

CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

An efficient microwave irradiated synthesis of 2-Oxo-substituted-phenyl-cyclohex-3-enecarboxylic acid ethyl ester and substituted-1,2,4,5-tetrahydro-indazol-3-one

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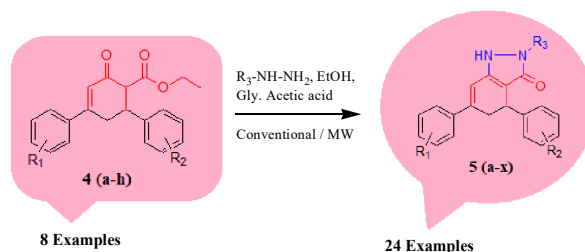
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Received 14 October 2019; Accepted 30 April 2020



Abstract: 2-Oxo-substituted-phenyl-cyclohex-3-enecarboxylic acid ethyl ester valuable intermediates in the synthesis of fused heterocycles have been prepared by 10% aqueous NaOH catalyzed cyclo-condensation of different Chalcones with ethyl acetoacetate. Twenty-four different substituted-1,2,4,5-tetrahydro-indazol-3-one synthesized from condensation reaction between substituted hydrazine and 2-Oxo-substituted-phenyl-cyclohex-3-enecarboxylic acid ethyl ester. Both the syntheses are carried out in conventional as well as modern methods i.e. under microwave irradiation. The yield in microwave irradiation synthesis is higher as compared to conventional method.

Keywords: Chalcone, Cyclohexenones, Indazoles, Michael addition, Cyclocondensation, 1,2,4,5-tetrahydro-indazol-3-one.

Introduction:

Heterocyclic compounds and their Chalcone

analogs are important intermediates in organic synthesis [1]. They also exhibit a large number of biological activities [2]. From a chemical

point of view, the important feature of chalcones is the ability to act as activated unsaturated systems in conjugated addition reactions with carbanions in the presence of base catalyst [3,4]. Generally this type of reaction is used for obtaining highly functionalized cyclohexene derivatives [5], but is more commonly and frequently used for the synthesis of 3,5-diaryl-6-carbethoxycyclohexenones via Michael addition of ethyl acetoacetate. The mentioned cyclohexenones derivatives are important intermediates used for the synthesis of fused benzisoxazoles and benzopyrazoles [6,7], heterocycles such as benzothiadiazoles and benzoselenadiazoles [8], as well as carbazole derivatives [9].

Indazole is two nitrogen containing benzene fused five-member heterocycles having great interest of researchers due to their wide range of biological importance. A large number of indazole derivatives possesses biological activities such as anti-depressant [10], anti-hypertensive [11], anti-tubercular [12,13], antiviral [14], antifungal [15], antioxidant [16,17], antibacterial [18,19], anti-inflammatory [20], neuro-protective [21], anticancer [22], anti-diabetic [23], and evaluated as potential drugs for variety of physiological activities [24].

Indazole is also a core part of various bioactive molecules like adjudin, a phase three molecule for male human contraceptive pill, which is a derivative of *IH*-indazole-3-carboxylic acid. It has shown to possess potent anti-spermatogenic activity also.

In this paper we are reporting the conventional and microwave irradiated method for base catalyzed synthesis of various 2-Oxo-substituted-phenyl-cyclohex-3-enecarboxylic acid ethyl ester and acid catalyzed synthesis of substituted-1,2,4,5-tetrahydro-indazol-3-one.

