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Novel tandem reactions of ethyl acetoacetate with aromatic aldehydes: product- and stereo-selective formation of highly functionalised cyclohexanones

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Abstract—The five-component tandem reaction of ethyl acetoacetate with aromatic aldehydes in the presence of pyrrolidine affords *t*(3),*t*(5)-diaryl-*t*(4)-[(*E*)-3-aryl-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanones stereoselectively in good yields presumably via a tandem Knoevenagel condensation–Michael addition–condensation via enamine-deethoxycarbonylation–Michael addition sequence. The same reactants in the presence of DBU led to the formation of *t*(3)-aryl-*r*(2),*c*(4)-bisethoxycarbonyl-*c*(5)-hydroxy-*t*(5)-methylcyclohexanones in excellent yields via a tandem Knoevenagel condensation–Michael addition–aldol reaction sequence.

1. Introduction

Cyclohexanone constitutes the backbone of many systems, which display biological activities such as herbicidal,[1] antibacterial,[2] antifungal,[2] convulsant,[3] anticonvulsant,[3,4] *anti*-implantation[5] and antiasthmone,[6] besides being useful in organic synthesis and in industry.

Tandem or cascade processes are one-pot multistep reactions providing rapid access to complex structures, and hence powerful for synthetic transformations.[7–10] Tandem reactions fall under the fold of green chemistry as the intermediates are not isolated and purified thus minimising the waste associated with solvent, adsorbent and loss of product during purification using crystallisation/column chromatography, besides minimising energy, labour and time.[11] In this paper, we report a one-pot tandem sequence for the diastereoselective synthesis of *t*(3),*t*(5)-diaryl-*t*(4)-[(*E*)-3-aryl-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanones and *t*(3)-aryl-*r*(2),*c*(4)-bisethoxycarbonyl-*c*(5)-hydroxy-*t*(5)-methylcyclohexanones (Fig. 1) by the reaction of ethyl acetoacetate with aromatic aldehydes in the presence of pyrrolidine or DBU, respectively, at ambient temperature. These cyclohexanones could serve as useful synthons in further synthetic endeavours, as the former has α,β-unsaturated carbonyl and β-keto ester functionalities and the latter has β-keto ester and β-hydroxy ester functionalities.

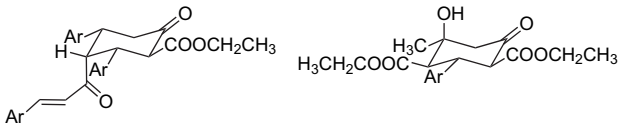
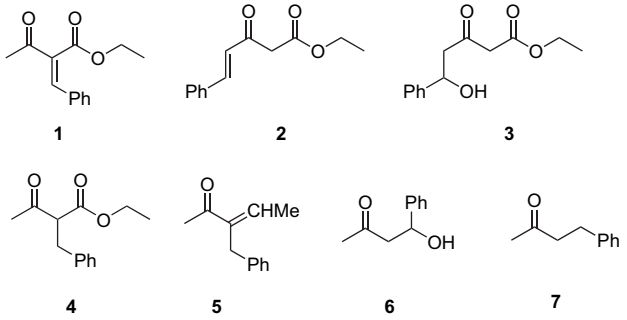


Figure 1.

The reaction of aromatic aldehydes with ethyl acetoacetate in the presence of different catalysts has been investigated.[12–23] The reaction of ethyl acetoacetate and benzaldehyde in the presence of piperidine,[12] sodium carbonate,[13,14] triethyl amine,[15] potassium carbonate–polyethylene glycol,[16] bismuth trichloride[17] and piperidine–acetic acid[18,19] afford ethyl 2-benzylidene-3-oxobutanoate **1**. The same reaction in the presence of titanium tetrachloride–triethyl amine,[15] sodium hydride–butyl lithium[20] and chlorotrimethylsilane–sodium iodide–acetonitrile[21] affords ethyl 3-oxo-5-phenylpent-4-enoate **2**, ethyl 5-hydroxy-3-oxo-5-phenylpentanoate **3** and ethyl 2-benzyl-3-oxobutanoate **4**, respectively. Alternatively in the presence of sodium



Keywords: Pyrrolidine; DBU; Ethyl acetoacetate; Tandem; Knoevenagal; Michael; Cyclohexanone; Enamine; Aldol; Aldehyde.
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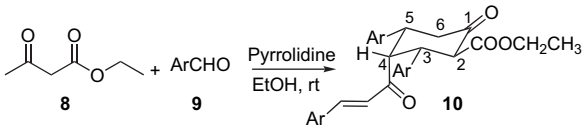
hydroxide–pyridine,[22] the reaction leads to a mixture of 3-phenylpent-3-en-2-one **5** and 4-hydroxy-4-phenylbutan-2-one **6**. The same reactants in the presence of potassium tetracarbonylhydridoferrate furnishes 4-phenylbutan-2-one **7**.[23]

2. Results and discussion

2.1. Synthesis of *t*(3),*t*(5)-diaryl-*t*(4)-[(*E*)-3-aryl-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanones

In the present investigation, the reaction of ethyl acetoacetate **8** with aromatic aldehydes **9** in a 2:3 molar ratio in the presence of pyrrolidine at ambient temperature affords after 2–5 days *t*(3),*t*(5)-diaryl-*t*(4)-[(*E*)-3-aryl-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanones **10** (Scheme 1). The products **10** were isolated in a pure state by flash chromatography in 58–68% yield.



