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Development of a novel ionic support and its application in the ionic liquid phase assisted synthesis of a potent antithrombotic ☆

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Abstract—The synthesis of ionic support **1** and its application in the preparation of a set of amides and sulfonamides is described. The potential of **1** is further exemplified by its use in a one-pot multistep ionic liquid phase assisted synthesis of tirofiban analogue **2**.

An important research objective within the pharmaceutical and the fine-chemical industries is the development of strategies that enable the rapid generation of new chemical entities. Ideally such synthesis strategies should be highly flexible, allow (semi-)high throughput chemistry, could be upscaled and should be environmentally clean. In this respect, solid phase synthesis has proven its merit in the combinatorial chemistry era.[1] A drawback of solid phase chemistry, however, is the fact that many organic reactions routinely performed in solution are often difficult to transfer to the solid support. Furthermore, the number of applications of solid phase chemistry on an industrial scale so far is limited. With the objective of ensuring the rapid generation of compound libraries, homogeneous phase chemistry strategies in combination with novel separation methods[2] are currently being pursued. Interesting techniques emerging in this area include the application of fluorous solvents and tags,[3] polyethylene glycol supports,[4] supercritical fluids,[5] soluble polystyrene supports,[6] microencapsulated catalysts[7] and solid supported (scavenger) reagents.[8]

Recently, ionic liquids have been recognised as novel, environmentally benign solvents in synthetic chemistry.[9] Ionic liquids have no detectable vapour pressure, are thermally stable and have the ability to form a separate phase[10] in the presence of both aqueous and organic solvents. Moreover, ionic liquids can be readily recycled[9] and are highly suitable for the recycling of a variety of reagents, including organometallic catalysts.[9b,11] Finally, they have found recent applications as additives in microwave accelerated synthesis.[12,14b]

The scope[13] of ionic liquids has recently been expanded by the introduction of additional functional groups in the ionic liquid structure. These so-called task-specific ionic liquids[14] can be utilised as (supported) reagents or catalysts with high affinity for the ionic liquid phase. Task-specific ionic liquids are compatible with a variety of organic transformations[14a–g] and have proven to be useful for the extraction[14h–j] of specific chemicals.

In this paper, we report our results obtained with ionic support **1**, which is equipped with an aldehyde for attaching amines by reductive amination. After transient anchoring of reactants to **1**, organic transformations can be performed in a single batch of ionic liquid (e.g., [bmim][PF_6], Fig. 1), while excess of reagent can be removed by extraction with an organic or aqueous phase. Finally, the products are obtained by acidic removal of the ionic support and extraction into an organic phase. We demonstrate the validity of our strategy in the synthesis of a range of (sulfon)amides. Furthermore, the application of **1** in the multistep ionic

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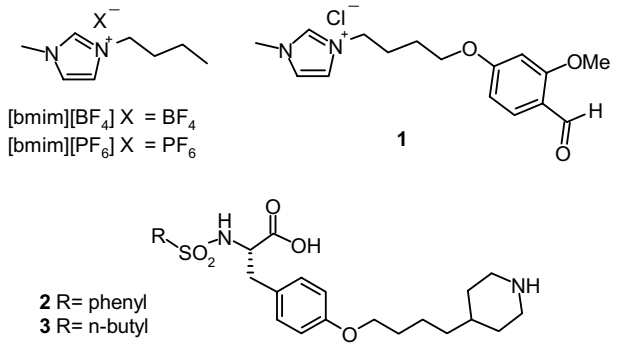
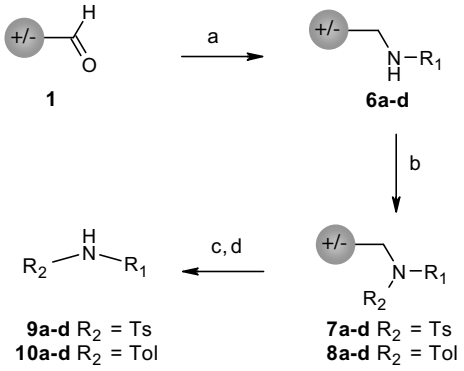


Figure 1.

