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Synthesis of Raspberry Ketone via Friedel-Crafts Alkylation Reaction Catalyzed by Sulfonic Acid-Functional Ionic Liquids[1]

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Abstract—Phenol and butanolone catalyzed by different SO_3H-functionalized ionic liquids (ILs) for synthesis of raspberry ketone (RK) had been investigated. The influences of different ionic liquids, reaction time, reaction temperature, reactant ratio, the amount of ionic liquid were investigated. The yield of raspberry ketone was 82.5% under the optimum reaction condition. In addition, the ILs (3-sulfo)propyltriamine bisulfate ($[TEA\text{-}PS][HSO_4]$) can be recycled up to five consecutive times without loss of activity. This method had the advantages of mild conditions, high product yield, easy to separate from the product, as well as environmentally friendly procedure. At the same time, the possible reaction mechanism was discussed.

Keywords: phenol, butanolone, SO_3H-functionalized ionic liquid, raspberry ketone, recycle, reaction mechanism

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INTRODUCTION

With the development of society and the improvement of our living standard, Fragrances are part of the daily life and can be found application in many consumer goods like household cleaners, perfumes, oils or even food [1]. To satisfy the growing demand for synthetic fragrances, raspberry ketone is absolutely essential as an important compound. In 1957, raspberry ketone was discovered by Schinz and Seidel [2, 3] as primary aroma component of red raspberries as it was already indicated by the name of this compound. Raspberry ketone has a large application potential in perfumery, cosmetics and as a food additive for soft drinks and sweets. As an important raw material and fine chemical intermediates, raspberry ketone is not only for the preparation of food and flavors daily flavor, but also for the synthesis of pharmaceuticals [4] and dye [5]. The derivatives of raspberry ketone have therapeutic effect on influenza [6]. Since natural abundance of raspberry ketone is very low with only 1–4 mg/kg raspberries, so it has to be prepared by synthesis [7, 8]. There are many methods for synthesis of raspberry ketone, catalysts are used for this reaction include Lewis acids, such as $AlCl_3$ and BF_3 [9], Brϕnsted acids, such as H_3PO_4, H_2SO_4, HF, $HClO_4$ [10], cation-exchange resin [11], mesoporous materials [12], zeolites [13, 14], molecular sieves [15], and also supercritical and near-supercritical water [16]. Liquid acid catalysts cause equipment corrosion and environmental pollution while solid acids deactivate rapidly due to the build-up of coke. Although cation-exchange resins show a good performance, thermal stability and fouling of the resins are also the major problems.

However, there is little information available in literature about synthesis of raspberry ketone catalyzed by ionic liquids. Ionic liquids are new kind of solvent which is entirely composed of ions. Their use as an environmentally benign alternative for conventional solvents has received much attention [17–23]. Recently, advancement in the field of ionic liquids research provides another route to achieve task-specific ionic liquids in which a functional group is covalently tethered to the cation or anion of the ionic liquid, especially to the N atom in the triethylamine [24–26]. When an alkane sulfonic acid group is covalently tethered to the IL cation, the IL would be a strong Brϕnsted acid [27]. These SO_3H-functionalized ionic liquids have exhibited great potential in replacement of conventional homogenous and heterogeneous acidic catalysts because they are fluxible, nonvolatile, noncorrosive and immiscible with many organic solvents [28–30].

In this work, we firstly reported an efficient and environmentally benign alkylation reaction of phenol with butanolone using SO_3H-functionalized ionic liq-

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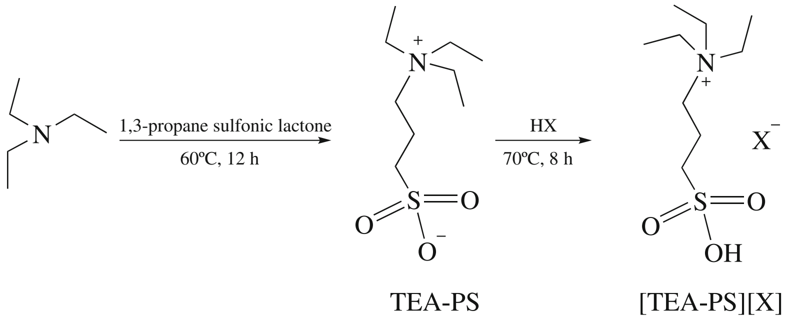
uids as a substitute for conventional homogenous and heterogeneous acidic catalysts. Then the reaction conditions were optimized and selected. This work also gave an insight into the proposed mechanism for the alkylation of phenol with butanolone.

