Indium Mediated Reduction of Hydroxylamines to Amines

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R_f values refer to TLC on 0.25 mm silica gel plates (Merck F₂₅₄) with the same eluent used for the chromatographic separation of the compound. ¹H and ¹³C NMR spectra were recorded in CDCl₃ solution (unless otherwise stated) at 200 MHz and 50.3 MHz, respectively, with a Varian Gemini spectrometer: the chemical shifts for ¹H and ¹³C NMR spectra are given in ppm from TMS. IR spectra were recorded with a Perkin-Elmer 881 spectrophotometer. Mass spectra (EI, 70 eV) were recorded with a QMD 1000 Carlo Erba instrument by direct inlet. Optical rotation measurements were carried out with a Jasco DIP-370 polarimeter. Elemental analyses were carried out with a Perkin-Elmer 2400 instrument.

Syntheses of Hydroxylamines 3-8 and Isoxazolidine 9. Hydroxylamine **1** has been purchased from Aldrich. Hydroxylamines **6**¹ and **7**² and isoxazolidine **9**³ have been prepared according to the literature. Hydroxylamines **3**⁴ and **4** have been prepared by addition of phenylmagnesium bromide and vinylmagnesium bromide, respectively, to the corresponding nitrones and hydroxylamine **5**⁵ by reduction of dihydroisoquinoline *N*-oxide with LiAlH₄.

(3*S*)-2-(2-Furyl)-1-hydroxy-3-[(triisopropylsilyl)oxy]pyrrolidine (**8**).

To a well-stirred solution of freshly distilled furan (3 equiv, 11.6 mmol, 0.789 g, 0.85 mL) in THF (20 mL), cooled to –80 °C, was added *n*-butyllithium (3.18 equiv, 7.55 mL of a 1.6 M solution in hexanes), and the mixture was stirred at 0 °C for 2 h. This solution was cooled at –80 °C and was treated with a solution of the nitron (1 equiv, 3.8 mmol, 1 g) in THF (15 mL) added

drop by drop. Stirring was continued for 30 min at 0 °C, then the reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) at -80 °C. Stirring was continued for 10 min at ambient temperature and then ethyl acetate (40 mL) was added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3x30 mL). The combined organic extracts were washed with brine and dried over sodium sulfate, and the solvent was evaporated under reduce pressure (90%, 3.4 mmol, 1.2 g). Column chromatography (hexane-ethyl acetate, 80:20) afforded pure hydroxylamine (35%, 1.3 mmol, 0.9 g).

^1H NMR (CDCl_3 , 300 MHz): 0.82-1.17 (m, 21H), 1.85 (tdd, 1H, $J = 2.9, 8.8, 13.2$ Hz), 2.23 (tdd, 1H, $J = 8.8, 10.3, 13.2$ Hz), 3.14 (dt, 1H, $J = 8.8, 10.3$ Hz), 3.27 (dt, 1H, $J = 2.9, 10.3$ Hz), 3.82 (d, 1H, $J = 5.8$ Hz), 4.53 (ddd, 1H, $J = 2.9, 5.8, 8.8$ Hz), 6.31 (s, 2H), 7.38 (s, 1H).

^{13}C NMR (CDCl_3 , 75.5 MHz): 11.8, 17.5, 17.6, 32.1, 55.8, 73.8, 74.3, 109.1, 110.1, 141.9, 152.1.

$[\alpha]_D^{25}$ (c 0.11, CHCl_3) = +23.8

I.R. 1174, 1204, 1242, 1565, 1600, 1722, 3350.

MS (FAB $M+1$): 326

Anal. Calcd for $\text{C}_{17}\text{H}_{31}\text{NO}_3\text{Si}$: C, 62.73; H, 9.60; N, 4.30. **Found:** C, 62.45; H, 9.78; N, 4.52.

General Procedure for the Reduction of Hydroxylamines with Stoichiometric In(0) . The hydroxylamine (1 mmol) is dissolved into a 2:1 solution of EtOH and sat. aq. NH_4Cl (6 mL) in a 25 mL round bottomed flask equipped with a Claisen condenser and a

magnetic stirring bar. The appropriate amount of In powder (see Tables) is then added and the mixture is heated under reflux. After completion of the reaction (TLC control), the mixture is cooled, filtered over Celite and concentrated. Then, a sat. Na_2CO_3 solution (15 mL) is added and the product is extracted with ethyl acetate (3x15 mL). The organic phase is dried over anhydrous Na_2SO_4 , then filtered and concentrated to afford the desired amine. When necessary, the amine has been purified by flash column chromatography.

General Procedure for the Reduction of Hydroxylamines with Catalytic In(0).

