Oxidative Deamination of Various Primary Amines to the Corresponding Carbonyl Compounds by Using *N*-*tert*-Butylphenylsulfinimidoyl Chloride

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Various linear and non-linear primary amines were oxidatively deaminated to afford the corresponding carbonyl compounds in good to excellent yields by the following procedure: (i) initial formation of their *N*-cyclohexylated or *N*-mesylated derivatives, (ii) subsequent oxidation of these derivatives by using *N*-*tert*-butylphenylsulfinimidoyl chloride (**1**) and DBU, (iii) one-pot acid-hydrolysis of thus formed imines to carbonyl compounds.

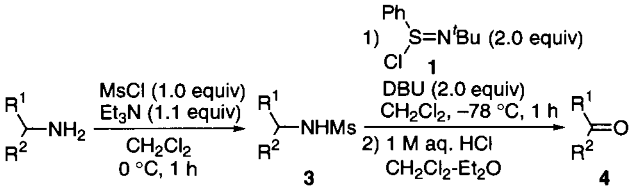
N-*tert*-Butylphenylsulfinimidoyl chloride (**1**) efficiently oxidized various secondary amines to afford the corresponding imines in the co-existence of DBU as was reported in the previous communication.[1] On the other hand, direct oxidation of primary amines was still unsuccessful. For example, cyclohexanone and 2-methoxybenzaldehyde were obtained only in 26% and 17% yields, respectively, when cyclohexylamine and 2-methoxybenzylamine were treated according to the above procedure, followed by acid-hydrolysis. Transformation of amino groups to carbonyl ones has sometimes been required in organic synthesis; however, known methods[2] for oxidative deamination of primary amines are not effective enough to be applied to various types of primary amines. Then, a new method for efficient and mild oxidative deamination of various primary amines to the corresponding carbonyl compounds by using **1** was studied.

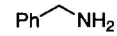
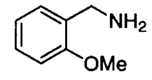
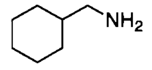
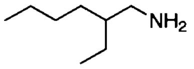
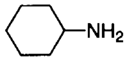
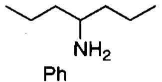
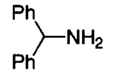
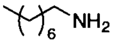
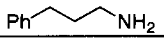
It was thought that difficult problems in oxidation of primary amines arose from the inherent instability of formed *N*-non-substituted imines.[3] Then, introduction of a suitable group in place of one hydrogen of primary amino groups was considered since formed *N*-substituted imines were more stable than *N*-non-substituted ones. First, benzoyl group was chosen as the nitrogen substituent; however, the oxidation of *N*-benzoylbenzylamine (**2**) by using **1** and DBU was found not to proceed even at room temperature. Instead, the oxidation of **2** proceeded under more basic conditions: i.e. the **1**-mediated oxidation took place when **2** was deprotonated with NaH in advance.

Nitrogen substituents were next changed from the benzoyl group to sulfonyl ones in order to increase the acidity of amino protons. Expectedly, *N*-sulfonyl amines were readily oxidized with **1** in the presence of DBU. It was consequently found that methanesulfonyl (mesyl) group was superior to other sulfonyl ones such as *p*-toluenesulfonyl and *o*-nitrobenzenesulfonyl groups. *N*-Mesylbenzylamine, easily prepared from benzylamine according to the conventional method (MsCl, Et_3N), was smoothly oxidized even at –78 °C by using **1** and DBU. Successive one-pot acid-hydrolysis of formed *N*-mesylbenzilideneamine by using 1 M HCl solution gradually proceeded at room temperature to give benzaldehyde in 98% yield (Table 1, entry 1). Further, these three steps for the above oxidative deamination of benzylamine, i.e. mesylation, oxidation, and hydrolysis, were smoothly carried out in a one-pot manner as shown in Scheme 1. Thus, a convenient and useful procedure for oxidative deamination of primary amines was established.

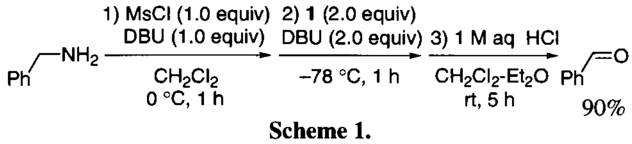
The above-mentioned procedure was applicable not only to benzylamine but also to other primary amines (Table 1). All of *N*-mesyl amines (**3**) were rapidly oxidized at –78 °C by the combined use of **1** and DBU. On the other hand, the rate of acid-hydrolysis depended strongly on the structure of parent primary amines. Acid-hydrolysis of *N*-mesyl-*β*-branched imines needed its reaction time slightly longer compared with *N*-mesylbenzylamines while that of *N*-mesyl-*α*-branched imines forming ketones was completed in a shorter time

Table 1. Oxidation of various primary amines



Entry	Primary amine	Yield/% **3**[a]	Hydrolysis conditions	Yield/% **4**[b]
1		98	rt, 6 h	98
2		>99	rt, 6 h	89
3		92	rt, 10 h	89
4		>99	rt, 24 h	73
5		96	rt, 1 h	90
6		98	rt, 1 h	88
7		98	rt, 6 h	98[c]
8		98	50 °C, 2 h	33
9		86	50 °C, 2 h	35

[a]Isolated yield. [b]Determined by GC-analysis using an internal standard unless otherwise noted. [c]Isolated yield after hydrolysis with 10% aq NaOH.

