



Ionic liquid $[Et_3NH][HSO_4]$ promoted One-pot Synthesis of 1, 3-Benzoxazoles with Substituted Thiazolidinone Moiety

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ABSTRACT

A significant, One-pot Synthesis of 1, 3-benzoxazoles with substituted thiazolidinone moiety using 2-(4-amino phenyl) benzoxazole, substituted aromatic aldehyde, and thioglycolic acid under $[Et_3NH][HSO_4]$ ionic liquid. Ionic liquid has been used as a rapid, greener, and reusesionic liquid for the synthesis of 1, 3-benzoxazoles with substituted thiazolidinone under solvent-free conditions. This methodology's numerous advantages are non-corrosiveness, safety, little waste, generality, simplicity, ease of isolation, short reaction times, better yields, and environmental friendliness.

Keywords: $[Et_3NH][HSO_4]$, Ionic liquid, 1, 3-benzoxazoles, thiazolidinone, multicomponent reactions.

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INTRODUCTION

Multi-component reactions have proven to be extremely effective at producing compounds in a single step and development of new MCRs, as well as the improvement of existing multi-component reactions, is a hot topic right now [1-4]. MCRs contribute significantly to the convergence synthesis of organic compounds' simple, commonly available starting components [5-7].

Sulfur heterocycles, such as the thiazole, have been labeled "privileged structures" because of their presence in biologically active natural compounds, medicines, and a variety of synthetic intermediates [8]. During the process of probing structural activity relationships (SAR) for lead optimization, thiazole can also be employed as an amide isostere or in a scaffold hopping strategy. As a result, thiazoles are commonly used as the main structure in the synthesis of chemical library resources or in drug design. Many thiazole compounds have been produced in recent decades and tested for a variety of biological activities [9]. Among these numerous classes, thiazolidine-4-ones are of special interest to researchers due to their efficacy in several biologically active compounds such as anti-bacterial [10-14], anti-tumor [15], anti-tubercular [16], anti-fungal [17], anti-viral [18], anti-inflammatory [19], and etc. Several of these procedures, however, have limitations such as extended reaction durations, dangerous organic solvent, high acidic conditions, time-consuming workups, and the use of significant amounts of catalyst.

ILs have environmentally acceptable solvents, catalysts, and reagents for chemical transformations due to their exceptional properties such as superior chemical stability, lack of flammability, and low volatility [21-27]. They have notable qualities such as low vapour pressure, nonflammability, recyclable capabilities, and organic substances. Because of their fascinating physical and chemical features, ionic liquids have been used in a variety of applications. ILs have been successfully employed in cyclo condensation reactions, Prins reactions, and Oxa-Michael additions, among other chemical reactions [28-30]. As a result, we developed a moderate generalized synthesis of 1, 3-benzoxazoles with substituted thiazolidinone moiety using ionic liquid $[Et_3NH][HSO_4]$ under solvent-free environments.

MATERIAL AND METHODS

The chemicals were bought in a store and used without purification. The melting points were measured in an open capillary tube with no corrections. $CDCl_3$ was used as the solvent for 1H and ^{13}C -NMR on a Bruker Avance II 400 spectrometer. The IR spectra were captured in KBr using a Perkin-Elmer RXI spectrometer.

General Procedure for Preparation [Et₃NH] [HSO₄] Ionic liquid.

H₂SO₄ (98 percent, 9.79 g, 0.1mmol) was dropped into Et₃N at 60 °C for 60 minutes (9.99 g, 0.1mmol). Following the addition, the reaction mixture was agitated for an extra 60 minutes at 80 °C to ensure that the reaction was complete. The remaining water is removed by heating. Yielding 98 percent, 18.5 g of IL [Et₃NH][HSO₄].

General Procedure for Synthesis of 3-[4-(1,3-benzoxazol-2-yl)phenyl]-2-aryl-1,3-thiazolidin-4-one.

A reaction mixture 2-(4-amino phenyl) benzoxazole 1a (1 mmol), substituted aromatic aldehyde 2a (1 mmol) and thioglycolic acid 3a (1 mmol) under ionic liquid [Et₃NH] [HSO₄] and the reaction mixture heated 80°C with constant string. Progress of the reaction is monitored by using TLC. After completing the reaction product was quenched into ice-cold water, the product was separated through filtration and characteristics data compared to literature. By removing the water under reduced pressure, the [Et₃NH] [HSO₄] was recycled.

Spectral Data.

