

An Eco-Friendly and Efficient Synthesis of Benzoylformic Acid and Methyl Benzoylformate from Styrene

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The HBr/H₂O₂ system was found to be highly efficient and green catalytic system for the selective oxidation of styrene to benzoylformic acid in excellent yields under water as solvent. The process of etherification is simple, highly efficient and inexpensive by using TiO₂/SO₄²⁻ as catalyst.

Key Words: Styrene, HBr/H₂O₂, Benzoylformic acid, Methyl benzoylformate, TiO₂/SO₄²⁻.

INTRODUCTION

α -Keto acids and their esters are compounds of high practical utility. Because they are versatile intermediates for the synthesis of kinds of important natural products, pharmaceuticals and agrochemicals¹, such as the 3-deoxy-2-ulosonic acids and their derivatives², glycopyrrolate bromide³, α -amino acids⁴ and precursors in the asymmetric synthesis of α -hydroxy carboxylic acids⁵, aryl triazole and triazine type compounds⁶. In addition, α -keto acid esters are also used as extremely important intermediates for the synthesis of bioactive compounds. For example, inhibitors of leukotriene A₄ hydrolase⁷, photopolymerization initiators⁸ and potent inhibitors of proteolytic enzymes⁹. Moreover, α -keto esters also show anti-sunburn effects¹⁰. Especially, they are found in many biologically relevant molecules in recently years¹¹.

In the past several decades, numerous methods have been developed for preparing α -keto acids and their esters. The α -keto acids were prepared *via* oxidation of mandelic acid or acetophenone with potassium permanganate in alkaline solution¹² or with selenium dioxide in dry pyridine¹⁰. They can also be obtained by hydrolyzing of acyl cyanides¹³, α -keto acid oximes or α -keto acid oxime esters¹⁴, dehydropeptides¹⁵, or hydrolyzing of addition products of Grignard reagents with diethyl oxalate¹⁶. Moreover, some other routes were reported including acid-catalyzed cleavage of α -acetyl amino α -methyl esters¹⁷, reaction of acylimidazolides with Grignard reagents followed by hydrolysis of the resulting α -keto acid ester¹⁵, oxidation of α -keto aldehydes in the presence of catalytic amounts of cyanide and an oxidizing agent¹⁸, epoxidation of

diethyl alkylidenemalonates¹⁹ and reaction of aromatic N-oxides with dibromomethyl aryl ketones²⁰.

Several routes were reported to prepare α -keto esters including oxidation of α -hydroxy esters with either PCC or Dess-Martin periodinane²¹, oxidative cleavage of cyano keto phosphoranes²², Friedel-Crafts acylation²³, hydrolysis and esterification of acyl cyanides⁸ and acylation or alkylation of mono-substituted 1,3-dithianes²⁴ and the reaction of organo-metallic species with oxalic ester derivatives²⁵. The most common route for the synthesis of α -keto esters is the reaction of Grignard reagents with oxalyl chloride²⁶. Though many of these methods provide good yields, some have drawbacks such as the use of expensive reagents, harsh reaction conditions, absolutely dry and inert media and tedious work-up procedure leading to the generation of a large amount of toxic waste. Thus, there is a need to develop an operationally simple, safe and widely usable method.

Organic reactions in water have received increasing attention primarily since their environmental acceptability, abundance, low cost, clean and more efficient technologies for the transformations of organic molecules²⁷. Moreover, water also improve reactivity and selectivity that can not be attained in conventional organic solvents²⁸.

With the increasingly environmental consciousness of academia and industry research, searching for more effective oxidants, such as hydrogen peroxide and molecular oxygen, is more necessarily. They are attractive 'green oxidants' offering the advantages such as cheap, environmentally benign, readily available and produces only water as a by-product²⁹.

The HBr/H₂O₂ system has been reported for a number of elegant bromination reactions by Iskra and co-workers³⁰. The direct use of HBr/H₂O₂ for the selective synthesis of bromohydrins from olefins has been reported by Patil *et al.*^{30c-g}. Inspired by these reports, we attempt to explore an unprecedented, mild and simple protocol for the synthesis of benzoylformic acid and methyl benzoylformate from styrene catalyzed by HBr/H₂O₂ in water to be shown in Fig. 1.

EXPERIMENTAL

General experimental procedure for the preparation of TiO₂/SO₄²⁻: 10 g TiO₂ was heated in a muffle furnace at 200 °C for 2 h and cooled at room temperature. Then the obtained TiO₂ was mixed with 50 mL 1 M H₂SO₄ and then fast stirred in a 250 mL three-necked flask for 6 h at room temperature followed standing for 14 h at room temperature. It was filtrated through a Buckner funnel and dried at 110 °C in a dryer for 3 h, then calcined at 450 °C in a muffle furnace for 3 h to obtain solid acid TiO₂/SO₄²⁻ and stored in vacuum desiccator. Using similar method for preparing TiO₂/SO₄²⁻ (0.5 M), TiO₂/SO₄²⁻ (1.5 M), ZrO₂/SO₄²⁻ (0.5 M), ZrO₂/SO₄²⁻ (1.0 M) and ZrO₂/SO₄²⁻ (1.0 M) under different calcinations temperature.

