Amide Activation by Tf_2O: Reduction of Amides to Amines by $NaBH_4$ under Mild Conditions

Shao-Hua Xiang,[a] Jian Xu,[a] Hong-Qiu Yuan,[a] Pei-Qiang Huang*[a,b]

[a] Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, P. R. of China
Fax +86(592)2186400; E-mail: pqhuang@xmu.edu.cn

[b] The State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. of China

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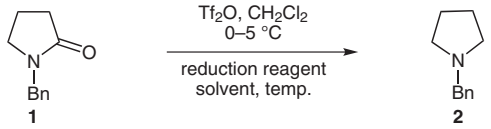
Abstract: An expeditious and practical method for the reduction of amides to amines is reported. The method is consisted of activation of amides with Tf_2O followed by reduction with sodium borohydride in THF at room temperature. Various amides/lactams gave the corresponding amines in good to excellent yields, even with hindered amides and secondary amides. This method also presents other advantages such as TBDPS-group tolerance, short reaction time, simple workup and purification procedure.

Key words: reduction, amides, amines, amide activation, triflic anhydride

Amines are of great medicinal interest and are an important class of compounds in chemistry.[1] The direct reduction of amides constitutes one of the main entries to amines.[2] Lithium aluminum hydride (LAH)[3] and diborane or borane complex[4] are, among others,[5] the most widely used reducing agents for amides reduction. The drawbacks of the reduction with LAH are the harsh conditions required for the reduction that renders the method low functionality tolerance,[6] difficulties in the reduction of secondary amides, and side reactions such as C–N bond cleavage with hindered tertiary amides.[7] In addition, difficulties are often encountered in the isolation of the product from the reaction mixture with these reducing agents due to formation of complex with the resultant amines.[8] Recently, transition-metal-complex-catalyzed organosilane reductions have emerged as attractive alternatives for amides reduction.[9,10] More recently, Charette and coworkers reported a highly chemoselective metal-free method for the reduction of tertiary amides via Tf_2O activation[11] and Hantzsch ester (HEH) reduction.[12] In connection with a recent work on the sequential reductive alkylation of amides via activation with Tf_2O,[13] we undertook an investigation on Charette's reduction aiming at the substitution of HEH by more commonly used reducing agents, and overcame the difficulty in the reduction of hindered tertiary amides as well as the reduction of secondary amides. The results are reported herein.

N-Benzyl-2-pyrrolidone (**1**) was selected as a substrate for our initial investigation. Thus, lactam **1** was treated with Tf_2O (1.1 mol equiv) in CH_2Cl_2 (0.1 M) in an ice bath for 30 minutes, and to the resultant activated intermediate was added a reducing agent. However, no reduction reaction occurred neither with triethylsilane (TES) (r.t. or reflux), Ph_3SiH, H_2 and Pd/C, nor $NaBH_4$ in CH_2Cl_2 (Table 1). The reaction with $NaBH_4$ in ethanol at room temperature gave, after workup, the desired pyrrolidine **2** in 37% yield, alongside with the recovered starting material **1** in 38% yield. Similar reaction in methanol at room temperature gave pyrrolidine **2** in 20% yield, along with the recovered starting material **1** in 75% yield.

Table 1 Attempted Tf_2O-Activated Reduction of Lactam **1** under a Variety of Conditions



Entry	Reducing reagent	Temp	Result
1	TES, CH_2Cl_2	r.t.	n.r.
2	TES, CH_2Cl_2	reflux	n.r.[a]
3	Ph_3SiH, CH_2Cl_2	r.t.	n.r.
4	10% Pd/C, H_2, CH_2Cl_2	r.t.	n.r.
5	$NaBH_4$, CH_2Cl_2	r.t.	n.r.[a]
6	$NaBH_4$, EtOH	r.t.	yield of **2**: 37% recovered **1**: 38%
7	$NaBH_4$, MeOH	r.t.	yield of **2**: 20% recovered **1**: 75%

[a] Only a small amount of starting material consumed with complex products formed as indicated by TLC.

