A Convenient Base-Mediated Diastereoselective Synthesis of 2-Oxo-*N*,4,6-triarylcyclohex-3-enecarboxamides *via* Claisen-Schmidt Condensation

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ABSTRACT: *Sodium acetate catalyzed the multi-component reaction of acetophenone, aromatic aldehydes, and acetoacetanilide in the water-ethanol mixture (1:1) at ambient temperature via Claisen-Schmidt condensation results in the formation of highly substituted cyclohexenones in 89–98% yields. The developed efficient catalytic approach to the substituted cyclohexenones – the promising compounds for inflammation and autoimmune diseases therapy and different biomedical applications – is beneficial from the viewpoint of diversity-oriented large-scale processes and represents facile, efficient and environmentally benign synthetic concept for multicomponent reactions strategy. This protocol offers several advantages including high yields, operational simplicity, clean reaction conditions, the minimum pollution of the environment, no need to column chromatography and simple work-up procedure.*

KEYWORDS: *Knoevenagel condensation; Michael reaction; Diastereoselective synthesis; Sodium acetate; 2-Oxo-N,4,6-triarylcyclohex-3-enecarboxamide.*

INTRODUCTION

Multi-Component Reactions (MCRs) are useful for the synthesis of various groups of compounds [1-3]. This strategy has been effectively used in the synthesis of various biologically active substances and natural products [4]. The MCRs strategy is provided significant advantages over conventional linear-type synthesis; in that three or more simple and flexible molecules are brought together to rapidly introduce structural complexity and diversity [5-11]. Additionally, MCRs have been extensively used for the efficient synthesis of organic compounds because of wide range availability of starting materials, the simplicity of one-pot procedures and the associated atom economy [12-18].

In this paper, a series of 2-oxo-*N*,4,6-triarylcyclohex-3-enecarboxamide derivatives were prepared by Claisen-Schmidt condensation and Michael addition between acetophenone, appropriate aromatic aldehydes, and acetoacetanilide. The product is prone to cyclization due to the presence of heterocyclic intermediate for the synthesis of joined heterocycles such as benzopyrazoles, benzisoxazoles, benzoselenadiazoles, benzothiadiazoles, 2*H*-indazoles, and carbazole derivatives [19-21]. Cyclohexenones have been widely used in drug design and natural products such as antibiotics, steroids and cortisone [22,23]. Besides, cyclohexenone derivatives are also lead molecules for the treatment of inflammation and

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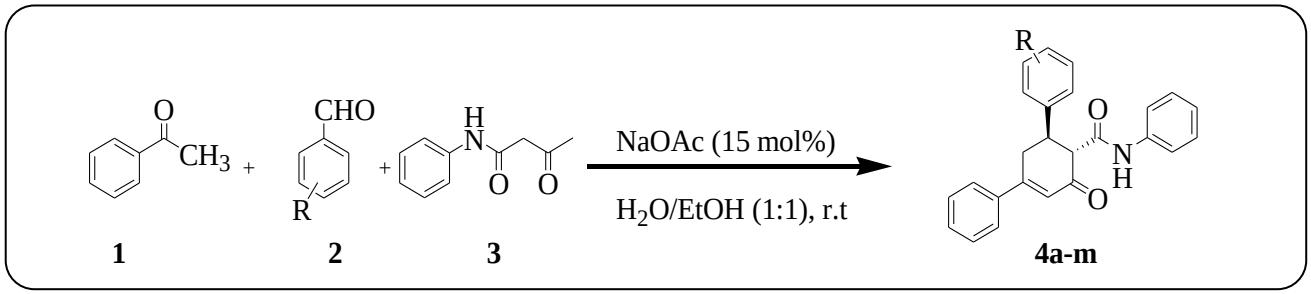


Scheme 1: NaOAc-catalyzed three-component synthesis of highly substituted cyclohexenones.

autoimmune diseases. Also, cyclohexenone and indazole derivatives are exhibited various pharmacological properties like antitumor, tyrosine kinases inhibitor, antipyretic, antiasthmatic, antiviral, antibacterial, anti-fungal, anti-cancer and anti-tubercular activity [24-29].

