

Indium-Mediated Cleavage of the Trityl Group from Protected 1H-Tetrazoles

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Dedicated to the memory of Prof. Manfred Schlosser

Abstract: On treatment with indium metal in MeOH/THF, the trityl group undergo reductive removal from 1-*H* protected tetrazoles; (including aliphatic, aromatic and heteroaromatic substituents), affording the corresponding free tetrazoles in excellent yields, without any decomposition of the tetrazole ring or reduction of any other group.

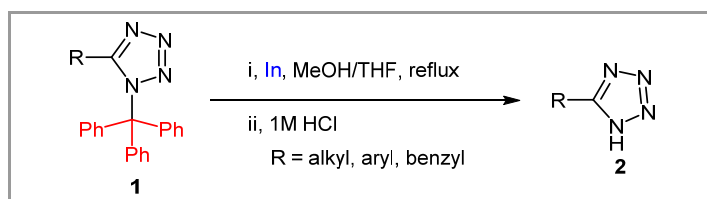
Keywords: tetrazole, indium, detritylation, cleavage.

Indium metal is an excellent useful reagent for a broad range of organic reductions.¹ Indium has a first electrode potential of 5.8 eV, which is similar to that of the alkali metals, such as sodium (5.1 eV) and lithium (5.4 eV), and much lower than that of zinc and magnesium.² Due to that, indium has demonstrated to be an excellent single-electron transfer reducing reagent, and has been used for the removal of many protecting groups. For instance, Moody *et al.* reported the general reductive removal of 4-nitrobenzyl oxygen-protecting group with this reagent. In this reaction, the nitro group is reduced first to give the corresponding aniline, which activates the benzylic carbon-oxygen bond towards the addition of an electron.³

In addition, reductive dehalogenations of α -halocarbonyl compounds with indium in the presence of a catalytic amount of sodium dodecyl sulfate in water were performed to afford the corresponding parent carbonyl compounds in excellent yields,⁴ and 2,2,2-trichloroethyl carboxylates smoothly underwent deprotection to carboxylic acids and reductive monodechlorination to 2,2-dichloroethyl esters.⁵ Furthermore, the selective cleavage of *tert*-butyldimethylsilyl ethers to give the corresponding alcohols by means of indium(III) chloride was also reported,⁶ this methodology being also applied to the chemoselective deprotection of different functional groups in polyfunctionalised substrates.

On the other hand, in the world drug, there are more than six types of sartans, which display different biological activities. Some of them, such as candesartan, irbesartan, losartan, olmesartan and valsartan bear a tetrazol unit in their structures and have a variety of therapeutic targets like angiotensin II receptor blocker, lowering blood pressure and playing a significant role in the progression of tissue damage in cardiovascular diseases.⁷

The protection and deprotection of the nitrogen atom of the tetrazole ring is a crucial operation during the synthesis of these Sartans. One group that can be used to protect the tetrazole nitrogen is the triphenylmethyl (trityl) group.⁸ Detritylation of tetrazole *N*-trityl protected Sartans derivatives to produce the free N-H bond was carried out under different conditions: hydrogenolysis in the presence of Pt/C (5%),⁹ or with aqueous NaOH in MeOH.⁸ Surprisingly, in the last case the removal took place without any side reaction and in excellent yields.



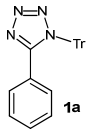
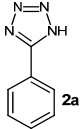
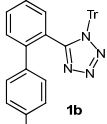
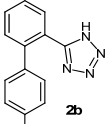
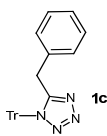
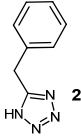
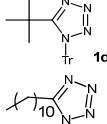
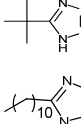
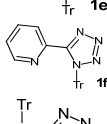
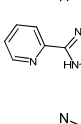
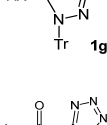
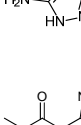
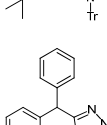
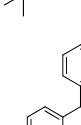
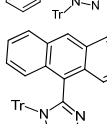
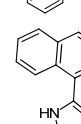
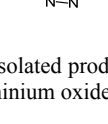
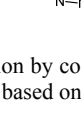
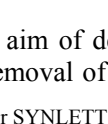
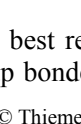
Equation 1

Our research group has already reported the removal of the trityl protecting unit in different functional groups using an arene catalysed lithiation. All these reactions were performed at -78 °C in excellent yields.¹⁰

In the course of developing deprotection methods of many protecting groups, we attempt to remove the trityl unit using different electron transfer sources. Such as lithium,

sodium, samarium and indium.^{10,11} The application of indium metal reductive removal of the trityl group from the nitrogen atom of several protected tetrazoles under mild reaction conditions is discussed below (Equation 1).

