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Synthesis and Biological investigation of some new 3, 5-diaryl-6-carboethoxy, 6-acetoxy cyclohexenone and indazole derivatives.

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ABSTRACT

The α, β- unsaturated carbonyl compounds have been converted into the corresponding 3, 5-diaryl-6-carboethoxy, and 6-acetoxy cyclohex-2-en-1-ones by the Michael condensation with ethyl acetoacetate and acetyl acetone in presence of ethanolic piperidine. These 6-carboethoxy cyclohex-2-en-1-ones (II) treated with hydrazine hydrate in ethanolic-acetic acid to yield corresponding indazoles (IV). The newly synthesized compounds were established on the basis of spectral analysis and have been screened for their antibacterial activity.

KEYWORDS

α, β-unsaturated carbonyl compounds;
Cyclohexenones;
Indazoles;
Antibacterial ctivity.

INTRODUCTION

The chemistry of chalcones (α, β-unsaturated carbonyl compounds) are potential precursors for the synthesis of variety of biodynamic heterocyclic compounds.[1-6] The Michael addition reaction is very useful for carbon-hetero atom and C-C bond formation.[7-10] Recently, synthesized cyclohexenones derivatives were reported as antibacterial agents.[11-12] The investigation of indazole derivatives showed analgesic, maximum electroseizure and anti-inflammatory activities.[13-16] In view of the above observations and in continuation work on the synthesis of bioactive heterocyclic compounds,[17] it was thought to synthesize some new different of cyclohexenones and indazole derivatives.

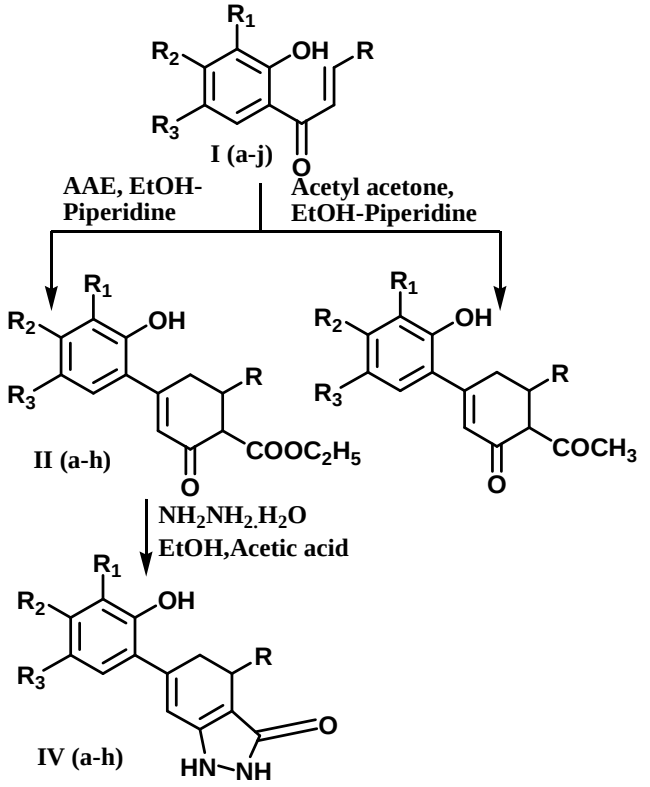
RESULT AND DISCUSSION

Ethyl acetoacetate and acetyl acetone reacts with chalcones system resulting in a variety of compounds *viz*. Michael adduct, pyrylium salt or cyclohexenone derivatives depending on the experimental conditions employed. Cylcohexenone derivatives have been isolated by the Michael addition of ethyl acetoacetate to chalcone followed by internal claisen condensation in presence of either dry K_2CO_3, and acetone or ethanolic piperidine. The cyclohexenone derivatives on treatment with hydrazine hydrate afforded indazoles with have shown significant biological activity.

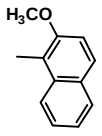
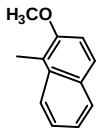
The starting substituted chalcones[6] (Ia-j) were prepared by Claisen-Schimdt condensation using appropriate acetophenones and aldehydes in ethanolic alkaline solution (NaOH/KOH).

