Asian Journal of Chemistry; Vol. 30, No. 5 (2018), 961-966

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2018.21028

Synthesis of Novel Acidic Ionic Liquid [BBSA-DBU][HSO_4] and Its Catalytic Activities for Synthesis of Pyrazolopyranopyrimidine Derivatives

M. PATIL, S. SHINDE, S. DAMATE and S. PATIL*

Synthetic Research Laboratory, P.G. Department of Chemistry, P.D.V.P. College, Tasgaon-416 312, India

*Corresponding author: E-mail: sanyujapatil@yahoo.com

Received: 6 September 2017; *Accepted*: 7 March 2018; *Published online*: 29 March 2018; AJC-18820

A novel Brønsted acid ionic liquid 1,8-*bis*(butanesulphonic acid)diazobicyclo[5.4.0]undec-7-enium hydrogen sulphate [BBSA-DBU][HSO_4] has been synthesized from 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU). The synthesised ionic liquid was characterized by ^{1}H and ^{13}C NMR spectroscopic techniques. The room-temperature derived ionic liquid is highly acidic due to presence of two -SO_3H groups and two -HSO_4^- anions. The ionic liquid [BBSA-DBU][HSO_4]showed high catalytic activity (5 mol %) for the synthesis pyrazolpyrano-pyrimidine derivatives with good to excellent yields in short reaction time at 60 °C under solvent-free conditions. Moreover, ionic liquid could be easily recovered and reused at least five times without change in its catalytic activity.

Keywords: Brønsted acid, SO_3-H, Bifunctionalized ionic liquid, Pyrazolopyranopyrimidine, Reusable catalyst.

INTRODUCTION

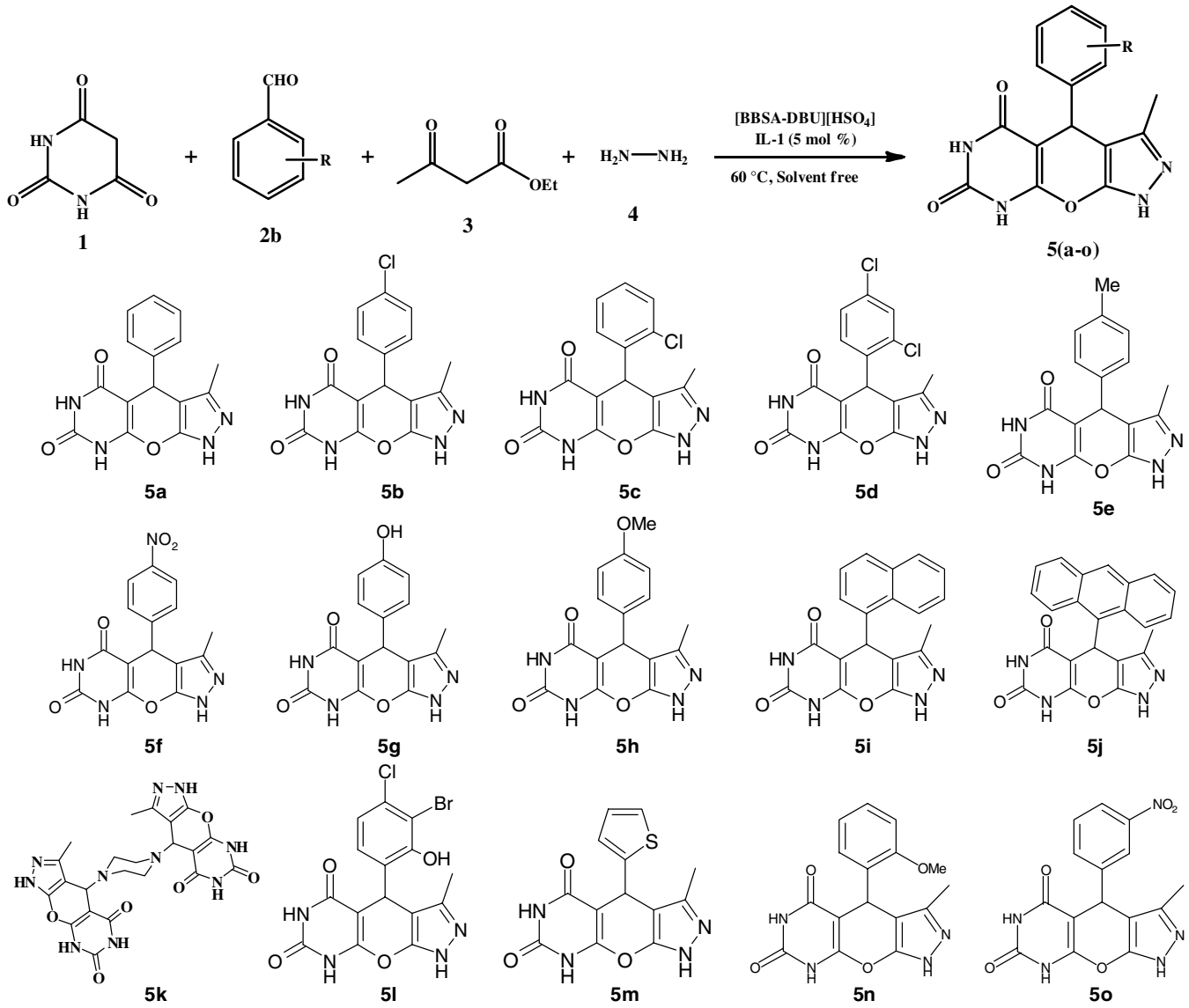
Ionic liquids (ILs), being familiar as environmentally benign media and widely used as solvent as well as catalysts for many reactions [1-6]. The great number of functional ionic liquids has been designed for different purposes [7,8]. Recently development of alternative synthetic tools for organic synthesis using ionic liquids have attracted significant attention, due to their distinctive properties like low vapour pressure, high thermal stability, excellent solvation ability, various liquid temperature range, better chemical stability, recyclability and solubility [9,10]. Especially, they shown efficient catalytic activities for many organic reactions like Diels-Alder [11], Aldol [12], Knoevenagel condensation [13], Michael addition [14], oxidation [15], *etc*.