EXPERIMENTAL

Materials and reagents. All solvents and chemicals in the experiment were commercially available and used without further purification unless otherwise stated. Triethylamine and 1,3-butane sultone were purchased from Aladdin. The products were examined using gas chromatography (Agilent 7890B; capillary column: Agilent DB-5, 30 m × 0.25 m × 0.25 μm; programmed oven temperature: 100°C, held for 5 min, ramped to 250°C at 5°C/min, held for 10 min; N_2 carrier gas).

Preparation of SO_3H-functional ILs [31]. In a typical procedure for the preparation of [TEA-PS] [X], a mixture of ethyl acetate (250 ml) and 1,3-butanesultone (0.5 mol) was charged into a round bottom flask (500 mL) , then added triethylamine (0.5 mol) to the round bottom flask. The resulting mixture was vigorously stirred for 12 h at 60°C. The solid product was washed with ethyl acetate (3 × 50 mL) after filtration, and dried under vacuum (70°C, 0.1 MPa). Then, zwitterions (0.1 mol) were dissolved in 50 mL of deionized water, and 0.1 mol of acid (sulfuric acid, hydrochloric acid, p-toluenesulfonic acid, phosphoric acid) was added dropwise with vigorous stirring, respectively and the resulting mixture was stirred for an additional 8 h at 70°C. Extra water was removed by rotary evaporation (70°C, 0.1 MPa), and SO_3H-functional ILs were obtained with a total yield of 68% (see Scheme 1).



Scheme 1. The synthesis process of [TEA-PS][X] ($X^- = HSO_4^-, Cl^-, PTSA^-, H_2PO_4^-$).

Characterization of ILs. The synthesized ILs were identified by ^{1}H NMR and ^{13}C NMR spectral data.

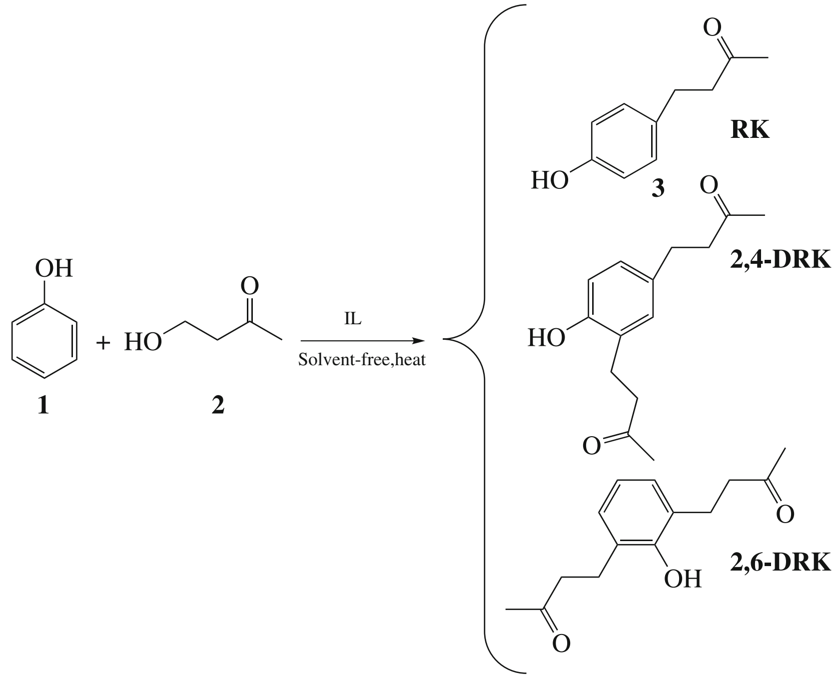
(3-sulfo)propyltriamine bisulfate ([TEA-PS][HSO_4]) ^{1}H NMR (500 MHz, D_2O) δ 2.78–2.56 (*m*, 8H), 2.44–2.21 (*m*, 2H), 1.47 (dd, *J* = 9.1, 4.5 Hz, 2H), 0.66 (*s*, 9H).^{13}C NMR (126 MHz, D_2O) δ 59.86, 54.46, 52.41, 47.59, 46.95, 29.97, 26.55, 16.88, 6.32.

