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Sodium Bicarbonate-Catalyzed Stereoselective Isomerizations of Electron-Deficient Propargylic Alcohols to (*Z*)-Enones

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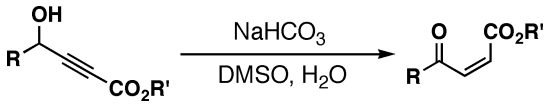
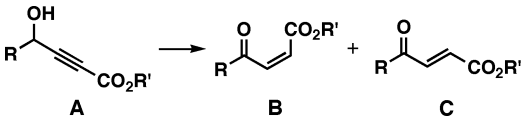


Redox isomerization is a synthetically important process because it creates two new functional groups in the product, among which is the isomerization of propargylic alcohols to conjugated enones. Although *E*-enones have been prepared by this approach, *Z*-enones could not be accessed. We previously reported DABCO-catalyzed *E*-selective isomerization of electron-deficient propargylic alcohols to enones and its mechanism. Based on this mechanism, we have now developed the first *Z*-selective redox isomerization of electron-deficient propargylic alcohol to enone using sodium bicarbonate as a catalyst.

Diversity-oriented organic synthesis has emerged as a new paradigm to discover small molecules that perturb biological processes. In this field, a new and exciting challenge is to develop synthetic methods to prepare skeletally and stereochemically diverse bioactive small molecules from common substrates.[1] As part of our efforts in this area, we became interested in *Z*- and *E*-γ-oxo-α,β-alkenyl esters (**B** and **C**, eq 1) and their derivatives. These moieties are part of biologically



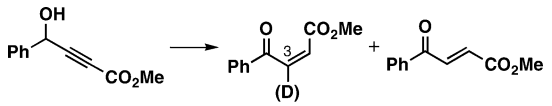
(1)

important natural and unnatural compounds[2−16] and are also important substrates in Diels−Alder cycloadditions[17−19] and potentially in many other cycloaddition reactions. *Z*- and *E*-γ-oxo-α,β-alkenyl esters **B** and **C** are interesting electrophiles as a result of their distinct reactivities, with the greater electrophilicity of **C** compared to that of **B**.[20] Presumably because of such differences, they exhibit distinct biological activities.[20] These distinctive chemical reactivities and biological activities prompted us to develop divergent synthetic methods to prepare a range of analogs **B** and **C** from common intermediates **A**.

We have recently reported the stereoselective isomerization of **A** (and other electron-deficient propargylic alcohols) to **C** using catalytic DABCO.[21,22] Despite the synthetic and biological importance of esters **B**, the only general approach toward **B** is the oxidation of 2-alkoxyfurans that are not readily accessible.[23] Presumably for this reason, the full synthetic and biological potential of **B** has not yet been explored. In this paper, we wish to describe a convenient and highly stereoselective method to produce **B** from readily available **A**.[24,25] This is the first stereoselective isomerization of electron-deficient propargylic alcohols to the corresponding *Z*-enones.

Prior to this work, we attempted the hydrogenation of **4** (Scheme 1); this deceptively straightforward Lindlar catalyst-

TABLE 1. Conversion of 1 to 2 and 3



1 (3-*d*-)**2** **3**

entry	base	solvents	$t_{1/2}$	**2:3**
1	^{i}Pr$_2$NEt	$CDCl_3$	60	1.2:1
2	^{i}Pr$_2$NEt	C_6D_6	126	1.0:1
3	^{i}Pr$_2$NEt	DMSO-d_6	12	1.6:1
4	^{i}Pr$_2$NEt	DMSO-d_6/D_2O (8:1)	n.d.	3-*d*-**2** only
5	$NaHCO_3$	DMSO-d_6/H_2O (8:1)	n.d.	**2** only

