

Synthesis of Phenylacetaldehyde from 1-Phenylethan-1,2-diol by Microwave-Assisted Dehydration in Water

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Abstract A highly efficient, simple and versatile acid catalyst is proposed for the selective dehydration of 1-phenylethan-1,2-diol to the phenylacetaldehyde as an industrial platform molecule. For the first time, common Lewis acids AlCl₃ and FeCl₃ and mineral acids HCl and H_2SO_4 had produced the acetaldehyde derivative under microwave irradiation in sub-critical water in good yield starting from the corresponding diol. *Graphical Abstract*



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1 Introduction

Phenylacetaldehyde is a natural product having a narcissuslike smell. This aldehyde is a molecule found in chocolate [1], buckwheat [2]. The chemical production of phenylacetaldehyde permits to use it in industry as upstream raw material and for downstream applications like preparation of fragrances [3] but also pharmaceuticals [4] and insecticides [5]. Different strategies afford the syntheses of phenylacetaldehyde: (i) isomerization of styrene oxide both in liquid or in gas phase (way A); (ii) Darzens glycidic ester condensation of benzaldehyde (way B) and (iii) dehydration of phenylethan-1,2-diol (way C) [6]. The main drawbacks of these methodologies were the formation of the corresponding enal due to competitive aldol condensation.

In regards of green chemistry and sustainable development, chemists can act at different levels and especially by using safer solvents and auxiliaries and by developing alternative technologies. Hydrothermal transformation using conventional heating or microwave activations permitted to realize the dehydration of polyols from biomass [7, 8] and fossil resources [9-11]. In this regards, dehydration of 1-phenylethan-1,2-diol (1) at 200 °C for 6 h without the presence of acid afforded phenylacetaldehyde (2) and the enal 3 in 24 and 41 % yields, respectively [9]. Using a similar strategy, Goettmann described the formation of compounds 2 and 3 in 22 and 21 % yields, respectively [10]. It was noteworthy that the addition of salts such as NaCl (1 M) permitted to increase the conversion of the diol 1 in favor of the enal derivative 3 (64 %). Recently, Len's group published the double dehydration of glycerol to acrolein and the synthesis of quinoline in sub-critical water under both conventional heating and microwave irradiation in batch [12, 13] and in

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continuous flow [14]. Following our continued interest in developing dehydration of alcohol in water, we now report a novel and efficient synthesis of phenylacetaldehyde and derivatives in sub-critical water under microwave technology.

2 Experimental

2.1 General

Substrate and product (1-phenylethan-1,2-diol and phenylacetaldehyde) were purchased from Acros. Catalysts were purchased from Acros [MnSO₄, FeCl₃, AlCl₃, FeSO₄, $CaCl_2$ and H_2SO_4 (96 %)], from Normapur [Fe₂(SO₄)₃₁, from Merck (ZnSO₄) and from Carlo Erba [hydrochloric acid (37 %) and NaCl]. All materials were used without further purification. Distilled H₂O was used for preparation of all aqueous solutions. ¹H and ¹³C 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:

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



Scheme 1 Proposed mechanism for the dehydration of diol 1 to aldehyde 2 with the $AlCl_3$ catalyst in water

2.2 General Procedure for the Synthesis of Phenylacetaldehyde (2) in Water Starting from 1-Phenylethan-1,2-diol (1)

In a typical experiment, a 10 mL glass vessel was charged with an aqueous solution (2 g) of 1-phenylethan-1,2-diol (1, 5 wt%) 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

$$Conversion X = \frac{(Initial \ reactant \ amount \ (mol) - Final \ reactant \ amount \ (mol))}{Initial \ amount \ of \ reactant \ (mol)} \times 100 \%$$

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

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

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 μ m, VWR).

