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Research Article

“$Mg(HSO_4).SiO_2$ Promoted Amidation Of Carboxylic Acid Under Microwave Irradiation”

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ABSTRACT

A new method for the direct synthesis of amides from carboxylic acids under microwave irradiation is described using magnesium hydrogen sulfate supported on silica as a low-cost and readily available catalyst. This methodology is particularly useful for the direct synthesis of secondary amides from carboxylic acid. Synthesis of amides using this technique is an economical, high yielding methodology with simple isolation process. This methodology tolerated most of the functional group and can be applicable at late stage amidation.

KEYWORDS: $Mg(HSO_4).SiO_2$, Amidation, Microwave irradiation.

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INTRODUCTION

Recently, silica supported catalysts have attracted the special attention of chemists [1-3] due to their eco-friendly nature, simple handling, recyclability, and high reactivity.

Similarly the significance of the amide functional group emerges out from different regions of chemistry such as pharmaceuticals, agrochemicals, academic research and medicinal chemistries due to their excellent biological activities. Because of this, it is very necessary to develop new methodologies for the proficient synthesis of amides. Conventional methods has requirement of conversion of the acid into the corresponding acid chloride which has limitations of moisture sensitivity as well as handling challenges.[1-6] Although amidation using catalysts or reagents resulted mild reaction conditions and good yields, but these reagents are required on stoichiometric amounts. Use of excess/ stoichiometric amount of reagents generates equivalent waste which is again a challenging task. New methodologies described for the synthesis of amides [5,6] from esters,[7-17] aldehydes,[18-27] alcohols,[28-33] nitriles,[34-45] and oximes.[46-56] were reported. The catalysts are used for the synthesis of amides such as rhodium, ruthenium, iridium, and palladium, copper, iron, titanium, hafnium, metal triflates, metal sulfates and zirconium have been recently reported.[57-60] Amidation reactions for the synthesis of secondary and tertiary amides [61-72] also reported.

A lot of work carried out in this area in last few decades and until now, several methods have been reported still a suitable method for solving this problem is not well established yet. Most of these strategies suffer from the drawback of green synthesis of amides, and have been associated with several shortcomings such as use of corrosive protic unrecyclable catalyst, long-reaction times and low product yields, difficult work-up procedure, limitations for sensitive functional groups and the use of organic solvents. Therefore, to come up with a new, inexpensive and eco-friendly method for the amidation is an important topic, and one which is an active ongoing research area. There is a scope for the further improvement towards green reaction conditions with improved yields. To the best of our knowledge, there is no report on amidation using magnesium hydrogen sulfate supported on silica under microwave irradiation.

We wish to report here a green and simple method for the amidation of carboxylic acid using catalytic quantity of silica supported magnesium hydrogen sulfate under microwave irradiation in excellent yields summarized in **Scheme 1**.

RESULTS AND DISCUSSION

On the basis of previously reported methodologies and current development reports, in the present study, we have described the use of cheaper and commercially available $Mg(HSO_4).SiO_2$ as a catalyst for the preparation of secondary amides **3(a-k)** of 2-(4-(benzo[d]thiazol-5-ylsulfonyl)piperazin-1-yl)acetic acid (**1**) and variety of anilines **2(a-k)** under microwave irradiation at 120 ^{0}C in high yields. Initially, 2-(4-(benzo[d]thiazol-5-ylsulfonyl)piperazin-1-yl)acetic acid, 3,5-dibromo aniline is selected as reference substrates, for optimization of reaction condition. Different time, temperature, solvent and catalysts were screened **[Table-1].** As a result of optimization studies, it was observed that less yield is obtained in absence of catalyst [Entry-1, Table-1]. A large number of catalysts were screened [Entry 2-13, Table-1], out of which $Mg(HSO_4).SiO_2$ [Entry 10, Table-1] is observed as a best catalyst and provided highest yield among all the catalysts. We have performed reaction at 100, 120 and 130 ºC and it is seemed that at 100 ºC yields are obtained lower side may be due to incomplete reaction while reaction at 130 oC did not improve the conversion. We have also screened time and solvent of the reaction and it is observed that 100 min., is the optimum time required for the reaction and longer reaction times did not show a substantial increase in the conversion while Xylene is the best solvent for reaction.

