Journal of Molecular Liquids 320 (2020) 114370

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Mechanistic studies on counter-ionic effects of camphorsulfonate-based ionic liquids on kinetics, thermodynamics and stereoselectivity of β-amino carbonyl compounds

Sabahat Sardar [a,b,c,*], Erum Jabeen [d], Cecilia Devi Wilfred [b], Ahmad Sazali Hamzah [c], Jean-Marc Leveque [e]

[a] *Sulaiman Bin Abdullah Aba Al-Khail - Centre for Interdisciplinary Research in Basic Sciences (SA-CIRBS), International Islamic University, H-10 Sector, Islamabad, Pakistan*
[b] *Center of Research in Ionic Liquids (CORIL), Universiti Teknologi PETRONAS, 32610 Seri Iskandar, Perak, Malaysia*
[c] *Institute of Science, Universiti Teknologi MARA, Puncak Alam 42300, Selangor, Malaysia*
[d] *Department of Chemistry, Allama Iqbal Open University, Islamabad 44400, Pakistan*
[e] *LCME/SCeM, Universite de Savoie Mont-Blanc, 73376 Le Bourget du Lac cedex, France*

ARTICLE INFO

Article history:
Received 20 August 2020
Received in revised form 13 September 2020
Accepted 18 September 2020
Available online 25 September 2020

Keywords:
β-Amino carbonyl compounds
Ionic liquids
Hammett acidity
DFT
Dual catalyst/solvent

ABSTRACT

Catalysis is important in various applications of organic chemistry and its output product control for stereoselective compounds is outrageous. Establishment of experimental facts of stereoselective compounds from catalysis and their validation using theoretical evidences is the key to understand various mechanisms of optically active compounds. A family of new ionic liquids (ILs) with various imidazolium cations and camphorsulfonate anion as environmentally benign liquid salts have been synthesized and deployed for catalysis of β-amino carbonyl compounds. The products were formed using ILs as a homogeneous catalyst with excellent product yield and diastereoselectivity. The effect of counter ions, Hammett acidity and viscosity of ILs along with solvent and temperature are explored in terms of reaction kinetics and product yields. Density functional theory (DFT) was used to investigate thermodynamical study of mechanistic pathway of the reaction. The DFT calculations predicted that the catalysis mechanism involved both counterions of the IL. Moreover, it is evidenced that the syn-pathway required lower activation energy while anti-pathway led to thermodynamically stable product. This study explores new avenues for using ILs as potential homogeneous catalysts for the production of stereoselective species.

1. Introduction

Optically active β-amino carbonyl compounds are essential building blocks for the synthesis of pharmaceutical and agrochemical target compounds. Thus obtained molecules can be used as versatile intermediates for preparation of amino alcohols, amino acids, peptides, lactams *etc.* [1,2]. Additionally, these molecules are valuable chiral starting materials for synthesis of bioactive natural products such as those belonging to alkaloid family. Enantioselective Mannich-type reactions provide an efficient strategy to synthesize chiral β-amino carbonyl derivatives. The condensed product of the reaction (Mannich base) is structural fragment of several bioactive compounds such as antibiotics, vitamins, peptides, nucleotides, alkaloids, steroid and hormones. These compounds show a broad range of bioactivities, like antimalarial, antitubercular, vasorelaxing, analgesic, anti-inflammatory, anticancer, antifungal, antioxidative *etc.* [3–5]. Remarkable contributions have been made in the development of proficient chiral catalysts to quench the quest of controlled enantioselectivity and/or diastereoselectivity. The various efforts include preformed enolates, enolizable β-dicarbonyl, use of chiral metal complexes, organocatalysts *etc.* for optimization of high enantioselective Mannich reaction. Recent approaches for catalysis of Mannich reaction include organocatalyst [6], Brönsted acid [7], Lewis acid [8], catalyst free and solvent free condition [9] *etc.* Conversely, these catalysts are accompanied by several hindrances, such as waste production, corrosion and environmental problems, which limit their usage. Other severe drawbacks include harsh reaction conditions, catalyst deactivation, difficulty in product separation, long reaction time and ultimately low yield [10–13]. Also the use of organic solvents in reaction mixture usually leads to serious safety issues such as volatility, flammability and toxicity [14].

Recently, ionic liquids (ILs), also regarded as liquid salts, have been used as promising alternates to traditional catalysts and/or solvents [15–17]. Notably, they have been excessively explored as environmentally benign solvents and/or efficient catalysts in construction of organic moieties [18]. Beside high activity and selectivity, these versatile liquids are centre of interest as they possess unique properties like stability in air, easy separation and purification processes, reusability, non-volatility, non-flammability, noncorrosive nature, controlled immiscibility, low toxicity,

---

[*] Corresponding author at: Sulaiman Bin Abdullah Aba Al-Khail - Centre for Interdisciplinary Research in Basic Sciences (SA-CIRBS), International Islamic University, H-10 Sector, Islamabad, Pakistan.

E-mail address: sabahat.sardar@iiu.edu.pk (S. Sardar).

https://doi.org/10.1016/j.molliq.2020.114370

Brönsted acidity, low vapor pressure, wide range of viscosities, high thermal, oxidative and chemical stabilities [19–22]. The usage of Brönsted-acidic ILs is in increased demand due to their high efficiency, recycling performance and easy separation on reaction completion. The mechanistic studies emphasizing the role of catalyst have also been performed for different catalysts including proline, Lewis and Brönsted acids and a wide variety of organocatalysts for synthesis of β-amino carbonyl compounds [23–25]. Among the reported multicomponent reactions (MCRs), the mechanism proposed for Mannich reaction is least controversial and reaction route is almost largely acceptable [26]. However, most of these suggested mechanisms focus on formation of C—C bond step, while formation of iminium ion is not much highlighted. Insight grip on mechanistic pathway is very significant to develop novel catalysts, upgrade greener reaction conditions, for synthetic estimates, innovative appliances and rational designs.

In this study, role of synthesized IL bearing camphorsulfonate moiety as anion with imidazolium-based cations as catalytic entities has been inspected deeply to develop a probable mechanism that is supported by both experimental and theoretical studies. The reaction proceeds *via* hydrogen bond-assisted mechanism and formation of iminium ion with release of water molecule has been found as rate determining step of the overall reaction. To extent of our knowledge, the current study is first detailed investigation on influence of camphorsulfonate-based IL on Mannich-type reactions and for iminium ion formation as a critical intermediate for the entire mechanism.

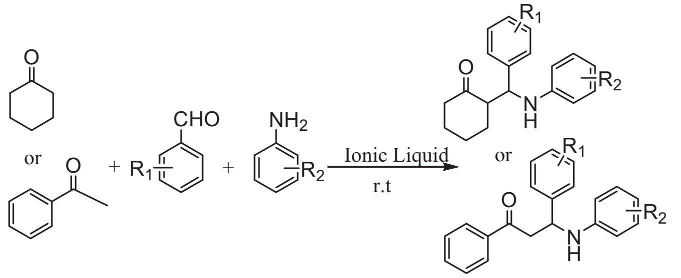
2. Experimental

2.1. Chemicals and instrumentation

The starting materials used for synthesis of protic ionic liquids (PILs), including 1,3-propane sultone 99%, 1,4-butane sultone 99%, 1-*H*-imidazole 98%, 1-methylimidazole 99%, 2-methylimidazole 99%, 1-ethylimidazole 99%, 2-ethylimidazole 98%, 1-butylimidazole 98%, 2-phenylimidazole 98%, benzimidazole 98%, hydrochloric acid 35–37%, trifluoroacetic acid 99%, sulfuric acid 99%, trifluoromethanesulfonic acid 99%, *p*-methylbenzenesulfonic acid 98%, phosphoric acid 85 wt% in H_2O, methanesulfonic acid 99.5% and (+)-10-camphorsulfonic acid 98% were purchased from Sigma Aldrich, Malaysia. NMR spectra were recorded on a 400 MHz NMR Joel spectrometer using D_2O or $CDCl_3$ as solvents. Chemical shifts were mentioned in ppm. IR spectra were recorded on a Nicolet FTIR spectrometer (400–4000 cm^{-1}).

