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Simple green dehydration in biphasic medium: Application to the synthesis of phenylacetaldehyde

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ABSTRACT

A highly efficient, simple and versatile acid catalyst is proposed for the selective acid dehydration of 1-phenylethan-1,2-diol to phenylacetaldehyde in water-CPME biphasic media under microwave irradiation. A high stability and recyclability of the catalyst is also observed under the investigated conditions.

1. Introduction

Phenylacetaldehyde, a natural compound found in chocolate [1], buckwheat [2], has a narcissus-like smell. Synthetical phenylacetaldehyde is used in industry as upstream raw material and for downstream applications like preparation of fragrances [3] but also pharmaceuticals [4] and insecticides [5]. Among the different syntheses of phenylacetaldehyde, isomerization of styrene oxide both in liquid or in gas phase, Darzens glycidic ester condensation of benzaldehyde and dehydration of phenylethan-1,2-diol [6,7] were the most useful. The main drawbacks of these methodologies were the competitive aldol condensation or the polymerization of aldehyde products.

Due to the depletion of petroleum resources, organic reactions in water as green solvent were developed. Hydrothermal transformation using conventional heating or microwave activations permitted to realize the dehydration of polyols from biomass [8,9] and fossil resources [10–12]. Recently, our group published dehydration of glycerol to acrolein and the synthesis of quinoline in sub-critical water under conventional heating and microwave irradiation in batch [13,14] and in continuous flow [15]. In a previous work, we optimized a method for the dehydration of 1-phenylethan-1,2-diol **1** in sole water under microwave irradiation [16]. Best conditions were a temperature of 170 °C and a reaction time of 30 min. Among the different homogeneous and heterogeneous catalysts tested, mineral acids H_2SO_4 and HCl and metal chlorides $FeCl_3$ and $AlCl_3$ gave the highest phenylacetaldehyde **2** yields (55–63%). However, in water, phenylacetaldehyde formation was limited by the formation of the aldol condensation product **3**. In the present work, we report an efficient strategy for the selective formation of phenylacetaldehyde **2** under microwave irradiation by the addition of an extracting co-solvent, cyclopentyl methyl ether (CPME). Already exemplified for the synthesis of furans [17,18], this strategy uses the partition coefficient of aldehyde **2** between water and organic solvent. After dehydration of diol **1** to aldehyde **2** in water, the affinity of aldehyde **2** with organic solvent should permit to transfer aldehyde **2** to the organic phase while limiting the formation of compound **3** (Scheme 1).

2. Materials and methods

2.1. Materials

Substrates and products (1-phenylethan-1,2-diol, phenylacetaldehyde and styrene oxide) were purchased from Acros. Catalysts were purchased from Acros ($FeCl_3$, $AlCl_3$, and H_2SO_4 (96%)) and from Carlo Erba (hydrochloric acid (37%)). Solvents were purchased from Fisher Scientific (acetonitrile, tetrahydrofu-

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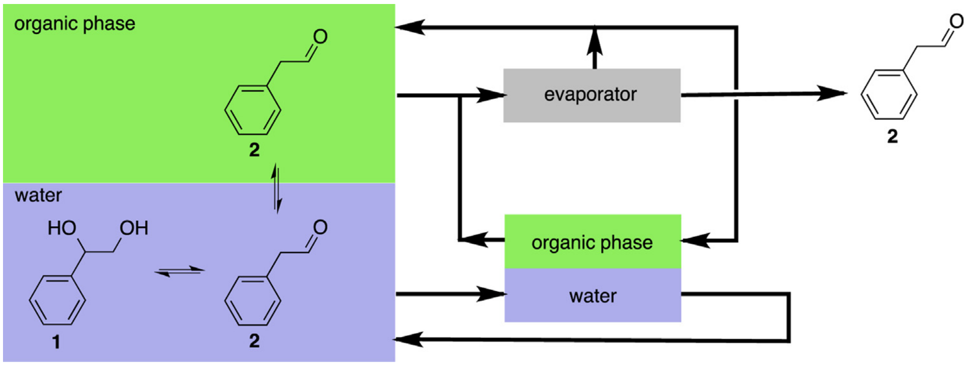


Scheme 1. Extraction of aldehyde 2 from water to the organic phase.

ran, toluene and ethyl acetate) and from Acros (cyclopentyl methyl ether and methyl-tetrahydrofuran). All materials were used without further purification. Distilled H_2O was used for preparation of all aqueous solutions.

