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Amide activation by TMSCl: Reduction of amides to amines by $LiAlH_4$ under mild conditions

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ABSTRACT

An expeditious and practical method for the reduction of amides to amines is reported. The method consists of activation of amides with TMSCl followed by reduction with LiAlH4. Various amides/lactams including hindered amides and secondary amides gave the corresponding amines in good to excellent yields. This novel protocol has a wide substrate scope and shows good functional group tolerance with high stereoretention.

Amines and their derivatives are of great pharmaceutical significance and are an important class of compounds for the drug development, due to their affinity towards various receptors in the biological system.[1] In this regard; wide scope and broad tolerance toward functional groups are the key factors for the acceptance and application of a newly developed methodology involving readily available reagents. Direct conversion of amides and lactams to the corresponding amines is one of the most important facets of chemistry but it is not as facile as it seems. There are many procedures available for the reduction of amides and lactams to amines. Lithium aluminum hydride (LAH)[2], diborane or borane complex[3] and others[4] are the widely used reducing agents for amide reductions. Recently, there have been impetus given for the reduction of amides, particularly, reduction of less reactive secondary amides employing hydrosiloxane,[5a] Cbz/$LiBH_4$,[5b] and TMDS/$Cu(OTf)_2$.[6] The other reducing agents e.g. DodBMS,[7] Red-Al,[8a,b] $NaBH_4$ in ionic liquids,[9] have been employed for reduction of secondary amides.. But reduction of tertiary amides into amines was carried out by using 9-BBN,[10] $Zn(OTf)_2$/methyl diethoxy silane[11] and hydrosilanes activated by Rh,[12a] Ru,[12b,c] Pt,[12d,e] Ti,[12f] In,[12g] Ir,[12h,i] Mn,[12j] Re,[12j] Os,[12j] Pd,[12j] Fe,[12k,l] Mo,[12m] and Zn[12n] derived catalysts/reagents. Reductive alkylation on tertiary amide yielding amine derivative is also reported.[13] In addition to this, Charette and coworkers reported a highly chemoselective metal-free method for the reduction of tertiary amides using Tf_2O and Hantzsch ester (HEH).[14] Primary amides were reduced using $NaBH_4$/diglyme.[15]

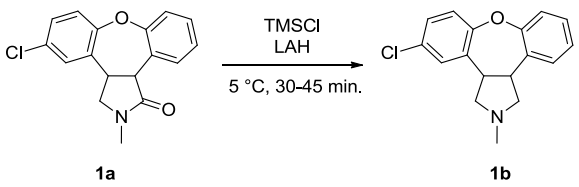
The reduction of amides and lactams to amines with lithium aluminum hydride[2] has many limitations. The drawback of using LAH is that it requires harsh conditions for the reduction that renders the method with poor efficiency,[16] and quite often it proceeds with great difficulty, particularly where secondary amines are to be generated. In addition to this, the side reactions due to NH proton acidity such as C–N bond cleavage with hindered tertiary amides[17] and formation of insoluble complexes are also encountered. Interestingly, the use of aluminum hydride for such reduction provides a convenient alternative to the use of lithium aluminum hydride-aluminum chloride mixtures.[18] During the reagent preparation, the lithium chloride precipitates and an ether solution of the reagent is obtained. Unfortunately, such solutions are metastable and, on standing, the aluminum hydride associates and precipitates from solution that led to the poor reducing profile of this reagent.[19] Considering all these limitations, we carried out an investigation on reduction by selecting commonly used Lewis acid, trimethylsilyl chloride over aluminium chloride in combination with LAH.[20]

This combination turned out to be very effective in the reduction of hindered tertiary amides as well as the reduction of secondary amides. Here in, we disclose the novel protocol for reduction and its application to various amide substrates including the drug molecule, Azenapine.

By taking a lead from a report disclosing LAH and TMSCl used in the reduction of phosphonate to phosphine we attempted this system for the first time to reduce amides to amines as shown in Scheme 1. Azenapine amide (**1a**) was selected as a model substrate for our initial investigation. Thus, lactam **1a** was treated with LAH (1.4 mol equiv) in THF in an ice bath for 1 h and complete conversion of the substrate with less yield and purity was obtained (Table 1). The reaction with LAH/$AlCl_3$ (1.4/1.1 mol equiv) in THF in an ice bath for 1 h offered complete conversion with moderate yield and purity. In spite of its utility, unstable nature of AlH_3 and concomitant formation of salt byproducts makes it difficult to optimize this procedure.

