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Facile Aldolization Catalyzed by Ionic Liquid [4-Sulfbmpyrazine][BF_4]

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The acidic functionalized ionic liquid 1-(4-sulfonic group)butyl-3-methylpyrazine tetrafluoroborate (abbreviated as [4-sulfbmpyrazine][BF_4]) was employed as the catalyst of the condensation of aromatic aldehyde and diols. The optimized condition was as follows: aromatic aldehyde (0.20 mol), diols (0.30 mol) and [4-sulfbmpyrazine][BF_4] (0.60 g) were refluxed in cyclohexane (10.00 mL) for 1 h. A series of aromatic aldehydes were studied and afforded the corresponding acetals products with good yields which were from 70.3 to 96.9 %. The ionic liquid catalyst could be recycled for four times without significant loss of catalyst reactivity.

Key Words: Aldolization, Ionic liquid, Aromatic aldehyde, Acetals.

INTRODUCTION

The demand of flavours is greatly increasing with the rapid development of chemical industry. Acetals are better than the parent carbonyl compounds in spices and become new fast developed flavours in recent years. Although aldehydes species play an extremely important role in the flavour of food, they can easily be oxidized and darken under the air, light and heat, *etc*. Carbonyl compounds are feasible to form stable acetals, most of which show the flavour of floral, woody and mint. In addition, the acetals are usually used to be the protected group of carbonyl compounds and reagent in the organic synthesis[1].

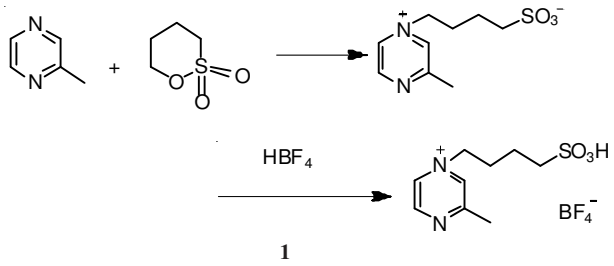
The traditional acetals syntheses meet many drawbacks, such as long reaction time, more byproducts, low reaction yields, deep colour of the products, corrosion of equipments and large amount of acid waste. Recently much attention has been paid to studies on acidic ionic liquid catalysts with stability and high catalytic activities. Ionic liquids are considered as the green solvents and catalysts in terms of low vapour pressure, high efficiency, easy separation of products and recyclability[2-7]. In this paper, we reported that the acid-functionalized ionic liquid 1-(4-sulfonic group) butyl-3-methylpyrazine tetrafluoroborate (abbreviated as [4-sulfbmpyrazine][BF_4]) catalyzed the acetalization of aromatic aldehydes and diols to afford acetals. The synthesis conditions of acetals were optimized. It was found that the ionic liquid showed excellent catalytic activity and was easily handled and recycled for at least four times without significant loss of activity.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AVANCE III 500 MHz spectrometer with TMS as an internal. ESI-MS spectra were recorded on a Micromass LCT KC317 spectrometer. Reagents and chemicals were purchased from commercial resource and used without further purification. All final products are known compounds; their physical and spectroscopic data were compared with those reported in the literatures and found to be identical.

Preparation of [4-sulfbmpyrazine][BF_4] (Scheme-I): 2-Methylpyrazine (0.94 g, 0.01 mol) was dissolved in acetonitrile, then added 1,4-butanesultone (2.72 g, 0.02 mol) and the mixture was heated to reflux. On completion, the mixture was cooled down to room temperature, filtered and the cake was washed for three times with ethyl acetate, dried in vacuum to give the intermediate **1** (1.92 g, yield is 83.5 %). And then HBF_4 (5.28 g, 0.06 mol) was dropped in the intermediate **1** (11.50 g, 0.05 mol) in the acetonitrile and heated at 60 ºC for 2 h. On completion, the solvent was removed and the residue was washed with acetone to afford a brown liquid [4-sulfbmpyrazine][BF_4] (14.66 g, yield is 92.4 %). Some spectra of [4-sulfbmpyrazine][BF_4]: ^{1}H NMR (500 MHz, D_2O) δ: 1.72-1.79 (m, 2H, CH_2), 2.11-2.15 (t, J = 7.6, 2H, CH_2), 2.75 (s, 3H, CH_3), 2.88-2.92 (t, J = 7.6, 2H, CH_2), 4.62-4.68 (m, 2H, CH_2), 8.77 (s, 1H, CH=CH), 8.89 (s, 1H, CH=CH), 9.19 (s, 1H, CH=N); MS(ESI): m/e 231.1.

