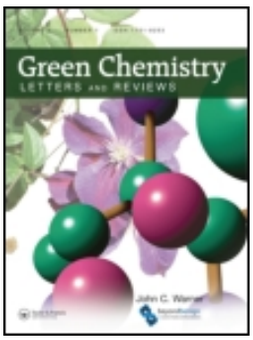

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RESEARCH LETTER

An efficient and practical synthesis of 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole using silica-supported sodium hydrogen sulfate as a heterogeneous catalyst

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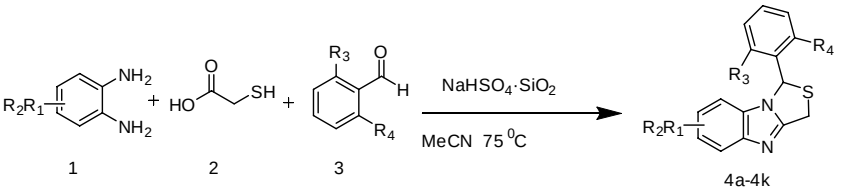
Silica-supported sodium hydrogen sulfate ($NaHSO_4{\cdot}SiO_2$) efficiently catalyzed the three-component reactions of *o*-phenylenediamine, 2-mercaptoacetic acid, and aromatic aldehydes, and it formed the corresponding 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole. The catalyst is inexpensive and eco-friendly and works under heterogeneous conditions.



Keywords: heterogeneous catalysis; silica-supported sodium hydrogen sulfate; multicomponent reaction; 1-aryl-1H,3H-thiazolo[3,4-a]benzimidazoles

Introduction

In natural products and drugs, one of the most widely observed active pharmacophores is benzimidazole. In modern days, it is attracting the interest of researchers for its various significant biological activities [1–5]; besides this, its derivatives have also found to be potential HIV-1 RT inhibitors. Furthermore, benzimidazoles have found and will continue to find extensive use in a myriad of synthetic contexts. So far, the reported synthetic methodologies for synthesis of benzimidazole and its derivatives involve condensation of various substrates under harsh reaction conditions [6–10] which suffer from demerits like poor yield, long reaction time, formation of side products, etc. [11]. The disadvantages faced during the synthesis of benzimidazole and its derivatives have made it an urgent necessity to develop new methods/protocols, which would eliminate many of the drawbacks of existing synthetic protocols and may meet the requirements of green chemistry to protect human health and also the environment. In this context, microwave-assisted and ionic liquid-mediated synthesis of benzimidazoles is reported by Pietro Monforte and coworkers and Ashok Yadav et al., respectively [12,13].

Indeed, multicomponent reactions have recently attracted a considerable attention in organic synthesis owing to their ability to produce the target products in a single operation without isolating the intermediates. They not only reduce the reaction time and energy but also reduce the waste product generation [14–16]. In the quest of selecting a promising, sustainable catalyst for multicomponent reactions, heterogeneous catalysts provide an efficient and a promising avenue toward realization of high yields of product pertinent to their inherent environmental and eco-friendly nature [17,18].

Thus, considering the above reports, advantages and applications of silica-supported sodium hydrogen sulfate as a heterogeneous catalyst, and as part of our ongoing project to explore green methodologies for the synthesis of bioactive heterocyclic compounds

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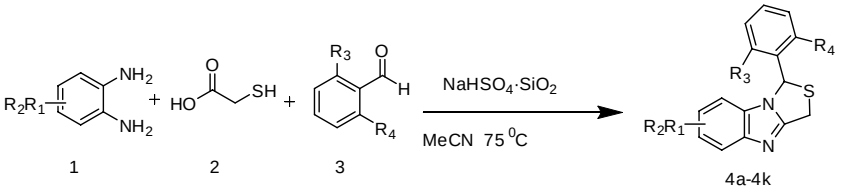


Scheme 1. Synthesis of 1-aryl-1*H*, 3*H*-thiazolo[3,4-*a*]benzimidazoles.

[19–21], herein we report the effective and practical one-pot synthesis of 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*]-benzimidazoles *via* the simple three-component condensation of 1,2-phenylenediamine, 2-mercaptoacetic acid, and aromatic aldehydes using catalytic amount of silica-supported sodium hydrogen sulfate, which served as heterogeneous catalyst (Scheme 1). The catalyst can easily be prepared [22] from readily available inexpensive ingredients like $NaHSO_4$ and properly activated silica gel (finer than 200 mesh). The mild reaction conditions and simple experimental procedure offer a better alternative to the existing methods.