2.2. General procedure for the synthesis of phenylacetaldehyde in water-CPME as biphasic media from 1-phenylethan-1,2-diol

In a typical experiment, a 10 mL glass vessel was charged with water (0.5 mL), CPME (1.4 mL), 1-phenylethan-1,2-diol (**1**, 100 mg, 0.725 mmol) and a catalyst (20 mol%). The vessel was sealed with a septum, placed in the microwave apparatus (AntonPaar Monowave 300) and heated to the desired temperature under magnetic stirring (600 rpm) for the desired time. Temperature in the vessel was measured by means of an IR sensor. At the end of the reaction, the vessel was cooled down to 40 °C using compressed air. Then, the reaction mixture was diluted in 100 mL of acetonitrile. An aliquot of the diluted solution was taken (ca. 1.5 mL) and filtered prior to analysis through a syringe filter (PTFE, 0.45 μm, VWR).

2.3. General procedure for the synthesis of phenylacetaldehyde in water-CPME as biphasic media from styrene oxide

In a typical experiment, a 10 mL glass vessel was charged with water (0.5 mL), CPME (1.4 mL), styrene oxide (**4**, 87 mg, 0.725 mmol) and a catalyst (20 mol%). The vessel was sealed with a septum, placed in the microwave apparatus (AntonPaar Monowave 300) and heated to the desired temperature under magnetic stirring (600 rpm) for the desired time. Temperature in the vessel was measured by means of an IR sensor. At the end of the reaction, the vessel was cooled down to 40 °C using compressed air. Then, the reaction mixture was diluted in 100 mL of acetonitrile. An aliquot of the diluted solution was taken (ca. 1.5 mL) and filtered prior to analysis through a syringe filter (PTFE, 0.45 μm, VWR).

2.4. Product analysis

^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker UltraShield 400 MHz/54 mm Ultra long hold. Chemical shifts (d) are quoted in ppm and are referenced to TMS as an internal standard. Coupling constants (J) are quoted in Hz. All reactions were monitored by HPLC. The column used is a GRACE Prevail C18. The detector used is a SPD-M20A photo diode array detector (Shimadzu). The mobile phase is a mixture of water and MeOH (20:80). Reactant and product concentrations were determined using calibration curves that were obtained from references samples. The product yield (Y_i), the conversion (X), the selectivity (S_i) and the ratio **2**/(**2** + **3**) were calculated by the following equations:

$$\text{Product yield } Y_i = \frac{\text{Final amount of product i (mol)}}{\text{Initial amount of reactant (mol)}} \times 100$$

$$\text{Conversion } X = \frac{(\text{Initial reactant amount (mol)} - \text{Final reactant amount (mol)})}{\text{Initial amount of reactant (mol)}}$$

$$\text{Selectivity } S_i = \frac{\text{Yield of product i}}{\text{Conversion of reactant}} \times 100\%$$

$$\text{Ratio } 2/(2+3) = \frac{\text{Final amount of product 2 (mol)}}{\text{Final amounts of product 2 + product 3 (mol)}} \times 100\%$$

3. Results and discussion

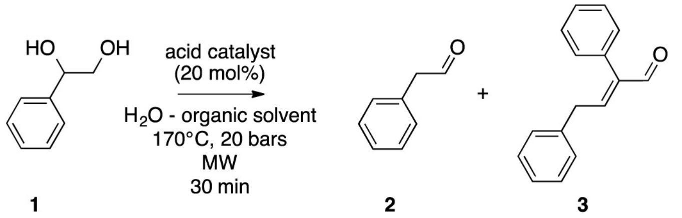
3.1. Effect of the nature of organic solvent

