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A Hierarchy of Aryloxide Deprotection by Boron Tribromide

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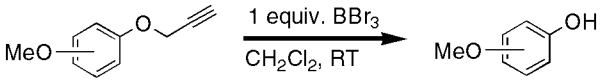
ABSTRACT



Aryl propargyl ethers and esters are cleaved selectively in the presence of aryl methyl ethers and esters by boron tribromide in dichloromethane. Under the same conditions, allyl ethers undergo very rapid Claisen rearrangement, and benzyl ethers are also cleaved more rapidly than propargyl. A mechanism involving intramolecular delivery of bromide to the propargyl terminus is proposed.

Cleavage of aryl ethers and esters by Lewis acids constitutes a common strategy for the unmasking of the ArOH and $ArCO_2H$ functional groups.[1] The methoxy unit, being stable to a vast array of reaction conditions, is particularly well utilized, although its deprotection with strong Lewis acids is not compatible with some functional groups. In contrast, the propargyloxy unit is rarely used in total synthesis, probably because of the lack of a convenient and selective deprotective protocol. The known methods include (1) palladium-catalyzed reactions, which usually proceed at elevated temperature in moderate to high yields;[2] (2) the use of low-valent titanium species, incompatible with subtrates presenting easily reduced functional groups such as nitro or carbonyl;[3] (3) nickel-catalyzed electroreductions;[4] (4) cleavage using a tetrathiomolybdate reagent, which has to be prepared in a first step;[5] and (5) a two-step protocol involving the isomerization of prop-2-ynyl ethers to the corresponding allenyl ethers, followed by cleavage under neutral and acidic conditions.[6] We report here an easy and efficient method for the selective deprotection of aryl propargyl ethers or esters. Most significantly, the protocol allows for selectivity among aryl benzyl, propargyl, and methyl protecting groups.

Table 1 summarizes the results. In independent reactions, propargyl 1-naphthyl ether was cleaved to 1-naphthol within 5 min at room temperature, whereas the methyl ether required 30 min (entries 1 and 2). When both functional groups were present on the same molecule, the propargyl ether was cleaved selectively by 1 equiv of BBr_3 at room temperature or −20 °C (entries 3 and 4). Depropargylation also occurred smoothly in the presence of bromide and nitro substituents (entries 5 and 6), but more time was required for the electron-deficient substrate. Similarly, propargyloxy cleavage was faster in the presence of *p*-methoxy substitution compared to *m*-methoxy or -carbomethoxy (entry 3 vs 4 and 7). The acid-sensitive tetrahydropyranyl group was not tolerated (entry 8). Allylic ethers underwent rapid BBr_3-mediated Claisen rearrangement,[7] leaving methyl and propargyl ethers untouched (entries 9 and 10). Similarly, a benzyl ether reacted more rapidly than propargyl (entry 11).[8]

Propargyl esters were cleaved to the carboxylic acids in the presence of methyl ether and methyl ester groups (entries 12 and 13). Propargylic amides, however, were resistant to

(1) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999. (b) Schelhaas, M.; Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2056−2083.

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(4) Oliviero, S.; Duñach, E. *Tetrahedron Lett.* **1997**, *38*, 6193−6196.

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(6) Mereyala, H. B.; Gurrala, S. R.; Mohan, S. K. *Tetrahedron* **1999**, *55*, 11331−11342.

(7) (a) Cairns, N.; Harwood, L. M.; Astles, D. P.; Orr, A. *J. Chem. Soc., Chem. Commun.* **1986**, 182−183. (b) Cairns, N.; Harwood, L. M.; Astles, D. P.; Orr, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3095−3100.

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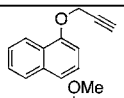
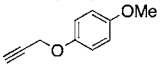
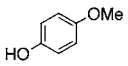
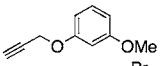
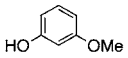
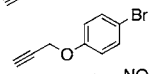
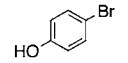
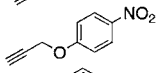
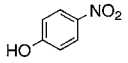
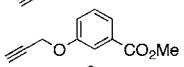
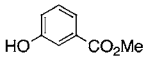
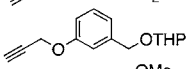
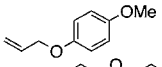
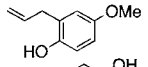
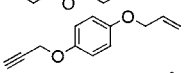
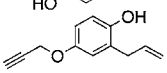
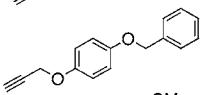
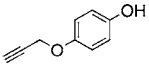
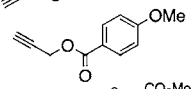
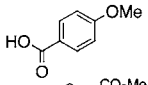
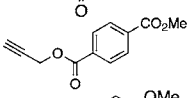
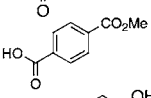
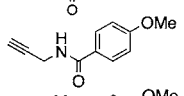
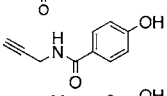
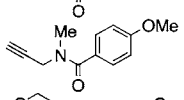
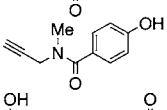
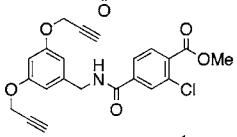
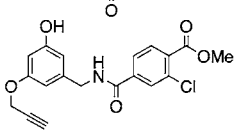
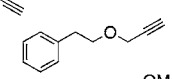
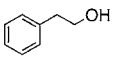
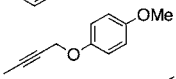
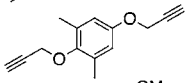
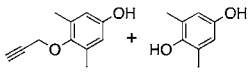
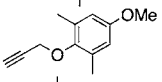
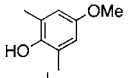
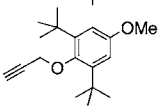
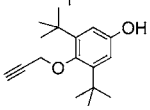
Table 1. Treatment of Ethers and Esters with BBr_3