To extend the scope of synthesis of this methodology, a range of substituted anilines 2(b-k) were also screened using optimized reaction conditions summarized in **Table-2**.

Scheme-1: *Synthesis of amides 3(a-k)*

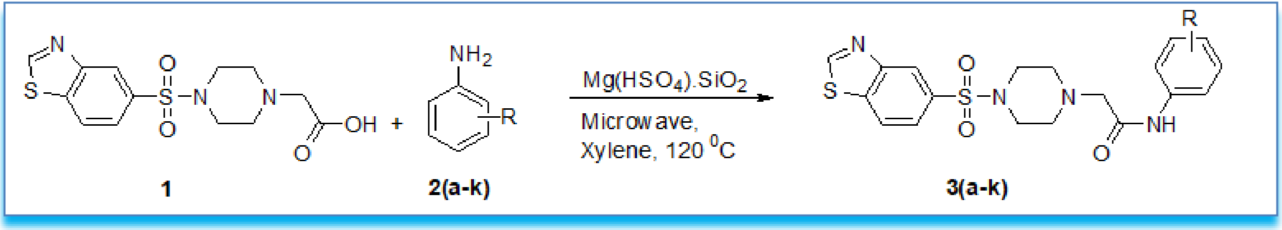
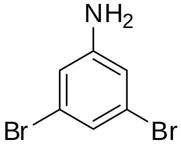
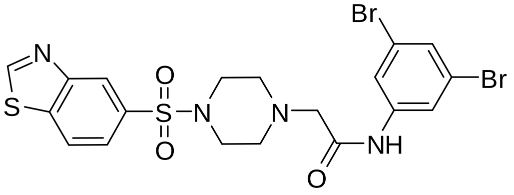
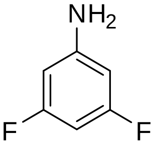
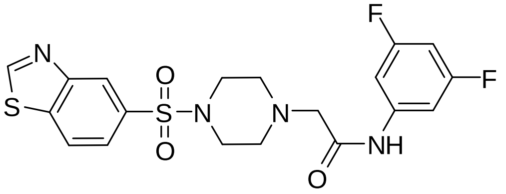
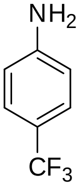
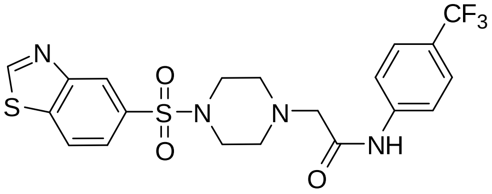
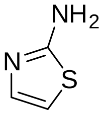
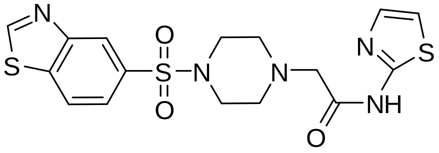
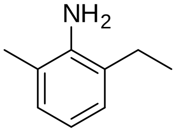
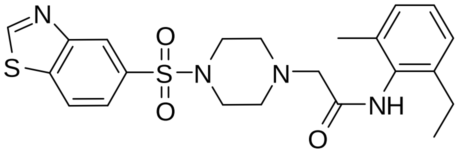
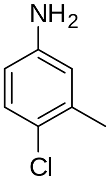
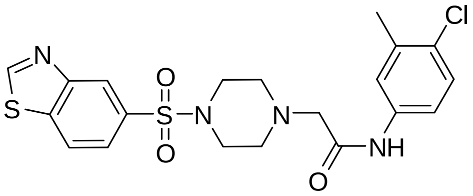
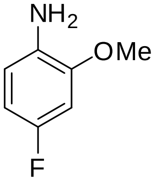
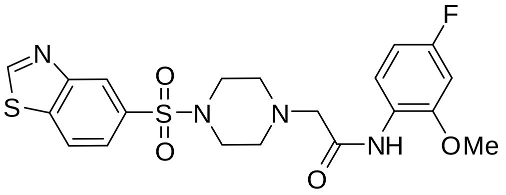


