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Indium-mediated cleavage of the trityl group from protected alcohols and diols

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ABSTRACT

The reaction of primary, secondary, allylic and benzylic trityl ethers with indium powder in MeOH/NH_4Cl led to reductive cleavage of the trityl-oxygen bond, affording the corresponding alcohols in good to excellent yield under very mild reaction conditions. The detritylation process could successfully be extended to mono and detritylated diols. This methodology represents a new and efficient detritylation procedure under mild reaction conditions.

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1. Introduction

The use of indium metal[1] in reduction processes applied to synthetic organic chemistry[2] is based on the fact that its electrode potential (5.8 eV) is rather similar to that of alkali metals, such as sodium (5.1 eV) or lithium (5.4 eV) and, therefore, indium metal behaves as an excellent single electron transfer reagent.[3] This ability has been used successfully for the cleavage of carbon–heteroatom bonds and, consequently, for the deprotection of several functionalities such as protected alcohols, amines or thioethers.[4] Among interesting protecting groups, the triphenylmethyl (trityl) unit has been extensively used in carbohydrate,[5] peptide,[6] and nucleoside chemistry,[7] mainly due to its steric demand. In addition, deprotection of the trityl group can be easily achieved by simple acid hydrolysis,[4] this procedure being useful only for compounds having functionalities not-sensitive to acidic conditions: as an example when nucleosides are tritylated at the 5′-OH position, its treatment with protic acids leads, together with the expected detritylation, to the hydrolysis of the *N*-glycosidic bond.[8]

In the last years, we have been interested in the deprotection of several oxygen, nitrogen and sulfur-containing compounds[9] using lithium and a catalytic amount of naphthalene[10] followed by hydrolysis. Among them, we investigated detritylation processes involving trityl ethers[9a] and trityl amines.[9g] In addition, more recently, we have explored the use of other metals, such as indium[11] or zinc,[12] in both cases in methanol, for the effective detritylation of 1-tritylterazoles.[13,14] In this paper, we report the indium-promoted detritylation of trityl ethers as an efficient method for the deprotection of this type of compounds under very mild reaction conditions.

2. Results and discussion

As a model reaction we treated *n*-nonadecyl trityl ether (**1a**) with indium metal (1:1.7 M ratio) under different reaction conditions finding that the optimal situation was the use of a mixture of methanol and aqueous ammonium chloride at reflux for 35 h (Table 1, entry 8). Using other solvent combinations or diminishing the reaction temperature or time, no reaction occurred (Table 1, entries 1–7).

Having the best reaction conditions in hand, we studied the scope of the process. Primary (**1a**–**d,** Table 2, entries 1–4) or secondary (**1e**–**g**, Table 2, entries 5–7) trityl ethers were easily

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Table 1
Assayed conditions for the In-promoted cleavage of **1a** for 24 h

Entry	Solvent	T (°C)	Yield (%)[a]
1	In/MeOH/THF	rt	0
2	In/MeOH/THF	Reflux	0
3	In/MeOH	rt	0
4	In/MeOH	Reflux	0
5	In/THF	rt	0
6	In/THF	Reflux	0
7	In/MeOH/THF/NH_4Cl	rt	0
8	In/MeOH/NH_4Cl	Reflux[b]	80

[a] Isolated yield.
[b] For 35 h.

deprotected to afford the expected alcohols **2a**–**g** with yields ranging from 62 to 80%. Mono (**1h**, Table 2, entry 8) and ditritylated diols (**1i,j**, Table 2, entries 9 and 10) were fully deprotected using the same reaction conditions with the corresponding stoichiometry, affording the expected diols **2h**–**j**. The low yield obtained for diols **2h**–**j** could be explained by their partial solubility in water during the extractive work-up; actually no byproducts were observed in the reaction crude. Also allylic or benzylic derivatives (**1k** and **1l**, respectively, Table 2, entries 11 and 12) were detritylated without any problem: allylic or benzylic carbon–oxygen cleavage was not observed in any case. Finally, the protected phenol **1m** (Table 2, entry 13) was submitted to the same protocol giving the parent phenol with reasonable yield.

