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Ionic Liquid-Supported Synthesis of Sulfonamides and Carboxamides

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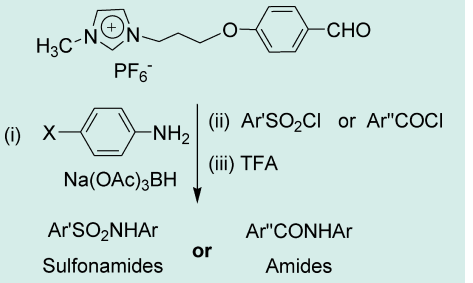
Supporting Information

ABSTRACT: An ionic liquid-supported aldehyde was designed and converted to ionic liquid-supported secondary aryl amines through reductive amination. The reaction of ionic liquid-supported aryl amines with sulfonyl chlorides and acid chlorides, respectively, followed by cleavage using trifluoroacetic acid (TFA) afforded sulfonamides and caboxamides. To introduce additional diversity in the synthesis of sulfonamides and caboxamides, ionic liquid-supported iodosubstituted aryl amine was synthesized using the same strategy, and underwent Suzuki coupling reaction, followed by reaction with a methanesulfonyl chloride to generate the corresponding biaryl sulfonamide. The advantages of the protocol over solid-phase synthesis are homogeneous reaction medium, high loading, easy separation of products, and characterization of intermediates.



KEYWORDS: *carboxamides, ionic liquids, parallel synthesis, sulfonamides, Suzuki coupling reaction*

INTRODUCTION

For the last several years, solid-phase synthesis has been utilized to generate large molecular libraries of small organic molecules in synthetic organic chemistry.[1−3] A significant number of organic reactions on various solid supports and a variety of linkers have been explored for the discovery of active compounds in pharmaceutical research.[4−11] Despite the success of solid-phase approaches for the generation of large libraries in combinatorial or parallel organic synthesis, they are associated with several disadvantages such as low-loading efficiency, difficulty in characterization of intermediates, prolonged validation-time in conversion of solution-phase protocols to solid-phase methods, inability to affect compound purification prior to the final cleavage from the solid support, use of large excesses of reagents, and difficulty and high cost of synthesis of compounds in adequate quantities for biological evaluation. Thus, particularly for smaller focused arrays, more attention has increasingly turned to the identification. Consequently, alternative solution-phase approaches that do not suffer from these limitations have been reported over the last few decades such as using fluorous-assisted synthesis,[12−16] PEG/solid-PEG supported synthesis,[17−19] soluble polymer supported synthesis,[20] polymer supported solution phase synthesis,[21] polymer-bound reagents, and scavengers and liquid phase combinatorial synthesis.[22] Ionic liquid supported synthesis has become the subject of major interest in the past few years due to easy preparation of ionic liquid supports. Under this approach, the reaction progress may be readily monitored by TLC and spectroscopic techniques. Room temperature ionic liquids are known to be green alternatives to the volatile organic solvents and have other useful properties, such as low vapor pressure, wide liquid range, and high thermal stability, and possess highly conductive solvation ability for a variety of organic substrates and catalysts including Lewis acids and enzymes.

In view of pharmacological importance of sulfonamides and amides, their synthesis has been an area of high interest in medicinal chemistry research. The amide bond is a key building unit in many natural and synthetic compounds. A number of small molecules with amide functionality have been shown to possess various biological activities such as antibacterial,[23] antitumor,[24] antiviral, Kv1.5 channel inhibitors,[25] and VEGFR-2 kinase inhibitors.[26] Sulfonamide moiety is a common pharmacophore in various biologically important molecules. Sulfonamides are pharmacologically significant as therapeutic agents as shown in sulfa antibiotics, serotonin antagonists, antifungal,[27,28] antibacterial,[29] and antitubercular[30] agents. Isoquinoline sulfonamides inhibit protein kinases by competing with ATP. In view of their importance in drug discovery, several solid-phase routes have been reported for the synthesis of a large number of structurally diversified sulfonamides and amides.[31−33]

To explore the synthetic utility of the ionic liquid-supported synthesis and to develop new and ecofriendly reaction methodologies,[34−37] herein, we describe the preparation and use of acid labile ionic liquids that facilitate a convenient method for ionic liquid-supported synthesis of sulfonamides and amides.

