

Accepted Manuscript

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PII: S0040-4039(16)30789-4
DOI: <http://dx.doi.org/10.1016/j.tetlet.2016.06.110>
Reference: TETL 47837

To appear in: *Tetrahedron Letters*

Received Date: 12 May 2016
Revised Date: 14 June 2016
Accepted Date: 23 June 2016

Please cite this article as: Behloul, C., Chouti, A., Chabour, I., Bey, H.B., Guijarro, D., Foubelo, F., Nájera, C., Yus, M., LiCl-mediated, easy and low-cost removal of the trityl group from protected alcohols and diols, *Tetrahedron Letters* (2016), doi: <http://dx.doi.org/10.1016/j.tetlet.2016.06.110>

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LiCl-mediated, easy and low-cost removal of the trityl group from protected alcohols and diols

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Received: The date will be inserted once the manuscript is accepted.

Dedicated to Professor Joaquín Plumet on occasion of his retirement

Keywords: lithium chloride, detritylation, trityl ethers, protected alcohols, protected diols

Abstract: The reaction of primary, secondary, phenyl, allyl and benzyl trityl ethers with lithium chloride in methanol at reflux led to deprotection of the trityl group affording the corresponding alcohol in good to excellent yields under mild reaction conditions.

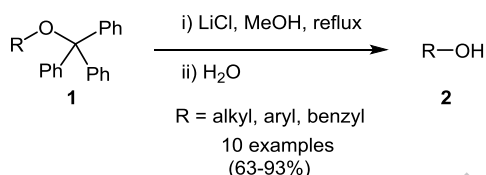
The trityl (triphenylmethyl) group is often employed for the selective protection of primary alcohols and amines in carbohydrate,¹ peptide² and nucleotide³ chemistry, due to its high steric demand. On the other hand, the cleavage of trityl ethers is involved in the manufacture of a number of pharmaceuticals, drugs and other fine chemicals.⁴

In the search for useful methods for the selective deprotection of trityl protected alcohols or phenols,⁵ various conditions for reductive cleavage of the trityl-oxygen bond have been reported including triethylsilane,⁶ or low-valent titanium reagents.⁷ Catalytic cerium(IV) ammonium nitrate adsorbed onto silica gel can efficiently oxidatively cleave the trityl-oxygen bond in nucleosides and nucleotides.⁸ This protecting group can be also easily removed using Brønsted⁹ and Lewis acids¹⁰ or bases,¹¹ electrolytically,¹² and by catalytic hydrogenation¹³ or reduction with sodium in liquid ammonia;¹⁴ however most of these procedures are incompatible with reducible functionalities, including multiple bonds.

In the last few years, our group has been interested in the deprotection of several functional groups using naphthalene-catalyzed lithiation,¹⁵ including trityl ethers,¹⁶ trityl amines,¹⁷ silylated alcohols, amines and thiols,¹⁸ Alloc- or Cbz- or Boc-protected alcohols, amines or thiols,¹⁹ esters, amides and thioesters,²⁰ and *N*-pivaloyltetrazoles.¹⁵ Other metals, such as indium²¹ or zinc²² under protic conditions (MeOH), have been used for the deprotection of *N*-tritylated tetrazoles.

In the present paper we describe the deprotection of trityl protected alcohols and diols with lithium chloride. This methodology represents a milder procedure than those already described and therefore may be more compatible with other functional groups present in a molecule.²³

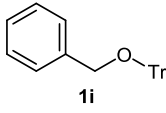
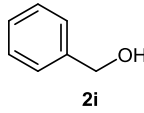
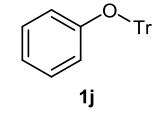
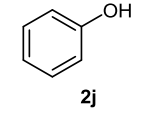
Treatment of several trityl ethers **1** with lithium chloride in methanol at reflux overnight gave, after hydrolysis with water, the expected alcohols **2** (Scheme 1 and Table 1).



Scheme 1. Deprotection of trityl ethers **1** using LiCl.

