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Direct sulfonylation of Baylis–Hillman alcohols and diarylmethanols with TosMIC in ionic liquid-[Hmim]HSO_4: an unexpected reaction

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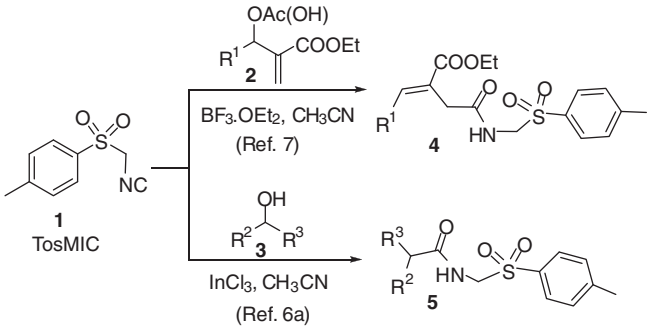
ABSTRACT

A Brønsted acidic ionic liquid-[Hmim]HSO_4 promoted unexpected reaction of Baylis–Hillman alcohols and diarylmethanols with *p*-toluenesulfonylmethyl isocyanide (TosMIC) affording the corresponding sulfone derivatives instead of *N*-tosylmethyl amides is reported. After isolation of the product, the ionic liquid [Hmim]HSO_4 was easily recycled for further use.

The tight restrictions on the release of waste and toxic emissions for the reduction of environmental pollution have induced a paradigmatic shift in the development of new synthetic strategies. Thus, in addition to the required mildness and selectivity, the issue of environmentally friendly reaction conditions has become increasingly important in designing alternate synthetic routes for fine chemicals. In this context, ionic liquids (ILs) are emerging as effective promoters and alternative solvents for green chemical reactions because of their many fascinating properties. ILs are simple, easy to recycle, inexpensive to prepare, and their properties can be fine tuned by changing the anion or the alkyl group attached to the cation.[1] Recently, Brønsted acidic ionic liquids have been deemed promising alternatives for acid catalyzed reactions and play a dual solvent–catalyst role in a variety of organic reactions.[2]

p-Toluenesulfonylmethyl isocyanide (TosMIC)[3] is a versatile and widely exploited reagent in a diverse range of organic reactions manifesting into valuable scaffolds, building blocks, and heterocycles. The broad synthetic utility stems from its varied functional groups: the isocyano group undergoes typical α-addition reactions, the acidic α-carbon atom and the sulfonyl group in the α-position serve two functions by acting both as a sulfonyl leaving group and contributing to the enhanced acidity of the α-carbon. TosMIC can be viewed as a specialized type of *N,S*-acetal due to the presence of the geminal isocyano and tosyl groups and reacts accordingly. Apart from the TosMIC mediated synthesis of *C*-nucleosides[4] and diastereoselective Passerini reactions,[5] recent endeavors show its application in transition metal catalyzed carbon–carbon bond formation by the reaction with aryl alcohols[6a] and 1,3-dicarbonyl compounds[6b] affording *N*-tosylmethyl amides and β-keto-(*E*)-enamino esters, respectively. Quite recently, Yadav et al.[7] have applied the Baylis–Hillman (BH) chemistry[8] to access functionalized allyl amides from the reaction between TosMIC **1** and BH acetates in the presence of Lewis acid (Scheme 1). In this report they have mentioned that TosMIC could also react with BH alcohols instead of BH acetates to afford allyl amides, but conversion rate was poor (20–45%) even after long reaction time.[7]



Scheme 1. Synthesis of *N*-tosylmethyl amides **4** and **5** using TosMIC.

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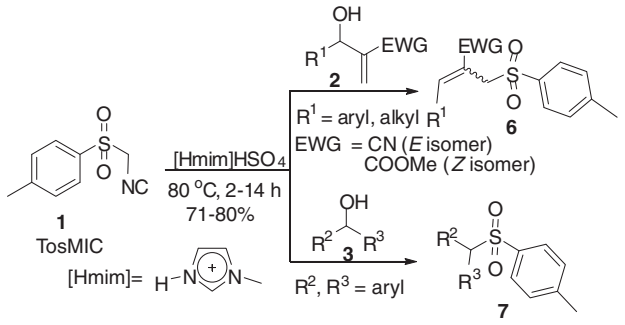


Scheme 2. Ionic-liquid promoted synthesis of sulfone derivatives **6** and **7** using TosMIC and alcohols.