On the basis of these preliminary trials, we next investigated the reduction of amide with $NaBH_4$ in THF. To our satisfaction, the reduction of lactam **1** with 1.3 mol equivalents of $NaBH_4$ in THF at room temperature for one hour afforded the desired pyrrolidine **2** in 75% yield.[14] It was observed that when 1.0 mol equivalent of $NaBH_4$ was used, the reaction was incomplete; while the use of 2.0 or more mol equivalents of $NaBH_4$ led to a borane complex of the desired pyrrolidine **2**, which required additional steps to deliver the free pyrrolidine **2**.[15]

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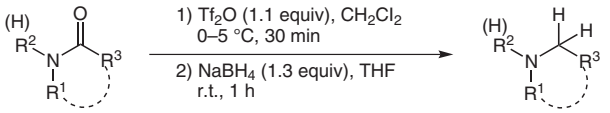
The reaction was then extended to a series of lactams and amides and the results are summarized in Table 2. As can be seen from Table 2, all reactions gave good to excellent yields (Table 2, entries 1–12), even with hindered amides (Table 2, entries 13–17). It should be noted that the reduction of hindered amides such as **1m–q** by Tf_2O–HEH gave only less than 5% yield.[12] Moreover, the reduction of secondary amides proceeded smoothly to give the desired amines in 75% and 73% yields (entries 18 and 19). While the reduction of (*S*)-pyroglutamate gave the fully reduced product prolinol (entry 20), the reduction of OTBDPS-protected (*S*)-2-oxoprolinol afforded the corresponding OTBDPS-protected (*S*)-prolinol in 70% yield (entry 21). These results showed that the reducing system Tf_2O–$NaBH_4$ is not only powerful for hindered amides, but also offers some chemoselectivity, because TBDPS was shown to be metal unstable in the reduction with $LiAlH_4$.[6] Reduction of chiral pyrrolidinone **1v**[16] gave pyrrolidine **2v** (entry 22), which is an intermediate for the synthesis of novel potential HIV protease inhibitors.[17]

Table 2 Tf_2O-Activated Reduction of Amides/Lactams with $NaBH_4$ in THF



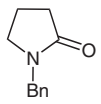
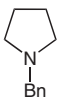
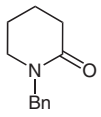
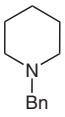
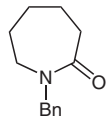
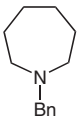
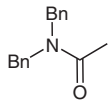
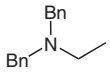
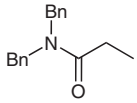
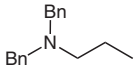
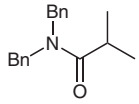
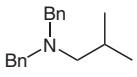
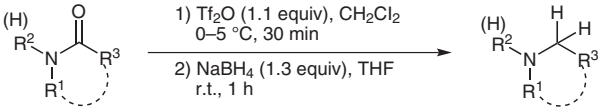
Entry	Amide **1**	Amine **2**	Isolated yield (%)
1	 **1a**	 **2a**	75
2	 **1b**	 **2b**	82
3	 **1c**	 **2c**	80
4	 **1d**	 **2d**	83
5	 **1e**	 **2e**	87
6	 **1f**	 **2f**	79

Table 2 Tf_2O-Activated Reduction of Amides/Lactams with $NaBH_4$ in THF (continued)



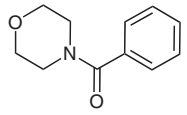
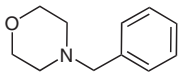
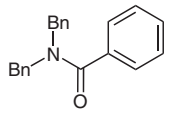
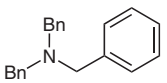
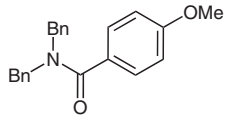
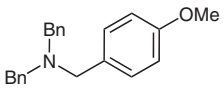
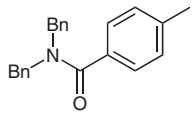
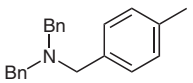
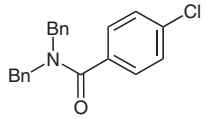
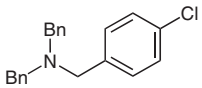
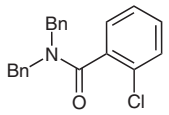
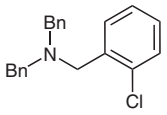
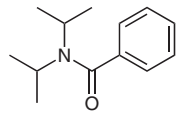
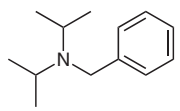
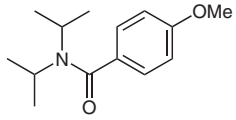
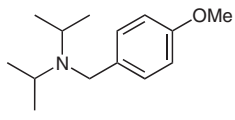
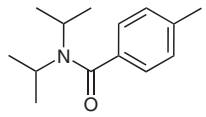
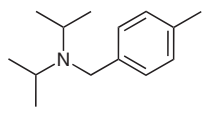
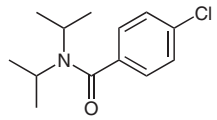
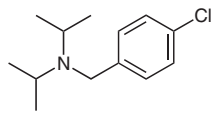
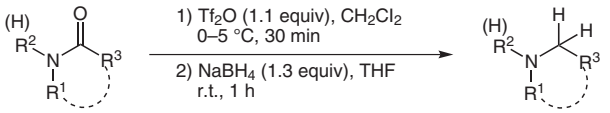
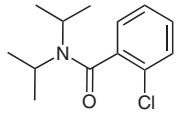
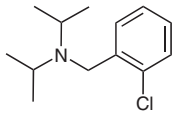
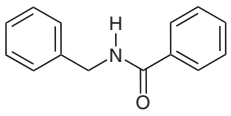
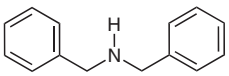
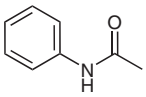
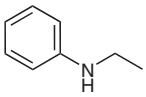
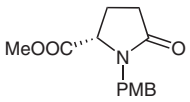
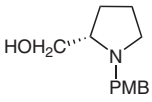
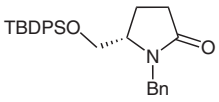
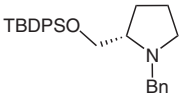
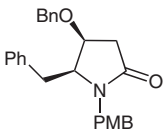
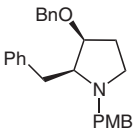
Entry	Amide **1**	Amine **2**	Isolated yield (%)
7	 **1g**	 **2g**	80
8	 **1h**	 **2h**	81
9	 **1i**	 **2i**	79
10	 **1j**	 **2j**	84
11	 **1k**	 **2k**	80
12	 **1l**	 **2l**	72
13	 **1m**	 **2m**	87
14	 **1n**	 **2n**	74
15	 **1o**	 **2o**	83
16	 **1p**	 **2p**	91

