Facile Synthesis of *ortho*-Halo-Substituted 4-Aryl-2-Aminobutyric Acids

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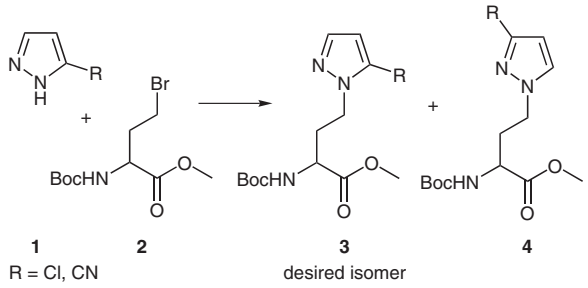
Received 15 October 2007; revised 13 December 2007

Abstract: Herein we describe an efficient and practical route for the regioselective synthesis of 4-(5-bromo/chloropyrazol-1-yl)-2-aminobutyric acids. The compounds have been prepared by regioselective C-5 halogenation of 1-(3,3-dimethoxypropyl)-1*H*-pyrazole followed by a Strecker synthesis. In addition, Boc-protected 2-amino-4-(2-chlorophenyl)butyric acid and 2-amino-4-(3-chloropyridin-2-yl)butyric acid have been synthesized.

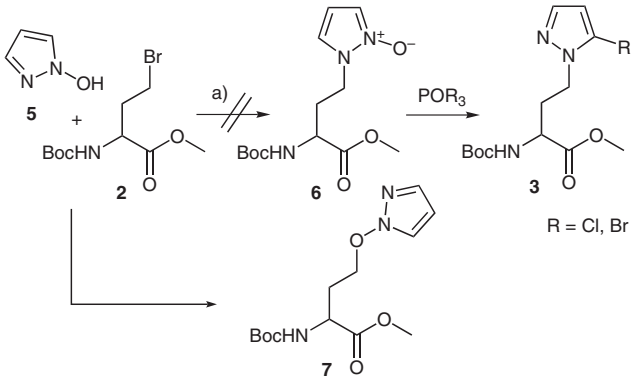
Key words: amino acids, 1-alkyl-5-halopyrazole, Strecker synthesis, Heck reaction, Grignard reaction

In the course of our research, we required a general method for the preparation of ortho-substituted 4-aryl-2-aminobutyric acids, particularly when aryl equals pyrazole. While chemistry to prepare amino acid derivatives containing (hetero)aryl side chains is known,[1] none of the reported methods appeared to allow the ready incorporation of different ortho-substituents on the (hetero)aryl ring. For the synthesis of a pyrazole-containing amino acid derivative such as **3**, we initially focused on alkylation of the anion of 5-substituted pyrazoles **1** (R = Cl, CN) with alkyl bromide **2**. As expected,[2] this alkylation produced a regioisomeric mixture of the 1,5- and 1,3-substituted pyrazoles **3** and **4** that proved difficult to separate (Scheme 1). Subsequently, we investigated an alternative synthesis of **3** with R = Br, with the intention of exploiting the bromine functionality in subsequent cross-coupling reactions.



Scheme 1 Regioisomeric mixture formed through direct alkylation

Two general routes are reported that regioselectively introduce a halogen at the 5-position of 1-alkylpyrazoles. One method constitutes the conversion of 1-alkylpyrazole-2-oxides (cf. **6**, Scheme 2) into 5-halo-1-alkylpyrazoles (cf. **3**, R = Cl, Br) via an oxyhalide-mediated halogenation with simultaneous deoxygenation.[3] Alkylpyrazole-2-oxides can be accessed through regioselective N-alkylation of hydroxypyrazole (**5**) with alkyl bromides. For example, heating **5** and *n*-butyl bromide in chloroform at 100 °C has been reported to furnish 1-butylpyrazole-2-oxide in 49% yield.