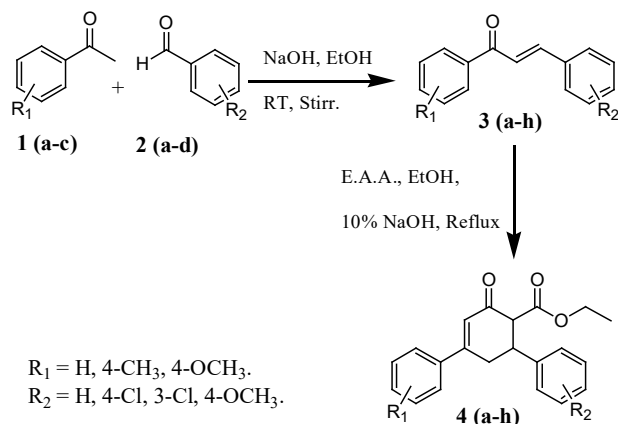
Materials and method

All the starting chemicals, reagents and solvents used were of analytical grade (AR) and used without further purification. Scientific Microwave oven used for irradiation is of make 'Catalyst microwave synthesizer Sr. No. 130602954'. IR spectra of the compounds obtained in potassium bromide (KBr) disks on a Bruker IR spectrometer. ¹H NMR and ¹³C spectra were recorded in CDCl₃ or DMSO solvent on a Bruker Avance-II 400 MHz spectrometer. Mass spectra were recorded on a Waters ZQ-4000 spectrometer. The yields of the synthesized compounds mentioned for isolated product. Melting point of all the synthesized compounds were taken on a precision melting point apparatus (DBK) instrument and are uncorrected.

Results and Discussion:

The acid or base catalyzed Aldol condensation reaction between aromatic aldehydes and aromatic ketones gives α,β -unsaturated ketones i.e. chalcone. The Michael condensation type of reaction between resultant chalcones with ethyl acetoacetate leads to three structurally different types of compounds depending on the experimental conditions, Michael addition products [25], pyrylium salts [26], and cyclohexenone derivatives [27]. The catalysts play important role in the formation of different end products, weak base catalyzed intramolecular cyclo-condensation of the methyl group from acetoacetic acid ester and the ketone function of the initial chalcone turn the intermediate Michael addition product into cyclohexenones, The Lewis acid such as boron trifluoride etherate forms pyrylium cations from the reaction of chalcones and acetoacetic acid esters. In the present study Aldol condensation reaction between substituted aromatic aldehydes **2 (a-d)** with aromatic ketones **1(a-c)** gives substituted chalcones. The reaction between substituted chalcones **3(a-h)** and ethyl acetoacetate produces cyclohexenones

by intermediate Michael adduct, as outlined in Scheme 1.



Scheme 1: Synthetic route of 2-Oxo-substituted-phenyl-cyclohex-3-enecarboxylic acid ethyl ester **4(a-h)**.

Precedent literature shows that K_2CO_3 [28] as a base catalyst or 0.5 ml of 10% sodium hydroxide [29,30] as catalyst was used for the synthesis of 2-Oxo-substituted-phenyl-cyclohex-3-enecarboxylic acid ethyl ester **4(a-h)**. In earlier reported methods time required for completion of reaction was 5-18 hours in K_2CO_3 and 4-5 hours in presence of dilute sodium hydroxide. We employed 1 ml of 10 % aqueous sodium hydroxide solution for present synthesis. The advantage of our method is maximum isolated yields within 2-3 hours using conventional method. On the other hand higher yields are achieved in microwave irradiation method within 10-15 minutes. The synthesis in presence of K_2CO_3 base and its concentration does not affect on ester functional group but the concentration of sodium hydroxide increases hydrolyzed products i.e. corresponding carboxylic acid. If the concentration of sodium hydroxide is increases to 15% or 20%, 1 ml of such solution used for the reaction it gives three spots on TLC plate.

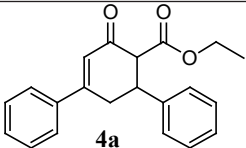
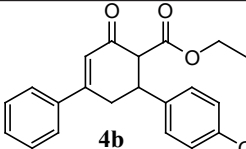
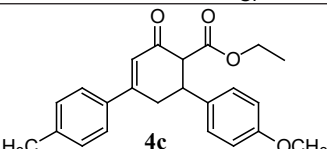
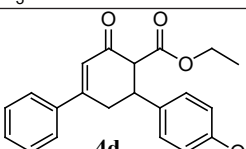
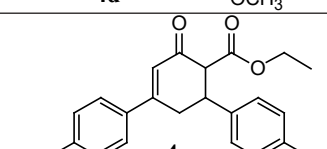
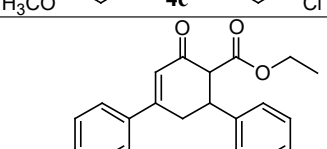
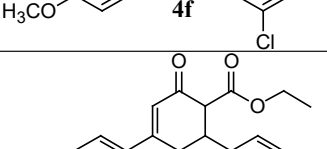
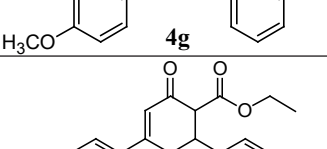
Similar results are obtained when we used more than 1 ml i.e. 1.5-2 ml 10% alkali