General experimental procedure for the synthesis of 2-bromo-1-phenylethanol from styrene using aqueous HBr/H₂O₂ system: Styrene (1.04 g, 10.0 mmol), water (15 mL),

40 % aqueous HBr (2.43 g, 12.0 mmol, 1.2 equiv) and tetrabutyl ammonium bromide (TBAB) (0.026 g, 2.5 wt % styrene) were placed in a 50 mL three-necked flask. The obtained mixtures were fast stirred for 20 min and 30 % aqueous H₂O₂ (1.70 g, 15.0 mmol, 1.5 equiv) was added dropwise for 1.5 h at room temperature (25 °C). Then it was heated up to 90 °C and continued stirring for 5 h. The processes were monitored by TLC. When the reaction was finished, the mixture was extracted by ethyl acetate. The organic layer was washed with dilute solutions of Na₂S₂O₃ to destroy the excess bromine. Finally, it was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get a crude product. The sample was analyzed by HPLC. Finally, the residue can be purified by silica gel column chromatography using petrol ether-ethyl acetate (95:5) as eluent. Identification of the isolated products was performed by ¹H NMR and melting point data.

General procedure for the synthesis of 2-bromo-1-phenylethanone from styrene: The compound **3** was obtained from the first stage. The above reaction mixture was attained at 90 °C and cooled to room temperature by stirred and another 0.5 equiv of 40 % aqueous HBr (1.01g, 5.0 mmol) was drop-added following by the gradual addition of 1.5 equiv of 30 % aqueous H₂O₂ (1.70 g, 15.0 mmol) for 1 h. Then the mixture was heated up to 90 °C and continued stirring for 3.5 h. Progress of the reaction was monitored by TLC. When the reaction was

