Protective Groups in Organic Synthesis, Third Edition. Theodora W. Greene, Peter G.M. Wuts

ISBNs: 0-471-16019-9 (Hardback); 0-471-22057-4 (Electronic)

3

PROTECTION FOR PHENOLS AND CATECHOLS

The phenolic hydroxyl group occurs widely in plant and animal life, both land based and aquatic, as demonstrated by the vast number of natural products that contain this group. In developing a synthesis of any phenol-containing product, protection is often mandatory to prevent reaction with oxidizing agents and electrophiles or reaction of the nucleophilic phenoxide ion with even mild alkylating and acylating agents. Many of the protective groups developed for alcohol protection are also applicable to phenol protection: thus, the chapter on alcohol protection should also be consulted. Ethers are the most widely used protective groups for phenols, and in general, they are more easily cleaved than the analogous ethers of simple alcohols.[1] Esters are also important protective groups for phenols, but are not as stable to hydrolysis as the related alcohol derivatives. Simple esters are easily hydrolyzed with mild base (e.g., $NaHCO_3$/aq. MeOH, 25°), but more sterically demanding esters (e.g., pivaloate) require harsher conditions to effect hydrolysis. Catechols can be protected in the presence of phenols as cyclic acetals or ketals, or cyclic esters. Some of the more important phenol and catechol protective groups are included in Reactivity Chart 4.[2]

1. For a review on ether cleavage, see M. V. Bhatt and S. U. Kulkarni, *Synthesis,* 249 (1983).
2. See also E. Haslam "Protection of Phenols and Catechols," in *Protective Groups in Organic Chemistry*, J. F. W. McOmie, Ed., Plenum, New York and London, 1973, pp. 145–182.

PROTECTION FOR PHENOLS

Ethers

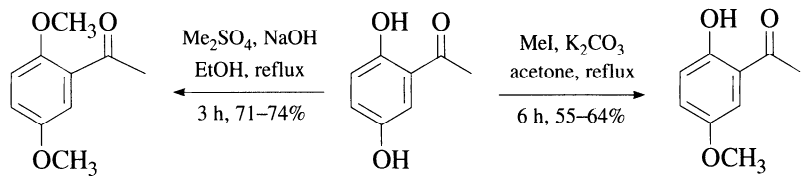
Historically, simple *n*-alkyl ethers formed from a phenol and a halide or sulfate were cleaved under rather drastic conditions (e.g., refluxing HBr). New ether protective groups have been developed that are removed under much milder conditions (e.g., via nucleophilic displacement, hydrogenolysis of benzyl ethers, or mild acid hydrolysis of acetal-type ethers) that often do not affect other functional groups in a molecule.

Methyl Ether: $ArOCH_3$ (Chart 4)

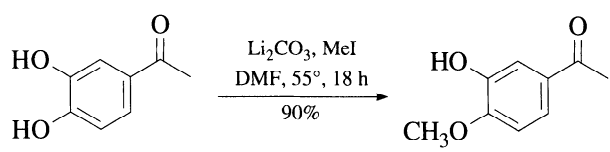
Deuteromethyl ethers have been used to protect phenols to prevent the methyl hydrogens from participating in free-radical reactions.[1]

Formation

1. MeI, K_2CO_3, acetone, reflux, 6 h.[2,3] This is a very common and often very efficient method for the preparation of phenolic methyl ethers. The method is also applicable to the formation of phenolic benzyl ethers.
2. Me_2SO_4, NaOH, EtOH, reflux, 3 h, 71–74% yield.[2]



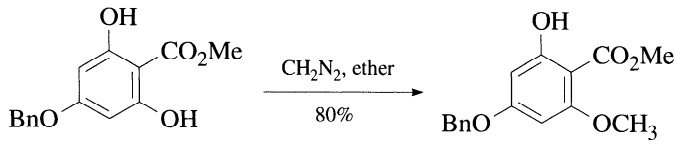
3. Li_2CO_3, MeI, DMF, 55°, 18 h, 54–90% yield.[4]



This method selectively protects phenols with $pK_a \leq 8$ as a result of electron-withdrawing *ortho*- or *para*-substituents.

4. RX, or R'_2SO_4, NaOH, CH_2Cl_2, H_2O, $PhCH_2N^+Bu_3Br^-$, 25°, 2–13 h, 75–95% yield.
   Ar = simple; 2- or 2,6-disubstituted[5,6]
   R = Me, allyl,  , *n*-Bu, *c*-C_5H_{11}, $PhCH_2$, $-CH_2CO_2Et$, R′ = Me, Et
5. Methyl, ethyl, and benzyl ethers have been prepared in the presence of tetraethylammonium fluoride as a Lewis base (alkyl halide, DME, 20°, 3 h, 60–85% yields).[6]

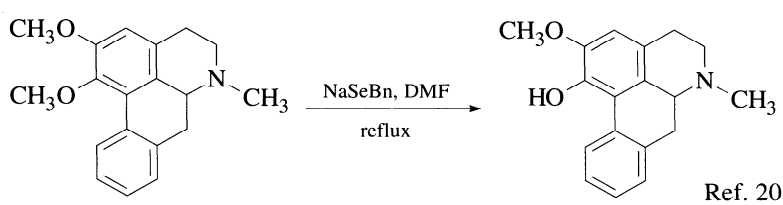
6. $p\text{-}NO_2\text{–}C_6H_4ONa + MeN(NO)CONH_2 \xrightarrow{DME,\ 0°\rightarrow 25°,\ 6\ h}$
   $[p\text{-}NO_2\text{–}C_6H_4O^- + CH_2N_2] \longrightarrow p\text{-}NO_2\text{–}C_6H_4OMe$, >90%[7]
7. Phenols protected as t-$BuMe_2Si$ ethers can be converted directly to methyl or benzyl ethers (MeI or BnBr, KF, DMF, rt, >90% yield).[8]
8. $TMSCHN_2$, MeOH, MeCN, rt, DIPEA, 31–100% yield.[9]
9. Diazomethane, ether, 80% yield.[10]



10. Dimethyl carbonate, $(Bu_2N)_2C{=}NMe$, 180°, 4.5 h, 54–99% yield.[11] In the presence of this guanidine, aromatic methyl carbonates are converted to methyl ethers with loss of CO_2.

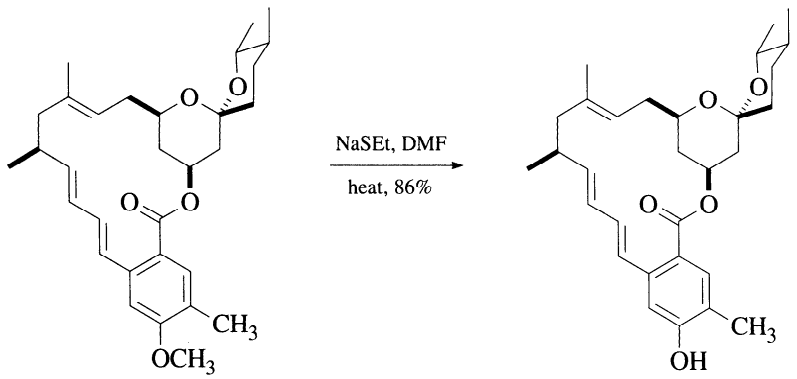
Cleavage

1. Me_3SiI, $CHCl_3$, 25–50°, 12–140 h.[12] Iodotrimethylsilane in quinoline (180°, 70 min) selectively cleaves an aryl methyl group, in 72% yield, in the presence of a methylenedioxy group.[13] Me_3SiI cleaves esters more slowly than ethers and cleaves alkyl aryl ethers (48 h, 25°) more slowly than alkyl alkyl ethers (1.3–48 h, 25°), but benzyl, trityl, and t-butyl ethers are cleaved quite rapidly (0.1 h, 25°).[12]
2. Toluene, potassium, 18-crown-6, 100% yield.[14] Tetrahydrofuran can also be used as the solvent in this process.[15]
3. Sodium, liquid ammonia.[16] The utility of this method depends on the nature of the substituents on the aromatic ring. Rings containing electron-withdrawing groups will be reduced, as in the classic Birch reduction.
4. EtSNa, DMF, reflux, 3 h, 94–98% yield.[17,18] Potassium thiophenoxide has been used to cleave an aryl methyl ether without causing migration of a double bond.[19] Sodium benzylselenide ($PhCH_2SeNa$) and sodium thiocresolate ($p\text{-}CH_3C_6H_4SNa$) cleave dimethoxyaryl compounds regioselectively, reportedly because of steric factors in the former case[20] and electronic factors in the latter case.[21]

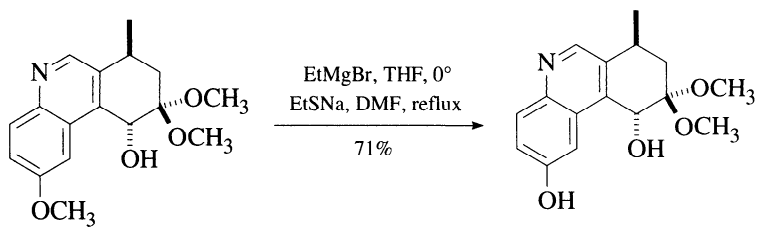


Ref. 20

5. Sodium ethanethiolate has been examined for the selective cleavage of aryl methyl ethers. Methyl ethers *para* to an electron-withdrawing group are cleaved preferentially.[22]



Ref. 23

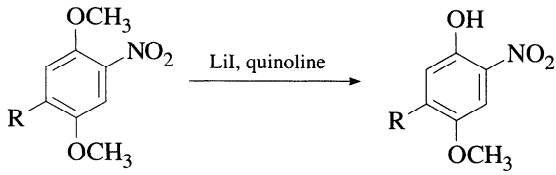


Ref. 24

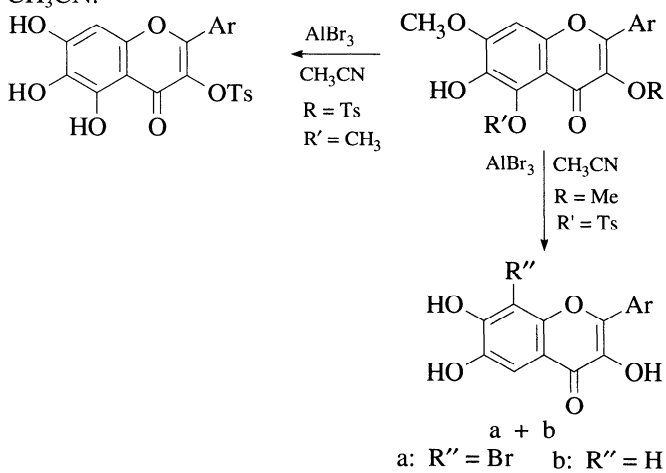
In this case, the magnesium alkoxide protects the ketal from cleavage.[24]

6. Sodium sulfide in *N*-methylpyrrolidone, NMP, (140°, 2–4 h) cleaves aryl methyl ethers in 78–85% yield.[25]
7. Me_3SiSNa, DMPU, 185°, 78–95% yield.[26]
8. PhSH, catalytic K_2CO_3, NMP, 60–97% yield.[27]
9. Lithium diphenyphosphide (THF, 25°, 2 h; HCl, H_2O, 87% yield) selectively cleaves an aryl methyl ether in the presence of an aryl ethyl ether.[28] It also cleaves a phenyl benzyl ether and a phenyl allyl ether to the phenol in 88% and 78% yield, respectively.[29,30]
10. $(TMS)_2NNa$ or LDA, THF, DMPU, 185°, 80–91% yield.[31]
11. DMSO, NaCN, 125–180°, 5–48 h, 65–90% yield.[32] This cleavage reaction is successful for aromatic systems containing ketones, amides, and carboxylic acids; mixtures are obtained from nitro-substituted aromatic compounds; there is no reaction with 5-methoxyindole (180°, 48 h).
12. LiI, collidine, reflux, 10 h, quant.[33] Aryl ethyl ethers are cleaved more slowly; dialkyl ethers are stable to these conditions.

13. LiI, quinoline, 140–180°, 10–30 min, 65–88% yield.[34]

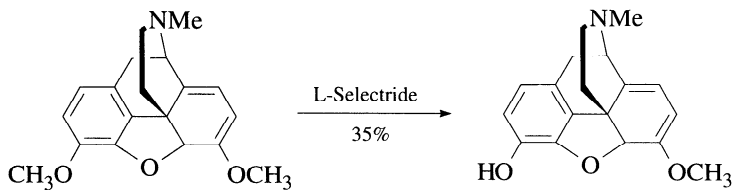


14. $AlBr_3$, EtSH, 25°, <1 h, 94% yield.[35] Both methyl aryl and methyl alkyl ethers are cleaved under these conditions. A methylenedioxy group, used to protect a catechol, is cleaved under similar conditions in satisfactory yields; methyl and ethyl esters are stable (0–20°, 2 h)[35].
15. $AlCl_3$, $HSCH_2CH_2SH$.[36]
16. $AlBr_3$, CH_3CN.[37]

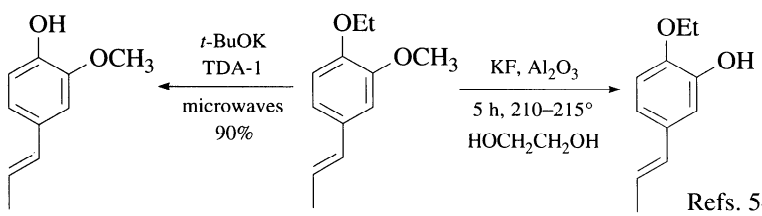


17. Regioselective cleavage of dimethoxyaryl derivatives with methanesulfonic acid/methionine has been reported.[38]
18. BBr_3, CH_2Cl_2, −80° → 20°, 12 h, 77–86% yield.[39] Methylenedioxy groups and diphenyl ethers are stable to these cleavage conditions. Benzyloxycarbonyl and *t*-butoxycarbonyl groups, benzyl esters,[40] and 1,3-dioxolanes are cleaved with this reagent. Boron tribromide is reported to be more effective than iodotrimethylsilane for cleaving aryl methyl ethers.[41]
19. Boron triiodide rapidly cleaves methyl ethers of *o*-, *m*-, or *p*-substituted aromatic aldehydes (0°, 25°; 0.5–5 min; 40–86% yield).[42] BI_3 complexed with *N,N*-diethylaniline is similarly effective, but benzyl ethers are converted to the iodide.[43]
20. $BBr_3 \cdot S(CH_3)_2$, $ClCH_2CH_2Cl$, 83°, 50–99% yield.[44] The advantage of this method is that the reagent is a stable, easily handled solid. Methylenedioxy groups are also cleaved by this reagent.

21. 9-Bromo-9-borabicyclo[3.3.0]nonane (9-Br–BBN), CH_2Cl_2, reflux, 87–100% yield.[45] 9-Br–BBN also cleaves dialkyl ethers, allyl aryl ethers, and methylenedioxy groups.
22. BH_2Cl–DMS, toluene, reflux, 95% yield. Acetonides and THP ethers are cleaved, and epoxides are converted to the chlorohydrin.[46]
23. Me_2Br, CH_2Cl_2, 70°, 30–36 h, 72–96% yield.[47] Alkyl methyl ethers are also cleaved, but tertiary methyl ethers are converted to the bromide.
24. 2-Bromo-1,3,2-benzodioxaborole, CH_2Cl_2 (cat. $BF_3{\cdot}Et_2O$), 25°, 0.5–36 h, 95–98% yield. Aryl benzyl ethers, methyl esters, and aromatic benzoates are also cleaved.[48]
25. Pyr·HCl, 220°, 6 min, 34% yield of morphine from codeine.[49]
26. Excess MeMgI, 155–165°, 15 min, 80% yield.[50]
27. Sodium *N*-methylanilide, xylene, HMPA, 60–120°, 70–95% yield. Methyl ethers of polyhydric phenols are cleaved to give the monophenol.[51] Benzyl ethers are also cleaved. Halogenated phenols are not effectively cleaved, because of competing aromatic substitution.
28. L-Selectride or Super Hydride, 67°, 88–92% yield.[52] Other methods for converting thebaine to oripavine have not been successful.[53]



29.

