IONIC LIQUID PROMOTED GREEN APPROACH FOR NOVEL AND EFFICIENT SYNTHESIS OF *N*-TOSYL IMINES

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An ionic liquid promoted green and environment friendly synthesis of *N*-tosyl imines of aromatic aldehydes is described. The present protocol involves use of ionic liquid without any added catalyst to afford the corresponding products in moderate to excellent yield (80-95%). The process is easy for isolation, tolerance towards both electron-donating and electron-withdrawing substrates which makes it as a valuable method in synthetic chemistry.

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Introduction

Ionic liquids (IL) are the molten organic salts which are liquid at temperatures below 100 °C. These salts are liquid at room temperature hence called as room temperature ionic liquids liquids. Ionic liquids have very low vapor pressure, high boiling points and their polarity can be varied in wide range depending on the nature of both anions and cations.

ILs are used as preferable solvents in a number of organic reactions. In addition, recycling and reuse of IL is possible and their application is so called "working solutions" wherein a catalyst is dissolved and this phase can be easily separated and reused. Ionic liquids have many fascinating properties which make them fundamental to all chemists.

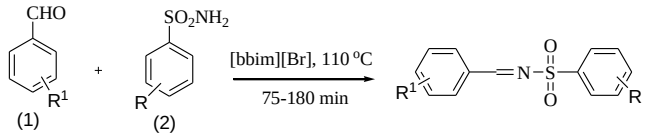
N-tosyl imines are versatile intermediates in organic synthesis.[1] *N*-tosyl imines find utility as electron deficient 1, 3-azabutadiene equivalents in inverse electron demand Diels-Alder chemistry,[2] electrophilic aza-aldehyde equivalents in addition reactions,[3] reactive olefin equivalents in ene reactions ,[4] or as precursors to *N*-sulfonyloxaziridines which have utility as chiral oxidants.[5] Due to the broad synthetic utility of tosylimines, numerous methods have been developed for their synthesis. These methods include utilization of tellurium metal and chloramines,[6] rearrangement of oxime *N*-sulfinates, [7] Lewis acid-promoted reaction of sulfonamide with aldehyde or acetals,[8] additions of *N*-sulfinyl sulfonamide to aldehydes in the presence of BF_3-Et_2O, using sodium benzenesulfinate in formic acid,[9] using $TiCl_4$,[10] and in the presence of trifluoroacetic anhydride as the dehydrating agent.[11] They are also synthesized from aziridines using palladium catalyst.[12] *N*-tosyl imines are difficult to prepare via condensation reactions. Typically the condensation of sulfonamides with arylaldehyde requires harsh conditions and usually results in lower yields in long time period. The classical reactions are generally carried out in benzene, toluene, DCM etc. and also suffer from various disadvantages such as use of environmentally hazardous solvents /reagents, tedious work-up procedure, prolonged long reaction period, less yield, expensive catalyst etc. Due to harsh reaction conditions, prolonged time period, less yield and to avoid molecular solvents, the development of new methods for the synthesis of *N*-tosyl imines under mild conditions is necessary. An ideal method would be general, atom economical and would not require toxic or other hazardous reagents.

Thus, the use of solvents such as water, supercritical fluids and ionic liquids has received much attention in recent times in the area of green synthesis. In this respect, ambient temperature ionic liquids have emerged as a set of green solvents with unique properties such as tunable polarity, high thermal stability and immiscibility with a number of organic solvents, negligible vapour pressure and recyclability.[13]

Their high polarity and ability to solubilise both organic and inorganic compounds can result in enhanced rates of chemical process and provide higher selectivity as compared to conventional solvents. Recently these ionic liquids are found to work as efficient dehydrating agents. They are emerging as novel replacements for volatile organic solvents in organic synthesis. Ionic liquids, however, have been used as promoters and solvents although they provide advantages of easy recovery and reuse of reaction media. Moreover, ionic liquids are inexpensive and simple to prepare and easy to recycle and their properties can be fine-tuned by changing the anion or the alkyl group attached to the cation.

In view of the emerging importance of the imidazolium based ionic liquids as novel reaction media and in our ongoing investigation on imidazolium based ionic liquids we wish to report an environmental friendly and recyclable solvent system for the synthesis of *N*-tosylimines of aryl aldehydes (Scheme 1).