Pyrazolopyranopyrimidines are a nitrogen and oxygen containing heterocyclic compounds and are useful in organic synthesis and medicinal chemistry because pyrazolopyrano-pyrimidines contain both pyranopyrimidine and pyranopyrazole as biological active nucleous [16]. Pyranopyrazoles derivatives have occupied a unique position in medicinal chemistry because of their biological and pharmacological activities [17], analgesic, antiinflammatory activity and act as vasodilators as well as hypotensive and hypoglycemic agents [18], antidepressant [19] and antitumor agents [20]. In addition, fused heterocycles systems like pyrazolopyridines, pyranopyrazoles and pyrazolopyrido-pyrimidines present interesting biological properties such as anticancer [21], cytotoxic [22] and antimicrobial activities [23].

However, these methods show varying degrees of success as well as limitations such as lower yields, use of expensive catalysts, prolonged reaction times, use of toxic organic solvents, and harsh reaction conditions. Therefore, we developed a new protocol for the synthesis of pyrazolopyranopirimidine using -SO_3H bifunctionalized Brønsted acidic ionic liquids. Herein, we wish to report a synthesis of series of novel -SO_3H bifunctionalized Brønsted acidic ionic liquids [BBSA-DBU][X]in aqueous solution and their application in organic synthesis. The Brønsted acidity strengths were determined by Hammett acidity function method performed on UV/visible spectra. This prepared ionic liquid used as catalyst for the pyrazolopyrano-pyrimidine synthesis in high yields (**Scheme-I**).

EXPERIMENTAL

All chemicals were purchased from Sigma Aldrich and used without further purification. Acidity of catalysts was checked by UV/visible spectrometer (Shimadzu model UV2401-PC). The purity of products and completion of reaction was checked by thin layer chromatography (TLC) on Merck silica gel (60 F_{254}) plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC (300 MHz) spectrometer using $CDCl_3$ or DMSO as a solvent. Chemical shifts are expressed in δ parts per million (ppm) values with tetramethylsilane (TMS) as the internal reference. Infrared spectra were measured with a Bruker FT-IR spectrophotometer. Melting points of all compounds were recorded on DBK-programmable melting point apparatus and compared with reported values.



Scheme-I: Synthesis of pyrazolopyranopirimidine using [BBSA-DBU][HSO_4]

Synthesis of zwitter ions: A 25 mL round bottom flask was charged with 1,8-diazobicyclo[5,4,0]undec-7-ene (DBU) (20 mmol) and 1,4-butane sulfonate (40 mmol) and stirred magnetically at room temperature for 5 min to get a white solid zwitter ions. Then solids zwitter ions were purified by washing twice with diethyl ether and dried in vacuum.

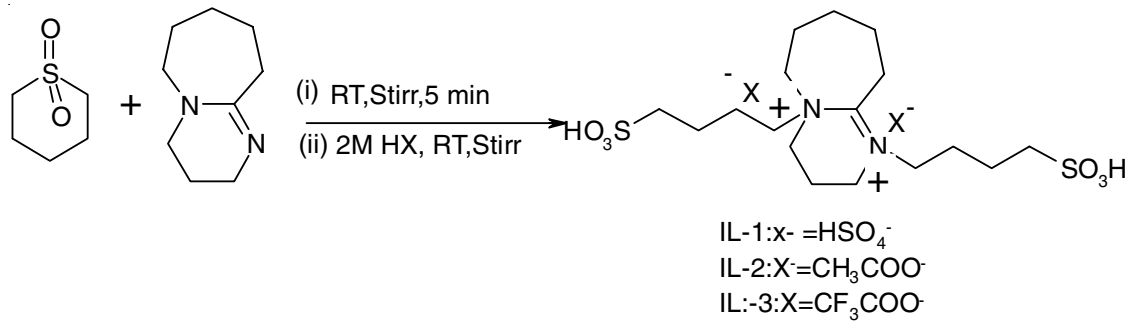
Synthesis of ionic liquids: The above obtained zwitter ions were acidified with dropwise addition of stoichiometric amount of sulphuric acid at room temperature with constant stirring to form IL-1. The pH of reaction mixture was checked successively during addition of acid on laboratory pH-meter (ProLab 3000). The produced IL -1 was purified by repeatedly washing with diethyl ether to remove non-ionic residues and dried in vacuum. The product was formed quantitatively and in high purity (**Scheme-II**).