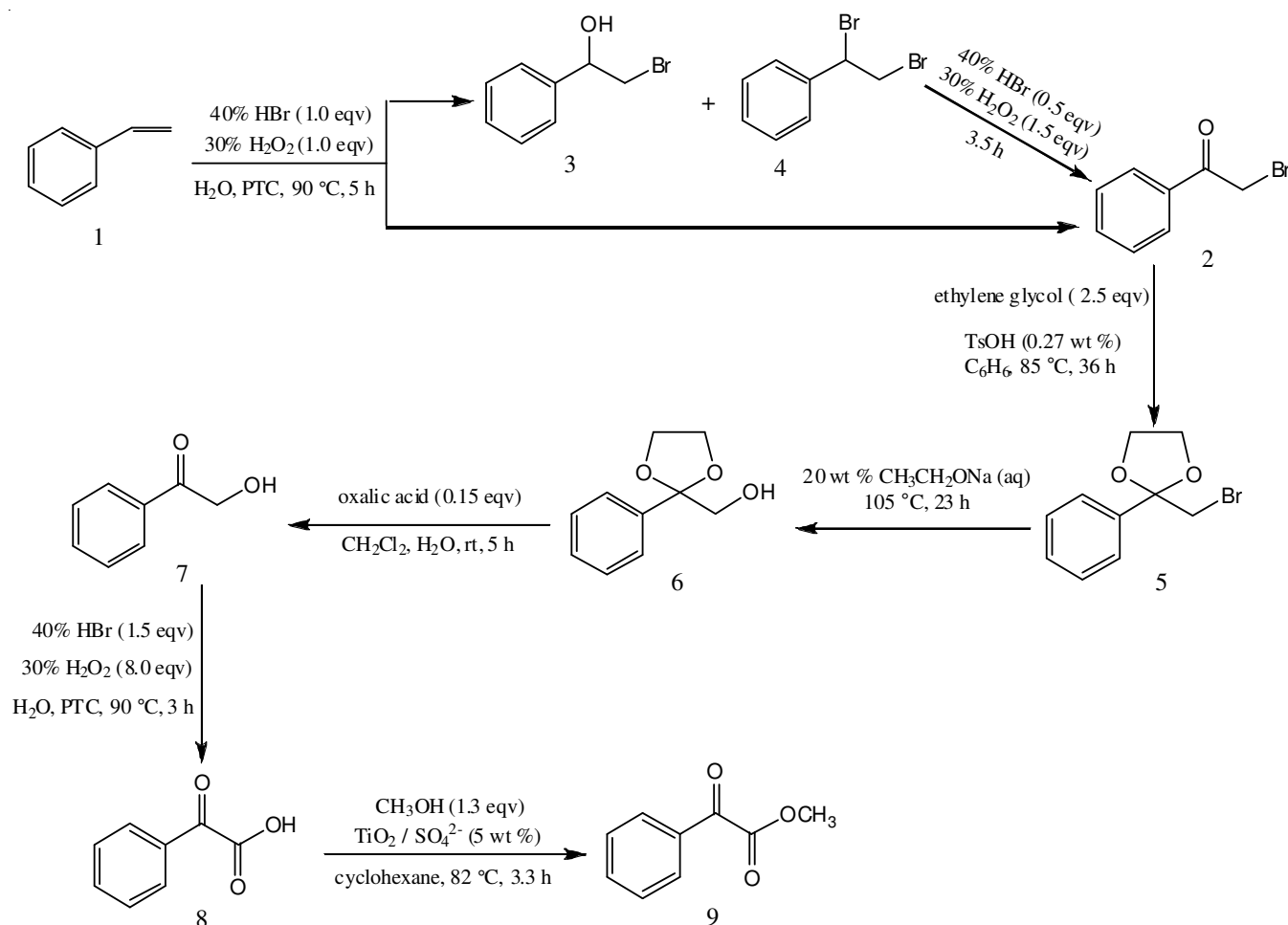


Fig. 1. Six-step sequential procedure to synthesize methyl benzoylformate

finished, dealing the mixture with the same method as mentioned above. Then the sample was analyzed by HPLC. Finally, the residue can be purified by silica gel column chromatography using petrol ether-ethyl acetate (95:5) as eluent. Identification of the isolated products was performed by ^1H NMR and melting point data.

Procedure for the synthesis of 2-bromomethyl-2-phenyl-1,3-dioxolane: 2 (1.39 g, 7.0 mmol), ethylene glycol (1.09 g, 17.5 mmol, 2.5 equiv), toluene-4-sulfonic acid monohydrate (TsOH) (0.038 g, 0.27 wt % 2) and dry benzene (80 mL) were placed in a 250 mL three-necked flask with water segregator. It was heated up to 85 °C and refluxed for 36 h (TLC). The resulting reaction mixture was cooled and dried over anhydrous K_2CO_3 and filtrated through a Buchner funnel and washed with benzene (10 mL). Then, the organic solvent was evaporated under reduced pressure to afford crude product. Then the sample was analyzed by HPLC. The residue can be purified by silica gel column chromatography using petrol ether-ethyl acetate (95:5) as eluent. Identification of the isolated product was performed by melting point data.

Procedure for the synthesis of 2-hydroxymethyl-2-phenyl-1, 3-dioxolane: 5 (1.46 g, 6 mmol), $\text{CH}_3\text{CH}_2\text{ONa}$ 20 wt % solution (10 mL) and TBAB (0.037 g, 2.5 wt % 5) were placed in a 50 mL three-necked flask. The above mixture was refluxed for 23 h (TLC). After completion of the reaction, the mixture was neutralized with dilute solutions of HCl and extracted with ethyl acetate (10 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 and filtrated through a Buchner funnel and washed with ethyl acetate (10 mL). Then, the organic solvent was evaporated under reduced pressure to afford a crude product. Then the sample was analyzed by HPLC. The crude product was purified by silica gel column chromatography using petrol ether-ethyl acetate (95:5) as eluent. Identification of the isolated products was performed by melting point data.

Procedure for the synthesis of 2-hydroxy-1-phenylethanone: 6 (0.90 g, 5 mmol), oxalic acid (0.095 g, 0.75 mmol), H_2O (5 mL), dichloromethane (5 mL) were placed in a 50 mL three-necked reaction flask. The obtained mixture was stirred for 5 h (TLC) at room temperature. After completion of the reaction, the organic layer was withdrawn and washed with dichloromethane (10 mL). It was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get a crude product. Then the sample was analyzed by HPLC. Finally, the residue can be purified by silica gel column chromatography using petrol ether-ethyl acetate (95:5) as eluent. Identification of the isolated products was performed by ^1H NMR and melting point data.

Procedure for the synthesis of benzoylformic acid: 7 (1.36 g, 10.0 mmol), water (10 mL), TBAB (0.034 g, 2.5 wt % 7) and 40 % aqueous HBr (3.03 g, 15.0 mmol, 1.5 equiv) were placed in a 100 mL three-necked reaction flask. The mixture was stirred for a minute and 30 % aqueous H_2O_2 (9.07 g, 80.0 mmol, 8 equiv) was added drop-wise for 2 h at room temperature. Then the above reaction mixture was heated up to 90 °C and continued stirring for 3 h. Procedure of the reaction was monitored by TLC. The resulting reaction mixture was cooled by stirred. To isolate the product, it was extracted with ethyl

acetate (15 mL \times 3). The combined organic layers were washed with dilute solutions of $\text{Na}_2\text{S}_2\text{O}_3$. Then removing the organic solvent by evaporation and 2 mol/L sodium hydroxide solution was added to the residue and some ethyl acetate followed. Subsequently 36-38 % concentrated hydrochloric acid was put into the mixture drop-wise and benzoylformic acid was separated out. Then the sample was analyzed by HPLC. Finally, the residue can be purified by silica gel column chromatography using petrol ether-ethyl acetate (95:5) as eluent. Identification of the isolated products was performed by ^1H NMR and melting point data.

