Oxidation of Methyl Heteroaryls with Molecular Oxygen: A Facile Synthesis of 2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-pyridinecarbaldehyde

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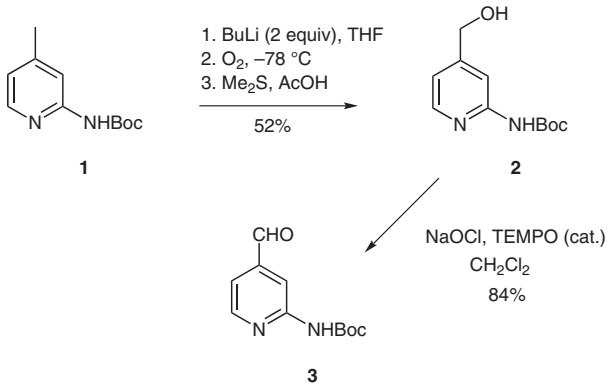
Abstract: Oxidation of nitrogen-based methyl heteroaryls with molecular oxygen resulted in the formation of the corresponding benzyl alcohols. While experimentally easy and amenable to large-scale preparations, this approach has limitations with respect to the particular nature of heterocyclic substrates. Using this methodology, the title compound, 2-[*N*-(*tert*-butoxycarbonyl)amino]-4-pyridinecarbaldehyde, considered to be a versatile pharmaceutical intermediate, was prepared on a multigram scale.

Key words: oxidation, oxygen, methyl heteroaryls, benzyl anion, benzyl alcohols

Despite rising interest in the 2-aminopyridine motif as a building block for biologically active molecules,[1] methods available for its incorporation into more complex structures are rather limited. 2-Amino-4-hydroxymethylpyridine has been prepared from the corresponding amino acid *N*-acetyl derivative[2] and is now commercially available. In conceptually similar, although somewhat lengthy approaches, Boc-protected 2-amino-4-hydroxymethylpyridine **2** was prepared in three steps from the same 2-acetylamino-4-pyridinecarboxylic acid[3] and in 4 steps from 2-chloro-4-pyridinecarboxylic acid.[4] Boc-protected 3-amino-5-pyridinecarbaldehyde was obtained in three steps from 3,5-pyridinedicarboxylic acid with the apparent implication that the same method was used to access 2-amino-4-pyridinecarboxaldehyde **3**.[5] However, an option of direct access to benzyl alcohol and/or aldehyde from the 2-amino-4-methylpyridine precursor without invoking carboxylic acid intermediates would be desirable. More straightforward in nature, this approach has the potential to be cheaper and more amenable to large scale synthesis. In a general sense, it may also offer the advantage of applicability to heterocycles for which no benzoic esters are commercially available and better compatibility with certain functional groups, in contrast to metal hydrides required for ester reduction. We describe here our efforts towards direct oxygenation of Boc-protected 2-amino-4-methylpyridine **1** and other nitrogen-containing heterocycles.

Attempts at direct oxidation of compound **1** with oxidants of moderate strength (e.g., SeO_2) were not successful, and complex mixtures containing largely unreacted starting material were obtained.[6] Ihle and co-workers have described use of the dianion derived from 2-[*N*-(*tert*-butoxycarbonyl)amino]-4-methylpyridine (**1**) in reactions with electrophiles.[7] We investigated the applicability of this approach toward our goal of obtaining alcohol **2** in a convenient large-scale procedure.

When predried molecular oxygen was passed through a –78 °C suspension of the dianion derived from **1**, the dark orange color quickly changed to bright yellow. After several hours, the reaction mixture was quenched with two equivalents of acetic acid together with an excess of dimethyl sulfide. The crude mixture was stirred for an additional 48 hours at room temperature, as it appeared by TLC that formation of alcohol **2**, presumably from its hydroperoxide precursor, was still being completed during this time. Gratifyingly, the desired alcohol **2** was isolated in 52% yield (Scheme 1). Conversion into aldehyde **3** was effected in high yield under NaOCl/TEMPO conditions.



Scheme 1 Synthesis of aldehyde **3**

The moderate yield of alcohol formation is not easy to explain, as no obvious side products have been isolated. However, the efficiency of the procedure, ease of scale-up and purification, as well as the low cost of starting 2-amino-4-methylpyridine appear to offer a viable option to the previously mentioned reductive methods.