(3-sulfo)propyltriethylamine hydrochloride ([TEA-PS][Cl]) ^{1}H NMR (500 MHz, D_2O) δ 3.27–2.95 (*m*, 8H), 2.74 (*t*, *J* = 7.1 Hz, 2H), 1.95–1.78 (*m*, 2H), 1.05 (*t*, *J* = 7.2 Hz, 9H). ^{13}C NMR (126 MHz, D_2O) δ 60.15, 54.74, 52.66, 47.94, 47.23, 30.25, 26.95, 17.20, 6.60.

(3-sulfo)propyltriethylamine p-toluenesulfonate ([TEA-PS][PTSA]) ^{1}H NMR (500 MHz, D_2O) δ 7.39 (dd, *J* = 5.1, 3.0 Hz, 2H), 7.04 (*d*, *J* = 4.8Hz, 2H), 3.02–2.78 (*m*, 8H), 2.65 (dd, *J* = 6.8, 4.0 Hz, 3H), 1.94–1.83 (*m*, 2H), 1.80–1.66 (*m*, 2H), 0.91 (*d*, *J* = 3.9 Hz, 9H).^{13}C NMR (126 MHz, D_2O) δ 142.19, 129.40, 125.36, 60.18, 54.75, 52.65, 47.96, 47.23, 20.45, 17.20, 6.57.

(3-sulfo)propyltriethylamine phosphate ([TEA-PS][H_2PO_4]) ^{1}H NMR (500 MHz, D_2O) δ 3.10–2.81 (*m*, 8H), 2.58 (*t*, *J* = 7.1 Hz, 2H), 1.78–1.63 (*m*, 2H), 0.89 (*t*, *J* = 7.2 Hz, 9H).^{13}C NMR (126 MHz, D_2O) δ 60.06, 54.69, 52.64, 47.84, 47.19, 30.24, 26.84, 17.14, 6.61.

Reaction procedure. In a typical reaction, Phenol (**1**, 0.5 mol), IL (0.03 mol) were added into a three-necked round bottom flask equipped with magnetic stirrer and butanolone (**2**, 0.1 mol) and dripped into the above solution slowly. The resulting mixture was heated to 50°C and magnetically stirred for 30 min when the drop was completed. After the reaction was completed (TLC detected), the upper organic phase was separated from IL by decantation and analyzed via gas chromatography (GC), IL was recovered from the aqueous solution by removing water at 70°C under vacuum for 6 h, and used directly for the next run (see Scheme 2).



Scheme 2. Synthesis of raspberry ketone by ILs. **RK**—raspberry ketone; **2,4-DRK**—2,4-Double replace raspberry ketone; **2,6-DRK—**2,6-Double replace raspberry ketone.

RESULTS AND DISCUSSION

Effect of different ILs. The experiments were carried out at a molar ratio of phenol/butanolone = 5/1 for two reasons: (i) to avoid the formation of large amounts of by-products, such as the oligomers of 1-butylene-2-keto, 2,4-Double replace raspberry ketone; 2,6-Double replace raspberry ketone, diphenyl ether ketone, raspberry ketone isomers; and (ii) to diminish the influence of the water formed by the dehydration of butanolone in situ. At the same time, the slight excess of phenol is enough to have a crucial influence on the alkylation reaction [32]. The influence of different ionic liquids on the catalytic activity in alkylation of phenol with butanolone was shown in Table 1.We can see the yield from ionic liquid [TEA-PS][HSO_4] as catalyst (entry 1) was slightly better than other ionic liquids (entries 2–4),which indicated that the anionic (HSO_4) improved the catalytic performance [33], due to sulfuric acid is a strong acid.