Acetals were synthesized *via* the acetalization of carbonyl compounds with diols (**Scheme-II**) catalyzed by [4-sulfbmpyrazine][BF_4]. In the typical procedure, carbonyl compounds



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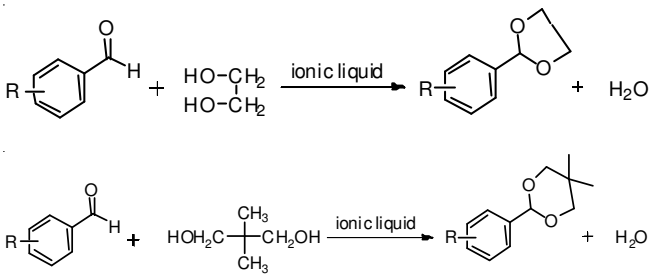
Scheme-I: Synthesis of [4-sulfbmpyrazine][BF_4]

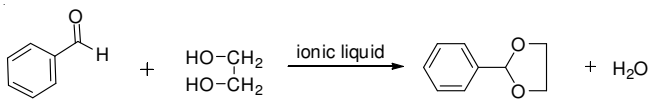


Scheme-2: Synthesis of acetals

(0.20 mol), cyclohexane 10.00 mL, diols (0.30 mol) and the [4-sulfbmpyrazine][BF_4] (0.60 g, 0.20 mol) were mixed together in a three necked round bottomed flask equipped with a magnetic stirrer and thermometer. Here a Dean-Stark apparatus was used to remove the water continuously from the reaction mixture. The mixture was refluxed for the specified time. On completion, the catalyst was recovered by centrifugation, washing with acetone and drying in an oven at 80 ºC for *ca.* 1 h.

RESULTS AND DISCUSSION

The synthesis of acetal was optimized by the orthogonal test method with the reaction of benzaldehyde with glycol as the representative reaction (**Scheme-III**) and the orthogonal experimental program was shown in Table-1. Four factors were the dosage of diol (A), the dosage of cyclohexane (B), the dosage of catalyst (C) and reaction time (D), respectively. Orthogonal experimental results and analysis were shown in Table-2.



Scheme-III: Synthesis of benzaldehyde ethylene glycol acetal

TABLE-1
FACTOR LEVEL OF THE SYNTHESIS OF BENZALDEHYDE ETHYLENE GLYCOL ACETAL

Level	Factor			
	Dosage of diol (A) (mol)	Dosage of cyclohexane (B) (mL)	Dosage of catalyst (C) (g)	Reaction time (D) (h)
1	0.20	5	0.20	1
2	0.30	10	0.40	2
3	0.40	15	0.60	3

The orthogonal test analysis showed that the best combination of factors was $A_2B_2C_3D_1$. And, the longer reaction time, the more byproducts. Therefore, the optimized reaction

TABLE-2
RESULTS OF THE $L_9(3^4)$ ORTHOGONAL EXPERIMENT OF ALDOLIZATION AND RANGE ANALYSIS

Entry	A	B	C	D	Yield (%)
1	A_1	B_1	C_1	D_1	36.8
2	A_1	B_2	C_2	D_2	54.6
3	A_1	B_3	C_3	D_3	48.7
4	A_2	B_1	C_2	D_3	53.3
5	A_2	B_2	C_3	D_1	87.4
6	A_2	B_3	C_1	D_2	68.5
7	A_3	B_1	C_3	D_2	54.5
8	A_3	B_2	C_1	D_3	59.7
9	A_3	B_3	C_2	D_1	82.5
K_1	140.10	144.60	165.00	206.70	–
K_2	209.20	201.70	190.40	177.60	–
K_3	196.70	199.70	190.60	161.70	–
k_1	46.70	48.20	55.00	68.90	–
k_2	69.73	67.23	63.47	59.20	–
k_3	65.57	66.57	63.53	53.90	–
Range	23.03	19.03	8.53	15.00	–
Primary-secondary	ABDC				
Optimal solution	$A_2B_2C_3D_1$				

conditions of synthesis of acetal were: the dosage of benzaldehyde (0.20 mol), diol (0.30 mol), cyclohexane (10.00 mL), catalyst (0.60 g), reaction time (1 h). The reaction gave the desired product in 88.3 % yield under the optimized conditions.

To recover the catalyst [4-sulfbmpyrazine][BF_4], the residue after extraction was washed with acetone and dried under vacuum to give regenerated [4-sulfbmpyrazine][BF_4]. In order to demonstrate the repeatability of functionalized ionic liquid [4-sulfbmpyrazine][BF_4], the recycle of catalyst [4-sulfbmpyrazine][BF_4] was also investigated by using the preparation of benzaldehyde ethylene glycol acetal (**a**) as a model. The recovered [4-sulfbmpyrazine][BF_4] was employed in the same aldolization, The yield of benzaldehyde ethylene glycol acetal was fluctuated at 88.3-86.4 % in the first four cycles (Fig. 1). Then it became less activity in the next run.

