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Et_3N catalyzed the diastereoselective synthesis of functionalized cyclohexanones by condensation of acetoacetanilide and various aldehydes in mild conditions

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Abstract A facile synthetic strategy has been reported for the diastereoselective synthesis of *N*,*N*′-diaryl-2-aryl-6-hydroxy-6-methyl-4-oxocyclohexane-1,3-dicarboxamide via Et_3N-catalyzed. Acetoacetanilide undergoes a diastereoselective condensation reaction with various aromatic and aliphatic aldehydes in EtOH at 50 °C to afford desirable products via one-pot pseudo-three-component reaction. The present protocol provides an inexpensive and efficient route to obtain functionalized cyclohexanones containing four quaternary stereogenic centers with high yields from the simple and readily available starting materials under mild conditions in shorter reaction times. The products have been characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. The stereoselectivity of compounds was established with crystallography and NMR spectroscopy.

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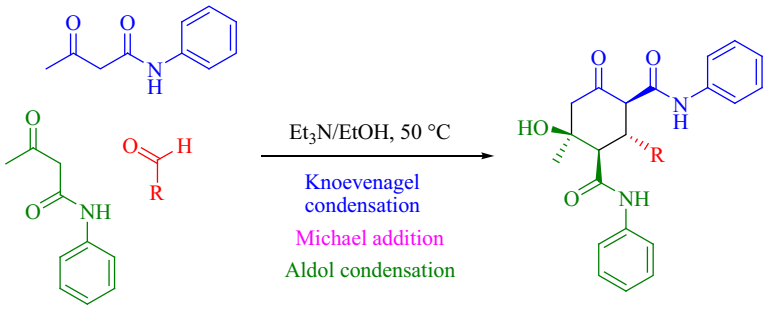
Graphical Abstract



Keyword Et_3N · Diastereoselective · One-pot · Functionalized cyclohexanones · Stereogenic centers

Introduction

Life exists in three-dimensional form and, in this regard, chirality has a leading role. Unceasing stereoselective synthesis of molecules continues in living organisms and dramatically in laboratories with the inspiration of nature [1]. The formation of stereogenic centers, a prevalent feature in many natural products and biologically important scaffolds, has transformed a challenging topic in organic synthesis. This property elevates the complexibility of a chemical synthesis. In the area of organic chemistry, synthesis of motifs while retaining maximum enantiomerical purity is very desirable, especially where several new carbon–carbon bonds are created in a single-pot operation in an atom-economic path [2–4]. In this context, multicomponent reactions effectively provide an answer to the issues of a high degree of pot, atom and step economy (PASE), multiple bond formation, efficiency, convergence and flexibility in the stereoselective construction of complex structural assembly libraries [5, 6].

Recently, organocatalysis, or small metal-free organic molecules, have been applied in organic chemistry and especially in the field of medicinal chemistry as essential tools for the synthesis of stereoselective, complex, molecular scaffolds. Compared to metal catalysts, enzymes or other bioorganic analogues have notable advantages such as higher resistance in rigorously anhydrous or anaerobic conditions and extremely high enantioselectivities that lead to savings in cost, time, and energy, and reduction in chemical waste [7, 8].

Functionalized cyclohexanones containing stereogenic centers as valuable building blocks are present at the core of an array of natural products and drug candidates, such as methoxetamine (a designer drug) [9] and S-(+)-ketamine (Ketanest S, a dissociative anesthetic and antidepressant drug; Fig. 1) [10]. They are biologically active agents with antibacterial [11], anticonvulsant [12], antifungal, and anticancer [13] properties. The antimicrobial feature of some*N*,*N*′-diaryl-2-aryl-

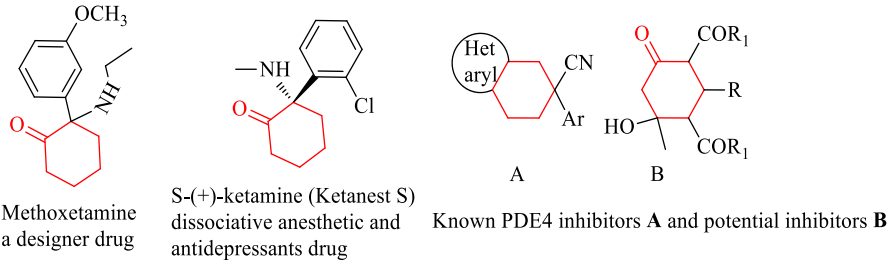
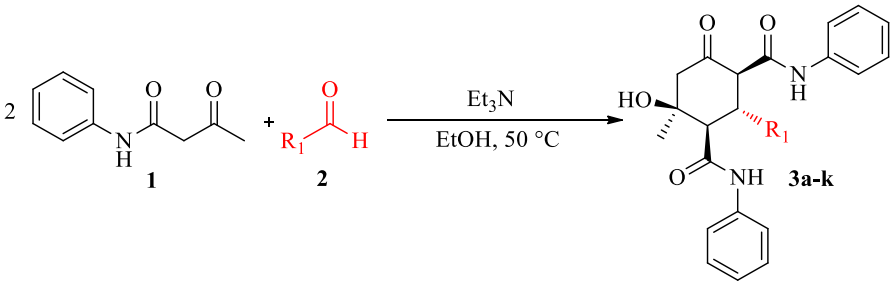


