Synthesis of Functionalized Chiral Ammonium, Imidazolium and Pyridinium-based Ionic Liquids derived from (-)-Ephedrine using solvent-free microwave activation. Applications for the Asymmetric Michael Addition

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Abstract—An efficient procedure for the synthesis of functionalized chiral ammonium, imidazolium and pyridinium-based ionic liquids derived from (1R, 2S)-ephedrine using solvent-free microwave activation has been described. Good yields were obtained in very short reaction time. These chiral ionic liquids were used as chiral reaction media for the asymmetric Michael addition, giving good yields and moderate enantioselectivities.

1. Introduction

Over the past decade, ionic liquids (ILs) have received considerable attention thanks to their ability to serve as effective reaction media for a wide range of organic reactions and other applications in chemistry.[1] By modifying the structure of the cations or anions of ionic liquids, it has been shown that their properties can be altered in order to influence the outcomes of reactions. Advances in ILs have made development of chiral ionic liquids (CILs), a subject of intense study in recent years.[2] Although a limited number of CILs have been designed and synthesized, they have already found promising applications in asymmetric synthesis,[3] stereoselective polymerization,[4] chiral chromatography,[5] liquid crystals,[6] chiral resolution, and as a NMR shift reagents.[7] Nowadays, the design and synthesis of novel CILs is growing rapidly. The study of CILs applications in asymmetric synthesis presents a challenge and an opportunity to researchers. It is, therefore, essential if not interesting to synthesize different kinds of CILs from various starting materials, especially derived from a chiral pool.

Microwave (MW) activation, a non-conventional energy source, has emerged as a powerful technique for promoting a variety of chemical reactions and has become a useful technology in organic chemistry.[8] The combination of solvent-free conditions and MW irradiation considerably reduces reaction time, enhances conversions as well as selectivity and presents certain environmental advantages.[9] This method has been successfully applied to the synthesis of several imidazolium-based ILs.[10]

In 2004, we reported the first synthesis of chiral ionic liquids possessing a chiral ephedrinium cation using solvent-free microwave irradiation conditions.[11] Recently, Cravotto *et al.*[12]

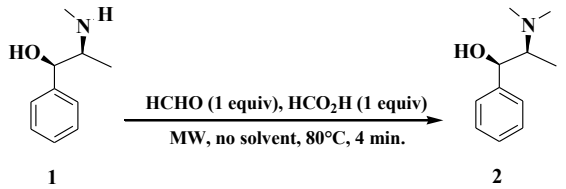
described an effective and rapid one-pot procedure to synthesize a second-generation ionic liquid using combined microwave / ultrasound irradiation.

In view of the emerging importance of the ILs as reaction media in organic synthesis and our general interests in MW-assisted chemical processes, we report here the synthesis of functionalized chiral ammonium, imidazolium and pyridinium-based ILs using solvent-free reactions under MW activation. These ILs were used as chiral reaction media in the asymmetric Michael addition.

2. Result and discussion

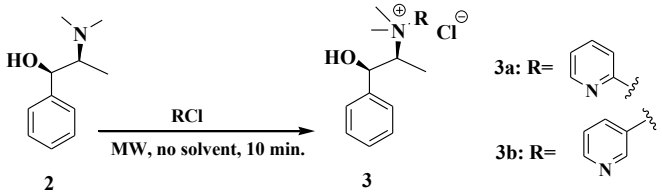
2.1. Solvent-free microwave assisted synthesis of functionalized chiral ammonium, imidazolium and pyridinium-based ionic liquids

Our synthesis was initiated by the synthesis of (*1R, 2S)-N*-methylephedrine **2** by reductive amination of (*1R, 2S*)-ephedrine using solvent-free microwave irradiation. The compound **2** was isolated with good yield (90%) for only 4 minutes, using 1 equivalent of formaldehyde along with formic acid in stoichiometric quantity (Scheme 1). It should be noted that using classical procedure,[13] the reaction must take longer time (around 5h) and the use of large excess of reagents is necessary.