Among the various types of important intermediates, the chalcones have been successfully used for the synthesis of cyclohexenone derivatives. Chalcones are 1,3-diphenyl-2-propene-1-ones, in which two aromatic rings are linked by a three-carbon *α,β*-unsaturated carbonyl system [30]. Chalcones possess conjugated double bonds and a completely delocalized *π*-electron system on both benzene rings. Thus, due to the enone system, such molecules can act as a Michael acceptor undergoing electron transfer [31]. Chalcones and its derivatives also comprise a significant biological and pharmacological properties such as antibacterial, anticonvulsant, anticancer, antifungal, antiprotozoal and antimalarial [32-42].

The conjugate addition of a stabilized carbanion to *α,β*-unsaturated carbonyl compounds is one of the fundamental C-C bond-forming reactions in organic synthesis. The Michael reaction of 1,5-diaryl-1,4-pentadiene-3-ones with active methylene compounds has long been employed to prepare highly substituted cyclohexanones in terms of their stereochemistry [43], and as precursors for the synthesis of spiro-heterocycles [44] with a broad spectrum of chemotherapeutic properties such as hypnotic, antitumor, antiviral, anticonvulsant and analgesic activities [45]. The attention of medicinal and organic chemists is increasingly being devoted to methods of synthesis of these compounds.

Recently, we have reported new diastereoselective multicomponent transformation of acetophenone, aromatic aldehydes, and acetoacetanilide into a series of novel poly substituted cyclohexenone derivatives under mild conditions [46-49]. These results present a challenge to design a simple and efficient multicomponent synthesis of cyclohexenone derivatives from the proposed reactants under base catalysis. In the present study, we report our results based on one-pot MCR between, acetophenone **1**, aldehydes **2** and acetoacetanilide **3** under ambient conditions, in a small quantity of water-alcohol (1:1) (Scheme 1).

EXPERIMENTAL SECTION

General

Melting points and IR spectra of all compounds were obtained on an Electrothermal 9100 apparatus and a JASCO FT/IR-460 plus spectrometer, respectively. ^{1}H and ^{13}C NMR spectra of compounds were recorded on a Bruker DRX-400 Avance instrument in DMSO or $CDCl_3$ as the solvent with TMS as an internal standard at 400 and 100 MHz, respectively. Elemental analyses for C, H, and N for the new compounds were performed using a Heraeus CHN-O-Rapid analyzer. The mass spectra of the new compounds were recorded on an Agilent Technology (HP) mass spectrometer, operating at an ionization potential of 70 eV. All reagents were purchased from Merck (Darmstadt, Germany), Acros (Geel, Belgium) and Fluka (Buchs, Switzerland), and used without further purification.

General procedure for the synthesis of 2-oxo-N,4,6-triarylcyclohex-3-enecarboxamides

To a solution of 15 mol% NaOAc in H_2O/EtOH (1:1, 5 mL), acetophenone (1 mmol), aryl aldehyde (1 mmol), and acetoacetanilide (1 mmol) were added and the resulting mixture was stirred at room temperature for the appropriate time as indicated in Table 2. After completion of the reaction, as indicated by TLC (ethylacetate/n-hexane, 1:3), the product was precipitated from the reaction mixtures, filtered off and washed with

H_2O/EtOH (2×5 mL) and the solid residue was crystallized from hot ethanol (98%) to give pure product **4** in high yield. Physical and spectral data for the selected compounds are represented below:

*2-Oxo-N,4-diphenyl-6-(pyridin-3-yl)cyclohex-3-enecarboxamide (**4b**)*

White solid, yield: (91%); mp: 194-196 ºC. ^{1}H NMR (400 MHz, DMSO): 3.09 (dd, *J* = 18.2, 4.4 Hz, 1H, H-5), 3.21 (ddd, *J* = 18.0, 11.4, 2.0 Hz, 1H, H'-5), 3.88 (td, *J* = 13.0, 4.8 Hz, 1H, H-6), 3.51 (d, *J* = 12.8 Hz, 1H, H-1), 6.60 (d, *J* = 2.0 Hz, 1H, H-3), 7.01 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.24 (t, *J* = 12.8 Hz, 2H, Ar-H), 7.35 (dd, *J* = 4.8, 7.6 Hz, 1H, Ar-H), 7.43 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.47 (dd, *J* = 2.4, 5.2 Hz, 2H, Ar-H), 7.75 (dd, *J* = 7.4, 2.4 Hz, 2H, Ar-H), 7.89 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.42 (dd, *J* = 4.8, 1.2 Hz, 1H, Ar-H), 8.65 (d, *J* = 1.6 Hz, 1H, Ar-H), 10.10 (s, 1H, NH).

