# Direct Microdroplet Synthesis of Carboxylic Acids from Alcohols by Preparative Paper Spray Ionization without Phase Transfer Catalysts

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S *Supporting Information*

ABSTRACT: Carboxylic acids are widely used in the production of fine chemicals. This study demonstrates rapid synthesis of carboxylic acids directly from alcohols in microdroplets by paper spray ionization under UV irradiation. Oxidation acceleration was contributed from paper substrate as a thin film format and microdroplets of smaller sizes by paper spray ionization. Yields can reach as high as 100% for all tested alcohols except 4-nitrobenzene alcohol (39%) in microdroplets compared to 1−10% for acids and 2−50% for aldehydes with methylbenzoate byproducts in bulk phase. Preparative paper spray ionization for scaling-up syntheses realized rates of 19 mg h^{-1}. Paper spray-based synthesis not only possesses all merits of microvolume synthesis by electro- and sonic spray, but also owns unique properties of no need for phase-transfer catalysts, and high ease to salt deposition typically occurred at the capillary tips for the latter. All these merits indicate it is a high-efficiency green methodology.

KEYWORDS: *Microsynthesis, Oxidation, Two-phase reaction, Direct transformation, Light irradiation, Green chemistry, High yield, Reaction acceleration*
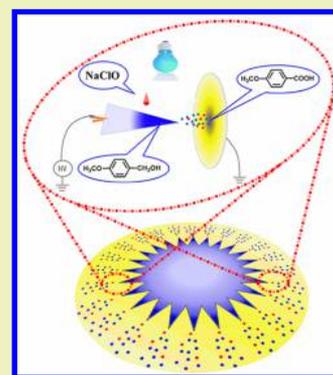
■ INTRODUCTION

Carboxylic acids are widely used in the production of fine chemicals, such as drugs, pesticides, dyes, coatings, plasticizers, spices and food preservatives.[1] Comprising a significant ingredient of the human diet, acids are found in almost all plant-derived foods, which are endogenously synthesized for protection against UV light, insects, viruses and bacteria.[2] In consideration of the significance and the above applications, the synthesis of aromatic acids has been extensively studied.[3]

Traditionally, acids have been synthesized by the oxidation of hydrocarbons,[4] alcohols and aldehydes, and the oxidative cracking of olefins and alkynes.[5] The oxidation reactions from these reactants are typically carried out in highly oxidative environments (using HNO_3, $KMnO_4$, $K_2Cr_2O_7$, etc.).[6] Large amounts of strong oxidants may lead to severe environmental problems. Hence relatively weak oxidative reagents are searched for green synthesis of acids in mild conditions, where noble metallic catalysts were necessary.[7] Recently, the carboxylation of CO_2 with aromatics has attracted considerable attention owing to widespread occurrence and nontoxicity. Carbon dioxide can be reacted with aryl halide,[8] unsaturated aromatic hydrocarbons,[9,10] and organoboron reagents (aryl boronate).[11] Due to low-reactive electrophile of CO_2, metallic catalysts are vitally important to activate this oxidant for carboxylation, and great progress has been made in transition

metal-catalyzed carboxylation reactions.[12] Despite a potential alternative to traditional methods, carboxylation reactions also suffered from several problems. For examples, excessive reduction metal reagents (zinc powder, manganese powder,[13] etc.) used were environmentally unfriendly. Additionally, it is tedious and sometimes difficult to isolate the products from these high-cost catalysts. Therefore, it is still essential to develop novel green carboxylation methodologies.