Typical procedure for the synthesis of compound 5b: A 25 mL round bottomed flask was charged with barbituric acid (1 mmol), 4-chloroaldehydes (1 mmol), ethyl acetoacetate (1 mmol) hydrazine hydrate (1 mmol) and IL-1 catalyst (5 mol %). The reaction mixture was stirred on preheated oil bath at 60 ºC. The formation of the product was monitored by TLC. After completion of the reaction, the reaction mixture often solidified in the round bottomed flask. To the solid reaction mixture 5 mL water was added and again stirred for 5 min, then filtered and washed with water to remove the catalyst. The product obtained was further purified by recrystallization with ethanol.

Spectral data

3-Methyl-4-phenyl-1,4-dihydropyrazolo[40,30:5,6]-pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (5a): IR (KBr, ν_{max}, cm^{-1}): 3424, 3398, 3143, 2770, 1742, 1678; ^1H NMR (300 MHz, DMSO): 13.6 (m, 5H, Ar-H) 10.4 (s, 2H, NH), 4.53 (s, 1H, CH), 7.02 (d, 2H, Ph), 7.02 (t, 1H, Ph), 7.11 (t, 2H, Ph), 5.3 (s, 1H, NH), 6.5 (s, 1H, NH), 12.23 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): 163.0, 155.5, 150.3, 133.2, 129.3, 128.3, 115.2, 112.1, 81.7, 36.2, 30.9, 12.5.

3-Methyl-4-(2-chlorophenyl)-1,4-dihydropyrazolo-[40,30:5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (5c): IR (KBr, ν_{max}, cm^{-1}): 3012 (br), 1638, 1556, 1355, 1388, 1358,



Scheme-II: Synthetic route for the novel catalyst [BBSA-DBU][X]IL-1, IL-2 and IL-3

857, 786, 560; ^{1}H NMR (400 MHz, DMSO): 2.22 (s, 3H, CH_3), 4.45 (s, 1H, CH), 7.03-7.6 (m, 3H, Ph), 9.41 (s, 1H, NH), 10.02 (s, 1H, NH), 10.04 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): 164.6, 156.2, 157.1, 134.0, 123.5, 121.1, 112.9, 76.6.

3-Methyl-4-(2,4-dichlorophenyl)-1,4-dihydropyrazolo-[40,30:5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (5d): IR (KBr, ν_{max}, cm^{-1}): 3092 (br), 1643, 1554, 1352, 1348, 1348, 856, 746, 530; ^{1}H NMR (400 MHz, DMSO): 2.29 (s, 3H, CH_3), 5.45 (s, 1H, CH), 7.33-7.4 (m, 3H, Ph), 9.51 (s, 1H, NH), 10.32 (s, 1H, NH), 10.24 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): 174.6, 165.2, 167.1, 123.0, 123.5, 111.1, 110.9, 74.6.

3-Methyl-4-(4-methylphenyl)-1,4-dihydropyrazolo-[40,30:5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (5e): IR (KBr, ν_{max}, cm^{-1}): 3292 (br), 1743, 1454, 1232, 1238, 1248, 866, 776, 520; ^{1}H NMR (400 MHz, DMSO): 2.23 (s, 3H, CH_3), 5.25 (s, 1H, CH), 7.34-7.46 (m, 4H, Ph), 10.51 (s, 1H, NH), 10.42 (s, 1H, NH), 10.12 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): 164.6, 165.2, 163.1, 124.0, 126.5, 131.1, 121.9, 74.6.

3-Methyl-4-(4-nitrophenyl)-1,4-dihydropyrazolo-[40,30:5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (5f): IR (KBr, ν_{max}, cm^{-1}): 3139 (br), 3056 (br), 2906 (br), 1689, 1595, 1515, 1471, 1349, 1274, 841, 547 cm-1; ^{1}H NMR (400 MHz, DMSO-d_6): 2.25 (s, 3H, CH_3), 5.51 (s, 1H, CH), 7.31 (d, J = 8.4 Hz, 2H, Ph), 8.11 (d, J = 8.8 Hz, 2H, Ph), 10.24 (s, 2H, 2NH), 13.26 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 160.5, 151.7, 151.1, 146.0, 144.1, 128.5, 123.6, 105.3, 91.5, 60.2, 31.5, 14.5, 10.5.

