



# Acidic-functionalized ionic liquid as an efficient, green, and metal-free catalyst for benzylation of sulfur, nitrogen, and carbon nucleophiles to benzylic alcohols



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## ABSTRACT

A series of  $\text{HSO}_4^-$  functionalized ILs was synthesized and used as efficient, green, and metal-free catalysts for benzylation. Notably, the catalytic system has wide substrate scopes and the ionic liquid catalysts were applied to investigate three different types of nucleophiles to give the desired benzylation products with moderate to excellent yields.

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## 1. Introduction

Over the past decades, ionic liquid (IL) research is undergoing an unprecedented explosion of interest, due to their particular physicochemical properties, such as negligible vapor pressure, excellent chemical, and thermal stability, good solvating ability, ease of recyclability and their potential to enhance reaction rates.<sup>1</sup> Some have been successfully used as an environmentally friendly alternative to conventional organic solvents or catalysts in a number of reactions,<sup>2</sup> such as Diels–Alder reaction,<sup>3</sup> Friedel–Crafts reaction,<sup>4</sup> esterification,<sup>5</sup> cracking reactions.<sup>6</sup> Among them, acidic-functionalized ILs has been intensively studied.<sup>7</sup> Especially, Brønsted acidic task-specific ionic liquids (TSILs) (Fig. 1), combining some useful characteristics of solid acids and mineral acids, which have been exploited as efficient catalysts and generally can afford higher yields and selectivities in chemical processes.<sup>8</sup>

The alkylation reaction of activated nucleophilic reagents, such as thiols, amines, indoles, is used as a powerful tool for the formation of carbon–carbon and carbon–heteroatom bonds, especially the benzylation (Scheme 1). The benzyl motif is ubiquitous in the realms of pharmacologically active agents and natural products. Particularly, *N*-benzyl amine scaffold and C3-benzyl indoles exhibit a wide range of biological activities. For example, *N*<sup>1</sup>-benzyl-*N*<sup>2</sup>,*N*<sup>2</sup>-dimethyl-*N*<sup>1</sup>-phenylethane-1,2-diamine, which is known as Antergan (Fig. 2, A),<sup>9</sup>

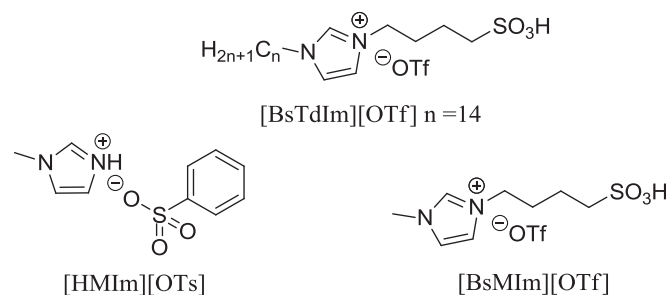
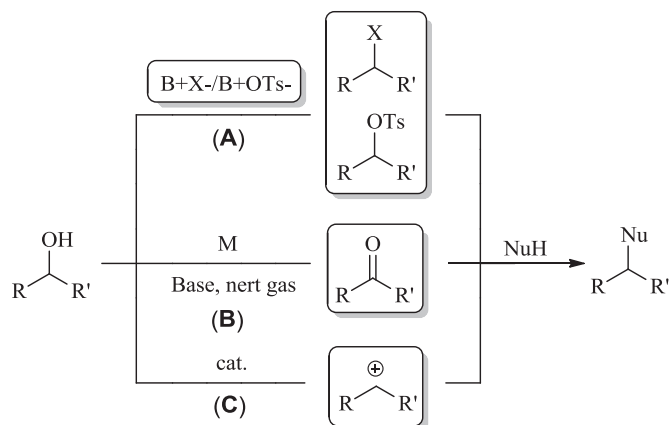


Fig. 1. Reported Brønsted acidic task-specific ionic liquids (TSILs) used in chemical processes.