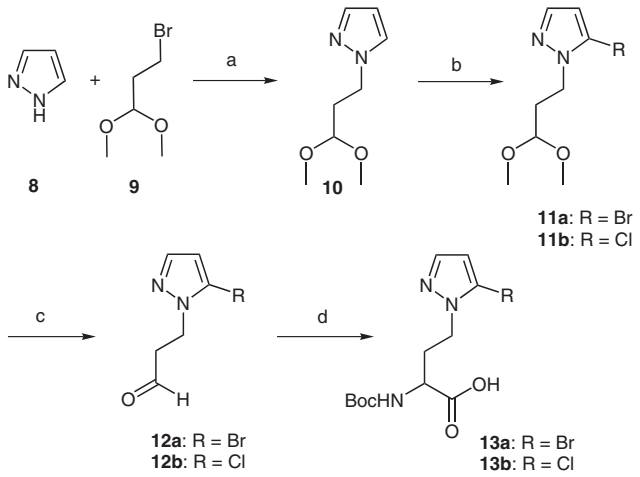
Scheme 2 O-Alkylation instead of N-alkylation. *Reagents and conditions*: (a) $CHCl_3$, 100 °C, 24 h, sealed tube.[3]

In our hands, heating a mixture of **5** and **2** in chloroform at 100 °C provided exclusively O-alkylated product **7** instead of the desired product **6** (Scheme 2). We attributed this failure to the functional groups present in **2** compared to non-functionalized alkyl bromides. Therefore, 3-bromo-1,1-dimethoxypropane (**9**), a less functionalized alkyl bromide, which could subsequently be converted into an amino acid, was evaluated. Reaction of hydroxypyrazole with **9** afforded the desired N-alkylated pyrazole-2-oxide, but only in less than 10% yield (major product: O-alkylation).

Since the pyrazole oxide route was unsuccessful, we investigated a second general method, which involves ortho-lithiation of 1-alkylpyrazoles.[4] Starting from alkyl bromide **9**, we envisioned 5-halopyrazole **11a** would be readily accessible and undergo a subsequent Strecker reaction to convert the aldehyde into the amino acid. Thus, alkylation of the anion of pyrazole (**8**) with commercially available bromide **9** provided acetal **10** in 75% yield. Lithiation of **10** at –78 °C with *n*-butyllithium, followed by addition of bromine, led to 5-bromopyrazole **11a**. The best yields (72%) were obtained when the reaction was quenched below –30 °C with saturated aqueous sodium carbonate; this avoided over-bromination of the pyrazole. Cleavage of the acetal with perchloric acid[5] afforded aldehyde **12a**. In a one pot sequence, aldehyde **12a** was first

SYNTHESIS 2008, No. 6, pp 0883–0886
Advanced online publication: 28.02.2008
DOI: 10.1055/s-2008-1032194; Art ID: M07707SS

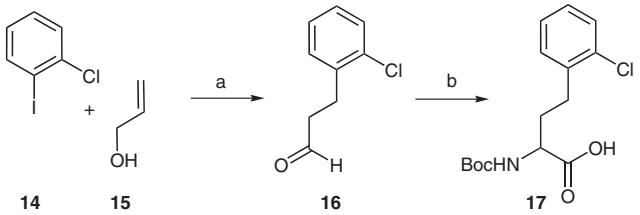
converted into the aminonitrile,[6] which was hydrolyzed under acidic conditions to the free amino acid. Subsequent Boc-protection provided the expected 4-(5-bromopyrazol-1-yl)-2-aminobutyric acid **13a** in an overall yield of 81% over three steps (Scheme 3).



Scheme 3 *Reagents and conditions*: (a) NaH, THF, 75%; (b) **11a**: *n*-BuLi, Br_2, 72%; **11b**: *n*-BuLi, C_2Cl_6, 75%; (c) $HClO_4$, THF, **12a**: 84%; **12b**: 92%; (d) (i) TMSCN, NH_3, cat. ZnI_2; (ii) 6N HCl; (iii) $NaHCO_3$, Boc_2O, **13a**: 81%; **13b**: 70%.

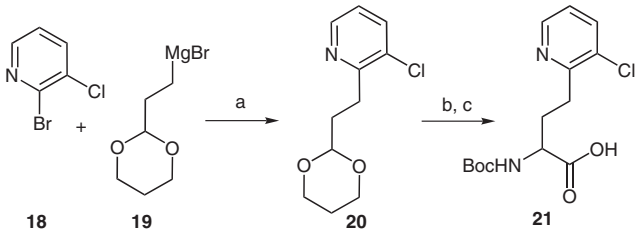
The corresponding chloro-analogue **11b** was prepared in a similar manner, using hexachloroethane in the halogenation step. Both compounds **13a** and **13b** were obtained in 36% yield starting from pyrazole over four isolated steps.

