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Highly Chemo- and Regioselective Reaction of Hydroxybenzenes in Acidic Ionic Liquid

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Highly chemo- and regioselective reaction of hydroxybenzenes with α,β-unsaturated compounds in acidic ionic liquid l-butyl-3-methylimidazolium hydrogen sulphate ([BMIM]HSO_4) was reported for the first time. A series of oxa-Michael adducts and Friedel-Crafts alkylated products were synthesized with good yields. The acidic ionic liquid could be easily recycled for at least 5 times with only minor loss in activity.

Key Words : Acidic ionic liquid, Hydroxybenzenes, α,β-unsaturated compounds, Friedel-Crafts alkylation, oxa-Michael addition

Introduction

The reaction of hydroxybenzenes with α,β-unsaturated compounds has attracted a great deal of attention since it could produce oxa-Michael adducts and Friedel-Crafts alkylated products.[1-9] There are a few examples about the selectivity tuning for the reaction of hydroxybenzenes with α,β-unsaturated compounds, however, these precedents did not give satisfactory results. Rudolf Aumann discovered that both oxa-Michael adduct and Friedel-Crafts alkylated product were produced from the reaction of 9-phenanthrol, while the reaction of phenol only afforded the oxa-Michael adduct.[10] Ryszard Bodalski found that the reaction of phenol with dicyclohexylammonium acrylates could produce oxa-Michael adduct or Friedel-Crafts alkylated product under different temperatures, however, isolation of the oxa-Michael adduct was inefficacious.[11] Velayutham Murugesan and co-workers tried to control the reaction selectivity of phenol by varying reaction conditions, however a mixture of oxa-Michael adduct, *para*-alkylated and *ortho*-alkylated products was produced.[12] Therefore, it is necessary to develop a direct and efficient method for the selectivity tuning of hydroxybenzenes.

Ionic liquids have been applied in many areas because of their unique physical and chemical properties, such as good solvating ability, negligible vapor pressure.[13-15] Some ionic liquids have been utilized in aerobic oxidation of benzylic alcohols,[16] mononitration of aromatic compounds,[17] synthesis of Hantzsch 1,4-dihydropyridines.[18] In this paper, we represent the first example of highly chemo- and regioselective reaction of hydroxybenzenes with α,β-unsaturated compounds in acidic ionic liquid and a series of valuable oxa-Michael adducts and Friedel–Crafts products were synthesized.

Experimental

Materials and General Methods. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Bruker AVANCE DMX 500 spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in ppm (δ), relative to tetramethylsilane (TMS) as the internal standard. IR spectra were measured with a Nicolet Nexus FTIR 670 spectrophotometer. All reactions were carried out with efficient stirring in a round bottom flask at room temperature, unless otherwise stated, and monitored by TLC. MVK was distilled before use, other chemicals were obtained from commercial suppliers and were used without further purification.

Preparation of Acidic Ionic Liquid [BMIM]HSO_4. Acidic ionic liquid [BMIM]HSO_4 was synthesized by the literature method.[19] The preparation was very convenient and the structure of the acidic ionic liquid was characterized by ^{1}H NMR spectroscopy.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 3H), 1.23 (t, 2H), 1.75 (t, 2H), 3.84 (s, 3H), 4.15 (t, 2H), 7.69 (s, 1H), 7.75 (s, 1H), 9.12 (s, 1H).

Typical Procedure for Alkylation of Hydroxybenzenes. To a mixture of *m*-cresol (0.5 mmol, 54 mg) in [BMIM]HSO_4 (0.5 mmol), MVK (0.5 mmol, 35 mg) was added. After addition, the reaction was stirred for 24 h at room temperature. The reaction was monitored by TLC. After the completion of reaction, reaction mixture was extracted with ethyl acetate. The ionic liquid could be further washed with ethyl acetate and reused several times without further purification. The solvent was evaporated and the product was isolated by column chromatography. Yellow oil; IR (neat) ν: 3376, 2944, 1702, 1586, 1504, 1456, 1359, 1233, 1160, 1106, 953, 863, 813, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.24 (s, 3H), 2.67 (t, 2H), 2.80 (t, 2H), 6.62 (d, 1H), 6.64 (s, 1H), 6.96 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 26.5, 30.2, 44.2, 112.8, 117.3, 130.0, 131.1, 137.6, 154.5, 209.7.

