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A Facile Radical Induced Selective Removal of N-Propargyl Protecting Groups Using Low Valent Titanium Reagents

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Abstract: Low valent titanium mediated cleavage of N-propargyl bonds offers a facile, mild, and high yielding method for the deprotection of amines under neutral conditions. The methodology could be used for the chemoselective removal of propargyl groups from amines in preference to the allyl/benzyl counterparts and can be performed chemoselectively in the presence of methoxy, methylenedioxy, and chloro functionalities.

Keywords: N-Propargyl amines; Selective deprotection; Low valent titanium

Designing efficient protecting groups is often a decisive factor in many demanding synthetic projects [1]. In particular, amino protection is of paramount importance for the synthesis of many compounds, including peptides [2,3]. A wide range of reagents has been developed for this purpose. Towards this end, a conceptually new approach to radical induced selective deprotection of N-benzyl/allyl amines was reported by us [4-6]. However, the yields were moderate and the reaction required prolonged reflux (~22 h). The yield of the reaction could be substantially improved by using the activated low valent titanium (LVT) reagent recently described by us [7], but methoxy and chloro groups were cleaved under the reaction conditions. This incompatibility of functionalities prompted us to develop better protecting groups which could be liberated under milder conditions with good yields. The presence of two orthogonal π-bonds in the propargyl group makes it attractive as an efficient protective group for alcohols/phenols [8,9]. Based on these considerations, we anticipated that N-propargyl amines should undergo facile cleavage. Although the involvement of organometallic η^3-allylic complexes in a number of synthetic endeavors is well documented [10,11], the potential of propargylic organometallic derivatives has been less explored. In addition to our work [9], few methods for the cleavage of propargyl ethers have been reported [12,13,14]. Herein we wish

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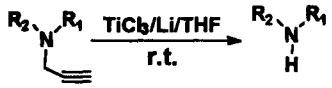
to report a protocol for the facile removal of N-propargyl group from amines (Scheme 1) using LVT reagents.



R_1, R_2 = Alkyl, Aryl, H

Scheme 1

N-Propargyl diphenyl amine (N-PDA) was used as a model substrate. When subjected to the LVT ($TiCl_3$-Li-THF) reagent, N-PDA underwent smooth deprotection to give diphenyl amine (75%) within only 35 min at 25 °C (Table, entry 1). In contrast, the cleavage of N-allyl diphenyl amine required refluxing of the reaction mixture for 20 h to yield diphenyl amine in 65% [4].

A typical experimental procedure is as follows: A mixture of $TiCl_3$ (1.54 g, 10 mmol) and lithium (231 mg, 33 mmol) was refluxed (3 h, argon) in dry THF (70 mL). To the LVT reagent thus prepared [15,16], N-PDA (518 mg, 2.5 mmol) in THF (5 mL) was added and stirred. After completion (TLC), the reaction mixture was diluted with hexane-ethyl acetate (70:30) mixture and passed through a celite bed. The filtrate was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by preparative TLC (SiO_2) to yield diphenyl amine (317 mg, 75%).

The generality and selectivity of the protocol have been shown by using a variety of primary (entries 2 and 3) and secondary amines (entries 4-12).

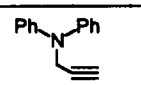
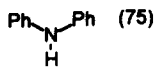
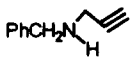
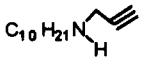
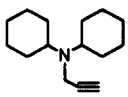
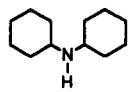
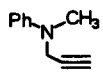
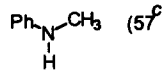
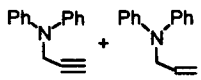
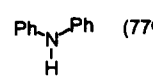
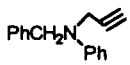
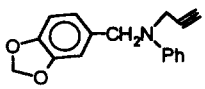
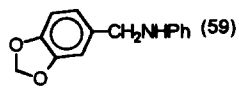
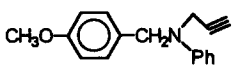
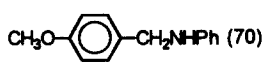
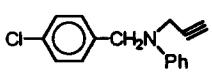
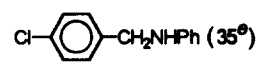
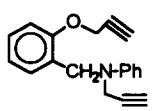
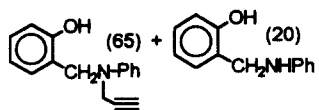
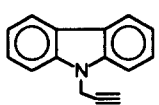
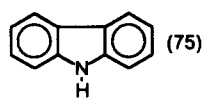
Both N-alkyl and N-aryl bonds do not undergo cleavage under the present reaction conditions (entries 1, 3-5, and 8-10). The cleavage of N-propargyl bonds could be carried out selectively in the presence of N-allyl (entry 6) and N-benzyl functionalities (entries 2 and 7).

Chemoselective removal of the N-propargyl group in functionalised amines adds to the novelty of the process. Otherwise reducible groups such as methylenedioxy, arylmethoxy, and arylchloro remain intact during the removal of N-propargyl groups (entries 8-10). It is important to note that both methoxy and chloro groups underwent complete cleavage without any amine deprotection under the conditions of N-allyl/benzyl bond cleavage with LVT [5].

The O-propargyl bond was cleaved in preference to the N-propargyl moiety, thereby offering selective deprotection in amino phenols. Thus, selective O-depropargylation of N-(2-propargyloxybenzyl)-N-propargyl aniline yielded N-(2-hydroxybenzyl)-N-propargyl aniline (65%) along with 20% of N-(2-hydroxybenzyl) aniline, generated as a result of secondary N-propargyl bond cleavage (entry 11).

The applicability of the protocol in the case of heterocycles such as carbazole has also been investigated wherein deprotection of N-propargyl carbazole yielded carbazole (75%) at 25 °C (entry 12).

Table: Low Valent Titanium ($TiCl_3$-Li-THF) Mediated Cleavage of N-Propargyl Bonds[a]

Entry	Substrate	Time	Product/s (%)[b]
1		35 min	 (75)
2		30 min	$PhCH_2NH_2$ (57[c])
3		1.0 h	$C_{10}H_{21}NH_2$ (55[c])
4		3.5 h	 (57[c])
5		3.0 h	 (57[c])
6		2.0 h	 (77[d])
7		45 min	$PhCH_2NHPh$ (65)
8		1.5 h	 (59)
9		10.0 h	 (70)
10		30.0 h	 (35[e])
11		2.5 h	 (65) + (20)
12		10.0 h	 (75)

[a] All the reactions were performed at 25 °C.
[b] Yields refer to pure, isolated products, unless otherwise stated. The products were characterised by ^1H NMR, IR, mass spectrum, physical data and also by comparing with authentic samples.
[c] GLC yields.
[d] unreacted *N*-allyl diphenyl amine was recovered quantitatively.
[e] 57 % of the unreacted starting compound was recovered.

In conclusion, an LVT mediated facile, mild, and high yielding method for the deprotection of propargyl amines in the presence of N-allyl, N-benzyl, chloro, methoxy, and methylenedioxy functionalities has been developed. Incidently this is the first report of the cleavage of the N-propargyl group by LVT under neutral conditions, with excellent chemoselectivity. The present investigation, along with our earlier reports, holds promise in protective group chemistry and will encourage the use of the propargyl group for blocking of the amino functionality in selective organic transformations.

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