Effect of reaction time. Figure 1 shows the yield of different products as a function of reaction time for alkylation of phenol with butanolone at 50°C with a molar ratio of phenol to butanolone of 5 : 1. In the early stages of the reaction, the products were RK, 2,4-DRK, 2,6-DKR, other products were very few. As the reaction going on, the RK was decreased, the 2,4-DRK and 2,6-DKR were slightly increased. Figure 1 also shows clearly that the reaction reached an equilibrium level after 180 min. In the process of reaction, ionic liquid could be well miscible with reactants, reaction was in a homogeneous phase. After butanolone addition was completed in an hour, the raspberry ketone content was the highest in the next 30 min, that is to say, 90 min is the best reaction time. Therefore we determine the optimal reaction time is 90 min.

Effect of reaction temperature. As can be seen from Fig. 2, the reaction temperature we set is 40–80°C. The yield of RK was up from 40 to 50°C, but it was

Table 1. Alkylation of phenol with butanolone in different ILs[a]

Entry	ILs	Yield of RK, %[b]	Yield of 2,4-DRK, %[b]	Yield of 2,6-DRK, %[b]
1	[TEA-PS][HSO_4]	81.1	13.2	3.9
2	[TEA-PS][Cl]	77.5	18.3	3.2
3	[TEA-PS][PTSA]	80.1	14.5	3.9
4	[TEA-PS][H_2PO_4]	78.9	11.4	1.2

[a] Reaction condiction: 50°C, phenol/but.nolone/ILs 5 : 1 : 0.03 mol/mol/mol, 5 h.
[b] Yield was achieved by GC analysis.

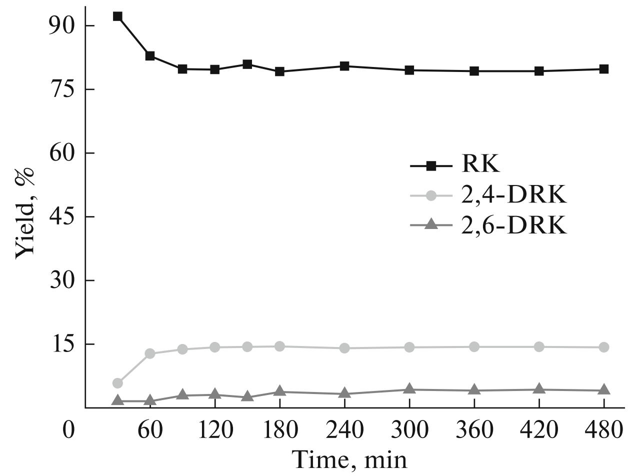


Fig. 1. Influence of reaction time on alkylation of phenol with butanolone. Reaction conditions: 50°C, phenol/butanolone/ILs ([TEAPS][HSO_4]) 5 : 1 : 0.3 mol/mol/mol.

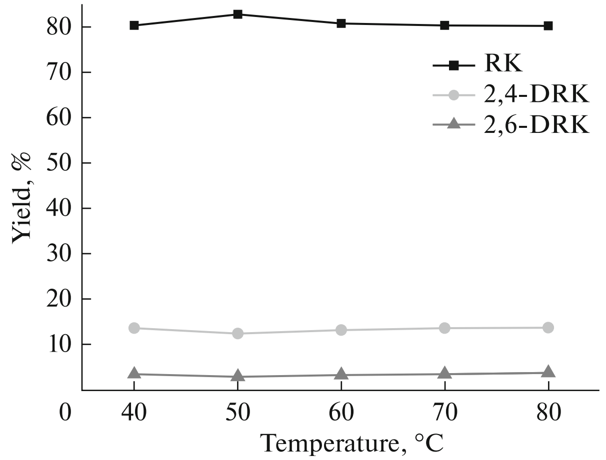


Fig. 2. Influence of reaction temperature on alkylation of phenol with butanolone. Reaction condictions: phenol/butanolone/ILs ([TEA-PS][HSO_4]) 5 : 1 : 0.3 mol/mol/mol, 90 min.

