

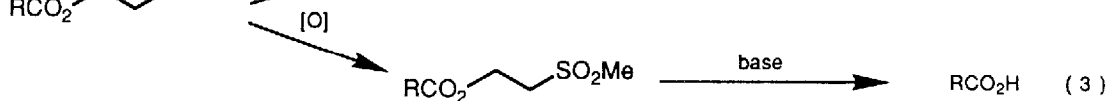
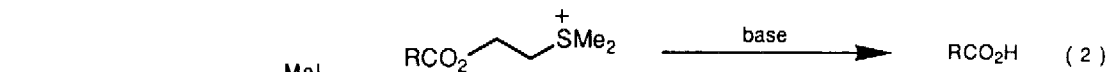
3-BUTENYL ESTERS AS CONVENIENT PROTECTING GROUPS FOR CARBOXYLIC ACIDS

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Abstract: Carboxylic acids were protected as their corresponding 3-butenyl esters. Deprotection was carried out via ozonolysis and β -elimination of the resultant 3-acyloxypropanal.

Recently we encountered difficulties in the hydrolysis of a carboxylic ester due to facile epimerization α to the carboxyl group. Thus we examined the use of 3-butenyl esters as protecting groups.¹ We anticipated that deprotection should be easily effected via ozonolysis and β -elimination² of the resultant 3-acyloxypropanal (equation 1). Such a protection strategy has indirect precedent in the use of 2-methylthioethyl esters. Such esters may be deprotected via S-methylation or S-oxidation, to produce the sulfone, and β -elimination (equations 2 and 3).^{1,3} However, the β -elimination process in equation 1 should take place more readily than in equations 2 or 3.⁴ Thus deprotection should be possible under milder conditions.

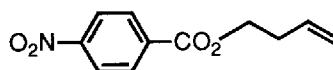


A series of 3-butenyl esters⁵ were prepared by direct esterification or via titanium tetra-isopropoxide catalyzed transesterification⁶ (Table). Ozonolysis of each ester with a dimethyl sulfide work up⁷ gave the corresponding labile 3-acyloxypropanal derivatives.

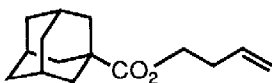
TABLE. Preparation and Deprotection of 3-Butenyl Esters

Ester (Method of Preparation^B, % Yield, % Yield of Regenerated Carboxylic Acid)

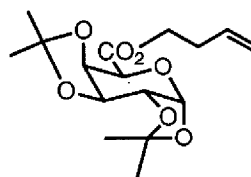
1 (A, 88, 98)



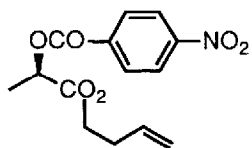
2 (A, 79, 99)



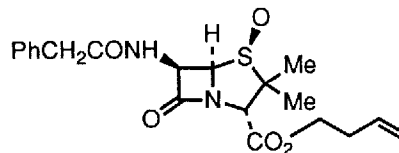
3 (A, 80, 99)



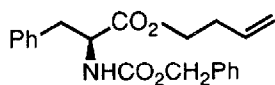
4 (B, 94, 96)



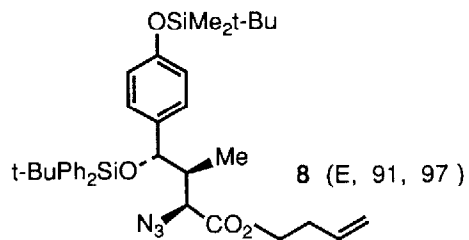
5 (C, 62, 85)



6 (D, 87, 79)



7 (D, 70, 82)



8 (E, 91, 97)