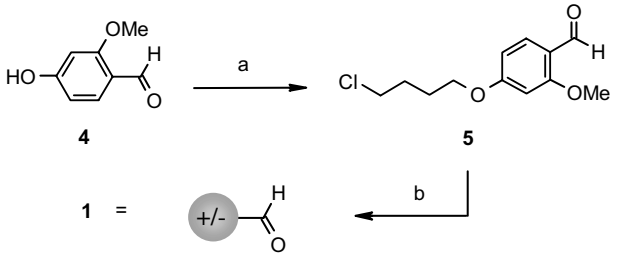


Scheme 2. Ionic phase synthesis of (sulfon)amides. All reactions were performed in [bmim][PF_6]. (a) R^1NH_2, $NaHB(OAc)_3$, 16 h; (b) TsCl or TolCl, Et_3N, 2 h. (c) 2% HPF_6, 10 min; (d) satd $NaHCO_3$, then extraction with Et_2O.

phase assisted synthesis of **2**, a potent analogue of the antiplatelet drug tirofiban **3**, is presented.

The synthesis of *N*-methylimidazolium based ionic support **1**, the ionic analogue of the known AMEBA solid support,[15] was readily accomplished by alkylation[16] of the phenol **4** with 1,4-dichlorobutane and subsequent substitution of chloride **5** with *N*-methylimidazole under microwave irradiation. Imidazolium chloride **1** (obtained in 75% yield over the two steps; 90% pure based on HPLC) could be readily dissolved in [bmim][PF_6] and showed neither leakage to the aqueous nor to the organic phase, thus avoiding any need to convert **1** into the corresponding PF_6^- salt. The solution of **1** in [bmim][PF_6] can be stored at room temperature for 6 months without any sign of decomposition (Scheme 1).

In order to determine the scope of ionic support **1** in ionic phase assisted synthesis, we set out to prepare (Scheme 2) a set of diverse sulfonamides and amides (see Table 1). Treatment of a solution of compound **1** in [bmim][PF_6] with four commercially available amines in the presence of $NaHB(OAc)_3$ gave, after reductive amination,[17] the ionic supported amines **6a**–**d**.The reaction mixtures were divided and the amines either sulfonylated with tosyl chloride (TsCl) or acylated with 4-methylphenylcarbonyl chloride (TolCl) to give ionic tagged sulfonamides **7a**–**d** and amides **8a**–**d**, respectively. After each step, excess of reagents were removed by consecutive extractions with diethyl ether and water.[18]



Scheme 1. (a) 1,4-Dichlorobutane, Bu_4NHSO_4, 3 M NaOH, reflux, 16 h, 75%; (b) 2.0 equiv *N*-methylimidazole, CH_3CN, microwave, 170 °C, 30 min, quant.

In the final step, the (sulfon)amides were liberated from the ionic support using acidic conditions. Upon treatment with trifluoroacetic acid (TFA) all target compounds were completely removed. Unfortunately, the high concentration of TFA required (upto 50%) led to the in situ formation of [bmim][TFA], which was present as a contaminant in all products.[19] To our satisfaction, however, short (10 min) exposure of the ionic supported (sulfon)amides to 2% HPF_6 followed by extraction (diethyl ether) from the ionic phase and concentration of the organic phase provided target compounds **9a**–**d** and **10a**–**d** in promising yields with reasonable to excellent purities (see Table 1).[20] Although extraction of the products from the ionic phase is still unoptimised, the yields and purities are comparable to those reported for the conventional AMEBA solid support.[†]