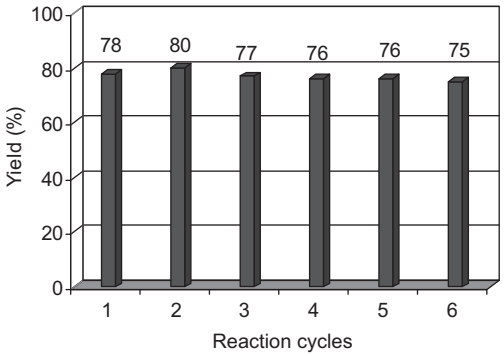
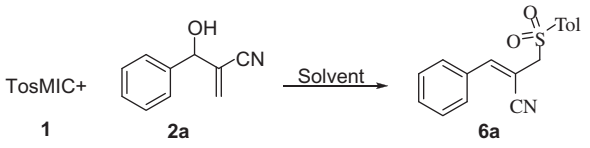


Figure 1. Reusability of ionic liquid [Hmim]HSO_4.

Table 1
Reaction of BH alcohol **2a** with TosMIC under different conditions[a]



Entry	Solvent[b]	Time (h)	Temp (°C)	Yield[c,d] (%)
1	[Hmim]HSO_4	10	80	48
2	[Hmim]HSO_4–H_2O	10	80	78
3	[Hmim]HSO_4–H_2O	15	50	42
4	[Hmim]HSO_4–H_2O	20	25	—
5	[Hmim]H_2PO_4–H_2O	10	80	52
6	[Bmim]Cl–H_2O	10	80	—
7	[Bmim]BF_4–H_2O	10	80	—
8	[Bmim]PF_6–H_2O	10	80	—
9	[Hmim]HSO_4–H_2O [e]	10	80	71
10	aq H_2SO_4 (20%)	10	80	39

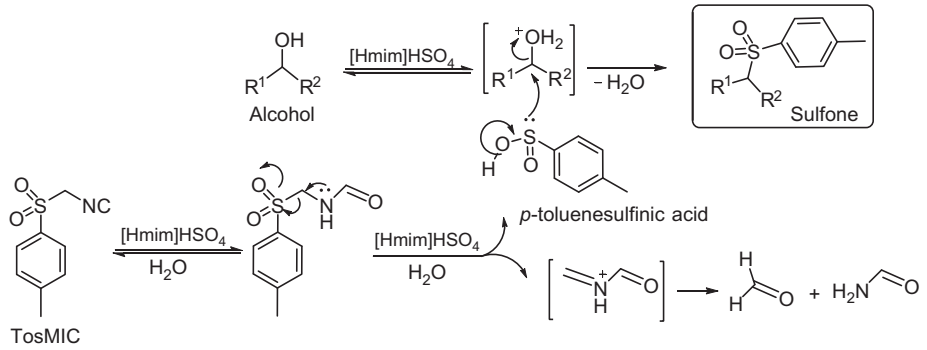
[a] All reactions were performed using 1 mmol of BH alcohol **2a** and 1.1 mmol TosMIC.
[b] 1 mL of solvent was taken. In case of ionic liquid–H_2O system the ratio was 10:1.
[c] Isolated yields after column chromatography.
[d] In all cases *E*/*Z* ratio was found to be >90:<10 in crude products as determined by ^{1}H NMR analysis.
[e] Instead of TosMIC, freshly prepared *p*-toluenesulfinic acid (1.2 mmol) was used.

Intrigued by the above reports[6a,7] and in continuation of our research program based on ionic liquid promoted organic synthesis[9] along with BH chemistry,[10] initially we attempted to develop a green protocol for TosMIC mediated synthesis of various amide derivatives (Scheme 1). Thus, BH alcohols and other aryl alcohols were reacted with TosMIC implementing reusable Brønsted acidic ionic liquid-[Hmim]HSO_4 to act both as a solvent and catalyst in order to replace metal derived Lewis acids and to minimize the use of common organic solvents. Surprisingly, instead *N*-tosylmethyl amides **4** and **5** (Scheme 1), unexpected sulfone derivatives **6** and **7** were obtained under the reaction conditions (Scheme 2).