Results and discussion

With a viewpoint to accomplish the best reaction condition, the initial efforts were devoted toward the investigation of an appropriate and efficient catalyst for the three-component synthesis of 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole. In order to observe the need of catalyst, we had run two sets of reactions, namely, control and test. In control set of reaction, *o*-phenylenediamine, 2-mercaptoacetic acid, and benzaldehyde in acetonitrile were reacted without addition of any catalyst. While in the test sets of reaction, all of the same substrates as mentioned in control set were allowed to react in the presence of various catalysts, namely, Amberlyst-15, PMA-SiO_2, mantmorillonite clay, KF-Al_2O_3, $NaHSO_4.SiO_2$, bismuth (III) salts, and Indion 190 resin. In the control set of reaction only trace yield was observed after 20 h at 75 °C, while in the test sets of reaction the yields obtained were in the range of 43–93%. During screening for efficiency considered in terms of product yield, $NaHSO_4.SiO_2$ was found to be the most efficient catalyst with 93% of product yield. This high yield of 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole is presumably due to the ability of $NaHSO_4.SiO_2$ to elevate the formation of imidazole through protonation, which apparently enhances the rate of reaction (Table 1 and Scheme 2).

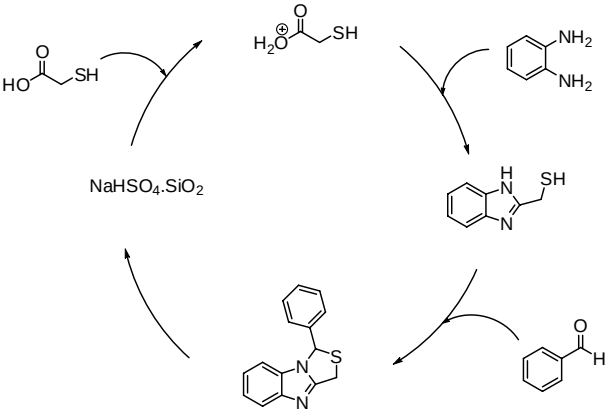
Table 1. Synthesis of 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*]-benzimidazole using various catalysts.[a]

Entry	Catalyst	Time (h)	Yield[b]
1	None	20	Trace
2	Amberlyst-15	1	79
3	PMA-SiO_2	1	85
4	Mantmorillonite clay	1	76
5	KF-Al_2O_3	1	43
6	$NaHSO_4.SiO_2$	1	93
7	Bismuth (III) salts	1	80
8	Indion 190 resin	1	75

[a]Reaction conditions: *o*-phenylendiamine (1 mmol), 2-mercaptoacetic acid (1 mmol) and benzaldehyde (1 mmol), catalyst (200 mg), time: 1 h, acetonitrile (5 mL), temp: 75 °C.
[b]Isolated yield.

Further to elucidate the effect of solvents, reactions were carried out in various solvents in the presence of $NaHSO_4.SiO_2$ as the catalyst. The control reaction was set in a neat condition. After completion of reactions, the organic solvents were removed under reduced pressure. The dichloromethane was added in the reaction mass and filtered off. The residue was further washed twice with the dichloromethane. The combined dichloromethane filtrate on evaporation afforded the product in the range of 40–93%. To our delight, best result was observed with acetonitrile (Table 2).

We observed that catalyst concentration also plays a pivotal role in the synthesis of 1*H*,3*H*-thiazolo[3,4-*a*]benzimidazoles. After experimenting with various concentrations of $NaHSO_4.SiO_2$, we got optimum yield of product with 200 mg of catalyst



Scheme 2. Possible mechanism.

Table 2. Effect of solvents on preparation of 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole.[a]

Entry	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	Methanol	55	4	40
2	Ethanol	75	4	53
3	DMF	120	4	45
4	Acetonitrile	75	1	93
5	Neat	100	24	17
6	Toluene	100	4	71

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), benzaldehyde (1 mmol), 2-mercaptoacetic acid (1 mmol), $NaHSO_4.SiO_2$ (200 mg), solvent (5 mL).
[b]Isolated yield.

(Table 3). On further increasing the amount of catalyst, the yield of corresponding product decreased, ascribable to the increased acidity.

Furthermore, temperature also played a crucial role in the synthesis of 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*]-benzimidazole. At 30 °C, only 40% conversion was observed. On subsequent rises in temperature the percentage yields of product were as follows: at 50 °C, 65%; at 75 °C, 93%, respectively (Table 4).

All the aforementioned results revealed that $NaHSO_4.SiO_2$ in acetonitrile is the best system for the synthesis of 1-aryl-1*H*, 3*H*-thiazolo[3,4-*a*]-benzimidazoles. To investigate the generality and feasibility of the protocol, we treated diverse substituted aldehydes and *o*-phenylenediamines with 2-mercaptoacetic acid. Good to high yields of the products were obtained. The optimized results are summarized in Table 5. Electron-releasing group on aldehyde and electron-withdrawing group on amine reduced the rate as well as yield of reaction. Products were characterized by ^{1}H-NMR, ^{13}C NMR, mass, and physical constant. Physical and spectral data of known compounds are in agreement with those reported in the literature [12,13].

Table 3. Optimization of the amount of $NaHSO_4.SiO_2$ for the synthesis of 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*]-benzimidazole.[a]

Entry	Weight of catalyst (mg)	Time (h)	Yield[b] (%)
1	50	1	40
2	100	1	60
3	150	1	82
4	200	1	93
5	250	1	85

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), benzaldehyde (1 mmol), 2-mercaptoacetic acid (1 mmol), $NaHSO_4.SiO_2$ (X mg), acetonitrile (5 mL), temperature: 75 °C.
[b]Isolated yield.