*6-(4-Cyanophenyl)-2-oxo-N,4-diphenylcyclohex-3-enecarboxamide (**4d**)*

White solid, yield: (96%); mp: 223-225 ºC. ^{1}H NMR (400 MHz, DMSO): 3.07 (dd, *J* = 18.0, 4.0 Hz, 1H, H-5), 3.18 (dd, *J* = 17.6, 10.4 Hz, 1H, H'-5), 3.95 (td, *J* = 13.2, 4.8 Hz, 1H, H-6), 4.02 (d, *J* = 13.2 Hz, 1H, H-1), 6.60 (d, *J* = 1.6 Hz, 1H, H-3), 7.01 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.24 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.44 (d, *J* = 8.8 Hz, 3H, Ar-H), 7.47 (d, *J* = 0.8 Hz, 2H, Ar-H), 7.66 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.73 (t, *J* = 5.2 Hz, 2H, Ar-H), 7.80 (d, *J* = 8.0 Hz, 2H, Ar-H), 10.10 (s, 1H, NH).

*6-(3-Chlorophenyl)-2-oxo-N,4-diphenylcyclohex-3-enecarboxamide (**4f**)*

White solid, yield: (97%); mp: 188-190 ºC. ^{1}H NMR (400 MHz, DMSO): 3.06 (dd, *J* = 18.0, 4.4 Hz, 1H, H-5), 3.17 (m, 1H, H'-5), 3.86 (td, *J* = 12.8, 4.4 Hz, 1H, H-6), 3.97 (d, *J* = 13.2 Hz, 1H, H-1), 6.58 (d, *J* = 2.0 Hz, 1H, H-3), 7.01 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.24 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.27 (t, *J* = 2.0 Hz, 1H, Ar-H), 7.34 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.40 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.44-7.47 (m, 5H, Ar-H), 7.55 (s, 1H, Ar-H), 7.74 (dd, *J* = 7.2, 2.4 Hz, 2H, Ar-H), 10.08 (s, 1H, NH).

*6-(2-Chlorophenyl)-2-oxo-N,4-diphenylcyclohex-3-enecarboxamide (**4h**)*

White solid, yield: (94%); mp: 225 ºC. ^{1}H NMR (400 MHz, DMSO): 3.03 (d, *J* = 7.2 Hz, 2H, H-5), 4.24 (d, *J* = 13.2 Hz, 1H, H-1), 4.30 (dd, *J* = 14.0, 7.2 Hz, 1H, H-6), 6.63 (s, 1H, H-3), 7.00 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.24 (t, *J* = 7.6 Hz, 3H, Ar-H), 7.35 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.46 (dd, *J* = 15.2, 9.2 Hz, 6H, Ar-H), 7.67 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.72 (d, *J* = 7.6 Hz, 2H, Ar-H), 10.26 (s, 1H, NH).

*6-(4-Methoxyphenyl)-2-oxo-N,4-diphenylcyclohex-3-enecarboxamide (**4i**)*

White solid, yield: (89%); mp: 218-220 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): 2.32 (s, 3H, OCH_3), 3.06 (dd, *J* = 18.4, 7.6 Hz, 1H, H-5), 3.36 (dd, *J* = 18.4, 4.8 Hz, 1H, H'-5), 3.71 (d, *J* = 8.0 Hz, 1H, H-1), 4.17 (dd, *J* = 12.8, 7.6 Hz, 1H, H-6), 6.58 (s, 1H, H-3), 7.08 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.12 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.21 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.28 (t, *J* = 8.4 Hz, 3H, Ar-H), 7.40-7.47 (m, 5H, Ar-H), 7.56 (t, *J* = 6.4 Hz, 2H, Ar-H), 8.01 (s, 1H, NH).

