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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7077–7079

A direct synthesis of α-(hydroxymethyl) and α-alkyl-vinyl alkyl ketones

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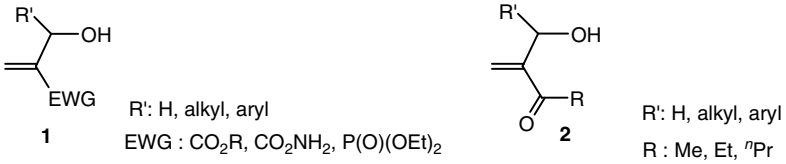
Received 9 March 2006; revised 7 July 2006; accepted 20 July 2006
Available online 14 August 2006

Abstract—Reaction of 2,4-diketoesters **3a–c** with aqueous formaldehyde using potassium carbonate solution as base affords the corresponding α-methylene-β-hydroxyalkanones **4a–c** which provide a route to α,β-unsaturated alkyl ketones **6a–e** via coupling of α-acetoxymethyl alkyl vinyl ketone **5a** with Grignard reagents in the presence of a catalytic amount of $LiCuBr_2$ at low temperature.

During the past decade, the preparation of α-hydroxyalkyl carbonyl compounds **1**[1–10] has attracted significant attention because of their ability to act as Michael acceptors[11,12] (Scheme 1). Furthermore, these compounds show a range of applications as starting materials for the preparation of α-methylene-γ-lactones,[13] α-methylene-γ-lactams[14] and cyclopentenones.[15]

Although studies have been reported,[16,17] there are only a few examples of the preparation of α-methylene-β-hydroxyalkanones **2**. According to the literature, the synthetic methods mainly consist of the alkoxyalkylation at the α-position of methyl vinyl ketones,[18] aldol condensation,[19] Wittig–Horner reaction of phosphonates and aqueous formaldehyde under heterogeneous conditions[3] and Baylis–Hilman reactions of aldehydes with α,β-unsaturated ketones in the presence of DABCO,[20–22] DBU[23] or 3-hydroxyquinuclidine[24] as catalysts. However, most of these methods suffer from low yields or the use of expensive chemicals and there is no general method which covers the different types of α-methylene-β-hydroxyalkanones **2**. To the best of our knowledge, α-hydroxyalkyl acrylic ketones **2**, where R = Ph, *p*-CH_3–C_6H_4, Et, R′ = H have not been reported in the literature with practical yields.[25]

In connection with our previous studies[2] on the development of new routes to **2**, we report herein a simple and convenient synthesis of β-hydroxy ketones **4** starting from 2,4-diketoesters **3** prepared according to the literature by condensation of ketones with diethyl oxalate in the presence of sodium ethoxide in ethanol.[26] As shown in Scheme 2, the condensation of aqueous formaldehyde with the 2,4-diketoesters **3**, at room temperature in the absence of any organic solvent gave the



Scheme 1.

Keywords: Baylis–Hillman; α-Hydroxmethyl alkyl vinyl ketones; α,β-Unsaturated alkyl ketones.
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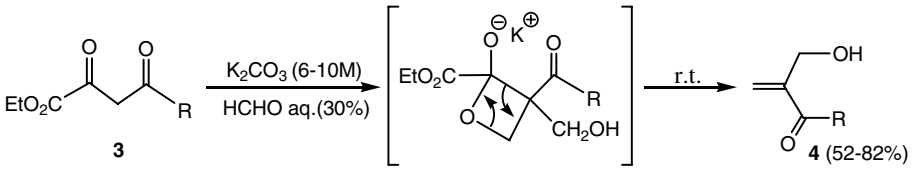
doi:10.1016/j.tetlet.2006.07.093



Scheme 2.

Table 1. α-Methylene-β-hydroxyalkanones **4a–c**

Product	R	Yield (%)[a]
4a	Ph	52
4b	*p*-CH_3–C_6H_5	56
4c	Et	82

[a] Yields refer to the pure isolated products characterized by IR, ^1H, ^{13}C NMR and mass spectrometry.

Table 2. α-Alkylated α,β-unsaturated ketones **6a–e**

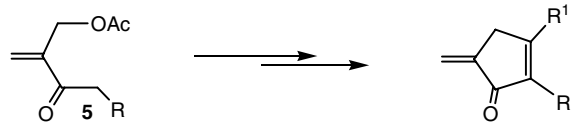
Product	RMgX (equiv)	Yield (%)[a]
6a	MeMgI (2.5)	54
6b	EtMgBr (2.2)	68
6c	*n*-PrMgCl (2.0)	87
6d	*i*-BuMgBr (2.3)	63
6e	$PhCH_2MgBr$ (2.0)	80

[a] Yields refer to the pure isolated products characterized by IR, ^1H, ^{13}C NMR and mass spectrometry.

novel α-methylene-β-hydroxyalkanones **4** via the well-established tandem hydroxymethylation–cyclisation–elimination mechanism, in acceptable to good yields. Spectroscopic data[27] were in accord with structures **4**. The results are summarized in Table 1.