Cyclopentyl methyl ether (CPME), ethyl acetate, toluene, methyltetrahydrofuran (Me-THF) and tetrahydrofuran (THF) as organic solvents were tested in the presence of different selected acids ($AlCl_3$, $FeCl_3$, HCl or H_2SO_4) in water under microwave irradiation to investigate their effect on aldehyde **2** yield. The ratio between the organic solvent and water was 1:1, v/v (Table 1). It should be noted that, whatever the solvent used, reactions performed without acid catalyst afforded no conversion of the starting diol **1**. With ethyl acetate, a large amount of aldehyde **3** (9–25%) was detected. In our conditions, ethyl acetate was degraded during the process and only one phase was obtained at the end of reaction preventing the transfer of aldehyde **2** in the organic phase. With Me-THF and THF, yields of the target compound **2** were comprised between 47% and 86% yields and formation of enal **3** was observed whatever the acid. In contrast, toluene gave selectively the aldehyde **2** with good yield for the four acids. However substitution of toluene as fossil solvent was recommended. The ether CPME gave excellent yield (>86%) in presence of $FeCl_3$, HCl or H_2SO_4 and low amount of compound **3** (<2%). Even if CPME is industrially produced from fossil carbon, it is considered as green solvent and as an alternative to ethereal solvents [19,20]. For these reasons, a mixture of CPME and water for the dehydration of diol **1** to aldehyde **2** was chosen.

3.2. Effect of the ratio water/CPME on the phenylacetaldehyde yield

Variation of the ratio between water and CPME was realized to optimize the selectivity of aldehyde **2** and the selectivity between the aldehyde **2** and the enal **3** (Table 2). Five ratios were tested (water-CPME, 3:1; 2:1; 1:1; 1:2; 1:3, v/v) in presence of $AlCl_3$, $FeCl_3$,

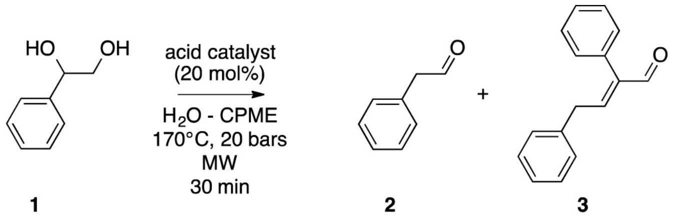
Table 1
Acid catalyzed dehydration of diol **1** to aldehyde **2** under microwave irradiation varying the nature of the organic solvent and the nature of the catalyst.[a]



Entry	Acid (20 mol%)	Organic solvent	Conversion (%)	Yield **2** (%)[b]	Yield **3** (%)[b]	Selectivity **2** (%)	**2**/(**2**+**3**) (%)
1	$AlCl_3$	CPME	64	56	1	87	98
2	$AlCl_3$	EtOAc	90	64	22	71	74
3	$AlCl_3$	toluene	80	78	0	97	100
4	$AlCl_3$	Me-THF	71	62	9	87	87
5	$AlCl_3$	THF	54	47	2	87	96
6	$FeCl_3$	CPME	98	86	1	88	99
7	$FeCl_3$	EtOAc	93	66	9	71	88
8	$FeCl_3$	toluene	99	88	0	89	100
9	$FeCl_3$	Me-THF	88	72	1	82	99
10	$FeCl_3$	THF	87	63	5	72	96
11	HCl	CPME	97	94	1	97	99
12	HCl	EtOAc	94	79	15	84	84
13	HCl	toluene	99	98	0	99	100
14	HCl	Me-THF	94	83	2	88	98
15	HCl	THF	91	67	8	74	89
16	H_2SO_4	CPME	98	95	2	97	98
17	H_2SO_4	EtOAc	99	70	25	71	74
18	H_2SO_4	toluene	99	98	0	99	100
19	H_2SO_4	Me-THF	91	86	1	94	99
20	H_2SO_4	THF	93	70	8	75	90

[a] Reaction conditions: 20 mol% catalyst, 0.725 mmol of 1-phenylethan-1,2-diol (**1**), 0.95 mL of water, 0.95 mL of organic solvent, 170 °C, 20 bars, 30 min, MW.
[b] The yield was calculated from HPLC analysis with a calibration curve.

