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A mild and selective method for *N*-dealkylation of tertiary amines

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Abstract—Alkyl groups can be cleaved efficiently and selectively from tertiary alkyl amines using propargyl chloroformate. The propargyloxycarbonyl (Poc) protected secondary amines thus obtained can be deblocked under neutral and mild conditions using benzyltriethylammonium tetrathiomolybdate. The generality and compatibility of the method have been studied with a wide range of functionalities.

N-Dealkylations, and more specifically debenzylations are important in organic synthesis and structural determination. Many carbon chloridates (chloroformates) have been used as reagents for acylative dealkylation of tertiary amines but most are expensive, and not very selective. Very often basic or acidic conditions are used for deblocking the carbamate formed.[1–4] Recently, cyanuric chlorides have been used as reagents for dealkylation of aliphatic tertiary amines, but secondary amines are formed as *s*-triazine derivatives.[5] Simple acid chlorides have also been used as dealkylating agents for tertiary amines to furnish tertiary amides.[6] For the selective dealkylation of the hydroxyethyl group derived from phenylglycinol in the presence of other functionalities, a two-step procedure has been reported using thionyl chloride followed by treatment with potassium cyanide.[7] Labile iron(II,III) complexes along with dioxygen are known to dealkylate tertiary amines to give secondary amines.[8] Though the dealkylation follows the specific reactivity towards chloroformates in accordance with the alkyl group, the corresponding carbamates might pose difficulties during their deprotection to give secondary amines.[3]

The search for a safe, effective, economical and mild methodology for *N*-dealkylation is still a challenging task in organic synthesis.

In this letter we introduce the use of propargyl chloroformate (Poc-Cl) **1** for dealkylation and the use of benzyltriethylammonium tetrathiomolybdate **2**[9] for effective deblocking of the Poc group under mild conditions.

Propargyl chloroformate was prepared from commercially available propargyl alcohol and diphosgene.[10] It has been shown in our laboratory that the Poc group is orthogonal to a variety of protecting groups as the cleavage is performed under neutral and mild conditions.[9,11] To substantiate the reactivity of propargyl chloroformate **1** towards tertiary amines and to illustrate the utility of **2** in selective deblocking, a series of model reactions have been carried out (Scheme 1).

Propargyl chloroformate **1** (1.2 equiv) was added dropwise to *N*-alkyl pyrrolidines/*N*-alkyl piperidines in chloroform at −23 °C under an argon atmosphere to generate intermediate salts (**X**).

The intermediates (**X**), *N*-alkyl *N*-propargyloxycarbonyl pyrrolidinium chlorides/*N*-alkyl *N*-propargyloxycarbonyl piperidinium chlorides when refluxed for an hour decomposed to furnish the *N*-Poc pyrrolidines/*N*-Poc piperidines, respectively, in moderate to excellent yields (Scheme 1 and Table 1; entries 1 and 2).

Encouraged by the initial success, the general applicability of this methodology was studied using a series of tertiary amines as substrates (Table 1; entries 3–5).

In all the cases studied (Table 1; entries 1–5) the formation of the *N*-Poc derivatives was very rapid and the products were obtained in good to excellent yields.