2.2. Synthesis of ionic liquids

The synthesis of PILs has been carried out by using a similar method as reported in literature with some modifications [27–29]. The method involved the solvent-less reaction of 1,3-propane sultone or 1,4-butane sultone with *N*-methylimidazole in equimolar ratio affording respective zwitterions that were further converted to PILs by acidification with different protic acids (Scheme 1). In a typical experiment, 1,3-propane sultone (12.2 g, 0.1 mol, 1 equiv.) was drawn into two-necked round bottom flask equipped with drying tube and 1-methylimidazole (8.21 g, 0.1 mol, 1 equiv.) was added drop wise at room temperature. Within 10 min, the liquid reaction mixture turned to viscous material and further to white solid. The synthesized zwitterion was washed several times with diethylether, dichloromethane and ethyl acetate (10 mL each). After drying, zwitterion was further taken in equimolar concentration with different protic acids (hydrochloric acid, trifluoroacetic acid, sulfuric acid, phosphoric acid, methane sulphonic acid, trifluoromethane sulphonic acid, *p*-toluenesulphonic acid and camphor-10-sulphonic acid) at 85–90 °C for 4–6 h (Scheme 1). The corresponding ILs were formed quantitatively with high purity as assessed by NMR.



Scheme 2. Mannich reaction catalysed by imidazolium based ILs.

2.3. Mannich reaction: a typical procedure

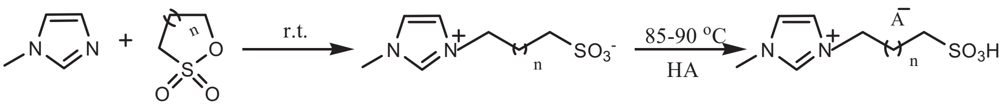
In a classic tryout, aniline (0.9 mL, 10 mmol, 1 equiv.), benzaldehyde (1 mL, 10 mmol, 1 equiv.), cyclohexanone/acetophenone (10 mmol, 1 equiv.) and stoichiometric amount of catalyst were placed in a round bottom flask with a magnetic stirrer at a constant temperature water bath at 25 °C (Scheme 2) [30,31]. The reaction mixture turned turbid within minutes and progress of reaction was continuously monitored by TLC. After completion of reaction, as indicated by TLC, the IL was separated from the product by adding 3–5 mL of water. The solid product was filtered, dried and then recrystallized using acetonitrile and further dried *in vacuo* until constant weight was obtained. Finally the water layer containing IL was concentrated using rotary evaporator. After washing with diethylether and ethyl acetate, IL was then vacuum dried at 70 °C for 12 h and was reused for next cycle.

2.4. UV–Vis acidity evaluation of PILs by Hammett equation

The camphorsulfonate-based ILs were dissolved in dried methanol and 4-nitroaniline was added as an indicator. The ILs and indicator were taken at concentration of 3×10^{-2} mol/L and 7.5×10^{-5} mol/L, respectively. The resulting solutions were shaken vigorously and then left to stand for overnight. Then UV–visible absorption study was carried out for the determination of Hammett acidity function in the range of 300–800 nm using Cary Series spectrophotometer of Agilent Technologies.

2.5. Viscosity measurement for camphorsulfonate-based PILs

Viscosity measurements were taken at ambient temperature using an Anton Paar viscometer (SVM 3000). The instrument was initially



Where $A^- = Cl^-, CF_3COO^-, HSO_4^-, H_2PO_4^-, CH_3SO_3^-, CF_3SO_3^-$, *p*-TS⁻, CS⁻

n= 1 and/or 2

Scheme 1. Schematic diagram of ionic liquid syntheses.

calibrated using ultrapure Millipore-grade water, for which data was established. The uncertainty of measurement is ±0.32%.

2.6. DFT calculations

The thermodynamic parameters were computed setting DFT/B3LYP/6-311G**(++) basis sets for DFT/B3LYP/6-311G level optimized structures of every step in proposed mechanism and their corresponding transition states using the Gaussian 03/Gauss view 09 software [16,32].

3. Results and discussion

The synthesized ILs were subjected to catalyse Mannich reaction using cyclohexanone, benzaldehyde and aniline as model substrates at ambient temperature. A variety of ILs were employed for this synthesis. For that purpose, propanesultone and butanesultone-based ILs were synthesized with same anions to check whether a small difference of one atom of carbon on the side alkyl chain could lead to noticeable difference in terms of yield. The data collection of experimental outcomes is outlined in Table 1. In the presence of IL, in mostly cases, reactions underwent smoothly leading to the formation of product within half hour to 1 h. Extending the reaction time beyond 60 min had practically no effect on the yield of the product (entries **3**, **8** and **9**). Over all of the tried ILs, [1MeimPS][CS] (entry **13**) appeared to be the best promoter for this reaction affording 93% of Mannich product in 15 min. The reactions which gave low yields were further tried with ethanol (as solvent) using same IL as catalyst and were also monitored at 70 °C but the results obtained were insignificant (entries **3**, **8** and **9**).

From these results, it can be highlighted that 'apparently' the role of cationic portion of ILs seemed to exert an insignificant role in the catalytic activity and the contribution of the engaged anion was the key parameter. It can be justified from those reactions in which low yields were observed (Table 1, entries **2**, **3**, **6**, **7**, **8**, **9** and **10**) where results were regardless of the cation but highly dependent on the nature of the anion. It was also observed that ILs formed from inorganic protic acids of low pKa gave poor yield and *vice versa*. While comparing the results of ILs bearing same anion, it was found that the ILs with 1-methylimidazolium-3-(3-propylsulfonic acid) ([1MeimPS] as cation) gave comparable yields in shorter reaction time as compared to 1-methylimidazolium-3-(4-butylsulfonic acid) [1MeimBS] which might be result of difference in viscosity of the respective ILs.

To further investigate the role of cation, some other imidazolium-based ILs were synthesized using camphorsulfonate (anion of best promoter) as anion. All the camphorsulfonate-based PILs were further used to catalyse the model reaction of cyclohexanone (5 mmol), benzaldehyde (5 mmol) and aniline (5 mmol) at room temperature (Table 1, entries **15**–**21**). The results suggested that the catalytic activity of ILs was not only depended on the nature of anion but cationic role was also significant. All the reactions were performed thrice and an average value of yield was reported for each IL. For the model reaction, all ILs gave high yields (84–94%) as shown in Table 1. It was observed that ILs prepared from 1-substituted imidazoles gave better yield than others. To determine the appropriate condition of temperature, the model reaction was also investigated in the presence of [1MeimPS][CS] for 30 min at different temperatures of 25, 40, 60, 80 °C and product was found in 93, 93, 90 and 86% yields, respectively. It was observed that increase in temperature caused negative effect on the yield of the product that may result from increased possibility of undesired product formation that could be facilitated at higher temperature.

The Brönsted acidities of camphorsulfonate-based PILs were investigated using Hammett method and measured by evaluating the protonation extent of indicator in ILs. The maximal absorbance of unprotonated 4-nitroaniline was observed at 371 nm in methanol. The experimental results are summarized in Fig. 1 and Table 2. As displayed in Table 2, the Hammett acidity function (H_0) can be expressed as:

$$H_0 = \mathrm{pKa}(\mathrm{In}) + \log([\mathrm{In}]/[\mathrm{InH}^+])$$

The corresponding H_0 values were 1.47, 1.34, 1.59, 1.35, 1.48, 1.40, 1.44, 1.46 and 1.70 for [imPS][CS], [1MeimPS][CS], [2MeimPS][CS], [1EtimPS][CS], [2EtimPS][CS], [1BuimPS][CS], [1MeimBS][CS], [2PhimPS][CS] and [bnzimPS][CS], respectively (Table 2). The results indicated that -SO_3H functionalized ILs exhibited strong Brönsted acidity and the acidity of [1MeimPS][CS] was strongest among the examined PILs and acidity of [1EtimPS][CS] was very close to that of [1MeimPS][CS]. It was observed that the catalytic activity of camphorsulfonate-based PILs for Mannich reaction was in excellent agreement with their acidity order indicating that the progress of Mannich reaction was also influenced by Brönsted acidities of respective PILs.