Table 2
Acid catalyzed dehydration of diol **1** to aldehyde **2** under microwave irradiation varying the volume of the organic solvent and the nature of the catalyst.[a]

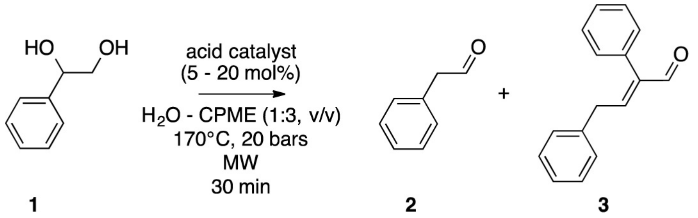


Entry	Acid (20 mol%)	H_2O-CPME v/v	Conversion (%)	Yield **2** (%)[b]	Yield **3** (%)[b]	Selectivity **2** (%)	**2**/(**2**+**3**) (%)
1	$AlCl_3$	3:1	76	63	2	83	97
2	$AlCl_3$	2:1	70	66	1	94	98
3	$AlCl_3$	1:1	64	56	1	87	98
4	$AlCl_3$	1:2	62	59	0	95	100
5	$AlCl_3$	1:3	47	45	0	96	100
6	$FeCl_3$	3:1	96	81	2	84	98
7	$FeCl_3$	2:1	98	81	2	83	98
8	$FeCl_3$	1:1	98	86	1	88	99
9	$FeCl_3$	1:2	98	85	1	87	99
10	$FeCl_3$	1:3	98	84	1	86	99
11	HCl	3:1	97	87	2	90	98
12	HCl	2:1	97	91	1	94	99
13	HCl	1:1	97	94	1	97	99
14	HCl	1:2	98	95	1	97	99
15	HCl	1:3	98	94	1	96	99
16	H_2SO_4	3:1	98	89	3	91	97
17	H_2SO_4	2:1	98	91	2	93	98
18	H_2SO_4	1:1	98	95	2	97	98
19	H_2SO_4	1:2	99	97	1	98	99
20	H_2SO_4	1:3	99	96	1	97	99

[a] Reaction conditions: 20 mol% catalyst, 0.725 mmol of 1-phenylethan-1,2-diol (**1**), 1.9 mL of a mixture of water and CPME, 170 °C, 20 bars, 30 min, MW.
[b] The yield was calculated from HPLC analysis with a calibration curve.

HCl or H_2SO_4. Among the different results, only $AlCl_3$ did not give a good conversion of the diol **1** (<76%) and a good yield of aldehyde **2** (<66%). Besides, contrary to expectations, when the amount of CPME was higher than that of water, only aldehyde **2** with a medium yield (<62 %) was observed. In contrast, when the amount of CPME was lower than that of water, conversion of the diol **1** and yield of aldehyde **2** were higher. With an excess of CPME, a complex between the aluminium atom and the CPME ether may be formed.

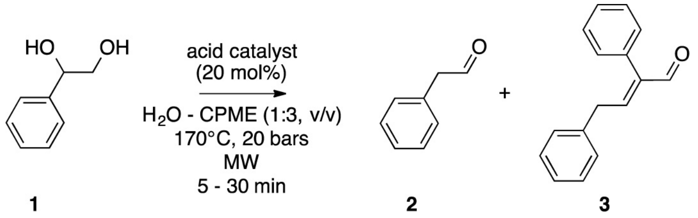
Table 3
Acid catalyzed dehydration of diol **1** to aldehyde **2** under microwave irradiation varying the concentration of the acids.[a]



Entry	Acid (mol%)	Conversion (%)	Yield **2** (%)[b]	Yield **3** (%)[b]	Selectivity **2** (%)	**2**/(**2** + **3**) (%)
1	$FeCl_3$ 5	63	55	0	87	55
2	$FeCl_3$ 10	86	80	0	93	80
3	$FeCl_3$ 20	98	84	1	86	99
4	HCl 5	77	73	0	95	100
5	HCl 10	90	87	0	97	100
6	HCl 20	98	94	1	96	99
7	H_2SO_4 5	85	67	0	79	100
8	H_2SO_4 10	95	86	0	91	100
9	H_2SO_4 20	99	96	1	97	99

[a] Reaction conditions: 5–20 mol% catalyst, 0.725 mmol of 1-phenylethan-1,2-diol (**1**), 0.5 mL of water, 1.4 mL of CPME, 170 °C, 20 bars, 30 min, MW.
[b] The yield was calculated from HPLC analysis with a calibration curve.

