Oxidation of Various Secondary Amines to Imines with *N*-*tert*-Butylphenylsulfinimidoyl Chloride

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(Received January 29, 2001; CL-010083)

Various secondary amines were smoothly oxidized to the corresponding imines at –78 °C by using *N*-*tert*-butylphenylsulfinimidoyl chloride and DBU.

Mild and efficient oxidation of amines to the corresponding imines[1] would provide a new synthetic possibility in organic synthesis because the formed imines are susceptible to nucleophilic additions which enable the introduction of a new substituent at the *β*-position of the amine functionality. In recent years, several trials of the amine-oxidation forming imines were reported in the field of natural products synthesis.[2] A variety of oxidants that realize this transformation have been developed to date: e.g. hypervalent iodine reagents,[3,2a] phenylselenic anhydride,[4] manganese dioxide,[5] and so on.[6] Oxidation of amines was also carried out by using a catalytic amount of ruthenium catalysts,[7,3c] cobalt-Shiff base complex,[8] or $NiSO_4$[9] in the presence of an appropriate co-oxidant. Most of these known methods have only been applied to oxidation of benzylic and allylic amines, which afford conjugated imines at room temperature or above, and a limited number of examples were reported for oxidation of aliphatic amines to non-conjugated imines. Therefore, a new amine-oxidizing reagent that has wider applicability and wider functional tolerance is now strongly desired.

Overton et al. reported that the oxidation of secondary amines by Swern oxidation method (DMSO-oxalyl chloride) yielded the corresponding imines along with considerable amounts of methylthiomethylamines as by-products.[10a] In the present study, oxidation of amines to the corresponding imines was examined by using a combination of *N*-*tert*-butylphenylsulfinimidoyl chloride (**1**) and DBU, which was previously reported to be the effective combination of reagents for oxidation of alcohols into carbonyl compounds.[11]

In the first place, oxidation of *N*-benzylaniline (**2a**) to *N*-benzylideneaniline (**3a**) was tried with the above-mentioned reagents. Expectedly, **2a** was oxidized instantaneously even at –78 °C by using two equivalents of **1** and DBU, and **3a** was detected by ^1H NMR in 92% yield.[12] The formation of **3a** was also confirmed by one-pot hydrolysis of **3a** with 1M HCl solution to afford benzaldehyde in 94% yield (Table 1, entry 1). The formed **3a** was methylated in a one-pot manner to afford *N*-(1-phenylethyl)aniline in 77% yield by adding three equivalents of methyllithium after the oxidation in THF. Further, the oxidations of *N*-benzyl-4-methoxyaniline (**2c**) and *N*-benzyl-4-fluoroaniline (**2b**) were examined in order to investigate the effect of aniline ring substituents. However, no differences were observed at all because the oxidations proceeded very quickly at –78 °C in both cases (Entries 2 and 3).

In addition to *N*-benzylideneamines, other conjugated imines and non-conjugated imines were also successfully formed at –78 °C by the present oxidation (Entries 4–9). Yields of non-conjugated imines were determined after hydrolysis into the corresponding aldehydes since the non-conjugated imines were easily hydrolyzed in aqueous work-up procedures. It was interesting to note that the oxidations of *N*-pentylaniline and *N*-(cyclohexylmethyl)aniline proceeded smoothly even at –78 °C in contrast to the cases of simple primary alcohols which were not oxidized completely with **1** and DBU at –78 °C.[11a]

The present oxidation reaction was applicable not only to *N*-substituted anilines but also to various *N*-substituted secondary amines (Entries 10–15). However, the oxidation of *N*-benzyl(triphenylmethyl)amine did not proceed at all probably due to the steric hindrance of triphenylmethyl group (Entry 12). In the cases of unsymmetrical secondary amines, two different imines are expected to form by the oxidation reaction. It was found that benzylic part was selectively oxidized in the oxidation of *N*-(cyclohexyl)benzylamine, and *N*-(benzilidene)cyclohexylamine was detected in 94% yield (Entry 13). This result can be explained by the unsuccessful formation of ketimines in the present oxidation; ketimines were hardly detected in the oxidation of *N*-cyclohexylaniline or *N*-(diphenylmethyl)aniline even at elevated temperatures. On the other hand, the oxidation of *N*-hexylbenzylamine took place on the either two alkyl groups to form two kinds of aldimines. Of these two products, the oxidation of benzylic part was moderately preferred (Entry 14). It was notable that the regioselectivity was also influenced by an electronic factor as exemplified in the oxidation of *N*-(2-methoxybenzyl)benzylamine, followed by one-pot hydrolysis giving benzaldehyde and 2-methoxybenzaldehyde in 32% and 53% yields, respectively (Entry 15). This result suggested that the electron-rich alkyl group facilitated the dehydrogenation to imines.