In addition to the above-mentioned salient features of ILs as reaction media, we have also recently shown that they can also promote and catalyse organic transformations of commercial importance under ambient conditions without the need for any added catalyst or ligand. As a part of our comprehensive ongoing programme on ionic liquid promoted organic transformations, we chose to evolve an efficient and ecofriendly process for the synthesis of *N*-tosyl imines in ambient temperature ionic liquid as reaction media and promoters in the absence of any added catalyst.



[bbim][Br] promoted synthesis of N-tosylimines

Scheme

Table 1. Condensation of different arylaldehyde (1) with p-toluene sulfonamide (2) in [Bbim]Br at 110 °C

Entry	R	R'	Melting point, ◦C	Product	Time (min)	[b]Yield, %	
						[Bbim][BF4]	[Bbim][Br]
1	CH_3	4-Me	116-118	3a	75	84	85
2	CH_3	4-MeO	124-128	3b	90	85	84
3	CH_3	4-NO_2	162-170	3c	80	82	82
4	CH_3	4-Cl	174-176	3d	105	90	90
5	CH_3	2-Cl	130-132	3e	150	88	88
6	CH_3	2-F	120–125	3f	120	85	86
7	CH_3	H	105–108	3g	90	95	95
8	CH_3	4-Br	200–204	3h	110	86	85
9	CH_3	2,5-MeO	120-124	3i	190	80	80
10	H	4-Me	110-112	3j	180	84	84
11	H	4-MeO	130-134	3k	140	85	85
12	H	4-NO_2	110-112	3l	110	82	82
13	H	4-Cl	128-132	3m	95	90	92
14	H	2-Cl	132-136	3n	130	87	89
15	H	2-F	119-125	3o	170	87	88
16	H	H	80-82	3p	90	92	94
17	H	4-Br	198-204	3q	120	82	84
18	H	2,5-MeO	118-124	3r	180	81	82

[a:] Isolated yield after crystallization

Herein we disclose a successful outcome of this endeavor in which sulfonamide is condensed with aromatic aldehydes in IL and afforded excellent to moderate yield of products in short reaction time.

Experimental

All chemicals were of research grade and were used as obtained from Aldrich or Fluka. The ionic liquid [bbim]Br was prepared as per the method already reported.[14] Melting points were uncorrected. IR spectra were recorded on Mattson Research Series FTIR spectrometer, mass spectra on Finnigan Mat-1020 automated GC/MS spectrometer and ^{1}H NMR spectra on Bruker-200 MHz spectrometer.

General procedure for the condensation of aldehyde (1) with p-toluene sulfonamide (2) in ionic liquid

To a mixture of aldehyde (1 mmol) and p-toluene sulfonamide (1 mmol) requisite amount of dry ionic liquid [Bbim]Br was added and the contents were stirred at 110-120 ºC temperature. The completion of reaction was followed by TLC using 40% EtOAc in petroleum ether as eluent. After completion, the reaction mixture was diluted with water (25 ml) and filtered. The product thus obtained was pure (single spot on TLC). It was subjected to further purification by crystallization using ethyl acetate to obtain pure product and characterized. The aqueous layer consisting IL was subjected to distillation (80 ºC, 10 mm Hg) for 2 h to remove water, leaving behind the IL, [Bbim]Br (recovery 98%), which was reused three times with minor loss in yield. All the compounds described herein are reported in literature. The compounds were characterized by spectral data and physical constants reported earlier.

The spectral data of compounds is mentioned below:

Product Table 1, entry 3a (E)-N-(4-methylbenzylidene)-4-methylbenzenesulfonamide: ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 6H), 7.20 (d, 2H), 7. 30 (d, 2H), 7.78 (d, 2H), 7.88 (d, 2H), 8.92 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 20.0, 124, 126.5, 130, 132, 130, 133, 137.4, 145.5, 172. Mass spectrum, m/z (relative intensity): 274.1(M+1).

Product Table 1, entry 3b (E)-N-(4-methoxy-benzylidene)-4-methylbenzenesulfonamide: ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H), 3.80 (s, 3H), 7.2 (d, 2H), 7.30 (d, 2H), 7.84 (d, 2H), 8.0 (d, 2H), 8.96 (s, 1H). ^{13}C NMR ($CDCl_3$): 20.2, 57.2, 117, 126, 129.2, 131, 135.4, 137.2, 146.2, 167, 171. Mass spectrum, m/z (relative intensity): 290.1(M+1).