Table 4
Acid catalyzed dehydration of diol **1** to aldehyde **2** under microwave irradiation at different reaction times.[a]



Entry	Acid (20 mol%)	Time (min)	Conversion (%)	Yield **2** (%)	Yield **3** (%)[b]	Selectivity **2** (%)	**2**/(**2** + **3**) (%)
1	$FeCl_3$	5	58	43	0	74	100
2	$FeCl_3$	10	82	67	0	82	100
3	$FeCl_3$	15	92	81	0	88	100
4	$FeCl_3$	20	96	84	0	87	100
5	$FeCl_3$	30	98	84	1	86	99
6	HCl	5	61	60	0	98	100
7	HCl	10	83	79	0	95	100
8	HCl	15	94	91	0	97	100
9	HCl	20	96	93	1	97	99
10	HCl	30	98	94	1	96	99
11	H_2SO_4	5	70	56	0	80	100
12	H_2SO_4	10	87	77	0	88	100
13	H_2SO_4	15	96	92	0	96	100
14	H_2SO_4	20	98	97	1	99	99
15	H_2SO_4	30	99	96	1	97	99

[a] Reaction conditions: 20 mol% catalyst, 0.725 mmol of 1-phenylethan-1,2-diol (**1**), 0.5 mL of water, 1.4 mL of organic solvent, 170 °C, 20 bars, 5–30 min, MW.
[b] The yield was calculated from HPLC analysis with a calibration curve.

In this case, the amount of free $AlCl_3$ was not enough to catalyze the dehydration of the diol. With $FeCl_3$, HCl or H_2SO_4, the amount of organic solvent has no influence on the diol conversion. However, we can notice that more the amount of CPME was important, more the yield of **2** was better. The experiments showed that the best results were obtained when the amount of CPME represented 66 to 75% of the total solvent amount (Table 2). Based on these results, dehydration of the diol **1** was realized in presence of $FeCl_3$, HCl or H_2SO_4 (20 mol%) in a biphasic system: water-CPME, 1:3, v/v as biphasic system at 170 °C for 30 min under microwave irradiation.

3.3. *Effect of catalyst loading variation*

In order to further evaluate influence of the catalyst concentration in the optimized biphasic system, experiments with different amounts (5,10 and 20 mol%) of $FeCl_3$, HCl and H_2SO_4 were carried out (Table 3). Decreasing the catalyst loading resulted in a lower conversion of the diol **1** and a lower formation of aldehyde **2**. Consequently, the amount of catalyst was maintained at 20 mol%. It was noteworthy that in these conditions a negligible aldol condensation (<1%) was observed.

3.4. *Effect of reaction time*

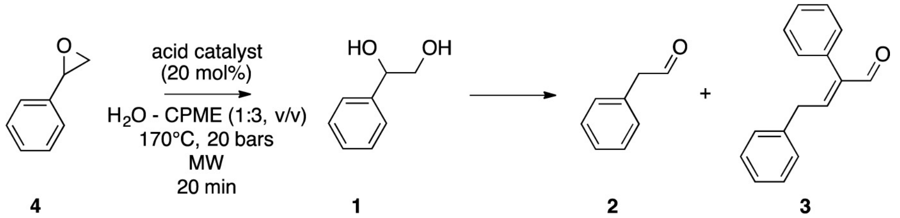
Experiments were conducted for 5, 10, 15, 20 and 30 min to study the effect of reaction time on the dehydration of the diol **1** to the aldehyde **2** (Table 4). From 5 to 30 min, the conversion of the diol **1** and the formation of aldehyde **2** increased. Between 20 and 30 min, low variations were detected and consequently the time of reaction of 20 min was chosen.

