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

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PROTECTION FOR THE CARBOXYL GROUP

Carboxylic acids are protected for a number of reasons: (1) to mask the acidic proton so that it does not interfere with base-catalyzed reactions, (2) to mask the carbonyl group to prevent nucleophilic addition reactions, and (3) to improve the handling of the molecule in question (e.g., to make the compound less water soluble, to improve its NMR characteristics, or to make it more volatile so that it can be analyzed by gas chromatography). Besides having stability to a planned set of reaction conditions, the protective group must also be removed without affecting other functionality in the molecule. For this reason, a large number of protective groups for acids have been developed that are removed under a variety of conditions, even though most can readily be cleaved by simple hydrolysis. Hydrolysis is an important means of deprotection, and the rate of hydrolysis is, of course, dependent upon steric and electronic factors that help to achieve differetial deprotection in polyfunctional substrates. These factors are also important in the selective protection of compounds containing two or more carboxylic acids. Hydrolysis using HOO^- is about 400 times faster than simple hydrolysis with hydroxide (phenyl acetate = substrate).[1]

Polymer-supported esters[2] are widely used in solid-phase peptide synthesis, and extensive information on this specialized protection is reported annually.[3] Some activated esters that have been used as macrolide precursors and some that have been used in peptide synthesis are also described in this chapter; the many activated esters that are used in peptide synthesis are discussed elsewhere.[3] A useful list, with references, of many protected amino acids (e.g., $-NH_2$, COOH, and side-chain-protected compounds) has been compiled.[4] Some general methods for the preparation of esters are provided at the beginning of this chapter;[5] conditions that are unique to a protective group are described with that group.[6] Some esters that have been used as protective groups are included in Reactivity Chart 6.

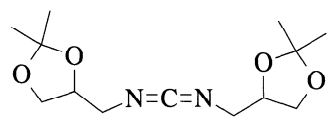
1. W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **90**, 2622 (1968).
2. See reference 22 (**Peptides**) in Chapter 1. See also P. Hodge, "Polymer-Supported Protecting Groups," *Chem. Ind. (London)*, 624 (1979); R. B. Merrifield, G. Barany, W. L. Cosand, M. Engelhard, and S. Mojsov, "Some Recent Developments in Solid Phase Peptide Synthesis," in *Peptides: Proceedings of the Fifth American Peptide Symposium*, M. Goodman and J. Meienhofer, Eds., Wiley, New York, 1977, pp. 488–502; J. M. J. Fréchet, "Synthesis and Applications of Organic Polymers as Supports and Protecting Groups," *Tetrahedron*, **37**, 663 (1981).
3. *Specialist Periodical Reports*: *Amino-Acids, Peptides, and Proteins*, Royal Society of Chemistry, London, Vols. 1–16 (1969–1983); *Amino Acids and Peptides*, Vols. 17–28 (1984–1997).
4. G. A. Fletcher and J. H. Jones, *Int. J. Pept. Protein Res.*, **4**, 347 (1972).
5. For classical methods, see C. A. Buehler and D. E. Pearson, *Survey of Organic Syntheses*, Wiley-Interscience, New York, 1970, Vol. 1, pp. 801–830; 1977, Vol. 2, pp. 711–726.
6. See also E. Haslam, "Recent Developments in Methods for the Esterification and Protection of the Carboxyl Group," *Tetrahedron*, **36**, 2409–2433 (1980); E. Haslam, "Activation and Protection of the Carboxyl Group," *Chem. Ind. (London)*, 610–617 (1979); E. Haslam, "Protection of Carboxyl Groups," in *Protective Groups in Organic Chemistry*, J. F. W. McOmie, Ed., Plenum, New York and London, 1973, pp.183–215; P. J. Kocienski, *Protecting Groups*, Thieme Medical Publishers, New York 1994, p. 118.

ESTERS

General Preparations of Esters

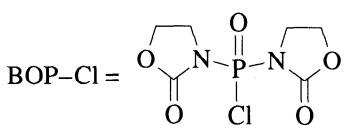
The preparation of esters can be classified into two main categories: (1) carboxylate activation with a good leaving group and (2) nucleophilic displacement of a carboxylate on an alkyl halide or sulfonate. The latter approach is generally not suitable for the preparation of esters if the halide or tosylate is sterically hindered, but there has been some success with simple secondary halides[1] and tosylates (ROTs, DMF, K_2CO_3, 69–93% yield).[2]

1. RCO_2H + R′OH, MeTHF, Me_3SiCl, (or Me_2SiCl_2, $MeSiCl_3$ or $SiCl_4$), rt, 15 min to 100 h, 90–97% yield.[3] In this case, both R and R′ can be hindered. Since the reaction conditions generate HCl, the substrates should be stable to strong acid.
2. RCO_2H, R′OH, DCC/DMAP, Et_2O, 25°, 1–24 h, 70–95% yield. This method is suitable for a large variety of hindered and unhindered acids and alcohols.[4] Carbodiimide **i** was developed to make the urea by-product water soluble and thus easily washed out.[5]



i

3. $(RCO_2)O$, R′OH, Bu_3P, excellent yields.[6] The nearly neutral esterification proceeds without the need for basic additives.
4. RCO_2H, R′OH, BOP–Cl, Et_3N, CH_2Cl_2, 23°, 2 h, 71–99% yield.[7] This is an excellent general method for the preparation of esters.



5. $RCO_2H \xrightarrow[\text{2. R′OH, DMAP, >95\% yield.}]{\text{1. 2,4,6-}Cl_3C_6H_2COCl,\ Et_3N,\ THF}{}^{8} \rightarrow RCO_2R'$

This method is best suited to the preparation of relatively unhindered esters; otherwise some esterification of the benzoic acid may occur at the expense of the acid to be esterified.

6. $RCO_2H + R'X \xrightarrow[25\text{–}80°,\ 1\text{–}10\ h]{\text{DBU, benzene}}{}^{9} RCO_2R'$, 70–95% yield

RCO_2H = alkyl, aryl, hindered acids
R′ = Et, *n*- and *s*-Bu, CH_3SCH_2, ...
X = Cl, Br, I

The reaction also proceeds well in acetonitrile, allowing lower temperatures (25°) and shorter times.[10]

7. $RCHCO_2H \xrightarrow[\text{pH 7}]{Cs_2CO_3} \xrightarrow[6\ h]{\text{R′X, DMF}}{}^{11} RCHCO_2R'$ (NHPG)

R′ = Me, 80%; $PhCH_2$, 70–90%; *o*-$NO_2C_6H_4CH_2$, 90%; *p*-$MeOC_6H_4CH_2$, 70%; Ph_3C, 40–60%; *t*-Bu, 14%; PhCOCH(Me), 80%; *N*-phthalimidomethyl, 80% yield.

A study of relative rates of this reaction indicates that $Cs^+ > K^+ > Na^+ > Li^+$; $I^- >> Br^- >> Cl^-$; HMPA > DMSO > DMF.[12]

8. $RCHCO_2H + R'X \xrightarrow[25°,\ 24\ h,\ 90–95\%]{NaHCO_3,\ DMF}{}^{13} RCHCO_2R'$
   NHPG NHPG
   R′ = Et, *n*-Bu, *s*-Bu X = Br, I

9. $RCHCO_2H + R'X \xrightarrow[25°,\ 3–24\ h,\ 70–95\%]{(C_8H_{17})_3\ N^+MeCl^-,\ aq.\ NaHCO_3,\ CH_2Cl_2}{}^{14} RCHCO_2R'$
   NHPG NHPG

10. $RCO_2H + R'_3O^+\ BF_4^- \xrightarrow[25°,\ 1–24\ h]{EtN\text{–}i\text{-}Pr_2,\ CH_2Cl_2}{}^{15} RCO_2R'$, 70–95% yield
    RCO_2H = hindered acids
    R′ = Me, Et

11. $RCO_2H + Me_2NCH(OR')_2 \xrightarrow{25–80°,\ 1–36\ h}{}^{16} RCO_2R'$, 80–95%
    RCO_2H = Ph, 2,4,6-$Me_3C_6H_2$–, *N*-protected amino acids
    R′ = Me, Et, $PhCH_2$, *s*-Bu

12. $RCO_2H + R'OH \xrightarrow[1–20°,\ 24\ h]{t\text{-BuNC}}{}^{17} RCO_2R'$, 36–98%
    RCO_2H = amino, dicarboxylic acids; ≠ $PhCO_2H$
    R′ = Me, Et, *t*-Bu

13. $RCO_2H + R'OH \xrightarrow[25°,12\ h,\ 75–85\%]{Ph_3P(OSO_2CF_3)_2,\ CH_2Cl_2}{}^{18} RCO_2R'$
    R = aryl
    R′ = Et

14. $RCO_2H \xrightarrow[Et_3N,\ DMAP]{ClCO_2R',\ CH_2Cl_2,\ 0°}{}^{19} RCO_2R'$, 89–98%

This reaction is not suitable for hindered carboxylic acids, since considerable symmetrical anhydride formation (52% with pivalic acid) results. Symmetrical anhydride formation can sometimes be suppressed by the use of stoichiometric quantities of DMAP.

15. $RCO_2H + R'X \xrightarrow[R''_4N^+X^-,\ rt,\ 80–99\%\ yield]{Electrolysis:\ pyrrolidone,\ DMF}{}^{20} RCO_2R'$

This method is based on the generation of the tetraalkylammonium salt of pyrrolidone, which acts as a base. The method is compatible with a large

variety of carboxylic acids and alkylating agents. The method is effective for the preparation of macrolides.

16. $\underset{\underset{\text{NHPG}}{|}}{\text{RCHCO}_2\text{H}} \xrightarrow[\text{DMAP, } CH_2Cl_2,\ 0°,\ \text{R'OH}]{\text{isopropenyl chloroformate}^{21}} \underset{\underset{\text{NHPG}}{|}}{\text{RCHCO}_2\text{R'}}$, 60–96%

17. $\text{RCO}_2\text{H} + \text{R'OH} \xrightarrow[0.1\text{–}48\ \text{h, } 67\text{–}98\%]{\text{TMSCl, } 22\text{–}78°\ ^{22}} \text{RCO}_2\text{R'}$

18. $\text{RCO}_2\text{H} \xrightarrow[\text{2. R'OH, reflux}\\ \text{5–120 min, 80–90\%}]{\text{1. TsCl, } K_2CO_3\text{, TEBAC}^{23}\\ 40°\text{–reflux, 5–60 min}} \text{RCO}_2\text{R'}$

$\text{TEBAC} = Et_3N^+CH_2Ph\ Cl^-$

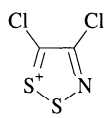
19. $\text{RCO}_2\text{H} \xrightarrow[50°,\ 12\text{–}48\ \text{h, } 50\text{–}99\%\ ^{24}]{\text{R'OH, } TiCl(OTf)_3\text{, } (Me_2SiO)_4} \text{RCO}_2\text{R'}$

20. $\text{RCO}_2\text{H} \xrightarrow[\text{rt, 0.5–17 h, 90–99\%}\ ^{25}]{\text{R'OH, } TiCl_4\text{,}AgClO_4\text{, } (ArCO)_2O\text{, TMSCl, } CH_2Cl_2} \text{RCO}_2\text{R'}$

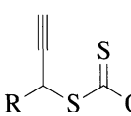
21. $\text{RCO}_2\text{TMS} + \text{R'OTMS} \xrightarrow[\text{rt, 80–99\%}]{TiCl_4\text{, } AgClO_4\text{, } (ArCO)_2O\text{, } CH_2Cl_2} \text{RCO}_2\text{R'}$

$Sn(OTf)_2$ has also been used as an effective catalyst.[26]

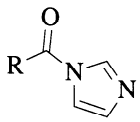
22. $\text{RCO}_2\text{H} \xrightarrow[\text{R'OH, 2,6-lutidine}^{27}\\ \text{39–84\%}]{} \text{RCO}_2\text{R'}$



23. $\text{RCO}_2\text{H} \xrightarrow[56\text{–}95\%]{\text{R'OH, EEDQ}^{28}} \text{RCO}_2\text{R'}$

24.  $\xrightarrow[\text{toluene}]{\text{R''CO}_2\text{H}}$ $\text{R''CO}_2\text{R'}$

Esterification proceeds with inversion Ref. 29

25. 

1. MeOTf, $ClCH_2CH_2Cl$
2. R′OH, NMM
82°, 1–10 h
70–90%
$\longrightarrow$ RCO_2R'

Ref. 30

The Mitsunobu reaction is used to convert an alcohol and an acid into an ester by the formation of an activated alcohol (Ph_3P, diethyl diazodicarboxylate), which then undergoes displacement with inversion by the carboxylate.[31] Although this reaction works very well, it suffers from the fact that large quantities of by-products are produced, which generally require removal by chromatography.

General Cleavage of Esters[32]

1. $RCO_2R' + Nu^-$ $\xrightarrow{\text{aprotic solvent}[33]}$ RCO_2H

Nu^- = LiS-*n*-Pr: HMPA, 25°, 1 h, ca. quant. yield[34]
= NaSePh: HMPA–THF, reflux, 7 h, 90–100% yield[35]
= LiCl: DMF or Pyr, reflux, 1–18 h, 60–90% yield[36]
= KO-*t*-Bu: DMSO, 50–100°, 1–24 h, 65–95% yield[37]
= NaCN (for decarboxylation of malonic esters): DMSO, 160°, 4 h, 70–80% yield[38]
= NaTeH from Te: DMF, *t*-BuOH, $NaBH_4$, 80–90°, 15 min, 85–98% yield[39]
= KO_2: 18-crown-6, benzene, 25°, 8–72 h, 80–95% yield[40]
= LiI: EtOAc, reflux, 26–98% yield.[41] Bn, PMB, PNB, *t*-Bu, and Me esters are all cleaved.

2. RCO_2R' $\xrightarrow[\text{reflux, 5–35 h, 70–90\%}]{\text{TMSCl, NaI, } CH_3CN\ [42\text{–}44]}$ RCO_2H

RCO_2H = alkyl, aryl, hindered acids
R′ = Me, Et, *i*-Pr, *t*-Bu, $PhCH_2$

This method generates Me_3SiI *in situ*. The reagent also cleaves a number of other protective groups.

3. RCO_2R' $\xrightarrow[41\text{–}96\%]{MgI_2, \text{ toluene, 1–3 days}[45]}$ $RCO_2H + R'I$

RCO_2H = alkyl, aryl, hindered acids
R′ = Me, Et, cHex, 1-Ad, 2-Ad, *t*-Bu, $PhCH_2$

4. RCO_2R' $\xrightarrow[\text{15–60 min, 36–98\% yield}]{\text{aq. NaOH, DMF; HCl}[46]}$ RCO_2H

5. $RCO_2R' \xrightarrow[80\text{–}100\%]{KO\text{-}t\text{-}Bu/H_2O\ (4:1),\ 25°,\ 2\text{–}48\ h}{}^{47} RCO_2H$

RCO_2H = Ph, aryl, hindered acids

R' = Me, *t*-Bu, alkyl

"Anhydrous hydroxide" also cleaves tertiary amides.

6. $\underset{\underset{NHPG}{|}}{RCHCO_2R'} \xrightarrow[-10°,\ 1\ h \rightarrow 25°,\ 2\ h]{BBr_3,\ CH_2Cl_2}{}^{48} \underset{\underset{NH_2}{|}}{RCHCO_2H},\ 60\text{–}85\%$

R' = Me, Et, *t*-Bu, $PhCH_2$

PG = $-CO_2CH_2Ph$, $-CO_2$–*t*-Bu; OMe, OEt, O–*t*-Bu, OCH_2Ph side-chain ethers

7. $RCO_2R' \xrightarrow[70\text{–}95\%]{AlX_3,\ R''SH,\ 25°,\ 5\text{–}50\ h}{}^{49,50} RCO_2H$

R = Ph, steroid side chain, ...

R' = Me, Et, $PhCH_2$–

R'' = Et, $HO(CH_2)_2$–

X = Cl, Br

8. $RCO_2R' \xrightarrow[benzene,\ 1\text{–}30\ h]{xs\ (Bu_3Sn)_2O,\ 80°}{}^{51\text{–}53} RCO_2H$, 40–95% yield

$R' = CH_2O_2CC(CH_3)_3$, Me, Et, Ph

1. T. Shono, O. Ishige, H. Uyama, and S. Kashimura, *J. Org. Chem.*, **51**, 546 (1986).
2. W. L. Garbrecht, G. Marzoni, K. R. Whitten, and M. L. Cohen, *J. Med. Chem.*, **31**, 444 (1988).
3. R. Nakao, K. Oka, and T. Fukomoto, *Bull. Chem. Soc. Jpn.*, **54**, 1267 (1981).
4. A. Hassner and V. Alexanian, *Tetrahedron Lett.*, 4475 (1978).
5. F. S. Gibson, M. S. Park, and H. Rapoport, *J. Org. Chem.*, **59**, 7503 (1994).
6. E. Vedejs, N. S. Bennett, L. M. Conn, S. T. Diver, M. Gingras, S. Lin, P. A. Oliver, and M. J. Peterson, *J. Org. Chem.*, **58**, 7286 (1993).
7. J. Diago-Meseguer, A. L. Palomo-Coll, J. R. Fernández-Lizarbe, and A. Zugaza-Bilbao, *Synthesis*, 547 (1980).
8. J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **52**, 1989 (1979).
9. N. Ono, T. Yamada, T. Saito, K. Tanaka, and A. Kaji, *Bull. Chem. Soc. Jpn.*, **51**, 2401 (1978).
10. C. G. Rao, *Org. Prep. Proced. Int.*, **12**, 225 (1980).
11. S.-S. Wang, B. F. Gisin, D. P. Winter, R. Makofske, I. D. Kulesha, C. Tzougraki, and J. Meienhofer, *J. Org. Chem.*, **42**, 1286 (1977).

12. P. E. Pfeffer and L. S. Silbert, *J. Org. Chem.*, **41**, 1373 (1976).
13. V. Bocchi, G. Casnati, A. Dossena, and R. Marchelli, *Synthesis*, 961 (1979).
14. V. Bocchi, G. Casnati, A. Dossena, and R. Marchelli, *Synthesis*, 957 (1979).
15. D. J. Raber, P. Gariano, A. O. Brod, A. Gariano, W. C. Guida, A. R. Guida, and M. D. Herbst, *J. Org. Chem.*, **44**, 1149 (1979).
16. H. Brechbühler, H. Büchi, E. Hatz, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **48**, 1746 (1965).
17. D. Rehn and I. Ugi, *J. Chem. Res., Synop.*, 119 (1977).
18. J. B. Hendrickson and S. M. Schwartzman, *Tetrahedron Lett.*, 277 (1975).
19. S. Kim, Y. C. Kim, and J. I. Lee, *Tetrahedron Lett.*, **24**, 3365 (1983).
20. T. Shono, O. Ishige, H. Uyama, and S. Kashimura, *J. Org. Chem.*, **51**, 546 (1986).
21. P. Jouin, B. Castro, C. Zeggaf, A. Pantaloni, J. P. Senet, S. Lecolier, and G. Sennyey, *Tetrahedron Lett.*, **28**, 1661 (1987).
22. M. A. Brook and T. H. Chan, *Synthesis*, 201 (1983).
23. Z. M. Jászay, I. Petneházy, and L. Töke, *Synthesis*, 745 (1989).
24. J. Izumi, I. Shiina, and T. Mukaiyama, *Chem. Lett.*, 141 (1995).
25. I. Shiina, S. Miyoshi, M. Miyashita, and T. Mukaiyama, *Chem. Lett.*, 515 (1994).
26. T. Mukaiyama, I. Shiina, and M. Miyashita, *Chem. Lett.*, 625 (1992).
27. J. J. Folmer and S. M. Weinreb, *Tetrahedron Lett.*, **34**, 2737 (1993).
28. B. Zacharie, T. P. Connolly, and C. L. Penney, *J. Org. Chem.*, **60**, 7072 (1995).
29. J. Boivin, E. Henriet, and S. Z. Zard, *J. Am. Chem. Soc.*, **116**, 9739 (1994).
30. G. Ulibarri, N. Choret, and D. C. H. Bigg, *Synthesis*, 1286 (1996).
31. D. L. Hughes, *Org. React.*, **42**, 335 (1992); O. Mitsunobu, *Synthesis*, 1 (1981).
32. For a review, see C. J. Salomon, E. G. Mata, and O. A. Mascaretti, *Tetrahedron*, **49**, 3691 (1993).
33. J. McMurry, "Ester Cleavages via S_N2-Type Dealkylation," *Org. React.*, **24**, 187–224 (1976).
34. P. A. Bartlett and W. S. Johnson, *Tetrahedron Lett.*, 4459 (1970).
35. D. Liotta, W. Markiewicz, and H. Santiesteban, *Tetrahedron Lett.*, 4365 (1977).
36. F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1960).
37. F. C. Chang and N. F. Wood, *Tetrahedron Lett.*, 2969 (1964).
38. A. P. Krapcho, G. A. Glynn, and B. J. Grenon, *Tetrahedron Lett.*, 215 (1967).
39. J. Chen and X. J. Zhou, *Synthesis*, 586 (1987).
40. J. San Filippo, L. J. Romano, C.-I. Chern, and J. S. Valentine, *J. Org. Chem.*, **41**, 586 (1976).
41. J. W. Fisher and K. L. Trinkle, *Tetrahedron Lett.*, **35**, 2505 (1994).
42. M. E. Jung and M. A. Lyster, *J. Am. Chem. Soc.*, **99**, 968 (1977).
43. T. Morita, Y. Okamoto, and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 874 (1978).
44. G. A. Olah, S. C. Narang, B. G. B. Gupta, and R. Malhotra, *J. Org. Chem.*, **44**, 1247 (1979).
45. A. G. Martinez, J. O. Barcina, G. H. del Veccio, M. Hanack, and L. R. Subramanian, *Tetrahedron Lett.*, **32**, 5931 (1991).
46. J. M. Khurana and A. Sehgal, *Org. Prep. Proced. Int.*, **26**, 580 (1994).

47. P. G. Gassman and W. N. Schenk, *J. Org. Chem.*, **42**, 918 (1977).
48. A. M. Felix, *J. Org. Chem.*, **39**, 1427 (1974).
49. M. Node, K. Nishide, M. Sai, and E. Fujita, *Tetrahedron Lett.*, 5211 (1978).
50. M. Node, K. Nishide, M. Sai, K. Fuji, and E. Fujita, *J. Org. Chem.*, **46**, 1991 (1981).
51. C. J. Salomon, E. G. Mata, and O. A. Mascaretti, *Tetrahedron Lett.*, **32**, 4239 (1991).
52. C. J. Salomon, E. G. Mata, and O. A. Mascaretti, *J. Org. Chem.*, **59**, 7259 (1994).
53. E. G. Mata and O. A. Mascaretti, *Tetrahedron Lett.*, **29**, 6893 (1988).

Transesterification

The process of transesterification is an important way to prepare a large number of esters from more complex or more simple esters without passing through the carboxylic acid. Transesterification can be used to convert one type of ester to another type that can then be removed under a different set of conditions. This section describes many of the methods that have been found effective for ester metathesis.[1]

1. ROH, DBU, LiBr. When a large excess of the alcohol is undesirable, the reaction can be run in THF/CH_2Cl_2 in the presence of 5Å ms. The combination of DBU–LiBr is required, since neither reagent is effective alone.[2]
2. Alkali metal alkoxides, *t*-butyl acetate neat, 45°, 30 min, 98% yield of *t*-butyl ester from methyl benzoate. The rate constant for the reaction increases with increasing ionic radius of the metal and with decreasing polarity of the solvent. Equilibrium for the reaction is achieved in <10 sec. Other examples are presented.[3,4]
3. M(O–*i*-Pr)$_3$; M = La[5], Nd, Gd, Yb.[6]
4. The use of 1,3-disubstituted 1,1,3,3-tetraalkyldistannoxanes for ester metathesis has been reviewed.[7,8]
5. Ti(O–*i*-Pr)$_4$, ROH, 50–90% yield.[9–11]
6. Mg, MeOH.[12]
7. From a β-keto ester: ROH, toluene, reflux, 95% yield. The reaction in this case is proposed to proceed through a ketene intermediate.[13]
8. From a β-keto ester: ROH, Sulfated-SnO_2, 50–97% yield.[14]
9. $Ce(SO_4)_2$–SiO_2, ROH, reflux, 0.25–2 h.[15]
10. $RCO_2R' + R''OH \xrightarrow[\text{Toluene >88\% yield}]{Bu_2Sn(OH)OSn(NCS)Bu_2 \text{ cat.}^{16}} RCO_2R'' + R'OH$

    This method is not effective for tertiary alcohols. It has a strong rate dependence on the polarity of the solvent, with less polar solvents giving faster rates.

1. J. Otera, *Chem. Rev.*, **93**, 1449 (1993).
2. D. Seebach, A. Thaler, D. Blaser, and S. Y. Ko, *Helv. Chim. Acta*, **74**, 1102 (1991).

3. M. G. Stanton and M. R. Gagné, *J. Am. Chem. Soc.*, **119**, 5075 (1997).
4. M. G. Stanton and M. R. Gagné, *J. Org. Chem.*, **62**, 8240 (1997).
5. T. Okano, K. Miyamoto, and J. Kiji, *Chem. Lett.*, 246 (1995).
6. T. Okano, Y. Hayashizaki, and J. Kiji, *Bull. Chem. Soc. Jpn.*, **66**, 1863 (1993).
7. J. Otera, *Adv. Detailed React. Mech.*, **3**, 167 (1994).
8. O. A. Mascaretti and R. L. E. Furlan, *Aldrichimica Acta*, **30**, 55 (1997).
9. D. Seebach, E. Hungerbühler, R. Naef, P. Schnurrenberger, B. Weidmann, and M. Züger, *Synthesis*, 138 (1982).
10. U. D. Lengweiler, M. G. Fritz, and D. Seebach, *Helv. Chim. Acta*, **79**, 670 (1996).
11. For a review of titanium compounds as catalysts for transesterification, see M. I. Siling and T. N. Laricheva, *Russ. Chem. Rev.*, **65**, 279 (1996).
12. Y.-C. Xu, E. Lebeau, and C. Walker, *Tetrahedron Lett.*, **35**, 6207 (1994).
13. A. G. Myers, N. J. Tom, M. E. Fraley, S. B. Cohen, and D. J. Madar, *J. Am. Chem. Soc.*, **119**, 6072 (1997).
14. S. P. Chavan, P. K. Zubaidha, S. W. Dantale, A. Keshavaraja, A. V. Ramaswany, and T. Ravindranathan, *Tetrahedron Lett.*, **37**, 233 (1996).
15. T. Nishiguchi and H. Taya, *J. Chem. Soc., Perkin Trans. 1*, 172 (1990).
16. J. Otera, T. Yano, A. Kawabata, and H. Nozaki, *Tetrahedron Lett.*, **27**, 2383 (1986); J. Otera, S. Ioka, and H. Nozaki, *J. Org. Chem.*, **54**, 4013 (1989).

Enzymatically Cleavable Esters

The enzymatic cleavage of esters is a vast and extensively reviewed area of chemistry.[1] Recently, several new esters have been examined primarily for the preparation of peptides and glycopeptides.

Heptyl Esters: $C_7H_{15}O_2CR$

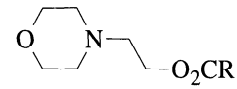
The heptyl ester was developed as an enzymatically removable protective group for C-terminal amino acid protection.

