Original Article

SYNTHESIS OF ALPHA, BETA UNSATURATED CYCLIC KETONES VIA ROBINSON ANNULATION REACTION

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Abstract

A Chalcones (3a-l) and (5a-c) were used to create some brand-new cyclohexanone compounds (6a-f) and (7a-c), respectively. Accordingly modified benzaldehyde, 2-hydroxy-1- naphthaldehyde, and cinnamaldehyde were base-condensed with 1-tetralone to produce the chalcones (3a–l), while benzaldehyde and 1-indanone were base-condensed with benzaldehyde to produce the chalcones (5a–c). The cyclohexenone (6a-f) was produced by the reaction of prepared chalcones with ethyl acetoacetate via Robinson annulation (7a-c). Physical and spectral approaches have been used to characterize all produced compounds.

Keywords: Robinson annulation, Tetralone, Indanone, chalcone.

1. Introduction

Tetralones, Indanones, and Indenones are significant classes of naturally occurring substances that serve as helpful building blocks in the synthesis of several carbocyclic and heterocyclic [1] molecules of biological significance [2, 3]. Due to their presence in many medications and pharmaceutical molecules, these structures can be crucial in medicinal chemistry [4, 5]. Through the Claisen-Schmidt condensation of 1-tetralone and 1-indanone numerous times with the suitable aryl aldehyde, the-unsaturated cyclic ketones were created [6]

By creating three new carbon-carbon bonds, the Robinson annulation is a chemical reaction used in organic chemistry to produce a six-membered ring. More specifically, this reaction completes the synthesis of cortisone [7]. A new six-membered ring containing-unsaturated cyclic ketone (cyclohexenone) is produced after the reaction begins with a Michael reaction and continues with an intramolecular aldol condensation [8].

2. Experimental

All of the chemicals were of analytical grade and came from BDH and Fluka in Switzerland. For the FTIR Spectroscopy analysis, a Shimadzu FT-IR-8400S was employed. Deuterated DMSO was utilized as the solvent for the ^{1}H NMR and ^{13}C NMR spectra on a Bruker Bio Spin GmbH 400MHz apparatus. For determining the melting points of synthesis compounds, electro thermal IA 9000 Digital series melting point (1998) was utilized. In addition to the intermediate material, the purity of the synthesized derivatives was tested using the thin layer

chromatography (TLC) method. A mixture of benzene and methanol (8:2) was utilized as the elute solvent for silica gel of the 60–100 mesh variety. The iodine vapour was employed for show spots.

2.1 synthesis of the chalcone compounds from 1-tetralone (3a-l) :

General procedure [9,10]

Benzaldehyde substitutes (2) were dissolved in ethanol (20 ml) and added to a round-bottomed flask (100 ml) with a magnetic stirrer in a basic medium of sodium hydroxide (10%). Next, equimolar (1.41 gm, 0.01 mol) 1-tetralone (1) was added, and the mixture was stirred at room temperature for several hours until a precipitate was formed, collected by filtration to give compound (3a-l), recrystallization from ethanol.

(E)-2-(2-chlorobenzylidene)-3,4-dihydronaphthalen-1(2H)-one (3a)

Compound 3a was purified as a white substance with a yield (78%), mp. 69-71°C. 3066 (=CH, ArH), 2951 (C-H), 1662 (C=O), and 1604 (C=C aliphatic) are the IR values. ^{1}H-NMR (DMSOd6): 3.34–3.36 (br, 4H, CH2); 7.39–7.41 (m, 1H); 7.44–7.47 (m, 3H); 7.53–7.55 (m, 1H); 7.55-7.63 (m, 2H); 7.74 (s, 1H); and 8.01 (d, 1H, J=8Hz).