Table 1
Effect of imidazolium based PILs on yield of Mannich base.[a]

Entry	Ionic liquid	Solvent used	Reaction time (min)	Isolated yield (%)
1	Without IL	–, EtOH[b,c]	24 h	9, 10[b], 13[c]
2	[1MeimPS][Cl]	–	30	22
3	[1MeimBS][Cl]	–, EtOH[b,c]	60, 24 h[b,c]	19, 20[b,c]
4	[1MeimPS][CF_3COO]	–	20	77
5	[1MeimBS][CF_3COO]	–	45	76
6	[1MeimPS][HSO_4]	–	30	31
7	[1MeimBS][HSO_4]	–	55	29
8	[1MeimPS][CF_3SO_3]	–, EtOH[b,c]	60, 24 h[b,c]	30, 30[b], 31[c]
9	[1MeimBS][CF_3SO_3]	–, EtOH[b,c]	60, 24 h[b,c]	16, NR[b], 19[c]
10	[1MeimPS][CH_3SO_3]	–	60	32
11	[1MeimPS][*p*-TS]	–	25	78
12	[1MeimPS][H_2PO_4]	–	35	74
13	[1MeimPS][CS]	–	15	93
14	[1MeimBS][CS]	–	25	90
15	[imPS][CS]	–	30	90
16	[2MeimPS][CS]	–	30	88
17	[1EtimPS][CS]	–	20	94
18	[2EtimPS][CS]	–	30	91
19	[1BuimPS][CS]	–	30	91
20	[2PhimPS][CS]	–	45	90
21	[bnzimPS][CS]	–	40	84

No reaction (NR).

[a] Reaction conditions: cyclohexanone (10 mmol), benzaldehyde (10 mmol), aniline (10 mmol) and IL (5 mmol); r.t.

[b] Yield in presence of solvent.

[c] Yield obtained at 70 °C.

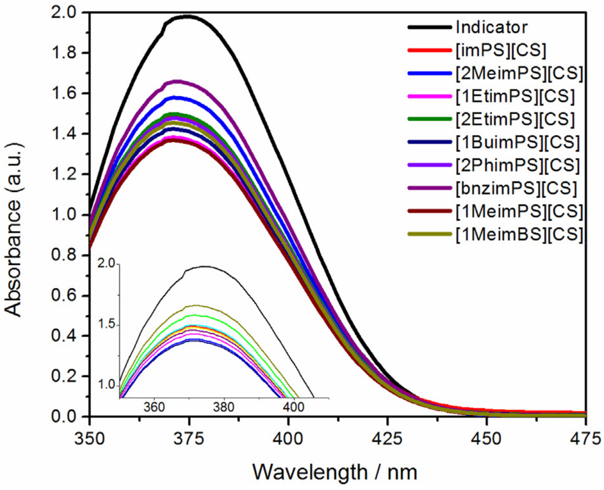


Fig. 1. The UV/Vis spectrum according to Hammett method.

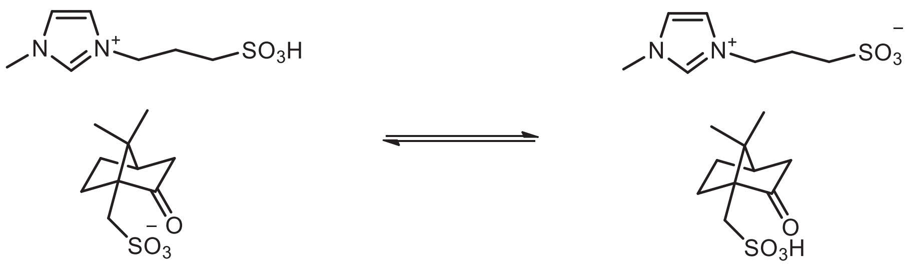
From these results, it is revealed that the nature of the anion affects the acidity of the sulfonic acid group which in turn affects its ability to function as an acid catalyst. Wang et al. reported that when the sulfonic acid and anion interaction is stronger, the IL has a stronger acidity [33]. Based on the minimum-energy geometries of sulfonic acid functionalized ILs (SFILs), they considered that the SFILs have two adjacent acid sites. One was the alkyl sulfonate group, and the other was the anion. The acidities of SFILs depended both on the characteristics of the anions and on the sulfonate group. When the interaction between the anion and the sulfonic acid proton was stronger, the dependence of the acidity of the SFIL on the anion was more significant. In addition to alkyl sulfonic acid group, the anion is also considered as available acidic site [34]. Hence the catalytic activities and acidities of –SO_3H based ILs depend on nature of anions as well. In present study, camphorsulfonate and the imidazolium sulfonic acid are both alkylsulfonic acids (albeit one contains a distant cationic group). They both might have a similar pKa and thus the proton can be located on both the imidazolium sulfonic acid and the camphorsulfonic acid, which therefore increases the number of possible acidic sites in the IL which in return aids in catalysis (Scheme 3).

To further explore the role of catalyst, the viscosities of camphorsulfonate-based PILs were measured at ambient temperature under atmospheric pressure as shown in Table 3. The viscosities of ILs increased in order [imPS][CS] < [1MeimPS][CS] < [2MeimPS][CS] < [2EtimPS][CS] < [1EtimPS][CS] < [1MeimBS][CS] < [1BuimPS][CS] < [2PhimPS][CS] < [BnzimPS][CS]. Generally, it was found that camphorsulfonate-based PILs with lower viscosities have shown better yields of Mannich product but the observed trend was not regular. For instance, the viscosity of [1MeimPS][CS] was 50.4% less than [1MeimBS][CS], although there was difference of only one methylene group in both PILs. The fast kinetics of [1MeimPS][CS] might be attributed to its low viscosity as compared with [1MeimBS][CS]. Furthermore,

Table 2
Hammett function values of investigated PILs.[a]

Entry	IL	Absorbance	[In]%[a]	[InH$^+$]%[b]	H_0[c]
1	None	1.98	100	0	–
2	[imPS][CS]	1.49	75.25	24.75	1.47
3	[1MeimPS][CS]	1.37	69.19	30.81	1.34
4	[2MeimPS][CS]	1.58	79.80	20.20	1.59
5	[1EtimPS][CS]	1.38	69.70	30.30	1.35
6	[2EtimPS][CS]	1.5	75.76	24.24	1.48
7	[1BuimPS][CS]	1.43	72.22	27.78	1.40
8	[1MeimBS][CS]	1.46	73.74	26.26	1.44
9	[2PhimPS][CS]	1.48	74.75	25.25	1.46
10	[bnzimPS][CS]	1.66	83.84	16.16	1.70

[a] [In] = molar concentration of indicator.
[b] [InH$^+$] = molar concentration of protonated indicator.
[c] H_0 = pKa(ln) + log([In]/[InH$^+$]); (pKa = 0.99); solvent: methanol; c (In) = 7.5 × 10^{-5} molL^{-1}; c (sample) = 3.0 × 10^{-2} molL^{-1}; temperature = 25 °C.

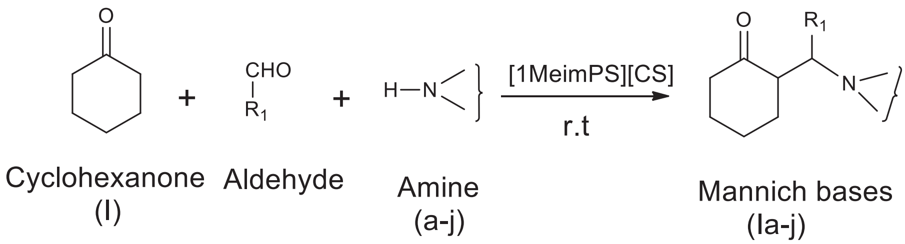


Scheme 3. Possible proton shift between sulfonate ions of [1MeimPS][CS]. Adapted from [33].