In the past several decades, small-volume reactors such as microdroplets, thin film and microcompartments in micro-fluidic systems are appealing to green synthesis because they overcome the reagent incompatibility and enhance the mixing of reagents,[14] and accelerates the reaction owing to confinement effect[15] and rapid evaporation of solvents[16−18] because of huge surface-to-volume ratios of microdroplets. In particular, many synthetic reactions that cannot be completed in bulk phase can be accomplished in microdroplets, i.e. two-phase oxidation of alcohols to aldehydes without phase transfer catalysts.[19,20] To date, accelerated reactions in microdroplets involve carbon−carbon bond formation, carbon−nitrogen bond formation, cyclization, oxidation−reduction, and multi-

component multistep reactions.[21,22] Microdroplets (charged or uncharged) with high synthetic efficiencies were generated by electrospray[23] and desorption electrospray,[24] sonic spray,[25,26] paper spray, etc. Paper spray ionization (PSI) is an ambient ionization method which originated from wick spray mass spectrometry by Professor Fenn.[27] In 2010, Cooks and Ouyang group equally introduced PSI into analytical community.[28−32] Because of facile operation, low-cost, simple separation, and little or no sample pretreatment, PSI has demonstrated its high potential in many analytical scientific areas since the advent, and PSI is proceeding to many new fields beyond analytical science, for instance, synthesis study to Claisen−Schmidt base catalyzed condensation and Haloform reaction.[33,34] Regardless of several successful syntheses, there is scarce literature regarding direct synthesis of carboxylic acids from alcohols in PSI. Notwithstanding highly accelerated reactions, small-volume reactors are limited by small amounts, which motivates researchers to scale up for meaningful synthesis. Multiplex and array sprayers[19,23,35] and high flux devices using the thin film format[36] or array internal-mix nozzles[37] are two wide strategies to produce more microdroplets for preparative synthesis, where rates of isolated products at several tens of milligram per minute were comparable to the bulk phase reaction. Therefore, preparative microdroplets synthesis of carboxylic acids from alcohols by preparative paper spray is another objective of this study.

■ EXPERIMENTAL SECTION

For microdroplet synthesis by PSI, qualitative rapid filter paper was cut into typical isosceles triangles of 30° (∼10 mm base wide). Another round qualitative rapid filter paper was directly pasted on a ground stainless steel disc to collect the sprayed microdroplets, which was placed 5 mm vertically away from the paper tip. 100 μL of 0.2 mol L^{-1} 4-methoxybenzyl alcohol in CH$_2$Cl$_2$ was dropped on the paper tip by a 100 μL pipettor to allow the evaporation of CH$_2$Cl$_2$ at room temperature in 1 min. Then a high voltage of +6.0 kV was applied on the paper tip under UV irradiation once dropwise adding 100 μL of NaOCl (∼6% m/m) containing 20% v/v methanol. PSI was maintained for microdroplet synthesis for 45 min. Five aliquots of 100 μL of NaOCl (∼6% m/m) containing 20% v/v methanol may be successively dropped on the surface of the spray paper substrate if all alcohols (∼20 μmol) was required to be extracted from the paper substrate for microdroplet oxidation. Thereafter the collection paper and the triangular spray paper were individually extracted with MeOH and then dried with anhydrous Na$_2$SO$_3$, followed by yield measurements by HPLC on a Shimadzu LC-20AT HPLC. HPLC separation of carboxylic acid, aldehyde and alcohol was achieved on a C$_{18}$ column by using mobile phase listed in Table S1 at 1 mL min^{-1} with UV detection at 254 nm. For bulk-phase oxidation, 100 μL of 0.2 mol L^{-1} 4-methoxybenzyl alcohol in CH$_2$Cl$_2$ (or MeOH) and 100 μL of NaOCl (∼6% m/m) containing 20% v/v methanol were stirred for 45 min under UV irradiation, followed by drying with anhydrous Na$_2$SO$_3$ and HPLC analysis for yield measurements.