Formation

Heptyl alcohol, TsOH, benzene, reflux, 66–92% yield.[2]

Cleavage

1. Lipase from *Rhizopus niveus*, pH 7, rt, 50–96% yield.[3]
2. Lipase from *Aspergillus niger*, 0.2 *M* phosphate buffer, acetone, pH 7, 37°, 50–96% yield. This lipase was used in the cleavage of phosphopeptide heptyl esters. These conditions are sufficiently mild to prevent the elimination of phosphorylated serine and threonine residues.[4]
3. Lipase M (*Mucor javanicus*), pH 7, 37°, 70–88% yield. In this case, α- and β-glycosidic peptide derivatives were deprotected. Acetates on the pyranosides were not affected.[5]

2-*N*-(Morpholino)ethyl ($MoC_2H_2O_2CR$) Ester: 

This ester was developed to impart greater hydrophilicity in C-terminal peptides that contain large hydrophobic amino acids, since the velocity of deprotection with enzymes often was reduced to nearly useless levels. Efficient cleavage is achieved with the lipase from *R. niveus* (pH 7, 37°, 16 h, H_2O, acetone, 78–91% yield).[6]

Choline Ester: $Me_3N^+CH_2CH_2O_2CR\ Br^-$

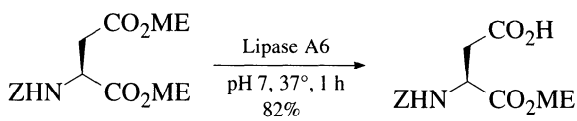
The choline ester is prepared by treating the 2-bromoethyl ester with trimethylamine. The ester is cleaved with butyrylcholine esterase (pH 6, 0.05 M phosphate buffer, rt, 50–95% yield). As with the morpholinoethyl ester, the choline ester imparts greater solubility to the C-terminal end of very hydrophobic peptides, thus improving the ability to cleave enzymatically the C-terminal ester.[7]

(Methoxyethoxy)ethyl (Mee) Ester: $CH_3OCH_2CH_2OCH_2CH_2O_2CR$

Because *O*-glycoproteins are susceptible to strong base and anomerization with acid, their preparation presents a number of difficulties, among which is the issue of mild and selective deprotection. Although in many cases the heptyl group was found quite useful because of the mild conditions associated with its enzymatic cleavage, in some cases the enzymatic cleavage would not proceed because the high level of hydrophobicity reduced solubility enough that the cleavage velocity approached zero. Increasing the hydrophilicity of the C-terminal protective group by incorporating some oxygen into the chain, as in the Mee ester, allows for reasonably facile cleavage with the lipase M from *M. javanicus* or papain. The pyranosidic acetates were not cleaved with these enzymes, but they could be cleaved with lipase WG.[8]

Methoxyethyl Ester (ME–O_2CR): $CH_3OCH_2CH_2O_2CR$

The advantages of the methoxyethyl ester over some of the other water-solubilizing esters are that many of the amino acid esters are crystalline and thus easily purified, are cleaved with a number of readily available lipases, and are useful for the synthesis of *N*-linked glycopeptides.[9]



1. (a) K. Faber and S. Riva, *Synthesis,* 895 (1992); (b) H. Waldmann and D. Sebastian, *Chem. Rev.*, **94**, 911 (1994); (c) K. Drauz and H. Waldmann, Eds., *Enzyme Catalysis in Organic Synthesis: A Comprehensive Handbook*, VCH, New York, 1995;

(d) T. Pohl, E. Nägele, and H. Waldmann, *Catal. Today*, **22**, 407 (1994); (e) H. Waldmann, P. Braun, and H. Kunz, *Chem. Pept. Proteins*, **5/6** (Pt. A), 227 (1993); (f) A. Reidel and H. Waldmann, *J. Prakt. Chem./Chem.-Ztg.*, **335**, 109 (1993); (g) C.-H. Wong and G. M. Whitesides, *Enzymes in Synthetic Organic Chemistry*, Pergamon, Oxford, U.K. (1994).

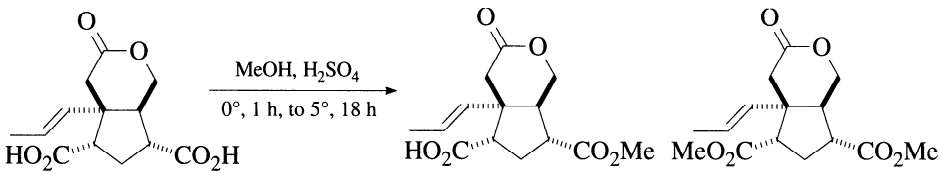
2. P. Braun, H. Waldmann, W. Vogt, and H. Kunz, *Synlett*, 105 (1990); *idem*, *Liebigs Ann. Chem.*, 165 (1991).
3. P. Braun, H. Waldmann, W. Vogt, and H. Kunz, *Liebigs Ann. Chem.*, 165 (1991).
4. D. Sebastian and H. Waldmann, *Tetrahedron Lett.*, **38**, 2927 (1997).
5. H. Waldmann, A. Heuser, P. Braun, and H. Kunz, *Indian J. Chem., Sect. B*, **31B**, 799 (1992); H. Waldmann, P. Braun, and H. Kunz, *Biomed. Biochim. Acta*, **50**, S 243 (1991); P. Braun, H. Waldmann, and H. Kunz, *Synlett*, 39 (1992).
6. G. Braum, P. Braun, D. Kowalczyk, and H. Kunz, *Tetrahedron Lett.*, **34**, 3111 (1993).
7. M. Schelhaas, S. Glomsda, M. Hänsler, H.-D. Jakubke, and H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, **35** 106 (1996).
8. J. Eberling, P. Braun, D. Kowalczyk, M. Schultz, and H. Kunz, *J. Org. Chem.*, **61**, 2638 (1996).
9. M. Gewehr and H. Kunz, *Synthesis*, 1499 (1997).

Methyl Ester: RCO_2CH_3 (Chart 6)

Formation

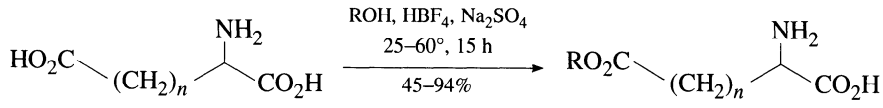
The section on general methods should also be consulted.

1. $H_2NCON(NO)Me$, KOH, DME, H_2O, 0°, 75% yield. This method generates diazomethane *in situ*.[1] *N*-Methyl-*N*-nitrosourea is a proven carcinogen.
2. Me_3SiCHN_2, MeOH, benzene, 20°.[2,3] This reagent does not react with phenols. This is a safe alternative to the use of diazomethane. A detailed, large-scale preparation of this useful reagent has been described.[4] The reagent reacts with various maleic anhydrides in the presence of an alcohol to form diesters (70–96% yield).[5]
3. $Me_2C(OMe)_2$, cat. HCl, 25°, 18 h, 80–95% yield.[6] These reaction conditions were used to prepare methyl esters of amino acids.
4. $(MeO)_2NH$, heat, 98% yield.[7] Amines are also alkylated.
5. MeOH, H_2SO_4, 0°, 1 h; 5°, 18 h, 98% yield.[8]



Ratio = 4:1

6. MeOH, HBF_4, Na_2SO_4, 25–60°, 15 h, 45–94% yield.[9] The selectivity observed here is also observed for Et, *i*-Pr, Bn, and cyclohexyl esters ($n = 1, 2$).

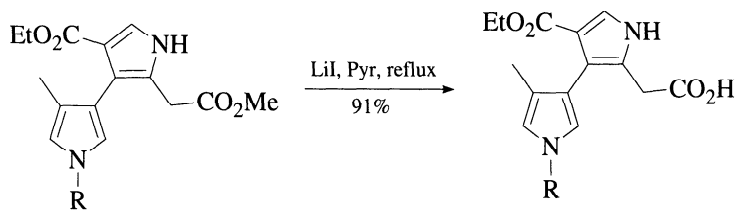


$n = 1, 2$ R = CH_3, Et, *i*-Pr, Bn, cyclohexyl

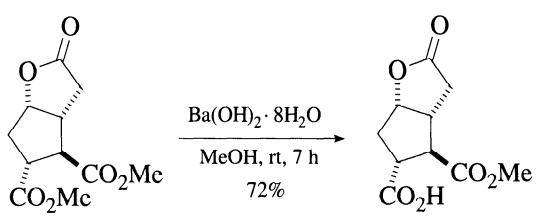
7. $NiCl_2 \cdot 6H_2O$, 10 mol%, MeOH, reflux, 9–93% yield.[10] Aromatic and conjugated acids are not effectively esterified under these conditions.

Cleavage

1. LiOH, CH_3OH, H_2O (3:1), 5°, 15 h.[11]
2. $AlBr_3$, tetrahydrothiophene, rt, 62 h, 99% yield.[12]
3. NaCN, HMPA, 75°, 24 h, 75–92% yield.[13] Ethyl esters are not cleaved under these conditions.
4. Cs_2CO_3, PhSH, DMF, 85°, 3 h, 91% yield. A methyl carbonate was cleaved simultaneously.[14]
5. LiI, Pyr, reflux, 91% yield.[15]

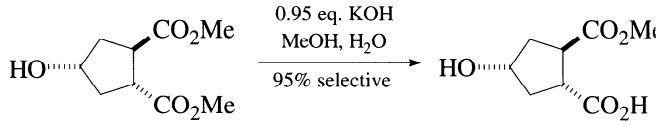


6. $(CH_3)_3SiOK$, ether[16] or THF, 4 h, 61–95% yield as the acid salt.[17]
7. $Ba(OH)_2 \cdot 8H_2O$, MeOH, rt, 7 h, 72% yield.[18]



These conditions gave excellent selectivity for an external methyl dienoate in the presence of a more hindered internal dienoate during a

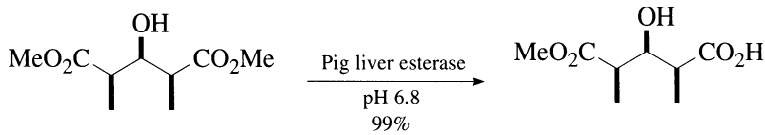
synthesis of the complex macrolide swinholide.[19] These conditions are also mild enough to prevent retroaldol condensation during ester hydrolysis.[20]

8. 

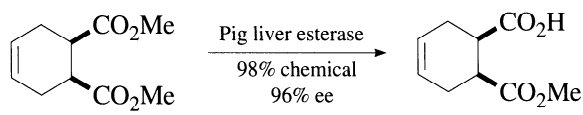
Ref. 21

The authors suggest that the selectivity is due to participation of the hydroxyl group.

9. $H_2NC_6H_4SH$, Cs_2CO_3, DMF, 85°, 1–3 h.[22]
10. Pig liver esterase is particularly effective in cleaving one ester of a symmetrical pair.[23–25]

11. 

Ref. 26

12. 

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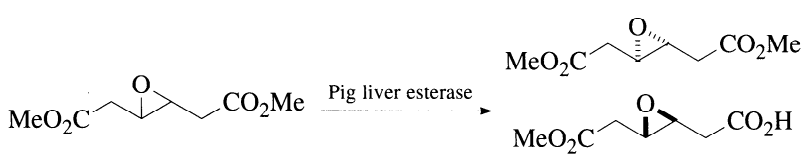
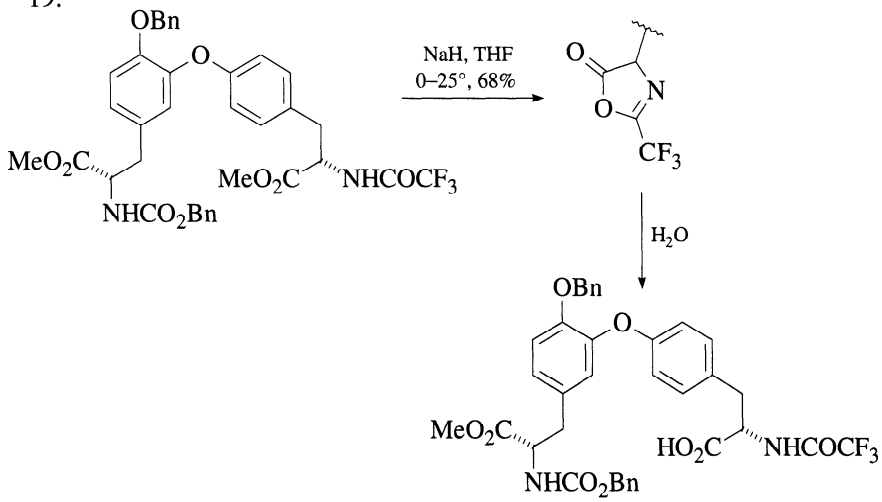
13 

E = 21.5 (enantiomeric ratio)

Ref. 28

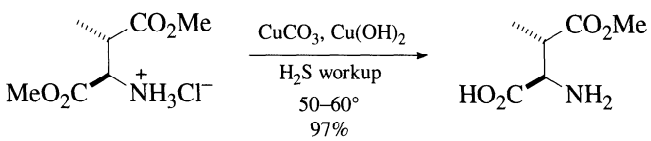
14. Carbonic anhydrase, H_2O, 23–83% yield. This enzyme was used for the selective hydrolysis of the D-form of methyl *N*-acetyl α-amino acids.[29]
15. Porcine pancreatic lipase, pH 7.5, 23° 4.5 h, 55% yield. These conditions were used to suppress facile racemization of 2-chlorocyclohexenone.[30]
16. Thermitase, pH 7.5, 55°, 50% DMSO, 3–140 min. This method was used to avoid the degradation of base-sensitive side chains during peptide synthesis. The method is compatible with the Fmoc group.[31]
17. BCl_3, 0°, 5–6 h, 90% yield.[32] In this example, a phenolic methyl group, normally cleaved with boron trichloride, was not affected.
18. $NaBH_4$, I_2, 3 h, rt.[33]

19.



Ref. 34

20. $(Bu_3Sn)_2O$, benzene, 80°, 2–24 h, 73–100% yield.[35] Only relatively unhindered esters are cleaved with this reagent. Acetates of primary and secondary alcohols and phenols are also cleaved efficiently.[36]
21. $CuCO_3$, $Cu(OH)_2$; H_2S workup, 50–60°.[37]

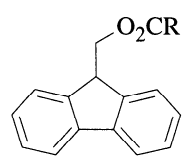


1. For example, see S. M. Hecht and J. W. Kozarich, *Tetrahedron Lett.*, 1397 (1973).
2. N. Hashimoto, T. Aoyama, and T. Shioiri, *Chem. Pharm. Bull.*, **29**, 1475 (1981).
3. Y. Hirai, T. Aida, and S. Inoue, *J. Am. Chem. Soc.*, **111**, 3062 (1989).
4. T. Shioiri, T. Aoyama, and S. Mori, *Org. Synth. Collect. Vol. VIII*, 612 (1993).
5. S. C. Fields, W. H. Dent, III, F. R. Green, III, and E. G. Tromiczak, *Tetrahedron Lett.*, **37**, 1967 (1996).
6. J. R. Rachele, *J. Org. Chem.*, **28**, 2898 (1963).
7. V. F. Rudchenko, S. M. Ignator, and R. G. Kostyanovsky, *J. Chem. Soc., Chem. Commun.*, 261 (1990).
8. S. Danishefsky, M. Hirama, K. Gombatz, T. Harayama, E. Berman, and P. Schuda, *J. Am. Chem. Soc.*, **100**, 6536 (1978); *idem, ibid.*, **101**, 7020 (1979).
9. R. Albert, J. Danklmaier, H. Hönig, and H. Kandolf, *Synthesis*, 635 (1987).
10. R. N. Ram and I. Charles, *Tetrahedron*, **53**, 7335 (1997).
11. E. J. Corey, I. Székely, and C. S. Shiner, *Tetrahedron Lett.*, 3529 (1977).
12. A. E. Greene, M.-J. Luche, and J.-P. Deprés, *J. Am. Chem. Soc.*, **105**, 2435 (1983).
13. P. Müller and B. Siegfried, *Helv. Chim. Acta*, **57**, 987 (1974).

14. D. Eren and E. Keinan, *J. Am. Chem. Soc.*, **110**, 4356 (1988); S. Bouzbouz and B. Kirschleger, *Synthesis*, 714 (1994).
15. P. Magnus and T. Gallagher, *J. Chem. Soc., Chem. Commun.*, 389 (1984).
16. E. D. Laganis and B. L. Chenard, *Tetrahedron Lett.*, **25**, 5831 (1984).
17. C. Rasset-Deloge, P. Martinez-Fresneda, and M. Vaultier, *Bull. Soc. Chim. Fr.*, **129**, 285 (1992).
18. K. Inoue and K. Sakai, *Tetrahedron Lett.*, 4063 (1977).
19. I. Paterson, K.-S. Yeung, R. A. Ward, J. D. Smith, J. G. Cumming, and S. Lamboley, *Tetrahedron*, **51**, 9467 (1995).
20. M. Nambu and J. D. White, *J. Chem. Soc., Chem. Commun.*, 1619 (1996).
21. M. Honda, K. Hirata, H. Sueoka, T. Katsuki, and M. Yamaguchi, *Tetrahedron Lett.*, **22**, 2679 (1981).
22. E. Keinan and D. Eren, *J. Org. Chem.*, **51**, 3165 (1986).
23. M. Ohno, Y. Ito, M. Arita, T. Shibata, K. Adachi, and H. Sawai, *Tetrahedron*, **40**, 145 (1984).
24. E. Alvarez, T. Cuvigny, C. Hervé du Penhoat, and M. Julia, *Tetrahedron*, **44**, 119 (1988).
25. K. Adachi, S. Kobayashi, and M. Ohno, *Chimia*, **40**, 311 (1986).
26. D. S. Holmes, U. C. Dyer, S. Russell, J. A. Sherringham, and J. A. Robinson, *Tetrahedron Lett.*, **29**, 6357 (1988).
27. S. Kobayashi, K. Kamiyama, T. Iimori and M. Ohno, *Tetrahedron Lett.*, **25**, 2557 (1984).
28. P. Mohr, L. Rösslein, and C. Tamm, *Tetrahedron Lett.*, **30**, 2513 (1989).
29. R. Chênevert, R. B. Rhlid, M. Lêtourneau, R. Gagnon, and L. D'Astous, *Tetrahedron: Asymmetry*, **4**, 1137 (1993).
30. H. Wild, *J. Org. Chem.*, **59**, 2748 (1994).
31. S. Reissmann and G. Greiner, *Int. J. Pept. Protein Res.*, **40**, 110 (1992).
32. P. S. Manchand, *J. Chem. Soc., Chem. Commun.*, 667 (1971).
33. D. H. R. Barton, L. Bould, D. L. J. Clive, P. D. Magnus, and T. Hase, *J. Chem. Soc. C*, 2204 (1971).
34. D. L. Boger and D. Yohannes, *J. Org. Chem.*, **54**, 2498 (1989).
35. E. G. Mata and O. A. Mascaretti, *Tetrahedron Lett.*, **29**, 6893 (1988).
36. C. J. Salomon, G. E. Mata, and O. A. Mascaretti, *J. Org. Chem.*, **59**, 7259 (1994).
37. J. M. Humphrey, J. B. Aggen and A. R. Chamberlin, *J. Am. Chem. Soc.*, **118**, 11759 (1996).

Substituted Methyl Esters

9-Fluorenylmethyl (Fm) Ester:



9-Fluorenylmethyl esters of *N*-protected amino acids were prepared using the DCC/DMAP method (50–89% yield)[1] or by imidazole-catalyzed transesterifi-

cation of protected amino acid active esters with FmOH.[2] Cleavage is accomplished either with diethylamine or piperidine in CH_2Cl_2 at rt for 2 h. No racemization was observed during formation or cleavage of the Fm esters.[1] The Fm ester is cleaved slowly by hydrogenolysis,[3] but complete selectivity for hydrogenolysis of the benzyloxycarbonyl group could not be obtained. Fm esters also improved the solubility of protected peptides in organic solvents.[2]

1. H. Kessler and R. Siegmeier, *Tetrahedron Lett.*, **24**, 281 (1983).
2. M. A. Bednarek and M. Bodanszky, *Int. J. Pept. Protein Res.*, **21**, 196 (1983).
3. A. Lender, W. Yao, P. A. Sprengeler, R. A. Spanevello, G. T. Furst, R. Hirschmann, and A. B. Smith, III, *Int. J. Pept. Protein Res.*, **42**, 509 (1993).

Methoxymethyl (MOM) Ester: $RCOOCH_2OCH_3$ (Chart 6)

Formation

The section on the formation of MOM ethers should be consulted, since many of the methods described there should also be applicable to the formation of MOM esters.

1. CH_3OCH_2Cl, Et_3N, DMF, 25°, 1 h.[1]
2. $CH_3OCH_2OCH_3$, Zn/$BrCH_2CO_2Et$, 0°; CH_3COCl, 0–20°, 2 h, 75–85%.[2] A number of methoxymethyl esters were prepared by this method, which avoids the use of the carcinogen chloromethyl methyl ether.

Cleavage

1. R'_3SiBr, trace MeOH. Methoxymethyl ethers are stable to these cleavage conditions.[3] Methoxymethyl esters are unstable to silica gel chromatography, but are stable to mild acid (0.01 *N* HCl, EtOAc, MeOH, 25°, 16 h).[4]
2. $MgBr_2$, Et_2O. MEM, MTM, and SEM ethers are cleaved as well.[5]
3. Solvolysis in MeOH/H_2O at 21°. This method was developed for a series of penicillin derivatives where conventional cleavage methods resulted in partial β-lactam cleavage.[6]
4. $AlCl_3$, $PhNMe_2$, 80–99% yield. MEM, MTM, Me, Bn, and SEM esters are cleaved similarly.[7]
5. Pyr, H_2O.[8]

1. A. B. A. Jansen and T. J. Russell, *J. Chem. Soc.*, 2127 (1965).
2. F. Dardoize, M. Gaudemar, and N. Goasdoue, *Synthesis*, 567 (1977).
3. S. Masamune, *Aldrichimica Acta*, **11**, 23–30 (1978); see p. 30.
4. L. M. Weinstock, S. Karady, F. E. Roberts, A. M. Hoinowski, G. S. Brenner, T. B. K. Lee, W. C. Lumma, and M. Sletzinger, *Tetrahedron Lett.*, 3979 (1975).

5. S. Kim, Y. H. Park, and I. S. Kee, *Tetrahedron Lett.*, **32**, 3099 (1991).
6. S. Vanwetswinkel, V. Carlier, J. Marchand-Brynaert, and J. Fastrez, *Tetrahedron Lett.*, **37**, 2761 (1996).
7. T. Akiyama, H. Hirofuji, A. Hirose, and S. Ozaki, *Synth. Commun.*, **24**, 2179 (1994).
8. M. Shimano, H. Nagaoka, and Y. Yamada, *Chem. Pharm. Bull.*, **38**, 276 (1990).

Methylthiomethyl (MTM) Ester: $RCOOCH_2SCH_3$ (Chart 6)

Formation

1. From RCO_2K: CH_3SCH_2Cl, NaI, 18-crown-6, C_6H_6, reflux, 6 h, 85–97% yield.[1]
2. $Me_2S^+ClX^-$, Et_3N, 0.5 h, $-70° \rightarrow 25°$, 80–85% yield.[2]
3. *t*-BuBr, DMSO, $NaHCO_3$, 62–98% yield.[3,4] This method was used to prepare the MTM esters of *N*-protected amino acids.

Cleavage

1. $HgCl_2$, CH_3CN, H_2O, reflux, 6 h; H_2S, 20°, 30 min, 82–98% yield.
2. MeI, acetone, reflux, 24 h; 1 *N* NaOH, 87–97% yield.[5]
3. CF_3COOH, 25°, 15 min, 80–90% yield.[6]
4. HCl, Et_2O, 6 h, 83–88% yield.[4] Acidic deprotection of the BOC group could not be achieved with complete selectivity in the presence of an MTM ester. The trityl and NPS (2-nitrophenylsulfenyl) groups were the preferred nitrogen protective groups.
5. H_2O_2, $(NH_4)_6Mo_7O_{24}$; NaOH, pH 11, 97% yield.[5] The MTM ester is converted to the much-more-base labile methylsulfonylmethyl ester. It is possible to hydrolyze the methylsulfonylmethyl ester in the presence of the MTM ester.
6. MCPBA converts the MTM ester to a methylsulfonylmethyl ester (78–98% yield), which can be hydrolyzed enzymatically with rabbit serum (pH 4.5 phosphate buffer, EtOH, 25–28°, 1 h, 84% yield).[7]

1. L. G. Wade, J. M. Gerdes, and R. P. Wirth, *Tetrahedron Lett.*, 731 (1978).
2. T.-L. Ho, *Synth. Commun.*, **9**, 267 (1979).
3. A. Dossena, R. Marchelli, and G. Casnati, *J. Chem. Soc., Perkin Trans. 1*, 2737 (1981).
4. A. Dossena, G. Palla, R. Marchelli, and T. Lodi, *Int. J. Pept. Protein Res.*, **23**, 198 (1984).
5. J. M. Gerdes and L. G. Wade, *Tetrahedron Lett.*, 689 (1979).
6. T.-L. Ho and C. M. Wong, *J. Chem. Soc., Chem. Commun.*, 224 (1973).
7. A. Kamal, *Synth. Commun.*, **21**, 1293 (1991).

Tetrahydropyranyl (THP) Ester: RCOO-2-tetrahydropyranyl (Chart 6)

Formation

1. Dihydropyran, TsOH, CH_2Cl_2, 20°, 1.5 h, quant.[1]

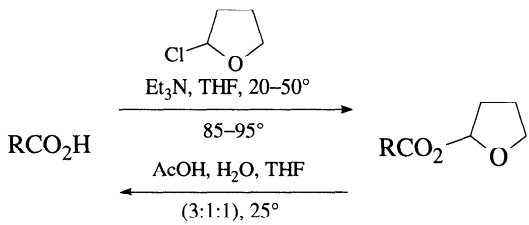
Cleavage

1. AcOH, THF, H_2O (4:2:1), 45°, 3.5 h.[1]

1. K. F. Bernady, M. B. Floyd, J. F. Poletto, and M. J. Weiss, *J. Org. Chem.*, **44**, 1438 (1979).

Tetrahydrofuranyl Ester: RCO_2-2-tetrahydrofuranyl

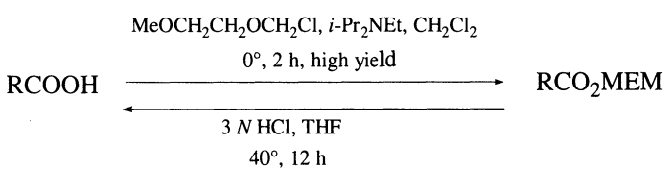
Formation/Cleavage[1]



1. C. G. Kruse, N. L. J. M. Broekhof, and A. van der Gen, *Tetrahedron Lett.*, 1725 (1976).

Methoxyethoxymethyl (MEM) Ester: $RCO_2CH_2OCH_2CH_2OCH_3$

Formation/Cleavage[1]



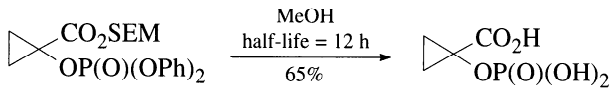
In an attempt to synthesize the macrolide antibiotic chlorothricolide, an unhindered –COOH group was selectively protected, in the presence of a hindered –COOH group, as a MEM ester that was then reduced to an alcohol group.[2] $MgBr_2 \cdot Et_2O$[3] and $AlCl_3$–dimethylaniline[4] efficiently cleave the MEM ester.

1. A. I. Meyers and P. J. Reider, *J. Am. Chem. Soc.*, **101**, 2501 (1979).

2. R. E. Ireland and W. J. Thompson, *Tetrahedron Lett.*, 4705 (1979).
3. A. J. Pearson and H. Shin, *J. Org. Chem.*, **59**, 2314 (1994).
4. T. Akiyama, H. Hirofuji, A. Hirose, and S. Ozaki, *Synth. Commun.*, **24**, 2179 (1994).

2-(Trimethylsilyl)ethoxymethyl (SEM) Ester: $RCO_2CH_2OCH_2CH_2Si(CH_3)_3$

The SEM ester was used to protect a carboxyl group where DCC-mediated esterification caused destruction of the substrate. It was formed from the acid and SEM chloride (THF, 0°, 80% yield) and was removed solvolytically. The ease of removal in this case was attributed to anchimeric assistance by the phosphate group.[1] Normally, SEM groups are cleaved by treatment with fluoride ion. Note that in this case the SEM group is removed considerably faster than the phenyl groups from the phosphate. Additionally, cleavage is effected with $MgBr_2$ in ether (61–100% yield),[2] HF in acetonitrile,[3] or neat HF.[4]



1. E. W. Logusch, *Tetrahedron Lett.*, **25**, 4195 (1984).
2. W.-C. Chen, M. D. Vera, and M. M. Joullié, *Tetrahedron Lett.*, **38**, 4025 (1997).
3. W.-R. Li, W. R. Ewing, B. D. Harris, and M. M. Joullié, *J. Am. Chem. Soc.*, **112**, 7659 (1990).
4. G. Jou, I. Gonzalez, F. Albericio, P. Lloyd-Williams, and E. Giralt, *J. Org. Chem.*, **62**, 354 (1997).

Benzyloxymethyl (BOM) Ester: $RCOOCH_2OCH_2C_6H_5$ (Chart 6)

Formation[1]

$$RCOONa + PhCH_2OCH_2Cl \xrightarrow{HMPA,\ 25°,\ 70\%} RCO_2BOM$$

Cleavage[1]

1. H_2/Pd–C, EtOH, 25°, 70–100% yield.
2. Aqueous HCl, THF, 25°, 2 h, 75–95% yield.

1. P. A. Zoretic, P. Soja, and W. E. Conrad, *J. Org. Chem.*, **40**, 2962 (1975).

Pivaloyloxymethyl Ester (POM–O_2CR): $(CH_3)_3CCO_2CH_2O_2CR$

The ester is prepared from the acid with $PvOCH_2I$ and Ag_2CO_3 in DMF.[1]

Cleavage

$(Bu_3Sn)_2O$, Et_2O, 3 h, 25°, 56% yield.[2–4]

1. D. V. Patel, E. M. Gordon, R. J. Schmidt, H. N. Weller, M. G. Young, R. Zahler, M. Barbacid, J. M. Carboni, J. L. Gullo-Brown, L. Hunihan, C. Ricca, S. Robinson, B. R. Seizinger, A. V. Tuomari, and V. Manne, *J. Med. Chem.*, **38**, 435 (1995).
2. C. J. Salomon, E. G. Mata, and O. A. Mascaretti, *Tetrahedron Lett.*, **32**, 4239 (1991).
3. C. J. Salomon, E. G. Mata, and O. A. Mascaretti, *J. Org. Chem.*, **59**, 7259 (1994).
4. E. G. Mata and O. A. Mascaretti, *Tetrahedron Lett.*, **29**, 6893 (1988).

