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One-pot carbon–carbon bond formation at the β-position of cyclic ketones: oxidative Michael addition with alkyl malonates

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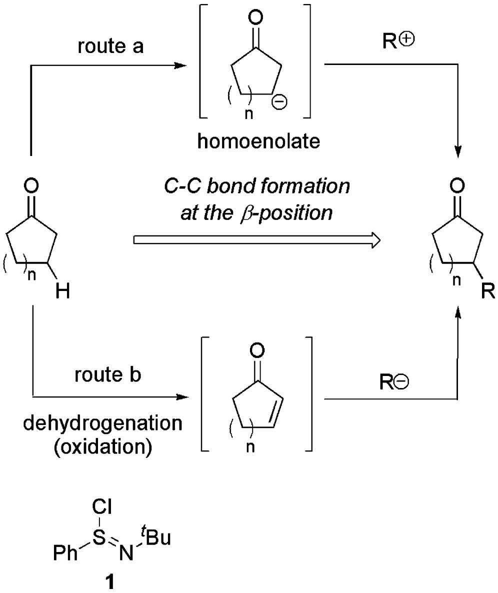
Abstract—A carbon–carbon bond was formed at the β-position of cyclic ketones in a one-pot manner by oxidation with *N-tert*-butylbenzenesulfinimidoyl chloride, followed by the reaction of malonic acid esters or potassium cyanide.

Direct carbon–carbon bond formation at the β-position of ketones still remains a difficult task in organic synthesis. Though homoenolate chemistry[1,2] offers an effective method for carbon–carbon bond formation with electrophiles at the β-position of carbonyl compounds, homoenolates are not prepared directly from the corresponding carbonyl compounds (Scheme 1, route a). On the other hand, carbon–carbon bond formation at the β-position of ketones with carbon nucleophiles is usually conducted by several steps. That is, ketones are first converted to the corresponding α,β-unsaturated ketones at the expense of two steps,[3–7] and the synthesized enones are next allowed to react with carbon nucleophiles to form a new carbon–carbon bond at their β-positions (route b). To the best of our knowledge, there is no report on one-pot carbon–carbon bond formation at the β-position of saturated ketones.

We have developed a new method for mild and direct dehydrogenation of carbonyl compounds to the corresponding α,β-unsaturated carbonyl compounds using *N-tert*-butylbenzenesulfinimidoyl chloride (**1**).[8,9] We considered that one-pot β-substitution of saturated ketones with carbon nucleophiles would be realized by dehydrogenation of ketone with **1** followed by 1,4-addition of carbon nucleophiles unless *N-tert*-butylbenzenesulfenamide, an oxidation co-product formed from **1**, interfered with carbon nucleophiles. In this communication, we present the results for the **1**-mediated one-pot β-substitution of cyclic ketones with diethyl malonates and potassium cyanide.



Scheme 1. Carbon–carbon bond formation at the β-position of ketones.

First, one-pot carbon–carbon bond formation at the β-position of α-benzoyl cyclic ketones with diethyl malonate was tried for two reasons: (i) the intermediate, α-acyl-α,β-unsaturated cyclic ketones,[10] are difficult to be prepared by the Knoevenagel condensation,[11] and (ii)

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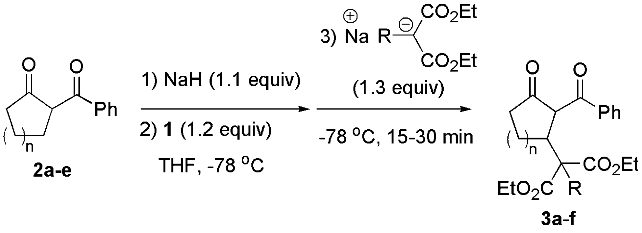
Table 1. One-pot oxidative Michael addition of diethyl malonate anion to α-benzoyl cyclic ketones **2a**–**e**



