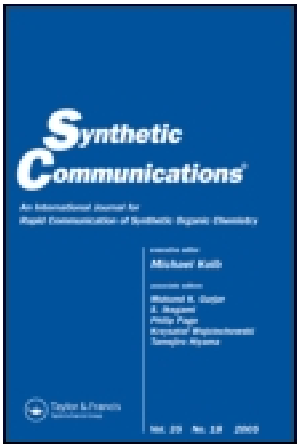

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Dimethyl Sulfoxide Pivaloyl Chloride: A New Reagent for Oxidation of Alcohols to Carbonyls

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India

Abstract: An efficient procedure for conversion of alcohols to the corresponding carbonyl compounds, an alternative to the classical Swern oxidation, is described. Pivaloyl chloride is employed as a mild and inexpensive electrophile. A possible reaction mechanism is proposed.

Keywords: alcohols, carbonyls, DMSO, pivaloyl chloride, Swern oxidation

INTRODUCTION

The oxidation of alcohols to the corresponding carbonyl compounds is one of the most important and frequently used synthetic procedures, and the development of such a procedure is still desirable in academic as well as in industrial research. The chemistry of dimethyl sulfoxide has been the subject of monographs[1] and reviews,[2] because it is one of the most studied solvents and reagents in organic synthesis. Dimethyl sulfoxide coupled with various electrophiles such as trifluoroacetic anhydride,[3] thionyl chloride,[4] oxalyl chloride,[5] *t*-butylhypochlorite,[6] acetic anhydride,[7] phosgene,[8] bis-(trichloromethyl)carbonate,[9] cyanuric chloride[10] and $Ph_3P \cdot X_2$[11] has been used in the classical Swern oxidation. Oxalyl chloride, which is a routinely used electrophile, has the following disadvantages: it is moisture sensitive, expensive, and toxic and its vapors are a powerful irritant, particularly to

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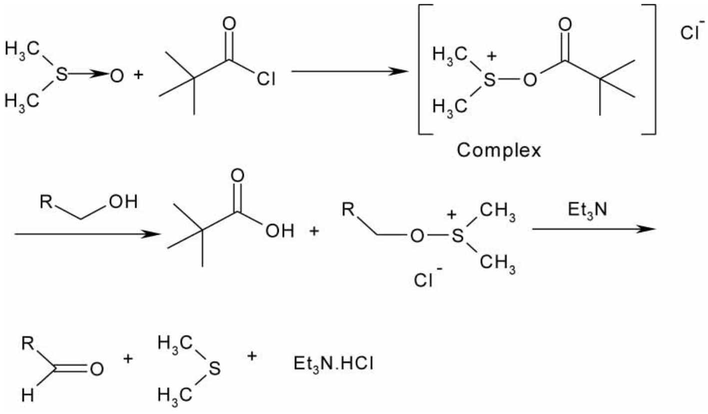
Scheme 1.

the respiratory system. Therefore use of a mild, efficient, and inexpensive electrophile is highly desirable. Herein, we report the oxidation of alcohols to carbonyl compounds employing pivaloyl chloride as an electrophile.

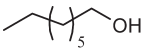
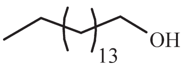
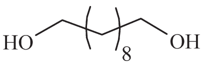
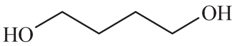
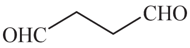
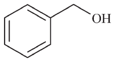
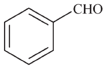
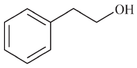
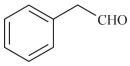
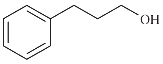
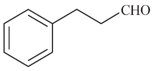
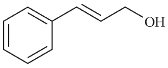
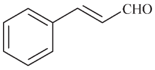
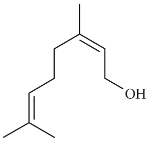
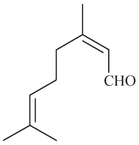
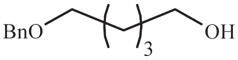
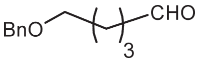
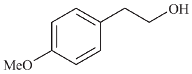
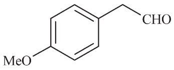
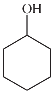
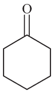
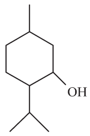
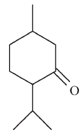
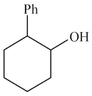
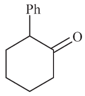
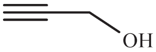
Although pivaloyl chloride has been commonly employed as a protecting group for various functional groups, its synthetic potential still remains unexplored. With a view to extend its synthetic utility in organic transformations, we envisioned that the activation of pivaloyl chloride with DMSO could be advantageous in the classical Swern oxidation reaction. In a typical experimental procedure, when alcohol was treated with 2 equiv of pivaloyl chloride and 3 equiv of dimethyl sulfoxide (DMSO) in CH_2Cl_2 at −78°C followed by treatment with 5 equiv of Et_3N, the corresponding carbonyl compound was obtained in good to excellent yield (Scheme 1).

