ORGANIC LETTERS

2010
Vol. 12, No. 5
944−947

Synthesis of γ,δ-Unsaturated Glycolic Acids via Sequenced Brook and Ireland−Claisen Rearrangements

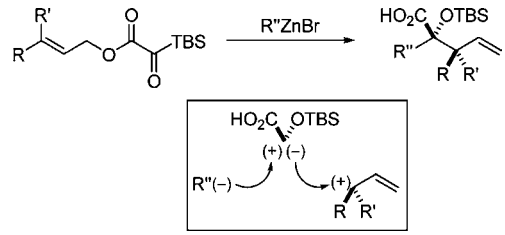
Daniel C. Schmitt and Jeffrey S. Johnson*

Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

jsj@unc.edu

Received December 21, 2009

ABSTRACT



Organozinc, -magnesium, and -lithium nucleophiles initiate a Brook/Ireland−Claisen rearrangement sequence of allylic silyl glyoxylates resulting in the formation of γ,δ-unsaturated α-silyloxy acids.

New methods to produce the glycolic acid moiety continue to be important in the creation of small-molecule building blocks.[1] γ,δ-Unsaturated glycolic acid derivatives represent a functional-group-rich subset of substituted α-hydroxy acids with significant potential for further elaboration. The preparation of such compounds may be achieved via Ireland−Claisen rearrangement of allyl glycolate esters.[2] While the standard Ireland−Claisen rearrangement is performed by sequential enolization and silylation of allylic esters, alternative approaches to the requisite silyl ketene acetal have been reported. Methods include 1,4-addition to enoates,[3] and silylene transfer followed by 6π-electrocyclization,[4] or by Rh-catalyzed reduction of enoates.[5] These methods allow for the generation of chiral products from achiral starting materials; however, a method that introduces multiple α substituents in a single-pot process could potentially allow a more rapid buildup of molecular complexity.

Silyl glyoxylates are reagents for the geminal linking of nucleophile/electrophile pairs at a glycolic acid junction.[6] Because multicomponent couplings involving silyl glyoxylates are believed to proceed through a glycolate enolate intermediate, the use of an allylic ester might allow [3,3]-sigmatropic rearrangement to proceed in preference to intermolecular addition to an electrophile (Scheme 1).

(1) Ley, S. V.; Sheppard, T. D.; Myers, R. M.; Chorghade, M. S. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1451–1472.

(2) (a) Ager, D. J. *Tetrahedron Lett.* **1982**, *23*, 3419–3420. (b) Bartlett, P. A.; Tanzella, D. A.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3941–3945. (c) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221–5228. (d) Sato, T.; Tanaka, A.; Tajima, K.; Fujisawa, T. *Chem. Lett.* **1987**, 1979–1980. (e) Fujiwara, K.; Goto, A.; Sato, D.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 3465–3468. (f) Gould, T. J.; Balestra, M.; Wittman, M. D.; Gary, J. A.; Rossano, L. T.; Kallmerten, J. *J. Org. Chem.* **1987**, *52*, 3889–3901.

(3) Chai, Y.; Hong, S. P.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905–2928.

(4) (a) Calad, S. C.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 2046–2047. (b) Howard, B. E.; Woerpel, K. A. *Org. Lett.* **2007**, *9*, 4651–4653. (c) Howard, B. E.; Woerpel, K. A. *Tetrahedron* **2009**, *65*, 6447–6453.

(5) Miller, S. P.; Morken, J. P. *Org. Lett.* **2002**, *4*, 2743–2745.

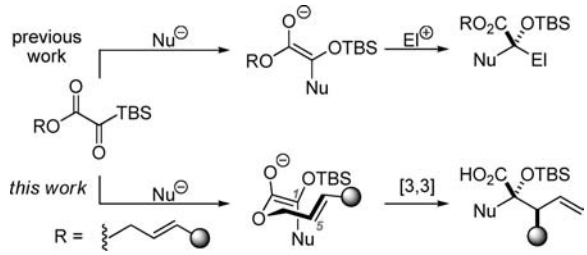
(6) (a) Nicewicz, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 6170–6171. (b) Greszler, S. N.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3689–3691.

(7) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77–84.

(8) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877. (b) *The Claisen Rearrangement: Methods and Applications*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, Germany, 2007.