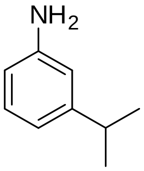
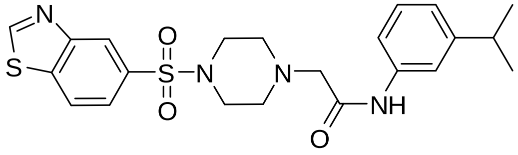
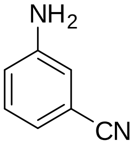
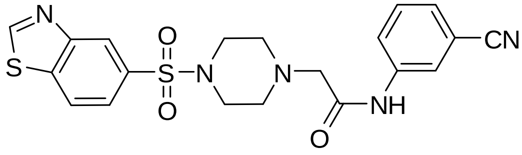
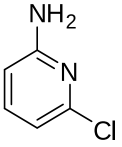
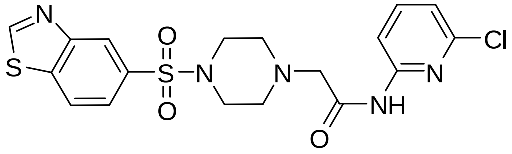
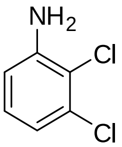
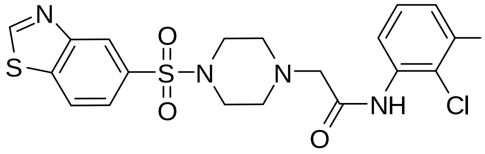
Table-1: ***Optimization of reaction condition***.

No.	Reagent	Temperature (ºC)	Reaction time (Min.)	Solvent	Yield (%)
1.	-	120	100	Xylene	23
2.	$ZnCl_2$	120	100	Xylene	73
3.	$Sc(OTf)_3$	120	100	Xylene	86
4.	$Mg(OAc)_2{\cdot}4H_2O$	120	100	Xylene	83
5.	$Zn(OAc)_2{\cdot}2H_2O$	120	100	Xylene	82
6.	$Mg(NO_3)_2{\cdot}6H_2O$	120	100	Xylene	88
7.	$Mg(OTf)_2$	120	100	Xylene	88
8.	$MgCl_2{\cdot}6H_2O$	120	100	Xylene	81
9.	$MgSO_4$	120	100	Xylene	93
10.	**$Mg(HSO_4).SiO_2$**	**120**	**100**	**Xylene**	**96**
11.	pTSA	120	100	Xylene	77
12.	Imidazole	120	100	Xylene	90
13.	DMAP	120	100	Xylene	88
14.	$Mg(HSO_4).SiO_2$	120	80	Xylene	85
15.	$Mg(HSO_4).SiO_2$	120	120	Xylene	96
16.	$Mg(HSO_4).SiO_2$	100	100	Xylene	75
17.	$Mg(HSO_4).SiO_2$	130	100	Xylene	91
18.	$Mg(HSO_4).SiO_2$	120	100	Toluene	83
19.	$Mg(HSO_4).SiO_2$	120	100	Chlorobenzene	69

***Optimized reaction condition:** *carboxylic acid (1.0 eq), Aniline (1.06 eq), Mg(HSO4).SiO2 (10 mol %), xylene (3 vol), 120 ºC, 24 h. b Isolated yields,*

Table-2: Substrate scope for the formation of secondary amides 3(a-k) from carboxylic acids using substituted anilines 2(a-k) and $Mg(HSO_4).SiO_2$

Anilines 2(a-k)	**Compounds 3(a-k)**	**Isolated Yields (%)**
	 **3a**	96
	 **3b**	93
	 **3c**	82
	 **3d**	83
	 **3e**	91
	 **3f**	88
	 **3g**	89

	 **3h**	92
	 **3i**	89
	 **3j**	83
	 **3k**	94

Biological Activity:
Tables 3 show the results of disc-diffusion assays used to assess the antibacterial activity of the produced compounds **3(a-k**) against *S. aureus* MCC 2010, *B. subtilis* MCC 2010, *E. coli* MCC 2412, *Pseudomonas aeruginosa* MCC 2080, *Candida albicans* MCC 1439, and *Saccharomyces cerevisiae*. These compounds' antibacterial effects were measured against those of streptomycin and fluconazole (**Tables 3**). *E. coli* MCC 2412 (14 mm), *Pseudomonas aeruginosa* MCC 2080 (10 mm), and *S. aureus* MCC 2010 (9 mm). Most of the compounds were observed active against these pathogens.