Table 5
Reusability of acid catalyst in the dehydration reaction of diol **1** to aldehyde **2** under microwave irradiation.[a]

Entry	Acid (20 mol%)	Run	Conversion (%)	Yield**2** (%)	Yield**3** (%)[b]	Selectivity**2** (%)	**2**/(**2** + **3**) (%)
1	$FeCl_3$	1	96	90	1	94	99
2	$FeCl_3$	2	95	93	0	98	100
3	$FeCl_3$	3	91	88	0	97	100
4	$FeCl_3$	4	86	81	0	94	100
5	$FeCl_3$	5	81	76	0	94	100
6	HCl	1	98	96	1	98	99
7	HCl	2	97	94	0	97	100
8	HCl	3	95	92	0	97	100
9	HCl	4	93	86	0	92	100
10	HCl	5	91	86	0	94	100
11	H_2SO_4	1	98	96	0	98	100
12	H_2SO_4	2	98	98	0	100	100
13	H_2SO_4	3	97	96	0	99	100
14	H_2SO_4	4	98	97	0	99	100
15	H_2SO_4	5	97	96	0	99	100

[a] Reaction conditions: 20 mol% catalyst, 0.725 mmol of 1-phenylethan-1,2-diol (**1**), 0.5 mL of water, 1.4 mL of organic solvent, 170 °C, 20 bars, 20 min, MW.
[b] The yield was calculated from HPLC analysis with a calibration curve.

Table 6
Dehydration of the epoxide **4** to aldehyde **2** under microwave irradiation.[a]



Entry	Acid (20 mol%)	Conversion (%)	[**1**] (%)[b]	Yield **2** (%)[b]	Yield **3** (%)[b]	Selectivity **2** (%)	**2**/(**2** + **3**) (%)
1	$FeCl_3$	100	3	86	0	94	99
2	HCl	100	2	95	1	98	100
3	H_2SO_4	100	2	94	0	97	100

[a] Reaction conditions: 20 mol% catalyst, 0.725 mmol of styrene oxide (**2**), 0.5 mL of water, 1.4 mL of organic solvent, 170 °C, 20 bars, 20 min, MW.
[b] The yield was calculated from HPLC analysis with a calibration curve.

3.5. *Reusability of the catalyst*

Besides activity and selectivity, one expected advantage of our system lies in the easy separation of the aqueous phase and the CPME. After a catalytic test, the aqueous phase was reused for a second catalytic cycle under the same conditions. The acid catalyst was recyclable for up to four cycles even if a progressive decrease in activity was observed for the acid catalysts $FeCl_3$ and HCl. No yield variation was observed with H_2SO_4 (Table 5). The analysis of the aqueous phase after the fifth cycle showed a clean phase and no accumulation of undesired compounds. Therefore, it appeared that the optimized system was to use H_2SO_4 as acid catalyst in water and CPME biphasic system under microwave irradiation at 170 °C for 20 min.

3.6. *Phenylacetaldehyde production from styrene oxide*

In order to vary the starting material, the use of styrene oxide **4** as cheaper compound was studied. Styrene oxide **4** was first hydrolyzed to 1-phenylethan-1,2-diol **1**, which was then dehydrated to form phenylacetaldehyde **2**. Application of the optimized dehydration method produced the target aldehyde **2** in similar yields: 86, 95 and 94% with $FeCl_3$, HCl and H_2SO_4 respectively (Table 6).

4. Conclusions

In conclusion, $FeCl_3$, HCl and H_2SO_4 are excellent acid catalysts for the selective production of phenylacetaldehyde starting from the corresponding diol in water-CPME biphasic solvents under microwave irradiation. Our optimized conditions produce selectively the target aldehyde in yield higher than 84–97% with a trace of aldol compound. Furthermore the system was stable after reuses under the investigated condition. Starting from styrene oxide, extension of the present methodology was reported in excellent yield.

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