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# Synthesis of Sterically Hindered Amine Containing Azide via Chemoselective Hydride Reduction

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# SYNTHESIS OF STERICALLY HINDERED AMINE CONTAINING AZIDE VIA CHEMOSELECTIVE HYDRIDE REDUCTION

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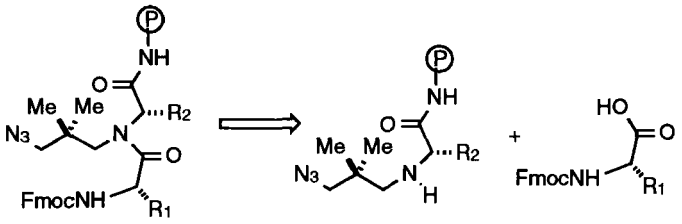
**ABSTRACT**: The chemoselective reduction of an ester in the presence of an azido group by $LiCl/NaBH_4$ is described. A sterically hindered secondary amine containing an azido group is synthesized by this method.

Recently we reported a facile synthesis of sterically hindered secondary amines[1] and their subsequent acylation[2] to prepare key intermediates for peptide secondary structure mimetics. During the course of our continuing research in this area,[3] we required intermediate **1** which incorporates orthogonal and solid phase compatible protecting groups. We envisioned that the use of an azido functionality and Fmoc protection ideally suited for this purpose.



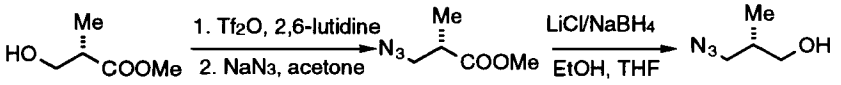
1 2

Azides have been used as masked amine functionality.[4] The azido group is known to be readily reduced by hydrogenolysis ($H_2$, Pd/C)[5], $PPh_3$,[4b,5] or metal hydride reduction.[5] In order to synthesize intermediate **2**, we required a mild chemoselective reduction method of an ester in the presence of azido group that is compatible with the solid phase synthesis. To the best of our knowledge, there does not appear to be a selective and mild protocol to reduce an ester to an alcohol in the presence of an azide.[6]

In this article we report an efficient synthesis of the azide protected amino-alkyl secondary amino ester **2b** via chemoselective reduction of an ester and reductive amination in the presence of an azido group.

As a preliminary study (**Scheme 1**), we chose (R)-methyl 3-azido-2-methyl propanoate (**4a**) as a model. The azido ester **4a** was prepared by the reaction of hydroxy ester **3a** with triflic anhydride and 2,6-lutidine,[7] followed by substitution with sodium azide[4] in quantitative yield. We employed $LiCl/NaBH_4$[8] as a reducing agent of the ester to the alcohol because of its mild reducing ability. Indeed, when ester **4a** was subjected to $LiCl/NaBH_4$ (EtOH/THF) at room temperature, the desired azido alcohol **5a** was obtained in 40% yield without any evidence of reduction of the azido group. The IR spectrum of **5a** showed a strong band at 2100 $cm^{-1}$ for the characteristic azide stretch.

**Scheme 1**




**3a** **4a** **5a**

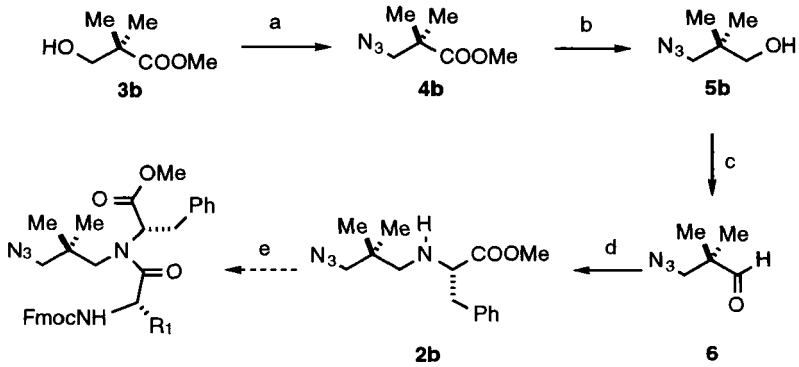
With the successful chemoselective reduction, we synthesized the sterically hindered secondary amine **2b** by the following sequence (**Scheme 2**). Treatment of the hydroxy ester **3b** with triflic anhydride, followed by the displacement with sodium azide provided the azido ester **4b** in 97% yield. The ester **4b** was reduced to the corresponding alcohol **5b** with $LiCl/NaBH_4$ in 65 % yield. Again, no evidence for the reduction of the azide to the amine was observed. The azido alcohol **5b** displayed a strong azide stretch at 2101 $cm^{-1}$ in the IR spectrum. The Swern oxidation of the azido alcohol **5b** to the corresponding aldehyde **6** was effected in quantitative yield. The aldehyde **6** was reductively aminated with phenylalanine methyl ester and $LiCl/NaBH_3CN$ to provide the desired sterically hindered secondary amine **2b** in a modest 32 % yield. However, the use of LiCl rather than an alternative Lewis acid[9] provided the desired amine **2b** without reduction of the azido group.

