

New Protecting Groups for 1,2-Diols (Boc- and Moc-ethylidene). Cleavage of Acetals with Bases

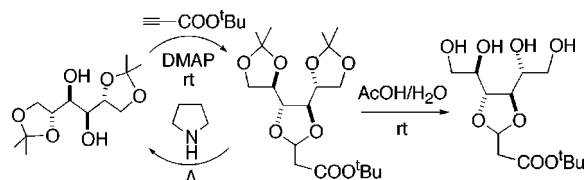
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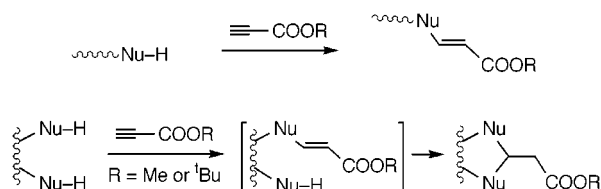
ABSTRACT



1,2-Diols react at rt with alkyl propynoates, in the presence of 4-dimethylaminopyridine, to give cyclic acetals which are quite stable to acid-catalyzed hydrolysis or methanolysis. 1,3-Diols and 1,4-diols do not form acetals with alkyl propynoates under the same conditions. Deprotection is accomplished with bases (via elimination and addition/elimination steps).

The addition of nucleophiles to triple bonds conjugated with electron-withdrawing groups has many synthetic applications.^{1–3} Often, as illustrated in Scheme 1 (top) for certain

Scheme 1



nucleophile additions to esters of propynoic acid (propionic acid), only the adduct of configuration *E* is obtained, although

there are exceptions.¹ In this context, we focused our attention on compounds with two nucleophilic sites close together, as shown in Scheme 1. Initially, one of the nucleophilic sites would become protected by a 2-(methoxycarbonyl)ethenyl group (Mocvinyl)⁴ or 2-(*tert*-butoxycarbonyl)ethenyl group (henceforward Bocvinyl). These reaction intermediates could react with the propynoate ester (remaining or in excess) either to afford a diprotected derivative or to cyclize intramolecularly (Scheme 1, bottom).^{5,6} In this second case, the two nucleophilic sites of the molecule would become protected by a 2-(methoxycarbonyl)ethylidene (Moc-ethylidene, “Mocdene”) or 2-(*tert*-butoxycarbonyl)ethylidene group (Boc-ethylidene, “Bocdene”). We report here on the formation, stability, and cleavage of these acetals, which show a striking

(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992; p 345. MacPherson, D. T.; Rami, H. K. In *Comprehensive Organic Functional Group Transformations*, Vol. 4; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Kirby, G. W., Eds.; Elsevier: Oxford, 1995; p 195. Arjona, O.; Iradier, F.; Medel, R.; Plumet, J. J. *Org. Chem.* **1999**, *64*, 6090, and references therein. For “anomalous” reactions (γ - or α -addition instead of β -addition, in the presence of Ph_3P and AcOH), see: Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819. Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595.

(2) Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241 (addition of primary alcohols to methyl propynoate, catalyzed by Bu_3P).

(3) Kuroda, H.; Tomita, I.; Endo, T. *Synth. Commun.* **1996**, *26*, 1539 (formation of dithioacetals via conjugate addition).

(4) Faja, M.; Ariza, X.; Gálvez, C.; Vilarrasa, J. *Tetrahedron Lett.* **1995**, *36*, 3261. Costa, A. M.; Faja, M.; Farràs, J.; Vilarrasa, J. *Tetrahedron Lett.* **1998**, *39*, 1835 (protection of N3 of pyrimidine nucleosides).

(5) For the formation of cyclic acetals via conjugate addition (of alkoxide to $\text{O}-\text{CH}=\text{CH}-\text{COOMe}$), see: Evans, P. A.; Garber, L. T. *Tetrahedron Lett.* **1996**, *37*, 2927.

(6) For the formation of cyclic acetals from dialkoxides and 1,2-bis-(phenylsulfonyl)ethene, see: Chéry, F.; Rollin, P.; De Lucchi, O.; Cossu, S. *Tetrahedron Lett.* **2000**, *41*, 2357, and references therein.

behavior, as they are quite stable to acidic media while they can be cleaved with strong bases.

