



Efficient Synthesis of Benzoylformic Acid Under Mild Conditions

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A new highly efficient synthesis protocol for benzoylformic acid was developed. Of three steps a key unit involved oxidation using clean aqueous hydrogen peroxide and hydrogen bromide systems.

Keywords: Benzoylformic acid, Oxidation, Hydrogen peroxide, Hydrogen bromide synthesis.

INTRODUCTION

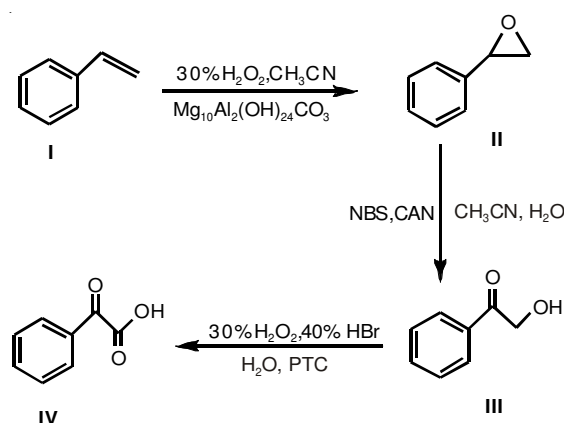
Benzoylformic acid and its esters have been widely applied to synthesize kinds of important natural analogues, pharmaceuticals and agrochemicals¹, such as the 3-deoxy-2-ulonic acids and their derivatives² and glycopyrrolate bromide³, etc. In the past several decades, the α -keto acids were prepared via oxidation of mandelic acid or acetophenone with potassium permanganate in alkaline solution⁴ or with selenium dioxide in dry pyridine⁵. Likewise they could be obtained by hydrolyzing of acyl cyanides⁶.

The clean aqueous hydrogen peroxide and hydrogen bromide systems have been studied for various elegant bromination and oxidation reactions by Iskra and co-workers⁷. Since aqueous hydrogen peroxide can be converted water of environmental economy once performing its functions. Moreover the development of chemical reactions involving aqueous reagents shows some advantages over the use of organic solvents⁸.

Inspired by these reports, we developed environmentally benign procedures of high atom economy in the preparation of title compound. The novel route could be conveniently used for industrial preparation (Scheme-I).

EXPERIMENTAL

Melting points were determined on a WPS-2 melting point apparatus and were uncorrected. ¹H NMR spectra were recorded on a Bruker Avance (400 MHz) spectrometer using CDCl₃ as the solvent. Spots were visualized with UV. HPLC (Shimadzu LC-10Avp Plus) and GC (Shimadzu GC-2014C) were utilized to determine product compositions. All chemicals were analytical grade without further purification.



Procedure for preparation of hydrotalcites¹⁵: To a solution of Al(NO₃)₃·9H₂O (0.01 mol) and Mg(NO₃)₂·6H₂O (0.05 mol) dissolved in deionized water (100 mL) were dropwise added a solution of sodium carbonate (0.03 mol) and sodium hydroxide (0.07 mol) in deionized water (60 mL). The resulting mixture was heated at 65 °C for 18 h with vigorous stirring. The white slurry at room temperature was filtered out, followed by washing and drying over night at 110 °C. And then the sample was calcined at 450 °C for 18 h in order to produce high decomposition of the anions located in the inter-layer space of the hydrotalcite. Hydrotalcite in constitution of Mg₁₀Al₂(OH)₂₄CO₃ were formed to use for reaction catalyst.

Procedure for synthesis of styrene epoxide: Into a reaction vessel with I (0.67 g, 6.4 mmol) successively placed catalyst (0.15 g) and acetonitrile (5 mL) was added dropwise 30 % aqueous hydrogen peroxide (2.4 mL) with stir at 25 °C during 1.5 h of period. Then the mixture was raised to 60 °C with stir

for an appropriate time. The catalyst was separated by filtration. GC quantitative analyses of the filtrate extracts showed yield of styrene oxide. The filtrate was diluted with deionized water (50 mL) and extracted with ethyl acetate (10 mL \times 3). The combined organic phase was concentrated and subjected to column chromatography on silica gel with a mixture of *n*-hexane/ethyl acetate (10:1) which afforded pure epoxides.