3-Methyl-4-(4-hydroxyphenyl)-1,4-dihydropyrazolo-[40,30:5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (5g): IR (KBr, ν_{max}, cm^{-1}): 3347, 3348 (br), 3243 (br), 1587, 1459, 1241, 1341, 1324, 1121, 840, 892, 346; ^{1}H NMR (400 MHz, DMSO-d_6): 2.12 (s, 3H, CH_3), 4.38 (s, 1H, CH), 7.92-7.30 (d, 4H, Ph), 10.37 (s, 2H, 2NH), 12.20 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 162.1, 141.1, 142.0, 134.0, 123.6, 119.0, 109.1, 106.5, 93.8, 54.5, 34.6, 24.0, 15.0, 12.5.

3-Methyl-4-(4-methoxyphenyl)-1,4-dihydropyrazolo-[40,30:5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (5h): IR (KBr, ν_{max}, cm^{-1}): 3357, 3658 (br), 3343 (br), 1587, 1429, 1341, 1231, 1124, 1131, 841, 882, 336; ^{1}H NMR (400 MHz, DMSO-d_6): 3.12 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.28 (s, 1H, CH), 7.92-7.30 (d, 4H, Ph), 10.37 (s, 2H, 2NH), 12.20 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 167.1, 142.3, 143.3, 135.3, 125.2, 115.3, 108.1, 103.4, 94.5, 53.4, 33.4, 25.0, 15.3, 11.3.

3-Methyl-4-(4-hydroxyphenyl)-1,4-dihydropyrazolo-[40,30:5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (5i): IR (KBr, ν_{max}, cm^{-1}): 3447, 3234 (br), 3213 (br), 1765, 1767, 1453, 1344, 1276, 1155, 845, 725, 546; ^{1}H NMR (400 MHz, DMSO-d_6): 2.11 (s, 3H, CH_3), 4.38 (s, 1H, CH), 6.52-7.12 (m, 7H, Ph), 10.27 (s, 2H, 2NH), 12.20 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 164.1, 154.3, 143.2, 134.0, 123.6, 118.0, 117.1, 105.5, 93.8, 52.3, 34.2, 23.4, 15.3, 12.3.

3-Methyl-4-(4-anthracene)-1,4-dihydropyrazolo-[40,30:5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (5j): IR (KBr, ν_{max}, cm^{-1}): 3357, 3354 (br), 3233 (br), 1455, 1457, 1343, 1234, 1096, 1045, 854, 744, 554; ^{1}H NMR (400 MHz, DMSO-d_6): 2.43 (s, 3H, CH_3), 4.45 (s, 1H, CH), 6.42-7.45 (m, 9H, Ph), 10.37 (s, 2H, 2NH), 12.24 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 164.3, 152.3, 144.5, 135.2, 124.5, 128.4, 113.4, 104.3, 92.4, 53.5, 32.1, 22.3, 17.1, 11.2.

Di-3-methyl-4-(4-piperazine)-1,4-dihydropyrazolo-[40,30:5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (5k): IR (KBr, ν_{max}, cm^{-1}): 3347, 3234 (br), 3254 (br), 1345, 1567, 1234, 1244, 1123, 1123, 834, 723, 545; ^{1}H NMR (400 MHz, DMSO-d_6): 2.84 (s, 3H, $2CH_3$), 5.15 (s, 1H, 2CH), 2.32-2.45 (m, 8H, $4CH_2$), 10.87 (s, 2H, 2NH), 12.24 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 163.2, 145.2, 145.2, 145.0, 123.6, 129.5, 112.4, 156.3, 93.5, 52.5, 33.1, 21.3, 14.5, 12.5.

3-Methyl-4-(4-chloro-3-bromo-2-hydroxy)-1,4-dihydro-pyrazolo[40,30:5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (5l): IR (KBr, ν_{max}, cm^{-1}): 3567, 3344 (br), 3244 (br), 1245, 1547, 1564, 1344, 1233, 1253, 834, 743, 523; ^{1}H NMR (400 MHz, DMSO-d_6): 1.84 (s, 3H, CH_3), 5.35 (s, 1H, CH), 7.32-7.45 (m, 2H, pH), 10.23 (s, 2H, 2NH), 12.34 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 153.1, 144.1, 145.3, 146.2, 124.5, 128.2, 114.1, 157.2, 91.3, 51.4, 32.4, 22.4, 13.2, 11.4.

3-Methyl-4-(2-thiophene)-1,4-dihydropyrazolo-[40,30:5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (5m): IR (KBr, ν_{max}, cm^{-1}): 3212, 3323 (br), 3123 (br), 1132, 1345, 1223, 1112, 1056, 1043, 832, 824, 568; ^{1}H NMR (400 MHz, DMSO-d_6): 2.24 (s, 3H, CH_3), 4.12 (s, 1H, CH), 6.22-7.15 (m, 3H, pH), 12.81 (s, 2H, 2NH), 10.21 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 163.1, 142.1, 144.2, 144.1, 123.5, 122.4, 111.5, 155.2, 94.2, 51.4, 32.4, 22.5, 12.6, 13.9.

