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MOPS Buffer Catalyzed Synthesis of Indolyl Pyrimidine 2,4,6 Triones Under Ultrasound Irradiation

Suchita S. Gadekar[1], Suryakant B. Sapkal[2] and Balaji R. Madje[1*]

[1] *Department of Chemistry Vasantrao Naik College, Aurangabad,, INDIA*
[2] *Department of Chemistry, Jawaharlal Nehru Engineering College, Aurangabad, INDIA*

[*] *Correspondence: E-mail: drmadjebr@rediffmail.com*

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ABSTRACT: Multicomponent one pot synthesis of Indolyl pyrimidine 2,4,6 trione derivatives has been described by the condensation of aromatic aldehydes, indole and barbituric acid in the presence of 3-morpholinopropane-1-sulfonic acid (MOPS) in acetone under ultrasound irradiation condition. Besides biochemical application, MOPS as an organocatalyst has been used in multicomponent organic transformation and succeeded along with virtues of green chemistry practices. Reaction is mechanized by zwitterionic interactions between organocatalyst and reactants to form targeted molecules.

Keywords: Organocatalyst; pyrimidine 2,4,6 trione; Ultrasound irradiation; Acetone; MOPS.

INTRODUCTION: Generally, because of the present environmental consequences scientists have to pay attention towards awareness about ecological sustainability aspects while working in the field of chemistry. One has to put this scenario in the eyeshot although experiments have been performed inside the four walls of the laboratory [1-3]. Keeping little focus on environmental degradability we have chosen MOPS as an organocatalyst to catalyze the proposed reaction. Literature investigation shows that MOPS plays crucial role in biochemical protocols to maintain near neutral pH as buffer media [4-8]. Catalytic application of MOPS we have done for multicomponent Hantzsch condensation reaction under microwave irradiation [9], for the synthesis of 3-amino alkylated indoles by conventional route [10], for the synthesis of benzimidazoles under ultrasonic irradiation in ethanol [11].

As we know in many natural products a pharmacodynamic nucleus of indole exhibited characteristic activities, therefore indole moiety gaining considerable importance [12]. In particular, 3-C-functionalized indoles are highly applicable for the synthesis of various indole impurities in support of active pharmaceutical ingredients (APIs) such as antibacterial [13], anti-inflammatory and analgesic agent [14], anticonvulsant [15], cardiovascular [16], HIV-1 inhibitor [17], antimigraine and to cure breast cancer [18]. Because of such wide spread medicinal applications of indolyl nucleus the chemists and pharmacists are consistently engaged in the development of competent methodologies for proposed nucleus by applying several conditions such as β-cyclodextrin [19], Silver triflate (AgOTf), Ionic liquids [20], Indiun/HCl [21], PMA-SiO2/CH3CN [22]. Moreover, 3-substituted indoles via reactive intermediates alkylidene indoleamine have also been attempted through state of the art conditions with considerable yields of the product in hand [23]. With this literature one of our attempts will add another noteworthy report in the field of organocatalysis.

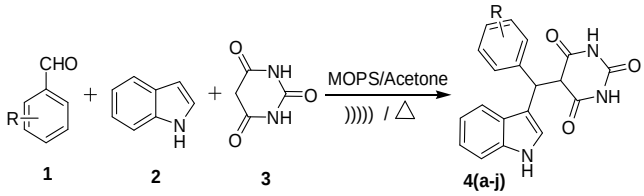
MATERIALS AND METHODS: Experimental Procedure for the preparation of Indolyl pyrimidine 2,4,6 trione derivatives.

In the hard glass test tube Bendaldehyde (0.221 g, 0.002 mol) and Barbituric acid (0.256 g, 0.002 mol) and MOPS (120 mg) in 25 mL acetone was subjected for ultrasound irradiation for 30-35 minutes. To this solution, Indole (0.290g, 0.002 mol) was added portion wise at same reaction vessel. The progress of the reaction was monitored after interval of each half hour by TLC. The reaction is completed after specified period of time. After completion the reaction mixture was extracted in ethyl acetate and water (60:40) as a solvent system. Organic layer was once washed by brine solution degassed on rotary evaporator. Thus obtained solid was dried and purified by recrystalliza-

tion in ethanol to yield a pure product. Similar procedure was applied for the synthesis of other derivatives. All compounds were characterized by spectroscopic analysis.