Product Table 1, entry (3d) (E)-N-(4-chlorobenzylidene)-4-methylbenzenesulfonamide: ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H), 7.20 (d, 2H), 7.40 (d, 2H), 7.90 (dd, 4H), 9.10 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 21.5, 127.4, 129.2, 130, 130.3, 131.7, 137, 142.5, 147, 170.4. Mass spectrum, m/z (relative intensity): 294.0 (M+1).

Product Table 1, entry 3e (E)-N-(2-Chloro-benzylidene)-4-methylbenzenesulfonamide: ^{1}H NMR ($CDCl_3$): δ 2.40 (s,

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3H), 7.4-7.8 (m, 8H), 9.20 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 21.5, 127.4, 129, 130, 131.2 132.4, 132.4, 135.2, 136.8, 171. Mass spectrum, m/z (relative intensity): 294.0 (M+1).

Product Table 1, entry 3g (E)-N-Benzylidene-4-methylbenzenesulfonamide: ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 7.30 (d, 2H), 7.52 (t, 2H), 8.02 (t, 1H), 7.68–7.78 (m, 4H), 9.10 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 20.6, 127.4, 128.6, 129.1, 130.2, 134.8, 142, 146.2, 168.1. Mass spectrum, m/z (relative intensity): 260.1(M+1).

Product Table 1, entry 3h (E)-N-(4-Bromobenzylidene)-4-methylbenzenesulfonamide: ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 7.20–7.68 (m, 8H), 8.6 (s, 1H). ^{13}C NMR ($CDCl_3$): 21.8, 123.8, 127.1, 130, 130.8, 131.5, 134.5, 169.0. Mass spectrum, m/z (relative intensity): 337.9 (M+1).

Product Table 1, entry 3i (E)-N-(2,5-Dimethoxy-benzylidene)-4-methylbenzenesulfonamide: ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H), 3.58 (s, 3H), 3.85 (s, 3H), 7.10–7.76 (m, 7H), 9.41 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 22.2, 54.2, 57.1, 109.8, 112.9, 120.6, 124.4, 128.2, 131.8, 135.2, 145.1, 152.8, 157.4, 166.8. Mass spectrum, m/z (relative intensity): 320.2 (M+1).

Product Table 1, entry 3o (E)-N-(2-Fluoro-benzylidene)benzenesulfonamide: ^{1}H NMR ($CDCl_3$) δ 9.32 (s, 1H), 8.21 (d, 1H), 7.85 (d, 2H), 7.40–7.52 (m, 3H), 7.32 (t, 2H), 7.18 (t,1H); ^{13}C NMR ($CDCl_3$): δ 20.5, 126.3, 128.4, 129.6, 130.2, 131.4, 132.4, 136.2, 137.2, 169.0. Mass spectrum, m/z (relative intensity): 264.15 (M+1).

Product Table 1, entry 3p (E)-N-benzylidenebenzenesulfonamide (3p): ^{1}H NMR ($CDCl_3$): 7.55 (m, 6H), 8.2 (m, 4H), 9.10 (s, 1H) Mass spectrum, m/z (relative intensity): 246.1 (M+1).

Result and Discussion

The reaction was tried at ambient temperature, but it does not proceed even when continued for longer time (24 h). But no progress in reaction was observed on TLC, so we increased temperatures slowly to 110 °C temperature. The reaction proceeds very well but below this temperature there was no reaction or no product formation was observed. This was due to reversible reaction. Higher temperature above 110 °C didn't show any shortening of reaction time.

As we got excellent results in the synthesis of tosyl imines using IL [bbim]BF_4 as compared to [bbim]Br with respective to yield and time period. So we except same results from [Hbim]BF_4, but unfortunately we didn't got similar results as [bbim]BF_4 with respect to yield and time. We had done this reaction in different ionic liquids as shown in Table 2, we found that [bbim]Br and [bbim]BF_4 giving excellent to moderate yield as compared to other ILs. [bbim]Br is water soluble and it facilitates easy isolation procedure so we used [bbim]Br for the remaining substrates.

Earlier the same reaction has been carried out under microwave irradiation. But as the microwave irradiations are non-conventional, it cannot be suitable for industrial purpose. Our process is a conventional process; hence can be used as industrial process.