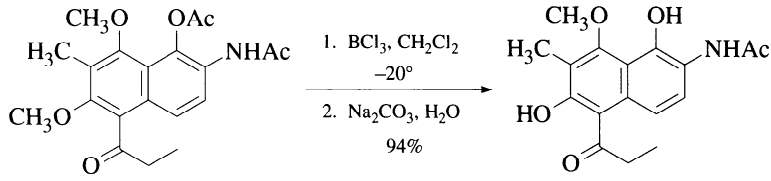


Refs. 54, 55

The loss of the ethyl group probably occurs by an E-2 elimination, whereas methyl cleavage occurs by an S_N-2 process.

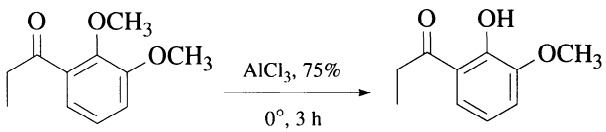
30. 48% HBr, AcOH, reflux, 30 min, 85%.[56] The efficiency of this method is significantly improved if a phase transfer catalyst (n-$C_{16}H_{33}P^+Bu_3\ Br^-$) is added to the mixture.[57] Methods that use HBr for ether cleavage can give bromides in the presence of benzylic alcohols.[58]
31. 48% HBr, $Bu_4N^+Br^-$, 100°, 6 h, 80–98% yield.[59]
32. HBr, NaI, 90–94°, sealed tube, 90% yield.[60]
33. TFA, thioanisole, TfOH, 2 h, 0°, 87% yield.[60]

34. BCl_3, CH_2Cl_2, −20°, 94% yield.[61]

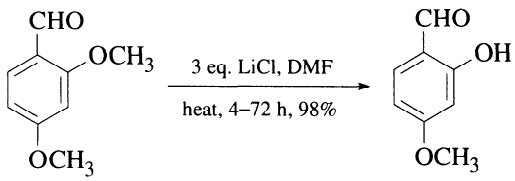


Either an aryl methyl ether or a methylenedioxy group can be cleaved with boron trichloride under various conditions.[62]

35. $AlCl_3$, 3 h, 0°, 75% yield.[63,64] A selectivity study on the demethylation of polymethoxy-substituted acetophenones has been performed using $AlCl_3$ in CH_3CN.[65]

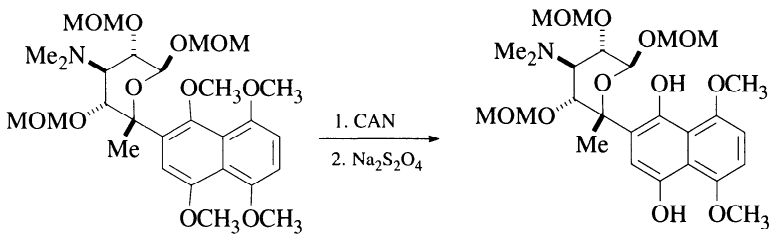


36. LiCl, DMF, heat, 4–72 h.[66]

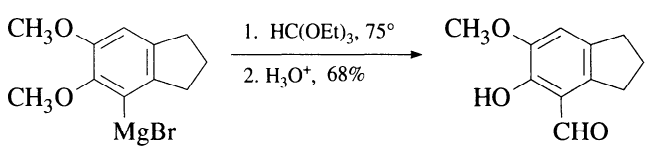


37. CF_3SO_3H, PhSMe, 0–25°.[67,68] In this case *O*-methyltyrosine was deprotected without evidence of O→C migration, which is often a problem when removing protective groups from tyrosine.

38. Ceric ammonium nitrate converts a 1,4-dimethoxy aromatic compound to the quinone, which is reduced with sodium dithionite to give a deprotected hydroquinone.[69]



39.



Ref. 70

1. D. L. J. Clive, M. Cantin, A. Khodabocus, X. Kong, and Y. Tao, *Tetrahedron*, **49**, 7917 (1993); D. L. J. Clive, A. Khodabocus, M. Cantin, and Y. Tao, *J. Chem. Soc., Chem. Commun.*, 1755 (1991).
2. G. N. Vyas and N. M. Shah, *Org. Synth., Collect. Vol. IV*, 836 (1963).
3. A. R. MacKenzie, C. J. Moody, and C. W. Rees, *Tetrahedron*, **42**, 3259 (1986).
4. W. E. Wymann, R. Davis, J. W. Patterson, Jr., and J. R. Pfister, *Synth. Commun.*, **18**, 1379 (1988).
5. A. McKillop, J.-C. Fiaud, and R. P. Hug, *Tetrahedron*, **30**, 1379 (1974).
6. J. M. Miller, K. H. So, and J. H. Clark, *Can. J. Chem.*, **57**, 1887 (1979).
7. S. M. Hecht and J. W. Kozarich, *Tetrahedron Lett.*, 1307 (1973).
8. A. K. Sinhababu, M. Kawase, and R. T. Borchardt, *Tetrahedron Lett.*, **28**, 4139 (1987).
9. T. Aoyama, S. Terasawa, K. Sudo, and T. Shioiri, *Chem. Pharm. Bull.*, **32**, 3759 (1984).
10. F. Bracher and B. Schulte, *J. Chem. Soc., Perkin Trans. 1*, 2619 (1996).
11. G. Barcelo, D. Grenouillat, J. P. Senet, and G. Sennyey, *Tetrahedron*, **46**, 1839 (1990).
12. M. E. Jung and M. A. Lyster, *J. Org. Chem.*, **42**, 3761 (1977).
13. J. Minamikawa and A. Brossi, *Tetrahedron Lett.*, 3085 (1978).
14. T. Ohsawa, K. Hatano, K. Kayoh, J. Kotabe, and T. Oishi, *Tetrahedron Lett.*, **33**, 5555 (1992).
15. U. Azzena, T. Denurra, G. Melloni, E. Fenude, and G. Rassa, *J. Org. Chem.*, **57**, 1444 (1992).
16. A. J. Birch, *Quart. Rev.*, **4**, 69 (1950).
17. G. I. Feutrill and R. N. Mirrington, *Tetrahedron Lett.*, 1327 (1970); *idem*, *Aust. J. Chem.*, **25**, 1719, 1731 (1972).
18. A. S. Kende and J. P. Rizzi, *Tetrahedron Lett.*, **22**, 1779 (1981).
19. J. W. Wildes, N. H. Martin, C. G. Pitt, and M. E. Wall, *J. Org. Chem.*, **36**, 721 (1971).
20. R. Ahmad, J. M. Saá, and M. P. Cava, *J. Org. Chem.*, **42**, 1228 (1977).
21. C. Hansson and B. Wickberg, *Synthesis*, 191 (1976).
22. J. A. Dodge, M. G. Stocksdale, K. J. Fahey, and C. D. Jones, *J. Org. Chem.*, **60**, 739 (1995).
23. A. B. Smith, III, S. R. Schow, J. D. Bloom, A. S. Thompson, and K. N. Winzenberg, *J. Am. Chem. Soc.*, **104**, 4015 (1982).
24. A. G. Myers, N. J. Tom, M. E. Fraley, S. B. Cohen, and D. J. Mader, *J. Am. Chem. Soc.*, **119**, 6072 (1997).
25. M. S. Newman, V. Sankaran, and D. R. Olson, *J. Am. Chem. Soc.*, **98**, 3237 (1976).
26. J. R. Hwu and S.-C. Tsay, *J. Org. Chem.*, **55**, 5987 (1990).
27. M. K. Nayak and A. K. Chakraborti, *Tetrahedron Lett.*, **38**, 8749 (1997).
28. R. E. Ireland and D. M. Walba, *Org. Synth., Collect. Vol. VI*, 567 (1988).
29. F. G. Mann and M. J. Pragnell, *Chem. Ind. (London)*, 1386 (1964).
30. H. Meier and U. Dullweber, *Tetrahedron Lett.*, **37**, 1191 (1996).
31. J. R. Hwu, F. F. Wong, J.-J. Huang, and S.-C. Tsay, *J. Org. Chem.*, **62**, 4097 (1997).
32. J. R. McCarthy, J. L. Moore, and R. J. Crege, *Tetrahedron Lett.*, 5183 (1978).

33. I. T. Harrison, *J. Chem. Soc., Chem. Commun.*, 616 (1969).
34. K. Kirschke and E. Wolff, *J. Prakt. Chem./Chem. Ztg.*, **337**, 405 (1995).
35. M. Node, K. Nishide, K. Fuji, and E. Fujita, *J. Org. Chem.*, **45**, 4275 (1980).
36. T. Inaba, I. Umezawa, M. Yuasa, T. Inoue, S. Mihashi, H. Itokawa, and K. Ogura, *J. Org. Chem.*, **52**, 2957 (1987).
37. T. Horie, T. Kobayashi, Y. Kawamura, I. Yoshida, H. Tominaga, and K. Yamashita, *Bull. Chem. Soc. Jpn.*, **68**, 2033 (1995).
38. N. Fujii, H. Irie, and H. Yajima, *J. Chem . Soc., Perkin Trans. 1*, 2288 (1977).
39. J. F. W. McOmie and D. E. West, *Org. Synth., Collect. Vol. V*, 412 (1973).
40. A. M. Felix, *J. Org. Chem.*, **39**, 1427 (1974).
41. E. H. Vickery, L. F. Pahler, and E. J. Eisenbraun, *J. Org. Chem.*, **44**, 4444 (1979).
42. J. M. Lansinger and R. C. Ronald, *Synth. Commun.*, **9**, 341 (1979).
43. C. Narayana, S. Padmanabhan, and G. W. Kabalka, *Tetrahedron Lett.*, **31**, 6977 (1990).
44. P. G. Williard and C. B. Fryhle, *Tetrahedron Lett.*, **21**, 3731 (1980).
45. M. V. Bhatt, *J. Organomet. Chem.*, **156**, 221 (1978).
46. P. Bovicelli, E. Mincione, and G. Ortaggi, *Tetrahedron Lett.*, **32**, 3719 (1991).
47. Y. Guindon, C. Yoakim, and H. E. Morton, *Tetrahedron Lett.*, **24**, 2969 (1983).
48. P. F. King and S. G. Stroud, *Tetrahedron Lett.*, **26**, 1415 (1985).
49. M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, **78**, 1380 (1956).
50. R. Mechoulam and Y. Gaoni, *J. Am. Chem. Soc.*, **87**, 3273 (1965).
51. B. Loubinoux, G. Coudert, and G. Guillaumet, *Synthesis*, 638 (1980).
52. G. Majetich, Y. Zhang, and K. Wheless, *Tetrahedron Lett.*, **35**, 8727 (1994).
53. A. Coop, J. W. Lewis, and K. C. Rice, *J. Org. Chem.*, **61**, 6774 (1996).
54. A. S. Radhakrishna, K. R. K. P. Rao, S. K. Suri, K. Sivaprakash, and B. B. Singh, *Synth. Commun.*, **21**, 379 (1991).
55. A. Oussaïd, L. N. Thach, and A. Loupy, *Tetrahedron Lett.*, **38**, 2451 (1997).
56. I. Kawasaki, K. Matsuda, and T. Kaneko, *Bull. Chem. Soc. Jpn.*, **44**, 1986 (1971).
57. D. Landini, F. Montanari, and F. Rolla, *Synthesis*, 771 (1978).
58. A. Kamai and N. L. Gayatri, *Tetrahedron Lett.*, **37**, 3359 (1996).
59. K. Hwang and S. Park, *Synth. Commun.*, **23**, 2845 (1993).
60. G. Li, D. Patel, and V. J. Hruby, *Tetrahedron Lett.*, **34**, 5393 (1993).
61. H. Nagaoka, G. Schmid, H. Iio, and Y. Kishi, *Tetrahedron Lett.*, **22**, 899 (1981).
62. M. Gerecke, R. Borer, and A. Brossi, *Helv. Chim. Acta*, **59**, 2551 (1976).
63. K. A. Parker and J. J. Petraitis, *Tetrahedron Lett.*, **22**, 397 (1981).
64. T.-t. Li and Y. L. Wu, *J. Am. Chem. Soc.*, **103**, 7007 (1981).
65. Y. Kawamura, H. Takatsuki, F. Torii, and T. Horie, *Bull. Chem. Soc. Jpn.*, **67**, 511 (1994).
66. A. M. Bernard, M. R. Ghiani, P. P. Piras, and A. Rivoldini, *Synthesis*, 287 (1989).
67. Y. Kiso, S. Nakamura, K. Ito, K. Ukawa, K. Kitagawa, T. Akita, and H. Moritoki, *J. Chem. Soc., Chem. Commun.*, 971 (1979).
68. Y. Kiso, K. Ukawa, S. Nakamura, K. Ito, and T. Akita, *Chem. Pharm. Bull.*, **28**, 673 (1980).
69. M. Kawaski, F. Matsuda, and S. Terashima, *Tetrahedron*, **44**, 5713 (1988).

70. P. Deslongchamps, A. Bélanger, D. J. F. Berney, H. J. Borschberg, R. Brousseau, A. Doutheau, R. Durand, H. Katayama, R. Lapalme, D. M. Leturc, C.-C. Liao, F. N. MacLachan, J.-P. Maffrand, F. Marazza, R. Martino, C. M. L. Ruest, L. Saint-Laurent, and R. S. et P. Soucy, *Can. J. Chem.*, **68**, 115 (1990).

Methoxymethyl (MOM) Ether: $ArOCH_2OCH_3$ (Chart 4)

Formation

1. $ClCH_2OCH_3$, CH_2Cl_2, NaOH–H_2O, Adogen (phase transfer cat.), 20°, 20 min, 80–95% yield.[1,2] This method has been used to protect selectively a phenol in the presence of an alcohol.[3]
2. $ClCH_2OCH_3$, CH_3CN, 18-crown-6, 80% yield.[4]
3. $CH_3OCH_2OCH_3$ TsOH, CH_2Cl_2, mol. sieves, N_2, reflux, 12 h, 60–80% yield.[5] This method of formation avoids the use of the carcinogen chloromethyl methyl ether.
4. $ClCH_2OCH_3$, acetone, K_2CO_3, 86% yield.[6]
5. $ClCH_2OCH_3$, DMF, NaH, 93% yield.[6]

Cleavage

1. HCl, *i*-PrOH, THF, 25°, 12 h, quant.[5]
2. 2 *N* HOAc, 90°, 40 h, high yield.[7] The group has been used in a synthesis of 13-desoxydelphonine from *o*-cresol, a synthesis that required the group to be stable to many reagents.[8]
3. NaI, acetone, cat. HCl, 50°, 85% yield.[9]
4. P_2I_4, CH_2Cl_2, 0° → rt, 30 min, 70–90% yield.[10] This method is also effective for removal of the SEM and MEM groups.
5. $(EtO)_3SiCl$, NaI, CH_3CN, CH_2Cl_2, −5°, 0.5 h, 74% yield. This method was reported to work better than TMSI.[11] TBDPS groups were not affected by this reagent.
6. TMSBr, CH_2Cl_2, 30° → 0°, 87% yield.[12]

1. F. R. van Heerden, J. J. van Zyl, G. J. H. Rall, E. V. Brandt, and D. G. Roux, *Tetrahedron Lett.*, 661 (1978).
2. W. R. Roush, D. S. Coffey, and D. J. Madar, *J. Am. Chem. Soc.*, **119**, 11331 (1997).
3. T. R. Kelly, C. T. Jagoe, and Q. Li, *J. Am. Chem. Soc.*, **111**, 4522 (1989).
4. G. J. H. Rall, M. E. Oberholzer, D. Ferreira, and D. G. Roux, *Tetrahedron Lett.*, 1033 (1976).
5. J. P. Yardley and H. Fletcher, III, *Synthesis*, 244 (1976).
6. M. Süsse, S. Johne, and M. Hesse, *Helv. Chim. Acta*, **75**, 457 (1992).
7. M. A. A.-Rahman, H. W. Elliott, R. Binks, W. Küng, and H. Rapoport, *J. Med. Chem.*, **9**, 1 (1966).
8. K. Wiesner, *Pure Appl. Chem.*, **51**, 689 (1979).