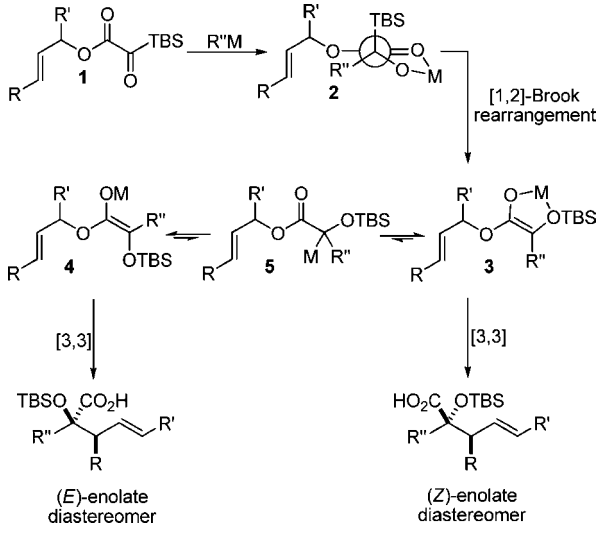
10.1021/ol9029353
Published on Web 02/09/2010

Scheme 1. Silyl Glyoxylate Reactivity



In the proposed reaction, the addition of a nucleophile to acylsilane would give a tetrahedral intermediate (Scheme 2). The proper alignment of the C−Si σ orbital with the

Scheme 2. Proposed Reaction



adjacent C=O π^* orbital in tetrahedral intermediate **2** would allow [1,2]-Brook rearrangement[7] to proceed, forming glycolate enolate **3**. At this point, the allylic ester enolate could undergo Ireland−Claisen rearrangement to afford a γ,δ-unsaturated acid.

Ireland−Claisen rearrangement proceeds via a well-understood transition state wherein the enolate geometry dictates the stereochemistry of the product.[8] The *E*/*Z* geometry of the intermediate glycolate enolate has not been established in reactions of silyl glyoxylates; therefore, determination of the enolate geometry would augment our understanding of the silyl glyoxylate reactivity and provide mechanistic insight for future endeavors. Furthermore, this process would create two new C−C bonds, allowing access to densely functionalized glycolic acids. Herein, we describe experiments directed toward these ends.

Preliminary work focused on defining a compatible nucleophilic component. Previously employed nucleophiles such as vinylmagnesium bromide and zinc acetylides were found to trigger oligomerization of silyl glyoxylate. This result underscores the chemoselectivity displayed in previously reported three-component coupling reactions, where the nucleophile reacts selectively with silyl glyoxylate, rather than the terminal electrophile, and the intermediate glycolate enolate reacts selectively with a terminal electrophile, rather than a second equivalent of silyl glyoxylate. The proposed Ireland−Claisen rearrangement requires a nucleophile capable of completely consuming silyl glyoxylate prior to oligomerization.

An assessment of other Grignard reagents revealed that MeMgBr had potential as an effective nucleophile because it cleanly added to cinnamyl silyl glyoxylate **1a** at 0 °C. In this case, Brook rearrangement did not occur below room temperature. When the reaction was allowed to warm, only decomposition was observed. Silyl ketene acetal formation was then attempted by the addition of MeMgBr at 0 °C, followed by warming to room temperature and the addition of TMSCl; however, this also resulted in decomposition. Given that no TMS incorporation had occurred, we turned to TMSOTf, which induced the desired Ireland−Claisen rearrangement and provided the γ,δ-unsaturated glycolic acid **7** in 55% yield (Table 1, entry 1). Silyl glyoxylates **1b** and **1c** reacted with similar efficiency (entries 2 and 3). The lithium enolate of ^{t}BuOAc also initiates the Brook/Ireland−Claisen sequence with excellent diastereoselectivity (Table 1, entry 4).

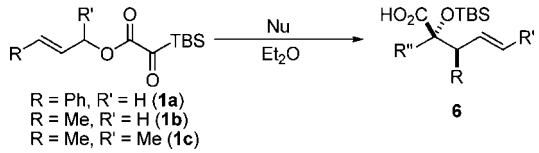
Organozinc nucleophiles were also found to be effective. $ZnEt_2$ serves as an efficient hydride donor, triggering the sequential Brook and Ireland−Claisen rearrangements, to afford glycolic acid **11** in 69% yield with good diastereoselectivity (Table 1, entry 5). The reduction of α-ketoesters with $ZnEt_2$ or EtMgBr has been previously reported; however, it is typically a minor byproduct to ethyl addition.[9] Allylzinc bromide and allenylzinc bromide were useful triggers as well (Table 1, entries 6−10).