3-Methyl-4-(2-methoxyphenyl)-1,4-dihydropyrazolo-[40,30:5,6]pyrano[2,3-d] pyrimidine-5,7(6H,8H)-dione (5n): IR (KBr, ν_{max}, cm^{-1}): 3529, 3461, 2960 (br), 2839 (br), 1693, 1612, 1485, 1462, 1394, 1294, 753; ^{1}H NMR (400 MHz, DMSO-d_6): 2.35 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 5.64 (s, 1H, CH), 6.81 (m, 2H, Ph), 7.11 (t, J = 7.4 Hz, 1H, Ph), 7.34 (d, J = 7.2 Hz, 1H, Ph), 10.10 (s, 2H, 2NH), 12.92 (br s, 1H,

NH); ^{13}C NMR (100 MHz, DMSO-d_6): 161.1, 157.1, 151.0, 144.2, 131.1, 129.0, 127.4, 120.0, 111.0, 106.5, 90.5, 61.0, 55.7, 31.8, 26.4, 10.7.

3-Methyl-4-(3-nitrophenyl)-1,4-dihydropyrazolo-[40,30:5,6]pyrano[2,3-d]pyrimidine-5,7(6H,8H)-dione (5o): IR (KBr, ν_{max}, cm^{-1}): 3616, 3476 (br), 3034 (br), 2923 (br), 1710, 1586, 1527, 1479, 1350, 1300, 810, 543 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 2.26 (s, 3H, CH_3), 5.53 (s, 1H, CH), 7.54 (m, 2H, Ph), 7.85 (s, 1H, Ph), 8.02 (m, 1H, Ph), 10.26 (s, 2H, 2NH), 13.44 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 160.5, 151.1, 148.1, 145.9, 143.9, 134.3, 129.9, 121.6, 121.2, 105.2, 91.3, 58.1, 31.2, 19.5, 10.5.

RESULTS AND DISCUSSION

Cole *et al*. [24] first reported sulfonic acid group functionalized ionic liquids with strong Brønsted acidity for several organic reactions. At first stage of this experiment, synthesized IL-1 was confirmed by ^{1}H and ^{13}C NMR analysis.

Spectral characterization of 1,8-*bis*(butanesulphonic acid)-diazobicyclo[5.4.0]undec-7-enium hydrogen sulfate [BBSA-DBU][HSO$_4$] (IL-1): ^{1}H NMR (300 MHz, D_2O, TMS): δ 1.06-1.11 (m, 2H), 1.59-1.66 (m, 6H), 1.94-2.07 (m, 6H), 2.58-2.65 (m, 2H), 2.97-3.05 (m, 2H), 3.33-3.46 (m, 10H), 3.62-3.37 (m, 4H), 8.26-8.29 (m, 4H); ^{13}C NMR (75 MHz, D_2O, TMS): δ 19.70, 21.83, 22.90, 25.49,27.10, 27.19, 27.93, 31.58, 46.64, 48.59, 50.69, 52.86, 54.06, 60.55, 74.65, 166.0.

Considering the crucial role of the acidity of ionic liquids in organic reactions, the Brønsted acidic scale of three sulfonic acid functional ionic liquids were measured on UV spectrometer with 4-nitroaniline as the indicator (Hammett method). We conducted this method by evaluating the protonation extent of uncharged indicator bases (named I) in dichloromethane by measuring the indicator ratio [I]/[IH]. Hammett function (H_o) was calculated using the following equation:

$$H_o = pka(IH^+) + \log\frac{[I]}{[IH]}$$

where , pka(IH^+) is pka value of indicator in dichloromethane (0.98), [I] is molar concentrations of unprotonated indicator and [IH^+] molar concentrations of protonated indicator.

As shown in Fig. 1, the maximum absorbance of unprotonated form of indicator was observed at 350 nm in DCM, which decreased to some extent after addition of acidic ionic liquids.Thus, the characteristic absorption peak was decreased with acidity of solution containing ionic liquids increased. H_o value of IL-1 is 1.30, which is slightly less than H_o value of IL-2 and IL-3 (Table-1). Hence, more is the acidity of ionic liquid, the better is it's activity in this cyclocondensation reaction. Hence, it is clear that IL-1 have stronger acidity than IL-2 and IL-3. Therefore IL-1 is preferred for synthesis of pyrazolopyranopyrimidine derivatives.