Table3: Antibacterial studies of 3(a-k) compounds

Compound	**Antibacterial Activity (zone of inhibition)**			
	S. aureus	***B. subtilis***	***E. coli***	***P. aeruginosa***
3a	7	11	8	10
3b	10	10	9	7
3c	11	6	6	11
3d	9	10	0	14
3e	0	6	6	0
3f	8	10	7	0
3g	9	9	10	9
3h	7	8	8	6
3i	12	12	0	8
3j	8	11	5	7
3k	10	9	1	9
Streptomycin	9	8	6	18

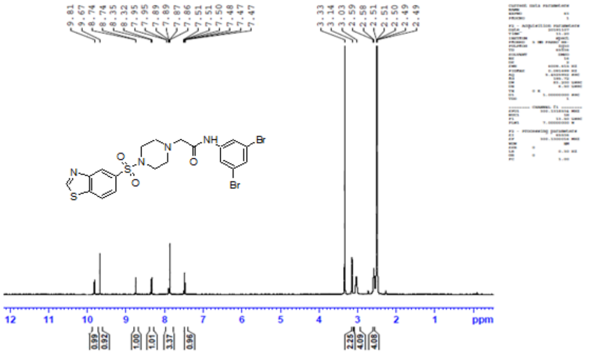
1. EXPERIMENTAL SECTION

Reagents were used straight out of the bottle, received from commercial suppliers without purification. TLC plates used to check the reaction's progress under a UV lamp. Melting points were measured with the use of the Lab-India MR. Vis+ device. Using TMS as the internal standard, the Bruker 400 MHz equipment was used to determine the ^{1}H-NMR spectra. Re-crystallization techniques used to purify the isolated compounds. 1H-NMR chemicals shift values and melting points of the synthesized compounds confirmed with literature data.

1.1 Preparation of 5-Aryl-1,3,4-oxadiazol-2-amines 2 (a-i):

To a stirred solution of 2-(4-(benzo[d]thiazol-5-ylsulfonyl)piperazin-1-yl)acetic acid **1** (1.0 eq.) in Xylene (3 rel vol.), 3,5-dibromoaniline (1.06 eq.) and $Mg(HSO_4).SiO_2$ (10 mol %.) were charged under stirring at ambient temperature and the reaction mass was irradiated using microwave at 120 ^{0}C for 100 min. Reaction progress was monitored by TLC. After completion of reaction, $Mg(HSO_4).SiO_2$ filtered off using celite and crude product was obtained by removing xylene under vacuum from filtrate mL. The isolated crude material was purified using ethanol to obtain light brown solid.

(3a): $[M+H]^+$=574.8, ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.81(d, 1H), 9.67(s, 1H), 8.74 (s, 1H), 8.32-8.35 (d, 1H), 7.86-7.95(m, 3H), 7.47-7.51(s, 1H), 3.33 (s, 2H), 3.03 (t, 4H), 2.58(t, 4H).



Similar protocol used for the preparation of **3(b-k).**

Antibacterial Activities:

The antibacterial efficiency was evaluated using the disc diffusion technique. Following microbe culture injection (300 ml), each sterile petri dish was inoculated with Hinton, Clint Agar. Each chemical under review was dissolved in DMSO to produce a 5 mg/mL solution. Filtered solutions with a pore size of 0.2 μm were employed. 6-mm-diameter discs were fashioned using Whatman filter paper no. 1, followed by sterilization in a hot air oven and placement in Petri dishes for testing. Agar plates were used to hold the discs. 20 ml of compounds were injected into each empty, sterilized disc. Following a 24-hour incubation period at 37°C, the dimensions of the inhibition zones on the plates were quantified in millimeters. There was no antibacterial activity demonstrated by solvent control (DMF). We compared the inhibition zones to those of reference discs that we had previously examined. The following reference discs are employed as a control: *streptomycin*, and *fluconazole*. The results of the disc diffusion method, including the diameters, are presented in **Table 3**.

CONCLUSION

$Mg(HSO_4).SiO_2$ promoted amidation under microwave irradiation is an effective, gentle, and environmentally friendly, process has been devloped. Some advantages of the established protocol are short reaction times, easy to handle, and eco-friendliness. It is hoped that this approach may find wider application future research of amidation chemistry.

In addition to this, the compounds which are exhibiting well to excellent biological activities will be preferred as a starting point for future research designing of molecules. These substances may be taken into consideration during the development of innovative bioactive molecules.

2. ACKNOWLEDGMENT

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