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A Comparative Study: Michael Adduct Reaction with Hydroxylamine Hydrochloride and Hydazine Hydrate: Formation of Oximes, Indazolones, Hydrazides, 2-Mercapto-1,3,4-Oxadiazoles, Iminobenzal-N-Amides of Cyclohexanones and Study of Their Antimicrobial Activity

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A comparative study reveals that 1,2,4,5-tetrahydro-4-6-diaryl-indazoline-3-one-6-yl, 3,5-diaryl-6-carbohydrazide-2-ene-cyclo hexanone-3-yl and 3,5-diaryl-6-carbethoxy-2-ene-cyclohexyl oxime were obtained by the reaction of 3,5-diaryl-6-carbethoxy-2-ene-cyclohexanone-3-yl with hydrazine hydrate and hydroxylamine hydrochloride in solvents S_1, S_2, S_3 and S_4 respectively. 3,5-Diaryl-6-carbohydrazide-2-ene-cyclohexanone-3-yl was further subjected to react with CS_2/KOH and benzaldehydes to get 2-mercapto-1,3,4-oxadiazoles and Schiff bases respectively.

INTRODUCTION

In continuation of our work[1], we now report a comparative study of Michael adduct with hydroxylamine hydrochloride and hydrazine hydrates. Various derivatives of Schiff bases are known to exhibit pharmacological properties like antimicrobial, anticancer[2] and antitubercular[3] activities. Some Michael addition products[4] and their aryl sydnones are reported and studied for the antimicrobial activity and found to be inactive. Similarly some mercapto-oxadiazole derivatives[5] are found to show 47% antiinflammatory activity. In view of this, and our interest in the synthesis of biologically active heterocyclic compounds, it was thought of interest to synthesize some differently substituted 3,5-diaryl-cyclohexanone and their derivatives, *i.e.*, oximes, indazolones, hydrazides, Schiff bases, mercapto oxadiazoles, etc. All synthesized compounds were screened for their antimicrobial activity.

The reaction sequence leading to the formation of different title compounds is outlined in Scheme-1 and Scheme-2. Chalcones[6] were condensed with ethylacetoacetate by Michael addition reaction. A comparative study of reaction between Michael adducts (2) with hydroxylamine hydrochloride and hydrazine hydrate has been undertaken by using different solvents such as acetic acid (S_1), ethanol (S_2), acetic acid-ethanol (S_3) and ethanol-KOH (S_4) and time ranging from 2–4 h for getting maximum yield.

It was observed that oximes (3) were obtained by the reaction of Michael adducts (2) and hydroxylamine hydrochloride in solvents S_1, S_2, S_3 and S_4. Similarly a reaction of Michael adducts (2) and hydrazine hydrate was carried out in different solvents S_1, S_2, S_3, S_4; the products obtained were different. Indazolones (4) were formed in solvent S_1, hydrazides (5) were obtained in solvent S_2. In solvents S_3 and

S_4, a mixture of (4) and (5) was obtained. The synthesized compounds were identified by spectral studies, m.p., mmp and Co-TLC to check the purity. Hydrazides (5) were further subjected to react with CS_2/ethanol-KOH and differently substituted benzaldehydes forming 2-mercapto-1,3,4-oxadiazoles (6) and iminobenzal-N-amido cyclohexanone-2-ene-3-yls (7).

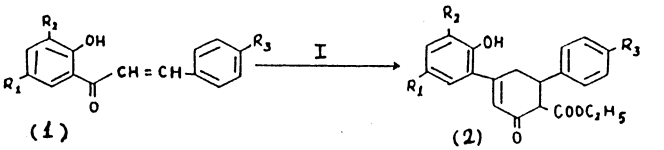
The synthesized compounds were studied for antimicrobial activity by using DMF as solvent at 100 μg against *S. aureus*, *B. subtilis*, *E. coli*, and *K. pneumoniae*. The compounds 2d, 4d, 5d, 6d and 7d showed moderate zone of inhibition. The sensitivity was compared with standard drugs streptomycin and penicillin. Zone of inhibition was measured in mm.

EXPERIMENTAL

All the melting points were determined in open capillaies and are uncorrected. The IR spectra (KBr) were recorded on magna IR 550 series II spectrometer. The ^{1}H-NMR spectra were recorded on AC-Brucker 300 MHz spectrophotometer using 5 mm tubes.

