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FULL-LENGTH PAPER

One-pot diastreoselective synthesis of highly functionalized cyclohexenones: 2-oxo-N,4,6-triarylcyclohex-3-enecarboxamides

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Abstract A series of 2-oxo-N,4,6-triarylcyclohex-3-enecarboxamides were synthesized by condensing acetophenone and aromatic aldehydes with acetoacetanilide in ethanol in the presence of 2-hydroxyethylammonium acetate (2-HEAA) as a basic ionic liquid at ambient conditions. This process is simple, efficient and environmentally benign and proceeds in high yield, short reaction times and there is no need for column chromatography purification.

Keywords Highly functionalized cyclohexenone · 2-Oxo-N,4,6-triarylcyclohex-3-enecarboxamide · Ionic liquid · One-pot · 2-Hydroxyethylammonium acetate

Introduction

Commonly, α,β-Enone is known as chalcone. Chalcones own an α,β-unsaturated grouping with two aromatic rings in the molecules. A highly electrophilic three-carbon α,β-unsaturated carbonyl system has interconnected the rings (Fig. 1) [1–4]. Chalcones are very reactive compounds and increase their reactivity due to a keto-ethylinic type (–CO–CH=CH–) conjugated double bond system present in the structure [5–7]. Chalcones have occupied a unique place in medicinal and biological chemistry. Chalcones and derivatives comprise a significant class of compounds possessing diverse biological and pharmacological properties including anti-bacterial [4,8,9], anticonvulsant [10], anti-cancer [11], anti-fungal [12,13], antiprotozoal [14], antimalarial [1,2,15], larvicidal [16], antifilarial [17], anti-inflammatory [18], antioxidant [19,20], and antimicrobial [21]. Also, they have been identified as inhibitors of enzymes, specifically mammalian alpha-amylase [3,22], monoamine oxidase (MAO) [23], and cyclo-oxygenase (COX)[24]. 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 [25–27]. Therefore, an important feature of chalcones is their ability to act as activated unsaturated systems in conjugated additions of carbanions in the presence of suitable basic catalysts [28,29]. For example, the Michael addition of ethylacetoacetate to chalcone yields 4,6-diaryl-2-oxo-cyclohex-3-ene-1-carboxylate derivatives which are efficient synthons for building spiranic compounds [30], and are also important intermediates in the synthesis of joined heterocycles, such as benzopyrazoles and benzisoxazoles [31], benzoselenadiazoles and benzothiadiazoles [32], 2H-indazoles [33], and carbazole derivatives [34]. Cyclohexenone derivatives are well-known lead molecules for the treatment of inflammation and autoimmune diseases [35,36]. Also, cyclohexenone and inazole derivatives exhibit a variety of pharmacological properties, such as antitumor [37], tyrosine kinases inhibitor [38], antipyretic [39], antiasthametic [40], antiviral [41], anti-bacterial, anti-fungal, anti-cancer, and anti-tubercular activity [42]. Because of the importance of cyclohexenone derivatives from a pharmaceutical and biological point of view, there is still a need to develop efficient, mild, and environmentally benign protocols for the synthesis of these compounds. Herein we present an eco-friendly procedure for the synthesis simple and effi cient and characterization of a novel series cyclohexenone derivatives called 2-oxo-N,4,6-triarylcyclohex-3-enecarboxamides via a one-pot three-component reaction using ace-

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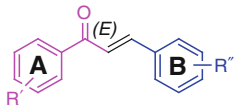
Fig. 1 Structure of chalcone



tophenone **1**, aromatic aldehydes **2**, and 3-oxo-N-phenylbutanami (acetoacetanilide) **3** in the presence of 2-hydroxyethylammonium acetate as a ionic liquid in ethanol at room temperature (Scheme 1).