Procedure for synthesis of 2-hydroxy-1-phenylethanone:

Into the solution of **II** (0.20 g, 1.6 mmol) in mixtures (5 mL) of acetonitrile and water in 9:1 (v/v) was added cerium ammonium nitrate (0.20 g, 0.36 mmol) then bromine sources (1 g) at 30 °C with stir. After completion of the reaction, the mixture was diluted with water and extracted with ethyl acetate (10 mL \times 3). The combined organic extract was dried over sodium sulfate and concentrated under vacuum. The product **III** was purified by column chromatography on silica gel using *n*-hexane/ethyl acetate (10:1) as eluent.

Procedure for synthesis of benzoylformic acid: Into a three-necked reaction flask with a reflux condenser were successively placed **III** (0.45 g, 3.3 mmol), water (10 mL), phase transfer catalyst (0.01 g) and 40 % aqueous hydrogen bromide (0.75 g, 5 mmol). Then 30 % aqueous hydrogen peroxide (3 g, 26.7 mmol) was added dropwise to the mixture at room temperature in no less than 0.5 h. The reaction was maintained at 65 °C for defined time with vigorous stirring by TLC track. After reaction, the mixture was cooled to room temperature and product was extracted with ethyl acetate (15 mL \times 3). The combined organic layer was washed with dilute solutions of sodium thiosulfate and dried with anhydrous sodium sulfate. The sample was purified by silica gel column chromatography using petroleum ether/ethyl acetate (95:5) as eluent.

Styrene epoxide (II): Pale oil; ¹H NMR (400 MHz, CDCl₃): δ = 7.33-7.30 (m, 5H), 3.9 (t, 1H), 3.1 (t, 1H), 2.8 (t, 1H).

2-Hydroxy-1-phenylethanone (III): Pale yellow solid; m.p. = 86-87 °C. ¹H NMR (400 MHz, CDCl₃): δ = 8.01-7.94 (m, 2H), 7.70-7.64 (m, 1H), 7.58-7.56 (m, 2H), 4.79 (s, 2H), 3.65 (s, 1H).

Benzoylformic acid (IV): White solid; m.p. = 62-63 °C. ¹H NMR (400 MHz, CDCl₃): δ = 9.19 (s, 1H), 8.04-8.01 (m, 2H), 7.73-7.70 (m, 1H), 7.54-7.52 (m, 2H).

RESULTS AND DISCUSSION

First of all, the feedstock styrene (**I**) was conveniently transferred styrene epoxide (**II**) by employing aqueous hydrogen peroxide as oxidant over various catalysts shown in Table-1.

It could be seen that the selectivity of epoxidation in a 91.0 % of substrate conversion could reach relatively high level in a yield of 73.4 % over hydrotalcite catalyst (entry 2 in Table-1) compared with blank and other solids. From Table-1, epoxidation was rather feeble in the absence of any catalyst (entry 1 in Table-1). Surprisingly, the reaction selections were poor to epoxidation although a 100 % conversion could be obtained in the presence of metal ion-exchanged zeolites catalysts (entries 5-8 in Table-1). We also selected metal oxides as catalysts to apply to the preparation of styrene epoxide (entries 9, 10 in Table-1). And 22.1 and 52.8 % yields in low substrate

TABLE-1
SYNTHESIS OF STYRENE EPOXIDE
UNDER VARIOUS CATALYSTS

Entry	Catalyst	Conversion ^a (%)	Yield ^{ab} (%)
1	–	> 99	Trace
2	Mg ₁₀ Al ₂ (OH) ₂₄ CO ₃	91.0	73.4
3 ^c	Mg ₁₀ Al ₂ (OH) ₂₄ CO ₃	95.0	86.4 ^d
4 ^e	Mg ₁₀ Al ₂ (OH) ₂₄ CO ₃	87.0	82.6
5	CuBEA-25	> 99	9.0
6	CoBEA-25	> 99	17.1
7	CuZSM-5	> 99	11.0
8	CoZSM-5	> 99	11.9
9 ^f	MoO ₃	22.5	22.1
10	MgO	39.2	52.8