The compounds **(Ia-j)** up on treatment with ethyl acetoacetate and acetyl acetone in presence of ethanolic piperidine furnish the title compounds (SchemeI). The formation of cyclohexenones exclusively in the above Michael addition is in marked contrast with the Michael condensation chalcones. The products were confirmed by its spectral analysis. Appearance of IR bands at 3250-3150 cm^{-1}(-OH), 1720-1710cm^{-1} (ester >CO) and 1645cm^{-1}(unsaturated >C=O) supported the structures. In ^1H NMR signal at δ 10.5-11.5 ppm indicates the presence of phenolic –OH. The multiplate at δ 7.05-

8.46 ppm to the aromatic protons. The singlet (III), triplet and quartet (II) signals at lower field region revealed the presence of acetoxy and carboethoxy groups in products. These 6-carboethoxy cyclohex-2en-1-ones (II) are treated with hydrazine hydrate in ethanolic acetic acid gave the corresponding indazoles (IV) (Scheme-I). The IR spectrum showed bands at 1730-1725 cm^{-1} and 3300-3250 cm^{-1} of 5-membered γ-ring. The PMR spectrum revealed the absence of carboethoxy group and presence of –NH protons of lactum ring. All the synthesized compounds were screened for antibacterial activity.



Substituents:

Entry	R_1	R_2	R_3	R
a	H	CH_3	Cl	
b	I	H	Cl	
c	H	H	Cl	
d	I	H	CH_3	
e	Br	H	Cl	
f	H	H	CH_3	
g	Br	H	CH_3	
h	I	H	I	
i	I	CH_3	Cl	
j	Br	H	Br	

SCHEME 1

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. All the chemicals and solvents used for laboratory grade and solvents were purified. Completion of the reaction was monitored by Thin Layer Chromatography on pre-coated sheets of silica gel-G. IR spectra were recorded in KBr (cm^{-1}) on FTIR-SCIMADZU spectrometer. PMR spectra were recorded in DMSO-d_6 on AVANCE 300 MHz spectrometer using TMS as an internal standard.

General procedure for 6-carboethoxy-3-(sub.phenyl)-5-(2-methoxy-1-napthyl)-cyclohex-2-en-1-ones (IIa-h)

A mixture of chalcone (I) (0.001 Mole), acetoacetic ester (0.003 Mole) was dissolved in ethanol (15 ml) and few drops of piperidine was added to it, the mixture was refluxed for 3 hrs. After completion of the reaction (monitored by TLC), mixture was cooled to room temperature then poured into ice cold water. Solid get separated out, filtered, dried and recrystallised from suitable solvent.

IIa: IR(KBr cm^{-1}): 3184 (-OH), 1718 (-C=O, ester), 1648 (-C=O, unsaturated), 1598 (-C=C) cm^{-1}; NMR(DMSO-d_6): δ 10.62 (s, 1H, OH), δ 6.81 (s, 1H, -C=C-H), δ 7.1-8.42 (m, 12H, Ar-H), δ 4.16 (q, 2H, $-CH_2CH_3$) δ 2.91 (s, 3H, OCH_3), δ 2.21 (s, 3H, CH_3), δ 1.12 (t, 3H, $-CH_2CH_3$) ppm

IIb: IR(KBr cm^{-1}): 3181 (-OH), 1711 (-C=O, ester), 1646 (-C=O, unsaturated), 1596 (-C=C) cm^{-1}; NMR(DMSO-d_6): δ 10.82 (s, 1H, OH), δ 6.86 (s, 1H, -C=C-H), δ 7.14-8.41 (m, 12H, Ar-H), δ 4.19 (q, 2H, $-CH_2CH_3$) δ 3.06 (s, 3H, OCH_3), δ 1.15 (t, 3H, $-CH_2CH_3$) ppm.

General procedure for 6-acetoxy-3-(sub.phenyl)-5-(2-methoxy-1-napthyl)-cyclohex-2en-1-ones (IIIa-j)

A mixture of chalcone (I) (0.001 Mole), acetyl acetone (0.003 Mole) was dissolved in ethanol (15 ml) and few drops of piperidine was added to it, the mixture was refluxed for 3 hrs. After completion of the reaction (monitored by TLC), mixture was cooled to room temperature then poured into ice cold water. Solid separates out, filtered, dried and recrystallised from suitable solvent.

TABLE 1 : Analytical and antibacterial data of synthesized compounds.

