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Go Green-Effective Synthesis of Isatin Containing Oxadiazole Moiety Based on Microwave-Assisted Heating Protocol

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ABSTRACT

An efficient microwave heating methodology for the synthesis of Isatin containing oxadiazole moiety is reported. Each compound was obtained with high yield and purity in a few minutes. The synthesized compounds (7a-d) were characterized using Infra-Red (IR), Proton Nuclear Magnetic Resonance (^{1}H-NMR) and mass spectra. Comparison with conventional synthesis indicated the enhanced yield with faster reactions under microwaves.

Keywords: Microwave, Conventional, Synthesis, Isatin, 1,3,4-oxadiazole

INTRODUCTION

Many important biochemical compounds and drugs of natural origin contain heterocyclic rings. Literature survey has revealed the diversified biological and pharmacological significance of several nitrogen and sulphur heterocycles. This aspect has been drawing the attention of many researchers towards exploiting the biological importance of various heterocyclic compounds and to establish the relationship between their biological, pharmacological potency and structural features. In the past decade, Microwave-induced Organic Reaction Enhancements (MORE) chemistry has increased attractiveness for quick synthesis of compounds and many organic chemists have described organic reactions [1]. MORE chemistry can also be expressed as e-chemistry due to its effective, economical nature, easy to handle and it is a step towards green chemistry [2].

Isatin possessing an indole nucleus having both the keto and lactam moiety has aroused tremendous curiosity due to its diverse biological and pharmacological studies. Isatin is an endogenous compound identified in humans that possesses wide range of biological activities. Isatin has anxiogenic [3], anticonvulsant [4] activity and acts as a potent antagonist on atrial natriuretic peptide receptors *in vitro* [5]. Isatin derivatives of Mannich bases had antibacterial [6-8], antifungal [9,10], antiviral [11-13], anti-HIV [14-16], antiprotozoal [17,18], anticancer [19], muscle relaxant [20], antiallergic [21] activity.

The 1,3,4-oxadiazoles moiety containing various heterocyclic nuclei possess various important pharmacological activities like antimicrobial [22] anti-inflammatory [23]. The key element in our approach is the novel utilization of 1,3,4-oxadiazole as well as isatin ring as a building block, a well-documented application to the construction of various nitrogen heterocycles of chemical and biological interest.

Therefore, it is planned to condense two nuclei with an aim to get synergistic activity. A number of conventional method for the synthesis of 1,3,4-oxadiazole have been reported which are time consuming resulting in limited yield of the final product, to overcome these draw backs of the conventional procedures microwave synthesis procedures are used here.

MATERIALS AND METHODS

General

Solvents were of reagent grade and dried using standard procedures. Melting points were determined on to an open glass capillary method and are uncorrected. All chemicals used were reagent grade and were used as received without further purification. ^{1}HNMR spectra were recorded at 400 MHZ on a Bruker Avance DPX (400 MHz) FT spectrometer in Deuterated Dimethyl Sulfoxide (DMSO-d_6) using Tetramethylsilane (TMS) as an internal reference. Mass spectra were recorded on a JEOL SX-102 Mass spectrometer at 70ev. A laboratory microwave oven operating at 2450 MHz and power output of 600 W and was used for all the experiments.

Elemental analyses were carried out using a Coleman automatic C, H and N analyzer. The progress of the reaction was monitored by Thin Layer Chromatography (TLC). The structures of synthesized compounds were confirmed by spectral and elemental analysis.

General procedure for synthesis of isatin (3a)

Following the previous literature oximinoacetanilide was prepared in 75% yield. After addition of concentrated sulphuric acid (14.66 ml) with dry oximinoacetanilide (4 g; 0.024 mol) at 70-80°C the solution was cooled to room temperature and poured upon 10-12 times of volume of crushed ice. The orange red crude solid product of (3a) was separated from the solution after half an hour which was filtered, washed well with cold water and dried in a vacuum desiccator. The orange red pure product of (3a) (yield 65%) was re-crystallized from ethyl acetate (2.32 g). Similarly compound 3b-3d were synthesized using the same procedure.