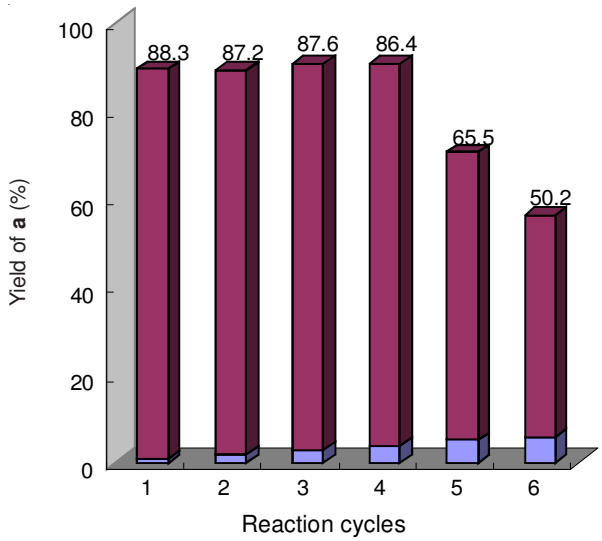
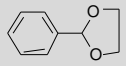
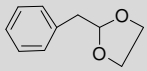
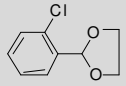
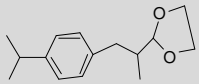
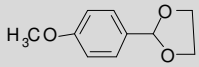
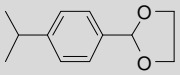
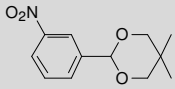
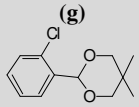
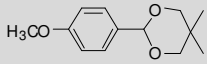
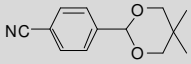
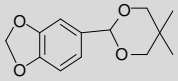
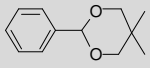


Fig. 1. Recyclability of regenerated [4-sulfbmpyrazine][BF_4]

Furthermore, in order to test the generality of [4-sulfbmpyrazine][BF_4] as catalyst for the aldolization, reactions of a variety of aromatic aldehydes with diols were carried out

TABLE-3
SYNTHESIS OF RAMIFICATION OF ALDOLIZATION CATALYZED BY [4-SULFBMPYRAZINE][BF_4]

Entry	Aromatic aldehydes	Diols	Product	Yield (%)
1	Benzaldehyde	Ethanediol	 **(a)**	88.3
2	Phenylacetaldehyde	Ethanediol	 **(b)**	78.9
3	*o*-Chlorobenzaldehyde	Ethanediol	 **(c)**	82.6
4	Cyclamen aldehyde	Ethanediol	 **(d)**	86.4
5	*p*-Methoxybenzaldehyde	Ethanediol	 **(e)**	76.8
6	Cuminaldehyde	Ethanediol	 **(f)**	70.3
7	*m*-Nitrobenzaldehyde	Neopentyl glycol	 **(g)**	85.7
8	*o*-Chlorobenzaldehyde	Neopentyl glycol	 **(h)**	87.6
9	*p*-Methoxybenzaldehyde	Neopentyl glycol	 **(i)**	87.7
10	*p*-Formyl-benzonitrile	Neopentyl glycol	 **(j)**	85.6
11	Piperonyl aldehyde	Neopentyl glycol	 **(k)**	88.0
12	Benzaldehyde	Neopentyl glycol	 **(l)**	96.9

under the optimized conditions established above and the results were shown in Table-3. The results demonstrated that the functionalized ionic liquid [4-sulfbmpyrazine][BF_4] exhibited high catalytic reactivity in the synthesis of acetals.

Benzaldehyde ethylene glycol acetal[8] (a): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.53-7.52 (m, 2H), 7.42-7.39 (m, 3H), 5.84 (s, 1H), 4.15 (t, *J* = 7.0 Hz, 2H), 4.05 (t, *J* = 7.0 Hz, 2H).

Phenylacetaldehyde ethylene glycol acetal[9] (b): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34-7.24 (m, 5H), 5.10 (t, *J* = 4.5 Hz, 1H), 3.97 (t, *J* = 7.0 Hz, 2H), 3.86 (t, *J* = 7.0 Hz, 2H), 2.30 (d, *J* = 5.0 Hz, 2H).

***o*-Chlorobenzaldehyde ethylene glycol acetal[10] (c):** ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.63-7.61 (m, 1H), 7.40-7.38 (m, 1H), 7.31-7.29 (m, 2H), 7.62 (s, 1H), 4.17 (t, *J* = 7.0 Hz, 2H), 4.08 (t, *J* = 7.0 Hz, 2H).