When, in a series of parallel experiments, (*S,S*)-1,2-diphenyl-1,2-ethanediol (**1**) was treated with 1.1 equiv of *tert*-butyl propynoate in CH₃CN at rt, in the presence of 0.5 equiv of 4-dimethylaminopyridine, triethylamine, or *N*-ethyl-diisopropylamine, *O*-substituted derivatives were formed at rates decreasing in this order. Thus, the experiment with DMAP gave 97% of acetal **1a** within 30 min (Table 1, entry

Table 1. Reaction of Diols with *tert*-Butyl Propynoate (1.1 equiv) and DMAP (0.5 equiv) in CH₃CN at Room Temperature,^a unless Otherwise Indicated

Entry	Diol	Time	Acetal	Yield, %
1		30 min		97
2		45 min		94 ^b
3		30 min	 	55 35
4		90 min	 	60 30
5 ^c		60 min	 	70 25
6		120 min ^d		90

^a At 0.1 M substrate concentrations. ^b Similar results in THF and in CH₂Cl₂. ^c 2.2 equiv of *tert*-butyl propynoate was used. ^d In DMF, with 2 equiv of *tert*-butyl propynoate; in CH₃CN (where **6** is scarcely soluble), with only 1.1 equiv of reagent, the yield was 99%, but 24 h was required to complete the reaction.

1), Et₃N required 1–2 h to complete the acetal formation, while the catalytic activity of *N*-ethyl-diisopropylamine was very low. Without base, no reaction took place, even in refluxing CH₃CN. With Me₃P or with Bu₃P,² the acetal yields never exceeded 50%. The *meso* form of 1,2-diphenyl-1,2-ethanediol (**2**) reacted similarly with *tert*-butyl propynoate to afford 94% of the acetal **2a** (Table 1, entry 2), with the “Bocdene” group *cis* to the phenyl groups, as shown by a NOESY experiment (in CDCl₃ at 500 MHz, summarized in Figure 1). 1-Phenyl-1,2-ethanediol (**3**), *cis*-1,2-cyclopentanediol (**4**),⁷ and 5'-*O*-trityluridine (**5**) gave the two possible stereoisomers. In general, the presence of epimers is a well-known handicap of ethylidene acetals, benzylidene acetals,

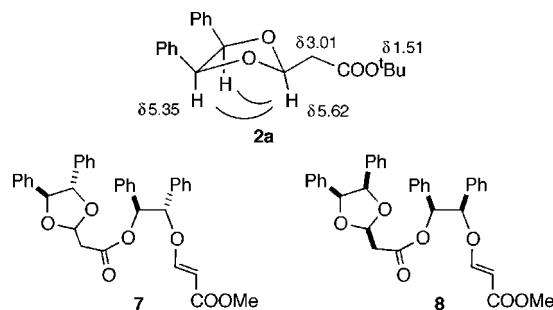
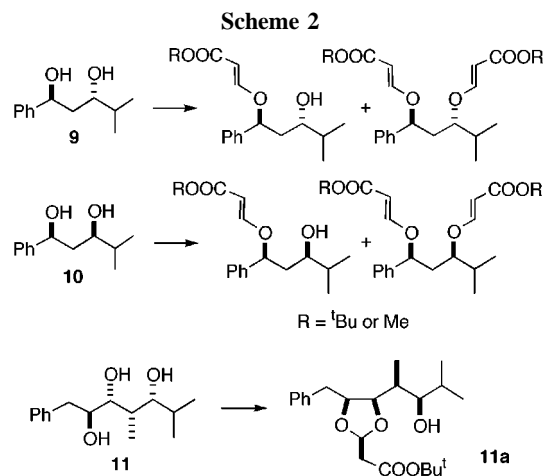


Figure 1. NOE noted in **2a**. Byproducts **7** and **8** (of the reactions of **1** and **2**, respectively, with methyl propynoate and DMAP at rt).

THP derivatives, etc.,⁸ as a new stereocenter is created during the protection step, but organic chemists are used to managing these cases. Finally, the diisopropylidene acetal of D-mannitol (**6**) afforded **6a** in excellent yield (Table 1, entry 6).

Methyl propynoate was also investigated as an alternative to *tert*-butyl propynoate, the corresponding “Mocdene” acetals forming equally well in most cases, with similar stereoselectivities. However, some byproducts were isolated in 15–25% yields, such as **7** (from **1**) and (±)-**8** (from **2**). Nevertheless, it sufficed to carry out the reactions between –20 and 0 °C, instead of at rt, to avoid the appearance of these transesterification byproducts.

1,3-Diols **9** and **10** did not afford the corresponding six-membered cyclic acetals but mixtures of mono-Bocvinyl and bis-Bocvinyl derivatives, or of the mono-Mocvinyl and bis-Mocvinyl derivatives (see Scheme 2), under our reaction



conditions (in which no alkoxide ions are involved⁵). With a large excess of alkyl propynoates, only the bis-derivatives

(7) As expected, no cyclized product was observed in the case of *trans*-1,2-cyclopentanediol.

