An efficient iodine-catalysed Knoevenagel condensation reaction in the presence of acetic anhydride

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A mild, simple and efficient iodine catalysed system has been developed for the Knoevenagel condensation of 1,3-dicarbonyl compounds with various aromatic aldehydes in the presence of acetic anhydride. The reaction gave good to excellent yields for a broad range of substrates.

Keywords: iodine, catalyst, acetic anhydride, Knoevenagel condensation

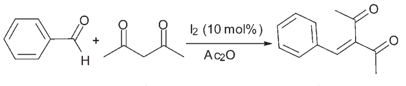
Knoevenagel condensation reactions play an important role in modern organic synthesis.[1] Recently, some novel catalytic systems for the Knoevenagel condensation reaction have been reported. In these processes, Lewis acids,[2,3] (S)-proline,[4] surfactants[5,6] and ionic liquids[7,8] have been employed to catalyse the Knoevenagel condensation reaction. However, the disposal of these metal salts or corrosive acids is troublesome and therefore prevents their large scale applications. The development of efficient and environmentally friendly catalysts and procedures for the Knoevenagel condensation reaction is still a useful topic.

Recently, molecular iodine has attracted attention as a simple, inexpensive, and non-toxic reagent in organic synthesis.[9–11] Ren and co-workers described an elegant example of the Knoevenagel condensation reaction catalysed by I_2/K_2CO_3.[12] However, the reaction failed under the reported conditions with 1,3-dicarbonyl compounds. The iodine catalysed benzylation reaction of 1,3-dicarbonyl compounds was also observed by our group.[13] When 1,1′-diacetoxytoluene was used, a Knoevenagel condensation product was obtained in excellent yield. Herein, we wish to describe the I_2-catalysed Knoevenagel condensation of 1,3-dicarbonyl compounds with various aromatic aldehydes in the present of acetic anhydride.

Initial exploration of the iodine-catalysed reaction of benzaldehydes (**1a**) with acetylacetone (**2a**) concentrated on varying the reaction conditions (Table 1). The addition of acetic anhydride remarkably improved the yield of **3a** (Table 1, entries 11, 12). Moreover, the effect of solvents on this reaction is important. Compared with other solvents (MeOH, EtOH, MeCN, or H_2O), this I_2-catalysed Knoevenagel reaction proceeded much better in nitromethane, dichloroethane (DCE) or without solvent (Table 1, entries 1–7). From these experiments, the best result with respect to yield was obtained when the reaction was performed with 10 mol % of iodine catalyst in the present of acetic anhydride in DCE at 80 °C (Table 1, entries 8, 11). The reaction proceeded smoothly without the exclusion of moisture and air from the reaction mixture.

Under the optimised conditions, we then investigated this I_2-catalysed Knoevenagel reactions with various aromatic aldehydes and 1,3-dicarbonyl compounds. It was shown that the reaction proceeded smoothly with both electron-rich and electron-poor aromatic aldehydes affording the corresponding Knoevenagel condensation products in excellent yields (Table 2, **3b–f**). A number of functional groups, such as Cl, Br,

Table 1 I_2 catalysed reaction of benzaldehyde with acetylacetone[a]

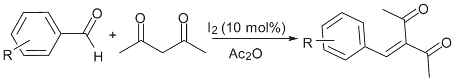


1a **2a** **3a**

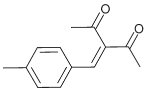
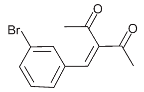
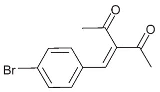
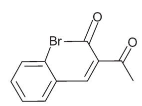
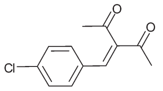
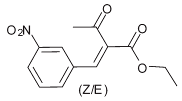
Entry	Solvent	**1a:2a**	Yield/%[b]
1	—	1:4	86
2	$MeNO_2$	1:4	83
3	MeCN	1:4	60
4	H_2O	1:4	0
5	MeOH	1:4	0
6	EtOH	1:4	0
7	$ClCH_2CH_2Cl$	1:4	91
8	$ClCH_2CH_2Cl$	1:2	94
9	$ClCH_2CH_2Cl$	1:1	87
10	$ClCH_2CH_2Cl$	1:1.5	87
11	$ClCH_2CH_2Cl$	1:1.2	91
12	$ClCH_2CH_2Cl$	1:1.2	32[c]

[a] All reaction were carried out by using 1 mmol of benzaldehyde, 2 mmol of Ac_2O and 0.1 mmol of I_2 at 80 °C in 2 mL of solvent.6 h.
[b] Isolated yield. [c] no acetic anhydride.