Table 4. Optimization of temperature for the synthesis of 1-aryl-1*H*, 3*H*-thiazolo[3,4-*a*]benzimidazole.[a]

Entry	Temperature (°C)	Time (h)	Conversion[b] (%)
1	30	1	40
2	50	1	65
3	75	1	93

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), benzaldehyde (1 mmol), 2-mercaptoacetic acid (1 mmol), $NaHSO_4.SiO_2$ (200 mg), and acetonitrile (5 mL).
[b]Isolated yield.

We emphasized on studying the recyclability and reusability of the catalyst so that our protocol can become more environment-friendly method and thus could belong to the domain of green chemistry methods. Upon the completion of the reaction, the catalyst was separated by filtration, further washed twice with dichloromethane and dried first under vacuum and then in oven. The activated catalyst was used for two more subsequent cycles. Interestingly, consistent performance of the catalyst was observed in all the cycles (Table 6).

Experimental

All commercial reagents were used as received without further purification, and all solvents were of reagent grade. The reaction was monitored by TLC using 0.25-mm E-Merck silica gel 60 F254 precoated plates, which were visualized using UV light. Melting points were measured in open capillaries. The IR spectra were recorded on a PerkinElmer 257 spectrometer using KBr disks. ^{1}H NMR and ^{13}C NMR

Table 5. Synthesis of 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*]-benzimidazole.[a]

Products	R_1	R_2	R_3	R_4	Yield[b] (%)	Physical constant observed (liter)
4a	H	H	Cl	Cl	89	133–134 (132–134)
4b	H	H	H	H	93	134–136 (134–135)
4c	H	H	H	NO_2	90	149–151 (150–152)
4d	H	H	H	Cl	87	125–127 (124–126)
4e	H	H	H	OH	85	482 (481.5)
4f	H	H	H	OMe	80	132–133 (133–134)
4g	H	H	F	F	91	140–141 (141–142)
4h	5-Me	H	F	F	92	160–161 (159–161)
4I	6-Me	7-Me	F	F	93	179–180 (178–179)
4j	8-Me	H	F	F	90	147–149 (149–150)
4k	3-NO_2	H	H	H	79	183–184 (182–183)

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), aldehydes (1 mmol), 2-mercaptoacetic acid (1 mmol), $NaHSO_4.SiO_2$ (200 mg), acetonitrile (5 mL), temperature: 75 °C, time: 1 h.
[b]Isolated yield.

Table 6. Reusability of the catalyst.[a]

Cycle	Yield (%)
1	93
2	91
3	87

[a]Reaction condition: *o*-phenylenediamine (1 mmol), benzaldehydes (1 mmol), 2-mercaptoacetic acid (1 mmol), $NaHSO_4.SiO_2$ (200 mg), acetonitrile (5 mL), temperature: 75 °C, time: 1 h.

spectra were recorded on a VXR-300 MHz instrument using TMS as an internal standard.

General experimental procedure

To a mixture of an *o*-phenylenediamine (1 mmol), 2-mercaptoacetic acid (1 mmol) and aromatic aldehydes (1 mmol) in MeCN (5 mL) $NaHSO_4.SiO_2$ (200 mg) was added and then stirred at 75 °C for 1 h. After cooling to room temperature, the reaction mixture was filtered and the residue was washed thoroughly with dichloromethane. The catalyst was recovered from the residue. The filtrate was concentrated under reduced pressure to isolate the crude product which was purified by column chromatography over silica gel using hexane-DCM (7:3) as eluent and eventually recrystalized using ethanol.

Representative spectral data

1−(2′,6′-Dichlorophenyl)-1H 3H-thiazolo[3,4-a]benzimidazole(4a): ^{1}H NMR (DMSO-d_6): 4.21 (d, $J =$ 14.1 Hz, 1H, H_3), 4.54 (dd, $J = 1.75$ and 14.2 Hz, 1H, H_3), 6.63 (s, 1H, H_1), 6.6–7.71 (m, 7H, Ar-H) ppm; ^{13}C NMR (DMSO-d_6): 162, 159.8, 159, 158.6, 156.2, 152, 149, 137.4, 135.1, 133, 126.5, 125, 123.3, 76, 70 ppm; **IR (KBr)**:1617, 772, 707 cm^{-1}; MS: (M + 2): 323.2.

Conclusion

In this study, we have investigated a novel, simple, and efficient protocol for the synthesis of 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole derivatives *via* cyclocondensation reaction of *o*-phenylenediamine, 2-mercaptoacetic acid, and aromatic aldehydes using $NaHSO_4.SiO_2$ as a catalyst. The method is associated with the benefits derived from multicomponent reaction and the application of a heterogeneous catalyst. We feel this eco-friendly and economically viable catalyst will find practical utility for the one-pot synthesis of various 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*]-benzimidazole derivatives.

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