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Synthesis of Substituted 3-Hydroxy-2-Furanone Derivatives via an Unusual Enolate Wittig Rearrangement/Alkylative Cyclization Sequence

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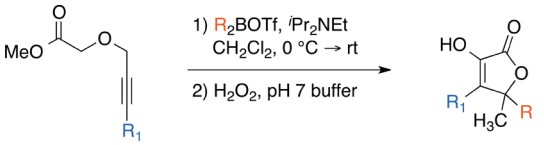
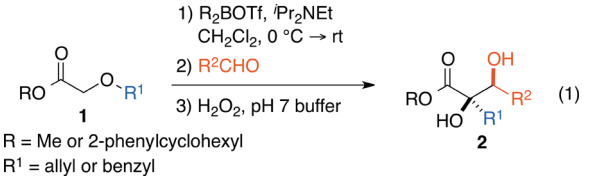
ABSTRACT



Treatment of methyl *O*-(alkynylmethyl) glycolate derivatives with dialkylboron triflates and Hünig's base leads to the formation of highly substituted 3-hydroxy-2-furanone derivatives. The transformations appear to proceed via an unusual mechanism involving initial 2,3-Wittig rearrangement of a boron ester enolate followed by an alkylative cyclization reaction that leads to incorporation of an alkyl group from the boron reagent into the product.

In recent years our group has explored the development and applications of boron-mediated cascade Wittig rearrangement/aldol reactions of glycolate ester derivatives **1** for the stereoselective construction of α-alkyl-α,β-dihydroxy esters **2** (eq 1).[1,2] These reactions proceed with excellent diastereoselectivity, and use of the readily available chiral auxiliary 2-phenylcyclohexanol provides access to enantiomerically enriched products with up to 94% ee after auxiliary cleavage. Although these reactions have demonstrated synthetic utility, the scope of this method is currently limited to substrates bearing *O*-allyl or *O*-benzyl migrating groups. Substrates that contain simple *O*-alkyl or *O*-aryl groups fail to undergo the initial Wittig rearrangement.



In order to further expand the scope of this method, we sought to employ substrates bearing *O*-propargyl groups. Related substrates are known to undergo 2,3-Wittig rearrangement when treated with a strong base,[3] and the resulting products **2** where R^1 is an allenyl group could be valuable intermediates for the construction of substituted heterocycles.[4] To this end we prepared ester substrate **3a** and subjected this compound to our standard reaction conditions whereby the ester was treated with Bu_2BOTf and $^iPr_2NEt$ and stirred at rt for ca. 15 min, and then an aldehyde was added to the resulting mixture. We were quite surprised to discover that **3a** failed to undergo the sequential rearrangement/aldol reaction and instead was transformed to the substituted 3-hydroxy-2-furanone **4a** (eq 2). Interestingly, although the aldehyde electrophile apparently did not participate in the reaction, a butyl group from the Bu_2BOTf reagent was incorporated at

(1) (a) Bertrand, M. B.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 4661–4663. (b) Giampietro, N. C.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 12556–12557.

(2) For related asymmetric Wittig rearrangement/Mannich reactions that generate amino alcohol products, see: Giampietro, N. C.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 2922–2924.

(3) (a) Marshall, J. A.; Robinson, E. D.; Zapata, A. *J. Org. Chem.* **1989**, *54*, 5854–5855. (b) Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 4913–4918. (c) Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1992**, *57*, 2747–2750.

(4) (a) Alcaide, B.; Almendros, P.; Carrascosa, R.; Martinez del Campo, T. *Chem.—Eur. J.* **2010**, *16*, 13243–13252. (b) Alcaide, B.; Almendros, P.; Carrascosa, R.; Martinez del Campo, T. *Chem.—Eur. J.* **2009**, *15*, 2496–2499.

