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A Combination of Phase Transfer Catalyst and Ultrasonic Irradiation Promotes Synthesis of Mandelic Acid

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A combination of phase transfer catalyst and ultrasonic irradiation used to promotes synthesis of mandelic acid from benzaldehyde with chloroform. The main advantages of this method are that the reaction time is much shorter and the yield is higher than those of the classical method. *p*-Methoxymandelic acid was also obtained in 58 % yield under the same reaction conditions.

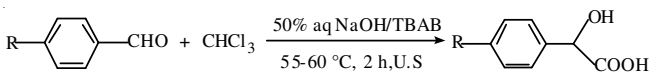
Keywords: Tetrabutyl ammonium bromide, Mandelic acid, Ultrasonic activation, Phase transfer catalysis.

INTRODUCTION

The mandelic acid, *i.e.*, α-hydroxyphenylacetic acid is a racemate and usually an important starting material for resolution to obtain (R)-mandelic acid and (S)-mandelic acid [1]. (R)-Mandelic acid is mainly used as a key intermediate for the production of semisynthetic cephalosporins and penicillins and also for the synthesis of other pharmaceuticals such as antitumour and antiobesity agents. Therefore, many approaches for the production of mandelic acid have been reported, but they usually require long reaction time and the yield was very low[2].

Sonication also increases the reaction rate and avoids the use of high reaction temperatures[3]. Numbers of organic reactions have been revisited by means of ultrasonic waves[4-6]. Compared with traditional methods this technique is more convenient and easily controlled and is more appropriate in the consideration of green chemistry concepts[7].

In this context, our attention was focused on the fact that phase transfer catalyst and ultrasonic irradiation could be a successful way to synthesize mandelic acid. This method is benefits from the rate enhancement effects found when using ultrasonic irradiation and phase transfer catalyst. Herein, we propose to present our studies toward the ultrasound-assisted synthesis of mandelic acid catalyzed by phase transfer catalyst tetrabutyl ammonium bromide (TBAB) (**Scheme-I**).



Scheme-I

Mandelic acid (3a): Yield: 83 %; white solid, m.p. 118-119 ºC; ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 7.25(5 H, m), δ_H 5.10 (1H, s), δ_H 4.70 (2H, s); EI-MS m/z151.9 (M^+).

***p*-Methoxymandelic acid (3b):** Yield: 58 %; white solid, 110-113 ºC; ^{1}H NMR (400 MHz, $CDCl_3$), δ_H 3.80 (3H, s), δ_H 5.20 (1H, s), δ_H 6.89(2H, d, J = 8.8 Hz), δ_H 7.34 (2H, d, J = 8.4 Hz); EI-MS m/z 182 (M^+).

EXPERIMENTAL

All the reagents employed in the synthesis were of analytical reagent grade. The materials were used as purchased and $CHCl_3$ was used directly without any additional purification. Melting points were uncorrected. FT-IR spectra were recorded on a Thermo Nicolet 67 FT-IR spectrophotometer with 4 cm^{-1} resolution. All NMR analyses were performed on a Bruker spectrometer (300 or 400 MHz) in $CDCl_3$; TMS (^{1}H NMR) was used as internal standards. Respectively, Sonication was performed in Shanghai SK-250LH ultrasonic cleaner with the frequency of 59 kHz.

General procedure: To the mixture of the distilled benzaldehyde (**1a**, 96 mmol), tetrabutyl ammonium bromide (TBAB, 3 mmol) and $CHCl_3$ (2.240 mmol) in100 mL three-neck rockered flask at 55-60 ºC under N_2, 50 % aq. NaOH (30 mL) was added dropwise in 1 h under ultrasonic irradiation, After adding, the above mixture continued to react at 55-60 ºC for 2 h under ultrasonic irradiation. Water (20 mL) was then added to the mixture, which was extracted by Et_2O (2 × 10 mL). The water phase was separated, collected, acidified the pH value to 1-2 by 50 % aq. H_2SO_4 and extracted by Et_2O (2 × 10 mL). Subsequently, the organic phase was combined, dried over

anhydrous Na_2SO_4, concentrated *in vacuo* and purified by recrystallization in toluene to give **3a**, which was characterized by ^{1}H NMR, EI-MS and m.p.

RESULTS AND DISCUSSION

The effects of ultrasound wave, tetrabutyl ammonium bromide, reaction time, ultrasonic radiation frequencies, base, reaction way and temperature on the reaction were investigated as summarized in Table-1.

