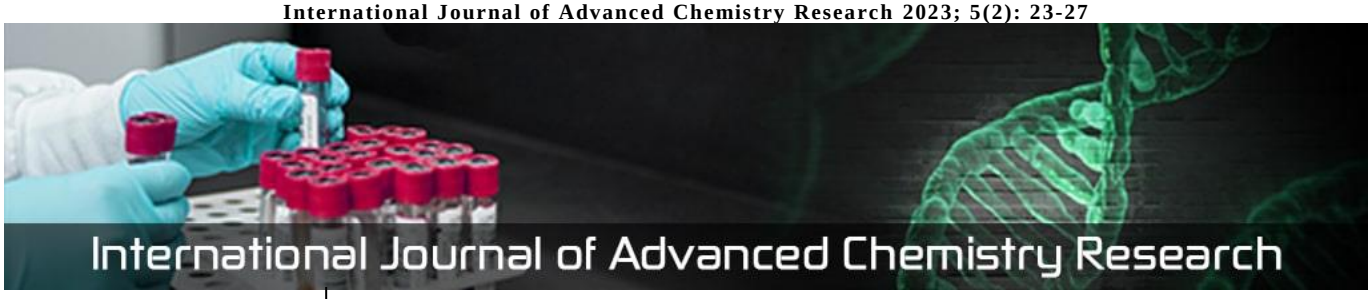

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Microwave assisted organic synthesis of nitrogen, oxygen and sulphur containing heterocycles

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Abstract
Microwave assisted organic synthesis is one among the handy methods included in Green Chemistry. The main objective of this work was to synthesize useful nitrogen, oxygen and sulphur containing heterocyclic compounds. Generally, such heterocyclic compounds are of prime interest when medicinal chemistry is concerned for their pronounced response towards various pharmacological tests. Apart from this, basically their synthetic route is of much importance. Use of solvent free reaction conditions enable eco-friendly synthesis of heterocycles. Likewise, coumarin, chalcone and amino thiadiazole derivatives were prepared using various starting materials to promote green synthesis. Knoevenagel, Schiff base formations etc. helped mechanistically to understand the way of product formations. Selected compounds were subjected for various characterization techniques like FT-IR, ^{1}H NMR, ^{13}C NMR and LCMS for strong conclusion.

Keywords: 3-acetyl coumarin, 3-cinnamoyl coumarin, 2-Amino 1, 3, 4-thiadiazole derivatives, 1, 3, 4-thiadiazol-2-yl-thiourea, 5-phenyl 1, 3, 4-thiadiazol-2-yl-thiourea, Microwave assisted organic synthesis

1. Introduction
Greener pathway of Organic synthesis is now an emerging field in the arena of synthetic organic chemistry research wherein Microwave heating is one of the major tools for combating the hazardous effects caused by toxic chemicals in the reactions [1]. The advantages of this technique have created its own impact in the eco-friendly approach towards healthy and safe environment. This can avoid the possibilities of unwanted side reactions, improved reproducibility and uniform heating throughout the course of reaction [2, 3]. The wide applications in the synthesis of heterocycles like benzimidazoles [4] and coumarins [5] via Pechmann condensation have been reported with efficient high yield. Coumarin-purine hybrids have been effectively synthesized using microwave source of radiation resulted in showing potent antioxidant activity [6]. Fused ring heterocycles containing Nitrogen and Oxygen have been effectively studied and reported encompassing green synthetic routes [7].
Oxadiazole derivatives were found to possess anti-tumor activity [8] while imidazo [1, 2-a] pyridine derivatives with antimicrobial activity [9] and served as PDE inhibitors [10] prepared via greener microwave synthetic protocols. The new synthetic strategies developed for 1, 3, 4 thiadiazole 2- amine derivatives by Kokovina *et al.* gave an idea of them exhibiting biological activity using one pot synthesis [11] whereas Mishra *et al.* developed via Microwave and Ultrasonic methods [12] proposed study on their biological evaluation. Chalcones derivatives synthesized under solvent free microwave conditions by Ajani and coworkers possessed antibacterial activity [13]. Imidazole based coumarin derivatives [14] synthesized under the influence of Microwave irradiation by Ashok *et al.*, manifested clear antimicrobial activity. Optimized Microwave assisted synthetic procedures have been inculcated for the synthesis of novel coumarin analogues and resulted in greater antifungal response with very low concentration [15]. Coumarin substituents have also been catalyzed by deep eutectic solvents like choline chloride/zinc chloride using Knoevenagel condensation [16].
Konradova *et al.*, carried out Witting reaction between salicylaldehyde and ylides which reported products in two cases; One at lesser exposure to microwave radiation obtained

coumarin and cinnamic ester derivatives while other gave only coumarin on prolonged reaction time [17]. Acetyl coumarins are found to be synthesized using amino acids like L- Proline as a green catalyst reacting with substituted salicylaldehyde and ethyl acetoacetate led multicomponent reaction with better yields [18].

