41 (2H, q, J=7.2 Hz), 3.87 (3H, s), 1.35 (3H, t, J=7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.3, 159.8, 154.3, 148.0, 146.5, 138.0, 136.7, 122.4, 119.3, 117.4, 61.6, 52.2, 14.4; MS (EI) *m/z* 274.0 (M^+, 100%). Anal. Calcd. for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.43. Found: C, 56.63; H, 4.97; N, 20.33%.

When the reaction was carried out at reflux for 15 min, product **17** (321 mg, 78% yield) was obtained.

A comparable reaction with 3-amino-6-chloropyrazine-2-carboxylic acid methyl ester **9b**,[16] 15 min at 60 °C, gave **17** in 62% yield.

4.2.8. 3-(2-Amino-4-trifluoromethylbenzene)-2-ethoxypyridine (18). Boronic acid **2** (284 mg, 1.7 mmol), 1-amino-2-bromo-5-(trifluoromethyl)benzene **10** (360 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (59.6 mg, 0.085 mmol), 1,4-dioxane (10 mL) and Na_2CO_3 (4 mL); reaction time 24 h; eluent DCM, gave **18** as a clear brown oil (300 mg, 71%); υ_{max}(KBr) 3464, 3378, 3054, 2982, 1633, 1579 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.27 (1H, dd, J=2.0, 3.2 Hz), 7.70 (1H, dd, J=2.0, 5.2 Hz), 7.26 (1H, d, J=

7.8 Hz), 7.20 (1H, s), 7.12 (1H, dd, J=2.0, 4.8 Hz), 7.04 (1H, d, J=7.8 Hz), 4.90 (2H, t, s), 4.48 (2H, q, J=7.2 Hz), 1.36 (3H, t, J=7.2 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 116.3, 147.5, 140.8, 132.4, 130.9 (q, J=32 Hz), 125.5 (q, J=270 Hz), 122.2, 117.8, 113.5, 112.2, 62.2, 14.8; HRMS (EI) calcd for $C_{14}H_{13}F_3N_2O$ (M^+) 282.09800, found 282.09820.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.02.070

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