Table 1. LiCl-mediated deprotection of trityl ethers **1** in MeOH at reflux

Entry	Substrate	t (h)	Product	Yield (%) ^a
1		12		88
2		12		72
3		25		71
4		12		71
5		12		60
6		12		93
7		12		84
8		12		63

9		12		87
10		12		80

^a Isolated yield

The starting trityl ethers **1** were prepared from the corresponding commercially available alcohols **2** by reaction with trityl chloride in the presence of triethylamine and catalytic 4-dimethylaminopyridine. They were fully characterized by comparison of their spectroscopic data with authentic samples.¹⁶ The reaction was first examined using trityl ether **1a** with LiCl (1:1 molar ratio) in DMSO at reflux for 24 h,²⁴ however the reaction failed and the starting material was recovered. However, the same reaction conducted in MeOH at reflux for 12 h afforded the expected alcohol **2a** in 88% yield (Table 1, Entry 1). Other protected primary or secondary alcohols, such as **1b**, **1f** and **1g** gave the corresponding products **2b**, **2f** and **2g**, respectively (Entries 2, 6, and 7). Mono and diprotected primary and secondary diols **1c-e** were fully deprotected under similar reaction conditions, with the monotritylated diol **1c** requiring a prolonged reaction time of 25 h (Entries 2-4). The allyl (**1h**) and benzyl (**1i**) ethers were deprotected without producing any deallylation or debenzylated products (Entries 8 and 9). Finally, aromatic trityl ether **1j** was deprotected liberating phenol (Entry 10).

Concerning a possible mechanism, we believe that a trityl cation is involved in the process and is captured by chloride to give trityl chloride which was isolated during the deprotection of **1a** in 65% yield.

In conclusion, we report a simple, mild and inexpensive method for the deprotection of trityl ethers derived from aliphatic primary and secondary alcohols, diols and phenol. This methodology can advantageously compete with other reported procedures, which are not so tolerant of other functional groups.²⁵

Acknowledgements

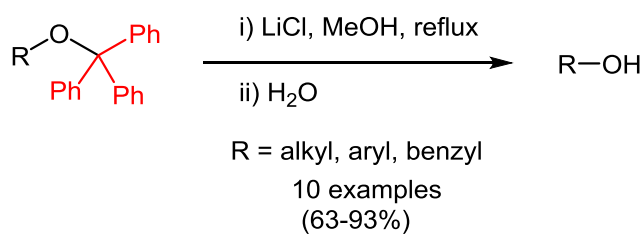
This work was financially supported by the Agence National pour le Développement de la Recherche en Santé (Algérie) and the Spanish Ministerio de Ciencia e Innovación (CTQ2011-24155, CTQ2011-24165), the Ministerio de Economía y Competitividad (CTQ2013-43446-P, CTQ2014-51912-REDC, CTQ2014-53695-P), FEDER, the Generalitat Valenciana (PROMETEO 2009/039,

PROMETEOII/2014/017), and the University of Alicante. We also thank the Spanish Ministerio de Asuntos Exteriores y de Cooperación (AP/039112/11).