9. D. R. Williams, B. A. Barner, K. Nishitani, and J. G. Phillips, *J. Am. Chem. Soc.*, **104**, 4708 (1982).
10. H. Saimoto, Y. Kusano, and T. Hiyama, *Tetrahedron Lett.*, **27**, 1607 (1986).
11. J. R. Falck, K. K. Reddy, and S. Chandrasekhar, *Tetrahedron Lett.*, **38**, 5245 (1997).
12. J. W. Huffman, X. Zhang, M.-J. Wu, H. H. Joyner, and W. T. Pennington, *J. Org. Chem.*, **56**, 1481 (1991).

Benzyloxymethyl (BOM) Ether: $C_6H_5CH_2OCH_2OAr$

Formation

1. BOMCl, NaH, DMF, >81% yield.[1]

Cleavage

1. MeOH, Dowex 50W-X8 (H^+), 90% yield.[1]

1. W. R. Roush, M. R. Michaelides, D. F. Tai, B. M. Lesur, W. K. M. Chong, and D. J. Harris, *J. Am. Chem. Soc.*, **111**, 2984 (1989).

Methoxyethoxymethyl (MEM)Ether: $ArOCH_2OCH_2CH_2OCH_3$ (Chart 4)

In an attempt to metalate a MEM-protected phenol with BuLi, the methoxy group was eliminated, forming the vinyloxymethyl ether. This was attributed to intramolecular proton abstraction.[1]

A 2-methoxyethoxymethyl ether was used to protect one phenol group during a total synthesis of gibberellic acid.[2]

Formation

1. NaH, THF, 0°; $MeOCH_2CH_2OCH_2Cl$, 0° → 25°, 2 h, 75% yield.[2]
2. $MeOCH_2CH_2OCH_2Cl$, DIPEA.[3]

Cleavage

1. CF_3CO_2H, CH_2Cl_2, 23°, 1 h, 74% yield.[2]
2. $(Ipc)_2BCl$, THF, 0°, 80 h. Cleavage occurred during the reduction of an acetophenone.[3]
3. For other methods of cleavage, the chapter on alcohol protection should be consulted.

1. J. Mayrargue, M. Essamkaoui, and H. Moskowitz, *Tetrahedron Lett.*, **30**, 6867 (1989).
2. E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, and J.-L. Gras, *J. Am. Chem. Soc.*, **100**, 8031 (1978).
3. E. T. Everhart and J. C. Craig, *J. Chem. Soc., Perkin Trans. 1*, 1701 (1991).

2-(Trimethylsilyl)ethoxymethyl (SEM) Ether: $(CH_3)_3SiCH_2CH_2OCH_2OAr$

Formation

1. SEMCl, DMAP, Et_3N, benzene, reflux, 3 h, 98% yield.[1]
2. SEMCl, $(i\text{-Pr})_2NEt$, CH_2Cl_2, 97% yield.[3]

Cleavage

1. $Bu_4N^+F^-$, HMPA, 40°, 2 h, >23–51% yield.[2]
2. H_2SO_4, MeOH, THF, 90% yield.[1]
3. P_2I_4, CH_2Cl_2, 0° → rt, 30 min, 62–86% yield.[3,4] These conditions also cleave methoxymethyl and methoxyethoxymethyl ethers.

1. T. L. Shih, M. J. Wyvratt, and H. Mrozik, *J. Org. Chem.*, **52**, 2029 (1987).
2. A. Leboff, A.-C. Carbonnelle, J.-P. Alazard, C. Thal, and A. S. Kende, *Tetrahedron Lett.*, **28**, 4163 (1987).
3. H. Saimoto, Y. Kusano, and T. Hiyama, *Tetrahedron Lett.*, **27**, 1607 (1986).
4. H. Saimoto, S.-i. Ohrai, H. Sashiwa, Y. Shigemasa, and T. Hiyama, *Bull. Chem. Soc. Jpn.*, **68**, 2727 (1995).

Methylthiomethyl (MTM) Ether: $ArOCH_2SCH_3$ (Chart 4)

Formation

1. NaOH, $ClCH_2SMe$, HMPA, 25°, 16 h, 91–94% yield.[1]

Cleavage

1. $HgCl_2$, CH_3CN–H_2O, reflux, 10 h, 90–95% yield.[1] Aryl methylthiomethyl ethers are stable to the conditions used to hydrolyze primary alkyl MTM ethers (e.g., $HgCl_2/CH_3CN$–H_2O, 25°, 6 h). They are moderately stable to acidic conditions (95% recovered from HOAc/THF–H_2O, 25°, 4 h).
2. Ac_2O, Me_3SiCl, 25 min, rt, 95% yield.[2]

1. R. A. Holton and R. G. Davis, *Tetrahedron Lett.*, 533 (1977).
2. N. C. Barua, R. P. Sharma, and J. N. Baruah, *Tetrahedron Lett.*, **24**, 1189 (1983).

Phenylthiomethyl (PTM) Ether: $C_6H_5SCH_2OAr$

Formation

1. NaI, $PhSCH_2Cl$, NaH, HMPA, 87–94% yield.[1]

Cleavage

1. $CH_3CN:H_2O$ (4:1), $HgCl_2$, 24 h, 90–94% yield. The methylthiomethyl ether group can be removed in the presence of the phenylthiomethyl ether.[1]

1. R. A. Holton and R. V. Nelson, *Synth. Commun.*, **10**, 911 (1980).

Azidomethyl Ether: N_3CH_2OAr

The azidomethyl ether, used to protect phenols and prepared by the displacement of azide on the chloromethylene group, is cleaved reductively with $LiAH_4$ or by hydrogenolysis (Pd–C, H_2). It is stable to strong acids, permanganate, and free-radical brominations.[1]

1. B. Loubinoux, S. Tabbache, P. Gerardin, and J. Miazimbakana, *Tetrahedron*, **44**, 6055 (1988).

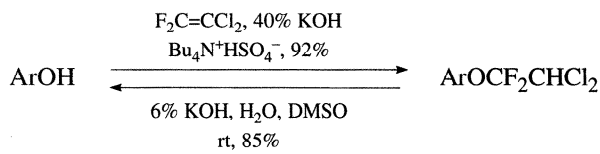
Cyanomethyl Ether: $ArOCH_2CN$

The cyanomethyl ether, formed from bromoacetonitrile (acetone, K_2CO_3, 97–100% yield), is cleaved by hydrogenation of the nitrile with PtO_2 in EtOH, in 98% yield.[1] The method has also been used for the protection of amines and carbamates.

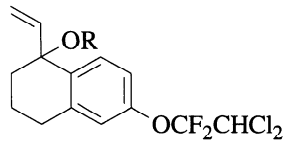
1. A. Benarab, S. Boye, L. Savelon, and G. Guillaumet, *Tetrahedron Lett.*, **34**, 7567 (1993).

2,2-Dichloro-1,1-difluoroethyl Ether: $CHCl_2CF_2OAr$

Formation/Cleavage



This group decreases the electron density on the aromatic ring and thus inhibits solvolysis of the tertiary alcohol **i** and the derived acetate **ii**.[1]



i R = H
ii R = Ac

1. S. G. Will, P. Magriotis, E. R. Marinelli, J. Dolan, and F. Johnson, *J. Org. Chem.*, **50**, 5432 (1985).

2-Chloro- and 2-Bromoethyl Ether: XCH_2CH_2OAr, X=Cl, Br

These ethers can be removed from naphthohydroquinones either by elimination to the vinyl ether followed by hydrolysis or by Finklestein reaction with iodide followed by reduction with zinc.[1]

1. H. Laatsch, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.*, **40B**, 534 (1985).

Tetrahydropyranyl (THP) Ether: ArO–2-tetrahydropyranyl

The tetrahydropyranyl ether, prepared from a phenol and dihydropyran (HCl/EtOAc, 25°, 24 h) is cleaved by aqueous oxalic acid (MeOH, 50–90°, 1–2 h).[1] Tonsil, Mexican Bentonite earth,[2] HSZ Zeolite,[3] and $H_3[PW_{12}O_{40}]$[4] have also been used for the tetrahydropyranylation of phenols. The use of $[Ru(ACN)_3(triphos)](OTf)_2$ in acetone selectively removes the THP group from a phenol in the presence of an alkyl THP group. Ketals of acetophenones are also cleaved.[5]

1-Ethoxyethyl (EE) Ether: $ArOCH(OC_2H_5)CH_3$

The ethoxyethyl ether is prepared by acid catalysis from a phenol and ethyl vinyl ether and is cleaved by acid-catalyzed methanolysis.[6]

1. H. N. Grant, V. Prelog, and R. P. A. Sneeden, *Helv. Chim. Acta*, **46**, 415 (1963).
2. R. Cruz-Almanza, F. J. Pérez-Floress, and M. Avila, *Synth. Commun.*, **20**, 1125 (1990).
3. R. Ballini, F. Bigi, S. Carloni, R. Maggi, and G. Sartori, *Tetrahedron Lett.*, **38**, 4169 (1997).
4. A. Moinar and T. Beregszaszi, *Tetrahedron Lett.*, **37**, 8597 (1996).
5. S. Ma and L. M. Venanzi, *Tetrahedron Lett.*, **34**, 8071 (1993).
6. J. H. Rigby and M. E. Mateo, *J. Am. Chem. Soc.*, **119**, 12, 655 (1997).

Phenacyl Ether: $ArOCH_2COC_6H_5$ (Chart 4)

4-Bromophenacyl Ether: $ArOCH_2COC_6H_4$-4-Br

Formation

1. $BrCH_2COPh$, K_2CO_3, acetone, reflux, 1–2 h, 85–95% yield.[1]

Cleavage

1. Zn, HOAc, 25°, 1 h, 88–96% yield.[1] Phenacyl and *p*-bromophenacyl ethers of phenols are stable to 1% ethanolic alkali (reflux, 2 h), and to 5 *N* sulfuric acid in ethanol–water. The phenacyl ether, prepared from β-naphthol, is cleaved in 82% yield by 5% ethanolic alkali (reflux, 2 h).

1. J. B. Hendrickson and C. Kandall, *Tetrahedron Lett.*, 343 (1970).

Cyclopropylmethyl Ether: $ArOCH2–c\text{-}C_3H_5$

For a particular phenol, the authors required a protective group that would be stable to reduction (by complex metals, catalytic hydrogenation, and Birch conditions) and that could be easily and selectively removed.

Formation

1. KO–*t*-Bu, DMF, 0°, 30 min; $c\text{-}C_3H_5CH_2Br$, 20°, 20 min → 40°, 6 h, 80% yield.[1]

Cleavage

1. aq. HCl, MeOH, reflux, 2 h, 94% yield. [1]

1. W. Nagata, K. Okada, H. Itazaki, and S. Uyeo, *Chem. Pharm. Bull.*, **23**, 2878 (1975).

Allyl Ether: $ArOCH_2CH{=}CH_2$ (Chart 4)

Formation

1. Allyl ethers can be prepared by reaction of a phenol and the allyl bromide in the presence of base.[1]
2. AllylOH, $Pd(OAc)_2$, PPh_3, $Ti(O–i\text{-}Pr)_4$, 73–87% yield.[2]

Cleavage

1. The section on the cleavage of allyl ethers of alcohols should also be consulted.

2. Pd–C, TsOH, H_2O or MeOH; 60–80°, 6 h, > 95% yield.[3]
3. SeO_2/HOAc, dioxane, reflux, 1 h, 40–75% yield.[4]
4. $NaAlH_2(OCH_2CH_2OCH_3)_2$, $PhCH_3$, reflux, 10 h, 62% yield.[5] An aryl allyl ether is selectively cleaved by this reagent (which also cleaves aryl benzyl ethers) in the presence of an *N*-allylamide.
5. $Ph_3P/Pd(OAc)_2$, HCOOH, 90°, 1 h.[6]
6. Pd° cat., Bu_3SnH, AcOH, *p*-NO_2-phenol.[7]
7. $Pd(Ph_3P)_4$, $LiBH_4$, THF, 88% yield.[8] $NaBH_4$ can also be used as an allyl scavenging agent.[9]
8. $Pd(Ph_3P)_4$, $PhSiH_3$, 20–40 min, 74–100% yield.[10]
9. Bis(benzonitrile)palladium(II) chloride, benzene, reflux, 16–20 h, 86% yield.[11]
10. EtOH, $RhCl_3$, reflux, 86% yield. [1]
11. $LiPPh_2$, THF, 4 h, reflux, 78% yield.[12]
12. $SiCl_4$, NaI, CH_2Cl_2, CH_3CN, 8 h, 84% yield.[13]
13. $NaBH_4$, I_2, THF, 0°, 84–95% yield.[14]
14. Electrolysis, $[Ni(bipy)_3](BF_3)$, Mg anode, DMF, rt, 40–99% yield.[15] Aryl bromides and iodides are reduced under these conditions.
15. Electrolysis, DMF, $Bu_4N^+Br^-$, $SmCl_3$, Mg anode, 67–90% yield.[16]
16. $TiCl_3$, Mg, THF, reflux, 3 h, 70% yield.[17]
17. *t*-BuOK, DMSO, 92% yield; MeOH, HCl, >75% yield.[18]
18. Chromium-pillared clay, *t*-BuOOH, CH_2Cl_2, 10 h, 80% yield. Simple allyl ethers are cleaved to give ketones, and allylamines are also deprotected (84–90% yield).[19]
19. Li, naphthalene, THF, 51–91% yield.[20]

1. See, for example; S. F. Martin and P. J. Garrison, *J. Org. Chem.*, **47**, 1513 (1982).
2. T. Satoh, M. Ikeda, M. Miura, and M. Nomura, *J. Org. Chem.*, **62**, 4877 (1997).
3. R. Boss and R. Scheffold, *Angew. Chem., Int. Ed. Engl.*, **15**, 558 (1976).
4. K. Kariyone and H. Yazawa, *Tetrahedron Lett.*, 2885 (1970).
5. T. Kametani, S.-P. Huang, M. Ihara, and K. Fukumoto, *J. Org. Chem.*, **41**, 2545 (1976).
6. H. Hey and H.-J. Arpe, *Angew. Chem., Int. Ed. Engl.*, **12**, 928 (1973).
7. P. Four and F. Guibe, *Tetrahedron Lett.*, **23**, 1825 (1982).
8. M. Bois-Choussy, L. Neuville, R. Beugelmans, and J. Zhu, *J. Org. Chem.*, **61**, 9309 (1996).
9. R. Beugelmans, S. Bourdet, A. Bigot, and J. Zhu, *Tetrahedron Lett.*, **35**, 4349 (1994).
10. M. Dessolin, M.-G. Guillerez, N. Thieriet, F. Guibé, and A. Loffet, *Tetrahedron Lett.*, **36**, 5741 (1995).
11. J. M. Bruce and Y. Roshan-Ali, *J. Chem. Res., Synop.*, 193 (1981).