The oxidation of cyclic secondary amines such as indoline and 1,2,3,4-tetrahydroisoquinoline gave indole and 3,4-dihydroisoquinoline, respectively, in moderate yields (Entries 16 and 17). Indoline was oxidized to indole in a better yield by using 1.2 equivalents of **1** and DBU. Additionally, the present oxidation method was applied to oxidative deamination of primary amines. As a preliminary experiment (Entry 18), benzophenone was obtained in 52% yield on treating benzhydrylamine with the combination of **1** and DBU, followed by acid hydrolysis.

It should be noted that various secondary amines were efficiently oxidized to the corresponding imines under mild conditions (at –78 °C) by using the combination of **1** and DBU. Further studies on oxidative deamination of primary amines into the corresponding carbonyl compounds by using **1** are now under way.

Typical experimental procedure (Table 1, entry 6) is as follows: to a stirred solution of *N*-cinnamylaniline (110 mg, 0.53 mmol) and DBU (146 mg, 0.96 mmol) in CH_2Cl_2 (3 mL) was added a solution of **1** (206 mg, 0.96 mmol) in CH_2Cl_2 (1 mL) at

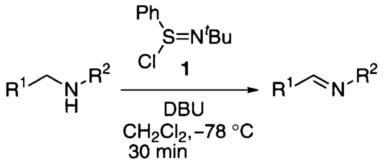
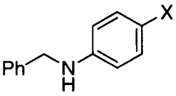
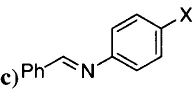
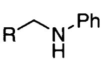
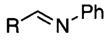
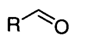
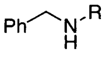
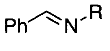
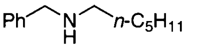
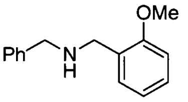
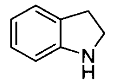
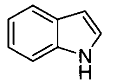
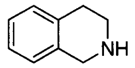
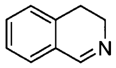
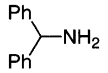
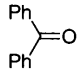


Table 1. Oxidation of various amines[a]

Entry	Amine		Product	Yield/%[b]
1	 **2a–c**	X=H (**2a**)	 **3a–c**	92 (94)[c]
2		X=F (**2b**)		92
3		X=OMe (**2c**)		quant.
4		R: 3-pyridyl		89
5		R: 2-furyl		96
6		R: CH=CHPh		98
7		R: CH=CH^{n}C$_3$H$_7$ (*trans*)		66
8		R: *n*-C$_5$H$_{11}$		81[c]
9		R: *c*-hexyl		81[c]
10		R: CH$_2$Ph		95
11		R: *t*-Bu		90
12		R: CPh$_3$		0
13		R: *c*-hexyl		94
14[d]			PhCHO + *n*-C$_5$H$_{11}$CHO	47[c] 31[c]
15			PhCHO + *o*-MeO-C$_6$H$_4$CHO	32[c] 53[c]
16[d]				62
17				65
18				52[c,e]

[a] **1** (2.0 equiv) and DBU (2.0 equiv) were used. [b] Determined by ^{1}H NMR spectra using an internal standard unless otherwise noted. [c] GC-yield of carbonyl compounds after hydrolysis of formed imines with 1M HCl solution at rt for 1 h. [d] **1** (1.2 equiv) and DBU (1.2 equiv) were used. [e] Isolated yield.

−78 °C. After the reaction mixture was stirred at the same temperature for 30 min, the reaction was quenched with saturated aqueous NaHCO$_3$ solution and the resulting mixture was extracted with CH$_2$Cl$_2$. The combined organic extracts were dried with anhydrous Na$_2$SO$_4$, filtrated, and concentrated to give a crude product. The formation of *N*-cinnamylideneaniline was confirmed by ^{1}H NMR spectrum by comparing it to that of an authentic sample, and its yield (0.51 mmol, 98%)[12] was determined by ^{1}H NMR spectrum using triphenylmethane (128 mg, 0.53 mmol) as an internal standard.

The present work was partially supported by Grant-in-Aids for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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12 The isolated yields were not shown here since the formed imines were partially decomposed during the isolation procedures such as silica gel or alumina column chromatography.