Table 1. Indium-Mediated Cleavage of the Trityl Group under Reflux from Protected 1*H*-Tetrazoles

Entry	Substrate	t (h)	Product	Yield (%) ^a
1		26		93
2		21		96
3		25.5		80
4		22		92
5		21		81
6		23		86
7		4		93
8		20		88
9		23		82
10		20		77

^a Yield of isolated product after purification by column chromatography (basic aluminium oxide, hexane/EtOAc), based on the starting material

With the aim of determining the best reaction conditions for the removal of the trityl group bonded to the nitrogen

in different tetrazoles, we took 5-phenyl-1-trityl-1*H*-tetrazole (**1a**) as the model compound. Unfortunately, no reaction occurred when tetrazole **1a** was treated with indium metal (1:1 molar ratio) in a mixture of MeOH and THF (2:1 volume ratio) at 0 °C for 24 h. However, total conversion was observed when this reaction mixture was heated at reflux temperature for 26 h, 5-phenyl-1*H*-tetrazole **2a** being isolated in 93% yield after column chromatography purification (Table 1, entry 1). In absence of indium the cleavage did not take place under the same reaction conditions. On the other hand, indium was partially consumed during the reaction, before the acidic hydrolysis. In order to broaden the scope of this indium-mediated detritylation, we applied the same reaction conditions to different 5-substituted tetrazoles. Detritylation of tetrazoles bearing aromatic (**1b** and **1j**) and benzylic (**1c** and **1i**) substituents at 5-position occurred also in high yields (Table 1, entries 2, 3, 9 and 10). Actually, compound **2b** is a direct precursor of sartans.⁹ Similar results were also obtained for aliphatic substituted tetrazoles. Thus, for compound **1d** with a sterically demanding *t*-butyl group at 5-position, detritylation produced 5-*t*-butyl-1*H*-tetrazole in 92% yield (Table 1, entry 4), meanwhile, in the case of tetrazole **1e** bearing a long linear aliphatic chain, the detritylated tetrazole **2e** was obtained in 81% yield (Table 1, entry 5).

These reaction conditions were also highly effective in the detritylation of functionalised tetrazoles. For instance, tritylated tetrazole with a heteroaromatic 2-pyridyl substituent at 5-position gave 5-(2-pyridyl)-1*H*-tetrazole (**2f**) in 86% yield (Table 1, entry 6). Even more interestingly, a double deprotection of ditritylated 5-amino substituted tetrazole **1g** was observed, leading to 5-amino-1*H*-tetrazole (**2g**) in 93% yield (Table 1, entry 7). Comparing with the lithium arene-catalyzed detritylation, this methodology seems to be superior since previous deprotonation with *n*-butyllithium of tetrazole **1g** was not necessary. The starting material **1g** has an N-H which is acidic enough to decompose the naphthalene radical-anion and dianion that act as lithiation agents. That is the reason why it has to be removed first when the lithium-arene combination is used in these reductive reactions. This methodology was also compatible with the presence of carbonyl groups. Detritylation of **1h** gave 1-(1*H*-tetrazol-5-yl)propan-2-one (**2h**) in 88% yield (Table 1, entry 8), taking place the removal of the trityl unit without affecting the carbonyl group under these reductive reaction conditions.

The progress of the reactions was monitored in all cases by TLC. Once the reaction went to completion, final hydrolysis with 1M HCl led to the corresponding tetrazoles **2**. After hydrolysis, triphenylmethane and the tetrazoles products

were extracted together with EtOAc and then easily separated by column chromatography.

The starting Tr-tetrazoles **1** were prepared by reaction of the corresponding tetrazole **2** with trityl chloride in the presence of triethylamine and a catalytic amount of 4-(dimethylamino)pyridine. Compounds **2a**, **2g** and **2i** were commercially available and **2b-2f**, **2h** and **2j** were prepared by us.¹² All of these compounds were characterised by comparison of their physical and spectroscopic data with authentic samples.

