Protic acidic ionic liquids promoted formation of 1,5-benzodiazepines: remarkable effects of cations and anions on their performances

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A series of protic acidic ionic liquids have been used as solvents and catalysts for the synthesis of 1,5-benzodiazepines. Success of the condensation appears to lie in the choice of cation–anion combinations and the ionic liquid [HBIm]CF_3SO_3 was found to be the best. Acidities of five protic acidic ionic liquids have also been investigated using Hammett method in 1,2-dichloromethane solutions. The ionic liquid [HBIm]CF_3SO_3 can be recovered conveniently and reused for five times without remarkable loss of activity.

Keywords: ionic liquid, determination of acidity, 1,5-benzodiazepines, Hammett method

Benzodiazepines and their polycyclic derivatives are a very important class of bioactive compounds. They are finding numerous new applications and are widely used as anticonvulsant, anti-inflammatory, analgesic, hypnotic, sedative, and antidepressive agents.[1,2] Some benzodiazepine derivatives are also used in industry, such as in photography (as dyes for acrylic fibres).[3] Moreover, benzodiazepines are used as synthons for the preparation of other fused ring systems such as triazolo-, oxadiazolo-, oxazino- or furanobenzodiazepines.[4] Due to their wide range of pharmacological activity, industrial, and synthetic applications, the synthesis of 1,5-benzodiazepines has received more attention and recently many methods have been reported for their synthesis. Generally these compounds are prepared by condensation of *o*-phenylenediamines with α,β-unsaturated carbonyl compounds, β-halo ketones or ketones. Many reagents or catalysts have been reported for this condensation reaction in the literature which include the use of BF_3-etherate,[5] $NaBH_4$,[6] polyphosphoric acid or SiO_2,[7] MgO/$POCl_3$,[8] Yb$(OTf)_3$,[9] sulfated zirconia,[10] silica gel,[11] $CeCl_3$/NaI/silica gel,[12] molecular iodine,[13] and Al_2O_3/P_2O_5 or AcOH in conjunction with microwave conditions.[14] However, a milder, selective, non-hazardous and inexpensive reagent is still in demand.

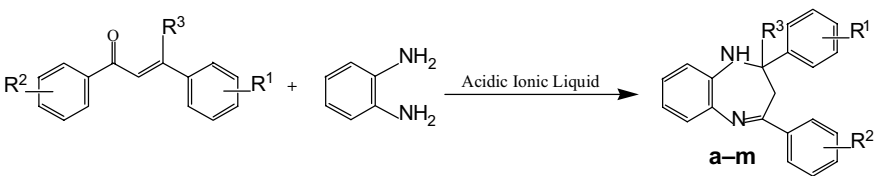
Recently, the application of ionic liquids as reaction media for a wide variety of synthetic processes is an area of intense research. Ionic liquids provide a vapourless, thermally stable and reusable 'green' solvent for chemical reactions.[15] The synthesis of benzodiazepines has also been reported in ionic liquids.[16] However, these synthetic proposals often involve the use of an additional acidic catalyst or corrosive and toxic bromide ion. Recent investigations on non-chloroaluminate functionalised acidic ionic liquids have opened up avenues for green acid catalysis.[17] Based on previous works,[18] we reasoned that employing the protic acidic ionic liquids (PAILs), which have been proved to be an efficient acidic catalysts for many organic transformations,[19] as the solvent and/or catalyst may have prominent advantages for the synthesis of 1,5-benzodiazepines through condensation of *o*-phenylenediamines with α,β-unsaturated carbonyl compounds. The PAILs might neutralise the interaction between basic substrate or product and acidic catalyst or solvent, which are disadvantageous for the condensation, because their active site (the proton covalently attached to 3-position in imidazolium ring) has been trapped with the nitrogen atom. Moreover, PAILs may avoid the use of additional acidic promoter, which is mainly responsible for the condensation.[7-10] Furthermore, ionic liquid can facilitate the formation of imine,[20] which is known as the intermediate for the synthesis of 1,5-benzodiazepines from α,β-unsaturated ketones and *o*-phenylenediamine. The above possibilities stimulated our study of the synthesis of 1,5-benzodiazepines carried out in the PAILs.

