Synthesis of racemic mandelic acids with the composite phase transfer catalyst β-cyclodextrin-[bmim]PF₆

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Ionic liquids were employed as a part of composite phase transfer catalyst to synthesise mandelic acid, and it is found that [bmim]PF₆ coupled with β-cyclodextrin is the most effective catalyst, which was also applicable to other reactions used to synthesise mandelic acid derivatives. Reaction conditions were optimized and the products were characterised by ^{1}H NMR and IR.

**Keywords:** mandelic acid, phase transfer catalyst, β-cyclodextrin, ionic liquid

Mandelic acid, known as 2-hydroxyl-2-phenylacetic acid, is a racemate which is readily resolved into its enantiomers (*R*)-mandelic acid and (*S*)-mandelic acid.[1–2] Its derivatives act as thrombin inhibitors and anticoagulants.[3] Mandelic acid and its derivatives have also found broad use as intermediates and resolving agents for the production of many pharmaceutical products such as semisynthetic penicillins or cephalosporins and other agricultural products.[4,5]

Due to the high level of interest in mandelic acid and its derivatives, a number of methods have been developed for their synthesis,[6–8] and two pathways are prominent. One is based on the hydrocyanation of benzaldehyde in the presence of chloroform, which gives the corresponding cyanohydrin, followed by chemical hydrolysis in the presence of strong acid. This process requires poisonous raw materials, and is not applicable to compounds with sensitive functional groups. The other pathways by chlorination of hypnone followed by hydrolysis in aqueous alkaline, yet involves many disadvantages, such as long reaction time, excess solvents and low yields. So, it is necessary to develop new synthetic methods making the use of less toxic commercial reagents.

Cyclodextrin is a cyclicoligomer consisting of α-1, 4-linked D-glucopyranose, have attracted growing attention for their ability to form inclusion complexes and act as efficient catalysts in various reactions. Ionic liquid is an eco-friendly reaction medium for a variety of organic transformations, is non-volatile, recyclable, easy to handle and thermally robust. Ionic liquid is also a quaternary ammonium salt which thus should also act as a phase transfer catalyst. We have attempted the combination of both β-cyclodextrin (β-CD) and ionic liquds to accelerate the reaction in a green chemical process.

To the best of our knowledge, the synthesis of mandelic acids by the combination of ionic liquids and β-CD has not yet been explicitly reported. A similar study is reported combining β-CD and triethylbenzylammonium chloride (TEBA) to catalyse the reaction.[9]

In continuation of our research interest in ionic liquid, we present our studies toward the synthesis of mandelic acids catalysed by ionic liquids and β-CD from the corresponding aromatic aldehyde with chloroform (see Scheme 1).
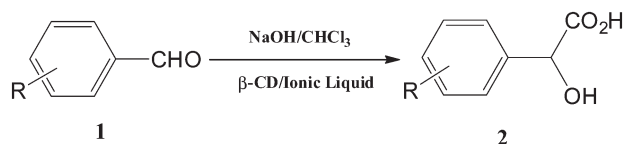
a: R=H; b. R=4-OH; c. R=4-CH₃O;
d. R=3-CH₃O-4-OH; e. R=4-NO₂

Scheme 1

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Table 1   Different single and composite catalysts[a]

single catalyst	Yield /%[b]	composite catalyst	Yield /%[b]
β-CD	57	--	20
TEBA	60	β-CD-TEBA	65
[bpy]Br[c]	55	β-CD-[bpy]Br	70
[bpy]BF₄[d]	51	β-CD-[bpy]BF₄	73
[bzpy]Cl[e]	46	β-CD-[bzpy]Cl	71
[bmim]PF₆[f]	40	β-CD-[bmim]PF₆	76

[a] All reactions were performed at 60 °C with stirring for 6 h under catalyst of 5% to benzaldehyde in mole fraction.
[b] Isolated yield based on benzaldehydes.
[c] *N*-butylpyridinium bromide.
[d] *N*-butylpyridinium tetrafluoroborate.
[e] 1-Benzylpyridinium chloride.
[f] 1-Butyl-3-methylimidazolium hexafluorophosphate.