Based on this route, which provided us with a reliable sequence to access 5-halopyrazole-containing amino acids, we investigated the synthesis of analogous amino acids with six-membered aryl rings such as phenyl **17** (Scheme 4)[7] and 2-pyridyl **21** (Scheme 5). Aldehyde **16** was prepared from 2-chloroiodobenzene (**14**) and allyl alcohol (**15**) in 73% yield by a Heck-type reaction developed by Jeffery.[8] Subsequent Strecker reaction gave butyric acid **17** in 55% yield (Scheme 4).



Scheme 4 *Reagents and conditions*: (a) $Pd(OAc)_2$, $NaHCO_3$, TBACl, DMF, 73%; (b) (i) TMSCN, NH_3, cat. ZnI_2; (ii) 6N HCl; (iii) $NaHCO_3$, Boc_2O, 55%.

In case of the pyridine analogue **21**, the corresponding aldehyde precursor could not be prepared from 2-bromo-3-chloropyridine (**18**) and allyl alcohol (**15**). We decided to revisit our strategy and investigated the synthesis of acetal **20** via a copper(I)-mediated Grignard addition as reported by Bell et al. for mono-halogenated pyridines.[9] Applying these conditions, reaction of doubly halogenated pyridine **18** and commercially available Grignard reagent **19** furnished acetal **20** in 56% yield. Subsequent transformations provided the Boc-protected 2-amino-4-(3-chloropyridin-2-yl)butyric acid (**21**) in 19% yield over three isolated steps (Scheme 5).



Scheme 5 *Reagents and conditions*: (a) CuBr, THF, 56%; (b) $HClO_4$, THF, 76%; (c) (i) TMSCN, NH_3, cat. ZnI_2; (ii) 6N HCl; (iii) $NaHCO_3$, Boc_2O, 45%.

In summary, an efficient and practical regioselective route to access 5-halopyrazole substituted 2-aminobutyric acids has been developed. Furthermore, this general route, starting from readily available materials, was applied to the syntheses of 2-chlorophenyl and 3-chloropyridyl containing amino acids by expanding known chemistry.

All chemicals used, including anhydrous solvents, were of reagent grade and used as supplied. Chromatography was carried out on silica gel; TLC were carried out on silica plates (Merck, Art. 5554). In general, the course of reactions was followed by TLC and/or LC-MS. NMR spectra were obtained on a Bruker DPX-400 spectrometer at 400 MHz. LC-MS data was recorded utilizing the electrospray (ESI) technique. Values for *m/z* are given; the mass ion quoted is $[M + H]^+$, which refers to the protonated mass ion. HRMS data was acquired using an Agilent LCMSD-TOF in the positive and negative ESI ionization modes. This instrument achieved a mass resolution of greater than 13,000 measured at *m/z* = 2722.

1-(3,3-Dimethoxypropyl)-1*H*-pyrazole (10)

To a solution of pyrazole (1.67 g, 24.6 mmol) in DMF (25 mL) at r.t. was added NaH (0.98 g, 60% in mineral oil, 24.6 mmol) in one portion. The resulting white suspension was stirred for 15 min before 3-bromo-1,1-dimethoxypropane (5.00 g, 90%, 24.6 mmol) was added. The reaction mixture was heated at 80 °C for 3 h. After cooling to r.t., the reaction was quenched with H_2O (25 mL) and the mixture was extracted with EtOAc (2 × 50 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a pale-yellow oil. Purification on silica gel (EtOAc–hexane, 0→50%) gave **10**.

Yield: 3.16 g (75%); colorless oil; R_f = 0.5 (EtOAc–hexane, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 2.0 Hz, 1 H), 7.37 (d, *J* = 2.0 Hz, 1 H), 6.23 (t, *J* = 2.0 Hz, 1 H), 4.26 (t, *J* = 5.8 Hz, 1 H), 4.20 (t, *J* = 7.0 Hz, 2 H), 3.32 (s, 6 H), 2.16 (dt, *J* = 7.0, 5.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.2, 129.1, 105.1, 101.9, 53.0, 47.6, 33.2.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_8H_{14}N_2O_2$: 171.1128; found: 171.1134.