The sulfones **6** and **7** are well known to serve as useful building blocks for a number of important carbon–carbon bond forming reactions due to the unique reactivity pattern of α-sulfonyl carbanions under various reaction conditions.[11,12] Additionally, they are the main constituents of some biologically important compounds that have potential for the treatment of Alzheimer's disease,[13] cancer, and abnormal cell proliferation diseases.[14] Although several new methods have recently been reported to access benzylic and allylic sulfones,[15,16] the application of TosMIC for the synthesis of sulfone derivatives from alcohols has not been yet documented and represents a unique and unprecedented protocol adding a new manifold in TosMIC chemistry.

In an exploratory experiment, 2-(hydroxyphenylmethyl) acrylonitrile (BH alcohol) **2a** (1 mmol) and TosMIC (1.1 mmol) were taken in a Brønsted acidic ionic liquid–water system [Hmim]HSO_4–H_2O (1 mL, 10:1) and the mixture was stirred at 80 °C. After 10 h, the reaction mixture was cooled to rt, and extracted with dichloromethane. The organic layer on usual processing and chromatography afforded a colorless crystalline solid (mp 125 °C) in 78% yield that to our surprise was found to be the trisubstituted allyl sulfone **6a** (Table 1, entry 1). The structure of **6a** was assigned on the basis of ^{1}H, ^{13}C NMR and mass spectroscopy as well as by comparison with the literature data.[16c] The *E*/*Z* ratio was found to be 94:6 as determined by ^{1}H NMR analysis of the crude product.

To get an insight into the mechanism, we also performed the reaction of TosMIC with a model substrate 2-(hydroxyphenylmethyl) acrylonitrile (BH alcohol) **2a** in various conditions and results are compiled in Table 1. As it is evident from Table 1, [Hmim]HSO_4–H_2O (pK_a = 1.88) was found to be the best solvent system



Scheme 3. Plausible mechanism for ionic-liquid promoted solfonylation of alcohols with TosMIC.

Table 2
Reaction of alcohols with TosMIC in [Hmim]HSO_4[a] (Scheme 2)

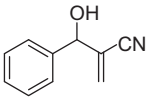
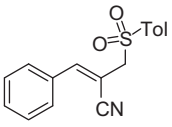
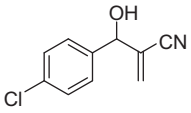
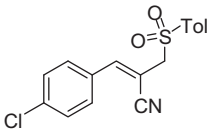
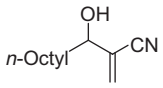
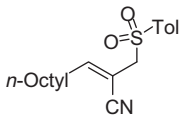
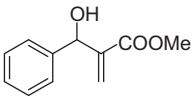
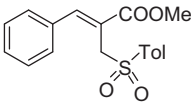
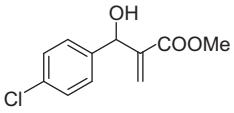
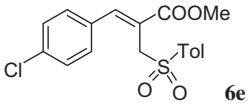
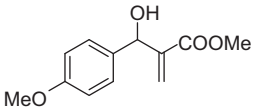
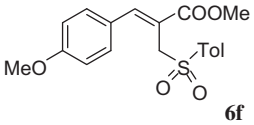
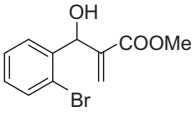
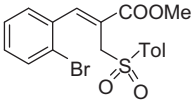
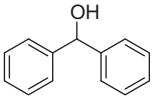
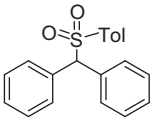
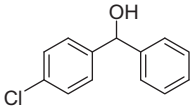
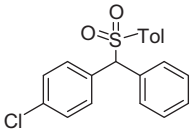
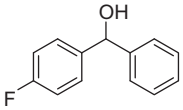
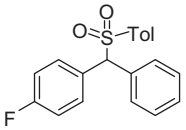
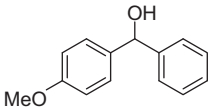
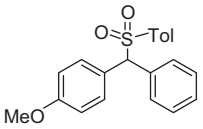
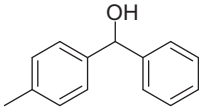
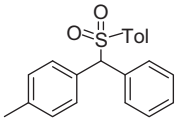
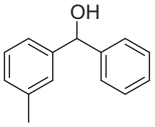
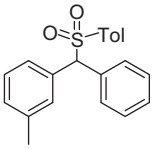
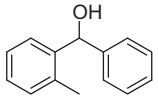
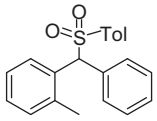
Entry	Alcohol	Product[b]	Time (h)	Yield[c] (%)	*E*/*Z* ratio[d]
1		 **6a**	10	78	94:6
2		 **6b**	14	74	92:8
3		 **6c**	10	70	90:10
4		 **6d**	12	72	4:96
5		 **6e**	14	71	5:95
6		 **6f**	10	76	7:93
7		 **6g**	14	74	3:97
8		 **7a**	10	79	–
9		 **7b**	3	76	–
10		 **7c**	4	74	–
11		 **7d**	2	80	–
12		 **7e**	3	74	–
13		 **7f**	3	76	–
14			3	72	–

