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DMOBO: An Improvement on the OBO Orthoester Protecting Group

José-Luis Giner

Department of Chemistry, SUNY-ESF, Syracuse, New York 13210

jlginer@syr.edu

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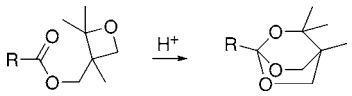
ABSTRACT

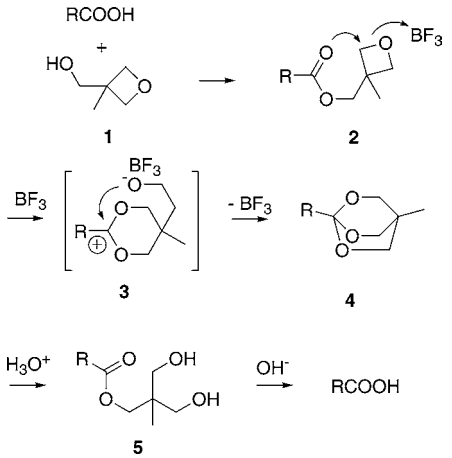


Conversion of a carboxylic acid to an orthoester provides protection toward nucleophiles and strong bases. The addition of methyl substituents to the oxetane precursor of the commonly used [2.2.2]-bicyclic OBO orthoester significantly increased the ease of orthoester formation and its resistance to hydrolysis. NMR kinetics show the DMOBO protecting group is formed 85 times faster than the OBO group, and that its stability toward aqueous hydrolysis is 36 times greater. Nucleophilic attack of the ester carbonyl on the oxetane ring was shown by ^{18}O-labeling to take place at the most substituted position.

The generation of an orthoester provides an effective way of protecting carboxylic acids and esters.[1] Analogous to the protection of a ketone as a ketal, the masking of the carboxylate carbonyl group as an orthoester confers stability to nucleophilic reagents, as well as toward base-promoted enolization. However, orthoesters cannot be prepared by the methods used for ketal formation, and other approaches are necessary. A general procedure for the protection of carboxylic acids as [2.2.2]-bicyclic orthoesters has been developed by Corey and Raju.[2] This method consists of the esterification of the carboxylic acid with 3-hydroxymethyl-3-methyloxetane (**1**), followed by Lewis acid-catalyzed rearrangement of the resulting oxetanyl ester **2** (Scheme 1). Although the OBO orthoester **4** is much more stable to acid-catalyzed hydrolysis than an acyclic orthoester, the carboxylic acid is easily recovered by mild acidic hydrolysis, followed by saponification of the resulting ester **5**.

More recently, an alternative [3.2.1]-bicyclic orthoester protecting group named ABO (**8**) has been described by Wipf and co-workers.[3] As part of our investigation of the epoxy ester−orthoester rearrangement,[4] we recently published a mechanistic study that demonstrates that the zirconocene reagent used by Wipf can be conveniently replaced with protic acids such as TFA (Scheme 2).[5] In addition, we determined that the rate of formation of **8** is 22 000 times greater than the formation of the OBO orthoester **4**, and that it is twice as stable toward acid hydrolysis as **4**. One

Scheme 1. Protection and Deprotection of a Carboxylic Acid as an OBO Orthoester, Shown for BF_3 Catalysis



(1) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 437−441. (b) Kocienski, P. J. *Protecting Groups*; Thieme: New York, 2000; pp 145−148.

(2) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571−5574.

(3) (a) Wipf, P.; Xu, W.; Kim, H.; Takahashi, H. *Tetrahedron* **1997**, *53*, 16575−16596. (b) Wipf, P.; Tsuchimoto, T.; Takahashi, H. *Pure Appl. Chem.* **1999**, *71*, 415−421.

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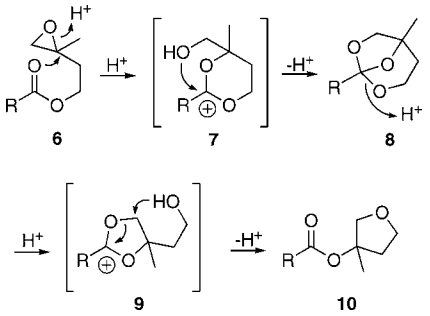
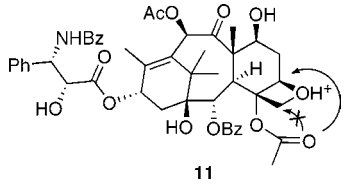
Scheme 2. Mechanism of Formation and Rearrangement of the ABO Orthoester, Shown for Protic Acid Catalysis



disadvantage of using [3.2.1]-bicyclic orthoesters such as **8** is the formation of 3-acyloxytetrahydrofuran side products (**10**).[3b] However, we have shown that THF **10** is formed from orthoester **8** via the dioxolanium ion (**9**), rather than directly from the epoxy ester **6**, and that its rate of formation is nearly 1000 times slower than that of the orthoester (**8**).[5] Therefore, by controlling the concentration of the acid catalyst and the time, this reaction can be minimized. In some cases, cyclic ether formation may actually be advantageous, since it provides a method of deprotection that does not involve aqueous acid.[3] Perhaps the greatest disadvantage of [3.2.1]-bicyclic orthoesters as a protecting groups compared to [2.2.2]-bicyclic orthoesters is that they are intrinsically chiral. This results in diastereomeric product mixtures if the carboxylic acid is also chiral, which is often the case in natural products synthesis. Although this problem can be solved by using an enantiomerically pure epoxide to generate a homochiral orthoester,[3] this approach is impractical.