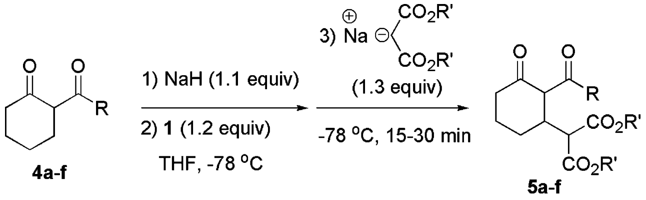
Entry	α-Benzoyl ketone	R	Product	Yield[a] (%)
1	$n = 1$ (**2a**)	H	**3a**	67
2	$n = 2$ (**2b**)	H	**3b**	84
3	$n = 3$ (**2c**)	H	**3c**	90
4	$n = 4$ (**2d**)	H	**3d**	50
5	$n = 8$ (**2e**)	H	**3e**	46[b]
6[c]	$n = 2$ (**2b**)	Me	**3f**	62

[a] Isolated yield unless otherwise noted.

[b] Determined by ^{1}H NMR analysis using an internal standard.

[c] A solution of sodium diethyl methylmalonate anion was added in the presence of HMPA (4.0 equiv).

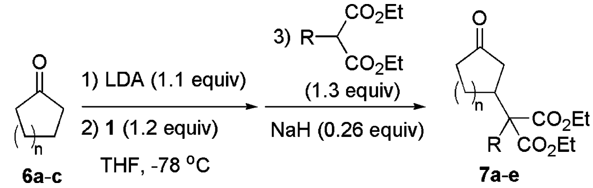
Table 2. One-pot oxidative Michael addition of malonic acid esters to various α-acylcyclohexanones **4a**–**f**

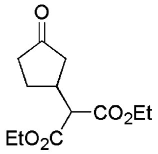
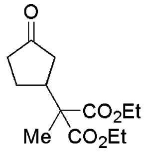
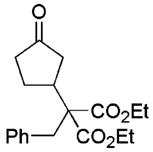
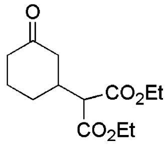
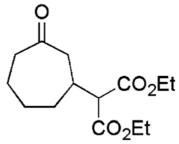


Entry	R	R′	Product	Isolated yield (%)
1	*o*-BrC_6H_4 (**4a**)	Et	**5a**	73
2	*p*-BrC_6H_4 (**4b**)	Et	**5b**	69
3	*p*-$MeOC_6H_4$ (**4c**)	Et	**5c**	85
4	Et (**4d**)	Et	**5d**	64
5	Pr (**4e**)	Et	**5e**	74
6	OMe (**4f**)	Bn	**5f**	74

these reactive intermediates should be employed without isolation in successive transformation. The procedure employed in Table 1 is as follows: α-benzoyl cyclic ke-

Table 3. One-pot oxidative Michael reaction of cyclic ketones **6a-c** with diethyl malonates



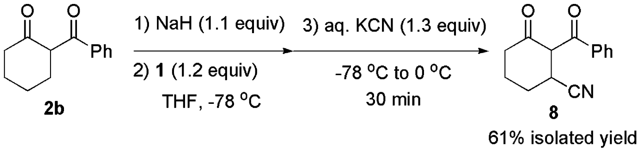
Entry	Cyclic ketone	R	Conditions	Product		Isolated yield (%)
1	**6a** ($n = 1$)	H	rt, 2 h		**7a**	82
2	**6a** ($n = 1$)	Me	rt, 3 h		**7b**	79
3	**6a** ($n = 1$)	Bn	rt, 3 h		**7c**	59
4	**6b** ($n = 2$)	H	Reflux, 6 h		**7d**	75
5	**6c** ($n = 3$)	H	Reflux, 26 h		**7e**	55

tones were dehydrogenated to the corresponding enones by treatment with sodium hydride followed by the reaction with **1** at −78 °C. The in situ formed enones were then treated at −78 °C with sodium diethyl malonate anion which was prepared in advance. It was found that the **1**-mediated dehydrogenation of α-benzoyl cyclic ketones **2a–e** proceeded smoothly at −78 °C in each case, and sodium diethyl malonate anion reacted with the formed enones at −78 °C. α-Benzoylcyclohexanone (**2b**) and α-benzoylcycloheptanone (**2c**) gave β-bis(ethoxycarbonyl)methyl ketones in high yields (entries 2 and 3), whereas five-membered ketone **2a** and medium-sized cyclic ketones such as **2d** and **2e** gave the corresponding β-substituted products in moderate yields (entries 1, 4, and 5).[12] Raising the reaction temperature from −78 °C to room temperature did not improve the yields of adducts. It was observed that adduct **3e** was unstable at room temperature and retro-Michael reaction proceeded. β-Substitution of **2b** with diethyl methylmalonate anion also proceeded in the presence of HMPA (entry 6).[13]