(1) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969.
(2) Nozoe, S.; Hirai, K.; Tsuda, K. *Tetrahedron Lett.* **1965**, *6*, 4675−4677.
(3) Aldridge, D. C.; Armstrong, J. J.; Speake, R. N.; Turner, W. B. *Chem. Commun.* **1967**, 26−27.
(4) Boeckman, R. K., Jr.; Fayos, J.; Clardy, J. *J. Am. Chem. Soc.* **1974**, *96*, 5954−5956.
(5) Michel, K. H.; Demarco, P. V.; Nagarajan, J. *J. Antibiot.* **1977**, *30*, 571−575.
(6) Nukina, M.; Sassa, T.; Ikeda, M. *Tetrahedron Lett.* **1980**, *21*, 301−302.
(7) Fex, T. *Tetrahedron Lett.* **1981**, *22*, 2703−2706.
(8) Ohmoto, T.; Koike, K. *Chem. Pharm. Bull.* **1984**, *32*, 3579−3583.
(9) Arai, K.; Rawlings, B. J.; Yoshizawa, Y.; Vederas, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 3391−3399.
(10) Hayashi, M.; Kim, Y. P.; Hiraoka, H.; Natori, M.; Takamatsu, S.; Kawakubo, T.; Masuma, R.; Komiyama, K.; Omura, S. *J. Antibiot.* **1995**, *48*, 1435−1439.
(11) Takamatsu, S.; Kim, Y. P.; Hayashi, M.; Hiraoka, H.; Natori, M.; Komiyama, K.; Omura, S. *J. Antibiot.* **1996**, *49*, 95−98.
(12) Goto, S.; Chen, K.-X.; Oda, S.; Hori, H.; Terada, H. *J. Am. Chem. Soc.* **1998**, *120*, 2457−2463.
(13) Zhang, H.; Tomoda, H.; Tabata, N.; Miura, H.; Namikoshi, M.; Yamaguchi, Y.; Masuma, R.; Omura, S. *J. Antibiot.* **2001**, *54*, 635−641.
(14) Evidente, A.; Andolfi, A.; Vurro, M.; Zonno, M. C.; Motta, A. *Phytochemistry* **2002**, *60*, 45−53.
(15) Berg, A.; Notni, J.; Dorfelt, H.; Grafe, U. *J. Antibiot.* **2002**, *55*, 660−662.
(16) Findlay, J. A.; Li, G. Q.; Miller, J. D.; Womiloju, T. O. *Can. J. Chem.* **2003**, *81*, 284−292.
(17) Angell, E. C.; Fringuelli, F.; Guo, M.; Minuti, L.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1988**, *53*, 4325−4328.
(18) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1998**, *63*, 812−816.
(19) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693−3695.
(20) Dal Pozzo, A.; Acquasaliente, M.; Donzelli, G.; DeMaria, P.; Nicoli, M. C. *J. Med. Chem.* **1987**, *30*, 1674−1677.
(21) Sonye, J. P.; Koide, K. *Synth. Commun.* **2006**, *36*, 599−602.
(22) Sonye, J. P.; Koide, K. *J. Org. Chem.* **2006**, *71*, 6254−6257.
(23) Antonioletti, R.; D'Auria, M.; De Mico, A.; Piancatelli, G.; Scettri, A. *Synthesis* **1984**, *3*, 280−281.
(24) Shahi, S. P.; Koide, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 2525−2527.
(25) Midland, M. M.; Tramontano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28−29.