3 Results and Discussion

The initial dehydration reaction was performed using 1-phenylethan-1,2-diol (1) in the presence of $AlCl_3$ (20 mol%) as a model reaction in neat water at 170 °C

under microwave irradiation. As expected the dehvdration reaction in presence of AlCl₃ in water is believed to be initiated by the hydrolysis of AlCl₃ which forms under microwave irradiation a cationic species [Al(OH)(H₂ O_{5}^{2+} and H⁺. It is notable that $[Al(OH)(H_2O_5)^{2+}]^{2+}$ and H^+ could react as a potential electrophile with the diol 1 and as acid catalyst, respectively (Scheme 1). Using these initial conditions, study of the rate of aldehyde 2 formation as a function of time was realized (Table 1). Conversion of the diol 1 increased with the time of the microwave irradiation and better yield of compound 2 was obtained after 30 min of reaction (Table 1, entry 3). After this time, the yield of compound 2 and selectivity between compounds 2 and 3 decreased due to the formation of the aldehyde 3. Consequently, 30 min of reaction have been selected for the next steps.

In contrast with previous reports [9, 10], aldol condensation of aldehyde 2 afforded the (E)-2,4-diphenylbut-2enal (3). The structure of compound 3 was established by NMR spectroscopy. ¹H NMR and ¹³C spectroscopy experiments were performed at 296 K in CDCl₃. The ¹H NMR spectrum showed that (i) the C(1)H gave one singlet at 9.67 ppm indicating no coupling with another hydrogen atom; (ii) the C(3)H gave one triplet at 6.88 ppm and (iii) the C(4)H gave one doublet at 3.71 ppm with an integral value for two hydrogen atoms. The coupling constant J = 7.6 Hz for C(3)H and C(4)H proved that the CH and CH₂ groups were neighbors. The ¹³C NMR spectrum showed the presence of an enal structure with the C(1)H at 193.51 ppm, a disubstituted carbon atom C(2) at 153.47 ppm and an electron deficient carbon atom C(4) at 138.02 ppm. The ¹H and ¹³C NMR experiments confirmed that compound **3** had a 2,4-disubstituted-but-2-enal



Fig. 1 Structure of enal 3 by ¹H and ¹³C NMR determination

structure. The configuration of the enal **3** was assigned to the *E* configuration since an NOE interaction between the C(3)H and the C(1)H was detected (Fig. 1).

Based on these results, dehydration of diol **1** was carried out using AlCl₃ (20 mol%) as catalyst in water for 30 min at different temperatures (Table 2). Conversion increased till 100 % after 30 min under microwave irradiation at 180 °C. With a temperature higher than 180 °C, the yield of aldehyde **2** decreased from 55 to 31 % and the aldol condensation furnishing compound **3** was preferred (Table 2, entries 6–8). Considering the results, temperature of 170 °C has been selected.

The next step consisted in studying variable catalyst concentrations of AlCl₃ for maximizing the aldehyde **2** yield (Table 3). Acid concentration had some influence on the conversion of the diol **1** to the aldehyde **2** since 5 mol% of AlCl₃ gave 60 % of conversion (Table 3, entry 1) and 50 mol% of AlCl₃ gave 91 % of conversion (Table 3, entry 6). In contrast, AlCl₃ concentration had a lower influence on the yield of aldehyde **2** (46–60 % yields) but a higher concentration of AlCl₃ increased the yield of compound **3**. In the next steps, the amount of AlCl₃ was fixed at 20 mol % due to a good equilibrium between yield of compound **2**, global selectivity and **2**/(**2** + **3**) balance.

		1	$\begin{array}{c} H_2 O \\ H_2 O \\ C, 20 \text{ bars} \\ MW \\ t \\ \end{array} $		<u>_</u>	
Entry	Time(min)	Conversion (%)	Yield 2 (%) ^a	Yield 3 (%) ^a	Selectivity 2 (%)	2/(2 + 3) (%)
1	10	51	36	1	71	97
2	20	64	48	1	75	98
3	30	80	55	3	69	95
4	40	86	53	7	61	88
5	50	94	53	12	56	82
6	60	98	48	10	49	83

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 Table 1
 Acid catalyzed dehydration of diol 1 to aldehyde 2 under microwave irradiation at different time of reaction

^a The yield was calculated from HPLC analysis with a calibration curve

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		HO OH	AICI ₃ (20 mol%) H_2O T, 20 bars MW 30 min			
Entry	T (°C)	Conversion (%)	Yield 2 (%) ^a	Yield 3 (%) ^a	Selectivity 2 (%)	2/(2 + 3) (%)
1	130	5	0	0	0	0
2	140	6	4	0	66	100
3	150	16	13	0	81	100
4	160	44	34	1	77	97
5	170	80	55	3	69	95
6	180	100	45	22	45	67
7	190	100	39	28	39	58
8	200	100	31	27	31	53