Keywords: *N*-Dealkylation; Propargyl chloroformate; Tetrathiomolybdate.
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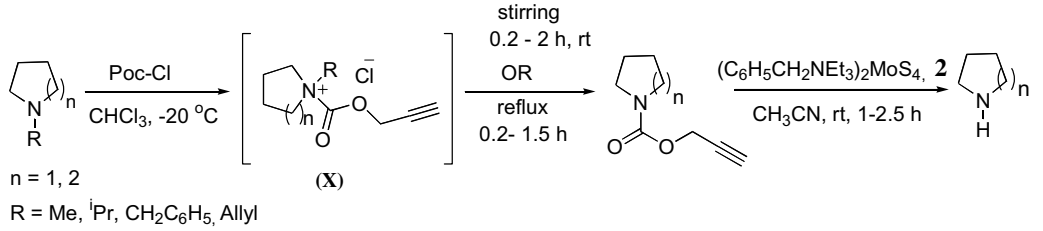
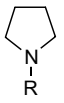
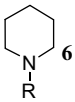
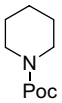
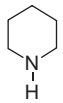
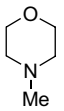
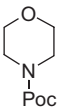
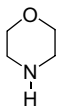
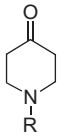
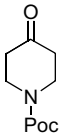
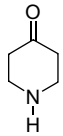
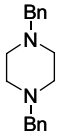
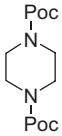
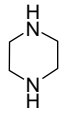
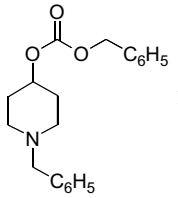
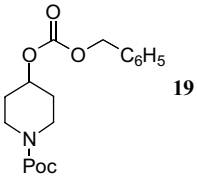
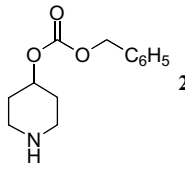
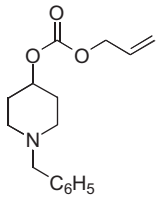
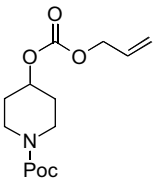
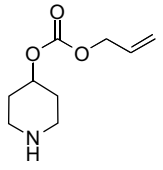
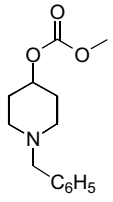
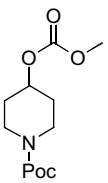
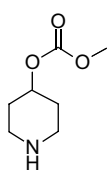


Scheme 1. General reaction pathway.

Table 1. *N*-Dealkylation of tertiary amines with Poc-Cl

Entry	Tertiary amine		Time (h) rt/reflux	*N*-Poc derivatives	Yield (%)	Time (h)	Secondary amine	Yield (%)
1	 **3**	R = (a) Me (b) ^{i}Pr (c) Allyl (d) Bn	2/1.5 2/1 1.5/0.5 0.2	 **4**	(a) 52 (b) 61 (c) 72 (d) 90	2.5	 **5**	97
2	 **6**	R = (a) Me (b) ^{i}Pr (c) Bn	2/1.5 1.5/1 0.2	 **7**	(a) 51 (b) 63 (c) 87	2	 **8**	96
3	 **9**		2/1	 **10**	59	2.5	 **11**	95
4	 **12**	R = (a) ^{i}Pr (b) Bn	1.75/0.75 0.2	 **13**	(a) 65 (b) 92	2	 **14**	97
5	 **15**		0.2	 **16**	86	2	 **17**	96
6	 **18**		0.2	 **19**	88	1.5	 **20**	97
7	 **21**		0.2	 **22**	86	2	 **23**	98
8	 **24**		0.2	 **25**	89	1.5	 **26**	96

Deblocking of the Poc group was achieved by treatment with tetrathiomolybdate **2** (CH_3CN, rt, 1–2.5 h) under neutral and nonhydrolytic conditions in almost quantitative yields.

Under dealkylation and Poc deprotection conditions, other functionalities present in the substrate were unaffected and we did not observe formation of any side products due to ring scission. Generally, the debenzylation was more rapid than other dealkylations. From the table it is clear that the selectivities for *N*-dealkylation followed the order benzyl > allyl > isopropyl > methyl. This can be explained on the basis of the electrophilicity of the carbon at the alkyl chain.

A typical dealkylation takes 0.2–2 h with stirring at room temperature or 0.2–1.5 h at reflux. As the propargyloxycarbonyl (Poc) group is stable to acidic and basic conditions and its deblocking is achieved by treatment with tetrathiomolybdate **2** under neutral conditions, the reactivity of the Poc group has been explored further as an orthogonal protecting group in organic synthesis. We synthesised three carbonates (Table 1: **18**, **21** and **24**) starting from *N*-benzyl 4-hydroxy piperidine. Treatment of compounds **18**, **21** and **24** with propargyl chloroformate **1** ($CHCl_3$, −23 °C) resulted in the formation of the corresponding *N*-Poc piperidine carbonates **19**, **22** and **25**, respectively, in excellent yields. Further treatment of **19**, **22** and **25** with tetrathiomolybdate **2**, (CH_3CN, rt, 2–2.5 h) resulted in the formation of the corresponding secondary amines **20**, **23** and **26**, respectively, in excellent yields. The carbonate protecting groups (Cbz, Alloc, Moc) were unaffected under the reaction conditions (Table 1).