Scheme 1: Solvent-free microwave synthesis of (*1R, 2S*)-*N*-methylephedrine

We proceeded to our synthesis by direct alkylation of *N*-methylephedrine **2** using solvent-free microwave irradiation conditions as previously reported by our group.[11] 2-(chloromethyl)- and 3-(chloromethyl)pyridine were used as alkylating agents for this study. All the MW reactions were performed in the CEM Discover monomode system with a strict control of power and temperature during the course of the reaction. Generally speaking, excellent yields were obtained in very short reaction time. Experiments using a thermostatted oil bath (conventional heating) were executed under identical reaction conditions (time, temperature, vessel, profile of rise in temperature, without solvent). A drop in yield was observed in all cases (Scheme 2, Table 1).



Scheme 2: Solvent-free microwave assisted synthesis of ephedrinium salts **3**.

Table 1: Solvent-free microwave-assisted *N*-alkylation of (*1R, 2S*)-methylephedrine with 2-(chloromethyl) or 3-(chloromethyl)pyridine.

Conditions: **2**: RCl = 1 : 1.2. Time: 10 min.

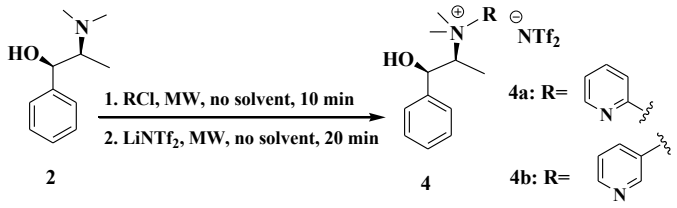
Entry	RCl	Temperature (°C)	Isolated yield (%)
1		90	90
2		100	98 (47)[b]
3		85	83
4[a]		85	90 (43)[b]

a) 1.3 equivalents of 3-(chloromethyl)pyridine was used. b) Yields obtained under conventional heating given in brackets.

The next step in the synthesis involves an anion exchange of ephedrinium chloride salts **3** with $LiNTf_2$. Generally, this step was carried out at reflux in a large excess of acetone as solvent for several hours or even some days.[14] Good yields were generally obtained in all cases.

As already reported by Varma *et al*.[9d] an anion exchange metathesis is easily performed under MW activation using a domestic oven. In this way, 1,3-dialkylimidazolium tetrafluoroborate salts were prepared in good yields after only a few minutes of reaction time.

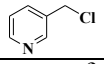
In order to simplify the overall procedure, we carried out the synthesis of chiral ammonium-based ionic liquids using a two-step one-pot sequence reaction as developed previously by our group.[11] All products (not isolated) resulting from the quaternisation step (first step) were directly submitted to an anion exchange step (Scheme 3). All the MW reactions were conducted in the absence of any solvent. The more significant results are given in Table 2.



Scheme 3: Solvent-free microwave assisted synthesis of chiral ionic liquids **4**

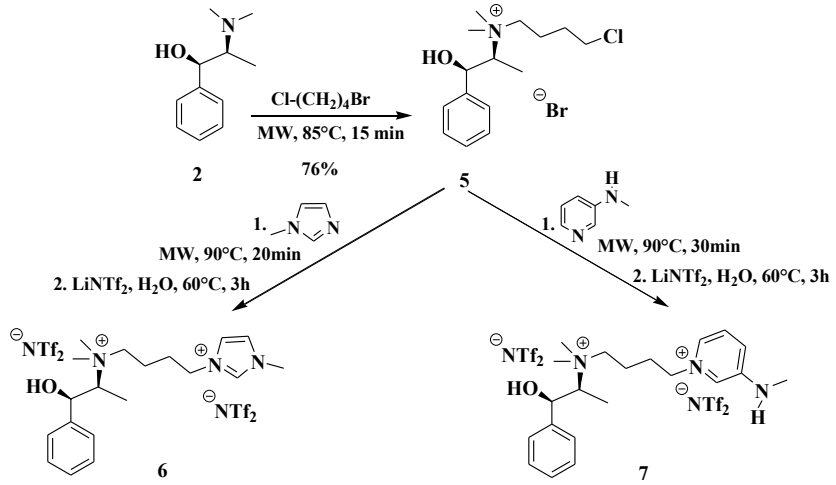
Table 2: Solvent-free microwave assisted synthesis of chiral ionic liquids 4 using a two-step one-pot sequence reaction.

Conditions: **2**: RCl = 1 : 1.2.

