A Mild and Efficient Alternative to the Classical Swern Oxidation

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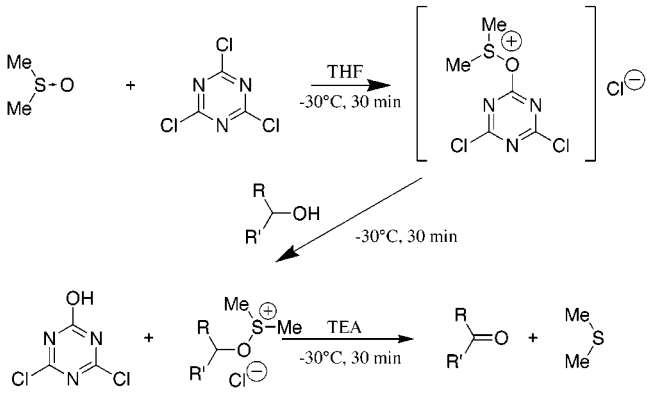
Carbonyl compounds are of great importance as intermediates to prepare other functional groups in organic synthesis. In particular, aldehydes and N-protected α-amino aldehydes[1] are important and versatile compounds.

Oxidation of alcohols to the corresponding carbonyl compounds is one of the most important synthetic procedures, and the development of selective and efficient reagents for that conversion, especially when other oxidizable functional groups are also present, has interested organic chemists for a long time. In this context, notwithstanding the availability of many preparative methods, the restrictions that accompany some of them make new, mild, and selective procedures highly desirable. Most of the methods for the oxidation of alcohols utilize dimethyl sulfoxide as a reagent via dimethyl alkoxysulfonium salts that react with a base to give the carbonyl compound and dimethyl sulfide. The electrophilic reagents that have been used to activate dimethyl sulfoxide include acetic anhydride,[2] methanesulfonic anhydride,[3] tosyl chloride,[4] sulfur trioxide/pyridine,[5] phosphorus pentoxide,[6] thionyl chloride,[7] and oxalyl chloride[7,8] among others. Generally, the activation of DMSO can be violent and exothermic, and successful activation requires low temperatures, usually −60 °C. Of all the activators, the highest yields of carbonyl compounds, with minimal byproduct formation, were obtained with thionyl chloride and oxalyl chloride, especially the latter. Unfortunately, oxalyl chloride is moisture sensitive and dangerously toxic, and its vapor is a powerful irritant, particularly to the respiratory system and to the eyes.

On this basis and following our interest in the use of [1,3,5]triazine derivatives in organic synthesis,[9] herein we report a mild and efficient alternative procedure for the quantitative conversion of alcohols into the corresponding carbonyl compounds. The method uses dimethyl sulfoxide (DMSO), activated by 2,4,6-trichloro[1,3,5]-triazine (cyanuric chloride, TCT), under the so-called Swern oxidation conditions.[10]

Scheme 1



We have observed that the activation of DMSO can be conveniently conducted with the very cheap cyanuric chloride, which can be used even for large-scale work, simply using THF as solvent. The procedure is based on treatment of TCT with 5 equiv of DMSO in THF at −30 °C for 30 min, followed by addition of the alcohol. After an additional 30 min, triethylamine (TEA, 4 equiv) was added (Scheme 1). The reaction mixture was then quenched with water and worked up to yield the carbonyl compound. Although formation of the dimethyl alkoxysulfonium salt occurred even at 0 °C without any apparent decomposition, the reactions were carried out at −30 °C to prevent eventual formation of undesirable byproducts, such as chloro derivatives or thiomethyl ethers.[11]

As shown in Tables 1 and 2, a variety of carbonyl compounds and N-protected amino aldehydes were prepared from commercially available alcohols. The yields were quantitative (>99%), and the conversion[12] was very high in most of the cases. The oxidation proceeds with satisfactory rates even when the alcohol has steric constrains. Only in the case of 9-fluorenemethanol was the reaction found to be very slow (20% conversion after 8 h). The oxidation of 2-phenylthioethanol is very slow too, possibly due to the competition of sulfur atom of the alcohol in the coordination with the TCT.

