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Research Article

AN EFFICIENT SOLVENT FREEONE-POT SYNTHESIS OF NAPHTHO PYRANOPYRIMIDINES UNDER MICROWAVE IRRADIATION CATALYZED BY SULFATED TIN OXIDE

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ABSTRACT
A mild and rapid protocol has been developed for the synthesis of naphthopyranopyrimidine derivatives in short reaction time to afford the products in excellent yield (72-96%). These derivatives were prepared by a microwave-assisted one-pot three-component coupling reaction between aromatic aldehydes, β-naphthol, and 1, 3-dimethylbarbituric acid under solvent-free in presence of sulfated tin oxide. Operational simplicity, clean reaction, high yield, easy work up and shortened reaction times are the significant advantages of the present protocol.

Keywords: *Multi-Component Reaction, Naphthopyranopyrimidine, Sulfated Tin Oxide, Microwave Irradiation, Solvent Free*

INTRODUCTION
The development of cleaner technologies for green chemistry has gained importance. Medium of large excess solvents required for chemical reaction causes ecological and economic concerns (Verma, 2001). The utilization of green chemistry techniques is dramatically reducing chemical waste and reaction times as it has recently been proven in several organic syntheses and chemical transformations. To illustrate these advantages in synthesis of bioactive heterocycles, using efficient and less hazardous energy sources such as microwave (MW) energy is highly recommended.
In the last decade microwave irradiation technique has been utilized as a powerful tool for various organic transformations (Loupy 2006; Kappe *et al.*, 2011; Kappe 2008). The main benefits of the use of microwave irradiation include improved reaction yields, selectivity, cleaner reactions, shortened reaction times, easy work-ups and/or solvent free reaction conditions.
Development of novel synthetic methodologies to facilitate the preparation of libraries of compounds is an important for modern medicinal and combinatorial chemistry (Thompson *et al.*, 2000; Nefzi *et al.*, 1997). Multi component reactions (MCRs) are highly efficient processes for the synthesis of fine-chemicals with value added, like pharmaceutical ingredients or ligands for catalysis. Multi-component reactions (MCRs), because of their productivity, simple procedures, facile execution, and atom economy are one of the best tools in the synthesis of diverse and complex compounds as well as small and drug like heterocycles. These one-pot reactions introduce the most efficient method to the molecular diversity (Sapi *et al.*, 2004; Hazeri *et al.*, 2007).
Naphthopyranopyrimidines and its derivatives plays essential and promising role in medicinal and pharmaceutical chemistry (Pan˜eda *et al.*, 2009). They display interesting biological activities such as antibacterial, antifungal and anticonvulsant properties (Radi *et al.*, 2009; Bedair *et al.*, 2009). They are also known to possess antiviral (Jamison *et al.*, 2009), antibacterial (El-Brashy *et al.*, 2004), and anti-inflammatory (Chibale *et al.*, 2003) activities and etc.
Lately, several multicomponent strategies have been reported for the synthesis of naphthopyranopyrimidines utilizing different types of acid catalysts (Laitinen *et al.*, 2004; Mashraqui *et al.*, 2004; Li *et al.*, 2008; Gao *et al.*, 2009; Nandi *et al.*, 2009; Kumar *et al.*, 2012). However, these reported methods show varying degrees of successes as well as limitations. Therefore, thereis a need to develop more general, efficient, economically viable and eco-compatible protocol for the synthesis of naphthopyranopyrimidines scaffolds of biological importance.

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Recently, sulfated tin oxide (STO) has been the focus of intensive research due to their high efficiency in organic transformations (Narayana *et al.,* 2012; Magar *et al.,* 2013). It has the strongest acidity on the surface. It is a mesoporous material containing both Bronsted and Lewis acid sites. STO has some advantages such as it is quite stable to moisture, air and heat, is easily separated, less corrosive to reactors and containers, and friendlier to the environment. Therefore, we decided to investigate a green and efficient protocol for the synthesis of naphthopyranopyrimidines and its derivatives, catalyzed by sulfated tin oxide under microwave method using solvent free conditions.