(E)-2-(4-bromobenzylidene)-3,4-dihydronaphthalen-1(2H)-one (3b)

Yellowish brown compound 3b with a yield of 91% was isolated. mp. 153-155°C. 3070, 3026 (=CH, ArH), 2945 (C-H), 1668 (C=O), and 1593 (C=C) are the IR values. ^{1}H-NMR: 2.93 to 2.99 (m, 2H), 3.07 (t, 2H, J=4Hz), 7.38 to 7.40 (m, 1H), 7.42 to 7.44 (m, 1H), 7.49 to 7.51 (m, 2H), 7.59 (t, 1H, J=4Hz), 7.66 to 7.68 (m, 3H), and 7.97 (d, 1H, J=8Hz).

(E)-2-(2-hydroxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (3c)

Compound 3c, with a yield of 66% and a dark brown melting point 125 (dec), was isolated. 2954(C-H), 1656(C=O), 1595(C=C), 3446(O-H), 3035(=CH, ArH), 2954(C-H), 2.80(m.4H), 6.64-6.73(m,2H), 6.84-6.91(m,3H), 7.22(t,1H, J=8Hz), 7.44(t,1H, J=8Hz), 7.58(d,1H, J=8Hz), 8.31(s,1H), and 9.92(s,1H, OH) are among the ^{1}H-NMR data.

methyl (E)-4-((1-oxo-3,4-dihydronaphthalen-2(1H)-ylidene)methyl)benzoate (3d)

Compound 3d was purified as a white, yield (64%), mp. 115-118 °C product. IR: 1707, 1666 (ester, ketone C=O), 1604 (C=C), 3074, 3054 (=CH, ArH), 2983 (C-H). ^{1}H-NMR data include the following: 1.34 (t, 3H, J=8Hz), 2.97 (t, 2H, J=4Hz), 3.10 (t, 2H, J=4Hz), 4.34 (q, J=4 Hz), 7.39–7.45 (m, 2H), 7.59 (t, 1H, J=8H), 7.66 (d, 2H, J=8Hz), 7.74 (s,1H), 7.98 (d,1H,J=8Hz), 8.03(d,2H,J=8Hz).^{13}C-NMR: 14.63 (CH_3), 27.20 (C_4), 28.31 (C_3), 61.35 (C_{16}), 127.55 (C_6), 127.93 (C_7), 129.09 (C_5), 129.71 (C_{4a}), 130.06 (C_{11}), 130.06 (C_{13}), 130.56 (C_{10}), 130.56 (C_{14}), 133.16 (C_9), 134.19 (C_{19}), 134.65 (C_8),137.87 (C_2), 140.41 (C_{8a}), 144.00 (C_{12}), 165.81 (C_1,C=O), 187.06 (C_{18},C=O). figure 1

(E)-2-((2-hydroxynaphthalen-1-yl)methylene)-3,4-dihydronaphthalen-1(2H)-one (3e)

Black compound 3e, mp. 95–98 °C, yield (62%), was obtained after separation. 3356 for OH, 3064 for (=C-H and ArH), 2866 for (CH2), 1680 for (C=O), and 1593 for(C=C).

(2E,2'E)-2,2'-(1,4-phenylenebis(methaneylylidene))bis(3,4-dihydronaphthalen-1(2H)-one) (3f). [12]

By condensing 2 moles of 1-tetralone with 1 mole of terphthaldehyde, compound 3f was created, yielding an 87% yield and having a pale yellow, mp. 260–263 °C, color. 3065, 3046 (=CH, ArH), 2956 (C-H), 1660 (C=O), and 1600 (C=C) in the IR. ^{1}H-NMR: 1.07 (t, 1H, J=8Hz), 2.61 (t, 1H, J=8Hz), 3.45 (q, 1H, J=8Hz), 4.19-4.23 (m, 1H), 7.13-7.25 (m, 1H), 7.34-7.78 (m, 11H), 7.98-8.01 (m,2H).