Fig. 1 Representative examples of compounds containing a cyclohexanone unit

6-hydroxy-6-methyl-4-oxocyclohexane-1,3-dicarboxamide derivatives has been proved [14]. The cyclohexanone scaffold has also been investigated in the discovery of phosphodiesterase 4 (PDE4) inhibitors as an agent for the treatment of chronic obstructive pulmonary diseases (COPD), asthma, and central nervous system (CNS)-related diseases (Fig. 1) [3, 15]. Additionally, these classes of scaffolds are striking, starting materials for organic synthesis [16]. Cyclohexanones contain in their structure a hydroxy group, and two alkoxycarbonyl or acyl structures are widely used in the preparation of functionalized carbocyclic or fused heterocyclic compounds [17]. Therefore, there has been extensive attention paid to the synthesis of functionalized cyclohexanones [18, 19].

One of the commonly used methods reported for the synthesis of functionalized cyclohexanones involves the condensation of aldehydes with β-keto esters or 1,3-diketones in the presence of a base [3, 12, 20]. In this context, and in continuation of our endeavors towards the development of catalytic methods for important organic conversions [21–26], herein, we reported an efficient one-pot, pseudo-three-component strategy for the rapid synthesis *N*,*N*′-diaryl-2-aryl-6-hydroxy-6-methyl-4-oxocyclohexane-1,3-dicarboxamide derivatives **3a–k** from reaction between acetoacetanilide and various aromatic and aliphatic aldehydes in the presence of triethylamine (Et_3N) as an efficient catalyst in EtOH at 50 °C (Scheme 1).

The stereoselectivity of highly substituted cyclohexanones including four quaternary stereogenic centers has been envisaged with crystallography analysis and nuclear magnetic resonance (NMR) spectroscopy.



Scheme 1 Et_3N catalyzed the synthesis of *N*,*N*′-diaryl-2-aryl-6-hydroxy-6-methyl-4-oxocyclohexane-1,3-dicarboxamides

Results and discussion

For the synthesis of *N*,*N*′-diaryl-2-aryl-6-hydroxy-6-methyl-4-oxocyclohexane-1,3-dicarboxamides via a more efficient route and shorter reaction time and minimizing the amount of catalyst, the reaction of acetoacetanilide (2.0 mmol) and 4-nitrobenzaldehyde (1.0 mmol) in EtOH was chosen as a model reaction to determine the optimal reaction conditions. Initially, to evaluate the effect of temperature, results showed 50 °C to be the best option in comparison with the other temperatures (Table 1, entry 3). Next, we envisaged the effect of various amounts of catalyst. The highest yield of product was achieved in the presence of 25 mol% of Et_3N in EtOH at 50 °C (Table 1, entry 10). Also, a test reaction was accomplished in catalyst-free conditions. In this state, the desired product was not afforded after 24 h at 50 °C, which showed the presence of catalyst is essential for the reaction (Table 1, entry 8).

In order to evaluate the range and feasibility of reactions, a variety of aromatic aldehydes including either electron-donating or electron-withdrawing groups were reacted with acetoacetanilide under the optimized reaction conditions. The desired products were obtained in good yields using small amounts of the catalyst, and the results are shown in Table 2. As shown, heteroaromatic aldehydes, namely 4-pyridinecarboxaldehyde and thiophene-2-carbaldehyde, also reacted efficiently, affording the corresponding products **3i** and **3j** in 87 and 91% yields, respectively (Table 2). Aliphatic aldehydes also participated well in the reaction with good yields (**3k**).

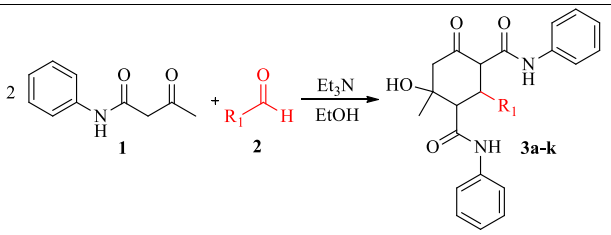
A tentative mechanism for the formation *N*,*N*′-diaryl-2-aryl-6-hydroxy-6-methyl-4-oxocyclohexane-1,3-dicarboxamides is proposed in Scheme 2. At first, Knoevenagel condensation acetoacetanilide **1** and aldehydes **2** produced intermediated products **A**, which upon Michael addition to another acetoacetanilide, provided the intermediate **B**. Intramolecular aldol condensation of **B** afforded the cyclized corresponding products (**3a–k**).