Procedure for the synthesis of methyl benzoylformate: 8 (1.50 g, 10.0 mmol), anhydrous methanol (0.42 g, 13.0 mmol, 1.3 equiv), $\text{TiO}_2/\text{SO}_4^{2-}$ (0.08 g, 5 wt % 8) and cyclohexane as water-carrying agent (10 mL) were placed in a 50 mL three-necked reaction flask with water segregator. The above reaction mixture was then refluxed for 3.3 h (TLC). The resulting reaction mixture was cooled, filtrated through a Buckner funnel and washed with anhydrous methanol (10 mL). Then, the organic solvent was evaporated under reduced pressure to afford a crude product. Then the sample was analyzed by HPLC. The residue was purified by silica gel column chromatography using petrol ether-ethyl acetate (95:5) as eluent to afford corresponding methyl benzoylformate. Identification of the isolated products was performed by ^1H NMR and melting point data.

2-Bromo-1-phenylethanone: White solid. m.p. 70-71 °C. ^1H NMR (400 MHz, CDCl_3): δ = 8.27-8.10 (m, 2H), δ = 7.89-7.78 (m, 1H), δ = 7.65-7.60 (m, 2H), δ = 4.39 (s, 2H).

2-Bromo-1-phenylethanol: Pale yellow oil. ^1H NMR (400 MHz, CDCl_3): δ = 7.39-7.23 (m, 5H), δ = 4.91-4.86 (m, 1H), δ = 3.63-3.45 (m, 2H), δ = 2.82 (s, 1H).

1,2-Dibromoethyl benzene: Pale yellow solid. m.p. 48-49 °C. ^1H NMR (400 MHz, CDCl_3): δ = 7.60 (t, 2H), δ = 7.43 (t, 1H), δ = 7.37-7.33 (m, 2H), δ = 5.15 (t, 1H), δ = 4.11-3.99 (m, 2H).

2-Hydroxy-1-phenylethanone: Pale yellow solid. m.p. = 86-87 °C. ^1H NMR (400 MHz, CDCl_3): δ = 8.01-7.94 (m, 2H), δ = 7.70-7.64 (m, 1H), δ = 7.58-7.56 (m, 2H), δ = 4.79 (s, 2H), δ = 3.65 (s, 1H).

Benzoylformic acid: White solid. m.p. = 62-63 °C. ^1H NMR (400 MHz, CDCl_3): δ = 9.19 (s, 1H), δ = 8.04-8.01 (m, 2H), δ = 7.73-7.70 (m, 1H), δ = 7.54-7.52 (m, 2H).

Methyl benzoylformate: pale yellow oil. ^1H NMR (400 MHz, CDCl_3): δ = 8.04-8.01 (m, 2H), δ = 7.73-7.70 (m, 1H), δ = 7.54-7.52 (m, 2H), δ = 3.76 (s, 3H).

RESULTS AND DISCUSSION

The system of HBr/ H_2O_2 with styrene to provide 2-bromo-1-phenylethanone **2** was investigated. Optimization of reaction conditions for synthesis of **2** from styrene **1** using HBr/ H_2O_2 system by one-pot method was studied. The conversion, yield of the oxidation and selectivity under different conditions were summarized in Table-1.

The effect of different solvents under similar reaction conditions was evaluated and the results were summarized in Table-1, entries 1-10. When the reaction was carried out with *n*-hexane as solvent with 1.7 equiv of 40 % aqueous HBr, the