In summary, in this paper we have presented a very efficient method for the detritylation of protected tetrazoles using indium as an electron source. The methodology has proved to be useful for the removal of the trityl group from Tr-tetrazoles substituted on the carbon atom of the ring by aromatic, heteroaromatic, aliphatic or benzylic carbon chains, with in some cases sensitive functionalities like carbonyl and amino groups. The double detritylation of a Tr-tetrazole in the presence of a secondary Tr-amine was also observed. This method represents a good alternative to the commonly used detritylation procedures, which are sensitive to air moisture and acidic conditions.^{13,14}

Acknowledgements

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References

- (1) (a) Woo, H. G.; Choi, H. T. *Indium Properties, Technological Applications and Health Issues*; Nova Science Publishers: New York, **2013**. (b) Perchyonok V. T. *Radical Reactions in Aqueous Media*; Royal Society of Chemistry: Cambridge, **2010**.
- (2) For reviews see: (a) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633. (b) Yadav, J. S.; Antony, A.; George, J.; Subba, R., B. V. *Eur. J. Org. Chem.* **2010**, 591. (c) Shen, Z. L.; Wang, S. Y.; Chok, Y. K.; Xu, Y. H.; Loh, T. P. *Chem. Rev.* **2013**, *113*, 271.
- (3) Moody, C. J.; Pitts, M. R. *Synlett* **1999**, 1575.
- (4) Leeyoung, P.; Gyochang K.; Soon, B. K.; Kwan, S. K.; Youseung, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4462.

- (5) Tomoko, M.; Hisao, K.; Takehisa, K. *Tetrahedron Lett.* **2007**, *48*, 5027.
- (6) Yadav, J. S.; Subba, B. V.; Madan C. *New J. Chem.* **2000**, *24*, 853.
- (7) Daugherty, A.; Cassis, L. *Trends Cardiovasc. Med.* **2004**, *14*, 117.
- (8) Srimurugan, S.; Suresh, P.; Babu, B.; Hiriyanna, S. G.; Pati, H. N. *Chem. Pharm. Bull.* **2008**, *56*, 383.
- (9) García, G.; Rodríguez-Puyol, M.; Alajarín, R.; Serrano, I.; Sánchez-Alonso, P.; Griera, M.; Vaquero, J.; Rodríguez-Puyol, D.; Álvarez-Builla, J.; Díez-Marqués, M. *J. Med. Chem.* **2009**, *52*, 7220.
- (10) (a) Yus, M.; Behloul, C.; Guijarro, D. *Synthesis* **2003**, 2179. (b) Behloul, C.; Guijarro, D.; Yus, M. *Synthesis* **2004**, 1274. (c) Behloul, C.; Guijarro, D.; Yus, M. *Tetrahedron* **2005**, *61*, 6908. (d) Behloul, C.; Guijarro, D.; Yus, M. *Tetrahedron* **2005**, *61*, 9319. (e) Behloul, C.; Guijarro, D.; Yus, M. *Synthesis* **2006**, 309. (f) Behloul, C.; Guijarro, D.; Yus, M. *ARKIVOC* **2007**, (vii), 41. (g) Behloul, C.; Bouchelouche, K.; Guijarro, D.; Najera, C.; Yus, M. *Synthesis* **2014**, 2065. (h) Behloul, C.; Chouti, A.; Guijarro, D.; Najera, C.; Yus, M. *Synthesis* **2015**, *47*, 507.
- (11) 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.; Ramón, D. J. *Latv. J. Chem.* **2002**, *79*. (e) Ramón, D. J.; Yus, M. *Rev. Cubana Quim.* **2002**, *14*, 76. (f) Yus, M. In *The Chemistry of Organolithium Compounds*; Rappoport, Z.; Mareck, I. Eds.; J. Wiley & Sons: Chichester, **2004**, Chapter 11. For a mechanistic study, see: (g) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2001**, *42*, 3455. (h) Yus, M.; Herrera, R. P.; Guijarro, A. *Chem. Eur. J.* **2002**, *8*, 2574. (i) Herrera, R. P.; Guijarro, A.; Yus, M. *Tetrahedron Lett.* **2003**, *44*, 1309.
- (12) With the aim of trying to broaden the substrate scope, we tried to prepare some other tetrazoles functionalized with either ester or amide groups but, unfortunately, all our attempts were unsuccessful.
- (13) In a **typical procedure**, a mixture of 5-phenyl-1-trityl-1H-tetrazole (**1a**, 0.230 g, 0.5 mmol) and indium powder (0.058 g, 0.5 mmol) in MeOH (6 mL) and THF (3 mL) was stirred at 78 °C for 26 h. Then the resulting mixture was cooled to room temperature, hydrolyzed with 1M HCl (2 mL), extracted with AcOEt (3 × 10 mL), dried over anhydrous MgSO₄, and evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield 5-phenyl-1H-tetrazole (**2a**, 0.134 g, 93%) as a white solid, mp 215-216 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 7.55-7.62 (m, 3H), 8.01-8.10 (m, 2H); ¹³C NMR (75 MHz, DMSO-d₆): δ 124.1 (2 × CH), 127.0 (C), 129.4 (CH), 131.3 (2 × CH), 155.3 (C).^{10h}
- (14) For all detailed procedures, see the attached Supporting Information.