Initial experimentation was undertaken in 1-butylimidazolium trifluoromethanesulfonate ([HBIm]CF_3SO_3, 10 mmol) using *o*-phenylenediamine (10 mmol) and chalcone (10 mmol) under atmospheric pressure, the mixture being heated at 80°C for 2 h without any particular precautions (Table 1, run 1). After extraction of organic compounds with diethyl ether, GC analysis of the solution indicated the formation of 1,5-benzodiazepine (**a**). Then, the solvent was removed under reduced pressure and the resulting crude product was purified by silica gel column chromatography (ethyl acetate/*n*-hexane: 2: 8) to yield 88% of pure product (Table 1, entry 1). When the experiment was carried out in 1-butylimidazolium methanesulfonate ([HBIm]CH_3SO_3) under identical conditions, we found that 1,5-benzodiazepine (**a**) was formed in *ca* 38% yield (entry 2). In analogous protic ionic liquid 1-butylimidazolium trifluoroacetate ([HBIm]CF_3CO_2), heat treatment of *o*-phenylenediamine and chalcone gave rise to a complex mixture of products

Table 1 Synthesis of 1,5-benzodiazepine (a) from *o*-phenylenediamine and chalcone over different protic ionic liquids

Entry	Catalyst	Temp./°C	Time/h	Yield/%
1	[HBIm]CF_3SO_3	80	2	88
2	[HBIm]CH_3SO_3	80	2	38
3	[HBIm]CF_3CO_2	80	2	< 2[a]
4	[HMIm]CF_3SO_3	80	2	72
5	[HMPy]CF_3SO_3	80	2	81
6	[HBIm]CF_3SO_3	50	2	61
7	[HBIm]CF_3SO_3	80	1	73

[a]Obtained from GC analysis.



Scheme 1 Synthesis of 1,5-benzodiazepines from *o*-phenylenediamine and chalcones.

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difficult to separate (entry 3). GC/MS analysis revealed that 1,5-benzodiazepine(**a**) was formed only in trace (< 2%). Other two trifluoromethanesulfonate PAILs, 1-methylimidazolium trifluoromethanesulfonate ([HMIm]CF_3SO_3) and 2-methylpyridinium trifluoro-methanesulfonate ([HMPy]CF_3SO_3), are also capable of promoting the reaction between *o*-phenylenediamine and chalcone, but the activities seems to be slightly inferior as compared with that of [HBIm]CF_3SO_3, the yields of 1,5-benzodiazepine (**a**) were reached to 72% and 81%, respectively (entries 4 and 5). Thus, the best catalyst should be [HBIm]CF_3SO_3. Subsequent experiments using ionic liquid [HBIm]CF_3SO_3 as solvent shown that the optimum condition should be 80°C and 2 h (entries 1, 6 and 7).

As described in above, the reaction between *o*-phenylenediamine and chalcone is a typical acid-catalysed reaction. Therefore, the outcome of the condensation reaction depended very much on Brønsted acidity of catalyst. We have investigated the relative Brønsted acidities of existing non-chloroaluminate functionalised acidic ionic liquids using Hammett method.[18b] Here, the acidity of [HBIm]CF_3SO_3 was also examined using 4-phenylazodiphenylamine (Hammett constant ($pK(I)_{aq}$) is 1.50) as indicator in 1,2-dichloroethane and the results are shown in Fig. 1. The maximal absorbance of the unprotonated form of the indicator was observed at 401 nm in 1,2-dichloroethane. When [HBIm]CF_3SO_3 was added, the absorbance of the unprotonated form of the indicator was decreased. In contrast, the absorbance of the protonated form of the indicator was increased at 540 nm. By taking as the initial reference the total unprotonated form of the indicator (no acid is added to the 1,2-dichloroethane solution, spectrum a), we could determine the [I]/[IH^+] ratio from the measured absorbance at each concentration (spectra b–e), and then the Hammett function (H_0) is calculated and the results are listed in Table 2. As the concentrations of [HBIm]CF_3SO_3 were increased from 1.22 mmol/l to 2.59 mmol/l, H_0 values of 1,2-dichloroethane solutions of [HBIm]CF_3SO_3 were decreased from 2.09 to 1.44, indicating [HBIm]CF_3SO_3 has a moderate acid strength at room temperature.