■ RESULTS AND DISCUSSION

The microdroplet oxidation of *p*-methoxybenzyl alcohol to *p*-methoxybenzoic acid by diluted sodium hypochlorite (NaOCl) was first taken as an example (Scheme 1). As shown in Figure 1A, *p*-methoxybenzyl alcohol in dichloromethane was initially pipetted on the paper substrate to allow solvent evaporation, followed by the deposition of diluted NaOCl with methanol. A round paper was placed against the paper tip for product collection once applying an electric potential at the paper tip. After 45 min of spraying, the collection paper and the paper substrate were both washed with MeOH immediately, and the

Scheme 1. Synthesis of Carboxylic Acids from Alcohols in Microdroplets
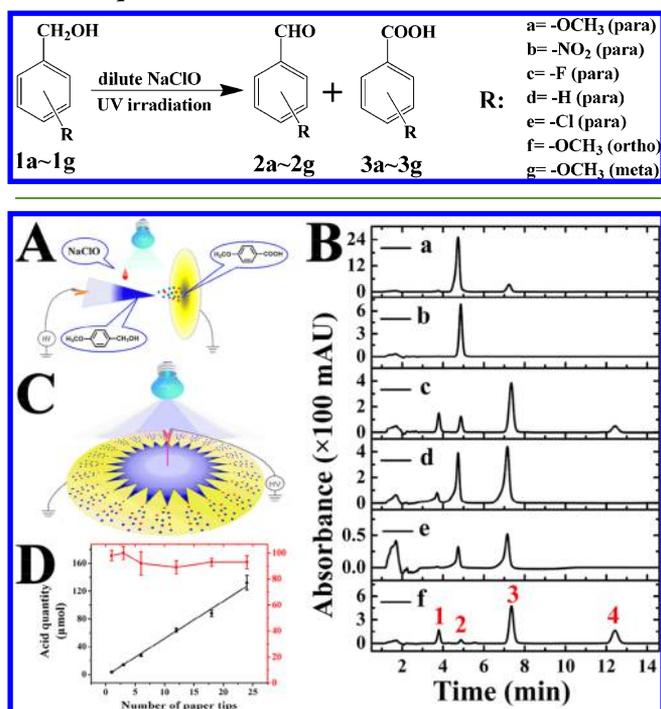
Figure 1. (A) Setup of single-tip paper spray for microdroplet oxidation of 4-methoxybenzyl alcohol with NaOCl. (B) HPLC chromatograms showing the oxidation on the paper substrate with (a) and without (d) UV irradiation, in micrordroplets with (b) and without (e) UV irradiation, and in bulk phase with (c) and without (f) UV irradiation (peak identity: 1, 4-methoxybenzyl alcohol; 2, 4-methoxybenzoic acid; 3, 4-methoxylbenzaldehyde; 4, 4-methoxy-2-methylbenzoate). (C) Setup of preparative paper spray for microdroplet oxidation. (D) Acid quantity versus the number of paper tips in preparative paper spray.

products were analyzed by high performance liquid chromatography (HPLC) for yield and quantity. As shown in Figure 1Ba−c, alcohol was completely converted into carboxylic acid in microdroplets whereas most of alcohols were major oxidized into acid (49%) and minor oxidized into aldehyde (11%) on the paper substrate. However, the same oxidation in bulk phase offered bad yields of 2% for acid and 17% for aldehyde.

In PSI, the spray solvent containing NaOCl formed a thin liquid film on the paper substrate when high electric fields drove it toward the paper tip to generate charged micrdroplets toward the ground collected paper. Alcohols on the paper substrate were extracted and oxidized by NaOCl in the spray solvent, which referred to thin-film microvolume reaction. A thin film format can enhance the reaction because of partial desolvation at the interface,[38] and also the improved transfer of two reactants at the interface.[24,36] A comparison oxidation was conducted only on the paper substrate without applying any high voltage. As shown in Figure S1, the alcohol was major oxidized to the corresponding carboxylic acid (increased from 18% in 5 min to 43% in 50 min) with aldehyde as a minor product (increased from 13% in 5 min to 28% in 50 min). The results demonstrate the superiority of thin-film microvolume reactors in reaction acceleration over bulk-phase reactors. However, the obtained yields on the paper substrate were far lower than those in microdroplets by PSI. Solvent evaporation and confinement effects in microdroplets was stronger to