Phenylacetoxymethyl Ester: $PhCH_2CO_2CH_2O_2CR$

This ester is conveniently formed from a penicillinic acid with $PhCH_2CO_2CH_2Cl$ and TEA. Cleavage is accomplished by enzymatic hydrolysis with penicillin G. acylase in 70–90% yield.[1,2]

1. E. Baldaro, C. Fuganti, S. Servi, A. Tahliani, and M. Terreni, in *Microbial Reagents in Organic Synthesis,* S. Servi, Ed., Kluwer Academic Pubs., Dordrecht (1992), pp. 175ff.
2. E. Baldaro, D. Faiardi, C. Fuganti, P. Grasselli, and A. Lazzzarini, *Tetrahedron Lett.*, **29**, 4623 (1988).

Triisopropylsilylmethyl Ester: $i\text{-}Pr_3SiCH_2O_2CR$

Formation

1. $i\text{-}Pr_3SiCHN_2$, 76–96% yield.[1] In contrast, when $TMSCHN_2$ is used to prepare an ester, the methyl ester is formed.

Cleavage

1. 3 *N* NaOH, EtOH, 6 h, reflux.

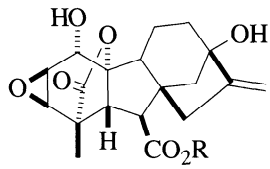
1. J. A. Soderquist and E. I. Miranda, *Tetrahedron Lett.*, **34**, 4905 (1993).

Cyanomethyl Ester: RCO_2CH_2CN

Formation

1. $ClCH_2CN$, TEA, 78–96% yield.[1]

2.



R = H Ref. 2

Cleavage

Na_2S, acetone, water, 74–90% yield.[1]

1. H. M. Hugel, K. V. Bhaskar, and R. W. Longmore, *Synth. Commun.*, **22**, 693 (1992).
2. S. Findlow, P. Gaskin, P. A. Harrison, J. R. Lenton, M. Penny, and C. L. Willis, *J. Chem. Soc., Perkin Trans. 1*, 751 (1997).

Acetol Ester: $CH_3COCH_2O_2CR$

Developed as a carboxyl protective group for peptide synthesis because of its stability to hydrogenolysis and acidic conditions, the acetol (hydroxy acetone) ester is prepared by DCC coupling (68–92% yield) of the acid with acetol. It is cleaved with TBAF in THF.[1]

1. B. Kundu, *Tetrahedron Lett.*, **33**, 3193 (1992).

Phenacyl Ester: $RCOOCH_2COC_6H_5$ (Chart 6)

Formation

1. $PhCOCH_2Br$, Et_3N, EtOAc, 20°,12 h, 83% yield.[1]
2. $PhCOCH_2Br$, KF/DMF, 25°, 10 min, 90–99% yield.[2] Hindered acids are protected at 100°.
3. From the K salt: $PhCOCH_2Br$, $Bu_4N^+ Br^-$, CH_3CN, rt, dibenzo-18-crown-6, 86–98% yield.[3]

Cleavage

1. Zn/HOAc, 25°, 1 h, 90% yield.[4]
2. Zn, acetylacetone, Pyr, DMF, 35°, 0.6 h, 90–98% yield.[5]
3. H_2/Pd–C, aq. MeOH, 20°, 1 h, 72% yield.[1]
4. PhSNa, DMF, 20°, 30 min, 72% yield.[1]
5. $CuCl_2$, O_2, DMF, H_2O, 23–92% yield.[6]
6. Photolysis, sensitizer, CH_3CN, 2 h, 76–100% yield.[7]

7. Irradiation of buffered solutions of *p*-hydroxyphenacyl esters releases the acid.[8]
8. PhSeH, DMF, rt, 48 h, 79% yield.[9] Under basic coupling conditions, an aspartyl peptide that has a β-phenacyl ester is converted to a succinimide.[10] The use of PhSeH prevents the α,β-rearrangement of the aspartyl residue during deprotection.
9. TBAF, THF or DMSO or DMF, 72–98% yield. 4-Nitrobenzyl and trichloroethyl esters of amino acids are also cleaved.[11]

A phenacyl ester is much more readily cleaved by nucleophiles than are other esters, such as the benzyl ester. Phenacyl esters are stable to acidic hydrolysis (e.g., concd. HCl;[1] HBr/HOAc;[1] 50% CF_3COOH/CH_2Cl_2;[12] HF, 0°, 1 h[12]).

1. G. C. Stelakatos, A. Paganou, and L. Zervas, *J. Chem. Soc. C*, 1191 (1966).
2. J. H. Clark and J. M. Miller, *Tetrahedron Lett.*, 599 (1977).
3. S. J. Jagdale, S. V. Patil, and M. M. Salunkhe, *Synth. Commun.*, **26**, 1747 (1996).
4. J. B. Hendrickson and C. Kandall, *Tetrahedron Lett.*, 343 (1970).
5. D. Hagiwara, M. Neya, and M. Hashimoto, *Tetrahedron Lett.*, **31**, 6539 (1990).
6. R. N. Ram and L. Singh, *Tetrahedron Lett.*, **36**, 5401 (1995).
7. A. Banerjee and D. E. Falvey, *J. Org. Chem.*, **62**, 6245 (1997).
8. R. S. Givens, A. Jung, C.-H. Park, J. Weber, and W. Bartlett, *J. Am. Chem. Soc.*, **119**, 8369 (1997).
9. J. L. Morell, P. Gaudreau, and E. Gross, *Int. J. Pept. Protein Res.*, **19**, 487 (1982).
10. M. Bodanszky and J. Martinez, *J. Org. Chem.*, **43**, 3071 (1978).
11. M. Namikoshi, B. Kundu, and K. L. Rinehart, *J. Org. Chem.*, **56**, 5464 (1991).
12. C. C. Yang and R. B. Merrifield, *J. Org. Chem.*, **41**, 1032 (1976).

p-Bromophenacyl Ester: $RCOOCH_2COC_6H_4$–*p*-Br

In a penicillin synthesis, the carboxyl group was protected as a *p*-bromophenacyl ester that was cleaved by nucleophilic displacement (PhSK, DMF, 20°, 30 min, 64% yield). Hydrogenolysis of a benzyl ester was difficult (perhaps because of catalyst poisoning by sulfur); basic hydrolysis of methyl or ethyl esters led to attack at the β-lactam ring.[1]

1. P. Bamberg, B. Eckström, and B. Sjöberg, *Acta Chem. Scand.*, **21**, 2210 (1967).

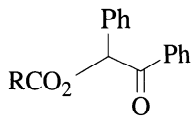
α-Methylphenacyl Ester: $RCO_2CH(CH_3)COC_6H_5$

p-Methoxyphenacyl Ester: $RCO_2CH_2COC_6H_4$–*p*-OCH_3

Phenacyl esters can be prepared from the phenacyl bromide, a carboxylic acid,

and potassium fluoride as base.[1] These esters can be cleaved by irradiation (313 nm, dioxane or EtOH, 20°, 6 h, 80–95% yield, R = amino acids;[2] >300 nm, 30°, 8 h, R = a gibberellic acid, 36–62% yield[3]). Another phenacyl derivative, $RCO_2CH(COC_6H_5)C_6H_3$–3,5-$(OCH_3)_2$, cleaved by irradiation, has also been reported.[4]

1. F. S. Tjoeng and G. A. Heavner, *Synthesis*, 897 (1981).
2. J. C. Sheehan and K. Umezawa, *J. Org. Chem.*, **38**, 3771 (1973).
3. E. P. Serebryakov, L. M. Suslova, and V. K. Kucherov, *Tetrahedron*, **34**, 345 (1978).
4. J. C. Sheehan, R. M. Wilson, and A. W. Oxford, *J. Am. Chem. Soc.*, **93**, 7222 (1971).

Desyl ester: 

Formation

Desyl bromide, DBU, benzene, reflux, 57–95% yield.[1] A polymer-supported version of this ester has been prepared.[2]

Cleavage

Photolysis, 350 nm, CH_3CN, H_2O. The by-product from the reaction is 2-phenylbenzo[*b*]furan. Cleavage with TBAF and $PhCH_2SH$ has been demonstrated (70–94% yield).[3] The related 3,5-dimethoxybenzoin analogue is cleaved with a rate constant of $>10^{10}$ sec^{-1}.[4] Photolytic cleavage occurs by heterolytic bond dissociation.[5]

1. K. R. Gee, L. W. Kueper, III, J. Barnes, G. Dudley, and R. S. Givens, *J. Org. Chem.*, **61**, 1228 (1996).
2. A. Routledge, C. Abell, and S. Balasubramanian, *Tetrahedron Lett.*, **38**, 1227 (1997).
3. M. Ueki, H. Aoki, and T. Katoh, *Tetrahedron Lett.*, **34**, 2783 (1993).
4. M. H. B. Stowell, R. S. Rock, D. C. Rees, and S. I. Chan, *Tetrahedron Lett.*, **37**, 307 (1996).
5. Y. Shi, J. E. T. Corrie, and P. Wan, *J. Org. Chem.*, **62**, 8278 (1997).

Carboxamidomethyl (Cam) Ester: $RCO_2CH_2CONH_2$

The carboxamidomethyl ester was prepared for use in peptide synthesis. It is formed from the cesium salt of an *N*-protected amino acid and α-chloroacetamide (60–85% yield). It is cleaved with 0.5 *M* NaOH or $NaHCO_3$ in DMF/H_2O. It is stable to the conditions required to remove BOC, Cbz, Fmoc, and *t*-butyl esters. It cannot be selectively cleaved in the presence of a benzyl ester of aspartic acid.[1]

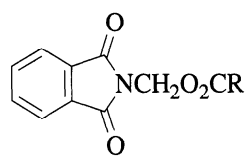
1. J. Martinez, J. Laur, and B. Castro, *Tetrahedron*, **41**, 739 (1985); *idem.*, *Tetrahedron Lett.*, **24**, 5219 (1983).

p-Azobenzenecarboxamidomethyl Ester: $C_6H_5N{=}NC_6H_4NHC(O)CH_2O_2CR$

This ester was developed for C-terminal amino acids during solution-phase peptide synthesis. Purification of intermediates can be monitored colorimetrically or visually. Protection is achieved by reacting the sodium salt of the *N*-protected amino acid with the bromoacetamide derivative to give the ester in 70–95% yield. Cleavage is effected by simple hydrolysis with K_2CO_3 or NH_4OH.[1] A related chromogenic ester, the ***p*-(*p*-(dimethylamino)phenylazo)benzyl ester**, has also been used for the same purpose, except that it can be cleaved by hydrogenolysis.[2]

1. V. G. Zhuravlev, A. A. Mazurov, and S. A. Andronati, *Collect. Czech. Chem. Commun.*, **57**, 1495 (1992).
2. G. D. Reynolds, D. R. K. Harding, and W. S. Hancock, *Int. J. Pept. Protein Res.*, **17**, 231 (1981).

N-Phthalimidomethyl Ester (Chart 6):



Formation

1. $RCO_2H + XCH_2$-*N*-phthalimido

   X = OH: Et_2NH, EtOAc, 37°, 12 h, 70–80% yield.[1]
   X = Cl: $(c\text{-}C_6H_{11})_2NH$, DMF or DMSO, 60°, few minutes, 70–80% yield.[1]
   X = Cl, Br: KF, DMF, 80°, 2 h, 65–75% yield.[2]

Cleavage

1. H_2NNH_2/MeOH, 20°, 3 h, 90% yield.[1]
2. Et_2NH/MeOH, H_2O, 25°, 24 h or refux, 2 h, 82% yield.[1]
3. NaOH/MeOH, H_2O, 20°, 45 min, 77% yield.[1]
4. Zn/HOAc, 25°, 12 h, 80% yield.[3]
5. g HCl/EtOAc, 20°, 16 h, 83% yield.[1]
6. HBr/HOAc, 20°, 10–15 min, 80% yield.[1]

1. G. H. L. Nefkens, G. I. Tesser, and R. J. F. Nivard, *Recl. Trav. Chim. Pays-Bas*, **82**, 941 (1963).
2. K. Horiki, *Synth. Commun.*, **8**, 515 (1978).
3. D. L. Turner and E. Baczynski, *Chem. Ind. (London)*, 1204 (1970).

2-Substituted Ethyl Esters

2,2,2-Trichloroethyl Ester: $RCO_2CH_2CCl_3$ (Chart 6)

Formation

1. CCl_3CH_2OH, DCC, Pyr.[1]
2. CCl_3CH_2OH, TsOH, toluene, reflux.[1,2]
3. CCl_3CH_2OCOCl, THF, Pyr, >60% yield.[3]

Cleavage

1. Zn, AcOH, 0°, 2.5 h. [1]
2. Zinc, THF buffered at pH 4.2–7.2 (20°, 10 min, 75–95% yield).[4]
3. Zinc dust, 1 *M* NH_4OAc, 66% yield.[5]
4. Electrolysis: −1.65 V, $LiClO_4$, MeOH, 87–91% yield.[6] A **tribromoethyl ester** is cleaved by electrolytic reduction at −0.70 V (85% yield); a **dichloroethyl ester** is cleaved at −1.85 V (78% yield).[6]
5. Cat. Se, $NaBH_4$, DMF, 40–50°, 1 h, 77–93% yield.[7]
6. SmI_2, THF, rt, 2 h, quantitative.[8]
7. Cd, DMF, AcOH, 25°, 15 h, 82% yield.[9]

1. R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrüggen, *J. Am. Chem. Soc.*, **88**, 852 (1966).
2. J. F. Carson, *Synthesis*, 24 (1979).
3. R. R. Chauvette, P. A. Pennington, C.W. Ryan, R. D. G. Cooper, F. L. José, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, *J. Org. Chem.*, **36**, 1259 (1971).
4. G. Just and K. Grozinger, *Synthesis*, 457 (1976).
5. G. Jou, I. Gonzalez, F. Albericio, P. Lloyd-Williams, and E. Giralt, *J. Org. Chem.*, **62**, 354 (1997).
6. M. F. Semmelhack and G. E. Heinsohn, *J. Am. Chem. Soc.*, **94**, 5139 (1972).
7. Z.-Z. Huang and X.-J. Zhou, *Synthesis*, 693 (1989).
8. A. J. Pearson and K. Lee, *J. Org. Chem.*, **59**, 2304 (1994).
9. Y. Génisson, P. C. Tyler, and R. N. Young, *J. Am. Chem. Soc.*, **116**, 759 (1994).

2-Haloethyl Ester: $RCOOCH_2CH_2X$, X = I, Br, Cl (Chart 6)

Cleavage

2-Haloethyl esters have been cleaved under a variety of conditions, many of which proceed by nucleophilic addition.

1. Li^+ or Na^+ Co(I)phthalocyanine/MeOH, 0–20°, 40 min–60 h, 60–98% yield.[1]
2. Electrolysis: Co(I)phthalocyanine, $LiClO_4$, EtOH, H_2O, −1.95 V, 95% yield.[2]
3. $NaS(CH_2)_2SNa/CH_3CN$, reflux, 2 h, 80–85% yield.[3]
4. NaSeH/EtOH, 25°, 1 h → reflux, 6 min, 92–99% yield.[4,5]
5. $(NaS)_2CS/CH_3CN$, reflux, 1.5 h, 75–86% yield.[6]
6. Mc_3SnLi/THF, 3 h → $Bu_4N^+F^-$, reflux, 15 min, 78–86% yield.[7]
7. NaHTe, EtOH, 2–60 min, 80–92% yield.[8]
8. Na_2S, 40–68% yield.[9]
9. Li(cobalt phthalocyanine).[10]
10. Cobalt phthalocyanine, $NaBH_4$.[11]
11. SmI_2, THF, rt, 2 h, 88–100% yield.[12] These conditions were found effective when many of the preceding reagents failed to give clean deprotection.

1. H. Eckert and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, **15**, 681 (1976).
2. R. Scheffold and E. Amble, *Angew. Chem., Int. Ed. Engl.*, **19**, 629 (1980).
3. T.-L. Ho, *Synthesis*, 510 (1975).
4. T.-L. Ho, *Synth. Commun.*, **8**, 301 (1978).
5. Z.-Z. Huang and X.-J. Zhou, *Synthesis*, 633 (1990).
6. T.-L. Ho, *Synthesis*, 715 (1974).
7. T.-L. Ho, *Synth. Commun.*, **8**, 359 (1978).
8. J. Chen and X. Zhou, *Synth. Commun.*, **17**, 161 (1987).
9. M. Joaquina, S. A. Amaral Trigo, and M. I. A. Oliveira Sartos, in *Peptides 1986*, D. Theodoropoulos, Ed., Walter de Gruyter & Co., Berlin, 1987, p. 61.
10. P. Lemmen, K. M. Buchweitz, and R. Stumpf, *Chem. Phys. Lipids*, **53**, 65 (1990).
11. H. Eckert, *Z. Naturforch., B: Chem. Sci.*, **45**, 1715 (1990).
12. A. J. Pearson and K. Lee, *J. Org. Chem.*, **59**, 2257, 2304 (1994); *idem, ibid.*, **60**, 7153 (1995).

ω-Chloroalkyl Ester: $RCOO(CH_2)_nCl$

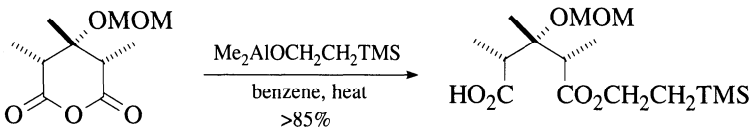
ω-Chloroalkyl esters ($n = 4, 5$) have been cleaved by sodium sulfide (reflux, 4 h, 58–85% yield). The reaction proceeds by sulfide displacement of the chloride ion, followed by intramolecular displacement of the carboxylate group by the (now) sulfhydryl group.[1]

1. T.-L. Ho and C. M. Wong, *Synth. Commun.*, **4**, 307 (1974).

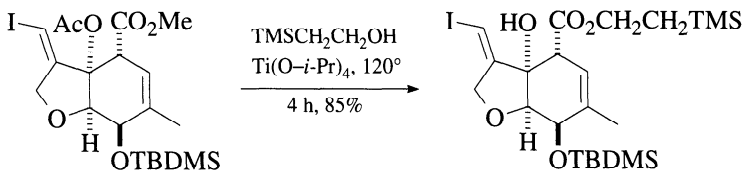
2-(Trimethylsilyl)ethyl (TMSE) Ester: $RCO_2CH_2CH_2Si(CH_3)_3$

Formation

1. $Me_3SiCH_2CH_2OH$, DCC, Pyr, CH_3CN, 0°, 5–15 h, 66–97% yield.[1]
2. From an acid chloride: $Me_3SiCH_2CH_2OH$, Pyr, 25°, 3 h.[2]
3. $Me_3SiCH_2CH_2OH$, Me_3SiCl, THF, reflux, 12–36 h.[3] This method of esterification is also effective for the preparation of other esters.
4. From an anhydride: $Me_2AlOCH_2CH_2SiMe_3$, benzene, heat, >85% yield.[4]



5. $Me_3SiCH_2CH_2OH$, 2-chloro-1-methylpyridinium iodide, Et_3N, 90% yield.[5]
6. From a methyl ester: $Me_3SiCH_2CH_2OH$, $Ti(O\textit{i}\text{-}Pr)_4$, 120°, 4 h, 85% yield.[6]



7. $Me_3SiCH_2CH_2OH$, EDC, DMAP, Pyr.[7]
8. $Me_3SiCH_2CH_2OH$, DEAD, Ph_3P, THF, >75% yield.[8]

Cleavage

1. $Et_4N^+F^-$ or $Bu_4N^+F^-$, DMF or DMSO, 20–30°, 5–60 min, quant. yield.[1,9]
2. DMF, $Bu_4N^+Cl^-$, $KF \cdot 2H_2O$, 42–62% yield (substrate = polypeptide).[10]
3. TBAF, SiO_2, 100% yield[7] or TBAF, DMF, 20 min.[11]
4. TBAF, TsOH, THF, 20°. Other conditions in this sensitive ivermectin analogue led to decomposition.[6]
5. Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS–F), DMF, >76% yield.[8]

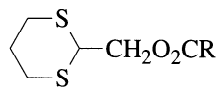
1. P. Sieber, *Helv. Chim. Acta*, **60**, 2711 (1977).
2. H. Gerlach, *Helv. Chim. Acta*, **60**, 3039 (1977).
3. M. A. Brook and T. H. Chan, *Synthesis*, 201 (1983).
4. E. Vedejs and S. D. Larsen, *J. Am. Chem. Soc.*, **106**, 3030 (1984).
5. J. D. White and L. R. Jayasinghe, *Tetrahedron Lett.*, **29**, 2139 (1988).
6. J.-P. Férézou, M. Julia, Y. Li, L. W. Liu, and A. Pancrazi, *Bull. Soc. Chim. Fr.*, **132**, 428 (1995).

7. A. M. Sefler, M. C. Kozlowski, T. Guo, and P. A. Bartlett, *J. Org. Chem.*, **62**, 93 (1997).
8. W. R. Roush, D. S. Coffey, and D. J. Madar, *J. Am. Chem. Soc.*, **119**, 11331 (1997).
9. P. Sieber, R. H. Andreatta, K. Eisler, B. Kamber, B. Riniker, and H. Rink, in *Peptides: Proceedings of the Fifth American Peptide Symposium*, M. Goodman and J. Meienhofer, Eds., Halsted Press, New York, 1977, pp. 543–545.
10. R. A. Forsch and A. Rosowsky, *J. Org. Chem.*, **49**, 1305 (1984).
11. C. K. Marlowe, *Bioorg. Med. Chem. Lett.*, **3**, 437 (1993).

2-Methylthioethyl Ester: $RCO_2CH_2CH_2SCH_3$

The 2-methylthioethyl ester is prepared from a carboxylic acid and methylthioethyl alcohol or methylthioethyl chloride ($MeSCH_2CH_2OH$, TsOH, benzene, reflux, 55 h, 55% yield; $MeSCH_2CH_2Cl$, Et_3N, 65°, 12 h, 50–70% yield).[1] It is cleaved by oxidation [H_2O_2, $(NH_4)_6Mo_7O_{24}$, acetone, 25°, 2 h, 80–95% yield → pH 10–11, 25°, 12–24 h, 85–95% yield][2,3] and by alkylation followed by hydrolysis (MeI, 70–95% yield → pH 10, 5–10 min, 70–95% yield).[1]

1. M. J. S. A. Amaral, G. C. Barrett, H. N. Rydon, and J. E. Willet, *J. Chem. Soc. C*, 807 (1966).
2. P. M. Hardy, H. N. Rydon, and R. C. Thompson, *Tetrahedron Lett.*, 2525 (1968).
3. S. Inoue, K. Okada, H. Tanino, K. Hashizume, and H. Kakoi, *Tetrahedron*, **50**, 2729 (1994).

1,3-Dithianyl-2-methyl (Dim) Ester: 

The Dim ester was developed for the protection of the carboxyl function during peptide synthesis. It is prepared by transesterification of amino acid methyl esters with 2-(hydroxymethyl)-1,3-dithiane and $Al(i\text{-}PrO)_3$ (reflux, 4 h, 75°, 12 torr, 75% yield). It is removed by oxidation [H_2O_2, $(NH_4)_2MoO_4$; pH 8, H_2O, 60 min, 83% yield]. Since it must be removed by oxidation it is not compatible with sulfur-containing amino acids such as cysteine and methionine. Its suitability for other, easily oxidized amino acids (e.g., tyrosine and tryptophan) must also be questioned. The Dim ester is stable to CF_3CO_2H and HCl/ether.[1,2]

1. H. Kunz and H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, **22**, 62 (1983).
2. H. Waldmann and H. Kunz, *J. Org. Chem.*, **53**, 4172 (1988).

2-(*p*-Nitrophenylsulfenyl)ethyl Ester: $RCO_2CH_2CH_2SC_6H_4$–*p*-NO_2

This ester is similar to the 2-methylthioethyl ester in that it is prepared from a thioethyl alcohol and cleaved by oxidation [H_2O_2, $(NH_4)_6Mo_7O_{24}$].[1]

1. M. J. S. A. Amaral, *J. Chem. Soc. C*, 2495 (1969).

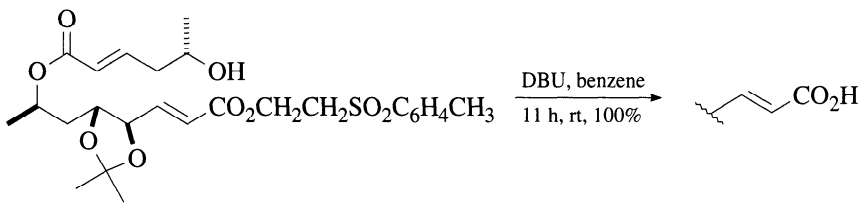
2-(*p*-Toluenesulfonyl)ethyl (Tse) Ester: $RCO_2CH_2CH_2SO_2C_6H_4$–*p*-CH_3 (Chart 6)

Formation

1. $TsCH_2CH_2OH$, DCC, Pyr, 0°, 1 h → 20°, 16 h, 70–90% yield.[1]

Cleavage

1. Na_2CO_3, dioxane, H_2O, 20°, 2 h, 95% yield.[1]
2. 1 *N* NaOH, dioxane, H_2O, 20°, 3 min, 60–95% yield.[1]
3. KCN, dioxane, H_2O, 20°, 2.5 h, 60–85% yield.[1]
4. DBN, benzene, 25°, quant.[2]
5. DBU, benzene, 11 h, 100% yield.[3]



6. $Bu_4N^+F^-$, THF, 0°, 1 h, 52–95% yield.[4] A primary alcohol protected as the *t*-butyldimethylsilyl ether was cleaved under these conditions, but a similarly protected secondary alcohol was stable.

1. A. W. Miller and C. J. M. Stirling, *J. Chem. Soc. C*, 2612 (1968).
2. E. W. Colvin, T. A. Purcell, and R. A. Raphael, *J. Chem. Soc., Chem. Commun.*, 1031 (1972).
3. H. Tsutsui and O. Mitsunobo, *Tetrahedron Lett.*, **25**, 2163 (1984).
4. H. Tsutsui, M. Muto, K. Motoyoshi, and O. Mitsunobo, *Chem. Lett.*, 1595 (1987).

2-(2′-Pyridyl)ethyl (Pet) Ester: $RCO_2CH_2CH_2$–2-C_5H_4N

Formation

1. DCC, HOBt, $HOCH_2CH_2$–2-C_5H_4N, 0° → rt, CH_2Cl_2 or DMF, overnight, 50–92% yield.[1,2]
2. DCC, DMAP, $HOCH_2CH_2$–2-C_5H_4N, CH_2Cl_2, 61–92% yield.[3]
3. The related **2-(4′-pyridyl)ethyl** ester has also been prepared from the acid chloride and the alcohol.[4]

Cleavage

1. MeI, CH_3CN; morpholine or diethylamine, methanol, 76–95% yield.[1,3] These conditions also cleave the 4′-pyridyl derivative.[4]

The Pet ester is stable to the acidic conditions required to remove the BOC and *t*-butyl ester groups, to the basic conditions required to remove the Fmoc and Fm groups, and to hydrogenolysis. It is not recommended for use in peptides that contain methionine or histidine, since these are susceptible to alkylation with methyl iodide.

1. H. Kessler, G. Becker, H. Kogler, and M. Wolff, *Tetrahedron Lett.*, **25**, 3971 (1984).
2. H. Kessler, G. Becker, H. Kogler, J. Friesse, and R. Kerssebaum, *Int. J. Pept. Protein Res.*, **28**, 342 (1986).
3. H. Kunz and M. Kneip, *Angew. Chem., Int. Ed. Engl.*, **23**, 716 (1984).
4. A. R. Katritsky, G. R. Khan, and O. A. Schwarz, *Tetrahedron Lett.*, **25**, 1223 (1984).

2-(*p*-Methoxyphenyl)ethyl Ester: p-$CH_3OC_6H_4CH_2CH_2O_2CR$

Formation of this ester proceeds under standard DCC coupling conditions (DMAP, THF, 28–93%). The ester is cleaved with 1% TFA[1] or dichloroacetic acid in CH_2Cl_2 by DDQ (reflux, CH_2Cl_2, H_2O, 5–15 h, 47–92% yield).[2] Hydrogenolysis (Pd/C, EtOAc, MeOH) cleaves the ester in 23 h, whereas a benzyl ester is cleaved in 10 min under these conditions.[1]

1. M. S. Bernatowicz, H.-G. Chao, and G. R. Matsueda, *Tetrahedron Lett.*, **35**, 1651 (1994).
2. S.-E. Yoo, H. R. Kim, and K. Y. Yi, *Tetrahedron Lett.*, **31**, 5913 (1990).

