

Brønsted acidic ionic liquid ([BMIm]HSO₄) as an efficient catalysts for the one-pot synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives

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ABSTRACT

The Brønsted acidic ionic liquid ([BMIm]HSO₄) catalyzed three-component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives at room temperature. The integrity of the ionic liquid remains reasonably unchanged when it is separated from the reaction mixture by water extraction, as it can be recycled several times without any loss of activity in each of the title syntheses. The products and ionic liquid could be conveniently separated from the reaction mixture, indicating that the whole process was performed as a green chemical transformation. The salient features of this one pot protocol are short reaction times, cleaner reaction profiles and simple workup.

Keywords: Ionic liquid, Reusable catalyst, Phthalazine moiety, Brønsted acid.

1. Introduction

During recent years, ionic liquids (ILs) have attracted increasing interest in the area of organic synthesis particularly by producing an alternative green reaction medium [1]. Recently, the ionic liquids have been found to possess a significant role as catalyst [2]. They can be also used as solvents due to their unique physical and chemical properties such as non-volatility, non-flammability, thermal stability and controlled miscibility [3-5]. A subdivision of ILs is protic ionic liquids (PILs), which are produced through the combination of a Brønsted acid and a Brønsted base [6]. These acidic ionic liquids have widely been applied in electrochemistry, synthesis of nanostructure materials, reaction media and catalyst.

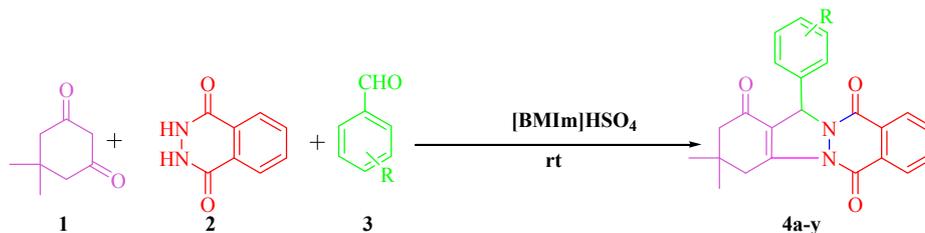
1-butyl-3-methylimidazolium hydrogensulphate ([BMIm]HSO₄) has not been explored [7] to great extent, in spite the fact that it holds great potential to catalyse various organic reactions. This Brønsted acidic ionic liquid has easily been synthesized and used as an efficient, inexpensive and reusable catalyst in organic synthesis [8-10]. Moreover, the present ionic liquid is halogen free and because of less carbon numbers, this ionic liquid has less toxicity [11].

Therefore, [BMIm]HSO₄ can be introduced as a green ionic liquid. Over the past few decades, a tremendous upsurge of interest has been observed in the synthesis of nitrogen containing heterocyclic compounds, owing to their abundance in nature and essentiality to life [12-16]. Among them, heterocycles containing phthalazine moiety are of interest because they show some pharmacological and biological activities such as Anticonvulsant [17], cardiotoxic [18], and vasorelaxant [19].

The synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives have been reported using *p*-TSA [20], ionic liquids [21], ultrasound [22], dodecylphosphonic acid (DPA) [23], heteropoly acids [24], Ce(SO₄)₂·4H₂O [25], CAN [26], montmorillonite K-10 [27], N-halosulfonamides [28], TMSCl [29], silica sulfuric acid [30], phosphomolybdic acid (PMA)-SiO₂ [31], [BMIm]Br [32] and PEG-6000 [33].

In continuation of our interest in finding new environmentally benign methods for the synthesis of various compounds [34-35] and use of various ionic liquids for organic synthesis [36], herein we want to report the rapid and selective synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione in the presence of [BMIm]HSO₄ ionic liquid as a Brønsted acidic ionic liquid (Scheme 1).

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Scheme 1. One-pot three-component reaction of dimedone, hydrazine monohydrate, phthalic anhydride and aldehyde catalyzed by [BMIm]HSO₄.

2. Experimental

2.1. Materials and equipments

Chemicals were purchased from Merck and Fluka Chemical Companies and used without further purification. The purity determination of the products was accomplished by TLC on silica gel polygram SIL G/UV 254 plates. All products were confirmed by their m.p., IR, NMR and comparison with data in the pointed references. Melting points were determined on an electrothermal type 9200 melting point apparatus. IR spectra were recorded using a Shimadzu IR-470 spectrometer with KBr plates. In all the cases the ¹HNMR spectra were recorded with Bruker Avance 300 MHz instrument. Chemical shifts are reported in parts per million in DMSO with tetramethylsilane as an internal standard. The ¹³CNMR data were collected on Bruker Avance 75 MHz instrument. Mass spectra were recorded on a shimadzu QP1100EX mass spectrometer operating at an ionization potential of 70 eV.