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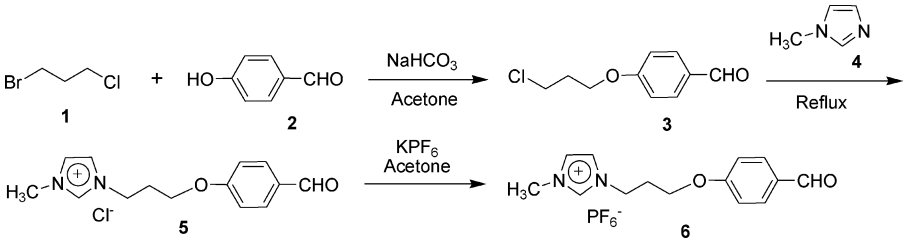
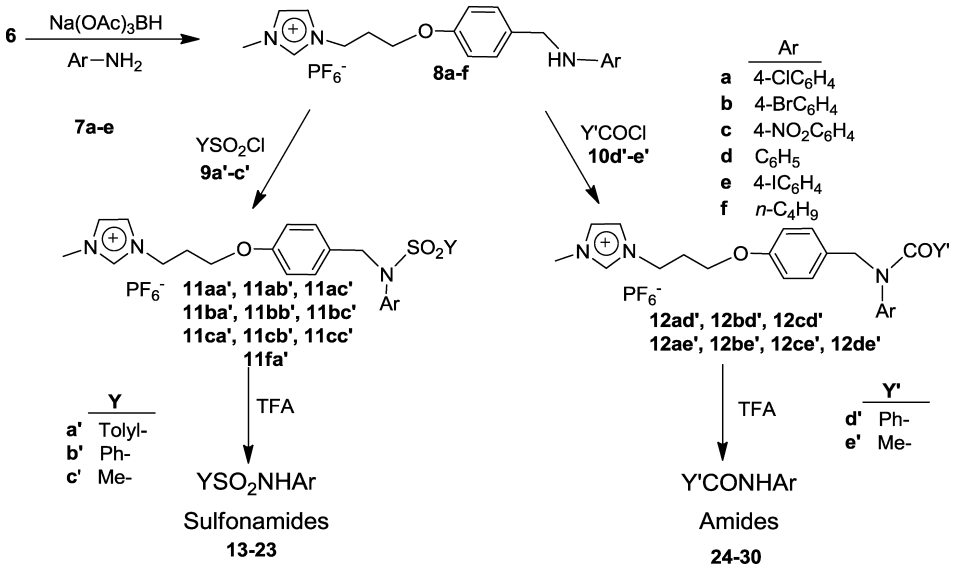
Scheme 1. Synthesis of Ionic Liquid-Supported Aldehyde Group



Scheme 2. Synthesis of Sulfonamides and Amides from Ionic Liquid-Supported Aldehyde 6



RESULTS AND DISCUSSION

Ionic liquid-supported aldehyde group **6** was prepared by selective monoalkylation of 4-hydroxybenzaldehyde (**2**) with 1-chloro-3-bromopropane (**1**), followed by reaction with 1-methylimidazole (**4**) under reflux and ion exchange (Scheme 1). The chloride anion of ionic liquid-supported aldehyde group was exchanged with hexafluorophosphate (PF_6^-) in dry acetone. The ionic liquid-supported aldehyde group was converted to ionic liquid-supported secondary amines through reductive amination and further substitution of amino functional groups.

To demonstrate the application of designed ionic liquid-supported aldehyde for the synthesis of diverse classes of compounds, ionic liquid-supported liquid phase synthesis of sulfonamides and amides is shown here (Scheme 2). Initially, reaction conditions were optimized for the reductive amination of ionic liquid-supported aldehyde group **6** with aniline using different borohydrides to afford the intermediate ionic liquid supported secondary amines as summarized in Table 1. Among different screened borohydrides, $NaBH(OAc)_3$ was found to give the highest yield of supported amine in $[bmim][BF_4]$ ionic liquid at 40 °C (entry 5, Table 1). Thus, $NaBH(OAc)_3$ was used with five different aromatic amines for the reductive amination reactions.