The reaction of benzaldehyde with chloroform was performed firstly under different single and composite catalysts including ionic liquid as an example to investigate the catalytic effects on the reaction, and the results were summarized in Table 1.

Though TEBA is not liquid at room temperature, it was still used for comparison. It was found that the lowest yield of only 20% was obtained in the absence of any catalyst, because phase transfer catalyst is necessary to accelerate the reaction in heterogeneous system. It also can be seen from Table 1 that both β-CD and single ionic liquid or TEBA as a phase transfer catalyst could not give satisfactory results comparing with composite phase transfer catalysts. Of all the investigated composite phase transfer catalysts, β-CD-[bmim]PF₆ was the most effective catalyst, under which the best yield of 76% was obtained for the reaction of benzaldehyde with chloroform. The composite phase transfer catalysts are more effective than any single catalyst, which presumably is due to some concerted catalytic effects collaboratively presented by β-CD and quatemary ammonium salts to enhance the reaction.[10]

The research was then focused on the reaction conditions with the composite phase transfer catalyst composed of ionic liquid [bmim]PF₆ and β-CD. The influences of the ratio of the reactants, the reaction time, the reaction temperature, the ratio of β-CD to [bmim]PF₆ and the amount of the composite phase transfer catalyst on the reaction yield were minutely examined and the results are summarized in Table 2.

The experimental results showed that the optimal reaction conditions were as follows: the reaction temperature 50 °C, the reaction time 6h, the ratio of benzaldehyde to chloroform 1:1.5 in mole fraction, the ratio of β-CD to [bmim]PF₆ 1:2 in mole fraction, the amount of the composite phase transfer catalyst β-CD-[bmim]PF₆ to benzaldehyde 10% in mass fraction, under which the yield could reach high to 85%. In addition, the effects of recycling of the composite catalyst β-CD-[bmim]PF₆ were also investigated, and decreasing yields were found partly as a result of some catalyst loss in the reaction treatments.

Table 2 Effects of reaction conditions on the yield of the reaction catalysed by β-CD-[bmim]PF$_6$

Entry	T /°C	Time /h	Ratio[a]	β-CD: ionic liquid[b]	cat./Reactant /%[c]	Yield /%[d]
1	40	6	1:2	1:1	5	62
2	50	6	1:2	1:1	5	80
3	60	6	1:2	1:1	5	76
4	70	6	1:2	1:1	5	68
5	50	2	1:2	1:1	5	65
6	50	4	1:2	1:1	5	75
7	50	8	1:2	1:1	5	77
8	50	6	1:1	1:1	5	60
9	50	6	1:1.5	1:1	5	81
10	50	6	1:2.2	1:1	5	80
11	50	6	1:1.5	2:1	5	70
12	50	6	1:1.5	1:2	5	82
13	50	6	1:1.5	1:3	5	78
14	50	6	1:1.5	1:2	2.5	64
15	50	6	1:1.5	1:2	10	85
16	50	6	1:1.5	1:2	20	79
17	50	6	1:1.5	1:2	10	80[e]
18	50	6	1:1.5	1:2	10	60[f]

[a] Ratio of benzaldehyde to chloroform in mole. [b] Ratio in mole. [c] In mole fraction. [d] Isolated yield based on benzaldehydes. [e] Catalyst is reused twice. [f] Catalyst is reused three times.

