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MICROWAVE ASSISTED SYNTHESIS OF 5H-2(SUBSTITUTED)PHENYLIMINO-5-PHENYLOXAZOLE-4-ONES

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Abstract:
A series of 5H-2(substituted)phenylimino-5-phenyloxazole-4-ones **(3)** and 5H-2(substituted)phenylimino-5-phenylthiazole-4-ones **(4)** have been synthesized by interaction of ethyl-2-bromo-2-phenylethanoate with urea and thiourea under microwave condition respectively. The technique consumes less time and gives excellent yield of **3** & **4**. These compounds were also synthesized by conventional method. Structure of compounds has been elucidated on the basis of spectral and laboratorial technique. Further, the compound has been scanned for their biological activities.

Keywords: phenyl acetic acid, urea, thiourea, oxazoles, thiazoles.

Introduction:

Five membered heterocyclic compounds possess interesting biological activity[i]. Among them the compounds bearing 1, 3- oxazole and 1, 3- thiazole has attracted attention of many synthetic chemists due to their presences in large number of natural products[ii]. Ample of evidence suggests that these compounds have significant anti-inflammatory[iii], antifungal[iv], antibacterial[v], analgesic[vi], antiviral[vii], and anticancer[viii] activities. In addition, many investigations demonstrated that biological activity of azoles derivatives were significantly influenced by the introduction of variable aromatic substituent.
In recent years the increase in the importance of microwave assisted method for synthesis of organic compound was greatly observed not only because the method is fast and effective but it also reduces the side reactions thereby causing an increase in the product yield[ix-xi]. In view of these finding and in continuation of our ongoing search for new heterocyclic systems of biological importance, we have synthesized the title compounds and screened them for their antimicrobial activities.

Materials and methods

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The purity of the compounds was monitored by thin layer chromatography on silica gel coated aluminium plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard

(chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

General Procedure:

Synthesis of 2-Bromo-2-phenylacetic acid (1):

In a conical flask mixture of phenyl acetic acid (0.1mole, 13.6g) and N-Bromosuccnimide (0.15mole, 26.7g) were allowed to reflux for 8-10 hrs in CCl_4 (30ml) as a solvent and small quantity of benzoyl peroxide as a catalyst. The progress of the reaction was monitored on TLC. Upon completion, reaction mixture was quenched into the water and CCl_4 (10ml). Organic layer was separated and washed with water. CCl_4 was distilled out completely to yield crystals of compound **1**. Yield =70%, m.p. =81-83^{0}C.

Synthesis of Ethyl-2-bromo-2-phenylethanoate (2):

Compound **1** (0.1mole, 21.5g) thus obtained was further treated with $SOCl_2$ (0.15mole, 10.9ml) in presence of CCl_4 (10ml) as a solvent. The reaction mixture was refluxed for 2-3 hrs and ethanol (20ml) was then added. The reaction mixture was stirred further for 5-10 mins and was washed using aqueous solution of Na_2CO_3 to remove traces of compound **1** if present. The organic layer so obtained was distilled off to obtain compound **2**. Yield =83%, b.p. =88-93^{0}C.

Synthesis of 5H-2(substituted)phenylimino-5-phenyloxazole-4-ones (3a-f):

A mixture of compound **2** (0.01mole), substituted urea (0.01mole) and KOH (0.015mole) in ethanol (10ml) were irradiated in microwave for 3-5 mins. The progress of the reaction was monitored on TLC. Upon completion, the reaction mixture was cooled to RT. The solid product thus obtained was filtered, washed with water and recrystallized using ethanol to yield **3**. Thus compounds **3a-f** were synthesized.

Spectral interpretation: 5H-2-phenylimino-5-phenyloxazole-4-ones. (3a)

Anal.Calcd for $C_{15}H_{12}N_2O_2$: C,71.42; H,4.76; N,11.11; O,12.69%.Found C,71.42; H,4.76; N,11.11; O,12.69%. IR(cm^{-1}): 3310 (N-H), 1650 (-C=N-), 1680 (-CO-NH-), 1135 (C-O), 750-700 (mono substituted aromatic ring) ^{1}H NMR(δ ppm): 4.85(s,1H,CH), 7.05-7.45 (m,10H,Ar-H), 8.08 (s,1H,NH) ^{13}C NMR(δ ppm): 46.1(CH), 127-135 (Ar-C),156 (C=N) and 173 (C=O)

5H-2-(4-methyl)phenylimino-5-phenyloxazole-4-ones. (3b)

Anal.Calcd for $C_{16}H_{14}N_2O_2$: C,72.18; H,5.26; N,10.52; O,12.03%.Found C,72.18; H,5.26; N,10.52; O,12.03%. IR(cm^{-1}): 3314 (NH), 1648 (-C=N-), 1679 (-CO-NH-), 1136 (C-O) ^{1}H NMR(δ ppm): 4.83(s,1H,CH), 2.35(s,3H,CH_3) 7.05-7.45 (m,9H,Ar-H), 8.13 (s,1H,NH) ^{13}C NMR(δ ppm): 30.6(CH3), 45.9(CH), 127-139 (Ar-C),157 (C=N) and 176 (C=O).