3-[4-(1,3-benzoxazol-2-yl)phenyl]-2-(4-chlorophenyl)-1,3-thiazolidin-4-one(4e): Solid; m. p. 119-122 °C; Yield: 94%; IR(KBr): ν_{\max} = 3052(-Ar-H), 2885(-C-H), 1685(>C=O), 751(C-S-C) cm⁻¹; ¹³C-NMR(100 MHz, DMSO-*d*⁶): δ 34.3(C2), 68.5(C5), 110.4 (C23), 113.8 (C8,C12), 119.9(C26), 124.2(C24), 124.9 (C25), 127.5(C10), 128.6(C17), 129.6(C14,C18), 129.5 (C15), 131.3(C9,C11), 135.17.(C16), 139.3(C13), 141.1(C21), 144.7(C7), 150.1(C20), 164.4(C19), 170.9(>C=O) ; ¹H-NMR(DMSO): δ 3.71 (d, *J* = 15.9 Hz, 1H, C2-H), 3.97 (d, *J* = 15.9 Hz, 1H, C2-H), 6.47 (s, 1H, C5-H), 7.26(ddd, *J* = 8.55, 7.56, 1.76, 1H, C24-H), 7.33(ddd, *J* = 7.92, 1.60, 0.45, 1H, C25), 7.54(ddd, *J* = 8.41, 1.54, 0.55, 2H, C15, 17-H), 7.65(ddd, *J* = 8.41, 1.49, 0.55, 2H, C14, 18), 7.71(ddd, *J* = 8.55, 1.60, 0.51, 1H, C23-H), 7.72(ddd, *J* = 8.19, 1.58, 0.44, 2H, C9, 11-H), 7.84(ddd, *J* = 8.19, 1.93, 0.45, 2H, C8, 12-H), 7.89 (ddd, *J* = 7.92, 1.76, 0.51, 1H, C26-H) ppm.

3-[4-(1,3-benzoxazol-2-yl)phenyl]-2-(4-nitrophenyl)-1,3-thiazolidin-4-one(4f): Solid; m. p. 175-178 °C; Yield: 92%; IR (KBr): ν_{\max} = 3066(Ar-H), 2933(CH), 1650(>C=O), 1519.274(Ar-C=C<), 1423(-C=N-), 775(C-S-C) cm⁻¹; ¹³C-NMR(100 MHz, DMSO-*d*⁶): δ 33.4(C2), 68.5(C5), 110.4(C24), 113.8 (C8,C12), 119.9 (C27), 124.2(C24), 124.9 (C25), 127.5(C10), 127.8 (C14,C18), 124.6 (C15,C17), 131.3(C9,C11), 139.3(C13), 141.1 (C21), 143.3 (C16), 144.7(C7), 150.1 (C20), 164.4(C19), 170.9(>C=O); ¹H-NMR(DMSO): δ 3.72 (d, *J* = 15.9 Hz, 1H), 3.97 (d, *J* = 15.9 Hz, 1H), 6.50(s, 1H), 7.25(ddd, *J* = 7.93, 2.25, 0.44, 1H, C24H), 7.33(ddd, *J* = 7.92, 0.56, 1.60, 1H, C25H), 7.41(ddd, *J* = 7.93, 2.225, 0.55, 2H, C14, 18H), 7.71 (ddd, *J* = 8.55, 1.60, 0.51, 2H, C23-H), 7.72(ddd, *J* = 8.19, 1.59, 0.44, 2H, C9, 11H), 7.84(ddd, *J* = 8.19, 1.93, 0.45, 2H, C8, 12-H), 7.89 (ddd, *J* = 7.92, 1.76, 0.51, 1H, C26H), 8.16(ddd, *J* = 7.93, 1.86, 0.44, 2H, C15, 17-H)

RESULT AND DISCUSSIONS

Here, we revealed an effective and greener route for the one pot Synthesis of 1, 3-Benzoxazoles with Substituted thiazolidinone moiety, 2-(4-amino phenyl) benzoxazole(1a, 1 mmol), substituted aromatic aldehyde (2a, 1 mmol) and thioglycolic acid(3a, 1 mmol) in the presence of [Et₃NH][HSO₄] act as a catalyst plus solvent [Scheme 1].