increase reagent concentration, leading to further accelerated conversion than thin-film reaction.[15,19,39,40] To demonstrate this effect, another comparison oxidation was performed in charged microdroplets by electrospray ionization using the similar setup in a previous work.[20] Briefly, p-methoxybenzyl alcohol of 0.2 mol L^{-1} in CH$_2$Cl$_2$ and NaOCl (∼6% m/m) + methanol (4:1 v/v) were delivered to two separate capillaries of 150 μm i.d. and 320 μm o.d. at 5 μL min^{-1}, which were surrounded by high-pressure nitrogen gas at 150 psi to generate charged microdroplets upon applying high voltages on both capillaries. The microdroplet plumes were mixed at an angle of 60° and a distance of 1.0 mm under UV irradiation, and a glass surface was used to collect the products. As shown in Figure S2, 12% carboxylic acid and 45.5% aldehyde were produced. Although the yields were superior over the bulk-phase reaction, there still existed a big gap between electrospray-based microdroplet synthesis and PSI-based microdroplet synthesis. Such a yield difference can be ascribed by the droplet sizes by two spray methods. Typical droplet sizes by PSI were distributed from one to two micrometers,[41] which were smaller than those by electrospray (around 10 μm or less). The smaller the microdroplets size, the larger surface-to-volume ratio of microdroplets, and the faster the evaporation. Therefore, reaction acceleration was facilitated with microdroplets of small sizes. We then decreased the microdroplet sizes by either using capillaries of different diameters (30−200 μm i.d.) under a constant sheath gas pressure of 150 psi or increasing the sheath gas pressure from 50 to 200 psi to enlarge the shearing force with the same capillary (100 μm i.d.). As shown in Figure S2, gradually improved product formation was observed for a small bore capillary (30 μm i.d. × 130 μm o.d.) and under a high gas pressure (150 psi), which agreed with the results by Yan et al.[19] The results proved that the microdroplet size played an important role in further accelerated reactions in micro-droplets. In addition, PSI-generated microdroplets might generate continuous renewable thin film on the collection paper (even thinner than that on the paper substrate for PSI) upon the deposition, which expedited the oxidation because of microthin mechanism for reaction acceleration.[42] Overall, the microdroplet synthesis by PSI combined the beneficial actions of both microdroplets and the thin film, and was also beneficial from the small droplet sizes.

Apart from high yields, microdroplet synthesis by PSI also avoided side reactions from the chromatograms (Figure 1B), where a byproduct (1%) was observed only in bulk-phase oxidation. The byproduct corresponded to 4-methoxy-2-methylbenzoate[43] by using the pure standard. To check how the ester was produced, a comparison experiment was performed by individual using 4-methoxybenzyl aldehyde and 4-methoxybenzoic acid as starting reactants. As demonstrated in Figure S3, the ester can only be found when the alcohol and aldehyde were used as the reactant, indicating that the ester was produced from aldehyde. When the alcohol and the aldehyde prepared in MeOH were individually mixed with 0.1 mol L^{-1} NaOH, the ester of a small amount can also be observed with the aldehyde. We also replaced methanol with acetonitrile as the spray solvent to repeat the above oxidation, which demonstrated no presence of this ester. It indicated the esterification of aldehyde with methanol rather than acids, which agreed well with a previous work.[43,44] Methanol was evaporated quickly on the paper substrate and in microdroplets to inhibit the formation of the methyl ester. And water was

moderately evaporated in small-volume reactors, which might be expected to promote conversion of the methyl ester to the final acid.[36] In addition, the synthetic aldehyde can be further oxidized to carboxylic acid in microdroplets and on the paper substrate immediately, avoiding the addition of methanol to aldehyde. However, the evaporation of methanol was moderate and the further oxidation of aldehyde to carboxylic acid was also slow in bulk phase, leading to aldehyde esterification.