Spectral analysis of representative compound
Compound 4a (Table 2): 5-((1H-indol-3-yl)(phenyl)methyl)pyrimidine-2,4,6(1H,3H,5H)-trione: M. P. 168-170 °C; 1H NMR (CDCl3) δ ppm; of 9.95 (S, 2H, N-H), 10.15 (S, 1H, N-H), 6.98-7.70 (m, 9H, Ar-H), 6.65 (S, 1H, C-H), 4.45 (s, 1H, tC-H), 4.10 (S, 1H, C-H); MS m/z = 333.4; IR (KBr); v cm-1 3065 (N-H Str.), 1721 (C=O Str.), 1461 (C=C Str.).

RESULTS AND DISCUSSION: To take a broad view of an experimental procedure we have optimized the reaction conditions by several methods out of which few successful reports have been demonstrated here with this discussion. Herein, at first attempt we tried the reaction of equimolar quantity of benzaldehyde, Indole and barbituric acid in aqueous solvents such as alcohol, methyl alcohol, isopropyl alcohol and other organic solvents like ethyl acetate, dichloromethane (DCM), acetone and carbon tetrachloride etc separately under ultrasound irradiation for model reaction but there was not considerable conversion of product we observed except in acetone. Further we turned our focus to perform this reaction for the synthesis Indolyl pyrimidine 2,4,6 trione derivatives (4) from aromatic aldehydes (1), indole (2) and barbituric acid (3) in the presence of MOPS in acetone under ultrasound irradiation we obtained good to better yield of the product (Scheme 1).



Scheme 1: MOPS catalyzed synthesis of pyrimidine 2,4,6 trione derivatives.

Then after, we decided to optimize the reaction with respect to catalyst concentration, reaction time and percent yield. After several experimental attempts we came to know that reaction proceed to completion by proper sequential addition of reactant and catalyst. Accordingly, benzaldehyde, barbituric acid and MOPS were irradiated by ultrasound energy for 30-35 minutes solid suspension is observed in the reaction vessel, which indicates formation of 5-benzylidenepyrimidine-2,4,6(1H,3H,5H)-trione as an intermediate followed by Knoevenagel condensation. Later on, indole is added in that reaction vessel portion wise under same reaction condition that leads to formation of targeted product by condensation manner within next couple of hours. During this protocol up to the completion of reaction because of continuous bombardment of ultrasound waves warming up of reaction vessel we observed. To establish the optimized protocol we examined stoichiometric study of catalyst concentration as shown in Table 1.

Table 1: Effect of catalyst concentration on the model reaction.

Sr. No	Catalyst (mg)	Time (Hrs)	Yield (%)
1	20	3.5	Only Intermediate
2	40	3.5	25
3	60	3.5	40
4	80	3.5	55
5	100	3.5	68
6	120	3.5	80
7	140	3.5	81

It has been experimentally reported after the successful screening of suitable solvent and stoichiometry determination of catalyst for the synthesis of Indolyl pyrimidine 2,4,6 trione by the condensation of benzaldehyde, Indole and barbituric acid in the presence of MOPS as a organocatalyst in acetone as a reaction medium under ultrasound irradiation. To prove the catalytic efficacy of MOPS we have implemented the same reaction conditions to the different aromatic aldehydes (Table 2).

Table 2: MOPS catalyzed synthesis of Indolyl pyrimidine 2,4,6 triones under ultrasonic technique.

Entry	R/Aldehyde	Time (Hrs)	Yield (%)
4a	H	3.5	80
4b	2-Cl	3.5	74
4c	4-Cl	3.5	71
4d	4-CH_3	3.5	76
4e	4-OH, 3-OCH_3	3.5	70
4f	2-CH_3	3.5	72
4g	3-NO_2	3.5	69
4h	4-$N(CH_3)_2$	3.5	79
4i	Acetaldehyde	3.5	64
4j	Furfuraldehyde	3.5	69

While performing experiments for derivatization it has been noted that aromatic aldehydes with different substitutions at different positions have been reacted smoothly with appreciable product yield. In conjunction with an output of the reaction in our hand heterocyclic reactants also give compatible yield of the product. Whereas, aliphatic aldehyde resulted comparatively less yield and took more time for transformation. The formation of products was confirmed by their physical constant and structures were elucidated by spectroscopic analysis.

CONCLUSION: Catalytic role of buffering agent MOPS would be the futuristic approach toward synthesis of Indolyl pyrimidine 2,4,6 trione derivatives. This strategy will be the user friendly synthetic protocol. The structural benefit of MOPS has been recognized by this high yielding methodology and may be applicable in industrial laboratories. This synthetic strategy also covers the advantages of one-pot multicomponent transformations which will make this research work practical and economically feasible and provides foresight for green chemistry aspects.

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