Preparation of 3,5-diaryl-6-carbethoxy-2-ene-cyclohexanone-3-yl (2)

A mixture of chalcone (1) (0.01 mol), ethylacetoacetate (0.02 mol), K_2CO_3 (0.04 mol) and dry acetone (20 mL) was taken in a beaker and stirred for 1 h. The reaction mixture was kept for 1 h at room temperature. It was neutralized by 1 : 1 dil. HCl, filtered and dried. Further it was crystallized from ethanol to get white crystalline compound. Yield 80% (Table-1, Scheme-I)



Scheme-I
(I. $CH_3COCH_2COOC_2H_5$—K_2CO_3, dry acetone)

Comp. (2d): NMR: ($CDCl_3$ + DMSO-d_6): δ(1.04, t, 3H, $COOCH_2\mathbf{CH_3}$) δ(4.05, q, 2H, $COO\mathbf{CH_2}CH_3$), δ(6.45, S, 1H, C_2—1H), δ(3.01–3.1, m, 2H, C_4—2H), δ(2.9, S, 1H=C—H enolic), δ(3.7, S, 1H,C_6—1H), δ(6.9–7.2, m, 8H; Ar—H), δ(9.6, S, 1H, Ar—H).

IR: (KBr): ν: 3102 ν(OH), 2932 (>CH_2), 1738 ν(C=O), 1664 ν(C=O—ester), 1602 ν(H-bonded carbonyl ester), 1288 ν(enolic —OH).

Reaction of 3,5-diaryl-6-carbethoxy-2-ene-cyclohexanone-3-yl and hydroxylamine-hydrochloride in solvents S_1, S_2, S_3, S_4: Formation of 3,5-diaryl-6-carbethoxy-2-ene-cyclohexyl oxime (3)

A mixture of compound (2) (0.01 mol) and hydroxylamine hydrochloride (0.02 mol) was taken in round-bottomed flask. To this mixture, acetic acid (S_1) (15 mL) was added. The reaction mixture was refluxed for 4 h in a water bath. Solvent was evaporated and a sticky mass was obtained. It was triturated with ethanol-