2.2. General procedure for preparation of [BMIm]HSO₄

The 1-butyl-3-methylimidazolium hydrogen sulfate was synthesized according the reported procedure for 1-hexyl-3-methylimidazolium hydrogen sulfate [HMIm]HSO₄ [40]. The [BMIm]HSO₄ was obtained by a dropwise addition of one equivalent of concentrated sulfuric acid (97%) to a cooled solution of butyl methyl imidazolium chloride (1 eq) in anhydrous methylene chloride. The mixture was refluxed for 48 h and the HCl by-product formed in the reaction was collected by dissolving it in deionized water at 0 °C (the acidity of the aqueous solution was measured by titration with NaOH as a control for completion of the reaction). After completion of the reaction, the solution was cooled to room temperature and dichloromethane was removed in a rotary evaporator. The ionic liquid was dried under high vacuum at 70 °C for 6 h.

2.3. General procedure for separation of [BMIm]HSO₄

For this aim, after completion of the reaction (monitored by TLC), water was added to the reaction mixture and then the solid was isolated by filtration.

The IL in water could be recovered easily by evaporation at 80 °C in a vacuum. The recovered IL was washed with diethyl ether and dried at 80°C in a vacuum for 1h.

2.4. General procedure for preparation of phthalazine derivative

A mixture of dimedone (1 mmol), phthalhydrazide (1 mmol), aldehyde (1mmol) and [BMIm]HSO₄ (1 ml) was sealed and stirred at room temperature under solvent-free conditions. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was washed with water (2×15 mL) and then recrystallized from EtOAc/*n*-hexane (1:2) to afford the pure product.

3. Results and Discussion

In order to determine the optimum conditions, we investigated the reaction of dimedone (1 mmol), phthalhydrazide (1 mmol), 2-chlorobenzaldehyde (1 mmol) and [BMIm]HSO₄ (1 ml) at variable temperatures and alternatively in closely related ionic liquids (Table 1). It could be seen that the best result was obtained with 1 mL of [BMIm]HSO₄ at room temperature (Table 1, entry 13). Increase in the reaction temperature did not improve the yield of the product (Table 1, entry 14 and 15). The results show that weak basic ionic liquids such as TMGT and Et₄NBr lead to the products in low yields and the reaction time is longer than acidic ionic liquids. The neutral ionic liquid, [BMIm]BF₄, was not as effective as [BMIm]HSO₄, however, it found comparable catalysis activity when contaminated with 20 mol% of *p*-TSA. the results was shown that different ILs exhibit a dramatic difference in the yield of **4a**, that is attributed to the tunable physical properties of ionic liquids. Among various other catalysts, [BMIm]BF₄, [BMIm] BF₄ / *p*-TSA, TiCl₄, DBU and K₃PO₄ afforded poor to moderate yields (30-74%), while, KSF, [HMIm]HSO₄, [BMIm]HSO₃ and [2-aemim][PF₆] gave good yields of the desired products (80-84%). The main disadvantage of some of the used solid catalysts is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. But [BMIm]HSO₄ catalyst is inexpensive, readily available and reusable.

Table 1. Influence of different catalysts on the reaction of dimedone, phthalhydrazide, and 2-chlorobenzaldehyde.^a

| Entry | Catalyst | Reaction time (min) | Yield(%) ^b |
|-------|--|---------------------|-----------------------|
| 1 | --- | 200 | trace |
| 2 | KSF | 40 | 84 |
| 3 | K ₃ PO ₄ | 120 | 72 |
| 4 | TiCl ₄ | 25 | 70 |
| 5 | DBU | 40 | 74 |
| 6 | [BMIm]BF ₄ | 120 | 41 |
| 7 | [HMIm]HSO ₄ | 15 | 83 |
| 8 | [BMIm] HSO ₃ | 120 | 81 |
| 9 | TMGT | 120 | 25 |
| 10 | [BMIm] BF ₄ / <i>p</i> -TSA | 25 | 60 |
| 11 | [2-aemim][PF ₆] | 25 | 80 |
| 12 | Et ₄ NBr | 120 | trace |
| 13 | [BMIm] HSO ₄ (25°C) | 5 | 97 |
| 14 | [BMIm] HSO ₄ (45°C) | 7 | 85 |
| 15 | [BMIm] HSO ₄ (65°C) | 9 | 80 |

^aReaction conditions: dimedone (1 mmol), phthalhydrazide (1 mmol), 2-chlorobenzaldehyde (1 mmol) and [BMIm] HSO₄ (1 ml).

^bIsolated yield.

In order to show the merit of the catalyst, we have compared the obtained results in the synthesis of 2H-indazolo[2,1-*b*]phthalazine-triones catalyzed by [BMIm] HSO₄, with some heterogeneous and homogeneous catalysts, as reported in the literature (Table 2). The harsh reaction conditions, longer reaction times, and lower yields of other methods make our system a better choice.