Table 3
Experimental viscosities (mPa.s) of camphorsulfonate-based PILs at ambient temperature and atmospheric pressure.[a]

IL	[imPS] [CS]	[1MeimPS] [CS]	[2MeimPS] [CS]	[1EtimPS] [CS]	[2EtimPS] [CS]	[1MeimBS] [CS]	[1BuimPS] [CS]	[2PhimPS] [CS]	[BnzimPS] [CS]
μ	176.64	183.18	199.71	248.35	241.45	363.41	477.39	639.98	673.65

[a] Standard uncertainty μ is μ(T) = 0.01 K and the combined expanded uncertainty is $\mu_c(\eta)$ 0.32% mPa.s.



Scheme 4. Synthesis of cyclohexanone-based Mannich bases.

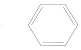
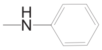
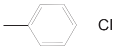
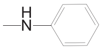
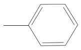
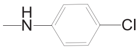
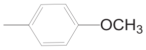
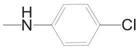
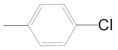
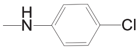
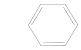
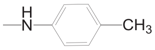
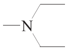
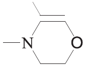
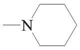
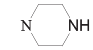
higher viscosities of [PhimPS][CS] and [BnzimPS][CS] might be resulted in increased reaction time.

The scope of the cyclohexanone-based Mannich bases with formaldehyde and some benzaldehydes was investigated using [1MeimPS][CS] as dual reagent (Scheme 4). Although, by using ILs as catalyst and/or solvent, aliphatic aldehydes have been reported to form Mannich adduct in very low yield [35], but the present methodology produced Mannich bases in high yield by using formaldehyde (Table 4, entries 7–10). All the reactions underwent smoothly affording 85–94% yields in 15–45 min. It was noted that aryl aldehyde bearing electron-donating substituent facilitated Mannich base in high yield as compared to electron withdrawing substituent (Table 4). While by using anilines, both electron-donating and electron with-drawing substituents proved to be equally advantageous for Mannich reaction as reported in literature [11,36]. [1MeimPS][CS] was successfully reused four times with slight decrease in activity. The IL retained its structure and purity after four cycles as confirmed by NMR analysis of recycled ILs.

3.1. Mechanistic insight for formation of Mannich adduct in the presence of [1MeimPS][CS]

The largely accepted mechanism suggests that iminium ion/enamine is formed as an intermediate and hydrogen bonding is found to be essential for C—C bond formation between imine and catalyst [37,38]. In the current study, two mechanistic pathways have been proposed emphasizing the role of Brönsted imidazolium (Fig. S1) and both counter ions of [1MeimPS][CS] (Fig. 2), as catalysing entities. To solve which of two proposed pathways is effectively pursued to get more insight into the reaction mechanism; DFT computational theory has been conducted. A comparison of transition states and respective energies formed along both routes has been made to investigate the role of catalyst for formation of C—N bond (first step) and C—C bond (second step). The DFT studies have suggested that mechanism 1(Fig. 2; involving role of both counter ions as catalytic sites) is more plausible than mechanism 2 (Fig. S1; showing $[1MeimPS]^+$ as catalyst). The probable route (mechanism 1) is based on hydrogen bonding-assisted mechanism where negative charge of camphorsulfonate anion is stabilized by labile proton of aniline, while Brönsted proton of imidazolium cation develops hydrogen bonding with carbonylic oxygen of benzaldehyde (Fig. 2). In other words, the reaction is initiated with interaction of cationic counter part of IL with carbonylic oxygen while negative charge of camphorsulfonate (anionic part of IL) shows interactions with labile proton of aniline. The first step involves nucleophile attack of aniline nitrogen atom on electrophilic carbonylic carbon of benzaldehyde leading to formation of C—N bond (intermediate **2**). This first step is supported with HOMO of aniline and LUMO of benzaldehyde. It can be observed from Fig. 3 that most electron rich area in aniline is nitrogen atom while most electron deficient area in benzaldehyde is carbon atom from carbonyl moiety. In other words, HOMO map of aniline suggests that HOMO can serve as delocalized orbital with substantial contribution from N-atom. Whereas LUMO map of benzaldehyde certainly reveals that the most deficient electron deficient area is carbonylic carbon. The new C—N bond is formed along with simultaneous proton transfer from side chain of imidazolium ion to carbonyl oxygen atom of benzaldehyde *via* first transition state (TS1). Under influence of interactions between counter ions of [1MeimPs][CS] and intermediate **2**, isomerization of intermediate **2** to more stable intermediate **3** takes place. Back donation of proton to imidazolium cation occurs by abstraction of hydrogen from positively charged nitrogen of intermediate **3** leading to of intermediate

Table 4
Preparation of cyclohexanone based Mannich bases using [1MeimPS][CS] as catalyst.[a]

Entry	Products	R_1	R_2	Reaction time (min)	Yield (%)	*anti/syn*[c]
1	Ia			15	93, 94[b]	100:0
2	Ib			20	89	99:1
3	Ic			20	91	100:0
4	Id			15	94	100:0
5	Ie			25	90	99:1
6	If			20	92	100:0
7	Ig	H		45	85	–
8	Ih	H		25	92	–
9	Ii	H		30	90	–
10	Ij	H		25	88	–

[a] Cyclohexanone (10 mmol), aldehyde (10 mmol), amine (10 mmol), [1MeimPS][CS] (3 mmol) at room temperature.

[b] Reaction at 50 mmol scale.

[c] Determined by ^1H NMR of crude reaction mixture.

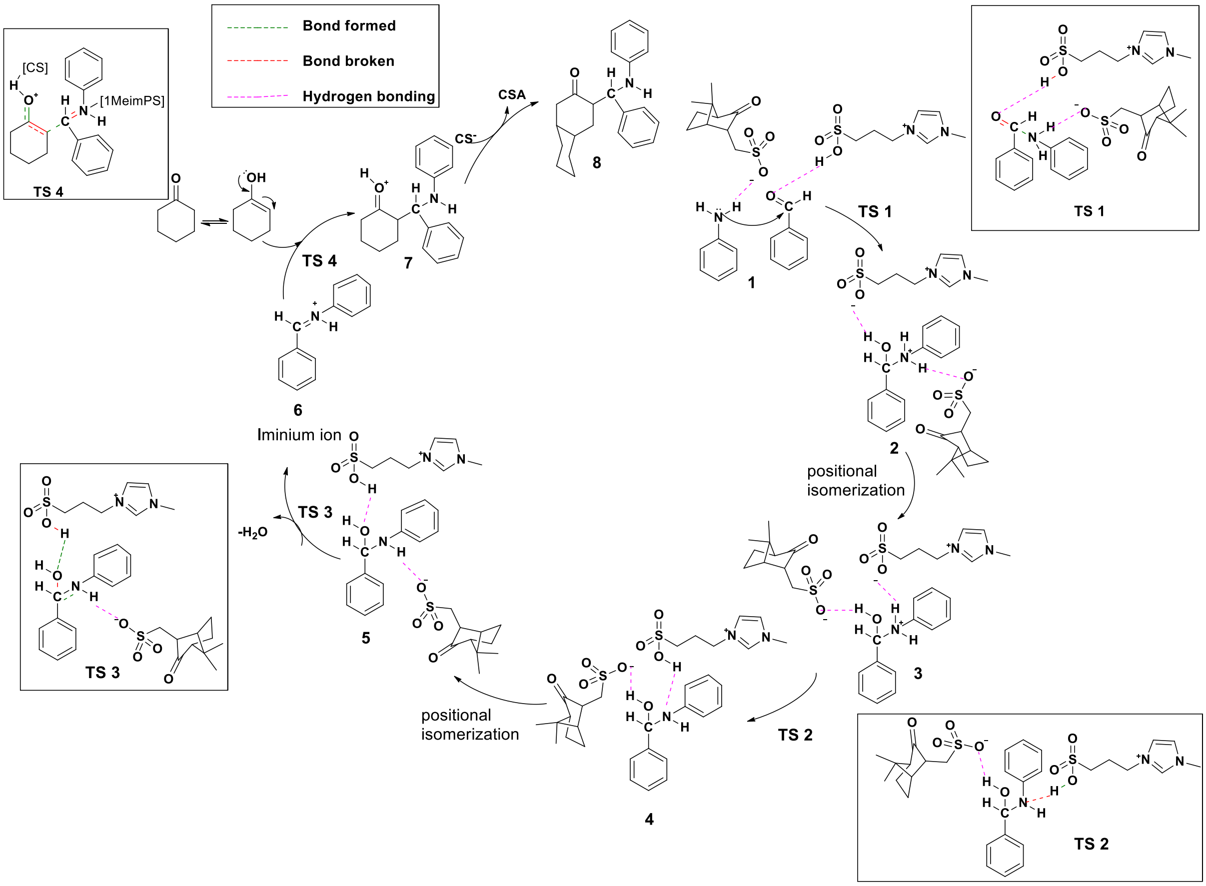
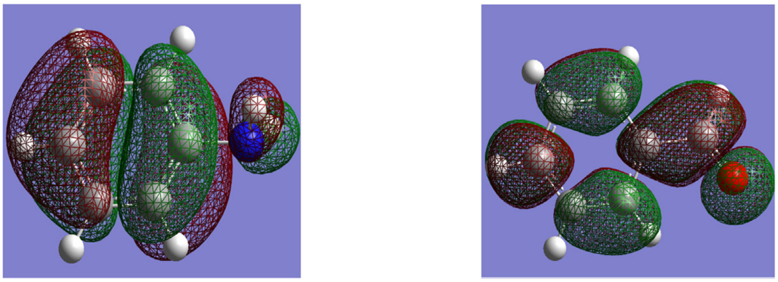
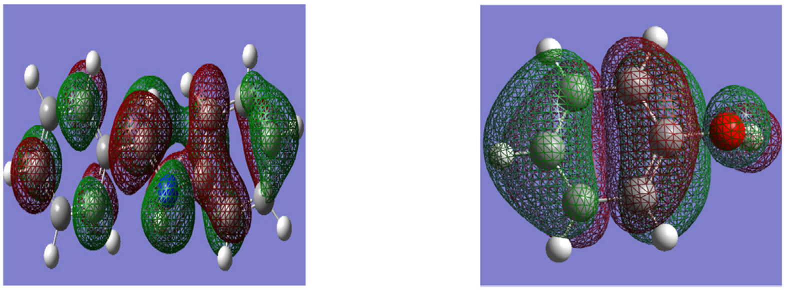


