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LETTERS

Indium-mediated chemoselective deprotection of trichloroethoxycarbonyl and trichloroacetyl groups

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Abstract—A new, mild, and chemoselective method for the deprotection of trichloroethoxylcarbonyl and trichloroacetyl groups is described. © 2001 Elsevier Science Ltd. All rights reserved.

Protecting groups play an important role in chemical synthesis, particularly for the total synthesis of natural products. Various protecting groups and deprotection methods have been developed to achieve chemoselective transformations.[1] 2,2,2-Trichloroethoxycarbonyl (Troc) and trichloroacetyl groups have been widely used as protecting groups in organic synthesis.[2–8] Though they are very useful protecting groups, only a few deprotection methods are available for their removal. The Troc group can be removed by zinc reduction,[2–4] electrolysis,[5] or alkenolysis.[6] In contrast, the trichloroacetyl group can be removed by ammonia[7] and alkali bases.[8] Since these conditions are not mild enough to accommodate several other functionalities, the development of a new mild method seemed worthwhile.

There has been growing interest in the use of metallic elements in synthetic chemistry.[9] Recent research using metallic indium[10,11] stimulated us to investigate its use in the deprotection of these chlorinated protecting groups.

$$\mathrm{R{-}OP} \xrightarrow[\text{MeOH}]{\text{indium, aq. NH}_4\text{Cl}} \mathrm{R{-}OH}$$

$$\mathrm{P = Cl_3CH_2OCO\text{-} \ or \ Cl_3CCO\text{-}}$$

Herein, we describe a mild, chemoselective, and general method for the release of alcohols from the corresponding trichloroethoxycarbonate and trichloroacetate derivatives by refluxing the protected alcohols in the presence of indium powder and aq. NH_4Cl in methanol.

To determine the general applicability of this methodology, various substrates having diverse functionality and protecting groups were prepared and subjected to deprotection. The reaction conditions were very mild and gave the corresponding alcohols in excellent yields (Table 1). Under these reaction conditions, chiral substrates did not undergo any racemization (entries 1, 4, 5, and 9). Deprotection of silyl-protected 1,2- and 1,3-diols (entries 3 and 4) led to the formation of the desired silyloxy alcohols, and migration of silyl group was not observed. It was possible to carry out the deprotection without affecting olefins (entries 1 and 3), alkyne (entry 6), alkoxy group (entry 7), or halogen (entry 8). This method is highly chemoselective in that many protecting groups, such as benzoyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, ethyl ester, and amide are stable to these reaction conditions. This method is also very effective in the unmasking of protected sterically hindered alcohol (entry 10).

In a typical experimental procedure, the Troc or trichloroacetyl protected alcohol (1 mmol) was combined with indium powder[12] (2 mmol), aqueous NH_4Cl (5N, 1 mL), and methanol (5 mL). The mixture was refluxed and monitored for completion by TLC. The solvent was removed by rotary evaporation under vacuum, and the residue was extracted with ethyl acetate (3×25 mL), washed with brine (50 mL), and dried over Na_2SO_4. The mixture was filtered, and the solvent was

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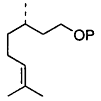
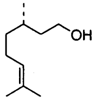
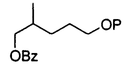
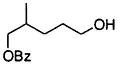
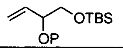
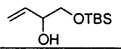
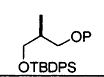
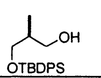
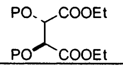
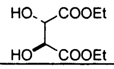
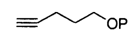
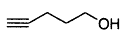
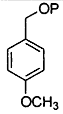
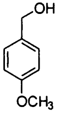
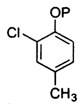
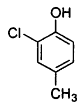
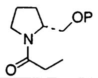
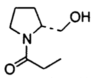
Table 1. Deprotection of Troc and trichloroacetyl groups using indium and aq. NH_4Cl

Entry	Starting Material	Product	Time^a (h)	Yield^{a,b} (%)	Time^c (h)	Yield^{b,c} (%)
1			1	98	0.5	95
2			1.5	94	0.5	98
3			3	89	0.5	85
4			1	95	0.5	94
5			2	85	1	89
6			0.5	98	0.5	87
7			1	91	1	94
8			1.5	84	1	82
9			3	82	1.5	85
10			1	98	0.5	90

a: Troc deprotection, b: All the products were purified by silica gel flash column chromatography and characterized by ^{1}H-NMR and HRMS, c: Trichloroacetyl deprotection

evaporated to provide the crude residue. Flash column chromatography on silica gel furnished analytically pure alcohols, which were confirmed by ^{1}H-NMR and HRMS.

In conclusion, this procedure provides an improvement over existing methods for the selective deprotection of Troc and trichloroacetyl groups. The conditions are mild and tolerate various other types of functionalities and protecting groups.

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