In summary, we have developed a facile synthetic method for the preparation of the sterically hindered secondary amino azide **2b**. The chemoselective reduction of an ester in the presence of an azide, is attributed to the modest reducing ability of $LiCl/NaBH_4$.

## EXPERIMENTAL SECTION

THF was distilled from sodium benzophenone ketyl prior to use. Dichloromethane was distilled from $CaH_2$. $^1H$ and $^{13}C$ NMR were recorded with a

**Scheme 2**




Reagents and Conditions: a). i) $Tf_2O$, 2,6-lutidine ii) $NaN_3$, acetone/$H_2O$, rt. b). LiCl, $NaBH_4$, THF/EtOH. c). $(COCl)_2$, DMSO, TEA. d). HCl· Phe-OMe, LiCl/$NaBH_3CN$, MeOH. e). reference 2.

Varian Unity 500 MHz spectrometer. IR spectra were recorded with a Nicolet Impact 400 spectrometer. TLC was performed on silica gel 60 $F_{254}$ plates and visualized by UV irradiation, iodine vapor and/or PMA solution. Preparative TLC was performed using silica gel 60 $F_{254}$ plates (500μm thickness).

**(S)-3-Azido-2-methylpropanol (5a)**: To a stirred solution of commercially available methyl (S)-3-hydroxy-2-methylpropionate (**3a**) (1.20g, 10 mmol) in $CH_2Cl_2$ (20 mL) was added $Tf_2O$ (2 mL, 12 mmol), followed by 2,6-lutidine (1.4 mL, 12 mmol) at 0 °C. The resulting solution was stirred for 15 min. After dilution with $CH_2Cl_2$ (50 mL), the solution was washed with 1N HCl (50 mL), brine (50 mL), dried ($Na_2SO_4$), and concentrated to provide an oil.

Without further purification, above oil was dissolved in acetone (20 mL) and water (20 mL). To this stirred solution was added $NaN_3$ (1.3 g, 20 mmol) and the resulting solution was stirred at rt overnight. After dilution with $Et_2O$ (200 mL), the solution was washed with brine (50 mL), brine (50 mL), dried ($Na_2SO_4$), and

concentrated by rotary evaporator (bath temp.; 25 $^0$C) to provide **4a** as an oil in quantitative yield.

To a stirred solution of the above azido ester **4a** (1.43 g, 10 mmol) in THF (10 mL) was added LiCl (860 mg, 20 mmol) and $NaBH_4$ (760 mg, 20 mmol), followed by EtOH (10 mL) at rt. The resulting solution was stirred at the same temperature for 18h. After addition of 0.5 M HCl (100 mL) the solution was extracted with $Et_2O$ (2x100 mL). The combined organic extracts were washed with brine (50 mL), dried ($Na_2SO_4$), and concentrated to provide an oil. The crude product was purified by flash chromatography (hexane:EtOAc = 80:20 to 70:30 to 60:40 to 50:50) to provide **5a** as a colorless oil (460 mg, 40% for three steps). TLC $R_f$ 0.25 (hexane:EtOAc = 60:40): $^1$H NMR ($CDCl_3$) δ 0.97 (d, 3H, *J*=7Hz, $CHCH_3$), 1.6 (br, 1H, OH), 1.95 (m, 1H, $CHCH_3$), 3.34 (ABq, AB of ABX, 2H, *J*=6, 6.5Hz, $N_3CH_2$-), 3.58 (ABq, AB of ABX, 2H, *J*=5, 6.5Hz, $CH_2OH$): IR (neat) 3358 (br), 2930, 2098 cm$^{-1}$.