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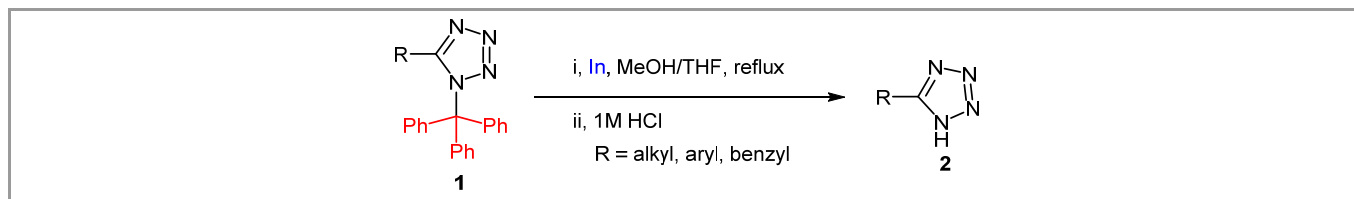
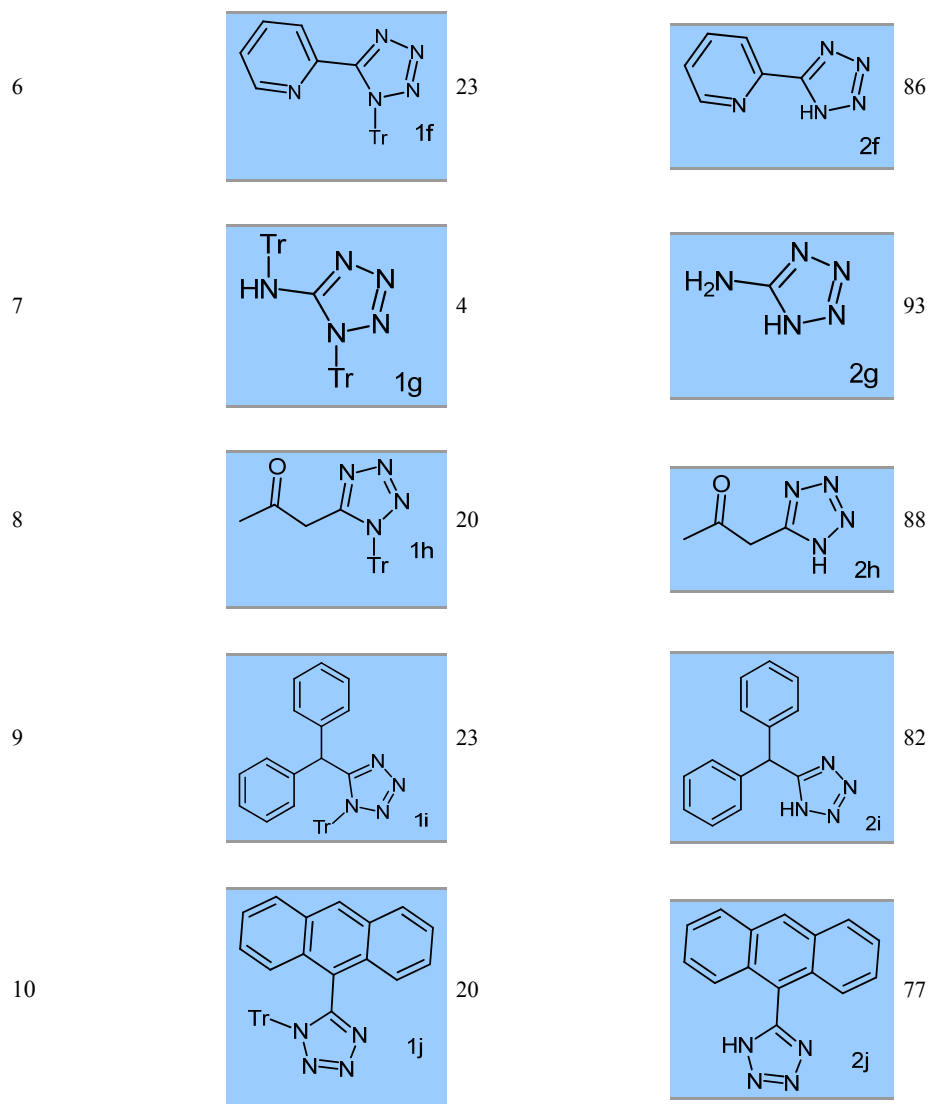


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^a Yield of isolated product after purification by column chromatography (basic aluminium oxide, hexane/EtOAc), based on the starting material