Fig. 2. Proposed catalytic cycle for mechanism 1 catalysed by [1MeimPS][CS]. Adapted from [16].

4 *via* TS2. The intermediate **4** further isomerises to more stable intermediate **5** by positional isomerization. The liberation of water molecule from intermediate **5** leads to formation of iminium ion (**6**) *via* TS3 through rate determining step. The LUMO and HOMO maps of the iminium ion and enol form of cyclohexanone show the most electron deficient and sufficient areas in respective molecules (Fig. 3). Hence, the nucleophilic attack of enol form of cyclohexanone on C═N bond of iminium ion (**6**) lead to formation of C—C bond (**7**) *via* TS4. The enol form of cyclohexanone and



HOMO of aniline E = - 0.335 eV	LUMO of benzaldehyde = E = 0.08150eV



LUMO of imminium ion = E = - 0.2741eV	HOMO of enol = E = - 0.335eV

Fig. 3. HOMO map of aniline and LUMO map of benzaldehyde (top), and LUMO map of iminium ion and HOMO map of enol form of cyclohexanone (bottom).

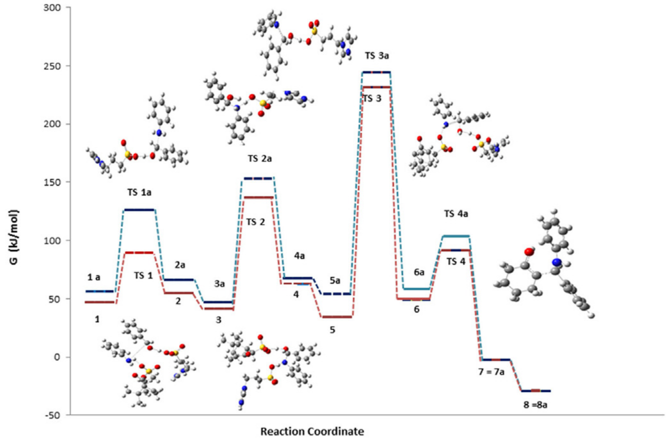
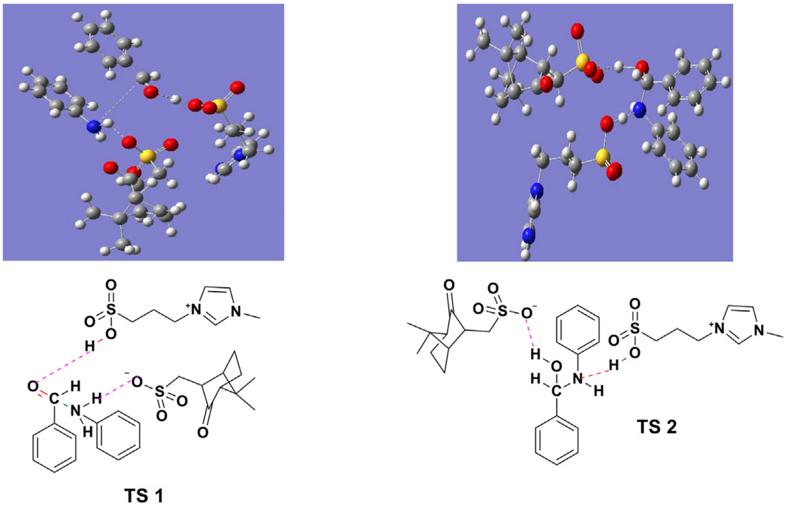


Fig. 4. Energy diagrams of the pathways for the formation of product (8) through proposed mechanisms and transition states; red lines reflect mechanism 1 (catalysed by [1MeimPS][CS]), while mechanism 2 is presented by blue lines (catalysed by $[1MeimPS]^+$).

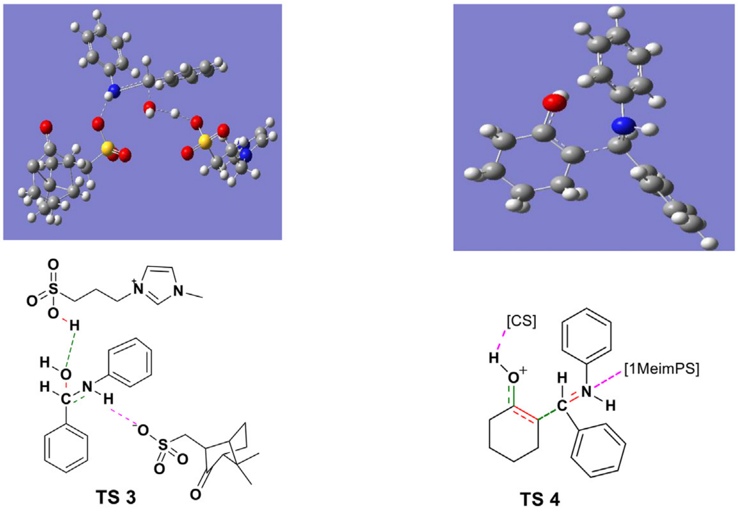
iminium ion (**6**) yielded protonated Mannich base *via syn*- and anti-pathways. The final product (**8**) is formed by deprotonation of 7.