5-Bromo-1-(3,3-dimethoxypropyl)-1*H*-pyrazole (11a)
To a solution of pyrazole **10** (3.15 g, 18.1 mmol) in THF (50 mL) at –78 °C was added *n*-BuLi (8.9 mL, 2.5 M in hexane, 22.2 mmol) dropwise. After stirring at –78 °C for 30 min, Br_2 (1.14 mL, 22.2 mmol) was added. The reaction was stirred for 1 h at –78 °C and was then allowed to reach –30 °C before sat. aq Na_2CO_3 (50 mL) was added. The resultant mixture was extracted with EtOAc (2 × 50 mL). The organic layer was washed with H_2O (25 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil. Purification on silica gel (EtOAc–hexane, 0→50%) gave **11a**.

Yield: 3.30 g (72%); colorless oil; R_f = 0.9 (EtOAc–hexane, 75%, $KMnO_4$ stain).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 2.0 Hz, 1 H), 6.27 (d, *J* = 2.0 Hz, 1 H), 4.36 (t, *J* = 5.8 Hz, 1 H), 4.24 (t, *J* = 7.0 Hz, 2 H), 3.34 (s, 6 H), 2.15 (dt, *J* = 7.0, 5.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2, 112.6, 108.4, 101.9, 53.2, 46.0, 32.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{13}BrN_2O_2$: 249.0233; found: 249.0245.

5-Chloro-1-(3,3-dimethoxypropyl)-1*H*-pyrazole (11b)
Prepared according to the procedure for **11a** from pyrazole **10** (2.14 g, 12.6 mmol), *n*-BuLi (6.03 mL, 15.1 mmol) and hexachloroethane (2.98 g, 12.6 mmol).

Yield: 1.94 g (75%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 2.0 Hz, 1 H), 6.18 (d, *J* = 2.0 Hz, 1 H), 4.35 (t, *J* = 5.8 Hz, 1 H), 4.20 (t, *J* = 7.0 Hz, 2 H), 3.33 (s, 6 H), 2.14 (dt, *J* = 7.0, 5.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.3, 126.8, 104.5, 101.9, 53.1, 44.8, 32.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{13}ClN_2O_2$: 205.0738; found: 205.0748.

3-(5-Bromopyrazol-1-yl)propionaldehyde (12a)
Acetal **11a** (1.87 g, 7.5 mmol) was dissolved in THF (10 mL) and cooled to 0 °C before a solution of perchloric acid (4.0 mL, 70%) in THF (15 mL) was added. H_2O (5 mL) was then added and the reaction was stirred at r.t. for 6 h, the mixture was poured into sat. aq $NaHCO_3$ and extracted with EtOAc (2 × 50 mL). The organic layer was washed with H_2O (25 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a pale-yellow oil. Purification on silica gel (EtOAc–hexane, 0→50%) gave **12a**.

Yield: 1.30 g (84%); colorless oil; R_f = 0.3 (EtOAc–hexane, 75%; $KMnO_4$ stain).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.84 (s, 1 H), 7.48 (d, *J* = 2.0 Hz, 1 H), 6.28 (d, *J* = 2.0 Hz, 1 H), 4.48 (t, *J* = 7.0 Hz, 2 H), 3.05 (t, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.9, 140.5, 112.8, 108.7, 43.5, 43.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_6H_7BrN_2O$: 202.9814; found: 202.9817.

3-(5-Chloropyrazol-1-yl)propionaldehyde (12b)
Acetal **11b** (1.93 g, 9.5 mmol) was hydrolyzed under the conditions described for **12a** to provide **12b**.

Yield: 1.39 g (92%); pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.84 (s, 1 H), 7.50 (d, *J* = 2.0 Hz, 1 H), 6.20 (d, *J* = 2.0 Hz, 1 H), 4.50 (t, *J* = 7.0 Hz, 2 H), 3.05 (t, *J* = 7.0 Hz, 2 H).