Six anilines were reacted with **6** to give ionic liquid-supported amines (**8a−f**) in 80−83% yield (Scheme 2). The excess of anilines was removed from the ionic liquid by extraction with ethyl acetate and then $NaBH(OAc)_3$ and $[bmim][BF_4]$ were removed by water washing leaving behind the supported secondary amines (**8**). All the ionic liquid-supported anilines

Table 1. Optimization of Reductive Amination Conditions.[a]

entry	reducing agent	temp (°C)	time (h)	yield (%)[b]
1	$NaBH_4$	35	7	66
2	$NaBH_4$	60	7	75
3	$NaBH_4$	60	8	72[c]
4	$NaBH_4$	35	6	60[d]
5	$NaBH(OAc)_3$	40	5	87
6	$NaBH(OAc)_3$	40	5	83[d]
7	$NaBH_3CN$	60	6	85
8	$NaBH_3CN$	60	6	79[d]

[a]Reaction conditions: Ionic liquid-supported aldehyde (**6**) (1 mmol), aniline (1 mmol), reducing agent (1.1 mmol), room temperature, $[bmim][BF_4]$ (1.0 mL). [b]Isolated yield. [c]Toluene used as a solvent in place of $[bmim][BF_4]$. [d]Methanol used as a solvent.

were characterized by IR, ^1H NMR, and mass spectrometry. In IR spectra, a peak around 1690−1700 cm^{-1} for stretching of aldehyde carbonyl disappeared and a broad peak appeared in the range of 3100−3200 cm^{-1} for secondary NH stretching. In NMR, a characteristic peak appeared around 4.10 ppm for CH_2NH group along with other aromatic protons of the phenyl ring.

Next, ionic liquid-supported secondary amines (**8**) were reacted with sulfonyl chlorides (**9**) to give ionic liquid-supported sulfonamides (**11**). After removal of excess of sulfonyl chloride from the reaction mixture, the ionic liquid-supported sulfonamides were cleaved using TFA to give sulfonamides **13−23** in high yields (82−91%) as shown in Table 2.

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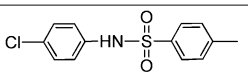
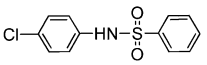
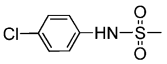
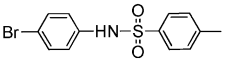
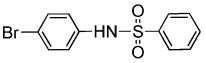
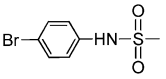
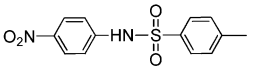
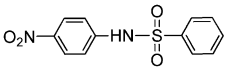
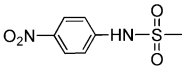
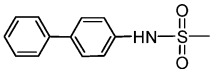
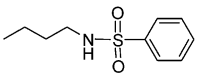
Table 2. Synthesis of Sulfonamides

Ar	Y	Product		Time (h)	% Yield[a]
4-ClC_6H_4	4-$CH_3C_6H_4$	**13**		8	87 (66)[b]
4-ClC_6H_4	C_6H_5	**14**		8	88 (65)[b]
4-ClC_6H_4	CH_3	**15**		10	86 (64)[b]
4-BrC_6H_4	4-$CH_3C_6H_4$	**16**		8	89 (64)[b]
4-BrC_6H_4	C_6H_5	**17**		8	85 (63)[b]
4-BrC_6H_4	CH_3	**18**		10	84 (61)[b]
4-$NO_2C_6H_4$	4-$CH_3C_6H_4$	**19**		8	85 (57)[b]
4-$NO_2C_6H_4$	C_6H_5	**20**		8	83 (55)[b]
4-$NO_2C_6H_4$	CH_3	**21**		10	82 (54)[b]
4-$C_6H_5C_6H_4$	CH_3	**22**		10	87 (56)[b]
n-C_4H_9	C_6H_5	**23**		10	91 (59)[b]

[a]Isolated yields after column chromatography. [b]Overall yield (from ionic liquid supported aldehyde **6**).

To demonstrate the utility of **6** in supported liquid phase synthesis, ionic liquid-supported secondary amines (**8**) were reacted with acid chlorides (**10**) to give ionic liquid-supported amides (**12**). The excess of acid chlorides were removed by ethyl acetate extraction followed by cleavage with TFA to afford desired amides **24**−**30**. All the amides were isolated in good yields (81−87%, Table 3) and excellent purities following final purification.