12. F. G. Mann and M. J. Pragnell, *J. Chem. Soc.*, 4120 (1965).
13. M. V. Bhatt and S. S. El-Morey, *Synthesis*, 1048 (1982).
14. R. M. Thomas, G. H. Mohan, and D. S. Iyengar, *Tetrahedron Lett.*, **38**, 4721 (1997).
15. S. Olivero and E. Duñach, *J. Chem. Soc., Chem. Commun.*, 2497 (1995).
16. B. Espanet, E. Duñach, and J. Perichon, *Tetrahedron Lett.*, **33**, 2485 (1992).
17. S. M. Kadam, S. K. Nayak, and A. Banerji, *Tetrahedron Lett.*, **33**, 5129 (1992).
18. F. Effenberger and J. Jäger, *J. Org. Chem.*, **62**, 3867 (1997).
19. B. M. Choudary, A. D. Prasad, V. Swapna, V. L. K. Valli, and V. Bhuma, *Tetrahedron*, **48**, 953 (1992).
20. E. Alonso, D. J. Ramon, and M. Yus, *Tetrahedron*, **42**, 14355 (1997).

Propargyl Ether: $HC{\equiv}CCH_2OAr$

Cleavage

1. Electrolysis, Ni(II), Mg anode, DMF, rt 77–99% yield. This method is not compatible with halogenated phenols, because of competing halogen cleavage.[1]
2. $TiCl_3$, Mg, THF, 54–92% yield.[2]

1. S. Olivero and E. Duñach, *Tetrahedron Lett.*, **38**, 6193 (1997).
2. S. K. Nayak, S. M. Kadam, and A. Banerji, *Synlett*, 581 (1993).

Isopropyl Ether: $ArOCH(CH_3)_2$

An isopropyl ether was developed as a phenol protective group that would be more stable to Lewis acids than would be an aryl benzyl ether.[1] The isopropyl group has been tested for use in the protection of the phenolic oxygen of tyrosine during peptide synthesis.[2]

Formation

1. Me_2CHBr, K_2CO_3, DMF, acetone, 20°, 19 h.[1]

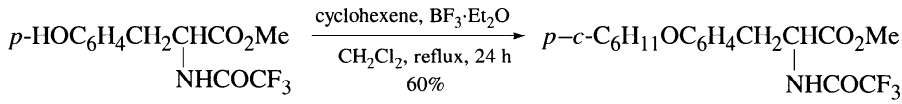
Cleavage

1. BCl_3, CH_2Cl_2, 0°, rapid; or $TiCl_4$, CH_2Cl_2, 0°, slower. There was no reaction with $SnCl_4$.[1]
2. $SiCl_4$, NaI, 14 h, CH_2Cl_2, CH_3CN, 80% yield.[3]

1. T. Sala and M. V. Sargent, *J. Chem. Soc., Perkin Trans. 1*, 2593 (1979).
2. See cyclohexyl ether in this section: M. Engelhard and R. B. Merrifield, *J. Am. Chem. Soc.*, **100**, 3559 (1978).
3. M. V. Bhatt and S. S. El-Morey, *Synthesis*, 1048 (1982).

Cyclohexyl Ether: ArO–*c*-C_6H_{11} (Chart 4)

Formation[1]



Cleavage[1]

1. HF, 0°, 30 min, 100% yield.
2. 5.3 *N* HBr/AcOH, 25°, 2 h, 99% yield. An ether that would not undergo rearrangement to a 3-alkyl derivative during acid-catalyzed removal of –NH protective groups was required to protect the phenol group in tyrosine. Four compounds were investigated: *O*-cyclohexyl-, *O*-isobornyl-, *O*-[1-(5-pentamethylcyclopentadienyl)ethyl]- and *O*-isopropyltyrosine.

The *O*-isobornyl- and *O*-[1-(5-pentamethylcyclopentadienyl)ethyl]- derivatives do not undergo rearrangement, but are very labile in trifluoroacetic acid (100% cleaved in 5 min). The cyclohexyl and isopropyl derivatives are more stable to acid, but undergo some rearrangement. The cyclohexyl group combines minimal rearrangement with ready removal.[1] A comparison has been made with several other common protective groups for tyrosine, and the degree of alkylation *ortho* to the phenolic OH decreases in the order Bn > 2-$ClC_6H_4CH_2$ >2,6-$Cl_2C_6H_3CH_2$ > cyclohexyl > *t*-Bu ~ benzyloxycarbonyl ~2-Br-benzyloxycarbonyl.[2]

1. M. Engelhard and R. B. Merrifield, *J. Am. Chem. Soc.*, **100**, 3559 (1978).
2. J. P. Tam, W. F. Heath, and R. B. Merrifield, *Int. J. Pept. Protein Res.*, **21**, 57 (1983).

***t*-Butyl Ether:** ArOC$(CH_3)_3$ (Chart 4)

Formation

1. Isobutylene, cat. concd. H_2SO_4, CH_2Cl_2, 25°, 6–10 h, 93% yield.[1] These conditions also convert carboxylic acids to *t*-Bu esters.
2. Isobutylene, CF_3SO_3H, CH_2Cl_2, −78°, 70–90% yield.[2] These conditions will protect a phenol in the presence of a primary alcohol.
3. *t*-Butyl halide, Pyr, 20–30°, few h, 65–95% yield.[3]

Cleavage

The section on *t*-butyl ethers of alcohols should also be consulted.

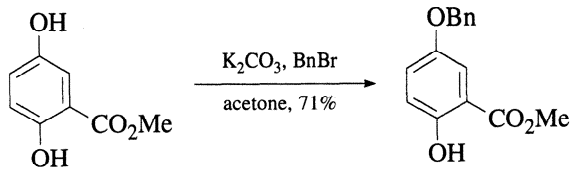
1. Anhyd. CF_3CO_2H, 25°, 16 h, 81% yield.[1]
2. CF_3CH_2OH, CF_3SO_3H, −5°, 60 sec, 100% yield.[2]

1. H. C. Beyerman and J. S. Bontekoe, *Recl. Trav. Chim. Pays-Bas*, **81**, 691 (1962).
2. J. L. Holcombe and T. Livinghouse, *J. Org. Chem.*, **51**, 111 (1986).
3. H. Masada and Y. Oishi, *Chem. Lett.*, 57 (1978).

Benzyl Ether: $ArOCH_2C_6H_5$ (Chart 4)

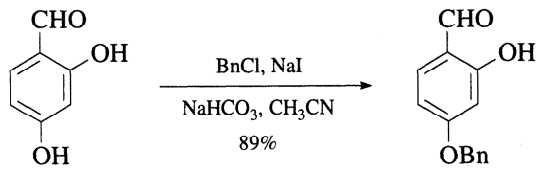
Formation

1. In general, benzyl ethers are prepared from a phenol by treating an alkaline solution of the phenol with a benzyl halide.[1]



Ref. 2

2.

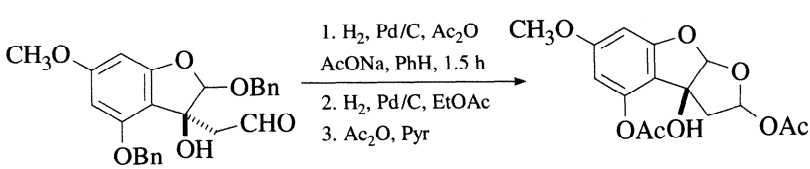


Ref. 3

3. $CHCl_3$, MeOH, K_2CO_3, BnBr, 4 h, heat.[4] In this case, some (5:1) selectivity was achieved for a less hindered phenol in the presence of a more hindered one.
4. Benzyl ethers of phenols can also be prepared by reaction with phenyldiazomethane.
5. $(BnO)_2CO$, DMF, 155°, 2 h, 80% yield. Active methylenes are also benzylated.[5]

Cleavage

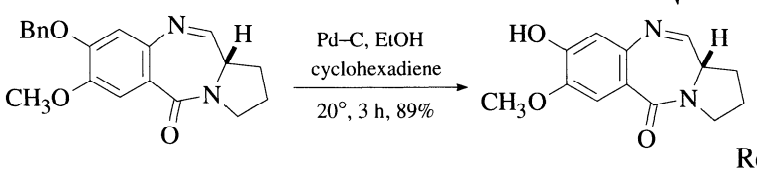
1.



Catalytic hydrogenation in acetic anhydride–benzene removes the aromatic benzyl ether and forms a monoacetate; hydrogenation in ethyl acetate removes the aliphatic benzyl ether to give, after acetylation, the diacetate.[6] Trisubstituted alkenes can be retained during the hydrogenolysis of a phenolic benzyl ether.[7]

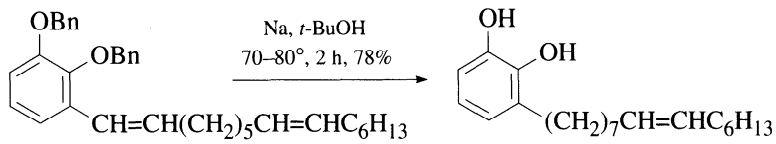
2. Pd–C, 1,4-cyclohexadiene, 25°, 1.5 h, 95–100% yield.[8]

Note: the imine is not reduced



Ref. 9

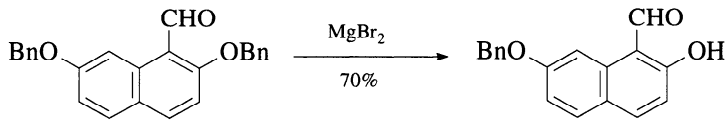
3. Palladium black, a more reactive catalyst than Pd–C, must be used to cleave the more stable aliphatic benzyl ethers.[8]
4. Na, *t*-BuOH, 70–80°, 2 h, 78%.[10]



In this example, sodium in *t*-butyl alcohol cleaves two aryl benzyl ethers and reduces a double bond that is conjugated with an aromatic ring; non-conjugated double bonds are stable.

5. $BF_3{\cdot}Et_2O$, EtSH, 25°, 40 min, 80–90% yield.[11] Addition of sodium sulfate prevents hydrolysis of a dithioacetal group present in the compound; replacement of ethanethiol with ethanedithiol prevents cleavage of a dithiolane group.
6. CF_3OSO_2F or CH_3OSO_2F, $PhSCH_3$, CF_3CO_2H, 0°, 30 min, 100% yield.[12] Thioanisole suppresses acid-catalyzed rearrangement of the benzyl group to form 3-benzyltyrosine. The more acid-stable 2,6-dichlorobenzyl ether is cleaved in a similar manner.
7. Me_3SiI, CH_3CN, 25–50°, 100% yield.[13] Selective removal of protective groups is possible with this reagent, since a carbamate, $=NCOOCMe_3$, is cleaved in 6 min at 25°; an aryl benzyl ether is cleaved in 100% yield, with no formation of 3-benzyltyrosine, in 1 h at 50°, at which time a methyl ester begins to be cleaved.
8. 2-Bromo-1,3,2-benzodioxaborole, CH_2Cl_2, 95% yield.[14]
9. NaI, $BF_3{\cdot}Et_2O$, 0°, 45 min, rt, 15 min. 75–90% yield.[15]
10. CF_3CO_2H, $PhSCH_3$, 25°, 3 h.[16] The use of dimethyl sulfide or anisole as a cation scavenger was not as effective because of side reactions. Benzyl ethers of serine and threonine were slowly cleaved (30% in 3 h; complete cleavage in 30 h). The use of pentamethylbenzene has been shown to increase the rate of deprotection of *O*-Bn-Tyrosine.[17]
11. $PhNMe_2$, $AlCl_3$, CH_2Cl_2, 78–91% yield.[18]

12. $MgBr_2$, benzene, Et_2O, reflux, 24 h, 63–95% yield.[19]



13. Dimethyldioxirane, acetone, 20°, 45 h, 69% yield.[20]
14. Calcium, ammonia, 95% yield.[21]
15. $SnBr_2$, AcBr, CH_2Cl_2, rt, 5–24 h, 76–86% yield. These conditions convert a benzyl ether to the acetate and are effective for alkyl benzyl ethers as well.[22]
16. $TiCl_3$, Mg, THF, reflux, 28–96% yield.[23]
17. TFA, pentamethylbenzene. This method was developed to minimize the formation of 3-benzyltyrosine during the acidolysis of benzyl-protected tyrosine.[24]

1. For example, M. C. Venuti, B. E. Loe, G. H. Jones, and J. M. Young, *J. Med. Chem.*, **31**, 2132 (1988).
2. N. R. Kotecha, S. V. Ley, and S. Montégani, *Synlett*, 395 (1992).
3. W. L. Mendelson, M. Holmes, and J. Dougherty, *Synth. Commun.*, **26**, 593 (1996).
4. H. Schmidhammer and A. Brossi, *J. Org. Chem.*, **48**, 1469 (1983).
5. M. Selva, C. A. Margues, and P. Tundo, *J. Chem. Soc., Perkin Trans. 1*, 1889 (1995).
6. G. Büchi and S. M. Weinreb, *J. Am. Chem. Soc.*, **93**, 746 (1971).
7. A. F. Barrero, E. J. Alvarez-Manzaneda, and R. Chahboun, *Tetrahedron Lett.*, **38**, 8101 (1997).
8. A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki, and J. Meienhofer, *J. Org. Chem.*, **43**, 4194 (1978).
9. D. E. Thurston, V. S. Murty, D. R. Langley, and G. B. Jones, *Synthesis*, 81 (1990).
10. B. Loev and C. R. Dawson, *J. Am. Chem. Soc.*, **78**, 6095 (1956).
11. K. Fuji, K. Ichikawa, M. Node, and E. Fujita, *J. Org. Chem.*, **44**, 1661 (1979).
12. Y. Kiso, H. Isawa, K. Kitagawa, and T. Akita, *Chem. Pharm. Bull.*, **26**, 2562 (1978).
13. R. S. Lott, V. S. Chauhan, and C. H. Stammer, *J. Chem. Soc., Chem. Commun.*, 495 (1979).
14. P. F. King and S. G. Stroud, *Tetrahedron Lett.*, **26**, 1415 (1985).
15. Y. D. Vankar and C. T. Rao, *J. Chem. Res., Synop.*, 232 (1985).
16. Y. Kiso, K. Ukawa, S. Nakamura, K. Ito, and T. Akita, *Chem. Pharm. Bull.*, **28**, 673 (1980).
17. H. Yoshino, Y. Tsuchiya, I. Saito, and M. Tsujii, *Chem. Pharm. Bull.*, **35**, 3438 (1987).
18. T. Akiyama, H. Hirofuji, and S. Ozaki, *Tetrahedron Lett.*, **32**, 1321 (1991).
19. J. E. Baldwin and G. G. Haraldsson, *Acta. Chem. Scand., Ser. B*, **B40**, 400 (1986).

