ORGANIC LETTERS

2004
Vol. 6, No. 9
1513−1514

Mild Cleavage of Aryl Mesylates: Methanesulfonate as Potent Protecting Group for Phenols

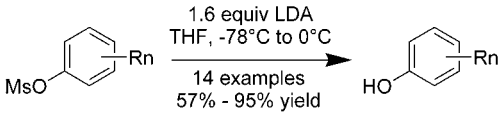
Tobias Ritter, Kyrill Stanek, Igor Larrosa, and Erick M. Carreira*

Laboratorium für Organische Chemie, ETH Hönggerberg, CH-8093 Zürich, Switzerland

carreira@org.chem.ethz.ch

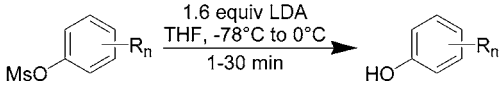
Received March 15, 2004

ABSTRACT



A mild protocol for the chemoselective deprotection of aryl methanesulfonates is described. The transformation can be conducted on highly functionalized substrates and renders the methanesulfonate a useful, previously underutilized protecting group for phenols.

Phenols are widely occurring subunits in natural products (e.g., aromatic steroids, canabinoids, macrolides, quinones, alkaloids, and iridoids), small-molecule pharmaceuticals (e.g., chloramphenicol, epinephrine, ethynylestradiol, and tamoxifen), and materials.[1−3] The most commonly employed protection regimens include methyl or benzyl ethers, with the former requiring harsh reagents or conditions for its removal. Methyl and arylsulfonates have also been employed as protecting groups;[4] however, these are generally avoided because of the vigorous conditions required for their removal that are often at odds with other functionality. In this paper, we expand the utility of methanesulfonate as a protecting group for phenols through the observation that they can be conveniently removed in a broad range of substrates upon exposure of methanesulfonate phenyl esters to lithium diisopropylamide (LDA) (eq 1). The mildness of the procedure is evident in the wide range of functionality that is compatible with the deprotection conditions.[5]



(1)

As phenol protecting groups, mesylates display ideal characteristics, namely, their facile and high-yielding introduction using inexpensive MsCl along with their high stability to a variety of conditions.[4]

As shown in Table 1, treatment of a broad range of aryl mesylates in THF with 1.6 equiv of LDA within a temperature range of −78 to +23 °C furnishes the corresponding alcohols in 57−96% yield.[6] Both electron-rich and electron-deficient phenols participate in the reaction as well as mesylated hydroxypyridines and -quinolines (entries 10 and 11). Of additional significance, the *N*-methanesulfonamide of 4-quinolone undergoes rapid deprotection at 0 °C in 72% yield (entry 12).

The mesylate of a phenol renders the aromatic ring considerably less electron-rich. We have exploited this

(1) (a) Steglich, W.; Fugmann, B.; Lang-Fugmann, S. *Naturstoffe*; Thieme, Stuttgart, 1997. (b) Lednicer, D. *Strategies for Organic Drug Synthesis and Design*; Wiley: New York, 1998.

(2) Pu, L. *Chem. Rev.* **2004**, *104*, 1687−1716.

(3) For recent examples, see the following. (a) Dynemicin: Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072−6094. (b) Ecteinascidin: Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552−6554. (c) Vancomycin: Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700−2704.

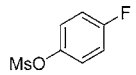
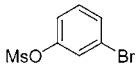
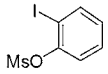
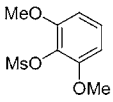
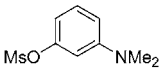
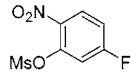
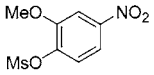
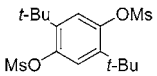
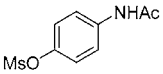
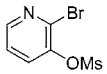
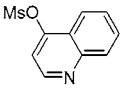
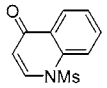
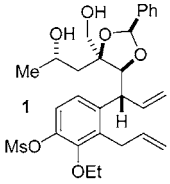
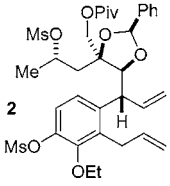
(4) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

(5) To the best of our knowledge only one example has been reported where a methanesulfonate is used as phenol protecting group and deprotected with LDA. However, no indication of the generality is provided. See ref 3c.