*6-(3-Nitrophenyl)-2-oxo-N,4-diphenylcyclohex-3-enecarboxamide (**4j**)*

Pale yellow solid, yield: (94%); mp: 203 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): 3.08 (dd, *J* = 8.4, 18.0 Hz, 1H, H-5), 3.38 (dd, *J* = 18.2, 4.8 Hz, 1H, H'-5), 3.76 (d, *J* = 8.8 Hz, 1H, H-1), 4.32 (dd, *J* = 13.1, 8.8 Hz, 1H, H-6), 6.63 (s, 1H, H-3), 7.10 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.28 (dd, *J* = 9.2, 5.2 Hz, 2H, Ar-H), 7.45 (d, *J* = 2.4 Hz, 2H, Ar-H), 7.48 (d, *J* = 7.2 Hz, 3H, Ar-H), 7.52 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.57 (t, *J* = 6.4 Hz, 2H, Ar-H), 7.69 (d, *J* = 7.6 Hz, 1H, Ar-H), 8.13 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.19 (s, 1H, Ar-H), 8.25 (s, 1H, NH).

*2-Oxo-N,4-diphenyl-6-o-tolylcyclohex-3-enecarboxamide (**4k**)*

White, yield: (97%); mp: 198-200 ºC. IR (KBr) (ν_{max}/cm^{-1}): 3392 (NH), 3253 (C=CH), 2948 (CH-C=O), 1676 (C=O), 1629 (C=O), 1602, 1558, 1445, 1370, 1234, 1191, 908, 866, 799, 760, 693, 682. ^{1}H NMR (400 MHz, DMSO): 2.37 (s, 3H, CH_3), 3.00 (s, 2H, H-5), 4.07 (s, 2H, H-6, H-1), 6.59 (s, 1H, H-3), 6.99 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.08 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.18 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.23 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.42-7.46 (m, 5H, Ar-H), 7.73 (dd, *J* = 2.4, 8.0 Hz, 2H, Ar-H), 10.04 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 35.3, 38.4, 59.9, 119.4, 123.7, 123.8, 126.4, 126.5, 126.9, 126.9, 129.1, 129.2, 130.8, 130.8, 136.3, 137.8, 139.2,

140.8, 159.3, 167.9, 196.2. MS (EI, 70 eV) *m/z* (%): 381 (M^+, 43), 320 (1), 289 (9), 261 (100), 239 (2), 215 (11), 193 (1), 171 (10), 145 (34), 115 (75), 93 (50), 65 (17), 43 (7). Anal. Calcd for $C_{26}H_{23}NO_2$: C, 81.86; H, 6.08; N, 3.67. Found: C, 82.04; H, 6.20; N, 3.73.

*6-(4-Fluorophenyl)-2-oxo-N,4-diphenylcyclohex-3-enecarboxamide (**4l**)*

White, yield: (98%); mp: 222-224 ºC. IR (KBr) (ν_{max}/cm^{-1}): 3298 (NH), 3203 (C=CH), 2954 (CH-C=O), 1682 (C=O), 1661 (C=O), 1605, 1550, 1508, 1444, 1364, 1289, 1242, 1226, 1199, 871, 838, 759, 759, 693, 522. ^{1}H NMR (400 MHz, DMSO): 3.04 (dd, *J* = 18.0, 4.4 Hz, 1H, H-5), 3.13 (dd, *J* = 10.8, 2.0 Hz, 1H, H'-5), 3.85 (td, *J* = 10.8, 4.4 Hz, 1H, H-6), 3.96 (d, *J* = 13.2 Hz, 1H, H-1), 6.59 (d, *J* = 2.0 Hz, 1H, H-3), 7.00 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.14 (t, *J* = 8.8 Hz, 2H, Ar-H), 7.24 (t, *J* = 8.4 Hz, 2H, Ar-H), 7.43 (d, *J* = 4.4 Hz, 2H, Ar-H), 7.45-7.50 (m, 5H, Ar-H), 7.74 (dd, *J* = 8.0, 2.8 Hz, 2H, Ar-H), 10.05 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.8, 42.7, 60.2, 115.5 (d, *J* = 21.0 Hz), 119.5, 123.8 (d, *J* = 14.4 Hz), 126.9, 129.1, 129.3, 129.9 (d, *J* = 8.0 Hz), 130.9, 137.9, 138.8 (d, *J* = 2.9 Hz), 139.1, 159.4, 160.3, 162.7, 167.7, 195.7. MS (EI, 70 eV) *m/z* (%): 385 (M^+, 28), 367 (1), 293 (4), 265 (100), 247 (8), 220 (6), 202 (3), 188 (1), 171 (4), 149 (32), 133 (6), 115 (23), 93 (40), 77 (12), 51 (3). Anal. Calcd for $C_{25}H_{20}FNO_2$: C, 77.90; H, 5.23; N, 3.63. Found: C, 77.98; H, 5.35; N, 3.72.