solution while decreasing the concentration of sodium hydroxide to 5% and perform same experiment, interestingly we got the product with single spot on TLC but time required for completion was 8-10 hours. From these sets of reaction conditions for above experiments and observations, we selected 1 ml of 10% of sodium hydroxide which is best suitable for the conversion of **3(a-h)** to **4(a-h)** with higher yields and this particular concentration of alkali is safe and does not hydrolyze the ester functional group is the key advantage of this synthesis.

The IR, HRMS and NMR investigations of synthesized cyclohexenone **4a** supports the formation carboxylic acid ester. The IR spectra of this compound has shown a sharp strong absorption band at 1710 cm^{-1} that can be for C=O stretching (ester) in compound **4a**, another sharp absorption band was observed at nearly 1670 cm^{-1} assigned for the carbonyl group conjugated with a carbon-carbon double bond. The HRMS and mass spectra of **4a** at 321.14 (M+1) also support the results of IR analysis. Finally the ^1H NMR signal for ethyl ester moiety a triplet at δ 1.15 ppm and a quartet at δ 4.02 ppm confirmed cyclohexenone **4a** bearing ester group in the structure.

Lastly the synthesis of substituted-1,2,4,5-tetrahydro-indazol-3-one **5(a-x)** from 2-Oxo-substituted-phenyl-cyclohex-3-enecarboxylic acid ethyl ester **4(a-h)** is carried out in presence of weak acid i.e. acetic acid. The reactions were carried out using conventional and modern method i.e. microwave irradiation as given in scheme 2.

Table no. 1 Substrate scope for the synthesis of 4 (a-h) from 3 (a-h).

Sr. No.	R ₁ , R ₂ .	Product	Time		Yield ^a (%)	
			Con. (h.)	MW (min.)	Con.	MW
1	R ₁ = H R ₂ = H	 4a	2	10	78	85
2	R ₁ = H R ₂ = 4-Cl	 4b	2.5	13	82	90
3	R ₁ = CH ₃ R ₂ = 4-OCH ₃	 4c	2	10	87	96
4	R ₁ = H R ₂ = 4-OCH ₃	 4d	2	15	76	91
5	R ₁ = 4-OCH ₃ R ₂ = 4-Cl	 4e	2.5	12	85	98
6	R ₁ = 4-OCH ₃ R ₂ = 3-Cl	 4f	3	15	80	94
7	R ₁ = 4-OCH ₃ R ₂ = H	 4g	2.5	14	75	90
8	R ₁ = 4-OCH ₃ R ₂ = 4-OCH ₃	 4h	2	10	88	96

^a isolated yields

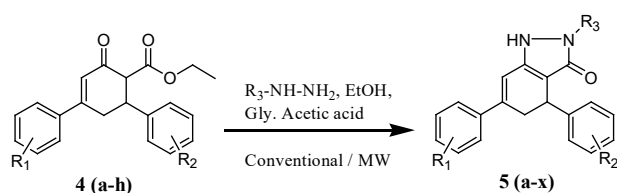
R₁, R₂ are Substituents

h. Time in hours.

min. Time in minutes.

Con. Conventional method

MW. Microwave irradiation (Modern method).



R₁ = H, 4-CH₃, 4-OCH₃,
 R₂ = H, 4-Cl, 3-Cl, 4-OCH₃,
 R₃ = H, -C₆H₅, 2,4-diNO₂C₆H₃.

