An Unprecedented DBU–MeOH Promoted One-pot γ-Arylidenation of Cyclic β-Ketoesters by a Directed γ-Aldol Reaction and Dehydration Sequence

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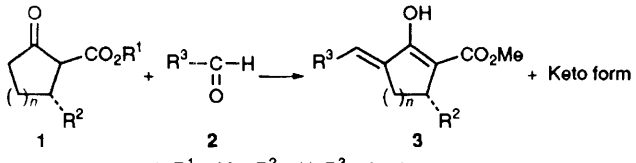
Cyclic β-ketoesters **1** undergo, in a one-pot process, an unprecedented DBU–MeOH promoted selective γ-arylidenation with aldehydes **2**, by a directed γ-aldol reaction and dehydration sequence, to afford stereoselectively synthetically valuable cycloalkenones **3** in good yields.

In conjunction with ongoing studies in our laboratory on the reactivity of carbanions derived from β-dicarbonyl compounds, we have recently shown the usefulness of cascade transformations initiated by the Michael addition of β-ketoesters to α,β-unsaturated electrophiles.[1] In this paper, we describe an unprecedented one-pot γ-arylidenation of cyclic β-ketoesters **1** with aldehydes **2**, by a 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) directed γ-aldol reaction and dehydration sequence, leading to synthetically valuable cycloalkenones **3**.

Whereas the directed γ-alkylation of β-dicarbonyl derivatives is well documented,[2,3] the related selective γ-alkylidenation has received little attention. To our knowledge, there is no precedent for the direct preparation of hitherto unknown carboxycycloalkenones **3** starting from simple cyclic β-ketoesters and aldehydes,[2] while in the acyclic version, the aldol type condensation of dianions derived from acetoacetates, combined with subsequent dehydration[4] or dehydrosulfenylation[5] and the Wadsworth–Emmons coupling of γ-phosphono β-ketothioesters[6] constitute interesting approaches.



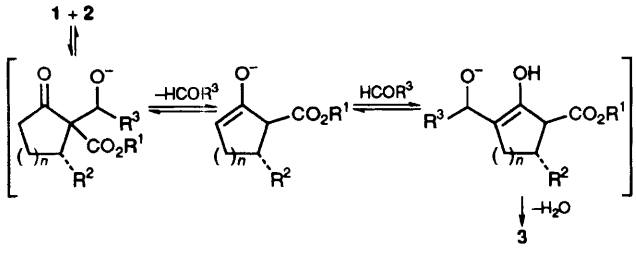
a $n = 1$, R^1 = Me, R^2 = H, R^3 = furyl
b $n = 1$, R^1 = Me, R^2 = H, R^3 = *o*-tolyl
c $n = 1$, R^1 = Me, R^2 = H, R^3 = *p*-(methoxycarbonyl)phenyl
d $n = 1$, R^1 = Me, R^2 = H, R^3 = phenyl
e $n = 1$, R^1 = R^2 = Me, R^3 = phenyl
f $n = 2$, R^1 = Et, R^2 = H, R^3 = *o*-tolyl
g $n = 2$, R^1 = Et, R^2 = H, R^3 = furyl
h $n = 2$, R^1 = Et, R^2 = H, R^3 = phenyl

Scheme 1 *Reagents and conditions*: 1 equiv. DBU, MeOH, room temp. to reflux, 4–24 h, 34–98%

Table 1 Preparation of ethylenic cycloalkanones **3**

β-Ketoester **1**	Aldehyde **2**	*t*/h	Product **3**	Yield (%)
a	a	24[a]	**a**	66
b	b	4[b]	**b**	71
c	c	6[b]	**c**	34
d	d	2[b]	**d**	70
e	e	3[b]	**e**	98
f	f	24[b]	**f**	50
g	g	19[a]	**g**	75
h	h	24[a]	**h**	86

[a] Room temp. [b] Reflux.

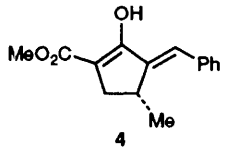


Scheme 2 Proposed mechanism for the cascade transformation

It is of interest to note that related unsaturated cyclic ketones are useful intermediates in the synthesis of natural products[7] and have also been used as precursors for potentially bioactive pyrimidine derivatives[8] and *trans*-disubstituted cycloalkanols.[9] On the other hand, the presence of three contiguous reactive centres such as two electrophilic and one nucleophilic sites should confer to intermediates **3** very interesting synthetic potentialities.

Our new one-pot γ-functionalization proceeds smoothly under mild conditions with various aldehydes **2** in MeOH in the presence of 1 equiv. of DBU (Scheme 1). The generality of the method is summarized in Table 1. Good unoptimized yields of **3** are generally obtained under the standard conditions reported above.† Compounds **3** exist as a mixture of keto and enol tautomers but only one stereoisomer having the *E* configuration is formed.[10]

The overall sequence is probably initiated by a reversible α-aldol reaction allowing the formation of the enolate, which reacts irreversibly with aldehydes **2** to give after dehydration the stable α-carboxy substituted, stereodefined and optically active ethylenic ketones such as **3e** (Scheme 2).‡ Experimental evidence for this pathway is provided by the structural elucidation of **3e**.§ The ^{1}H NMR spectrum shows a characteristic signal for the vinylic proton at δ 6.92 as a triplet with ^4J = 2.6 Hz, which after a selective irradiation of the allylic proton (δ 2.42, 1H, br d, J 17.7 Hz) appears as a doublet with ^4J = 2.6 Hz. These results are in complete agreement with the proposed structure for **3e**. An alternative mechanism involving a 1,3-ester shift through a cyclobutane-1,3-dione monohemiketal intermediate[11] leading to **4** can thus be ruled out.



The use of DBU in MeOH seems to be crucial since only starting materials are recovered with K_2CO_3 or NaOMe even after refluxing in MeOH for prolonged time. Moreover the condensation of ethyl cyclohexan-2-onecarboxylate with benzaldehyde is ineffective after 24 h in refluxing THF containing 1 equiv. of DBU and a very slow reaction of methyl cyclopentan-2-onecarboxylate is observed in the same conditions leading to **3d** in only 10% isolated yield.¶ Finally, when ethyl β-ketoesters **1f–h** are used, a complete transesterification occurs leading exclusively to methyl esters **3f–h**.

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Footnotes

† All new compounds gave satisfactory analytical and/or spectral data.

‡ We are grateful to one of the referees for fruitful comments on the mechanistic pathway.

§ **3e**: (Enol form) white crystals, R_f = 0.57 (diethyl ether–pentane, 1/1); IR (neat) ν/cm^{-1} 3054, 2985, 1708, 1655, 1650, 1601, 1264; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (3H, d, *J* 6.6 Hz), 2.42 (1H, br d, *J* 17.7 Hz), 3.04–3.15 (2H, m), 3.81 (3H, s), 6.92 (1H, t, *J* 2.6 Hz), 7.23–7.27 (1H, m), 7.36 (2H, t, *J* 7.5 Hz), 7.44 (2H, br d, *J* 7.5 Hz), 10.05 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 33.2, 36.2, 51.4, 110.9, 124.8, 127.7, 128.7 (2CH), 129.3 (2CH), 137.3, 136.8, 169.5, 170.7

¶ Obtained after 5 days at room temp. or 2 days at reflux.

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