Heterocycle variation in a series of biologically active analogues stimulated our interest in the application of this oxidative approach to the synthesis of other heteroaryl-derived benzyl alcohols. From the outset, however, we had to consider conceptual limitations of this strategy. In particular, electron-poor nitrogen heteroaryls can be expected to be susceptible to nucleophilic attack from alkylmetal bases[8] or aryllithium intermediates, possibly arising from

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the direct ring metalation.[9] Replacement of butyllithium with LDA did not change the outcome, as adducts with pyrimidines and pyridazines (e.g., LDA adduct with **4**) were isolated in both cases. Direct ring metalation can also shift the reactivity from the methyl group to the heteroaryl nucleus,[10] although intermediate quenching of the more reactive ring position with a removable blocking group can potentially be envisioned. Functional group compatibility with reaction conditions was not systematically investigated, but complex mixtures were formed with specific substrates **5** and **6** (Figure 1). In the case of nitro substitution *ortho* to the methyl group (compound **7**), the easily formed deep blue benzylic anion was completely unreactive towards oxygen, and starting material was fully recovered. Similarly, subjecting ethylpyridine **8** to the reaction conditions returned unchanged starting material.

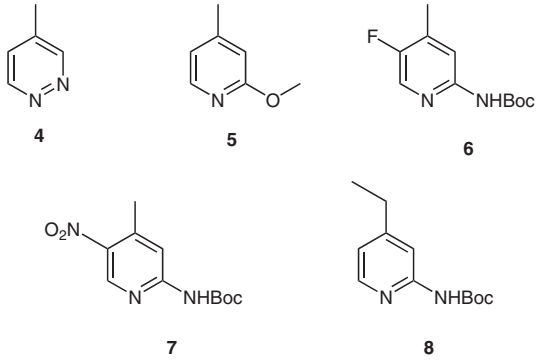


Figure 1 Unsuccessful benzylic oxygenation substrates

However, when the methodology was applied to the 4-amino-6-methylpyrimidine,[11] the desired alcohol **10** was isolated in 49% yield (Table 1). The approach also proved moderately successful in the case of 2-fluoro-4-methylpyridine[12] which produced the desired alcohol **11**,[13] but also 2-fluoro-4-methylpyridine dimer **13** (Figure 2) in comparable 31% yield. Oxidation of 3,4-lutidine occurred selectively at the 4-methyl group to yield 4-hydroxymethyl-3-methylpyridine (**12**),[14] in contrast to the previously reported unsuccessful approach to 4-hydroxymethyl-2-methylpyridine under similar conditions.[15] Dimer formation (compound **14**),[16] however, was also observed (15%) although in a lower yield compared to the 2-fluoro analogue **13**. Interestingly, attempted oxidation of 2-(*tert*-butoxycarbonyl)amino-4,6-dimethylpyridine (**15**) (Figure 2) resulted in intractable mixture. While the mechanism of dimer formation is not quite clear at this point, formation of **13** appears to be attributable to the reaction of the starting 2-fluoro-4-methylpyridine with the alcohol **11** under the workup conditions. This was demonstrated by the full conversion of starting methyl heteroaryl into the dimer **13** (as followed by TLC) upon exposure to equimolar amount of the corresponding alcohol **11** and catalytic amount of acetic acid. However, subjecting a mixture of 3,4-dimethylpyridne and alcohol **12** to similar conditions did not lead to **14**. Further investigations into the process of methyl heteroaryl dimer formation will be reported in due course.