9 and 10	Ar
a	C_6H_5
b	4-ClC_6H_4
c	4-$CH_3C_6H_4$
d	4-$CH_3OC_6H_4$
e	2-ClC_6H_4
f	2-$CH_3OC_6H_4$
g	2-$CH_3C_6H_4$

Scheme 1.

This reaction was investigated in different solvents with varying amounts of pyrrolidine with a view to (i) investigating the influence of the solvent on the course of the reaction and (ii) optimising the yield of **10**. The data furnished (Table 1) reveal that the yield of **10** remains constant when the amount of pyrrolidine employed in this reaction is between 25 and 100 mol % and the reaction was found to be slow in the presence of 10 mol % or less. The reaction of ethyl acetoacetate with aromatic aldehydes in a 2:3 molar ratio using 25 mol % of pyrrolidine in DMSO took 4 days for completion, affording **10a** in 58% (entry 1). In ethanol, the reaction was complete within 2 days furnishing a slightly enhanced yield of **10a** (62%; entry 4). In both the solvents, the amount of pyrrolidine was varied, viz. 25, 50, 100 mol %, whereupon the yield does not alter. The use of CH_3OH, DMF or CH_3CN as solvent has little effect on the yield of **10a** (entries 7–9) revealing that this tandem reaction is unaffected by the solvent.

Table 1. Pyrrolidine-catalysed reactions of ethyl acetoacetate with aromatic aldehydes affording **10**

Entry	Compound	Pyrrolidine (mol %)	Solvent	Yield	Reaction time (days)
1	**10a**	25	DMSO	58	4
2	**10a**	50	DMSO	59	4
3	**10a**	100	DMSO	60	3
4	**10a**	25	EtOH	62	2
5	**10a**	50	EtOH	63	2
6	**10a**	100	EtOH	63	2
7	**10a**	25	MeOH	61	4
8	**10a**	25	DMF	60	5
9	**10a**	25	CH_3CN	58	4
10	**10b**	25	EtOH	66	2
11	**10c**	25	EtOH	62	2
12	**10d**	25	EtOH	60	2
13	**10e**	25	EtOH	68	2
14	**10f**	25	EtOH	68	2
15	**10g**	25	EtOH	59	3
16	**10h**	25	EtOH	58	3

The structure of ketone **10** is in accord with the NMR spectroscopic data as illustrated for the representative example **10a**. The one proton doublet at 4.93 ppm (J=12.9 Hz) is assigned to H-2, as this is the only ring proton that has one coupling partner, viz. H-3. The proton, H-3, gives a doublet of doublets at 3.94 ppm (J=12.9 and 4.4 Hz), ascribed respectively, to vicinal couplings with adjacent H-2 and H-4. The triplet at 3.85 ppm (J=4.4 Hz) for one proton is assigned to H-4, which couples equally with the adjacent axial protons, H-3 and H-5. These assignments are also supported by H–H-COSY and HMBC correlations shown by thick bonds and curved arrows, respectively, in Figure 2. The HMBC correlation is also useful in assigning the ^{13}C signal at 202.7 ppm to the carbonyl of the 3-aryl-2-propenonyl moiety attached to C-4.

That the multiplet at 3.67 ppm is due to H-5 is evident from a H–H-COSY correlation with H-4 and the diastereotopic methylene protons (6-CH_2). The H-6eq appears as a doublet of doublets at 2.66 ppm (J=12.9 and 1.8 Hz) arising from geminal and vicinal axial–equatorial couplings, while the H-6ax appears as a triplet at 3.69 ppm (J=12.9 Hz), the diaxial and geminal couplings being fortuitously equal. The HMBC correlation (Fig. 2) between the H-6eq/H-6ax protons and the carbon at 206.1 ppm points to the assignment of the latter to C-1. The multiplet at 4.06 ppm for two protons is assigned to the diastereotopic CH_2 protons of the ester group, which also shows a HMBC correlation with the ester carbonyl at 169.7 ppm. The above ^1H NMR spectroscopic features reveal that the ester function at C-2 and the aryl rings at C-3 and C-5 are all equatorially oriented, while the (*E*)-3-aryl-2-propenonyl group at C-4 is oriented axially.

The doublets at 5.78 and 6.83 ppm (J=16.2 Hz) of **10a** are assigned to H-α and H-β of the (*E*)-3-aryl-2-propenonyl group. These assignments are evident from the HMBC correlations of H-α and H-β with the neighbouring carbons, especially from the correlation of H-β with the signal at 127.8 ppm due to the *ortho*-carbon in the phenyl ring of the cinnamoyl group (Fig. 2). Both these protons appear unusually upfield than would normally be expected for an α,β-unsaturated carbonyl system, presumably due to shielding by the neighbouring two aryl rings at the C-3 and C-5 positions. This conclusion is also in accord with the MM2 minimised structure of **10a** given in Figure 3.

