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On the Mechanism of DABCO-Catalyzed Isomerization of γ-Hydroxy-α,β-alkynoates to γ-Oxo-α,β-(*E*)-alkenoates

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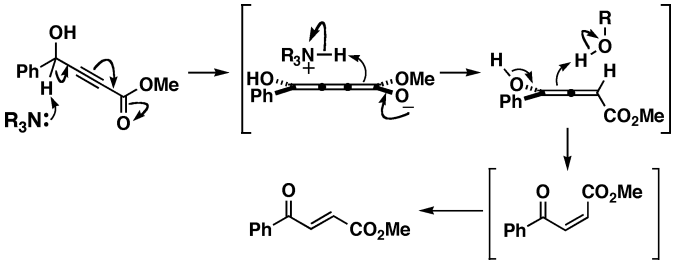
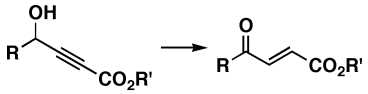
ABSTRACT



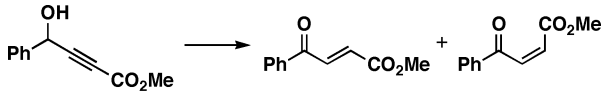
Since the discovery of organic base-catalyzed isomerization of γ-hydroxy-α,β-acetylenic esters to γ-oxo-α,β-*trans*-alkenyl esters in 1949, the mechanism has not been elucidated. This study shows that the mechanism involves cumulene formation, protonation with the conjugate acid of the amine, and protonation of the resulting allenol with water.

γ-Oxo-α,β-*trans*-alkenyl esters (**B**, Scheme 1) are substrates for various types of organic reactions[1] and part of peptidomimetic[2] and some natural products.[3] Compounds **B** can be formed via the redox isomerization of readily accessible[4,5] γ-hydroxy-α,β-alkynyl esters **A**. In 1949, the first example of such an isomerization was reported by the Raphael group (Scheme 2),[6] whereby **1** was subjected to excess Et_3N at 23 °C and the subsequent distillation afforded **E2**. The high E-selectivity is presumably due to the isomerization of **Z2**

Scheme 1. Redox Isomerization of **A** to **B**



Scheme 2. Redox Isomerization of **1** to **E2** and **Z2**



(1) (a) Angell, E. C.; Fringuelli, F.; Guo, M.; Minuti, L.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1988**, *53*, 4325. (b) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693. (c) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1998**, *63*, 812. (d) Hirayama, T.; Oshima, K.; Matsubara, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3293.

(2) Vabeno, J.; Brisander, M.; Lejon, T.; Luthman, K. *J. Org. Chem.* **2002**, *67*, 9186.

(3) (a) Nozoe, S.; Hirai, K.; Tsuda, K. *Tetrahedron Lett.* **1965**, *6*, 4675. (b) Hayashi, M.; Kim, Y. P.; Hiraoka, H.; Natori, M.; Takamatsu, S.; Kawakubo, T.; Masuma, R.; Komiyama, K.; Omura, S. *J. Antibiot.* **1995**, *48*, 1435. (c) Takamatsu, S.; Kim, Y. P.; Hayashi, M.; Hiraoka, H.; Natori, M.; Komiyama, K.; Omura, S. *J. Antibiot.* **1996**, *49*, 95.

(4) Midland, M. M.; Tramontano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28.

(5) Shahi, S. P.; Koide, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 2525.

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to **E2** at an elevated temperature in the presence of Et_3N as suggested in more recent literature.[7] The pathway of the Raphael reaction was "conjectured" to go through an allenol intermediate, PhC(OH)═C═$CHCO_2Me$ (**3**). Although the Raphael reaction has been used for many decades for the conversion of **A** to **B**,[7,8] neither the intermediacy of **3** nor the mechanism have been studied.

We have recently reported a more convenient transformation of **1** to **E2** using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a catalyst (10 mol %) at 23 °C,[9] and this method has been found to be applicable to other substrates **A**.[10] We have become interested in the mechanism of this DABCO-catalyzed isomerization because it could also be related to the mechanism of the Raphael reaction. Herein, we report our mechanistic studies of the Raphael-like reaction catalyzed by DABCO.

By monitoring the DABCO-catalyzed isomerization of **1** by ^{1}H NMR spectroscopy, we found that the half-life of **1** was approximately 90 min under the reaction conditions (10 mol % of DABCO, initial [**1**] = 0.25 M, DMSO-d_6, 23 °C). The yield of **E2** was approximately 95% based on the internal standard (Bn_2O) and the **E2**:**Z2** ratio was 33:1. The kinetic studies of the isomerization of **1** by ^{1}H NMR analysis revealed that the reaction rate was second order overall (Figure 1a) and first order with respect to DABCO (Figure 1b), indicating that the rate-determining step involves one molecule of DABCO and one molecule of **1** in the transition state.