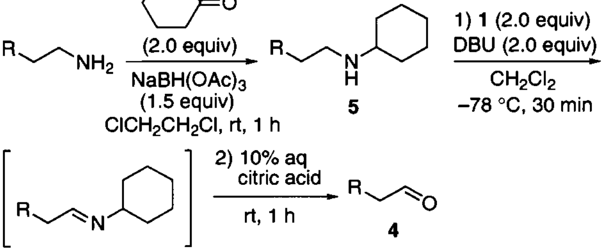


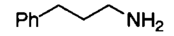
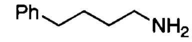
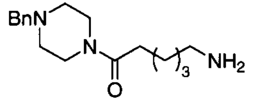
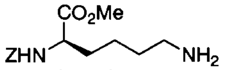
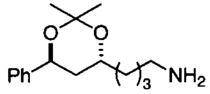
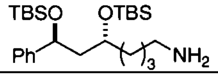
Scheme 1.

(Entries 3–6). Interestingly, *N*-mesylbenzhydrylideneamine which was formed after oxidation of *N*-mesylbenzhydrylamine was difficult to be hydrolyzed with aqueous HCl solution and 98% of the imine was isolated after purification with silica gel-column chromatography. On the other hand, one-pot hydrolysis of *N*-mesylbenzhydrylideneamine was smoothly carried out by using 10% aqueous NaOH solution and benzophenone was isolated in 98% yield. It was noted that *N*-mesyl ketimines were readily formed by the present oxidation of *N*-mesyl amines (Table 1, Entries 5–7), though it was previously reported that oxidation of secondary amines giving *N*-alkyl ketimines did not proceed smoothly by using **1** and DBU.[1]

Linear primary amines such as octylamine and 3-phenylpropylamine, however, were not effectively oxidized to the corresponding aldehydes by the above method probably due to the instability of formed *N*-mesyl aldimines[4] under the present oxidation conditions (Table 1, Entries 8 and 9). Other nitrogen substituents such as dimethylphosphinyl, 2-nitrobenzenesulfenyl, and 2-pyridyl groups were further examined, and alkyl groups were found to be better than electron-withdrawing ones. Then, cyclohexyl group[5] was chosen as a promising alkyl substituent as it was directly introduced to primary amines under reductive conditions.[6] The desirable oxidation at primary alkyl groups of *N*-cyclohexylated linear primary amines was also thought to take place selectively even in the presence of cyclohexyl group because of the steric reasons.

Table 2. Oxidation of linear primary amines via the corresponding *N*-cyclohexylamines



Entry	Linear primary amine	Yield/%[a] 5	Yield/%[a] 4
1		91	98[b]
2[c]		99	94[b]
3[c]		90	78
4		92	81
5		91	65
6		60	84
7		92	78
8		71	72
9		93	84
10		91	85

[a]Isolated yield unless otherwise noted. [b]Determined by GC-analysis using an internal standard. [c]*N*-cyclohexylation was carried out under the following conditions: $NaBH_3CN$ (2.0 equiv), cyclohexanone (1.5 equiv), HCl (pH 6), MeOH, rt, 1 h.[6b]

The oxidative deamination of 3-phenylpropylamine to afford 3-phenylpropanal was improved up to 98% by changing nitrogen substituents from mesyl (33%) to cyclohexyl group. Various linear primary amines were also successfully employed in the oxidative deamination which consisted of *N*-cyclohexylation, oxidation, and hydrolysis (Table 2). Most of *N*-cyclohexylations of linear primary amines were carried out by using cyclohexanone and $NaBH(OAc)_3$,[6a] and all of *N*-cyclohexyl secondary amines (**5**) were oxidized smoothly at –78 °C by the combined use of **1** and DBU. Formed *N*-cyclohexyl aldimines were hydrolyzed in a one-pot manner by using 10% aqueous citric acid to give linear aldehydes in good yields. It was noted that protecting groups such as acetonide, trityl, and ester groups were kept safely during these reactions.

General experimental procedure is as follows: (Oxidation of *N*-mesyl amines, Table 1): under argon atmosphere, a solution of **1** (1.08 mmol) in CH_2Cl_2 was added to a stirred mixture of *N*-mesyl amines (0.54 mmol) and DBU (1.08 mmol) in CH_2Cl_2 (3.0 mL) at –78 °C. The reaction mixture was stirred for 1 h at –78 °C and quenched by adding 1 M HCl solution (2.0 mL) and ether (20 mL). After stirring the mixture at room temperature, yields of carbonyl products were determined by GC-analysis. (Oxidation of *N*-cyclohexyl amines, Table 2): the oxidation of *N*-cyclohexyl amines was carried out as described above for 30 min at –78 °C and was quenched by adding 10% aqueous citric acid solution (2 mL). After the resulting mixture was stirred for 1 h at room temperature, linear aldehydes were isolated by the usual work-up procedure.

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References and Notes

1 T. Mukaiyama, A. Kawana, Y. Fukuda, and J. Matsuo, *Chem. Lett.*, **2001**, 390.

2 Review: R. J. Baumgarten, *J. Chem. Educ.*, **43**, 398 (1966). Recent reports: R. V. Hoffman and A. Kumar, *J. Org. Chem.*, **49**, 4011 (1984) and references are cited therein.

3 R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

4 a) F. Chemla, V. Hebbe, and J-F. Normant, *Synthesis*, **2000**, 75. b) J. Sisko and S. M. Weinreb, *J. Org. Chem.*, **55**, 393 (1990).

5 The *N*-cyclohexyl group was used as a nitrogen substituent for thermal elimination of sulfinamides. However, only benzylic amines were dehydrogenated by that method and rather high temperatures were needed for the elimination reaction. See: B. M. Trost and G. Liu, *J. Org. Chem.*, **46**, 4617 (1981).

6 a) A. F. Abdel-Magid, C. A. Maryanoff, and K. G. Carson, *Tetrahedron Lett.*, **39**, 5595 (1990). b) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).