^aDetermined by GC using an internal standard technique; ^bBased on the styrene; ^cThe reaction was carried out with acetonitrile-benzene media of volume ratio of 1 : 9 instead of acetonitrile as the solvent; ^dIsolated yield; ^eThe reaction was carried out with acetonitrile-formamide media of volume ratio of 1 : 9 instead of acetonitrile as the solvent; ^fThe reaction was carried out with tert-butyl hydroperoxide (2.4 mL) instead of aqueous hydrogen peroxide as the solvent

conversion were only obtained respectively. Therefore much attention has been focused on developing the novel catalytic processes based on efficient hydrotalcite catalysts with easy workup. In the presence of Mg₁₀Al₂(OH)₂₄CO₃ in acetonitrile-benzene media of volume ratio of 1:9, the yield of styrene epoxide could be promoted to 86.4 % of isolated yield in a 95 % substrate conversion (entry 3 in Table-1). Similarly the yield could be raised to 82.6 % in acetonitrile-formamide media of volume ratio of 1:9 (entry 4 in Table-1). It is likely that the Brønsted basic sites derived from surface hydroxyl groups on the hydrotalcite play an important role in the epoxidation of olefins in the presence of nitriles⁹⁻¹³.

Next, the synthesis of the desired *a*-hydroxyketone(**III**) began with substrate **II** using Rao's procedure¹⁴. A 96 % of yield was achieved with 30 % aqueous hydrogen peroxide, cerium ammonium nitrate (CAN) and *N*-bromosuccinimide in acetonitrile and water media (entry 1 in Table-2). It was found that *N*-bromosuccinimide in reaction media play a key role in promoting reaction selectivity. Especially, the moisture was imperative since only trace of product was detected by high performance liquid chromatography under anhydrous conditions (entry 2 in Table-2). Other various bromine sources such as potassium bromide, sodium bromide and hydrogen bromide under similar conditions gave poor yield of α -hydroxyketone (entries 3-5 in Table-2).

TABLE-2
SYNTHESIS OF 2-HYDROXY-1-PHENYLETHANONE
UNDER SOME BROMINATION REAGENTS

Entry	Bromination reagent	Time (h)	Conversion ^a (%)	Yield ^a (%)
1	NBS	4	> 99	96.0 ^b
2 ^c	NBS	10	> 99	Trace
3	HBr	4.5	> 99	16.6
4	KBr	5	> 99	59.6
5	NaBr	4.5	> 99	19.2

^aCalculated from HPLC peak area

Finally, the formation of benzoylformic acid (**IV**) was extensively optimized under reaction conditions involving different amount ratios of **III** to aqueous hydrogen peroxide,

etc. by the promotion of 40 % aqueous hydrogen bromide in the presence of phase transfer catalysts (PTC). It was found that the conversion of **III** was promoted from partial conversion of 57 to full conversion of 99 % above with the increase in ratio of **III** to aqueous hydrogen peroxide from 1 to 10 (Table-3). However a 90.1 % IV of maximum yield was achieved in the molar ratio of aqueous hydrogen peroxide to **III** of 8 over PEG400 (entry 3 in Table-3). Large excess amounts of aqueous hydrogen peroxide did not improve the yield actively.

TABLE-3
SYNTHESIS OF BENZOYLFORMIC ACID WITH
DIFFERENT AMOUNTS OF H₂O₂ AS OXIDANT IN
THE PRESENCE OF PHASE TRANSFER CATALYSTS

Entry	n(II): n(H ₂ O ₂)	Time (h)	PTC	Conversion ^a (%)	Yield ^a (%)
1	1:1	17	PEG400	57.0	37.7
2	1:4	7	PEG400	73.5	54.6
3	1:8	5	PEG400	97.6	90.1 ^b
4	1:10	4.5	PEG400	> 99	87.7
5	1:8	5	tetra-Butyl ammonium bromide	> 99	84.2
6	1:8	5.5	Benzyltriethyl ammonium chloride	> 99	89.1

^aCalculated from HPLC peak areas; ^bIsolated yield

Conclusion

In conclusion, we have developed an efficient procedure for the synthesis of benzoylformic acid in 74.7 % of total yield starting from styrene by the use of clean aqueous hydrogen peroxide under mild conditions.

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