RESULTS AND DISCUSSION

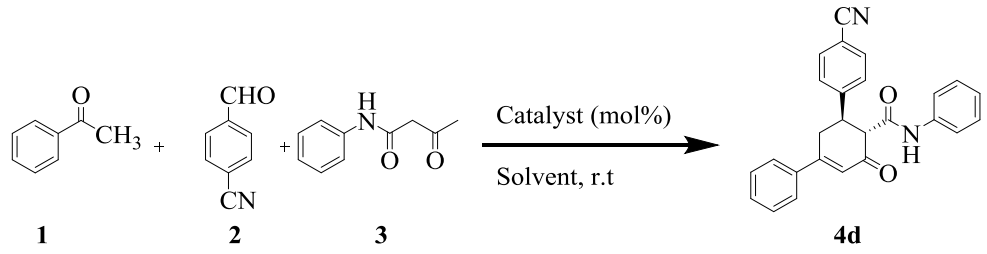
As part of our plan in the search for new and green multi-component reactions [50-53], and as it follows a background of study from introduction we are prompted to design a green, convenient and facile catalytic multi-component reaction methodology for the efficient multi-component synthesis of highly functionalized cyclohexenone. Thus, in the present study, we report our results based on the study of sodium acetate as a weak base catalyzed multi-component chain transformation of acetophenone **1**, aryl aldehydes **2** and acetoacetanilide **3** into substituted 2-oxo-*N*,4,6-triarylcyclohex-3-enecarboxamides **4a–m** under mild conditions in water-alcohol medium (Scheme 1, Table 2). We have performed a set of preliminary experiments on acetophenone, 4-cyanoaldehyde, and acetoacetanilide in the presence of 10 mol% catalyst as a model reaction. The results are shown in Table 1. In the initial inspection, different Lewis acids and bases were screened as a catalyst in the model reaction (Table 1, entries 2-7). As seen in Table 1, the reaction did not progress even after 48 h in the absence of a catalyst. Also, the reaction in the presence of $Y(NO_3)_3.4H_2O$, $La(NO_3)_3.6H_2O$ and $ZrCl_4$ was performed, and no product was obtained even after 48 h (enties 2-4). Therefore, acidic catalysts are not an appropriate media for this reaction. When sodium oxalate and $Na_2S_2O_4$ were used as a catalyst at room temperature, the product was obtained in low yields 35% and 28% respectively (enties 5 and 6). However, 15 mol% NaOAc proved to be an efficient catalyst giving high yields. Increasing the catalyst loading did not further improve the results (Table 1, entry 8). Moreover, when the reaction was carried out under solvent-free conditions, the trace product was obtained after 48 h. This may be due to the lack of effective interaction of reactants with the catalyst in the absence of solvent (Table 1, entry 13).

Moreover, we tested the effects of two green solvents (H_2O and EtOH), with various ratios or used alone. Among the screened solvent systems, (50:50) of water/ethanol was the solvent of choice, since the reaction proceeded smoothly and afforded the desired adducts in high yields. Since we are going to present a green and environmentally benign protocol for the synthesis of substituted cyclohexenones, we did not test organic solvents for this reaction.

Encouraged by the remarkable results obtained from above conditions, and in order to show the general applicability of the procedure, the optimized conditions were used to construct a variety of substituted cyclohexenones (**4a**–**m**). This reaction extended to various aromatic aldehydes in the presence of electron-withdrawing or electron-releasing substituents, both of which gave the desired product in good yields using the catalytic amount of catalyst. The results are shown in Table 2. As shown in Table 2, the electron withdrawing or donating group on the phenyl rings did not affect the reaction, with the exception of **4m** which, unfortunately, we did not get the desired cyclohexenone derivative after 48 h of stirring (Table 2).

The cyclo-condensation of acetoacetanilide with chalcones leads to the generation of two chiral centers at **C-1** and **C-6** in the structure of cyclohexenones (Fig. 1).

Table 1: Different catalytic systems and catalytic activity evaluation for the synthesis of highly substituted cyclohexenone 4d.