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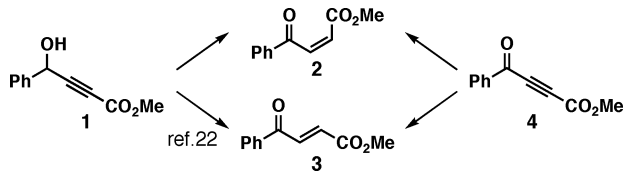
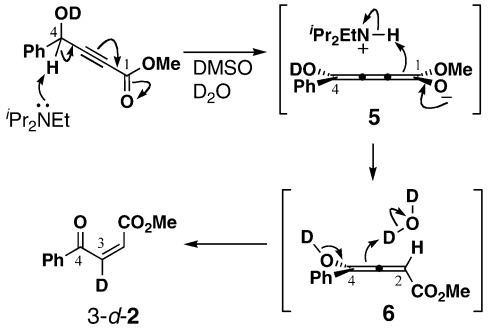
SCHEME 1. Model Systems Used in This and Previous Studies



SCHEME 2. Proposed Mechanism

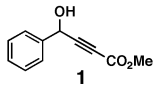
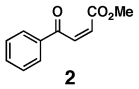
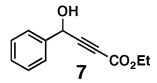
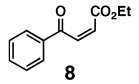
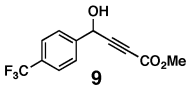
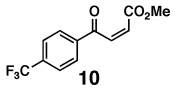
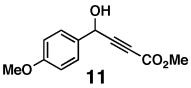
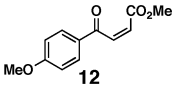
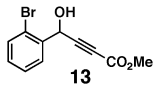
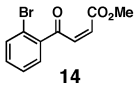
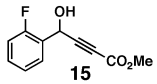
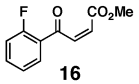
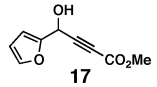
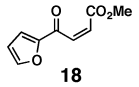
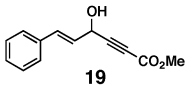
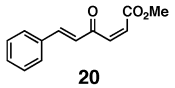
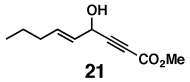
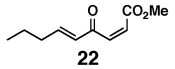
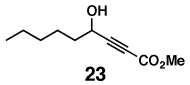
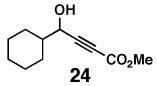


based hydrogenation of **4** was not *Z*-selective, providing a mixture of **2** and **3** in a 1:5 ratio in favor of **3**. Therefore, the lack of a convenient method to prepare **2** prompted us to develop a new synthetic methodology so that we would be able to prepare both **2** and **3** stereoselectively from the same precursor **1**.

We previously screened various organic bases (DBU, DMAP, DABCO, Et_3N, $^iPr_2NEt$) in NMR solvents ($CDCl_3$, C_6D_6, DMSO-d_6, CD_3CN) to convert **1** to **3**.[22] As Table 1 shows, we discovered that $^iPr_2NEt$ catalyzed the conversion of **1** to **2** and **3** in $CDCl_3$ (entry 1) and C_6D_6 (entry 2) and more rapidly in DMSO-d_6 (entry 3). In the presence of $^iPr_2NEt$, the *E*:*Z* ratio remained the same even after **1** was consumed, excluding the possibility for isomerization of **2** to **3**. Although the stereoselectivity was less than desirable at this point, ranging from 1:1 to 1.6:1, we became interested in the mechanism of this moderately *Z*-selective transformation. To determine how hydrogen atoms are transferred in the $^iPr_2NEt$-catalyzed isomerization of **1**, we subjected **1** to 10 mol % of $^iPr_2NEt$ in a DMSO-d_6−D_2O mixture (8:1) at 23 °C and monitored the reaction in an NMR tube. To our surprise, this experiment generated exclusively 3-*d*-**2** (entry 4) and no *E*-isomer! This high *Z*-selectivity is not due to the potential selective degradation of **3** since compound **3** was found to be stable under the reaction conditions.