entry	substrate	product	conditions[a]	yield (%)[b]
1			RT, 5 min	72
2			RT, 35 min	99
3			-20°C, 30 min RT, 3 min	89 99
4			RT, 15 min	90
5			RT, 3 min	78
6			RT, 35 min	75
7			RT, 10 min	99
8		—	RT, 5 h complex mixture	— —
9			-40°C, 3 min	98
10			RT, 3 min	84
11			RT, 3 min -20°C, 30 min	61 72
12			RT, 15 min	88
13			RT, 3 min	86
14			RT, 5 h (no reaction) 3 equiv. BBr_3, RT, 2 h	— 35
15			RT, 15 h (no reaction) 2 equiv. BBr_3, RT, 15 min	— 41
16			RT, 20 min 2 equiv. BBr_3	71
17			RT, 3 min	52
18		——	RT or –40°C, 3 min, complex mixture	—— ——
19			RT, 30 min	55 + 6
20			RT, 30 min	83
21			RT, 30 min	68

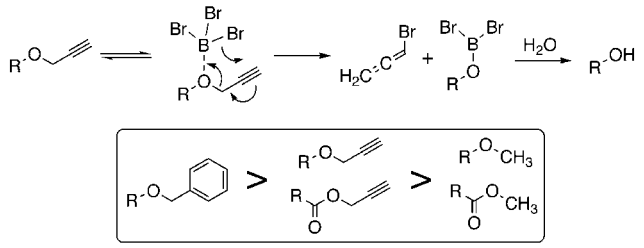
[a] Unless otherwise indicated, all reactions were performed with 1 equiv of BBr_3 (1 M in CH_2Cl_2) and monitored by TLC. Each was quenched by the addition of water; the products were extracted with CH_2Cl_2 or ethyl acetate and purified by flash chromatography. [b] Isolated yields of pure compounds after chromatography.

cleavage. Thus, both secondary and tertiary propargyl amides bearing methyl ether groups were recovered intact after extended treatment at room temperature with 1 equiv of BBr_3. The corresponding methyl-cleaved phenols were obtained in modest yield (but as the major component of mixtures) with only the use of excess reagent (entries 14 and 15). These observations suggest that amides bind to the boron center and passivate the Lewis acid. The more complex structure

shown in entry 16 gave further evidence of this hypothesis, being cleanly mono-depropargylated when treated with 2 equiv of BBr_3. This result also shows that propargyl ethers can be cleaved in preference to methyl esters. A preliminary test demonstrated that an aliphatic propargyl ether was also deprotected by BBr_3, albeit in lower yield (entry 17).

A suggested reaction mechanism for depropargylation is shown in Scheme 1. Activation of the propargyl group by

Scheme 1



coordination of the Lewis acid is proposed to lead to intra- or intermolecular delivery of bromide to give bromoallene by concomitant C−O bond cleavage.[9] Consistent with this hypothesis was the observed failure of a methylated (2-butynyl) derivative to undergo clean deprotection (entry 18), presumably because bromide addition is hindered. The importance of the precoordination step is supported by three observations. (a) The reaction does not occur in donor solvents (THF, diethyl ether). (b) It is slowed by electron-withdrawing substituents (see above). (c) Steric hindrance *ortho* to the propargyl ether moiety inhibits the process. Thus, substantial selectivity was observed for the 4-position of the 2,6-dimethyl-1,4-dipropargyl ether shown in entry 19: while a small amount of the doubly deprotected hydroquinone was isolated, none of the 4-propargyloxy-1-phenol was observed. 2,6-Dimethyl substitution was not sufficient to overcome the more reactive nature of the propargyl ether in entry 20, but *tert*-butyl groups served to direct BBr_3 to the unguarded 4-methoxy position in entry 21.

These studies establish the order of reactivity for deprotection by BBr_3 depicted in Scheme 1. Benzyl, propargyl, and methyl ethers can thereby be deprotected sequentially using stoichiometric amounts of boron tribromide, adding an additional level of selectivity to protecting group operations for the phenolic unit.

Acknowledgment. We thank the NIH (R01-ED000432-02) and the Skaggs Institute for Chemical Biology for support of this work.

Supporting Information Available: Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0489898

(9) Deuterium NMR monitoring of the reaction of $ArOCH_2CCD$ (Ar = 1-naphthyl) with BBr_3 showed the formation of a signal in the aliphatic region (4.2 ppm) and several vinylic resonances (6−8 ppm), but none corresponding to the intact propargyl unit (see the Supporting Information). This suggests that the alkyne unit participates in propargyl ether cleavage, as opposed to simple rupture or displacement of the $O-CH_2$ bond. The data also suggest the presence of benzofuran and related compounds as minor byproducts derived from propargylic Claisen rearrangement: (a) Box, V. G. S.; Meleties, P. C. *Heterocycles* **1998**, *48*, 2173−2183. (b) Cruz-Almanza, R.; Perez-Florez, F.; Brena, L.; Tapia, E.; Ojeda, R.; Fuentes, A. *J. Heterocycl. Chem.* **1995**, *32*, 219−222. (c) Otter, B. A.; Saluja, S. S.; Fox, J. J. *J. Org. Chem.* **1972**, *37*, 2858−2864.