Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 667–669
Tetrahedron Letters

Guaiacol transprotection: replacement of the phenoxy isopropyl protecting function by acetyl

Craig M. Williams[a,*] and Lewis N. Mander[b]

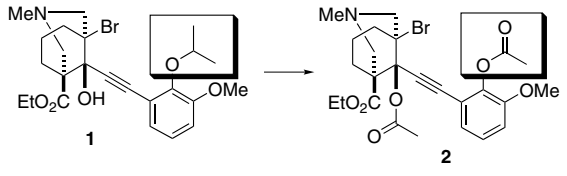
[a]*Department of Chemistry, School of Molecular and Microbial Sciences, University of Queensland, St. Lucia, Brisbane 4072, QLD, Australia*
[b]*Research School of Chemistry, Australian National University, Canberra 0200, ACT, Australia*

Received 15 October 2003; revised 7 November 2003; accepted 14 November 2003

Abstract—A one-step method for the conversion of isopropyl protected guaiacols to the corresponding acetates is reported. Treating 6-substituted isopropyl protected guaiacols with trimethylsilyl trifluoromethanesulfonate in a mixture of acetic anhydride and acetonitrile affords 6-substituted guaiacol acetates in yields ranging from 35% to 99%.

Methods to effect transprotection are valued tools in organic synthesis for the simple fact that they eliminate two synthetic sequences, deprotection and subsequent reprotection. Transprotection on alkyl nitrogen (e.g., interconversion of carbamates,[1] 2,4-dinitrobenzenesulfonamides to acetates, thioacetates, ureas and thioureas,[2] and *N*-benzoyl to *N*-dialkylaminomethylene[3]), alkyl oxygen (e.g., tetrahydropyran to acetate[4] or silyl ethers,[5] silyl ethers to acetates,[6,4c,d] *p*-methoxybenzyl ethers to methoxymethyl ethers,[7] benzyl ethers to acetates,[8] trityl ethers to esters,[9] methoxymethyl ethers to acetates[4f]) and alkyl sulfur (e.g., thiolacetate to disulfide,[10] enol ethers to thiolacetals[11]) have been reported. However, transprotection of non-benzylic aryl ethers, has, as far as we can determine, yet to be reported.

Recently, we described an expeditious synthesis of an advanced intermediate for C-20 diterpene alkaloid synthesis.[12] This work unexpectedly revealed that the isopropyl protecting group in guaiacol derivatives could be replaced in one step under especially mild conditions using trimethylsilyl trifluoromethanesulfonate (TMSOTf) and acetic anhydride in acetonitrile; **1**, for example, could be transformed into **2** in 89% yield (Scheme 1). We have now explored the scope and utility



Scheme 1.

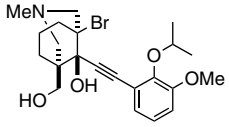
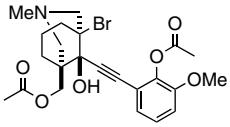
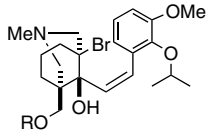
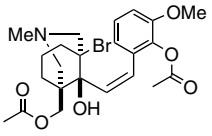
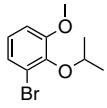
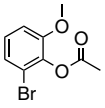
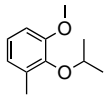
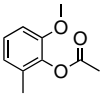
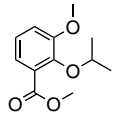
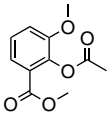
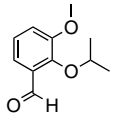
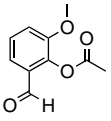
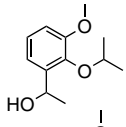
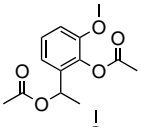
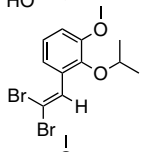
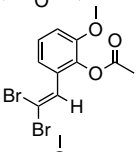
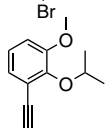
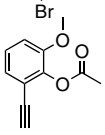
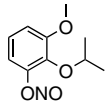
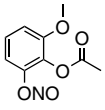
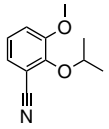
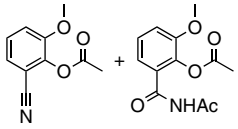
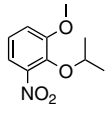
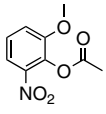
of this methodology, establishing that it provides a useful extension to the utility of the isopropyl protecting group for phenols.[13] The outcome is disclosed in this letter.