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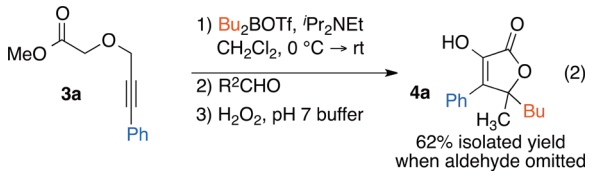
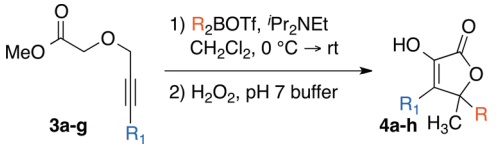
the product C5 position. Omission of the aldehyde from the reaction mixture led to the formation of **4a** in 62% yield.



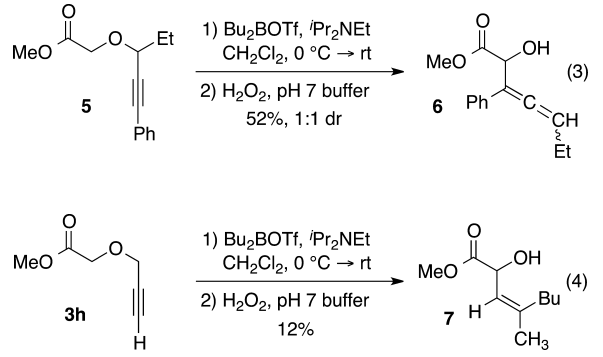
Given the potential synthetic utility and biological relevance of substituted furanone derivatives,[5] we sought to further examine this unusual transformation. Efforts to optimize reaction conditions by modifying temperature, solvent, base, etc. did not lead to significant improvements in yield. As such, we proceeded to explore the effect of substrate structure on reactivity. As shown in Table 1, the best results were obtained with substrates bearing aryl groups on the alkyne moiety (entries 1–4 and 8). These substrates were converted to substituted furanones in moderate yield. In contrast, substrates that contain alkyl-substituted alkynes were transformed in low yields (entries 5–7).[6] Attempts to employ substrate **5** bearing an ethyl group at the propargylic position led to formation of allene **6** in 52% yield; no furanone product was observed (eq 3). The rearrangement/cyclization reactions appear to be limited to internal alkyne substrates, as subjection of terminal alkyne substrate **3h** to the standard reaction conditions resulted in generation of substituted allylic alcohol **7** in low yield rather than a substituted furanone (eq 4).[7]

Table 1. Tandem Wittig Rearrangement/Alkylative Cyclization Reactions[a]

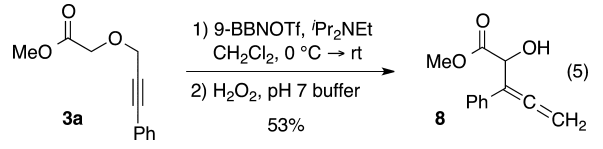


entry	R	R^1	yield[b]
1	Bu	Ph	62
2	Bu	*p*-F-C_6H_4	47
3	Bu	2-naphthyl	56
4	Bu	*p*-Me-C_6H_4	43
5	Bu	$Ph(CH_2)_2$	29
6	Bu	^{i}Pr	23
7	Bu	Me	20
8	Et	Ph	50

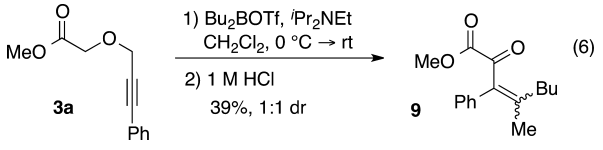
[a] Conditions: (*i*) 1.0 equiv of **3**, 3.2 equiv of R_2BOTf, 4.0 equiv of $^i Pr_2NEt$, CH_2Cl_2, 0.25 M, 0 °C → rt. (*ii*) H_2O_2, pH 7 buffer. [b] Isolated yields (average of two experiments).