In consideration of light role in reaction acceleration in our previous work,[20] the effect of light irradiation on the conversion was investigated (Figure 2). A small amount of
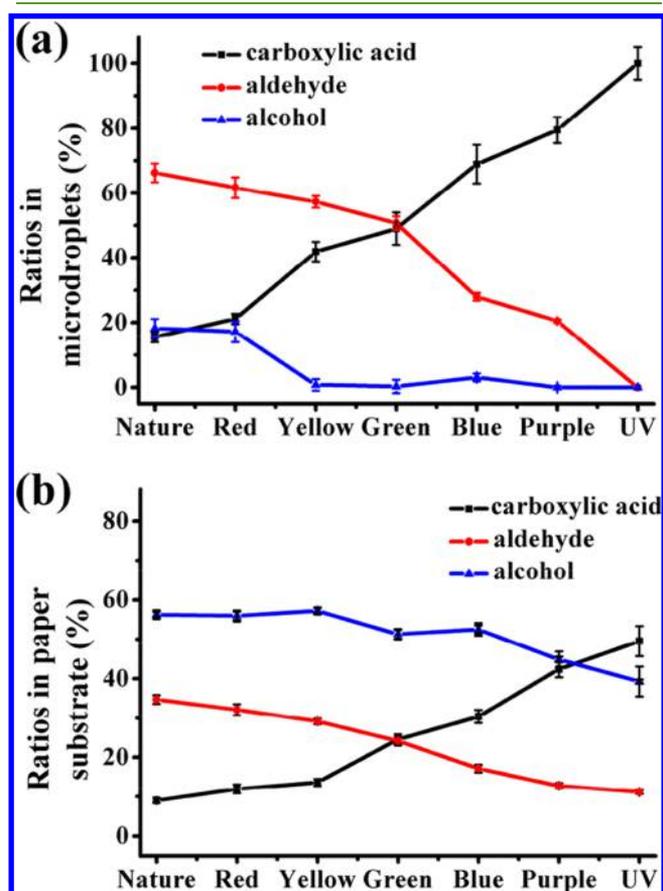
Figure 2. Effects of different lights on the ratios of alcohol, aldehyde and carboxylic acid in microdroplets (a) and on the paper substrate (b).

alcohol was converted into the major aldehyde (34.7%) and the minor acid (9.0%) on the paper substrate under natural light. In microdroplets by PSI, higher yields of aldehyde (66%) and acid (17%) were obtained than on the paper substrate. More and more alcohols were oxidized in microdroplets and on the paper substrate when decreasing the wavelength of the used lamps. At the same time, the aldehydes were rapidly further oxidized into acids, leading to higher acid yields under the light irradiation of shorter wavelengths. Alcohol was 100% oxidized to aldehyde and carboxylic acid in microdroplets under light irradiation of wavelengths less than 570 nm. When lights of wavelengths lower than 485 nm, acid was the major product with aldehyde as the minor product in microdroplets and on the paper substrate. It was worth noting that all alcohols were converted into carboxylic acid in microdroplets under UV irradiation. The contrast can be ascribed by the

Table 1. Yields for Oxidation of Various Alcohols in Microdroplets by PSI and in Bulk Phase

			yields by PSI-based microdroplet synthesis (%)				yields in bulk phase (%)[a]			
			single tip		24 paper tips		CH_2Cl_2		MeOH	
alcohols	aldehydes	carboxylic acids	acid	aldehyde	acid	aldehyde	acid	aldehyde	acid	aldehyde
1a (liquid)[b]	2a (liquid)	3a (soild)	100	0	99	1	2	17	1	6
1b (soild)	2b (soild)	3b (soild)	39	0	34	1	1	2	1	1
1c (liquid)	2c (liquid)	3c (soild)	100	0	100	0	3	3	0	5
1d (liquid)	2d (liquid)	3d (soild)	100	0	100	0	9	29	1	5
1e (soild)	2e (soild)	3e (soild)	96	4	91	5	10	50	1	11
1f (liquid)	2f (soild)	3f (soild)	99	1	93	7	7	14	0	3
1g (liquid)	2g (liquid)	3g (soild)	98	2	98	2	2	22	0	4

[a]Alcohols were prepared in CH_2Cl_2 (or MeOH) and mixed with NaOCl in 20% MeOH to perform bulk-phase oxidation. [b]Phase states (solid or liquid) of alcohols, aldehydes and carboxylic acids in ambient conditions were described in parentheses.

photoinduced decomposition of NaOCl into such reactive oxygen species (ROS) as oxygen radical ($O^{\bullet-}$) and hydroxyl radical (HO·). The ROSs have stronger oxidation capabilities than its precursor molecules (HOCl and ClO^-), which can oxidize alcohols into aldehyde and finally carboxylic acid. The light energy was strengthened with the decrease of the light wavelength, which promoted the decomposition of NaOCl to form more radicals for oxidation acceleration. Therefore, the oxidation was assisted under UV irradiation followingly.