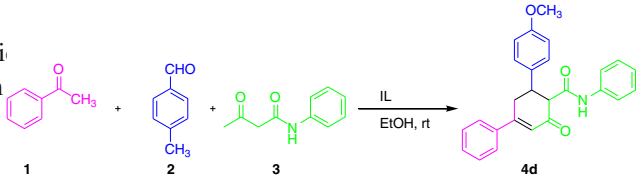
Results and discussion

We first examined the reaction of 4-methoxy benzaldehyde and acetophenone with acetoacetanilide using 15 mol% of different catalysts. In the initial search for an efficient catalyst, four different ionic liquids were screened in our model reaction. The reaction did not progress even after 48 h in the absence of catalyst. As shown in Table 1, the reaction was performed in the presence of diethylammonium hydrogen sulfate (DEAS), triethylammonium hydrogen sulfate (TEAS), and triethylammonium dihydrogen phosphate (TEAP), the desired product was obtained in low yields along with undesired by-products. However, after optimizing the catalyst amount, we found that 20 mol% 2-hydroxyethylammonium acetate (2-HEAA) gave desired product in high yields. Increasing the catalyst loading did not improve product yields (entries, 8 and 9). Also, we found that when the reactions were run under solvent-free and under optimized conditions, the reaction did not lead to the desired product (Table 1, entry 10) which could be due to the lack of effective interaction between reactants and the catalyst in the absence of solvent.

During the course of screening a variety of reaction conditions such as solvent, reaction temperature, and the amount of the catalyst, we found that the use of ethanol as a solvent was essential for the efficient conversion of raw materials to (1R,6S)/(1S,6R)-6-(4-methoxyphenyl)-2-oxo-N,4-diphenylcyclohex-3-enecarboxamide **4d**. It is remarkable that, ethanol is a green solvent. The structure of (1R,6S)/(1S,6R)-6-(4-methoxyphenyl)-2-oxo-N,4-diphenylcyclohex-3-enecarboxamide **4d** was confirmed by spectral techniques, such as like ^{1}H-NMR, ^{13}C-NMR, elemental, and mass spectral analysis. The products obtained in this work are chiral compounds. They have two chiral centers on **C-1** and **C-6**, with protons in *anti*-configuration. Also, the protons on **C-5** are diastereotopic. This reaction leads to the creation of two stereogenic centers (Fig. 2).

To explore the scope of our methodology, we extended this reaction to various aromatic aldehydes in the presence of electron-withdrawing (NO_2, Cl, CN, and Br) and electron-releasing (OMe) substituents, both of which gave the desired

Table 1 Condensation reaction of acetophenone, 4-methoxy benzaldehyde, and acetoacetanilide in the presence of different loadings of various catalysts at ambient conditions[a]



Entry	Catalyst	Solvent	Catalyst (mol%)	Time (h)	Yield (%)[a]
1	–	EtOH	–	24	–
2	DEAS	EtOH	15	120	30
3	TEAS	EtOH	15	100	38
4	TEAP	EtOH	15	60	40
5	2-HEAA	EtOH	5	55	80
6	2-HEAA	EtOH	10	50	82
7	**2-HEAA**	**EtOH**	**20**	**45**	**96**
8	2-HEAA	EtOH	25	40	88
9	2-HEAA	EtOH	30	45	90
10	2-HEAA	–	20	24	–

[a] All the reactions were carried out using, acetophenone 1 mmol, 4-methoxy benzaldehyde 1 mmol and acetoacetanilide 1 mmol with varying amounts of catalysts in EtOH (5 mL) at room temperature
[b] Yield refers to the pure isolated products

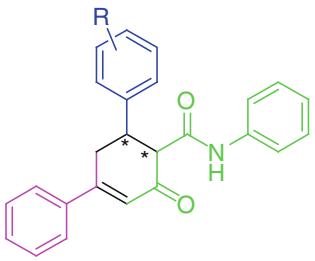


Fig. 2 Stereogenic centers on the structure of 2-oxo-N,4,6-triarylcyclohex-3-enecarboxamides

Scheme 1 Synthesis of diastreoselective 2-oxo-N,4,6-triarylcyclohex-3-enecarboxamides

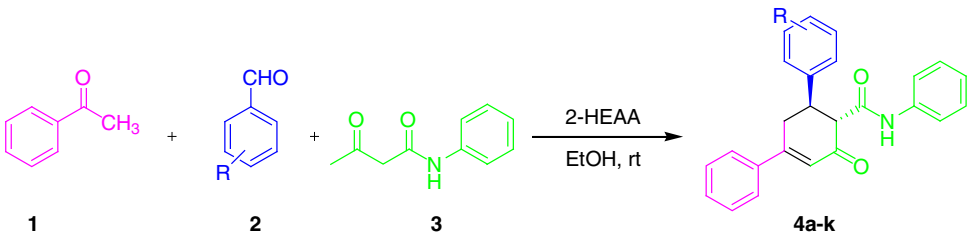


Table 2 Synthesis of 2-oxo-N,4,6-triarylcyclohex-3-enecarboxamides in the presence of ethanol ammonium acetate

