A Mild and Efficient Oxidation of Alcohols with *N*-*tert*-Butylphenylsulfinimidoyl Chloride in the Coexistence of Zinc Oxide

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Various primary and secondary alcohols bearing β-aryl, alkenyl, or alkoxy moiety were efficiently oxidized to the corresponding labile aldehydes and ketones under mild conditions with *N*-*tert*-butylphenylsulfinimidoyl chloride (**1**) in the coexistence of zinc oxide.

A number of useful carbon–carbon bond forming reactions using aldehydes and ketones have been developed to date, and efficient and reliable methods for preparing various types of aldehydes and ketones are important in organic synthesis. Especially, oxidation of alcohols to the desired carbonyl compounds is considered as a convenient tool for this purpose, although most current oxidations are carried out under either acidic or basic conditions which sometimes cause the decomposition, polymerization, isomerization, or epimerization of the prepared labile aldehydes and ketones.[1] In order to prevent such unfavorable side reactions, it may be worthwhile to conduct the oxidation under almost neutral conditions.

It was recently reported from our laboratory that primary and secondary alcohols were efficiently oxidized with *N*-*tert*-butylphenylsulfinimidoyl chloride (**1**) in the presence of DBU.[2] Although a variety of primary and secondary alcohols were efficiently oxidized by this new oxidation method, some types of aldehydes such as α-aryl and α-ketoaldehydes were not obtained in sufficient yields. For example, 3-phenylpropanol was smoothly oxidized to 3-phenylpropanal by using **1** and DBU (94%) while oxidation of 2-phenylethanol (**2**) gave phenylacetaldehyde (**3**) in only 24% yield (Table 1, entry 1). Swern et al. also reported that the oxidation of **2** using dimethyl sulfoxide activated with oxalyl chloride afforded **3** in a low yield (23%).[3a] These results suggested that the formed **3** decomposed under these basic oxidation conditions. In fact, 40%, 51%, and 55% of **3** decomposed in the presence of two equivalents of DBU giving a complex mixture in CH_2Cl_2 at 0 °C after 5 min, 30 min, and 1 h, respectively. In order to prevent the decomposition of the formed carbonyl product, the oxidation using **1** must be conducted under as neutral conditions as possible. Therefore, the original procedure was changed by replacing DBU with another suitable scavenger of hydrogen chloride, which was liberated during the formation of an intermediate, alkoxysulfilimine, from **1** and an alcohol. Then, it was thought that an insoluble solid base would be suitable because it would not cause the decomposition of the formed carbonyl compounds. In search for appropriate solid bases, zinc oxide turned out to be the most effective, and in this communication we would like to describe a mild and efficient oxidation of primary and secondary alcohols to the corresponding sensitive aldehydes and ketones with **1** in the coexistence of zinc oxide.

Suitable solid bases were examined taking the oxidation of 2-phenylethanol (**2**) to phenylacetaldehyde (**3**) by using 1.5 equivalents of **1** in dichloromethane as a model reaction (Table 1). In the first place, molecular sieves 4A (MS4A) was tested as a solid base because it was reported to work as a neutral scavenger of hydrogen chloride.[4] When MS4A (1 g/mmol) was used, the yield of **3** was sufficiently improved (73%, entry 3). When other types of zeolites such as MS3A and 5A were used, on the other hand, the oxidation did not proceed smoothly. It was then noted that MS4A was a preferred scavenger of hydrogen chloride among the three types of molecular sieves. Cesium fluoride, which is known as a hydrogen bond-assisted dehydrohalogenating agent, was ineffective in this oxidation. Next, the oxidation was further tried in the coexistence of several metal oxides since magnesium oxide[5] and zinc oxide[6] were shown to be effective acid-scavengers in Friedel–Crafts type reactions. Of several metal oxides screened,[7] zinc oxide was the most effective acid-scavenger in this reaction and it was experimentally shown that zinc oxide itself did not work as an oxidant (entry 12). Because the yield of **3** dropped significantly when the amount of zinc oxide decreased from five to two equivalents, experiments thereafter were carried out by using five equivalents of zinc oxide.

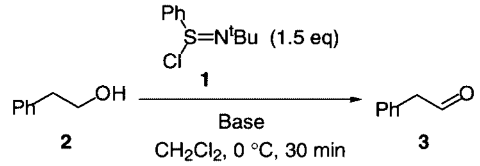


Table 1. Effect of bases

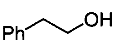
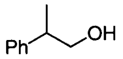
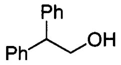
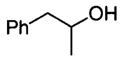
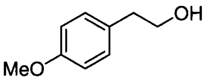
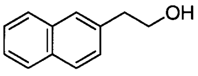
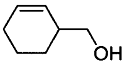
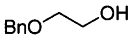
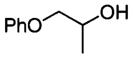
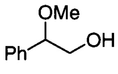
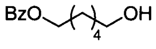
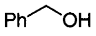
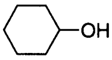
Entry	Base	Yield/%[a]
1	DBU (2 eq)	24
2	MS3A (1 g/mmol)	21
3	MS4A (1 g/mmol)	73 (56)[b]
4	MS5A (1 g/mmol)	35
5	CsF (5 eq)	6
6	MgO (10 eq)	58
7	CaO (5 eq)	56
8	BaO (5 eq)	70
9	TiO_2 (5 eq)	0
10	NiO (5 eq)	trace
11	CuO (5 eq)	37
12	ZnO (5 eq)	91 (35)[c] (0)[d]
13	Al_2O_3 (5 eq)	trace

[a] Determined by GC analysis using an internal standard. [b] MS4A (3 g/mmol) was used. [c] ZnO (2 eq) was used. [d] **1** was not used.

