Stereoselective Synthesis of Tetrahydrofurans *via* the Lewis Acid Promoted Reaction of β-Benzyloxy Aldehydes and Ethyl Diazoacetate

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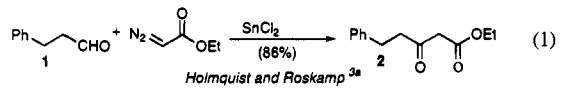
During the course of unrelated work on the synthesis of (+)-pancratistatin, we discovered a new method for the stereoselective synthesis of tetrahydrofurans.[1] The wide occurrence of natural products possessing tetrahydrofuran subunits led us to explore the scope and limitations of this reaction. We report here our initial studies of this new methodology.[2]

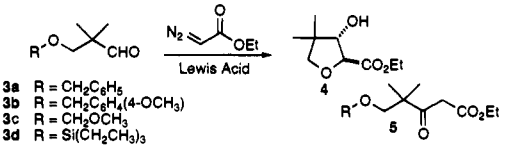
Roskamp and co-workers have reported the efficient homologation of aldehydes to β-keto esters upon treatment with ethyl diazoacetate and stannous chloride (eq 1).[3,4] We found that when this reaction is carried out on a β-benzyloxy aldehyde, a tetrahydrofuran product is also formed. In spite of the high yield of β-keto esters in the Roskamp homologation, we have optimized the reaction conditions such that tetrahydrofurans can be prepared in high yield.[5,6]



(1)

A study of the factors affecting the ratio of tetrahydrofuran to β-keto ester products is presented in Table 1. Treatment of a methylene chloride solution of **3** (0.125 M) and ethyl diazoacetate (2.0 equiv) with the appropriate Lewis acid afforded tetrahydrofuran **4**, β-keto ester **5**, or mixtures of the two. Analysis of the crude reaction mixtures by ^{1}H NMR and TLC showed that they consisted of **4**, **5**, and unreacted starting materials, with little or no side products. It is interesting to note that **4** is obtained as a single diastereomer in every case examined.[7,8]

Table 1. Tetrahydrofuran Annulation with Aldehyde **3** and Ethyl Diazoacetate



entry	SM	Lewis acid	(equiv)	temp, °C	time, h	product (yield, %)[a]	
1	**3a**	$TiCl_4$	(0.5)	−78	0.5 h	**4** (44)	**5a** (13)
2	**3a**	$TiCl_4$	(1.1)	−78	0.5 h	**4** (60)	**5a** (18)
3	**3a**	$SnCl_4$	(0.5)	−78	0.5 h	**4** (76)	**5a** (12)
4	**3a**	$ZrCl_4$	(0.5)	−78	3 h	**4** (50)[b]	
5	**3b**	$SnCl_4$	(0.2)	−78	2 h	**4** (76)	**5b** (12)
6	**3b**	$SnCl_4$	(0.5)	−78	0.5 h	**4** (84)	
7	**3b**	$SnCl_4$	(1.0)	−78	0.5 h	**4** (59)	
8	**3b**	$SnCl_2$	(2.0)	−78 to rt[c]	10 h		**5b** (45)
9	**3b**	$BF_3{\cdot}OEt_2$	(0.2)	−78	0.5 h	**4** (34)	**5b** (15)
10	**3c**	$SnCl_4$	(0.5)	−78	0.5 h	**4** (60)	
11	**3d**	$SnCl_4$	(0.5)	−78	0.5 h	**4** (81)[d]	

[a] For conditions, see general experimental (footnote 8). [b] Three equivalents of ethyldiazoacetate was used. [c] Room temperature. [d] The crude product, which consisted of a mixture of silyl ether and alcohol, was treated with pyridine−HF to afford the indicated yield of product.

Treatment of **3a** and ethyl diazoacetate with 0.5 equiv of $TiCl_4$ afforded **4** in 44%, **5a** in 13% yield, and recovered **3a** in 37% yield (Table 1, entry 1). After accounting for recovered starting material the yields of **4** and **5a** were 70% and 21%, respectively. Increasing the amount of $TiCl_4$ to 1.1 equiv led to the production of **4** in 60% yield and recovered **3a** in approximately 20% yield (entry 2). Employing $SnCl_4$ (0.5 equiv) at −78 °C led to the isolation of tetrahydrofuran **4** in 76% yield and β-keto ester **5a** in 12% yield (entry 3). Using 0.5 equiv of $ZrCl_4$ (entry 4), 3.0 equiv of ethyl diazoacetate, and 3 h reaction time at −78 °C afforded **4** in 50% yield and unreacted starting material (40%). No β-keto ester was observed by ^{1}H NMR analysis.