Entry	Product	R	Time(h)	Yield (%)[a]	M.p.(°C)
1	**4a**	2-Br	15	99	220–222
2	**4b**	3-NO_2	20	96	200–202
3	**4c**	2-Cl	40	97	224–226
4	**4d**	4-OMe	45	96	217–219
5	**4e**	4-NO_2	18	94	202–204
6	**4f**	2,6-Cl_2	15	95	188–190
7	**4g**	4-CN	25	99	224–226
8	**4h**	3-Cl	30	95	187–189
9	**4i**	3-pyridin-	45	92	195–197
10	**4j**	4-pyridin-	10	97	202–204
11	**4k**	2,3-$(OMe)_2$	35	90	196–198

Bold represents the best conditions for the reaction during the course of the screening of different catalysts

[a] Yields refer to the pure isolated products

product. The results are shown in Table 2. These results show that the functional groups did not play any significant role in the reactivity of the substrate.

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. The products were fully characterized by melting points, elemental analyses, IR, ^{1}H and ^{13}C NMR, and mass spectra. For example, the IR spectra of **4g** revealed a sharp absorption band at 3308 cm^{-1} associated to NH, while a strong stretching band at 2230 cm^{-1} was attributed to C ≡ N. Furthermore, two sharp strong absorption bands were noticed at approximately 1672 and 1656 cm^{-1} and were 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 **4g** recorded a molecular ion signal (M^+) at $m/z = 392$, which is consistent with the proposed structure. The ^{1}H NMR spectrum of compound **4g**, exhibited two doublets of doublets at 3.07 ppm ($J = 18.0, 4.0$ Hz) and 3.18 ppm ($J = 17.6, 10.4$ 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 (td) at δ 3.95 ppm ($J = 13.2, 4.8$ Hz) and another methine proton (H-1) appeared as a doublet at δ 4.02 ppm ($J = 13.2$ Hz). The vinyl proton (H-3) was observed as a doublet at 6.60 ppm (J = 1.6 Hz). The aromatic protons were recorded as doublets and triplets at δ 7.01–7.80 ppm. The NH proton was observed at δ 10.10 ppm, indicating an intramolecular hydrogen bond interaction with the vicinal carbonyl group on cyclohexenone ring. The ^{13}C-NMR spectrum of compound **4g** showed 20 distinct signals consistent with the cyclohexenone structure. According to the structure of **4g**, 25 carbon signals should be present in the ^{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 **4g**, on the ^{13}C NMR spectrum one signal is observed for each of the pairs. In the ^{13}C NMR spectrum of this compound, the **C-6** carbon was observed at δ 35.1 ppm and **C-5** at δ 43.4 ppm. The **C-1**, **C-3**, and **C-4** carbon signals were observed at δ 59.3, 126.9, and 159.2 ppm, respectively. The C ≡ N and aromatic carbons were found at δ 110.2-148.3 ppm. In addition, the carbon of carbonyl of amide group was shown at δ 167.4 ppm. And, the carbon of carbonyl of conjugated double bond C=C system (**C-2**) was observed at 195.3 ppm.

A part of the ^{1}H NMR spectrum of **4b** is shown in Fig. 3. In this figure, four protons of cyclohexenone, H-5, H'-5, H-1, and H-6 were characterized and assigned.

A reasonable pathway for the synthesis of highly substituted cyclohexenone derivatives is given in Scheme 2. The Claisen-Schmidt condensation method for the synthesis of chalcones is very attractive, since it specifically generates the trans (E)-isomer [43–45]. Hence, the reaction of acetophenone **1** with different aryl aldehydes **2** in the presence of catalytic amount of 20 mol% 2-hydroxyethylammonium acetate afforded the desired chalcone **5**. Subsequently, Michel addition of chalcone with acetoacetanilide **3** in the presence of IL followed by internal Claisen condensation gives 2-oxo-N,4,6-triarylcyclohex-3-enecarboxamides **4**.

In conclusion, we have disclosed an extremely facile and environmentally benign synthesis of a series of 2-oxo-N,4,6-triarylcyclohex-3-enecarboxamides via reaction of acetophenone and different aromatic aldehydes with acetoacetanilide under room temperature with ethanol as green solvent by the use of a catalytic amount of 2-hydroxyethylammonium acetate (2-HEAA). This work not only offers substantial improvements in reaction rates and yields, but also avoids the use of hazardous catalysts or solvents. Moreover, the mild reaction conditions, high yields, easy work-up, and clean reaction profiles are some of the advantages of this procedure. Therefore, this protocol is eco-friendly.