Starting ethers **1** were easily prepared from the corresponding commercially available alcohols **2** by a standard procedure: reaction of **2** with trityl chloride in the presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine.[9a]

Concerning a possible reaction mechanism, we believe that after the first single electron transfer (SET) from the metal to the ether, a trityl radical is formed, which after a second SET process gives the corresponding anion that in the reaction medium captures a chloride from ammonium chloride, giving trityl chloride. The alkoxide formed in the first step also traps a proton from the protic reaction medium to give the alcohol **2**. Actually, in order to support this proposal we were able to isolate trityl chloride (65%; column chromatography, silica gel hexane–EtOAc 9:1) in the detritylation of **1a** under the conditions shown in Table 2.

As a conclusion, we have reported here a simple, versatile and useful methodology for the detritylation of protected primary and secondary alcohols, as well as mono- or diprotected diols, and tritylated phenol, using indium in a protic medium.

3. Experimental part

3.1. General

FTIR spectra were recorded on a Nicolet Impact 400D spectrophotometer and Fourier Shimadzu FTIR-8201 PC using KBr pellets. NMR spectra were recorded on a Bruker AC-300 spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C) and a Bruker AC-400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) using $CDCl_3$, DMSO-d_6, or CD_3OD as solvent and TMS (δ=0.00 ppm, ^1H) or $CDCl_3$ (δ=77.0 ppm, ^{13}C), DMSO-d_6 (δ=2.50 ppm, ^1H; δ=39.75 ppm, ^{13}C), or CD_3OD (δ=4.87 ppm, ^1H; δ=49.0 ppm, ^{13}C), Fourier BRUCKER DPX 250 (250 MHz for ^1H and 62.5 MHz for ^{13}C) as internal standards; chemical shifts are given in δ (ppm) and coupling constants (J) in Hz. Multiplicities are given as s: singlet, d: doublet, t: triplet, td: triplet of doublet, m: multiplet. Elemental analyses were measured by the Technical Services at the University of Alicante. Column chromatography was performed using silica gel 60 (35–70 mesh). All reagents used for the synthesis of trityl ethers were of the best commercial grade and were uses as received.

3.2. General procedure for tritylation of alcohols 2. Preparation of ethers 1[9a,13]

A solution of the commercially available alcohol **2** (5.0 mmol) in CH_2Cl_2 (2.5 mL) was added to a solution of trityl chloride (1.55 g, 5.5 mmol), Et_3N (1.25 mL, 8.8 mmol) and DMPA (46 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) at rt and the mixture was stirred overnight. The reaction was then quenched with water (2.5 mL) and extracted with EtOAc (3×10 mL) and the combined organic phases were washed with brine (2.5 mL) and dried over sodium sulfate. After evaporation of the solvents (15 Torr), the resulting residue was purified by column chromatography (silica gel, hexane–EtOAc) affording the expected trityl ethers **1**. When diols were used (as precursor of ethers **1h**–**j**), a mixture of mono and deprotected products were obtained in variable proportions, which could be easily separated by column chromatography. Physical, spectroscopic and analytical data for the tritylated alcohols **1** follow.

*3.2.1. Stearyl trityl ether (**1a**).*[13] White solid; yield 2.45 g (95%); mp: 70 °C; IR (cm^{-1}): 3000, 2950, 2400, 1500, 1450, 1300, 1050, 1010, 650; ^1H NMR (400 MHz, $CDCl_3$): δ 0.81 (t, 3 H, J=4.0 Hz, CH_3), 1.18–1.56 [m, 24H, $CH_3(CH_2)_{12}$], 2.20–2.22 (m, 6H, 3 CH_2), 2.49–2.52 (m, 2H, CH_2CO), 2.96 (t, 2H, J=6.7 Hz, CH_2O), 7.13–7.25 (m, 9H, ArH), 7.36–7.38 (m, 6H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (CH_3), 22.6, 26.2, 29.3, 29.6 (8C), 30.0, 31.9, 39.9, 40.1, 40.3 [$CH_3(CH_2)_{16}$], 63.6 (CH_2O), 86.5 (CO), 126.7 (3C), 127.6 (6C), 128.6 (6C), 144.5 (3C, ArC); MS m/z (%): 435 (M^+-Ph, 8), 244 (39), 243 (100), 183 (29), 165 (15), 105 (16); Anal. Calcd for $C_{37}H_{52}O$: C, 86.66; H, 10.22. Found: C, 86.62; H, 10.26.