Without isolation these were reacted briefly with triethylamine (esters 1-7) or DBU (ester 8) to regenerate the carboxylic acid. The mildness of this deprotection sequence is underscored by its application to the diester **5**, penicillin sulfoxide **6** and the configurationally labile α -azido ester **8**. In a typical procedure pyridine (1.25 mL) and phosgene in PhMe (1.9 M; 3.65 mL) were added to (L)-N-Cbz-phenylalanine (1.5 g) and 3-buten-1-ol (0.94 mL) in Me₂CO (5 mL) at -78 °C. The solution was allowed to warm up to room temperature, stirred for 40 h and added to water (50 mL). The aqueous layer was extracted with PhMe (2 x 20 mL) and the combined organic extracts washed with hydrochloric acid (1 M; 20 mL) and saturated aqueous NaHCO₃ (10 mL) and dried (Na₂SO₄). Evaporation and chromatography on silica (eluant CH₂Cl₂) gave ester **7** (1.23 g, 70%) as a colorless oil. Ozone was bubbled through a solution of **7** (213mg) in CH₂Cl₂ (2 mL) and MeOH (2 mL) at -78 °C to a blue end point. Me₂S (0.5 mL) was added and the solution allowed to warm up to room temperature. After 3 h, Et₃N (0.5 mL) was added and stirring continued for 1 h. The solution was evaporated, H₂O (20 mL) added and the mixture extracted with pentane (2 x 10 mL). The aqueous phase was carefully acidified to pH 4 with hydrochloric acid (0.05 M) and extracted with EtOAc (3 x 15 mL). The extracts were dried (Na₂SO₄) and evaporated to afford pure (L)-N-Cbz-phenylalanine (147 mg, 82%).

Acknowledgement:

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3. For the use of 2-methylthioethyl esters as carboxylic acid protecting groups see P.M. Hardy, H. N. Rydon, and R.C. Thompson, *Tetrahedron Lett.*, **1968**, 2525. Alternative

protecting groups that are removed by E_{1c}b elimination of carboxylate include 2-cyanoethyl esters which are cleaved using K₂CO₃ in MeOH, see P.K. Misra, S.A.N Hashmi, W. Haq, and S.B. Katti, *Tetrahedron Lett.* **1989**, *30*, 3569; 2-(2-pyridyl)ethyl esters which are cleaved by sequential reaction with iodomethane and diethylamine, see H. Kessler, G. Becker, H. Kogler, and M. Wolff, *Tetrahedron Lett.*, **1984**, *25*, 3971; and 2-(diphenylphosphino)ethyl esters which are cleaved by P-methylation followed by β-elimination using KF or K₂CO₃, see D. Chantreux, J.-P. Gamet, R. Jacquier, and J. Verducci, *Tetrahedron*, **1984**, *40*, 3087.

4. Sulfones are less (CH) acidic than aldehydes or ketones see H.O. House, "Modern Synthetic Reactions", W.A. Benjamin Inc, Menlo Park, **1972**, p. 494.
5. All new compounds were fully authenticated by spectroscopic data and microanalyses or high resolution mass spectra. The acid derived from the ester **8** was characterized as the *p*-nitrophenyl ester.
6. D. Seebach, E. Hungerbühler, R. Naef, P. Schnurrenberger, B. Weidmann, and M. Züger, *Synthesis*, **1982**, 138.
7. J.J. Pappas, W.P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, **1966**, 4273.
8. The esters were prepared by (A) reaction of the acid chloride and 3-buten-1-ol in CH₂Cl₂ and pyridine at 25 °C; (B) reaction of the carboxylic acid, 3-buten-1-ol and DCC in CH₂Cl₂ at 0-25 °C; (C) reaction of (R)-lactic acid with 3-nitrobenzoyl chloride (2 equiv.) and pyridine in CH₂Cl₂ at 25 °C followed by 3-buten-1-ol and pyridine; (D) reaction of the carboxylic acid with pyridine and phosgene in Me₂CO at -78 °C followed by 3-buten-1-ol at -78 to 25 °C; (E) reaction of **9** with 3-buten-1-ol and (iso-PrO)₄Ti in PhH at 80 °C followed by silylation of the resultant phenol **10** using *t*-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine in THF at -78°C, see E.J. Corey, H. Cho, C. Rücker, and D.H. Hua, *Tetrahedron Lett.*, **1981**, *22*, 3455.