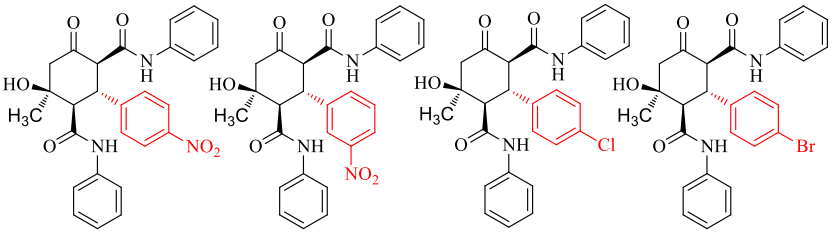
The IR and NMR spectrum all of the products clearly indicated the formation of desirable compounds. For example, the ^{1}H NMR spectrum of compound **3f** showed

Table 1 Optimization of reaction conditions for synthesis of **3a**

Entry	Temperature (°C)	Catalyst (mol%)	Time (min)	Isolated yield (%)
1	r.t.	20	24	70
2	40	20	12	78
3	50	20	4	88
4	60	20	4	89
5	50	5	6	81
6	50	10	5	82
7	50	15	4	86
8	**50**	**25**	**4**	**92**
9	50	30	4	92
10	50	–	24	N.R.

Table 2 Synthesis and molecular structure of *N*,*N*′-diaryl-2-aryl-6-hydroxy-6-methyl-4-oxocyclohexane-1,3-dicarboxamide derivatives (**3a–k**)



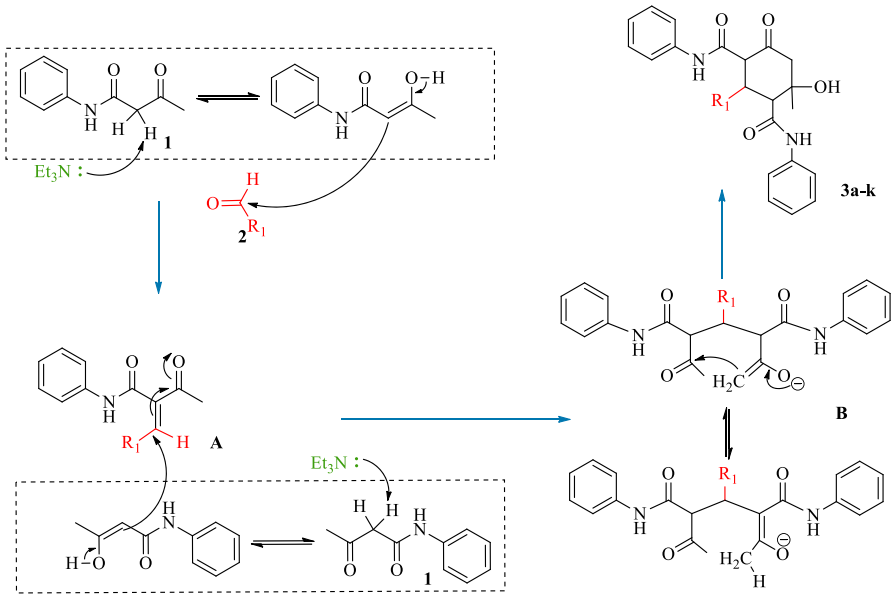


3a, 4h, 92% **3b, 7h, 87%** **3c, 6h, 90%** **3d, 5h, 91%**

3e, 7h, 88% **3f, 8h, 85%** **3g, 6h, 90%**

3h, 7h, 89% **3i, 6h, 87%** **3j, 5h, 91%** **3k, 6h, 89%**

one sharp singlet at 1.30 ppm related to the protons of methyl groups. Four doublets were observed at 2.45, 2.79, 3.15, and 3.84 ppm related to methylene protons in the 5-position and two protons in the 1- and 3-position, respectively. A triplet was observed at 4.01 ppm related to the proton at the 2-position. A broad singlet was observed at 5.08 ppm for the hydroxy group of the cyclohexanone ring. The chemical shift of aromatic protons has shown the presence of 14 protons related to aromatic protons. Three singlets at 9.16, 9.66, and 9.70 related to OH and NH



Scheme 2 The proposed mechanism for the synthesis of *N,N′*-diaryl-2-aryl-6-hydroxy-6-methyl-4-oxocyclohexane-1,3-dicarboxamides

protons were apparent (Fig. 2). The ^{13}C NMR spectrum of compound **3f** exhibited 22 signals in agreement with the suggested motifs.