(E)-2-((E)-3-phenylallylidene)-3,4-dihydronaphthalen-1(2H)-one (3g)

By condensation of 1 mol of cinnamaldehyde with 1 mol of 1-tetralone, which was obtained as a pale yellow, mp. 118-121°C yield (77%), compound 3g was created. 3061, 3038 (=CH, ArH), 2946 (C-H), 1657 (C=O), and 1594 (C=C) are the IR values). ^{1}H-NMR: 2.98–3.01 (m, 2H), 3.05–3.08 (m, 2H), 7.17–21 (m, 1H), 7.34–7.36 (m, 1H), 7.38–7.44 (m, 5H), 7.57(t, 1H, J=8Hz), 7.69 (m, 2H), and 7.95 (d, 1H, J=4Hz).

(E)-2-(3-nitrobenzylidene)-3,4-dihydronaphthalen-1(2H)-one (3h)

Compound 3h was purified as a light yellow yield (72%), mp. 129-133 °C. IR: 3070 (ArH), 2939, 2845 (C-H), 1662 (C=O), 1593 (C=C), 1348 (NO2 sym), and 1454 (C=C) (NO2 Asym). ^{1}H-NMR data include the following: 2.97 (t, 2H, J=8Hz), 3.10 (t, 2H, J=8Hz), 7.39–7.45 (m, 2H), 7.61 (t, 1H, J=8Hz), 7.75–7.79 (m, 2H), 7.97–8.00 (m, 2H), 8.24(d, 1H, J=8Hz), and 8.33 (s,1H).^{13}C-NMR: 27.04 (CH_2), 28.26 (CH_2), 123.66 (C_6), 124,52 (C_7), 127.01 (C_{4a}), 127.57 (C_{13}), 129.01 (C_5), 130.58 (C_8), 136.56 (C_{14}), 134.26 (C_9), 136.61 (C_{15}), 137.39 (C_{8a}), 137.65 (C_2), 138.28 (C_{12}), 143.99 (C_{10}), 148.42 (C_{11}), 186.95 (C_1, C=O). figure (2)

(E)-2-(4-nitrobenzylidene)-3,4-dihydronaphthalen-1(2H)-one (3i)

Compound 3i, with a yield of 61% and mp of 177–180 °C, was isolated. IR: 3103 (ArH), 2927, 2843 (C-H), 1664 (C=O), 1591 (C=C), 1340 (NO2 sym), and 1454 (C=C) (NO2 Asym).

(E)-2-(4-(dimethylamino)benzylidene)-3,4-dihydronaphthalen-1(2H)-one (3j)

Compound 3j, mp. 143–150 °C, yield (80%), was isolated as a yellowish brown substance. 3056, 3031 (=CH, ArH), 2955 (C-H), 1664 (C=O), and 1591 (C=C) are the IR numbers.

(E)-2-(3-hydroxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (3k)

Compound 3k was purified as a brown, yielding (65%), mp. 116-119 °C product. 3269 (OH), 3030 (ArH), 2943 (C-H), 1649 (C=O), and 1591 (C=C) on the IR scale.

(E)-2-(2,4-dichlorobenzylidene)-3,4-dihydronaphthalen-1(2H)-one (3l)

The whitish, mp. 107-109 °C, compound 3l was isolated. 3091, 3059 (ArH, =CH), 2926 (C-H), 1668 (C=O), and 1612 (C=C) on the IR scale.

2.2 synthesis of ethyl 3-oxo-1,2,3,9,10,10a-hexahydrophenanthrene-2-carboxylate substituted (6a-f).

General procedure [12,13]

Equimolar (0.01 mol) mixtures of chalcone (3a-3f) and ethyl acetoacetate that were previously made dissolve in 15 ml of ethanol in a basic sodium hydroxide solution (15–20 drops, NaOH, 10%). The reaction mixture was heated under TLC control for 3 to 4 hours, then cooled and poured into ice water (20 ml) while stirring. The precipitate that formed was then collected by filtration, washed with water (5 ml total), recrystallized from water and ethanol, dried, and given compound (6a-f).

ethyl 1-(2-chlorophenyl)-3-oxo-1,2,3,9,10,10a-hexahydrophenanthrene-2-carboxylate (6a)