We also briefly examined the influence of the dialkylboron reagent structure on reactivity. As anticipated, use of diethylboron triflate resulted in the formation of furanone product **4h** in which an ethyl group had been incorporated at C5 (Table 1, entry 8). However, use of the hindered and less electrophilic Cy_2BCl reagent led to no observable reaction. Interestingly, treatment of **3a** with 9-BBN-OTf/$^i Pr_2NEt$ led to clean formation of allene **8** in 53% yield (eq 5).



During the course of our initial optimization studies, we examined an alternative workup procedure in which the reaction of substrate **3a** with Bu_2BOTf/$^i Pr_2NEt$ was quenched with aqueous HCl rather than treated with H_2O_2 and pH 7 buffer. Interestingly, use of this acidic workup led to the formation of **9** (39% yield) (eq 6); the furanone product was not observed by NMR analysis of the crude reaction mixture.



Taken together, the results illustrated in eqs 3–6 provide a considerable amount of information about the likely mechanism of the rearrangement/cyclization reactions. The conversions of **5** to **6**, **3a** to **8**, and **3h** to **7** suggest the mechanism of this unusual rearrangement/alkylation involves initial 2,3-Wittig rearrangement of the substrate to generate an intermediate allene.[8] A subsequent alkyl

(5) (a) Nicoll-Griffith, D. A.; Chauret, N.; Houle, R.; Day, S. H.; D'Antoni, M.; Silva, J. M. *Drug. Metab. Dispos.* **2004**, *32*, 1509–1515. (b) Leblanc, Y.; Roy, P.; Wang, Z.; Li, C. S.; Chauret, N.; Nicoll-Griffith, D. A.; Silva, J. M.; Aubin, Y.; Yergey, J. A.; Chan, C. C.; Riendeau, D.; Brideau, C.; Gordon, R.; Xu, L.; Webb, J.; Visco, D. M.; Prasit, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3317–3320. (c) Leblanc, Y.; Roy, P.; Boyce, S.; Brideau, C.; Chan, C. C.; Charleson, S.; Gordon, R.; Grimm, E.; Guay, J.; Leger, S.; Li, C. S.; Riendeau, D.; Visco, D.; Wang, Z.; Webb, J.; Xu, L. J.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2207–2212.

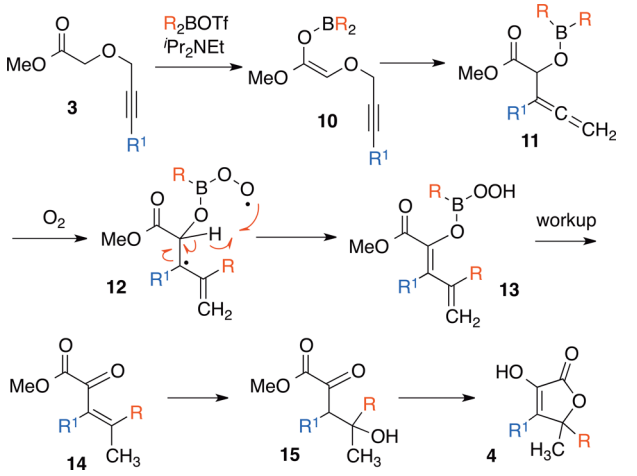
(6) The modest yields appear to be due to difficulties with the isolation of these products or the formation of volatile or water soluble side products.

(7) Compound **7** was the only isolable product obtained from this reaction. The low yield may be due to the volatility of either the product or of other low molecular weight side products.

(8) For a recent synthesis of furan-2-ones via addition of Grignard reagents to allenyl alcohols followed by trapping with CO_2, see: Li, S.; Miao, B.; Yuan, W.; Ma, S. *Org. Lett.* **2013**, *15*, 977–979.

transfer from the boron reagent to the allene leads to C−C bond formation and likely proceeds via a radical pathway that is presumably initiated by small amounts of oxygen.[9−12] Finally, the fact that the modified (acidic) workup generates **9** rather than **4** suggests that α-ketoester **9** may be an intermediate in the alkylation/cyclization reactions and that conversion of **9** to **4** may occur during the H_2O_2/ pH 7 buffer workup step.