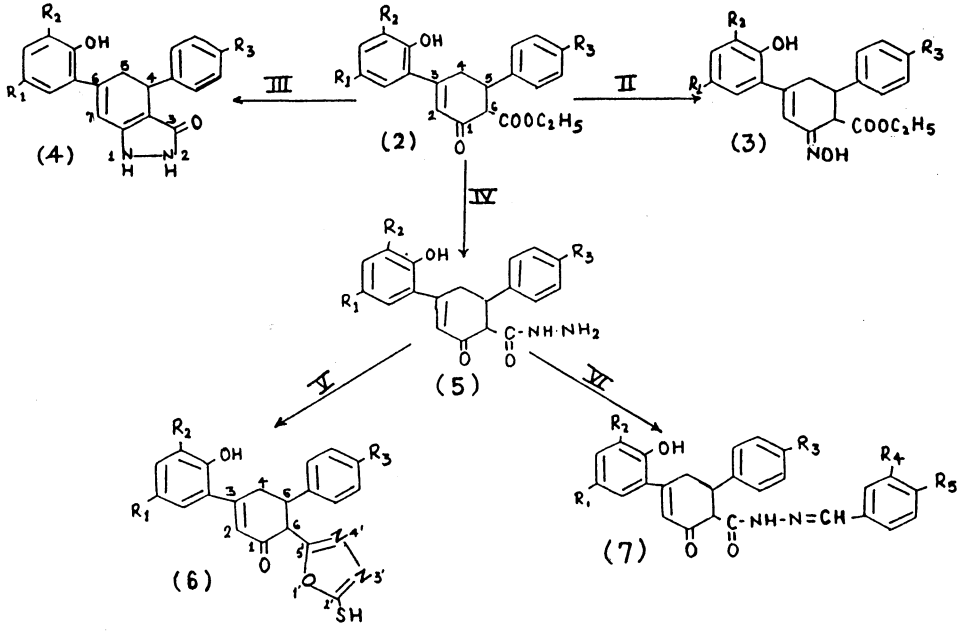
PHYSICAL CHARACTERISATION OF COMPOUNDS

Comp. No.	R_1	R_2	R_3	R_4	R_5	Yield (%)	m.p. (°C)	m.f.	% Analysis C	H	N
2a	CH_3	H	H	–	–	60	150	$C_{22}H_{22}O_4$	75	7	–
2b	CH_3	H	OCH_3	–	–	75	146	$C_{23}H_{24}O_5$	72.6	6.3	–
2c	CH_3	NO_2	H	–	–	42	132	$C_{22}H_{21}O_6N$	67	5.4	3.5
2d	Cl	H	H	–	–	80	152	$C_{21}H_{19}O_4Cl$	69	5.3	–
2e	Cl	H	OCH_3	–	–	90	142	$C_{22}H_{21}O_5Cl$	89	5.25	–
2f	Cl	Br	H	–	–	55	165	$C_{21}H_{18}O_4BrCl$	57	4.2	–
3a	CH_3	H	H	–	–	30	165	$C_{22}H_{22}O_4N$	72.5	6.2	3.7
3b	CH_3	H	OCH_3	–	–	32	170	$C_{23}H_{25}O_5N$	69.8	6.4	3.3
3c	CH_3	NO_2	H	–	–	31	140	$C_{22}H_{22}O_6N_2$	67	5.4	6.5
3d	Cl	H	H	–	–	40	169	$C_{21}H_{20}O_4N{\cdot}Cl$	65.7	5.2	3.2
3e	Cl	H	OCH_3	–	–	60	176	$C_{22}H_{22}O_5N{\cdot}Cl$	63.6	5.3	3.3
3f	Cl	Br	H	–	–	40	190	$C_{21}H_{19}O_4NBr.Cl$	54.3	4.01	3.0
4a	CH_3	H	H	–	–	60	260	$C_{20}H_{18}O_2N_2$	75.4	5.7	8.4
4b	CH_3	H	OCH_3	–	–	70	259	$C_{21}H_{20}O_3N_2$	72.3	5.8	8.05
4c	CH_3	NO_2	H	–	–	90	260(d)	$C_{20}H_{17}O_4N_3$	69	4.9	11.6
4d	Cl	H	H	–	–	90	255	$C_{19}H_{15}O_2N_2Cl$	69	4.5	12.3
4e	Cl	H	OCH_3	–	–	80	249	$C_{20}H_{17}O_3N_2Cl$	65	4.6	11.4
4f	Cl	Br	H	–	–	40	260	$C_{19}H_{14}O_2N_2Br{\cdot}Cl$	54.6	3.8	10.0
5a	CH_3	H	H	–	–	80	276	$C_{20}H_{19}O_3N_2$	68.7	5.4	12.1
5b	CH_3	H	OCH_3	–	–	82	268	$C_{21}H_{22}O_4N_2$	68.8	6.0	7.65
5c	CH_3	NO_2	H	–	–	91	270(d)	$C_{20}H_{19}O_5N_3$	62.4	4.9	10.8
5d	Cl	H	H	–	–	90	260	$C_{19}H_{17}O_3N_2Cl$	64	4.8	7.3
5e	Cl	H	OCH_3	–	–	90	256	$C_{20}H_{19}O_4N_2Cl$	62.3	4.9	7.1
5f	Cl	Br	H	–	–	40	278	$C_{19}H_{16}O_3N_2Br{\cdot}Cl$	55.0	3.9	6.3
6a	CH_3	H	H	–	–	30	210	$C_{21}H_{17}O_3N_2S$	66.8	4.9	7.4
6b	CH_3	H	OCH_3	–	–	35	205	$C_{22}H_{20}O_4N_2S$	65.3	4.9	6.9
6c	CH_3	NO_2	H	–	–	20	190	$C_{21}H_{17}O_7N_3S$	60.0	4.03	9.7
6d	Cl	H	H	–	–	50	206	$C_{20}H_{15}O_3N_2SCl$	60.0	3.79	7.0
6e	Cl	H	OCH_3	–	–	50	200	$C_{21}H_{17}O_4N_2SCl$	58.8	3.9	6.5
6f	Cl	Br	H	–	–	30	216	$C_{20}H_{14}O_3N_2SBr{\cdot}Cl$	50.5	2.9	5.8
7a1	CH_3	H	H	H	H	90	280	$C_{27}H_{24}O_3N_2$	77.0	5.6	6.6
7a2	CH_3	H	H	NO_2	H	80	260(d)	$C_{27}H_{23}O_5N_3$	70.0	4.9	8.7
7a3	CH_3	H	H	H	OCH_3	92	285	$C_{28}H_{26}O_4N_2$	75	5.9	6.0
7a4	CH_3	H	H	H	OH	70	250	$C_{27}H_{24}O_4N_2$	75	5.6	6.2
7b1	CH_3	H	OCH_3	H	H	80	275	$C_{28}H_{26}O_4N_2$	75	5.8	5.9
7b2	CH_3	H	OCH_3	NO_2	H	75	270(d)	$C_{28}H_{25}O_6N_3$	67.2	5.2	8.6
7b3	CH_3	H	OCH_3	H	OCH_3	90	278	$C_{29}H_{28}O_5N_2$	72	6.2	5.6
7b4	CH_3	H	OCH_3	H	OH	70	268	$C_{28}H_{26}O_5N_2$	71.5	6.1	5.3