It seemed likely that a benzyl ether with an electron-rich aromatic ring would increase the yield of tetrahydrofuran product. Accordingly, a *p*-methoxybenzyl group (**3b**) was examined (Table 1, entries 5−9). Again, $SnCl_4$ proved to be the optimal Lewis acid, and the yield of tetrahydrofuran vs amount of $SnCl_4$ was briefly examined (Table 1, entries 5−7). Entry 6 shows that the optimum conditions were 0.5 molar equiv of $SnCl_4$, which afforded **4** in 84% yield. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy showed that less

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(2) For recent leading references on the synthesis of tetrahydrofurans, see: (a) Burke, S. D.; Jung, K. W. *Tetrahedron Lett.* **1994**, *35*, 5837−5840. (b) Bugianesi, R. L.; Ponpipom, M. M.; Parsons, W. H.; Hwang, S.-B.; Doebber, T. W.; Lam, M.-H.; Wu, M. S.; Alberts, A. W.; Chabala, J. C. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 181−184. (c) Aller, E.; Cox, G. G.; Miller, D. J.; Moody, C. J. *Tetrahedron Lett.* **1994**, *35*, 5949−5952. (d) Carless, H. A. J.; Swan, D. I.; Haywood, D. J. *Tetrahedron* **1993**, *49*, 1665−1674. (e) Cerè, V.; Mazzini, C.; Paolucci, C.; Pollicino, S.; Fava, A. *J. Org. Chem.* **1993**, *58*, 4567−4571. (f) Grese, T. A.; Hutchinson, K. D.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468−2477. (g) Guindon, Y.; Yoakim, C.; Gorys, V.; Ogilvie, W. W.; Delorme, D.; Renaud, J.; Robinson, G.; Lavallée, J.-F.; Slassi, A.; Jung, G.; Rancourt, J. *J. Org. Chem.* **1994**, *59*, 1166−1178. (h) Kang, S. H.; Lee, S. B. *Tetrahedron Lett.* **1993**, *34*, 7579−7582. (i) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868−9870. (j) Rao, A. V. R.; Reddy, K. L. N.; Reddy, K. A. *Indian J. Chem., Sect. B* **1993**, *32*, 1203−1208. (k) Zhao, Y.; Quayle, P. *Tetrahedron Lett.* **1994**, *35*, 4179−4182.

(3) (a) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258−3260. (b) For a similar reaction with diazo sulfones and diazo phosphine oxides, see: Holmquist, C. R.; Roskamp, E. J. *Tetrahedron Lett.* **1992**, *33*, 1131−1134. (c) For a related reaction, see: Padwa, A.; Hornbuckle, S. F.; Zhang, Z.; Zhi, L. *J. Org. Chem.* **1990**, *55*, 5297−5299.

(4) For applications of the Roskamp homologation, see: (a) Hecker, S. J.; Werner, K. M. *J. Org. Chem.* **1993**, *58*, 1762−1765. (b) Nomura, K.; Iida, T.; Hori, K.; Yoshii, E. *J. Org. Chem.* **1994**, *59*, 488−490. (c) Meyer, S., D.; Miwa, T.; Nakatsuka, M.; Schreiber, S. L. *J. Org. Chem.* **1992**, *57*, 5058−5060.

(5) For a recent review of diazocarbonyl compounds, see: Ye, T.; McKervey, A. *Chem. Rev.* **1994**, *94*, 1091−1160.

(6) For reactions in which an *O*-nucleophile reacts with an α-diazocarbonyl compound, see: (a) Marshall, J. R.; Walker, J. *J. Chem. Soc.* **1952**, 467−475. (b) Canet, J.-L.; Fadel, A.; Salaün, J. *J. Org. Chem.* **1992**, *57*, 3463−3473. (c) Brouwer, A. C.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1975**, 807−810.