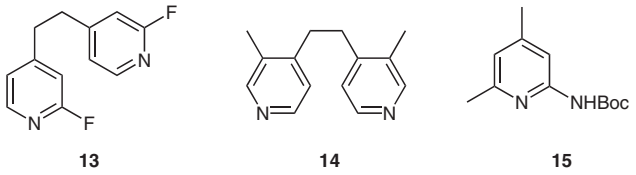
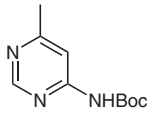
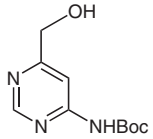
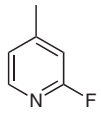
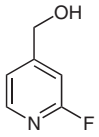
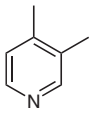
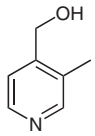


Figure 2 Compounds **13**–**15**

Table 1 Benzylic Oxidations of Methyl Heteroaryls[a]

Starting material	Product	Isolated yield (%)
 **9**	 **10**	49
	 **11**	33
	 **12**	49

[a] Procedures analogous to the conversion **1** into **2** were used. One equiv of BuLi was used in the syntheses of **11** and **12**. Anion of 2-fluoro-4-methylpyridine was maintained at –78 °C throughout the reaction.

Having established an efficient and reliable synthetic route to aldehyde **3**, we explored its use as a pharmaceutical intermediate. The 2-amino-4-pyridyl motif can be variably linked into more complex structures with the nature of connection dependent on the functional elaboration of the initial aldehyde **3** (Scheme 2). The 2-aminopyridine motif often conveys unique biological properties to the targets of interest. Information in this regard will be reported in due course.

All reactions were carried out under N_2 with anhyd solvents (Sigma-Aldrich) under anhydrous conditions, unless otherwise noted. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Flash chromatography was carried out with EM science Silica gel 60 (neutral, 230–400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 500 NMR Spectrometer with chemical shifts measured relative to residual or deuterated solvent and reported in ppm relative to external TMS. HRMS was recorded on a Micromass QT of Ultima API US mass spectrometer by FAB. IR spectra were recorded on ATI Mattson Genesis FTIR spectrometer. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ, USA. Melting points were measured on Thomas Hoover capillary melting point apparatus, Thomson Scientific, USA.

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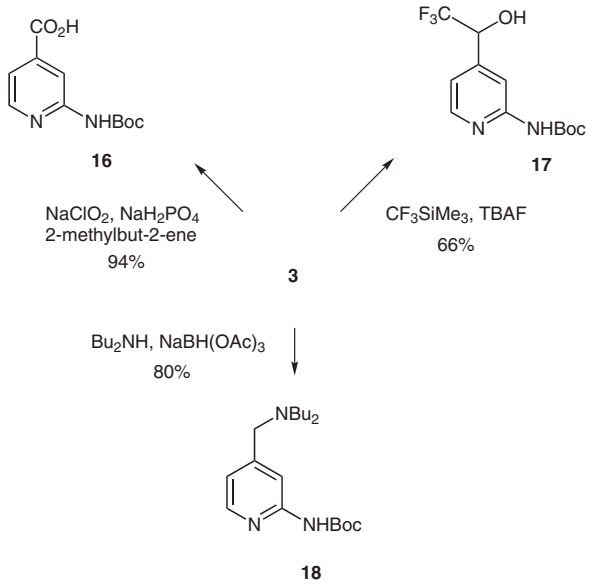

Scheme 2 Synthetic transformations of aldehyde **3**

2-(*tert*-Butoxycarbonylamino)-4-hydroxymethylpyridine (2)

To a –78 °C solution of picoline **1** (35.96 g, 173 mmol) in THF (1.4 L), was added a 1.4 M BuLi solution in hexanes (272 mL, 381 mmol) in portions over 30 min. The mixture was then allowed to warm up and stirred for 2 h at r.t., which resulted in the formation of an orange precipitate. The mixture was cooled back to –78 °C, and predried O_2 (passed through a Drierite column) was bubbled through the suspension for 6 h while the temperature was maintained at –78 °C. The color of the mixture changed to yellow during this time. It was then quenched at –78 °C with Me_2S (51.4 mL, 700 mmol) followed by AcOH (22 mL, 384 mmol). The mixture was allowed to warm up and stirred for 48 h at r.t. Dilution with H_2O (3 L) and extraction with EtOAc (2 × 500 mL) were followed by concentration and flash chromatography of the residue (0–15% acetone–CH_2Cl_2) to provide 20.15 g (52%) of alcohol **2** as a pale yellow solid; mp 133–134 °C.