Cyclamen aldehyde ethylene glycol acetal[11] (d): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.16-7.11 (m, 4H), 4.77 (d, *J* = 4.0 Hz, 1H), 4.00 (t, *J* = 4.5 Hz, 2H), 3.90 (t, *J* = 4.5 Hz, 2H), 2.93-2.87 (m, 2H), 2.39 (dd, *J* = 13.5 Hz, *J* = 4.5 Hz, 1H), 1.25 (d, *J* = 7.0 Hz, 6H), 0.90 (d, *J* = 7.0 Hz 3H).

***p*-Methoxybenzaldehyde ethylene glycol acetal[12] (e):** ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 10.0 Hz, 2H), 6.89 (d, *J* = 10.0 Hz, 2H), 6.21 (s, 1H), 3.97 (t, *J* = 7.0 Hz, 2H), 3.85 (t, *J* = 7.0 Hz, 2H), 3.61 (s, 3H).

Cuminaldehyde ethylene glycol acetal[13] (f): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43-7.41 (m, 2H), 7.27-7.25 (m, 2H), 5.81 (s, 1H), 4.14 (t, *J* = 7.0 Hz, 2H), 4.04 (t, *J* = 7.0 Hz, 2H), 2.84 (dd, *J* = 14.0 Hz, *J* = 7.0 Hz, 1H), 1.26 (d, *J* = 7.0 Hz, 6H).

***m*-Nitrobenzaldehyde neopentyl glycol acetal[14] (g):** m.p. 49-50 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.22 (t, *J* = 10.0 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 2H), 5.29 (s, 1H), 3.81 (d, *J* = 10.0 Hz, 2H), 3.69 (d, *J* = 10.0 Hz, 2H), 1.31 (s, 3H), 0.85 (s, 3H).

***o*-Chlorobenzaldehyde neopentyl glycol acetal[15] (h):** ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.77 (d, *J* = 10.0 Hz, 1H), 7.30-

7.37 (m, 3H), 5.77 (s, 1H), 3.71-3.81 (m, 4H), 1.34 (s, 3H), 0.83 (s, 3H).

***p*-Methoxybenzaldehyde neopentyl glycol acetal[16] (i):** m.p. 60-61 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45 (d, *J* = 10.0 Hz, 2H), 6.91 (d, *J* = 10.0 Hz, 2H), 5.37 (s, 1H), 3.83 (s, 3H), 3.77 (d, *J* = 10.0 Hz, 2H), 3.65 (d, *J* = 10.0 Hz, 2H), 1.32 (s, 3H), 0.82 (s, 3H).

***p*-Formyl-benzonitrile neopentyl glycol acetal[17] (j):** m.p. 106-109 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 10.0 Hz, 2H), 7.63 (d, *J* = 10.0 Hz, 2H), 5.44 (s, 1H), 3.79 (d, *J* = 15.0 Hz, 2H), 3.67 (d, *J* = 10.0 Hz, 2H), 1.29 (s, 3H), 0.84 (s, 3H).

Piperonyl aldehyde neopentyl glycol acetal[18] (k): m.p. 44-45 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.05 (s, 1H), 6.98 (d, *J* = 10.0 Hz, 1H), 6.81 (d, *J* = 5.0 Hz, 1H), 5.97 (s, 2H), 5.33 (s, 1H), 3.76 (d, *J* = 15.0 Hz, 2H), 3.64 (d, *J* = 10.0 Hz, 2H), 1.31 (s, 3H), 0.81 (s, 3H).

Benzaldehyde neopentyl glycol acetal[19] (l): m.p. 32-33 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.54 (t, *J* = 10.0 Hz, 3H), 7.38 (d, *J* = 15.0 Hz, 2H), 5.43 (s, 1H), 3.80 (d, *J* = 10.0 Hz, 2H), 3.68 (d, *J* = 10.0 Hz, 2H), 1.34 (s, 3H), 0.83 (s, 3H).

Conclusion

We reported herein the synthesis of acetals catalyzed by functionalized acidic ionic liquid 1-(4-sulfonic group) butyl-3-methylpyrazine tetrafluoroborate (abbreviated as [4-sulfbmpyrazine][BF_4]). The reaction conditions were optimized by orthogonal analysis and a variety of substituted aromatic aldehydes and diols were examined and afforded the corresponding acetals products with the yield 70.3-96.9 %. The catalyst could be recovered by simple work-up after extraction. The results of recycle experiments showed that the regenerated functionalized ionic liquid [4-sulfbmpyrazine][BF_4] could be reused at least four times without losing its activity, which the yields of desired compound were fluctuated between 88.3-86.4 %. Further applications of this catalytic system in the aldolization with a broader scope of substrates and in other valuable reactions have been undergone in our group.

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