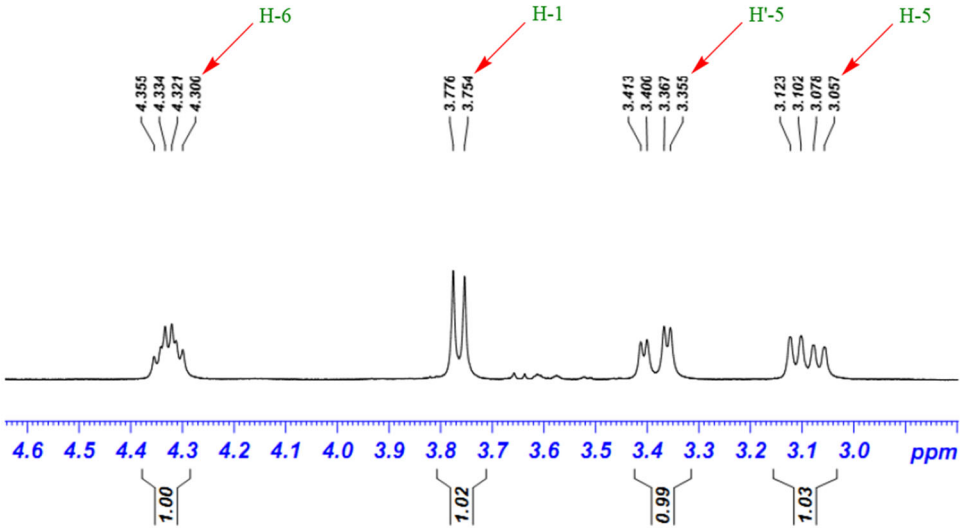
It is worth noting that literature procedures generally point to the synthesis of cyclohexenone derivatives in two steps. Such as in the first step chalcone is synthesized from the reaction of aldehyde and acetophenone. After isolation, purification and characterization, in the second step chalcone would react in new conditions for preparing cyclohexenone derivatives. But in the present work, synthesis of novel cyclohexenones (2-oxo-N,4,6-triarylcyclohex-3-enecarboxamides) is discussed in a one-pot three-component reaction.

