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A REUSABLE MORPHOLINIUM BISULFATE PROMOTED SYNTHESIS OF 2-ARYL BENZOTHIAZOLE DERIVATIVES UNDER GRIND-STONE METHOD

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Abstract: In this protocol, we have synthesized the 2-arylbenzothiazoles using highly inexpensive, reusable and mild morpholinium bisulfate [morH][HSO_4] ionic liquid as a catalyst with the condensation reaction of 2-aminothiophenol and aromatic aldehydes under grind-stone method. The use of highly efficient with high catalytic activity is one more advantages of this protocol.

Keywords: 2-Arylbenzothiazoles, Ionic liquid, Grind-stone method, 2-Aminothiophenol, Recyclable.

Introduction

Benzothiazole heterocycles are an important part of heterocyclic compounds. Highly reactive compounds 2-aminobenzothiazoles are widely used as reactants or reaction intermediates for the synthesis of several fused heterocyclic compounds.[i] Medicinal chemists more concentration was drawn to this series of compounds, when pharmacological profile of Riluzole (Figure 1) was observed as clinically available anticonvulsant drug.[ii] Also, Erythrazoles A and Erythrazoles B were separated from mangrove sediments (Figure 1).[iii] 2-arylbenzothiazoles heterocyclic compounds possess diverse of biological and pharmacological activities[iv-vi], such as antimicrobial[vii-viii], antitumor[ix], anti-convulsant[x-xi] and antidiabetic[xii] activities. Moreover, in the area of organic optoelectronic material they have also found wide range of application[xiii-xvii].

2-arylbenzothiazoles heterocyclic compounds possess diverse of biological and pharmacological activities. Because of their importance, numerous methods have been developed for the synthesis of 2-arylbenzothiazoles, which mostly includes condensation reaction of 2-aminothiophenols and carboxylic acids/ acid chlorides/ aldehydes/ esters/ nitriles/ ketones/ thioesters such as Bi_2O_3 nanoparticles[xviii], cerium (IV) ammonium nitrate[xix], NH_2SO_3H[xx], pTSA[xxi].

However, many among these methods suffer from one or more limitations such as unbearable reaction conditions, prolonged reaction time period, poor yields with formation of

many side products and use of large quantity of volatile organic solvents. So, the development of a clean, high yielding and eco-friendly approach is still desirable. In recent years, room temperature ionic liquids (RTILs) were introduced because of their unique physical and chemical properties of non-volatility, non-flammability, thermal stability, and recyclability[xxii]. Also, RTILs promising as greener alternative reaction media as well as catalyst towards conventional organic solvents which is an essential part of today's force towards sustainable chemistry.[xxiii]

In continuation of our ongoing research to develop novel methodologies in synthetic chemistry[xxiv-xxviii], we have investigated here an efficient, low cost, and environmentally benign protocol for the synthesis of 2-arylbenzothiazole using morpholinium bisulfate [morH][HSO_4] ionic liquid a simple, reusable and inexpensive catalyst under solvent-free grindstone method.