Various α-acylcyclohexanones were employed in order to investigate the scope and limitations of the present one-pot carbon–carbon bond formation (Table 2). The kind of substituent on the aromatic α-acyl group gave a little effect on the present reaction. Thus, **4c** bearing *p*-methoxy group was converted to **5c** in a slightly better yield than **4a** or **4b** bearing *o*- or *p*-bromo group (entries 1–3). Cyclohexanones having an aliphatic α-acyl group **4d–e** also gave the adducts **5d–e** in good yields (entries 4 and 5). In addition to β-diketones, β-ketoester **4f** reacted effectively with sodium dibenzyl malonate anion to give **5f** in 74% yield (entry 6).

Next, one-pot carbon–carbon bond formation of simple cyclic ketones such as cyclopentanone (**6a**), cyclohexanone (**6b**) and cycloheptanone (**6c**) were examined (Table 3). In situ formation of enone was performed by deprotonation with LDA followed by reaction with **1** at −78 °C in THF.[9] The addition of malonic acid esters was carried out by using a catalytic amount[14] of sodium hydride at room temperature. It was found that dehydrogenation of **6a–c** with **1** proceeded rapidly at −78 °C, and cyclopentenone generated directly from cyclopentanone (**6a**) reacted with diethyl malonate more smoothly than did cyclohexenone and cycloheptenone generated from **6b** and **6c**, respectively, (entries 1–3 vs entries 4–5). Various diethyl 2-alkylmalonates such as diethyl methylmalonate and diethyl benzylmalonate reacted with in situ formed cyclopentenone to give adducts **7b–c** in good yields (entries 2 and 3).

β-Cyano ketones are valuable synthetic intermediates in organic synthesis and they are often prepared by hydrocyanation of α,β-unsaturated ketones.[15] One-pot substitution at the β-position of ketone with cyanide ion was performed by using α-benzoylcyclohexanone (**2b**) as a model substrate (Scheme 2). Addition of an aqueous solution of potassium cyanide to enone directly formed by using **2b** and **1** resulted in the formation of a desirable carbon–carbon bond to afford **8**.



Scheme 2. One-pot β-substitution of **2b** with cyanide ion.

In summary, we have developed an efficient and convenient one-pot carbon–carbon bond formation at the β-position of cyclic ketones with malonic acid esters and cyanide ion. The present procedure will be applicable to other carbon nucleophiles to form various types of carbon–carbon bonds at the β-position of carbonyl compounds.

Acknowledgments

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Supplementary data

Supplementary data including spectral data of the products (**3a–f**, **5a–f**, **7a–e**, and **8**) and experimental procedures can be found. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.059.

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12. *Typical procedure (Table 1, entry 3)*: To a stirred mixture of sodium hydride (60%, 21.7 mg, 0.54 mmol) in THF (2 mL) was added a solution of **2c** (99.5 mg, 0.46 mmol) in THF (1.5 mL) at room temperature, and the mixture was stirred for 30 min. A solution of **1** (122 mg, 0.57 mmol) in THF (1.5 mL) was added at −78 °C, and the mixture was stirred for 30 min. Then a solution of diethyl malonate anion (prepared by diethyl malonate and NaH, 0.60 mmol) in THF (1.9 mL) was added at −78 °C, and the mixture was stirred for 30 min. After adding saturated aqueous sodium bicarbonate solution, the mixture was extracted with ethyl acetate (three times), and the extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by thin-layer chromatography on silica gel (hexane–ethyl acetate = 2:1) to afford **3c** (154.3 mg, 0.412 mmol, 90%).
13. In the absence of HMPA, the 1,4-addition did not proceed.
14. β-Substitution of **6b** with a stoichiometric amount of sodium diethylmalonate anion gave **7d** in 55–57% yields.
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