Scheme 2: Synthetic route of substituted-1,2,4,5-tetrahydro-indazol-3-one **5(a-x)**.

In the reaction of **4(a-h)** with hydrazine hydrate and phenyl hydrazine we used excess amount of both reagents, but equimolar amount of **4(a-h)** and 2,4-dinitro phenyl hydrazine is used for the synthesis. Removing unreacted/excess of hydrazine hydrate or phenyl hydrazine by recrystallization is easier but 2,4-dinitro phenyl hydrazine is not easily removed from product, hence we use it in equimolar proportion. The excess amount of above said two reagents shift equilibrium towards the product formation in short time period with good percent yields of the products. But in case of 2,4-DNP the electron withdrawing nature of two nitro groups on phenyl ring and equimolar amount adversely affected on the reaction time as well as percent yields of the product as outlined in table no. 2. Both the conventional as well as microwave irradiation methods were works successively but modern method is more superior and less time consuming process with higher yields as reported in table no. 2.

The IR, NMR and mass spectral analysis of synthesized compounds supports the formation of above product mentioned in table no. 2. The IR spectra of the compound **5b** absence of bands 1710 cm⁻¹ and 1670 cm⁻¹ for C=O in ester and conjugated carbonyl group which was observed in **4a**, while it shows strong absorption band at 1598 for cyclic amide and at 3059 for N-H bond. Molecular ion peaks in positive ion mass spectroscopy observed at 365.31 (M+1). Both NMR studies also shows that peaks are absent

of CH₃ and CH₂. It supports the formation of aimed products in good yields.

General procedure for the synthesis of the derivative of Chalcones 3(a-h):

A mixture of 05 mmol of **1(a-c)** and 05 mmol of substituted aldehydes **2(a-h)** in absolute ethanol (25 ml) was stirred at room temperature in conical flask for 1-2 hours using 6N NaOH as a catalyst to make the solution strongly basic (slight exotherm is observed). After the formation of thick precipitate, then the reaction mixture was poured in ice cold water. The crude 1,3-substituted diphenyl-propenone **3(a-h)** was isolated and recrystallized from hot ethanol.

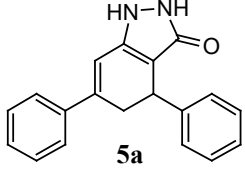
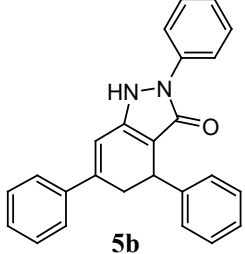
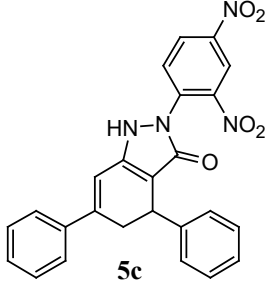
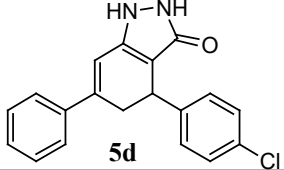
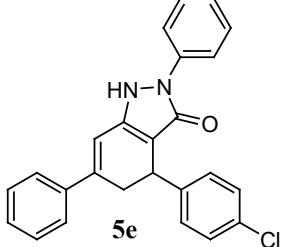
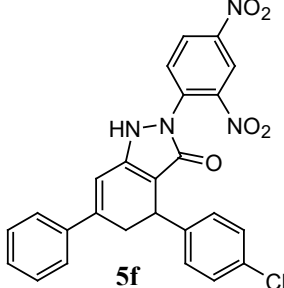
General procedure for the synthesis of 2-Oxo-substituted-phenyl-cyclohex-3-enecarboxylic acid ethyl ester 4(a-h):

