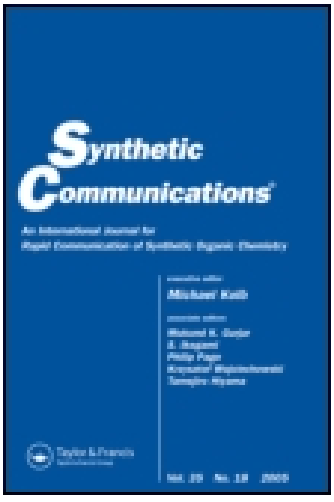

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Organic Base-Catalyzed Stereoselective Isomerizations of 4-Hydroxy-4-phenyl-but-2-ynoic Acid Methyl Ester to (*E*)- and (*Z*)-4-Oxo-4-phenyl-but-2-enoic Acid Methyl Esters

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Abstract: We have developed a 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalyzed isomerization of 4-hydroxy-4-phenyl-but-2-ynoic acid methyl ester to (*E*)-4-oxo-4-phenyl-but-2-enoic acid methyl ester and an *N*,*N*-diisopropylethylamine-catalyzed isomerization of the same substrate to (*Z*)-4-oxo-4-phenyl-but-2-enoic acid methyl ester.

Keywords: 1,4-Diazabicyclo[2.2.2]octane, *N*,*N*-diisopropylethylamine, γ-hydroxy-α,β-alkynoic esters, isomerization, γ-oxo-α,β-alkenoic esters

Both (*E*)- and (*Z*)-γ-oxo-α,β,-alkenoic esters (***E*-A** and ***Z*-A**, Figure 1) have been used as intermediates in complex molecule syntheses[1–5] and also found in peptidomimetics[6] and natural products such as cytochalasins A,[7] L,[8] vermiculine,[9] pyrenophorin,[10] and A26771B.[11] Although Wittig-type condensations[6] and other methods[12–14] have been employed to form ***E*-A**, additional methods would involve γ-hydroxy-α,β-alkynoic esters **B** as precursors. These esters are easy to prepare[15,16] even in the presence of reactive functional groups.[16] In principle, concomitant oxidation of the γ-hydroxy group and reduction of alkyne of **B** should afford ***E*-A** or ***Z*-A**.

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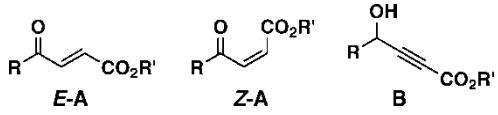
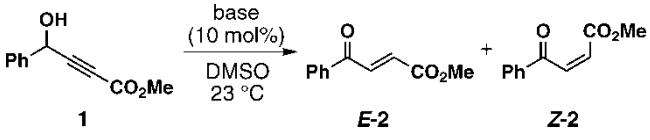


Figure 1. Structures of (*E*)- and (*Z*)-γ-oxo-α,β-alkensic esters and γ-hydroxy-α,β-alkynoic esters.

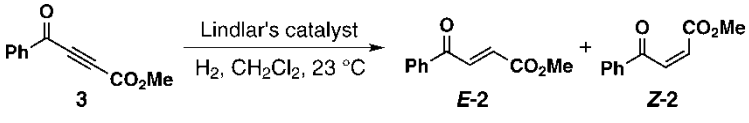
Such transformations have been achieved by three methods: (1) treatment of **B** with 0.5 equiv of Et_3N at 23°C, generating only ***E*-A** after distillation (our study and others[17] indicate that ***Z*-A** might have been isomerized to ***E*-A** during distillation in the presence of Et_3N);[17] (2) treatment of **B** with 1 equiv of *n*-Bu_3N at 23°C, generating a mixture of ***E*-A** and ***Z*-A**;[18] (3) treatment of **B** with 3 mol% of $Rh(PPh_3)_3Cl$, air-sensitive tri-*n*-butylphosphine,[19] and high temperature (110°C), generating ***E*-A**.[20] Although these methods can be used to prepare ***E*-A**, there are few general methods to prepare ***Z*-A** stereoselectively.[21] Herein, we report convenient organic base-catalyzed methods to convert **B** to ***E*-A** and **B** to ***Z*-A** stereoselectively.