Experimental

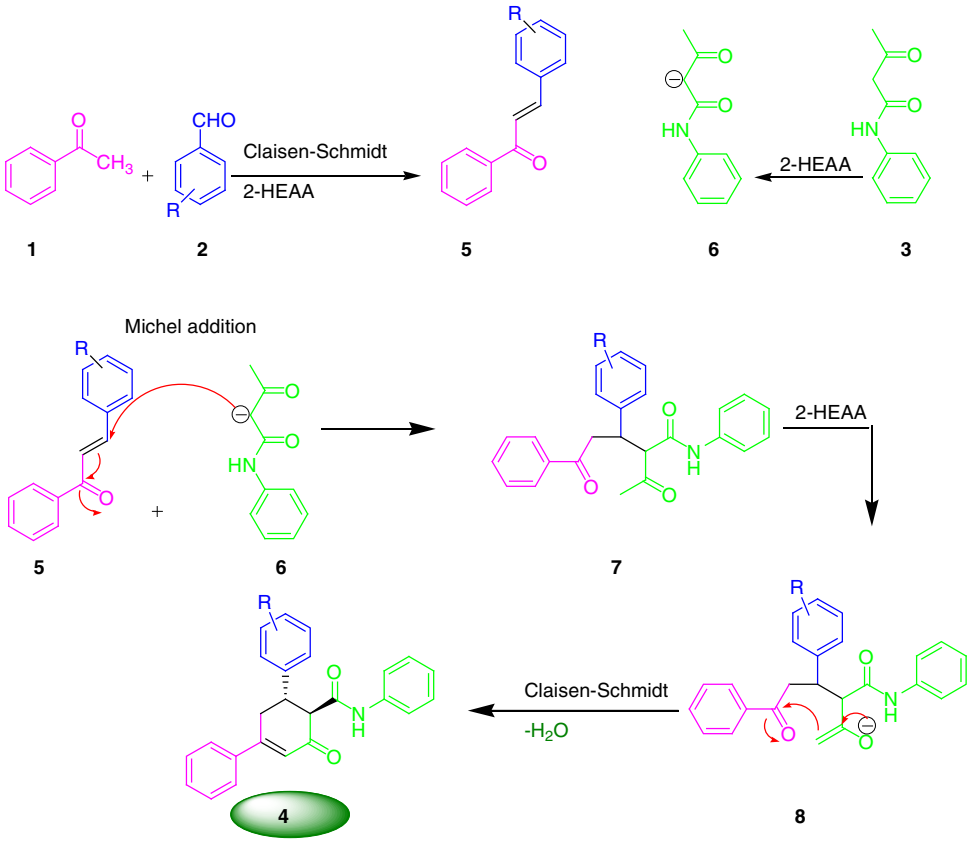
General

Melting point and IR spectra of all compounds were obtained on an Electrothermal 9100 apparatus and a JASCO FT/IR-

Fig. 3 ^{1}H NMR spectrum of **4b**



Scheme 2 Suggested pathway for the synthesis of highly substituted cyclohexenone derivatives



460 plus spectrometer, respectively. ^{1}H and ^{13}C NMR spectra of compounds were recorded on a Bruker DRX-400 Avance instrument using DMSO or $CDCl_3$ as the solvent and 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 for 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 (Darmastadt, Germany), Acros (Geel, Belgium) and Fluka (Buchs, Switzerland), and use without further purification.

Typical procedure for the preparation of 2-hydroxyethylammonium acetate (2-HEAA)

As reported in the literature [46,47], for the synthesis of ionic liquid (2-HEAA) a solution of acetic acid (50 mmol, 3.00 g) in EtOH (1.5 mL) was added dropwise to a stirring solution of 2-aminoethanol (50 mmol, 3.05 g) in EtOH (1.5 mL) at room

temperature within 1 h. The resulting solution was stirred at room temperature for another 20 h. Ethanol was removed in vacuo and the residual was dried in vacuo at 50 °C for 48 h to give 2-hydroxyethylammonium acetate (2-HEAA) as a light yellow, viscous liquid.

General procedure for the preparation 2-oxo-N,4,6-triarylcyclohex-3-enecarboxamide derivatives

To a solution of acetophenone (1 mmol), aromatic aldehyde (1 mmol), and acetoacetanilide (1 mmol) was added 2-HEAA 20 mol%. The resulting mixture was stirred for the appropriate time (Table 2) at room temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/n-hexane, 1:3), a thick precipitate was obtained. The solid was filtered, washed with ethanol, and crystallized from ethanol to give pure product. The pure products were characterized by conventional spectroscopic methods. Physical and spectral data for the synthesized compounds are represented below:

*6-(2-bromophenyl)-2-oxo-N,4-diphenylcyclohex-3-enecarboxamide (**4a**)*

White solid, yield: (99 %); mp 220–222 °C. IR (KBr) (ν_{max}/cm^{-1}): 3411, 1676, 1629, 1601, 1557, 1445, 1370, 1248, 1181, 757, 693. ^{1}H NMR (400 MHz, DMSO): 3.01 (s, 2H, H-5), 4.20 (d, J = 13.2 Hz, 1H, H-1), 4.26 (dd, J= 9.6, 5.2 Hz, 1H, H-6), 6.63 (s, 1H, H-3), 7.01 (t, J = 7.2 Hz, 1H, Ar-H), 7.17 (t, J = 7.2 Hz, 1H, Ar-H), 7.24 (t, J = 7.6 Hz, 2H, Ar-H), 7.40 (t, J = 7.6 Hz, 1H, Ar-H), 7.46 (d, J = 6.0 Hz, 5H, Ar-H), 7.62 (dd, J = 11.6, 8.0 Hz, 2H, Ar-H), 7.72 (d, J = 7.6 Hz, 2H, Ar-H), 10.21 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO): δ 34.8, 42.2, 58.7, 119.5, 123.8, 123.9, 124.5, 126.8, 128.2, 128.5, 129.1, 129.3, 129.4, 131.0, 133.4, 137.6, 139.1, 141.1, 158.7, 167.3, 195.7. MS (EI, 70 eV) m/z (%): 447 ($M^+ + 1$, 19), 366 (98), 327 (20), 298 (1), 273 (19), 247 (31), 215 (19), 183 (8), 157 (17), 115 (44), 93 (100), 65 (18). Anal. Calcd. for $C_{25}H_{20}BrNO_2$: C, 67.27; H, 4.52; N, 3.14. Found: C, 67.40; H, 4.64; N, 3.22.