Entry	RCl	Temperature (°C)	Isolated yield (%)
1		100[a] / 75[b]	84 (37)[c]
2		85[a] / 95[b]	78 (41)[c]

a) Temperature for the first step. b) Temperature for the second step. c) Yields obtained under conventional heating given in brackets.

We then proceeded to synthesize some other functionalized CILs **6**, possessing the imidazolium skeleton, and **7**, having the methylaminopyridinium function. These secondary basic groups could serve as activator function of the substrates via a hydrogen bonding formation. Using the same strategy previously described in Scheme 3, CILs **6** and **7** were obtained respectively in 45% and 49% overall yield in 3 steps, from (-)-N-methylephedrine. Lower yields (25% for **6** and 18% for **7**) were observed under conventional heating. Scheme 4 summarizes the synthesis of these new CILs.



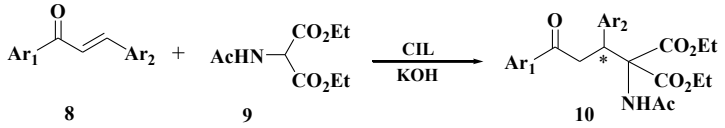
Scheme 4: Synthesis of CILs **6** and 7

To sum up, we have developed an efficient procedure for the synthesis of ammonium, imidazolium and pyridinium-based ionic liquids using a two-step one-pot reaction under solvent-free microwave activation. These chiral salts can be used as catalysts for the asymmetric Michael addition.

2.2. Chiral ionic liquids-based (-)-ephedine as catalysts for the asymmetric Michael addition.

The conjugate addition of nucleophiles, usually called Michael addition, is one of the fundamental bond-forming processes in organic chemistry[15] and its asymmetric version offers an extremely powerful tool for the synthesis of a variety of useful chiral functionalized organic molecules.[16] Efforts toward achieving asymmetric conjugate addition of malonates to α,ß-unsaturated ketones in the presence of chiral catalyst have been the subject of several reports. As a result, a variety of chiral metal catalysts[17] as well as organocatalysts[18] including imidazoline catalysts,[19] L-proline-derived catalysts,[20] phase-transfer catalysts,[21] pyrrolidylalkyl ammonium hydroxide,[22] and chiral ammonium salts.[23] have been developed for this transformation. There are also publications reporting Michael addition reaction catalyzed by chiral ionic liquids.[18a,24] However, these reactions employ highly activated Michael acceptors, such as nitroalkenes. Enantioselective catalytic conjugate addition of ketones with enones remains a challenging reaction.

After achieving the synthesis of CILs containing a chiral moiety, a free hydroxyl group and a basic function, we were interested in testing their potential for asymmetric induction. Initially, the Michael addition reaction of diethyl-2- acetamidomalonate **9** to chalcone **8** (Ar_1: Ph, Ar_2: Ph) was selected for catalyst evaluation (Scheme 5).



Scheme 5: Asymmetric Michael addition reaction

A screening of CILs was examined as shown in Table 3. The reaction was conducted in the presence of 1 equiv. of CIL, without any organic solvent, using catalytic amount of KOH (6 mol %) as co-basic catalyst, at 60°C for 1 hour. Optimization of reaction conditions was carried out and the main results obtained were listed in Table 3.

Table 3: Screening of CIL for the asymmetric Michael addition reaction of diethyl-2-acetamidomalonate **9** to chalcone **8**

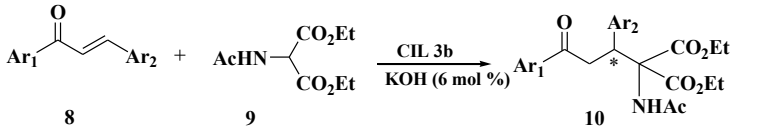
Entry	CIL	Yield **10** (%)	(*S*)-**10** ee (%)[a]
1	**4a**	60	58
2	**4b**	51	64
3	**7**	58	47
4	**6**	52	40
5	**3a**	51	70
6	**3b**	**55**	**70**
7[b]	**3b**	52	66
8[c]	**3b**	51	59
9[d]	**3b**	76	52

a) ee determined by chiral HPLC[25] and configuration (*S*)-**10** was determined by comparison of optical rotation with the literature value[21c]. b) CIL: 10 mol %. c) Temperature: 40°C. d) Toluene (0.3 mL) was added.