Experimental

General

Melting points and IR spectra of all compounds were determined by an Electrothermal 9100 apparatus and a JASCO FT-IR-460 Plus spectrometer. The ^{1}H and ^{13}C NMR spectra of known compounds were recorded on a Bruker DRX-400 Avance instrument in DMSO at 300 MHz. Mass spectra were obtained on an Agilent Technology (HP) spectrometer operating at an ionization potential of 70 eV. All chemicals were provided from chemical producers Merck (Darmastadt, Germany) and Fluka (Buchs, Switzerland) and used without further purification.

General procedure for preparation of N,N′-diaryl-2-aryl-6-hydroxy-6-methyl-4-oxocyclohexane-1,3-dicarboxamides

A mixture of acetoacetanilide (2.0 mmol), aldehydes (1.0 mmol), and Et_3N (20 mol%) were stirred at 50 °C in EtOH for an appropriate time. The progress of the reaction was monitored through thin layer chromatography (TLC). After completion of the reaction, the mixture was washed with EtOH for separation of the

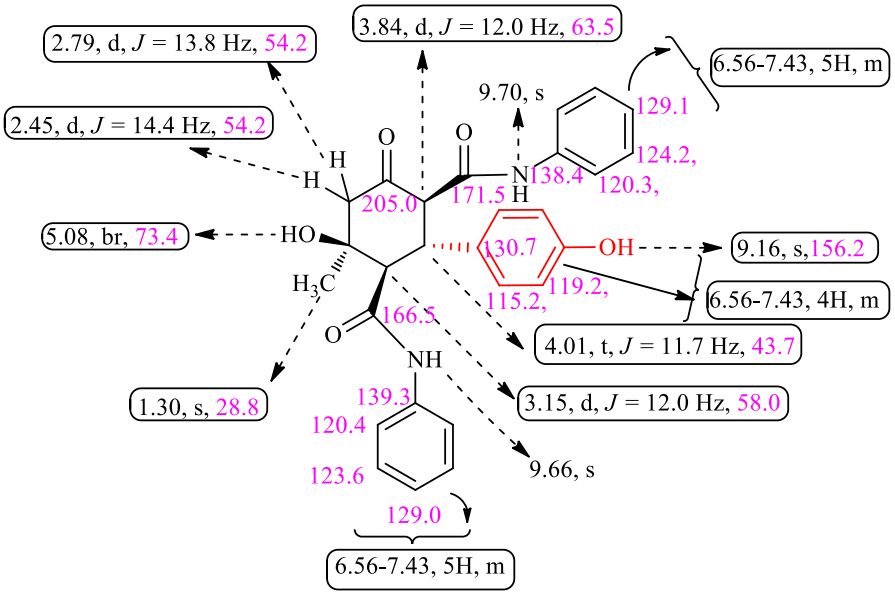


Fig. 2 NMR data of compound **3f**

product. Finally, the crude product was recrystallized from ethanol to afford the pure cyclohexane derivatives.

Characterization data of compounds

6-hydroxy-6-methyl-2-(4-nitrophenyl)-4-oxo-*N*,*N*′-diphenylcyclohexane-1, 3-dicarboxamide (**3a**): White solid; Yield 92%; mp: 234–235 °C. IR (KBr) (νmax, cm^{-1}): 3405, 3372, 2969, 1719, 1682, 1525, 1443, 1348, 753, 686. ^{1}H NMR (300 MHz, DMSO-*d*6): δ 1.34 (s, 3H, CH_3), 2.51 (d, 1H, CH_2), 2.95 (d, 1H, J = 13.8 Hz, CH_2), 3.34 (d, 1H, J = 12.0 Hz, CH_2), 4.01 (d, 1H, J = 12.3 Hz, CH), 4.35 (t, 2H, J = 12.3 Hz, CH), 5.21 (s, br, 1H, OH), 6.96-7.42 (m, 10H, ArH), 7.65 (d, 2H, J = 8.1 Hz, ArH), 8.12 (d, 2H, J = 8.7 Hz, ArH), 9.70, 9.82 (2 s, 2H, 2NH). ^{13}C NMR (75.65 MHz, DMSO-*d*6): δ 28.5, 44.1, 54.6, 62.6, 73.5, 119.2, 119.3, 119.9, 120.1, 120.4, 120.5, 123.6, 123.7, 124.2, 129.0, 129.1, 130.2, 138.3, 139.0, 146.8, 148.9, 166.0, 170.2, 204.2. MS m/z (%): 93.2 (100), 141.2 (10), 173.2 (12), 230.2 (16), 350.2 (9), 487.3 (M + , 0.2).