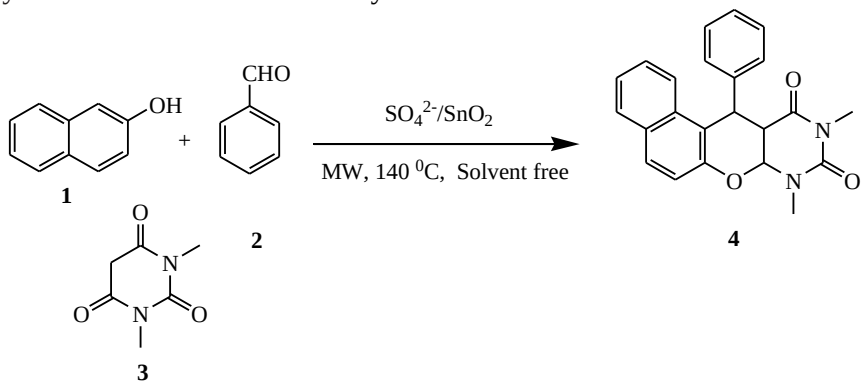
MATERIALS AND METHODS

All essential chemicals and reagents were purchased from Merck, Sigma Aldrich and Fluka of high purity grade and used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu JASCO FTIR-460 plus spectrophotometer using KBr pellet. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker DRX-500 Avance spectrometers. Chemical shifts (δ) are reported in parts per million and TMS as an internal reference. GC-Mass analysis was performed on a GC-Mass (Varian Saturn) model: 2100T. For MWI a Milestone MicroSYNTH microwave oven was used. All the products are known compounds, which were identified by comparison of their mp, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data with those of authentic samples.

Synthesis of Sulfated tin Oxide (SO_4^{2-}/SnO_2) Catalyst

In a typical method, 100 g of $SnCl_2{\cdot}2H_2O$ (99% purity) was dissolved in 500 ml of distilled water and few drops of concentrated HNO_3 was added and kept under vigorous stirring at 80^0C, later it was cool to 30°C and an aqueous solution of NH_4OH (25 vol%) was added with continuous stirring so that the solution reaches to pH 8. The pale yellow gel type precipitate obtained was filtered and suspended in a 4% CH_3COONH_4 solution for 30 min. Then, the Sn $(OH)_2{\cdot}xH_2O$ gels was impregnated with 1 M H_2SO_4 solution to obtain sulfated tin oxide. After, this gel was dried at 110 °C for 24 h and calcined at 500-600 °C for 3 h.

In our continued efforts towards the development of new catalysts and methods in organic synthesis. Herein, we report a simple and efficient method for the preparation of naphthopyranopyrimidines and its derivatives using a three component cyclocondensation reaction between 2-napthol (**1**), benzaldehyde (**2**) and 1,3-dimethylbarbutric acid (**3**) as a model reaction under solvent-free conditions in presence of sulfated tin oxide as an efficient and versatile catalyst by microwave irradiation technique to obtain the product (**4**) in excellent yield (**Scheme 1**). To the best, we feel that our efforts are first for the synthesis of naphthopyranopyrimidines and its derivatives by this method.



Scheme 1

RESULTS AND DISCUSSION

Initially, we selected sulfated tin oxideto evaluate the catalytic efficiency for the current multicomponent reaction (MCR). The model reaction was carried out between 2-napthol (1), benzaldehyde (2) and 1,3-dimethylbarbutric acid (3) in presence of sulfated tin oxide under microwave irradiation to obtain the

desired product (4). Further, we evaluated reaction in various solvents and under solvent-free conditions and results are summarized in Table 1. After much experimentation for optimization of solvent, it was found that use of a less-polar solvent like xylene and toluene showed no reaction (Entries 1 and 4 Table 1). Polar solvents like ethanol and acetonitrile afforded corresponding naphthopyranopyrimidines in low yield (Entries 2 and 3 Table 1). It was found under solvent-free condition, the sulfated tin oxide catalyst gave excellent conversion to naphthopyranopyrimidines with 96% yield (Entry 5, Table 1).

Table 1: Screening of the solvents for synthesis of naphthopyranopyrimidines

yrtnE	tnevloS	Time (min)	Yield (%)
1	enelyX	20	N. R
2	Ethanol	18	35
3	elitinotecA	18	30
4	enuloT	20	N. R
5	eerf tnevloS	10	96

To find the optimum reaction temperature, the reaction was carried out in presence of catalyst under solvent-free condition and the results are presented in Table 2. Only 15% yield of naphthopyranopyrimidines was obtained when the reaction was conducted at 100^0C, further rise in temperature to 120^0C the desired product yield was improved to 50% (Entries 2 and 3 Table 2). So we decided to increase the temperature to 140^0C and the corresponding product was obtained in excellent yield 96% (Entry 4 Table 2). Further, increase in temperature 160^0C (Entry 5 Table 2), leads to decomposition of the product. Therefore, the optimized temperature was proved to be 140 ^{0}C.