Compound 6a was purified as a yellow crystal with a yield of (52%), mp 141-143 °C. 3061 for Ar-H, 2989 for C-H, 1672 for C=O ester, 1645 for C=O ketone, and 1618 for C=C. ^{1}H-NMR: 1.03 (t,3H, J=8Hz), 2.71 (m, 2H, CH2 cyclic), 3.31-3.36 (m, 2H, CH2 cyclic), 3.45 (q, 1H), 3.45 (m, 1H), 3.66-3.70 (m, 1H), 3.99-4.03 (m,2H, OCH2), 4.71(d,1H, J=8Hz), 4.96(s,1H) (m,1H), 6.85 (s, 1H), 7.10–7.15 (m, 2H), 7.20–7.34 (m, 3H), 7.29–7.31 (m, 2H), and 7.38 (m,1H). Mass m/z: 380 [M^{+}]

ethyl 1-(4-bromophenyl)-3-oxo-1,2,3,9,10,10a-hexahydrophenanthrene-2-carboxylate (6b)

Compound 6b was purified as a white, yield (54%), mp. 63-65 °C product. IR: 3059 (=C-H), 2929 (C-H), 1622 (C=C), 1670 (C=O ketone), and 1739 (C=O ester) 1.09 (t,2H, J=4Hz), 2.64–2.96 (m, 3H), 4.06 (d, 2H, J=8Hz), 4.16-4.19 (m, 1H), 4.34 (t, 1H, J=4 Hz), and 7.20–8.01 are the ^{1}H-NMR values (m,9H). Mass m/z: 424 [M^{+}]

ethyl 1-(2-hydroxyphenyl)-3-oxo-1,2,3,9,10,10a-hexahydrophenanthrene-2-carboxylate (6c)

Compound 6c was isolated as a dark brown, yielding 48 percent, mp. 104-106 °C. IR:3275-3444(OH), 3025 (ArH) (ArH). 2981(C-H). 1649 (C=O ketone), 1699 (C=O ester), and 1597 (C=C). ^{1}H-NMR: 1.03(t,3H, J=8Hz, CH3); 1.16-1.68 (m,1H); 2.61 (s, 2H); 4.05(d, 1H, J=8Hz); 4.31(m,1H); 4.42(m,2H); 4.50(m,1H); 6.72-7.32 (m,9H, Ar-H, C=CH); 8.30 (s,1H, OH). Mass m/z: 362 [M^{+}]

ethyl 1-(4-(ethoxycarbonyl)phenyl)-3-oxo-1,2,3,9,10,10a-hexahydrophenanthrene-2-carboxylate(6d)

Compound 6d was isolated as a dark brown, yielding (45%), mp. 103-106 °C product. IR: 3033 (ArH), 2980, 2933(C-H), 1723, 1712 (C=O ester), 1662 (C=O ketone), and 1608 (C=C). ^{1}H-NMR: 0.80-0.89 (m, 1H), 1.17-1.34 (m, 4H), 2.38-2.94 (m, 4H), 3.31-3.42 (m, 4H), 3.86 (q, 1H, J=8Hz), 4.29-4.33 (m, 3H), 6.76-6.84 (m, 1H), 7.15-7.43 (m, 3H), 7.58 (d, 2H, J=8Hz), 7.73-7.84 (m, 1H (m,2H).

ethyl 1-(2-hydroxynaphthalen-1-yl)-3-oxo-1,2,3,9,10,10a-hexahydrophenanthrene-2-carboxylate (6e)

Black compound 6e, mp 88–91 °C, yield (43%), was isolated, IR: 3406 (OH), 4045(=C-H), 2927,2870 (C-H), 1715(C=O ester),1676 (C=O ketone), 1589 (C=C).