Table 2 (*continued*)

Entry	Alcohol	Product[b]	Time (h)	Yield[c] (%)	*E*/*Z* ratio[d]
		 **7g**			

[a] See Ref. 17 for general procedure.
[b] All the products are known compounds[15c,e,16c] and were characterized by comparison of their mp and spectral data with those of reported in the literature.
[c] Yields of pure isolated products after column chromatography.
[d] The selectivity was determined by ^{1}H NMR analysis.

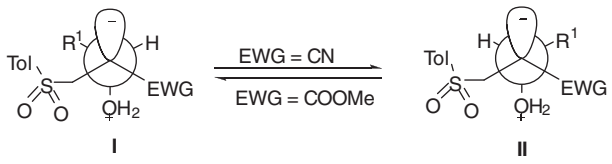


Figure 2.

to access the corresponding sulfone **6a**. Its superiority over [Hmim]HSO_4 (Table 1, entries 1 and 2) indicates the role of water in hydrolysis of TosMIC (Scheme 3). The temperature appears crucial because lowering the reaction temperature from 80 to 50 °C lowered the product yield, and the reaction did not take place appreciably at 25 °C even after stirring for 20 h (Table 1, entries 3 and 4). The reaction was unsuccessful in ionic liquid–water systems such as [Bmim]Cl–H_2O, [Bmim]BF_4-H_2O, and [Bmim]PF_6-H_2O, which indicates that a Brønsted acid is necessary to catalyze the present reaction. However, the reaction proceeded in the [Hmim]H_2PO_4-H_2O system but relatively low yield (52 %) of sulfone **6a** was obtained (Table 1, entry 5). This is probably due to the lower Brønsted acidity associated with [H_2PO_4].

We also attempted the direct sulfonylation of alcohols using TosMIC in 20% aq. H_2SO_4 (pKa = 2.0) under the same reaction conditions, but a reduced product yield was obtained (Table 1, entry 10). Eventually, the recycling performance of ionic liquid [Hmim]HSO_4 in the same model reaction was also investigated. After isolation of product **6a**, the ionic liquid [Hmim]HSO_4 was easily recovered, and reused[17] at least in five runs without appreciable decrease in catalytic activity as shown in Figure 1. Thus, [Hmim]HSO_4 plays a dual role, that is, as an acid catalyst and as well as a good reusable solvent for the present unprecedented protocol for the direct sulfonylation of alcohols with TosMIC. Owing to the presence of the organic moiety in [Hmim]HSO_4, it is a better solvent than aq 20% H_2SO_4 for organic reactants **1**–**3**. Here, TosMIC is decomposed to expel *p*-toluenesulfinic acid which acts as the actual nucleophile. A reaction of freshly prepared *p*-toluenesulfinic acid with BH alcohol **2a** proceeds smoothly supporting the role of *p*-toluenesulfinic acid as the nucleophile (Table 1, entry 9). The stabilized *p*-toluenesulfinate anion is commonly used in the preparation of sulfones,[16a,c,18] but the use of TosMIC as a source of the *p*-toluenesulfinate anion for the direct sulfonylation of alcohols under acidic conditions has not been explored so far. Although our conceptualization of a novel synthesis of *N*-tosylmethyl amides by avoiding the commonly used Lewis acid in volatile organic solvents did not materialize (Scheme 1), the preparative value of this transformation proceeding in reusable solvent cum catalyst-[Hmim]HSO_4–H_2O system and its mechanistic importance prompted us to pursue the reaction in some detail. Thus, we turned our attention to apply this protocol on other alcohols and the results are summarized in Table 2.