Physical properties of isatin (3a)

Molecular formula	$C_8H_5NO_2$
molecular weight	147 g
melting point	180-182°C
TLC (Solvent system)	Petroleum ether: Ethyl acetate (3:2)

Synthesis of 3-(4-fluorophenyimino)-1H-indol-2-one (4a)

A mixture of indole-2,3-dione (1.47 g, 0.01 mol) and 4-fluoroaniline (1.11 ml, 0.01 mol) in absolute ethanol (20 ml) in the presence of 2-3 drops of glacial acetic acid was irradiated in a microwave oven for 4 min. On cooling, crystals reported out which were filtered and recrystallized from ethanol to give 3-(4-fluorophenylimino)-1H-indol-2-one (yield 86%) as yellow needles.

Physical properties of 3-(4-fluorophenyimino)-1H-indol-2-one (4a)

Molecular formula	$C_{14}H_9FN_2O$
molecular weight	240 g
melting point	210-216°C
TLC (Solvent system)	Benzene: Methanol (4:1)

Synthesis of 3-(4-fluorophenyl imino)-2-oxo-1-indol-ethyl acetate (5a)

A mixture of (4a) (2.40 g, 0.01 mol), ethylchloro acetate (1.22 ml, 0.01 mol) and potassium carbonate (2.2 g, 0.015 mol) in dry acetone was placed in a Round Bottom Flask (RBF) placed in a microwave oven and irradiated for 10 min. After completion of reaction (monitored by TLC), the mixture was cooled and the resulting solid was filtered, dried and recrystallized from methanol (yield 78%) as a yellow compound (1.89 g).

Physical properties of 3-(4-fluorophenyl imino)-2-oxo-1-indol-ethyl acetate (5a)

Molecular formula	$C_{18}H_{11}FN_2O_3$
molecular weight	326 g
melting point	105-106°C
TLC (Solvent system)	Benzene: Methanol (4:1)

Synthesis of 3-(4-fluorophenylimino)-2-oxo-1-indol-acetyl hydrazide (6a)

A mixture of (5a) (3.26 g, 0.01 mol) and hydrazine hydrate (99%, 0.5 ml, 0.01 mol) in methanol (10 ml) was subjected to Microwave Irradiation (MWI) at 140 W. TLC was run after every half a min to monitor the progress of reaction. On completion of the reaction, the reaction mixture was poured over crushed ice. The solid obtained was collected and washed with water. It was dried and recrystallized from ethanol (yield 78%) as a yellow coloured solid (2.43 g).

Physical properties of 3-(4-fluorophenylimino)-2-oxo-1-indol-acetyl hydrazide (6a)

Molecular formula	$C_{16}H_{13}FN_4O_2$
molecular weight	312g
melting point	225-226°C
TLC (Solvent system)	Toluene: Ethyl acetate (4.5:0.5)

Synthesis of 5-mercapto-2-[3(4-fluorophenyl imino)-1-methyl-indol-2-one]-1,3,4-oxadiazole (7a)

A mixture of (6a) (3.12 g, 0.01 mol) was dissolved in ethanolic KOH (15 ml) and the solution was cooled to 0°C, CS_2 (0.75 ml, 0.01 mol) was added. The reaction mixture was subjected to MWI at 140 W. TLC was run after every half a minute to monitor the progress of the reaction. Then the reaction mixture was concentrated to a small volume, water was added to it, it was neutralized with 1 N HCl and the resulting solid was extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to furnish the desired compound (7a) (yield 84%) as a yellow powder (2.62 g).