The potential energy diagram corresponding to both proposed mechanisms is given as Fig. 4. The potential energy diagram clearly revealed that the reaction pathway labelled from 1 to 8 is associated with lower potential energy barrier for all steps as compared with the reaction path corresponding of proposed mechanism 2 (1a-8a). When the activation energy barriers were calculated, it was found that path 1a-8a presented 28 kJ/mol higher barrier to reach first transition state ($\Delta G_{TS1a} > \Delta G_{TS1}$), 22 kJ/mol higher barrier for 2nd transition state ($\Delta G_{TS2a} > \Delta G_{TS2}$) while 9 kJ/mol lower barrier towards 3rd transition state ($\Delta G_{TS3a} < \Delta G_{TS3}$). For instance, the overall potential energy barrier for steps 1a-8a is higher as compared with the potential energy barrier for 1–8, so the action path 1–8 can be regarded to be more feasible as the reaction will prefer to adopt the route with lower starting energy barrier. The reaction path for 7–8 step is same in energy terms for both mechanisms as in both cases, camphorsulfonate ion has to quench proton prom protonated product (7) to afford (8) as displayed in Fig. 4. The optimized geometries of transition states involved in mechanism 1 catalysed by [1MeimPS][CS] are shown in Fig. 5. While the optimized geometries of transition states involved in mechanism 2 catalysed by



TS1; ΔG= 42.01 KJ/mol

TS2; ΔG= 94.08 KJ/mol



TS3; ΔG= 198.09 KJ/mol

TS4; ΔG= 42.5 KJ/mol

Fig. 5. Optimized geometries of transition states involved in mechanism 1 catalysed by [1MeimPS][CS].

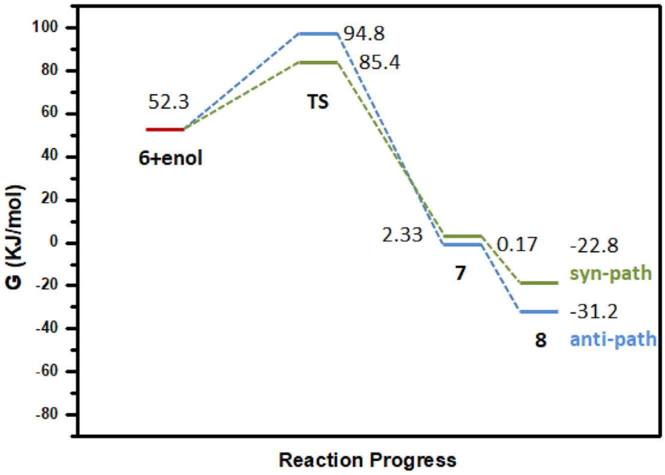


Fig. 6. Energy profile of stereocontrol step for syn- and anti-pathways.

[1MeimPS]$^+$ are shown in supplementary information as Fig. S2. The energy profile diagrams of mechanism 1 catalysed by [1MeimPS][CS] and mechanism 2 catalysed by [1MeimPS]$^+$ are also provided in supporting information as Figs. S3 and S4.

Theoretically, iminium ion (**6**) and enol form of cyclohexanone can lead to protonated Mannich product (**8**) *via syn*- and anti-pathways. It was noteworthy that, based on ^{1}H NMR spectra of the crude products, syn-isomer was not detected in the reaction mixture (Table 4). Interaction of counterions of [1MeimPS][CS] with reactant substrates controls the stereochemical outcome. The chair form of camphorsulfonate moiety may serve as an effective stereocontrolling chiral element resulting in excellent diastereocontrol. Theoretically, syn-product requires lower activation energy *i.e.* 85.4 KJ/mol and anti-product needs 94.8 KJ/mol activation energy (Fig. 6). The anti-pathway yields the product which is thermodynamically more stable *i.e.* −31.2 KJ/mol (Thermodynamically favored product) while syn-pathway yields kinetically favored product *i.e.* −22.8 KJ/mol (Fig. 6). Fig. 7 shows possible interactions of [1MeimPS][CS] with enol-form of cyclohexanone and iminium ion (**6**), for formation of anti-product (**8**).

One pot three component condensation reaction of acetophenone with different aldehydes and amines was further carried out under previously optimized reaction conditions. Using [1MeimPS][CS], all the reactions underwent smoothly giving 86–97% yields and were completed within the time periods ranging from 15 to 55 min to provide high yields of β–amino carbonyl compounds (Table 5). The effect of reaction temperature on yield of model reaction (using acetophenone, benzaldehyde and aniline) was determined by varying temperature from 25 °C to 60 and 80 °C (Table 5, entry **2**). It was found that the yield dropped from 96% to 93 and 88% when reaction temperature was increased from 25 °C to 60 and 80 °C, respectively. As the best yield was obtained at 25 °C so further reactions were performed at 25 °C. Notably, it was observed that among various amines, diethyl amine gave lowest yield and took longer time to react and the reason might be attributed to steric factors. Among methyl-substituted acetophenones, 3′-methyl acetophenone gave comparable yield in less time duration as compared to 2′-methyl acetophenone and 4′-methyl acetophenone. Among the studied acetophenones, the reactivity of acetophenones (in terms of reaction time) bearing electron withdrawing substituents was found to be higher as compared to those having electron donating substituents. The electron withdrawing substituents withdrew the electron density of aromatic ring and ultimately carbonyl carbon became more electron deficient making hydrogens of methyl group more labile. The products were separated by filtration after addition of small amount of water. The filtrate was reused without further purification in next run after rotary evaporation. The catalyst was recycled up to five times without significant decrease in catalytic activity. The systematic equation for reaction between acetophenone(s), aldehydes and amines is represented in Scheme 5.

4. Conclusion

Present methodology gives a simple and effective way to synthesize Mannich adducts in high yield by straight forward one-pot condensation of Mannich reagents at ambient temperature in shorter reaction time using camphorsulfonate-based PILs. The effect of anions followed

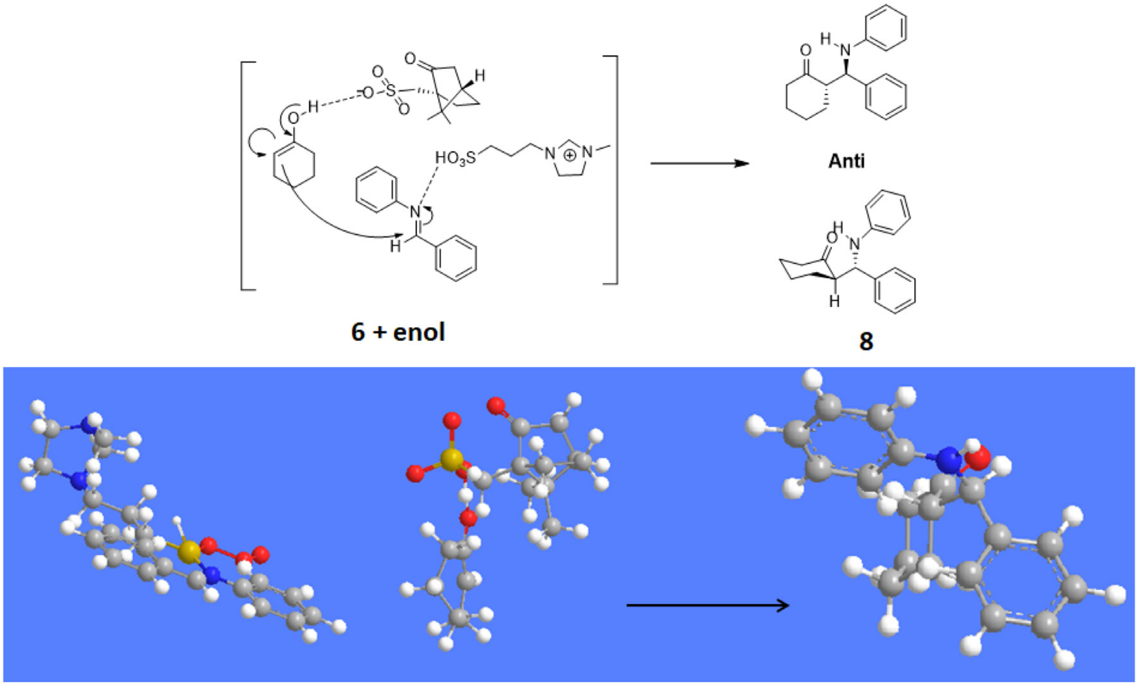
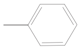
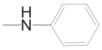
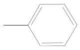
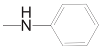
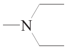
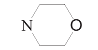
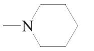
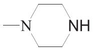
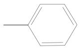
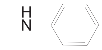
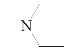
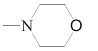
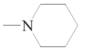
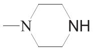
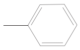
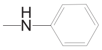
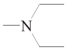
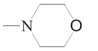
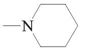
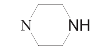
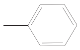
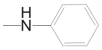
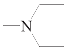
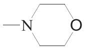
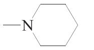
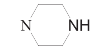
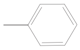
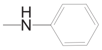
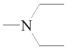
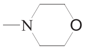
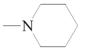
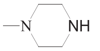
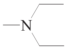
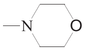
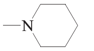
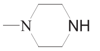