The reaction of TosMIC with methyl 2-(hydroxyphenylmethyl) acrylate in [Hmim]HSO_4 proceeded to give predominantly trisubstituted allylic sulfone-(*Z*)-methyl 3-phenyl-2-(tosylmethyl)acrylate (Table 2, entry 4). Other acrylate derived BH alcohols such as *p*-chloro, *p*-methoxy, *o*-bromo derivatives reacted cleanly with TosMIC under similar protocol to afford the corresponding trisubstituted allylic sulfones (Table 2, entries 5–7) in good yields (71–78%) with high diastereoselectivity (*E*/*Z* ratio from 3:97 to 7:93). Significantly, the reaction is highly stereoselective for both acrylonitrile/acrylate ester-derived BH alcohols, but with reversed stereochemical directive effect, that is, acrylonitrile-derived BH alcohols (**2a–c**, EWG = CN) predominantly afforded *E*-allyl sulfones (Table 1, entries 1–3) while acrylate ester-derived BH alcohols (**2d–g**, EWG = COOMe) selectively afforded *Z*-allyl sulfones (Table 2, entries 4–7) under the same reaction conditions. The configuration of trisubstituted allyl sulfones **6a–g** was assigned by comparing the ^{1}H NMR and ^{13}C NMR data with those of the published ones,[15c,16c] and was further confirmed by NOE experiments. The products **6a–g** were studied by NOE experiments. Products **6a–c** showed NOE between methylene protons and vinyl protons confirming the *E* configuration, and products **6d–g** showed NOE between methylene protons and aromatic protons and showed no NOE between methylene and vinyl protons confirming the *Z* configuration. Although no mechanistic studies have been carried out, related stereochemical reversals are attributed to differences in relative stabilities of intermediates as explained earlier by considering models (**I** and **II**) depicted in Figure 2.[19] When R^1 is a large group (R^1 = COOMe), model **I** is favored and thus predominantly forms the *Z* isomer. If R^1 is a small group (R^1 = CN), then model **II** is favored and, therefore, predominantly forms the *E* isomer.

The present protocol was also found suitable for the direct sulfonylation diarylmethanols containing both electron withdrawing and electron donating substituents (Table 2, entries 8–14) and afforded the corresponding benzylic sulfones in good yields (72–80%). Unfortunately, the reaction of 1-phenylethanol with TosMIC did not afford the corresponding benzylic sulfone under the present reaction conditions. Based on an observation presented in Table 1, a plausible mechanism for this reaction is depicted in Scheme 3.

In conclusion, we have uncovered a Brønsted acidic ionic liquid-[Hmim]HSO_4 promoted unprecedented reaction of *p*-toluensulfonylmethyl isocyanide (TosMIC) with alcohols affording the corresponding sulfone derivatives in good yields. The present work has explored TosMIC formally as a source of tosyl nucleophile in substitution reaction with alcohols, which opens up a new aspect of synthetic utility of both TosMIC and Brønsted acidic ionic liquids.

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17. *General procedure for the synthesis of [E]- and [Z]-allyl sulfones (**6**) and benzyl sulfones (**7**)*: A stirred solution of *p*-toluenesulfonylmethyl isocyanide (TosMIC) (1.1 mmol) and alcohols **2** or **3** (1 mmol) in 1 mL of [Hmim]HSO_4–H_2O (10:1) was heated at 80 °C for 2–14 h (Table 2). The reaction progress was monitored by TLC. Upon completion, the reaction mixture was cooled to rt and extracted with dichloromethane (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting crude product was purified by silica gel column chromatography using a gradient mixture of hexane/ethyl acetate (8:2) as eluent to give the corresponding pure sulfone derivatives **6** and **7**. All the products are known compounds[15c,e,16c] and were characterized by comparison of their mp and spectral data with those of reported in the literature. After isolation of the product, the remaining mother liquid containing the ionic liquid was washed with dichloromethane (2 × 5 mL) to remove any organic impurity, dried under vacuum at 90 °C to afford [Hmim]HSO_4 in an excellent yield (96%), which was used in subsequent runs without further purification (Fig. 1). The recovery yield of [Hmim]HSO_4 in subsequent runs was >93%.
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