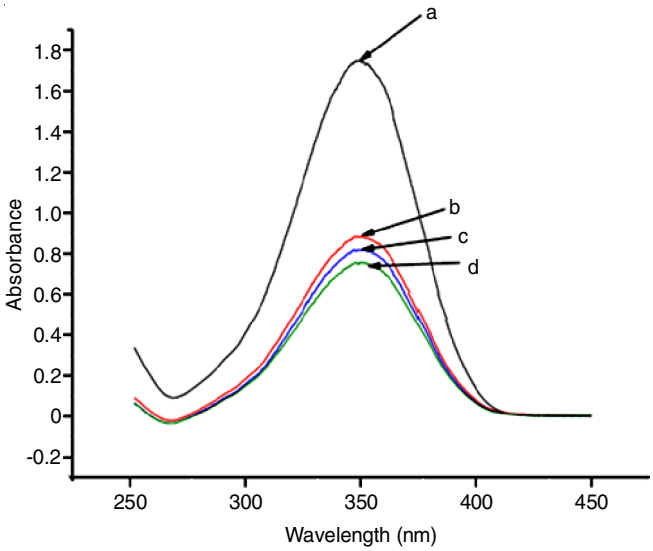


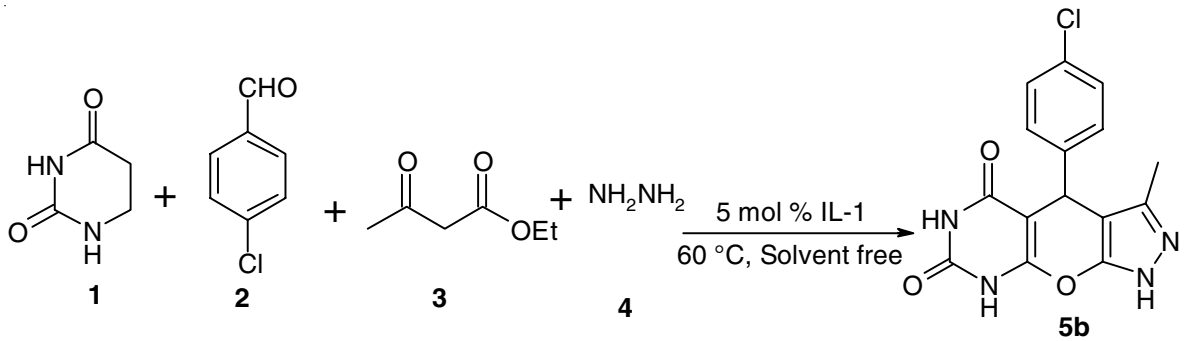
Fig. 1. Absorption spectra of 4-nitroaniline in three ILs in dichloromethane: (a) blank, (b) IL-3 (c) IL-2(d) IL-1

TABLE-1
BRØNSTED ACIDITY OF IONIC LIQUIDS IN DCM

	Ils	λ_{max}	[B] (%)	H_2O [BH^+] (%)	H_0
1	–	1.79	100	0	–
2	IL-1	0.78	61.74	38.06	1.30
3	IL-2	0.79	68.62	25.58	1.47
4	IL-3	0.82	62.25	26.72	1.54

Indicator: 4-nirtoaniline (pKa = 0.98).

To optimize the various reaction conditions, a preliminary investigation of the title reaction was carried out using IL-1 catalyst, while reaction of barbituric acid, 4-chlorobenzaldehyde, ethyl acetoacetate and hydrazine hydrate were chosen as a model reaction (**Scheme-III**). At first we focused on systematic evolution of appropriate amount of catalyst, hence the model reaction was performed by using various amount of IL-1 (3, 5 and 10 mol %). As presented in Table-2, it was found that catalyst and temperature play an essential role to carry out desired conversion. The model reaction did not proceed in absence of the catalyst at room temperature and as well as at elevated



Scheme-III: Synthesis of compound **5b** using IL-1

temperature (40/60/80 ºC) under solvent free conditions after prolonged reaction time (entry 1-4, Table-2). These negative results indicated the necessity of catalyst and temperature conditions for the conversion of reactants into product. Therefore, we examined the model reaction using IL-1at room temperature and at elevated temperature conditions(40/60/80 ºC) under solvent free condition. To our surprise, IL-1 (5 mol %) showed outstanding activity for the formation of desired product with excellent yield within a very shorter time, when reaction was performed at 60 ºC (entry 7, Table-2). A further increase in the temperature and catalyst amount did not improve the yields (entry 8-9, Table 2), however 3 mol % catalyst was used under same reaction conditions for comparison, moderate yield was obtained after 60 min (entry 10, Table 2). Furthermore, in order to check the effect of solvents on model reaction several organic solvents such as methanol, ethanol, THF, acetonitrile as well as water were screened. The results reveal that the reactions were not performed in proper direction and only reactants were observed on TLC after longer reaction time (entry 11-15, Table-2). The model reaction was also examined for IL-2 and IL-3 under same reaction conditions for comparing the catalytic performance of the all prepared ionic liquids (entry 16-17, Table-2). Thus the results proved that IL-1 is very active (entry 7, Table-2), leading to 93 % conversion of reactants into products of model reaction. In other words, the optimal conditions were determined that the reaction was catalyzed by 5 mol % of IL-1 under solvent free conditions at 60 ºC.