Analytical Data				Antimicrobial activity*	
Entry	Mol. Formula	Yield (%)	M.P °C	*S.aureus*	*E.coli*
IIa	$C_{27}H_{25}O_5Cl$	65	156	16	14
IIb	$C_{26}H_{22}O_5ICl$	68	172	21	18
IIc	$C_{26}H_{23}O_5Cl$	69	132	11	14
IId	$C_{27}H_{25}O_5I$	66	185	16	17
IIe	$C_{26}H_{22}O_5BrCl$	65	144	20	15
IIf	$C_{27}H_{26}O_5$	64	176	11	10
IIg	$C_{27}H_{25}O_5Br$	66	162	13	15
IIh	$C_{26}H_{22}O_5I_2$	67	191	19	20
IIIa	$C_{26}H_{25}O_4Cl$	66	128	16	12
IIIb	$C_{25}H_{20}O_4ICl$	65	155	12	09
IIIc	$C_{25}H_{21}O_4Cl$	67	140	15	14
IIId	$C_{26}H_{23}O_4I$	62	180	19	16
IIIe	$C_{25}H_{20}O_4BrCl$	65	202	13	16
IIIf	$C_{26}H_{24}O_4$	64	176	11	14
IIIg	$C_{26}H_{23}O_4Br$	62	151	18	17
IIIh	$C_{25}H_{20}I_2$	66	212	20	22
IIIi	$C_{26}H_{22}O_4ICl$	68	163	16	14
IIIj	$C_{25}H_{20}Br_2$	69	174	14	17
IVa	$C_{25}H_{23}O_3N_2Cl$	65	179	18	15
IVb	$C_{24}H_{20}O_3N_2ICl$	66	210	22	19
IVc	$C_{24}H_{21}O_3N_2Cl$	64	158	19	12
IVd	$C_{25}H_{23}O_3N_2I$	68	160	22	20
IVe	$C_{24}H_{20}O_3N_2Cl$	65	192	23	19
IVf	$C_{25}H_{24}O_3N_2$	64	225	20	16
IVg	$C_{25}H_{23}O_3N_2Br$	62	184	21	19
IVh	$C_{24}H_{20}O_3N_2I_2$	66	172	24	20
	Ampicillin(Standard)			32	26

***Diameter of Zone of inhibition measured in mm**

IIIa: IR(KBr cm^{-1}): 3182.5 (-OH), 1685 (-C=O, $COCH_3$), 1646 (C=O, unsaturated), 1595 (-C=C) cm^{-1}; NMR(DMSO-d_6): δ 10.68 (s, 1H, OH), δ 6.91 (s, 1H, -C=C-H), δ 7.13-8.36 (m, 12H, Ar-H), δ 3.21 (q, 3H, -$COCH_3$), δ 2.78 (s, 3H, OCH_3), δ 2.24 (s, 3H, CH_3) ppm

IIIc: IR(KBr cm^{-1}): 3192.5 (-OH), 1681 (-C=O, $COCH_3$), 1645.41(C=O, unsaturated), 1598 (-C=C) cm^{-1}; NMR(DMSO-d_6): δ 10.75 (s, 1H, OH), δ 6.88 (s, 1H, -C=C-H), δ 7.14-8.41 (m, 13H, Ar-H), δ 3.11 (q, 3H, -$COCH_3$), δ 2.69 (s, 3H, OCH_3) ppm.

General procedure for 4-(sub.phenyl)-6-(2-methoxy-1-napthyl)-tetrahydro-2H-indazoles (IVa-h)

A mixture of compound (II) (0.001 Mole), hydrazine hydrate (0.002 Mole) was added in ethanolic acetic acid (20 ml). The reaction mixture was refluxed for 4 hrs on water bath. After completion of the reaction (checked by TLC), excess of alcohol distilled off, residue was filtered and washed with cold water. The solid thus separated was collected and crystallized from proper solvent.

Similarly, all other compounds were prepared and analytical data was given in TABLE 1.