The several ILs and model reaction was carried out 2-(4-amino phenyl) benzoxazole(1a, 1 mmol), benzaldehyde (2a, 1 mmol), and thioglycolic acid (3a, 1 mmol) under [Et₃NH][HSO₄] ionic liquid. All of the ILs tested were shown to be capable of initiating the product 3-[4-(1,3-benzoxazol-2-yl) phenyl]-2-phenyl-1,3-thiazolidin-4-one derivatives (4a-h). However, a yield of the corresponding 1, 3-Benzoxazoles with Substituted thiazolidinone moiety was outstanding (Table 1, entry 6). Formerly, several reaction parameters were examined, including temp., and IL quantity (Table 1).

With these results in hand, we were inspired to make a variety of 1, 3-Benzoxazoles with substituted thiazolidinone moiety (4a-h) and the synthesis (4a) compound shows shorter time 35 min and 95 % yield. Table 2 shows the results, which show that the product 3-[4-(1,3-benzoxazol-2-yl) phenyl] contains both electron-poor and electron-rich substituents. The simple and easy to make -2-phenyl-1,3-thiazolidin-4-one analogs, all were obtained with excellent yields. [Et₃NH][HSO₄] catalyst for ionic liquid. In the reaction to synthesize 3-[4-(1,3-benzoxazol-2-yl) phenyl], the reusability of the [Et₃NH][HSO₄] catalyst were investigated. Under ideal reaction conditions, (4a). When the reaction was finished and cool to room temp. After being added to water, and precipitated mixture was filtered and separated the crude components. The water and [Et₃NH][HSO₄] were evaporated in the presence of decreasing pressure after completely washing the solid products, and the catalyst was retrieved and utilized for the next round. Without losing any activity, the recovering catalyst was reapplied for at least four runs. (Figure 1&2)

Scheme: 1 One-pot Synthesis of 1, 3-Benzoxazoles with Substituted Thiazolidinone Moiety

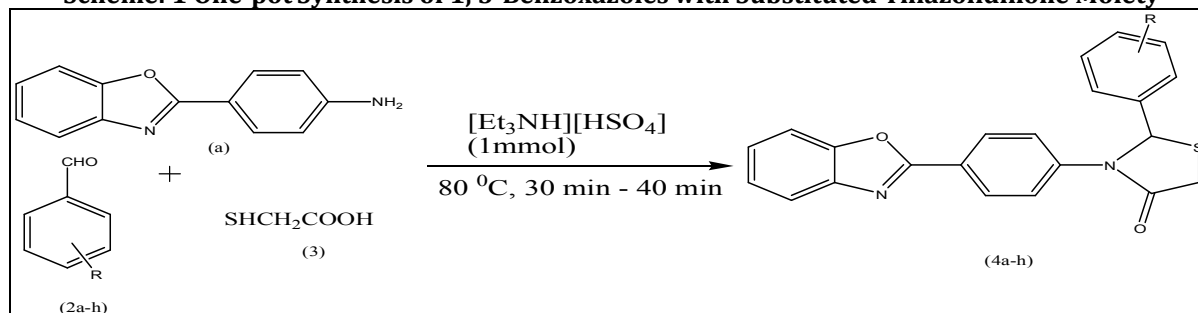


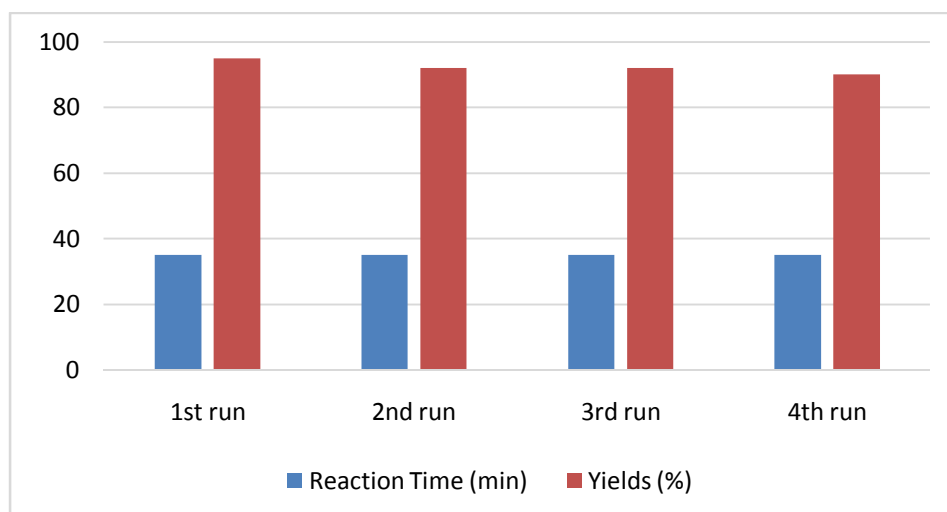
Table 1: Synthesis of (4a): Optimization of Reaction Parameters