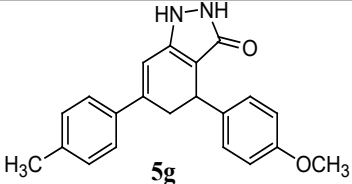
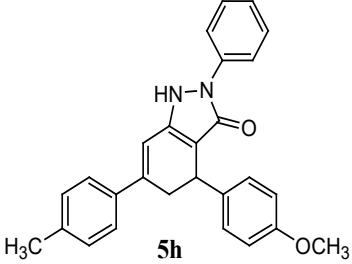
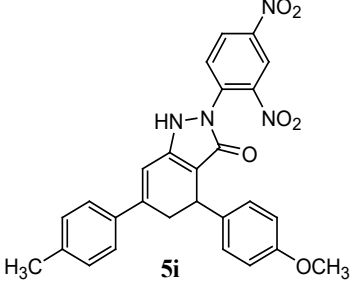
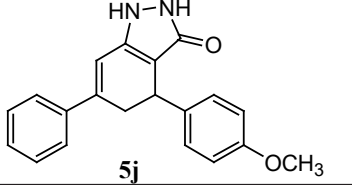
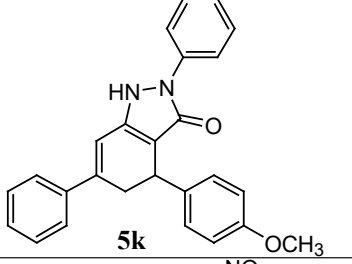
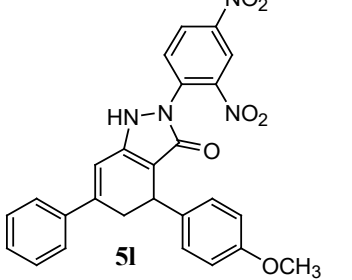
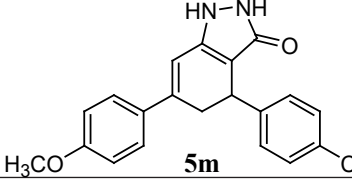
The equimolar amount of different 1,3-substituted diphenyl-propenone **3(a-h)** (3 mmol) and ethyl acetoacetate (3 mmol) were mixed and refluxed for various time intervals as mentioned in table no.1 in 10 ml ethanol in the presence 1 ml of 10% aqueous NaOH, progress of reaction was monitored on continuous TLC. After completion observed by TLC, then the reaction mixture was cooled to room temperature and poured with good stirring into 300 ml ice-cold water and kept at room temperature until the reaction product separated as a solid, which was filtered off and recrystallized from ethanol. Similar reaction was carried out in microwave irradiation.

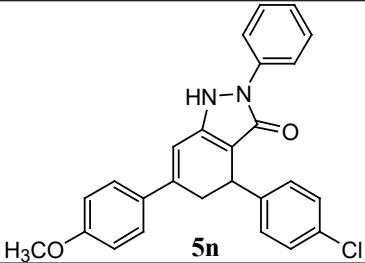
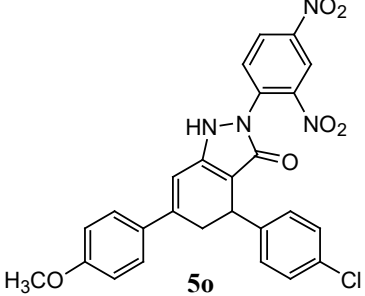
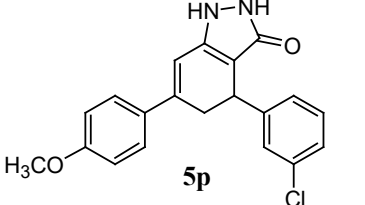
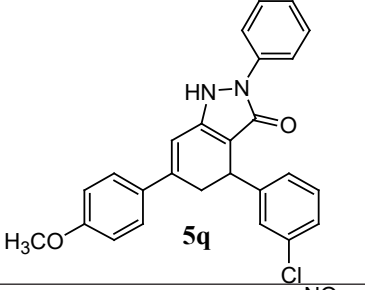
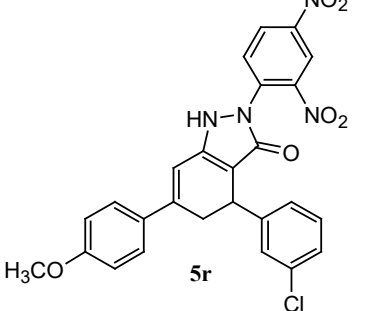
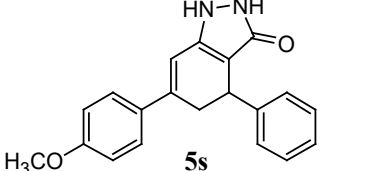
2-Oxo-4,6-diphenyl-cyclohex-3-enecarboxylic acid ethyl ester (4a)