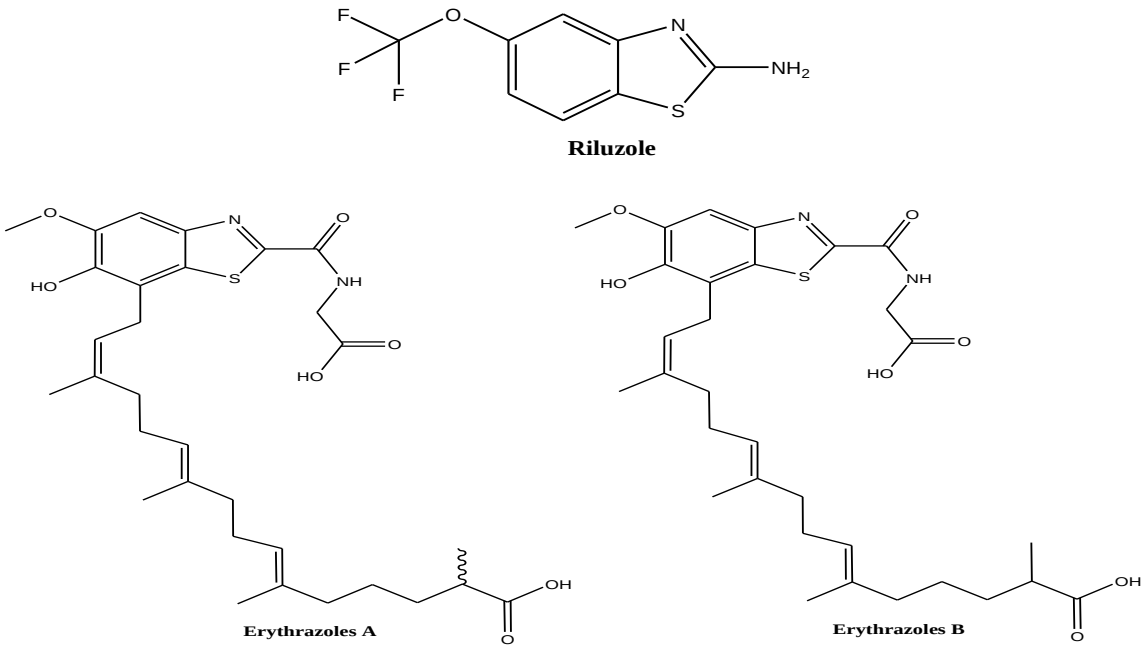


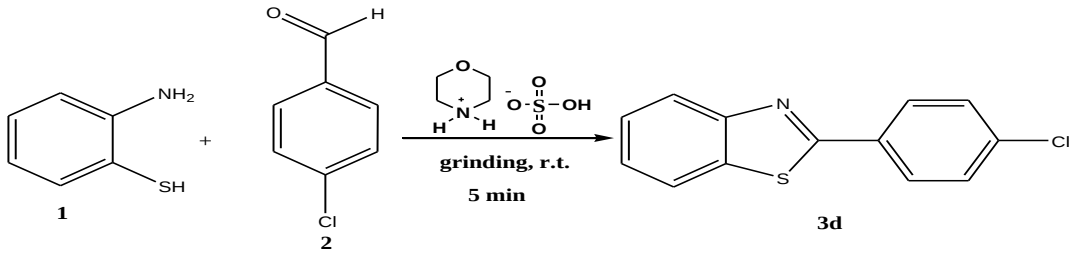
Figure 1: Naturally occurring benzothiazoles

Result and Discussion

To explore the use of morpholinium bisulfate [morH][HSO_4] ionic liquid as a catalyst for the synthesis of 2-arylbenzothiazole from the condensation reaction of 2-aminothiophenol and aromatic aldehydes under the grind-stone method. We have considered as standard model reaction of 2-aminothiophenol and 4-chlorobenzaldehyde in the presence of ionic liquid [morH][HSO_4] under grinding method (Scheme 1). Initially, we have optimized the amount of ionic liquid catalyst required for the formation of the product (Table 1). During this study, we have observed that the reaction smoothly carried out using 10 mol% of morpholinium bisulfate [morH][HSO_4] ionic liquid. Furthermore, same reaction work up with absence of catalyst then there is no desired product formed it means the catalyst was must be required for the initiation of reaction.

Encouraging by this results, we build the generality of reaction with electron donating and electron withdrawing group. When we carried out the reaction with both substituent's there is no observe any strong effect of nature of the substituent's on the yield and time of the products. In other terms, when electron-donating (–OCH_3, –CH_3, –OH) and electron-withdrawing groups (–Cl, –NO_2) were employed the reaction smoothly with less reaction time

and gives high to excellent yields. All obtained results are mentioned in the (Table 2 entries 3a-k).

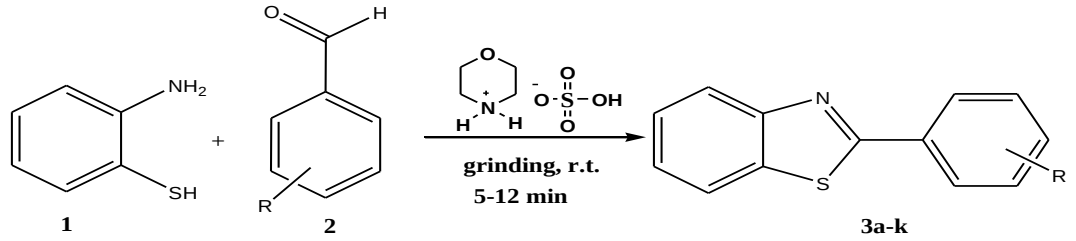


Scheme 1

Table 1 Optimization of catalyst[a]