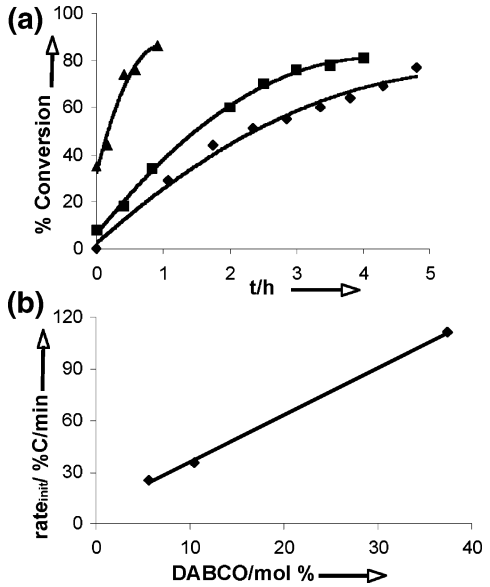
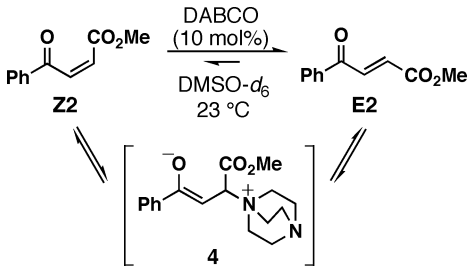


Figure 1. Kinetic studies of DABCO-catalyzed isomerization. (a) Conversion of the isomerization of **1** to **E2** catalyzed by 5.6 mol % (◆), 10 mol % (■), and 37 mol % (▲) of DABCO in DMSO-d_6 at 23 °C; (b) initial reaction rate vs DABCO in mol % of the isomerization of **1** to **E2** in DMSO-d_6 at 23 °C. R^2 = 0.999.

To determine whether this E-selective isomerization is thermodynamically controlled, compound **Z2** was subjected to 10 mol % of DABCO in DMSO-d_6 at 23 °C (Scheme 3).

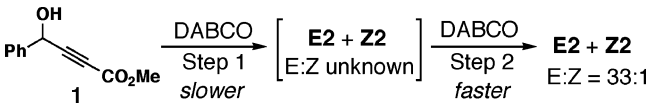
Scheme 3. DABCO-Catalyzed Isomerization of **Z2** to **E2**



^{1}H NMR analysis showed that the reaction mixture rapidly ($t_{1/2}$ < 5 min) reached nearly the same E:Z ratio (30:1), indicating that the origin of the high E-selectivity was a thermodynamic preference. A plausible mechanism for the isomerization between **Z2** and **E2** may involve intermediate **4**, which can be formed by the conjugate addition of DABCO toward **Z2** and **E2**.

At this point, we speculated that the DABCO-catalyzed isomerization of **1** proceeded in two steps (Scheme 4). In Step 1, **1** is transformed to the mixture of **E2** and **Z2** in an unknown ratio. In Step 2, the DABCO-catalyzed equilibrium between **E2** and **Z2** (see Scheme 3) is established to predominantly yield **E2**. Throughout the transformation of **1** to **E2**, compound **Z2** was hardly detectable by NMR analysis, which is consistent with the notion that the second step is much faster than the first step ($t_{1/2}$ = ~90 min for the overall process, whereas $t_{1/2}$ < 5 min for the isomerization of **Z2** to **E2**). Even though we cannot exclude the possibility that the high E-selectivity is due to a kinetic control, an alternative thermodynamic control is more likely because the kinetic pathway should involve the protonation of allenol **3** from the less hindered face to form **Z2** (see Scheme 7).

Scheme 4. Two Steps in the Isomerization of **1** to **E2**



To address this, we hypothesized that the intermediacy of **4** might be supported if the conversion of **Z2** to **E2** in the presence of D_2O resulted in the deuterated **E2**. To determine the position of the deuterium atom in **E2**, we required the unambiguous assignment of olefinic protons in the ^{1}H NMR spectrum (Figure 2). Toward this objective, an HMBC experiment proved to be informative, which revealed a coupling between the methyl hydrogens and C2 (see the

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(9) Sonye, J. P.; Koide, K. *Synth. Commun.* Accepted for publication.
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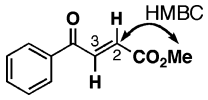
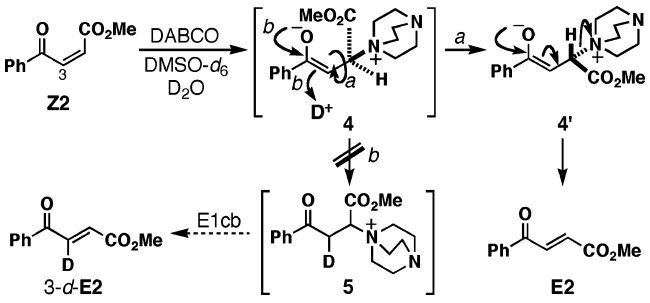


Figure 2. Key HMBC signal to assign 2-H and 3-H.