The scope of the ionic liquid-supported aldehyde **6** was further extended to increase functional diversity. Compound **6** was converted to ionic liquid-supported iodosubstituted aryl amine **8e** as described above (Scheme 1). The ionic liquid-supported aryl amine **8e** was transformed to ionic liquid-supported biaryl secondary amines **31** using Suzuki coupling reaction conditions (Scheme 3). The ionic liquid-supported secondary amine with biphenyl was characterized with ^{1}H NMR and mass spectrometry. The resulting secondary amine was transformed to the corresponding sulfonamide (**32**) by reaction with methanesulfonyl chloride using the standardized reaction conditions and finally cleaved to give sulfonamide (**22**). Structure of both **31** and **32** was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy (Supporting Information).

In conclusion, a new acid-labile ionic liquid-supported aldehyde was developed to facilitate the rapid and parallel solution-phase synthesis of sulfonamides and carboxamides. The use of ionic liquid supported-aldehyde group avoids the cumbersome conditions and makes the environmentally clean protocol for the synthesis of useful sulfonamides and carboxamides with the experimental ease. Functionalization of substituted ionic liquid-supported secondary amines followed by sulfonylation or acylation can be used to generate library of structurally diversified sulfonamides and carboxamides, respectively. The protocol represented here would improve the paradigm of sulfonamide and carboxamides and provide insights for potential application of ionic liquid-supported aldehydes and amines for generation of other compounds.

EXPERIMENTAL PROCEDURES

General. 1-Methyl imidazole, 1-chloro-3-bromopropane, 4-hydroxybenzaldehyde, KPF_6, and sodium triacetoxyborohydride were purchased from Sigma-Aldrich and were used without further purification. Aryl amines, sulfonyl chlorides, and acid chlorides were purchased from S. D. Fine Chemicals Ltd., Mumbai. Silica gel (100−200 mesh) was used for column chromatography. Thin-layer chromatography (TLC) was performed on Merck-precoated silica gel 60-F_{254} plates. All the other solvents and chemicals were obtained from commercial sources and purified using standard methods. The products were analyzed by NMR and mass spectroscopic techniques. The ^{1}H and ^{13}C NMR spectra were recorded on a

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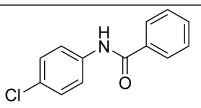
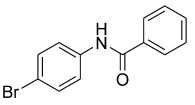
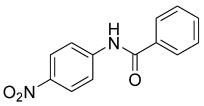
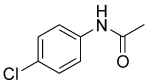
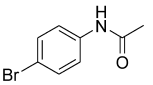
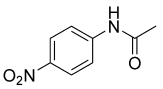
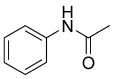
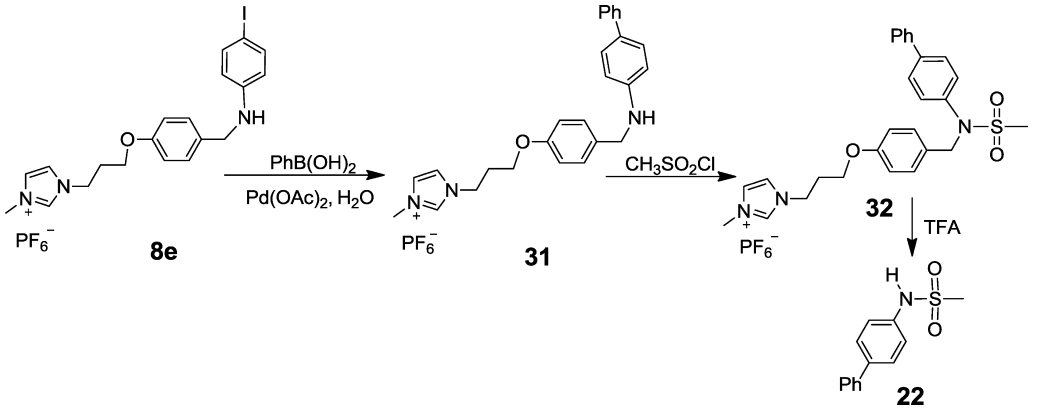
Table 3. Synthesis of Carboxamides

Ar	Ar'	Product		Time (h)	% Yield[a]
4-ClC_6H_4	C_6H_5	**24**		8	85 (63)[b]
4-BrC_6H_4	C_6H_5	**25**		7	83 (59)[b]
4-$NO_2C_6H_4$	C_6H_5	**26**		8	81 (55)[b]
4-ClC_6H_4	CH_3	**27**		8	86 (63)[b]
4-BrC_6H_4	CH_3	**28**		8	81 (62)[b]
4-$NO_2C_6H_4$	CH_3	**29**		8	82 (53)[b]
C_6H_5	CH_3	**30**		7	87 (56)[b]

[a]Isolated yields after column chromatography. [b]Overall yield (from ionic liquid supported aldehyde **6**).

