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Tandem Wittig Rearrangement/Aldol Reactions for the Synthesis of Glycolate Aldols

Myra Beaudoin Bertrand and John P. Wolfe*

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109-1055

jpwolfe@umich.edu

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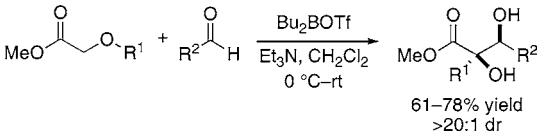
ABSTRACT



A new tandem Wittig Rearrangement/aldol reaction of *O*-benzyl or *O*-allyl glycolate esters is described. This reaction generates two carbon–carbon bonds and two contiguous stereocenters in a single step from simple starting materials. The [1,2]-Wittig rearrangement proceeds under very mild reaction conditions that do not require the use of a strong base, and the 1,2-diol products are obtained in good yield with excellent diastereoselectivity (>20:1).

The [1,2]-Wittig rearrangement of α-alkoxy carbanions has been known for over 60 years.[1,2] However, despite the fact that this reaction has considerable potential utility as a carbon−carbon bond-forming process, its use in organic synthesis remains relatively uncommon due to the need for strongly basic reaction conditions and the fact that many transformations proceed in low yield.[3] Thus, the ability to effect [1,2]-Wittig rearrangement under milder conditions and/or in tandem reaction sequences that lead to the generation of more than one C−C bond could result in significantly expanded synthetic utility.

During the course of an ongoing project directed toward the synthesis of a natural product, we sought to effect a stereoselective boron-mediated aldol reaction between acrolein and methyl *O*-benzyl glycolate (**1**).[4] This reaction failed to proceed at −78 °C, but when the transformation was attempted at 0 °C, an interesting result was obtained. The expected aldol product **2** was not generated in significant amounts, but instead, the 1,2-diol **3** resulting from benzyl migration was formed with >20:1 diastereoselectivity (Scheme 1).

The conversion of **1** to **3** presumably involves the unprecedented combination of a [1,2]-Wittig rearrangement and an aldol reaction. This tandem reaction sequence generates two C−C bonds and two contiguous stereocenters in a single step from simple starting materials[5] Furthermore, substituted dihydroxy esters are precursors for a wide array of biologically active molecules.[6] The conversion of **1** to **3** is also mechanistically intriguing, as [1,2]-Wittig rearrangements of enolates are rare and previously have only been effected using strongly basic reagents.[7,8] Moreover, the observed diastereoselectivity of the aldol reaction is unusually high. The few existing examples of aldol reactions involving unprotected α-hydroxy carbonyl compounds that afford

(1) Wittig, G.; Löhmann, L. *Liebigs Ann.* **1942**, *550*, 260.

(2) (a) Tomooka, K.; Yamamoto, H.; Nakai, T. *Liebigs Ann./Recueil* **1997**, 1275. (b) Tomooka, K. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: London, 2004; Vol. 2, pp 749−828.

(3) For examples of [1,2]-Wittig rearrangements in the context of complex molecule synthesis, see: (a) Tomooka, K.; Yamamoto, H.; Nakai, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 4500. (b) Tomooka, K.; Kikuchi, M.; Igawa, K.; Suzuki, M.; Keong, P.-H.; Nakai, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 4502. (c) Schreiber, S. L.; Goulet, M. T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 4718.

(4) Boron aldol reactions of methyl *O*-benzyl glycolate with aliphatic aldehydes proceed at −78 °C without rearrangement. See: Sugano, Y.; Naruto, S. *Chem. Pharm. Bull.* **1989**, *37*, 840.

(5) For a one-step, three-component synthesis of glycolate aldol products bearing tertiary alcohols, see: Nicewicz, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 6170.

(6) (a) Trost, B. M.; Probst, G. D.; Schoop, A. *J. Am. Chem. Soc.* **1998**, *120*, 9228. (b) Hecker, S. J.; Werner, K. *J. Org. Chem.* **1993**, *58*, 1762.

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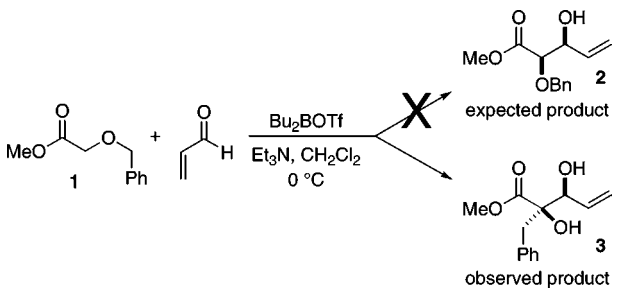
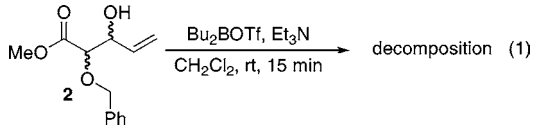
tertiary alcohol products proceed with modest (ca. 3:1) diastereoselectivities.[9,10] In this communication, we describe our preliminary studies on the scope and mechanism of new tandem Wittig rearrangement/aldol reactions of *O*-alkyl methyl glycolate derivatives.