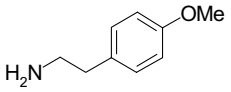
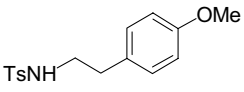
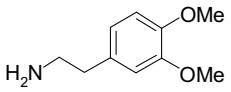
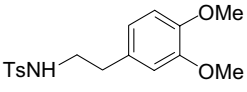
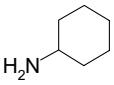
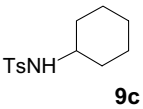
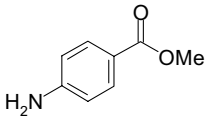
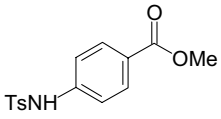
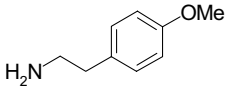
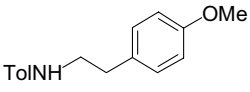
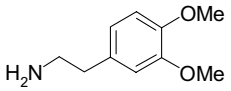
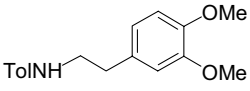
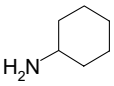
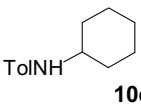
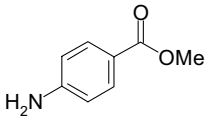
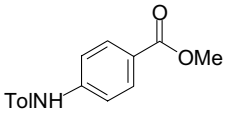
An important advantage of the sequence of reactions outlined here is the possibility of monitoring all reactions by HPLC/MS,[21] as is demonstrated for the conversion of **1** into **9b** (see Fig. 2). Of further interest is our observation that in all examples presented here no leakage of the ionic supported substrates into the aqueous or organic phase occurred.

Having established the effectiveness of ionic support **1** in the synthesis of (sulfon)amides, we set out to explore its potential in the multistep synthesis of sulfonylated tyrosine derivative **2**, a highly potent analogue of the antithrombotic drug tirofiban (**3**, Fig. 1).

A solution of ionic support **1** (0.125 M) in [bmim][PF_6] was charged by reductive amination with *O*-allyl-L-tyrosine(*O*-allyl) **11**[22] to give intermediate **12**. Sulfonylation of the secondary amine function in **12** with phenylsulfonyl chloride was complete after 1 h as judged by HPLC/MS analysis. After extractive work-up (water followed by diethyl ether), the resulting intermediate **13** was deprotected by a Pd-catalysed deallylation,[23] which

[†] Products **9a**,**c** and **10a** have been previously prepared on the AMEBA solid support.[15]

Table 1. IL phase synthesis of (sulfon)amides

Entry	Amine (R^1NH_2)	Product	Yield (%)	Purity[a] (%)
1		 **9a**	50	99 (95)
2		 **9b**	50	89 (90)
3		 **9c**	54	100 (>95)
4		 **9d**	32	65 (55)[b]
5		 **10a**	52	100 (95)
6		 **10b**	26	95 (95)
7		 **10c**	52	100 (95)
8		 **10d**	41	80 (85)[b]

[a] Numbers in parentheses denote purity based on ^1H NMR analysis.
[b] Only impurity observed was disulfonylated or acylated product resulting from poor extraction of the excess aniline.

proceeded smoothly at elevated temperature to yield **14**. In the penultimate step, the phenolic hydroxyl group in **14** was alkylated in a regioselective manner with *N*-Boc-4-(4-iodobutyl)-piperidine[24] under the influence of NaH to give product **15**.

Finally, cleavage from the ionic support and concomitant deprotection of the product was effected by treatment with 2% HPF_6. Quenching of the reaction mixture with Et_3N and extraction with water gave, after purification by preparative HPLC/MS chromatography, target compound **2** in 11% yield over the five steps (based on **1**). All the spectroscopic data of tirofiban analogue **2** were in full accordance with those reported[25] (Scheme 3).

