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

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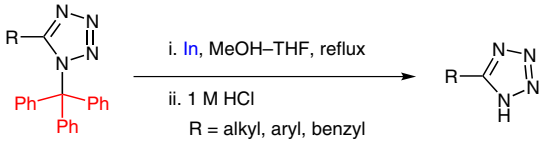
Dedicated to the memory of Prof. Manfred Schlosser



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Abstract On treatment with indium metal in MeOH–THF, trityl groups 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.

Key words tetrazole, indium, detritylation, cleavage

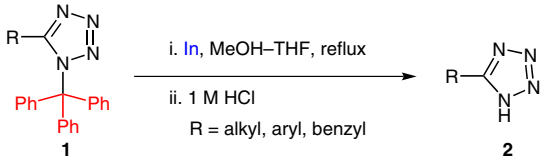
Indium metal is an excellent, useful reagent for a broad range of organic reductions.[1] Indium has a first electrode potential of 5.8 eV, which is similar to that of the alkali metals, such as sodium (5.1 eV) and lithium (5.4 eV), and much lower than that of zinc and magnesium.[2] Due to that, indium 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 benzilic 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 polyfunctionalized 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 sartan derivatives to produce the free N–H bonds 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.

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



Equation 1

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

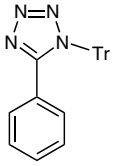
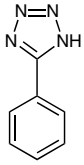
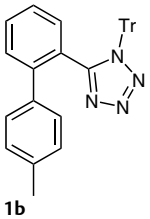
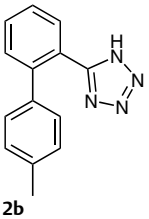
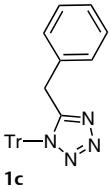
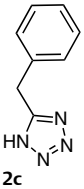
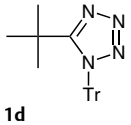
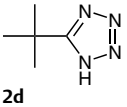
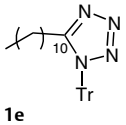
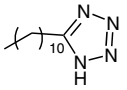
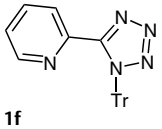
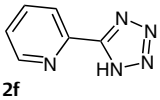
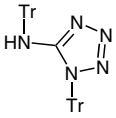
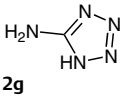
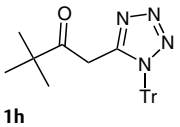
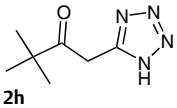
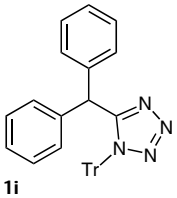
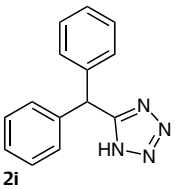
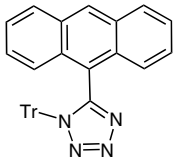
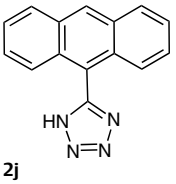
Entry	Substrate	Time (h)	Product	Yield (%)[a]
1	 **1a**	26	 **2a**	93
2	 **1b**	21	 **2b**	96
3	 **1c**	25.5	 **2c**	80
4	 **1d**	22	 **2d**	92
5	 **1e**	21	 **2e**	81
6	 **1f**	23	 **2f**	86
7	 **1g**	4	 **2g**	93

Table 1 (continued)

Entry	Substrate	Time (h)	Product	Yield (%)[a]
8	 **1h**	20	 **2h**	88
9	 **1i**	23	 **2i**	82
10	 **1j**	20	 **2j**	77

[a] Yield of isolated product after purification by column chromatography (basic aluminum 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 hours. However, full conversion was observed when this reaction mixture was heated at reflux temperature for 26 hours, 5-phenyl-1*H*-tetrazole (**2a**) being isolated in 93% yield after purification by column chromatography (Table 1, entry 1). In the 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 the 5-position occurred also in high yields (Table 1, entries 2, 3, 9, and 10). Actually, compound **2b** is a direct precursor of the sartans.[9] Similar results were also obtained for aliphatic substituted tetrazoles. Thus, for compound **1d** with a sterically demanding *tert*-butyl group at the 5-position, detritylation produced 5-*tert*-butyl-1*H*-tetrazole in 92% yield (Table 1, entry 4). 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 functionalized tetrazoles. For instance, tritylated tetrazole with a heteroaromatic 2-pyridyl substituent at the 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, because previous deprotonation with *n*-butyllithium of tetrazole **1g** was not necessary. The starting material **1g** has an N–H bond which is acidic enough to decompose the naphthalene radical anion and dianion that act as lithiation agents. This is the reason why it has to be removed first, beforethe 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), the removal of the trityl unit taking place without affecting the carbonyl group under these reductive reaction conditions.

The progress of the reactions was monitored in all cases by thin-layer chromatography. Once the reaction went to completion, final hydrolysis with 1 M HCl led to the corresponding tetrazoles **2**. After hydrolysis, the triphenylmethane and the tetrazole products were extracted 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**,**g**,**i** are commercially available and **2b–f**,**h**,**j** were prepared by us.[12] All of these compounds were characterized 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 proven 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]

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379933.

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(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) **Typical Procedure**
In a typical procedure, a mixture of 5-phenyl-1-trityl-1*H*-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 r.t., hydrolyzed with 1 M HCl (2 mL), extracted with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$, and evaporated (20 mbar). The resulting

residue was purified by column chromatography (silica gel, hexane–EtOAc) to yield 5-phenyl-1*H*-tetrazole (**2a**, 0,134 g, 93%) as a white solid, mp 215–216 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7. 55–7.62 (m, 3 H), 8.01–8.10 (m, 2 H). ^{13}C NMR (75 MHz, DMSO-d_6): 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.