(6) Preliminary results in our laboratories suggest that the corresponding *p*-toluenesulfonates also participate in this desulfonation reaction.

10.1021/ol049514j CCC: $27.50
Published on Web 04/01/2004

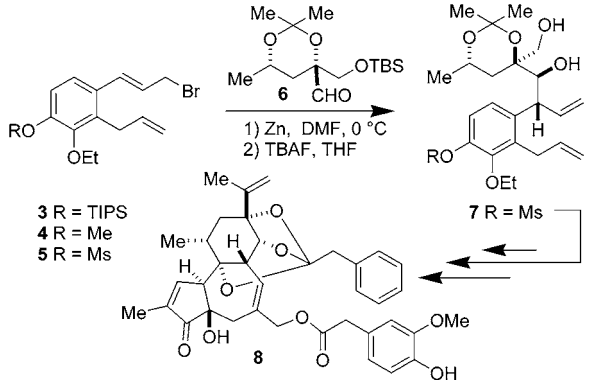
Table 1. Deprotection of Arylmethanesulfonates (See eq 1)[a]

entry	substrate	temp.	yield
1		0 °C	92%
2		0 °C	95%
3		0 °C	93%
4		0 °C	95%
5		0 °C	89%
6		0 °C	67%
7		0 °C	65%
8		0 °C	70%
9		23 °C	66%[b]
10		-78 °C	57%
11		0 °C	68%
12		0 °C	72%
13		0 °C	82%[c]
14		-78 °C	79%

[a] 1.6 equiv per phenolic mesylate group of LDA in THF was used. [b] 6 equiv of LDA was used. [c] 4 equiv of LDA was used.

noteworthy feature in the context of our interest in the total synthesis of resiniferatoxin **8** (Scheme 1). In our efforts to improve upon our previously reported route, we were interested in effecting the metalation of a cinnamyl bromide for subsequent coupling with aldehyde **6**.[7] However, the

Scheme 1



handling and purification of the electron-rich cinnamyl bromides (e.g., **3** and **4)** proved difficult due to decomposition. The instability of electron-rich benzyl and cinnamyl halides is to be expected as a consequence of their known propensity to undergo ionization. In this respect, the rate of solvolysis of *p*-methoxybenzyl chloride in aqueous acetone at 60 °C is 10^4 faster than that of benzyl chloride.[8] In contrast, the mesylated cinnamyl bromide **5** proved to be a stable, conveniently handled material that was amenable to metalation. Thus, treatment of **5** with Zn in DMF at 0 °C furnished an intermediate allylic zinc species which underwent addition to aldehyde **6** to give 41% yield of **7** after desilylation. After a sequence of steps, **7** was converted into compounds **1** and **2** (entries 13 and 14), which underwent deprotection in good yield. It is noteworthy that the phenolic mesylate in **2** smoothly undergoes chemoselective deprotection in good yield in the presence of an aliphatic mesylate ester.

In summary, we have demonstrated the efficient, chemoselective deprotection of aryl methanesulfonates with LDA to afford the corresponding phenols in up to 95% yield. The use of mesylates to stabilize cinnamyl and benzyl halides derived from electron-rich aromatics expands the opportunities to use more complex organometallic reagents in the synthesis of natural products. Due to low cost, efficient introduction, stability, and convenient removal under conditions that are tolerant of a wide range of functionality, this protecting group should find numerous future applications in academic and industrial processes.

Acknowledgment. We thank the Swiss National Science Foundation and the F. Hoffmann-La Roche Ltd as well as Merck & Co., Inc., and Eli Lilly and Company. T.R. thanks the Fonds der Chemischen Industrie for a Kekulé Fellowship.

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

OL049514J

(7) Jackson, S. R.; Johnson, M. G.; Mikami, M.; Shiokawa, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2694−2697.
(8) Simonetta, M.; Favini, G. *J. Chem. Soc.* **1954**, 1840−1844.