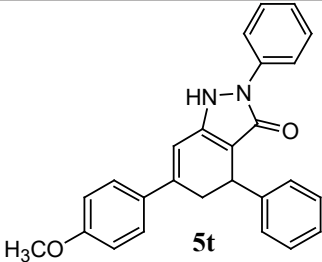
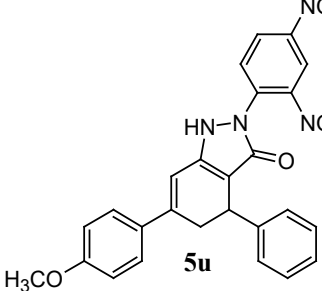
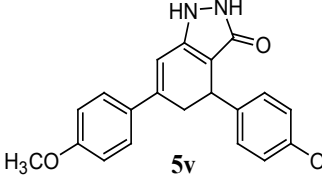
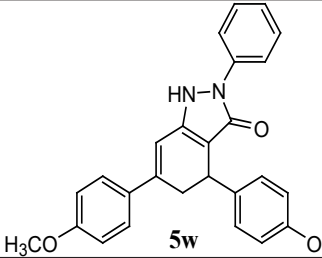
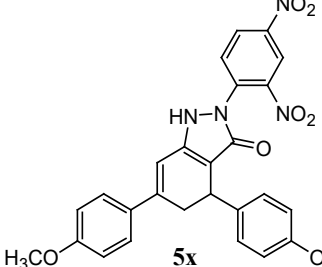
M/Z: m/z 321.14 [M+1]. IR (cm⁻¹): 1525, 1600 (aromatic C=C), 1710 (ester), 1329 (-CH₃), 1460 (-CH₂), 1670 (ketones). ¹H NMR: δ 1.15 (t, 3H), 4.02 (q, 2H), 2.98 (d, 2H), 3.56 (d, 1H), 3.66 (dt, 1H), 6.39 (s, 1H), 7.24-7.53 (m, 10H).

Table no. 2 Substrate scope for the synthesis of 5 (a-x) from 4 (a-h).

Sr. No.	R ₁ , R ₂ , R ₃ .	Product	Time		Yield ^a (%)		m.p. °C
			Con. (h.)	M W. (min.)	Con.	M.W.	
1	R ₁ = H R ₂ = H R ₃ = H	 5a	4	15	81	86	142-144
2	R ₁ = H R ₂ = H R ₃ = C ₆ H ₅	 5b	3.5	13	80	85	96-98
3	R ₁ = H R ₂ = H R ₃ = 2,4-di-NO ₂ C ₆ H ₃	 5c	4.5	19	74	84	194-197
4	R ₁ = H R ₂ = 4-Cl R ₃ = H	 5d	3.5	14	79	88	82-84
5	R ₁ = H R ₂ = 4-Cl R ₃ = C ₆ H ₅	 5e	3	13	82	90	146
6	R ₁ = H R ₂ = 4-Cl R ₃ = 2,4-di-NO ₂ C ₆ H ₃	 5f	4.5	16	74	86	156-158