(7) The stereochemistry of 4 and **11** was assigned by reduction to the alcohol ($LiAlH_4$) and formation of the acetonides. See supporting information for details. Tetrahydrofuran **11** is an inseparable 8.1:1 (^{1}H NMR integration vs impurity; see supporting information for details) mixture of two compounds. The minor component may be a diastereomer of **11** or some other byproduct. Resubmission of 4 to the reaction conditions afforded recovered 4 (>95% mass recovery).

(8) General experimental procedure: Ethyl diazoacetate (2 mmol) and $SnCl_4$ (0.5 mmol) were sequentially added to a stirred −78 °C solution of aldehyde (1 mmol) in CH_2Cl_2 (0.125 M). The reaction was followed by TLC until starting material was no longer detected (30 min), and then the reaction mixture was poured into a stirred solution of $NaHCO_3$. After being stirred for 5 min, the reaction mixture was diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (2×), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to afford crude product. Flash chromatography on silica gel (230−400 mesh; ethyl acetate/hexane mixtures) afforded product(s) in the yields shown.

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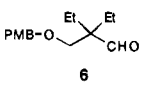
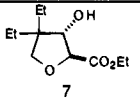
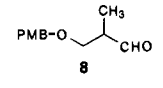
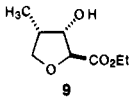
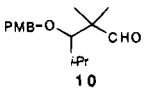
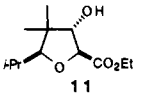
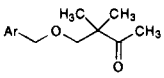
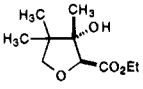
Table 2. Tetrahydrofuran Synthesis from Aldehydes and Ketones[a]

Entry	Aldehyde/Ketone	Conds.	Furan	Yield
1	 **6**	0.5 equiv. $SnCl_4$ -78 °C, 1 h -30 °C, 0.5 h	 **7**	(77%)
2	 **8**	0.5 equiv. $SnCl_4$ -78 °C, 0.5 h	 **9**	(75%)
3	 **10**	0.5 equiv. $SnCl_4$ -78 °C, 8 h 0 °C to rt, 12 h	 **11**	(78%)
		1.0 equiv. $ZrCl_4$		
4	**12a** Ar = Ph	note a	**13**	(72%)
5	**12b** Ar=C_6H_4(*p*-OCH_3)	note b		(80%)

[a] All compounds are racemic. PMB = *p*-methoxybenzyl. Reactions were run according to the general experimental procedure (footnote 8) 0.125 M in CH_2Cl_2 with the following exceptions. Note a: three equivalents of ethyl diazoacetate was used, 0 °C, 1 h. Note b: six equivalents of ethyl diazoacetate was used, −78 to 0 °C, overnight.

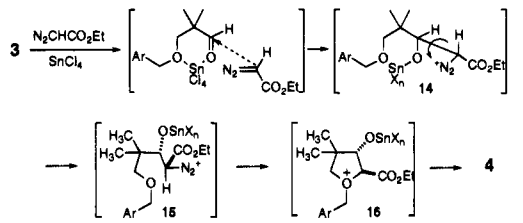
than 5% of β-ketoester **5b** had formed under these conditions. One equivalent of $SnCl_4$ again afforded only **4** albeit in a lower yield of 59% (entry 7). To judge the effect of the *p*-methoxybenzyl group on the reaction, we next examined $SnCl_2$, the Lewis acid Roskamp[3] had found to be optimal for β-keto ester production. Treatment of **3b** and ethyl diazoacetate with 2 equiv of $SnCl_2$ provided no reaction at −78 °C, and warming the reaction mixture to room temperature afforded **5b** in 45% yield; no tetrahydrofuran product **4** was obtained. Entry 9 shows that $BF_3{\cdot}OEt_2$ also afforded **4**, but in lower yield than $SnCl_4$ and $TiCl_4$.

Direct comparison of the benzyl and *p*-methoxybenzyl groups under identical conditions (entries 3 and 6; 0.5 equiv $SnCl_4$) showed that the *p*-methoxybenzyl group afforded a slightly better yield of tetrahydrofuran **4**. The methoxymethyl-protected (MOM-protected) substrate **3c** also afforded tetrahydrofuran **4** (60% yield) under these conditions (entry 10); however, the reaction mixture was noticeably more complex than with the benzyl or *p*-methoxybenzyl functionalities. Triethylsilyl-protected substrate **3d** initially afforded a ca. 1:1 mixture of alcohol **4** and the corresponding silyl ether, which was treated with pyridine−HF (THF) to afford **4** in 81% yield (entry 11). In this case, β-keto ester **5d** was not detected (^{1}H NMR analysis). This brief survey shows that a *p*-methoxybenzyl ether is the optimal group, but other common alcohol protecting groups are also compatible with the reaction. The data in Table 1 shows $SnCl_4$ (0.5 equiv) to be the Lewis acid of choice to maximize tetrahydrofuran formation.