TABLE 2
OPTIMIZATION OF REACTION CONDITIONS FOR SYNTHESIS OF **5b**[a]

Entry	ILs (mol %)	Solvent	Time (min)	Temp. (°C)	Yields[b] (%)
1	–	Solvent free	120	Rt	NR
2	–	Solvent free	120	40	NR
3	–	Solvent free	120	60	NR
4	–	Solvent free	120	80	NR
5	IL-1 (5)	Solvent free	30	Rt	NR
6	IL-1 (5)	Solvent free	30	40	Trace
7	IL-1 (5)	Solvent free	10	60	93
8	IL-1 (5)	Solvent free	10	80	93
9	IL-1 (10)	Solvent free	10	60	93
10	IL-1 (3)	Solvent free	10	60	78
11	IL-1 (5)	Methanol	30	Reflux	NR
12	IL-1 (5)	Ethanol	30	Reflux	NR
13	IL-1 (5)	THF	30	Reflux	NR
14	IL-1 (5)	Acetonitrile	30	Reflux	NR
15	IL-1 (5)	Water	30	Reflux	NR
16	IL-2 (5)	Solvent free	30	60	86
17	IL-3 (5)	Solvent free	30	60	88

[a]Reaction condition: barbituric acid(1 mmol), 4-chlorobenzaldehydes (1 mmol), ethyl acetoacetate (1 mmol) and hydrazine hydrate (1 mmol); [b]Isolated yields.

Reusability of IL-1 as catalyst: Reusability of ionic liquid for the synthesis of pyrazolopyranopyrimidine was examined. As shown in Table-3, ionic liquid was utilized repeatedly for five times without significant change in conversion and selectivity. It is therefore indicated that ionic liquid have excellent reusability. As the catalyst is soluble in water, after complication of reaction, water (5 mL) was added and reaction mixture was filtered to recover the catalyst from filtrate. The good reusability of ionic liquid was attributed to the stable covalent bond between cation of ionic liquid and alkyl sulfonic acid, which played the main role of catalysis in the reactions.

TABLE-3
RECYCLABILITY OF CATALYST[a]

Number of runs	Yield[b] (%)
1	93
2	93
3	93
4	92
5	92

[a]Reaction condition: Barbituric acid (1 mmol), 4-chlorobenzaldehydes (1 mmol), ethyl acetoacetate (1 mmol) and hydrazine hydrate (1 mmol) and IL-1 (5 mol %) at 60 °C under solvent-free conditions. [b]Isolated yields.

Encouraged by the remarkable results (Table-2) obtained with the above motioned reaction conditions and to show generality and scope of this new protocol, we extended these optimized protocol for the preparation of range of pyrazolopyranopyrimidine and the results are given in Table-4. In all cases, aromatic aldehydes with different substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the expected products in high yields and short reaction times.

TABLE-4
[BBSA-DBU][HSO_4] CATALYSED PYRAZOLOPYRANOPYRIMIDINE

Entry	Compd.	Time (min)	Yields (%)	m.p. (°C)
1	**5a**	05	93	185-187
2	**5b**	10	93	201-202
3	**5c**	10	93	200-202
4	**5d**	10	89	205-206
5	**5e**	10	91	199-201
6	**5f**	05	93	183-184
7	**5g**	05	94	183-184
8	**5h**	05	91	192-193
9	**5i**	05	93	284-285
10	**5j**	05	92	209-210
11	**5k**	20	70	254-255
12	**5l**	15	79	251-252
13	**5m**	10	82	249-251
14	**5n**	7	79	248-250
15	**5o**	10	89	247-248

Conclusion

Three novel -SO_3H bifunctionalized Brønsted acidic ILs were synthesized and their catalytic activities were evaluated for one-pot synthesis of pyrazolopyranopyrimidine *via* a four component cyclocondensation reaction under solvent free condition. Further investigation revealed that acidity of ionic liquids plays a key role in the acid catalysed probe reactions. Remarkable advantages of this protocol are simple experimental procedure, shortest reaction time, high catalytic activity, excellent yields and reusability of catalyst.

ACKNOWLEDGEMENTS

One of the authors (SKS) is thankful to Council of Scientific and Industrial research (CSIR), New Delhi, India for the award of fellowship.

