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A novel and simple method to prepare γ-hydroxy-α,β-(*E*)-alkenoic esters from γ-keto-alkynoic esters

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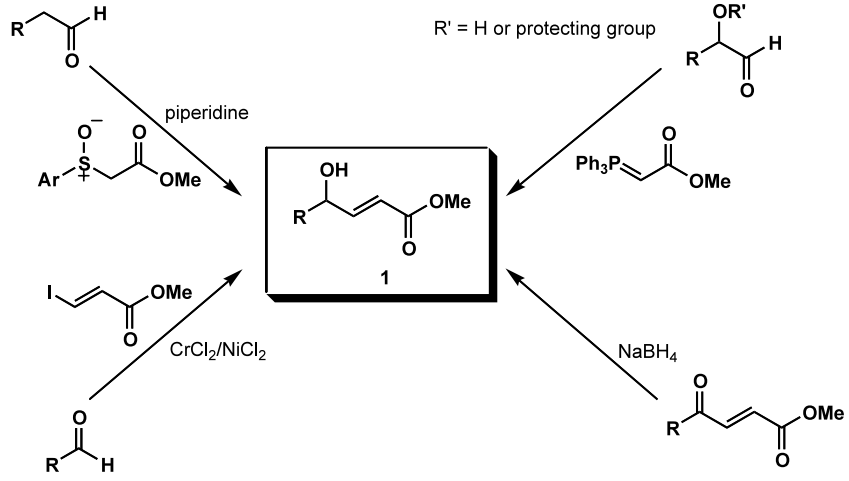
Abstract—A method to convert γ-keto-alkynoic esters to γ-hydroxy-α,β-(*E*)-alkenoic esters is described. This functional group transformation was accomplished in one step by means of $NaBH_4$ reduction in methanol.

γ-Hydroxy-α,β-(*E*)-enoates **1** (Scheme 1) are versatile synthetic intermediates[1–17] and part of many natural products.[18–28] This functionality has been prepared mostly by means of Wittig reactions,[29] rearrangements via vinylic sulfoxides,[30] reduction of γ-keto-α,β-(*E*)-alkenoates with $NaBH_4$, or the Nozaki–Hiyama–Kishi reaction.[10] Due to the lack of a synthetic method to convert ynoates to α,β-(*E*)-enoates, ynoate intermediates have not been used as precursors for α,β-(*E*)-enoates.

Herein we report that methyl 4-oxo-2-ynoates can be converted to methyl 4-hydroxy-2-(*E*)-alkenoates **1** in one step by means of $NaBH_4$ reduction. This method should render γ-keto-ynoic esters as viable precursors for the preparation of γ-hydroxy-α,β-(*E*)-alkenoic esters.

In an attempt to prepare a racemic form of compound **2a** (Fig. 1) during our synthetic studies toward FR901464, we synthesized keto ynoate **6a**[31] by coupling silver acetylide **4**,† prepared from the corresponding



Scheme 1. Known methods to prepare 4-hydroxy-(*E*)-2-alkenoic ester **1**.

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† It is noteworthy to comment on the safety of silver acetylide **4**. Since some silver acetylides are potentially explosive with a shock (especially using a metal spatula in the labs) and/or heat, we tested the safety of this silver acetylide; 20 mg of dry acetylide **4** was stirred in a glass vial with a sharp needle made of steel at 150°C. Although the color of this compound changed from pale pink to black upon heating, acetylide **4** did not exhibit any nature of explosiveness under these conditions. While it may be premature to draw a conclusion about the safety of acetylide **4** from this experiment, we have not had any accidents associated with this compound in our laboratory.

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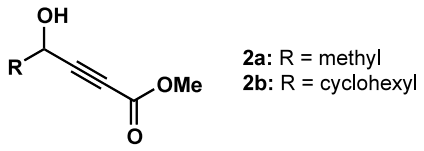
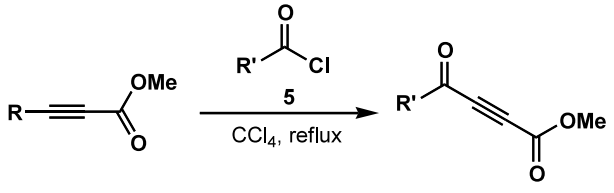


Figure 1. Structures of methyl 4-hydroxy-2-alkynoates.

alkyne **3**, with acetyl chloride in refluxing CCl_4 (Scheme 2).[32] This protocol does not require the use of a strong base such as LDA to deprotonate the acetylenic proton to form the C–C bond, which often results in undesired products. This one-step method to prepare ynones is more efficient than conventional two-step protocol (1. addition of metal acetylide to an aldehyde; 2. oxidation of the resulting alcohol).