Synthesis of 5H-2(substituted)phenylimino-5-phenylthiazole-4-ones (4a-f):

Compound **2** (0.01mole), substituted thiourea (0.01mole) and KOH (0.015mole) in ethanol (10ml) were irradiated in microwave for 3-5 mins. The progress of the reaction was monitored on TLC. Upon completion, the reaction mixture was cooled to RT. The solid product thus obtained was filtered, washed with water and recrystallized using ethanol to yield **4**. Thus compounds **4a-f** were synthesized.

5H-2-phenylimino-5-phenylthiazole-4-ones. (4a)
Anal.Calcd for $C_{15}H_{12}N_2OS$: C,67.16; H,4.47; N,10.44; O,5.97; S,11.94%. Found C,67.16; H,4.47; N,10.44; O,5.97; S,11.94%. IR(cm^{-1}): 3290 (NH), 1648 (-C=N-), 1670 (-CO-NH-), 1340 (C-S) ^{1}H NMR(δ ppm): 4.04(s,1H,CH), 6.95-7.23 (m,10H,Ar-H), 8.18 (s,1H,NH) ^{13}C NMR(δ ppm): 49.1(CH), 126-142 (Ar-C),154 (C=N) and 176 (C=O).

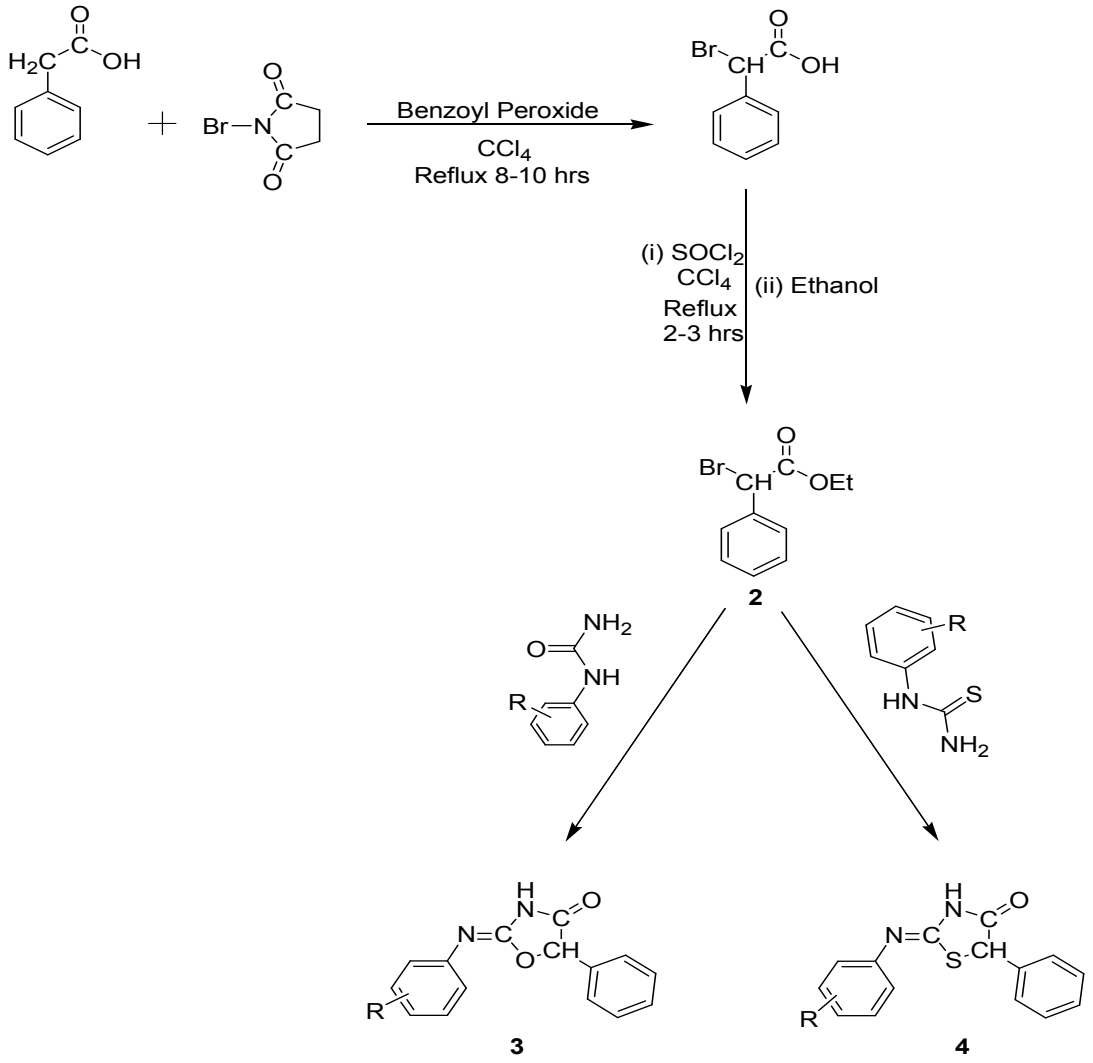
5H-2-(4-methyl)phenylimino-5-phenylthiazole-4-ones. (4b)
Anal.Calcd for $C_{16}H_{14}N_2OS$: C,68.08; H,4.96; N,9.92; O,5.67; S,11.34%.Found C,68.08; H,4.96; N,9.92; O,5.67; S,11.34%. IR(cm^{-1}): 3264 (NH), 1644 (-C=N-), 1677 (-CO-NH-), 1620-1440 (Ar ring), 1345(C-S),\ ^{1}H NMR(δ ppm): 4.82(s,1H,CH), 2.36(s,3H,CH_3) 6.95-7.43 (m,9H,Ar-H), 7.90 (s,1H,NH) ^{13}C NMR(δ ppm): 29.6(CH_3), 43.9(CH), 122-136 (Ar-C),151 (C=N) and 171 (C=O).