The ^{13}C NMR spectra of compounds **10a–h** are also in agreement, their spectra having one signal in the range of 206.0–207.5 ppm and another in the range of 201.4–202.9 ppm ascribable to C-1 and the 3-aryl-2-propenonyl

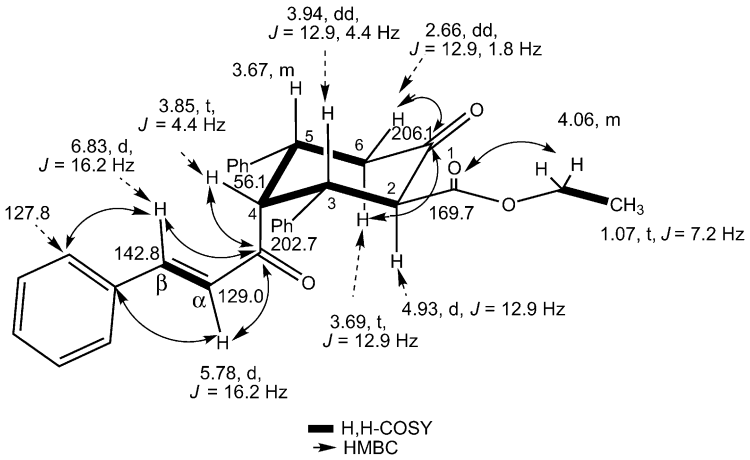


Figure 2. Selected ^{1}H and ^{13}C NMR parameters and 2D NMR correlations for **10a**.

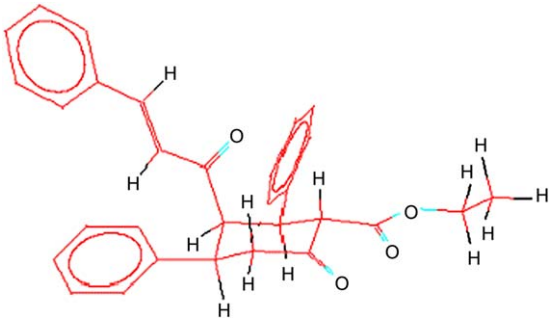


Figure 3. Geometry for **10a** optimised by molecular mechanics calculations.

carbonyls, respectively. The spectra of **10a–h** have a signal in the range of 169.6–170.6 ppm due to the ester carbonyl at C-2. The resonances of **10a–h** in the range 114.7–142.8 ppm are due to the aromatic carbons, among which the less intense ones in the region, 130.2–142.8 ppm, are attributed to the *ipso* carbons. The cyclohexanone ring carbon signals, C-2 to C-6, occur in the range, 42.1–61.8 ppm, and individual assignments are readily achieved from the proton chemical shifts and C–H-COSY correlations (Table 2).

This reaction can be envisaged to occur via an initial Knoevenagel condensation of the aromatic aldehyde with ethyl acetoacetate, affording **1**, followed by Michael addition of ethyl acetoacetate to **1** furnishing symmetrical intermediate **11**. Dione **11** could then condense with two molecules of the aromatic aldehyde via dienamine **12** to afford **13**, which subsequently could suffer deethoxycarbonylation with concomitant intramolecular Michael addition either simultaneously or in a stepwise manner affording **10** (Scheme 2). It is also possible that the latter two reactions occur in the reverse order, first Michael and then deethoxycarbonylation, although this sequence appears to be less likely in view of the steric hindrance due to the two aryl rings at the 2- and 6-positions of the cyclohexanone that would be formed during the Michael addition. Our efforts to isolate and characterise one or more of the intermediates such as **1**, **11** or **13** in Scheme 2 by intercepting and analysing the reaction mixture at different stages during the course of the reaction before completion were unsuccessful as the reaction mixture comprised a mixture of products/intermediates with similar R_f.

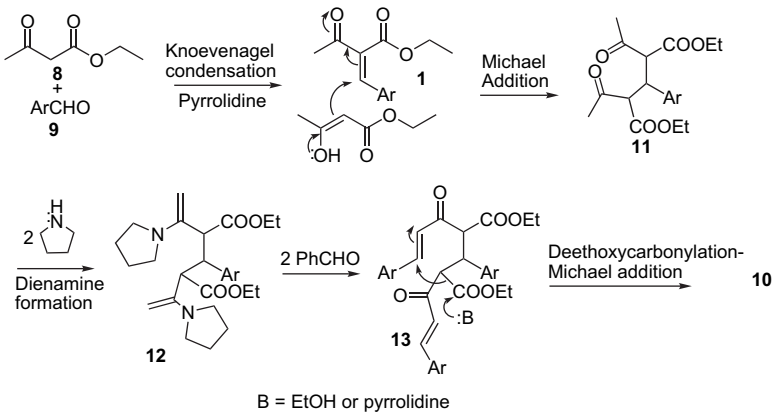
Table 2. ^{1}H and ^{13}C NMR spectroscopic data of **10a**