Supporting Information). On the basis of these results, the chemical shifts of 2-H and 3-H were assigned to be 6.89 and 7.93 ppm, respectively. With the proton assignment, we proceeded to study the isomerization of **Z2** to **E2** (Scheme 5); however, treatment of **Z2** with 10 mol % of DABCO in DMSO-d_6/D_2O (16:1) afforded **E2** and not 3-*d*-**E2** after 3 h. This experiment neither supports nor excludes the intermediacy of **4**, but indicates that the putative intermediate **4** undergoes the bond rotation-E1cb reaction (pathway a; **4** → **4′**) faster than protonation (pathway b). Importantly, this result suggested that deuterium incorporation in the isomerization of **1** to **E2** in DMSO-d_6/D_2O would elucidate the mechanism of Step 1 shown in Scheme 4.

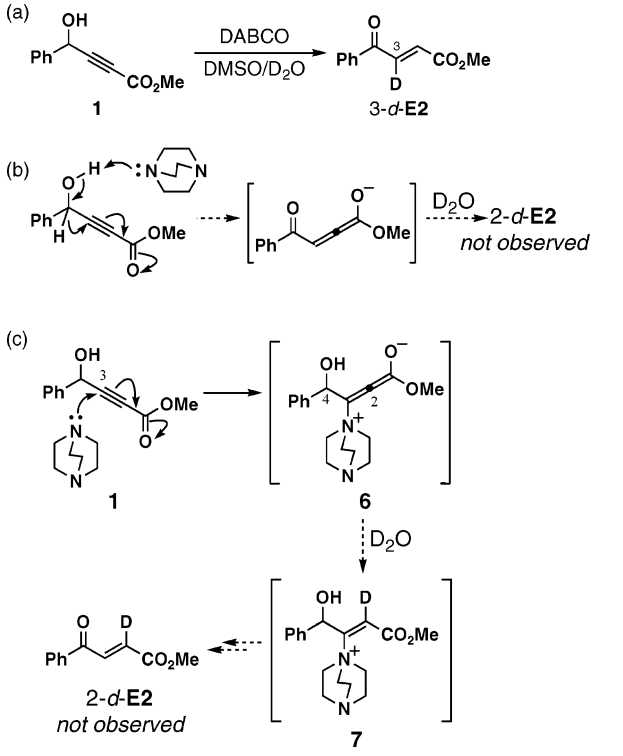
Scheme 5. No Deuterium Incorporation in the Isomerization of **Z2** to **E2**



Encouraged by this perspective, we turned our attention to Step 1. We treated **1** with 10 mol % of DABCO in DMSO-d_6/D_2O (16:1), which exclusively generated 3-*d*-**E2** (Scheme 6a). This result ruled out any mechanisms invoking a 1,2-hydride shift from C4 to C3 induced by the 4-OH deprotonation by DABCO (Scheme 6b). As an alternative mechanism, DABCO could undergo a conjugate addition toward acetylenic esters to generate intermediate **6** (Scheme 6c). This intermediate would be quenched by D_2O to form 2-*d*-**E2** via **7**. However, 2-*d*-**E2** was not observed; therefore, although **6** may be formed in a reversible manner, the subsequent pathway does not proceed in the DABCO-catalyzed isomerization of **1** to **E2**.

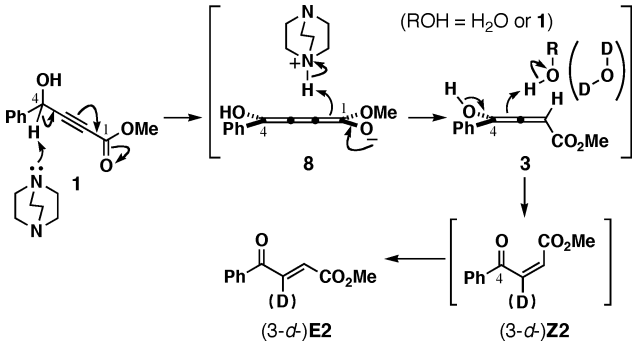
On the basis of the results described thus far, we postulated the mechanism shown in Scheme 7: the 4-H of **1** is abstracted by DABCO to form intermediate **8** and the protonated DABCO. The protonated DABCO species is far more acidic (pK_a = 9 in DMSO) than H_2O (or D_2O; pK_a = 32 for H_2O in DMSO), providing the source of the proton in the next step to form allenol **3**. The following tautomerization occurs by abstracting a proton from residual H_2O or

Scheme 6. Deuterium Incorporation Experiment



1 (or a deuterium from D_2O) in the less sterically hindered face[11] to generate 3-*d*-**Z2**. Finally, as described in Scheme 3, this intermediate isomerizes in the presence of DABCO to form 3-*d*-**E2**.