During the course of investigating numerous mono-, di- and tri-substituted phenols with single isopropyl protection, it was determined that for transprotection to proceed, the substitution pattern seen with the original discovery must be maintained, that is, the isopropyloxy group must be flanked by substituents on both *ortho*-positions (Table 1). If this substitution pattern is ignored, for example, as with isopropyl phenyl ether, then Friedel–Crafts acetylation is the dominant reaction pathway and in many cases no transprotection products are observed; 4-isopropoxyacetophenone is formed in 48% yield. Moreover, transprotection proceeds most efficiently when one substituent is both bulky and electron withdrawing; cf. entries 3, 5, 8, 11 and 12 (Table 1). Poor yields, not surprisingly, were obtained when sensitive functional groups such as benzyl alcohols (entry 7), benzaldehydes (entry 6), and terminal acetylenes

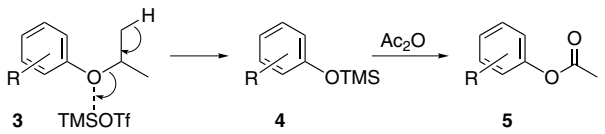
Keywords: Transprotection; Isopropyl phenyl ether; Trimethylsilyl trifluoromethanesulfonate.
* Corresponding author. Tel.: +61-7-3365-3530; fax: +61-7-3365-4299; e-mail: c.williams3@mailbox.uq.edu.au

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.11.065

Table 1. One-step conversion of 6-substituted isopropyl protected guaiacols to acetates[15]

Entry	Isopropyl ether	Acetate	Yield (%)
1			77
2			68 (R = H) 86 (R = Ac)
3			98
4			62
5			96
6			35
7			0
8			75
9			35
10			99
11			60 + 12
12			50 (100)

(entry 9) were present. We note that terminal acetylenes are also sensitive to other isopropyl ether deprotection protocols.[13] In the case of the benzonitrile (entry 11) the cyano group was partially converted into an imide (12%), whereas, for no apparent reason, the nitrobenzene (entry 12) could only be driven to 50% completion; however, based on recovered starting material, the yield was 100%. Use of the solvent acetonitrile seems to be essential for transprotection. Dichloromethane, for example, substantially decreased the rate of reaction, while the addition of nitrogen bases to neutralise trifluoromethanesulfonic acid reduced yields significantly. Lower yields were obtained with the alternative silylating reagents TESOTf and TBDMSOTf. Mecha-



Scheme 2.

nistically, the isopropyl group (e.g., **3**), under the strongly acidic conditions, possibly undergoes elimination to the silylated phenol **4**, which is then acetylated with acetic anhydride, activated by excess Lewis acid, affording the acetate **5** (Scheme 2).[14]

In conclusion, we have discovered that 6-substituted isopropyl protected guaiacols undergo transprotection in one step when treated with TMSOTf in acetonitrile. When the substituent at position 6 is bulky and electron withdrawing the reaction proceeds in very high yield. Unfortunately, mono- and di-substituted isopropyl phenyl ethers do not undergo transprotection but rather Friedel–Crafts acetylation occurs.

Acknowledgements

The authors thank the following people for their assistance: Dr. Tri Le for performing NMR analysis and Mr. Graham McFarlane for mass spectroscopy.