H-atom	δ_H	δ_C
2	4.93 (1H, d, *J*=12.9 Hz)	58.1
3	3.94 (1H, dd, *J*=12.9, 4.4 Hz)	49.3
4	3.85 (1H, t, *J*=4.4 Hz)	56.1
5	3.67 (1H, m)	46.4
6ax	3.69 (1H, t, *J*=12.9 Hz)	42.3
6eq	2.66 (1H, dd, *J*=12.9, 1.8 Hz)	
α-H	5.78 (1H, d, *J*=16.2 Hz)	129.0
β-H	6.83 (1H, d, *J*=16.2 Hz)	142.8
Aromatic	7.03–7.26 (m, 15H)	127.5, 127.8, 127.9, 128.6, 128.7, 129.0, 129.2, 130.8, 134.5, 139.3, 140.2
Ethyl	4.06 (m), 1.07 (t, *J*=7.2 Hz)	14.4, 61.3
Carbonyl	—	202.7 (3-aryl-2-propenonyl), 206.1 (C-1), 169.7 (ester)

2.2. Diastereoselective synthesis of *t*(3)-aryl-*r*(2),*c*(4)-bisethoxycarbonyl-*c*(5)-hydroxy-*t*(5)-methylcyclohexanones (15)

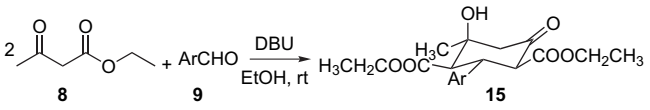
The formation of the cyclohexanones **10** provided impetus to investigate the reaction between ethyl acetoacetate and aromatic aldehyde in the presence of DBU, a stronger base which cannot form enamine intermediates, in order to understand (i) the roles of different bases in these tandem reactions and (ii) whether the formation of **10** in the pyrrolidine-catalysed reaction requires the intervention of the enamine intermediates depicted in Scheme 2.

It was found that even when aromatic aldehydes and ethyl acetoacetate were taken in a 3:2 molar ratio in the presence of DBU, only **15** was obtained. Under these conditions, the cyclohexanones **10** could not be detected even in trace amounts. This can probably be taken as indirect evidence for the formation of **10**, in the presence of pyrrolidine, via enamine intermediates (Scheme 2). In the present work, eight compounds **15a–h** were synthesised by the reaction of ethyl acetoacetate with aromatic aldehydes in a molar ratio of 2:1 in the presence of DBU (Scheme 3). During the preparation of the manuscript we happen to find the work of Pandiarajan et al.[24] on the synthesis of the keto esters **15** by condensing ethyl acetoacetate with aromatic aldehyde



Scheme 2. Mechanism for the pyrrolidine-catalysed formation of **10**.

in the presence of methylamine as base. A significantly increased yield of **15a–h** 85–95% (Table 3) is obtained in the present work relative to 65–75% reported by Pandiarajan et al.[24]



9 and **15**	Ar
a	C_6H_5
b	4-ClC_6H_4
c	4-$CH_3C_6H_4$
d	4-$CH_3OC_6H_4$
e	4-$O_2NC_6H_4$
f	4-FC_6H_4
g	3-$O_2NC_6H_4$
h	2-ClC_6H_4

Scheme 3.

The structure of the cyclohexanones **15a–h** has been elucidated using elemental analysis and NMR spectroscopic data as illustrated below for ketone **15a**. The three-proton singlet at 1.34 ppm is assigned to the methyl group. The H–H-COSY spectrum shows that the triplets at 0.79 and 1.04 ppm and the multiplets at 3.84 and 4.01 ppm are ascribable to the ethyl ester. The 1H doublet at 3.68 ppm with J=12.6 Hz is assigned to H-2, which has a H–H-COSY correlation with the multiplet centred at 4.00 ppm assignable to H-3. The other doublet at 3.03 ppm is assigned to H-4 since it shows H–H-COSY correlation with H-3. That the diastereotopic protons at C-6 give one doublet at 2.72 ppm (J=14.2 Hz) and a doublet of doublets at 2.51 ppm (J=14.2 and 2.5 Hz), is evident from their HMBC correlations (Fig. 4) with the signal of the C-1 at 201.7 ppm. The doublet at 3.73 ppm (J=2.5 Hz) is due to the OH proton, which has a long-range coupling with H-6ax due to W arrangement (Fig. 4), which is probably stabilised by some electrostatic attraction between the ester carbonyl and the OH proton. That the W arrangement is possible only between the OH proton and H-6ax (but not with H-6eq) is helpful in distinguishing the signals of H-6ax and H-6eq. The appearance of the signal of the OH proton upfield at 3.73 ppm suggests that the intramolecular hydrogen bonding between the ester carbonyl and the OH is not strong. Probably, the distance between the OH proton and the ester carbonyl is more than that required for optimal hydrogen bonding in this system. The fairly large ^4J value of 2.5 Hz suggests that the rotamer depicted in Figure 4 probably is the most populated one enabling facile W arrangement between the hydroxyl and H-6ax protons.

Table 3. Yields and mp of *t*(3)-aryl-*r*(2),*c*(4)-bisethoxycarbonyl-*c*(5)-hydroxy-*t*(5)-methylcyclohexanones **15**

Compd	mp °C (lit. mp °C)	Lit. yield (%)	Yield (%)
15a	155 (156)[24]	75	90
15b	160 (162)[24]	73	95
15c	146[a]	—	86
15d	142 (144)[24]	75	88
15e	189 (188)[24]	68	86
15f	162[a]	—	91
15g	151 (152)[24]	65	85
15h	154[a]	—	87

[a] New compounds.