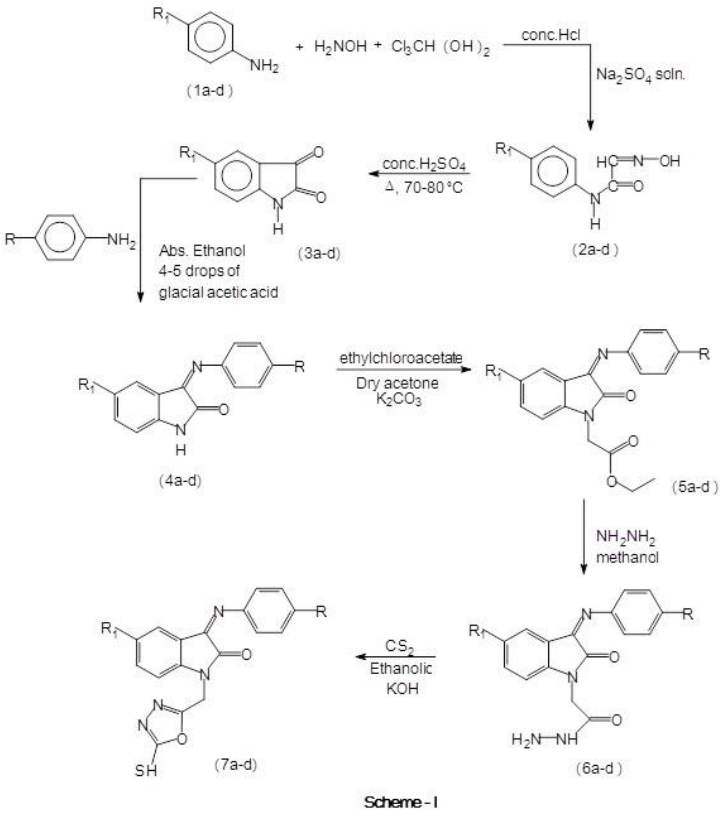
Physical properties of 5-mercapto-2-[3(4-fluorophenyl imino)-1-methyl-indol-2-one]-1,3,4-oxadiazole (7a)

Molecular formula	$C_{17}H_{11}FN_4O_2S$
molecular weight	354 g
melting point	125°C
TLC (Solvent system)	Benzene: Ethyl acetate (3:2)

All the other compounds (7b-7d) are synthesized by following the above mentioned procedure.

Spectral data

(7a)-IR (KBr): υ(cm^{-1}): 1076 (C-F), 1313 g (C-N), 1614 (C=N), 1676 (C-S), 1743 (> C = O), 1606 (> C = O isatin), 2565 (S-H), ^{1}H-NMR: δ (ppm): 3.4 (S, H,-SH), 5.1 (S, 2H, N-CH_2), 6.7-7.4 (m, 8H, Ar-H). MS: (m/z): 354 [M^+], 246 ($C_{11}H_9N_3O_2S^+$), 131 ($C_8H_6NO^+$), 115 ($C_3H_3N_2OS^+$), 108 ($C_6H_4NF^+$), 101 ($C_2H_2N_2OS$+), 90 ($C_6H_5N^+$), 76 ($C_6H_4^+$) (100%). (7b)-IR (KBr): υ (cm^{-1}): 500 (C-Cl), 1016 (C-F), 1310 (C-N), 1622 (C = N), 1739 (> C = O), 1606 (χ=0 isatin), 2565 (S-H). (7c-IR (KBr): υ (cm^{-1}): 1076 (C-F), 1313 (C-N); 1612 (C = N), 1649 (C-S), 1676 (> C = O), 1606 (> C = O isatin), 2565 (S-H). (7d)-IR (KBr): υ (cm^{-1}): 1024 (C - F), 1309 (C - N), 1614 (C = N), 1647 (C-CH_3), 1720 (> C = O), 2565 (S-H).



Scheme 1: The Microwave-Assisted Organic Synthesis of 5-mercapto-2-[5-substituted-3-(4-arylimino)-1-methyl-indol-2-one]-1,3,4-oxadiazole (7a-d)

RESULTS AND DISCUSSION

The focus of the Scheme 1 is the Microwave-Assisted Organic Synthesis (MAOS) of 5-mercapto-2-[5-substituted-3-(4-arylimino)-1-methyl-indol-2-one]-1,3,4-oxadiazole (7a-d) analogs and the comparison of this method with the conventional one. In the present work, condensation of appropriate indol-2,3-diones with halogen substituted anilines under microwave irradiation at a power level of 140 watts yields 5-substituted-3-(4-arylimino)-indol-2-one (4a-d). In the next step, 4a-g on treatment with ethyl chloroacetate in anhydrous K_2CO_3 and dry acetone furnished [5-substituted-3-(4-arylimino)-2-oxo]-1-indole-ethylacetate (5a-d) which on reaction with hydrazine hydrate in methanol gave [5-substituted-3-(4-arylimino)-2-oxo]-1-indole acetyl hydrazide (6a-d). In the last step, a solution of compounds (6a-d) in ethanolic KOH on treatment with CS_2 gave title compounds 5-mercapto-2-[5-substituted-3-(4-arylimino)-1-methyl-indol-2-one]-1,3,4-oxadiazole (7a-d) (Figure 1) under microwave irradiation at a power of 140 watts. MW irradiation led to higher yields in much less time than that by conventional methods.