6-hydroxy-6-methyl-2-(3-nitrophenyl)-4-oxo-*N*,*N*′′-diphenylcyclohexane-1, 3-dicarboxamide (**3b**): White solid; Yield 87%; mp: 229–230 °C [12]. IR (KBr) (νmax, cm^{-1}): 3587, 3309, 2923, 1709, 1691, 1530, 1443, 1349, 756, 691. ^{1}H NMR (300 MHz, DMSO-*d*6): δ 1.35 (s, 3H, CH_3), 2.49 (d, 1H, J = 9 Hz, CH_2), 2.93 (d, 1H, J = 13.8 Hz, CH_2), 3.38 (d, 1H, J = 13.2 Hz, CH), 4.04 (d, 1H, J = 12.0 Hz, CH), 4.35 (t, 2H, J = 12.0 Hz, CH), 5.30 (s, br, 1H, OH), 6.96-7.55 (m, 10H, ArH), 7.55 (t, 1H, J = 8.1 Hz, ArH), 7.79 (d, 1H, J = 7.5 Hz, ArH), 8.00 (d, 1H, J = 8.1 Hz, ArH), 8.32 (s, 1H, ArH), 9.71, 9.84 (2 s, 2H, 2NH). ^{13}C NMR

(75.65 MHz, DMSO-*d*6): δ 28.7, 44.0, 54.6, 62.7, 73.5, 119.4, 120.5, 120.6, 122.5, 123.1, 123.8, 124.3, 129.0, 129.1, 130.0, 136.1, 138.3, 139.0, 143.1.7, 147.9, 166.1, 170.4, 204.2.

2-(4-chlorophenyl)-6-hydroxy-6-methyl-4-oxo-*N*,*N*′-diphenylcyclohexane-1, 3-dicarboxamide (**3c**): White solid; Yield 90%; mp: 246–247 °C [12]. IR (KBr) (νmax, cm^{-1}): 3393, 3303, 2971, 1713, 1660, 1531, 1445, 752, 695. ^{1}H NMR (300 MHz, DMSO-*d*6): δ 1.32 (s, 3H, CH_3), 2.48 (d, 1H, $J = 15$ Hz, CH_2), 2.86 (d, 1H, $J = 13.5$ Hz, CH_2), 3.25 (d, 1H, $J = 12.0$ Hz, CH), 3.92 (d, 1H, $J = 12.0$ Hz, CH), 4.17 (t, 2H, $J = 12.0$ Hz, CH), 5.20 (s, br, 1H, OH), 6.97-7.43 (m, 14H, ArH), 9.68, 9.77 (2 s, 2H, 2NH). ^{13}C NMR (75.65 MHz, DMSO-*d*6): δ 28.6, 43.8, 54.5, 63.0, 73.4, 119.2, 119.3, 120.3, 120.5, 123.7, 124.2, 128.4, 129.0, 129.1, 130.6, 131.7, 138.4, 139.1, 139.7, 166.2, 170.7, 204.5.

2-(4-bromophenyl)-6-hydroxy-6-methyl-4-oxo-*N*,*N*′-diphenylcyclohexane-1, 3-dicarboxamide (**3d**): White solid; Yield 91%; mp: 236–237 °C. IR (KBr) (νmax, cm^{-1}): 3573, 3312, 2976, 1712, 1702, 1686, 1547, 1443, 752, 690. ^{1}H NMR (300 MHz, DMSO-*d*6): δ 1.33 (s, 3H, CH_3), 2.49 (d, 1H, $J = 13.2$ Hz, CH_2), 2.87 (d, 1H, $J = 13.8$ Hz, CH_2), 3.26 (d, 1H, $J = 12.0$ Hz, CH_2), 3.92 (d, 1H, $J = 12.0$ Hz, CH_2), 4.16 (t, 2H, $J = 12.0$ Hz, CH), 5.21 (s, br, 1H, OH), 6.97-7.44 (m, 14H, ArH), 9.69, 9.78 (2 s, 2H, 2NH). ^{13}C NMR (75.65 MHz, DMSO-*d*6): δ 28.6, 43.8, 54.5, 63.0, 73.4, 113.7, 119.2, 119.3, 120.3, 120.3, 120.5, 123.7, 124.2, 129.0, 129.1, 129.7,130.9, 131.3, 138.4, 139.1, 140.2, 166.2, 170.7, 204.5. MS m/z (%): 93.2 (100), 141.1 (12), 184.2 (20), 263.1 (37), 384.2 (11), 520.3 (M + , 0.2).