1 **2** **3** **4d**

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[a]
1	-	H_2O/EtOH	48	-
2	$Y(NO_3)_3.4H_2O$ (10)	H_2O/EtOH	48	-
3	$La(NO_3)_3.6H_2O$ (10)	H_2O/EtOH	48	-
4	$ZrCl_4$ (10)	H_2O/EtOH	48	-
5	Sodium Oxalate (10)	H_2O/EtOH	24	35
6	$Na_2S_2O_4$ (10)	H_2O/EtOH	24	28
7	NaOAc (10)	H_2O/EtOH	18	84
8	**NaOAc (15)**	**H_2O/EtOH**	**12**	**97**
9	NaOAc (20)	H_2O/EtOH	12	90
10	NaOAc (25)	H_2O/EtOH	14	90
11	NaOAc (30)	H_2O/EtOH	16	86
12	NaOAc (40)	H_2O/EtOH	20	85
13	NaOAc (15)	-	48	Trace

a) Yield refers to the pure isolated product.

The structure of all known products was characterized by comparison of the melting points and the analytical data (IR, ^{1}H NMR) with those reported in our previous works that their results are published recently [56-58]. The constitution of the synthesized product has been characterized by using elemental analysis, infrared spectroscopy and ^{1}H and ^{13}C-nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy. For example, the IR spectrum of **4l** revealed a sharp absorption band at 3298 cm^{-1} due to NH. Furthermore, two sharp strong absorption band were noticed at approximately 1682 and 1661 cm^{-1} are assigned to the carbonyl groups. The ^{1}H and ^{13}C NMR, and mass spectra substantiated the results of the IR analysis. The mass spectrum of **4l** displayed molecular ion peak (M^+) at *m/z* = 385, which consistent with the proposed structure. The ^{1}H NMR spectrum of compound **4l**, exhibited two doublets of doublets at 3.04 ppm (*J* = 18.0, 4.4 Hz) and 3.13 ppm (*J* = 10.8, 2.0 Hz) for methylene protons of cyclohexenone ring (H-5, H'-5), respectively. One of the methine protons of cyclohexenone ring (H-6) was observed as a triplet of doublet at δ 3.85 ppm (*J* = 10.8, 4.4 Hz) and another methine proton (H-1) appeared as a doublet at δ 3.96 ppm (*J* = 13.2 Hz). The vinyl proton (H-3) was observed as a doublet at 6.59 ppm (*J* = 2.0 Hz). The aromatic protons resonance observed as doublets and triplets at δ 7.00-7.74 ppm. The NH proton was observed as a singlet at δ 10.05 ppm, which indicating intramolecular hydrogen bond formation with the vicinal carbonyl group on cyclohexenone ring. The ^{13}C NMR spectrum of compound **4l** showed 19 distinct resonances consistent with the cyclohexenone structure. According to the structure of **4l**, it should be containing 25 carbons in ^{13}C NMR spectrum. However, due to the same carbons of (**C-3**, **C-5**) and (**C-2**, **C-6**) in the aromatic rings in the structure of **4l**, on the ^{13}C NMR spectrum, one peak is

Table 2: NaOAc catalyzed the three-component synthesis of highly substituted cyclohexenone derivatives.[a]