IR (neat): 3434, 3206, 1727, 1618, 1579, 1540, 1432, 1293 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.52 (s, 3 H), 3.04 (br s, 1 H, OH), 4.71 (s, 1 H), 6.98 (d, *J* = 5.5 Hz, 1 H), 7.95 (s, 1 H), 8.26 (d, *J* = 5.5 Hz, 1 H), 9.39 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.29, 63.65, 80.89, 109.60, 115.67, 147.60, 152.66, 152.73, 152.91.

HRMS-FAB: *m*/*z* calcd for $C_{11}H_{17}N_2O_3$ $[M + H]^+$: 225.1239; found: 225.1236.

Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.91; H, 7.26; N, 12.34.

2-(*tert*-Butoxycarbonylamino)-4-pyridinecarbaldehyde (3)

To a solution of the alcohol **2** (19.15 g, 85.5 mmol) in CH_2Cl_2 (640 mL) was added aq sat. $NaHCO_3$ [prepared from 8.62 g (103 mmol) of $NaHCO_3$ in H_2O (90 mL)] and NaBr (444 mg, 4.3 mmol). The mixture was cooled to 0 °C, and TEMPO (140 mg, 0.90 mmol) was introduced. Commercial bleach solution (5.25% in NaOCl, 122 mL of 0.7 M, 85.4 mmol) was added, in portions, to the vigorously stirred mixture over 40 min. After additional 20 min at 0 °C, the mixture was quenched with aq sat. $Na_2S_2O_3$ (200 mL) and allowed to warm to r.t. Dilution with H_2O (600 mL) and extraction with CH_2Cl_2 (200 mL) were followed by concentration and flash chromatography (from 30% hexanes–CH_2Cl_2 to 0–2% acetone–CH_2Cl_2) to afford 15.97 g (84%) of aldehyde **3** as an off-white solid; mp 125–126 °C.

IR (neat): 3206, 1725, 1580, 1535, 1432, 1290 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.56 (s, 9 H), 7.37 (dd, *J* = 5.0, 1.5 Hz, 1 H), 8.47 (br s, 1 H), 8.50 (br d, *J* = 5.0 Hz, 1 H), 9.75 (br s, 1 H, NH), 10.04 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.30, 81.57, 113.78, 114.90, 143.91, 148.74, 152.66, 154.33, 191.66.

HRMS-FAB: *m*/*z* calcd for $C_{11}H_{15}N_2O_3$ $[M + H]^+$: 223.1083; found: 223.1079.

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.37; H, 6.23; N, 12.70.

4-(*tert*-Butoxycarbonylamino)-6-methylpyrimidine (9)

The mixture containing 4-amino-6-methylpyrimidine (1.04 g, 9.50 mmol), di-*tert*-butyl dicarbonate (2.71 g, 12.4 mmol) and DMAP (0.122 g, 1.00 mmol) in *t*-BuOH (25 mL) was stirred for 6 h at r.t. With starting material still present, an additional amount of di-*tert*-butyl dicarbonate (1.00 g, 4.58 mmol) was added, and the mixture was stirred at r.t. overnight. The mixture was concentrated, the residue dry-loaded on silica gel, and flash-chromatographed (5–12% acetone–CH_2Cl_2) to afford 0.73 g (37%) of pyrimidine **9** as a white solid.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 9 H), 2.49 (s, 3 H), 7.84 (s, 1 H), 8.73 (s, 1 H), 8.82 (br s, 1 H, NH).

HRMS-FAB: *m*/*z* calcd for $C_{10}H_{16}N_3O_2$ $[M + H]^+$: 210.1243; found: 210.1245.

Anal. Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.53; H, 7.39; N, 20.18.

4-(*tert*-Butoxycarbonylamino)-6-hydroxymethylpyrimidine (10)

In a procedure analogous to that described for **2**, pyrimidine **9** (350 mg, 1.67 mmol) yielded 185 mg (49%) of pyrimidine alcohol **10**.

^1H NMR (500 MHz, CD_3OD): δ = 1.57 (s, 9 H), 4.64 (s, 2 H), 8.16 (s, 1 H), 8.64 (s, 1 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 27.44, 63.78, 81.62, 104.51, 152.81, 157.29, 160.20, 171.18.