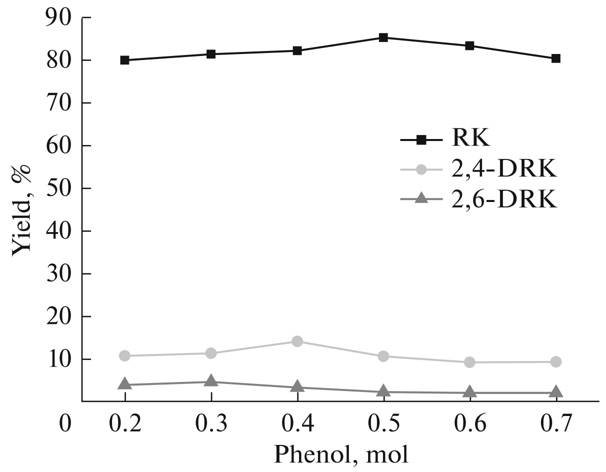


Fig. 3. Influence of the amount of phenol on alkylation of phenol with butanolone. Reaction conditions: 50°C, 90 min, 0.1 mol butanolone, 0.03 mol ILs.

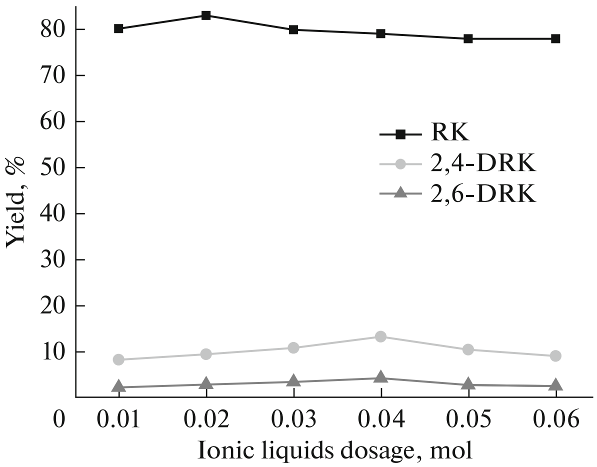


Fig. 4. Influence of the amount of ionic liquids on alkylation of phenol with butanolone. Reaction conditions: 50°C, 90 min, phenol : butanolone = 0.5 : 0.1 mol/mol.