We recently noted that taxol oxetanyl ester rearranges under acidic conditions with inversion at the more substituted center of the oxetane (Scheme 3).[4d] This phenomenon is

Scheme 3. Rearrangement of the Taxol Oxetane, Shown for Protic Acid Catalysis

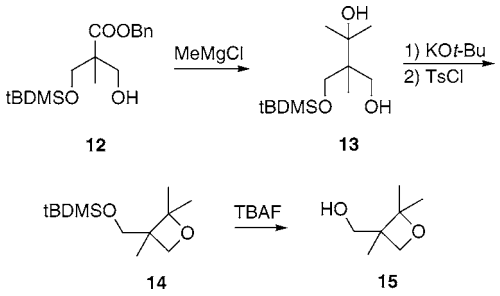


similar to the situation encountered with epoxides, where alkyl substitution increases the reactivity by stabilizing carbocationic character in the protonated epoxy intermediate.[6]

Applying this effect to enhance the reactivity of the oxetane precursor should make it possible to prepare [2.2.2]-bicyclic orthoesters under much milder conditions.

To test this hypothesis, alkyl substituents were added to the oxetane ring of OBO precursor **1**. Dimethyl-substituted oxetanyl alcohol **15** was prepared from 2,2-bis(hydroxymethyl)propionic acid via its benzyl ester tBDMS ether **12**[7] (Scheme 4). Introduction of the methyl groups with a

Scheme 4. Synthesis of 3-Hydroxymethyl-2,2,3-trimethyloxetane (**15**)



Grignard reagent, followed by Williamson ether synthesis and desilylation provided rapid access to the desired product (**15**). The oxetane ring was prepared in a modification of a one-pot procedure[8] in which 2 equiv of KOt-Bu were added to diol **13**, followed immediately by 1 equiv of tosyl chloride. The dimethyl oxetanyl alcohol (**15**) thus obtained was esterified with dihydrocinnamic acid and the reactivity of oxetanyl ester **16** was compared with the corresponding OBO precursor **18**.

The rates of reaction of the two orthoester precursors (**16** and **18**) were measured simultaneously by ^{1}H NMR kinetics to ensure identical conditions (Figure 1). Treatment of a mixed sample of **16** and **18** with 0.2 mM BF_3 etherate in $CDCl_3$ resulted in the rapid reaction of the dimethyl-substituted oxetane **16** and the much slower reaction of the OBO precursor **18** (Figure 1, graph a). Under these reaction conditions, the BF_3 reagent appeared to decompose as shown by steadily decreasing rates over time. However, useful data were obtained from the initial 10 min of the reaction, which indicated a 20-fold greater reactivity for **16**. A more accurate comparison was obtained with TFA catalysis by using a reactivity scale that we previously established (Figure 1, graph b).[5] In this experiment, the formation of the dimethyl-substituted OBO (DMOBO) orthoester **17** could be shown to be 85 times faster than that of the OBO orthoester **19**, since the reaction of **20** was 1.8 times faster than that of **16**, and **20** had been found to be 160 times more reactive than **18**.[5]

The stability of the OBO and DMOBO orthoesters **17** and **19** toward aqueous acid was measured by comparing their rates of hydrolysis at pH 4.75 (Figure 1, graph c). Under