HRMS-FAB: *m*/*z* calcd for $C_{10}H_{16}N_3O_3$ $[M + H]^+$: 226.1192; found: 226.1181.

Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.66. Found: C, 53.22; H, 6.63; N, 18.40.

2-Fluoro-4-hydroxymethylpyridine (11) and 1,2-Bis(2-fluoro-4-pyridyl)ethane (13)

To a –78 °C solution of 2-fluoro-4-methylpyridine (4.1 g, 36.9 mmol) in THF (150 mL), was added dropwise a 2.4 M solution of BuLi in hexanes (15.4 mL 36.9 mmol). The mixture was stirred for 2 h at –78 °C, after which predried O_2 was passed through the solution for 4 h. The mixture was then quenched with AcOH (2.2 mL, 38.7 mmol) and Me_2S (5.1 mL, 70 mmol) and allowed to warm to r.t. The mixture was concentrated, the residue was dry-loaded on silica gel and subjected to flash chromatography (2% acetone–CH_2Cl_2) to give 1.5 g (33%) of **11**[13] and 1.25 g (31%) of **13**.

Compound **13**:

^1H NMR (500 MHz, $CDCl_3$): δ = 3.02 (s, 2 H), 6.76 (s, 1 H), 6.99 (d, *J* = 5.1 Hz, 1 H), 8.15 (d, *J* = 5.1 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.12, 109.08 (d, *J* = 37 Hz), 121.42 (d, *J* = 4 Hz), 147.69 (d, *J* = 16 Hz), 154.93 (d, *J* = 7 Hz), 164.05 (d, *J* = 239 Hz).

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HRMS-FAB: *m/z* calcd for $C_{12}H_{11}F_2N_2$ $[M + H]^+$: 221.0890; found: 221.0905.

Anal. Calcd for $C_{12}H_{10}F_2N_2$: C, 65.45; H, 4.58; N, 12.72; F, 17.25. Found: C, 65.23; H, 4.52; N, 12.32; F, 17.04.

4-Hydroxymethyl-3-methylpyridine (12)

To a –78 °C solution of 3,4-lutidine (10.0 mL, 89 mmol) in THF (400 mL), was added dropwise a 2.5 M solution of BuLi in hexanes (35.7 mL, 89 mmol). The resulting mixture was stirred at –78 °C for 25 min and then slowly warmed up to r.t. over 1.5 h. The mixture was cooled back to –78 °C, and predried O_2 was bubbled through the solution for 1 h. The mixture was warmed up to r.t. over 1 h while the stream of O_2 was maintained. The mixture was cooled to –30 °C, and Me_2S (26 mL, 350 mmol) was added, followed by Et_3N (50 mL, 360 mmol). The resulting mixture was warmed to r.t. and stirred for an additional 20 h. The mixture was diluted with H_2O (800 mL), extracted with EtOAc (2 × 150 mL), the combined organic phases were dried (Na_2SO_4), and concentrated. The brown oily residue was subjected to flash chromatography (5% of 0.4 M NH_3 in MeOH–CH_2Cl_2) to afford 5.35 g (49%) of alcohol **12**[14] as white crystals.

^{1}H NMR (500 MHz, CD_3OD): δ = 2.26 (s, 3 H), 4.67 (s, 2 H), 7.51 (d, *J* = 5.0 Hz, 1 H), 8.26 (s, 1 H), 8.35 (d, *J* = 5.0 Hz, 1 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 14.4, 60.5, 121.0, 131.4, 146.8, 149.1, 150.6.

HRMS-FAB: *m/z* calcd for $C_7H_{10}NO$ $[M + H]^+$: 124.0762; found: 124.0756.

2-(*tert*-Butoxycarbonylamino)-4-pyridinecarboxylic Acid (16)

To a solution of the aldehyde **3** (2.07 g, 9.32 mmol) in *t*-BuOH (80 mL) was added aq sat. NaH_2PO_4 (5.75 g, 47.9 mmol) and 2-methylbut-2-ene (6 mL, 56.6 mmol), followed by $NaClO_2$(3.38 g, 37.3 mmol). The mixture was stirred overnight at r.t., concentrated, and the residue was dry-loaded on silica gel and flash-chromatographed (30–50% MeOH–CH_2Cl_2) to afford 2.08 g (94%) of acid **16** as a white solid.