*6-(3-nitrophenyl)-2-oxo-N,4-diphenylcyclohex-3-enecarboxamide (**4b**)*

Pale yellow solid, yield: (98 %); mp 200–202 °C. IR (KBr) (ν_{max}/cm^{-1}): 3413, 1632, 1601, 1558, 1531, 1445, 1353, 758, 689. ^{1}H NMR (400 MHz, $CDCl_3$): 3.08 (dd, J = 18.0, 8.4 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.8, 41.0, 58.5, 120.0, 122.0, 122.3, 124.4, 124.6, 126.3, 128.9, 129.0, 129.8, 131.0, 134.2, 137.3, 137.3 148.5, 159.6, 164.4, 194.5. MS (EI, 70 eV) m/z (%): 412 (M^+, 29), 369 (1), 344 (1), 320 (9), 293 (87), 270 (1), 246 (16), 224 (1), 202 (30), 176 (39), 144 (27), 115 (69), 93 (100), 65 (24). Anal. Calcd. for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79. Found: C, 72.86; H, 4.96; N, 6.85.

*6-(2-chlorophenyl)-2-oxo-N,4-diphenylcyclohex-3-enecarboxamide (**4c**)*

White solid, yield: (97 %); mp 224–226 °C. IR (KBr) (ν_{max}/cm^{-1}): 3383, 3084, 1674, 1627, 1601, 1559, 1445, 1249, 1180, 757, 693. ^{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). ^{13}C NMR (100 MHz, DMSO): δ 34.6, 39.6, 58.6, 119.4, 123.7, 124.0, 126.8, 127.0, 127.9, 128.4, 128.9, 129.1, 129.3, 130.1, 131.0, 133.4, 137.6, 139.2, 139.6, 158.7, 167.4, 195.7. MS (EI, 70 eV) m/z (%): 401 (M^+, 3), 347 (2), 283 (3), 265 (4), 236 (3), 219 (5), 197 (3), 179 (5), 160 (4), 132 (5), 108 (48), 81 (28), 52 (100). Anal. Calcd. for $C_{25}H_{20}ClNO_2$: C, 74.71; H, 5.02; N, 3.49. Found: C, 74.75; H, 5.06; N, 3.55.

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

White solid, yield: (96 %); mp 217–219 °C. IR (KBr) (ν_{max}/cm^{-1}): 3306, 3203, 1680, 1666, 1651, 1603, 1547, 1444, 1362, 1175, 759, 692. ^{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). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 34.1, 40.9, 59.5, 124.2, 124.3, 126.3, 126.4, 127.2, 128.8, 128.9, 129.4, 129.4, 130.6, 136.7, 137.6, 137.8 139.2, 160.0, 165.4, 195.8; MS (EI, 70 eV) m/z (%): 397 (M^+, 1), 392 (1), 381 (35), 344 (1), 289 (4), 261 (100), 228 (6), 202 (3), 171 (4), 145 (25), 115 (23), 93 (37), 65 (6). Anal. Calcd. for $C_{25}H_{20}N_2O_4$: C, 78.57; H, 5.83; N, 3.52. Found: C, 78.70; H, 5.94; N, 3.60.

*6-(4-nitrophenyl)-2-oxo-N,4-diphenylcyclohex-3-enecarboxamide (**4e**)*

Pale yellow solid, yield: (94 %); mp 202–204 °C. IR (KBr) (ν_{max}/cm^{-1}): 3415, 3304, 1663, 1606, 1555, 1517, 1445, 1349, 1176, 854, 759, 752, 692. ^{1}H NMR (400 MHz, $CDCl_3$): 3.05 (dd, J = 18.0, 8.4 Hz, 1H, H-5), 3.33 (dd, J = 18.0, 4.8 Hz, 1H, H′ − 5), 3.76 (d, J = 9.2 Hz, 1H, H-1), 4.27 (m, 1H, H-6), 6.58 (s, 1H, H-3), 7.09 (t, J= 7.2 Hz, 1H, Ar-H), 7.27 (t, J = 8.0 Hz, 2H, Ar-H), 7.39–7.48 (m, 5H, Ar-H), 7.49–7.55 (m, 4H, Ar-H), 8.16 (d, J = 8.4 Hz, 2H, Ar-H), 8.32 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.8, 41.3, 58.4, 120.0, 124.0, 124.2, 124.7, 126.3, 126.3, 128.4, 128.7, 128.9, 129.0, 131.0, 137.2, 137.3 146.9, 149.8, 159.5, 164.7, 194.7. MS (EI, 70 eV) m/z (%): 412 (M+, 44), 344 (7), 320 (7), 292 (82), 266 (14), 228 (4), 202 (12), 157 (30), 115 (27), 93 (100), 66 (19). Anal. Calcd. for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79. Found: C, 72.87; H, 4.94; N, 6.85.