The position of the deuterium incorporation indicates that the mechanism is analogous to the DABCO-catalyzed *E*-selective isomerization, except that the final *Z* to *E* isomerization does not take place. In other words, as shown in Scheme 2, $^iPr_2EtN$ first abstracts the 4-H to form cumulenoate **5**. This intermediate is then protonated by iPr_2EtNH^+ to form the allene intermediate **6**. It is worthwhile to mention here that iPr_2EtNH^+ reacts faster with **6** than with D_2O (i.e., no proton exchange with water) during this process, analogous to our previous studies.[26] Intermediate **6** then abstracts a deuterium atom from D_2O to generate 3-*d*-**2**. An alternative mechanism has recently been described for a closely related transformation, in which the authors proposed a 1,3-hydride shift.[27] Their transformation can also be explained by extending our mechanism presented here and in our previous communication,[26] which does not involve the 1,3-hydride shift that is known to be antarafacial and thus requires extremely high temperature.[28]

TABLE 2. Scope of *Z*-Isomerization

Entry	Substrate	Product	Time (h)	Yield (%)
1	 **1**	 **2**	25	76
2	 **7**	 **8**	73	55
3	 **9**	 **10**	3	50
4	 **11**	 **12**	18	58
5	 **13**	 **14**	54	20
6	 **15**	 **16**	38	22
7	 **17**	 **18**	7.5 (0.9 equiv of LiBr was added)	57
8	 **19**	 **20**	7.5	53
9	 **21**	 **22**	24	52
10	 **23**		75	Complex mixture
11	 **24**		44	Complex mixture

With such high *Z*-selectivity in wet DMSO, we screened other non-nucleophilic bases and found that $NaHCO_3$ also catalyzed the conversion of **1** to **2** (entry 5, Table 1). After some optimization efforts, we found that this transformation was efficient when **1** was treated with 0.5 equiv of $NaHCO_3$ and 0.1 mol % of hydroquinone (as a possible stabilizer of **1** and **2**) in an 8:1 DMSO−H_2O mixture. Under these conditions, **2** was obtained in 76% yield with trace **3** (∼1%) after 24 h at 23 °C (Table 2, entry 1).

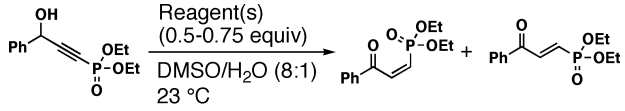
We then set out to determine the scope of this method. Unless specifically noted, the following reactions provided exclusively *Z*-products. To verify that the optimized conditions can be applied to other types of esters, the ethyl ester **7** (entry 2) was treated with $NaHCO_3$ to generate **8** in 55% isolated yield. The

(26) Sonye, J. P.; Koide, K. *Org. Lett*. **2006**, *8*, 199−202.

(27) Wang, S.-H.; Tu, Y.-Q.; Wang, M. *Tetrahedron Lett.* ***2006***, *47*, 8621−8623.

(28) Baldwin, J. E.; Fleming, R. H. *J. Am. Chem. Soc*. **1972**, *94*, 2140−2142.

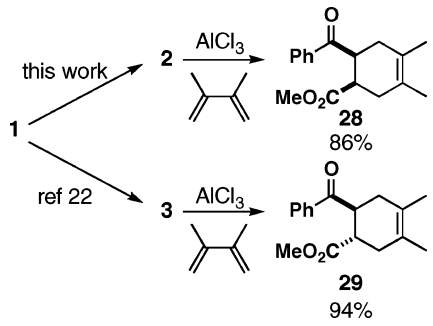
TABLE 3. Isomerization of Phosphonate 25



25 26 27

entry	reagent(s)	time (h)	**26**:**27**	combined yield (%)
1	$NaHCO_3$	52	1:2	45
2	$NaHCO_3$ + LiBr	52	1:>20	50
3	$KHCO_3$	50	1:4	n.d.
4	$CsHCO_3$ (40 °C)	29	1:>20	38

SCHEME 3. Diels−Alder Reactions of *Z*- and *E*-γ-Oxo-α,β-Alkenyl Esters



more electron-deficient trifluoromethyl derivative **9** (entry 3) and the electron-rich substrate **11** (entry 4) underwent the isomerizations smoothly, providing the *Z*-products **10** and **12** in 50% and 58% yields, respectively. The *o*-bromo derivative **13** (entry 5) was converted to its derivative **14** in 20% yield after 48 h. We also recovered the starting material **13** in 20% yield. Similarly to this example, another *ortho* halo-substituted compound proved to be a poor substrate: the *o*-fluoro derivative **15** (entry 6) underwent isomerization to give **16** in 22% yield.