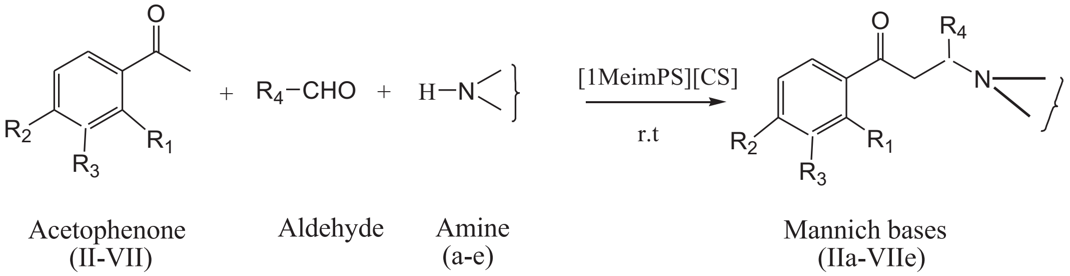
Fig. 7. Proposed interactions of [1MeimPS][CS] with enol-form and iminium ion (6), for formation of anti-product (8).
Adapted from [39].

Table 5
Synthesis of β–amino ketones using [1MeimPS][CS] as catalyst.[a]

Entry	Products	R_1	R_2	R_3	R_4	R_5	Reaction time (min)	Yield (%)
1	IIa	-H	-H	-H			120[b,c,d,e]	16[b], 17[c], 21[d], 26[e]
2	IIa	-H	-H	-H			20, 15[f], 30[g]	96, 93[f], 88[g]
3	IIb	-H	-H	-H	-H		40	89, 91[f]
4	IIc	-H	-H	-H	-H		30	95
5	IId	-H	-H	-H	-H		30	96
6	IIe	-H	-H	-H	-H		25	94
7	IIIa	$-CH_3$	-H	-H			30	95
8	IIIb	$-CH_3$	-H	-H	-H		55	86
9	IIIc	$-CH_3$	-H	-H	-H		35	93
10	IIId	$-CH_3$	-H	-H	-H		40	92
11	IIIe	$-CH_3$	-H	-H	-H		35	92
12	IVa	-H	$-CH_3$	-H			20	95
13	IVb	-H	$-CH_3$	-H	-H		45	88
14	IVc	-H	$-CH_3$	-H	-H		25	94
15	IVd	-H	$-CH_3$	-H	-H		25	94
16	IVe	-H	$-CH_3$	-H	-H		30	93
17	Va	-F	-H	-H			15	97
18	Vb	-F	-H	-H	-H		40	91
19	Vc	-F	-H	-H	-H		25	95
20	Vd	-F	-H	-H	-H		25	96
21	Ve	-F	-H	-H	-H		25	96
22	*VIa*	-OH	-H	-H			15	96
23	VIb	-OH	-H	-H	-H		45	91
24	VIc	-OH	-H	-H	-H		25	93
25	VId	-OH	-H	-H	-H		25	94
26	VIe	-OH	-H	-H	-H		30	93
27	VIIb	-H	-H	$-CH_3$	-H		55	86
28	VIIc	-H	-H	$-CH_3$	-H		30	91
29	VIId	-H	-H	$-CH_3$	-H		35	92
30	VIIe	-H	-H	$-CH_3$	-H		30	91

Where [a]acetophenone (10 mmol), aldehyde (10 mmol), amine (10 mmol), [1MeimPS][CS] (3.5 mmol) at room temperature.
[b,c,d & e]Reaction without IL at 25 °C, 40 °C, 60 °C and 80 °C, respectively.
[f, g]Reaction with [1MeimPS][CS] at 60 °C and 80 °C, respectively.

by effect of cations was probed using different cations and anions to find the best promoter for the reaction. Among the tried combinations of different cations and anions, [1MeimPS][CS] was found as an efficient catalyst for catalysis of Mannich bases. Experimentally, it was found that both cation and anion of [1mMeimPS][CS] were active participants in catalysis pathway. Based on DFT outcomes of mechanistic study, it can be concluded that hydrogen bonded chiral organocatalysis serves a significant role in formation of C—N and C—C bond. The release of water molecule during formation of iminium ion has been depicted as rate determining step of the whole reaction. Additionally, the final phase of



Scheme 5. Synthesis of acetophenone based Mannich bases.

reaction, that is formation of C—C bond along with deprotonation of oxygen atom is also facilitated by presence of both counterions of [1MeimPS][CS]. The *syn*-route needs lesser activation energy as compared to hypothetic anti-pathway but yields a less stable kinetically favored product. The anti-pathway results in formation of thermodynamically favored product, which depicts that the pathway catalysed with [1MeimPS][CS] is thermodynamically controlled.

CRediT authorship contribution statement

All authors have contributed equally and there is no conflict of interest.

Declaration of competing interest

The findings of this work were based on a research project embarked by a group of staff of Universiti Teknologi PETRONAS, Malaysia, Universiti Teknologi MARA, Malaysia and LCME/SCeM, Universite de Savoie Mont-Blanc, France. It is confirmed that all the authors are agreed to the content and publication of the submitted manuscript. All authors have contributed equally and there is no conflict of interest.

Acknowledgment

The authors would like to thank Center of Research in Ionic Liquids (CORIL) at Universiti Teknologi PETRONAS (Seri Iskandar) and Universiti Teknologi MARA (Puncak Alam) for lab facilities and chemicals provided. The project is funded by URIF (0153AA-B35).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molliq.2020.114370.