20. B. A. Marples, J. P. Muxworthy, and K. H. Baggaley, *Synlett*, 646 (1992).
21. J. R. Hwu, Y. S. Wein, and Y.-J. Leu, *J. Org. Chem.*, **61**, 1493 (1996).
22. T. Oriyama, M. Kimura, M. Oda, and G. Koga, *Synlett*, 437 (1993).
23. S. M. Kadam, S. K. Nayak, and A. Banerji, *Tetrahedron Lett.*, **33**, 5129 (1992).
24. H. Yoshino, M. Tsujii, M. Kodama, K. Komeda, N. Niikawa, T. Tanase, N. Asakawa, K. Nose, and K. Yamatsu, *Chem. Pharm. Bull.*, **38**, 1735 (1990).

2,6-Dimethylbenzyl Ether: $2,6\text{-}(CH_3)_2C_6H_3CH_2OAr$

The 2,6-dimethylbenzyl ether is considerably more stable to hydrogenolysis than the benzyl ether. It has a half-life of 15 h at 1 atm of hydrogen in the presence of Pd–C, whereas the benzyl ether has a half-life of ~45 min. This added stability allows hydrogenation of azides, nitro groups, and olefins in the presence of a dimethylbenzyl group.[1]

1. R. Davis and J. M. Muchowski, *Synthesis*, 987 (1982).

4-Methoxybenzyl (MPM–OAr or PMB–OAr) Ether: $4\text{-}CH_3OC_6H_4CH_2OAr$

Formation

1. $MeOC_6H_4CH_2Cl$, $Bu_4N^+I^-$, K_2CO_3, acetone, 55°, 96% yield.[1] Sodium iodide can be used in place of $Bu_4N^+I^-$.[2]
2. $MeOC_6H_4CH_2Br$, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, rt, 80% yield.[3]

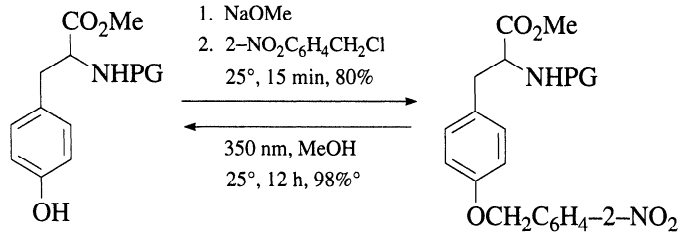
Cleavage

1. CF_3CO_2H, CH_2Cl_2, 85% yield.[1]
2. Camphorsulfonic acid, $(CH_3)_2C(OCH_3)_2$, rt.[3]
3. $BF_3{\cdot}Et_2O$, $NaCNBH_3$, THF, reflux, 6–10 h, 65–77% yield.[4]
4. 18-Crown-6, toluene, K, 2–3 h, 81–96% yield.[5]
5. Acetic acid, 90°, 89–96% yield.[6] Benzyl groups are not affected by these conditions.
6. DDQ, 35% yield.[7] The DDQ-promoted cleavage of phenolic MPM ethers can be complicated by overoxidation, especially with electron-rich phenolic compounds.
7. 5% Pd–C, H_2. In the presence of pyridine, hydrogenolysis of the MPM group is suppressed.[8]

1. J. D. White and J. C. Amedio, Jr., *J. Org. Chem.*, **54**, 736 (1989).
2. I. A. McDonald, P. L. Nyce, M. J. Jung, and J. S. Sabol, *Tetrahedron Lett.*, **32**, 887 (1991).

3. H. Nagaoka, G. Schmid, H. Iio, and Y. Kishi, *Tetrahedron Lett.*, **22**, 899 (1981).
4. A. Srikrishna, R. Viswajanani, J. A. Sattigeri, and D. Vijaykumar, *J. Org. Chem.*, **60**, 5961 (1995).
5. T. Ohsawa, K. Hatano, K. Kayoh, J. Kotabe, and T. Oishi, *Tetrahedron Lett.*, **33**, 5555 (1992).
6. K. J. Hodgetts and T. W. Wallace, *Synth. Commun.*, **24**, 1151 (1994).
7. O. P. Vig, S. S. Bari, A. Sharma, and M. A. Sattar, *Indian J. Chem., Sect. B*, **29B**, 284 (1990).
8. H. Sajiki, H. Kuno, and K. Hirota, *Tetrahedron Lett.*, **38**, 399 (1997).

o-Nitrobenzyl Ether: *o*-NO_2–$C_6H_4CH_2OAr$ (Chart 4)



An *o*-nitrobenzyl ether can be cleaved by photolysis. In tyrosine, this avoids the use of acid-catalyzed cleavage and the attendant conversion to 3-benzyltyrosine.[1] (Note that this unwanted conversion can also be suppressed by the addition of thioanisole; see benzyl ether cleavage.)

1. B. Amit, E. Hazum, M. Fridkin, and A. Patchornik, *Int. J. Pept. Protein Res.*, **9**, 91 (1977).

2,6-Dichlorobenzyl Ether: $ArOCH_2C_6H_3$–2,6-Cl_2

This group is readily cleaved by a mixture of CF_3SO_3H, $PhSCH_3$, and CF_3CO_2H.[1,2] Of the common benzyl groups used to protect the hydroxyl of tyrosine, the 2,6-dichlorobenzyl shows a low incidence of alkylation at the 3-position of tyrosine during cleavage with HF/anisole. A comparative study of the deprotection of X-Tyr in HF/anisole gives the following percentages of side reactions for various X groups: Bn, 24.5; 2-ClBn, 9.8; 2,6-Cl_2Bn, 6.5; cyclohexyl, 1.5; *t*-Bu, <0.2; Cbz, 0.5; 2-Br-Cbz, 0.2.[3]

3,4-Dichlorobenzyl Ether: 3,4-$Cl_2C_6H_3CH_2OAr$

The electron-withdrawing chlorine atoms confer greater acid stability to this group than that conferred on the usual benzyl group. It is cleaved by hydrogenolysis (Pd/C–H_2).[4]

1. Y. Kiso, M. Satomi, K. Ukawa, and T. Akita, *J. Chem. Soc., Chem. Commun.*, 1063 (1980).
2. J. Deng, Y. Hamada, and T. Shioiri, *Tetrahedron Lett.*, **37**, 2261 (1996).
3. J. P. Tam, W. F. Heath, and R. B. Merrifield, *Int. J. Pept. Protein Res.*, **21**, 57 (1983).
4. D. A. Evans, C. J. Dinsmore, D. A. Evrard, and K. M. DeVries, *J. Am. Chem. Soc.*, **115**, 6426 (1993).

4-(Dimethylamino)carbonylbenzyl Ether: $(CH_3)_2NCOC_6H_4CH_2OAr$

The 4-(dimethylamino)carbonylbenzyl ether has been used to protect the phenolic hydroxyl of tyrosine. It is stable to CF_3CO_2H (120 h), but not to HBr/AcOH. (Complete cleavage occurs in 16 h.) It can also be cleaved by hydrogenolysis (H_2/Pd–C).[1]

1. V. S. Chauhan, S. J. Ratcliffe, and G. T. Young, *Int. J. Pept. Protein Res.*, **15**, 96 (1980).

4-Methylsulfinylbenzyl (Msib) Ether: $CH_3S(O)C_6H_4CH_2OAr$

The Msib group has been used for the protection of tyrosine. It is cleaved by reduction of the sulfoxide to the sulfide, which is then deprotected with acid. Reduction is achieved with DMF–SO_3/$HSCH_2CH_2SH$ or $Bu_4N^+I^{-1}$ or with $SiCl_3$/TFA.[2]

1. S. Futaki, T. Yagami, T. Taike, T. Ogawa, T. Akita, and K. Kitagawa, *Chem. Pharm. Bull.*, **38**, 1165 (1990).
2. Y. Kiso, S. Tanaka, T. Kimura, H. Itoh, and K. Akaji, *Chem. Pharm. Bull.*, **39**, 3097 (1991).

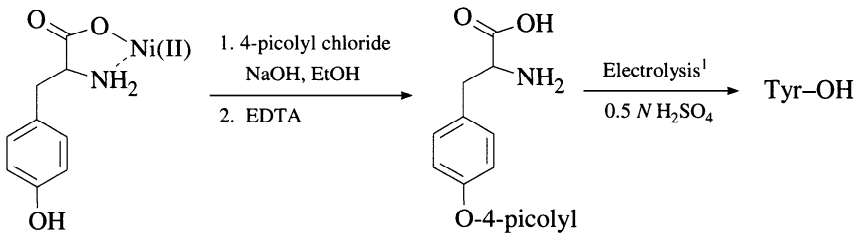
9-Anthrylmethyl Ether: $ArOCH_2$–9-anthryl (Chart 4)

9-Anthrylmethyl ethers, formed from the sodium salt of a phenol and 9-anthrylmethyl chloride in DMF, can be cleaved with CH_3SNa (DMF, 25°, 20 min, 85–99% yield). They are also cleaved by CF_3CO_2H/CH_2Cl_2 (0°, 10 min, 100% yield); they are stable to CF_3CO_2H/dioxane (25°, 1 h).[1]

1. N. Kornblum and A. Scott, *J. Am. Chem. Soc.*, **96**, 590 (1974).

4-Picolyl Ether: $ArOCH_2$–4-pyridyl (Chart 4)

***Formation*[1]*/Cleavage*[1,2]**

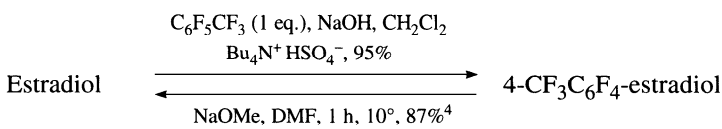


An aryl 4-picolyl ether is stable to trifluoroacetic acid, used to cleave an *N*-*t*-butoxycarbonyl group.[2]

1. A. Gosden, D. Stevenson, and G. T. Young, *J. Chem. Soc., Chem. Commun.*, 1123 (1972).
2. P. M. Scopes, K. B. Walshaw, M. Welford, and G. T. Young, *J. Chem. Soc.*, 782 (1965).

Heptafluoro-*p*-tolyl and Tetrafluoro-4-pyridyl Ethers: $ArOC_6F_4$–CF_3, $ArOC_5F_4N$

***Formation/Cleavage*[1–3]**



If 2 eq. of reagent are used, both hydroxyls can be protected, and the phenolic hydroxyl can be selectively cleaved with NaOMe. The tetrafluoropyridyl derivative is introduced under similar conditions. The use of this methodology has been reviewed.[5]

1. M. Jarman and R. McCague, *J. Chem. Soc., Chem. Commun.*, 125 (1984).
2. M. Jarman and R. McCague, *J. Chem. Res., Synop.*, 114 (1985).
3. J. J. Deadman, R. McCague, and M. Jarman, *J. Chem. Soc., Perkin Trans. 1*, 2413 (1991).
4. S. Singh and R. A. Magarian, *Chem. Lett.*, 1821 (1994).
5. M. Jarman *J. Fluorine Chem.*, **42**, 3 (1989).

Silyl Ethers

Aryl and alkyl trimethylsilyl ethers can often be cleaved by refluxing in aqueous methanol, an advantage for acid- or base-sensitive substrates. The ethers are stable to Grignard and Wittig reactions and to reduction with lithium aluminum hydride at −15°. Aryl *t*-butyldimethylsilyl ethers and other sterically more demanding silyl ethers require acid- or fluoride ion-catalyzed hydrolysis for removal. Increased steric bulk also improves their stability to a much harsher set of conditions. An excellent review of the selective deprotection of alkyl silyl ethers and aryl silyl ethers has been published.[1]

1. T. D. Nelson and R. D. Crouch, *Synthesis*, 1031 (1996).

Trimethylsilyl (TMS) Ether: $ArOSi(CH_3)_3$

Formation

1. Me_3SiCl, Pyr, 30–35°, 12 h, satisfactory yield.[1]
2. $(Me_3Si)_2NH$, cat. concd. H_2SO_4, reflux, 2 h, 97% yield.[2]
3. A large number of other silylating agents have been described for the derivatization of phenols, but the first two are among the most common.[3]

Cleavage

Trimethylsilyl ethers are readily cleaved by fluoride ion, mild acids, and mild bases. If the TMS derivative is somewhat hindered, it also becomes less susceptible to cleavage. A phenolic TMS ether can be cleaved in the presence of an alkyl TMS ether [Dowex 1-x8 (HO^-), EtOH, rt, 6 h, 78% yield].[4]

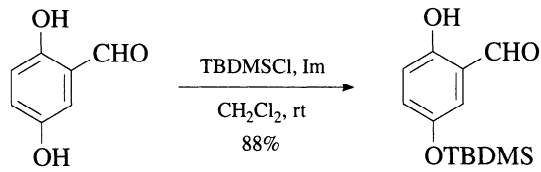
1. Cl. Moreau, F. Roessac, and J. M. Conia, *Tetrahedron Lett.*, 3527 (1970).
2. S. A. Barker and R. L. Settine, *Org. Prep. Proced. Int.*, **11**, 87 (1979).
3. G. van Look, G. Simchen, and J. Heberle, *Silylating Agents*, Fluka Chemie, AG, 1995.
4. Y. Kawazoe, M. Nomura, Y. Kondo, and K. Kohda, *Tetrahedron Lett.*, **28**, 4307 (1987).

t-Butyldimethylsilyl (TBDMS) Ether: $ArOSi(CH_3)_2C(CH_3)_3$ (Chart 4)

The section on alcohol protection should be examined, since many of the methods for the formation and cleavage of TBDMS ethers are similar.

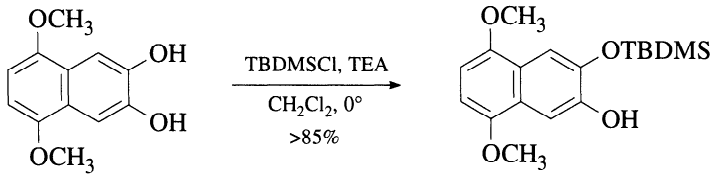
Formation

1. *t*-$BuMe_2SiCl$, DMF, imidazole, 25°, 3 h, 96% yield.[1, 2]

2. 

Ref. 3

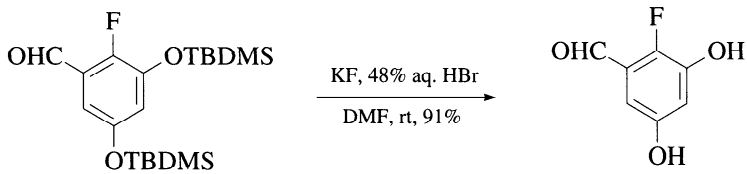
3. *t*-$BuMe_2SiOH$, Ph_3P, DEAD, 86% yield. In this case, the standard methods for silyl ether formation were unsuccessful.[4]

4. 

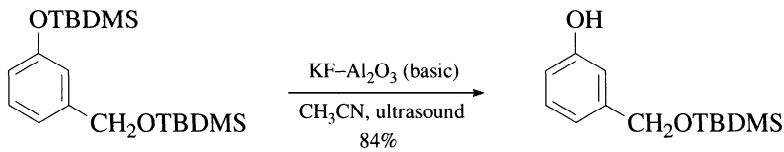
Ref. 5

Cleavage

1. 0.1 *M* HF, 0.1 *M* NaF, pH 5, THF, 25°, 2 days, 77% yield.[1] In this substrate, a mixture of products resulted from the attempted cleavage of the *t*-butyldimethylsilyl ether with tetra-*n*-butylammonium fluoride, the reagent generally used.[6]
2. KF, 48% aq. HBr, DMF, rt, 91% yield.[7]



The use of $Bu_4N^+F^-$ results in decomposition of this substrate.

3. 