In our continued endeavor, lactam **1a** was treated with LAH/TMSCl (1.4/1.2 mol equiv) in THF in an ice bath for 1 h, only 30% conversion was observed. In order to achieve better conversion, reverse mode of addition of reagent was employed and it afforded complete conversion. In a typical procedure, lactam **1a** was treated with TMSCl (1.2 mol equiv) in THF in an ice bath for 15 min and to the resultant reaction mass was added a reducing agent, LAH (1.4 mol equiv). The reaction was

completed in less than 1 h. By this observation, we envisaged that the lactam **1a** might have been activated with TMSCl by forming imine *in situ* thereafter the reduction of amide to amine with LAH would have proceeded. When the same reaction was conducted in DCM, the results were comparable to that in THF medium.



1a **1b**

Scheme 1. Novel amide reduction approach to **1b**

Table 1. Reduction of lactam **1a** under various Lewis acid-LAH reaction conditions.

S.No.	LAH (equiv)	Lewis acid (equiv)	Sol.	T (°C)	Conv. (%)	Yield[a] (%) (Purity)
1	1.4	--	THF	5	100	55(70)
2	1.4	$AlCl_3$/ (1.1)	THF	5	100	70(98)
3	1.4	TMSCl (1.2)	THF	5	100	85(98)
4.	1.4	TMSCl (1.2)	DCM	5	100	85(98)

[a] *isolated as maleate salt*

On the basis of these preliminary trials, we next focused on optimization of critical reaction parameters (Table 2) for the reduction of amide with LAH/TMSCl in DCM. As expected, only 45% conversion occurred with 0.5 mol of TMSCl. In contrast, with 1.2 mol of TMSCl, complete conversion with high isolated yield and purity were obtained. At higher temperature, we encountered poor yields which could possibly be due to the destabilized Lewis acid activated amides leading to decompostion of transient amide. The results are summarized in Table 2 (entry 3).

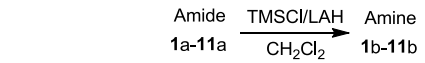
Table 2. Screening of the reaction conditions for reduction of Lactam (**1a**)

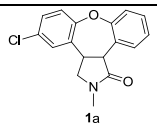
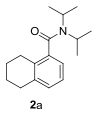
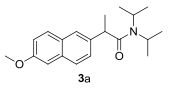
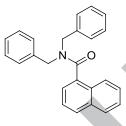
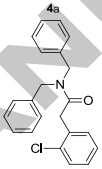
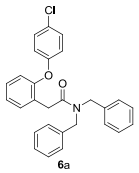
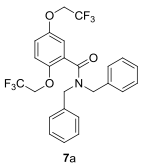
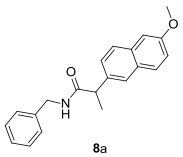
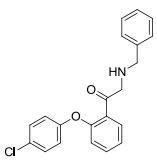
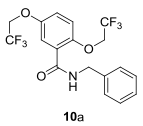
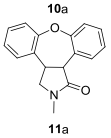
Entry	LAH (equiv)	TMSCl (equiv)	T (°C)	Conv[a].(%)	Yield[b] (%)
1	1.0	1.0	5	50	35
2	1.2	1.0	5	70	55
3	1.3	1.2	5	100	85
4	1.3	1.2	25	100	50

[a] *Determined by TLC*
[b] *isolated as maleate salt*

With optimized conditions in hand, the scope of LAH in presence of Lewis acid, TMSCl for reduction of hindered tertiary and secondary amides was explored. The reaction was then extended to a series of lactams and amides including aromatic and aliphatic and the results are summarized in Table 3. Delightfully, all the reactions afforded good to excellent yields (Table **3**), even with hindered amides and the structure of the products are shown in Figure 1.