Scheme 1

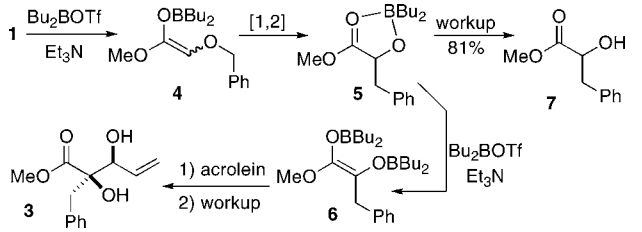


In our preliminary experiments, we sought to determine which of the two sequential reactions that lead to the conversion of **1** to **3** occurs first, as this knowledge could aid in the development of optimal conditions for this transformation. The possibility that the sequence is initiated by an initial aldol reaction of **1** was rapidly discounted. The expected product of the boron−aldol reaction, *β*-hydroxy ester **2**, was prepared as a mixture of diastereomers[11] and treated with a mixture of Bu_2BOTf and Et_3N in CH_2Cl_2 at room temperature for 15 min. As shown in eq 1, these conditions resulted predominantly in the decomposition of the starting material and provided only trace amounts (<5%) of **3**.



The failure of **2** to undergo clean conversion to **3** suggests that the transformation of **1** to **3** likely proceeds via an initial [1,2]-Wittig rearrangement of boron ester enolate **4** to generate **5** (Scheme 2). This hypothesis is supported by the

Scheme 2. Proposed Mechanism



fact that treatment of methyl *O*-benzyl glycolate (**1**) with Bu_2BOTf/Et_3N for 15 min at room temperature followed by aqueous workup affords rearranged product **7** in 81% yield.[12]

Following the initial Wittig rearrangement, conversion of **5** to boron enolate **6** presumably occurs with high selectivity for *E*(*O*)-enolate generation due to chelation between the ester carbonyl and the adjacent boron alkoxide. Enolate **6** then undergoes aldol reaction to provide the observed *syn*-diol product **3** with excellent stereoselectivity. Evidence for the intermediacy of doubly borylated ester enolate **6** was obtained through HRMS analysis of a reaction mixture resulting from treatment of **1** with Bu_2BOTf/Et_3N for 15 min at room temperature. A signal was observed for *m*/*z* 428.3650 (calculated mass = 428.3633) with an isotopic distribution in accord with the calculated pattern for **6**.

With knowledge of the reaction mechanism in hand, improved conditions were developed in which **1** was treated with excess Bu_2BOTf/Et_3N and allowed to undergo rearrangement before introduction of the aldehyde. In a representative experiment, **1** was added to a solution of Et_3N (4 equiv) and Bu_2BOTf (3.2 equiv) in CH_2Cl_2 at 0 °C and then warmed to room temperature for 15 min. The mixture was then cooled to 0 °C. Acrolein (1.5 equiv) was added, and the reaction mixture was allowed to warm to room temperature and stir for 1 h. Upon workup, the diol product **3** was obtained in 67% yield with >20:1 diastereoselectivity (Table 1, entry 1).

To probe the scope of the tandem Wittig rearrangement/aldol reaction, **1** was treated with a variety of different aldehydes using the optimized conditions described above. As shown in Table 1, the diol products were all obtained in good yields with excellent diastereoselectivities.[13] The transformation is effective with aromatic aldehydes

(7) For examples of [1,2]-Wittig rearrangements of enolates, see: (a) Curtin, D. Y.; Proops, W. R. *J. Am. Chem. Soc.* **1954**, *76*, 494. (b) Paquette, L. A.; Zeng, Q. *Tetrahedron Lett.* **1999**, *40*, 3823. (c) Vilotijevic, I.; Yang, J.; Hilmey, D.; Paquette, L. A. *Synthesis* **2003**, 1872. (d) Garbi, A.; Allain, L.; Chorki, F.; Ourevitch, M.; Crousse, B.; Bonnet-Delpon, D.; Nakai, T.; Begue, J.-P. *Org. Lett.* **2001**, *3*, 2529.

(8) For examples of [2,3]-Wittig rearrangements of boron ester enolates, see: (a) Oh, T.; Wrobel, Z.; Rubenstein, S. M. *Tetrahedron Lett.* **1991**, *32*, 4647. (b) Fujimoto, K.; Matsuhashi, C.; Nakai, T. *Heterocycles* **1996**, *42*, 423.

(9) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169.