The hydroxylamine (1 mmol) is dissolved into a 2:1 solution of EtOH and sat. aq. NH_4Cl (6 mL) in a 25 mL round bottomed flask equipped with a Claisen condenser and a magnetic stirring bar. The appropriate amount of In powder (2-10%, see Tables) and Zn or Al (2 mmol) are added and the mixture is heated under reflux. After completion of the reaction (TLC control), the mixture is cooled, filtered over Celite and concentrated. Then, a sat. Na_2CO_3 solution (15 mL) is added and the product is extracted with ethyl acetate (3x15 mL). The organic phase is dried over anhydrous Na_2SO_4 , then filtered and concentrated to afford the desired amine. When necessary, the amine has been purified by flash column chromatography.

Syntheses of Amines 2 and 10-16.

Dibenzylamine (2)

$^1\text{H-NMR}$: 7.47-7.31 (m, 10 H, ArH), 3.91 (s, 4H, 2CH_2), 1.81 (bs, 1H, NH).

$^{13}\text{C-NMR}$: 140.2 (C), 128.2 (CH), 128.0 (CH), 126.8 (CH), 53.1 (CH_2).

N-(Diphenylmethyl)methylamine (10)

$^1\text{H-NMR}$: 7.52-7.22 (m, 10H, ArH), 4.78 (s, 1H, CH), 2.49 (s, 3H, CH_3), 2.18 (bs, 1H, NH).

$^{13}\text{C-NMR}$: 143.7 (C), 128.3 (CH), 127.1 (CH), 126.9 (CH), 69.4 (CH), 34.9 (CH_3).

3-(N-methylamino)-3-phenylprop-1-ene (11)⁶

¹H-NMR: 7.30-7.15 (m, 5H, ArH), 5.96-5.77 (m, 1H, ArCH), 5.22-5.02 (m, 2H, CH=CH₂), 4.03-3.97 (m, 1H CH=CH₂), 2.32 (s, 3H, Me), 1.48 (bs, 1H, NH).

¹³C-NMR: 142.4 (C), 140.5 (CH), 128.3(CH), 127.6 (CH), 127.0 (CH), 114.9 (CH₂), 67.8 (CH), 34.1 (CH₃).

Tetrahydroisoquinoline (12)

¹H-NMR: 7.16-6.95 (m, 4 H, ArH), 4.00 (s, 2H, ArCH₂NH), 3.12 (m, 2H, ArCH₂CH₂NH), 2.78 (m, 2H, ArCH₂CH₂NH), 2.75 (bs, 1H, NH).

¹³C-NMR: 135.5 (C), 134.4 (C), 129.0 (CH), 125.9 (CH), 125.7 (CH), 125.5 (CH), 48.0 (CH₂), 43.6 (CH₂), 28.9 (CH₂).

3,4-cis-Isopropylidenedioxypyrrolidine (13)⁷

¹H-NMR: 4.66-4.57 (m, 2H), 3.15-3.06 (m, 2H), 2.88 (bs, 1H, NH), 2.60-2.48 (m, 2H), 1.45 (s, 3H, CH₃), 1.30 (s, 3H, CH₃).

(3S)-3-Methoxymethoxypyrrolidine (14)

¹H-NMR: 4.70-4.55 (m, 2H, OCH₂O), 4.35-4.15 (m, 1H), 3.65-3.50 (m, 1H), 3.35 (s, 3H, CH₃), 2.85-2.70 (m, 1H), 2.30-1.90 (m, 4H), 1.85 (bs, 1H, NH).

¹³C-NMR: 95.5 (CH₂), 77.2 (CH), 55.5 (CH₃), 52.4 (CH₂), 31.7 (CH₂), 29.6 (CH₂).

(3S)-2-(2-Furyl)-3-[(triisopropylsilyl)oxy]pyrrolidine (15)

¹H-NMR: 7.40 (s, 2H), 6.30 (s, 2H), 4.54 (td, 1H, *J*=4.5, 5.1 Hz), 4.17 (d, 1H, *J*=5.1 Hz), 3.15-3.28 (m, 2H), 2.10 (ddt, 1H, *J*=11.4 Hz, 8.2 Hz, 4.5 Hz), 1.78-1.92 (m, 1H), 0.92 (m, 21H).

¹³C-NMR: 153.5, 141.9, 110.2, 107.2, 76.7, 64.7, 44.6, 35.1, 17.8, 17.7, 12.2.

MS (m/z): 309 (*M*⁺, 9), 283 (12), 108 (100), 75 (18).

IR 3162 (s), 2895 (s), 1385 (m), 1368 (w), 1245 (m), 855 (m).

Anal calcd for C₁₇H₃₁NO₂Si: C 65.97%; H 10.10%; N 4.53%; found: C 65.45%; H 9.93%; N 4.73%.