Table 2: Condensation of benzaldehyde (**1a**) with p-toluene sulfonamide (**2**) at 110 °C

Entry	ILs	Yield[a,] (%)	Time, h
1	[Bbim]Br	81	4
2	[Bbim]BF_4	81	4
3	[Bbim]PF_6	78	12
4	[Bbim]ClO_4	65[b]	12
5	[Hbim]Br	64[b]	12
6	[Hbim]BF_4	70	7
7	[Hbim]PF_6	55[b]	12
8	[Hbim]ClO_4	45[b]	12

[a]Isolated yield after crystallization; [b]Remaining unreacted starting material was recovered

We also tried to condense arylaldehyde (benzaldehyde **1a**) with p-toluene sulfonamide (**2**) in different molecular solvents such as methanol, ethanol, dioxane, DMF and DMSO without any added catalyst at reflux temperature for 12 h. But no product formation was observed. When it was refluxed in toluene for same time period it gives little bit product (23-25 %) formation as shown in Table 3.

Table 3: Condensation of benzaldehyde with p-toluene sulphonamide at refluxed temperature of respective molecular solvent

Sr. No.	Molecular solvent	Yield[a]	Time, h
1	Toluene	25	12
2	Methanol	-	12
3	Ethanol	-	12
4	Dioxane	-	12
5	DMF	-	12
6	DMSO	-	12

[a]Isolated yield

From this we concluded that inherent Lewis/Bronsted acidity of imidazolium ionic liquids promoted this facile synthesis. We tried to perform this reaction using catalytic amount of ionic liquid in molecular solvent, but we observed that this reaction does not proceed without using equivalent amount of ionic liquid. As in some cases reaction was not completed after long time period also so we isolated the products and to obtain pure product we loaded on silica-gel, but we observed that some of these compounds are decomposed on acidic silica gel so we purified the compound after crystallization using appropriate solvents and in some cases column chromatography was essential using neutral silica gel.

Herein, we have developed a new method for neither the synthesis of *N*-tosyl imines that requires neither harsh conditions nor the use of any hazardous acids or bases or any expensive catalyst. Reaction tolerates very well both electron-donating as well electron withdrawing substrates; also the reaction was successful on heterocyclic aldehyde.

Recyclability of IL, mild reaction conditions, short reaction time, excellent to moderate yield, simple isolation procedure and tolerance towards both electron-donating as well electron withdrawing substrates make this procedure amenable for scale up.

Conclusion

In conclusion we have demonstrated an efficient, green and environmentally non-hazardous protocol for the synthesis of *N*-tosyl imines using [bbim][Br] ionic liquid. The advantages associated with our strategy are excellent to moderate yield (80-95%), simple isolation procedure, ILs as solvent as well as promoter, short reaction period (75-180 min), reaction tolerance towards both electrons donating as well as electron withdrawing substrates, recyclability and reusability of ionic liquid without any loss of yield. Hence we believe our protocol as an efficient tool for the synthesis of N-tosyl imines.

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References

[1]Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131.

[2](a)Krow, G. R.; Pyun, C.; Rodebaugh, R.; Marakowski, J. *Tetrahedron* **1974**, *30*, 2977. (b) Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 1517. (c) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713. (d) Sisko, J.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 3037.

[3]Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 393.

[4](a)Tschaen, D. M.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058. (b) Melnick, M. J.; Freyer, A. J.; Weinreb, S. M. *Tetrahedron Lett.* **1988**, 29, 3891.

[5]Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387.

[6]Trost, B. M.; Marra, C. *J. Org. Chem.* **1991**, *56*, 6468.

[7]Boger, D. L.; Corbett, W. L. *J. Org. Chem.* **1992**, *57*, 4777.

[8](a) Jennings, W. B.; Lovely, C. J. *Tetrahedron Lett.* **1988**, *29*, 3725. (b) Glass, R. S.; Hoy, R. C. *Tetrahedron Lett.* **1976**, *17*, 1781.

[9]Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, *75*, 75.[10]Wynne, J. H. ; Price, S. E. ; Rorer, J. R. ; Staick, W. M. *Synth. Comm.* 2003, *33*, 2.

[11]Lee, K. Y.; Lee, C. G.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 1231.

[12]Wolfe, J. P.; Ney, J. E. *Org. Lett.* **2003**, *5*, 4607.

[13](a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071. (b) Wasserschied, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3772.

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