Table 3 Reduction of amides/lactams with LAH/TMSCl in DCM



Substrate	Product[a]	TMSCl/ LAH (equiv)	h	Yield (%)[b]
	**1b**	1.2/1.4	0.45	85[c]
	**2b**	1.2/1.4	0.75	78[d]
	**3b**	1.2/1.4	1.0	79[d]
	**4b**	1.2/1.5	1.0	77[d]
	**5b**	1.2/1.5	0.75	81[d]
	**6b**	1.2/1.5	1.25	75[d]
	**7b**	1.2/1.4	1.25	77[d]
	**8b**	1.2/1.5	0.75	81[d]
	**9b**	1.2/1.4	1.0	74[d]
	**10b**	1.2/1.5	1.25	84[d]
	**11b**	1.2/1.4	1.0	79[e]

[a] *The products were characterized by IR, ^{1}H NMR data*
[b] *Yields of the isolated pure compound*
[c] *isolated as maleate salt in IPA*
[d] *isolated as hydrochloride salt in diisopropyl ether*
[e] *isolated as amine*

It is well established that the use of LAH for reductions can potentially cause racemization of chiral center(s) present in the system.[21] In most of the cases, when the reduction of chiral amides was carried out with LAH, it ended with racemic amines. Therefore, we explored the possibility of reduction on such compounds, to investigate the fate of chirality of reduced chiral amines by reduction with lithium aluminum hydride in the presence of trimethylsilyl chloride. As it can be seen from Table 4, all the reactions afforded good to excellent yields, with excellent *ee/de* of the products. The results are summarized in Table 4 and the structure of products is shown in Figure 2. This strategy was also employed to access pharmaceutically relevant molecules like Asenapine maleate (**1**b') and Dexpramipexole (KNS-760704) (**12**b).

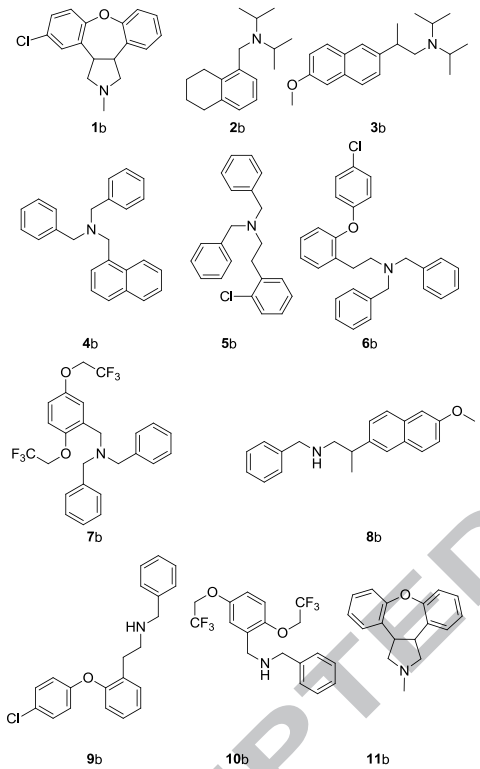
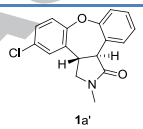
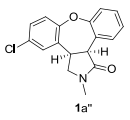
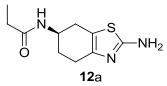
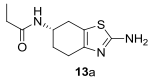
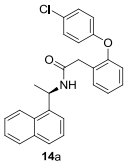
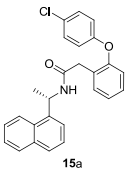
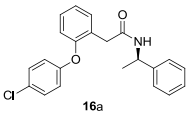
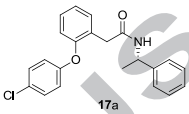


Figure 1. Structure of amines (**1**b-**11**b)

Table 4 Reduction of chiral Amides/Lactams with LAH/TMSCl in DCM

Entry	Substrate	Product[a]	Yield[b] (%)	h	%ee/ de
1	 1a'	**1b'**	85[c]	0.45	99[e]
2	 1a''	**1b''**	79[c]	1.0	99[e]
3	 12a	**12b**	77[d]	0.50	>98.5[f]
4	 13a	**13b**	72[d]	1.0	>98.5[f]
5	 14a	**14b**	81[d]	1.1	99[f]
6	 15a	**15b**	79[d]	1.3	99[f]
7	 16a	**16b**	82[d]	1.2	>98.5[f]
8	 17a	**17b**	79[d]	1.4	>98.5[f]