2-(3-bromophenyl)-6-hydroxy-6-methyl-4-oxo-*N*,*N*′-diphenylcyclohexane-1, 3-dicarboxamide (**3e**): White solid; Yield 88%; mp: 216–217 °C. IR (KBr) (νmax, cm^{-1}): 3399, 3308, 2923, 1723, 1663, 1553, 1443, 1357, 756, 691. ^{1}H NMR (300 MHz, DMSO-*d*6): δ 1.33 (s, 3H, CH_3), 2.51 (d, 1H, CH_2), 2.87 (d, 1H, $J = 13.5$ Hz, CH_2), 3.27 (d, 1H, $J = 12.0$ Hz, CH), 3.94 (d, 1H, $J = 11.7$ Hz, CH), 4.16 (t, 2H, $J = 11.7$ Hz, CH), 5.20 (s, br, 1H, OH), 7.00–7.59 (m, 14H, ArH), 9.70, 9.79 (2 s, 2H, 2NH). ^{13}C NMR (75.65 MHz, DMSO-*d*6): δ 28.6, 44.1, 54.5, 62.8, 73.4, 119.4, 120.1, 120.4, 120.5, 120.6, 121.7, 123.7, 124.3, 128.0, 129.0, 129.1, 130.2, 130.5, 131.3, 138.3, 139.1, 143.5, 166.2, 170.7, 204.4. MS m/z (%): 93.2 (100), 141.1 (14), 209.0 (15), 265.1 (46).

6-hydroxy-6-methyl-2-(4-hydroxyphenyl)-4-oxo-*N*,*N*′-diphenylcyclohexane-1, 3-dicarboxamide (**3f**): White solid; Yield 85%; mp: 233–234 °C. IR (KBr) (νmax, cm^{-1}): 3289, 3145, 2969, 1714, 1672, 1548, 1445, 1381, 1253, 752, 691. ^{1}H NMR (300 MHz, DMSO-*d*6): δ 1.30 (s, 3H, CH_3), 2.45 (d, 1H, $J = 14.4$ Hz, CH_2), 2.79 (d, 1H, $J = 13.8$ Hz, CH_2), 3.15 (d, 1H, $J = 12.0$ Hz, CH), 3.84 (d, 1H, $J = 12.0$ Hz, CH), 4.01 (t, 2H, $J = 11.7$ Hz, CH), 5.08 (s, br, 1H, OH), 6.56-7.43 (m, 14H, ArH), 9.16 (s, 1H, OH), 9.66, 9.70 (2 s, 2H, 2NH). ^{13}C NMR (75.65 MHz, DMSO-*d*6): δ 28.8, 43.7, 54.2, 58.0, 63.5, 73.4, 115.2, 119.2, 120.3, 120.4, 123.6, 124.2, 129.0, 129.1, 130.7, 138.4, 139.3, 156.2, 166.5, 171.5, 205.0. MS m/z (%): 93.2 (83), 147.1 (30), 201.2 (100), 321.3 (13).

2-(4-methoxyphenyl)-6-Hydroxy-6-methyl-4-oxo-*N*,*N*′-diphenylcyclohexane-1, 3-dicarboxamide (**3g**): White solid; Yield 90%; mp: 227–228 °C [13]. IR (KBr) (νmax, cm^{-1}): 3393, 3308, 2970, 1718, 1654, 1542, 1444, 1252, 753, 691. ^{1}H NMR (300 MHz, DMSO-*d*6): δ 1.31 (s, 3H, CH_3), 2.48 (d, 1H, $J = 15$ Hz, CH_2), 2.82 (d, 1H, $J = 13.8$ Hz, CH_2), 3.21 (d, 1H, $J = 12.0$ Hz, CH), 3.62 (s, 3H, OCH_3), 3.88 (d, 1H, $J = 12.0$ Hz, CH), 4.09 (t, 2H, $J = 12.0$ Hz, CH), 5.11 (s, br, 1H, OH), 6.75-7.44 (m, 14H, ArH), 9.67, 9.72 (2 s, 2H, 2NH). ^{13}C NMR (75.65 MHz, DMSO-*d*6): δ 28.7, 54.3, 55.2, 56.5, 63.4, 73.4, 113.7, 119.2, 120.4, 123.6, 124.1, 129.0, 129.1, 129.7, 132.5, 138.4, 139.1, 139.3, 158.2, 166.5, 171.3, 204.9. MS m/z (%): 93.1 (58), 161.1 (20), 215.2 (100), 335.3 (14), 472.3 (M + , 0.3).