The derivatives of coumarin having influential Acetylcholinesterase (AChE) enzyme inhibition serve as vital targets for the treatment of Alzheimer disease [19-21]. Other than the medicinal applications, class of cyanocoumarins [22] and iminocoumarins [23] is found to be fluorescent in nature with splendid optical properties. Apart from coumarins, bioactive 1, 3, 4-thiadiazole 2-amine derivatives, as the part of our interest, have been exclusively reported for exhibiting unique phenomena called dual fluorescence effect [24–27].

2. Materials and Methods

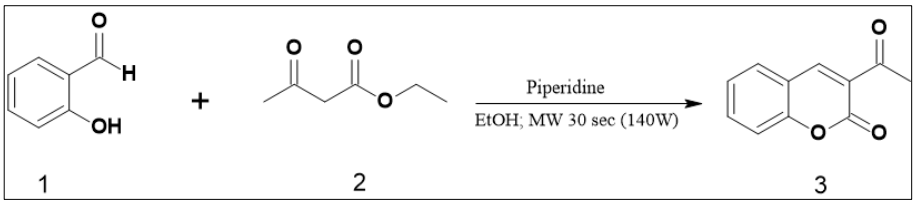
2.1 Materials: Salicylaldehyde, Ethyl acetoacetate, Piperidine, Ethanol, Benzaldehyde, Formic Acid, Benzoic acid, Thiosemicarbazide, Ammonium acetate, dil. HCl, dil. NaOH used were of analytical grade and employed without any further purification. All chemicals were procured from Loba Chemie Pvt. Ltd.

230 V-50 Hz; 1050 W Microwave instrument was used for irradiation.

Perkin Elmer Spectrum Two Universal ATR device with LiTaO3 detector was used to record FT-IR Spectrum. ^{1}H and ^{13}C NMR spectrum was recorded using 400 MHz JNM-ECZ400S/L1 Jeol NMR Spectrometer and Bruker Avance III HD NMR Spectrometer. Chloroform-d and DMSO-d_6 solvent containing 99.8 atom % D and 0.03% (v/v) TMS as reference standard were procured from Sigma Aldrich. LCMS (ESI) 1525u Binary HPLC and Xevo G2-XS QTof models employed for characterization were developed by Waters USA.

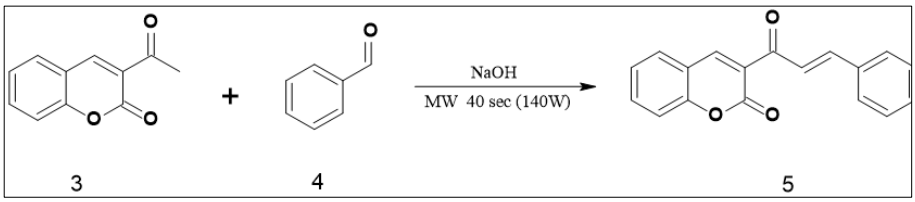
2.2 Synthesis of 3-acetyl coumarin (3)

3-acetyl coumarin (3) was synthesized via Knoevenagel condensation reaction by Valizadeh *et al.* [28] with certain modifications in the reaction conditions. 9 mmol Salicylaldehyde (1) and 12 mmol Ethyl acetoacetate (2) were mixed with few drops of Piperidine in the presence of minimum quantity of E thanol. The reaction mixture was then kept for Microwave irradiation at 140W and the reaction was carried out for 30 sec as described in the Scheme 1. The crude was recrystallized using Ethanol.



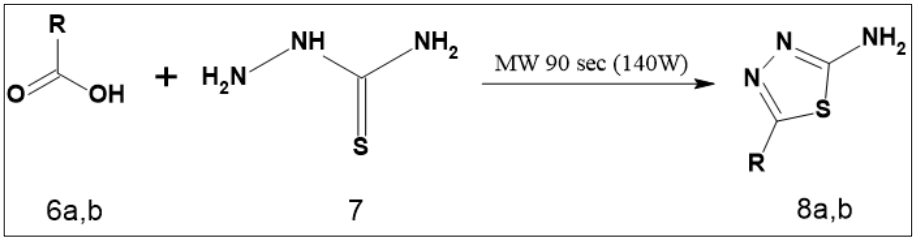
Scheme 1: Synthesis of 3-acetyl coumarin (3)

2.3 Synthesis of 3-cinnamoyl coumarin (5): 1 mmol 3-acetyl coumarin (3) obtained above was reacted with 1 mmol Benzaldehyde (4) in the presence of dil. NaOH to give 3-cinnamoyl coumarin (5). The reaction was carried out at 140W MW irradiation for 40 sec as shown in the Scheme 2. The product was recrystallized with Ethanol.



Scheme 2: Synthesis of 3-cinnamoyl coumarin (5)

2.4 Synthesis of 2-Amino 1, 3, 4-thiadiazole derivatives (8a, b): 2-Amino 1, 3, 4-thiadiazole derivatives was prepared in contrast to Zheng Li *et al.*, [29] without polymer support. 1 mmol of an acid (6a, b) is treated with 1 mmol thiosemicarbazide (7) and kept for MW irradiation at 140 W for 90 sec to give 2-Amino 1, 3, 4-thiadiazole derivatives (8a, b) as depicted in the Scheme 3. The products were recrystallized using Ethanol.