Results and Discussion

For the beginning of this study, the reaction of *m*-cresol with methyl vinyl ketone (MVK) was employed as the model. The effect of amount of ionic liquid on the reaction was strong. As can be seen in Table 1, the yield of the reaction

Table 1. The effect of amount of ionic liquid on the alkylation reaction[a]

Entry	Amount of ionic liquid	Yield[b] (%)
1	2 mmol	61
2	1 mmol	67
3	0.5 mmol	75
4	0.1 mmol	68

[a]Reactions were carried out on 0.5 mmol scale of *m*-cresol with 2 equiv of MVK in [BMIM]HSO_4 at room temperature for 24 h. [b]Yield determined by HPLC.

Table 2. The effect of reactant ratios on the alkylation reaction[a]

Entry	Reactant ratio (*m*-cresol/MVK)	Yield[b] (%)
1	1:1	71
2	1:2	75
3	1:4	56

[a]Reactions were carried out on 0.5 mmol scale of *m*-cresol with MVK in 0.5 mmol [BMIM]HSO_4 at room temperature for 24 h. [b]Yield determined by HPLC.

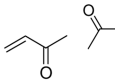
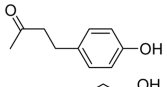
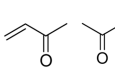
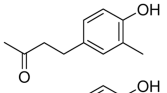
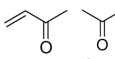
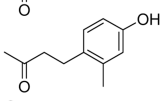
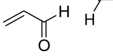
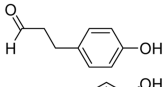
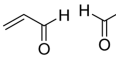
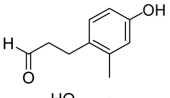
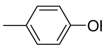
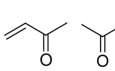
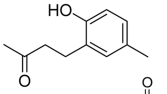
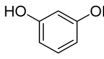
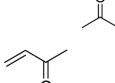
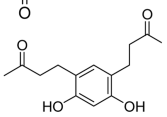
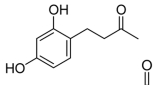
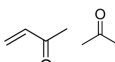
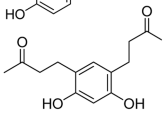
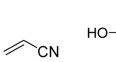
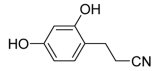
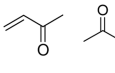
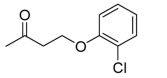
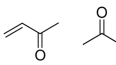
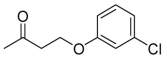
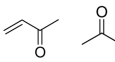
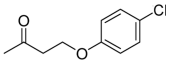
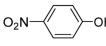
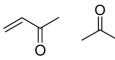
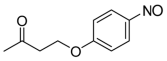
would increase from 61% to 75% when the amount of ionic liquid decreased from 2 mmol to 0.5 mmol (Table 1, entries 1-3). But, the yield of the reaction would decrease from 75% to 68% when the amount of ionic liquid decreased from 0.5 mmol to 0.1 mmol (Table 1, entry 4). After the screening, the optimal amount of ionic liquid was about 0.5 mmol.

Then different reactant ratios were tested and the results were represented in Table 2. The yield of the reaction would increase slightly when the quantity of MVK increase from 0.5 mmol to 1 mmol (Table 2, entries 1, 2). But, the yield of the reaction was very low when the quantity of MVK was higher than 2 mmol because of the formation of byproduct (Table 2, entry 3). Therefore, the optimal ratio was 1:1.

With the optimal reaction conditions in hands, we then examined the generality of this strategy for other structurally diverse substrates, the results were listed in the Table 3. The *para*-alkylated products were obtained when phenol, *o*-cresol and *m*-cresol reacted with MVK (Table 3, entries 1-3). Acrylaldehyde could also react with hydroxybenzenes and the similar *para*-alkylated products were produced (Table 3, entries 4, 5). But the *ortho*-alkylated product was obtained when *p*-cresol reacted with MVK (Table 3, entry 6). The results demonstrated that the Friedel-Crafts reaction of hydroxybenzenes in [BMIM]HSO_4 was regioselective, and the position of substituent had important effect.