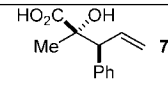
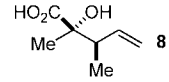
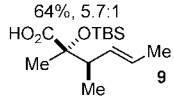
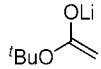
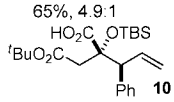
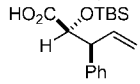
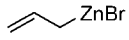
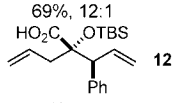
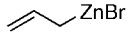
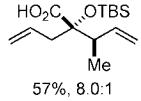
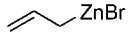
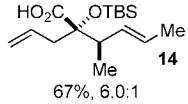
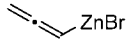
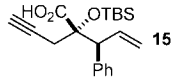
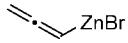
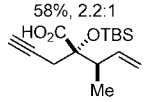
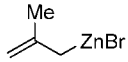
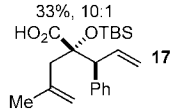
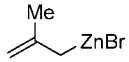
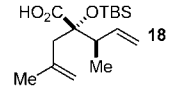
Substituted allylic zinc nucleophiles were also competent initiators. Methallylzinc bromide provided the desired products with slightly diminished diastereoselectivity relative to allylzinc bromide (Table 1, entries 11 and 12). The reaction was also tolerant of crotyl- and cinnamylzinc reagents; however, products were obtained as a complex mixture of diastereomers (not shown). Notably, none of the organozinc nucleophiles required silyl ketene acetal formation because the zinc enolate underwent [3,3]-rearrangement spontaneously.

Extension to other organozinc bromides proved challenging. Benzylzinc bromide, propynylzinc bromide, and Reformatsky nucleophiles resulted in alkene dimer **19** (Scheme 3). This dimer was cleanly formed by the addition of the glycolate enolate to a second equivalent of silyl glyoxylate. The derived alkoxide suffered Brook rearrangement and elimination. It appears that allyl- and allenylzinc bromide nucleophiles consumed silyl glyoxy-

(9) (a) Hameury, T.; Guillemont, J.; Van Hijfte, L.; Bellosta, V.; Cossy, J. *Org. Lett.* **2009**, *11*, 2397. (b) Fennie, M. W.; DiMauro, E. F.; O'Brien, E. M.; Annamalai, V.; Kozlowski, M. C. *Tetrahedron* **2005**, *61*, 6249–6265.

Table 1. Sequential Brook/Ireland−Claisen Rearrangements of Silyl Glyoxylates



entry	silyl glyoxylate	Nu	yield, dr
1	**1a**	MeMgBr/TMSOTf	 **7** 55%, 5.0:1
2	**1b**	MeMgBr/TMSOTf	 **8** 64%, 5.7:1
3	**1c**	MeMgBr/TMSOTf	 **9** 65%, 4.9:1
4	**1a**		 **10** 31%, 20:1
5	**1a**	$ZnEt_2$	 **11** 69%, 12:1
6	**1a**		 **12** 68%, 1.8:1
7	**1b**		 **13** 57%, 8.0:1
8	**1c**		 **14** 67%, 6.0:1
9	**1a**		 **15** 58%, 2.2:1
10	**1b**		 **16** 33%, 10:1
11	**1a**		 **17** 74%, 1:1
12	**1b**		 **18** 61%, 4.9:1

late more rapidly, and therefore dimerization was not competitive.

Geranyl silyl glyoxylate **20** underwent the title transformation when treated with allenylic or allylic zinc bromides, providing glycolic acid derivatives in moderate diastereoselectivity (Table 2). These results demonstrate that the Brook/Ireland−Claisen sequence may show promise for the construction of adjacent chiral quaternary centers.

Scheme 3. Dimerization Limits Nucleophile Scope

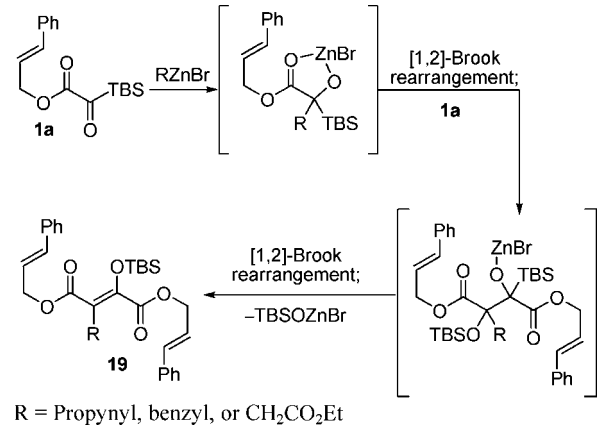
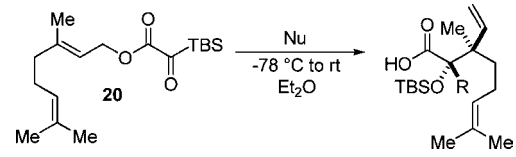
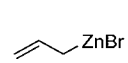
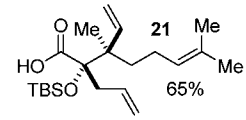
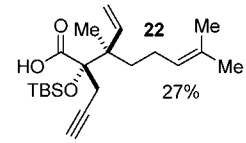
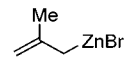
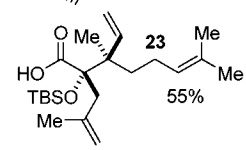