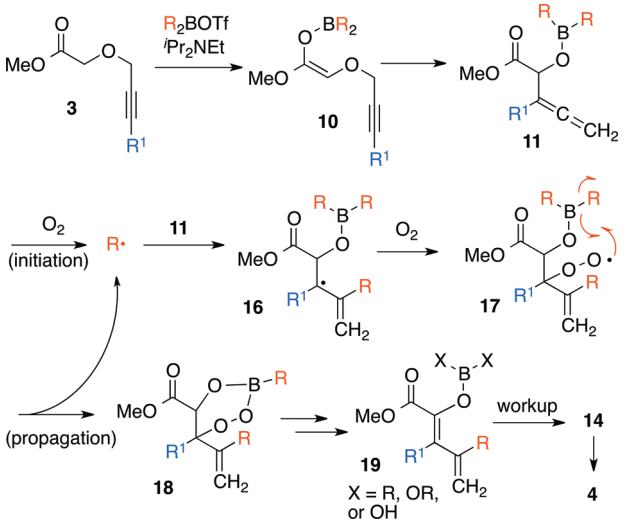
Scheme 1. Radical Cage Mechanism for Conversion of **11** to **13**



On the basis of these results, two plausible mechanisms for the conversion of **3** to **4** are illustrated in Schemes 1−2; the former involves a radical cage process, whereas the latter proceeds via a radical chain mechanism. In both pathways treatment of ester **3** with the dialkylboron triflate and Hünig's base leads to formation of boron enolate **10**, which undergoes 2,3-Wittig rearrangement to afford allene **11**. In the cage mechanism (Scheme 1), the oxygen-mediated transfer of an alkyl radical from the boron group to the allene would occur within a solvent cage to generate allyl radical **12**.[9] An intramolecular 1,5-hydrogen atom transfer of **12** would then afford enolate **13**. Upon workup, protonation of the enolate would generate **14**, which can then undergo conjugate addition of water or hydroxide to provide alcohol **15**.[13] Intramolecular acylation of the alcohol then yields the product **4**.[14]

Alternatively, the radical reaction may also occur via a chain mechanism (Scheme 2) whereby oxygen could lead to generation of an alkyl radical from **11** in the initiation step. Propagation would then involve addition of the alkyl radical to a second molecule of **11** to yield **16**, which could be captured by oxygen to afford **18** along with another alkyl radical. Base-mediated elimination of **18** (or the analogous boronate ester derived from homolysis of the O−O bond and rearrangement) would provide **19**, which upon workup could be transformed to **14** and then **4**.

Scheme 2. Radical Chain Mechanism



Regardless of which pathway is operational, the formation of allene product **6** in the reaction of ethyl-substituted substrate **5** may result from steric inhibition of alkyl radical addition to the more highly substituted allene intermediate. The reason behind the failed cyclization of terminal alkene substrate **3h** is less clear. However, the radical intermediate generated from rearrangement and alkyl transfer of **3h** (**12**, R^1 = H) is considerably less stable than analogous intermediates derived from internal alkynes.

In order to further probe the question of cage vs chain mechanism, we carried out a crossover experiment in which the rearrangement of **3a** was carried out in the

(9) For select recent examples of alkyl radical addition to allenes, see: (a) Ma, Z.; Zeng, R.; Fu, C.; Ma, S. *Tetrahedron* **2011**, *67*, 8808–8818. (b) Kippo, T.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2011**, *13*, 3864–3867. (c) Yang, D.; Cwynar, V.; Donahue, M. G.; Hart, D. J.; Mbogo, G. *J. Org. Chem.* **2009**, *74*, 8726–8732. (d) Ma, Z.; Ma, S. *Tetrahedron* **2008**, *64*, 6500–6509. (e) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Redondo, M. C. *J. Org. Chem.* **2007**, *72*, 1604–1608. (f) Shen, L.; Hsung, R. P. *Org. Lett.* **2005**, *7*, 775–778. For a review on free-radical addition to allenes, see: (g) Hartung, J.; Kopf, T. in *Modern Allene Chemistry*; Krause, N., Hashimi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 701−726.

