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Synthesis of Tetrahydrofurans from Protected β-Hydroxyaldehydes: Optimization of the Alcohol Protecting Group

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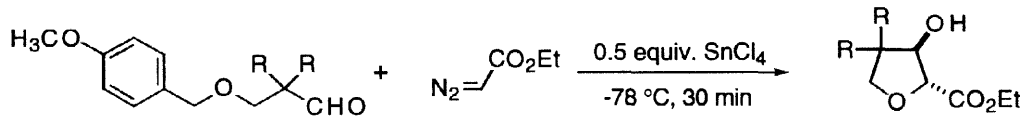
Abstract: As part of an effort to generalize the synthesis of substituted tetrahydrofurans from protected β-hydroxy aldehydes, a series of common alcohol protecting groups was screened for compatibility with the methodology. Employing a β-(triisopropylsilyloxy)aldehyde resulted in a low yield of tetrahydrofuran, while the other protecting groups all afforded good yields of tetrahydrofurans.

We have recently reported a new method for the synthesis of substituted tetrahydrofurans which involves condensation of a protected β-hydroxy aldehyde with ethyl diazoacetate.[1] We examined several different aldehydes and found that most of them afford tetrahydrofurans in 50-95% yield. For example, treatment of β-benzyloxyaldehyde **1a** with ethyl diazoacetate afforded THF **2a** in 84% yield as a single stereoisomer (eq. 1). However, aldehyde **1b** afforded only small amounts of THF product **2b.**

(eq. 1)



1a, R = Me
1b, R = H

2a (84%)
2b (>5%)

We have continued to explore this interesting reaction from both a mechanistic and synthetic perspective and found it to be extremely sensitive to the purity of the ethyl diazoacetate and stannic chloride. Accordingly, we sought to develop a general protocol for the synthesis of tetrahydrofurans by optimizing the alcohol protecting group.

The first problem we addressed was the purity of the ethyl diazoacetate. After considering the dangers associated with distillation of this potentially explosive compound,[2] we elected to prepare benzyl diazoacetate.[2b] Diazotization of benzyl glycine followed by flash chromatography afforded benzyl diazoacetate that was homogeneous by ^{1}H NMR and TLC analysis.

The second problem addressed was the oxygen protecting group. While β-benzyloxy aldehydes normally afforded tetrahydrofuran products in reasonable yields, several reactions of

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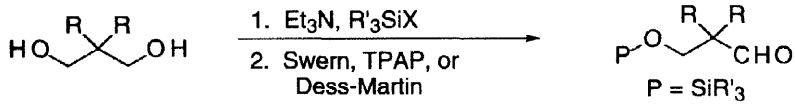
these substrates led to complex mixtures of products. We attributed these by-products to polymerization of benzylic cations formed in the reaction.[3] In an effort to eliminate this complication and hopefully enhance the generality of the methodology, we decided to systematically study a range of silyl protecting groups on the β-hydroxy aldehydes **5** and **6** (eq. 2). Aldehydes **5** and **6** represent the best and worst substrates in the THF synthesis with a *p*-methoxybenzyl protecting group as shown in equation 1.

Several of the requisite β-alkoxypropanals **5** and **6** were easily prepared from commercially available 1,3-propanediols **3** and **4** in two steps (eq. 2). Monoprotection of diol **3** with an appropriate chlorosilane, or silyltriflate,[4] followed by oxidation gave good to moderate yields of the β-alkoxypropanals **5**. The preparation and isolation of aldehydes **6** were somewhat problematic; these volatile compounds were sensitive to both acid and base. Monoprotection of **4** followed by oxidation under Swern conditions[5] or with TPAP[6] led to rapid decomposition of the aldehyde products, presumably through retro-Michael reactions. However, oxidation with Dess-Martin periodinane[7] afforded good yields of aldehydes **6** in all but one case, 3-(trimethylsilyl)oxypropanal (**6**, P = $Si(CH_3)_3$).[8]

(eq. 2)



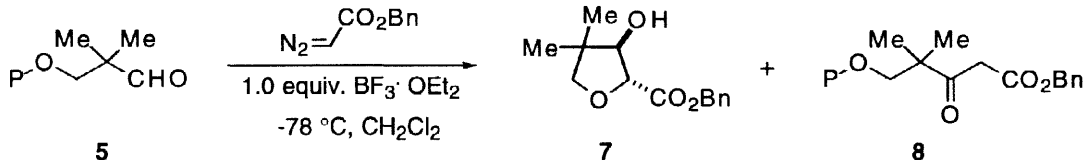
3, R = Me
4, R = H

5, R = Me
6, R = H

The results for aldehydes **5** are shown in Table 1. A survey of Lewis acids showed boron trifluoride etherate to be slightly superior to the other Lewis acids examined ($TiCl_4$, Et_2AlCl, $EtAlCl_2$, $SnCl_4$, $ZrCl_4$). The trimethylsilyl and triethylsilyl protecting groups (Table 1, entries 1 and 2) gave the highest yield of THF **7** with a minimal amount of β-keto ester **8**.[9-11] In the case of the trimethylsilyl protecting group, we were not able to observe any β-keto ester in the ^1H NMR spectrum of the crude reaction mixture. In the case of the triethylsilyl protecting group, the β-keto ester was isolated in 5% yield. The trimethylsilylethyl and *t*-butyldimethylsilyl protecting groups (Table 1, entries 3 and 4) also gave comparable yields of **7** with only a slight increase in the yield of **8**. Employing a triisopropylsilyl protecting group resulted in a dramatic increase in the amount of β-keto ester isolated (43%; Table 1, entry 5) with a corresponding decrease in the amount of THF isolated. An important trend is shown in Table 1: increasing the steric bulk around silicon

resulted in a decrease in the yield of THF **7** and an increase in the yield of β-keto ester **8**. It is also important to note that THF **7**, possessing a *trans*-orientation between the ester and alcohol groups,[12] was the only diastereomer formed in the reaction; none of the corresponding *cis*-diastereomer was isolated.