To understand the reaction pathway, the oxidation of 1-octanol was carried out at different temperatures. At −78°C and −60°C, the reaction was complete, and the desired product was obtained in high yield (95%); however, at −40°C and −30°C, the reaction was incomplete, and the oxidized product was obtained in less than 50% yield along with the recovered alcohol. At 0°C, the reaction did not proceed at all, and the starting material was completely recovered. This could probably be attributed



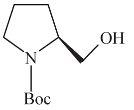
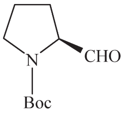
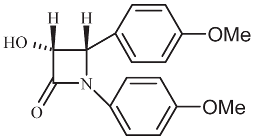
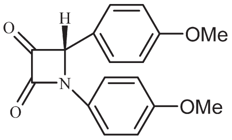
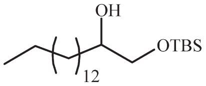
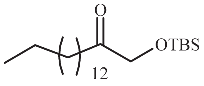
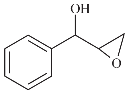
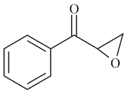
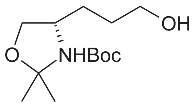
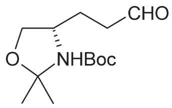
Scheme 2. Proposed mechanism for oxidation of alcohols to carbonyls.

Table 1. Dimethyl sulfoxide-piraloyl chloride mediated oxidation of alcohols to carbonyls

Number	Substrate	Product[a]	Yield (%)[b]
1			95
2			92
3			89
4			86
5			96
6			92
7			94
8			88
9			94
10			86
11			84
12			96
13			89
14			88
15			72

(*continued*)

Table 1. Continued

Number	Substrate	Product[a]	Yield (%)[b]
16			85[c]
17			60[c]
18			85[c]
19			85
20			70

[a] Products were characterized by spectral data (IR, ^{1}H NMR, ^{13}C NMR) and also by comparison with authentic samples.

[b] Isolated pure yields.

[c] The optical purity was checked by measuring the optical rotation of the products.

to the nature of complex formed during the reaction which may not be stable at high temperature (Scheme 2).

The present procedure is quite general as a wide range of structurally varied alcohols (such as primary, secondary, allylic, homoallylic, benzylic, and acetylenic) could be oxidized to carbonyl compounds in high yields. The superiority of this procedure can be clearly visualized in oxidation of *β*-amino alcohols leading to the corresponding carbonyls in good yields (Table 1, entries 16, 17). It should be mentioned that the oxidation of *N*-protected *β*-amino alcohol using DMSO/cyanuric reagent required a prolonged reaction time, leading to an *N*-deprotected compound along with the desired product.[10] A noteworthy feature of this reaction is that the epimerization of a chiral center could not be observed under the reaction conditions employed (Table 1, entries 16, 17). The oxidation of an alcohol having silyl ethers could also be carried out successfully in high yields (Table 1, entry 18). Similarly, epoxy alcohol could be smoothly converted into epoxy ketone in reasonably good yield (Table 1, entry 19).

CONCLUSION

In conclusion, we have demonstrated that the DMSO–pivaloyl chloride combination serves as an efficient reagent to effect the oxidation of a variety of alcohols to carbonyl compounds. This could be used as an alternative to the classical Swern oxidation reaction.