With ketone **6a** in hand, we attempted to prepare alcohol **2a** by the action of $NaBH_4$. In effect, upon addition of 1.2 equiv. of $NaBH_4$ to ketone **6a**, we isolated *E*-enoate **1a** as a single product in 70% yield (Scheme 3). The spectroscopic data of compound **1a** were identical to the literature.[33] We were unable to detect either the corresponding *Z*-enoate or the desired ynoate **2a** by NMR analysis of the crude reaction mixture.



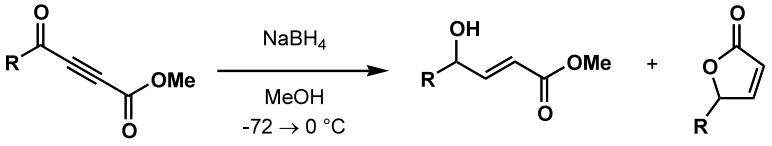
R '	time (h)	yield (%)
methyl	3	50
cyclohexyl	3	89
tert-butyl	3	99
phenyl	48	61

Scheme 2. Preparation of 4-oxo-2-alkynoates **6**.

To investigate the generality of this novel functional group transformation, we prepared ketones **6b**, **6c** and **6d**, which were subjected to the similar conditions. The result is summarized in Scheme 3. For these bulkier ketones, more equivalents of $NaBH_4$ were necessary. With only 1–2 equivalents of $NaBH_4$ in the reduction of **6b**, we isolated alcohol **2b** (Fig. 1) in addition to alcohol **1b**. The stereoselectivity of this reduction with these two substrates was determined to be 5.5:1 in favor of *trans*. Although the chemical yields of these reduction reactions are modest to good, we did not observe any by-products by NMR analysis of the crude mixture.

This simple functional group conversion reported herein should be applicable to syntheses of a wide variety of γ-hydroxy-α,β-(*E*)-alkenoic esters. Further studies of this methodology will be reported in due course.

Experimental: Sodium borohydride (203 mg; 5.36 mmol) was added to a solution of ketone **6b** (208 mg; 1.07 mmol) in methanol (3.6 mL) in one portion at −72°C. The temperature of the reaction mixture was then gradually raised to 0°C over 30 min, and the reaction mixture was stirred at the same temperature for an additional 30 min. The reaction mixture was quenched by the addition of diethyl ether (20 mL) and saturated aqueous NH_4Cl (8 mL) at 0°C, and the resulting solution was stirred at room temperature for 1 h. This mixture was separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL× 1) and brine (10 mL×1), and dried over Na_2SO_4. The organic layer was then concentrated in vacuo, and the resulting residue was purified by silica gel column chromatography (5→15% ethyl acetate in hexanes) to afford an inseparable mixture of alcohol **1b** and lactone **7b** (159 mg; 75% yield) as colorless oil. Data for compound **1b**: R_f 0.28 (20% ethyl acetate in hexanes); ^1H



6a: R = methyl
6b: R = cyclohexyl
6c: R = *tert*-butyl
6d: R = phenyl

1a: R = methyl
1b: R = cyclohexyl
1c: R = *tert*-butyl
1d: R = phenyl

7a: R = methyl
7b: R = cyclohexyl
7c: R = *tert*-butyl
7d: R = phenyl

	yield(%)	
R	**1**	**7**
methyl	70	not detected
cyclohexyl	63	12
tert-butyl	47	9
phenyl	60	not detected

Scheme 3. Reduction of methyl 4-oxo-2-alkynoates **6**.

NMR (300 MHz, 293 K, $CDCl_3$) $\delta = 6.97$ (dd, 1H, $J = 15.7$, 5.2 Hz), 6.04 (dd, 1H, $J = 15.7$, 1.7 Hz), 4.10 (broad dd, 1H, $J = 8.9$, 5.2 Hz), 3.75 (s, 3H), 1.99–1.01 (m, 11H); HRMS (CI+) calcd for $C_{10}H_{15}O_2$ (M^+–OMe) 167.1072; found 167.1072 m/z.

1a, **1c**, **1d**: The spectra were consistent with the literature.[33,34]

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