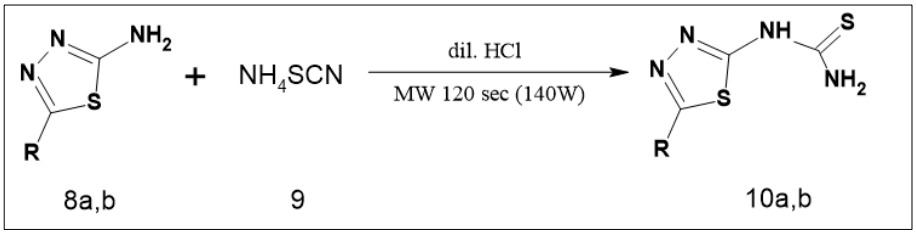


Component No.	R
a	H
b	C_6H_5

Scheme 3: Synthesis of 2-amino 1, 3, 4-thiadiazole derivatives (8)

2.5 Synthesis of 5-substituted 1, 3, 4-Thiadiazol-2-yl-thiourea (10a, b)

1 mmol 5-substituted 2-Amino 1, 3, 4 thiazole (8) obtained in Scheme 3 is mixed with 1 mmol ammonium thiocyanate (9) in the presence of dil. HCl. The reaction vessel is MW irradiated at 140W for 120 sec to give 5-substituted 1, 3, 4-Thiadiazol-2-yl-thiourea (10a, b). The obtained products were recrystallized using Ethanol.



Component No.	R
a	H
b	C_6H_5

Scheme 4: Synthesis of 5-substituted 1, 3, 4-Thiadiazol-2-yl-thiourea (10a, b)

3. Results and Discussion: The following Table 1. Shows the overall results of the products synthesized in the above reaction schemes.

Table 1: Overall Reaction Results

Sl. No.	Component	Product	Reaction Time under MW (sec)	Melting Point (°C)	Yield (%)
1	3	3-acetyl coumarin	30	114-116	88
2	5	3-cinnamoyl coumarin	40	181-183	62
3	8a	2-amino 1, 3, 4-thiadiazole	90	192-194	85
4	8b	2-amino 5-phenyl 1, 3, 4-thiadiazole	90	219-222	80
5	10a	1, 3, 4-thiadiazol-2-yl-thiourea	120	192-195	73
6	10b	5-phenyl 1, 3, 4-thiadiazol-2-yl-thiourea	120	206-208	61

Spectral interpretation of selected products is given below

3-acetyl coumarin (3): Yellow-orange solid. Yield: 88% FT-IR (ν cm^{-1}): 1734 (lactone), 1678 (C=O), 1549 (aromatic C=C), 1203 (C-O), 760 (monosubstituted ring). ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.73 (3H, s), 7.32 – 7.39 (2H, 7.34 (ddd, J = 7.6, 6.8, 0.8 Hz), 7.37 (ddd, J = 9.2, 5.6, 1.2 Hz)) 7.63 – 7.67 (2H, 7.64 (ddd, J = 5.6, 4.0, 1.6), 7.66 (ddd, J = 6.0, 3.2, 1.6)), 8.50 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$): δ_C 30.53 (CH_3, s), 116.69 (1C, s), 118.26 (1C, s), 124.55 (1C, s), 124.96 (1C, s), 130.21 (1C, s), 134.37 (1C, s), 147.44 (1C, s), 155.33 (1C, s), 159.22 (C=O, lactone, s), 195.48 (C=O, ketone, s). MS (LCMS; ESI): m/z calcd for $C_{11}H_8O_3$ 188.05, found 189.06 [M+H].

1, 3, 4-Thiadiazol-2-yl-thiourea (10a): Faded white solid. Yield: 73%. FT-IR (ν cm^{-1}): 3370, 3302 (primary N-H stretch), 3049 (aromatic C-H), 1556 (C=N thiadiazole), 1476 (-NH bending), 1201 (C=S). ^1H NMR (400 MHz, DMSO-d_6): δ_H 3.4038 (1H, s, NH disappeared on D_2O exchange), 8.267 (1H, s), 13.353 (2H, s, NH_2 disappeared on D_2O exchange). ^{13}C NMR (400 MHz, DMSO-d_6): δ_C 140.93 (1C, C-H, s), 160.95 (1C, s) 182.12 (1C, C=S, s). MS (LCMS; ESI): *m/z* calcd for $C_3H_4N_4S_2$ 160, found 160 [M^+].

4. Conclusion

After the successful reactions upon microwave irradiation, the selected products were satisfactorily proved through the characterization tools being used for the analysis. Products obtained were of good yield with the application of uniform power. The time duration is comparatively less when compared with the literature study. Various heterocycles synthesized could be subjected for biological activities as their synthesis is convenient and follow eco-friendly approach.

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