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

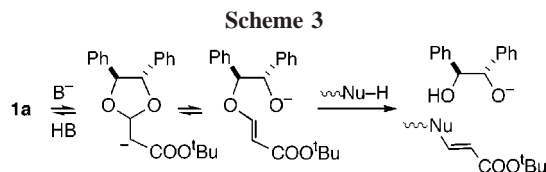
were obtained. 1,2-Benzenedimethanol (a 1,4-diol) did not give a seven-membered cyclic acetal, either. Therefore, 1,3- and 1,4-diols did not show any trend to form “Bocdene” or “Mocdene” acetals. It means that, in polyol systems, five-membered rings (dioxolanes) can be selectively obtained with respect to six- (dioxanes) and seven-membered (dioxepanes) rings. To check this assumption, triol **11**⁹ was treated with 1.1 equiv of *tert*-butyl propynoate and 0.5 equiv of DMAP in CH₃CN at rt for 90 min: **11a** was formed exclusively (as indicated by TLC) and was isolated in 91% yield.

Stability of “Bocdene” and “Mocdene” Acetals to Acids Is Noteworthy. The usual mechanism of acetal hydrolysis through protonation of one oxygen atom, cleavage of one C—O bond to give an oxonium-like cation, and so on (i.e., the reversal of the acid-catalyzed acetal formation) does not work in these acetals; it is likely that the alkoxycarbonyl group (like other EWG)⁶ disfavors the first two steps. The results of the hydrolysis experiments may be summarized as follows: (i) at rt, “Bocdene” and “Mocdene” acetals are stable against AcOH/H₂O, 1 M HCl/THF, and TsOH/MeOH;⁸ in practice we hydrolyzed quantitatively the isopropylidene acetals of **6a** with 70:30 AcOH/H₂O without touching at all its “Bocdene” acetal; (ii) on heating at 65 °C for 5 days in 80:20 AcOH/H₂O, the *tert*-butyl ester group of **1a** is hydrolyzed to carboxylic acid (95% yield) but no further hydrolysis is detected; (iii) with 5 equiv of TFA in CH₂Cl₂ at rt, conversion of the *tert*-butyl ester of **1a** into the carboxyl group is completed in a few days, but the acetal group remains; and (iv) on heating for 1 day in refluxing MeOH, in the presence of 1 equiv of TsOH or camphorsulfonic acid, only the expected transesterification, of *tert*-butyl to methyl ester, is observed for **1a**–**3a**, while no change occurs with the corresponding “Mocdene” acetals, even with a larger excess of TsOH.

In short, the *tert*-butyl ester of “Bocdene”, although it is less reactive than standard Boc groups, may be eventually removed by forcing the reaction conditions, but the acetal function stands. Only when the carboxylic acid arising from **1a** was heated in refluxing 2 M HCl/THF for 3–4 days we were able to recover 60% of diol **1**, accompanied by byproducts. To summarize, acidic hydrolysis of “Bocdene” and “Mocdene” acetals, to recover the diol, is difficult and not useful in practice.

(9) Esteve, C.; Ferreró, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1999**, *40*, 5079. Esteve, C. Masters Thesis, Universitat de Barcelona, 1999.

Deprotection of “Bocdene” and “Mocdene” Acetals Can Be Accomplished with a Base. Our hypothesis was that a base was needed to produce the elimination that would yield the Bocvinyl intermediate (Scheme 3), which could



be cleaved⁴ in situ by a good nucleophile such as pyrrolidine via an addition–elimination mechanism. In practice, treatment of **1a** with pyrrolidine (5.0 equiv) and butyllithium (2.0–2.5 equiv) in THF for 16 h at rt afforded **1** in 85–90% yields. Compound **2a** was similarly converted into diol **2**. Deprotection can also be achieved by an alternative procedure: by heating in a water bath the **3a/3b** mixture with neat pyrrolidine, 93% of **3** was recovered. Similarly, heating of **6a** in neat pyrrolidine yielded **6** in 94% yield.

In conclusion, via conjugate (hetero-Michael) additions, with nucleophilic and basic catalysis, 1,2-diols have been converted into “Bocdene” and “Mocdene” acetals in excellent yields. Though the scope of these protecting groups (and related NuNu’CHCH₂-EWG systems) deserves to be studied further, we have shown that the use of appropriate bases is the method of choice for leading the reverse reaction to completion. The rule that acetals are formed and cleaved under acid catalysis, while being stable to bases, does not work here: it has been overturned by the electronic effect of the substituent.

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Supporting Information Available: Typical procedures for protection and deprotection and spectral data for compounds **1a**, **2a**, **3a**, **3b**, **4a**, **4b**, **5a**, **5b**, **6a**, and **11a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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