Comp. No.	R_1	R_2	R_3	R_4	R_5	Yield (%)	m.p. (°C)	m.f.	% Analysis C	H	N
7d1	Cl	H	H	H	H	90	265	$C_{26}H_{21}O_3N_2Cl$	70.1	4.7	6.8
7d2	Cl	H	H	NO_2	H	70	269(d)	$C_{26}H_{20}O_5N_3Cl$	65	4.1	8.5
7d3	Cl	H	H	H	OCH_3	90	275	$C_{27}H_{23}O_4N_2Cl$	68.3	5.0	5.3
7d4	Cl	H	H	H	OH	75	255	$C_{26}H_{21}O_4N_2Cl$	69.0	5.2	6.0
7e1	Cl	H	OCH_3	H	H	80	260	$C_{27}H_{23}O_4N_2Cl$	69	4.9	5.4
7e2	Cl	H	OCH_3	NO_2	H	70	261(d)	$C_{27}H_{22}O_6N_3Cl$	64	4.3	8.1
7e3	Cl	H	OCH_3	H	OCH_3	90	282	$C_{28}H_{25}O_5N_2Cl$	67	5.1	5.5
7e4	Cl	H	OCH_3	H	OH	60	258	$C_{27}H_{23}O_5N_2Cl$	67	4.7	5.3

(d): decomposed

acetic acid and recrystallized from ethanol. Same reaction was carried out in solvents S_2, S_3 and S_4 and it was found that similar compounds (3) were obtained. The compounds were compared with authentic sample and identified by spectral studies, m.p, mmp, Co-TLC (yield 40%) (Table 1, Scheme-II).



II. $NH_2OH{\cdot}HCl$, S_1, S_2, S_3, S_4, Δ 3–4 h
III. $NH_2NH_2{\cdot}H_2O$, S_1, Δ 4 h
IV. $NH_2NH_2{\cdot}H_2O$, S_2, Δ 2 h
V. CS_2 ethanol-KOH, Δ 10 h
VI. $C_6H_3{\cdot}R_4R_5CHO$, ethanol-acetic acid, conc. H_2SO_4, Δ 2 h

Scheme-II

Comp (3d): NMR: ($CDCl_3$ + DMSO-d_6): δ(1.00, t, 3H, $COOCH_2\mathbf{CH_3}$), δ(3.9–4.04, q, 2H, $COO\mathbf{CH_2}CH_3$), δ(3.06 m, 2H, C_4—2H), δ(3.7, S, 2H, C_6—1H and C_5—1H), δ(6.5, S, 1H, C_2—1H), δ(6.8–7.3, m, 8H, Ar—H), δ(9.3, S, 1H, Ar—OH), δ(11.2, b, 1H, N—OH).

IR (KBr): ν_{max} (cm^{-1}): 3400 ν(OH), 3397 ν(N=OH), 2931 ν(=CH_2), 1645 ,ν(C=N), 1736 ν(C=O ester), 1610 ν(H-bonded carbonyl ester)

Reaction of 3,5-diaryl-6 carbethoxy-2-ene-cyclohexanone-3 yl and hydrazine hydrate in solvent S_1 acetic acid: Formation of 1,2,4,5-tetrahydro-4,6,-diarylindazoline-3-one-6-yl (4).

To the mixture of compound (2) (0.01 mol) and hydrazine hydrate (0.02 mol), 15 mL of acetic acid (S_1) was added. The reaction mixture was refluxed for 4 h in a water bath. A bright yellow needle-shaped compound was obtained. It was filtered and recrystallized from ethanol (yield 70%) (Table-1, Scheme-II).

Comp. 4d: NMR: ($CDCl_3$ + DMSO-d_6): δ(6.7–8.09, m, 11H, Ar–H), δ(8.5, S, 1H, Ar—OH), δ(9.7, S, 1H, NH), δ(11.13, S, 1H, NH).

IR: cm^{-1} (KBr): 3388.99 ν(NH), 3150 ν(NH), 2931 ν(=CH_2), 1705 ν(C=O), 1593 δ (Amide II, NH-bending), 1512 ν (Amide I, C=O), 1252 ν (enolic —OH).

Reaction of 3,5-diaryl-6-carbethoxy-2-ene-cyclohexanone-3-yl and hydrazine hydrate in solvent S_2 (ethanol): Formation of-3,5-diaryl-6-carbohydrazide-2-ene-cyclohexanone-3-yl (5)

A mixture of compound (2) (0.01 mol), hydrazine hydrate (0.02 mol) and (S_2) ethanol (20 mL) was taken in round-bottomed flask and refluxed for 2 h in a water bath. Silver white shining crystals were obtained. It was filtered and recrystallized from ethanol (yield 90%) (Table-1, Scheme-II).