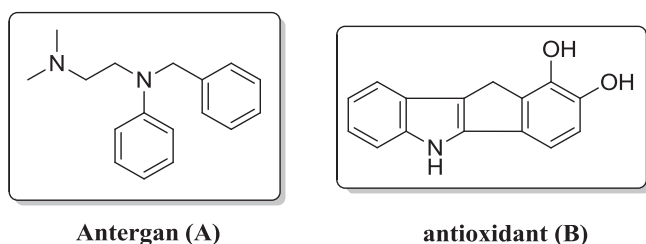
is among the first antihistamine drugs to be sold and its structure provide the framework for antihistamine agents; B has effective antioxidant power and radical scavenging activities (Fig. 2, B).<sup>10</sup>

Generally, this transformation is performed with benzyl halides or activated benzyl alcohols,<sup>11</sup> in presence of stoichiometric amount of base, which results in the generation of large quantities of waste salts, have intrinsic drawbacks in terms of atom economy (Scheme 1, path A).<sup>12</sup> One popular concept to overcome the poor reactivity of the most benzylic alcohols is to temporarily convert them into corresponding carbonyl intermediates by the metal-catalyzed removal of hydrogen, which is well known as 'Hydrogen autotransfer processes' (Scheme 1, path B).<sup>13</sup> Another proposed mechanism is carbocation mechanism (Scheme 1, path C), using Lewis acid or Brønsted acids, such as  $\text{BF}_3 \cdot \text{OEt}_2$ ,<sup>14</sup>  $\text{InCl}_3$ ,<sup>15</sup>  $\text{Bi}(\text{OTf})_3$ ,<sup>16</sup> or H-

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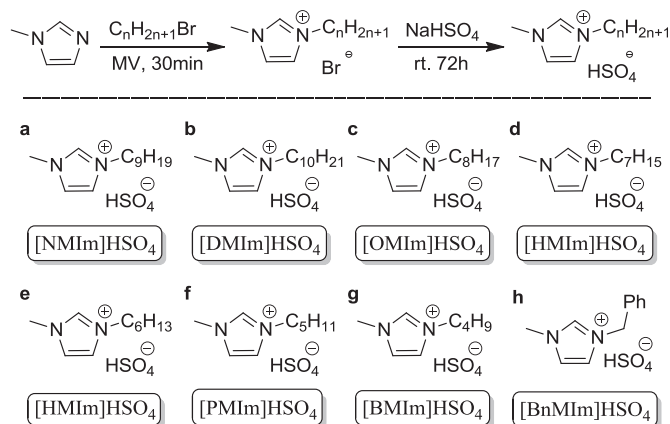
**Scheme 1.** Nucleophilic substitution reactions of alcohols by preactivation (A) and direct catalytic substitutions (B) and (C).



**Fig. 2.** The medicinal and other applications of *N*-benzyl amine scaffolds (A) and C3-benzyl indoles (B).

montmorillonite,<sup>17</sup> *p*-toluenesulfonic acid,<sup>18</sup> triflic acid,<sup>19</sup> benzhydryl alcohols can be turned to carbocations, which are then attacked by nucleophiles.

Almost all of these catalytic systems suffered from below one or more disadvantages: (1) expensive transition metals with additives are essential; (2) the catalysts are sensitive to air; (3) nucleophiles are excessive. To the best of our knowledge, the direct benzylation reactions catalyzed by acidic-functionalized ionic liquids are still relatively rare.<sup>20</sup> Moreover, when we are preparing this paper, Xia's group reported sulfonic acid-functionalized ionic liquids used as catalysts for the direct amination of alcohols.<sup>8d</sup> However, in our method more inexpensive acidic-functionalized ionic liquids catalysts could be obtained with simple work-up. On the other hand, rarely reported catalysts were applied to investigate three different types of nucleophiles in details. As a continuation of our interests in ILs mediated reactions<sup>21</sup> and acidic-functionalized ionic liquids catalyzed reactions,<sup>22</sup> herein, we report the development of a simple procedure utilizing acidic-functionalized ionic liquids (Scheme



**Scheme 2.** Preparation of  $\text{HSO}_4^-$  functionalized ionic liquids.

2), as metal-free, green, and efficient catalysts for the benzylation of benzothiazole-2-thiols, *N*-containing substrates, and indoles, and synthesize a series of *S*, *N*, *C*-benzyl scaffold derivatives under mild conditions.