TABLE-1
OPTIMIZATION OF REACTION CONDITIONS FOR SYNTHESIS OF **2** FROM **1**
USING HBr/H₂O₂ SYSTEM BY ONE-POT METHOD^a

Entry	Reaction conditions ^b		Time (h) ^c	Conv. (%) ^d	Yield (%) ^e	Product ratio (%) ^f		
	H ₂ O ₂ -Bromine source (mmol:mmol)	Solvent				2	3	4
1 ^g	3H ₂ O ₂ -1.7HBr	<i>n</i> -Hexane	8.0	>99	87.4	52.7	20.8	26.5
2 ^g	3H ₂ O ₂ -1.7HBr	Cyclohexane	7.5	>99	97.3	14.3	5.9	79.8
3 ^g	3H ₂ O ₂ -1.7HBr	CCl ₄	9.5	>99	75.0	28.6	5.2	66.2
4 ^g	3H ₂ O ₂ -1.7HBr	Benzene	9.0	>99	78.9	75.7	19.6	4.7
5 ^g	3H ₂ O ₂ -1.7HBr	CH ₂ Cl ₂	9.5	>99	63.7	70.9	28.9	0.2
6 ^g	3H ₂ O ₂ -1.7HBr	THF	8.5	>99	76.0	74.3	20.4	5.3
7 ^g	3H ₂ O ₂ -1.7HBr	CHCl ₃	7.5	>99	78.4	13.7	54.9	31.4
8 ^g	3H ₂ O ₂ -1.7HBr	Acetonitrile	7.0	>99	81.5	8.3	48.6	43.1
9 ^g	3H ₂ O ₂ -1.7HBr	DMSO	10.5	>99	73.0	80.5	18.7	0.8
10 ^g	3H ₂ O ₂ -1.7HBr	H ₂ O	18.0	>99	92.3	93.8	3.4	2.8
11 ^h	3H ₂ O ₂ -1.7HBr	H ₂ O	11.0	>99	94.0	94.7	5.3	–
12 ^h	3H ₂ O ₂ -1.7KBr	H ₂ O	12.5	>99	86.1	92.4	7.6	–
13 ^h	3H ₂ O ₂ -1.7NaBr	H ₂ O	12.0	>99	85.3	90.4	8.9	0.7
14 ^{h,i}	3H ₂ O ₂ -0.85Br ₂	H ₂ O	10.0	>99	86.7	77.4	4.7	17.9
15 ^h	3H ₂ O ₂ -1.7NBS	H ₂ O	12.5	>99	92.3	96.7	2.7	0.6
16 ^j	3H ₂ O ₂ -1.7HBr	H ₂ O	11.5	>99	91.4	91.7	1.5	6.8
17 ^j	3H ₂ O ₂ -1.7HBr	H ₂ O	10.5	>99	84.7	89.6	7.2	3.2
18 ^j	3H ₂ O ₂ -1.7HBr	H ₂ O	9.5	>99	91.2	92.2	3.7	4.1
19 ^j	3H ₂ O ₂ -1.7HBr	H ₂ O	15.5	>99	83.9	85.8	6.3	7.9
20 ^h	3H ₂ O ₂ -1.5HBr	H ₂ O	14.0	>99	87.3	79.3	20.4	0.3
21 ^h	3H ₂ O ₂ -2HBr	H ₂ O	10.5	>99	90.3	79.4	16.4	4.2
22 ^{h,k}	3H ₂ O ₂ -1.7HBr	H ₂ O	52.0	34.6	23.7	15.1	67.4	17.5
23 ^{h,k}	3H ₂ O ₂ -1.7HBr	H ₂ O	47.0	56.9	34.6	39.2	47.6	13.2
24 ^{h,k}	3H ₂ O ₂ -1.7HBr	H ₂ O	21.5	67.3	65.6	95.5	4.5	–
25 ^{h,k}	3H ₂ O ₂ -1.7HBr	H ₂ O	9.5	>99	83.8	98.6	1.4	–

^aAll reactions were carried out using one-pot method. ^bReaction conditions: styrene (1.04 g, 10.0 mmol), 30 % aqueous H₂O₂ (3.40 g, 30.0 mmol, 3.0 equiv) and solvent (15 mL) at 90 °C, unless otherwise noted. ^cMonitored by TLC until all the styrene was consumed. ^dDetermined by HPLC. ^eCombined yield of **2**, **3** and **4** based on consumed **1**. ^fCalculated from HPLC peak areas, excluding by-products. ^gPhase transfer catalyst (PTC) was not added for entries 1-10. ^hTBAB (0.026 g, 2.5 wt % styrene) was added for entries 11-15 and 20-25. ⁱStyrene (1.04 g, 10.0 mmol), water (15 mL), 30% aqueous H₂O₂ (1.70 g, 15.0 mmol, 1.5 equiv) and TBAB (0.026 g, 2.5 wt % styrene) were placed in a 50 mL three-necked reaction flask. The obtained mixture was stirred quickly for 20 min and Br₂ (0.96 g, 6.0 mmol, 0.6 equiv) was added drop-wise for 1.5 h at room temperature (25 °C). Then the reaction mixture was heated up to 90 °C and continued stirring for 5 h, and then cooled to room temperature under stirring, and another 1.5 equiv of 30 % aqueous H₂O₂ (1.70 g, 15.0 mmol) was added followed by the gradual addition of 0.25 equiv of Br₂ (0.40 g, 2.5 mmol) during 1 h. Then the reaction mixture was heated up to 90 °C and lasted for 3.5 h. ^jTetrabutyl ammonium chloride (TBAC), polyethylene glycol-200 (PEG-200), PEG-400 and PEG-20000 was added for entries 16-19, respectively. Their amounts were 2.5 wt % styrene. ^kThe reactions temperature were 0, °C, 25 °C (r.t.), 50 and 100 °C for entries 22-25, respectively.