Table 2 I_2 catalysed reaction of different aromatic aldehyde with acetylacetone[a]



1 **2a** **3**

Entry	Main product	M.p.	Yield/%[b]
1	 **3b**[2]	Liquid oil	92
2	 **3c**[14]	Liquid oil	80
3	 **3d**[14]	76–78 °C lit. [18]76–77 °C	83
4	 **3e**	Liquid oil	86
5	 **3f**[2]	Liquid oil	91
6	 **3g**[15]	Liquid oil	47 (3:2)[c]

[a] All reaction were carried out by using 1 mmol of aromatic aldehyde, 1.2 mmol of 1,3-dicarbonyl compounds and 0.1 mmol of I_2 at 80 °C in 2 mL of DCE.
[b] Isolated yield.
[c] ethyl 3-oxobutanoate be used. The ratio of the two diastereomers is given in parentheses.

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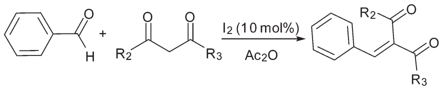
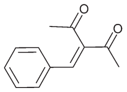
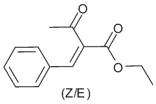
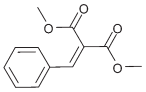
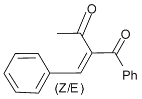
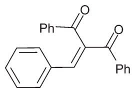
Table 3 I_2 catalysed reaction of different 1,3-dicarbonyl compounds with benzaldehyde[a]



1a **2** **3**

Entry	Product	M.p.	Yield/%[b]
1	 **3a**[2]	Liquid oil	94
2	 **3h**[2]	Liquid oil	73(69:31)
3	 **3i**[16]	Liquid oil	60
4	 **3j**[17]	97–98 °C	87(5:4)
5	 **3k**[2]	81–82 °C lit.[2] 81 °C	72

[a] All reaction were carried out by using 1 mmol of benzaldehyde, 1.2 mmol of 1,3-dicarbonyl compounds and 0.1 mmol of I_2 at 80 ºC in 2 mL of DCE.

[b] Isolated yield. The ratio of the two diastereomers is given in parentheses.

and NO_2 were tolerated. However, the reaction with the highly electron-deficient *m*-nitrobenzaldehyde only gave a 47% yield (Table 2, **3g**).

Further investigations were concentrated on the scope and limitations of this reaction (Table 3). Various active methylenes compounds, such as ethyl acetoaectate (Table 3, **3h**, 73%), benzoylacetone (Table 3, **3i**, 85%), dibenzoylmethane (Table 3, **3j**, 82%), gave corresponding products in good isolated yields.

From these results, we considered that aldehydes react with acetic anhydride to form the more reactive geminal diacetates *in situ* [11], and alkylation of 1,3-dicarbonyl compounds with diacetates then provides the Knoevenagel products. The moderate yields of **3g** might be due to the difficult step of benzylation reactions.

In summary, we have developed a general and efficient I_2-catalysed Knoevenagel condensation reaction of aromatic aldehydes with 1,3-dicarbonyl compounds. The reactions proceeded well in good to excellent yield under mild and non-metallic conditions and can be utilised for a broad range of substrates.

Experimental

GC analyses were performed on an Agilent 4890D spectrometer equipped with the same column and in the same conditions as the GC.

^1H and ^{13}C NMR spectra were recorded at room temperature on a Bruker 400MHz spectrometer with $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a LC-MSD-Trap-XCT instrument by electrospray ionisation (ESI) mass spectrometer. High resolution mass spectra were recorded on a Waters Q-Tof micro™ spectrometer by electrospray ionisation (ESI). IR spectra were recorded on a Bruker IFS25 Infrared Spectrometer. Melting points were uncorrected and measured on a XT-5 apparatus.

Synthesis of **3a–j**

I_2 (25.4 mg, 0.1 mmol) was added to a mixture of the aromatic aldehyde (1 mmol), Ac_2O (2 mmol), 1,3-dicarbonyl compound (1.2 mmol) and DCE (2 mL). The reaction mixture was stirred magnetically at 80 °C. After completion of the reaction (GC), the solvent was concentrated under reduced pressure by an aspirator, and the residue was purified by preparative TLC using 10:1 petroleum: ethyl acetate as an eluent to afford products. All procedures were carried out under air. All products were characterised by ^1H NMR and ^{13}C NMR. For example **3a**: Liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1 H), 7.40 (s, 5 H), 2.43 (s, 3 H), 2.29 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.7, 196.6, 142.7, 139.9, 132.8, 130.7, 129.7, 129.0, 31.7, 26.5. MS (ESI) *m/z* = 211.0 $[M + Na]^+$. **3e**: Liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.65 (d, J = 7.08 Hz, 1H), 7.30 (m, 2H), 7.27 (m, 1H), 2.46 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 196.3, 168.3, 144.2, 139.0, 133.2, 131.5, 130.3, 127.8, 124.3, 31.6, 26.7. IR (neat): 793, 1124, 1476, 1615, 1658, 1708, 2854, 2925 cm^{-1}. HRMS Calcd for $C_{12}H_{11}BrO_2$ (M+Na): 288.9840. Found:288.9844.

Electronic Supplementary Information

The ^1H and ^{13}C NMR and, where relevant, HRMS data for all the products have been deposited in the ESI available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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