

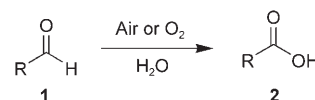
Highly Efficient Organic Reactions “on Water”, “in Water”, and Both**

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Water is the most abundant and environmentally friendly solvent in nature. Yet, its application in organic synthesis is currently limited.^[1] As most organic compounds have low solubility in water, much effort has been invested in the development of organic microenvironments in the aqueous phase, for example, in micellar catalysis.^[2,3] Recently, reactions of water-insoluble organic compounds that take place in aqueous suspensions (“on water”) have received a great deal of attention because of their high efficiency and straightforward synthetic protocols.^[4] Nevertheless, such reactions are still rare and lack generality. Herein we report a general procedure toward a common aerobic oxidation of aldehydes that takes place “on water” and its use in the consecutive three-component Passerini reaction both “on water” and “in water”.

The oxidation of aldehydes by oxygen or oxygen/nitrogen mixtures is a well-known reaction.^[5] Organic chemistry textbooks pay very little attention to the use of air in the synthesis of carboxylic acids from aldehydes. Notably, air is the ultimate “green” oxidant, more so than hydrogen peroxide, which is considered “green” for synthetic oxidation processes. In industry, aldehyde oxidation reactions are usually performed in bulk liquid aldehyde or organic solvents, with the stream of gas passing through the liquid phase.^[6] Various additives are often introduced into the system,^[7] but the role of these is still unclear.^[8] As the solubility of nonpolar gases, such as molecular oxygen, is generally low in any solvent,^[9] we hypothesized that the solvent is unnecessary or even detrimental to the oxidation process. An aldehyde oxidation taking place in thin layers of aldehyde, which increases the surface of interaction between the reagents, has also been reported, however, the yields were poor.^[10] Alternatively, such an increase in surface interaction can be achieved by mixing the aldehyde with water in the presence of oxygen. Indeed, we found that hydrophobic aliphatic (branched and linear) and aromatic aldehydes undergo facile oxidation upon simply stirring their aqueous emulsions in air to give the corresponding carboxylic acids in high yields

(Scheme 1).^[11] As both the starting materials and products are insoluble in water, they can be easily separated from the aqueous phase at the end of the reaction. The bubbling of gas



Scheme 1. Aldehyde oxidation “on water”.

through the liquid phase was not required, thus making the use of a condenser or other reactant traps unnecessary. The reactions proceeded smoothly both on a small scale (1 mmol) and on a relatively large laboratory scale (50 mmol). Table 1

Table 1: Aldehyde oxidation “on water”.^[a]

Entry	Aldehyde	Oxidation conditions	Yield [%]
1	<i>cyclo</i> -C ₆ H ₁₁ CHO (1a)	A	87
2	1a	B	87
3	1a	C	66
4	<i>n</i> C ₇ H ₁₅ CHO (1b)	A	50
5	1b	B	60
6	2-ethyl hexanal (1c)	A	86
7	1c	B	88
8	1c	C	75 ^[b]
9	benzaldehyde (1d)	A	83
10	1d	B	81
11	1d	C	53
12	<i>n</i> C ₄ H ₉ CHO (1e)	A	11

[a] See the Experimental Section for detailed reaction conditions. [b] 90% yield after 2 h with O₂.

shows typical results of the oxidation of liquid aldehydes “on water”. The reaction was especially straightforward for the preparation of solid carboxylic acids, such as benzoic acid, which precipitated from the reaction mixture and could be isolated by simple filtration. Importantly, very low amounts of by-products (mainly the corresponding formate) were observed in the “on water” reaction compared with the same reaction performed in bulk aldehyde. No oxidation was observed under the same conditions when the reaction was carried out in methanol or dichloromethane instead of water. Moreover, the addition of THF (5%) also completely inhibited the reaction.

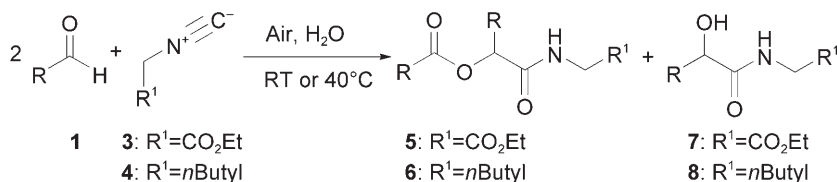
The highly efficient conversion of aldehydes into carboxylic acids described above inspired us to explore the possibility of coupling this reaction with a known “on

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water” accelerated process. Recently, Pirrung et al. reported elegant multicomponent Passerini- and Ugi-type reactions that were accelerated by using water as a solvent.^[4a,12,13] This finding led us to explore the possibility of using an aldehyde as the source of both carbonyl and ester functions in the Passerini reaction (Scheme 2).^[14] In this three-component



Scheme 2. Tandem aldehyde oxidation/Passerini reaction “on water”.