References and notes

1. (a) Roos, E. C.; Bernabé, P.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Boesten, W. H. J. *J. Org. Chem.* **1995**, *60*, 1733–1740; (b) Beugelmans, R.; Neuville, L.; Bois-Choussy, M.; Chastanet, J.; Zhu, J. *Tetrahedron Lett.* **1995**, *36*, 3129–3132; (c) Furlán, R. L. E.; Mata, E. G. *Tetrahedron Lett.* **1998**, *39*, 6421–6422; (d) Shapiro, G.; Marzi, M. *J. Org. Chem.* **1997**, *62*, 7096–7097; (e) Dessolin, M.; Guillerez, M.-G.; Thieriet, N.; Guibe, F.; Loffet, A. *Tetrahedron Lett.* **1995**, *36*, 5741–5744.
2. (a) Messeri, T.; Sternbach, D. D.; Tomkinson, N. C. O. *Tetrahedron Lett.* **1998**, *39*, 1669–1672; (b) Messeri, T.; Sternbach, D. D.; Tomkinson, N. C. O. *Tetrahedron Lett.* **1998**, *39*, 1673–1676.
3. Endova, M.; Masojidkova, M.; Rosenberg, I. *Nucleos. Nucleot.* **1997**, *16*, 2151–2164.
4. (a) Chandrasekhar, S.; Ramachandar, T.; Reddy, M. V.; Takhi, M. *J. Org. Chem.* **1995**, *60*, 1733–1740; (b) Schwarz, M.; Waters, R. M. *Synthesis* **1972**, 567; (c) Reddy, C. S.; Smitha, G.; Chandrasekhar, S. *Tetrahedron Lett.* **2003**, *44*, 4693–4695; (d) Chandra, K. L.; Saravanan, P.; Singh, V. K. *Tetrahedron Lett.* **2001**, *42*, 5309–5311; (e) Ranu, B. C.; Hajra, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 355–357; (f) Ranu, B. C.; Hajra, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2262–2265; (g) Oriyama, T.; Kobayashi, K.; Suzuki, T.; Oda, M. *Green Chem.* **2002**, *4*, 30–31.
5. Oriyama, T.; Yatabe, K.; Sugawara, S.; Machiguchi, Y.; Koga, G. *Synlett* **1996**, 523–525.
6. Oriyama, T.; Oda, M.; Gono, J.; Koga, G. *Tetrahedron Lett.* **1994**, *35*, 2027–2030.
7. Oriyama, T.; Kimura, M.; Koga, G. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 885–887.
8. (a) Yang, G.; Ding, X.; Kong, F. *Tetrahedron Lett.* **1997**, *38*, 6725–6728; (b) Ganem, B.; Small, V. R., Jr. *J. Org. Chem.* **1974**, *39*, 3728–3730.
9. (a) Bergmeier, S. C.; Arason, K. M. *Tetrahedron Lett.* **2000**, *41*, 5799–5802; (b) Kobayashi, K.; Watahiki, T.; Oriyama, T. *Synthesis* **2003**, 484–486.
10. Iimura, S.; Manabe, K.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 101–103.
11. Martel, A.; Chewchanwuttiwong, S.; Dujardin, G.; Brown, E. *Tetrahedron Lett.* **2003**, *44*, 1491–1494.
12. Williams, C. M.; Mander, L. N. *Org. Lett.* **2003**, *5*, 3499–3502.
13. Banwell, M. G.; Flynn, B. L.; Stewart, S. G. *J. Org. Chem.* **1998**, *63*, 9139–9144.
14. A similar process has been observed in the presence of TiO_2/SO_4^-: Jin, T.-S.; Li, Y.-W.; Sun, G.; Li, T.-S. *J. Chem. Res. (S)* **2003**, 98–100.
15. Typical procedure: 1-bromo-2-isopropoxy-3-methoxybenzene (100 mg, 0.041 mmol) was dissolved in acetic anhydride (0.4 mL) and anhydrous acetonitrile (0.4 mL) under nitrogen. TMSOTf (90 μL, 0.049 mmol) was then added dropwise over 30 s. The reaction mixture was stirred at room temperature. After 20 min the reaction was quenched with a saturated solution of sodium hydrogen carbonate (5 mL), extracted with diethyl ether (3×5 mL), dried (Na_2CO_3) and evaporated. The residue was subjected to column chromatography (dichloromethane/light petroleum) affording 2-acetoxy-3-bromo-1-methoxybenzene (98 mg, 98%) as a colourless oil, which slowly solidified on standing, mp 37 °C (lit.[16] 39 °C). Spectral data are in exact agreement to that reported.[16]
16. Mabic, S.; Vaysse, L.; Benezra, C.; Lepoittevin, J.-P. *Synthesis* **1999**, 1127–1134.