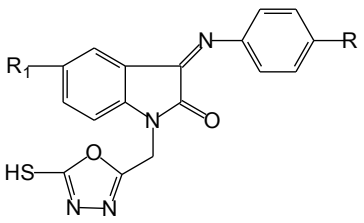


Figure 1: 5-mercapto-2[5-substituted-3-(4-arylimino)-1-methyl]-indole-2-one-1,3,4-oxadiazole analogs

The structure of isatin (3) has been confirmed by its IR, ^{1}H-NMR and mass spectra. The physical data of all synthesized compounds (7a-d) are shown in Table 1. In the elemental analysis, the percentage of C, H and N atoms are present in the range of ± 0.06, which is shown in Table 1.

IR spectroscopy of final compound (7a) exhibited isatin carbonyl at 1743 cm^{-1} and S-H of 5-mercapto oxadiazole at 2565 cm^{-1}, which confirms the formation of the final compound. In the ^{1}H-NMR (DMSO-d_6) spectra of (7a), all protons were seen according to the expected chemical shifts and integral values at δ=3.4 (S, H, -SH), 5.1 (S, 2H, N-CH_2) 6.7-7.4 (m, 8H, Ar-H).

The fragmentation pattern of representative compound (7a) is presented as an additional evidence for the proposed structure. The m/z ratio of 76 was found at 100% abundance i.e., base peak. In the mass spectra of (7a), the molecular ion peak at 354 [M^+] confirms the formation of final structure. The fragment ion peaks were observed at 246 ($C_{11}H_9N_3O_2S^+$), 131 ($C_8H_6NO^+$), 115 ($C_3H_3N_2OS^+$), 108 ($C_6H_4NF^+$), 101 ($C_2H_2N_2OS^+$), 90 ($C_6H_5N^+$), 76 ($C_6H_4^+$) (100%). Structure of the compound (7a) was confirmed by the spectral data (IR, ^{1}H-NMR and MS) and elemental analysis. A comparative study of microwave and conventional synthesis is shown in Table 2.

Table 1: The physical data of all synthesized compounds (7a-d) analogs

S. No.	R	R_1	Molecular formula	Molecular weight	Melting point (°C)	Elemental analysis Calc./found		
						C	H	N
7a	F	H	$C_{17}H_{11}N_4O_2SF$	354	125-128	57.6 (57.62)	3.05 (3.10)	14.76 (15.81)
7b	F	Cl	$C_{17}H_{11}N_4O_2SFCl$	388	125-130	52.51 (52.57)	2.53 (2.57)	14.47 (14.43)
7c	F	CH_3	$C_{18}H_{13}N_4O_2SF$	368	180-185	58.71 (58.69)	3.51 (3.53)	15.14 (15.21)
7d	F	Br	$C_{17}H_{11}N_4O_2SFBr$	433	138-145	47.04 (47.11)	2.25 (2.30)	12.85 (12.93)

Table 2: Comparative data of microwave and conventional methods in the synthesized compounds 7(a-d)

S. No.	Sample code	R_1	R	Microwave methods		Conventional method	
				Time (min)	Yield (%)	Time (h)	Yield (%)
1	7a	H	F	4	82	4	64
2	7b	Cl	F	4.5	85	3.5	63
3	7c	CH_3	F	5.5	81	4	70
4	7d	Br	F	6	88	4	72

CONCLUSION

We have developed a simple and efficient MW assisted synthesis of Isatin containing oxadiazole moiety using a laboratory microwave oven. The use of microwave irradiation offers many advantages over conventional heating; it remarkably decreases reaction time, requires less solvent, thus facilitating reaction workups, and increases yields.

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