The ^{13}C NMR spectra of each of the compounds of **15a–h** have two signals in the range 166.8–174.5 ppm ascribable to the ester carbonyl carbons at C-2 and C-4. They also have a signal in the range of 200.8–203.7 ppm ascribable to C-1. The signals of **15a–h** in the range 114.1–158.8 ppm are due to the aromatic carbons, among which the less intense ones in the region, 130.2–158.8 ppm, arise from the *ipso* carbons. The saturated carbon signals of the ring system, C-2 to C-6, occur in the range 43.5–73.8 ppm, assigned using proton chemical shifts and C–H-COSY correlations. The NMR spectroscopic data and assignments of the signals for **15** in the present work are in good agreement with those reported for five compounds in the literature.[24]

The probable mechanism for the formation of **15**, in the presence of DBU via intermediate **11** is depicted in Scheme 4. This intermediate **11** is common to the formation of **10** as well (Scheme 2). In the presence of DBU, **11** presumably forms enol **14**, which undergoes an intramolecular aldol reaction resulting in the formation of the six-membered ring **15** (Scheme 4). This occurs preferentially to the intermolecular reaction with an aromatic aldehyde, which could subsequently lead to the formation of **10** explicable by entropy considerations. The formation of **15** from the dienamine in

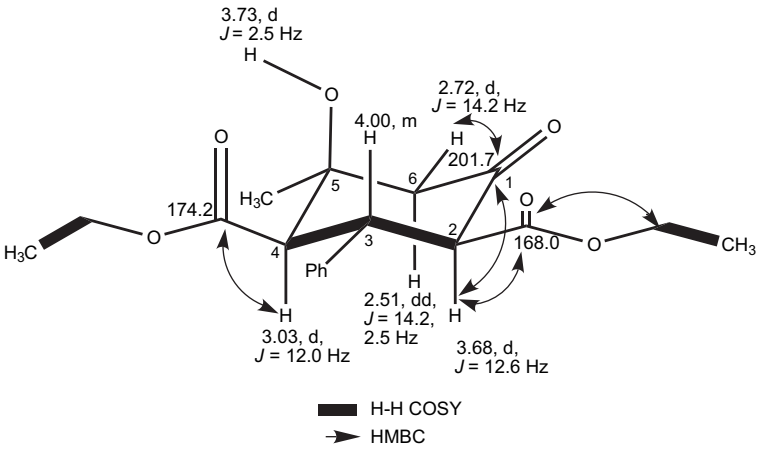
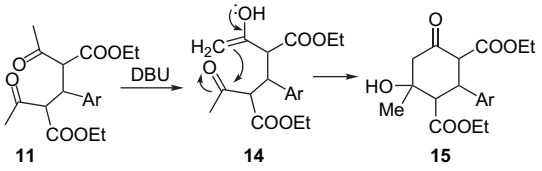
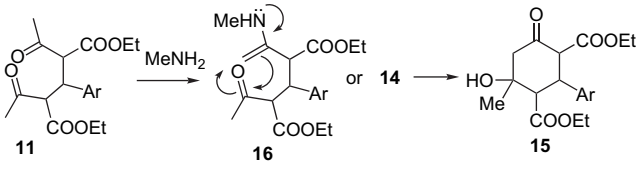


Figure 4. Selected 1D NMR data and 2D NMR correlations for **15a**.

the pyrrolidine-catalysed reaction appears unlikely as this would require the reaction between two nucleophilic enamine functionalities. From the selective formation of **10** in the presence of pyrrolidine, it is further clear that the monoenamine that would be formed initially from **11** en route to **12**, also presumably finds it facile either to undergo an intermolecular reaction with an aldehyde or to form the dienamine, relative to the intramolecular reaction with the keto functionality which would yield **15**. In the case of methylamine,[24] enamine intermediates (mono- and di-enamines) can be formed. However, in view of the diminished steric hindrance associated with the monoenamine **16** (relative to the pyrrolidine enamine), **16** can undergo an intramolecular reaction with the acetyl group affording **15** (Scheme 5). It is also possible for the methylamine catalysed reaction to proceed via the mechanism depicted in Scheme 4 alternatively through enol **14**. Thus the product selectivity of the reaction of ethyl acetoacetate with aromatic aldehyde is delicately tuned by the nature of the catalysts employed.



Scheme 4. Mechanism for the DBU catalysed formation of **15**.



Scheme 5. Mechanism for the methylamine catalysed formation of **15**.

3. Conclusion

A rapid one-pot five-component tandem protocol has been developed for the stereoselective synthesis of novel cyclohexanones **10** from ethyl acetoacetate and aromatic aldehydes in the presence of pyrrolidine. Further advantages of this method are the ready availability of the reagents, their low cost and mild conditions rendering it a useful and attractive strategy for the rapid synthesis of cyclohexanones **10**. The reaction of ethyl acetoacetate with aromatic aldehydes in the presence of DBU provided a better yield of **15** than the literature method. The present work demonstrates that the product selectivity of the reaction of ethyl acetoacetate with aromatic aldehyde can be fine-tuned by employing appropriate catalysts, which incidentally provides a deeper insight into the mechanistic aspects underlying these reactions.