Ref. 8

4. $PdCl_2(CH_3CN)_2$, aq. acetone, 75°, 10–96% yield.[9]
5. $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 8 h.[10]
6. K_2CO_3, Kriptofix 222, CH_3CN, 55°, 2 h, 70–95% yield.[11,12] Phenolic silyl ethers are cleaved selectively, but when TsOH or $BF_3{\cdot}Et_2O$ is used, alkyl TBDMS groups are cleaved in preference to phenolic derivatives.

7. Amberlite IRA-400 fluoride form, CH_2Cl_2 or DMF; then elute with aq. HCl, 80–90% yield.[13]

Table 1 gives the relative half-life to acid or base hydrolysis of a number of silylated *p*-cresols.[14]

Table 1. Susceptibility of Silylated Cresols to Hydrolysis

	Half-life ($t_{1/2}$, min) at 25°	
Substrate	Acid Hydrolysis 1% HCl in 95% MeOH	Base Hydrolysis 5% NaOH in 95% MeOH
p-$MeC_6H_4OSiEt_3$	≤1[a]	≤1[a]
p-MeC_6H_4OSi–*i*-$BuMe_2$	≤1[a]	≤1[a]
p-MeC_6H_4OSi–*t*-$BuMe_2$	273	3.5
p-MeC_6H_4OSi–*t*-$BuPh_2$	100 (h)	6.5
p-MeC_6H_4OSi–*i*-Pr_3	100 (h)	188

[a] A $t_{1/2}$ of 1 min is a minimum value because of sampling methods.

1. P. M. Kendall, J. V. Johnson, and C. E. Cook, *J. Org. Chem.*, **44**, 1421 (1979).
2. R. C. Ronald, J. M. Lansinger, T. S. Lillie, and C. J. Wheeler, *J. Org. Chem.*, **47**, 2541 (1982).
3. A. Liu, K. Dillon, R. M. Campbell, D. C. Cox, and D. M. Huryn, *Tetrahedron Lett.*, **37**, 3785 (1996).
4. D. L. J. Clive and D. Kellner, *Tetrahedron Lett.*, **32**, 7159 (1991).
5. A. Kojima, T. Takemoto, M. Sodeoka, and M. Shibasaki, *J. Org. Chem.*, **61**, 4876 (1996).
6. E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
7. A. K. Sinhababu, M. Kawase, and R. T. Borchardt, *Synthesis*, 710 (1988).
8. E. A. Schmittling and J. S. Sawyer, *Tetrahedron Lett.*, **32**, 7207 (1991).
9. N. S. Wilson and B. A. Keay, *Tetrahedron Lett.*, **37**, 153 (1996).
10. S. Mabic and J.-P. Lepoittevin, *Synlett*, 851 (1994).
11. C. Prakash, S. Saleh, and I. A. Blair, *Tetrahedron Lett.*, **35**, 7565 (1994).
12. N. S. Wilson and B. A. Keay, *Tetrahedron Lett.*, **38**, 187 (1997).
13. B. P. Bandgar, S. D. Unde, D. S. Unde, V. H. Kulkarni, and S. V. Patil, *Indian J. Chem., Sect. B*, **33B**, 782 (1994).
14. J. S. Davies, C. L. Higginbotham, E. J. Tremeer, C. Brown, and R. C. Treadgold, *J. Chem. Soc., Perkin Trans. 1*, 3043 (1992).

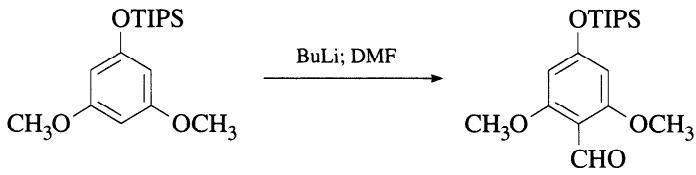
t-Butyldiphenylsilyl (TBDPS) Ether: $(CN_3)_3C(C_6H_5)_2SiOR$

The TBDPS ether has been used for the monoprotection of a catechol (TBDPSCl, Im, DMF, 5 h, 83% yield)[1] or simple phenol protection. It is cleaved with $Bu_4N^+F^-$ (THF, 94% yield).[2]

1. J. C. Kim and W.-W. Park, *Org. Prep. Proced. Int.*, **26**, 479 (1994).
2. A. B. Smith, III, J. Barbosa, W. Wong, and J. L. Wood, *J. Am. Chem. Soc.*, **118**, 8316 (1996).

Triisopropylsilyl (TIPS) Ether: $((CN_3)_2CH)_3SiOR$

The bulk of the TIPS group, introduced with TIPSCl (DMF, Im, 92% yield), directs metallation away from the silyl group as illustrated.[1]



1. J. J. Landi, Jr., and K. Ramig, *Synth. Commun.*, **21**, 167 (1991).

Esters

Aryl esters, prepared from the phenol and an acid chloride or anhydride in the presence of base, are readily cleaved by saponification. In general, they are more readily cleaved than the related esters of alcohols, thus allowing selective removal of phenolic esters. 9-Fluorenecarboxylates and 9-xanthenecarboxylates are also cleaved by photolysis. To permit selective removal, a number of carbonate esters have been investigated: aryl benzyl carbonates can be cleaved by hydrogenolysis; aryl 2,2,2-trichloroethyl carbonates by Zn/THF-H_2O. Esters of electron-deficient phenols are good acylating agents for alcohols and amines.

Aryl Formate: HCO_2Ar

The formate ester of phenol is rarely formed, but can be prepared from the phenol, formic acid, and DCC, 94–99% yield. The formate ester is not very stable to basic conditions or to other good nucleophiles.[1]

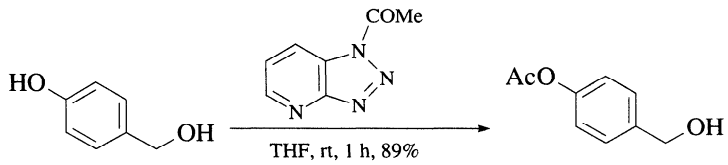
1. J. Huang and H. K. Hall, Jr., *J. Chem. Res., Synop.*, 292 (1991).

Aryl Acetate: $ArOCOCH_3$ (Chart 4)

Formation

1. AcCl, NaOH, dioxane, $Bu_4N^+HSO_4^-$, 25°, 30 min, 90% yield.[1] Phase-transfer catalysis with tetra-*n*-butylammonium hydrogen sulfate effects acylation of sterically hindered phenols and selective acylation of a phenol in the presence of an aliphatic secondary alcohol.

2. 1-Acetyl-*v*-triazolo[4,5-*b*]pyridine, THF, 1 *N* NaOH, 30 min.[2]



This method is also effective in the selective introduction of a benzoate ester.

3. IPA, NaOH, Ac_2O, pH 7.8. Phenols are selectively esterified in the presence of other alcohols.[3] These authors also showed that an alcohol could be acetylated in the presence of an amine using Ac_2O and Amberlyst 15 resin.
4. *Chromobacterium viscosum* lipase, cyclohexane, vinyl acetate, THF, 40°.[4]

Cleavage

1. $NaHCO_3$/aq. MeOH, 25°, 0.75 h, 94% yield.[5]
2. 3 *N* HCl, acetone, reflux, 2 h.[6]
3. Aq. NH_3, 0°, 48 h.[6]
4. $NaBH_4$, $HO(CH_2)_2OH$, 40°, 18 h, 87% yield.[7] Lithium aluminum hydride can be used to effect efficient ester cleavage if no other functional group is present that can be attacked by this strong reducing agent.[8]
5. $NaBH_4$, LiCl, diglyme. A diacylated guanidine was not deacylated under these conditions, whereas the usual basic conditions for acetate hydrolysis also resulted in guanidine deacylation.[9]
6. Sm, I_2, EtOH, 82–100% yield. Esters of other alcohols are similarly deacylated.[10]

The following conditions selectively remove a phenolic acetate in the presence of a normal alkyl acetate:

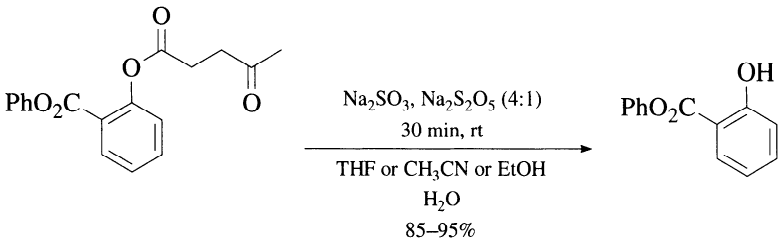
7. TsOH, SiO_2, toluene, 80°, 6–40 h, 79–100% yield.[11]
8. $(NH_2)_2C{=}NH$, MeOH, 50°, 95% yield.[12]
9. $Me_2NCH_2C(O)N(OH)Me$, MeOH or THF/H_2O, 84% yield.[13]
10. Zn, MeOH, 91–100% yield.[14]
11. Neutral alumina, microwaves, 82–96% yield.[15]
12. Bi(III)-mandelate, DMSO, 80–125°, 44–96% yield. Phenolic acetates with strong electron-withdrawing groups are hydrolyzed the fastest.[16]
13. Porcine pancreatic lipase, 28–30°, 95% yield.[17]
14. *Candida cylindracea* lipase, BuOH, hexane, 3 h, 25°, 40–100% yield.[18]

1. V. O. Illi, *Tetrahedron Lett.*, 2431 (1979).
2. M. P. Paradisi, G. P. Zecchini, and I. Torrini, *Tetrahedron Lett.*, **27**, 5029 (1986).
3. V. Srivastava, A. Tandon, and S. Ray, *Synth. Commun.*, **22**, 2703 (1992).

4. G. Nicolosi, M. Piattelli, and C. Sanfilippo, *Tetrahedron*, **48**, 2477 (1992).
5. For example, see G. Büchi and S. M. Weinreb, *J. Am. Chem. Soc.*, **93**, 746 (1971).
6. E. Haslam, G. K. Makinson, M. O. Naumann, and J. Cunningham, *J. Chem. Soc.*, 2137 (1964).
7. J. Quick and J. K. Crelling, *J. Org. Chem.*, **43**, 155 (1978).
8. H. Mayer, P. Schudel, R. Rüegg, and O. Isler, *Helv. Chim. Acta*, **46**, 650 (1963).
9. D. Huber, G. Leclerc, and G. Andermann, *Tetrahedron Lett.*, **27**, 5731 (1986).
10. R. Yanada, N. Negoro, K. Bessho, and K. Yanada, *Synlett*, 1261 (1995).
11. G. Blay, M. L. Cardona, M. B. Garcia, and J. P. Pedro, *Synthesis*, 438 (1989).
12. N. Kunesch, C. Miet, and J. Poisson, *Tetrahedron Lett.*, **28**, 3569 (1987).
13. M. Ono and I. Itoh, *Tetrahedron Lett.*, **30**, 207 (1989).
14. A. G. González, Z. D. Jorge, H. L. Dorta, and F. R. Luis, *Tetrahedron Lett.*, **22**, 335 (1981).
15. R. S. Varma, M. Varma, and A. K. Chatterjee, *J. Chem. Soc., Perkin Trans. 1*, 999 (1993).
16. V. Le Boisselier, M. Postel, and E. Duñch, *Tetrahedron Lett.*, **38**, 2981 (1997).
17. V. S. Parmar, A. Kumar, K. S. Bisht, S. Mukherjee, A. K. Prasad, S. K. Sharma, J. Wengel, and C. E. Olsen, *Tetrahedron*, **53**, 2163 (1997).
18. G. Pedrocchi-Fantoni and S. Servi, *J. Chem. Soc., Perkin Trans. 1*, 1029 (1992).

Aryl Levulinate: $CH_3COCH_2CH_2CO_2Ar$

Cleavage[1]

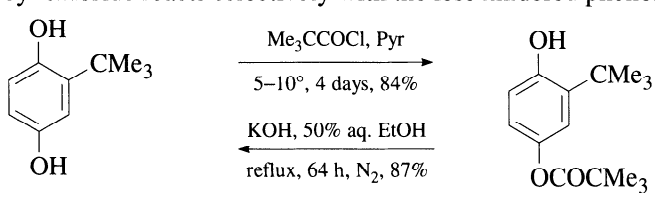


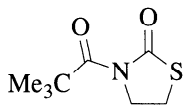
1. M. Ono and I. Itoh, *Chem. Lett.*, 585 (1988).

Aryl Pivaloate (ArOPv): $(CH_3)_3CCO_2Ar$ (Chart 4)

Formation/Cleavage[1]

1. Pivaloyl chloride reacts selectively with the less hindered phenol group.



2.  NaH, THF, 99% yield.[2] This method works well for the esterification of a phenol in the presence of an aniline. When the thiazolidone is reacted with a hydroxyaniline in the absence of base, only the nitrogen is derivatized to form a pivalamide.[3]

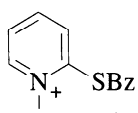
1. L. K. T. Lam and K. Farhat, *Org. Prep. Proced. Int.*, **10**, 79 (1978).
2. K. C. Nicolaou and W.-M. Dai, *J. Am. Chem. Soc.*, **114**, 8908 (1992).
3. W.-M. Dai, Y. K. Cheung, K. W. Tang, P. Y. Choi, and S. L. Chung, *Tetrahedron*, **51**, 12263 (1995).

Aryl Benzoate: $ArOCOC_6H_5$ (Chart 4)

Aryl benzoates, stable to alkylation conditions using K_2CO_3/Me_2SO_4, are cleaved by more basic hydrolysis (KOH).[1] They are stable to anhydrous hydrogen chloride,[2] but are cleaved by hydrochloric acid.[3]

Formation

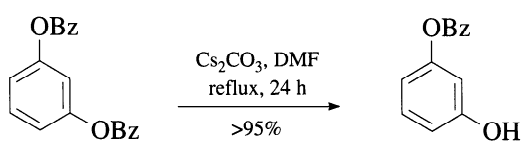
1. $(ClCO)_2$, Me_2NCHO, PhCOOH; Pyr, 20°, 2 h, 90% yield.[4]



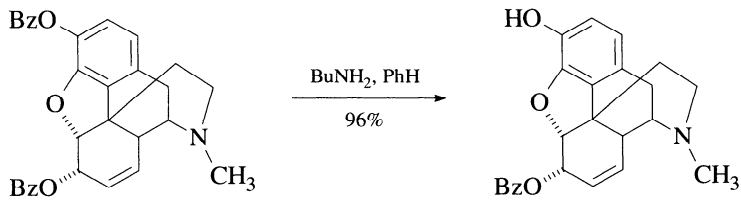
2. CH_3 Cl^- aq. $NaHCO_3$ or aq. NaOH, 80% yield.[5] This reagent forms aryl benzoates under aqueous conditions. (It also acylates amines and carboxylic acids.)
3. Monoesterification of a symmetrical dihydroxy aromatic compound can be effected by reaction with polymer-bound benzoyl chloride (Pyr, benzene, reflux, 15 h) to give a polymer-bound benzoate, which can be alkylated with diazomethane to form, after basic hydrolysis (0.5 *M* NaOH, dioxane, H_2O, 25°, 20 h, or 60°, 3 h),[6] a monomethyl ether.
4. $Fe_2(SO_4)_3$–SiO_2, methyl benzoate, 97% yield.[7]

Cleavage

1. Under anhydrous conditions, cesium carbonate or bicarbonate quantitatively cleaves an aryl dibenzoate or diacetate to the monoester; yields are considerably lower with potassium carbonate.[8]



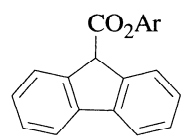
2. $BuNH_2$, benzene, rt, 1–24 h, >85% yield.[9] This method is generally selective for phenolic esters.