2.3 synthesis of 1,1'-(1,4-phenylene)bis(1,9,10,10-tetrahydrophenanthren-3(2H)-one) (6f)

Chalcone (3f), which was earlier synthesized, and ethyl acetoacetate, which was previously synthesized, were combined and dissolved in 15 ml of ethanol in a basic sodium hydroxide solution (15–20 drops, NaOH 10%). The reaction mixture was heated under TLC control for 3 to 4 hours, then cooled and poured into ice water (20 ml) while stirring. The precipitate that formed was then collected by filtration, washed with water (5 ml total), recrystallized from water and ethanol, dried, and given compound (6f).

1,1'-(1,4-phenylene)bis(1,9,10,10-tetrahydrophenanthren-3(2H)-one) (6f)

Compound 6f was separated as a brown precipitate, mp. 60-63 °C, yield (54%). IR: 2848(C-H), 1735 (C=O, ester), 1658 (C=O ketone),1604 (C=C). ^{1}H-NMR: 0.84-0.88(m,5H), 1.06 (t,2H, J=4Hz), 1.21-1.23 (m, 5H), 1.99-2.04 (m, 3H), 2.41-2.42 (m, 2H), 2.60 (s, 1H), 2.93-2.95 (m,2H), 3.84-4.04 (m,4H), 7.11-7.11 (m,14H, Ar-H).

2.4 Synthesis of Chalcone compounds from 1-indanone (5a-e)

General method

Dissolve 0.01 mol of substituted benzaldehyde in 20 ml of ethanol in a round-bottomed flask (100 ml) with a magnetic stirrer in a sodium hydroxide (10%) solution, in room temperature (0.01 mol, 1.4 ml) of 1-indanon (4) was added, with continued stirring for several hours (3-4 hrs.) until the precipitate was produced. Filtering and recrystallization from ethanol, drying to give the chemicals after separation (5a-e).

(E)-2-(2-chlorobenzylidene)-2,3-dihydro-1H-inden-1-one (5a)

Compound 5a was purified as a white precipitate with a yield of 90% and mp of 149–151 °C. IR: 3064 (ArH), 2924(C-H), 1697 (C=O), 1624 (C=C), ^{1}H-NMR: 4.13(s,2H), 7.46-7.53 (m,3H), 7.62-7.76 (m, 3H), 7.82-7.83 (m, 2H), 7.96-7.99 (m, 1H).

(E)-2-(4-bromobenzylidene)-2,3-dihydro-1H-inden-1-one (5b)

Compound 5b was purified as a white precipitate with a yield of 92% and mp of 180–184 °C. IR: 1693 (C=O), 3028 (=C-H), 2929 (C-H), and 1622 (C=C). ^{1}H-NMR: 4.12 (s,2H), 7.00–7.22 (m,1H), 7.31–7.31 (m,1H), 7.39–7.33 (m,1H), 7.49–7.53 (m,2H), and 7.68–78.2 (m,4H).

(E)-2-(4-nitrobenzylidene)-2,3-dihydro-1H-inden-1-one (5c)

Compound 5c was purified as a yellow precipitate with a yield of 77% at mp 232-235 °C. IR: 3033(=C-H), 2945 (C-H), 1689 (C=O), 1600 (C=C). ^{1}H-NMR: 4.12 (s,2H), 7.00–7.22 (m,1H), 7.31–7.31 (m,1H), 7.39–7.33 (m,1H), 7.49–7.53 (m,2H), and 7.68–78.2 (m,4H).

2.5 synthesis of 2-acetyl-1,2,9,9a-tetrahydro-3H-fluoren-3-one substituted (7a-c)

General method

Equimolar amounts of produced chalcone (5a-e) and ethyl acetoacetate (0.01 mol) were dissolved in 15 ml of ethanol using sodium hydroxide as the basic medium (10 drops, NaOH 10%), the reaction mixture was reacted for three to four hours (under TLC control), cooled, and then put into a beaker containing ice water (20 ml) while being stirred. The precipitate that developed was then collected by filtration and washed with water (five times), recrystallized from water and ethanol to give compounds (7a-e)

ethyl 1-(2-chlorophenyl)-3-oxo-2,3,9,9a-tetrahydro-1H-fluorene-2-carboxylate (7a)