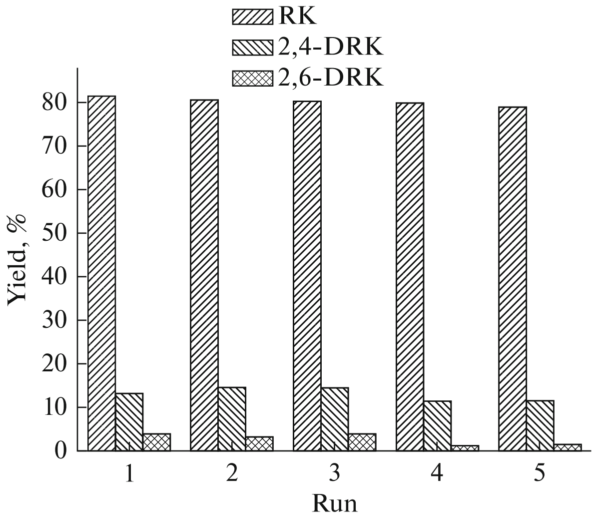


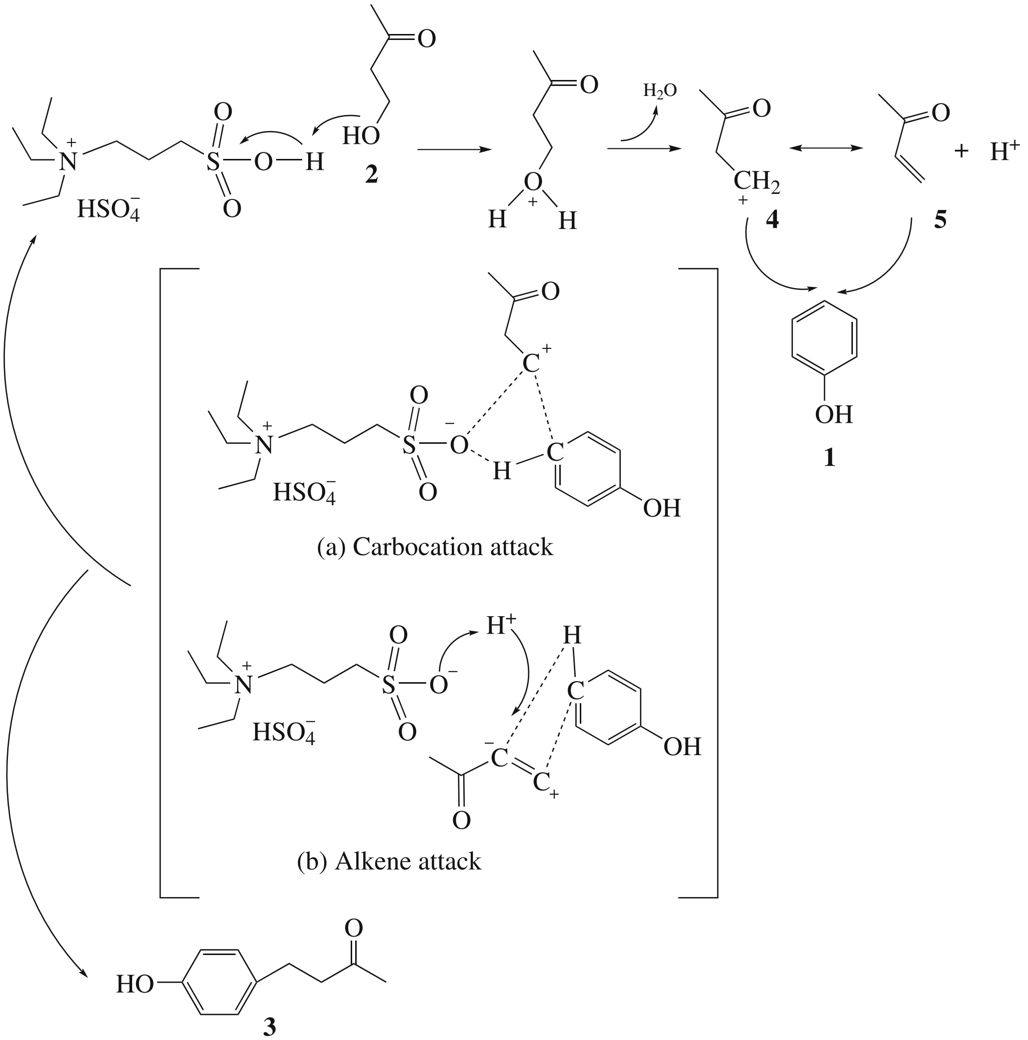
Fig. 5. Reaction conditions: 50°C, phenol : butanolone : ILs = 5 : 1 : 0.2 mol/mol/mol, 90 min.

down firstly and then remained unchanged with increase of temperature, and it reached the maximum at 50°C. The possible causes of this phenomenon is due to the adverse event increased when the temperature was too high, thus leading to the drop of RK yield. The content of 2,4-DRK had a slight increase firstly and then remained unchanged, however, the content of 2,6-DRK had a slight decline continually. We have done experiments at the lower temperature. At room temperature, phenol is solid, experiment cannot be carried out. Below 40°C, the ionic liquid viscosity is large, low catalytic activity, no product generation. Therefore, the best reaction temperature is 50°C.