When other bases, for example, potassium or sodium hydroxide were used, the reaction was not reproducible and only low yields of ketones **4** were obtained. In order to investigate the potential synthetic utility of α-methylene-β-hydroxyalkanone **4a**, we studied the electrophilic reactivity of the allylic acetate derivative **5a** using organometallics as nucleophilic reagents. Indeed, the conjugate addition of dialkyl organocuprates, generated in situ at low temperature from Grignard reagents in the presence of a catalytic amount of $LiCuBr_2$, to the acetate **5a** led to the corresponding α,β-unsaturated alkyl ketones **6**[27] in good yields through tandem reaction[28] involving nucleophilic S_N2' addition–elimination (Scheme 3). The results are summarized in Table 2.

In conclusion, a simple and expedient method for the direct synthesis of α-methylene-β-hydroxyalkanones **4a–c** is described which completes the existing routes[18–24] for preparation of α-functional alkyl-vinyl ones **2**. We have also demonstrated that allylic acetate **5a** can be easily displaced by organometallic species, at low temperature, to provide the corresponding α,β-unsaturated phenyl ketones **6a–e**. Moreover, the allylic acetate **5** could be used as an electrophilic synthon in the total synthesis of various natural products such as methylenomycin B[29,30] and various analogues[31] (Scheme 4). This work will be the subject of a future report.



Scheme 4.

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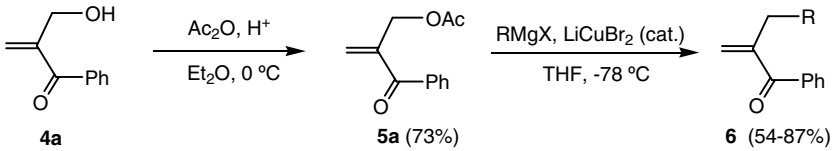

Scheme 3.

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27. *Synthesis of* α-*methylene*-β-*hydroxypropanone* **4a**: To a magnetically stirred mixture of 2,4-diketoester **3a** (16 mmol) and 30% aqueous formaldehyde (3.5 mL) was added at room temperature a gelatinous solution of potassium carbonate (6–10 M, 33 mmol). The heterogeneous reaction mixture was stirred for 3 h then treated with water. The solution was extracted with ether (3×25 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane, 3:7) to afford ketone **4a**. IR ν_{max} neat/cm^{-1} 3300, 1650, 1445: ^{1}H NMR (300 MHz, $CDCl_3$): 7.74 (2H, d, $J = 7.5$ Hz), 7.54 (1H, t, $J = 7.35$ Hz), 7.45 (2H, t, $J = 7.5$ Hz), 6.15 (1H, s), 5.81 (1H, s), 4.50 (2H, s), 2.77 (1H, m,); ^{13}C NMR (75 MHz, $CDCl_3$): 197.9 (C=O), 146.23 (CH_2=), 137.2 (=C), 132.4 ($CH_{aromatic}$), 129.3 ($CH_{aromatic}$), 128.2 ($CH_{aromatic}$), 127.3 ($C_{aromatic}$), 63.0 (CH_2); Mass (EI, 70 eV) *m*/*z* (%): 51 (35), 77 (89), 105 (100), 116 (13), 144 (9), 161 (96).
Organocuprate addition to allylic acetate **5a**: *Typical procedure*: A solution of propylmagnesium chloride ^{n}PrMgCl (2 equiv) was added dropwise over a period of 15 min to a mixture of α-acetoxymethyl phenyl vinyl ketone **5a** (2 mmol) and a 1 M solution of $LiCuBr_2$ (0.15 mL) diluted in dry THF (10 mL) at −78 °C under nitrogen. After a few minutes (TLC), the reaction mixture was quenched with saturated NH_4Cl solution (10 mL) then extracted with ether (3×15 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane, 2:8) to afford 2-methylene-1-phenylhexan-1-one **6c**. IR ν_{max} neat/cm^{-1} 1630, 1670, ^{1}H NMR (300 MHz, $CDCl_3$): 7.78 (2H, d, $J = 7.50$ Hz), 7.59 (1H, t, $J = 7.35$ Hz), 7.45 (2H, t, $J = 7.50$ Hz), 5.81 (1H, s), 5.56 (1H, s), 2.47 (2H, t, $J = 6.9$ Hz), 1.42 (4H, m), 0.92 (3H, t, $J = 7.35$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 198.5 (C=O), 148.5 (CH_2=), 137.9 (=C), 132.1 ($CH_{aromatic}$), 129.5 ($CH_{aromatic}$), 128.1 ($CH_{aromatic}$), 125.0 ($C_{aromatic}$), 32.0 (CH_2), 30.3 (CH_2), 22.4 (CH_2), 13.9 (CH_3). Mass (EI, 70 eV) *m*/*z* (%): 51 (19), 77(67), 105 (100), 145 (24), 159 (22), 188 (14).
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