2-(Diphenylphosphino)ethyl (Dppe) Ester: $(C_6H_5)_2PCH_2CH_2O_2CR$

The Dppe group was developed for carboxyl protection in peptide synthesis. It is formed from an *N*-protected amino acid and the alcohol (DCC, DMAP, 3–12 h, 0°, rt). It is most efficiently cleaved by quaternization with MeI, followed by treatment with fluoride ion or K_2CO_3. The ester is stable to HBr/AcOH, $BF_3{\cdot}Et_2O$, and CF_3CO_2H.[1]

1. D. Chantreux, J.-P. Gamet, R. Jacquier, and J. Verducci, *Tetrahedron*, **40**, 3087 (1984).

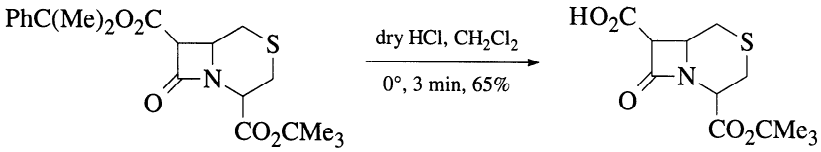
1-Methyl-1-phenylethyl (Cumyl) Ester: $RCO_2C(CH_3)_2C_6H_5$

Formation

1. $C_6H_5C(CH_3)_2OC(=NH)CCl_3$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, cHex, 82% yield.[1,2]

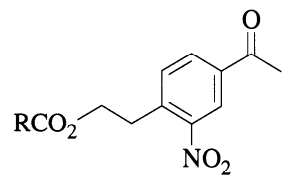
Cleavage

1. TFA/CH_2Cl_2, rt, 15 min, 86% yield. BOC and *t*-BuO groups were stable.[1]

2. 

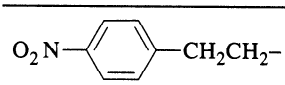
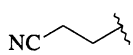
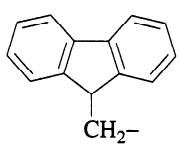
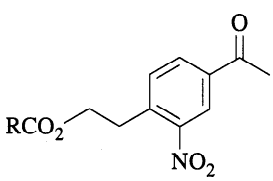
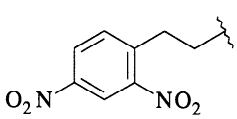
Note that a cumyl ester can be selectively cleaved in the presence of a *t*-butyl ester and a β-lactam.[3]

1. C. Yue, J. Thierry, and P. Potier, *Tetrahedron Lett.*, **34**, 323 (1993).
2. J. Thierry, C. Yue, and P. Potier, *Tetrahedron Lett.*, **39**, 1557 (1998).
3. D. M. Brunwin and G. Lowe, *J. Chem. Soc., Perkin Trans. 1*, 1321 (1973).

2-(4-Acetyl–2-nitrophenyl)ethyl (Anpe) Ester: 

This ester was designed as a base-labile protective group. Monoprotection of aspartic acid was achieved using the DCC/DMAP protocol. Cleavage is

Relative Lability of Aspartic Acid β-Carboxyl Protective Groups

Carboxyl Protective Group	Abbreviation	Deprotection time
	Npe	1.5–2 h
	Cne	45 min
	Fm	<5 min
	Anpe	< 5 min
$O_2NCH_2CH_2-$	Ne	*a*
	Dnpe	*a*

a. Not prepared because of a lack of stability.

promoted with 0.1 *M* TBAF. A comparison with other base-labile esters for the β-carboxyl group of aspartic acid to 0.1 *M* TBAF is provided in the preceding table.[1]

1. J. Robles, E. Pedroso, and A. Grandas, *Synthesis*, 1261 (1993).

2-Cyanoethyl Ester: $NCCH_2CH_2O_2CR$

Formation

$HOCH_2CH_2CN$, DCC, DMAP, CH_2Cl_2, 86–97% yield.[1]

Cleavage

1. TBAF, DMF/THF, 64–100% yield. Cleavage occurs in the presence of TMSE and benzyl esters and acetates.[1]
2. K_2CO_3, MeOH, H_2O.[2] Acetates and most other simple esters are cleaved under these conditions.
3. Na_2S, MeOH, 67–91% yield.[3]

1. Y. Kita, H. Maeda, F. Takahashi, S. Fukui, T. Ogawa, and K. Hatayama, *Chem. Pharm. Bull.*, **42**, 147 (1994).
2. P. K. Misra, S. A. N. Hashmi, W. Haq, and S. B. Katti, *Tetrahedron Lett.*, **30**, 3569 (1989).
3. T. Ogawa, K. Hatayama, H. Maeda, and Y. Kita, *Chem. Pharm. Bull.*, **42**, 1579 (1994).

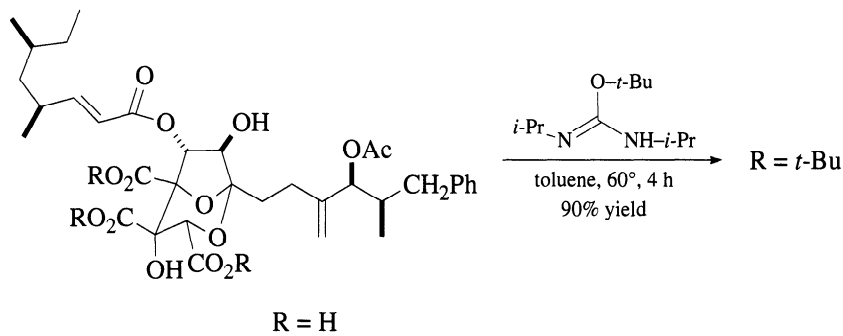
t-Butyl Ester: $RCO_2C(CH_3)_3$ (Chart 6)

Formation

The *t*-butyl ester is a relatively hindered ester, and many of the following methods for its formation should be, and in many cases are, equally effective for the preparation of other hindered esters. The related **1- and 2-adamantyl esters** have been used for the protection of aspartic acid[1] and other amino acids (1-AdOH, toluene, dimethyl sulfate, cat. TsOH, 70–80% yield).[2]

1. Isobutylene, concd. H_2SO_4, Et_2O, 25°, 2–24 h, 50–60% yield.[3] This method works for the preparation of *t*-Bu esters of alkyl acids, amino acids,[4,5] and penicillins.[6]
2. Isobutylene, CH_2Cl_2, H_3PO_4 (P_2O_5), $BF_3{\cdot}Et_2O$, −78°, 2 h, → 0°, 24 h.[7]

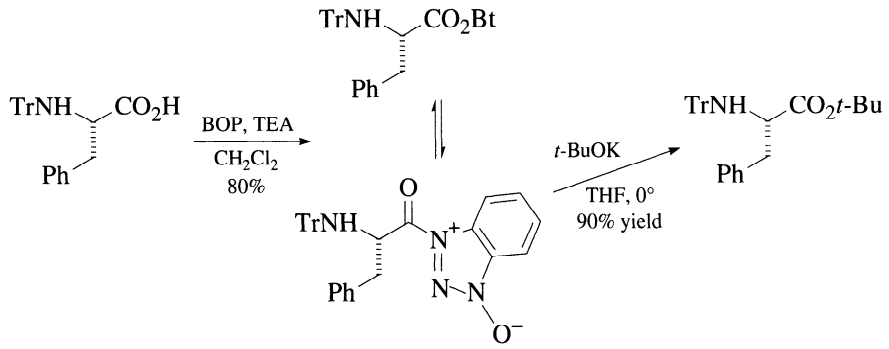
3. $(COCl)_2$, benzene, DMF, 7–10°, 45 min; *t*-BuOH, Et_3N, CH_2Cl_2, 0°, 3 h, 75% yield.[8]
4. From an aromatic acid chloride: LiO–*t*-Bu, 25°, 15 h, 79–82% yield.[9]
5. 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF; *t*-BuOH, DMAP, benzene, 25°, 20 min, 90% yield.[10]
6. *t*-BuOH, Pyr, $(Me_2N)(Cl)C{=}N^+Me_2Cl^-$, 77% yield.[11] This method is also effective for the preparation of other esters.
7. $(Im)_2CO$ (*N,N'*-carbonyldiimidazole), *t*-BuOH, DBU, 54–91% yield.[12]
8. Bu_3PI_2, Et_2O, HMPA; *t*-BuOH, 73% yield.[13]
9. *t*-BuOH, EDCI (EDCI = 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride, DMAP, CH_2Cl_2, 88% yield.[14] Cbz-Proline was protected without racemization.
10. *i*-PrN=C(O–*t*-Bu)NH–*i*-Pr, toluene, 60°, 4 h, 90% yield.[15]



R = H

11. Cl_3C(*t*-BuO)C=NH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, cyclohexane, 70–92% yield.[16] This reagent also forms *t*-butyl ethers from alcohols.
12. $(t\text{-BuO})_2CHNMe_2$, toluene, 80°, 30 min, 82% yield.[17,18]
13. From an acid chloride: *t*-BuOH, AgCN, benzene, 20–80°, 60–100% yield.[19] Alumina also promotes the conversion of an acid chloride to a *t*-Bu ester in 79–96% yield.[20]
14. 2-Cl-3,5-$(NO_2)_2C_5H_2N$, Pyr, rt → 115°, *t*-BuOH.[21] Other esters are also prepared effectively using this methodology.
15. *t*-BuOCOF, Et_3N, DMAP, CH_2Cl_2, *t*-BuOH, rt, 82–96% yield.[22]
16. $(BOC)_2O$, *t*-BuOH or THF, DMAP, 99% yield. This methodology is effective for the preparation of allyl, methyl, ethyl, and benzyl esters as well.[23]
17. *t*-BuBr, K_2CO_3, BTEAC, DMAC, 55°, 72–100% yield.[24]
18. By transesterification of a methyl ester with *t*-BuOH and sulfated SiO_2.[25]

19.



Thermodynamically favored

Ref. 26

Cleavage

t-Butyl esters are stable to mild basic hydrolysis, to hydrazine, and to ammonia; they are cleaved by moderately acidic hydrolysis, with the release of the *t*-Bu cation that often must be scavenged to prevent side reactions.

1. HCO_2H, 20°, 3 h.[27]
2. CF_3COOH, CH_2Cl_2, 25°, 1 h.[28] The addition of Et_3SiH to the deprotection step improves the yields over that obtained with the normal cation scavengers.[29]
3. AcOH, HBr, 10°, 10 min, 70% yield.[4] Phthaloyl or trifluoroacetyl groups on amino acids are stable to these conditions; benzyloxycarbonyl (Cbz) or *t*-butoxycarbonyl (BOC) groups are cleaved.
4. HCl, AcOH, CH_2Cl_2, 5°, 2 h. A *t*-butyl ether and an Fmoc group were not affected.[30]
5. TsOH, benzene, reflux, 30 min, 76% yield.[4] A *t*-butyl ester is stable to the conditions needed to convert an α,β-unsaturated ketone to a dioxolane ($HOCH_2CH_2OH$, TsOH, benzene, reflux).[31]
6. KOH, 18-crown-6, toluene, 100°, 5 h, 94% yield.[32] These conditions were used to cleave the *t*-butyl ester from an aromatic ester; they are probably too harsh to be used on more highly functionalized substrates.
7. 190–200°, 15 min, 100% yield.[33] A thermolysis in quinoline was found advantageous when acid-catalyzed cleavage resulted in partial debenzylation of a phenol.[34] Thermolytic conditions also cleave the BOC group from amines.
8. Bromocatecholborane.[35] Ethyl esters are not affected by this reagent, but it does cleave other groups; see the section on methoxymethyl (MOM) ethers.
9. TMSOTf, TEA, 53–90% yield. *t*-Butyl esters are cleaved in preference to *t*-butyl ethers.[36]

10. MgI_2, toluene, 46–111°, 1–3 days, 41–96% yield.[37]
11. Thermitase, pH 7.5, 45°, 20% DMF, 70–89% yield.[38]
12. Pig liver esterase.[39]
13. LiI, EtOAc, reflux,[40]
14. $TiCl_4$, CH_2Cl_2, $-10°$ to 0°, 54–91% yield. These conditions were developed for use with cephalosporin *t*-butyl esters.[41]

1. Y. Okada and S. Iguchi, *J. Chem. Soc., Perkin Trans. 1*, 2129 (1988).
2. S. M. Iossifidou and C. C. Froussios, *Synthesis*, 1355 (1996).
3. A. L. McCloskey, G. S. Fonken, R. W. Kluiber, and W. S. Johnson, *Org. Synth., Collect. Vol. IV*, 261 (1963).
4. G. W. Anderson and F. M. Callahan, *J. Am. Chem. Soc.*, **82**, 3359 (1960).
5. R. M. Valerio, P. F. Alewood, and R. B. Johns, *Synthesis*, 786 (1988).
6. R. J. Stedman, *J. Med. Chem.*, **9**, 444 (1966).
7. C.-Q. Han, D. DiTullio, Y.-F. Wang, and C. J. Sih, *J. Org. Chem.*, **51**, 1253 (1986).
8. C. F. Murphy and R. E. Koehler, *J. Org. Chem.*, **35**, 2429 (1970).
9. G. P. Crowther, E. M. Kaiser, R. A. Woodruff, and C. R. Hauser, *Org. Synth., Collect. Vol. VI*, 259 (1988).
10. J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **52**, 1989 (1979).
11. T. Fujisawa, T. Mori, K. Fukumoto, and T. Sato, *Chem. Lett.*, 1891 (1982).
12. S. Ohta, A. Shimabayashi, M. Aona, and M. Okamoto, *Synthesis*, 833 (1982).
13. R. K. Haynes and M. Holden, *Aust. J. Chem.*, **35**, 517 (1982).
14. M. K. Dhaon, R. K. Olsen, and K. Ramasamy, *J. Org. Chem.*, **47**, 1962 (1982).
15. R. M. Burk, G. D. Berger, R. L. Bugianesi, N. N. Girotra, W. H. Parsons, and M. M. Ponpipom, *Tetrahedron Lett.*, **34**, 975 (1993).
16. A. Armstrong, I. Brackenridge, R. F. W. Jackson, and J. M. Kirk, *Tetrahedron Lett.*, **29**, 2483 (1988).
17. U. Widmer, *Synthesis*, 135 (1983).
18. J. Deng, Y. Hamada, and T. Shioiri, *J. Am. Chem. Soc.*, **117**, 7824 (1995).
19. S. Takimoto, J. Inanaga, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **49**, 2335 (1976).
20. K. Nagasawa, S. Yoshitake, T. Amiya, and K. Ito, *Synth. Commun.*, **20**, 2033 (1990); K. Nagasawa, K. Ohhashi, A. Yamashita, and K. Ito, *Chem. Lett.*, 209 (1994).
21. S. Takimoto, N. Abe, Y. Kodera, and H. Ohta, *Bull. Chem. Soc. Jpn.*, **56**, 639 (1983).
22. A. Loffet, N. Galeotti, P. Jouin, and B. Castro, *Tetrahedron Lett.*, **30**, 6859 (1989).
23. K. Takeda, A. Akiyama, H. Nakamura, S.-i. Takizawa, Y. Mizuno, H. Takayanagi, and Y. Harigaya, *Synthesis*, 1063 (1994).
24. P. Chevallet, P. Garrouste, B. Malawska, and J. Martinez, *Tetrahedron Lett.*, **34**, 7409 (1993).
25. S. P. Chavan, P. K. Zubaidha, S. W. Dantale, A. Keshavaraja, A. V. Ramaswamy, and T. Ravindranathan, *Tetrahedron Lett.*, **37**, 233 (1996).

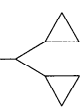
26. K. M. Sliedregt, A. Schouten, J. Kroon, and R. M. J. Liskamp, *Tetrahedron Lett.*, **37**, 4237 (1996).
27. S. Chandrasekaran, A. F. Kluge, and J. A. Edwards, *J. Org. Chem.*, **42**, 3972 (1977).
28. D. B. Bryan, R. F. Hall, K. G. Holden, W. F. Huffman, and J. G. Gleason, *J. Am. Chem. Soc.*, **99**, 2353 (1977).
29. A. Mehta, R. Jaouhari, T. J. Benson, and K. T. Douglas, *Tetrahedron Lett.*, **33**, 5441 (1992).
30. G. M. Makara and G. R. Marshall, *Tetrahedron Lett.*, **38**, 5069 (1997).
31. A. Martel, T. W. Doyle, and B.-Y. Luh, *Can. J. Chem.*, **57**, 614 (1979).
32. C. J. Pedersen, *J. Am. Chem. Soc.*, **89**, 7017 (1967).
33. L. H. Klemm, E. P. Antoniades, and D. C. Lind, *J. Org. Chem.*, **27**, 519 (1962).
34. J. W. Lampe, P. F. Hughes, C. K. Biggers, S. H. Smith, and H. Hu, *J. Org. Chem.*, **61**, 4572 (1996).
35. R. K. Boeckman, Jr., and J. C. Potenza, *Tetrahedron Lett.*, **26**, 1411 (1985).
36. A. Trzeciak and W. Bannwarth, *Synthesis*, 1433 (1996).
37. A. G. Martinez, J. O. Bardina, G. H. del Veccio, M. Hanack, and L. R. Subramanian, *Tetrahedron Lett.*, **32**, 5931 (1991).
38. M. Schultz, P. Hermann, and H. Kunz, *Synlett*, 37 (1992).
39. K. A. Stein and P. L. Toogood, *J. Org. Chem.*, **60**, 8110 (1995).
40. J. W. Fisher and K. L. Trinkle, *Tetrahedron Lett.*, **35**, 2505 (1994).
41. M. Valencic, T. van der Does, and E. de Vroom, *Tetrahedron Lett.*, **39**, 1625 (1998).

3-Methyl-3-pentyl (Mpe) Ester: $(C_2H_5)_2CCH_3O_2CR$

This tertiary ester was developed to reduce aspartimide and piperidide formation during the Fmoc-based peptide synthesis by increasing the steric bulk around the carboxyl carbon. A twofold improvement was achieved over the the standard *t*-butyl ester. The Mpe ester is prepared from the acid chloride and the alcohol and can be cleaved under conditions similar to those used for the *t*-butyl ester.[1]

1. A. Karlström and A. Undén, *Tetrahedron Lett.*, **37**, 4243 (1996).

Dicyclopropylmethyl (Dcpm) Ester: RCO_2



The Dcpm group can be removed in the presence of a *t*-butyl or *N*-trityl group with 1% TFA in CH_2Cl_2.[1]

1. L. A. Carpino, H.-G. Chao, S. Ghassemi, E. M. E. Mansour, C. Riemer, R. Warrass, D. Sadat-Aalaee, G. A. Truran, H. Imazumi, A. El-Faham, D. Ionescu, M. Ismail, T. L. Kowaleski , C. H. Han, H. Wenschuh, M. Beyermann, M. Bienert, H. Shroff, F. Albericio, S. A. Triolo, N. A. Sole, and S. A. Kates, *J. Org. Chem.*, **60**, 7718 (1995).

2,4-Dimethyl-3-pentyl (Dmp) Ester: $(i\text{-Pr})_2CHO_2CR$

Formation

1. 2,4-Dimethyl-3-pentanol, DCC, DMAP, CH_2Cl_2, 4 h. This group was developed as an improvement over the use of cylcohexanol for aspartic acid protection during peptide synthesis.[1]

Cleavage

Cleavage is effected with acid. The following table compares the acidolysis rates with Bn and cyclohexyl esters in TFA/phenol at 43°. The Dmp group reduces aspartimide formation during Fmoc-based peptide synthesis.

Protective Group	$t_{1/2}$ (h)
Bn	6
Dmp	40
cHex	500

1. A. H. Karlström and A. E. Unden, *Tetrahedron Lett.*, **36**, 3909 (1995).

Cyclopentyl Ester: RCO_2–*c*-C_5H_9

Cyclohexyl Ester: RCO_2–*c*-C_6H_{11}

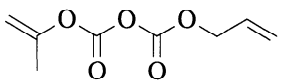
Cycloalkyl esters have been used to protect the β-CO_2H group in aspartyl peptides to minimize aspartimide formation during acidic or basic reactions.[1] Aspartimide formation is limited to 2–3% in TFA (20 h, 25°), 5–7% with HF at 0°, and 1.5–4% TfOH (thioanisole in TFA). Cycloalkyl esters are also stable to Et_3N, whereas use of the benzyl ester leads to 25% aspartimide formation during Et_3N treatment. Cycloalkyl esters are stable to CF_3COOH, but are readily cleaved with HF or TfOH.[2–4]

1. For an improved synthesis of cyclohexyl aspartate, see G. K. Toth and B. Penke, *Synthesis*, 361 (1992).
2. J. Blake, *Int. J. Pept. Protein Res.*, **13**, 418 (1979).
3. J. P. Tam, T.-W. Wong, M. W. Riemen, F.-S. Tjoeng, and R. B. Merrifield, *Tetrahedron Lett.*, 4033 (1979).
4. N. Fujii, M. Nomizu, S. Futaki, A. Otaka, S. Funakoshi, K. Akaji, K. Watanabe, and H. Yajima, *Chem. Pharm. Bull.*, **34**, 864 (1986).

Allyl Ester: $RCO_2CH_2CH{=}CH_2$

The use of various allyl protective groups in complex molecule synthesis has been reviewed.[1]

Formation

1. Allyl bromide, Aliquat 336, $NaHCO_3$, CH_2Cl_2, 83% yield.[2] The carboxylic acid group of Z-serine (Z = Cbz = benzyloxycarbonyl) is selectively esterified without affecting the alcohol.
2. $R'R''C{=}CHCH_2OH$, NaH, THF, 1–3 days, 80–95% yield.[3] A methyl ester is exchanged for an allyl ester under these conditions.
3. Allyl bromide, Cs_2CO_3, DMF, 84% yield.[4]
4. Allyl alcohol, TsOH, benzene, $-H_2O$.[5] These conditions were used to prepare esters of amino acids.
5. By transesterification of an ethyl ester: AllylOH, DBU, LiBr, 0°, 12 h, >54% yield.[6]
6. $AllylOCO_2CO_2allyl$, THF, DMAP.[7]
7.  DMAP, 81–100% yield.[8]
8. $AllylOC{=}NH(CCl_3)$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, cyclohexane, 67–96% yield.[9]
9. Vinyldiazomethane, CH_2Cl_2, 80–92% yield.[10]
10. From the Oppolzer sultam by exchange: AllylOH, $Ti(OR)_4$, 67–95% yield.[11]

Cleavage

1. $Pd(OAc)_2$, sodium 2-methylhexanoate, Ph_3P, acetone.[12] Triethyl phosphite could be used as the ligand for palladium.[13]
2. $(Ph_3P)_3RhCl$ or $Pd(Ph_3P)_4$, 70°, EtOH, H_2O, 91% yield.[14]
3. $Pd(Ph_3P)_4$, pyrrolidine, 0°, 5–15 min, CH_3CN, 70–90% yield.[15] Morpholine has also been used as an allyl scavenger in this process.[2,4] Allylamines are not affected by these conditions.[16]
4. $PdCl_2(Ph_3P)_2$, dimedone, THF, 95% yield.[17] This method is also effective for removing the allyloxycarbonyl group from alcohols and amines.
5. $Pd(Ph_3P)_4$, 2-ethylhexanoic acid[18] or barbituric acid (THF, 3 h, 93% yield).[19] Tributylstannane can serve as an allyl scavenger.[20]
6. Me_2CuLi, Et_2O, 0°, 1 h; H_3O^+, 75–85% yield.[21]
7. $PhSiH_3$, $Pd(Ph_3P)_4$, CH_2Cl_2, 74–100% yield.[22] $CF_3CON(SiMe_3)CH_3$ was also used to scavenge the allyl group from the Alloc and allyl ether protected deriviatives.
8. $Pd(Ph_3P)_4$, $BnONH_2$, CH_2Cl_2, 80% yield.[23]
9. $Pd(OAc)_2$, Ph_3P, TEA, HCO_2H, dioxane, 96% yield.[24,25]
10. Papain, DTT, DMF.[26]

11. $TiCl_4$, Mg–Hg, THF, 40–70% yield.[27] Benzyl esters are also cleaved.
12. $Pd(Ph_3P)_4$, RSO_2Na, CH_2Cl_2 or THF/MeOH, 70–99% yield. These conditions were shown to be superior to the use of sodium 2-ethylhexanoate. Methallyl, allyl, crotyl, and cinnamyl ethers, the Alloc group, and allylamines are all efficiently cleaved by this method.[28]

Methallyl Ester: $CH_2{=}C(CH_3)CH_2O_2CR$

Cleavage of the methallyl ester is achieved in 80–95% yield by solvolysis in refluxing 90% formic acid. Cinnamyl and crotyl alcohols are similarly cleaved.[29]

2-Methylbut-3-en-2-yl Ester: $CH_2{=}CHC(CH_3)_2O_2CR$

This ester is cleaved with $Pd(OAc)_2$, Ph_3P, Et_3N–H_2CO_2H, rt, 30 min.[30]

3-Methylbut-2-enyl (Prenyl) Ester: $(CH_3)_2C{=}CHCH_2O_2CR$

Cleavage

1. I_2 in cyclohexane, rt, 75–97% yield.[31]
2. $Pd(OAc)_2$, TPPTS, CH_3CN, H_2O, 75 min, 100% yield. The Alloc group is readily released in the presence of this ester.[32]

3-Buten-1-yl Ester: $CH_2{=}CHCH_2CH_2O_2CR$

This ester, formed from the acid ($COCl_2$, toluene; then $CH_2{=}CHCH_2CH_2OH$, acetone, $-78°$ warm to rt, 70–94% yield), can be cleaved by ozonolysis followed by Et_3N or DBU treatment (79–99% yield). The ester is suitable for the protection of enolizable and base-sensitive carboxylic acids.[33]

4-(Trimethylsilyl)-2-buten-1-yl Ester: $RCO_2CH_2CH{=}CHCH_2Si(CH_3)_3$

This ester is formed by standard procedures and is readily cleaved with $Pd(Ph_3P)_4$ in CH_2Cl_2 to form trimethylsilyl esters that readily hydrolyze on treatment with water or alcohol or on chromatography on silica gel (73–98% yield). Amines can be protected using the related carbamate.[34]

Cinnamyl Ester: $RCO_2CH_2CH{=}CHC_6H_5$ (Chart 6)

The cinnamyl ester can be prepared from an activated carboxylic acid derivative and cinnamyl alcohol or by transesterification with cinnamyl alcohol in the presence of the H-Beta Zeolite (toluene, reflux, 8 h, 59–96% yield).[35] It is cleaved under nearly neutral conditions [$Hg(OAc)_2$, MeOH, 23°, 2–4 h; KSCN, H_2O, 23°, 12–16 h, 90% yield][36] or by treatment with Sulfated-SnO_2, toluene, anisole, reflux.[37] The latter conditions also cleave crotyl and prenyl esters.

α-Methylcinnamyl (MEC) Ester: $RCO_2CH(CH_3)CH{=}CHC_6H_5$

Formation

1. PhCH=CHCH(CH_3)OH, DCC, DMAP, THF, 98% yield.[38]
2. From an acid chloride: PhCH=CHCH(CH_3)OH, Pyr, DMAP, 75–88% yield.[38]

Cleavage

$Me_2Sn(SMe)_2$, $BF_3{\cdot}Et_2O$, $PhCH_3$, 0°, 3–24 h; AcOH, 75–100% yield.[33,38] An ethyl ester can be hydrolyzed in the presence of an MEC ester with 1 *N* aqueous NaOH–DMSO (1 : 1), and MEC esters can be cleaved in the presence of ethyl, benzyl, cinnamyl, and *t*-butyl esters, as well as the acetate, TBDMS, and MEM groups.

1. F. Guibé, *Tetrahedron*, **54**, 2967–3041 (1998).
2. S. Friedrich-Bochnitschek, H. Waldmann, and H. Kunz, *J. Org. Chem.*, **54**, 751 (1989).
3. N. Engel, B. Kübel, and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, **16**, 394 (1977).
4. H. Kunz, H. Waldmann, and C. Unverzagt, *Int. J. Pept. Protein Res.*, **26**, 493 (1985).
5. H. Waldmann and H. Kunz, *Liebigs Ann. Chem.*, 1712 (1983).
6. M. J. I. Andrews and A. B. Tabor, *Tetrahedron Lett.*, **38**, 3063 (1997); D. Seebach, A. Thaler, D. Blaser, and S. Y. Ko, *Helv. Chim. Acta*, **74**, 1102 (1991).
7. K. Takeda, A. Akiyama, H. Nakamura, S.-i. Takizawa, Y. Mizuno, H. Takayamagi, and Y. Harigaya, *Synthesis*, 1063 (1994).
8. K. Takeda, A. Akiyama, Y. Konda, H. Takayanagi, and Y. Harigaya, *Tetrahedron Lett.*, **36**, 113 (1995).
9. G. Kokotos and A. Chiou, *Synthesis*, 168 (1997).
10. S. T. Waddell and G. M. Santorelli, *Tetrahedron Lett.*, **37**, 1971 (1996).
11. W. Oppolzer and P. Lienard, *Helv. Chim. Acta*, **75**, 2572 (1992).
12. L. N. Jungheim, *Tetrahedron Lett.*, **30**, 1889 (1989).
13. M. Seki, K. Kondo, T. Kuroda, T. Yamanaka, and T. Iwasaki, *Synlett*, 609 (1995).
14. H. Kunz and H. Waldmann, *Helv. Chim. Acta*, **68**, 618 (1985).
15. R. Dcziel, *Tetrahedron Lett.*, **28**, 4371 (1987).
16. J. E. Bardaji, J. L. Torres, N. Xaus, P. Clapés, X. Jorba, B. G. de la Torre, and G. Valencia, *Synthesis*, 531 (1990).
17. H. X. Zhang, F. Guibé, and G. Balavoine, *Tetrahedron Lett.*, **29**, 623 (1988).
18. P. D. Jeffrey and S. W. McCombie, *J. Org. Chem.*, **47**, 587 (1982).
19. H. Kunz and J. März, *Synlett*, 591 (1992).
20. B. G. de la Torre, J. L. Torres, E. Bardají, P. Clapés, N. Xaus, X. Jorba, S. Calvet, F. Albericio, and G. Valencia, *J. Chem. Soc., Chem. Commun.*, 965 (1990).
21. T.-L. Ho, *Synth. Commun.*, **8**, 15 (1978).