Interestingly, the isomerization of compound **17** (entry 7) under the above conditions generated a mixture of *Z*-product **18** and its *E*-isomer in a 3.5:1 ratio (not shown). However, the presence of LiBr (0.9 equiv) as an additive allowed for the exclusive formation of **18** in 57% yield, indicating compatibility with furans. The cinnamylalcohol derivative **19** (entry 8) underwent the isomerization more rapidly (7.5 h) than most other substrates to afford the diene compound **20** in 53% yield. The aliphatic alkene derivative **21** (entry 9) provided the expected product **22** in 52% yield, whereby the crude NMR did not indicate any byproduct formation. This result shows that the $NaHCO_3$-catalyzed isomerization is not limited to aromatic compounds. Unfortunately, substrates **23** and **24** (entries 10 and 11) generated intractable mixtures under the reaction conditions.

(29) Friess, S. L.; Farnham, N. *J. Am. Chem. Soc.* **1950**, *72*, 5518−5521.

The isomerization of phosphonate **25** under the above conditions gave a 1:2 mixture of **26** and **27** in 45% combined yield (Table 3, entry 1). In an attempt to improve the *Z*-selectivity, we screened related bases. Because $LiHCO_3$ is not commercially available, we mixed $NaHCO_3$ with LiBr (1:1) to test the effect of cations. Interestingly, these modified conditions increased the *E*-selectivity (entry 2). With other bases such as $KHCO_3$ (entry 3) and $CsHCO_3$ (entry 4), we were only able to improve the *E*-selectivity. Thus, this challenging transformation would require further substantial investigation for the *Z*-olefin formation.

To demonstrate the viability of our base-dependent isomerization methods in the context of diversity-oriented synthesis, we subjected compounds **2** and **3** to Diels−Alder reactions with 2,3-dimethyl-1,3-butadiene (10 equiv) in the presence of $AlCl_3$ (0.2 equiv)[17,18] for 1.5 h (Scheme 3). From the *Z*-compound **2**, the corresponding *cis* Diels−Alder product **28** was generated in 86% yield without epimerization. The *E*-substrate **3** afforded **29** in 94% yield. Since a cyclohexyl group has a higher migratory aptitude than a phenyl group in Baeyer−Villiger oxidation reactions,[29] the benzoyl groups in **28** and **29** could serve as precursor for benzoyl-protected hydroxy groups.

In conclusion, we have developed the first method to stereoselectively transform **A** to **B** using catalytic $NaHCO_3$ in DMSO−water. This divergent approach to prepare **B** and **C** from **A** should allow for the preparation of stereochemically diverse small molecule libraries.

Experimental Section

General Procedure for the Preparation of *Z*-Olefins. To a solution of alkynoate (0.2500 mmol) in 1:8 H_2O−DMSO (1.25 mL total) at 23 °C was added a 0.01 M solution of hydroquinone in DMSO (25 μL, 2.5 μmol). Subsequently, $NaHCO_3$ (15.8 mg, 50.0 μmol) was added in one portion, and the resulting solution was stirred at the same temperature for the indicated time. The reaction was then diluted with water (25 mL) and then acidified to pH 3 with a pH 3 phosphate buffer. The resulting aqueous mixture was extracted with Et_2O (25 mL × 3). The combined organic layers were then washed with water (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (EtOAc in hexanes) to afford the corresponding *Z*-olefin.

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Supporting Information Available: ^1H NMR, ^{13}C NMR, IR, and HRMS analysis data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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