products **2**, **3** and 1,2-dibromo-1-phenylethane **4** were obtained in 52.7, 20.8 and 26.5 % yields, respectively (by HPLC) (Table-1, entry 1). When the reaction was performed in cyclohexane and CCl₄ (entries 2 and 3), the yield of product **2** was reduced to 14.3 and 28.6 %, **4** being the major product in 79.8 and 66.2 % along with 5.9 and 5.2 % of product **3**, respectively. However, when the reaction was conducted in benzene, CH₂Cl₂, tetrahydrofuran, dimethyl sulfoxide and H₂O, respectively (entries 4-6 and 9-10), gave product **2** in 75.7, 70.9, 74.3, 80.5 and 93.8 % yields as major product, respectively, **3** in 19.6, 28.9, 20.4, 80.5 and 93.8 % yields and **4** in 4.7, 0.2, 5.3, 0.8 and 2.8 % yields. Whereas chloroform and acetonitrile provided desired product **2** in 13.3 and 8.3 % yields, respectively and products **3** and **4** were obtained as major ones (entries 7 and 8). The results clearly indicated that the best yield of the desired product could be obtained in water with 1.7 equiv of 40 % aqueous HBr.

To evaluate the effect of various bromine sources, the oxidation of **1** was studied using catalytic amount of different bromine sources (the dosage was equal to HBr) in place of aqueous HBr with 30 % aqueous H₂O₂ as an oxidant under

similar reaction conditions and the results were presented in Table-1, entries 11-15. Although the use of salts such as NaBr, KBr and N-bromosuccinimide (NBS) obtained good yields (Table-1, entry 12, 13 and 15), the use of molecular bromine gave poor ratio of product **2** (77.4 %) (Table-1, entry 14). Nevertheless, N-bromosuccinimide was more expensive than others. The discussion distinctly indicated that the excellent yield of the target product **2** could be achieved with 1.7 equiv 40 % aqueous HBr as catalyst (Table-1, entry 11).

As shown in Table-1, entries 11, 20 and 21, changing the molar ratios of styrene/H₂O₂/HBr can significantly alter the ratios of products **2**, **3** and **4**. By increasing the amount of HBr from 1.5-2.0 equiv of styrene, the yield (by HPLC) of **2** was increased from 79.3-94.7 % (Table 1, entries 11, 20 and 21). The selectivity towards formation of more useful **2** was generally obtained in dramatical yield (94.7 %), low **3** (5.3 %) and without **4**, when styrene/H₂O₂/HBr was maintained at the ratio 1:3:1.7 (Table-1, entry 11). Therefore, we chose the molar ratios of styrene/H₂O₂/HBr as 1:3:1.7 for preparing **2**.

For further shortening reaction time, we used kinds of phase transfer catalysts in a two-phase system (aqueous and

organic) (Table-1, entries 10-11 and 16-19). Reaction time was markedly shortened by using tetrabutyl ammonium bromide (TBAB) with 2.5 wt % of styrene (Table-1, entries 10-11). Although the reaction time can be further decreased by using polyethylene glycol-400 (PEG-400) (Table-1, entry 18), the yield and the ratios of products **2** were lower than using TBAB (Table-1, entry 11). Accordingly, we chose TBAB as phase transfer catalysts for synthesizing **2** from **1** under HBr/H₂O₂ system.

The effect of different reaction temperature under similar reaction conditions was evaluated and the results were presented in Table-1, entries 11 and 22-25. When the reaction was carried out at 0 °C, 25 °C (room temperature) with water as solvent with 1.7 equiv of 40 % aqueous HBr, the product ratio (by HPLC) were reduced to 34.6 and 56.9 %, respectively (Table-1, entries 22, 23), only gave target product **2** in 15.1 and 39.2 % yields, **3** being the major product in 67.4 and 47.6 % along with 17.5 and 13.2 % of product **4**, respectively and reaction spent much more time. When the reaction was performed at 50, 90 and 100 °C (entries 11, 24 and 25), the reaction conversion and the yield of products markedly increased. Especially, styrene was efficiently converted to the desired product **2** in excellent yields (95.5, 94.7 and 98.6 %). Increasing the reaction temperature could improve conversion and yield of target product and also could shorten reaction time. The best reaction time and temperature for preparing **2** was found to be 11.0 h at 90 °C with water as solvent (Table-1, entry 11).

As shown in **Scheme-II**, HBr reacted with H₂O₂ and produced free bromine. The generated bromine continued the bromination process and oxidized by H₂O₂ to give the corresponding **2** resulting in moderate to good yield.