$$H_0 = pK(I)_{aq} + \log ([I]_s/[IH^+]_s)$$

For comparison purposes, [HMIm]CF_3SO_3, [HMPy]CF_3SO_3, [HBIm]CH_3SO_3 and [HBIm]CF_3CO_2 were also examined using 4-phenylazodiphenylamine as indicator in 1,2-dichloroethane. The tendencies of [HMIm]CF_3SO_3 and [HMPy]CF_3SO_3 to reduce the absorbance of the unprotonated form of 4-phenylazodiphenylamine is the same as that observed with [HBIm]CF_3SO_3 but the magnitude is much more important with the latter (Table 3). In the case of [HBIm]CH_3SO_3 and [HBIm]CF_3CO_2, the measured peaks were superimposed on the blank peak, indicating that their Brønsted acidities

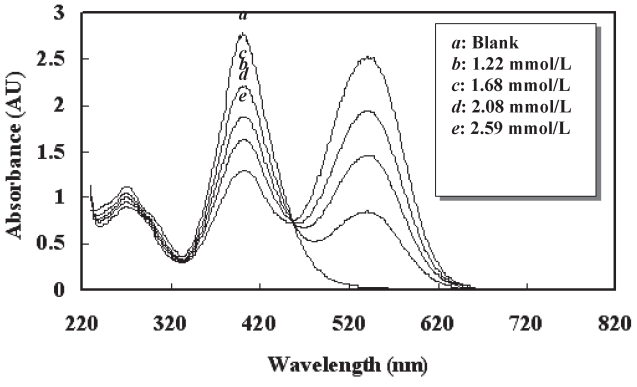

Fig 1 Absorption spectra of 4-phenylazodiphenylamine for various 1, 2-dichloromethane solutions of [HBIm]CF_3SO_3.

Table 2 H_0 values of ionic liquid [HBIm]CF_3SO_3 in 1,2-dichloroethane[a]

Conc./mmol/l[b]	Absorbance/AU	[I]/%	[HI^+]/%	H_0
0	2.783	100	0	–
1.22	2.210	79.4	20.6	2.09
1.68	1.877	67.4	32.6	1.82
2.08	1.626	58.4	41.6	1.65
2.59	1.292	46.4	53.6	1.44

[a] Using 4-phenylazodiphenylamine (Hammett constant ($pK(I)_{aq}$) is 1.50) as indicator.
[b] Concentrations of [HBIm]CF_3SO_3 in 1, 2-dichloroethane.

are weaker than that of trifluoromethanesulfonate PAILs. To make the acid strength sequence clear, a stronger base, methyl yellow, was chosen as Hammett indicator (Hammett constant is 3.3). In our hands, methyl yellow indicator has proved to be able to respond the addition of [HBIm]CH_3SO_3 but failed to [HBIm]CF_3CO_2 (no absorbance decrease has been observed). This fact implies that Brønsted acidity of [HBIm]CF_3CO_2 is weaker than that of [HBIm]CH_3SO_3. Further, from the results of Table 4, as the concentrations of [HBIm]CH_3SO_3 were increased from 1.36 mmol/l to 3.38 mmol/l, H_0 values of 1,2-dichloroethane solutions of [HBIm]CH_3SO_3 were decreased from 3.96 to 3.26, indicating [HBIm]CH_3SO_3 has a weak acidic scale at room temperature.

In light of above discussion, it can be seen that the trifluoromethanesulfonate PAILs have moderate acidities, and the relative strength should be [HBIm]CF_3SO_3 [HMPy]CF_3SO_3 [HMIm]CF_3SO_3; In contrast, the same cations with methanesulfonate [CH_3SO_3] and trifluoromethanesulfonate [CF_3SO_3] anions offer low to very low acidity at room temperature. This is good agreement with the order of catalytic performances observed in the reaction between *o*-phenylenediamine and chalcone.