Although alcohols were completely oxidized into carboxylic acids in microdroplets, the acid quantity from microdroplet synthesis was much small (approximately 12−21% in the theoretical amount from the chromatograms in Figure 1B). It may be ascribed by the low extraction efficiency by PSI. To transfer alcohol into microdroplets by PSI as much as possible, we continuously pipetted the oxidant on the paper substrate to maintain spraying for microdroplet synthesis. It was found that most of alcohols (>97%) on the paper substrate was extracted and oxidized into acid after five replicated addition of 100 μL oxidant. However, the total spraying time was too long (∼4 h), leading to low synthetic rate (0.1 mg h^{-1}). Therefore, we optimized the parameters that affected paper spray ionization, which are discussed in Supporting Information.

The satisfactory conversion yield (∼100%) of p-methoxylbenzoic acid from p-methoxylbenzene alcohol in microdroplets by PSI urges us to extend to several other benzyl alcohols with different substituents (Table 1). Except p-nitrobenzene alcohol, the other tested alcohols can be eventually oxidized to carboxylic acid with high yields in microdroplets. In comparison, small amounts of alcohols were transformed into aldehydes with minimal carboxylic acids for all bulk-phase oxidations no matter the alcohols were prepared in CH_2Cl_2 or MeOH. The results demonstrate the advantage of microdroplet synthesis in reaction acceleration.

Despite high yields in microdroplets by PSI, the obtained amounts of all products were much smaller (less than 0.8 mg h^{-1}) than other microdroplet synthesis by electrospray[23] and desorption electrospray[24] and sonic spray,[19] which deterred its application to practical large-scale synthesis. Therefore, preparative experiments in Figure 1C were carried out by using array paper tips (schematic diagram shown in Figure S10) to prove the practicability. It is observable from Figure 1D that the isolated acid quantity was proportional to the number of triangle filter paper with any loss in the yield, which indicated a rate of 19 mg h^{-1}. The results implied that comparable acid rates to other microdroplet synthesis using high flux can be realized by using further more paper tips.

Given the exploration, we further examined the oxidations of the above tested alcohols by preparative PSI (Table 1). HPLC chromatograms of the crude acids are shown in Figures S11−S17, and ^{1}H NMR spectra and mass spectra are shown in Figures S18−S31. The microdroplet oxidations by preparative PSI had similarities to those by single-tip PSI in the yields, proving the practical utility of the scaling up microdroplet synthesis using preparative PSI.

CONCLUSION

In summary, we directly synthesized carboxylic acids from alcohols in microdroplets under UV irradiation by paper spray ionization for the first time. Complete oxidations of alcohols in microdroplets (near 100% yields) were attributed to the combinational actions of paper substrate as a thin film format and microdroplets of small sizes. Scaling-up syntheses of acids were further accomplished by preparative paper spray ionization. Overall, microdroplet synthesis by paper spray ionization not only achieved ∼100% oxidation in dramatically shortened reaction time in the absence of phase-transfer catalysts without side reactions, but also saved organic solvents and decreased the waste amounts dramatically at high ease of salt deposition typically at the capillary tips in electrospray or sonic spray ionization, demonstrating its potential to scalable syntheses. This work also paves a way to undergo the synthesis of carboxylic acids from alcohols under the expectations of green chemistry.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.9b00427.

> Chemicals and reagents, instruments, optimization of synthetic conditions, HPLC chromatograms of products under different conditions, and ^{1}H NMR and high-resolution mass spectra of carboxylic acids (PDF)

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The authors declare no competing financial interest.

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