Compound 7a was separated as a brown precipitate, mp. 74-77 °C, yield (50%). IR: 3066 (ArH), 2980 (C-H), 1734 (C=O, ester), 1660 (C=O ketone), 1602 (C=C). ^{1}H-NMR: 0.59-1.36(m,4H), 3.81(s,1H), 3.83-4.17 (m,3H), 4.25 (s,1H), 4.28 (d, 1H, J=8Hz), 6.57-7.89 (m,9H).

ethyl 1-(4-bromophenyl)-3-oxo-2,3,9,9a-tetrahydro-1H-fluorene-2-carboxylate (7b)

Compound 7b was separated as a yellow precipitate, mp. 51-61 °C, yield (48%). IR: 3049 (ArH), 2981 (C-H), 1708 (C=O, ester), 1654 (C=O ketone), 1600 (C=C). ^{1}H-NMR: 1.03 (t,3H, J=4Hz), 2.75-3.12 (m,3H), 3.46-4.13 (m,4H), 7.17-7.58 (m,9H).

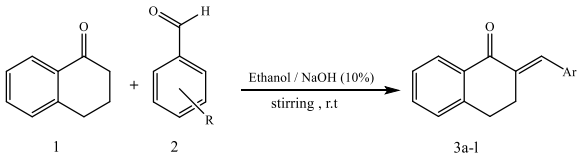
Ethyl 1-(4-nitrophenyl)-3-oxo-2,3,9,9a-tetrahydro-1H-fluorene-2-carboxylate (7c)

Compound 7c was separated as a yellow precipitate, mp. 51-61 °C, yield (44%). IR: 3030 (ArH), 2952 (C-H), 1732 (C=O, ester), 1660 (C=O ketone), 1604 (C=C).

3. Results and discussion

The *trans* Chalcones (3a-l) and (5a-c) were synthesized by a base catalysed Claisen–Schmidt condensation of 1-tetralone and 1-indanone with substituted aryl aldehydes in ethanol in presence sodium hydroxide as catalyst with stirrer at room temperature Scheme 1 and Scheme 4. In this work, the reaction involve is Robinson Annulation reaction where it is involve the Michael addition reaction followed by an Aldol condensation reaction to yield product of an α,β-unsaturated cyclic ketone (6a-f) and (7a-c). The synthesized *trans* chalcone (3a-l) and (5a-c) is prepared and react with ethyl acetoacetate in ethanol as a solvent and presence of sodium hydroxide as catalyst under reflux to yield the dicarbonyl ester product, this reaction is Michael addition reaction, The product is undergoing intramolecular aldol condensation to produce β-hydroxyketo compounds which eliminate water on reflux to yield an α,β-unsaturated cyclic ketone (6a-f) Scheme 2 and (7a-c) Scheme 5. The compound 3f was prepared by a base catalysed Claisen–Schmidt condensation of 2mol of 1-tetralone with 1mol of Terphthaldehyde, compound 6f was synthesized through Robinson Annulation reaction by reaction of 1mol of compound 3f with 2mol of ethyl acetoacetate under reflux in presence of sodium hydroxide as catalyst in ethanol as solvent scheme 3

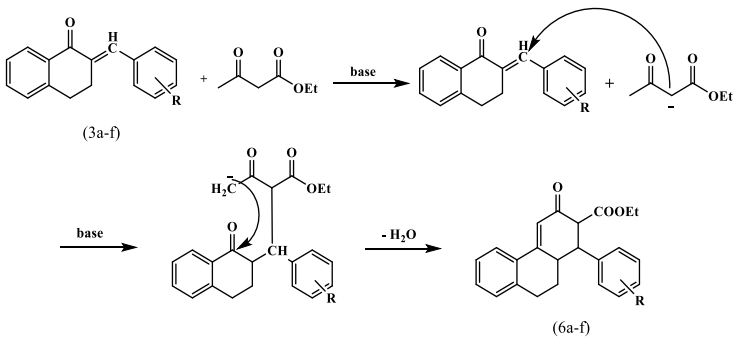
Scheme (1)