IVa: IR(KBr cm^{-1}): 3362, 3296 (-NH), 3189 (-OH), 1726 (-C=O, γ-ring), 1595 (-C=C) cm^{-1}; NMR(DMSO-d_6): δ 10.76 (s, 1H, OH), δ 9.61 (s, 1H, NH), δ8.56 (s,1H,NH), δ 6.98 (s, 1H, -C=C-H), δ 7.18-8.32 (m, 11H, Ar-H), δ 3.05 (s, 3H, OCH_3), δ 2.26 (s, 3H, CH_3) ppm

IVb: IR(KBr cm^{-1}): 3371, 3287 (-NH), 3202 (-OH), 1728.43 (-C=O, γ-ring), 1596 (-C=C) cm^{-1}; NMR(DMSO-d_6): δ 11.02 (s, 1H, OH), δ 9.56 (s, 1H, NH), δ8.46 (s, 1H ,NH), δ 6.89 (s, 1H, -C=C-H), δ 7.14-8.21 (m, 11H, Ar-H), δ 3.01 (s, 3H, OCH_3) ppm

IVc: IR (KBr cm^{-1}): 3358, 3291 (-NH), 3194 (-OH), 1722 (-C=O, γ-ring), 1592 (-C=C) cm^{-1}; NMR(DMSO-d_6): δ 10.52 (s, 1H, OH), δ 9.51 (s, 1H, NH), δ8.41 (s,1H,NH), δ 6.86 (s, 1H, -C=C-H), δ 7.12-8.28 (m, 12H, Ar-H), δ 2.98 (s, 3H, OCH_3) ppm

Biological activity

All the synthesized compounds were screened for their antibacterial activity against *S.aureus* and *E.Coli* at various concentrations such as 25, 50 and 100µg/ml. The activity was carried out using cup-plate method.[18] The zone of inhibition was measured in mm. and DMSO was used as solvent .The activities of the compounds were compared with standard A*mpicillin* drug (TABLE 1).

CONCLUSION

In the present paper we reported a series of novel substituted cyclohexenones and their derivatives by above mentioned methods. All the synthesized compounds gave satisfactory spectral and analytical data .The newly synthesized compounds were screened for antibacterial activity. It was also concluded that compounds cyclohexenone derivatives IIb, IId, IIe, IIh, IIId, IIIg, IIIh, and indazole derivatives IVb, IVd, IVe,

IVg and IVh were showed moderate to good active.

The activity of above compounds significant against bacterial strains. This might be due to presence of halo groups in aryl nucleus, none can reach the activity of standard drug.

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REFERENCES

[1] P.Boeck, C.A.Bandeira; Falcao, Bioorg.Med.Chem., **14**, 1538 **(2006)**.
[2] M.Satyanayarayana, P.Tiwari, B.K.Tripathi; Bioorg.Med.Chem., **12**, 883 **(2004)**.
[3] X.Liu, Mei-Lin Go; Bioorg.Med.Chem., **14**, 153 **(2006)**.
[4] F.Chimenti, E.Maccioni, D.Scci; J.Med.Chem., **48**, 7113 **(2005)**.
[5] B.S.Dawane, R.B.Bhosale, S.S.Pekamwar; J.Pharm.Res., **6(2)**, 119 **(2007)**.
[6] B.S.Dawane, Y.B.Vibhute, V.P.Chavan, A.S.More, M.S.Singare; Korean J.Med.Chem., **10**, 78 **(2000)**.
[7] H.O.House; Modern Synthetic Reaction, 2nd ed., W.A.Benjamin Inc., New York, Amsterdam, 595 **(1972)**.
[8] G.Raso, J.G.Raso, B.Campaner, R.Mastres, J.V.Sinisterra; Synthesis., 1037 **(1982)**.
[9] F.M.Menger, J.H.Smith; J.Am.Chem.Soc., **91**, 421 **(1969)**.
[10] M.F.Toda, H.Takumi; Heterocycles., **47**, 1 **(1998)**.
[11] Mrs.A.M.Rahatgaonkar; Asian J.Chem., **11(4)**, 1385 **(1999)**.
[12] Vijayvergiya, S.Kothari, D.B.L.Verma; Ind.J.Chem., **13**, 105 **(2003)**.
[13] A.C.Jain, P.Arya; Ind.J.Chem., **24(B)**, 645 **(1985)**.
[14] C.Jain, P.Arya; Ind.J.Chem., **26(B)**, 150 **(1987)**.
[15] D.Raffa, G.Daidone, B.Raffa; Arch.Pharm., **332**, 317 **(1999)**.
[16] K.Hosamani, B.V.Badami; Ind.J.Het.Chem., **7**, 254 **(1998)**.
[17] S.Dawane, Y.B.Vibhute, S.G.Konda, M.R.Mali; Asia J.Chem., **20(6)**, 4199 **(2008)**.
[18] H.Collins; 'Microbiological Methods' Buterworths, London, 364 **(1967)**.