Effect of the reactant ratio. As is shown in Fig. 3, we kept the amount of butanolone (0.1 mol) remained unchanged and increased of phenol proportionally, the content of RK increased and the content of RK reached to the maximum when the reactant ratio reached 5, then the content of RK was reduced with the reactant ratio increased, which is possible that too much phenol will have a dilution effect on catalyst, and in consequence, reduce the activity of the catalyst. But the maximum of 2,4-DRK formation at 0.4 mol (phenol) possible reason is that ionic liquid is excess, according to the principle of phenol positioning, ortho- and para-priority is occupied, so the amount of 2,4-DRK is large, but with the addition of phenol, ionic liquid is diluted, para-priority is occupied, so the maximum of RK formation at 0.5 mol (phenol), if continue to add phenol, ionic liquid is excessively diluted, the catalytic effect is reduced. there was an obvious characteristic that 2,4-DRK and 2,6-DRK were the minimum value when the rk content was the maximum. thus we can come to such a conclusion that the best raw material ratio is phenol : butanolone = 0.5 mol : 0.1 mol.

Effect of the amount of ILs. We can see in Fig. 4 that the RK content was increased and reached to the maximum value when the amount of catalyst was 0.02 mol, then the RK content had a slight decline with the increase of the amount of ionic liquid. And the content of 2,4-DRK and 2,6-DRK had a similar change rule. The side reaction is also increased at the same time when catalyst dosage increases, so we must control the amount of the catalyst. Thus we can conclude that the best amount of the catalyst is 0.02 mol.

Recyclability of ILs. In order to examine the regenerability of the ILs, we tried to recover the IL catalyst. Because the ILs were stratified at the end of the reaction, we could approximately get 90 percent of the ILs by decantation easily, the remaining ILs were extracted by *n*-hexane, then the recovered ILs were dried under vacuum for 5 h at 80°C and then reused for another cycle. The same procedure was repeated five times. The IL was assessed by ^{1}H NMR spectroscopy and no traces of products and reactant were detected. The results of the recycling experiments are shown in Fig. 5. It could be seen that ionic liquid [TEA-PS][HSO_4] (1) was utilized repeatedly over five times without any apparent loss of catalytic activity.



Scheme 3. The possible mechanism for catalytic synthesis of raspberry ketone.

The proposed mechanism for the alkylation of phenol with butanolone [34]. The strong acidic ionic liquids could protonate the hydroxyl group in butanolone which can liberate H_2O to form carbocation **4** [35]. The carbocation could either directly attack the *ortho*- or *para*- position of phenol via formation of transition state (a) as shown in Scheme 3 (which shows only ortho-attack) to give the *ortho*- or *para*- alkyl phenol; or it can undergo elimination of proton to form the alkene **5** [36] which could also attack the *ortho*- or *para*- position of phenol via formation of transition state (b).

CONCLUSIONS

In this study, SO_3H-functional ionic liquids were prepared and used for the synthesis of RK under solvent-free conditions. The result demonstrated the optimized conditions for this reaction were the molar ratio of phenol : butanolone : ILs ([TEA-PS][HSO_4]) = 5 : 1 : 0.2 at 50°C over 90 min, the biggest yield of RK was 82.5% under these conditions. Furthermore, the used IL catalyst could be easily recovered by simple separation and reused up to five times without any apparent reduction in its activity. Therefore, we come to a conclusion that the alkylation of phenol with butanolone catalyzed by Brϕnsted acidic ionic liquid ([TEA-PS][HSO_4]) indicates a great potential for producing raspberry ketone.