Finally, several substituted mandelic acids (**2**) were synthesised from corresponding substituted benzaldehyde (**1**) and chloroform under the above optimized conditions catalysed by the composite catalyst β-CD-[bmim]PF$_6$, and the results being listed in Table 3. It is shown that the composite phase transfer catalyst β-CD-[bmim]PF$_6$ was also applicable to reactions of some substituted benzaldehyde with function group *p*-hydroxyl, *p*-methoxyl, and 3-methoxyl-4-hydroxyl but *p*-nitryl group. Melting points of the product **2** were consistent with the literature data except **2e** which is much more like to be *p*-nitrobenzoic acid (lit.[11] m.p. 236–240 °C), and ^{1}H NMR chemical shift for hydrogen of **2e** can also verify that **2e** is not *p*-nitromandelic acid but *p*-nitrobenzoic acid. In fact, *p*-nitromandelic acid is sporadically reported in the literature and its synthesis, unlike that of its other isomer, is surprisingly difficult to synthesise.[12] The strong electron-withdrawing of *p*-nitryo group could lead severely to Cannizzaro reaction under the employed experimental conditions to give *p*-nitrobenzoic acid.

In conclusion, a new procedure employing the composite phase transfer catalyst β-CD-[bmim]PF$_6$ was presented with appropriately yield results. β-CD coupled with ionic liquid may presumably take on some concerted catalytic effects on the investigated reactions of aromatic aldehydes with chloroform. The procedure is efficient, practical, and simple to carry out, and further work on ionic liquid as both catalyst and solvent in this reaction is in progress.

Experimental

Mandelic acid (**2a**): Benzaldehyde, chloroform, and the phase transfer catalyst were placed in a three-neck 100mL flask, and stirred in water bath at 50 °C. Then 13 ml 50% aq. sodium hydroxide was added dropwise in 0.5h. After addition, the reaction was continued at 50 °C for 6 h. Then reaction mixture was quenched in 100ml water, and the aqueous layer and organic layer were separated. The phase transfer catalyst was separated from the organic layer by distillation under reduced pressure and directly recycled for reuse. The aqueous layer was acidified to a pH value of approximately one by using 50% aq. sulfuric acid, and then extracted with the ethyl ether (15 mL×3). The combined extracts were distilled to remove ethyl ether under reduced pressure. After recrystallisation from toluene, pure crystalline mandelic acid was obtained by filtration.

Melting points measured on MRS-1A apparatus are uncorrected. IR spectra were recorded as KBr pellets on Nicolet IR 200 spectrophotometer. ^{1}H NMR spectra were determined on Bruker (400 MHz) spectrometer in DMSO-d$_6$ using TMS as an internal standard.

Mandelic acid (**2a**): IR(cm^{-1}) 3400, 2965, 2630, 1714, 1450, 1378, 1298, 1063, 731, 695. ^{1}H NMR δ 12.55 (1H, s, -COOH), 7.18–7.27 (5H, m, ArH), 5.28 (1H, s, ArCH*(OH)-), 3.63 (1H, brs, ArCH(OH*)-).

p-Hydroxymandelic acid (**2b**): IR(cm^{-1}) 3415, 1621, 1384, 824. ^{1}H NMR δ 12.38 (1H, s, -COOH), 6.85 (2H, d, *J*=8.6Hz, ArH), 7.30 (2H, d, *J* = 8.6 Hz, ArH), 5.33 (1H, s, ArOH), 5.40 (1H, s, ArCH*(OH)-), 3.68 (1H, brs, ArCH(OH*)-).

p-Methoxymandelic acid (**2c**): IR(cm^{-1}) 3404, 2968, 1718, 1611, 1514, 1392, 1258, 1179, 1072, 827. ^{1}H NMR δ 12.37 (1H, s, -COOH), 7.32 (2H, d, *J* = 8.6 Hz, ArH), 6.89 (2H, d, *J* = 8.6 Hz, ArH), 5.20 (1H, s, ArCH*(OH)-), 3.80 (3H, s, -OCH$_3$), 3.45 (1H, brs, ArCH(OH*)-).