7	$R_1 = 4\text{-CH}_3$ $R_2 = 4\text{-OCH}_3$ $R_3 = \text{H}$	 <p style="text-align: center;">5g</p>	4.5	12	78	89	142
8	$R_1 = 4\text{-CH}_3$ $R_2 = 4\text{-OCH}_3$ $R_3 = \text{C}_6\text{H}_5$	 <p style="text-align: center;">5h</p>	3.5	10	80	92	116-118
9	$R_1 = 4\text{-CH}_3$ $R_2 = 4\text{-OCH}_3$ $R_3 = 2,4\text{-di-NO}_2\text{C}_6\text{H}_3$	 <p style="text-align: center;">5i</p>	4.5	18	65	84	243
10	$R_1 = \text{H}$ $R_2 = 4\text{-OCH}_3$ $R_3 = \text{H}$	 <p style="text-align: center;">5j</p>	3.5	15	78	94	1.7-109
11	$R_1 = \text{H}$ $R_2 = 4\text{-OCH}_3$ $R_3 = \text{C}_6\text{H}_5$	 <p style="text-align: center;">5k</p>	3.5	14	85	92	98
12	$R_1 = \text{H}$ $R_2 = 4\text{-OCH}_3$ $R_3 = 2,4\text{-di-NO}_2\text{C}_6\text{H}_3$	 <p style="text-align: center;">5l</p>	5	19	69	85	198
13	$R_1 = 4\text{-OCH}_3$ $R_2 = 4\text{-Cl}$ $R_3 = \text{H}$	 <p style="text-align: center;">5m</p>	3.5	16	72	96	127-129

14	$R_1 = 4\text{-OCH}_3$ $R_2 = 4\text{-Cl}$ $R_3 = \text{C}_6\text{H}_5$	 <p style="text-align: center;">5n</p>	3	15	72	90	78-80
15	$R_1 = 4\text{-OCH}_3$ $R_2 = 4\text{-Cl}$ $R_3 = 2,4\text{-di-NO}_2\text{C}_6\text{H}_3$	 <p style="text-align: center;">5o</p>	4.5	17	70	82	196-198
16	$R_1 = 4\text{-OCH}_3$ $R_2 = 3\text{-Cl}$ $R_3 = \text{H}$	 <p style="text-align: center;">5p</p>	4	12	84	94	108
17	$R_1 = 4\text{-OCH}_3$ $R_2 = 3\text{-Cl}$ $R_3 = \text{C}_6\text{H}_5$	 <p style="text-align: center;">5q</p>	3.5	13	85	88	97-98
18	$R_1 = 4\text{-OCH}_3$ $R_2 = 3\text{-Cl}$ $R_3 = 2,4\text{-di-NO}_2\text{C}_6\text{H}_3$	 <p style="text-align: center;">5r</p>	4.5	17	79	85	218
19	$R_1 = 4\text{-OCH}_3$ $R_2 = \text{H}$ $R_3 = \text{H}$	 <p style="text-align: center;">5s</p>	4	14	73	96	126-127

20	$R_1 = 4\text{-OCH}_3$ $R_2 = \text{H}$ $R_3 = \text{C}_6\text{H}_5$	 $5t$	3	13	71	89	84
21	$R_1 = 4\text{-OCH}_3$ $R_2 = \text{H}$ $R_3 = 2,4\text{-di-NO}_2\text{C}_6\text{H}_3$	 $5u$	5	20	68	87	205-207
22	$R_1 = 4\text{-OCH}_3$ $R_2 = 4\text{-OCH}_3$ $R_3 = \text{H}$	 $5v$	3.5	12	81	91	132
23	$R_1 = 4\text{-OCH}_3$ $R_2 = 4\text{-OCH}_3$ $R_3 = \text{C}_6\text{H}_5$	 $5w$	3.5	12	82	86	87-89
24	$R_1 = 4\text{-OCH}_3$ $R_2 = 4\text{-OCH}_3$ $R_3 = 2,4\text{-di-NO}_2\text{C}_6\text{H}_3$	 $5x$	4.5	18	76	81	224

^aIsolated yields.

R_1 , R_2 and R_3 are Substituents

h. Time in hours.

min. Time in minutes.

Con. Conventional method

MW. Microwave irradiation (Modern method).

m.p. melting point in °C.

^{13}C NMR: δ 14.16, 61.45, 65.98, 76.80, 77.11, 77.43, 112.40, 121.96, 122.62, 127.63, 132.23, 157.16, 157.45, 168.56.