EXPERIMENTAL

All reactions requiring anhydrous conditions were performed under positive pressure of argon using oven-dried glassware (110°C), which was cooled under argon. Dichloromethane (DCM) and triethyl amine were distilled from CaH_2 and stored over molecular sieves and potassium hydroxide (KOH), respectively. Solvents used for chromatography were distilled at their boiling points using known procedures. Infrared spectra were recorded with an ATI Matsion RS-1 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on Brucker AC-200, Brucker MSL-300, and Brucker DRX-500 instruments using deuterated solvent. Chemical shifts are reported in parts per million (ppm). All melting points were uncorrected in degrees Celsius and recorded on a Thermonik melting-point apparatus. Elemental analyses were carried out with a Carlo Erba CHNS-O analyzer.

General Procedure for the Oxidation of Alcohols to Carbonyls

Pivaloyl chloride (2 equiv.) in dry DCM was added to a stirred solution of DMSO (3 equiv.) in DCM, and the solution was cooled to $-78^\circ C$. The reaction mixture was stirred for 15 min, and the alcohol (1 equiv.) in dry DCM was added dropwise. After consumption of the starting material (nearly 1 h), Et_3N (5 equiv.) was added, and the reaction mixture was stirred at $-78^\circ C$ for further 30 min, brought to rt, and stirred again for 30 min. The reaction mixture was quenched with saturated NH_4Cl and water, and the organic layer was separated. The aqueous layer was extracted with dichloromethane, and combined organic layers were washed with brine solution and concentrated to near dryness. The crude product was purified using silica-gel column chromatography and characterized by comparison with authentic samples and spectral data.

Physical and spectroscopic data of compounds (Table 1, entries 1–13, 15, and 20) were in agreement with known values.

Data

2-Phenylcyclohexanone (Entry 14)

Yellow crystalline solid; mp = 37°C [lit.[12a] mp 37–38°C]; IR ($CHCl_3$): 1700, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.43–1.52 (m, 4H), 1.58–1.70 (m, 2H), 2.24–2.34 (m, 1H), 2.68–2.81 (m, 1H), 5.14–5.17 (m, 1H), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.5, 27.1, 34.4, 41.4, 56.4, 126.0, 127.5, 127.9, 138.3, 209.1.

(*S*)-*tert*-Butyl-2-formylpyrrolidine-1-carboxylate (Entry 16)[12b]

$[\alpha]_D^{25}$ −99.49 (c 0.66, $CHCl_3$). Colorless liquid; IR ($CHCl_3$): 1724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.44 (d, $J = 9.8$ Hz, 9H), 1.73–2.21 (m, 4H), 3.41–3.61 (m, 2H), 4.0–4.22 (m, 1H), 9.45 (s, 1H); ^{13} C NMR ($CDCl_3$, 50 MHz): δ 23.5, 24.2, 26.3, 27.5, 46.3, 64.9, 80.2, 200.2.

(*S*)-3,4-Bis-(4-methoxyphenyl)-azetidine-2,3-dione (Entry 17)

Yellow solid; mp = 143°C [lit.[12c] mp 144°C]; IR ($CHCl_3$): 1832, 1809, 1753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.79 (s, 3H), 3.89 (s, 3H), 5.52 (s, 1H), 6.86–6.95 (m, 4H), 7.25 (d, $J = 8.8$ Hz, 2H), 7.46 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): 55.2, 55.4, 74.4, 114.6, 114.8, 119.6, 123.5, 127.7, 129.8, 157.8, 160.1, 160.4, 191.1.

1-*tert*-Butyldimethylsilyloxy)-pentadecan-2-one (Entry 18)

Colorless syrupy liquid; IR ($CHCl_3$): 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ.04–09 (m, 6H), 0.84–0.92 (m, 12H), 1.18–1.26 (m, 26H), 4.16 (s, 2H)); ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.7, 14, 18.2, 22.6, 23.3, 25.6, 25.8, 26.4, 26.9, 29.2, 29.3, 29.6, 31.9, 38.2, 211.02. Anal. calcd. for $C_{22}H_{46}O_2Si$: C, 71.28; H, 12.51. Found: C, 71.11; H, 12.32.

Oxirane-2-yl-(phenyl)-methanone (Entry 19)[12d]

White solid; mp = 44°C; IR ($CHCl_3$): 1692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.97 (dd, $J = 2.5$, 6.6 Hz, 1H), 3.13 (dd, $J = 4.6$, 6.6 Hz, 1H), 4.25 (dd, $J = 2.5$ Hz, 4.4 1H), 7.47–7.68 (m, 3H), 8.02–8.08 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.4, 50.9, 128.1, 128.7, 133.8, 135.2, 194.5.

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