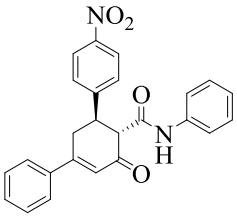
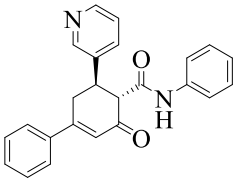
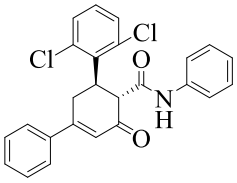
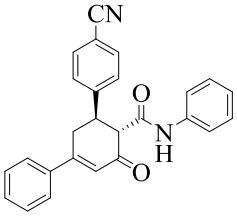
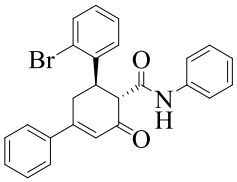
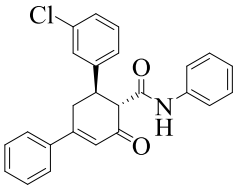
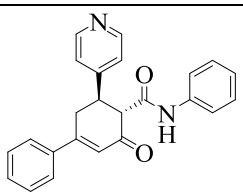
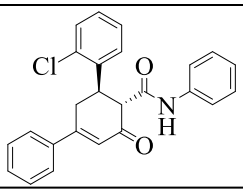
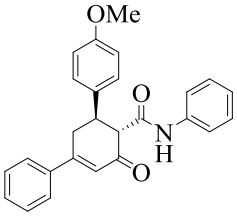
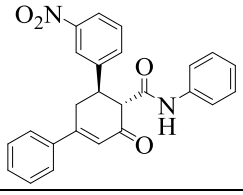
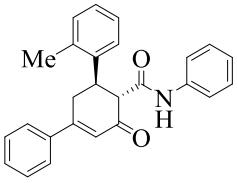
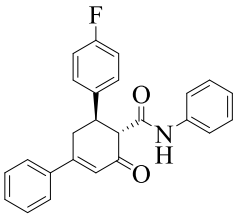
Product	R	Structure	Time (h)	Yield (%)[b]	M.p. (ºC)	Lit. m.p. (°C) [Ref]
4a	4-NO_2		11	97	205-207	204-206 [48]
4b	3-pyridin-		28	91	194-196	195-197 [46]
4c	2,6-Cl_2		15	98	189-191	186-188 [47]
4d	4-CN		18	96	223-225	224-226 [46]
4e	2-Br		10	95	219-221	220-222 [46]
4f	3-Cl		21	97	188-190	186-188 [48]
4g	4-pyridin-		25	93	203-205	202-204 [46]
4h	2-Cl		19	94	225	223-225 [47]

Table 2: NaOAc catalyzed three-component synthesis of highly substituted cyclohexenone derivatives.[a]

4i	4-OMe		25	89	218-220	218-220 [47]
4j	3-NO_2		18	94	203	200-202 [46]
4k	2-Me		17	97	198-200	This work[c]
4l	4-F		12	98	222-224	This work[c]
4m	2-H_2N	-	48	d	-	-

a) Acetoacetanilide, acetophenone, and aldehyde were taken in 1:1:1 ratio in presence of 15 mol% NaOAc at r.t. b) Isolated yield. C) New compounds synthesized. d) No reaction.

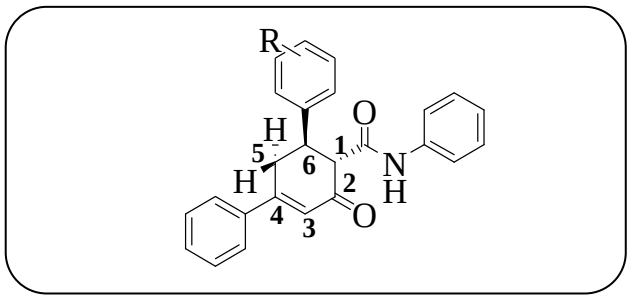
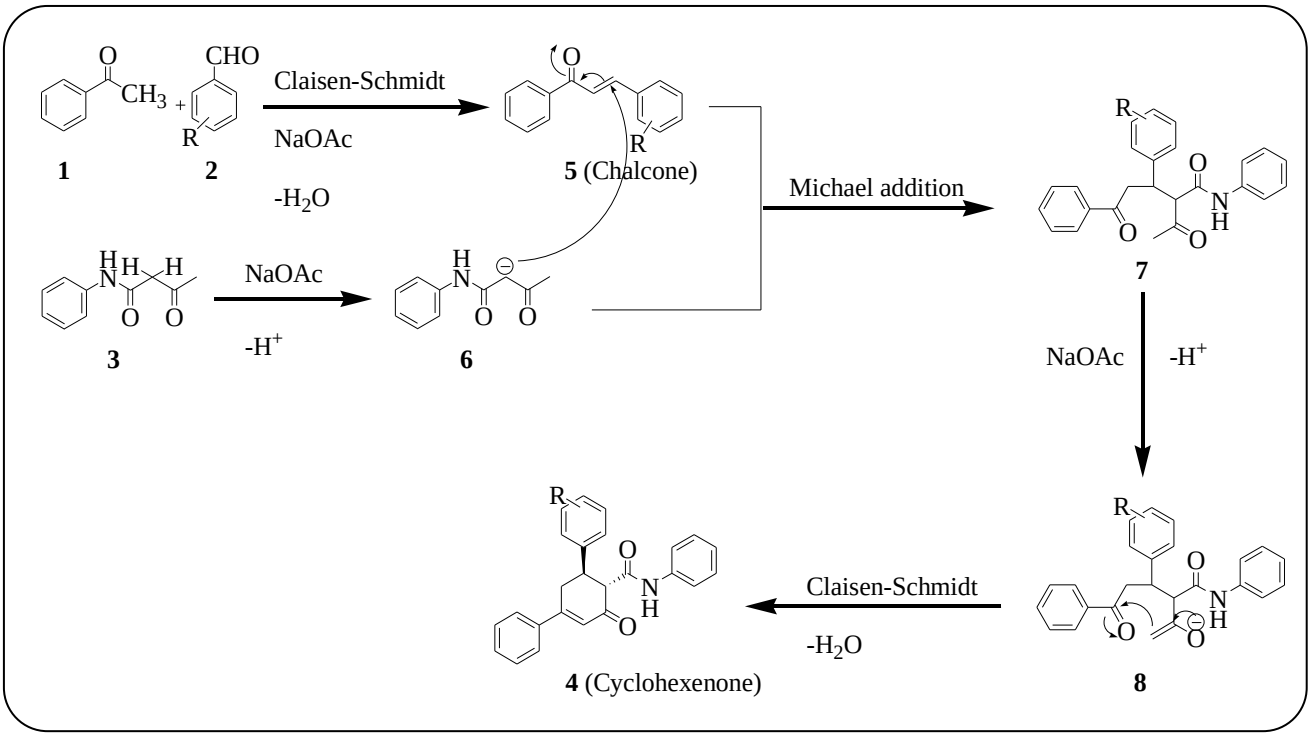