[α]_D²⁵ (c 2.21, CHCl₃) = +24.4

1,3-Diphenyl-3-(*N*-methylamino)-1-propanol (16)³

¹H-NMR: 7.45-7.18 (m, 10H, *ArH*), 5.08-4.93 (m, 1H, *ArCHOH*), 4.09 (bs, 2H, *OH&NH*), 3.88-3.61 (m, 1H, *ArCHNH*), 2.30 (s, 3H, *NCH*₃), 2.20-1.19 (m, 2H, *CH*₂).

Reduction-Acetylation of Hydroxylamine 6.

The hydroxylamine (0.27 mmol) is dissolved in THF (1.4 mL) into a 5 mL round bottomed flask equipped with a Claisen condenser and a magnetic stirring bar. Then AcOH (1.08 mmol), Ac₂O (1.62 mmol) and indium powder (0.54 mmol) are added and the mixture is heated under reflux. After 6.5 h the mixture is cooled, H₂O (2 mL) and a sat. Na₂CO₃ solution (1.5 mL) are added and the product is extracted with ethyl acetate (3x10 mL). The organic phase is dried over anhydrous Na₂SO₄, then filtered and concentrated. The acetamide **17** is purified by flash column chromatography (silica gel; AcOEt/MeOH = 10/1; *R*_f = 0.32).

¹H-NMR: 4.79-4.69 (m, 2H, 2CHO), 3.98 (d, *J*=13.6 Hz, 1H), 3.67 (d, *J*=12.1 Hz, 1H), 3.48 (dd, 1H, *J*=12.2 Hz, *J*=4.2 Hz), 3.30 (dd, 1H, *J*=14.0 Hz, *J*=4.1 Hz), 2.04 (s, 3H, CH₃CO), 1.44 (s, 3H, Me), 1.30 (s, 3H, Me).

¹³C-NMR: 169.4 (C), 111.9 (C), 79.3 (CH), 78.3 (CH), 53.2 (CH₂), 50.8 (CH₂), 27.0 (CH₃), 24.9 (CH₃), 22.1 (CH₃).

MS (m/z): 185 (M⁺, 0.3), 170 (M⁺-15, 5), 111 (20), 97 (31), 85 (55), 83 (100).

IR (KBr): 2992 (m), 2939 (m), 2868 (w), 2246 (m), 2639 (s), 1447 (s), 1376 (s), 1213 (s), 1061 (m).

One-Pot Grignard Additions-Reductions to Nitrone 18.

C-Phenyl-*N*-methylnitrone (1.5 mmol) is dissolved in dried THF (5 mL) into a 50 mL round bottomed flask equipped with a magnetic stirring bar. The solution is cooled in an ice bath, the appropriate Grignard reagent (1.8 mmol) is then added dropwise and the mixture is stirred at room temperature. After 10-15 hours a 2:1 solution of EtOH and sat. aq. NH₄Cl (6 mL) and indium powder (1.8-2.6 mmol) are added; this mixture is heated under reflux. After completion of the reaction (TLC control), the mixture is cooled, filtered over Celite and concentrated. Then, a sat. Na₂CO₃ solution (15 mL) is added and the product is extracted with ethyl acetate (3x15 mL). The organic phase is dried over anhydrous Na₂SO₄, then filtered and concentrated to afford the desired amine **10** or **11**.

One-Pot Conjugated Addition-Reduction of Hydroxylamine to Ethyl Acrylate.

Ethyl acrylate (4.6 mmol) is dissolved in EtOH (10 ml) into a 25 mL round bottomed flask equipped with a magnetic stirring bar. A 30% NH₃ solution (0.5 mL) and hydroxylamine hydrochloride (1.48 mmol) are added. The mixture is stirred overnight at room temperature. A sat. NH₄Cl solution (5 mL) and indium powder (3.3 mmol) are added; the mixture is heated under reflux. After 7.5 h, the mixture is cooled, filtered over Celite and concentrated. A sat. Na₂CO₃ solution (15 mL) is added and the product is extracted with ethyl acetate (3x15 mL). The organic phase is dried over anhydrous Na₂SO₄, then filtered and concentrated to afford the desired amine **21**.⁸

¹H-NMR: 4.10 (q, *J*=7.0 Hz, 4H, OCH₂CH₃), 2.85 (t, *J*=6.2 Hz, 4H, NCH₂CH₂CO), 2.46 (t, 4H, *J*=6.2 Hz NCH₂CH₂CO), 1.22 (t, *J*=7.2 Hz, 6H, OCH₂CH₃).

¹³C-NMR: 172.4 (C), 60.3 (CH₂), 44.8 (CH₂), 34.6 (CH₂), 14.1 (CH₃).

References and Notes

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