22. M. Dessolin, M.-G. Guillerez, N. Thieriet, F. Guibé, and A. Loffet, *Tetrahedron Lett.*, **36**, 5741 (1995).
23. B. T. Lotz and M. J. Miller, *J. Org. Chem.*, **58**, 618 (1993).
24. G. Casy, A. G. Sutherland, R. J. K. Taylor, and R. G. Urben, *Synthesis*, 767 (1989).
25. E. J. Corey and S. Choi, *Tetrahedron Lett.*, **34**, 6969 (1993).
26. N. Xaus, P. Clapés, E. Bardají, J. L. Torres, X. Jorba, J. Mata, and G. Valencia, *Tetrahedron*, **45**, 7421 (1989).
27. K. Satyanarayana, N. Chidambaram, and S. Chandrasekaran, *Synth. Commun.*, **19**, 2159 (1989).
28. M. Honda, H. Morita, and I. Nagakura, *J. Org. Chem.*, **62**, 8932 (1997).
29. C. R. Schmid, *Tetrahedron Lett.*, **33**, 757 (1992).
30. M. Yamaguchi, T. Okuma, A. Horiguchi, C. Ikeura, and T. Minami, *J. Org. Chem.*, **57**, 1647 (1992).
31. J. Cossy, A. Albouy, M. Scheloske, and D. G. Pardo, *Tetrahedron Lett.*, **35**, 1539 (1994).
32. S. Lemaire-Audoire, M. Savignac, E. Blart, G. Pourcelot, J. P. Genêt, and J-M. Bernard, *Tetrahedron Lett.*, **35**, 8783 (1994).
33. A. G. M. Barrett, S. A. Lebold, and X.-an Zhang, *Tetrahedron Lett.*, **30**, 7317 (1989).
34. H. Mastalerz, *J. Org. Chem.*, **49**, 4092 (1984).
35. B. S. Balaji, M. Sasidharan, R. Kumar, and B. Chandra, *J. Chem. Soc., Chem. Commun.*, 707 (1996).
36. E. J. Corey and M. A. Tius, *Tetrahedron Lett.*, 2081 (1977).
37. S. P. Chavan, P. K. Zubaidha, S. W. Dantale, A. Keshavaraja, A. V. Ramaswamy, and T. Ravindranathan, *Tetrahedron Lett.*, **37**, 237 (1996).
38. T. Sato, J. Otera, and H. Nozaki, *Tetrahedron Lett.*, **30**, 2959 (1989).

Prop-2-ynyl (Propargyl) Ester: $HC{\equiv}CCH_2O_2CR$

Cleavage

1. Benzyltriethylammonium tetrathiomolybdate in CH_3CN in 61–97% yield. Deprotection is compatible with esters such as benzyl, allyl, acetate, and *t*-butyl esters.[1]
2. $Pd(Ph_3P)_2Cl_2$ (Bu_3SnH, benzene)[2] or cobalt carbonyl.[3] The palladium method cleaves allyl esters, propargyl phosphates, and propargyl carbamates as well.
3. SmI_2.[4,5]
4. Hydrogenolysis.[6]
5. Electrolysis, Ni(II), Mg anode, DMF, rt, 77–99% yield. This method is not compatible with halogenated phenols because of competing halogen cleavage.[7]

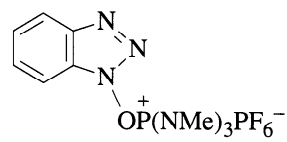
1. P. Ilankumaran, N. Manojans, and S. Chandrasekaran, *J. Chem. Soc., Chem. Commun.*, 1957 (1996).

2. H. X. Zhang, F. Guibé, and G. Balavoine, *Tetrahedron Lett.*, **29**, 619, 623 (1988).
3. B. Alcaide, J. Perez-Castels, B. Sanchez-Vigo, and M. A. Sierra, *J. Chem. Soc., Chem. Commun.*, 587 (1994).
4. J. Inanaga, Y. Sugimoto, and T. Hanamoto, *Tetrahedron Lett.*, **33**, 7035 (1992).
5. J. M. Aurrecoechea and R. F.-S. Anton, *J. Org. Chem.*, **59**, 702 (1994).
6. J. Tsuji and T. Mandai, *Synthesis*, 1 (1996); J. Tsuji and T. Mandai, *Angew. Chem., Int. Ed. Engl.*, **34**, 2589 (1995).
7. S. Olivero and E. Duñach, *Tetrahedron Lett.*, **38**, 6193 (1997).

Phenyl Ester: $RCO_2C_6H_5$

Phenyl esters can be prepared from *N*-protected amino acids (PhOH, DCC, CH_2Cl_2, $-20° \rightarrow 20°$, 12 h, 86% yield[1]; PhOH, BOP, Et_3N, CH_2Cl_2, 25°, 2 h, 73–97% yield[2]). Phenyl esters are readily cleaved under basic conditions (H_2O_2, H_2O, DMF, pH 10.5, 20°, 15 min).[3]

BOP =



1. I. J. Galpin, P. M. Hardy, G. W. Kenner, J. R. McDermott, R. Ramage, J. H. Seely, and R.G. Tyson, *Tetrahedron*, **35**, 2577 (1979).
2. B. Castro, G. Evin, C. Selve, and R. Seyer, *Synthesis*, 413 (1977).
3. G. W. Kenner and J. H Seely, *J. Am. Chem. Soc.*, **94**, 3259 (1972).

2,6-Dialkylphenyl Esters

2,6-Dimethylphenyl Ester

2,6-Diisopropylphenyl Ester

2,6-Di-*t*-butyl-4-methylphenyl Ester

2,6-Di-*t*-butyl-4-methoxyphenyl Ester

These esters were prepared from the phenol and the acid chloride, plus DMAP (or from the acid plus trifluoroacetic anhydride). Although the diisopropyl derivative can be cleaved with hot aqueous NaOH, the di-*t*-butyl derivatives could only be cleaved with NaOMe in a mixture of toluene and HMPA.[1] The related 2,6-di-*t*-butyl-4-methoxyphenyl ester can be cleaved oxidatively with ceric ammonium nitrate.[2] These hindered esters have been used to direct the aldol condensation.[3]

1. T. Hattori, T. Suzuki, N. Hayashizaka, N. Koike, and S. Miyano, *Bull. Chem. Soc. Jpn.*, **66**, 3034 (1993).

2. M. P. Cooke, Jr., *J. Org. Chem.*, **51**, 1637 (1986); C. H. Heathcock, M. C. Pirrung, S. H. Montgomery, and J. Lampe, *Tetrahedron,* **37**, 4087 (1981).
3. C. H. Heathcock, in *Asymmetric Synthesis*, J. D. Morrison, Ed., Academic, New York, 1984, Vol. 3, pp. 111–212; D. A. Evans, J. V. Nelson, and T. R. Tabor, in *Top. Stereochem.*, N. L. Allinger, E. L. Eliel, and S. H. Wilen, Eds., Wiley Interscience, New York, **13**, 1 (1982); C. H. Heathcock, in *Comprehensive Organic Synthesis*, B. M. Trost and I. Fleming, Eds., Pergamon, Oxford, U.K. 1991, Vol. 2, pp. 133–238.

p-(Methylthio)phenyl Ester: $RCO_2C_6H_4$–*p*-SCH_3

The *p*-(methylthio)phenyl ester has been prepared from an *N*-protected amino acid and 4-$CH_3SC_6H_4OH$ (DCC, CH_2Cl_2, 0°, 1 h → 20°, 12 h, 60–70% yield). The *p*-(methylthio)phenyl ester serves as an unactivated ester that is activated on oxidation to the sulfone (H_2O_2, AcOH, 20°, 12 h, 60–80% yield), which then serves as an activated ester in peptide synthesis.[1]

1. B. J. Johnson and T. A. Ruettinger, *J. Org. Chem.*, **35**, 255 (1970).

Pentafluorophenyl (Pfp) Ester: $C_6F_5O_2CR$

This active ester was used for carboxyl protection of Fmoc-serine and Fmoc-threonine during glycosylation.[1,2] The esters are then used as active esters in peptide synthesis.

Formation

1. $C_6F_5O_2CCF_3$, Pyr, DMF, rt, 45 min, 92–95% yield.[3] This reagent converts amines to the trifluoroacetamide.[4]
2. C_6F_5OH, DCC, dioxane or EtOAc and DMF, 0°, 1 h then rt, 1 h, 75–99% yield. [5]

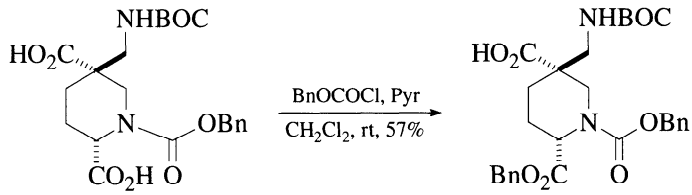
1. M. Meldal and K. Bock, *Tetrahedron Lett.*, **31**, 6987 (1990).
2. M. Meldal and K. J. Jensen, *J. Chem. Soc., Chem. Commun.*, 483 (1990).
3. M. Green and J. Berman, *Tetrahedron Lett.*, **31**, 5851 (1990).
4. L. M. Gayo and M. J. Suto, *Tetrahedron Lett.*, **37**, 4915 (1996).
5. L. Kisfaludy and I. Schön, *Synthesis,* 325 (1983); I. Schön and L. Kisfaludy, *ibid.*, 303 (1986).

Benzyl Ester: $RCO_2CH_2C_6H_5$, RCO_2Bn (Chart 6)

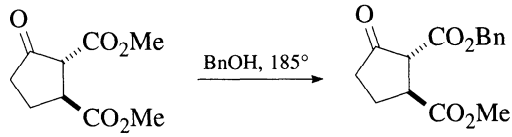
Formation

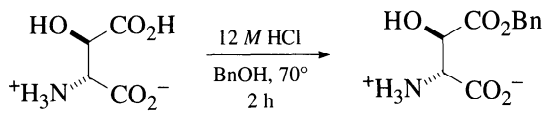
Benzyl esters are readily prepared by many of the classical methods (see the introduction to this chapter), as well as by many newer methods, since benzyl alcohol is unhindered and relatively acid stable.

1. BnOCOCl, Et_3N, 0°, DMAP, CH_2Cl_2, 30 min, 97% yield.[1] In the case of very hindered acids the yields are poor, and formation of the symmetrical anhydride is observed. Useful selectivity can be achieved for a less hindered acid in the presence of a more hindered one.[2]



2. A methyl ester can be exchanged thermally (185°, 1.25 h, –MeOH) for a benzyl ester.[3]



3. For amino acids: DCC, DMAP, BnOH, 92% yield.[4]
4. BnOC=NH(CCl_3), BF_3·Et_2O, CH_2Cl_2, cyclohexane, 60–98% yield.[5,6]
5. 

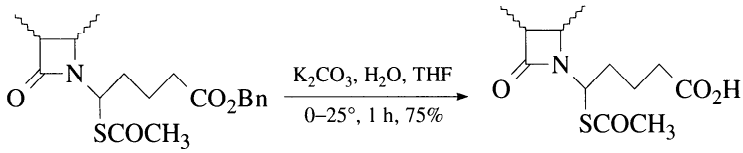
Ref. 7
6. $(BnO)_2CHNMe_2$.[8]
7. BnBr, DBU, CH_3CN, 75% yield.[9]
8. BnBr, Cs_2CO_3, CH_3CN, reflux, 93–100% yield.[10] Other esters are prepared similarly.
9. cHexN=C(OBn)NHcHex.[6]
10. From an anhydride, BnOH, Bu_3P, CH_2Cl_2.[11]

Cleavage

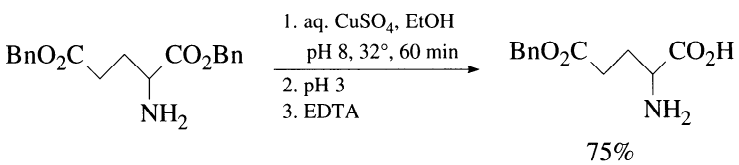
The most useful property of benzyl esters is that they are readily cleaved by hydrogenolysis.

1. H_2/Pd–C, 25°, 45 min–24 h, high yields.[12] Catalytic transfer hydrogenation (see entries 2 and 3) can be used to cleave benzyl esters in some compounds that contain sulfur, a poison for hydrogenolysis catalysts.
2. Pd–C, cyclohexene[13] or 1,4-cyclohexadiene,[14] 25°, 1.5–6 h, good yields. Some alkenes,[6] benzyl ethers, BOM groups, and benzylamines[15] are compatible with these conditions.
3. Pd–C, 4.4% HCOOH, MeOH, 25°, 5–10 min in a column, 100% yield.[16]

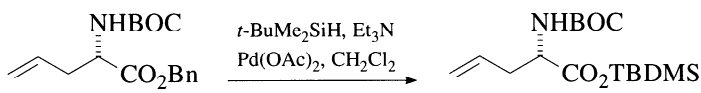
4. K_2CO_3, H_2O, THF, 0° → 25°, 1 h, 75% yield.[17]



5. $AlCl_3$, anisole, CH_2Cl_2, CH_3NO_2, 0° → 25°, 5 h, 80–95% yield.[18] These conditions were used to cleave the benzyl ester in a variety of penicillin derivatives.
6. BCl_3, CH_2Cl_2, −10°→ rt, 3 h, 90% yield.[19]
7. Na, ammonia, 50% yield.[20] These conditions were used to cleave the benzyl ester of an amino acid; the Cbz and benzylsulfenamide derivatives were also cleaved.
8. Aq. $CuSO_4$, EtOH, pH 8, 32°, 60 min; pH 3; EDTA (ethylenediaminetetraacetic acid), 75% yield.[21]



9. Benzyl esters can be cleaved by electrolytic reduction at −2.7 V.[22]
10. *t*-$BuMe_2SiH$, $Pd(OAc)_2$, CH_2Cl_2, Et_3N, 100% yield.[23] Cbz groups and Alloc groups are also cleaved, but benzyl ethers are stable. $PdCl_2$ and Et_3SiH have also been used to cleave a benzyl ester.[24]



11. NaHTe, DMF, *t*-BuOH, 80–90°, 5 min, 98% yield.[25] Methyl and propyl esters are also cleaved (13–97% yield).
12. W2 Raney nickel, EtOH, Et_3N, rt, 0.5 h, 75–85% yield.[26] A disubstituted olefin was not reduced.
13. Acidic alumina, microwaves, 7 min, 90% yield.[27]
14. NBS, CCl_4, Bz_2O, reflux, 61–97% yield.[28] Substituted benzyl esters are cleaved similarly.
15. Alcatase, *t*-BuOH, pH 8.2, 35°, 0.5 h, 91% yield.[29]
16. *P. Fluorescens*, ROH, MTBE convert a benzyl ester by transesterification to Me, Et, and Bu esters.[30]
17. Pronase, 25°, pH 7.2, aq. EtOH, 70–73% yield.[31]

18. Alkaline protease from *Bacillus subtilis* DY, pH 8, 37°, 80–85% yield.[32] Methyl esters are cleaved similarly.
19. Bis(tributyltin) oxide, toluene, 70–90°, 36–96 h, 60–69% yield.[33]

1. S. Kim, Y. C. Kim, and J. I. Lee, *Tetrahedron Lett.*, **24**, 3365 (1983); S. Kim, J. I. Lee, and Y. C. Kim, *J. Org. Chem.*, **50**, 560 (1985).
2. J. E. Baldwin, M. Otsuka, and P. M. Wallace, *Tetrahedron*, **42**, 3097 (1986).
3. W. L. White, P. B. Anzeveno, and F. Johnson, *J. Org. Chem.*, **47**, 2379 (1982).
4. B. Neises, T. Andries, and W. Steglich, *J. Chem. Soc., Chem. Commun.*, 1132 (1982).
5. G. Kokotos and A. Chiou, *Synthesis*, 169 (1997).
6. K. C. Nicolaou, E. W. Yue, Y. Naniwa, F. D. Riccardis, A. Nadin, J. E. Leresche, S. La Greca, and Z. Yang, *Angew. Chem., Int. Ed.. Engl.*, **33**, 2184 (1994).
7. J. F. Okonya, T. Kolasa, and M. J. Miller, *J. Org. Chem.*, **60**, 1932 (1995).
8. G. Emmer, M. A. Grassberger, J. G. Meingassner, G. Schulz, and M. Schaude, *J. Med. Chem.*, **37**, 1908 (1994).
9. M. J. Smith, D. Kim, B. Horenstein, K. Nakanishi, and K. Kustin, *Acc. Chem. Res.*, **24**, 117 (1991).
10. J. C. Lee, Y. S. Oh, S. H. Cho, and J. I. Lee, *Org. Prep. Proced. Int.*, **28**, 480 (1996).
11. E. Vedejs, N. S. Bennett, L. M. Conn, S. T. Diver, M. Gingras, S. Lin, P. A. Oliver, and M. J. Peterson, *J. Org. Chem.*, **58**, 7286 (1993).
12. W. H. Hartung and R. Simonoff, *Org. React.*, **VII**, 263–326 (1953).
13. G. M. Anantharamaiah and K. M. Sivanandaiah, *J. Chem. Soc., Perkin Trans. 1*, 490 (1977).
14. A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki, and J. Meienhofer, *J. Org. Chem.*, **43**, 4194 (1978).
15. J. S. Bajwa, *Tetrahedron Lett.*, **33**, 2299 (1992).
16. B. ElAmin, G. M. Anantharamaiah, G. P. Royer, and G. E. Means, *J. Org. Chem.*, **44**, 3442 (1979).
17. W. F. Huffman, R. F. Hall, J. A. Grant, and K. G. Holden, *J. Med. Chem.*, **21**, 413 (1978).
18. T. Tsuji, T. Kataoka, M. Yoshioka, Y. Sendo, Y. Nishitani, S. Hirai, T. Maeda, and W. Nagata, *Tetrahedron Lett.*, 2793 (1979).
19. U. Schmidt, M. Kroner, and H. Griesser, *Synthesis*, 294 (1991).
20. C. W. Roberts, *J. Am. Chem. Soc.*, **76**, 6203 (1954).
21. R. L. Prestidge, D. R. K. Harding, J. E. Battersby, and W. S. Hancock, *J. Org. Chem.*, **40**, 3287 (1975).
22. V. G. Mairanovsky, *Angew. Chem., Int. Ed. Engl.*, **15**, 281 (1976).
23. M. Sakaitani, N. Kurokawa, and Y. Ohfune, *Tetrahedron Lett.*, **27**, 3753 (1986).
24. K. M. Rupprecht, R. K. Baker, J. Boger, A. A. Davis, P. J. Hodges, and J. F. Kinneary, *Tetrahedron Lett.*, **39**, 233 (1998).
25. J. Chen and X. J. Zhou, *Synthesis*, 586 (1987).
26. S.-i. Hashimoto, Y. Miyazaki, T. Shinoda, and S. Ikegami, *Tetrahedron Lett.*, **30**, 7195 (1989).

27. R. S. Varma, A. K. Chatterjee, and M. Varma, *Tetrahedron Lett.*, **34**, 4603 (1993).
28. M. S. Anson and J. G. Montana, *Synlett*, 219 (1994).
29. S. T. Chen, S. C. Hsiao, C. H. Chang, and K. T. Wang, *Synth. Commun.*, **22**, 391 (1992).
30. A. L. Gutman, E. Shkolnik, and M. Shapira, *Tetrahedron*, **48**, 8775 (1992).
31. M. Pugniere, B. Castro, N. Domerque, and A. Previero, *Tetrahedron: Asymmetry*, **3**, 1015 (1992).
32. B. Aleksiev, P. Schamlian, G. Videnov, S. Stoev, S. Zachariev, and E. Golovinskii, *Hoppe-Seylers Z. Physiol. Chem.*, **362**, 1323 (1981).
33. C. J. Salomon, E. G. Mata, and O. A. Mascaretti, *J. Chem. Soc., Perkin Trans. 1*, 995 (1996).

Substituted Benzyl Esters

Triphenylmethyl Ester: $RCO_2C(C_6H_5)_3$ (Chart 6)

Triphenylmethyl esters are unstable in aqueous solution, but are stable to oxymercuration.[1]

Formation

$$RCO_2^-M^+ + Ph_3CBr \xrightarrow[3\text{–}5\text{ h, }85\text{–}95\%]{\text{Benzene, reflux}^2} RCO_2CPh_3$$

$M^+ = Ag^+, K^+, Na^+$

$$RCO_2SiMe_3 \xrightarrow[0°,\ 0.5\text{ h, }86\%]{Ph_3COTMS,\ TMSOTf,\ CH_2Cl_2{}^3} RCO_2CPh_3$$

Cleavage

1. $HCl{\cdot}H_2NCH_2CO_2CPh_3 \xrightarrow[\substack{18°,\ 5\text{ h, }72\%;\ 18°,\ 24\text{ h, }98\% \\ 100°,\ 1\text{ min, }98\%^4}]{\text{MeOH or } H_2O\text{/dioxane}}$; $HCl{\cdot}H_2NCH_2CO_2H$

2. Trityl esters have been cleaved by electrolytic reduction at –2.6 V.[5]

1. W. A. Slusarchyk, H. E. Applegate, C. M. Cimarusti, J. E. Dolfini, P. Funke, and M. Puar, *J. Am. Chem. Soc.*, **100**, 1886 (1978).
2. K. D. Berlin, L. H. Gower, J. W. White, D. E. Gibbs, and G. P. Sturm, *J. Org. Chem.*, **27**, 3595 (1962).
3. S. Murata and R. Noyori, *Tetrahedron Lett.*, **22**, 2107 (1981).
4. G. C. Stelakatos, A. Paganou, and L. Zervas, *J. Chem. Soc. C*, 1191 (1966).
5. V. G. Mairanovsky, *Angew. Chem., Int. Ed. Engl.*, **15**, 281 (1976).

Diphenylmethyl (Dpm) Ester: $RCO_2CH(C_6H_5)_2$

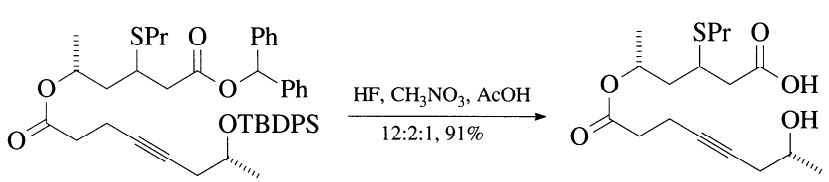
Diphenylmethyl esters are similar in acid lability to *t*-butyl esters and can be cleaved by acidic hydrolysis from *S*-containing peptides that poison hydrogenolysis catalysts.

Formation

1. Ph_2CN_2, acetone, 0°, 30 min → 20°, 4 h, 70%.[1,2]
2. $Ph_2C{=}NNH_2$, I_2, AcOH, >90% yield.[3]
3. $Ph_2C{=}NNH_2$, Oxone supported on wet Al_2O_3, cat. I_2, 0°, 66–95% yield.[4]
4. $(Ph_2CHO)_3PO$, CF_3COOH, CH_2Cl_2, reflux, 1–5 h, 70–87% yield.[5] Free alcohols are converted to the corresponding Dpm ethers. This reaction has also been used for the selective protection of amino acids as their tosylate salts (CCl_4, 15 min–3 h, 63–91% yield).[6]
5. $Ph_2C{=}NNH_2$, $PhI(OAc)_2$, CH_2Cl_2, cat. I_2, −10° → 0°, 1 h, 73–93% yield.[7]
6. Ph_2CHOH, cat. TsOH, benzene, azeotropic removal of water, 78–83% yield.[8]
7. $Ph_2CH{=}NNH_2$, AcOOH, 91% yield.[9]

Cleavage

1. H_2/Pd black, MeOH, THF, 3 h, 90% yield.[1,10]
2. CF_3COOH, PhOH, 20°, 30 min, 82% yield.
3. AcOH, reflux, 6 h.[11]
4. $BF_3{\cdot}Et_2O$, AcOH, 40°, 0.5 h → 10°, several hours, 65% yield.[12] The sulfur–sulfur bond in cystine is stable to these conditions.
5. H_2NNH_2, MeOH, reflux, 60 min, 100% yield.[13] In this case, the ester is converted to a hydrazide.
6. Diphenylmethyl esters are cleaved by electrolytic reduction at −2.6 V.[14]
7. HF, CH_3NO_2, AcOH (12:2:1), 91% yield.[15]



8. HCl, CH_3NO_2, < 5 min, 25°.[16]
9. 98% HCOOH, 40–50°, 70–97% yield[2].
10. 1 *N* NaOH, MeOH, rt.[6]
11. $AlCl_3$, CH_3NO_2, anisole, 3–6 h, 73–95% yield.[17,18] These conditions also

cleaved the *p*-$MeOC_6H_4CH_2$ ester and ether in penam- and cephalosporin-type intermediates.

12. 1 eq. TsOH, benzene, reflux, 78–95% yield.[8]

1. G. C. Stelakatos, A. Paganou, and L. Zervas, *J. Chem. Soc. C*, 1191 (1966).
2. T. Kametani, H. Sekine, and T. Hondo, *Chem. Pharm. Bull.*, **30**, 4545 (1982).
3. R. Bywood, G. Gallagher, G. K. Sharma, and D. Walker, *J. Chem. Soc., Perkin Trans. 1*, 2019 (1975).
4. M. Curini, O. Rosati, E. Pisani, W. Cabri, S. Brusco, and M. Riscazzi, *Tetrahedron Lett.*, **38**, 1239 (1997).
5. L. Lapatsanis, *Tetrahedron Lett.*, 4697 (1978).
6. C. Froussios and M. Kolovos, *Synthesis*, 1106 (1987).
7. L. Lapatsanis, G. Milias, and S. Paraskewas, *Synthesis*, 513 (1985).
8. R. Paredes, F. Agudelo, and G. Taborda, *Tetrahedron Lett.*, **37**, 1965 (1996).
9. R. G. Micetich, S. N. Maiti, P. Spevak, M. Tanaka, T. Yamazaki, and K. Ogawa, *Synthesis*, 292 (1986).
10. S. De Bernardo, J. P. Tengi, G. J. Sasso, and M. Weigele, *J. Org. Chem.*, **50**, 3457 (1985).
11. E. Haslam, R. D. Haworth, and G. K. Makinson, *J. Chem. Soc.*, 5153 (1961).
12. R. G. Hiskey and E. L. Smithwick, *J. Am. Chem. Soc.*, **89**, 437 (1967).
13. R. G. Hiskey and J. B. Adams, *J. Am. Chem. Soc.*, **87**, 3969 (1965).
14. V. G. Mairanovsky, *Angew. Chem., Int. Ed. Engl.*, **15**, 281 (1976).
15. L. R. Hillis and R. C. Ronald, *J. Org. Chem.*, **50**, 470 (1985).
16. R. C. Kelly, I. Schletter, S. J. Stein, and W. Wierenga, *J. Am. Chem. Soc.*, **101**, 1054 (1979).
17. T. Tsuji, T. Kataoka, M. Yoshioka, Y. Sendo, Y. Nishitani, S. Hirai, T. Maeda, and W. Nagata, *Tetrahedron Lett.*, 2793 (1979).
18. M. Ohtani, F. Watanabe, and M. Narisada, *J. Org. Chem.*, **49**, 5271 (1984).