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

White solid, yield: (95 %); mp 188–190 °C. IR (KBr) (ν_{max}/cm^{-1}): 3418, 3387, 1698, 1659, 1600, 1517, 1436, 1360, 1172, 768, 757, 691. ^{1}H NMR (400 MHz, $CDCl_3$): 2.98 (dd, J = 18.0, 4.8 Hz, 1H, H-5), 3.60 (ddd, J = 18.8, 12.0, 2.4 Hz, 1H, H′ − 5), 4.78 (d, J = 13.2 Hz, 1H, H-1), 5.01 (td, J = 12.4, 4.8 Hz, 1H, H-6), 6.64 (d, J = 2.4 Hz, 1H, H-3), 7.05 (t, J = 7.2 Hz, 1H, Ar-H), 7.15 (t, J = 8.0 Hz, 1H, Ar-H), 7.25 (t, J = 8.0 Hz, 2H, Ar-H), 7.30 (d, J = 8.0 Hz, 1H, Ar-H), 7.41 (dd, J = 8.0, 1.2 Hz, 1H, Ar-H), 7.44 (d, J = 3.2 Hz, 2H, Ar-H), 7.46–7.49 (m, 3H, Ar-H), 7.59–7.61 (m, 2H, Ar-H), 8.21 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.4, 38.7, 55.6, 120.1, 124.2, 126.2, 128.8, 128.9, 129.3, 130.2, 130.7, 133.9, 135.9, 137.1, 137.5 137.6, 159.6, 165.5, 195.1. MS (EI, 70 eV) m/z (%): 436 (M^+, 6), 435 (14), 400 (100), 372 (1), 343 (6), 316 (36), 281 (36), 256 (9), 226 (6), 199 (32), 157 (35), 115 (45), 93 (71), 65 (20). Anal. Calcd. for $C_{25}H_{19}Cl_2NO_2$: C, 68.82; H, 4.39; N, 3.21. Found: C, 68.88; H, 3.30; N, 6.85.

*6-(4-cyanophenyl)-2-oxo-N,4-diphenylcyclohex-3-enecarboxamide (**4g**)*

White solid, yield: (99 %); mp 224–226 °C. IR (KBr) (ν_{max}/cm^{-1}): 3308, 2230, 1672, 1656, 1603, 1543, 1443, 757, 692. ^{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). ^{13}C NMR (100 MHz, DMSO): δ 35.1, 43.4, 59.3, 110.2, 119.2, 119.5, 123.8, 123.9, 126.9, 129.1, 129.2, 129.3, 131.0, 132.8, 137.7 139.0, 148.3, 159.2, 167.4, 195.3. MS (EI, 70 eV) m/z(%): 392 (M^+, 41), 344 (5), 300 (7), 272 (100), 243 (6), 196 (4), 157 (38), 115 (35), 93 (70), 65 (14). Anal. Calcd. for $C_{26}H_{20}N_2O_2$: C, 79.57; H, 5.14; N, 7.14. Found: C, 79.70; H, 5.22; N, 7.21.

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

White solid, yield: (95 %); mp 187–189 °C. IR (KBr) (ν_{max}/cm^{-1}): 3368, 3302, 3086, 1665, 1628, 1600, 1560, 1498, 1445, 1368, 1247, 758, 692. ^{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). ^{13}C NMR (100 MHz, DMSO): δ 35.5, 43.1, 59.7, 119.6, 123.8, 126.8, 126.9, 127.3, 128.0, 129.1, 129.3, 130.6, 130.9, 133.4, 137.8, 139.1, 145.1, 159.4, 167.6, 195.5. MS (EI, 70 eV) m/z (%): 401 (M^+, 39), 342 (3), 309 (7), 281 (90), 252 (5), 228 (13), 202 (13), 179 (1), 157 (34), 115 (45), 93 (100), 65 (20). Anal. Calcd. for $C_{25}H_{20}ClNO_2$: C, 74.71; H, 5.02; N, 3.49. Found: C, 74.78; H, 5.15; N, 3.62.