As shown in Table-1, in the absence of ultrasound, when benzaldehyde (**1a**, 96 mmol), $CHCl_3$ (2.240 mmol) and tetrabutyl ammonium bromide (3 mmol) was reacted for 2 h at 55-60 ºC after adding 50 % aq. NaOH (30 mL), mandelic acid (**3a**) was obtained in a 52 % yield (entry 18); while under ultrasonic irradiation, **3a** was obtained in a 83 % yield (entry 7). Therefore, it was clear that the ultrasound could accelerate the synthesis of mandelic acid.We then studied the reaction conditions under ultrasound. When TBAB was added to the above reaction mixture used as phase transfer catalyst under ultrasonic irradiation for 2 h at 55-60 ºC, the yield of **3a** was increase from 35 to 83 % (entries 14 *vs.* 7), which encouraged us to observe the influence of the amount of TBAB on the reaction yields (entries 8, 14-16). It was found that the best yield of **3a** was obtained when 3 mmol of TBAB was used as phase transfer catalyst. The possible reason was: TBAB could be collapsed to form a cavity, for example, the inner and the external parts of which have the lipophilic and the hydrophilic properties, respectively. When TBAB was used as phase transfer catalyst, the benzaldehyde entered into the inner part of a cavity of the TBAB, while the corresponding external part was used to incorporate the TBAB from $CHCl_3$. Consequently, the benzaldehyde was easily to approach the trichloromethyl anion to complete the reaction (83 %, entry 7). If the amount of TBAB was too less, the reaction rate would be decreased and the corresponding yield of **3a** was reduced (entries 7, 14-16). Moreover, the influences of the reaction temperature (ultrasonic radiation frequencies, base and time on the reaction yields were also studied and the best result was achieved when the reaction temperature was at 55-60 ºC and the reaction time was 2 h (83 %, entry 7), respectively. It was obvious that the best yield of **3a** could not be obtained even if the reaction time prolonged to 3 h (75 %, entry 20) and the reaction temperature was raised to 70-80 ºC (54 %, entry 10).

The effect of various base used in the formation of **3a** was studied and NaOH was found to be the best base for the reaction when NaOH was used as base, the yield of **3a** was 83 %, whereas the yield is 79 and 0 % respective when reaction use KOH or K_2CO_3 as base (entry 18, 19). The best result was achieved when the ultrasonic radiation frequencies was at 59 kHz and the reaction time was 2 h (83 %, entry 7), whereas the yield is 63 % when the ultrasonic radiation frequencies was at 43 kHz (entry 21).

Finally, adding way was studied, when the mixture of benzaldehyde, TBAB and $CHCl_3$ in100 mL three-neck rockered flask at 55-60 ºC, 50 % aq. NaOH was added dropwise in 1 h under ultrasonic irradiation, then continues to react 2 h and to give the good yield (83 %, entry 7), whereas the yield is only 53 % using one-pot reaction (entry 22).

Evidently, of the ultrasound wave, TBAB, reaction time, ultrasonic radiation frequencies, base and temperature screened, the best yield of **3a** (83 %) was obtained when the molar ratio of benzaldehyde/$CHCl_3$ /TBAB/was 96/240/3/ and the reaction was proceeded 55-60 ºC for 2 h under ultrasonic irradiation . In additionally, *p*-methoxymandelic acid (**3b**) was also prepared in a 58 % yield by using the above same reaction conditions (**Scheme-I**).

TABLE-1
SYNTHESIS OF **3a** UNDER SONICATION

Entry	Temperature (ºC)	Ultrasonic radiation frequencies	Base	Amount of TBAB (mmol)	Adding time (h)	Reaction time (h)	Isolated yields (%)
1	35-40	59	NaOH	3	1	0.5	37
2	40-45	59	NaOH	3	1	0.5	35
3	45-50	59	NaOH	3	1	0.5	42
4	50-55	59	NaOH	3	1	1.0	53
5	55-60	59	NaOH	3	1	1.0	58
6	55-60	59	NaOH	3	1	1.5	62
7	55-60	59	NaOH	3	1	2.0	83
8	60-65	59	NaOH	3	1	2.0	72
9	65-70	59	NaOH	3	1	2.0	66
10	70-80	59	NaOH	3	1	2.0	54
11[a]	55-60	59	NaOH	3	1	2.5	51
12[a]	55-60	59	NaOH	3	1	2.0	53
13[c]	55-60	0	NaOH	3	1	2.0	26
14	55-60	59	NaOH	0	1	2.0	35
15	55-60	59	NaOH	2	1	2.0	59
16	55-60	59	NaOH	2.5	1	2.0	78
17	55-60	0	NaOH	2	1	2.0	52
18	55-60	59	KOH	2	1	2.0	79
19	55-60	59	Na_2CO_3	2	1	2.0	0
20	55-60	59	NaOH	3	1	3.0	75
21	55-60	43	NaOH	3	1	2.0	63
22	55-60	59	NaOH	3	0	3.0	53

[a]One-pot reaction, [b]Reaction time, [c]Stirred without sonication and TBAB.

Conclusion

In summary, we have found an efficient and practical procedure for the preparation of mandelic acid and *p*-methoxymandelic acid by using tetrabutyl ammonium bromide as phase transfer catalyst under ultrasonic irradiation.

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