Having these results in hand, other chalcones have been subjected to the conditions of run 7 in Table 1, and the results are listed in Table 5. The ionic liquid [HBIm]CF_3SO_3 proved to be active toward all substrates. Both chalcones with electron-donating groups and with electron-withdrawing groups except for hydroxy group reacted with *o*-phenylenediamine without any significant difference to give the corresponding 1,5-benzodiazepines in good yields (entries 1–10). In our system, acid-labile substrates such as 3-(4-methoxyphenyl)-

Table 3 H_0 values of ionic liquid [HBIm]CF_3SO_3 in 1,2-dichloroethane[a]

Ionic liquids	Conc. /mmol/l[b]	Absorbance /AU	[I]/%	[HI^+]/%	H_0
–	0	1.729	100	0	–
[HBIm]CF_3SO_3	2.89	0.755	43.7	56.3	1.38
[HMIm]CF_3SO_3	4.38	1.639	94.8	5.2	2.76
[HMPy]CF_3SO_3	4.38	1.434	82.9	17.1	2.19

[a]Using 4-phenylazodiphenylamine (Hammett constant ($pK(I)_{aq}$) is 1.50) as indicator.
[b]Concentrations of [HBIm]CF_3SO_3 in 1, 2-dichloroethane.

Table 4 H_0 values of ionic liquid [HBIm]CH_3SO_3 in 1,2-dichloroethane[a]

Conc./mmol/l[b]	Absorbance/AU	[I]/%	[HI^+]/%	H_0
0	2.208	100	0	–
1.36	1.812	82.1	17.9	3.96
1.99	1.485	67.3	32.7	3.61
2.57	1.282	58.1	41.9	3.44
3.38	1.053	47.7	52.3	3.26

[a]Using methyl yellow (Hammett constant ($pK(I)_{aq}$) is 3.30) as indicator.
[b]Concentrations of [HBIm]CH_3SO_3 in 1,2-dichloroethane.

1-phenylprop-2-en-1-one and 3-(4-bromophenyl)-1-(3,4-methylenedioxyphenyl)prop-2-en-1-one all worked well (entries 11 and 12). Reusability of the ionic liquid, [HBIm]CF_3SO_3, was also studied. After each cycle, the used ionic liquid was extracted with diethyl ether (4 ml × 3) and treated under vacuum (12 mmHg) at 90°C for 0.5 h before using for the next cycle. The activity of the ionic liquid was unaffected even after five cycles (entry 13).

In summary, many protic ionic liquids were synthesised and used in the synthesis of 1,5-benzodiazepines from *o*-phenylenediamine and chalcones as solvents and promoters. Success of the condensation appears to lie in the choice of cation-anion combinations and the ionic liquid [HBIm]CF_3SO_3 proved to be best. In the reaction of *o*-phenylenediamine and chalcone, the ionic liquid can be recovered conveniently and reused to three times without appreciable loss of activity. Determination of ionic liquid acidity with Hammett method revealed that the acid strength sequence of the protic ionic liquids should be [HBIm]CF_3SO_3 [HMPy]CF_3SO_3 [HMIm]CF_3SO_3 [HBIm]CH_3SO_3 [HBIm]CF_3CO_2, this is good agreement with the order of catalytic performances observed in the model reaction. Moreover, this methodology offers significant improvements with regard to yield of products, simplicity in operation, and green aspects avoiding toxic catalysts. The moderate reaction conditions and recyclability of the nonvolatile ionic liquid makes this an environment friendly methodology amenable for scale-up.