Bis(*o*-nitrophenyl)methyl Ester: $RCOOCH(C_6H_4\text{–}o\text{-}NO_2)_2$ (Chart 6)

Bis(*o*-nitrophenyl)methyl esters are formed and cleaved by the same methods used for diphenylmethyl esters. They can also be cleaved by irradiation ($h\nu = 320$ nm, dioxane, THF, ..., 1–24 h, quant. yield).[1]

1. A. Patchornik, B. Amit, and R. B. Woodward, *J. Am. Chem. Soc.*, **92**, 6333 (1970).

9-Anthrylmethyl Ester: $RCOOCH_2$–9-anthryl (Chart 6)

Formation

1. 9-Anthrylmethyl chloride, Et_3N, MeCN, reflux, 4–6 h, 70–90% yield.[1]

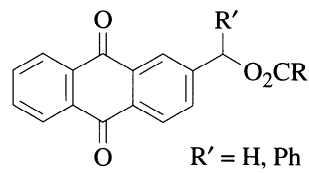
2. N_2CH–9-anthryl, hexane, 25°, 10 min, 80% yield.[2,3]

Cleavage

1. 2 *N* HBr/HOAc, 25°, 10–30 min, 100% yield.[1]
2. 0.1 *N* NaOH/dioxane, 25°, 15 min, 97% yield.[1]
3. MeSNa, THF–HMPA, −20°, 1 h, 90–100% yield.[4]

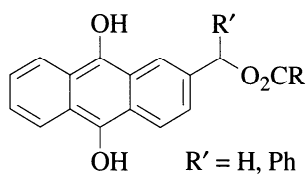
1. F. H. C. Stewart, *Aust. J. Chem.*, **18**, 1699 (1965).
2. M. G. Krakovyak, T. D. Amanieva, and S. S. Skorokhodov, *Synth. Commun.*, **7**, 397 (1977).
3. K. Hör, O. Gimple, P. Schreier, and H.-U. Humpf, *J. Org. Chem.*, **63**, 322 (1998).
4. N. Kornblum and A. Scott, *J. Am. Chem. Soc.*, **96**, 590 (1974).

2-(9,10-Dioxo)anthrylmethyl Ester (Chart 6):



This derivative is prepared from an *N*-protected amino acid and the anthrylmethyl alcohol in the presence of DCC/hydroxybenzotriazole.[1] It can also be prepared from 2-(bromomethyl)-9,10-anthraquinone (Cs_2CO_3).[2] It is stable to moderately acidic conditions (e.g., CF_3COOH, 20°, 1 h; HBr/HOAc, $t_{1/2}$ = 65 h; HCl/CH_2Cl_2, 20°, 1 h)[1]. Cleavage is effected by reduction of the quinone to the hydroquinone **i**; in the latter, electron release from the –OH group of the hydroquinone results in facile cleavage of the methylene–carboxylate bond.

The related **2-phenyl-2-(9,10-dioxo)anthrylmethyl** ester has also been prepared, but is cleaved by electrolysis (−0.9 V, DMF, 0.1 *M* $LiClO_4$, 80% yield).[3]



i

Cleavage[1]

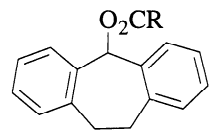
This derivative is cleaved by hydrogenolysis and by the following conditions:

1. $Na_2S_2O_4$, dioxane–H_2O, pH 7–8, 8 h, 100% yield.
2. Irradiation, *i*-PrOH, 4 h, 99% yield.
3. 9-Hydroxyanthrone, Et_3N/DMF, 5 h, 99% yield.

4. 9,10-Dihydroxyanthracene/polystyrene resin, 1.5 h, 100% yield.

1. D. S. Kemp and J. Reczek, *Tetrahedron Lett.*, 1031 (1977).
2. P. Hoogerhout, C. P. Guis, C. Erkelens, W. Bloemhoff, K. E. T. Kerling, and J. H. Boom, *Recl. Trav. Chim. Pays-Bas*, **104**, 54 (1985).
3. R. L. Blankespoor, A. N. K. Lau, and L. L. Miller, *J. Org. Chem.*, **49**, 4441 (1984).

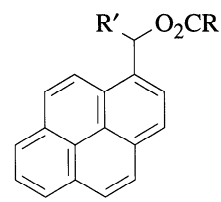
5-Dibenzosuberyl Ester:



The dibenzosuberyl ester is prepared from dibenzosuberyl chloride (which is also used to protect –OH, –NH, and –SH groups) and a carboxylic acid (Et_3N, reflux, 4 h, 45% yield). It can be cleaved by hydrogenolysis and, like *t*-butyl esters, by acidic hydrolysis (aq. HCl/THF, 20°, 30 min, 98% yield).[1]

1. J. Pless, *Helv. Chim. Acta*, **59** 499 (1976).

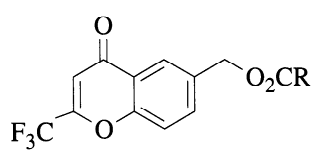
1-Pyrenylmethyl Ester (R′= H, Me, Ph):



These esters are prepared from the diazomethylpyrenes and carboxylic acids in DMF (R′ = H, 60% yield, R′ = Me, 80% yield, R′ = Ph, 20% yield for 4-methylbenzoic acid). They are cleaved by photolysis at 340 nm (80–100% yield, R′ = H).[1,2] The esters are very fluorescent.

1. M. Iwamura, T. Ishikawa, Y. Koyama, K. Sakuma, and H. Iwamura, *Tetrahedron Lett.*, **28**, 679 (1987).
2. M. Iwamura, C. Hodota, and M. Ishibashi, *Synlett*, 35 (1991).

2-(Trifluoromethyl)-6-chromonylmethyl (Tcrom) Ester:



The Tcrom ester is prepared from the cesium salt of an *N*-protected amino acid by reaction with 2-(trifluoromonethyl)-6-chromonylmethyl bromide (DMF, 25°,

4 h, 53–89% yield). Cleavage of the Tcrom group is effected by brief treatment with *n*-propylamine (2 min, 25°, 96% yield). The group is stable to HCl/dioxane, used to cleave a BOC group.[1]

1. D. S. Kemp and G. Hanson, *J. Org. Chem.*, **46**, 4971 (1981).

2,4,6-Trimethylbenzyl Ester: $RCOOCH_2C_6H_2$–2,4,6-$(CH_3)_3$

The 2,4,6-trimethylbenzyl ester has been prepared from an amino acid and the benzyl chloride (Et_3N, DMF, 25°, 12 h, 60–80% yield); it is cleaved by acidic hydrolysis (CF_3COOH, 25°, 60 min, 60–90% yield; 2 *N* HBr/HOAc, 25°, 60 min, 80–95% yield) and by hydrogenolysis. It is stable to methanolic hydrogen chloride, used to remove *N*-*o*-nitrophenylsulfenyl groups or triphenylmethyl esters.[1]

1. F. H. C. Stewart, *Aust. J. Chem.*, **21**, 2831 (1968).

***p*-Bromobenzyl Ester:** $RCOOCH_2C_6H_4$–*p*-Br

The *p*-bromobenzyl ester has been used to protect the β-COOH group in aspartic acid. It is cleaved by strong acidic hydrolysis (HF, 0°, 10 min, 100% yield), but is stable to 50% CF_3COOH/CH_2Cl_2, used to cleave *t*-butyl carbamates. The *p*-bromobenzyl ester is five to seven times more stable toward acid than is a benzyl ester.[1]

1. D. Yamashiro, *J. Org. Chem.*, **42**, 523 (1977).

***o*-Nitrobenzyl Ester:** $RCOOCH_2C_6H_4$–*o*-NO_2

***p*-Nitrobenzyl Ester:** $RCOOCH_2C_6H_4$–*p*-NO_2

The *o*-nitrobenzyl ester, used in this example to protect penicillin precursors, can be cleaved by irradiation (H_2O/dioxane, pH 7). Reductive cleavage of benzyl or *p*-nitrobenzyl esters occurred in lower yields.[1,2]

p-Nitrobenzyl esters have been prepared from the Hg(I) salt of penicillin precursors and the phenyldiazomethane.[3] They are much more stable to acidic hydrolysis (e.g., HBr) than are *p*-chlorobenzyl esters and are recommended for terminal –COOH protection in solid-phase peptide synthesis.[4]

p-Nitrobenzyl esters of penicillin and cephalosporin precursors have been cleaved by alkaline hydrolysis with Na_2S (0°, aq. acetone, 25–30 min, 75–85% yield).[5] They are also cleaved by electrolytic reduction at –1.2 V,[6] by reduction with $SnCl_2$ (DMF, phenol, AcOH),[7] by reduction with sodium dithionite, or by hydrogenolysis.[8]

1. L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 8006 (1978).
2. For a review covering the photolytic removal of protective groups, see V. N. R. Pillai, *Synthesis*, 1 (1980).
3. W. Baker, C. M. Pant, and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 668 (1978).
4. R. L. Prestidge, D. R. K. Harding, and W. S. Hancock, *J. Org. Chem.*, **41**, 2579 (1976).
5. S. R. Lammert, A. I. Ellis, R. R. Chauvette, and S. Kukolja, *J. Org. Chem.*, **43**, 1243 (1978).
6. V. G. Mairanovsky, *Angew Chem., Int. Ed. Engl.*, **15**, 281 (1976).
7. M. D. Hocker, C. G. Caldwell, R. W. Macsata, and M. H. Lyttle, *Pept. Res.*, **8**, 310 (1995).
8. J. W. Perich, P. F. Alewood, and R. B. Johns, *Aust. J. Chem.*, **44**, 233 (1991).

p-Methoxybenzyl Ester: $RCOOCH_2C_6H_4$–*p*-OCH_3

Formation

1. *p*-Methoxybenzyl esters have been prepared from the Ag(I) salt of amino acids and the benzyl halide (Et_3N, $CHCl_3$, 25°, 24 h, 60% yield).[1]
2. *p*-Methoxybenzyl alcohol, $Me_2NCH(OCH_2$–*t*-$Bu)_2$, CH_2Cl_2, 90% yield.[2]
3. Isopropenyl chloroformate, $MeOC_6H_4CH_2OH$, DMAP, 0°, CH_2Cl_2, 91%.[3]
4. *p*-Methoxyphenyldiazomethane in CH_2Cl_2, 80–96% yield.[4]
5. *p*-Methoxybenzyl chloride, $NaHCO_3$, DMF, 45°, 89% yield.[5]
6. $MeOC_6H_4CHN_2$.[4]

Cleavage

1. CF_3COOH/PhOMe, 25°, 3 min, 98% yield.[6]
2. HCOOH, 22°, 1 h, 81% yield. [1]
3. TFA, phenol, 1 h, 45°, 73–93% yield.[7,8] These conditions were developed for the mild cleavage of acid-sensitive esters of β-lactam-related antibiotics. Diphenylmethyl and *t*-butyl esters were cleaved with similarly high efficiency.
4. $AlCl_3$, anisole, CH_2Cl_2 or CH_3NO_2,–50°; $NaHCO_3$, –50°, 73–95% yield.[9,10]
5. $CF_3CO_2H/B(OTf)_3$.[11]

1. G. C. Stelakatos and N. Argyropoulos, *J. Chem. Soc. C*, 964 (1970).
2. J. A. Webber, E. M. Van Heyningen, and R. T. Vasileff, *J. Am. Chem. Soc.*, **91**, 5674 (1969).
3. P. Jouin, B. Castro, C. Zeggaf, A. Pantaloni, J. P. Senet, S. Lecolier, and G. Sennyey, *Tetrahedron Lett.*, **28**, 1661 (1987).
4. S. T. Waddell and G. M. Santorelli, *Tetrahedron Lett.*, **37**, 1971 (1996).
5. D. L. Boger, M. Hikota, and B. M. Lewis, *J. Org. Chem.*, **62**, 1748 (1997).

6. F. H. C. Stewart, *Aust. J. Chem.*, **21**, 2543 (1968).
7. H. Tanaka, M. Taniguchi, Y. Kameyama, S. Torii, M. Sasaoka, T. Shiroi, R. Kikuchi, I. Kawahara, A. Shimabayashi, and S. Nagao, *Tetrahedron Lett.*, **31**, 6661 (1990).
8. S. Torii, H. Tanaka, M. Taniguchi, Y. Kameyama, M. Sasaoka, T. Shiroi, R. Kikuchi, I. Kawahara, A. Shimabayashi, and S. Nagao, *J. Org. Chem.*, **56**, 3633 (1991).
9. M. Ohtani, F. Watanabe, and M. Narisada, *J. Org. Chem.*, **49**, 5271 (1984).
10. T. Tsuji, T. Kataoka, M. Yoshioka, Y. Sendo, Y. Nishitani, S. Hirai, T. Maeda, and W. Nagata, *Tetrahedron Lett.*, 2793 (1979).
11. S. D. Young and P. P. Tamburini, *J. Am. Chem. Soc.*, **111**, 1933 (1989).

2,6-Dimethoxybenzyl Ester: $2,6\text{-}(CH_3O)_2C_6H_3CH_2OOCR$

2,6-Dimethoxybenzyl esters prepared from the acid chloride and the benzyl alcohol are readily cleaved oxidatively by DDQ (CH_2Cl_2, H_2O, rt, 18 h, 90–95% yield). A 4-methoxybenzyl ester was found not to be cleaved by DDQ. The authors have also explored the oxidative cleavage (ceric ammonium nitrate, CH_3CN, H_2O, 0°, 4 h, 65–97% yield) of a variety of 4-hydroxy- and 4-amino-substituted phenolic esters.[1]

1. C. U. Kim and P. F. Misco, *Tetrahedron Lett.*, **26**, 2027 (1985).

4-(Methylsulfinyl)benzyl (Msib) Ester: $4\text{-}CH_3S(O)C_6H_4CH_2O_2CR$

The 4-(methylsulfinyl)benzyl ester was recommended as a selectively cleavable carboxyl protective group for peptide synthesis. It is readily prepared from 4-(methylsulfinyl)benzyl alcohol (EDCI, HOBt, $CHCl_3$, 78–100% yield) or from 4-methylthiobenzyl alcohol followed by oxidation of the derived ester with MCPBA or H_2O_2/AcOH. The Msib ester is exceptionally stable to CF_3COOH (cleavage rate = 0.000038% ester cleaved/min) and undergoes only 10% cleavage in HF (anisole, 0°, 1 h). Anhydrous HCl/dioxane rapidly reduces the sulfoxide to the sulfide (Mtb ester), which is completely cleaved in 30 min with CF_3CO_2H. A number of reagents readily reduce the Msib ester to the Mtb ester, with $(CH_3)_3SiCl/Ph_3P$ as the reagent of choice.[1]

1. J. M. Samanen and E. Brandeis, *J. Org. Chem.*, **53**, 561 (1988).

4-Sulfobenzyl Ester: $Na^+{}^-O_3SC_6H_4CH_2O_2CR$

4-Sulfobenzyl esters were prepared (cesium salt or dicyclohexylammonium salt, $NaO_3SC_6H_4CH_2Br$, DMF, 37–95% yield) from *N*-protected amino acids. They are cleaved by hydrogenolysis (H_2/Pd), or hydrolysis (NaOH, dioxane/water). Treatment with ammonia or hydrazine results in the formation of the amide or

hydrazide. The ester is stable to 2 *M* HBr/AcOH and to CF_3SO_3H in CF_3CO_2H. The relative rates of hydrolysis and hydrazinolysis for different esters are as follows:

Hydrolysis: $NO_2C_6H_4CH_2O- >> C_6H_4CH_2O- > {}^-O_3SC_6H_4CH_2O- >$ MeO–
Hydrazinolysis: $NO_2C_6H_4CH_2O- > {}^-O_3SC_6H_4CH_2O- > C_6H_5CH_2O- >$ MeO–

A benzyl ester can be cleaved in the presence of the 4-sulfobenzyl ester by CF_3SO_3H.[1,2]

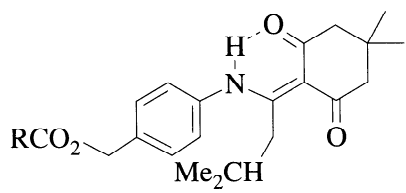
1. R. Bindewald, A. Hubbuch, W. Danho, E. E. Büllesbach, J. Föhles, and H. Zahn, *Int. J. Pept. Protein Res.*, **23**, 368 (1984).
2. A. Hubbuch, R. Bindewald, J. Föhles, V. K. Naithani, and H. Zahn, *Angew. Chem., Int. Ed. Engl.*, **19**, 394 (1980).

4-Azidomethoxybenzyl Ester: $N_3CH_2OC_6H_4CH_2O_2CR$

This ester, developed for peptide synthesis, is prepared by the standard DCC coupling protocol and is cleaved reductively with $SnCl_2$ (MeOH, 25°, 5 h) followed by treatment with mild base to effect quinonemethide formation with release of the acid in 75–95% yield.[1]

1. B. Loubinoux and P. Gerardin, *Tetrahedron*, **47**, 239 (1991).

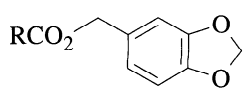
4-{*N*-[1-(4,4-Dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl]amino}benzyl (Dmab) Ester:



The Dmab group was developed for glutamic acid protection during Fmoc/*t*-Bu based peptide synthesis. The group shows excellent acid stability and stability toward 20% piperidine in DMF. It is formed from the alcohol using the DCC protocol for ester formation and is cleaved with 2% hydrazine in DMF at rt.[1]

1. W. C. Chan, B. W. Bycroft, D. J. Evans, and P. D. White, *J. Chem. Soc., Chem. Commun.*, 2209 (1995).

Piperonyl Ester (Chart 6):



The piperonyl ester can be prepared from an amino acid ester and the benzyl alcohol (imidazole/dioxane, 25°, 12 h, 85% yield) or from an amino acid and the

benzyl chloride (Et_3N, DMF, 25°, 57–95% yield). It is cleaved, more readily than a *p*-methoxybenzyl ester, by acidic hydrolysis (CF_3COOH, 25°, 5 min, 91% yield).[1]

1. F. H. C. Stewart, *Aust. J. Chem.*, **24**, 2193 (1971).

4-Picolyl Ester: RCO_2CH_2–4-pyridyl

The picolyl ester has been prepared from amino acids and picolyl alcohol (DCC/CH_2Cl_2, 20°, 16 h, 60% yield) or picolyl chloride (DMF, 90–100°, 2 h, 50% yield). It is cleaved by reduction (H_2/Pd–C, aq. EtOH, 10 h, 98% yield; Na/NH_3, 1.5 h, 93% yield) and by basic hydrolysis (1 *N* NaOH, dioxane, 20°, 1 h, 93% yield). The basic site in a picolyl ester allows its ready separation by extraction into an acidic medium.[1]

1. R. Camble, R. Garner, and G. T. Young, *J. Chem. Soc. C*, 1911 (1969).

***p-P*-Benzyl Ester:** $RCOOCH_2C_6H_4$–*p-P*

The first,[1] and still widely used, polymer-supported ester is formed from an amino acid and a chloromethylated copolymer of styrene–divinylbenzene. Originally, it was cleaved by basic hydrolysis (2 *N* NaOH, EtOH, 25°, 1 h). Subsequently, it has been cleaved by hydrogenolysis (H_2/Pd–C, DMF, 40°, 60 psi, 24 h, 71% yield)[2] and by HF, which concurrently removes many amine protective groups.[3]

Monoesterification of a symmetrical dicarboxylic acid chloride can be effected by reaction with a hydroxymethyl copolymer of styrene–divinylbenzene to give an ester; a mono salt of a diacid was converted into a dibenzyl polymer.[4]

1. R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149 (1963).
2. J. M. Schlatter and R. H. Mazur, *Tetrahedron Lett.*, 2851 (1977).
3. J. Lenard and A. B. Robinson, *J. Am. Chem. Soc.*, **89**, 181 (1967).
4. D. D. Leznoff and J. M. Goldwasser, *Tetrahedron Lett.*, 1875 (1977).

Silyl Esters

Silyl esters are stable to nonaqueous reaction conditions. A trimethylsilyl ester is cleaved by refluxing in alcohol; the more substituted, and therefore more stable, silyl esters are cleaved by mildly acidic or basic hydrolysis.

Trimethylsilyl Ester: $RCOOSi(CH_3)_3$ (Chart 6)

Some of the more common reagents for the conversion of carboxylic acids to trimethylsilyl esters follow. For additional methods that can be used to silylate acids, the section on alcohol protection should be consulted, since many of the methods presented there are also applicable to carboxylic acids. Trimethylsilyl esters are cleaved in aqueous solutions.

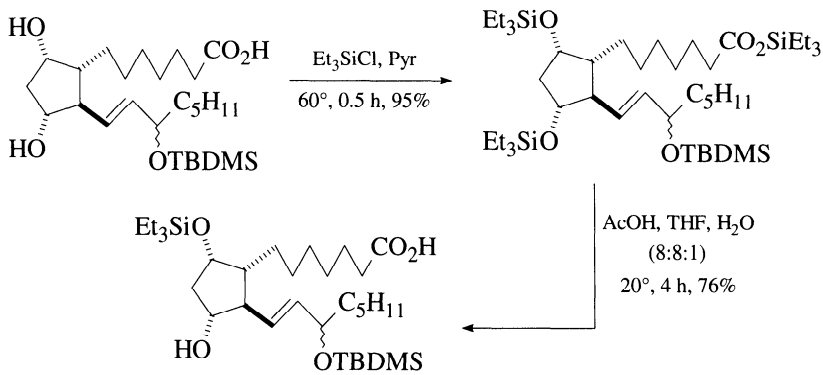
Formation

1. Me_3SiCl/Pyr, CH_2Cl_2, 30°, 2 h.[1]
2. $MeC(OSiMe_3)=NSiMe_3$, HBr, dioxane, α-picoline, 6 h, 80% yield.[2]
3. $MeCH=C(OMe)OSiMe_3/CH_2Cl_2$, 15–25°, 5–40 min, quant.[3]
4. $Me_3SiNHSO_2OSiMe_3/CH_2Cl_2$, 30°, 0.5 h, 92–98% yield.[4]

1. B. Fechti, H. Peter, H. Bickel, and E. Vischer, *Helv. Chim. Acta*, **51**, 1108 (1968).
2. J. J. de Koning, H. J. Kooreman, H. S. Tan, and J. Verweij, *J. Org. Chem.*, **40**, 1346 (1975).
3. Y. Kita, J. Haruta, J. Segawa, and Y. Tamura, *Tetrahedron Lett.*, 4311 (1979).
4. B. E. Cooper and S. Westall, *J. Organomet. Chem.*, **118**, 135 (1976).

Triethylsilyl Ester: $RCOOSi(C_2H_5)_3$

Formation/cleavage[1]



1. T. W. Hart, D. A. Metcalfe, and F. Scheinmann, *J. Chem. Soc., Chem. Commun.*, 156 (1979).

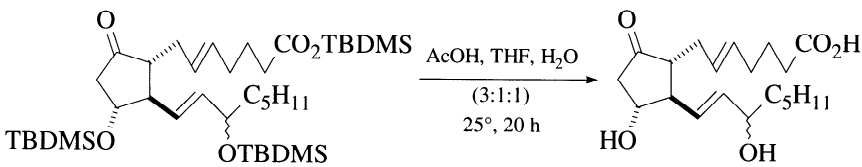
t-Butyldimethylsilyl (TBDMS) Ester: $RCOOSi(CH_3)_2C(CH_3)_3$ (Chart 6)

Formation

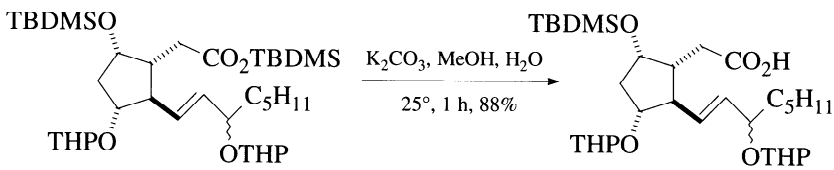
1. *t*-$BuMe_2SiCl$, imidazole, DMF, 25°, 48 h, 88%.[1]
2. Morpholine, TBDMSCl, THF, 2 min, 20°, >80% yield.[2] In this case, the ester was formed in the presence of a phenol.
3. *t*-$BuMe_2SiH$, Pd/C, benzene, 70°.[3]

Cleavage

1. AcOH, H_2O, THF, (3:1:1), 25°, 20 h.[1]



2. $Bu_4N^+F^-$, DMF, 25°.[1]
3. K_2CO_3, MeOH, H_2O, 25°, 1 h, 88% yield.[4]



4. The TBDMS ester can be converted directly to an acid chloride [DMF, $(COCl)_2$, rt, CH_2Cl_2] and then converted to another ester, with different properties, by standard means. This procedure avoids the generation of HCl during the acid chloride formation and is thus suitable for acid-sensitive substrates.[5]

1. E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
2. J. W. Perich and R. B. Johns, *Synthesis*, 701 (1989).
3. K. Yamamoto and M. Takemae, *Bull. Chem. Soc. Jpn.*, **62**, 2111 (1989).
4. D. R. Morton and J. L. Thompson, *J. Org. Chem.*, **43**, 2102 (1978).
5. A. Wissner and G. V. Grudzinskas, *J. Org. Chem.*, **43**, 3972 (1978).

i-Propyldimethylsilyl Ester: $RCOOSi(CH_3)_2CH(CH_3)_2$

The *i*-propyldimethylsilyl ester is prepared from a carboxylic acid and the silyl chloride (Et_3N, 0°). It is cleaved at pH 4.5 by conditions that do not cleave a tetrahydropyranyl ether (HOAc–NaOAc, acetone–H_2O, 0°, 45 min → 25°, 30 min, 91% yield).[1]

1. E. J. Corey and C. U. Kim, *J. Org. Chem.*, **38**, 1233 (1973).

Phenyldimethylsilyl Ester: $RCOOSi(CH_3)_2C_6H_5$

The phenyldimethylsilyl ester has been prepared from an amino acid and phenyldimethylsilane (Ni/THF, reflux, 3–5 h, 62–92% yield).[1]

1. M. Abe, K. Adachi, T. Takiguchi, Y. Iwakura, and K. Uno, *Tetrahedron Lett.*, 3207 (1975).

Di-*t*-butylmethylsilyl (DTBMS) Ester: $(t\text{-Bu})_2CH_3SiO_2CR$

The DTBMS ester was prepared (THF, DTBMSOTf, Et_3N, rt) to protect an ester so that a lactone could be reduced to an aldehyde. The ester is cleaved with aq. HF/THF or $Bu_4N^+F^-$ in wet THF. A THP derivative can be deprotected (pyridinium *p*-toluenesulfonate, warm ethanol) in the presence of a DTBMS ester.[1]

1. R. S. Bhide, B. S. Levison, R. B. Sharma, S. Ghosh, and R. G. Salomon, *Tetrahedron Lett.*, **27**, 671 (1986).

Triisopropylsilyl (TIPS) Ester

A TIPS ester, prepared by silylation with TIPSCl, TEA, and THF, is cleaved with HF–Pyr (Pyr, THF, 0°).[1]

1. D. A. Evans, B. W. Trotter, B. Côté, P. J. Coleman, L. C. Dias, and A. N. Tyler, *Angew. Chem., Int. Ed. Engl.*, **36**, 2744 (1997).

Activated Esters

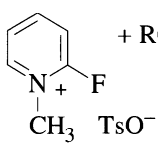
Thiol Esters

Thiol esters, more reactive to nucleophiles than the corrresponding oxygen esters, have been prepared to activate carboxyl groups, for both lactonization and peptide bond formation. For lactonization, *S*-*t*-butyl[1] and *S*-2-pyridyl[2] esters are widely used. Some methods used to prepare thiol esters are as follows (the *S*-*t*-butyl ester is included in Reactivity Chart 6):

1. $RCOOH + R'SH \xrightarrow[0°,\ 5\ min \rightarrow 20°,\ 3\ h]{DCC,\ DMAP,\ CH_2Cl_2}{}^{3} RCOSR'$ 85–92%

   $R' = Et,\ t\text{-Bu}$

DMAP = 4-dimethylaminopyridine (10^4 times more effective than pyridine)

2.  + RCOOH $\xrightarrow[-15°,\ 1\ h]{Et_3N,\ CH_2Cl_2}$ $\xrightarrow[2\ h,\ 75–95\%]{R'H,\ Et_3N,\ CH_2Cl_2}$ RCOSR′[4]

R′ = *n*-Bu, *s*-Bu, *t*-Bu, Ph, 2-pyridyl

3. RCOOH + R′SH $\xrightarrow[25°,\ 1\ h,\ 70–100\%]{Me_2NPOCl_2,\ Et_3N,\ DME}$ RCOSR′

R′ = Et, *i*-Pr, *t*-Bu, *c*-C_6H_{11}, Ph

These neutral conditions can be used to prepare thiol esters of acid- or base-sensitive compounds, including penicillins.[5]

4. $\underset{\underset{NHPG}{|}}{RCHCOOH}$ + Ph_2POCl $\xrightarrow[0°,\ 30\ min]{Et_3N,\ CH_2Cl_2}$ $\xrightarrow{R'SH,\ Et_3N}$ $\xrightarrow[25°,\ 1\ h]{\text{or } R'STl,\ Et_3N}$ $\underset{\underset{NHPG}{|}}{RCHCOSR}$

R′ = *t*-Bu, Ph, $PhCH_2$ 70–100%[6]

5. RCOOH + R′SH $\xrightarrow[Et_3N,\ DMF,\ 25°,\ 3\ h,\ 70–85\%]{(EtO)_2POCN \text{ or } (PhO)_2PON_3}$ RCOSR′[7]

R = alkyl, aryl, benzyl, amino acids; penicillins
R′ = Et, *i*-Pr, *n*-Bu, Ph, $PhCH_2$

6. RCOCl + *n*-Bu_3SnSR' $\xrightarrow{CHCl_3}$ RCOSR′[8]

R′ = *t*-Bu: 60°, 0.5 h, 90–95% yield
R′ = Ph: 25°, 12 h, 92–95% yield
R′ = $PhCH_2$: 25°, 0.5–1 h, 87–96% yield

7. RCOOR′ + Me_2AlS–*t*-Bu $\xrightarrow[25°,\ 75–100\%]{CH_2Cl_2}$ RCOS–*t*-Bu[9]

R′ = Me, Et

This reaction avoids the use of toxic thallium compounds.