*2-oxo-N,4-diphenyl-6-(pyridin-3-yl)cyclohex-3-enecarboxamide (**4i**)*

White solid, yield: (92 %); mp 195–197 °C. IR (KBr) (ν_{max}/cm^{-1}): 3399, 3086, 1696, 1633, 1607, 1557, 1444, 1369, 1235, 1176, 756, 715, 693. ^{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). ^{13}C NMR (100 MHz, DMSO): δ 35.2, 41.1, 59.6, 119.5, 123.9, 126.9, 129.1, 129.3, 130.9, 135.5, 137.8, 137.9, 139.0, 148.6, 149.7, 159.4, 167.5, 195.4. MS (EI, 70 eV) m/z (%): 368 (M^+, 43), 344 (1), 309 (2), 281 (39), 248 (100), 220 (14), 197 (3), 157 (21), 132 (28), 93 (96), 65 (13). Anal. Calcd. for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 78.31; H, 5.58; N, 7.69.

*2-oxo-N,4-diphenyl-6-(pyridin-4-yl)cyclohex-3-enecarboxamide (**4j**)*

White solid, yield: (97 %); mp 202–204 °C. IR (KBr) (ν_{max}/cm^{-1}): 3467, 3267, 3073, 1695, 1647, 1603, 1555, 1497, 1444, 1366, 1177, 756, 692. ^{1}H NMR (400 MHz, DMSO): 3.08 (dd, J = 18.0, 4.8 Hz, 1H, H-5), 3.17 (dd, J = 17.6, 11.4, Hz, 1H, H′ − 5), 3.87 (td, J = 13.2, 4.8 Hz, 1H, H-6), 4.01 (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), 7.25 (t, J = 8.0 Hz, 2H, Ar-H), 7.45 (t, J = 7.6 Hz, 7H, Ar-H), 7.74 (t, J = 5.6 Hz, 2H, Ar-H), 8.51 (d, J = 6.0 Hz, 2H, Ar-H), 10.13 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO): δ 34.8, 42.7, 59.0, 119.5, 123.4, 123.8, 123.9, 126.9, 129.1, 129.3, 131.0, 137.7, 139.0, 150.1, 151.3, 159.2, 167.4, 195.2. MS (EI, 70 eV) m/z (%): 368 (M^+, 30), 344 (1), 309 (2), 281 (29), 248 (19), 220 (10), 197 (3), 171 (15), 144 (34), 115 (55), 93 (100), 65 (25). Anal. Calcd. for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 78.31; H, 5.58; N, 7.69.

*6-(2,3-dimethoxyphenyl)-2-oxo-N,4-diphenylcyclohex-3-enecarboxamide (**4k**)*

White solid, yield: (90 %); mp 196–198 °C. IR (KBr) (ν_{max}/cm^{-1}): 3413, 1666, 1600, 1556, 1477, 1445, 1365, 1274, 1073, 1002, 756, 693. ^{1}H NMR (400 MHz, $CDCl_3$): 3.01 (d, J = 17.6 Hz, 1H, H-5), 3.44 (ddd, J = 17.5, 10.0, 3.2 Hz, 1H, H′ − 5), 3.88 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 4.49 (d, J = 8.8 Hz, 2H, H-1 and H-6), 6.53 (d, J = 2.8 Hz, 1H, H-3), 6.79 (dd, J = 8.0, 1.2 Hz, 1H, Ar-H), 6.96 (t, J = 8.0 Hz, 1H, Ar-H), 7.08 (t, J = 7.2 Hz, 1H, Ar-H), 7.22 (dd, J = 8.0, 1.2 Hz, 1H, Ar-H), 7.32 (t, J = 8.4 Hz, 3H, Ar-H), 7.39 (d, J = 7.2 Hz, 2H, Ar-H), 7.51-7.55 (m, 4H, Ar-H), 8.24 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.6, 36.0, 55.6, 58.2, 60.8, 111.3, 119.8, 120.3, 121.6, 123.9, 124.8, 125.1, 126.4, 127.7, 128.9, 130.5, 135.7, 137.7, 146.7, 152.9, 160.1, 165.5, 196.0. MS (EI, 70 eV) m/z (%): 354 ($M^+ - 1$, 2), 368 (3), 344 (1), 299 (7), 265 (1), 241 (100), 198 (26), 172 (1), 150 (74), 115 (15), 91 (7), 57 (9). Anal. Calcd. for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.28. Found: C, 75.95; H, 5.94; N, 3.40.

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