After optimizing the reaction conditions, a variety of aromatic aldehydes were employed under similar circumstances to evaluate the substrate scope of this reaction. The results were summarized in Table 3. Electronic effects and the nature of substituents on the aromatic ring showed a little effect in terms of the yield and reaction time under the optimized reaction

conditions. As shown in Table 3, when halogen substituted aromatic aldehydes such as 2-, 3-, 4-(chloro), 2-, 3-, 4-(bromo), 3-, 4-(fluoro) and 2,4-, 2,6-(dichloro) substrates were employed under the reaction conditions excellent yields (91-97%) of the corresponding products were obtained (Table 3, entries 2-11). Aromatic aldehydes possessing electron-donating substituents such as 2-methyl, 4-methyl, 4-methoxy and 3,4-dimethoxy have afforded the phthalazine moiety in 90-92% yields (Table 3, entries 12-15 and 22-23). Similarly, electron withdrawing aromatic aldehydes possessing 4-nitro, 2-nitro and 3-nitro groups also afforded the referred derivatives in 96%, 95% and 91% yields respectively (Table 3, entries 12-14).

Table 2. Comparison of [BMIm]HSO₄ with other catalysts for the synthesis of 13-(2-chlorophenyl)-3,4-dihydro-3,3-dimethyl-2H-indazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione.

| Entry | Catalyst and Conditions | Reaction time (min) | Yield(%) | Ref. |
|-------|--|---------------------|----------|-----------|
| 1 | <i>p</i> -TSA/Neat/80 °C | 15 | 88 | [20] |
| 2 | Silica sulfuric acid/Neat/100 °C | 10 | 88 | [30] |
| 3 | Ce(SO ₄) ₂ ·4H ₂ O | 8 | 80 | [25] |
| 4 | [BMIm]Br/Sonocation/r.t. | 10 | 91 | [32] |
| 5 | PEG-6000/Neat/reflux | 10 | 87 | [32] |
| 6 | [BMIm]HSO ₄ /Neat/r.t. | 5 | 96 | This work |

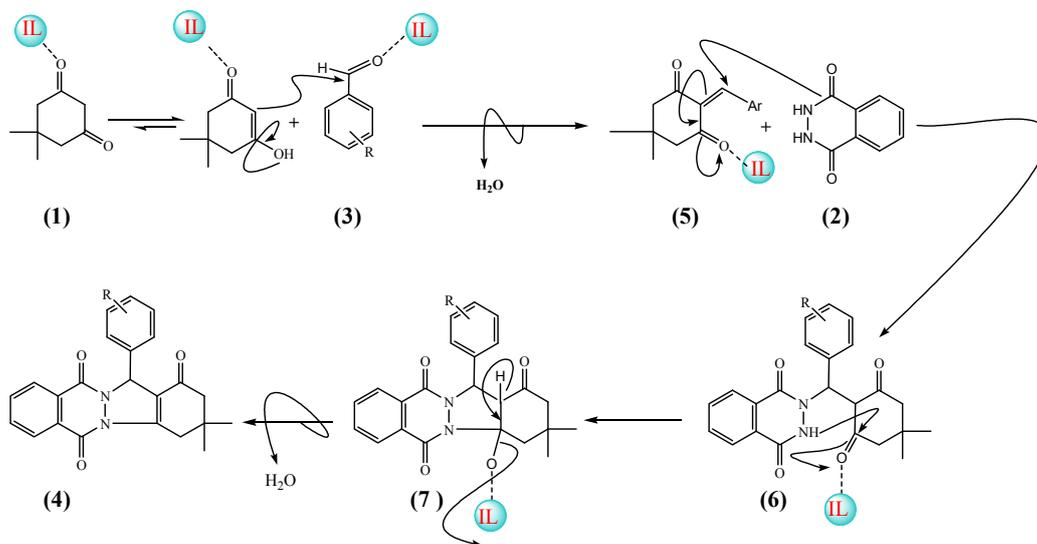
Table 3. [BMIm]HSO₄ catalyzed synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives via a one-pot, three-component reaction.