References and notes

- Dekker, C. A.; Goodman, L. In *Chemistry and Biochemistry*; Pigman, W.; Horton, D., Eds.; Academic Press: New York, 1970; Vol. IIA, p. 22.
- Bodanszky, M. *Principles in Peptide Synthesis*, 2nd Ed.; Springer-Verlag: New York, 1993; p. 88.
- Köster, H.; Hoppe, N.; Kohli, V.; Kröpelin, M.; Kaut, H.; Kulikowski, K. *Nucleic Acids Symposium Series*; Oxford University Press: 1980; p. 39.
- Zhuan, F; Guo-Chuan, Z; Shi-Long, Z; Guang-Li, H; Ju-Lian, L; Ling, H; Di, B. *J. Mol. Catal. A: Chem.* **2007**, *274*, 16.
- Wuts, P. G. M.; Greene, T. W. *Green's Protective Groups in Organic Synthesis*, 4th Ed.; John Wiley & Sons: Hoboken, 2007.
- Imagawa, H.; Tsuchihashi, T.; Singh, R. K.; Yamamoto, H.; Sugihara, T.; Nishizawa, M. *Org. Lett.* **2003**, *5*, 153.
- Rele, S.; Nayak, S. K. *Synth. Commun.* **2002**, *32*, 3533.
- Hwu, J. R.; Jain, M. L.; Tsai, F.-Y.; Tsay, S.-C.; Balakumar, A.; Hakimelahi, G. H. *J. Org. Chem.* **2000**, *65*, 5077.
- (a) Pathak, A. K.; Pathak, V.; Seitz, L. E.; Tiwari, K. N.; Akhtar, M. S.; Reynolds, R. C. *Tetrahedron Lett.* **2001**, *42*, 7755; (b) Maltese, M. *J. Org. Chem.* **2001**, *66*, 7615.
- (a) Koster, H.; Sinha, N. D. *Tetrahedron Lett.* **1982**, *23*, 2641; (b) Sabitha, G.; Reddy, E. V.; Swapna, R.; Mallikarjun, R. N.; Yadav, J. S. *Synlett* **2004**, 1276.
- (a) Das, V.; Srinivas, K. V. N. S. *Synth. Commun.* **2002**, *32*, 3027; (b) Oussaïd, A; Thach, L.N; Loupy, A. *Tetrahedron Lett.* **1997**, *38*, 2451.
- Marianovsky, V. G. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 281.
- Hanessian, S.; Rancourt, G. *Pure Appl. Chem.* **1977**, *49*, 1201.
- Hanessian, S.; Gooke, N. G.; Dehoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276.
- For reviews, see: (a) Yus, M. *Chem. Soc. Rev.* **1996**, *25*, 155; (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225; (c) Yus, M. *Synlett* **2001**, 1197; (d) Yus, M. *Pure Appl. Chem.* **2003**, *75*, 1453; (e) Yus, M. *The Chemistry of Organolithium Compounds*; Rappoport, Z.; Marek, I., Eds.; J. Wiley & Sons: Chichester: 2004; Ch. 11; (f) Candela, P.; Gómez, C.; Yus, M. *Russ. J. Org. Chem.* **2004**, *40*, 795; (g) Yus, M. *Contrib. Sci.* **2010**, *6*, 155; For an asymmetric version, see: (h) Martínez, R.; Pastor, I. M.; Yus, M. *Arkivoc* **2014**, (ii), 71; For mechanistic studies, see: (i) Yus, M.; Herrera, R. P.; Guijarro, A. *Chem. Eur. J.* **2002**, *8*, 2574; (j) de la Viuda, M.; Yus, M.; Guijarro, A. *J. Phys. Chem. B.* **2011**, *115*, 14610; (k) For the previous paper on this chemistry, see: (l) Behloul, C.; Chouti, A.; Guijarro, D.; Nájera, C.; Yus, M. *Synthesis* **2015**, *47*, 507.
- Yus, M.; Behloul, C.; Guijarro, D. *Synthesis* **2003**, 2179.
- Behloul, C.; Guijarro, D.; Yus, M. *Synthesis* **2004**, 1274.
- Behloul, C.; Guijarro, D.; Yus, M. *Tetrahedron* **2005**, *61*, 6908.
- (a) Behloul, C.; Guijarro, D.; Yus, M. *Tetrahedron* **2005**, *61*, 9319; (b) Almansa, R.; Behloul, C.; Guijarro, D.; Yus, M. *Arkivoc* **2007**, (vii), 41.
- Behloul, C.; Guijarro, D.; Yus, M. *Synthesis* **2006**, 309.
- Behloul, C.; Bouchelouche, K.; Guijarro, D.; Foubelo, F.; Nájera, C.; Yus, M. *Synlett* **2015**, *26*, 2399.
- Behloul, C.; Bouchelouche, K.; Hadji, Y.; Benseghir, S.; Guijarro, D.; Nájera, C.; Yus, M. *Synthesis* **2016**, *48*, 0000 (DOI: 10.1055/s-0035-1561609)

23. For the use of LiCl in delalkoxycarbonylations, see: (a) Krapcho, A. P. *Synthesis* **1982**, 893; (b) Krapcho, A. P. *Synthesis* **1982**, 893; for a general monograph, see: (c) *Handbook of Reagents for Organic Synthesis. Activation Agents and Protecting Groups*; Pearson, A. J.; Roush, W. R., Eds.; J. Wiley & Sons: Chichester, 2004; p. 248.
24. Bernard, A. M.; Ghiani, M. R.; Piras, P. P.; Rivoldini, A. *Synthesis* **1989**, 287.
25. *Typical Procedure*: LiCl (0.1 g, 2.36 mmol) was added to a solution of the substrate (1 mmol) in MeOH (3 mL) and the mixture heated at reflux overnight (Table 1). The cooled reaction mixture was quenched with water (2.5 mL) and extracted with EtOAc (3 × 5 mL) and the combined organic phases washed with brine (2.5 mL) and dried over Na₂SO₄. After solvent evaporation (15 Torr), the residue was purified by column chromatography.



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Highlights

Inexpensive deprotection of trityl ethers with LiCl was reported.

Mild reaction conditions included methanol at reflux.

Tritylated alcohols, diols and phenols were easily deprotected.

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