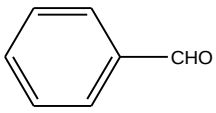
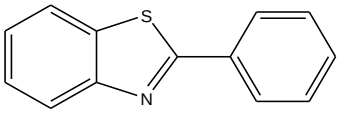
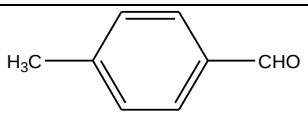
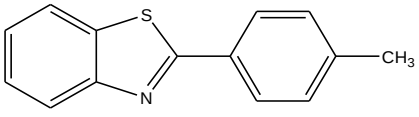
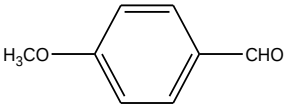
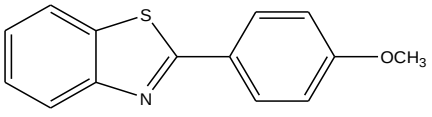
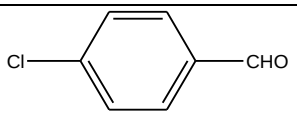
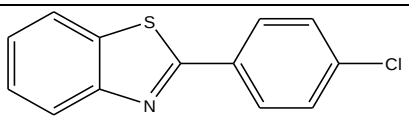
Entry	Catalyst mol%	Time (min)	Yield[b] %
1	-	20	No reaction
2	2	20	45
3	5	10	85
4	**10**	**05**	**95**
5	15	05	94

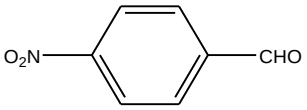
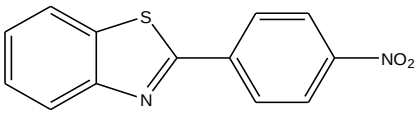
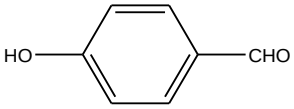
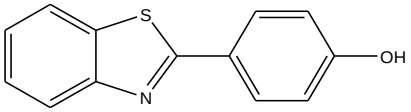
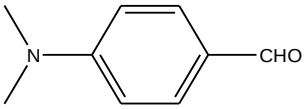
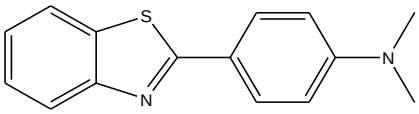
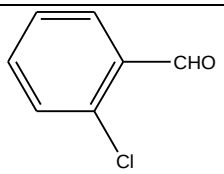
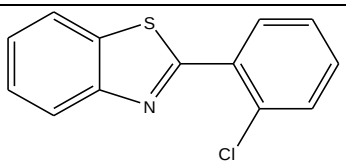
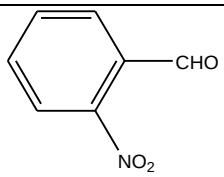
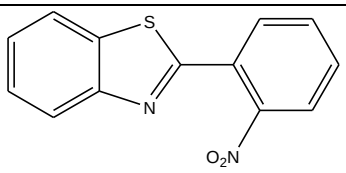
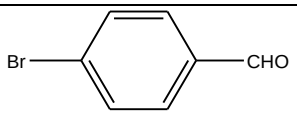
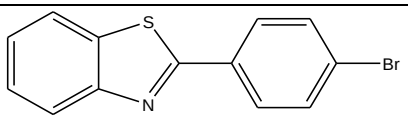
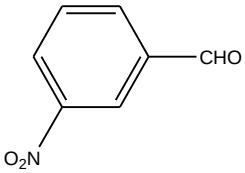
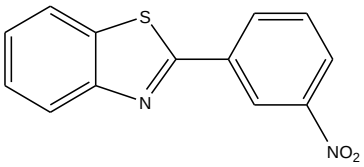
[a]**Reaction conditions:** 4-chlorobenzaldehyde(1 mmol), 2-aminothiophenol (1 mmol), morpholinium bisulfate [morH][HSO_4] (10 mol%) under grind-stone method, [b]Isolated yield.