Table 2: Effect of the reaction temperature for the synthesis of naphthopyranopyrimidines catalyzed by SO_4^{2-}/SnO_2

yrtnE	Temperature (^{0}C)	Yield (%)
1	Room temperature	N. R
2	100	15
3	120	50
4	140	96
5	160	60

To optimize the catalyst loading, the model reaction was investigated with different concentration such as 5 mol%, 10mol%, 20mol%, 30mol%, of sulfated tin oxide at 140 °C without solvent under microwave irradiation. The results are summarized in Table 3. A 10 mol% of sulfated tin oxide was adequate to afford the desired product in good yield. Further increase in loading of catalyst to 20 mol% and 30 mol% respectively, the desired product was obtained with decrease in yield (Entries 3 and 4 Table 3). When the similar reaction was carried out with 5 mol% the reaction took longer time and desired product yield was observed low (Entry 1 Table 3). Therefore, 10mol% loading of sulfated tin oxide was found to be sufficient to promote the reaction and increased amounts of the catalyst did not lead to any significant changes in the product yield.

Table 3: Effect of the catalyst concentration for the synthesis of naphthopyranopyrimidines

yrtnE	Catalyst (mol %)	Yield (%)
1	5	50
2	10	96
3	20	60
4	30	55

With optimized reaction parameters in hand. We then evaluated the scope and generality of the three component cyclocondensation reaction of 2-naphthol, 1,3-dimethylbarbutic acid using a variety of substituted aldehydes and the corresponding naphthopyranopyrimidines were obtained in 72-96% yields.

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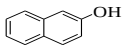
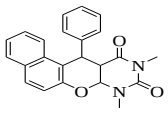
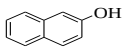
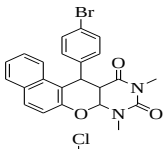
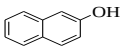
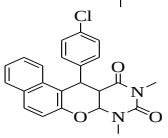
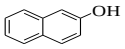
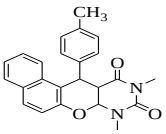
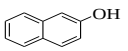
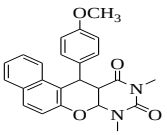
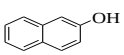
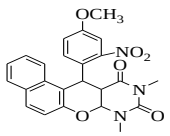
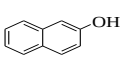
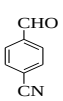
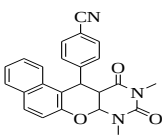
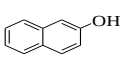
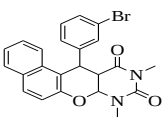
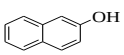
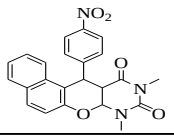
The results are summarized in Table 4. The results show benzaldehyde and aromatic aldehydes with electron withdrawing groups -Cl, -NO_2, -Br and –CN (Entries 1, 2, 3, 6, 7, 8 and 9 Table 4) and electron donating groups -OCH_3 and -CH_3 (Entries 4 and 5 Table 4) have all provided high yields of the products.

General Procedure for the Synthesis Naphthopyranopyrimidines

A mixture of aldehyde (1.0mmol), 2-naphthol (1.0 mmol), 1,3-dimethylbarbituric acid (1.2 mmol) and sulfated tin oxide (10mol%) were placed in a 10 ml microwave quartz flask under solvent free condition. The mixture was stirred at 140 ^{0}C for the appropriate time as mentioned in Table 4. After completion of the reaction as monitored by TLC using ethyl acetate and petroleum ether (30:70) as eluent, the mixture was allowed to cool to room temperature and quenched with water and extracted with ethyl acetate (3 x 15 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, concentrated under vacco and purified by column chromatography (ethyl acetate: petroleum ether) to afford the pure products. These products were fully characterized by spectral analysis.

Table 4: Synthesis of naphthopyranopyrimidines catalyzed by SO_4^{2-}/SnO_2 under microwave irradiation

S. No.	2-Naphthol	Aldehyde	1, 3-Dimethylbarbutric Acid	Product	Time (min)	Yield (%)
1					10	96
2					12	88
3					12	92
4					10	90
5					10	92
6					14	88
7					14	72
8					12	86
9					13	90

Conclusion

In summary, we have developed a simple, one-pot three component facile synthesis of naphthopyranopyrimidines and its derivatives catalyzed by sulfated tin oxide. Simple work up procedure, general applicability, microwave irradiation and solvent free conditions makes this protocol eco-friendly and distinctly superior to many other methods reported earlier.

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