The methodology is cleanly applicable to N-protected *β*-amino alcohols:[13] the corresponding aldehydes are recovered as pure products and in good conversions even if the reaction requires a longer time (90 min after the addition of TEA). Only *N*-Boc *β*-amino alcohols seem to react more slowly and in some cases may deprotect partially under the reaction conditions (e.g., Table 2, run 3).

On these results, α-amino aldehydes could be efficiently prepared in total good yield by using TCT/$NaBH_4$ reduction[9a] of N-protected α-amino acid followed by

(1) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.
(2) Albright, J. D.; Goldman, L. *J. Org. Chem.* **1967**, *32*, 2416.
(3) Murray, R. W.; Gu, D. *J. Chem. Soc., Perkin Trans. 2* **1994**, 451.
(4) Albright, J. D. *J. Org. Chem.* **1974**, *39*, 1977.
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(7) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(8) Marx, M.; Tidwell, T. T. *J. Org. Chem.* **1984**, *49*, 788. Liu, Y.; Vederas, J. C. *J. Org. Chem.* **1996**, *61*, 7856.
(9) (a) Falorni, M.; Porcheddu, A.; Taddei, M. *Tetrahedron Lett.* **1999**, *40*, 4395. (b) Falorni, M.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* **1999**, *64*, 8962. (c) Falchi, A.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *Synlett* **2000**, 275. (d) De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534. (e) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 1519.
(10) The use of TCT was already cited but the author reported only two examples, where TCT was used dissolved in a very toxic, possibly carcinogenic solvent such as HMPA.[4]
(11) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(12) Determined by NMR analysis of the crude product after 30 min of the addition of TEA.
(13) In the case of *N*-Fmoc α-amino alcohol, diisopropylethylamine (DIPEA) was used instead of TEA.

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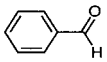
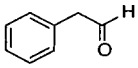
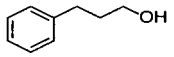
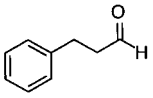
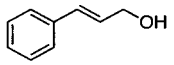
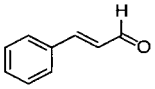
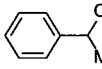
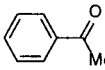
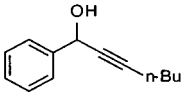
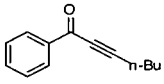
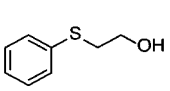
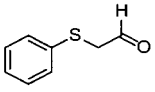
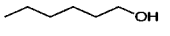
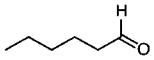
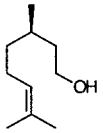
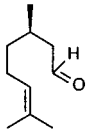
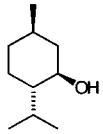
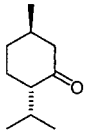
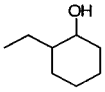
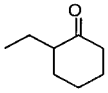
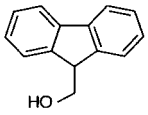
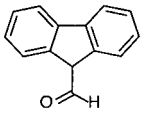
Table 1. Conversion of Alcohols into the Corresponding Carbonyl Compounds

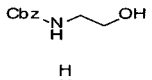
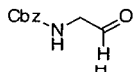
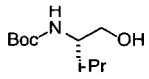
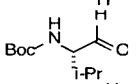
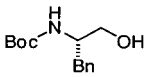
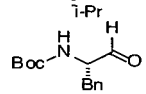
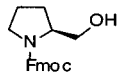
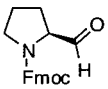
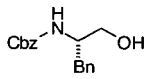
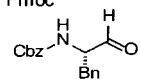
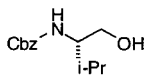
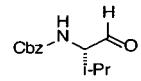
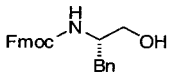
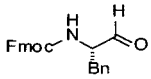
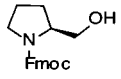
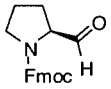
entry	alcohol	product	Conversion[a] (%)
1			91
2			89
3			90[b]
4			93
5			94
6			90
7			30[c]
8			70
9			74
10			90
11			90
12			20[c]

[a] After 30 min from addition of TEA. [b] The compound polymerizes when pure. [c] Conversion after 8 h.

oxidation according to the present procedure. Thus, (*S*)-*N*-benzyloxycarbonyl-2-amino-3-phenylpropionaldehyde, $[\alpha]^{20}_D$ −52.3 (*c* 0.7, MeOH) was recovered, without significant racemization of the chiral center,[14] from (*S*)-*N*-benzyloxycarbonylphenylalanine. This method could avoid some problems encountered in the synthesis of the aldehydes by controlled DIBAL reduction of α-amino esters[15] or in the reduction of N-protected α-amino acids by H_2 and Pd/C.[9b]

In conclusion, the method presented in this report is operationally simple and can be used as a valid alternative to the classical Swern oxidation, requiring milder conditions and cheaper reagents.