Table I: Characterization data of compounds 3(Urea derivative) and 4 (Thiourea derivative)

Compounds	R	Melting point ^{0}C	Yield %
3a	H	120-123	70
3b	4-CH_3	145-148	73
3c	2-CH_3	128-130	69
3d	4-OCH_3	110-113	80
3e	4-Cl	114-116	75
3f	-	95-98	71
4a	H	89-92	82
4b	4-CH_3	126-128	74
4c	2-CH_3	105-108	72
4d	4-OCH_3	136-139	85
4e	4-Cl	102-104	78
4f	-	80-83	81

Antibacterial Evaluation
The newly synthesized representative compounds were tested for their antimicrobial activity against the following microorganisms: (a) Gram-negative: Escherichia coli, P.aeruginosa;
(b) Gram-positive: S.aureus, C.diphtheria. The preliminary screening of the investigated compounds was performed using the filter paper disc-diffusion method. The compounds were tested at a concentration of 100 Kg/ml. The zone of inhibition was measured in mm and compared with reference standard ampicillin trihydrate (100 Kg/ml). The compounds tested displayed promising antimicrobial activity. The results of antibacterial screening studies are reported in **Table II**.

General Scheme



Results and Discussion

In the present study, a series of 1,3-Oxazole and 1,3-Thiazole derivatives were designed and synthesized , it involves three steps , the compounds **3a-f** and **4a-f** were synthesized in high yields by reacting substituted urea and thiourea with compound **2** in the presence of KOH as a catalyst and ethanol as a solvent. The representative compounds were evaluated for their antifungal and antibacterial activity, which showed promising activity. The structures of all the synthesized compounds were characterized on the basis of the chemical and spectral techniques such as IR, ^{1}H NMR, ^{13}C NMR and elemental analysis techniques.

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Table II. **Antimicrobial activities of some newly synthesized compounds.**

Compounds	**Inhibition Zone (mm)**			
	Gram-negative		**Gram-positive**	
	E.coli	**P.aeruginosa**	**S.aureus**	**C.diphtheria**
3a	18	20	22	16
3b	20	19	17	22
3c	17	22	24	18
3d	15	16	18	20
3e	12	15	14	17
3f	13	21	16	26
4a	16	11	21	13
4b	19	20	17	16
4c	15	18	23	24
4d	18	12	15	22
4e	14	17	19	20
4f	11	13	20	18
Amphicilin trihydrate	21	24	26	28
DMSO	0	0	0	0

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