Table 2 presents several additional examples of this new tetrahydrofuran synthesis. Entry 1 shows that the additional steric hindrance resulting from the two ethyl groups at the α-carbon of aldehyde **6** does not impede the reaction; tetrahydrofuran **7** was obtained in 77% yield. The presence of an α-stereogenic center in **8** (entry 2) results in the stereoselective formation of **9** in 75% yield as a ≥10:1 mixture of diastereomers (^{1}H NMR analysis).[9] The effect of a β-stereogenic center was next examined. Aldehyde **10** afforded tetrahydrofuran **11** in 78% yield as a ≥8.1:1 mixture of diastereomers (entry 3).[7]

In an attempt to extend the methodology to ketones, **12a** was subjected to the standard conditions (0.5 equiv of $SnCl_4$, −78 °C) but failed to afford any tetrahydrofuran product. However, treatment of **12a** and 3 equiv of ethyl diazoacetate with $ZrCl_4$ (1.0 equiv, CH_2Cl_2, 0 °C, 1 h) afforded tetrahydrofuran **13** in 72% yield.[10] Employing a *p*-methoxybenzyl ether (**12b**) under these conditions led to some cleavage of the *p*-methoxybenzyl ether protecting group and the formation of **13** in 50% yield. When 6 equiv of ethyl diazoacetate was used with **12b**, **13** was obtained in 80% yield.

Scheme 1



A possible mechanism for the reaction that accounts for the observed stereochemistry is presented in Scheme 1. Condensation of the α-diazo ester with the Lewis acid activated aldehyde **3** via a transition state that minimizes steric interactions should afford **14**. Rotation about the new C−C bond to place the N_2^+ group anti to the benzylic ether oxygen should afford **15**. S_N2-type intramolecular displacement of N_2 would then afford oxonium ion **16**. Loss of the benzylic group upon displacement by a nucleophile (e.g., halide) would afford tetrahydrofuran **4**.[11] This mechanism accounts for the observed trans orientation between the ester and alcohol functionalities. The stereochemical outcome for aldehyde **8** with an α-stereogenic center is consistent with a chelation-controlled addition to the aldehyde as shown in Scheme 1. However, the stereochemical outcome for the **10** to **11** transformation does not agree with this model. This may be due to steric interactions between the isopropyl and the adjacent methyl substituents in the chelate which lead to an open transition state being favored. The stereochemical aspects of this transformation will be discussed in a full account of this work.

In summary, we have developed a new stereoselective synthesis of tetrahydrofurans. The reaction shows a high degree of stereoselectivity. Further extension of the methodology to the synthesis of highly substituted tetrahydrofurans, exploitation of other nucleophiles, formation of other size rings, and application to other diazo compounds are currently underway.

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Supporting Information Available: Copies of NMR spectra for compounds **4**, **7**, **9**, **11**, **13**, ***i-a***, ***i-b***, ***ii***, and ***iii*** and ORTEP drawings of ***ii*** and ***iii*** (28 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(9) The stereochemistry of **9** was assigned by an X-ray crystal structure of a derivative. See supporting information for details. Tetrahydrofuran **9** is an inseparable 10:1 (^{1}H NMR) mixture of two compounds (^{1}H NMR integration vs impurity; see supporting information for details). The minor component may be a diastereomer of **9** or some other byproduct.

(10) The structure of **13** was assigned by an X-ray crystal structure of a derivative. See supporting information for details.

(11) In support of this notion, *p*-methoxybenzyl chloride was isolated in several reaction mixtures. For other tetrahydrofuran syntheses in which a benzyl ether plays a similar role, see: (a) Dehmlow, H.; Mulzer, J.; Seilz, C.; Strecker, A. R.; Kohlmann, A. *Tetrahedron Lett.* **1992**, *33*, 3607−3610. (b) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963−3964.