**Methyl 3-Azido-2,2-dimethyl propanoate (4b):** To a stirred solution of hydroxy propionate **3b** (1.32 g, 10 mmol) in $CH_2Cl_2$ (20 mL) was added $Tf_2O$ (2 mL, 12 mmol), followed by 2,6-lutidine (1.4 mL, 12 mmol) at 0 °C. The resulting solution was stirred for 15 min. After dilution with $CH_2Cl_2$ (100 mL), the solution was washed with 1N HCl (60 mL), dried ($Na_2SO_4$), and concentrated to provide an oil.

Without further purification, above oil was dissolved in acetone (20 mL) and water (20 mL). To this stirred solution was added $NaN_3$ (1.3 g, 20 mmol) and the resulting solution was stirred at rt overnight. After dilution with $Et_2O$ (200 mL), the solution was washed with brine (100 mL), dried ($Na_2SO_4$), and concentrated to provide an oil (1.52 g, 97%). $^1$H NMR ($CDCl_3$) δ 1.20 (two s, 6H), 3.39 (s, 2H), 3.70 (two s, 3H): $^{13}$C NMR ($CDCl_3$) δ 23.24, 43.80, 52.33, 59.80, 176.34: IR

(neat) 2105, 1736 $cm^{-1}$. The product was pure enough to be used for the next reaction without further purification.

**3-Azido-2,2-dimethylpropanol (5b):** To a stirred solution of the azido ester **4b** (780 mg, 5 mmol) in THF (10 mL) was added LiCl (430 mg, 10 mmol) and $NaBH_4$ (380 mg, 10 mmol), followed by EtOH (10 mL) at rt. The resulting solution was stirred at the same temperature overnight. After dilution with $Et_2O$ (50 mL), the solution was washed with 0.5 M HCl (50 mL). The aqueous phase was extracted with $Et_2O$ (50 mL). The combined organic extracts were washed with brine (50 mL), dried ($Na_2SO_4$), and concentrated to provide an oil (420 mg, 65 %). $^1H$ NMR ($CDCl_3$) δ 0.92 (s, 6H), 3.23 (s, 2H), 3.39 (s, 3H): $^{13}C$ NMR ($CDCl_3$) δ 22.41, 37.24, 59.57, 69.46: IR (neat) 2101 $cm^{-1}$. The product was pure enough to be used for the next reaction without further purification.

**N-(3-Azido-2,2-dimethylpropyl)phenylalanine Methyl Ester (2b):** To a stirred solution of $(COCl)_2$ (0.4 mL, 4 mmol) in $CH_2Cl_2$ (2 mL) was added DMSO (0.4 mL, 6 mmol) at -78 °C. After 5 min, to this stirred solution was added a solution of the alcohol **5b** (400 mg, 3 mmol) in $CH_2Cl_2$ (8 mL). The resulting solution was stirred at the same temperature for 20 min and TEA (2.8 mL, 20 mmol) was added. After warming to rt, the milky solution was taken up in $CH_2Cl_2$ (50 mL) and washed with 1N HCl (50 mL). Aqueous phase was extracted with $CH_2Cl_2$ (50 mL). The combined organic extracts were washed with brine (50 mL), dried ($Na_2SO_4$), and concentrated to provide an oil (420 mg).

Without further purification, above oil was used for the next reaction.

To a stirred solution of the aldehyde **6b** (38 mg, 0.3 mmol) with HCl Phe-OMe (130 mg, 0.6 mmol) in MeOH (2 mL) was added a solution of LiCl (22 mg, 0.5 mmol) and $NaBH_3CN$ (38 mg, 0.6 mmol) in MeOH (3 mL) at rt. After stirring

at rt for 18 h, the solution was concentrated and the residue was taken up in EtOAc (10 mL), washed with sat. $NaHCO_3$ (10 mL). The aqueous phase was extracted with EtOAc (10 mL). The combined organic extracts were washed with brine (10 mL), dried ($Na_2SO_4$), and concentrated to provide an oil. The crude product was purified by preparative TLC (hexane:EtOAc = 90:10) to provide an oil (28 mg, 32%). $^1H$ NMR ($CDCl_3$) δ 0.84 (two s, 6H, $C(CH_3)_2$), 1.50 (br, 1H, NH). 2.18 and 2.47 (two d, 2H, *J*= 12.5, 12 Hz, $CH_2$), 2.91 (m, 2H, CH), 3.02 and 3.16 (two d, 2H, *J*= 12 Hz, $CH_2$), 3.43 (t, 1H, CHNH), 7.1-7.3 (m, 5H, phenyl): IR (neat) 3035, 2950, 2099, 1737 $cm^{-1}$: MS CI($NH_3$) m/z 291.3 ($M+H^+$).

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