In conclusion, we have disclosed a novel readily accessible ionic support **1** and have demonstrated its use in ionic liquid phase assisted organic synthesis. To our knowledge this is the first time a multistep synthesis comprising five consecutive steps has been carried out in a single batch of ionic liquid. Our method represents an attractive alternative to classical solid and fluorous phase synthesis strategies and combines the advantage of performing homogeneous chemistry on a relatively large scale while avoiding of large excesses of reagents.

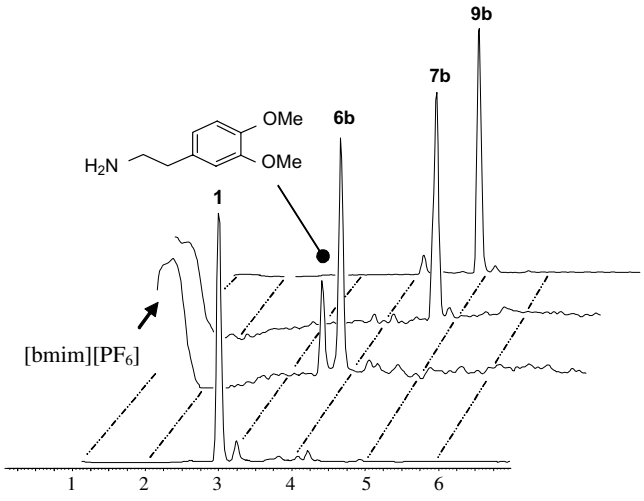
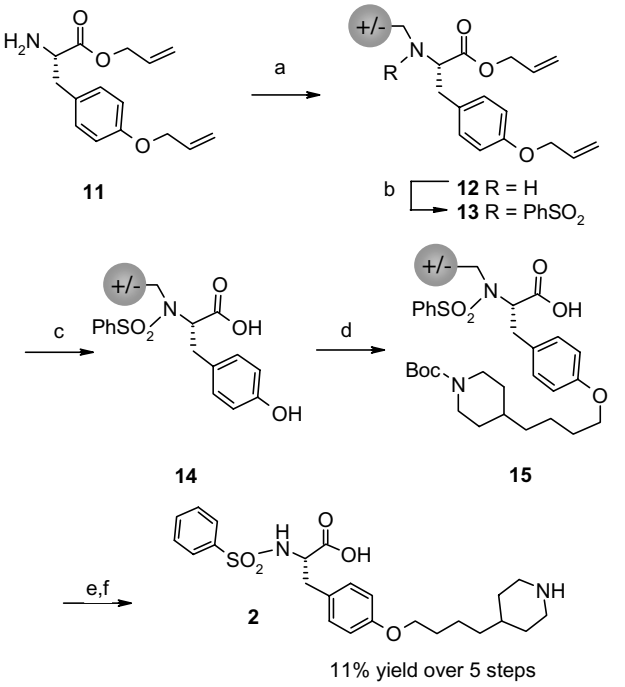


Figure 2. HPLC traces of crude ionic phase reaction mixtures (**1** → **6b** → **7b** → **9b**; entry 2, Table 1). Column: Luna C18; gradient: 7 min, 1/9 → 9/1, v/v, MeCN/H_2O containing 0.05% TFA.



Scheme 3. Ionic phase assisted synthesis of tirofiban analogue **2**. All reactions are performed in [bmim][PF_6]. (a) $NaBH(OAc)_3$, HOAc, 16 h; (b) $PhSO_2Cl$, Et_3N, 1 h; (c) 2 mol% $Pd(PPh_3)_4$, pyrrolidine, 90 °C, 45 min; (d) NaH, then *N*-Boc-4-(4-iodobutyl)-piperidine, 16 h; (e) 2% HPF_6, 10 min; (f) Et_3N, then extraction with H_2O.

An attractive feature of this ionic phase approach is the fact that reactions can be monitored at all times by common techniques such as HPLC/MS. The rapidly increasing number of publications on organic reactions in ionic liquids is an impetus to expand the utilisation of ionic phase assisted synthesis strategies. Expansion of the method presented here towards differently functionalised ionic supports, and the synthesis of more complex target molecules are currently being pursued.