Strecker Synthesis of Boc-Protected Amino Acids; General Procedure
In a pressure tube, TMS-CN (1.5 mmol) and a catalytic amount of ZnI_2 (~5 mol%) were added to a solution of aldehyde (1.0 mmol) in anhydrous THF (2 mL). After stirring for 15 min at r.t., a solution of NH_3 in MeOH (7 M, 5 mL) was added. The tube was sealed and the reaction mixture was stirred at 60 °C for 3 h, after which time the formation of the aminonitrile intermediate was complete (monitored by LC-MS). After evaporation of the solvent, HCl (6 N, 5 mL) was added to the residue and the mixture was heated to reflux for 8 h (or until complete hydrolysis to the amino acid was observed by LC-MS). After cooling to r.t., the mixture was cautiously neutralized with sat. aq $NaHCO_3$. Additional sat. aq $NaHCO_3$ (15 mL) and dioxane (20 mL), followed by Boc_2O (4.0 mmol), were added. After 4 h (reaction monitored by LC-MS) the mixture was extracted with EtOAc (3 × 20 mL) and the organic layer was discarded. The aqueous layer was acidified to pH 5 with HCl (2 N) and extracted with EtOAc (3 × 25 mL). The organic layer was washed with H_2O (25 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the product in >90% purity. The products could be further purified on silica gel (MeOH–CH_2Cl_2, 0→10%).

4-(5-Bromopyrazol-1-yl)-2-*tert*-butoxycarbonylaminobutyric Acid (13a)
According to the general Strecker procedure, aldehyde **12a** (1.27 g, 6.3 mmol) gave product **13a**.

Yield: 1.76 g (81%); colorless, waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (br s, 1 H), 7.53 (d, *J* = 2.0 Hz, 1 H), 6.32 (d, *J* = 2.0 Hz, 1 H), 5.44 (d, *J* = 7.0 Hz, 1 H), 4.45–4.26 (m, 3 H), 2.46–2.37 (m, 1 H), 2.32–2.23 (m, 1 H), 1.43 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 155.5, 139.9, 114.0, 109.1, 80.3, 51.2, 46.5, 32.2, 28.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}BrN_3O_4$: 348.0553; found: 348.0569.

2-*tert*-Butoxycarbonylamino-4-(5-chloropyrazol-1-yl)butyric Acid (13b)
According to the general Strecker procedure, aldehyde **12b** (1.39 g, 8.8 mmol) gave product **13b**.

Yield: 1.86 g (70%); colorless, waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 2.0 Hz, 1 H), 6.27 (d, *J* = 2.0 Hz, 1 H), 5.44 (br s, 1 H), 4.48–4.39 (m, 1 H), 4.36–4.23 (m, 2 H), 2.34–2.27 (m, 2 H), 1.43 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 155.5, 139.2, 128.0, 105.2, 80.2, 51.2, 45.3, 32.1, 28.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}ClN_3O_4$: 304.1058; found: 304.1073.

3-(2-Chlorophenyl)propionaldehyde (16)
In a pressure tube under argon, 2-chloroiodobenzene (5.86 g, 24.6 mmol), allyl alcohol (2.51 mL, 36.8 mmol), $Pd(OAc)_2$ (0.11 g, 0.5 mmol), $NaHCO_3$ (5.16 g, 61.4 mmol) and TBACl (6.83 g, 24.6 mmol) were mixed together in anhydrous DMF (100 mL). The mixture was stirred at 30 °C for 24 h before H_2O (100 mL) was added. The mixture was extracted with EtOAc (3 × 40mL) and the organic layer was washed with H_2O (25 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting black residue was purified on silica gel (EtOAc–hexane, 0→50%) to give **16**.

Yield: 3.00 g (73%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.83 (t, *J* = 1.2 Hz, 1 H), 7.35 (dd, *J* = 7.3, 2.0 Hz, 1 H), 7.24 (dd, *J* = 7.3, 2.0 Hz, 1 H), 7.22–7.14 (m, 2 H), 3.06 (t, *J* = 7.4 Hz, 2 H), 2.80 (dt, *J* = 7.4, 1.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1, 138.0, 133.8, 130.5, 129.6, 127.9, 127.0, 43.5, 26.2.

MS (EI, 70 eV): *m*/*z* (%) = 210 (100) $[M(H_2O) + Na + H]^+$.

2-*tert*-Butoxycarbonylamino-4-(2-chlorophenyl)butyric Acid (17)

According to the general Strecker procedure, aldehyde **16** (2.20 g, 13.1 mmol) gave product **17**.

