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LETTERS

Selective Reduction of Secondary Amides to Amines in the Presence of Tertiary Amides

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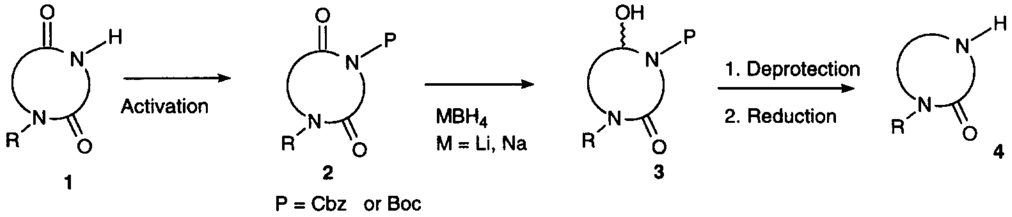
Abstract: Secondary amides activated with a Cbz group can be reduced to their corresponding hemiaminals using lithium borohydride. Hydrogenation then removes the Cbz and hydroxyl groups to produce the related amine. Tertiary amides are not affected. © 1999 Elsevier Science Ltd. All rights reserved.

In connection with other work, we found it necessary to selectively reduce a secondary amide in the presence of a tertiary amide. Although a number of methods[3] are available for the reduction of amides to amines,[1] tertiary amides are usually reduced faster than the secondary amides[2] and tend to produce mixtures of products when both types of amide are present. We herein report a method for reducing secondary amides in the presence of tertiary amides with a very high degree of selectivity. Attaching an oxycarbonyl moiety (e.g., Cbz or Boc[4]) to the secondary amide nitrogen of amide **1** of mixed types gives activated amide **2** (Scheme 1). The carbonyl of the secondary amide moiety is thereby rendered more susceptible to reduction with $LiBH_4$ or $NaBH_4$ to produce the related hemiaminal **3** while the carbonyl of the tertiary amide group remains unchanged. Deprotection and hydrogenation then leads to amine **4** with its tertiary amide intact.

Scheme 1.



Although Boc and other oxycarbonyl groups can be used where functional groups sensitive to hydrogenation are present, we prefer the Cbz group where applicable since hydrogenation removes both the Cbz-group and the hydroxyl of the hemiaminal at the same time. Examples using both Boc and Cbz activation are shown in Scheme 2. A typical experimental procedure follows. Compound **14** (660 mg, 2 mmol) was dissolved in MeOH (50 mL) and treated with $LiBH_4$ (110 mg, 5 mmol) at 0 °C. The mixture was stirred for 0.5 h at 0 °C, taken up in EtOAc (100 mL) and washed with 1N HCl and brine. The organic layer was separated, dried

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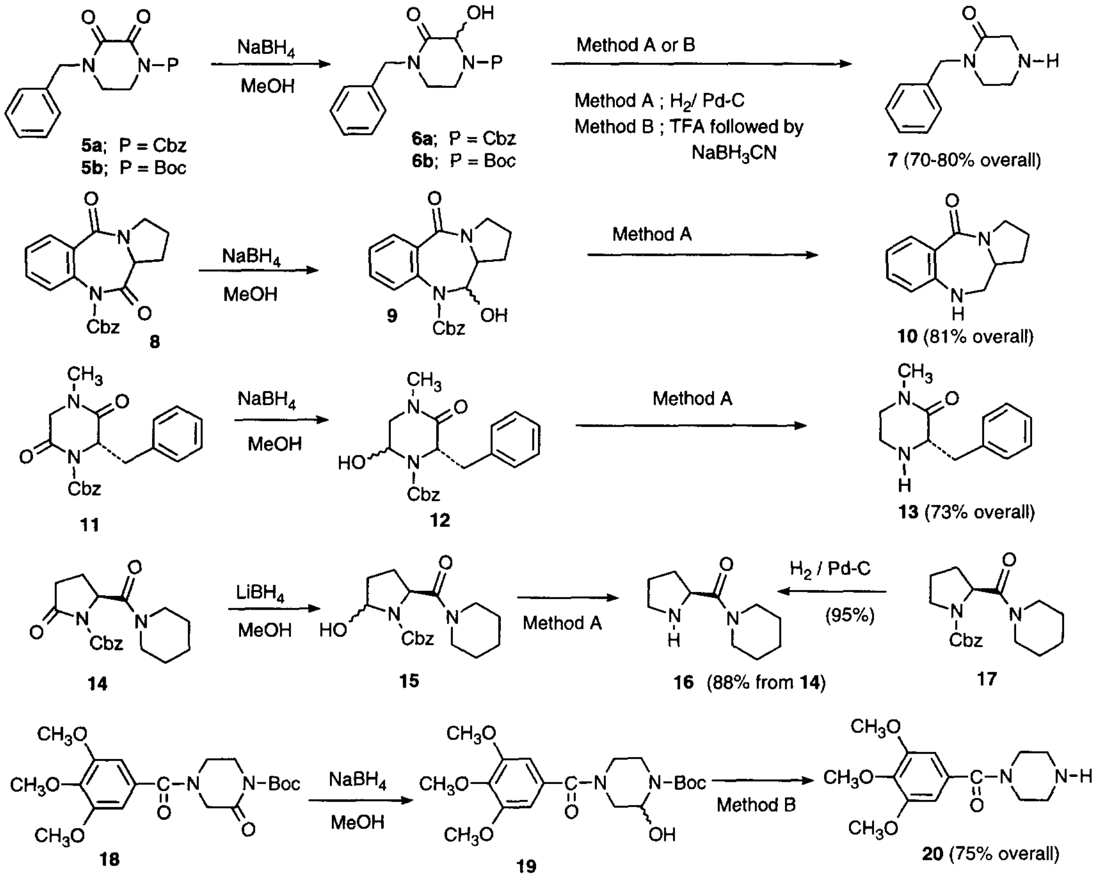
($MgSO_4$) and concentrated to give **15**. This was hydrogenated (40 psi, 200 mg of 10% Pd-C) in MeOH at room temperature for 6 h. After removing the catalyst by filtration, the filtrate was concentrated to give **16** as an oil (320 mg) in 88% yield. Compound **16** was also obtained from **17** by hydrogenation.

Scheme 2.



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