^{1}H NMR (300 MHz, CD_3OD): δ = 1.53 (s, 9 H), 7.44 (dd, *J* = 5.6, 2.3 Hz, 1 H), 8.27 (dd, *J* = 5.6, 1.1 Hz, 1 H), 8.28 (br s, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 28.58, 81.70, 113.63, 118.97, 146.83, 148.90, 154.36, 171.27.

HRMS-FAB: *m/z* calcd for $C_{11}H_{15}N_2O_4$ $[M + H]^+$: 239.1032; found: 239.1035.

2-(*tert*-Butoxycarbonylamino)-4-[(2,2,2-trifluoro-1-hydroxy)ethyl]pyridine (17)

To the solution of the aldehyde **3** (1.11 g, 5.0 mmol) in THF (10 mL) was added a 0.5 M solution of CF_3SiMe_3 in THF (20 mL, 10.0 mmol), followed by a 1 M solution of TBAF in THF (10 mL, 10.0 mmol) predried over 4 Å MS. The mixture was stirred overnight at r.t., and subjected to aq NH_4Cl [100 mL of a sat. soln diluted with H_2O (200 mL)] workup and EtOAc extraction (2 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated, and the residue was flash-chromatographed (5–8% acetone–CH_2Cl_2) to afford 0.96 g (66%) of alcohol **17** as a white foam.

^{1}H NMR (300 MHz, CD_3OD): δ = 1.53 (s, 9 H), 5.05 (q, *J* = 7.0 Hz, 1 H), 7.14 (d, *J* = 5.5 Hz, 1 H), 8.04 (s, 1 H), 8.24 (d, *J* = 5.5 Hz, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 28.59, 72.09 (q, *J* = 32 Hz), 81.81, 112.63, 118.26, 125.80 (q, *J* = 282 Hz), 148.33, 148.79, 154.08, 154.38.

HRMS-FAB: *m/z* calcd for $C_{12}H_{16}F_3N_2O_3$ $[M + H]^+$: 293.1113; found: 293.1108.

Anal. Calcd for $C_{12}H_{15}F_3N_2O_3$: C, 49.32; H, 5.17; N, 9.59; F, 19.50. Found: C, 49.83; H, 5.12; N, 9.71; F, 18.95.

2-(*tert*-Butoxycarbonylamino)-4-(*N*,*N*-dibutylaminomethyl)pyridine (18)

To a solution of the aldehyde **3** (344 mg, 1.55 mmol) and Bu_2NH (261 μL, 1.86 mmol) in CH_2Cl_2 (10 mL) was added AcOH (1 drop). The mixture was stirred for 1 h at r.t., after which $NaBH(OAc)_3$ (493 mg, 2.33 mmol) was added. The mixture was stirred for 20 h at r.t., subjected to aq $NaHCO_3$ [30 mL of a sat. soln diluted with H_2O (30 mL)] workup and CH_2Cl_2 extraction (2 × 40 mL). The organic phase was dried, concentrated, and the residue was flash-chromatographed (0–2% 2.3 M NH_3 in MeOH–CH_2Cl_2) to afford 415 mg (80%) of amine **18** as a clear oil which solidified under vacuum.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.2 Hz, 6 H), 1.22–1.35 (m, 4 H), 1.37–1.48 (m, 4 H), 2.39 (t, *J* = 7.1 Hz, 4 H), 3.53 (s, 2 H), 7.06 (d, *J* = 5.2 Hz, 1 H), 7.90 (s, 1 H), 8.25 (d, *J* = 5.2 Hz, 1 H), 9.28 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.06, 20.55, 28.38, 29.29, 53.91, 58.24, 80.58, 112.12, 118.28, 147.33, 151.91, 152.52, 152.82.

HRMS-FAB: *m/z* calcd for $C_{19}H_{34}N_3O_2$ $[M + H]^+$: 336.2651; found: 336.2647.

Anal. Calcd for $C_{19}H_{33}N_3O_2$: C, 68.02; H, 9.91; N, 12.53. Found: C, 68.00; H, 9.87; N, 12.40.

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