4. Experimental

4.1. General methods

The mp of the cyclohexanones are uncorrected. Unless stated otherwise, solvents and chemicals were obtained from commercial sources and were used without further purification. Flash chromatography was performed on silica gel (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz Bruker (Avance) NMR spectrometer at 300 and 75 MHz, respectively, and the chemical shifts are reported as δ values (ppm) relative to tetramethylsilane. Two-dimensional NMR spectra were also measured in the same instrument employing standard Bruker software throughout. Elemental analyses were performed on a Perkin–Elmer 2400 Series II Elemental CHNS Analyser. Optimisation of molecular geometry using MM2 calculations was performed by Hyperchem version 7.0 software. Petroleum ether employed in column chromatographic purification refers to the fraction, which boils at 40–60 °C.

4.2. General procedure for the synthesis of *t*(3),*t*(5)-diaryl-*t*(4)-[(*E*)-3-aryl-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanones 10a–g

To a mixture of pyrrolidine (0.08 ml, 0.98 mmol) and ethyl acetoacetate **8** (0.5 ml, 3.9 mmol), aromatic aldehyde **9** (Ar=C_6H_5) (0.6 ml, 5.9 mmol) and ethanol (3 ml) were added and the reaction mixture stirred at room temperature for 2–6 days to ensure completion of the reaction, which was monitored using TLC. Then the reaction mixture was extracted with chloroform (15 ml), washed with water, dried over (Na_2SO_4) and concentrated under reduced pressure.

The crude product was purified by flash column chromatography on silica gel [pet. ether/ethyl acetate (4:1 v/v) as eluent].

4.2.1. *t*(3),*t*(5)-Diphenyl-*t*(4)-[(*E*)-3-phenyl-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanone 10a. Isolated as a pale yellow solid (63%), mp=208 °C; IR (KBr) ν 1740, 1733, 1704, 1648 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 1.08 (t, J=7.2 Hz, 3H), 2.66 (dd, J=12.9 and 1.8 Hz, 1H), 3.67 (m, 1H), 3.69 (t, J=12.9 Hz, 1H), 3.85 (t, J=4.4 Hz, 1H), 3.94 (dd, J=12.9 and 4.4 Hz, 1H), 4.06 (m, 2H), 4.93 (d, J=12.9 Hz, 1H), 5.78 (d, J=16.2 Hz, 1H), 6.83 (d, J=16.2 Hz, 1H), 7.03–7.26 (m, 15H). ^{13}C NMR: δ 14.4, 42.3, 46.4, 49.3, 56.1, 58.1, 61.3, 127.5, 127.8, 127.9, 128.6, 128.7, 129.0, 129.0, 129.2, 130.8, 134.5, 139.3, 140.2, 142.8, 169.7, 202.7, 206.1.

Anal. Calcd for $C_{30}H_{28}O_4$: C, 79.62; H, 6.24; Obsd C, 79.55; H, 6.15.

4.2.2. *t*(3),*t*(5)-Bis(4-chlorophenyl)-*t*(4)-[(*E*)-3-(4-chlorophenyl)-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanone 10b. Isolated as a pale yellow solid (66%), mp=215 °C; IR (KBr) ν 1749, 1718, 1697, 1643 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 1.09 (t, J=7.2 Hz, 3H), 2.63 (dd, J=12.9 and 2.2 Hz, 1H), 3.64 (m, 1H), 3.71 (t, J=12.9 Hz, 1H), 3.83 (t, J=4.4 Hz, 1H), 3.97 (dd, J=12.9 and 4.4 Hz, 1H), 4.12 (m, 2H), 4.98 (d, J=12.9 Hz, 1H), 5.82 (d, J=15.9 Hz, 1H), 6.91 (d, J=15.9 Hz, 1H), 7.12–7.29 (m, 12H). ^{13}C NMR: δ 14.1, 42.6, 46.5, 49.1, 56.5, 58.4, 61.2, 127.1, 127.6, 127.7, 128.4, 128.6, 129.2, 129.3, 129.5, 130.4, 134.8, 139.8, 140.7, 142.4, 169.9, 202.3, 206.0.

Anal. Calcd for $C_{30}H_{25}Cl_3O_4$: C, 64.82; H, 4.53; Obsd C, 64.76; H, 4.49.

4.2.3. *t*(3),*t*(5)-Bis(4-methylphenyl)-*t*(4)-[(*E*)-3-(4-methylphenyl)-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanone 10c. Isolated as a pale yellow solid (62%), mp=193 °C; IR (KBr) ν 1742, 1727, 1701, 1652 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 1.08 (t, J=7.2 Hz, 3H), 2.21 (s, 6H), 2.23 (s, 3H), 2.65 (dd, J=12.9 and 1.8 Hz, 1H), 3.60 (m, 1H), 3.69 (t, J=12.9 Hz, 1H), 3.84 (t, J=4.4 Hz, 1H), 3.96 (dd, J=12.9 and 4.4 Hz, 1H), 4.15 (m, 2H), 4.95 (d, J=12.9 Hz, 1H), 5.78 (d, J=16.2 Hz, 1H), 6.95 (d, J=16.2 Hz, 1H), 7.10–7.41 (m, 12H). ^{13}C NMR: δ 13.9, 21.0, 21.1, 21.2, 42.2, 46.3, 49.1, 56.7, 58.5, 61.6, 127.3, 127.9, 128.1, 128.6, 128.8, 129.5, 129.6, 129.8, 130.7, 135.1, 139.9, 140.8, 142.7, 170.2, 201.4, 207.1.