Scheme 7. Proposed Mechanism



If the above mechanism is correct and the deprotonation of 4-H is the rate-determining step, the substitution of 4-H of **1** with a deuterium atom should substantially retard the reaction by virtue of a primary isotope effect. Additionally, the product formed in DMSO−H_2O should be 2-*d*-**E2**

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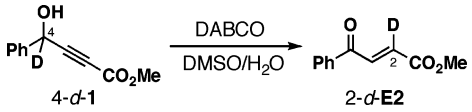
Scheme 8. Deuterium Transfer and Kinetic Isotope Effect

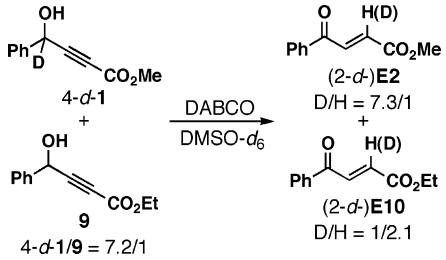


because the *N*-deuterated DABCO would quench cumulene **7** at the C2 position (Scheme 8). To test this hypothesis, 4-*d*-**1**, prepared by coupling PhCDO with Ag−C≡C−CO_2-Me,[5] was subjected to 20 mol % of DABCO in DMSO-d_6/H_2O (16:1) at 23 °C to find that 2-*d*-**E2** was indeed formed as the sole product. Furthermore, similarly to the enolization of 2,4-dimethyl-3-pentanone with NaOH (k_H/k_D = 6.1) at 25 °C,[12] a large kinetic isotope effect, k_H/k_D = 6.4, was observed at 23 °C. Thus, the proposed mechanism shown in Scheme 4 is consistent with this experiment and the dramatic reaction-rate acceleration in DMSO (the isomerization does not occur in nonpolar solvents such as $CHCl_3$ and benzene), a solvent that facilitates the formation of charged species such as **8** and the protonated DABCO. The results shown in Schemes 6a and 8 also indicate that the protonated DABCO does not undergo proton exchange with H_2O, which is not surprising because H_2O is far less acidic than the protonated DABCO in DMSO ($\Delta pK_a \approx 23$).

An unanswered question at this point was whether intermediate **8** formed a tight ion pair with the protonated DABCO. To address this question, a mixture of 4-*d*-**1** and **9** (7.2:1) in DMSO-d_6 was treated with 10 mol % of DABCO at 23 °C (Scheme 9). After the reaction, it was found that 12% of the methyl ester product contained H and 32% of the ethyl ester product contained D at their 2-positions. Due to the formation of protonated **E2** and deuterated 2-*d*-**E10**, it is deduced that intermediate **8** does not form a strong ion pair with the protonated DABCO.

(12) Lynch, R. A.; Vincenti, S. P.; Lin, Y. T.; Smucker, L. D.; Subba Rao, S. C. *J. Am. Chem. Soc.* **1972**, *94*, 8351.

Scheme 9. Crossover Experiment



Despite these observations, we cannot entirely exclude an alternative mechanism in which DABCO undergoes a conjugate addition with **1** to form intermediate **6**. To be consistent with our results, both the OH deprotonation of **7** by an additional DABCO molecule and a disrotatory 1,3-hydride shift from C4 to C2 occur at the same time. Alternatively, the conjugate addition of DABCO and the hydride shift occur simultaneously. Although we do not have any evidence to exclude these mechanisms, the stringent requirement for the timing of either of the two processes involving the kinetically unfavorable hydride shift would be less likely than the mechanism described above.

In conclusion, we have gained significant mechanistic insight into the DABCO-catalyzed isomerization of γ-hydroxy-α,β-alkynyl esters to γ-oxo-α,β-*trans*-alkenyl esters. The order of proton additions and the sources of each olefinic proton determined in this study could facilitate the development of related synthetic methods with various electrophiles.

Acknowledgment. Financial support was provided by the University of Pittsburgh. We thank a reviewer for suggesting the crossover experiment.

Supporting Information Available: NMR spectra for 3-*d*-**E2**, 2-*d*-**E2**, and the crossover experiment. This material is available free of charge via the Internet at http://pubs.acs.org.

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