For avoiding **2** to take place the aldol reaction in the presence of aqueous bases, we converted **2** into 2-bromomethyl-2-phenyl-1,3-dioxolane **5** by ethylene glycol/TsOH with benzene as solvent at 85 °C and **5** could be obtained in 91 % yield (by HPLC). The crude product was recrystallized by dichloromethane. The purified **5** was hydrolyzed by kinds of aqueous bases to give 2-hydroxymethyl-2-phenyl-1,3-dioxolane **6**. The effect of various base sources under similar reaction conditions was evaluated and the results were presented in Table-2. All the reaction conversions (by HPLC) were almost 100 %. Product **6** could be obtained in excellent yield from 76.4-87.0 % and reaction time was significantly shortened from 44.0-8.0 h (Table-2). When the reaction was carried out under aqueous CH₃CH₂ONa, the hydrolytic process tended to proceed more rapidly and cleanly, gave in excellent yields (87.0 %). Hence, the best reaction condition was chosen (Table-2, entry 7). Subsequently, product **6** was translated into 2-hydroxy-1-phenylethanone **7** in acid solution without purification.

The reaction conditions for synthesis of benzoylformic acid **8** from **7** by using HBr/H₂O₂ system were optimized and the results were summarized in Table-3. By changing the molar ratio of H₂O₂/HBr can markedly alter reaction conversion, yield of **8** and reaction time. By increasing the dosage of H₂O₂ from 1.5-9.0 equiv of HBr, the reaction conversion (by HPLC) was significantly increased from 54.0 % to almost 100 % and product **8** was obtained in good yield from 35.7-78.7 % and reaction time was markedly reduced from 16.0-5.0 h (Table-3).

TABLE-2
EFFECT OF VARIOUS BASE SOURCES FOR
PREPARING OF **6** BY HYDROLYSIS OF **5**^a

Entry	Base source	Time (h) ^b	Conv. (%) ^c	Yield (%) ^d
1	NaHCO ₃	44.0	>99	76.4
2	Na ₂ CO ₃	32.5	>99	80.3
3	K ₂ CO ₃	23.0	>99	82.0
4 ^e	K ₂ CO ₃	28.0	>99	78.2
5 ^e	K ₂ CO ₃	20.3	>99	83.4
6	NaOH	9.5	>99	85.7
7	CH ₃ CH ₂ ONa	8.0	>99	87.0

^aReaction conditions: 2-bromomethyl-2-phenyl-1,3-dioxolane **5** (1.46 g, 6 mmol), 20 wt % base solution (10 mL) and TBAB (0.037 g, 2.5 wt % **5**) under reflux conditions. ^bMonitored by TLC until all the **5** was consumed. ^cDetermined by HPLC. ^dCalculated from HPLC peak areas, excluding by-products. ^e10 wt % base solution and 30 wt % base solution were added for entries 4 and 5, respectively.

TABLE-3
OPTIMIZATION OF REACTION CONDITIONS FOR
SYNTHESIS OF **8** FROM **7** USING HBr/H₂O₂ SYSTEM

Entry	Reaction conditions ^a	Time (h) ^b	Conv. (%) ^c	Yield (%) ^d
1	1.5HBr-1.5H ₂ O ₂	16.0	54.0	35.7
2	1.5HBr-3H ₂ O ₂	16.0	69.5	44.8
3	1.5HBr-4.5H ₂ O ₂	12.0	78.6	53.1
4	1.5HBr-5.5H ₂ O ₂	9.0	86.8	68.3
5	1.5HBr-7H ₂ O ₂	7.0	95.7	74.7
6	1.5HBr-8H ₂ O ₂	5.0	>99	83.0
7	1.5HBr-9H ₂ O ₂	5.0	>99	78.7

^aReaction conditions: **7** (1.36 g, 10.0 mmol), water as solvent (10 mL), TBAB (0.034 g, 2.5 wt % **7**) and 40 % aqueous HBr (3.03 g, 15.0 mmol, 1.5equiv) at 90 °C. ^bMonitored by TLC until all the **5** was consumed. ^cDetermined by HPLC. ^dCalculated from HPLC peak areas, excluding by-products.

Accordingly, the best reaction condition was chosen (Table-3, entry 7).