Table 1.



Entry	Protecting Group (P)	% Yield 7[a]	% Yield 8[a]
1	Me_3Si	82	[b]
2	Et_3Si	76	5
3	$Me_3SiCH_2CH_2$	70	<7[c]
4	*t*-$BuMe_2Si$	70	11[c]
5	*i*-Pr_3Si	36	43

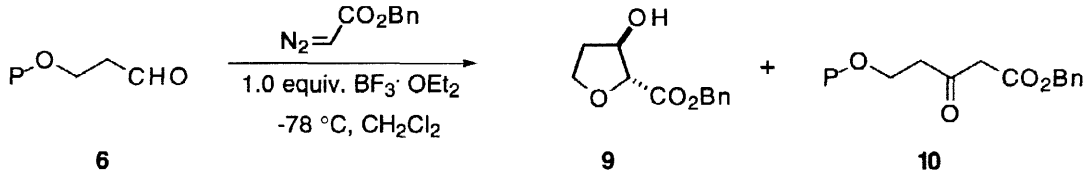
[a] Isolated yields after chromatography. [b] Unable to detect by ^1H NMR. [c] Yield determined by ^1H NMR.

The results for the reaction of aldehydes **6** with benzyl diazoacetate are given in Table 2. The use of the silyl protecting groups provided a great advantage with this substrate. Reaction of **6** under our previous conditions,[1] P = PMB (Table 2, entry 1; $SnCl_4$ used in place of BF_3•OEt_2), afforded THF **9** in 5% yield. When a triethylsilyl group was employed (entry 2) a 30% yield of THF **9** was obtained. While the yields of THF products were considerably lower than for the α,α-dimethylaldehyde **5**, the THF was isolated albeit in modest yields. The low yields were likely due to the instability of aldehydes **6**. The trimethylsilylethyl protecting group gave the highest yield of **9**, 33%, along with 5% of β-keto ester **10**. Increasing the steric bulk around silicon resulted in a decrease in the yield of THF **9** and an increase in the yield of β-keto ester **10**, consistent with the results in Table 1. The *t*-butyldimethylsilyl protected alcohol (Table 2, entry 4) afforded THF **9** in 22% yield and **10** in 15% yield. The triisopropylsilyl ether (Table 2, entry 5) afforded THF **9** in 11% yield and **10** in 25% yield. The product THF, **9**, was a single diastereomer by ^1H and ^{13}C NMR analysis.[13]

In summary, we have shown that trimethylsilyl, triethylsilyl, *t*-butyldimethylsilyl, and 2-(trimethylsilyl)ethyl ethers can be used in this novel THF synthesis. The yield of THF products decreases with increasing steric bulk about the silicon. The implication of these results on the

reaction mechanism is currently under investigation. In addition, benzyl diazoacetate proved to be a reliable source of diazoester for the reaction.

Table 2.



6 9 10

Entry	Protecting Group (P)	% Yield 9[a]	% Yield 10[a]
1	(p-OCH_3)$C_6H_4CH_2$[b]	5	<5[c]
2	Et_3Si	30	<5[c]
3	$Me_3SiCH_2CH_2$	33	5
4	t-$BuMe_2Si$	22	15[c]
5	i-Pr_3Si	11	25

[a]Isolated yields after chromatography. [b]$SnCl_4$ was used, not BF_3·OEt_2. [c] Yield determined by ^1H NMR.

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References and Notes

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7. (a) For preparation of Dess-Martin periodinane see: Ireland R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899. (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156.
8. Monoprotection of **4** with chlorotrimethylsilane followed by oxidation with Dess-Martin periodinane gave 3-(trimethylsilyl)oxypropanal (**6**, P = $Si(CH_3)_3$) in 0.7% yield. Attempts to improve the yield by other oxidation methods failed.
9. All new compounds were homogeneous by chromatography and were characterized by ^1H NMR, ^{13}C NMR, IR, MS, and HRMS.
10. Formation of the β-keto ester is due to a competitive Roskamp homologation, see: (a) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258-3260. (b) Holmquist, C. R.; Roskamp, E. J. *Tetrahedron Lett.* **1992**, *33*, 1131-1134.
11. General experimental procedure: Boron trifluoride etherate was added over 30 min to a -78 °C solution of protected β-hydroxy propanal (1.0 mmol) and benzyl diazoacetate (1.1 mmol) in CH_2Cl_2 (0.2 M). The reaction was followed by TLC until no starting material was detected (1 h). The reaction was then poured into a stirred solution of saturated $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. Drying ($MgSO_4$) and concentration afforded crude product(s). Flash chromatography on silica gel (ethyl acetate or ethyl ether/hexane mixtures) gave product(s) in the yields shown.
12. The stereochemistry of **7** was assigned based on coupling constant correlation to a previously reported ethyl ester derivative, see reference 1.
13. Stereochemistry of **9** was determined by reduction to the diol and comparison of the spectral data with those reported in the literature: Placec, J.; Tong, W.; Chattopadhyaya, J. *J. Am. Chem. Soc.* **1993**, *115*, 9734-9746.