1 2 3a-l

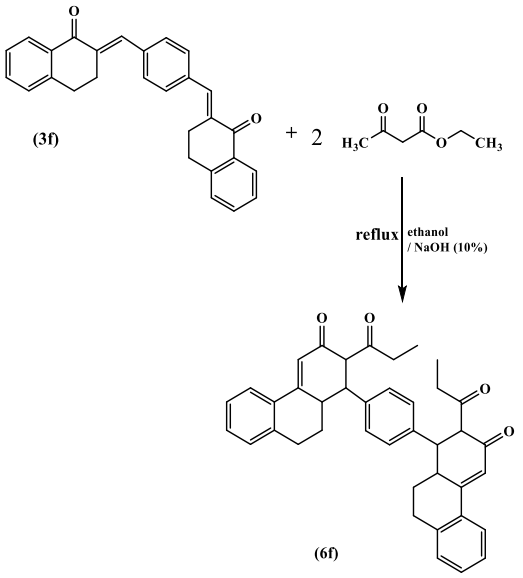
synthesis of the chalcone compounds from 1-tetralone (3a-l).

Scheme (2)



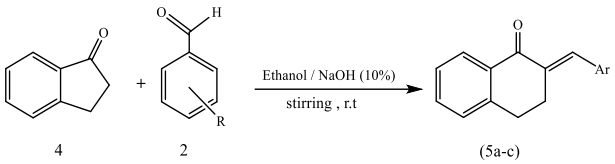
synthesis of ethyl 3-oxo-1,2,3,9,10,10a-hexahydrophenanthrene-2-carboxylate substituted (6a-f).

Scheme(3)



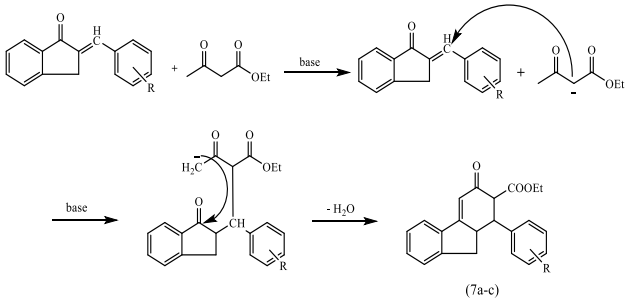
Scheme 3: synthesis of 1,1'-(1,4-phenylene) bis(1,9,10,10-tetrahydrophenanthren-3(2H)-one) (6f)

Scheme (4)



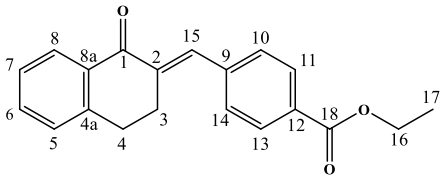
synthesis of Chalcone compounds from 1-indanone (5a-c).

Scheme (5)



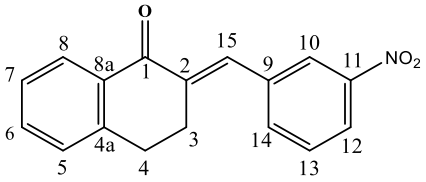
synthesis of the following compounds of [of 2-acetyl-1,2,9,9a-tetrahydro-3H-fluoren-3-one derivatives] (7a-e).

figure (1)



ethyl (*E*)-4-((1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)methyl)benzoate

Figure (2)



(*E*)-2-(3-nitrobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one

Conclusion

New cyclohexenone compounds were synthesized via Robison annulation reaction via Michael addition reaction followed by aldol condensation reaction of ethyl acetoacetate to chalcones derived from 1-tatralone and 1-1ndanone.

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