Table 2. Conversion of N-Protected α-Amino Alcohols into N-Protected α-Amino Aldehydes

entry	alcohol	product	Conversion[a] (%)
1			60
2			35
3			20[b]
4			50
5			90
6			80
7			60
8			86

[a] After 90 min from addition of the tertiary amine. [b] The compound was recovered partially deprotected (25%).

Experimental Section

All the solvents and the reagents were used in the commercially available grade of purity. The N-protected *β*-amino alcohols were prepared from the corresponding α-amino acids according to the literature,[9b] and their purity was established before utilization by melting point and optical rotation. Cyanuric chloride was purchased from Avocado.

Elemental analyses were performed on a Perkin-Elmer 420 B analyzer, optical rotations were measured with a Perkin-Elmer 241 automatic polarimeter in a 1 dm tube. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) were obtained with a Varian VXR-300 spectrometer from $CDCl_3$ solutions.

General Procedure for the Synthesis of Aldehydes and Ketones. The procedure for the preparation of *N*-benzyloxycarbonyl-2-amino-3-phenylpropionaldehyde is representative. DMSO (1.25 mL, 17.6 mmol) was added to a solution of TCT (0.66 g, 3.6 mmol) in THF (20 mL) stirred and maintained at −30 °C. After 30 min, *N*-benzyloxycarbonyl-2-amino-3-phenylpropan-1-ol, $[\alpha]^{20}_D$ − 41.0 (*c* 1, MeOH) (0.86 g, 3 mmol), in THF (10 mL) was added slowly at −30 °C with stirring, followed by TEA (2 mL, 14.3 mmol) after an additional 30 min. After 15 min, the mixture was warmed to room temperature, the solvent evaporated under vacuum, and Et_2O (50 mL) added to the solid formed. The mixture was quenched with 1 N HCl, and the organic phase washed with 15 mL of a saturated solution of $NaHCO_3$, followed by brine. The organic layer was dried (Na_2SO_4) and the solvent evaporated to yield pure *N*-benzyloxycarbonyl-2-amino-3-phenylpropionaldehyde (0.77 g, 90%): mp 79 °C; $[\alpha]^{20}_D$ − 52.3 (*c* 0.7, MeOH);[14] ^{1}H NMR *δ* 9.63 (s, 1H), 7.37 (m, 10H), 5.31 (s, 1H), 5.11 (s, 2H), 4.50 (m, 1H), 3.15 (d, 2H).

Simple aldehydes and ketones obtained were characterized by usual spectral data and compared with authentical samples, when commercial, or with the literature values. The following α-amino aldehydes were already described: *N*-benzyloxycarbonylglycinal,[16] *N-tert*-butoxycarbonyl-L-phenylalaninal,[14b,17] *N*-

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tert-butoxycarbonyl-L-isoleucinal,[17] *N*-benzyloxycarbonyl-L-valinal,[16] *N*-(9-fluorenylmethoxycarbonyl)-L-phenylalaninal,[18] *N*-benzyloxycarbonyl-L-prolinal.[14]

***N*-(9-Fluorenylmethoxycarbonyl)-L-prolinal** (0.83 g, 86%): ^{1}H NMR δ 9.44 (s, 0.6H), 9.13 (s, 0.4H), 7.82−7.23 (m, 8H) 4.47−3.98 (m, 3H), 3.89 (m, 1H), 3.40 (m, 2H), 2.03−1.60 (m, 4H); ^{13}C NMR δ 199.4, 157.4,140.1, 132.6, 128.2, 124.9, 120.8, 67.0, 64.8, 47.2 46.3, 27.6, 23.5. Anal. Calcd for $C_{20}H_{19}NO_3$ (321.14): C, 74.75; H, 5.96; N, 4.36. Found: C, 74.75; H, 5.99; N, 4.34.

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