6-hydroxy-6-methyl-4-oxo-2-(4-methylphenyl)-*N*,*N*′-diphenylcyclohexane-1, 3-dicarboxamide (**3h**): White solid; Yield 89%; mp: 230–231 °C. IR (KBr) (νmax, cm^{-1}): 3670, 3319, 2977, 1714, 17.04, 1686, 1545, 1443, 751, 690. ^{1}H NMR (300 MHz, DMSO-*d*6): δ 1.32 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.49 (d, 1H, $J = 14.4$ Hz, CH_2), 2.83 (d, 1H, $J = 14.1$ Hz, CH_2), 3.23 (d, 1H, $J = 12.0$ Hz, CH), 3.92 (d, 1H, $J = 12.3$ Hz, CH), 4.12 (t, 2H, $J = 12.0$ Hz, CH), 5.1 (s, br, 1H, OH), 6.96-7.45 (m, 14H, ArH), 9.68, 9.73 (2 s, 2H, 2NH). ^{13}C NMR (75.65 MHz, DMSO-*d*6): δ 21.0, 28.7, 44.0, 54.4, 63.3, 73.5, 119.2, 120.4, 123.5, 124.1, 128.5, 129.0, 129.1, 136.0, 137.6, 138.4, 139.3, 166.4, 171.2, 204.9. MS m/z (%): 93.2 (100), 145.1 (52), 199.2 (100), 318.2 (16), 456.3 (M + , 0.7).

6-hydroxy-6-methyl-4-oxo-*N*,*N*′-diphenyl-2-(pyridin-4-yl)cyclohexane-1, 3-dicarboxamide (**3i**): White solid; Yield 87%; mp: 181–183 °C. IR (KBr) (νmax, cm^{-1}): 3405, 3293, 2969, 1728, 1658, 1556, 1446, 1381, 1255, 753, 692. ^{1}H NMR (300 MHz, DMSO-*d*6): δ 1.35 (s, 3H, CH_3), 2.88 (d, 1H, $J = 13.8$ Hz, CH_2), 3.29 (d, 1H, $J = 12.3$ Hz, CH_2), 3.35 (d, 1H, CH), 3.98 (d, 1H, $J = 12.3$ Hz, CH), 4.19 (t, 2H, $J = 12.0$ Hz, CH), 5.22 (s, br, 1H, OH), 6.98-7.42 (m, 12H, ArH), 8.43 (d, 2H, $J = 5.7$ Hz, ArH), 9.70, 9.78 (2 s, 2H, 2NH). ^{13}C NMR (75.65 MHz, DMSO-*d*6): δ 28.6, 43.8, 54.5, 62.2, 73.6, 119.4, 120.5, 123.8, 124.1, 124.3, 129.0, 129.1, 138.3, 139.0, 149.5, 149.8, 166.0, 170.4, 204.1. MS m/z (%): 93.2 (100), 132.1 (24), 186.2 (62), 305.1 (23), 443.3 (M + , 0.3).

6-hydroxy-6-methyl-4-oxo-*N*,*N*′-diphenyl-2-(thiophen-2-yl)cyclohexane-1, 3-dicarboxamide (**3j**): White solid; Yield 91%; mp: 247–248 °C. IR (KBr) (νmax, cm^{-1}): 3455, 3308, 2970, 1718, 1664, 1539, 1444, 1252, 753, 691. ^{1}H NMR (300 MHz, DMSO-*d*6): δ 1.32 (s, 3H, CH_3), 2.48 (d, 1H, CH_2), 2.76 (d, 1H, $J = 14.1$ Hz, CH_2), 3.22 (d, 1H, $J = 12.0$ Hz, CH), 3.92 (d, 1H, $J = 12.3$ Hz, CH), 4.29 (t, 2H, $J = 12.0$ Hz, CH), 5.03 (s, br, 1H, OH), 6.11-7.51 (m, 13H, ArH), 9.87, 9.89 (2 s, 2H, 2NH). ^{13}C NMR (75.65 MHz, DMSO-*d*6): δ 28.5, 38.4, 54.2, 55.9, 60.8, 73.1, 107.2, 110.7, 119.3, 120.5, 123.7, 124.3, 129.1, 129.1, 138.5, 139.3, 142.6, 154.1, 166.3, 171.2, 204.0. MS m/z (%): 93.2 (86), 147.2 (15), 175.2 (100), 294.1 (38).

2-ethyl-6-hydroxy-6-methyl-4-oxo-*N*,*N*′-diphenylcyclohexane-1,3-dicarboxamide (**3k**): White solid; Yield 89%; mp: 248–249 °C. IR (KBr) (νmax, cm^{-1}): 3450, 3283, 2924, 1720, 1668, 1634, 1542, 1444, 743, 698. ^{1}H NMR (300 MHz, DMSO-