6-(4-Chloro-phenyl)-4-(4-methoxy-phenyl)-2-oxo-cyclohex-3-enecarboxylic acid ethyl ester (4e)

M/Z: m/z 385.11 [M+1]. IR (cm^{-1}): 1508, 1573 (aromatic C=C), 1715 (ester), 1339 ($-\text{CH}_3$), 1435 ($-\text{CH}_2$), 1665 (ketones). ^1H NMR: δ 1.28 (t, 3H), 2.48 (d, 2H), 3.60 (d, 1H), 3.72 (dt, 1H), 3.80 (s, 3H), 4.16 (q, 2H), 6.02 (s, 1H), 7.07-7.98 (m, 8H). ^{13}C NMR: δ 13.68, 25.51, 39.88, 56.02, 63.72, 115.00, 118.92, 126.08, 127.02, 128.69, 131.06, 146.81, 154.49, 156.22, 164.29, 166.81, 172.00, 197.68.

General procedure for the synthesis of substituted-1,2,4,5-tetrahydro-indazol-3-one 5(a-x):

A mixture of 05 mmol of **4(a-h)** and 10 mmol hydrazine hydrate or phenyl hydrazine (05 mmol of 2,4-dinitrophenyl hydrazine) and catalytic amount of glacial acetic acid were refluxed in ethanol (25 ml) for different time intervals mentioned in table no. **2**. The completion of reaction was monitored by continuous TLC. After reaction completes observed by TLC, the mixture was cooled to room temperature and poured on 300 ml ice cooled water, obtained ppt. were filtered and recrystallized in absolute ethanol. The same reaction was carried out in microwave irradiation.

2,4,6-Triphenyl-1,2,4,5-tetrahydro-indazol-3-one (5b)

M/Z: m/z 365.31 [M+1]. IR (cm^{-1}): 1312, 1449 (aromatic C=C), 1598 (Amide), 3059 (N-H). ^1H NMR: δ 2.39 (s, 1H), 2.48 (d, 2H), 3.45 (t, 1H), 6.28 (s, 1H), 7.18-8.03 (m, 15H). ^{13}C NMR: δ 35.59, 40.12, 109.82, 117.78, 126.28, 127.72, 128.17, 128.47, 134.94, 140.02, 142.32, 155.53,

158.06, 161.47, 163.49, 164.23, 165.12, 168.56.

2-(2,4-Dinitro-phenyl)-4,6-diphenyl-1,2,4,5-tetrahydro-indazol-3-one (5c)

M/Z: m/z 455.02 [M+1]. IR (cm^{-1}): 1250, 1453 (aromatic C=C), 1599 (Amide), 3015(N-H). ^1H NMR: δ 2.22 (s, 1H), 2.38 (t, 1H) 2.47 (d, 2H), 6.32 (s, 1H), 7.11-7.81 (m, 10H), 7.18 (d, 1H), 8.12 (d, 1H), 9.06 (s, 1H). ^{13}C NMR: δ 35.71, 40.52, 108.17, 124.85, 126.08, 127.70, 128.47, 128.49, 130.56, 132.58, 133.62, 134.91, 136.32, 138.18, 140.95, 142.83, 148.05, 150.79, 155.12, 156.48, 157.11.

Conclusion:

The 2-Oxo-substituted-phenyl-cyclohex-3-enecarboxylic acid ethyl esters are successively synthesized by using dilute aqueous sodium hydroxide as catalyst. The formed products then reacted with substituted hydrazines to afford substituted-1,2,4,5-tetrahydro-indazol-3-one with maximum of 98% isolated yields. Both the conventional as well as microwave irradiation method work well not only for the synthesis of intermediate but also for the final products.

Acknowledgment:

One of the authors Raut S. V. is thankful to CSIR for Senior Research Fellowship (SRF) for this work. The Authors are thankful to the Principal, Maulana Azad Collage Aurangabad for providing Library and Laboratory facilities. We are also thankful to SAIF Chandigarh for spectral analysis.

Conflict of interest:

The authors declare that there are no conflicts of interest with any person or agency

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