| Entry | Product | Aldehyde | Yield (%) ^a | Reaction time (min) | m.p. (°C) (found) | m.p. (°C) reported | Ref. |
|-------|---------|--|------------------------|---------------------|-------------------|------------------------|------|
| 1 | 4a | C ₆ H ₅ | 94 | 7 | 205-207 | 204-206 | [17] |
| 2 | 4b | 2-Cl-C ₆ H ₄ | 97 | 5 | 237-239 | 238-240 | [33] |
| 3 | 4c | 3-Cl-C ₆ H ₄ | 91 | 6 | 268-270 | 270-272 | [17] |
| 4 | 4d | 4-Cl-C ₆ H ₄ | 96 | 6 | 222-224 | 223-225 | [17] |
| 5 | 4e | 2-Br-C ₆ H ₄ | 94 | 7 | 261-263 | 262-264 | [38] |
| 6 | 4f | 3-Br-C ₆ H ₄ | 92 | 6 | 266-268 | 267-269 | [38] |
| 7 | 4g | 4-Br-C ₆ H ₄ | 93 | 7 | 261-263 | 262-264 | [37] |
| 8 | 4h | 2,4 di-Cl-C ₆ H ₃ | 92 | 6 | 218-220 | 219-221 | [37] |
| 9 | 4i | 2,6 di-Cl-C ₆ H ₃ | 94 | 6 | 261-263 | 260-262 | [33] |
| 10 | 4j | 3-F-C ₆ H ₄ | 91 | 5 | 261-263 | 271-273) | [38] |
| 11 | 4k | 4-F-C ₆ H ₄ | 97 | 4 | 219-221 | 218-220) ³⁷ | [37] |
| 12 | 4l | 2-NO ₂ -C ₆ H ₄ | 95 | 8 | 263-265 | 264-266) ¹⁸ | [18] |
| 13 | 4m | 3-NO ₂ -C ₆ H ₄ | 91 | 7 | 202-204 | 204-206) ¹⁸ | [18] |
| 14 | 4n | 4-NO ₂ -C ₆ H ₄ | 96 | 8 | 261-263 | 262-264) ¹⁷ | [17] |
| 15 | 4o | 2-MeO-C ₆ H ₄ | 91 | 7 | 240-242 | 242-243) ³² | [32] |
| 16 | 4p | 3-MeO-C ₆ H ₄ | 92 | 7 | 209-211 | 210-212) ³³ | [33] |
| 17 | 4q | 4-MeO-C ₆ H ₄ | 92 | 8 | 219-221 | 220-222) ³⁸ | [38] |
| 18 | 4r | 3,4 di-MeO-C ₆ H ₃ | 90 | 8 | 184-186 | 185-186) ²¹ | [21] |
| 19 | 4s | 3,4,5-tri-MeO-C ₆ H ₃ | 91 | 8 | 225-227 | 232-234) ³⁹ | [39] |
| 20 | 4t | 4-OH-3-MeO-C ₆ H ₃ | 90 | 6 | 251-253 | 250-252) ³⁹ | [39] |
| 21 | 4u | 4-CN-C ₆ H ₄ | 92 | 6 | 223-225 | 224-226) ³³ | [33] |
| 22 | 4v | 4-Me-C ₆ H ₄ | 92 | 7 | 225-227 | 227-229) ¹⁷ | [17] |
| 23 | 4w | 4-isopropyl-C ₆ H ₄ | 92 | 7 | 225-227 | 226-228) ³³ | [33] |
| 24 | 4x | C ₆ H ₅ -CO | 90 | 7 | 227-229 | 228-230) ³³ | [33] |
| 25 | 4y | 2-Naphthyl | 90 | 7 | 250-252 | 251-253 | [33] |

^aIsolated yield.

These results show that the [BMIm]HSO₄ promoted protocol has successfully accommodated wide range of aromatic aldehydes possessing broad array of functional groups and substitution patterns. The formations of products were confirmed by physical and spectroscopic data and are in good agreement with reported one. The simple experimental and product isolation procedure combined with ease of recovery and reusability of ionic liquid is expected to the

development of green strategy for the synthesis of phthalazine moiety. Finally, the recovery and reuse of the ionic liquid [BMIm]HSO₄ were studied in the preparation of **4b** as a model. The ionic liquid is recovered from the aqueous extracts of the reaction mixtures by evaporation of water under reduced pressure. The reaction medium can be recycled at least five times without significant decrease of the yields, ranging from 97% to 94%.



Scheme 2. Plausible mechanism for the synthesis of product (4).

According to these observations, A possible mechanism for the formation of 2*H*-indazolo[2,1-*b*]phthalazine-trione is shown in Scheme 2. In the first step, via Knoevenagel condensation of dimerone (1) with aromatic aldehyde (3) intermediate (5) was formed. Subsequent Michael-type addition of the phthalhydrazide (2) with intermediate (5) formed another intermediate (6), which underwent intramolecular cyclization to afford the final product (4).

4. Conclusions

In summary, an efficient protocol for the one-pot preparation of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives from the three-component condensation reaction of dimerone, phthalhydrazide and aldehyde using an environmental friendly and reusable ionic liquids, [BMIm]HSO₄, as catalyst was described. The reactions were carried out under solvent-free conditions with short reaction time and produced the corresponding products in good to excellent yields. The simplicity of the procedure, ecofriendly, non-volatile, easy handling, safety and reusability of catalyst are the advantages of these methods. These methods not only afford the products in excellent yields but also avoid the problems associated with catalyst cost, and pollution.

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