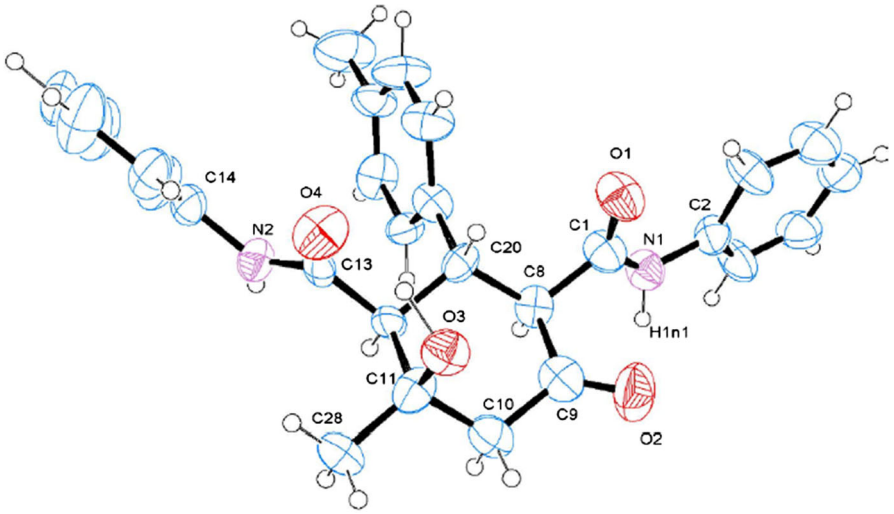


Fig. 3 *ORTEP* representation of the X-ray structure of **3h**

*d*6): δ 0.94 (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 1.30 (s, 3H, CH_3), 1.34-1.50 (m, 2H, CH_2CH_3), 2.40 (d, 1H, $J = 14.1$ Hz, CH_2), 2.60 (d, 1H, $J = 14.1$ Hz, CH_2), 2.86 (d, 1H, $J = 12.0$ Hz, CH), 2.97-3.06 (m, 1H, CH), 3.48 (d, 1H, $J = 11.7$ Hz, CH), 4.93 (s, br, 1H, OH), 7.05-7.64 (m, 10H, ArH), 9.95, 10.09 (2 s, 2H, 2NH). ^{13}C NMR (75.65 MHz, DMSO-*d*6): δ 8.8, 12.2, 23.7, 28.7, 37.9, 54.0, 60.5, 73.3, 119.5, 120.3, 123.7, 124.4, 129.2, 129.3, 138.6, 139.4, 167.3, 172.4, 205.6. MS m/z (%): 93.2 (100), 137.2 (58), 202.1 (18), 256.1 (46), 394.3 (M + , 7).

Crystallographic data

The molecular **3h** crystallized as a colorless crystal in the monoclinic space group I2/c with cell parameters a = 24.275 (5) Å, b = 8.8819 (18) Å, c = 27.842 (6) Å, $\alpha = 90°$, $\beta = 110.06(3)°$, $\gamma = 90°$, V = 5639 (2) Å^3, $D_{calc} = 1.076$ gcm^{-3}, and Z = 8 (Fig. 3). The final *R* value is 0.0597 for 19398 reflections. Crystallographic data and the refinement procedures for **3h** are given in Table 3.

Conclusion

In conclusion, a practical and efficient protocol for the synthesis of *N*,*N*′-diaryl-2-aryl-6-hydroxy-6-methyl-4-oxocyclohexane-1,3-dicarboxamides via a one-pot, pseudo-three-component Knoevenagel–Michael aldol condensation of acetoacetanilide, and various aldehydes is developed. The reaction can proceed in EtOH at 50 °C. High yields of products with short reaction time in a clean process in addition to an easy work-up and minimizing the use of catalyst are the advantageous aspects of this method. Also, the products have four stereocenters and are

Table 3 Crystal data and structure (1R, 2R, 3S, 6S)-6-hydroxy-6-methyl-4-oxo-2-(4-methylphenyl)-*N*,*N*′-diphenylcyclohexane-1,3-dicarboxamide

Empirical formula	$C_{28}\ H_{28}N_2O_4$
Formula weight	456.52
Temperature (K)	293
Crystal system	Monoclinic
Space group	I2/c (no. 15)
Unit cell dimensions	$a = 24.275$ (5) Å
	$b = 8.8819$ (18) Å
	$c = 27.842$ (6) Å
	$\alpha = 90°$
	$\beta = 110.06(3)°$
	$\gamma = 90°$
Volume	5639 (2) $Å^3$
Z	8
Density (calculated)	1.076
μ/mm^{-1}	0.072
$F(000)$	1936
Crystal size	$0.20 \times 0.40 \times 0.52\ mm^3$
θ range for data collection	1.6 to 25.0
Observed data [$I > 2\sigma\ (I)$]	702
Dataset	−28: 28; −10: 10; −32: 32
Data collected	19,398
Unique data, R(int)	4916, 0.188
Parameters	317
R, wR_2, S	0.0597, 0.1488, 0.49
Max, min [$e \cdot Å^{-3}$]	−0.16, 0.16
CCDC	1,552,865

$w = 2[(F_O^2) + (0.0449P)^2]$
$P = (F_O^2 + 2F_C^2)/3'$

synthesized with diastereocontrol completely. Owing to these features, this protocol would find vast applications in the field of organic synthesis of complex molecules.

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