Fig. 1: Chiral centers of the synthesized highly substituted cyclohexenone.

observed for each of the pairs. In ^{13}C NMR spectrum of this compound, the **C-6** carbon was observed at δ 35.8 ppm and **C-5** was exhibited at δ 42.7 ppm. The **C-1**, **C-3** and **C-4** carbons were observed at δ 60.2, 126.9 and 159.4 ppm, respectively. The aromatic carbons were exhibited at δ 115.5-162.7 ppm. In addition, the carbon of carbonyl of amide group was shown at δ 167.7 ppm. Also, the carbon of carbonyl of the conjugated double bond C=C system (**C-2**), was observed at 195.7 ppm.

The synthetic pathway via Claisen-Schmidt condensation and Michael reaction for the preparation of highly functionalized cyclohexenones is illustrated in the Scheme 2. This reaction may proceed via Claisen-Schmidt condensation for the formation of chalcones (**5**) upon the loss of a water molecule. Therefore, in this research, the reaction of acetophenone (**2**) with different aryl aldehydes (**3**) in the presence of catalytic amount of NaOAc afforded the desired chalcone (**5**) upon the loss of a water molecule. Afterward, Michel addition of chalcone with acetoacetanilide (**3**) in presence of NaOAc pursued by internal Claisen condensation give 2-oxo-*N*,4,6-triarylcyclohex-3-enecarboxamides (**4**) by the loss of a water molecule.



Scheme 2: A mechanistic pathway for the synthesis of highly functionalized cyclohexenone 4.

In the ^{1}H NMR spectra, the deshielded CH (H-3) group on the cyclohexene ring, which in all of these derivatives resonates as a singlet and in some cases as a doublet at δ> 6.5 ppm, can be reliable evidence for the formation of the cyclohexenone framework.

CONCLUSIONS

In conclusion, sodium acetate is a simple and efficient catalyst for the diastereoselective multi-component assembling of acetophenone **1**, aromatic aldehydes **2** and acetoacetanilide **3** into medicinally relevant 2-oxo-*N*,4,6-triarylcyclohex-3-enecarboxamides (highly substituted cyclohexenones) **4a-m** in excellent yields. The reaction is performed in water-alcohol emulsion under mild conditions. The procedure utilizes simple equipment; it is easily carried out and is valuable from the viewpoint of diversity-oriented large-scale processes. The results obtained represent a new synthetic concept for multi-component reactions, and allow for the combination of the synthetic virtues of MCR processes in emulsion with ecological benefits. The catalyst shows an environmental friendly character which is inexpensive, clean, safe, nontoxic, and easily obtained. Moreover, the procedure offers several advantages including high yields, operational simplicity, clean reaction conditions, and the minimum pollution of the environment, which make it a useful and attractive process for the synthesis of these compounds.

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