References

[1] Y. Shi, Q. Wang, S. Gao, Recent advances of intramolecular Mannich reaction in natural products total synthesis, Organic Chemistry Frontiers 5 (6) (2018) 1049–1066, https://doi.org/10.1039/C7QO01079F.
[2] S. Pandeya, N. Rajput, Synthesis and analgesic activity of Mannich & Schiff bases of 1, 5-benzodiazepines, Indo Global Journal of Pharmaceutical Sciences 2 (2012) 76–84.
[3] C. Cheng, X. Lu, L. Ge, J. Chen, W. Cao, X. Wu, et al., Effective asymmetric vinylogous Mannich reaction of isatin imines with α, α-dicyanoolefins in the presence of a simple chiral amide phosphonium bifunctional phase transfer catalyst, Organic Chemistry Frontiers 4 (2017) 101–114.
[4] J.-Y. Zhu, W.-L. Yang, Y.-Z. Liu, S.-J. Shang, W.-P. Deng, A copper (I)-catalyzed asymmetric Mannich reaction of glycine Schiff bases with isatin-derived ketimines: enantioselective synthesis of 3-substituted 3-aminooxindoles, Organic Chemistry Frontiers 5 (2018) 70–74.
[5] J.-L. Ye, H. Chen, Y.-F. Zhang, P.-Q. Huang, A versatile access to vicinal diamine motifs by highly anti-selective asymmetric vinylogous Mannich reactions: an efficient total synthesis of (+)-absouline, Organic Chemistry Frontiers 3 (2016) 683–692.
[6] Y. Zhu, Y. Li, Q. Meng, X. Li, An organocatalytic enantioselective vinylogous Mannich reaction of α, α-dicyanoolefins with isatin N-Boc ketimines, Organic Chemistry Frontiers 3 (2016) 709–713.
[7] X. Chen, H. Sun, Y. Luo, Y. Jian, Y. Wu, W. Zhang, et al., Polyelectrolyte Brønsted acid catalyzed three-component Mannich reactions accelerated by emulsion, RSC Adv. 6 (2016) 39343–39347.
[8] L. Min, B. Pan, Y. Gu, Synthesis of quinoline-fused 1-benzazepines through a Mannich-type reaction of a C, N-bisnucleophile generated from 2-aminobenzaldehyde and 2-methylindole, Org. Lett. 18 (2016) 364–367.
[9] S.B. Dongare, H.V. Chavan, P.S. Bhale, Y.B. Mule, A.S. Kotmale, B.P. Bandgar, A catalyst-and solvent-free multicomponent synthesis of 7-azagramine analogues via a Mannich type reaction, Chin. Chem. Lett. 27 (2016) 99–103.
[10] A. Hajipour, F. Rafiee, Basic ionic liquids. A short review, J. Iran. Chem. Soc. 6 (2009) 647–678.
[11] A.A. Hullio, G. Mastoi, Designing, synthesis and applications of task specific ionic liquids, Orient. J. Chem. 27 (2011) 1591.
[12] S.G. Subramaniapillai, Mannich reaction: a versatile and convenient approach to bioactive skeletons, J. Chem. Sci. 125 (2013) 467–482.
[13] N. Suryawanshi, P. Jain, M. Singhal, I. Khan, Mannich synthesis under ionic liquid [Et3NH][HSO4] catalysis, J. Appl. Chem. 1 (2012) 18–23.
[14] K. Gong, D. Fang, H.-L. Wang, Z.-L. Liu, Basic functionalized ionic liquid catalyzed one-pot Mannich-type reaction: three component synthesis of β-amino carbonyl compounds, Monatshefte für Chemie/Chemical Monthly 138 (2007) 1195–1198.
[15] W. Senapak, R. Saeeng, U. Sirion, Acid-ionic polymer as recyclable catalyst for one-pot three-component Mannich reaction, RSC Adv. 7 (2017) 30380–30384.
[16] V.P. Petrović, D. Simijonović, V.M. Milovanović, Z.D. Petrović, Acetophenone Mannich bases: study of ionic liquid catalysed synthesis and antioxidative potential of products, R. Soc. Open Sci. 5 (2018) 181232.
[17] H. Dong, Q. Liu, Y. Tian, Y. Qiao, Tartaric acid–zinc nitrate as an efficient Brønsted acid-assisted Lewis acid catalyst for the Mannich reaction, J. Chem. Res. 42 (2018) 463–466.
[18] A.C. Cole, J.L. Jensen, I. Ntai, K.L.T. Tran, K.J. Weaver, D.C. Forbes, et al., Novel Brønsted acidic ionic liquids and their use as dual solvent–catalysts, J. Am. Chem. Soc. 124 (2002) 5962–5963.
[19] P.J. Dyson, T.J. Geldbach, Applications of ionic liquids in synthesis and catalysis, Interface-Electrochemical Society 16 (2007) 50–53.
[20] P. Cserjési, K. Bélafi-Bakó, N. Nemestóthy, L. Gubicza, Recent trends on application of ionic liquids in organic synthesis, Hung. J. Ind. Chem. (2008) 36.
[21] S. Sardar, C.D. Wilfred, A. Mumtaz, J.-M. Leveque, A.S. Khan, S. Krishnan, Physico-chemical properties, Brönsted acidity and ecotoxicity of imidazolium-based organic salts: non-toxic variants of protic ionic liquids, J. Mol. Liq. 269 (2018) 178–186.
[22] S. Sardar, C.D. Wilfred, A. Mumtaz, Z. Rashid, J.-M. Leveque, Synthesis, thermophysical properties, Hammett acidity and COSMO-RS study of camphorsulfonate-based Brönsted acidic ionic liquids, J. Mol. Liq. 271 (2018) 621–630.
[23] H.G. Alvim, E.N. da Silva Junior, B.A. Neto, What do we know about multicomponent reactions? Mechanisms and trends for the Biginelli, Hantzsch, Mannich, Passerini and Ugi MCRs, RSC Adv. 4 (2014) 54282–54299.
[24] Q. Chang, J. Zhou, L.H. Gan, Theoretical study on the mechanisms of proline-catalyzed Mannich reaction between acetaldehyde and N-Boc imines, J. Phys. Org. Chem. 25 (2012) 667–673.
[25] M.J. Di Maso, K.M. Snyder, F. De Souza Fernandes, O. Pattawong, D.Q. Tan, J.C. Fettinger, et al., Diastereoselective synthesis of and mechanistic understanding for the formation of 2-piperidinones from imines and cyano-substituted anhydrides, Chem. Eur. J. 22 (2016) 4794–4801.
[26] H.G. Alvim, G.A. Bataglion, L.M. Ramos, A.L. de Oliveira, H.C. de Oliveira, M.N. Eberlin, et al., Task-specific ionic liquid incorporating anionic heteropolyacid-catalyzed Hantzsch and Mannich multicomponent reactions. Ionic liquid effect probed by ESI-MS (/MS), Tetrahedron 70 (2014) 3306–3313.
[27] K. Kondamudi, P. Elavarasan, P.J. Dyson, S. Upadhyayula, Alkylation of p-cresol with tert-butyl alcohol using benign Bronsted acidic ionic liquid catalyst, J. Mol. Catal. A Chem. 321 (2010) 34–41.
[28] X. Han, L. Zhou, Optimization of process variables in the synthesis of butyl butyrate using acid ionic liquid as catalyst, Chem. Eng. J. 172 (2011) 459–466.
[29] J. Fraga-Dubreuil, K. Bourahla, M. Rahmouni, J.P. Bazureau, J. Hamelin, Catalysed esterifications in room temperature ionic liquids with acidic counteranion as recyclable reaction media, Catal. Commun. 3 (2002) 185–190.
[30] G. Zhao, T. Jiang, H. Gao, B. Han, J. Huang, D. Sun, Mannich reaction using acidic ionic liquids as catalysts and solvents, Green Chem. 6 (2004) 75–77.
[31] K.K. Mak, J. Siu, Y. Lai, P.-k. Chan, Mannich reactions in room temperature ionic liquids (RTILs): an advanced undergraduate project of green chemistry and structural elucidation, J. Chem. Educ. 83 (2006) 943.
[32] Z.D. Petrović, D. Simijonović, J. Đorović, V. Milovanović, Z. Marković, V.P. Petrović, One-pot synthesis of tetrahydropyridine derivatives: liquid salt catalyst vs glycolic

acid promoter. Structure and antiradical activity of the new products, ChemistrySelect 2 (2017) 11187–11194.
[33] H. Xing, T. Wang, Z. Zhou, Y. Dai, The sulfonic acid-functionalized ionic liquids with pyridinium cations: acidities and their acidity–catalytic activity relationships, J. Mol. Catal. A Chem. 264 (2007) 53–59.
[34] A.S. Amarasekara, Acidic ionic liquids, Chem. Rev. 116 (2016) 6133–6183.
[35] S.B. Sapkal, K.F. Shelke, B.R. Madje, B.B. Shingate, M.S. Shingare, 1-Butyl-3-methyl imidazolium hydrogen sulphate promoted one-pot three-component synthesis of amidoalkyl naphthols, Bull. Kor. Chem. Soc. 30 (2009) 2887–2889.
[36] G. Zhao, M. Lu, One-pot green procedure for the Mannich reaction catalyzed by a task-specific ionic liquid, Chiang Mai Journal of Science 39 (2012) 49–58.
[37] H. Li, A. Fu, H. Shi, Theoretical studies of stereoselectivities in the direct organocatalytic Mannich reactions involving ketimine, J. Mol. Catal. A Chem. 303 (2009) 1–8.
[38] A. Fu, H. Li, F. Tian, S. Yuan, H. Si, Y. Duan, Theoretical studies of stereoselectivities in the direct anti-and syn-aldol reactions catalyzed by different amino acid derivatives, Tetrahedron Asymmetry 19 (2008) 1288–1296.
[39] Y. Shi, Q. Wang, S. Gao, Recent advances in the intramolecular Mannich reaction in natural products total synthesis, Organic Chemistry Frontiers 5 (2018) 1049–1066.