Anal. Calcd for $C_{33}H_{34}O_4$: C, 80.13; H, 6.93; Obsd C, 80.20; H, 6.96.

4.2.4. *t*(3),*t*(5)-Bis(4-methoxyphenyl)-*t*(4)-[(*E*)-3-(4-methoxyphenyl)-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanone 10d. Isolated as a pale yellow solid (60%), mp=185 °C; IR (KBr) ν 1738, 1719, 1706, 1660 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 1.04 (t, J=7.2 Hz, 3H), 2.61 (dd, J=13.2 and 2.2 Hz, 1H), 3.62 (m, 1H), 3.71 (t, J=13.2 Hz, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 3.84 (t, J=4.4 Hz, 1H), 3.95 (dd, J=13.2 and 4.4 Hz, 1H), 4.11 (m, 2H), 4.95 (d, J=13.2 Hz, 1H), 5.84 (d, J=16.2 Hz, 1H), 6.90 (d, J=16.2 Hz, 1H), 6.89–7.27 (m, 12H). ^{13}C NMR: δ 13.8, 42.1, 45.9, 48.6, 54.9, 55.0, 55.1, 55.9, 58.1, 61.4, 114.7, 115.0, 115.3, 127.1, 128.1, 128.4, 129.0, 129.3, 130.2, 134.7, 139.6, 140.5, 142.3, 169.9, 202.9, 206.1.

Anal. Calcd for $C_{33}H_{34}O_7$: C, 73.04; H, 6.32; Obsd C, 72.93; H, 6.25.

4.2.5. *t*(3),*t*(5)-Bis(2-chlorophenyl)-*t*(4)-[(*E*)-3-(2-chlorophenyl)-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanone 10e. Isolated as a pale yellow solid (68%), mp=210 °C; IR (KBr) ν 1745, 1730, 1697, 1647 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 1.06 (t, J=7.2 Hz, 3H), 2.65 (dd, J=12.9 and 1.8 Hz, 1H), 3.65 (m, 1H), 3.70 (t, J=12.9 Hz, 1H), 3.85 (t, J=4.4 Hz, 1H), 3.97 (dd, J=12.9 and 4.4 Hz, 1H), 4.11 (m, 2H), 4.99 (d, J=12.9 Hz, 1H), 5.83 (d, J=16.2 Hz, 1H), 6.90 (d, J=16.2 Hz, 1H), 7.12–7.35 (m, 12H). ^{13}C NMR: δ 14.0, 42.7, 46.6, 49.2, 56.6, 58.5, 61.1, 127.0, 127.3, 127.6, 127.7, 128.1, 128.3, 128.4, 128.6, 129.1, 129.2, 129.3, 129.5, 129.7, 130.3, 134.7, 139.9, 140.6, 142.3, 142.6, 169.7, 201.8, 206.9.

Anal. Calcd for $C_{30}H_{25}Cl_3O_4$: C, 64.82; H, 4.53; Obsd C, 64.70; H, 4.44.

4.2.6. *t*(3),*t*(5)-Bis(2-methoxyphenyl)-*t*(4)-[(*E*)-3-(2-methoxyphenyl)-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanone 10f. Isolated as a pale yellow solid (59%), mp=172 °C; IR (KBr) ν 1741, 1722, 1690, 1651 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 1.06 (t, J=7.2 Hz, 3H), 2.60 (dd, J=13.2 and 1.8 Hz, 1H), 3.63 (m, 1H), 3.70 (t, J=13.2 Hz, 1H), 3.77 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 3.85 (t, J=4.4 Hz, 1H), 3.96 (dd, J=13.2 and 4.4 Hz, 1H), 4.13 (m, 2H), 4.97 (d, J=13.2 Hz, 1H), 5.86 (d, J=15.8 Hz, 1H), 6.96 (d, J=15.8 Hz, 1H), 6.85–7.37 (m, 12H). ^{13}C NMR: δ 13.5, 42.5, 46.2, 48.8, 54.9, 55.0, 55.1, 56.2, 58.3, 61.5, 114.9, 115.1, 115.5, 127.1, 127.2, 128.3, 128.5, 128.6, 129.2, 129.7, 129.8, 129.9, 130.2, 130.6, 130.9, 134.7, 139.6, 140.5, 142.5, 169.6, 201.7, 206.6.

Anal. Calcd for $C_{33}H_{34}O_7$: C, 73.04; H, 6.32; Obsd C, 73.13; H, 6.25.