Experimental

Preparation of ionic liquids

Take the synthesis of 2-methylpyridinium trifluoromethanesulfonate ([HMPy]CF_3SO_3) for example: 2-methylpyridine (0.3 mol) and 30 ml $CHCl_3$ were placed in a three-necked flask, which was equipped with a magnetic stirring and condenser. Then trifluoromethanesulfonic acid (0.3 mol) was added slowly over a period of 60 min while stirring and cooling to maintain the temperature at 0–5°C. Then, the reaction mixture was stirred for an additional period of 4 h at 50°C. After the solvent was removed by distillation under reduced pressure, the product was dried under vacuum at 80°C for 2 h. Synthesis and purification of the other ionic liquids (Table 1) were analogous to the above procedure. [HMPy]CF_3SO_3: white solid, m.p. 72°C. ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 2.89 (s, 3H), 7.28–7.89 (m, 2H), 8.41–8.45 (m, 1H), 8.70 (d, J = 6.0 Hz, 1H), 15.01(brs, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δppm: 154.1, 146.3, 141.2, 128.0, 124.7, 120.2, 19.7; IR (KBr) ν/cm^{-1}: 3275, 2972, 1640, 1294, 1252, 1164, 1029, 777, 640. Elemental analysis: $C_7H_8F_3NO_3S$, calcd (%): C 34.57, H 3.32, N 5.76, S 13.18; found: C 34.52, H 3.41, N 5.74, S 13.23.

Typical procedure

In a typical experiment, ionic liquid (10.0 mmol) was dissolved into the mixture of chalcone (10.0 mmol) and *o*-phenylenediamine (10.0 mmol) in a 25 ml round bottom flask equipped with a distillation condenser. The content was stirred vigorously for desired time at 80°C. At the end of reaction, the reaction mixture was cooled to room temperature. The liquid mixture should be solidified at ambient temperature. Diethyl ether was then added to extract the organic components (4 ml × 3). Then, the organic phase was concentrated under reduced pressure and the product purified by silica gel column chromatography (ethyl acetate/*n*-hexane: 2:8) to yield 88% of the desired product. 2,3-Dihydro-2-(3,4-dichloropheny)l-4-phenyl-1H-1,5-benzodiazpine (**i**): yellow solid, m.p. 150–151°C. ^{1}H NMR (400 MHz, d_6-DMSO), δ_H (ppm) 2.45 (m, 2H), 3.05–3.16 (m, 1H), 5.21 (s, 1H), 6.99–7.85 (m, 13H). ν/cm^{-1} 1612 (C=N), 3341 (N-H); MS: *m/z* = 366 (M^+), 351, 289, 263, 221, 119, 103, 91, 77, 65; $C_{21}H_{16}Cl_2N_2$ (367.277): calcd. C 68.68, H 4.39, N7.63; found C 68.76, H 4.43, N 7.81.

UV-Vis acidity evaluation

1,2-Dichloroethane solutions of ionic liquids were prepared from dried 1,2-dichloroethane and ionic liquids (dried under vacuum at 80°C for 2 h). All the spectra were obtained with an Agilent B453 spectrophotometer.

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Table 5 Synthesis of 1,5-benzodiazepines over [HBIm]CF_3SO_3[a]

Entry	R^1	R^2	R^3	Time/h	Yield/%	M.p./°C$^{Ref.}$
b	*p*-OCH_3	H	H	3	88	147–148 (146–147)[21a]
c	*p*-Cl	H	H	3	89	143–144 (144–145)[21b]
d	*p*-NO_2	*p*-CH_3	H	2	81	170–171 (169–171)[21b]
e	H	*p*-Cl	H	2	90	129–130 (129–130)[21a]
f	*p*-Br	H	H	2	91	141–142 (142–143)[21a]
g	H	*p*-CH_3	H	2	93	126–127 (127)[21b]
h	H	*p*-NO_2	H	3	89	104–105 (104–105)[21a]
i	3,4-Cl	H	H	2	88	150–151
j	H	H	CH_3	2	90	151–152.5 (150–152)[13]
k	*p*-CH_3	*p*-CH_3	CH_3	2	87	142–144 (141–143)[13]
l	H	*p*-OCH_3	H	2	82	139–140 (139–140)[21a]
m	3,4-OCH_2O	*p*-Br	H	2	80	244–245 (246)[14 c]
a[b]	H	H	H	2	87	129–130 (129–130)[11]

[a]Reaction conditions: *o*-phenylenediamine, 10 mmol; chalcone, 10 mmol; ionic liquid, 10 mmol; temperature: 80°C.
[b]Reused for the fifth time.

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