The reaction conditions for synthesis of methyl benzoylformate **9** from **8** using solid superacid as catalyst were optimized. The reaction conversion, yield of the **9** and reaction time under different conditions were summarized in Table-4. As shown in Table-4, entries 1-3, raising the sulfuric acid concentration significantly increased the yield (by HPLC) of product from 72.5-87.2 % and markedly shortened reaction time from 5.0-3.2 h. The effect of different calcination temperature under similar reaction conditions was evaluated and the results were presented in Table-4, entries 3-6. When calcination temperature was 500 °C, good yield of the product **9** was obtained. The effect of various water-carrying agent was evaluated (Table-4, entries 2 and 7, 8). When the reaction was performed with cyclohexane, benzene and toluene as water-carrying agent, the yield of **9** was obtained in 87.6, 88.0 and 85.3 % yields, respectively. Although the use of benzene as water-carrying agent gave a little higher yield than cyclohexane, cyclohexane was little poisonous. By changing the molar ratio of **8** and anhydrous methanol significantly altered the yield of **9** (Table-4, entries 3 and 9, 10). The **9** was given in 87.2, 64.3 and 88.1 % yields. The gradual increase of the dosage of solid superacid 2, 5, 8 and 10 wt % of the **8** and gave **9** in 71.3, 87.2, 87.3 and 85.8 % yields, respectively (Table-4, entries 3 and 11-13). The effect of various solid superacids was evaluated

TABLE-4
OPTIMIZATION OF REACTION CONDITIONS FOR SYNTHESIS OF **9** FROM **8** USING SOLID SUPERACID CATALYST

Entry	Reaction conditions ^a			Time (h) ^b	Conv. (%) ^c	Yield (%) ^d
	c(H ₂ SO ₄) (mol/L)	Solid super acid source	Calcination temp. (°C)			
1 ^e	0.5	TiO ₂ /SO ₄ ²⁻	500	5.0	>99	72.5
2 ^e	1.0	TiO ₂ /SO ₄ ²⁻	500	3.3	>99	87.6
3 ^e	1.5	TiO ₂ /SO ₄ ²⁻	500	3.2	>99	87.2
4 ^e	1.0	TiO ₂ /SO ₄ ²⁻	400	7.6	>99	63.1
5 ^e	1.0	TiO ₂ /SO ₄ ²⁻	450	6.5	>99	85.0
6 ^e	1.0	TiO ₂ /SO ₄ ²⁻	550	8.0	>99	79.4
7 ^f	1.0	TiO ₂ /SO ₄ ²⁻	500	3.1	>99	88.0
8 ^f	1.0	TiO ₂ /SO ₄ ²⁻	500	3.6	>99	85.3
9 ^{e-g}	1.0	TiO ₂ /SO ₄ ²⁻	500	13	85.0	64.3
10 ^{e-g}	1.0	TiO ₂ /SO ₄ ²⁻	500	3.2	>99	88.1
11 ^{e,h}	1.0	TiO ₂ /SO ₄ ²⁻	500	5.5	91.0	71.3
12 ^{e,h}	1.0	TiO ₂ /SO ₄ ²⁻	500	3.3	>99	87.3
13 ^{e,h}	1.0	TiO ₂ /SO ₄ ²⁻	500	3.7	>99	85.8
14 ^e	0.5	ZrO ₂ /SO ₄ ²⁻	550	4.6	>99	84.9
15 ^e	1.0	ZrO ₂ /SO ₄ ²⁻	550	5.7	>99	77.3
16 ^e	1.5	ZrO ₂ /SO ₄ ²⁻	550	6.3	>99	74.1

^aReaction conditions: **8** (1.50 g, 10.0 mmol), anhydrous methanol (0.42 g, 13.0 mmol, 1.3 equiv), and solid superacid weight (5 wt % **8**) and water-carrying agent (10 mL) under reflux conditions. ^bMonitored by TLC until all the styrene was consumed. ^cDetermined by HPLC. ^dCalculated from HPLC peak areas, excluding by-products. ^eCyclohexane as water-carrying agent for entries 1-6 and 9-16. ^fBenzene and toluene were used as water-carrying agent for entries 7 and 8, respectively. ^g**8** (1.50 g, 10.0 mmol), n (**8**): n(anhydrous methanol) = 1:1 and n (**8**): n(anhydrous methanol) = 1:1.5 for entries 9 and 10, respectively. ^hSolid superacid weight of 2 wt % **8**, 8 wt % **8** and 10 wt % **8** were added for entries 11-13, respectively.

and the results were presented in Table-4, entries 1-6 and 14, 15. The results clearly indicated that the good yield of the desired product **9** could be obtained by using TiO₂/SO₄²⁻ (1 M H₂SO₄) calcined at 500 °C, amount of 5 wt % **8** with 1.3 equiv of anhydrous methanol and cyclohexane as water-carrying agent.

Conclusion

In summary, a novel method for preparing benzoylformic acid *via* using the aqueous HBr/H₂O₂ system with water as solvent serves as an efficient and green reagent was discovered. In addition, compared to conventional methods by direct oxybromination of styrene **1**, this procedure offered significant improvements with regard to reaction conditions, excellent yield and user-friendly operation and avoiding the use of hazardous molecular bromine. Solid superacid was used as catalyst in the esterification step. This was a simple, highly efficient and inexpensive catalytic method. Further investigations to expand the scope of this reaction are currently under active investigation in our laboratory.

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