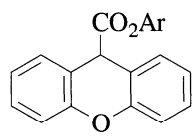
3. 2-Bromo-1,3,2-benzodioxaborole, CH_2Cl_2 (cat. $BF_3{\cdot}Et_2O$), 25°, 0.25 h, 71% yield.[10]

1. M. Gates, *J. Am. Chem. Soc.*, **72**, 228 (1950).
2. D. D. Pratt and R. Robinson, *J. Chem. Soc.*, 1577 (1922).
3. A. Robertson and R. Robinson, *J. Chem. Soc.*, 1710 (1927).
4. P. A. Stadler, *Helv. Chim. Acta*, **61**, 1675 (1978).
5. M. Yamada, Y. Watabe, T. Sakakibara, and R. Sudoh, *J. Chem. Soc., Chem. Commun.*, 179 (1979).
6. C. C. Leznoff and D. M. Dixit, *Can. J. Chem.*, **55**, 3351 (1977).
7. T. Nishiguchi and H. Taya, *J. Chem. Soc., Perkin Trans. 1*, 172 (1990).
8. H. E. Zaugg, *J. Org. Chem.*, **41**, 3419 (1976).
9. K. H. Bell, *Tetrahedron Lett.*, **27**, 2263 (1986).
10. P. F. King and S. G. Stroud, *Tetrahedron Lett.*, **26**, 1415 (1985).

Aryl 9-Fluorenecarboxylate (Chart 4):



Aryl 9-fluorenecarboxylates (designed to be cleaved photolytically) were prepared from the phenol and the acid chloride (9-fluorenecarbonyl chloride, Pyr, C_6H_6, 25°, 1 h, 65% yield) and cleaved by photolysis ($h\nu$, Et_2O, reflux, 4 h, 60% yield). The related aryl **xanthenecarboxylates**, **i**, were prepared and cleaved in the same way.[1]



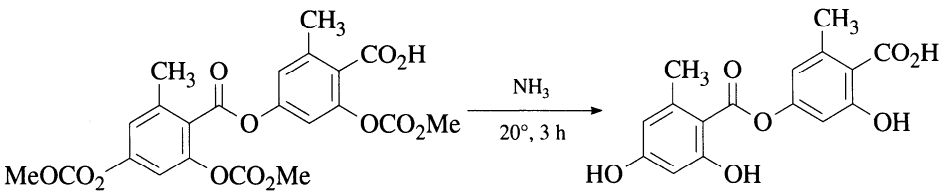
i

1. D. H. R. Barton, Y. L. Chow, A. Cox, and G. W. Kirby, *J. Chem. Soc.*, 3571 (1965).

Carbonates

Aryl Methyl Carbonate: $ArOCO_2CH_3$ (Chart 4)

In an early synthesis, a methyl carbonate, prepared by reaction of a phenol with methyl chloroformate, was cleaved selectively in the presence of a phenyl ester.[1]



More recently, an ethyl carbonate was cleaved by refluxing in acetic acid for 6 h.[2]

1. E. Fischer and H. O. L. Fischer, *Ber.*, **46**, 1138 (1913).
2. E. Haslam, R. D. Haworth, and G. K. Makinson, *J. Chem. Soc.*, 5153 (1961).

1-Adamantyl Carbonate (Adoc-OAr)

The adamantyl carbonate is prepared from $Adoc_2CO_3$ (DMAP, CH_3CN, >79% yield)[1] or, in the case of electron-deficient phenols, the fluoroformate (THF, Pyr, 54–95% yield).[2] It is somewhat more stable to TFA than the adamantyl carbamate.

1. B. Nyasse and U. Ragnarsson, *Acta Chem. Scand.*, **47**, 374 (1993).
2. I. Niculescu-Duvaz and C. J. Springer, *J. Chem. Res., Synop.*, 242 (1994).

The BOC derivative of phenols can be prepared using a phase transfer protocol (BOC_2O, $Bu_4N^+HSO_4^-$ or 18-crown-6, NaOH, CH_2Cl_2, 80% yield)[1] or by direct acylation with BOC_2O and DMAP as a catalyst (79–100% yield).[2] Cleavage is achieved by refluxing a mixture of the carbonate with 3 *M* HCl in dioxane. The use of TFA for cleavage often results in *t*-butylation of the phenol.[2]

1. F. Houlihan, F. Bouchard, J. M. J. Frechet, and C. G. Willson, *Can. J. Chem.*, **63**, 153 (1985).
2. M. M. Hansen and J. R. Riggs, *Tetrahedron Lett.*, **39**, 2705 (1998).

4-Methylsulfinylbenzyl Carbonate (Msz–OAr): $CH_3S(O)C_6H_4CH_2OCO_2Ar$

Tyrosine-½Cu is protected with 4-methylthiobenzyl 4′-nitrophenyl carbonate ($NaHCO_3$, DMF, H_2O). Release of the copper protection followed by BOC protection of the nitrogen gives a fully protected tyrosine, the sulfide of which is oxidized with $NaBrO_3 \cdot 3H_2O$ to generate the acid stable Msz-protected tyrosine. Cleavage is achieved by reductive acidolysis with $SiCl_4$/TFA.[1]

1. Y. Kiso, S. Tanaka, T. Kimura, H. Itoh, and K. Akaji, *Chem. Pharm. Bull.*, **39**, 3099 (1991).

2,4-Dimethylpent-3-yl Carbonate (Doc–OAr): $(i\text{-Pr})_2COCO_2Ar$

The Doc group, used for the protection of the phenolic hydroxyl group in tyrosine, is introduced with the chloroformate (DIPEA, CH_3CN). It has a half-life in 20% piperidine/DMF of 8 h, compared with 30 sec for the 2-BrZ (2-BrCbz) group. The 2-BrZ group is only slightly more stable to acid than the Doc group. The Doc group is completely cleaved by HF.[1]

1. K. Rosenthal, A. Karlström, and A. Undén, *Tetrahedron Lett.*, **38**, 1075 (1997).

Aryl 2,2,2-Trichloroethyl Carbonate: $ArOCOOCH_2CCl_3$ (Chart 4)

Formation

1. Cl_3CCH_2OCOCl, Pyr or aq. NaOH, 25°, 12 h.[1]

Cleavage

1. Zn, HOAc, 25°, 1–3 h, or Zn, CH_3OH, heat, few min.[1]
2. Zn, THF–H_2O, pH 4.2, 25°, 4 h.[2] The authors suggest that selective cleavage should be possible by this method, since, at pH 4.2, 25°, 2,2,2-trichloroethyl esters are cleaved in 10 min, 2,2,2-trichloroethyl carbamates are cleaved in 30 min, and the 2,2,2-trichloroethyl carbonate of estrone, formed in 87% yield from estrone and the acid chloride, is cleaved in 4 h (97% yield).

1. T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, 2555 (1967).
2. G. Just and K. Grozinger, *Synthesis*, 457 (1976).

Aryl Vinyl Carbonate: $ArOCO_2CH{=}CH_2$ (Chart 4)

Formation

1. $CH_2{=}CHOCOCl$, Pyr, 95% yield.[1]

Cleavage

1. Na_2CO_3, warm aq. dioxane, 96% yield. Selective protection of an aryl —OH or an amine—NH group is possible by reaction of the compound with vinyl chloroformate. Vinyl carbamates ($RR'NCO_2CH{=}CH_2$) are stable to the basic conditions (Na_2CO_3) used to cleave vinyl carbonates. Conversely, vinyl carbonates are stable to the acidic conditions ($HBr/CH_3OH/CH_2Cl_2$) used to cleave vinyl carbamates. Vinyl carbonates are cleaved by more acidic conditions: 2 *N* anhyd. HCl/dioxane, 25°, 3 h, 10% yield; HBF_4, 25°, 12 h, 30% yield; 2 *N* $HCl/CH_3OH–H_2O$(4:1), 60°, 8 h, 100% yield.[1]

1. R. A. Olofson and R. C. Schnur, *Tetrahedron Lett.*, 1571 (1977).

Aryl Benzyl Carbonate: $ArOCOOCH_2C_6H_5$ (Chart 4)

Formation

1. $PhCH_2OCOCl$, Pyr, CH_2Cl_2, THF.[1]

Cleavage

1. H_2/Pd–C, EtOH, 20°.[1]

o-Bromobenzyl carbonates have been developed for use in solid-phase peptide synthesis. An aryl *o*-bromobenzyl carbonate is stable to acidic cleavage (CF_3CO_2H) of a *t*-butyl carbamate; a benzyl carbonate is cleaved. The *o*-bromo derivative is quantitatively cleaved with hydrogen fluoride (0°, 10 min).[2]

1. M. Kuhn and A. von Wartburg, *Helv. Chim. Acta*, **52**, 948 (1969).
2. D. Yamashiro and C. H. Li, *J. Org. Chem.*, **38**, 591 (1973).

Aryl Carbamate: ArOCONHR

Formation

1. RNCO (R = Ph, *i*-Bu), 60°, 2 h, 65–85% yield.[1]

Cleavage

1. 2 *N* NaOH, 20°, 2 h, 78% yield.[1]
2. $H_2NNH_2{\cdot}H_2O$, DMF, 20°, 3 h, 59–87% yield.[1]

1. G. F. Jäger, R. Geiger and W. Siedel, *Chem. Ber.*, **101**, 2762 (1968).

Phosphinates

Dimethylphosphinyl Ester (Dmp–OAr): $(CH_3)_2P(O)OAr$

Formation

1. $Me_2P(O)Cl$, Et_3N, $CHCl_3$, 76% yield.[1] The Dmp group was used to protect tyrosine for use in peptide synthesis. It is stable to 1 *M* HCl/MeOH, 1 *M* HCl/AcOH, CF_3CO_2H, HBr/AcOH, and H_2/Pd–C.

Cleavage

The Dmp group can be cleaved by the following reagents: liq. HF (0°, 1 h); 1 *M* Et_3N/MeOH (rt, 7 h); 0.1 *M* NaOH (rt, < 5 min); 5% aq. $NaHCO_3$ (rt, 5 h); 20% hydrazine/MeOH (rt, < 5 min); 50% pyridine/DMF (rt, 6 h); $Bu_4N^+F^-$ (rt, < 5 min).[1]

Dimethylphosphinothioyl Ester (Mpt–OAr): $(CH_3)_2P(S)OAr$

Formation

1. MptCl, CH_2Cl_2, Et_3N, 66% yield.[2]

Cleavage

The *O*-Mpt group is quite stable to acidic conditions (HBr/AcOH, CF_3CO_2H, 1 *M* HCl/AcOH), but is slowly cleaved under basic conditions (1 *M* NaOH/MeOH, 5 min; 1 *M* Et_3N/MeOH, reflux, 12 h). In contrast, the *N*-Mpt group is readily cleaved with acid (CF_3CO_2H, 60 min; 1 *M* HCl/AcOH, 15 min; HBr/AcOH, 5 min), but not with base. The Mpt group was used to protect tyrosine during peptide synthesis.[2] The Mpt group can be removed with aq. $AgNO_3$ or $Hg(OAc)_2$,[3] or fluoride ion.[4]

Diphenylphosphinothioyl Ester (Dpt–OAr): $(C_6H_5)_2P(S)OAr$

The diphenylphosphinothioyl ester, used to protect a tryptophan, is cleaved with $Bu_4N^+ F^-$-$3H_2O$/DMF.[5]

1. M. Ueki, Y. Sano, I. Sori, K. Shinozaki, H. Oyamada, and S. Ikeda, *Tetrahedron Lett.*, **27**, 4181 (1986).
2. M. Ueki and T. Inazu, *Bull. Chem. Soc. Jpn.*, **55**, 204 (1982).
3. M. Ueki and K. Shinozaki, *Bull. Chem. Soc. Jpn.*, **56**, 1187 (1983).
4. M. Ueki and K. Shinozaki, *Bull. Chem. Soc. Jpn.*, **57**, 2156 (1984).
5. Y. Kiso, T. Kimura, Y. Fujiwara, M. Shimokura, and A. Nishitani, *Chem. Pharm. Bull.*, **36**, 5024 (1988).

Sulfonates

An aryl methane- or toluenesulfonate ester is stable to reduction with lithium aluminum hydride, to the acidic conditions used for nitration of an aromatic ring (HNO_3/HOAc),[1] and to the high temperatures (200–250°) of an Ullmann reaction. Aryl sulfonate esters, formed by reaction of a phenol with a sulfonyl chloride in pyridine or aqueous sodium hydroxide, are cleaved by warming in aqueous sodium hydroxide.[2]

1. E. M. Kampouris, *J. Chem. Soc.*, 2651 (1965).
2. F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **79**, 717 (1957).

Aryl Methanesulfonate: $ArOSO_2CH_3$ (Chart 4)

In a synthesis of decinine, a phenol was protected as a methanesulfonate that was stable during an Ullmann coupling reaction and during condensation, catalyzed by calcium hydroxide, of an amine with an aldehyde. Aryl methanesulfonates are cleaved by warm sodium hydroxide solution.[1,2]

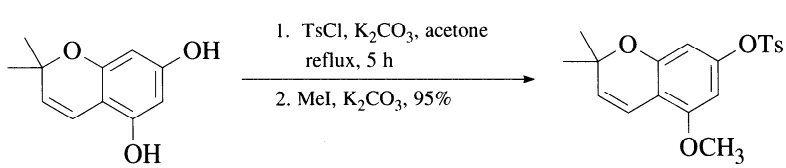
An aryl methanesulfonate was cleaved to a phenol by phenyllithium or phenylmagnesium bromide;[3] it was reduced to an aromatic hydrocarbon by sodium in liquid ammonia.[4]

1. I. Lantos and B. Loev, *Tetrahedron Lett.*, 2011 (1975).
2. J. E. Rice, N. Hussain, and E. J. LaVoie, *J. Labelled Compd. Radiopharm.*, **24**, 1043 (1987).
3. J. E. Baldwin, D. H. R. Barton, I. Dainis, and J. L. C. Pereira, *J. Chem. Soc. C*, 2283 (1968).
4. G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 522 (1955).

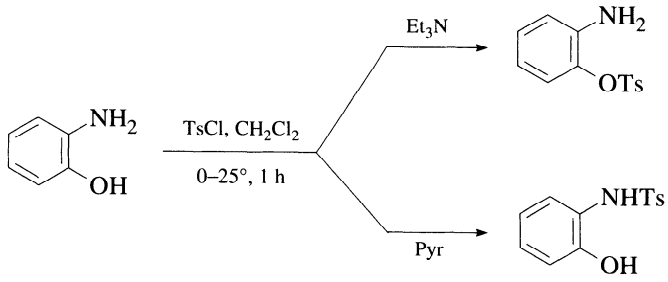
Aryl Toluenesulfonate: $ArOSO_2C_6H_4$–*p*-CH_3

Formation[1]

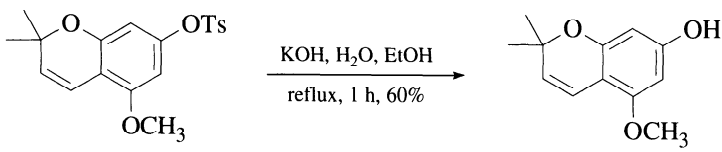
1.