Table 2 Acid catalyzed dehydration of diol 1 to aldehyde 2 under microwave irradiation varying the temperature

^a The yield was calculated from HPLC analysis with a calibration curve

Table 3 Acid catalyzed dehydration of diol 1 to aldehyde 2 under microwave irradiation varying the concentration of AlCl₃

		HO OH 17	AICI ₃ H ₂ O 70°C, 20 bars MW 30 min 2			
Entry	AlCl ₃ (mol %)	Conversion (%)	Yield 2 (%)	Yield 3 (%) ^a	Selectivity 2 (%)	2/(2+3) (%)
1	5	60	46	1	77	98
2	10	73	51	2	70	96
3	20	80	55	3	69	95
4	30	81	49	4	60	92
5	40	91	58	6	64	91
6	50	91	60	9	66	87

^a The yield was calculated from HPLC analysis with a calibration curve

Afterwards, different acids such as Lewis acid, Brønsted acid, metal sulfate and salts were tested in sole water at 170 °C for 30 min under microwave irradiations in order to isolate selectively the target aldehyde **2** (Table 4). From those experiments one could see that Lewis acids AlCl₃ and FeCl₃ (Table 1, entries 1, 2) and Brønsted acids HCl and H₂SO₄ (Table 1, entries 3, 4) had a major impact on the dehydration. Using FeCl₃, HCl and H₂SO₄, a full conversion of the starting material **1** was detected and aldehyde **2** was obtained with higher yields than with AlCl₃. However, the global selectivity was more important when AlCl₃ was used. In contrast with the results obtained by Vogel [15, 16] and Goettmann [10] for the dehydration of different alcohols, metal sulfates (Table 1, entries 5–8) and chloride salts (Table 1, entries 9 and 10) did not permit to furnish aldehyde **2** in good yield. In our hands, optimized dehydration of the diol **1** in sub-critical water under microwave irradiation was realized in the presence of AlCl₃, FeCl₃, HCl or H₂SO₄ at 170 °C for 30 min. In these conditions, the target aldehyde **2** was selectively obtained in 55–63 % yields with both good global selectivity and excellent selectivity for aldehyde **2** over aldehyde **3** (Table 4, entries 1–4). To the best of our knowledge, this is the first time that phenylacetaldehyde (**2**) was produced in liquid phase in yield higher than 45 % starting from the corresponding diol (**1**).

	HO OH acid catalyst (20 mol%) H_2O $170^\circC, 20 \text{ bars}$ MW 30 min 2 3						
Entry	Acid (20 mol %)	Conversion (%)	Yield 2 (%)	Yield 3 (%) ^a	Selectivity 2 (%)	2/(2 + 3) (%)	
1	AlCl ₃	80	55	3	69	95	
2	FeCl ₃	99	59	6	60	91	
3	HCl	96	63	4	66	94	
4	H_2SO_4	97	62	4	64	94	
5	MnSO ₄	0	0	0	0	0	
6	ZnSO ₄	3	2	0	67	100	
7	FeSO ₄	2	1	0	50	100	
8	$Fe_2(SO_4)_3$	54	26	0	48	100	
9	NaCl	1	1	0	100	100	
10	CaCl ₂	4	4	0	100	100	

Table 4 Acid catalyzed dehydration of diol 1 to aldehyde 2 under microwave irradiation varying the nature of the catalyst

^a The yield was calculated from HPLC analysis with a calibration curve

4 Conclusion

In conclusion, AlCl₃, FeCl₃, HCl and H_2SO_4 are excellent acid catalysts for the selective production of phenylacetaldehyde starting from the corresponding diol in subcritical water under microwave irradiation. Whereas mineral acids such as HCl and H_2SO_4 are the best catalysts in point of view of yield, Lewis acid such as FeCl₃ and AlCl₃ show a good alternative thanks to their safer handling. In contrast to literature, low amount of the product obtained by aldol condensation was detected.

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