8. RCOOH + PhSCN $\xrightarrow[25°,\ 30\ min,\ 80–95\%]{Bu_3P,\ CH_2Cl_2}$ RCOSPh[10]

9. RCOOH + ClCOS-2-pyridyl $\xrightarrow[0.5\ h,\ 95–100\%]{Et_3N,\ 0°}$ RCOS-2-pyridyl + $Et_3N{\cdot}HCl$[11]

10. RCO_2H + hydroxybenzotriazole $\xrightarrow{DCC}$ $\xrightarrow[70\text{–}100\%^{6}]{R'SH,\ Et_3N}$

or $\xrightarrow{R'\ STl}$ $RCOSR'$

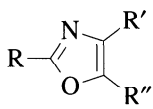
$R' = t$-Bu, Ph, $PhCH_2$

Cleavage

1. $AgNO_3$, H_2O, dioxane, (1:4), 2 h.[12]
2. ROH, $Hg(O_2CCF_3)_2$, 90% yield.[1]
3. Electrolysis, $Bu_4N^+Br^-$, H_2O, CH_3CN, $NaHCO_3$.[13] This method is unsatisfactory for primary and secondary alcohols, aldehydes, olefins, and amines.
4. MeI, ROH (R = t-Bu, PhSH, etc.), 68–97% yield.[14]
5. Treatment of the phenylthio ester with Pd/C and TESH results in reduction to the aldehyde.[15]

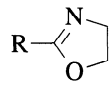
1. S. Masamune, S. Kamata, and W. Schilling, *J. Am. Chem. Soc.*, **97**, 3515 (1975).
2. T. Mukaiyama, R. Matsueda, and M. Suzuki, *Tetrahedron Lett.*, 1901 (1970); E. J. Corey, P. Ulrich, and J. M. Fitzpatrick, *J. Am. Chem. Soc.*, **98**, 222 (1976).
3. B. Neises and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, **17**, 522 (1978).
4. Y. Watanabe, S.-i. Shoda, and T. Mukaiyama, *Chem. Lett.*, 741 (1976).
5. H. -J. Liu, S. P. Lee, and W. H. Chan, *Synth. Commun.*, **9**, 91 (1979).
6. K. Horiki, *Synth. Commun.*, **7**, 251 (1977).
7. S. Yamada, Y. Yokoyama, and T. Shiori, *J. Org. Chem.*, **39**, 3302 (1974).
8. D. N. Harpp, T. Aida, and T. H. Chan, *Tetrahedron Lett.*, 2853 (1979).
9. R. P. Hatch and S. M. Weinreb, *J. Org. Chem.*, **42**, 3960 (1977).
10. P. A. Grieco, Y. Yokoyama, and E. Williams, *J. Org. Chem.*, **43**, 1283 (1978).
11. E. J. Corey and D. A. Clark, *Tetrahedron Lett.*, 2875 (1979).
12. A. B. Shenvi and H. Gerlach, *Helv. Chim. Acta*, **63**, 2426 (1980).
13. M. Kimura, S. Matsubara, and Y. Sawaki, *J. Chem. Soc., Chem. Commun.*, 1619 (1984).
14. D. Ravi and H. B. Mereyala, *Tetrahedron Lett.*, **30**, 6089 (1989).
15. Fukuyama, S.-C. Lin, and L. Li, *J. Am. Chem. Soc.*, **112**, 7050 (1990).

Miscellaneous Derivatives

Oxazoles: 

Oxazoles, prepared from carboxylic acids (benzoin, DCC; NH_4OAc, AcOH, 80–85% yield), have been used as carboxylic acid protective groups in a variety

of synthetic applications. They are readily cleaved by singlet oxygen followed by hydrolysis (ROH, TsOH, benzene[1] or K_2CO_3, MeOH[2]).

2-Alkyl-1,3-oxazoline (Chart 6): 

2-Alkyl-1,3-oxazolines are prepared to protect both the carbonyl and hydroxyl groups of an acid. They are stable to Grignard reagents[3] and to lithium aluminum hydride (25°, 2 h).[4]

Formation

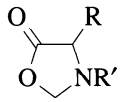
1. $HOCH_2C(CH_3)_2NH_2$, $PhCH_3$, reflux, 70–80% yield.[5]
2. From an acid chloride: $HOCH_2C(CH_3)_2NH_2$; $SOCl_2$, CH_2Cl_2, 25°, 30 min, >80% yield.[6]
3. Dimethylaziridine, DCC; 3% H_2SO_4, Et_2O or CH_2Cl_2, rt, 6–16 h, 50–80% yield.[4]
4. $H_2NCH_2CH_2OH$, Ph_3P, Et_3N, CCl_4, CH_3CN, Pyr, rt, 70% yield.[7]
5. From an acid chloride: $BrCH_2CH_2NH_3^+Br^-$; Et_3N, benzene, reflux, 24 h, 46–67% yield.[8]

Cleavage

1. 3 *N* HCl, EtOH, 90% yield.[3]
2. MeI, 25°, 12 h; 1 *N* NaOH, 25°, 15 h, 94% yield.[9]
3. (a) TFA, H_2O; (b) Ac_2O, Pyr; (c) *t*-BuOK, H_2O, THF, quantitative.[10]
4. (a) TFAA; (b) H_2O; (c) diazomethane; (d) KOH, DMSO, 56–88% yield.[11]

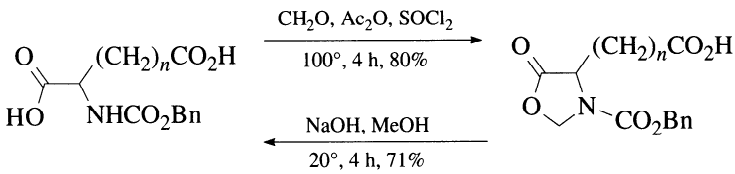
1. H. H. Wasserman, K. E. McCarthy, and K. S. Prowse, *Chem. Rev.*, **86**, 845 (1986).
2. M. A. Tius and D. P. Astrab, *Tetrahedron Lett.*, **30**, 2333 (1989).
3. A. I. Meyers and D. L. Temple, *J. Am. Chem. Soc.*, **92**, 6644 (1970).
4. D. Haidukewych and A. I. Meyers, *Tetrahedron Lett.*, 3031 (1972).
5. H. L. Wehrmeister, *J. Org. Chem.*, **26**, 3821 (1961).
6. S. R. Schow, J. D. Bloom, A. S. Thompson, K. N. Winzenberg, and A. B. Smith, III, *J. Am. Chem. Soc.*, **108**, 2662 (1986).
7. H. Vorbrüggen and K. Krolikiewicz, *Tetrahedron Lett.*, **22**, 4471 (1981).
8. C. Kashima and H. Arao, *Synthesis*, 873 (1989).
9. A. I. Meyers, D. L. Temple, R. L. Nolen, and E. D. Mihelich, *J. Org. Chem.*, **39**, 2778 (1974).
10. T. D. Nelson and A. I. Meyers, *J. Org. Chem.*, **59**, 2577 (1994).
11. D. P. Phillion and J. K. Pratt, *Synth. Commun.*, **22**, 13 (1992).

4-Alkyl-5-oxo-1,3-oxazolidine:

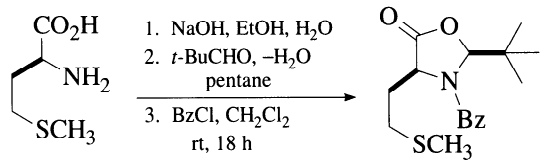


1,3-Oxazolidines are prepared to allow selective protection of the α- or ω-CO_2H groups in aspartic and glutamic acids and α-hydroxy acids.

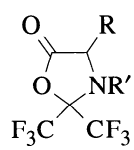
Formation/Cleavage[1]



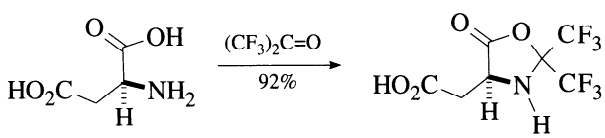
The use of paraformaldehyde and acid is equally effective (80–94% yield).[2] The related **2-*t*-butyl** derivative has been prepared and used to advantage as a temporary protective group for the stereogenic center of amino acids during alkylations.[3]



2,2-Bistrifluoromethyl-4-alkyl-5-oxo-1,3-oxazolidine:



Formation[4,5]

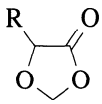


Cleavage is achieved with H_2O, IPA, or MeOH.[5] These derivatives also serve as active esters in peptide bond formation.[6]

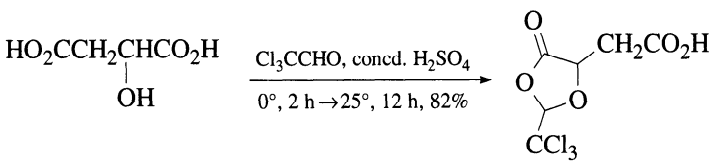
1. M. Itoh, *Chem. Pharm. Bull.*, **17**, 1679 (1969).
2. M. R. Paleo and F. J. Sardina, *Tetrahedron Lett.*, **37**, 3403 (1996); M. W. Walter, R. M. Adlington, J. E. Baldwin, J. Chuhan, and C. J. Schofield, *Tetrahedron Lett.*, **36**, 7761 (1995).

3. D. Seebach and A. Fadel, *Helv. Chim. Acta*, **68**, 1243 (1985).
4. K. Burger, M. Rudolph, and S. Fehn, *Angew. Chem., Int. Ed. Engl.*, **32**, 285 (1993).
5. K. Burger, E. Windeisen, and R. Pires, *J. Org. Chem.*, **60**, 7641 (1995).
6. K. Burger, M. Rudolph, E. Windeisen, A. Worku, and S. Fehn, *Monatsh. Chem.*, **124**, 453 (1993).

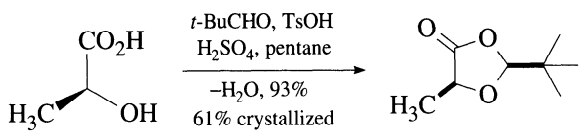
5-Alkyl-4-oxo-1,3-dioxolane:

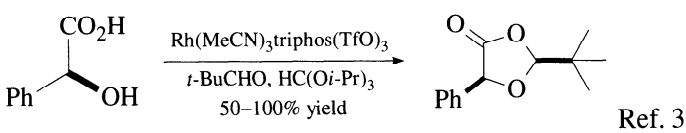


These derivatives are prepared to protect α-hydroxy carboxylic acids; they are cleaved by acidic hydrolysis of the acetal structure (HCl, DMF, 50°, 7 h, 71% yield) or basic hydrolysis of the lactone.[1]

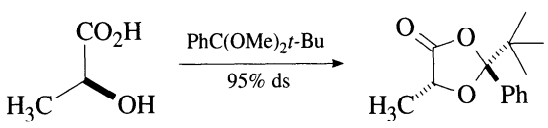


The **2-alkyl** derivatives have been prepared to protect the stereogenic center of the α-hydroxy acid during alkylations.[2]





Ref. 3

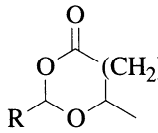


Ref. 4

This methodology is also effective for the protection of β-hydroxy acids.[5]

1. H. Eggerer and C. Grünewälder, *Justus Liebigs Ann. Chem.*, **677**, 200 (1964).
2. D. Seebach, R. Naef, and G. Calderari, *Tetrahedron*, **40**, 1313 (1984).

3. J. Ott, G. M. R. Tombo, B. Schmid, L. M. Venanzi, G. Wang, and T. R. Ward, *Tetrahedron Lett.*, **30**, 6151 (1989).
4. A. Greiner and J.-Y. Ortholand, *Tetrahedron Lett.*, **31**, 2135 (1990).
5. D. Seebach, R. Imwinkelried, and T. Weber, "EPC Synthesis with C,C Bond Formation via Acetals and Enimines," in *Modern Synthetic Methods 1986*, Vol. 4, R. Scheffold, Ed., Springer-Verlag, New York, 1986, p. 125.

Dioxanones:  $n = 0, 1$

Dioxanones have been prepared to protect α- or β-hydroxy acids.

Formation

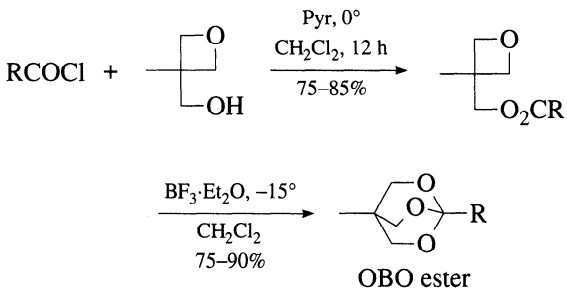
1. RR′C=O, $Sc(NTf_2)_3$ or $Sc(OTf)_3$, CH_2Cl_2, $MgSO_4$ or azeotropic water removal, 54–96% yield. In the case of aldehydes, better stereoselectivity is achieved using $MgSO_4$ as a water scavenger.[1]
2. From a silylated hydroxy acid: RCHO, TMSOTf, 2,6-di-*t*-butylpyridine, 77% yield.[2–4]
3. From a hydroxy acid: pivaldehyde, acid catalyst.[5,6]
4. From a hydroxy acid: $RCH(OR)_2$, PPTS, 20–62% yield.[7,8]

1. K. Ishihara, Y. Karumi, M. Kubota, and H. Yamamoto, *Synlett*, 839 (1996).
2. W. H. Pearson and M.-C. Cheng, *J. Org. Chem.*, **51**, 3746 (1986); *idem*, *ibid.*, **52**, 1353 (1987).
3. S. L. Schreiber and J. Reagan, *Tetrahedron Lett.*, **27**, 2945 (1986).
4. T. R. Hoye, B. H. Peterson, and J. D. Miller, *J. Org. Chem.*, **52**, 1351 (1987).
5. D. Seebach and J. Zimmerman, *Helv. Chim. Acta*, **69**, 1147 (1986).
6. D. Seebach, R. Imwinkelried, and G. Stucky, *Helv. Chim. Acta*, **70**, 448 (1987).
7. N. Chapel, A. Greiner, and J.-Y. Ortholand, *Tetrahedron Lett.*, **32**, 1441 (1991).
8. J.-Y. Ortholand, N. Vicart, and A. Greiner, *J. Org. Chem.*, **60**, 1880 (1995).

Ortho Esters: $RC(OR')_3$

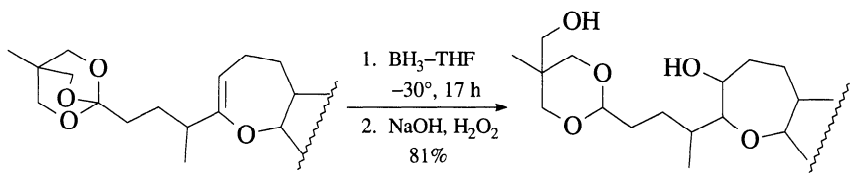
Ortho esters are one of the few derivatives that can be prepared from acids and esters that protect the carbonyl against nucleophilic attack by hydroxide or other strong nucleophiles such as Grignard reagents. In general, ortho esters are difficult to prepare directly from acids and are therefore more often prepared from the nitrile.[1,2] Simple ortho esters derived from normal alcohols are the least stable in terms of acid stability and stability toward Grignard reagents, but as the ortho ester becomes more constrained, its stability increases.

Formation

1. 

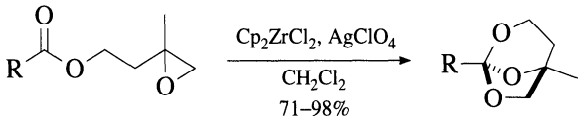
Ref. 3

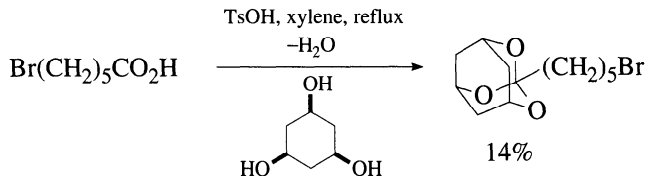
This is one of the few methods available for the direct and efficient conversion of an acid, via the acid chloride, to an ortho ester. The preparation of the oxetane is straightforward, and a large number of oxetanes have been prepared [triol, $(EtO)_2CO$, KOH].[4] In addition, the ***t*-butyl** analogue has been used for the protection of acids.[5] During the course of a borane reduction, the ortho ester was reduced to form a ketal. This was attributed to an intramolecular delivery of the hydride.[6]



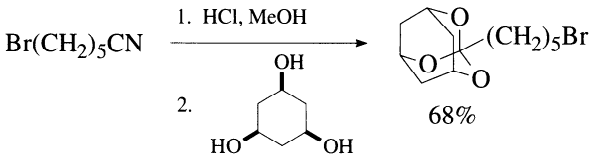
The OBO ester (2,6,7-trioxabicyclo[2.2.2]octyl ester) can also be prepared from a secondary or tertiary amide (Tf_2O, CH_2Cl_2, Pyr then 2,2-bis(hydroxymethyl)-1-propanol, 10–88% yield).[7]

2. The complementary ABO ester (2,7,8-trioxabicyclo[3.2.1]octyl ester) is prepared from the epoxy ester by rearrangement with $Cp_2ZrCl_2/AgClO_4$. The OBO ester is more easily cleaved by Brønsted acids than is the ABO ester, but the ABO ester is cleaved more easily by Lewis acids, thus forming an orthogonal set. The ABO ester can be cleaved with PPTS (MeOH, H_2O, 22°, 2 h; LiOH); the OBO ester is cleaved at 0° in 2 min.[8]

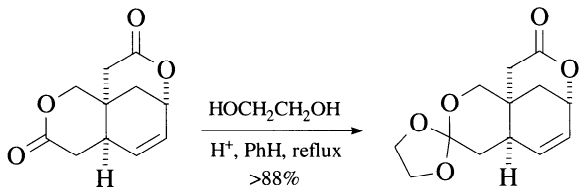


3. 

Refs. 9, 10

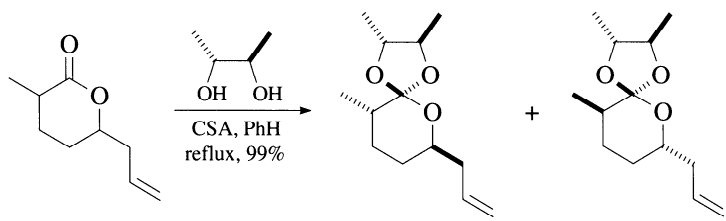
4. 

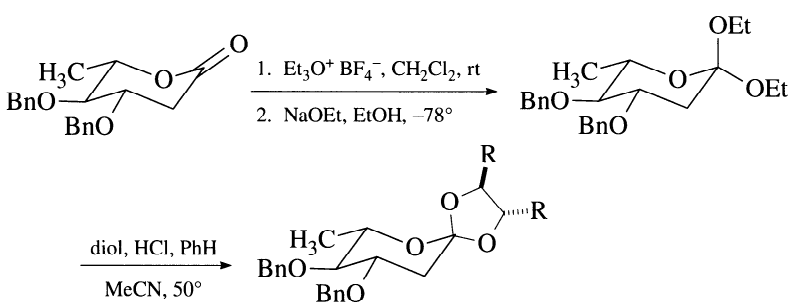
Ref. 9

5. 

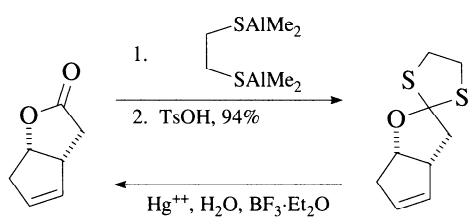
Refs. 11, 12

Note that this method does not work on simple esters. In addition, $TMSOCH_2CH_2OTMS/TMSOTF$ has been used to effect this conversion.[13] The same process was used to introduce the **cyclohexyl** version of this ortho ester in a quassinoid synthesis. Its cleavage was effected with DDQ in aqueous acetone.[14] (*R*,*R*)-2,3-Butanediol can be used to resolve the lactone.[15]

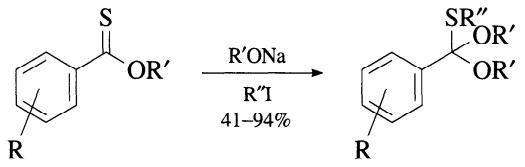




2-Substituted gulonolactones failed to react with Meerwein's salt.[16]

6. 

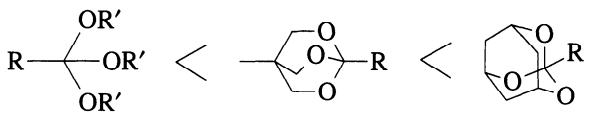
Refs. 17, 18

7. 

Ref. 19

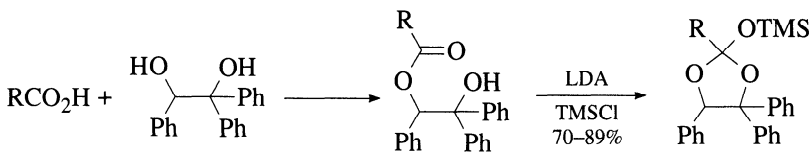
Cleavage

Oxygen ortho esters are readily cleaved by mild aqueous acid (TsOH·Pyr, H_2O;[20] $NaHSO_4$, 5:1 DME, H_2O, 0°, 20 min[21]) to form esters that are then hydrolyzed with aqueous base to give the acid. Note that a trimethyl ortho ester is readily hydrolyzed in the presence of an acid-sensitive ethoxyethyl acetal.[20] The order of acid stability is as follows:



The Braun Ortho Ester

Formation/Cleavage[22]



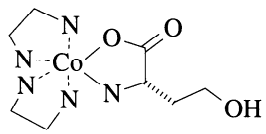
The derivative is stable to *n*-BuLi, *t*-BuLi (−78°), and pH 6–8. It is cleaved with NaOH, MeOH/H_2O at reflux (96% yield).

1. S. M. McElvain and J. W. Nelson, *J. Am. Chem. Soc.*, **64**, 1825 (1942).
2. The synthesis and interconversion of simple ortho esters has been reviewed: R. H. DeWolfe, *Synthesis*, 153 (1974).
3. E. J. Corey and N. Raju, *Tetrahedron Lett.*, **24**, 5571 (1983).
4. C. J. Palmer, L. M. Cole, J. P. Larkin, I. H. Smith, and J. E. Casida, *J. Agric. Food Chem.*, **39**, 1329 (1991).
5. B. R. DeCosta, A. Lewin, J. A. Schoenheimer, P. Skolnick, and K. C. Rice, *Heterocycles*, **32**, 2343 (1991); B. R. DeCosta, A. H. Lewin, K. C. Rice, P. Skolnick, and J. A. Schoenheimer, *J. Med. Chem.*, **34**, 1531 (1991).
6. K. C. Nicolaou, E. A. Theodorakis, F. P. J. T. Rutjes, M. Sato, J. Tiebes, X.-Y. Xiao, C.-K. Hwang, M. E. Duggan, Z. Yang, E. A. Couladouros, F. Sato, J. Shin, H.-M. He, and T. Bleckman, *J. Am. Chem. Soc.*, **117**, 10239 (1995).

7. A. B. Charette and P. Chua, *Tetrahedron Lett.*, **38**, 8499 (1997).
8. P. Wipf, W. Xu, H. Kim, and H. Takahashi, *Tetrahedron*, **53**, 16575 (1997).
9. G. Voss and H. Gerlach, *Helv. Chim. Acta*, **66**, 2294 (1983).
10. C. Müller, G. Voss, and H. Gerlach, *Liebigs Ann. Chem.*, 673 (1995).
11. T. Wakamatsu, H. Hara, and Y. Ban, *J. Org. Chem.*, **50**, 108 (1985).
12. J. D. White, S.-c. Kuo, and T. R. Vedananda, *Tetrahedron Lett.*, **28**, 3061 (1987).
13. D. J. Collins, L. M. Downes, A. G. Jhingran, S. B. Rutschman, and G. J. Sharp, *Aust. J. Chem.*, **42**, 1235 (1989).
14. S. Vasudevan and D. S. Watt, *J. Org. Chem.*, **59**, 361 (1994).
15. A. B. Smith, III, J. W. Leahy, I. Noda, S. W. Remiszewski, N. J. Liverton, and R. Zibuck, *J. Am. Chem. Soc.*, **114**, 2995 (1992).
16. C. Zagar and H. D. Scharf, *Liebigs Ann. Chem.*, 447 (1993).
17. E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **95**, 5829 (1973).
18. M. Nakada, S. Kobayashi, S. Iwasaki, and M. Ohno, *Tetrahedron Lett.*, **34**, 1035 (1993).
19. J. Voss and B. Wollny, *Synthesis*, 684 (1989).
20. G. Just, C. Luthe, and M. T. P. Viet, *Can. J. Chem.*, **61**, 712 (1983).
21. E. J. Corey, K. Niimura, Y. Konishi, S. Hashimoto, and Y. Hamada, *Tetrahedron Lett.*, **27**, 2199 (1986).
22. D. Waldmüller, M. Braun, and A. Steigel, *Synlett*, 160 (1991).

Pentaaminecobalt(III) Complex: $[RCO_2Co(NH_3)_5](BF_4)_3$

The pentaaminecobalt(III) complex has been prepared from amino acids to protect the carboxyl group during peptide synthesis [$(H_2O)Co(NH_3)_5(ClO_4)_3$, 70°, H_2O, 6 h; cool to 0°; filter; HBF_4, 60–80% yield]. It is cleaved by reduction [$NaBH_4$, NaSH, or $(NH_4)_2S$, Fe(II)EDTA]. These complexes do not tend to racemize and are stable to CF_3CO_2H that is used to remove BOC groups.[1–3] The related **bisethylenediamine** complex of amino acids has been prepared. It is stable to strong acids and is cleaved with ammonium sulfide.[4]



1. S. Bagger, I. Kristjansson, I. Soetofte, and A. Thorlacius, *Acta Chem. Scand. Ser. A*, **A39**, 125 (1985).
2. S. S. Isied, A. Vassilian, and J. M. Lyon, *J. Am. Chem. Soc.*, **104**, 3910 (1982).
3. S. S. Isied, J. Lyon, and A. Vassilian, *Int. J. Pept. Protein Res.*, **19**, 354 (1982).
4. P. M. Angus, B. T. Golding, and A. M. Sargeson, *J. Chem. Soc., Chem. Commun.*, 979 (1993).

Stannyl Esters

Triethylstannyl Ester: $RCOOSn(C_2H_5)_3$

Tri-*n*-butylstannyl Ester: $RCOOSn(n\text{-}C_4H_9)_3$

Stannyl esters have been prepared to protect a –COOH group in the presence of an $-NH_2$ group [$(n\text{-}Bu_3Sn)_2O$ or $n\text{-}Bu_3SnOH$, C_6H_6, reflux, 88%].[1] Stannyl esters of *N*-acylamino acids are stable to reaction with anhydrous amines and to water and alcohols;[2] aqueous amines convert them to ammonium salts.[2] Stannyl esters of amino acids are cleaved in quantitative yield by water or alcohols (PhSK, DMF, 25°, 15 min, 63% yield or HOAc, EtOH, 25°, 30 min, 77% yield).[2]

1. P. Bamberg, B. Ekström, and B. Sjöberg, *Acta Chem. Scand.*, **22**, 367 (1968).
2. M. Frankel, D. Gertner, D. Wagner, and A. Zilkha, *J. Org. Chem.*, **30**, 1596 (1965).

AMIDES AND HYDRAZIDES

To a limited extent, carboxyl groups have been protected as amides and hydrazides, derivatives that complement esters in the methods used for their cleavage. Amides and hydrazides are stable to the mild alkaline hydrolysis that cleaves esters. Esters are stable to nitrous acid, effective in cleaving amides, and to the oxidizing agents [including $Pb(OAc)_4$, MnO_2, SeO_2, CrO_3, and $NaIO_4$;[1] $Ce(NH_4)_2(NO_3)_6$;[2] Ag_2O;[3] and $Hg(OAc)_2$[4]] that have been used to cleave hydrazides.