2. *o*-Aminophenol can be selectively protected as a sulfonate or a sulfonamide.[2]

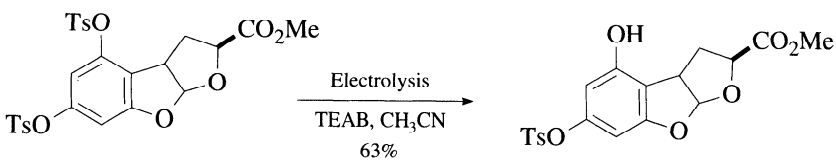


Cleavage[1]

1. 

An aryl toluenesulfonate is stable to lithium aluminum hydride (Et_2O, reflux, 4 h) and to *p*-toluenesulfonic acid ($C_6H_5CH_3$, reflux, 15 min).

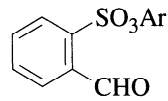
2. Electrolysis: Hg anode, Pt cathode, DMF, O_2, cyclohexene, $Bu_4N^+Br^-$, 62% yield.[3]

3. 

Ref. 4

4. Na(Hg), MeOH, 96.7% yield.[5]
5. Mg, MeOH, 4–6 h, 90–95% yield.[6]

1. M. L. Wolfrom, E. W. Koos, and H. B. Bhat, *J. Org. Chem.*, **32**, 1058 (1967).
2. K. Kurita, *Chem. Ind. (London)*, 345 (1974).
3. S. Dwivedi and R. A. Misra, *Indian J. Chem., Sect. B*, **B31**, 282 (1992).
4. E. R. Civitello and H. Rapoport, *J. Org. Chem.*, **59**, 3775 (1994).
5. R. S. Tipson, *Methods Carbohydr. Chem.*, **2**, 250 (1963).
6. M. Sridhar, B. A. Kumar, and R. Narender, *Tetrahedron Lett.*, **39**, 2847 (1998).

Aryl 2-Formylbenzenesulfonate: 

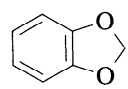
The formylbenzenesulfonate prepared from a phenol (2-CHO–$C_6H_4SO_2Cl$, Et_3N) can be cleaved with NaOH (aq. acetone, rt, 5 min) in the presence of a hindered acetate.[1]

1. M. S. Shashidhar and M. V. Bhatt, *J. Chem. Soc., Chem. Commun.*, 654 (1987).

PROTECTION FOR CATECHOLS (1,2-Dihydroxybenzenes)

Catechols can be protected as diethers or diesters by methods that have been described to protect phenols. However, formation of cyclic acetals and ketals (e.g., methylenedioxy, acetonide, cyclohexylidenedioxy, and diphenylmethylenedioxy derivatives) or cyclic esters (e.g., borates or carbonates) selectively protects the two adjacent hydroxyl groups in the presence of isolated phenol groups.

Cyclic Acetals and Ketals

Methylene Acetal (Chart 4): 

The methylenedioxy group, often present in natural products, is stable to many reagents. Efficient methods for both formation and removal of the group are available.

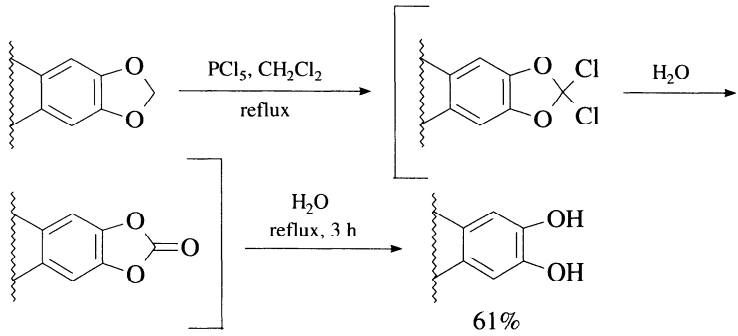
Formation

1. CH_2Br_2, NaOH, H_2O, Adogen, reflux, 3 h, 76–86% yield,[1] [Adogen = $R_3N^+CH_3Cl^-$, phase transfer catalyst (R = C_8–C_{10} straight-chain alkyl groups)]. Earlier methods required anhydrous conditions and aprotic solvents.
2. CH_2X_2 (X = Br, Cl), DMF, KF or CsF, 110°, 1.5 h, 70–98% yield.[2]
3. $BrCH_2Cl$, DMF, Cs_2CO_3, 70–110°, 86–97% yield.[3]
4. CH_2Cl_2, CsF, DMF, reflux, 91% yield.[4]

Cleavage

1. $AlBr_3$, EtSH, 0°, 0.5–1 h, 73–78% yield.[5] Aluminum bromide cleaves aryl and alkyl methyl ethers in high yield; methyl esters are stable.

2. PCl_5, CH_2Cl_2, reflux; H_2O; reflux, 3 h, 61% yield.[6]



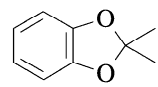
3. BCl_3, CH_3SCH_3, $ClCH_2CH_2Cl$, 83°, 98% yield.[7] Selective cleavage of an aryl methylenedioxy group or an aryl methyl ether by boron trichloride has been investigated.[8–10]
4. 9-Br–BBN, 24 h, 40°, CH_2Cl_2.[11]
5. A 4-nitro-1,2-methylenedioxybenzene has been cleaved to a catechol with 2 *N* NaOH, 90°, 30 min;[12] a similar compound substituted with a 4-nitro or 4-formyl group has been cleaved by $NaOCH_3$/DMSO, 150°, 2.5 min (13–74% catechol, 6–60% recovered starting material).[13]
6. $Pb(OAc)_4$, benzene, 50°, 8 h.[14]
7. $(TMS)_2NNa$ or LDA, THF, DMPU, 93–99% yield.[15]
8. $AlBr_3$, EtSH, 0°, 93% yield.[16]

1. A. P. Bashall and J. F. Collins, *Tetrahedron Lett.*, 3489 (1975).
2. J. H. Clark, H. L. Holland, and J. M. Miller, *Tetrahedron Lett.*, 3361 (1976).
3. R. E. Zelle and W. J. McClellan, *Tetrahedron Lett.*, **32**, 2461 (1991).
4. T. Geller, J. Jakupovic, and H.-G. Schmalz, *Tetrahedron Lett.*, **39**, 1541 (1998).
5. M. Node, K. Nishide, M. Sai, K. Ichikawa, K. Fuji, and E. Fujita, *Chem. Lett.*, 97 (1979).
6. G. L. Trammell, *Tetrahedron Lett.*, 1525 (1978).
7. P. G. Williard and C. B. Fryhle, *Tetrahedron Lett.*, **21**, 3731 (1980).
8. M. Gerecke, R. Borer, and A. Brossi, *Helv. Chim. Acta*, **59**, 2551 (1976).
9. S. Teitel, J. O'Brien, and A. Brossi, *J. Org. Chem.*, **37**, 3368 (1972).
10. F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Lett.*, 4153 (1966).
11. M. V. Bhatt, *J. Organomet. Chem.*, **156**, 221 (1978).
12. E. Haslam and R. D. Haworth, *J. Chem. Soc.*, 827 (1955).
13. S. Kobayashi, M. Kihara, and Y. Yamahara, *Chem. Pharm. Bull.*, **26**, 3113 (1978).
14. Y. Ikeya, H. Taguchi, and I. Yoshioka, *Chem. Pharm. Bull.*, **29**, 2893 (1981).
15. J. R. Hwu, F. F. Wong, J.-J. Huang, and S.-C. Tsay, *J. Org. Chem.*, **62**, 4097 (1997).
16. Y.-Z. Hu and D. L. J. Clive, *J. Chem. Soc., Perkin Trans. 1*, 1421 (1997).

Pivaldehyde Acetal

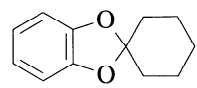
The acetal is prepared from a catechol and pivaldehyde with TMSCl catalysis.[1]

1. Y. Nishida, M. Abe, H. Ohrui, and H. Meguro, *Tetrahedron: Asymmetry*, **4**, 1431 (1993).

Acetonide Derivative (Chart 4): 

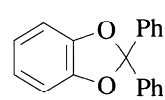
A catechol can be protected as an acetonide (acetone, 70% yield). It is cleaved with 6 *N* HCl (reflux, 2 h, high yield)[1] or by refluxing in acetic acid/H_2O (100°, 18 h, 90% yield).[2]

1. K. Ogura and G.-i. Tsuchihashi, *Tetrahedron Lett.*, 3151 (1971).
2. E. J. Corey and S. D. Hurt, *Tetrahedron Lett.*, 3923 (1977).

Cyclohexylidene Ketal: 

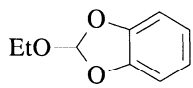
The cyclohexylidene ketal, prepared from a catechol and cyclohexanone (Al_2O_3/TsOH, CH_2Cl_2, reflux, 36 h),[1] is stable to metallation conditions (RX/BuLi) that cleave aryl methyl ethers.[2] The ketal is cleaved by acidic hydrolysis (concd. HCl/EtOH, reflux, 1.5 h, → 20°, 12 h); it is stable to milder acidic hydrolysis that cleaves tetrahydropyranyl ethers (1 *N* HCl/EtOH, reflux, 5 h, 91% yield).[3]

1. G. Schill and E. Logemann, *Chem. Ber.*, **106**, 2910 (1973).
2. G. Schill and K. Murjahn, *Chem. Ber.*, **104**, 3587 (1971).
3. J. Boeckmann and G. Schill, *Chem. Ber.*, **110**, 703 (1977).

Diphenylmethylene Ketal (Chart 4): 

The diphenylmethylene ketal prepared from a catechol (Ph_2CCl_2, Pyr, acetone, 12 h),[1] (Ph_2CCl_2, ncat, 170°, 5 min, 59%),[2] or [$Ph_2C(OMe)_2$, H_2SO_4, CH_2Cl_2, 40°, >83% yield][3] can be cleaved by hydrogenolysis (H_2/Pd–C, THF).[4,5] It has also been prepared from a 1,2,3-trihydroxybenzene (Ph_2CCl_2, 160°, 5 min, 80% yield) and cleaved by acidic hydrolysis (HOAc, reflux, 7 h).[6,7]

1. W. Bradley, R. Robinson, and G. Schwarzenbach, *J. Chem. Soc.*, 793 (1930).
2. S. Bengtsson and T. Högberg, *J. Org. Chem.*, **54**, 4549 (1989).
3. M. D. Shair, T. Y. Yoon, K. K. Mosny, T. C. Chou, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **118**, 9509 (1996).
4. E. Haslam, R. D. Haworth, S. D. Mills, H. J. Rogers, R. Armitage, and T. Searle, *J. Chem. Soc.*, 1836 (1961).
5. K. S. Feldman, S. M. Ensel, and R. D. Minard, *J. Am. Chem. Soc.*, **116**, 1742 (1994).
6. L. Jurd, *J. Am. Chem. Soc.*, **81**, 4606 (1959).
7. T. R. Kelly, A. Szabados, and Y.-J. Lee, *J. Org. Chem.*, **62**, 428 (1997).

Ethyl Orthoformate: 

The orthoformate is formed by the acid-catalyzed reaction of a catechol with triethyl orthoformate (82% yield) and is cleaved by acid-catalyzed hydrolysis (TsOH, MeOH, H_2O, rt, 16 h, 80–88% yield.).[1]

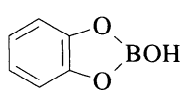
1. A. Merz and M. Rauschel, *Synthesis*, 797 (1993).

Diisopropylsilylene Derivative: $[(CH_3)_2CH]_2Si(OR)_2$

The diisopropylsilylene, formed from a catechol with $(i\text{-Pr})_2Si(OTf)_2$ and 2,6-lutidine in 96% yield, is cleaved with KF (MeOH, 2 eq. HCl).[1]

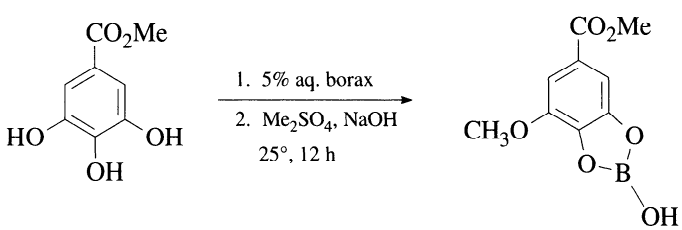
1. E. J. Corey and J. O. Link, *Tetrahedron Lett.*, **31**, 601 (1990).

Cyclic Esters

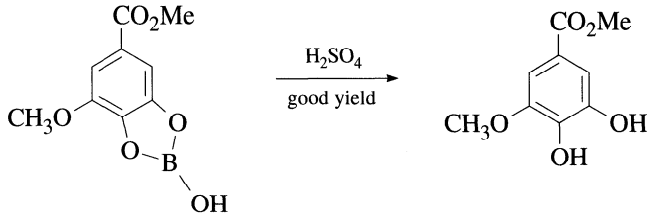
Cyclic Borate (Chart 4): 

A cyclic borate can be used to protect a catechol group during base-catalyzed alkylation or acylation of an isolated phenol group; the borate ester is then readily hydrolyzed by dilute acid.[1]

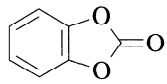
Formation[1]



Cleavage[1]

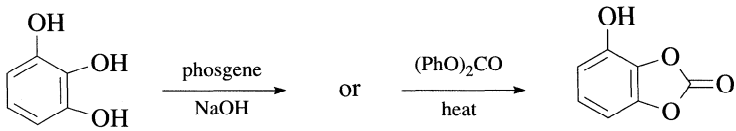


1. R. R. Scheline, *Acta Chem. Scand.*, **20**, 1182 (1966).

Cyclic Carbonate (Chart 4): 

Cyclic carbonates have been used to a limited extent only (since they are readily hydrolyzed) to protect the catechol group in a polyhydroxy benzene.

Formation[1]



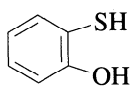
Cleavage

The cyclic carbonate is easily cleaved by refluxing in water for 30 min.[2] It can be converted to the 1,2-dimethoxybenzene derivative (aq. NaOH, Me_2SO_4, reflux, 3 h).[3]

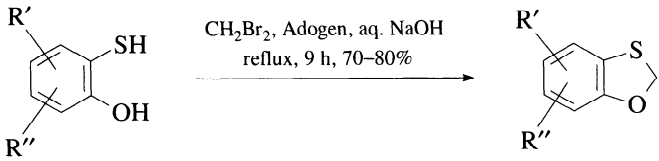
1. A. Einhorn, J. Cobliner, and H. Pfeiffer, *Ber.*, **37**, 100 (1904).
2. H. Hillemann, *Ber.*, **71**, 34 (1938).
3. W. Baker, J. A. Godsell, J. F. W. McOmie, and T. L. V. Ulbricht, *J. Chem. Soc.*, 4058 (1953).

PROTECTION FOR 2-HYDROXYBENZENETHIOLS

Two derivatives have been prepared that may prove useful as protective groups for 2-hydroxybenzenethiols.



Formation

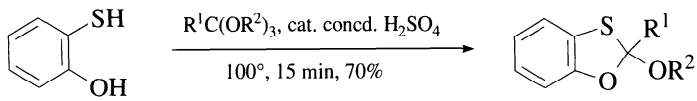


R′, R″ = H, Me, Cl

Adogen = $MeR_3N^+Cl^-$, phase transfer catalyst

R = C_8–C_{10} straight chain alkyl groups

Ref. 1



R^1 = H, Me, Ph; R^2 = Me, Et

Ref. 2

1. S. Cabiddu, S. Melis, L. Bonsignore, and M. T. Cocco, *Synthesis*, 660 (1975).
2. S. Cabiddu, A. Maccioni, and M. Secci, *Synthesis*, 797 (1976).