Comparing with other oxidation methods (Table 2, entries 1–5), the combined use of **1** and zinc oxide was more effective than Swern,[3] PDC,[8] and TPAP–NMO[1a] oxidations. On the other hand, Dess–Martin periodinate (DMP)[9] was also effective in the oxidation of **2** to **3**.[10] These results indicate that the present oxidation could be carried out under milder conditions than those of Swern, PDC, and TPAP–NMO oxidations.

In addition to **2**, primary and secondary alcohols bearing *β*-aryl, alkoxy, or phenoxy moiety were oxidized smoothly by the present oxidation method of using **1** and zinc oxide (entries 6–15). However, oxidation of secondary alcohols was slower than that of primary ones, and yields of ketones were moderate to good. Compared to the original procedure using DBU as a base, the present oxidation was carried out under slightly acidic conditions and a cleavage of trimethylsiloxy group was observed while an ester group survived during this oxidation. Also, simple primary and secondary alcohols were oxidized to the corresponding aldehydes and ketones by the present oxidation, although higher yields of the corresponding carbonyl compounds were achieved by the original procedure of using DBU as a base (entries 17–19).

Table 2. Oxidation of various alcohols

Entry	Alcohol	Conditions[a]	Yield/%[b]
1	 (**2**)	0 °C, 30 min	91 (24)
2	**2**	Swern Oxidation	23[c], 73[d]
3		PDC	31
4		TPAP/NMO	trace
5		Dess-Martin Oxidaiton	96
6	 (**4**)	0 °C, 30 min	94 (0)
7	**4**	Swern Oxidation	38[c]
8		0 °C, 30 min	91
9		rt, 30 min	66 (62)
10		0 °C, 30 min	84[e]
11		-78 °C, 2 h	52[f]
12		0 °C, 30 min	84
13		0 °C, 1 h	78
14		rt, 30 min	60
15		0 °C, 30 min	78
16		0 °C, 4 h	78[f]
17		-78 °C, 30 min	90 (98)
18		0 °C, 30 min	92 (94)
19		0 °C, 30 min	77 (91)

[a] Reaction conditions: **1** (1.5 eq), ZnO (5 eq) in CH_2Cl_2. [b] Determined by GC analyses using internal standards unless otherwise noted. Numbers in parentheses were yields of carbonyl products obtained by the original method using DBU (2 eq) as a base. [c] Ref. 3a. [d] By Walba's procedure. See Ref. 3b. [e] Isolated yield of its 2,4-dinitrophenylhydrazone. [f] Isolated yield.

Thus, various alcohols, especially, primary alcohols bearing *β*-aryl, alkenyl, or alkoxy moiety were smoothly oxidized to the corresponding carbonyl compounds with the combined use of the oxidizing agent **1** and zinc oxide. The oxidation described here is accomplished under mild conditions and successfully applied to the preparation of sensitive carbonyl compounds.

A typical experimental procedure is given for the oxidation corresponding to Table 2, entry 1. To a stirred white suspension of **2** (70 mg, 0.57 mmol) and zinc oxide[11] (233 mg, 2.86 mmol) in dry CH_2Cl_2 (1.5 mL) was added a solution of **1** (185 mg, 0.86 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The reaction mixture was stirred for 30 min at the same temperature and then quenched with water (5 mL). The mixture was filtered through Celite and the filter cake was washed with CH_2Cl_2 and water. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The yield of **3** (0.52 mmol, 91%) was determined by GC analyses of the combined organic phase using an internal standard.

References and Notes

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6 a) T. Mukaiyama, H. Kitagawa, and J. Matsuo, *Tetrahedron Lett.*, **41**, 9383 (2000). For other examples, see ref 6b and 6c. b) J. L. Charlton, *Can. J. Chem.*, **64**, 720 (1986). c) J. L. Charlton and M. M. Alauddin, *J. Org. Chem.*, **51**, 3490 (1986).

7 Only in the case of NiO, a considerable amount (55%) of (2-chloroethyl)benzene was detected (Table 1, entry 10).

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10 The oxidation of **2** to **3** was carried out under following conditions. Entry 3: PDC (1.5 equiv), CH_2Cl_2, rt, 12 h. Entry 4: TPAP (20 mol%), NMO (1.5 equiv), MS4A (500 mg/mmol), CH_2Cl_2, 0 °C, 1 h. Entry 5: DMP (1.5 equiv), wet CH_2Cl_2, rt, 30 min.

11 Commercial zinc oxide (purchased from Kanto Chemical Co., Inc.) was used without purification, because the oxidation of **2** by using dried zinc oxide (in vacuo, 150 °C, 5 h) and **1** gave **3** in a comparable yield (89%).