*3.2.2. Hexyl trityl ether (**1b**).*[13] Colorless oil; yield 1.18 g (62%); IR (cm^{-1}): 3166, 3058, 3028, 1593, 1488, 1080, 1068; ^1H NMR (250 MHz, $CDCl_3$): δ 1.22 (d, 3H, J=6.1 Hz, CH_3), 1.53–1.81 [m, 6H, $CH_3(CH_2)_3$], 3.08–3.17 (m, 2H, CH_2CH_2O), 3.76–3.88 (m, 2H, CH_2O), 7.23–7.37 (m, 9H, ArH), 7.42–7.50 (m, 6H, ArH); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 23.6 (CH_3), 26.5, 36.4 (2C), 63.8 [$CH_3(CH_2)_4$], 68.0 (CH_2O), 86.7 (CO), 127.0 (3C), 127.8 (6C), 128.7 (6C), 144.3 (3C, ArC); MS m/z (%): 243 (M^+–Ph–CH_2=CH_2, 100), 183 (30), 167 (11), 166 (7), 165 (21), 105 (31), 77 (20); Anal. Calcd for $C_{25}H_{28}O$: C, 87.16; H, 8.19. Found: C, 87.18; H, 8.16.

*3.2.3. n-Decyl trityl ether (**1c**).*[9a] Colorless oil; yield 1.85 g (76%); IR (cm^{-1}): 3085, 3057, 3031, 1596, 1489, 1086, 1068; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 3H, J=8.0 Hz, CH_3), 1.24–1.36 [m, 14H, $CH_3(CH_2)_7$], 1.51–1.65 (m, 2H, CH_2CO), 3.03 (t, 2H, J=6.7 Hz, CH_2O), 7.19–7.31 (m, 9H, ArH), 7.43–7.46 (m, 6H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (CH_3), 22.8, 26.4, 29.4, 29.6, 29.7 (2C), 30.2, 32.0 [$CH_3(CH_2)_8$], 63.8 (CH_2O), 86.3 (CO), 126.9 (3C), 127.8 (6C), 128.8 (6C), 144.6 (3C, ArC); MS m/z (%): 400 (M^+, 12), 323 (16), 244 (36), 243 (100), 183 (35), 165 (39), 105 (40).

*3.2.4. Isoamyl trityl ether (**1d**).*[15] Colorless oil; yield 1.24 g (75%); IR (cm^{-1}): 3070, 3024, 2912, 1485, 1446, 1083; ^1H NMR (400 MHz, $CDCl_3$): δ 0.80 (d, 6H, J=8.0 Hz, [m, 1H, $CH(CH_3)_2$], 1.47–1.53 (m, 2H, CH_2CH_2O), 1.72–1.79 [m, 1H, $CH(CH_3)_2$], 3.06 (t, 2H, J=8.0 Hz, CH_2O), 7.25–7.36 (m, 9H, ArH), 7.49–7.51 (m, 6H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8 ($2CH_3$), 25.2 (CH), 39.1 (CH_2), 68.2 (CH_2O), 86.4 (CO), 126.9 (3C), 127.8 (6C), 128.8 (6C), 144.6 (3C, ArC); MS m/z (%): 330 (M^+, 10), 244 (32), 243 (100), 253 (11), 183 (33), 165 (32), 105 (25); Anal. Calcd for $C_{24}H_{26}O$: C, 87.23; H, 7.93. Found: C, 87.25; H, 7.90.

*3.2.5. 2-Trityloxyoctane (**1e**).*[9a] Colorless oil; yield 1.60 g (78%); IR (cm^{-1}): 3055, 2925, 1598, 1489, 1075, 1026; ^1H NMR (400 MHz, $CDCl_3$): δ 0.83 (t, 3H, J=8.0 Hz, CH_3CH_2), 0.86 (d, 3H, J=4.0 Hz, CH_3CO), 1.05–1.23 [m, 10H, $(CH_2)_5$], 3.51–3.58 (m, 1H, CHO), 7.19–7.30 (m, 9H, ArH), 7.49–7.52 (m, 6H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (CH_3CH_2), 21.3 (CH_3CO), 22.7, 25.0, 29.5, 31.9, 37.6 [$(CH_2)_5$], 70.2

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