Scheme 2

Table 2 Synthesis of 2-arylbenzothiazole using morpholinium bisulfate [a]

Entry	Aldehydes	Products	Time (min)	Yield (%)[b]
3a			5	94
3b			5	94
3c			8	93
3d			5	95

3e			6	95
3f			12	88
3g			8	90
3h			7	92
3i			7	90
3j			5	94
3k			7	92

[a]**Reaction conditions:** Aromatic aldehyde(1 mmol), 2-aminothiophenol (1 mmol), morpholinium bisulfate [morH][HSO_4] (10 mol%) under grind-stone method, [b]Isolated yield.

Finally, we have studied the reusability of catalyst; reaction of 4-chlorobenzaldehyde (1.0 mmol) and 2-aminothiophenol (2.0 mmol) was selected as standard model reaction for this study. After completion of reaction, the reaction mixture was extracted with ethyl acetate and placed till to formation of two phases. The aqueous layer of ionic liquid phase was easily separated by separating funnel and washed with ether dried under reduced pressure and the catalyst can also be reused even after three runs for the same model reaction.

Table 3 Reusability of catalyst

Runs	**Time (min)**	**Yield[b] %**
Fresh	5	95
1	5	95
2	6	93
3	7	92

[b]Isolated Yield

Experimental

All the required chemicals were purchased from commercial suppliers either from S. D. Fine, Spectrochem and they were used without further purification. Melting points were recorded by the open tube capillary method and are uncorrected. The progress of the reaction was tested by thin-layer chromatography (TLC) analytical silica gel plates (Merck 60 F250). ^{1}HNMR and ^{13}CNMR spectra were characterized by Bruker Avance (400 and 100 MHz, respectively) instrument in $CDCl_3$ solvent, chemical shifts are specified in δ ppm comparative to tetramethylsilane (TMS) and coupling constants (*J*) are expressed in Hz.

Preparation of Morpholinium bisulfate [morH][HSO$_4$]

Morpholinium bisulfate acidic ionic liquid as a stable reagent is easily prepared as reported by the reaction of morpholine with conc. sulfuric acid (Yield 80%) [xxix]

General procedure for the preparation of 2-aryl benzothiazole (3a-k)

A mixture of aldehyde (1 mmol) and 2-aminothiophenol (1 mmol) was taken in mortar in the presence of morpholinium bisulfate (10 mol%)and was crushed with pestle for appropriate time at room temperature. The path of the reaction was monitored by TLC. After completion of the reaction, the ice cold water pour into mixture and solid product obtained was separated by filtration. Further purification was performed by recrystallization from ethanol.

Selected Spectral data:

2-Phenyl-1,3-benzothiazole (Table 2, Entry 3a)

Yellow solid, Yield: 94%, M.P-112-114 ^{o}C; IR (KBr): *v/max* 1562, 1612, 3020, 3058 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.6 Hz, 1H), 7.51 – 7.47 (m, 4H), 7.90 (d, *J* = 8.0 Hz, 1H), 8.10 – 8.07 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.6, 123.2, 125.2, 126.3, 127.6, 129.0, 130.9, 133.6, 135.1, 154.1, 168.1; ESI-MS: *m/z* 212 $[M+H]^+$.

2-(4-N,N-Dimethylphenyl)-benzothiazole (Table 2 Entry 3g)

Yellow solid, Yield: 90%, M.P-174-176 ^{o}C; IR (KBr) ν (cm^{-1}); 3060, 2901, 1594, 1544, 1440, 1372, 1240, 1162, 815, 745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.86 (2H, d, *J*=8.5 Hz); 7.62 (1H, d, *J*=7.8 Hz); 7.16 (1H, t, *J*=7.7 Hz); 7.08 (1H, t, *J*=7.6 Hz); 7.02 (1H, d, *J*=7.6Hz); 6.75 (2H, d, *J*=8.9 Hz); 3.07(6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 159.5, 152.7, 149.7, 131.8, 130.8, 128.8, 126.5, 125.8, 125.5, 124.4, 117.1, 111.5, 40.1; MS: m/z 254.09, 157.9, 131.9, 114.0, 102.1, 86.2, 72.4.

Conclusion

In summary, we have used highly efficient, mild and effective methodology for the synthesis of 2-arylbenzothiazole from the condensation reaction of 2-aminothiophenol and aromatic aldehydes in the presence of morpholinium bisulfate [morH][HSO$_4$] (10 mol%) under grind-stone method. The use of reusable, inexpensive with high catalytic activity is the advantage of this protocol. In difference to other acids, no need of special precautions for storage and handling of this catalyst and it can be stored on the bench top for weeks without losing its catalytic activity.

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