REFERENCES

1. N. Gupta, Sonu, G.L. Kad and J. Singh, *Catal. Commun.*, **8**, 1323 (2007); https://doi.org/10.1016/j.catcom.2006.11.030.
2. R. Sugimura, K. Qiao, D. Tomida and C. Yokoyama, *Catal. Commun.*, **8**, 770 (2007); https://doi.org/10.1016/j.catcom.2006.08.049.
3. A. Kamal and G. Chouhan, *Tetrahedron Lett.*, **44**, 3337 (2003); https://doi.org/10.1016/S0040-4039(03)00580-X.
4. X. Liu, Z. Song and H. Wang, *Struct. Chem.*, **20**, 509 (2009); https://doi.org/10.1007/s11224-009-9448-6.
5. D. Fang, X. Zhou, Z. Ye and Z. Liu, *Ind. Eng. Chem. Res.*, **45**, 7982 (2006); https://doi.org/10.1021/ie060365d.
6. Y.Y. Wang, X. Gong, Z. Wang and L. Dai, *J. Mol. Catal. Chem.*, **322**, 7 (2010); https://doi.org/10.1016/j.molcata.2010.01.011.
7. S. Tang, G.A. Baker and H. Zhao, *Chem. Soc. Rev.*, **41**, 4030 (2012); https://doi.org/10.1039/c2cs15362a.
8. D.B. Zhao, Z. Fei, T.J. Geldbach, R. Scopelliti and P.J. Dyson, *J. Am. Chem. Soc.*, **126**, 15876 (2004); https://doi.org/10.1021/ja0463482.
9. D. Kuang, S. Uchida, R. Humphry-Baker, S.M. Zakeeruddin and M. Grätzel, *Angew. Chem. Int. Ed.*, **47**, 1923 (2008); https://doi.org/10.1002/anie.200705225.
10. T. Singh and A. Kumar, *J. Phys. Chem.*, **112**, 4079 (2008); https://doi.org/10.1021/jp711711z.
11. F. Fu, Y.C. Teo and T.P. Loh, *Org. Lett.*, **8**, 5999 (2006); https://doi.org/10.1021/ol062481i.
12. P.N. Davey, S.A. Forsyth, H.Q.N. Gunaratne, C. Hardacre, A. McKeown, S. McMath, D.W. Rooney and K.R. Seddon, *Green Chem.*, **7**, 224 (2005); https://doi.org/10.1039/B416021E.
13. C. Yue, A. Mao, Y. Wei and M. Lu, *Catal. Commun.*, **9**, 1571 (2008); https://doi.org/10.1016/j.catcom.2008.01.002.
14. Y.O. Sharma and M.S. Degani, *J. Mol. Catal. Chem.*, **277**, 215 (2007); https://doi.org/10.1016/j.molcata.2007.07.053.
15. L.D. Pinto, J. Dupont, R.F. de Souza and K. Bernardo-Gusmão, *Catal. Commun.*, **9**, 135 (2008); https://doi.org/10.1016/j.catcom.2007.05.025.
16. M.M. Heravi, F. Mousavizadeh, N. Ghobadi and M. Tajbakhsh, *Tetrahedron Lett.*, **55**, 1226 (2014); https://doi.org/10.1016/j.tetlet.2014.01.004.
17. G. Nawwar, F. Abdelrazek and R. Swellam, *Arch. Pharm.*, **324**, 875 (1991); https://doi.org/10.1002/ardp.2503241110.
18. (a) S. Kuo, L. Huang and H. Nakamura, *J. Med. Chem.*, **27**, 539 (1984); https://doi.org/10.1021/jm00370a020.
(b) L. Huang, M.-J. Hour, C.-M. Teng and S.-C. Kuo, *Chem. Pharm. Bull. (Tokyo)*, **40**, 2547 (1992); https://doi.org/10.1248/cpb.40.2547.
19. Y.R. Prasad, A.L. Rao, L. Prasoona, K. Murali and P.R. Kumar, *Bioorg. Med. Chem. Lett.,* **15**, 5030 (2005); https://doi.org/10.1016/j.bmcl.2005.08.040.
20. J.-L. Wang, D. Liu, Z.-J. Zhang, S. Shan, X. Han, S.M. Srinivasula, C.M. Croce, E.S. Alnemri and Ziwei Huang, *Proc. Natl. Acad. Sci. U.S.A.* **97**, 7124 (2000); https://doi.org/10.1073/pnas.97.13.7124.
21. E. Grivsky, S. Lee, C.W. Sigle, D.S. Duch and C.A. Nichol, *J. Med. Chem.*, **23**, 327 (1980); https://doi.org/10.1021/jm00177a025.
22. P.J. Chen, A. Yang, Y.F. Gu, X.S. Zhang, K.P. Shao, D.Q. Xue, P. He, T.F. Jiang, Q.R. Zhang and H.M. Liu, *Bioorg. Med. Chem. Lett.,* **24**, 2741 (2014); https://doi.org/10.1016/j.bmcl.2014.04.037.
23. N.R. Kamdar, D.D. Haveliwala, P.T. Mistry and S.K. Patel, *Eur. J. Med. Chem.,* **45**, 5056 (2010); https://doi.org/10.1016/j.ejmech.2010.08.014.
24. A.C. Cole, J.L. Jensen, I. Ntai, K.L.T. Tran, K.J. Weaver, D.C. Forbes and J.H. Davis, *J. Am. Chem. Soc.*, **124**, 5962 (2002); https://doi.org/10.1021/ja026290w.