Table 2. Generation of Contiguous Quaternary Centers



entry	nucleophile	product (yield)	dr
1		 **21** 65%	3.0:1
2		 **22** 27%	3.7:1
3		 **23** 55%	2.5:1

The enolate geometry was inferred by examination of the relative stereochemistry of the γ,δ-unsaturated glycolic acid products. The products could be converted to cyclic products by iodolactonization or ring-closing metathesis, allowing for NOESY analysis.[10] In each case, the major diastereomer was found to be consistent with a (*Z*)-glycolate enolate.

The degree of diastereocontrol depended on the identity of both the nucleophile and the ester. While cinnamyl silyl

(10) See the Supporting Information for experimental details and NOESY data.

glyoxylate **1a** reacted with allylzinc bromide (Table 1, entry 6) and allenylzinc bromide (entry 9) with modest diastereocontrol, analogous reactions with crotyl silyl glyoxylate **1b** resulted in substantially higher diastereomeric ratios (entries 7 and 10). The formation of the chelated alkoxide **2** appears likely in light of the established tendencies for bidentate coordination in α-dicarbonyl electrophiles and the derived addition products.[11] Stereoelectronic considerations would suggest the subsequent formation of (*Z*)-enolate **3** arising from Brook rearrangement. The resulting silyl ether will dramatically weaken chelation,[12] potentially permitting enolate equilibration (via the C−Zn tautomer **5**) to compete with [3,3]-rearrangement from the *Z* isomer. The rate of sigmatropic rearrangement should be linked to steric demand at C1 and C6, where a less hindered substrate undergoes more rapid [3,3]-rearrangement;[13] therefore, it is hypothesized that the more encumbered **1a** undergoes enolate equilibration to a greater extent prior to sigmatropic rearrangement. The result is an erosion of the initial enolate geometric ratio and a corresponding decrease in the product diastereoselectivity. This proposal is consistent with the experimental observations within the organozinc nucleophile series: the product diastereomer ratio increases as the nucleophile bulk at C1 decreases (hydride > propargyl ≈ allyl > methallyl).

It is notable that MeMgBr initiates Ireland−Claisen rearrangement with diastereoselectivity independent of the ester. This may be a result of silyl ketene acetal formation prior to sigmatropic rearrangement. Provided there is no enolate equilibration after TMSOTf trapping, the diastereoselectivity reflects the *Z*/*E* magnesium enolate ratio at the time of silylation.

The high diastereoselectivity observed for the lithium enolate (Table 1, entry 4) can be explained if generation of the C−Li tautomer **5** is slow and sigmatropic rearrangement outcompetes enolate equilibration. This may be directly contrasted with a recent reaction between zinc enolates and silyl glyoxylates that do undergo facile enolate equilibration.[6b]

In summary, we have developed a one-pot Brook/Ireland−Claisen rearrangement sequence that generates γ,δ-unsaturated glycolic acids containing two new C−C bonds and two contiguous stereocenters. To our knowledge, this is the first report of a Brook rearrangement initiating a [3,3]-sigmatropic process. The reaction is tolerant of various reaction partners, but diastereoselectivity is linked to the identity of the metal cation and the ester. In diastereoselective cases, the stereochemical outcome of the reaction is consistent with a (*Z*)-enolate intermediate proceeding through a chairlike transition state. The work suggests that diastereocontrol and the enolate geometry in reactions of silyl glyoxylates can be tuned with the judicious selection of the metal cation and that the rate of the "second stage" reaction can have an impact.

Acknowledgment. This research was supported by the National Institutes of Health (National Institute of General Medical Sciences Grant GM084927) and Novartis. We thank a reviewer for a detailed analysis of the mechanism and some suggestions that were incorporated herein.

Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9029353

(11) (a) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686–699. (b) Masuyama, Y.; Tsunoda, T.; Kurusu, Y. *Chem. Lett.* **1989**, 1647–1650.

(12) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265–268.

(13) (a) Hiersemann, M.; Abraham, L. *Org. Lett.* **2001**, *3*, 49–52. (b) Wilcox, C. S.; Babston, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 6636–6642.