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17. Howarth, J.; James, P.; Ryan, R. *Synth. Commun.* **2001**, 2935–2938.
18. Procedure for **7** and **8**: Four 2 mL portions of a 0.125 M solution of ionic support **1** in [bmim][PF_6] were vigorously stirred with the amine (0.38 mmol, see Table 1) in the presence of $NaHB(OAc)_3$ (0.16 g, 0.75 mmol) and AcOH (6 μL, 0.1 mmol). After 16 h, the ionic phases were extracted with Et_2O (3×3 mL) and H_2O (3×3 mL) and dried in vacuo (5 mbar) at 60 °C for 2 h. The ionic phases containing **6a–d** were then treated with Et_3N (88 μL, 0.63 mmol), followed by TsCl (47 mg, 0.25 mmol) or TolCl (33 μL, 0.25 mmol). After 2 h the excesses of reagents were removed by extractive work-up (3×2 mL H_2O and Et_2O, respectively).
19. Traces of this contaminant could be easily removed by filtration through SiO_2.
20. Procedure for **9** and **10**: The [bmim][PF_6] solutions containing ionic supported **7** or **8** were each treated with 30 μL of 60% aq HPF_6 (CAUTION! – corrosive) while stirring for 10 min. The dark red coloured ionic phase (containing 2% HPF_6) was washed with satd aq $NaHCO_3$ (2×1 mL) and extracted with Et_2O (3×2 mL). The combined organic phases were rinsed with H_2O (2×1 mL), dried ($MgSO_4$) and the target compounds **9a–d** and **10a–d** were obtained by removal of Et_2O under reduced pressure. ^1H NMR ($CDCl_3$, 400 MHz), **9a**: δ 2.43 (s, 3H), 2.70 (t, 2H), 3.18 (q, 2H), 3.79 (s, 3H), 4.27 (t, 1H), 6.81 (d, 2H), 6.99 (d, 2H), 7.29 (d, 2H), 7.70 (d, 2H); **9b**: δ 2.43 (s, 3H), 2.71 (t, 2H), 3.19 (q, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 4.27 (t, 1H), 6.56 (d, 1H), 6.63 (dd, 1H), 6.77 (d, 1H), 7.28 (d, 2H), 7.67 (d, 2H); **9c**: δ 1.06–1.27 (m, 5H), 1.47–1.78 (m, 6H), 2.43 (s, 3H), 3.12 (q, 2H), 4.32 (d, 1H), 7.30 (d, 2H), 7.76 (d, 2H); **9d**: δ 2.38 (s, 3H), 3.87 (s, 3H), 4.20 (t, 1H), 7.11 (d, 2H), 7.34 (d, 2H), 7.72 (d, 2H), 7.92 (d, 2H); **10a**: δ 2.38 (s, 3H), 2.87 (t, 2H), 3.67 (q, 2H), 3.81 (s, 3H), 6.06 (b, 1H), 6.87 (d, 2H), 7.15 (d, 2H), 7.21 (d, 2H), 7.59 (d, 2H); **10b**: δ 2.39 (s, 3H), 2.88 (t, 2H), 3.69 (q, 2H), 3.84 (s, 3H), 3.88 (s, 3H), 6.74–6.84 (m, 3H), 7.21 (d, 2H), 7.59 (d, 2H); **10c**: δ 1.16–1.29 (m, 3H), 1.38–1.49 (m, 2H), 1.62–1.70 (m, 1H), 1.72–1.79 (m, 2H), 1.99–2.08 (m, 2H), 2.39 (s, 3H), 3.92–4.02 (m, 1H), 6.11 (bs, 1H), 7.22 (d, 2H), 7.64 (d, 2H); **10d**: δ 2.44 (s, 3H), 3.92 (s, 3H), 7.31 (d, 2H), 7.74 (d, 2H), 7.78 (d, 2H), 8.06 (d, 2H).
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