(10) For an example of furan-2-one synthesis that is initiated by radical initiation to an allene, see: Wu, Z.; Huang, X. *Synthesis* **2007**, 45–50.

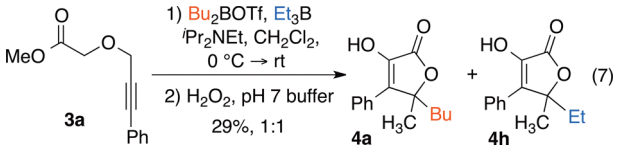
(11) For a review on the generation and reaction of alkyl radicals from organoboron reagents, see: Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415–3434.

(12) Reactions of **3a** conducted with measured amounts of added air failed to provide improved results over the standard conditions. However, a rearrangement of **3a** conducted in a nitrogen-filled glovebox afforded a ca. 2:1 mixture of allene **8** and lactone **4a**, which suggests a stoichiometric amount of oxygen is needed to facilitate the transformation of **3** to **4**.

(13) β,γ-Unsaturated α-ketoesters that are structurally similar to **14** have been shown to undergo conjugate addition of water followed by lactonization to generate 3-hydroxy-furan-2-ones analogous to **4**. See: (a) Mageswaran, S.; Ollis, W. D.; Southam, D. A.; Sutherland, I. O.; Thebtaranonth, Y. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1969–1980. (b) Babakhanyan, A. V.; Ovsepyan, V. S.; Kocharyan, S. T.; Panosyan, G. A. *Russ. J. Org. Chem.* **2003**, *39*, 814–819. (c) Ovsepyan, V. S.; Babakhanyan, A. V.; Manukyan, M. O.; Kocharyan, S. T. *Russ. J. Gen. Chem.* **2004**, *74*, 1376–1382. For an asymmetric two-step conjugate addition/ring-closing reaction for the conversion of β,γ-unsaturated α-ketoesters to 3-hydroxy-furan-2-ones, see: (d) Xiong, X.; Ovens, C.; Pilling, A. W.; Ward, J. W.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 565–567.

(14) Attempts to subject **9** to the workup conditions failed to generate significant amounts of product **4**. However it is possible that cleavage of the B−O bond is relatively slow and that either **13** or a boron-complexed ketone analog of **14** is the actual electrophile that participates in the conjugate addition of water or hydroxide.

presence of 3.2 equiv of Et_3B (eq 7). This reaction provided a ca. 1:1 mixture of **4a** and **4h**, which indicates an intermolecular (i.e., noncage) alkyl radical transfer to the allene is a viable mechanistic pathway and suggests that the mechanism illustrated in Scheme 2 may be operational (although this does not unambiguously rule out the radical cage mechanism shown in Scheme 1).[15]



In conclusion, we have discovered an unusual Wittig rearrangement/alkylative cyclization reaction of methyl *O*-propargyl glycolate derivatives. The reactions produce potentially useful 3-hydroxy-furan-2-one products in moderate yield and appear to proceed via radical alkylation of an intermediate allene. Future studies will be directed toward improving and expanding the scope of these transformations.

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Supporting Information Available. Experimental procedures, characterization data for all new compounds, descriptions of stereochemical assignments with supporting structural data, and copies of ^1H and ^{13}C NMR spectra for all new compounds reported in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) Treatment of **3a** with $Bu_2BOTf/{}^iPr_2NEt$ in the presence of excess (5 equiv) TEMPO as a radical trap resulted in no reaction; substrate **3a** was unchanged. This may be due to inhibition of enolate generation due to an undesired reaction of the Lewis acidic Bu_2BOTf with TEMPO.

The authors declare no competing financial interest.