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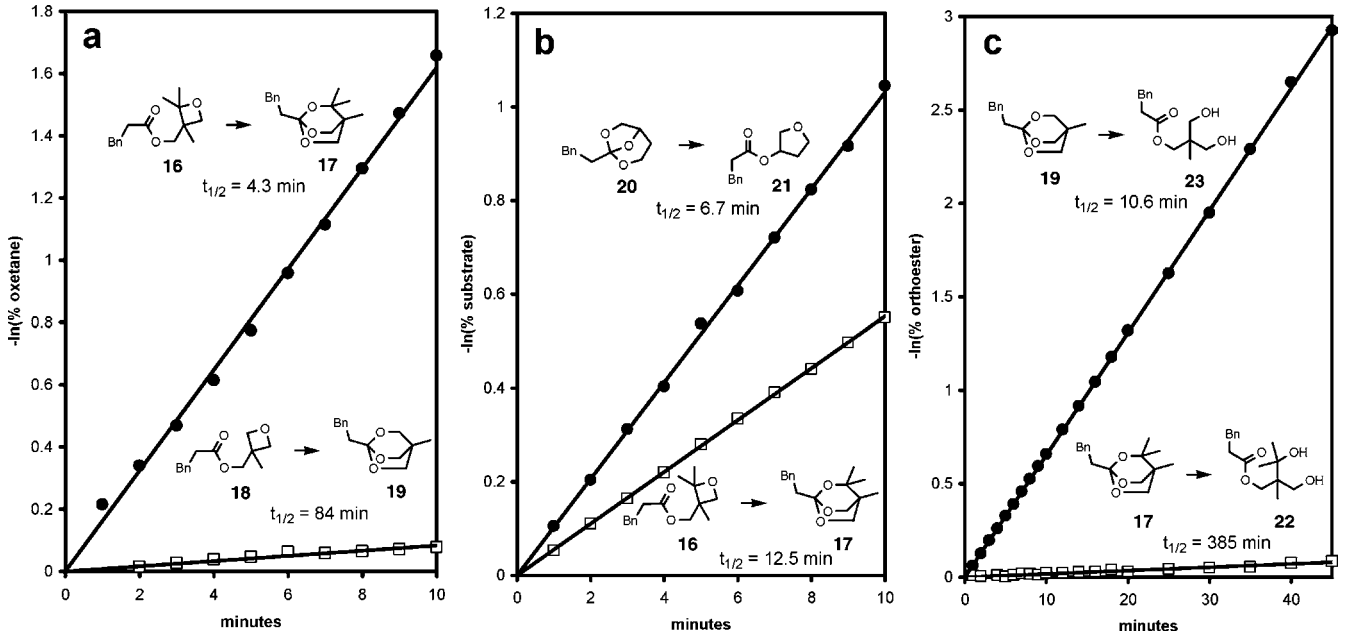

Figure 1. Comparative rates of the formation and hydrolysis of DMOBO and OBO measured by 600-MHz ^{1}H NMR at 30 °C: (a) rearrangement of **16** and **18** in 0.2 mM $BF_3-Et_2O/CDCl_3$; (b) rearrangement of **16** and [3.2.1]bicyclic orthoester **20** in 40 mM TFA/$CDCl_3$; and (c) hydrolysis of **17** and **19** in 50 mM NaOAc/D_2O at pH 7.5, buffer/acetone-d_6 1:2.

these conditions, the DMOBO orthoester (**17**) is 36 times more stable than the OBO orthoester (**19**).

The enhanced reactivity of oxetane **16** was predicted based on the hypothetical activating effect of the dimethyl substituents. To prove this and to show that the reaction is initiated at the more highly substituted position of the oxetane, an ^{18}O-labeling experiment was carried out. Isomerization of ester **16** bearing 55 atom % in the carbonyl oxygen yielded a sample of the DMOBO orthoester **17** in which all of the label was located at the oxygen connected to the dimethyl-substituted site (Figure 2). This result demonstrates that the reactivity of an oxetane ring toward nucleophiles under acidic conditions is enhanced by alkyl substituents adjacent to the ring oxygen atom, in much the same way as it is in epoxides.[6]

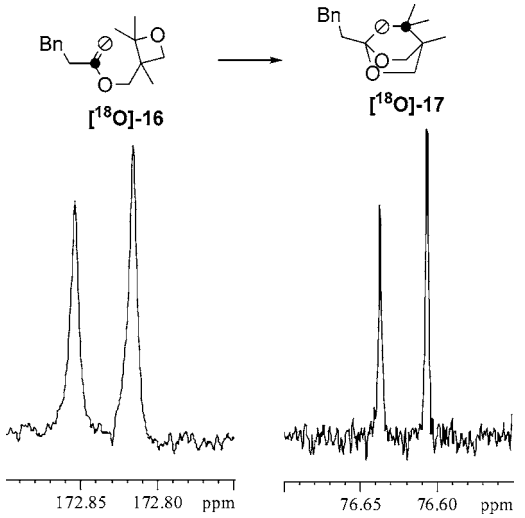

Figure 2. ^{18}O-labeling experiment. The location of the label is shown by 151-MHz ^{13}C NMR. Signals of carbon atoms are shifted due to the presence of 55% ^{18}O (the signal of the ^{18}O-labeled carbon is the one on the right of each pair): ● = observed carbon atom; ∅ = location of ^{18}O.

Because it can be prepared under much milder conditions, and because it is considerably more stable toward hydrolysis, the DMOBO orthoester represents an improvement on the OBO protecting group. Compared to the ABO protecting group, formation of the DMOBO group requires significantly stronger conditions, but it is much more stable to hydrolysis. Furthermore, it is not chiral, nor is it subject to further rearrangement. These advantageous properties of the DMOBO group suggest that it is likely to find application in protecting group strategies for the synthesis of complex organic molecules. Efforts to develop a more efficient synthesis of the DMOBO precursor **15** are underway.

Supporting Information Available: Experimental details, diagrams of rearrangement kinetics, and ^{13}C NMR spectra of ^{18}O-labeled compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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