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REFERENCES

1. K. J. Rossiter, Chem. Rev. **96**, 3201 (1996).
2. H. Schinz and C. F. Seidel, Helv. Chim. Acta **40**, 1839 (1957).
3. H. Schinz and C. F. Seidel, Helv. Chim. Acta **44**, 278 (1961).
4. D. Yoshida, JP Patent No. 6 321 850 (1988).
5. I. Matsuji, A. Masashi, and Y. Yoshio, JP Patent No. 63258444 (1988).
6. T. Nishimura, S. Yoshii, H. Toku, and B. Nomiya, DE Patent No. 2142494 (1972).
7. A. Deifel and Z. Lebensm, Unters Forsch. **188**, 330 (1989).
8. J. Beekwilder, I. M. van der Meer, O. Sibbesen, M. Broekgaarden, I. Qvist, J. D. Mikkelsen, and R. D. Hall, Biotechnol. J. **2**, 1270 (2007).
9. G. Sartori, F. Bigi, G. Casiraghi, G. Carnati, L. Chiesi, and A. Arduini, Chem. Ind. **22**, 762 (1985).
10. A. A. Carlton, J. Org. Chem. **13**, 120 (1948).
11. W. A. Herrmann and V. P. W. Bohm, J. Organomet. Chem. **572**, 141 (1999).
12. A. Sakthivel, S. K. Badamali, and P. Selvam, Micropor. Mesopor. Mater. **39**, 457 (2000).
13. A. V. Krishnan, K. Ojha, and N. C. Pradhan, Org. Process. Res. Dev. **6**, 132 (2002).
14. K. Zhang, H. Zhang, G. Xua, S. Xiang, D. Xu, S. Liu, and H. Li, Appl. Catal., A. **207**, 183 (2001).
15. S. Sumbramanian, A. Mitra, C. V. V. Satyanarayana, and D. K. Chakrabarty, Appl. Catal., A. **159**, 229 (1997).
16. T. Sato, G. Sekiguchi, T. Adschiri, and K. Arai, Chem. Commun. **17**, 1566 (2001).
17. P. Wasserscheid and W. Keim, Angew. Chem. Int. Ed. **39**, 3772 (2000).
18. J. Dupont, R. F. de Souza, and P. A. Z. Suarez, Chem. Rev. **102**, 3667 (2002).
19. C. M. Gordon, Appl. Catal., A. **222**, 101 (2002).
20. H. J. Olivier, Mol. Catal. **146**, 285 (1999).
21. T. Welton, Chem. Rev. **99**, 2071 (1999).
22. H. Olivier and L. Magna, J. Mol. Catal. A **419**, 182 (2002).
23. J. D. Holbrey and K. R. Seddon, Clean Prod. Process. **1**, 223 (1999).
24. K. W. Kottsieper, O. Stelzer, and P. Wasserscheid, J. Mol. Catal. A **175**, 285 (2001).
25. E. D. Bates, R. D. Mayton, I. Ntai, and J. H. Davis, J. Am. Chem. Soc. **124**, 926 (2002).
26. J. Gui, Y. Deng, Z. Hu, and Z. Sun, Tetrahedron Lett. **45**, 2681 (2004).
27. A. C. Cole, J. L. Jensen, I. Ntai, K. L. T. Tran, K. J. Weave, D. C. Forbes, and J. H. Davis, J. Am. Chem. Soc. **124**, 5962 (2002).
28. D. C. Forbes and K. J. Weaver, J. Mol. Catal. A **214**, 129 (2004).
29. Y. Gu, F. Shi, and Y. Deng, J. Mol. Catal. A **212**, 71 (2004).
30. J. Gui, X. Cong, D. Liu, X. Zhang, Z. Hu, and Z. Sun, Catal. Commun. **5**, 473 (2004).
31. H. Qian and D. B. Liu, Ind. Eng. Chem. Res. **50**, 1146 (2011).
32. E. Dumitriu and V. Hulea, J. Catal. **218**, 249 (2003).
33. X. Y. Liao, S. G. Wang, X. M. Xiang, Y. L. Zhu, X. C. She, and Y. W. Li, Fuel Process. Technol. **96**, 74 (2012).
34. K. M. Hello, F. Adam, and T. H. Ali, J. Taiwan Inst. Chem. E. **45**, 134 (2014).
35. K. U. Nandhini, J. H. Mabel, B. Arabindoo, M. Palanichamy, and V. Murugesan, Micropor. Mesopor. Mater. **96**, 21 (2006).
36. K. Song, J. Guan, S. Wu, Y. Yang, B. Liu, and Q. Kan, Catal. Lett. **126**, 333 (2008).