Yield: 2.25 g (55%); pale-yellow, waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (dd, *J* = 7.4, 1.5 Hz, 1 H), 7.24–7.13 (m, 3 H), 5.07 (d, *J* = 5.9 Hz, 1 H), 4.35 (br s, 1 H), 2.83 (t, *J* = 7.9 Hz, 2 H), 2.26–2.16 (m, 1 H), 2.03–1.93 (m, 1 H), 1.46 (s, 9 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 174.9, 156.9, 138.7, 133.7, 130.5, 129.3, 127.7, 127.0, 79.4, 53.4, 31.7, 29.6, 27.5.

HRMS (ESI): *m*/*z* $[M - H]^-$ calcd for $C_{15}H_{20}ClNO_4$: 312.1008; found: 312.1004.

3-Chloro-2-(2-[1,3]dioxan-2-ylethyl)pyridine (20)

Under argon, a mixture of anhydrous CuBr (1.79 g, 12.5 mmol), anhydrous THF (30 mL) and dioxan-2-yl-ethylmagnesium bromide (50 mL, 0.5 M in THF, 25.0 mmol) was stirred at –78 °C for 20 min. 2-Bromo-3-chloropyrdine (0.60 g, 3.1 mmol) was added and the reaction mixture was stirred for 3 h at –78 °C then allowed to warm to r.t. overnight. The reaction mixture was quenched by dropwise addition of NH_4OH (5 M, 10 mL) and then extracted with EtOAc (3 × 20 mL). The organic layer was washed with H_2O (25 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a brown oil. Purification on silica gel (EtOAc–hexane, 0→50%) gave **20**.

Yield: 0.40 g (56%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (dd, *J* = 4.8, 1.5 Hz, 1 H), 7.57 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.04 (dd, *J* = 8.0, 4.8 Hz, 1 H), 4.58 (t, *J* = 5.0 Hz, 1 H), 4.09–4.05 (m, 2 H), 3.76–3.69 (m, 2 H), 3.03–2.99 (m, 2 H), 2.11–1.99 (m, 3 H), 1.32–1.26 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6, 147.1, 136.5, 131.2, 122.2, 101.6, 66.9, 33.1, 29.7, 25.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{14}ClNO_2$: 228.0785; found: 228.0792.

2-*tert*-Butoxycarbonylamino-4-(3-chloropyridin-2-yl)butyric Acid (21)

Acetal **20** (192 mg, 0.8 mmol) was hydrolyzed under the conditions described for **12a** providing 3-(2-chloropyridin-2-yl)propionaldehyde.

Yield: 108 mg (76%); pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (br s, 1 H), 8.42 (d, *J* = 4.5 Hz, 1 H), 7.67 (d, *J* = 8.0 Hz, 1 H), 7.14 (dd, *J* = 8.0, 4.5 Hz, 1 H), 3.30 (t, *J* = 7.0 Hz, 2 H), 2.94 (dt, *J* = 7.0, 1.2 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* (%) = 170.4 (100) $[M + H]^+$.

According to the general Strecker procedure, 3-(2-chloropyridin-2-yl)propionaldehyde (62 mg, 0.4 mmol) gave product **21**.

Yield: 52 mg (45%); colorless, waxy solid.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.38 (d, *J* = 4.8 Hz, 1 H), 7.79 (d, *J* = 8.2 Hz, 1 H), 7.25 (dd, *J* = 8.2, 4.8 Hz, 1 H), 4.10 (br s, 1 H), 3.10–3.02 (m, 1 H), 2.99–2.91 (m, 1 H), 2.29–2.20 (m, 1 H), 2.06–1.97 (m, 1 H), 1.44 (s, 9 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 178.7, 159.6, 157.9, 148.2, 138.9, 138.6, 132.6, 124.2, 80.3, 32.5, 32.0, 28.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{19}ClN_2O_4$: 315.1087; found: 315.1091.

Acknowledgment

We thank Scott Leonard for confirming the regiochemistry of the halogenation by NMR, and Keith McKellop for HRMS experimentation. Additional thanks to Dr. Daniel Goldberg and Dr. Neil Moss for proofreading the manuscript and Dr. Derek Cogan for helpful discussions.

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