Entry	Catalyst (mmol)	Temperature ($^\circ\text{C}$)	Time (min)	^a Yield (%)
1	Solvent-free	120	20h	35
2	EtOH	80	16h	35
3	[DBUH][Im] (1)	80	40	75
4	[DBUH][OAc]	80	40	79
5	$[\text{Et}_3\text{NH}][\text{HSO}_4]$ (0.5)	80	35	85
6	$[\text{Et}_3\text{NH}][\text{HSO}_4]$ (1)	80	35	95
7	$[\text{Et}_3\text{NH}][\text{HSO}_4]$ (1.5)	80	35	95
8	$[\text{Et}_3\text{NH}][\text{HSO}_4]$ (2)	80	35	95

Table 2: One-pot Synthesis of 1, 3-Benzoxazoles with Substituted Thiazolidinone Moiety

Entry	Aromatic aldehyde	Time (min)	^a Yield (%)	^b Melting point
4a	-H	35	95	150-153
4b	-4-F	35	92	109-111
4c	-2-OH	35	94	248-250
4d	-2-OH-OMe	38	93	209-211
4e	-4-Cl	38	94	119-122
4f	-4-NO ₂	40	92	175-178
4g	-3-Br	35	94	279-281
4h	-2-NO ₂	40	94	178-180

^aIsolated yields. ^bAll m.p. compared with literature[31].

Figure 1: Recycling of ionic liquid $[\text{Et}_3\text{NH}][\text{HSO}_4]$ of synthesis (4a) compound.

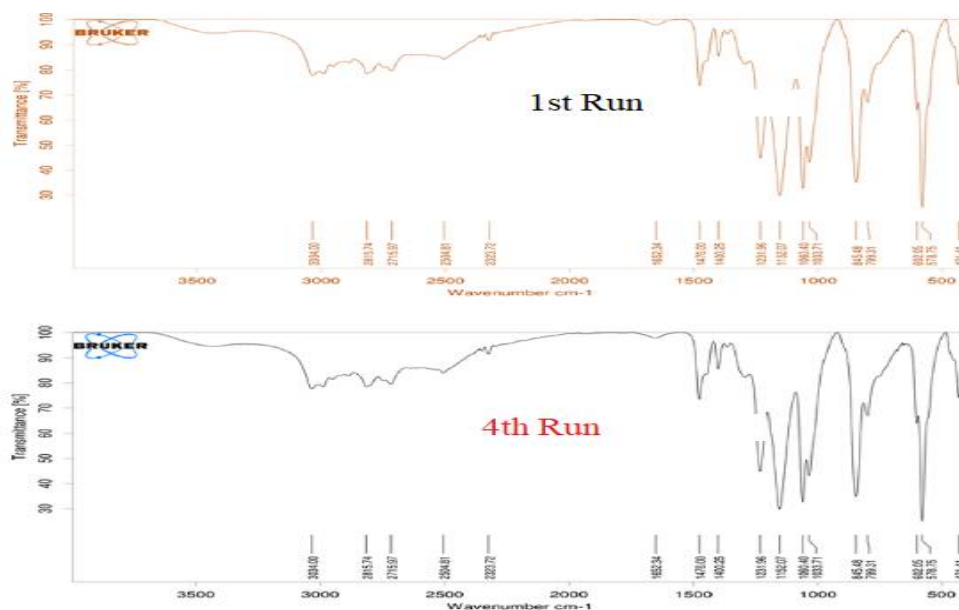


Figure 2: IR Spectra shows reusability of ionic liquid $[\text{Et}_3\text{NH}][\text{HSO}_4]$.

CONCLUSION

A conclusion, one-pot Synthesis of 1, 3-benzoxazoles with substituted thiazolidinone moiety by using ionic liquid $[\text{Et}_3\text{NH}][\text{HSO}_4]$. Every one of the reactions were carried out at 80°C with 1 mmol $[\text{Et}_3\text{NH}][\text{HSO}_4]$, and the desired products were generated with excellent yield in shorter reaction times. This approach is environmentally sustainable, with benefits such as strong yields, facile catalyst preparation/separation, high catalytic activity, catalyst recyclability, and ease of use.

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