In conclusion, we have developed a new, efficient and mild methodology for dealkylation of tertiary amines. This method provides an excellent protocol for *N*-dealkylation in general, and *N*-debenzylation in particular without using any strong base or acid. The propargyloxycarbonyl group was deblocked under neutral, mild and nonhydrolytic conditions. Orthogonality of the Poc group can be exploited for a wide range of functionalities.

A typical procedure for N-dealkylation: To the tertiary amine (4 mmol) in dry chloroform (5 mL) cooled to −23 °C, propargyl chloroformate **1** (5 mmol, 0.5 mL) was added dropwise under inert atmosphere (N_2). The intermediate Poc-amine salt (**X**) was either allowed to warm to room temperature with stirring (2–2.5 h) or the reaction mixture was refluxed for 0.2–1.5 h. The dealkylation was monitored by TLC. The reaction mixture was diluted with diethyl ether (30 mL) and was washed with water and brine solution. The organic layer was dried over anhydrous sodium sulfate. The *N*-Poc protected products were purified by column chromatography on silica gel.

Deprotection of the propargyloxycarbonyl (Poc) group: *A general procedure.* To a solution of the propargyl urethane (carbamate) (4 mmol) in acetonitrile (5 mL), benzyltriethylammonium tetrathiomolybdate **2** (1.2 equiv, 4.8 mmol) was added. The Poc group was deblocked completely within 2–2.5 h. The deprotection was monitored by TLC. After the reaction, the solvent was removed and the residue was taken up in CH_2Cl_2 (3 mL) and diethyl ether (10 mL) and the solution was filtered through a pad of Celite. The filtrate was concentrated and the product was purified by column chromatography on silica gel to give the secondary amine in almost quantitative yield.

Acknowledgements

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References and notes

1. Brewster, J. H.; Eliel, E. L. In *Organic Reactions*; Adams, R., Ed.; John Wiley and Sons: New York, 1953; Vol. VII, p 142.
2. Olofoson, R. A.; Schur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567.
3. Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1, and references cited therein.
4. Campbell, A. L.; Pilipauskas, D. R.; Khanna, I. K.; Rhodes, R. A. *Tetrahedron Lett.* **1987**, *28*, 2331.
5. Reddy, N. D.; Elias, A. J.; Vij, A. *J. Chem. Res. (S)* **1998**, 504.
6. Miller, M. W.; Vice, S. F.; McCombie, S. W. *Tetrahedron Lett.* **1998**, *39*, 3429; Dave, P. R.; Kumar, K. A.; Duddu, R.; Axenrod, T.; Dai, R.; Das, K. K.; Guan, X. P.; Trivedi, N. J.; Gilardi, R. D. *J. Org. Chem.* **2000**, *65*, 1207.
7. Agami, C.; Couty, F.; Evano, G. *Tetrahedron Lett.* **1999**, *40*, 3709.
8. Narog, D.; Lechowicz, U.; Pietryga, T.; Sobkowiak, A. *J. Mol. Catal. A* **2004**, *212*, 25.
9. Prabhu, K. R.; Devan, N.; Chandrasekaran, S. *Synlett* **2002**, 1762.
10. To a stirred solution of diphosgene (1.2 mL, 10 mmol) in dry diethyl ether (30 mL), activated charcoal (0.05 g) was added and the suspension was stirred overnight at room temperature (25 °C). The solution was cooled to 0 °C and propargyl alcohol (0.9 mL, 15 mmol) in dry diethyl ether (10 mL) was added dropwise. The resultant solution was stirred for 12 h and filtered. The ethereal layer was distilled under reduced pressure and the liquid obtained was used without further purification.
11. (a) Sinha, S.; Ilankumaran, P.; Chandrasekaran, S. *Tetrahedron Lett.* **1999**, *40*, 771; (b) Sridhar, P. R.; Chandrasekaran, S. *Org. Lett.* **2002**, *4*, 4731.