Scheme 3. Ionic Liquid-Supported Suzuki Reaction and Synthesis of Sulfonamide



Varian (500 MHz) spectrometer in DMSO-d_6 with ^1H resonant frequency of 500 MHz and ^{13}C resonant frequency of 126 MHz. The chemical shifts are expressed in parts per million (δ) and coupling constants (J) in Hz. The Mass spectra were recorded on QSTAR ELITE LX/MS/MS from Applied Biosystems.

Synthesis of Ionic Liquids-Supported Aldehyde. 1-Methylimidazole, **4** (4.43 g, 0.054 mol), was mixed with 4-(3-chloropropyloxy)benzaldehyde, **3** (9.75 g, 0.05 mol), and heated at 80 °C for 6 h. After the completion of the reaction, a thick liquid was obtained. The reaction mixture was cooled down to room temperature, and unreacted 1-methylimidazole and 4-(3-chloropropyloxy)benzaldehyde were removed by extraction with diethyl ether/ethyl acetate (2 × 25 mL, 1:1 v/v). The ionic liquid layer was concentrated under vacuum on a rotatory evaporator to give chloride salt **5**. Ion exchange was carried out in dry acetone (50 mL) using potassium hexafluorophosphate (7.67 g) at room temperature for 48 h. Acetone was evaporated; resulting solution was dissolved in water (25 mL) and extracted with DCM (3 × 50 mL). The DCM layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford pure **6** (yield 18.30 g, 96%).

General Procedure for the Synthesis of Ionic Liquid Supported Amines. Compound **6** (1 g, 2.5 mmol) was refluxed with corresponding amine **7** (3.0 mmol) in methanol or ethanol for overnight. The obtained solid was reduced using sodium triacetoxyborohydride (700 mg, 3.3 mmol) in [bmim]-[BF_4] for 5 h at 40 °C. The excess of amine was removed by extracting with ethyl acetate (3 × 20 mL). The inorganic

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impurities were removed by washing with water (2 × 10 mL) and the organic layer was dried on a rotatory evaporator to give ionic liquid-supported amine **8**.

General Procedure for the Synthesis of Sulfonamides/Carboxamides. To the stirred reaction mixture of **8** (1 mmol) and triethylamine (1.5 mmol) in dichlorormethane (3.0 mL) at 0 °C was added sulfonyl chloride/acid chloride (1.2 mmol) dropwise. The reaction mixture was brought to room temperature and stirred for 7−10 h (Table 1). After completion of the reaction, the mixture was washed with diethyl ether (3 × 10 mL) and water (2 × 10 mL), respectively. The sulfonamide/carboxamide-supported on ionic liquid was cleaved using trifluoroacetic acid (TFA, 1 mL). The resulting solution was neutralized with 10% aqueous $NaHCO_3$ solution and extracted with hexane/ethyl acetate (1:1 v/v) (2 × 10 mL). The combined organic extracts were concentrated under reduced pressure and purified by column chromatography on silica gel (60−120 mesh) using hexane and ethyl acetate as eluents.

General Procedure for Suzuki Coupling on Ionic Liquid Support. To a solution of ionic liquid-supported 4-iodoaniline (0.67 mmol) in water (5.0 mL) at 80 °C under nitrogen was added phenylboronic acid (0.19 mmol) and Cs_2CO_3 (1.34 mmol). The resulting mixture was stirred at 80 °C for 15 min, followed by the addition of $Pd(OAc)_2$ (0.097 mmol). The reaction mixture was then stirred vigorously for 23 h at 80 °C under nitrogen atmosphere. After completion of the reaction, the mixture was washed with water (3 × 15 mL), and finally the residue was dissolved in DCM (10 mL). The DCM layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give **31**. Yield: 423 mg (85%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedure for synthesis of 4-(3-chloropropoxy)-benzaldehyde, chemical structures of ionic liquid-supported amines and ionic liquid supported sulfonamides and amides, and spectroscopic and physical data of synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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