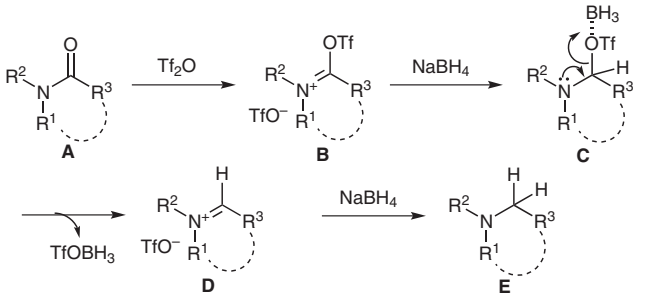
Table 2 Tf_2O-Activated Reduction of Amides/Lactams with $NaBH_4$ in THF (continued)



Entry	Amide **1**	Amine **2**	Isolated yield (%)
17	 **1q**	 **2q**	93
18	 **1r**	 **2r**	75
19	 **1s**	 **2s**	73
20	 **1t**	 **2t**	69
21	 **1u**	 **2u**	70
22	 **1v**	 **2v**	72

A plausible mechanism[12] for the lactam/amide reduction via activation with Tf_2O is shown in Scheme 1. The reaction of Tf_2O with the carbonyl of amide **A** generates a highly electrophilic iminium triflate intermediate **B**, which reacts with $NaBH_4$ to give *N*,*O*-acetal **C**. Then, elimination of $^-$OTf assisted by both the nitrogen lone pair of electrons and BH_3 complexation leads to the formation of iminium ion **D**, which is trapped by a second hydride to give amine **E**.

To summarize, we have developed an expeditious method for the reduction of amides and lactams with $NaBH_4$ under mild conditions. The method is not only efficient for the reduction of hindered tertiary amides, but also works well with secondary amides, which complements the method of Charette. Comparing with the classical methods utilizing lithium aluminum hydride, diborane or borane complex as the reducing agents, this new method is more efficient, milder, with simpler workup and purification procedure.



Scheme 1 Plausible mechanism for the amide/lactam reduction via activation with Tf_2O

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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General Procedure for the Preparation of Amines from Amides

To a solution of an amide (1.0 mmol) in anhyd CH_2Cl_2 (10 mL) was added Tf_2O (1.1 mmol) in an ice bath. After stirring for 30 min, $NaBH_4$ (1.3 mmol) was added in one portion, and THF (5 mL) was added dropwise. After stirring for 60 min at r.t., the reaction was quenched with H_2O (5 mL). The solution was brought to pH 10.5–11.0 by addition of a sat. aq Na_2CO_3 solution at 0 °C. The cooled aqueous solution was extracted with Et_2O (5 × 15 mL). The combined organic layers were washed with brine (5 mL), dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to give the corresponding amine (yields 69–93%). All new compound gave satisfactory spectral and analytical data (see Supporting Information).

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