During our efforts to develop diversity-oriented synthetic pathways using **1** (Equation (1)) as a pluripotent substrate, we found that treatment of **1** with Et_3N in CH_2Cl_2 at 23°C gave ***E*-2** and ***Z*-2** in approximately 70% yield (*E:Z* = 2 : 1). After some screening efforts, we found that 10 mol% of DABCO catalyzed such transformation in a highly *E*-selective manner (*E:Z*= 33 : 1) in 70% yield (DMSO, 23°C, 7 h). This is presumably a thermodynamically controlled reaction because the treatment of ***Z*-2** with 10 mol% DABCO in DMSO gave the same product distribution in 77% yield.



(1)

Catalytic *i*-Pr_2NEt (10 mol%) in DMSO/H_2O (4 : 1) isomerized **1** to ***Z*-2** and ***E*-2** in 47% combined yield in 10 : 1 ratio in favor of ***Z*-2**. In the absence of water, the *Z* : *E* stereoselectivity is only 2 : 1. Although the yield is currently moderate (not optimized), we found that the ***E*-2** was intact under similar conditions (10 mol% *i*-Pr_2NEt, DMSO/H_2O = 2 : 1, 23°C, 5 d), excluding the possibility that ***E*-2** selectively decomposed under the reaction conditions. It is noteworthy that the hydrogeratian of **3** using Lindlar's catalyst gave the mixture of ***E*-2** and ***Z*-2** in a 5 : 1 ratio presumably because of the quinoline-catalyzed isomerization of ***Z*-2** to ***E*-2** (Equation (2)).



(2)

We are currently studying the scope and mechanisms of these two new processes, which will be reported in due course.[24] In summary, we have developed the first metal-free catalytic processes for the stereoselective transformation of **1** to ***E*-2** and ***Z*-2**.

EXPERIMENTAL

Conversion of **1** to ***E*-2**. DABCO (2.8 mg, 0.0250 mmol) was added to a solution of **1** (47.6 mg, 0.250 mmol) in DMSO (1.0 mL) at 23°C, and the resulting solution was stirred at the same temperature for 7 h. The reaction was then quenched with 0.1 N HCl (0.3 mL) and water (20 mL), and the resulting aqueous mixture was extracted with Et_2O (30 mL × 5). The combined organic layers were then washed with water (20 mL × 3), dried over Na_2SO_4, filtered, and evaporated in vacuo. The resulting residue was purified by silica-gel chromatography (5 → 20% EtOAc in hexanes) to generate ***E*-2** (33.2 mg, 70%) as a pale yellow oil. The ^{1}H NMR spectrum of this product was consistent with the literature.[22]

Conversion of **1** to ***Z*-2**. *i*-Pr_2NEt (9.0 μL, 0.052 mmol) was added to a solution of **1** (99.7 mg, 0.52 mmol) in DMSO (0.8 mL) and water (0.2 mL) at 23°C, and the resulting solution was stirred at the same temperature far 2 d. The reaction was then quenched with 0.1 N HCl (0.6 mL) and water (20 mL), and the resulting aqueous mixture was extracted with EtOAc (15 mL × 3). The combined organic layers were then washed with water (20 mL × 1), brine (20 mL × 1), dried over Na_2SO_4, filtered, and evaporated in vacuo. The resulting residue was purified by silica-gel chromatography (5 → 20% EtOAc in hexanes) to generate a mixture of ***Z*-2** and ***E*-2** (47.2 mg, 47%; ***Z*-2** : ***E*-2** = 10 : 1, determined by ^{1}H NMR) as a pale yellow oil. The ^{1}H NMR spectrum of these products was consistent with the literature and showed no detectable impurities.[22,23]

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