Formation

Classically, amides and hydrazides have been prepared from an ester or an acid chloride and an amine or hydrazine, respectively; they can also be prepared directly from the acid as shown in the following equations:

1. $\underset{\text{NHPG}}{\text{RCHCOOH}} + R'NH_2 \xrightarrow[20°,\ 4\ h,\ 70\text{–}90\%]{\text{DCC, THF or } CH_2Cl_2\ [5]} \underset{\text{NHPG}}{\text{RCHCONHR}'}$

2. $\underset{\text{NHPG}}{\text{RCHCOOH}} \xrightarrow{H_2NNH_2,\ N\text{-hydroxybenzotriazole}\ [6]} \underset{\text{NHPG}}{\text{RCHCONHNH}_2}$

3. $\text{RCOOH} + \text{R}'\text{R}''\text{NH} \xrightarrow{Ph_3P\ [7]\ \text{or}\ Bu_3P/o\text{-}NO_2\text{–}C_6H_4SCN\ [8]} \text{RCONR}'\text{R}''$

4. $RCOOH + R'NH_2 \xrightarrow{C_6H_2F_3B(OH)_2,\ \text{toluene, heat}^{9}} RCONHR'$

5. $RCO_2R' + NaEt_2Al(NR''_2)_2 \xrightarrow[83\text{–}96\%^{10}]{} RCONR''_2$

6. $RCOOH \xrightarrow[\text{dioxane, Pyr, 4–16 h}^{11}]{NH_4OCO_2H,\ (BOC)_2O} RCONH_2$

7. $RCOOH + R'OCOCl + TEA \longrightarrow RCO_2CO_2R' \xrightarrow{R''_2NH} RCONR''_2$

This is a very general and mild method for the preparation of amides, applicable to large structural variations in both the acid and the amine. A variety of chloroformates can be employed, but isobutyl chloroformate is used most often. The solvent is not critical, but generally, THF is used.

Cleavage

Equations 1–10 illustrate some mild methods that can be used to cleave amides. Equations 1 and 2 indicate the conditions that were used by Woodward[12] and Eschenmoser,[13] respectively, in their synthesis of vitamin B_{12}. Butyl nitrite,[14] nitrosyl chloride,[15] and nitrosonium tetrafluoroborate ($NO^+BF_4^-$)[16] have also been used to cleave amides. Since only tertiary amides are cleaved by potassium *t*-butoxide (eq. 3), this method can be used to effect selective cleavage of tertiary amides in the presence of primary or secondary amides.[17] (Esters, however, are cleaved by similar conditions.) [18] Photolytic cleavage of nitro amides (eq. 4) is discussed in a review.[19]

1. $RCONH_2 \xrightarrow{N_2O_4/CCl_4\ ^{12,20}} RCOOH$

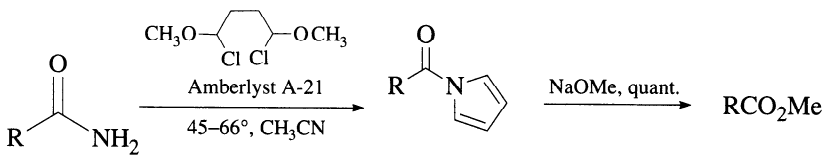
2. $RCONH_2 \xrightarrow{[ClCH_2CH{=}N(\rightarrow O)\text{-}c\text{-}C_6H_{11} + AgBF_4]\ ^{13}} \xrightarrow{H_3O^+} RCOOH$

3. $RCONR'R'' \xrightarrow[24°,\ 2\text{–}48\ h,\ 88\text{–}96\%]{KO\text{-}t\text{-}Bu/H_2O\ (6:2),\ Et_2O\ ^{17}} RCOOH$

   $R', R'' \neq H$

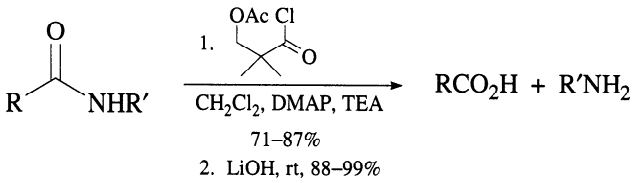
4. a, b, or c $\xrightarrow[5\text{–}10\ h,\ 70\text{–}100\%]{350\ nm\ ^{19}} RCOOH$

   a = *o*-nitroanilides[21]
   b = *N*-acyl-7-nitroindoles[22]
   c = *N*-acyl-8-nitrotetrahydroquinolines[23]

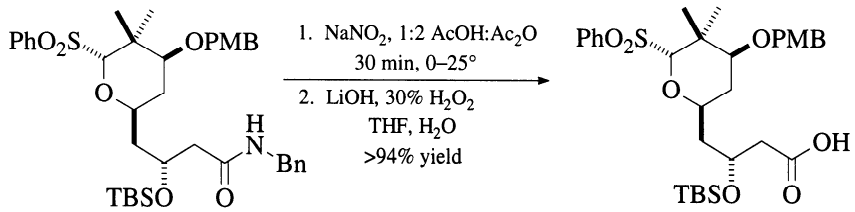
5. 

Treatment of acyl pyrroles with primary and secondary amines affords amides.[24]

6. The following cleavage proceeds via intramolecular assistance from the alkoxide formed on base treatment:[25,26]



7. For primary and secondary amides: $CuCl_2$, glyoxal, H_2O, pH 3.5, reflux, 92% yield.[27]
8. For primary amides: DMF dimethyl acetal, MeOH, 92–100% yield. The methyl ester is formed, but if MeOH is replaced with another alcohol, other esters can be prepared with similar efficiency.[28]
9. $NaNO_2$, AcOH, Ac_2O, 30 min, 0°–rt,[29] then hydrolysis with LiOOH. These conditions were developed as a mild method to cleave an amide that was prone to decomposition under the more basic conditions.[30]



10. N_2O_4, −20°, CH_3CN, 66–100% yield. Additionally, these conditions cleave hydroxamic acids, anilides, and sulfonamides.[31,32]

Hydrazides have been used in penicillin and peptide syntheses. In the latter syntheses, they are converted by nitrous acid to azides to facilitate coupling.

Some amides and hydrazides that have been prepared to protect carboxyl groups are included in Reactivity Chart 6.

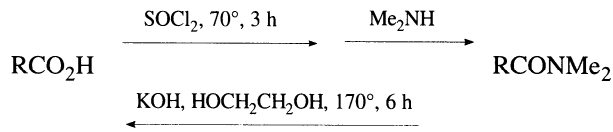
1. M. J. V. O. Baptista, A. G. M. Barrett, D. H. R. Barton, M. Girijavallabhan,

R. C. Jennings, J. Kelly, V. J. Papadimitriou, J. V. Turner, and N. A. Usher, *J. Chem. Soc., Perkin Trans. 1*, 1477 (1977).
2. T.-L. Ho, H. C. Ho, and C. M. Wong, *Synthesis*, 562 (1972).
3. Y. Wolman, P. M. Gallop, A. Patchornik, and A. Berger, *J. Am. Chem. Soc.*, **84**, 1889 (1962).
4. J. B. Aylward and R. O. C. Norman, *J. Chem. Soc. C*, 2399 (1968).
5. J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).
6. For example, see S. S. Wang, I. D. Kulesha, D. P. Winter, R. Makofske, R. Kutny, and J. Meienhofer, *Int. J. Pept. Protein Res.*, **11**, 297 (1978).
7. L. E. Barstow and V. J. Hruby, *J. Org. Chem.*, **36**, 1305 (1971).
8. P. A. Grieco, D. S. Clark, and G. P. Withers, *J. Org. Chem.*, **44**, 2945 (1979).
9. K. Ishihara, S. Ohara, and H. Yamamoto, *J. Org. Chem.*, **61**, 4196 (1996).
10. T. B. Sim and N. M. Yoon, *Synlett*, 827 (1994).
11. V. F. Posdnev, *Tetrahedron Lett.*, **36**, 7115 (1995).
12. R. B. Woodward, *Pure Appl. Chem.*, **33**, 145 (1973).
13. U. M. Kempe, T. K. Das Gupta, K. Blatt, P. Gygax, D. Felix, and A. Eschenmoser, *Helv. Chim. Acta*, **55**, 2187 (1972).
14. N. Sperber, D. Papa, and E. Schwenk, *J. Am. Chem. Soc.*, **70**, 3091 (1948).
15. M. E. Kuehne, *J. Am. Chem. Soc.*, **83**, 1492 (1961).
16. G. A. Olah and J. A. Olah, *J. Org. Chem.*, **30**, 2386 (1965).
17. P. G. Gassman, P. K. G. Hodgson, and R. J. Balchunis, *J. Am. Chem. Soc.*, **98**, 1275 (1976).
18. P. G. Gassman and W. N. Schenk, *J. Org. Chem.*, **42**, 918 (1977).
19. B. Amit, U. Zehavi, and A. Patchornik, *Isr. J. Chem.*, **12**, 103 (1974).
20. T. Itoh, K. Nagata, Y. Matsuya, M. Miyazaki, and A. Ohsawa, *Tetrahedron Lett.*, **38**, 5017 (1997).
21. B. Amit and A. Patchornik, *Tetrahedron Lett.*, 2205 (1973).
22. B. Amit, D. A. Ben-Efraim, and A. Patchornik, *J. Am. Chem. Soc.*, **98**, 843 (1976).
23. B. Amit, D. A. Ben-Efraim, and A. Patchornik, *J. Chem. Soc., Perkin Trans. 1*, 57 (1976).
24. S. D. Lee, M. A. Brook, and T. H. Chan, *Tetrahedron Lett.*, **24**, 1569 (1983).
25. T. Tsunoda, O. Sasaki, and S. Itô, *Tetrahedron Lett.*, **31**, 731 (1990).
26. T. Tsunoda, O. Sasaki, O. Takenchi, and S. Ito, *Tetrahedron*, **47**, 3925 (1991).
27. L. Singh and R. N. Ram, *J. Org. Chem.*, **59**, 710 (1994).
28. P. L. Anelli, M. Brocchetta, D. Palano, and M. Visigalli, *Tetrahedron Lett.*, **38**, 2367 (1997).
29. I. R. Vlahov, P. I. Vlahova, and R. R. Schmidt, *Tetrahedron Lett.*, **33**, 7503 (1992).
30. D. A. Evans, P. H. Carter, C. J. Dinsmore, J. C. Barrow, J. L. Katz, and D. W. Kung, *Tetrahedron Lett.*, **38**, 4535 (1997).
31. Y. H. Kim, K. Kim, and Y. J. Park, *Tetrahedron Lett.*, **31**, 3893 (1990).
32. D. S. Karanewsky, M. F. Malley, and J. Z. Gougoutas, *J. Org. Chem.*, **56**, 3744 (1991).

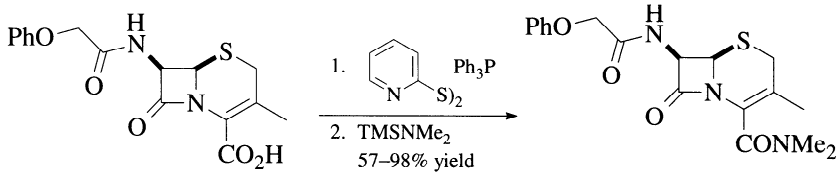
Amides

N,N-Dimethylamide: $RCON(CH_3)_2$ (Chart 6)

Formation/Cleavage[1]



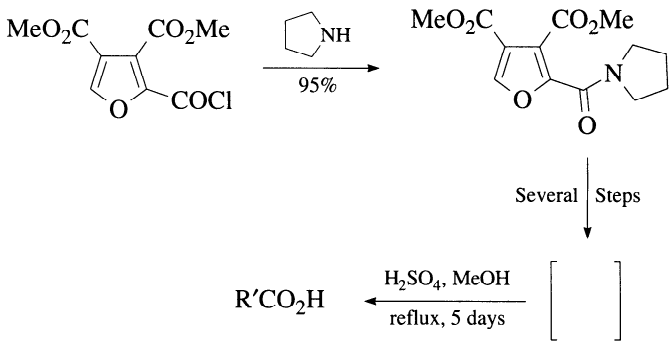
In these papers, the carboxylic acid to be protected was a stable, unsubstituted compound. Harsh conditions were acceptable for both formation and cleavage of the amide. Typically, a simple secondary amide is very difficult to cleave. As the pK_a of the conjugate acid of an amide decreases, the rate of hydrolysis of amides derived from these amines increases. The dimethylamide of a cephalosporin was prepared as follows using 2,2′-dipyridyl disulfide.[2]



1. D. E. Ames and P. J. Islip, *J. Chem. Soc.*, 351 (1961); *idem, ibid.*, 4363 (1963).
2. R. DiFabio, V. Summa, and T. Rossi, *Tetrahedron*, **49**, 2299 (1993).

Pyrrolidinamide: RCONR′R″, [R′R″= $(-CH_2-)_4$]

Formation/Cleavage[1]

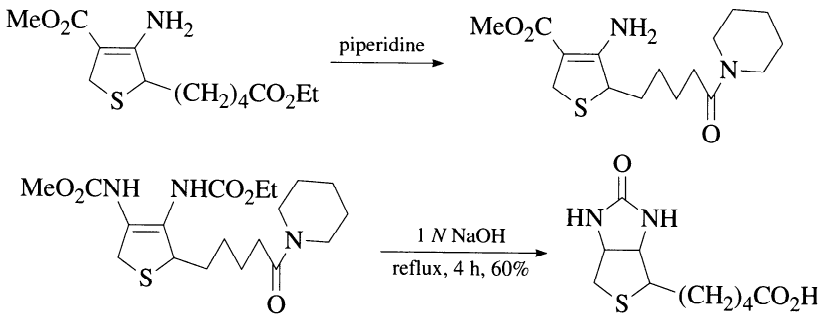


R′CO_2H = precursor to DL-camptothecin

1. A. S. Kende, T. J. Bentley, R. W. Draper, J. K. Jenkins, M. Joyeux, and I. Kubo, *Tetrahedron Lett.*, 1307 (1973).

Piperidinamide: RCONR′R″, [R′R″ = $(-CH_2-)_5$]

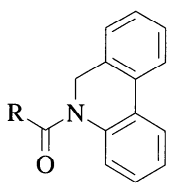
Formation/Cleavage[1]



biotin

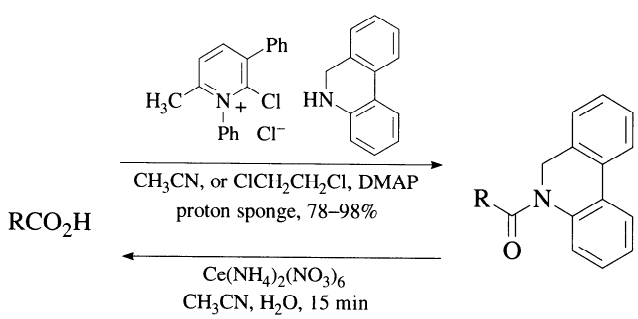
1. P. N. Confalone, G. Pizzolato, and M. R. Uskokovic, *J. Org. Chem.*, **42**, 1630 (1977).

5,6-Dihydrophenanthridinamide:



Formation/Cleavage[1]

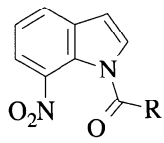
This amide is stable to HCl or KOH (THF, MeOH, H_2O, 70°, 10 h) and MeMgI, THF, HMPA, −78°. It can also be formed directly from the acid chloride.



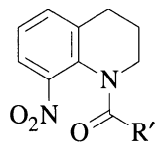
1. T. Uchimaru, K. Narasaka, and T. Mukaiyama, *Chem. Lett.*, 1551 (1981).

o-Nitroanilide: $RCONR'C_6H_4$–o-NO_2, $R' \neq H$

***N*-7-Nitroindolylamide** (Chart 6):



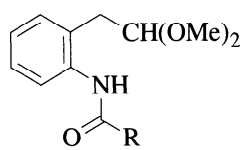
***N*-8-Nitro-1,2,3,4-tetrahydroquinolylamide:**



o-Nitroanilides (R′ = Me, *n*-Bu, *c*-C_6H_{11}, Ph, $PhCH_2$; ≠ H),[1] nitroindolylamides,[2] and tetrahydroquinolylamides[3] are cleaved in high yields under mild conditions by irradation at 350 nm (5–10 h).

1. B. Amit and A. Patchornik, *Tetrahedron Lett.*, 2205 (1973).
2. B. Amit, D. A. Ben-Efraim, and A. Patchornik, *J. Am. Chem. Soc.*, **98**, 843 (1976).
3. B. Amit, D. A. Ben-Efraim, and A. Patchornik, *J. Chem. Soc., Perkin Trans. 1*, 57 (1976).

2-(2-Aminophenyl)acetaldehyde Dimethyl Acetal Amide:



Formation

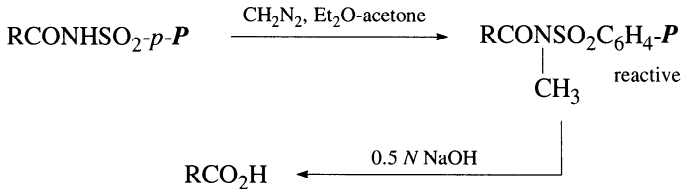
This amide is readily prepared from the acid chloride (Pyr, rt, 1 h, 77–86% yield) or the acid (DCC, DMAP, CH_2Cl_2, rt, 1 h, 88% yield). Treatment of the amide with camphorsulfonic acid forms an *N*-acylindole. The acid can be regenerated from the *N*-acylindole by $LiOH/H_2O_2/THF/H_2O$ or NaOH/MeOH. Alternatively, it can be transesterified with MeOH/TEA, converted to an amide, by heating with an amine or converted to an aldehyde by DIBAH (62–85% yield).[1]

1. E. Arai, H. Tokuyama, M. S. Linsell, and T. Fukuyama, *Tetrahedron Lett.*, **39**, 71 (1998).

p-P*-Benzenesulfonamide:** $RCONHSO_2C_6H_4$–*p*-P***

A polymer-supported sulfonamide, prepared from an amino acid activated ester

and a polystyrene–sulfonamide, is stable to acidic hydrolysis (CF_3COOH; HBr/HOAc). It is cleaved by the "safety-catch" method as shown.[1]



1. G. W. Kenner, J. R. McDermott, and R. C. Sheppard, *J. Chem. Soc., Chem. Commun.*, 636 (1971).

Hydrazides

Hydrazides: $RCONHNH_2$ (Chart 6)

Cleavage

1. NBS/H_2O, 25°, 10 min, 74% yield.[1]
2. 60% $HClO_4$, 48°, 24 h, 100% yield.[2]
3. $POCl_3$, H_2O, 94% yield.[2]
4. HBr/HOAc or HCl/HOAc, 94% yield.[2]
5. $CuCl_2$, H_2O, THF.[3] If an alcohol such as ethanol is substituted for H_2O in this reaction, the ester is produced instead of the acid.

1. H. T. Cheung and E. R. Blout, *J. Org. Chem.*, **30**, 315 (1965).
2. J. Schnyder and M. Rottenberg, *Helv. Chim. Acta*, **58**, 521 (1975).
3. O. Attanasi and F. Serra-Zannetti, *Synthesis*, 314 (1980).

***N*-Phenylhydrazide:** $RCONHNHC_6H_5$ (Chart 6)

Formation

Phenylhydrazides have been prepared from amino acid esters and phenylhydrazine in 70% yield.[1]

Cleavage

1. $Cu(OAc)_2$, 95°, 10 min, 67% yield.[2]
2. $FeCl_3$/1 *N* HCl, 96°, 14 min, 85% yield.[3]

3. Dioxane, DMF, 1 *M* aq. Pyr-AcOH buffer, AcOH, $CuCl_2$, 48 h, air, 86% yield.[4]
4. Horse radish peroxidase, H_2O_2 or Laccase, pH 4, 2% DMSO or DMF. Cleavage occurs by the formation of a phenyldiimide, which decomposes to the acid, nitrogen, and benzene. The laccase method is compatible with the readily oxidized tryptophan and methionine because it does not use peroxide.[5]

1. R. B. Kelly, *J. Org. Chem.*, **28**, 453 (1963).
2. E. W.-Leitz and K. Kühn, *Chem. Ber.*, **84**, 381 (1951).
3. H. B. Milne, J. E. Halver, D. S. Ho, and M. S. Mason, *J. Am. Chem. Soc.*, **79**, 637 (1957).
4. A. N. Semenov and I. V. Lomonosova, *Int. J. Pept. Protein Res.*, **43**, 113 (1994).
5. A. N. Semenov, I. V. Lomonosova, V. I. Berezin, and M. I. Titov, *Biotechnol. Bioengin.*, **42**, 1137 (1993).

N,N′-Diisopropylhydrazide: $RCON(i\text{-}C_3H_7)NH\text{–}i\text{-}C_3H_7$ (Chart 6)

The *N,N′*-diisopropylhydrazide, prepared to protect penicillin derivatives, is cleaved oxidatively by the following methods:[1]

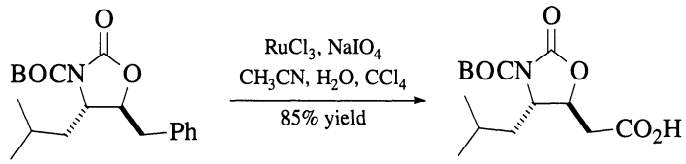
1. $Pb(OAc)_4$/Pyr, 25°, 10 min, 90% yield.
2. $NaIO_4/H_2O$–THF, H_2SO_4, 20°, 5 min, 89% yield.
3. Aq. NBS/THF–Pyr, 20°, 10 min, 90% yield.
4. CrO_3/HOAc, 25°, 10 min, 65% yield.

A number of di- and trisubstituted hydrazides of penicillin and cephalosporin derivatives were prepared to study the effect of *N*-substitution on the ease of oxidative cleavage.[2]

1. D. H. R. Barton, M. Girijavallabhan, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 929 (1972).
2. D. H. R. Barton and eight co-workers, *J. Chem. Soc., Perkin Trans. 1*, 1477 (1977).

Phenyl Group: C_6H_5–

The phenyl group became a practical "protective" group for carboxylic acids when Sharpless published a mild, effective one-step method for its conversion to a carboxylic acid.[1] Recently, the group has been used in a synthesis of the amino acid statine, in which it served as a masked or carboxylic acid equivalent.[2]



The furan group also serves as a protected carboxylic acid.[3]

1. P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, *J. Org. Chem.*, **46**, 3936 (1981).
2. S. Kano, Y. Yuasa, T. Yokomatsu, and S. Shibuya, *J. Org. Chem.*, **53**, 3865 (1988).
3. S. Sasaki, Y. Hamada, and T. Shioiri, *Tetrahedron Lett.*, **38**, 3013 (1997).

Tetraalkylammonium Salts: $R'_4N^+ {}^-O_2CR$

In a rather nontraditional approach to acid protection, the tetraalkylammonium salts of amino acids allow for coupling of HOBt-activated amino acids in yields of 55–84%.[1]

1. S.-T. Chen and K.-T. Wang, *J. Chem. Soc., Chem. Commun.*, 1045 (1990).

PROTECTION OF SULFONIC ACIDS

Few methods exist for the protection of sulfonic acids. Imidazolides and phenolic esters are too base labile to be useful in most cases. Simple sulfonate esters often cannot be used because these are obviously quite susceptible to nucleophilic reagents.

Neopentyl Ester: $(CH_3)_3CCH_2OSO_2R$

The neopentyl alcohol, prepared from the sulfonyl chloride (Pyr, 95% yield), is cleaved nucleophilically under rather severe conditions ($Me_4N^+ Cl^-$, DMF, 160°, 16 h, 100% yield).[1]

N-BOC-4-Amino-2,2-dimethylbutyl Sulfonate: $BOCNHCH_2CH_2C(CH_3)_2CH_2OSO_2R$

This sulfonate, prepared from $BOCNHCH_2CH_2C(CH_3)_2CH_2OH$ and the sulfonyl chloride (Pyr, 100% yield) is cleaved by initial BOC cleavage to release the free amine after pH adjustment to 7–8. Intramolecular displacement occurs to release the sulfonate and a pyrrolidine.[1]

Isobutyl Sulfonate: $(CH_3)_2CHCH_2OSO_2R$

The isobutyl sulfonate was examined as a replacement for the isopropyl sulfonate, which had undesirable stability properties. Cleavage occurs with 2 eq. of $Bu_4N^+ I^-$ and proceeds much more readily than cleavage of the isopropyl sulfonate.[2]

Isopropyl Sulfonate: $(CH_3)_2CHOSO_2R$

This sulfonate is cleaved with $Bu_4N^+ I^-$ or ammonia. [3] The group has been reported to suffer from stability problems upon storage and use.[2]

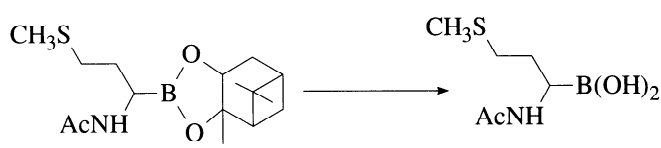
1. J. C. Roberts, H. Gao, A. Gopalsamy, A. Kongsjahju, and R. J. Patch, *Tetrahedron Lett.*, **38**, 355 (1997).
2. M. Xie and T. S. Widlanski, *Tetrahedron Lett.*, **37**, 4443 (1996).
3. B. Musicki and T. S. Widlanski, *Tetrahedron Lett.*, **32**, 1267 (1991); B. Musicki and T. S. Widlanski, *J. Org. Chem.*, **55**, 4231 (1990).

PROTECTION OF BORONIC ACIDS

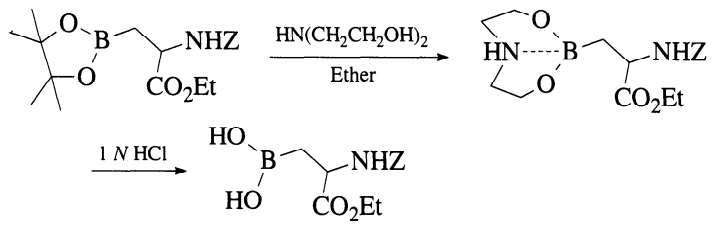
Boronic esters are easily prepared from a diol and the boronic acid with removal of water, either chemically or azeotropically. (See Chapter 2 on the protection of diols.) Sterically hindered boronic esters, such as those of **pinacol**, can be prepared in the presence of water. Boronic esters of simple unhindered diols are quite sensitive to water and hydrolyze readily. On the other hand, very hindered esters, such as the **pinacol** and **pinanediol** derivatives, are exceedingly difficult to hydrolyze and often require rather harsh conditions to achieve cleavage.

Cleavage

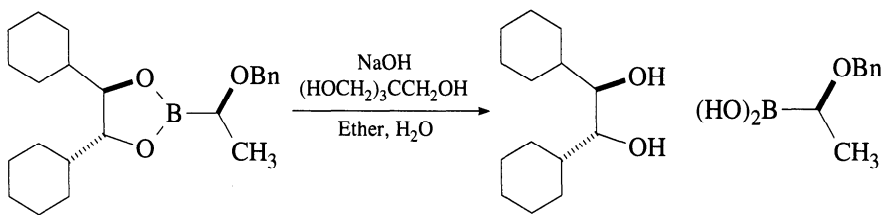
1. Ether, water, phenylboronic acid. Cleavage occurs by transesterification.[1,2]
2. (a) $NaIO_4$, NH_4OAc, acetone, water, 24–48 h; (b) pH 3 with HCl, 55–71% yield.[1]
3. BCl_3, −78°, CH_2Cl_2, 8 h, 83% yield.[3]



4. $LiAlH_4$, Et_2O; MeONa, 1,3-propanediol.[4] These conditions reduce the boronate to the hydride.
5. $HN(CH_2CH_2OH)_2$, ether; 1 *N* HCl, ~80% yield.[5,6]



6.



This method was only partially successful with the pinanediol boroanate.[7]

1,2-Benzenedimethanol

This ester is formed quantitatively in THF from the diol in the presence of a dehydrating agent such as sodium sulfate. It can be cleaved by hydrogenolysis, but it is also quite susceptible to hydrolytic cleavage.[8]

1,3-Diphenyl-1,3-propanediol

Esterification is readily achieved in THF in the presence of a dehydrating agent.[9] The boronate is stable to chromatography, has good stability to 2 *M* TFA/CH_2Cl_2, but is not stable to aqueous 1 *M* NaOH. Cleavage is also achieved by hydrogenolysis.[8]

1. S. J. Coutts, J. Adams, D. Krolikowski, and R. J. Snow, *Tetrahedron Lett.*, **35**, 5109 (1994).
2. J. Wityak, R. A. Earl, M. M. Abelman, Y. B. Bethel, B. N. Fisher, G. S. Kauffman, C. A. Kettner, P. Ma, J. L. McMillan, L. J. Mersinger, J. Pesti, M. E. Pierce, F. W. Rankin, R. J. Chorvat, and P. N. Confalone, *J. Org. Chem.*, **60**, 3717 (1995).
3. D. S. Matteson, T. J. Michnick, R. D. Willett, and C. D. Patterson, *Organometallics*, **8**, 726 (1989).
4. M. V. Rangaishenvi, B. Singaram, and H. C. Brown, *J. Org. Chem.*, **56**, 3286 (1991).
5. D. H. Kinder and M. M. Ames, *J. Org. Chem.*, **52**, 2452 (1987).
6. D. S. Matteson and R. Ray, *J. Am. Chem. Soc.*, **102**, 7590 (1980).
7. D. S. Matteson and H.-W. Man, *J. Org. Chem.*, **61**, 6047 (1996).
8. C. Malan, C. Morin, and G. Preckher, *Tetrahedron Lett.*, **37**, 6705 (1996).
9. C. Malan and C . Morin, *Synlett*, 167 (1996).