As illustrated in Table 3, the structural variation of cations has significant impact on the asymmetric induction. The best ee (up to 70%) were observed by using CIL **3a** and **3b** The bis-cation CILs **6** and **7** catalysed the reaction with lower enantioselectivities (Entries 3 and 4). In all cases, moderate yields (up to 76%) were obtained. It can be explained by a bad stirring of the reaction medium which was not homogeneous. The reaction worked better when using toluene as solvent, but a drop in ee was observed (entries 6 and 9). Some other optimization parameters were investigated. The reaction temperature was not critical in this reaction (Entries 6 and 8), affording the same yield with only 59% ee. Catalyst loading did not really affect the studied reaction. When using 10 mol % **3b** a slight drop in yield and ee was observed (Entry 7).

The scope of the Michael addition reaction was next explored under the optimized reaction conditions described above (1 equiv. of **3b**, 6 mol % KOH, 60°C, 1 h). A range of chalcone derivatives bearing either electron-withdrawing or electron-donating substitutes was applicable in the reaction with diethyl acetylaminomalonate **9** (Scheme 5). The reaction smoothly proceeded to afford the corresponding products 10 with moderate to good yields. Substitutes on C4 position of benzene demonstrated dramatic effect on the enantioselectivity. In all cases, lower until poor ee were observed with these chaconne derivatives (Table 4).

The recyclability and reusability of CILs was briefly tested. After reaction, the catalyst could be easily recycled by dilution in dichloromethane (5mL) and then washed with water (2 x 2mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo to afford the recycled ionic liquid. Spectra data (IR, 1H and 13C) were identical to the initial ionic liquid sample. The CIL **3b** could be recycled and reused for three times, maintaining similar activity and stereoselectivity (Table 4, entry 1). Loss of activity was observed in the fourth reuse.



8 9 10

10a: Ar_1 = Ph; Ar_2 = Ph
10b: Ar_1 = Ph; Ar_2 = 4-MeO-C_6H_4-
10c: Ar_1 = Ph; Ar_2 = 4-NO_2-C_6H_4-
10d: Ar_1 = Ph; Ar_2 = 4-Cl-C_6H_4-
10e: Ar_1 = 4-MeO-C_6H_4-; Ar_2 = Ph
10f: Ar_1 = 4-Cl-C_6H_4-; Ar_2= Ph
10g: Ar_1 = 2-Cl-C_6H_4-; Ar_2 = Ph

Scheme 5: Substrates scope for the asymmetric Michael addition reaction

Table 4: Substrates scope for the asymmetric Michael addition reaction of diethyl-2-acetamidomalonate **9** to chalcone derivatives 8, using CIL **3b** as a catalyst

Entry	Ar_1	Ar_2	Yield **10** (%)[a]	**10** ee (%)[b]
1	C_6H_5	C_6H_5	55 (56,55, 56)[c]	70 (70, 72,70)[c]
2[c]	C_6H_5	4-CH_3O-C_6H_4	67	10
3	C_6H_5	4-NO_2-C_6H_4	67	25
4[d]	C_6H_5	4-ClC_6H_4	73	4
5[d]	4-CH_3O-C_6H_4	C_6H_5	60	42
6[d]	4-Cl-C_6H_4	C_6H_5	80	4
7	C_6H_5	2-Cl-C_6H_4	61	56

a) Isolated yield. b) ee determined by chiral HPLC. c) Results obtained by reaction with recycled IL are given in brackets. d) Toluene (0.3 mL) was added.

3. Conclusion

In summary, we have designed and synthesized novel functionalized chiral ammonium, imidazolium and pyridinium-based ionic liquids derived from (-)-ephedrine as a chiral pool. The synthesis of these ionic liquids is easy and practical using solvent-free reaction under MW activation. Applications of these new CILs as chiral catalyst for the asymmetric Michel addition reaction of diethyl acetylaminomalonate to chalcone derivatives have been studied. Moderate to good yields and enantioselectivities (up to 80% yield and 70% ee) were observed. Based on these preliminary results, the design of novel CILs, which is expected to afford higher levels of enantioselectivities for asymmetric induction, is currently underway in our laboratory.

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25. See experimental section, 4.5.1. for compound 10a.