## 2. Results and discussion

As we know, sulfur-containing compounds are difficult to use in the presence of Lewis acidic metals because of their strong coordinating and adsorptive properties to poison these catalysts, although some advances have been developed.<sup>23</sup> Therefore, the development of a more efficient catalytic system for benzylation of thiols becomes highly desirable. To verify the practicability of the projected route, a series of  $\text{HSO}_4^-$  based ILs with different cations were synthesized according to our previous methods (Scheme 2)<sup>22</sup> with some changes and their performance in the direct nucleophilic substitution of alcohols was studied. 1,3-Benzothiazole-2-thiol (**1a**), the fragment is featured in a wide variety of pharmacologically and biologically active compounds,<sup>12</sup> could be used in the model reaction as an agent reacted with (4-methoxy-phenyl)-methanol (**2a**) to synthesize benzylic thioethers, the results are shown in Table 1. At the outset, the reaction was carried out in the presence of an ionic liquid **a** (10 mol %) at room temperature in various solvents for 24 h (Table 1, entries 1–8). When  $\text{CH}_3\text{CN}$  or  $\text{CHCl}_3$  was selected as the solvent, the desired product 2-(4-methoxy-benzylsulfanyl)-benzothiazole (**3aa**) was obtained in 86% yield (Table 1, entries 4 and 8). Other solvents, such as toluene, EtOH, DMF, DMSO, and THF, were inferior to  $\text{CH}_3\text{CN}$  (Table 1, entries 2–7). Additionally, further expansion of this protocol to other thiols compounds was limited, although the highest yield (87%) of product **3aa** was obtained when water was employed (Table 1, entry 1). Subsequently, other functionalized ionic liquids were investigated (Table 1, entries 9–15). Interestingly, it was found that the yield decreased with the carbon number of the side chain of imidazolium cations increasing from five to eight and dramatically increased when further increasing the carbon number. Only 26% yield was obtained when [BnMI]HSO<sub>4</sub> was used (Table 1, entry 15). The results indicated that the side chain has a certain impact on the activities of ionic liquids, **b** and **f** were found to be the most effective (Table 1, entries 9 and 13). Compared with these ionic liquids, NaHSO<sub>4</sub> was selected as the candidate here to determine whether the catalytic reactivities of ionic liquids were due to the same anion (Table 1, entries 3, 4 and 7). Otherwise, only low yield of the desired product was produced (see the Supplementary data, Table S1), making us confirmed that ionic liquids present high activity primarily ascribed to its imidazole cation. We also screened other commonly used Brønsted or Lewis acid catalysts, no better results were observed in these cases (Table 1, entries 16 and 18).

With the optimal reaction conditions in hand, we continued to explore the scope of the reaction by using various related electron-rich alcohols and the results were summarized in Table 2. Similar to the case of **2a**, the reaction of benzothiazole-2-thiol (**1a**) with benzylic alcohols bearing donating groups, such as methoxyl and methyl, moderate to high yields *S*-alkylated products could be formed (Table 2, entries 1–4). It is noteworthy that benzylic alcohol with steric hindered substituents at 2-position has dramatic detrimental effect on this reaction. Moreover, benzylic alcohols bearing two or more substituted methoxyl groups showed good activities, owing to the electronic effect and sometimes steric effect, and the corresponding products were obtained with 84% and 71% yields, respectively (Table 2, entries 2 and 3). Further, the conditions were also applied to the reaction with other aromatic alcohols, such as thiophen-2-yl-methanol (**2e**) and benzo[1,3]dioxol-5-yl-methanol (**2f**), affording the designed products with 49% and 72% yields, respectively (Table 2, entries 5 and 6). Secondary alcohol, 1-(ferrocenyl) ethanol (**2g**) was also chosen to detect the

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