[a]*The product were characterized by IR, ^{1}H NMR data*
[b]*Yields of the Isolated pure compound*
[c]*isolated as maleate salt in IPA*
[d]*isolated as hydrochloride salt in diisopropyl ether*
[e]*%de;* [f]*%ee*

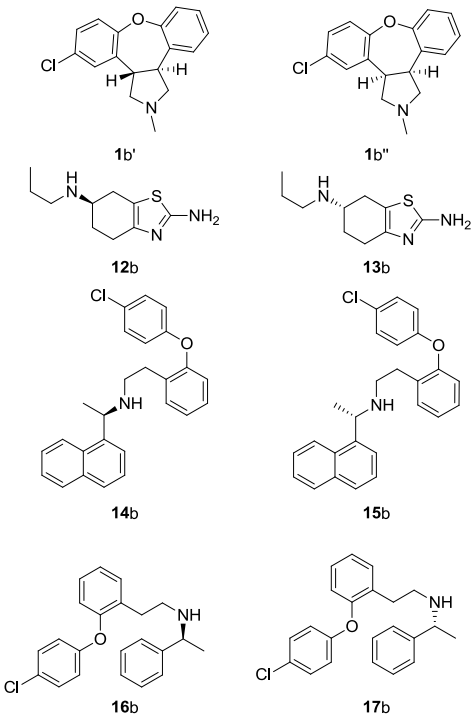
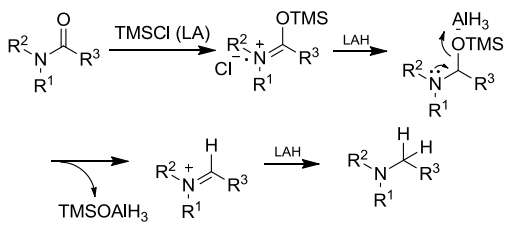


Figure 2. Structure of chiral amines (**1**b'-**17**b)



Scheme 2. Plausible mechanism for the amide/lactam reduction via activation with TMSCl

Mechanistically, trimethylsilyl chloride as a Lewis acid activates the carbonyl functionality and provides very reactive electrophile source. *In situ* generated imine can further be reduced with lithium aluminum hydride affording the products as shown in Scheme 2. Our approach allowed us to have quick access of the products as the rate of the reaction was found to be very fast in comparison with the lithium aluminum hydride-aluminum chloride mixtures-mediated reactions[22,23] and a typical experimental procedure is described in reference section.[24]

In conclusion, we have reported the reducing system employing lithium aluminum hydride, (LAH) activated by trimethylsilyl chloride (TMSCl) which reduces even the tertiary and secondary amides to the corresponding amines with high enantio-or diastereoretention and excellent yields.

Supplementary Material

Experimental procedures and compound characterization data are described in supplementary material.

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24. In a typical experimental procedure, amide, **1a** (10 g, 33.43 mmol) and dichloromethane (100 mL) were charged into a round bottomed flask and stirred under nitrogen atmosphere for 10-15 min and cooled to 0-5 ˚C. Trimethylsilyl chloride (5.1 mL, 40.12 mmol) was then added to the mixture over 10-15 min. and stirred for 10-15 min. at same temperature. Lithium aluminum hydride (19.5 mL, 46.81 mmol) in tetrahydrofuran solution is added dropwise at -10 to 0 ˚C. After complete addition, the solution is allowed to stir for 1-2 h at 0 to 10 ˚C. After completion of reaction (TLC), the reaction mass was quenched by slow dropwise addition of 2M sodium hydroxide (30 mL) and reaction mixture was extracted with dichloromethane (25 mL). The organic layers were combined, washed with 20% sodium chloride solution. The solvent was evaporated under reduced pressure to get the crude material which was dissolved in isopropyl alcohol (50 mL). Then maleic acid (5.0 g, 43.46 mmol) was added and stirred for 2-3 h at ambient temperature followed by cooling it to 0-10 ˚C for additional 2-3 h. The obtained solid was collected by filtration, washed with isopropyl alcohol (10 mL) and dried at 50-55 ˚C to afford the title compound **1b'** as white solid (11.5 g, 85%).

Graphical Abstract

Amide activation by TMSCl: Reduction of amides to amines by $LiAlH_4$ under mild conditions

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