The reaction of resorcinol with MVK was also investigated, both mono-alkylated product and bis-alkylated product were obtained (Table 3, entry 7). Bis-alkylated product could be obtained with high yield by using 2 equiv of MVK (Table 3, entry 8). However, it was difficult to provide mono-alkylated product exclusively by varying the ratio and the reaction temperature. The mono-alkylated product of resorcinol could be obtained exclusively when acrylonitrile was used as acceptor, this could be related to the weak activity of acrylonitrile (Table 3, entry 9).

Table 3. The reaction promoted by ionic liquid[a]

Entry	Donor	Acceptor	Product	Yield[b] (%)	Selectivity (%)
1				51	100
2				62	100
3				71	100
4				35	100
5				31	100
6				36	100
7				40	-
				7	-
8				95[c]	100
9				30[c]	100
10				35[d]	100
11				40[d]	100
12				27[d]	100
13				30[d]	100
14				28[d]	100
15				30[e]	100
16				36[e]	100
17			-	[e]	-
18				34[e]	100

[a]Reactions were carried out on 0.5 mmol scale of substrate with 1 equiv of acceptor (entries 1-5, 7, 9, Table 3) in 0.5 mmol [BMIM]HSO_4 at room temperature for 24 h. [b]yield of separated compound. [c]Reactions were carried out on 0.5 mmol scale of substrate with 2 equiv of acceptor (entry 8, Table 3) in 0.5 mmol [BMIM]HSO_4 at room temperature for 24 h. [d]Reactions were carried out on 0.5 mmol scale of substrate with 1 equiv of acceptor (entries 6, 10-14, Table 3) in 0.5 mmol [BMIM]HSO_4 at 37 °C for 24 h. [e]Reactions were carried out on 0.5 mmol scale of substrate with 2 equiv of acceptor (entries 15-16, Table 3) in 0.5 mmol [BMIM]BF_4 at 50 °C for 24 h.

Table 4. Recycling of [BMIM]HSO_4 in the reaction[a]

Run	Yield[b] (%)
1	71
2	71
3	71
4	70
5	69

[a]Reactions were carried out on 0.5 mmol scale of *m*-cresol with 1 equiv of MVK in 0.5 mmol [BMIM]HSO_4 at room temperature for 24 h. [b]Yield determined by HPLC.

In addition to the substrates with electron-donating groups, substrates with electron-withdrawing groups were also investigated. To our surprise, instead of affording the preconceived Friedel-Crafts alkylated product, an unexpected and interesting oxa-Michael adduct of 2-chlorophenol was obtained according to the ^{1}H NMR and IR (Table 3, entry 10). We subjected other hydroxybenzenes with electron-withdrawing substituents to the reaction and the corresponding oxa-Michael adducts were produced regardless of the positions and kinds of substituents (Table 3, entries 11-14).

It was known that hydroxybenzenes underwent oxa-Michael reaction or Friedel-Crafts alkylation exclusively regardless of the effect of substituent when acids were used as catalyst.[20,21] Furthermore, the oxa-Michael adducts of hydroxybenzenes were obtained exclusively in ionic liquid $BMIMBF_4$ (Table 3, entries 15-18). While highly chemo- and regioselective results were achieved in acidic ionic liquid [BMIM]-HSO_4, and the selectivity could be related to the nature of substituent. The reactions of hydroxybenzenes with electron-donating substituent in [BMIM]HSO_4 produced Friedel-Crafts alkylated products, this might be due to the activation ability of electron-donating substituent to the carbon on the aromatic ring. On the contrary, the reactions of hydroxybenzenes with electron-withdrawing substituent in [BMIM]-HSO_4 gave the oxa-Michael adducts, this might be due to the passivation ability of electron-withdrawing substituent to the carbon on aromatic ring.

Upon completion of the reaction, the product was easily separated by extraction with ethyl acetate. The ionic liquid [BMIM]HSO_4 could be reused without any additional operation. The reaction of *m*-cresol with MVK was repeated 5 times and the results were shown in Table 4. It could be seen that the ionic liquid remained consistent activity during the reaction.

Conclusion

In conclusion, a direct and efficient method for the selectivity tuning of hydroxybenzenes was reported for the first time. Highly chemo- and regioselective results were obtained, and a series of valuable Friedel-Crafts alkylated products and oxa-Michael adducts were produced smoothly under mild reaction conditions. The ionic liquid could be reused for at least 5 times with consistent activity.

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