Comp. 5d: NMR: ($CDCl_3$ + DMSO-d_6): δ(1.9, S, 2H, C_6—1H and enolic —OH), δ(2.8, dd, 1H, C_4—1H), δ(3.1, dd, 1H, C_4—1H), δ(4.2, q, 1H, C_5—1H), δ(6.6, S, 1H, C_2—1H), δ(6.7–7.6, m, 8H, Ar—H), δ(8.6, b, 4H, NH, NH_2 and Ar—OH).

IR: (KBr): ν_{max} cm^{-1}; 3500 ν(OH), 3178 ν(NH), 2500 ν(NH_2), 2833 ν(=CH_2), 1589 ν(Amide II NH bending), 1510 ν(Amide I C=O), 1249 ν(enolic —OH).

Reaction of 3,5-diaryl-6-carbethoxy-2-ene-cyclohexanone-3-yl and hydrazine hydrate in solvents S_3 and S_4: Formation of mixture of Indazolones (4) and hydrazides (5)

A mixture of compound (2) (0.01 mol), hydrazine hydrate and solvent S_3 ethanol-acetic acid (10 mL + 10 mL) was taken in round-bottom flask. The reaction mixture was refluxed for 4 h in a water bath. Solvent was evaporated and recrystallized from ethanol. It was found that the product obtained was the mixture of indazolone (4) 30% and hydrazide (5) 60%. It was compared with authentic samples and identified by spectural studies, m.p., mmp and Co- TLC. Same reaction was carried out in solvent S_4, ethanol/KOH (20 mL + 5 mL) to obtain a mixture of both compounds (4) and (5) (yield as 30 : 60).

Preparation of 3,5-diaryl-6-(2-mercapto-1,3,4-oxadiazole)-2-ene-cyclohexanone-3-yl(6)

To the mixture of compound (5) (0.01 mol) and ethanol/KOH (30 mL + 5 mL), dry CS_2 (5mL) was added and the reaction mixture was refluxed for 10 h in a water bath. The solvent was evaporated and crude mass was neutralized with 1 : 1 dil. HCl. It was filtered, dried and crystallized from ethanol : dioxane (yield 60%). (Table-1, Scheme-II).

Comp 6e: NMR ($CDCl_3$ + DMSO-d_6): δ(2.8, dd, 1H, C_4—1H), δ(3.1, m, 1H, C_4—1H), δ(4.1, q, 1H, C_5—1H), δ(3.7, S, 3H, Ar—OCH_3), δ(6.6, s, 1H, C_2—1H), δ(6.7–7.1 m, 7H, Ar—H), δ(7.9, S, 1H, S=C—NH), δ(9.8, b, 1H, Ar—OH).

IR: (KBr): ν_{max} (cm^{-1}) 3400 ν(OH), 3179 ν(NH), ν(=CH_2) 2550 ν (—SH streching), 1589 δ (Amide II NH bending), 1510 (Amide I, S=C—NH), 1250 ν (enolic = C–OH), 1175 ν(C=S).

Preparation of 3,5-diaryl-6-(iminobenzal-N-amido)-2-ene-cyclohexanone-3-yl (7)

A mixture of compound (5) (0.001 mol) and ethanol (10 mL) was taken in a round-bottomed flask. To this mixture benzaldehyde (0.001 mol) was added. 5 drops of acetic acid and 2 drops of conc. H_2SO_4 were added to the solution. The reaction mixture was refluxed for 2 h in water bath. The product was filtered and recrystallized from ethanol : dioxane (yield 90%) (Table-1 and Scheme-II)

Comp 7e$_3$: NMR: ($CDCl_3$ + DMSO-d_6): δ(0.9–1.22, m, 2H, C_6—1H and OH enolic), δ(2.8, dd, 1H, C_4—1H), δ(3.1, m, 1H, C_4—1H), δ(4.1, m, 1H, C_5—1H), δ(3.71, S, 3H, Ar—OCH_3), δ(3.75, S, 3H, Ar—OCH_3) δ(6.6, S, 1H, C_2—1H), δ(6.7, S, 1H, N=CH), δ(6.8–7.2, m, 11H, Ar—H), δ(7.8, S, 1H, O=C—NH), δ(9.6, b, 1H, Ar—OH).

IR: (KBr): ν_{max} (cm^{-1}) 3400 ν(OH), 3224 ν(NH), 2905 ν (=CH_2), 1639 ν(C=N), 1627 ν(O=C— Amide-I), 1580 δ(amide II NH-bending), 1248 ν(enolic —OH).

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