3-Methoxy-4-hydroxymandelic acid (**2d**): IR(cm^{-1}) 3441, 3229, 1732, 1525, 1377, 1150, 1033, 830. ^{1}H NMR δ 12.41 (1H, s, -COOH), 7.02–7.30 (3H, m, ArH), 5.40 (1H, s, ArCH*(OH)-), 5.37(1H, s, ArOH), 4.01 (3H, s, -OCH$_3$), 3.55 (1H, brs, ArCH(OH*)-).

p-Nitrobenzoic acid (**2e**): IR(cm^{-1}) 2600–3400, 1692, 1606, 1534, 1351, 1310, 1294, 718. ^{1}H NMR δ 13.69(1H, s, -COOH), 8.32(2H, d, *J* = 8.8 Hz, ArH), 8.16(2H, d, *J* = 8.8 Hz, ArH).

References

1   W.J. Choi, K.Y. Lee, S.H. Kang and S.B. Lee, *Sep. Purif. Technol.*, 2007, 178.
2   P. Saravanan and V.K. Singh, *Tetrahedron Lett.*, 1998, **39**, 167.
3   M. Landwehr, L. Hochrein, C.R. Otey, A. Kasrayan, J.-E. Backvall and F.H. Arnold, *J. Am. Chem. Soc.*, 2006, **128**, 6058.
4   G. DeSantis, Z. Zhu, W.A. Greenberg, K. Wong, J. Chaplin, S.R. Hanson, B. Farwell, L.W. Nicholson, C.L. Rand, D.P. Weiner, D.E. Robertson and M.J. Burk, *J. Am. Chem. Soc.*, 2002, **124**, 9024.
5   Y. Yamazaki and H. Maeda, *Agric. Biol. Chem.*, 1986, **50**, 2621.
6   S.H. Lee, J.H. Choi, S.H. Park, J.I. Choi and S.Y. Lee, *Enzyme Microb. Technol.*, 2004, **35**, 429.
7   H.R. Huang, J.H. Xu, Y. Xu, J. Pan and X. Liu, *Tetrahedron: Asymm.*, 2005, **16**, 2113.
8   G.M. Whitesides, M.A. Patterson and R.P. Szajewski, *J. Org. Chem.*, 1981, **46**, 4682.
9   Zhou, D.-Q. Yuan and R.-G. Xie, *Synth. Commun.*, 1994, **24**, 43.
10 M. Xiao, S.X. Wang, F. Hu, B.X. Liang, Y. Muramatsu and Z.L. Li, *Chin. Chem. Reag.*, 1997, **19**, 270.
11 M.M. Khodaei, A.R. Khosropour and H. Moghanian, *J. Iran. Chem. Soc.*, 2007, **4**, 336.
12 J. Morrison, P. Wan, J.E.T. Corrie and V.R.N. Munasinghe, *Can. J. Chem.*, 2003, **81**, 586.
13 H. Xu and Y. Chen, *Ultrason. Sonochem.*, 2008, **15**, 930.
14 K. Ladenburg, K. Folkers and R.T. Major, *J. Am. Chem. Soc.*, 1936, **58**, 1292.
15 R. G. Kalikar, R.S. Deshpande and S.B. Chandalia, *J. Chem. Tech. Biotechnol.*, 1986, **36**, 38.

Table 3 Synthesis of **2** with composite β-CD-[bmim]PF$_6$ as phase transfer catalyst.[a]

Compound.	Colour	Yield/%[b]	M.p./°C)	Lit. m.p. (°C)
2a	White	85	120–121	117.3–118.5[13]
2b	White	78	110–112	109.5–110.5[14]
2c	White	75	104–108	105–106[13]
2d	White	67	130–132	131[15]
2e	–	–[c]	–	128.5–130[12]

[a] All reactions were performed at 50 °C with stirring for 6 h under catalyst of 10% to benzaldehyde in mole fraction. [b] Isolated yield based on benzaldehydes. [c] *p*-Nitromandelic acid was obtained as yellow solid with the yield 35%, m.p. 238–240 °C (lit.[11] m.p. 236–240 °C).