4.2.7. *t*(3),*t*(5)-Bis(2-methylphenyl)-*t*(4)-[(*E*)-3-(2-methylphenyl)-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanone 10g. Isolated as a pale yellow solid (58%), mp=178 °C; IR (KBr) ν 1750, 1720, 1695, 1640 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 1.12 (t, J=7.2 Hz, 3H), 2.23 (s, 3H), 2.24 (s, 3H), 2.26 (s, 3H), 2.68 (dd, J=12.9 and 1.8 Hz, 1H), 3.65 (m, 1H), 3.70 (t, J=12.9 Hz, 1H), 3.89 (t, J=4.4 Hz, 1H), 4.01 (dd, J=12.9 and 4.4 Hz, 1H), 4.16 (m, 2H), 4.96 (d, J=12.9 Hz, 1H), 5.83 (d, J=16.2 Hz, 1H), 6.98 (d, J=16.2 Hz, 1H), 7.07–7.58 (m, 12H). ^{13}C NMR: δ 13.4, 21.0, 21.1, 21.2, 42.6, 46.7, 49.5, 56.8, 58.9, 61.8, 126.8, 127.1, 127.4, 127.7, 127.9, 128.2, 128.4, 128.6, 128.8, 129.5, 129.6, 129.7, 129.8, 130.5, 130.7, 135.3, 139.4, 140.5, 142.3, 170.6, 202.5, 207.5.

Anal. Calcd for $C_{33}H_{34}O_4$: C, 80.13; H, 6.93; Obsd C, 80.26; H, 6.90.

4.3. General procedure for the synthesis of *t*(3)-aryl-*r*(2),*c*(4)-bisethoxycarbonyl-*c*(5)-hydroxy-*t*(5)-methylcyclohexanones[25]

A mixture of ethyl acetoacetate (0.5 ml, 3.9 mmol), aromatic aldehyde (2 mmol) and DBU (0.15 ml, 1 mmol) in ethanol (3 ml) was stirred at room temperature for about 5–10 h. The precipitate formed was filtered and purified by recrystallisation from ethanol.

4.3.1. *t*(3)-(4-Methylphenyl)-*r*(2),*c*(4)-bisethoxycarbonyl-*c*(5)-hydroxy-*t*(5)-methylcyclohexanone 15c. Isolated as colourless needles (86%), mp=146 °C; IR (KBr) ν 3432, 1741, 1724 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 0.83 (t, J=7.2 Hz, 3H), 1.03 (t, J=7.2 Hz, 3H), 1.34 (s, 3H), 2.53 (dd, J=14.2 and 2.4 Hz, 1H), 2.73 (d, J=14.2 Hz, 1H), 3.04 (d, J=12.0 Hz, 1H), 3.67 (d, J=12.6 Hz, 1H), 3.74 (d, J=2.4 Hz, O*H*), 3.86 (m, 2H), 3.99 (m, 1H), 4.03 (m, 2H), 7.15–7.26 (m, 4H). ^{13}C NMR: δ 14.1, 14.3, 29.1, 45.5, 53.2, 57.5, 61.7, 63.1, 73.7, 128.6, 129.5, 129.9, 138.5, 168.1, 174.4, 201.4.

Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23; Obsd C, 66.17; H, 7.21.

4.3.2. *t*(3)-(4-Fluorophenyl)-*r*(2),*c*(4)-bisethoxycarbonyl-*t*(5)-hydroxy-*c*(5)-methylcyclohexanone 15f. Isolated as colourless needles (91%), mp=162 °C; IR (KBr) ν 3513, 1735, 1714 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 0.84 (t, J=7.2 Hz, 3H), 1.11 (t, J=7.2 Hz, 3H), 1.39 (s, 3H), 2.56 (dd, J=14.2 and 2.2 Hz, 1H), 2.70 (d, J=14.2 Hz, 1H), 3.06 (d, J=12.2 Hz, 1H), 3.69 (m, 2H), 3.95 (m, 3H), 4.08 (m, 2H), 7.15–7.28 (m, 4H). ^{13}C NMR: δ 14.3, 14.5, 29.3, 45.2, 53.1, 57.5, 61.9, 63.0, 73.8, 124.5, 124.8, 127.6, 127.8, 132.4, 135.4, 166.8, 174.2, 202.6.

Anal. Calcd for $C_{19}H_{23}FO_6$: C, 62.29; H, 6.33; Obsd C, 62.25; H, 6.38.

4.3.3. *t*(3)-(2-Chlorophenyl)-*r*(2),*c*(4)-bisethoxycarbonyl-*t*(5)-hydroxy-*c*(5)-methylcyclohexanone 15h. Isolated as colourless needles (87%), mp=154 °C; IR (KBr) ν 3470, 1748, 1710 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 0.81 (t, J=7.2 Hz, 3H), 1.04 (t, J=7.2 Hz, 3H), 1.31 (s, 3H), 2.48 (dd, J=14.2 and 2.2 Hz, 1H), 2.68 (d, J=14.2 Hz, 1H), 2.94 (d, J=12.0 Hz, 1H), 3.56 (m, 2H), 3.78 (m, 3H), 4.05 (m, 2H), 7.11–7.35 (m, 4H). ^{13}C NMR: δ 14.5, 14.7, 28.7, 44.5, 52.6, 56.8, 61.4, 62.4, 73.1, 118.7, 119.3, 129.7, 129.9, 133.5, 136.7, 168.1, 174.2, 203.7.

Anal. Calcd for $C_{19}H_{23}ClO_6$: C, 59.61; H, 6.06; Obsd C, 59.69; H, 6.16.

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25. Only for the new compounds (**15c**, **15f** and **15h**) belonging to series **15**, elemental analysis and NMR data are furnished in Section 4. Data for the other compounds (**15a–d** and **15g**) are available in Ref. 24.