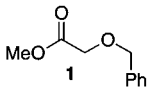
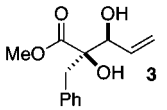
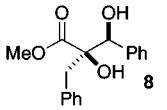
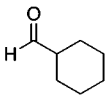
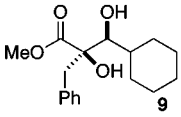
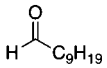
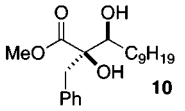
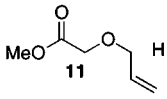
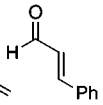
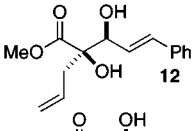
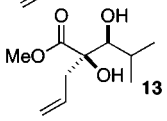
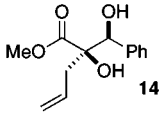
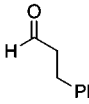
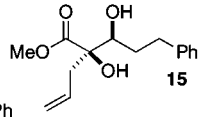
(10) Aldol reactions of O-protected 2-hydroxycarbonyl compounds that afford tertiary alcohol products also generally proceed with modest diastereoselectivity unless BHT esters or chiral auxiliaries are employed. See: (a) Murata, Y.; Kamino, T.; Hosokawa, S.; Kobayashi, S. *Tetrahedron Lett.* **2002**, *43*, 8121. (b) Kamino, T.; Murata, Y.; Kawai, N.; Hosokawa, S.; Kobayashi, S. *Tetrahedron Lett.* **2001**, *42*, 5249. (c) Montgomery, S. H.; Pirrung, M. C.; Heathcock, C. H. *Carbohydr. Res.* **1990**, *202*, 13. (d) Heathcock, C. H.; Pirrung, M. C.; Young, S. D.; Hagen, J. P.; Jarvi, E. T.; Badertscher, U.; Märki, H.-P.; Montgomery, S. H. *J. Am. Chem. Soc.* **1984**, *106*, 8161.

(11) Ester **2** was prepared through an aldol reaction between acrolein and the lithium enolate of **1** at −78 °C.

(12) Efforts to directly effect the boron-mediated aldol reaction of α-hydroxy ester **7** via treatment with excess Et_3N/Bu_2BOTf or 1 equiv of KH followed by excess Et_3N/Bu_2BOTf were unsuccessful. Boron-mediated aldol reactions of unprotected glycolate esters have also not been described in the literature. This suggests that **7** is not an intermediate along the reaction pathway and that formation of enolate **6** from borylated ester **5** occurs more rapidly than protonolysis of **5** to afford **7**.

(13) In most cases, only one stereoisomer was observed by ^1H NMR analysis of crude reaction mixtures. Product stereochemistry was assigned through ^1H NMR nOe analysis of an acetonide derivative of **3**. See the Supporting Information for complete details.

Table 1. Tandem Wittig Rearrangement/Aldol Reaction[a]

entry	ester	aldehyde	product	dr[b]	yield[c]
1				>20:1	67%
2				>20:1	72%
3				>20:1[d]	75%
4				>20:1	78%
5				>20:1[e]	61%
6				>20:1[f]	66%
7				>20:1	75%
8				>20:1	71%

[a] Conditions: 1.0 equiv of ester, 3.2 equiv of Bu_2BOTf, 4.0 equiv of Et_3N, CH_2Cl_2, 0.2 M, rt, 15 min, then add 1.5 equiv of aldehyde, 0 °C to rt. [b] Diastereomeric ratio obtained upon purification. In most cases, the crude product was obtained in >20:1 dr prior to purification. [c] Yields represent average isolated yields of two or more experiments. [d] The crude product was obtained in 14:1 dr. [e] The crude product was obtained in 17:1 dr. [f] The crude product was obtained in 20:1 dr.

(entry 2), α,β-unsaturated aldehydes (entry 1), and both branched and linear aliphatic aldehydes (entries 3 and 4).

This transformation was also readily extended to tandem [2,3]-Wittig rearrangement[8]/aldol reactions of methyl *O*-allyl glycolate **11** (Table 1, entries 5−8). A range of aliphatic and aromatic aldehydes were coupled with this substrate to afford the desired products with good yields and diastereoselectivities similar to those obtained in reactions of **1**.

Although *O*-benzyl and *O*-allyl glycolate esters are excellent substrates for the tandem Wittig rearrangement/aldol reactions, transformations of other *O*-alkyl glycolate esters remain challenging. For example, *O*-cyclohexyl and *O*-ethyl glycolate methyl esters failed to undergo [1,2]-Wittig rearrangement when treated with Bu_2BOTf/Et_3N. The bulky *O*-diphenylmethyl glycolate methyl ester undergoes facile [1,2]-Wittig rearrangement under these conditions, but the subsequent aldol reaction with benzaldehyde is slow. Further studies directed toward expanding the scope and developing asymmetric versions of these transformations are currently underway.

In conclusion, we have developed a new tandem Wittig rearrangement/aldol reaction for the synthesis of glycolate aldol products bearing tertiary alcohols. The reactions are effective for a wide array of aldehydes and proceed with excellent diastereoselectivity for the *syn*-diol products. The [1,2]-Wittig rearrangement occurs under very mild conditions that will likely be applicable to the future development of other tandem reaction sequences.

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Supporting Information Available: Characterization data for all new compounds in Table 1 (27 pages), mass spectral data for **6**, details of stereochemical assignments, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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