reaction, only two components would be added to the reaction mixture, with the third one generated in situ from one of the reagents. As many aldehydes and carboxylic acids show considerable solubility in water, it was important to establish to what extent the reactions proceed “in water” rather than “on water”.^[15] To this end, we studied the reaction of various aldehydes with water-insoluble isocyanides, which gave the Passerini products in the oxidation/three-component reaction sequence, (Table 2). As isocyanides slowly hydrolyze upon stirring with water, a slight excess of the aldehyde was used.^[16] Interestingly, the reactions between the highly hydrophobic aldehydes and the isocyanides “on water” and in air were complete after 3–4 hours at room temperature or upon

slight heating (40°C) to give the Passerini reaction products. On the other hand, more water soluble aldehydes gave mixtures of the Passerini products with another product—the α -hydroxyamide (Scheme 2). The ratio between the products roughly followed the solubility properties of the aldehyde (Table 2). Both propionic aldehyde and acetaldehyde, which

are fully miscible with water, formed geminal diols in 100% yield in aqueous solutions.^[17] α -Hydroxyamides were the only products obtained for these two aldehydes (Table 2, entries 15 and 16, 17 and 18, respectively). Although water-miscible aldehydes do not readily oxidize under these conditions, the lack of a carboxylic acid moiety was not responsible for the absence of the three-component Passerini products with such aldehydes. The reaction

between acetaldehyde, isocyanide, and acetic acid resulted in the formation of the α -hydroxyamide as the only product, which suggests that the reaction “in water” only gives this compound. In contrast, the reaction between octanoic aldehyde, isocyanide, and acetic acid gave only the Passerini product. It is likely that the formation of a *gem*-diol significantly decreases the concentration of the water-soluble aldehyde in the reaction. In addition, water competes favorably with the carboxylate in the nucleophilic addition to the carbonyl carbon atom when the reaction takes place “in water”.

In all cases, water-insoluble aldehydes gave the three-component Passerini products in high yields, while partially soluble aldehydes gave mixtures of both products, thus indicating the competition between the “in water” and “on water” reactions. Also, more hydrophobic pentyl isocyanide (**4**) reacted significantly faster than ethyl isocyanoacetate (**3**) and gave significant amounts of the Passerini product, even with partially water soluble aldehydes (Table 2, entries 11 and 14.). In support of the heterogeneous nature of the reaction mixture, the product distribution showed some dependence on the stirring rates (Table 2, compare entries 11 and 12).^[18] Importantly, almost no reaction was observed when the reactions were performed in methanol or dichloromethane under the same conditions. Furthermore, the reaction “in water” was significantly slower than the reaction “on water” even when the reactants were partially water soluble.^[19]

We further investigated the mechanism of the “on water” oxidation–Passerini reaction sequence by using isotope labeling experiments. When 1-octanal (**1b**) was stirred with H_2^{18}O (2 mL) under oxygen for 5 hours, about 60% of the 1-octanoic acid (**2b**) obtained had one labeled oxygen atom incorporated in the structure (Table 3, entry 1). As no ^{18}O incorporation was observed when nonlabeled 1-octanoic acid was stirred with H_2^{18}O , the incorporation of this isotope occurs prior to the formation of the carboxylic acid. Two possible pathways may account for this labeling: either rapid aldehyde/*gem*-diol equilibration^[20] on the water surface or an exchange reaction in one of the peroxo or radical species that are postulated in the oxidation of aldehydes by molecular oxygen (Scheme 3).^[5] Interestingly, when the Passerini reaction (Scheme 2) was performed in H_2^{18}O , the incorporation of

Table 2: Aldehyde oxidation/Passerini reaction “on water” and “in water”.^[a]

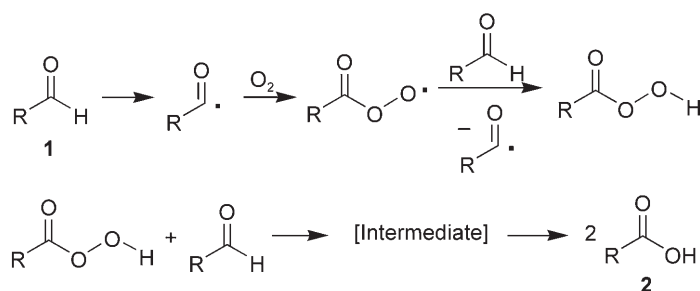
Entry	Aldehyde RCHO	Isonitrile R ¹ CH ₂ NC	5	7	Product ratio [%]	6	8
1	1a	3	80	0	—	—	—
2	1a	4	—	—	81 (90) ^[b,d]	0	—
3	1b	3	90	0	—	—	—
4	1b	3	84 ^[c]	0	—	—	—
5	1b	4	—	—	90 (71) ^[d]	0	—
6	1d	3	30 ^[e]	0	—	—	—
7	1d	4	—	—	57 ^[e]	0	—
8	1e	3	12	37	—	—	—
9	1e	4	—	—	37	11	—
10	R = <i>i</i> Pr, 1f	3	5 ^[d]	74 ^[d]	—	—	—
11	R = <i>i</i> Pr, 1f	4	—	—	35 (30) ^[d]	42 (34) ^[d]	—
12	R = <i>i</i> Pr, 1f	4	—	—	28 ^[f]	60 ^[f]	—
13	R = <i>n</i> Pr, 1g	3	2	51	—	—	—
14	R = <i>n</i> Pr, 1g	4	—	—	36	44	—
15	R = Et, 1h	3	0	58	—	—	—
16	R = Et, 1h	4	—	—	7 (4) ^[d]	32 (30) ^[d]	—
17	R = Me, 1i	3 ^[g]	0	72	—	—	—
18	R = Me, 1i	4 ^[g]	—	—	0	59	—

[a] Conditions: The mixture of the aldehyde and isocyanide in a 3:1 ratio was stirred at 1100 rpm for 3 h at 40°C. The organic products were extracted with CH_2Cl_2 , the solvent was evaporated, and the mixture analyzed by ^1H NMR spectroscopy. [b] After 4 h. [c] The reaction was performed at room temperature. [d] Yield of isolated product. [e] Benzoic acid precipitates during the reaction, which results in lower yields. [f] The reaction was stirred at 300 rpm. [g] An aldehyde/isocyanide ratio of 10:1 was used.

Table 3: ^{18}O Isotope distribution in aldehyde oxidation–Passerini reactions “on H_2^{18}O ”.[a]

Entry	Reaction on “ H_2^{18}O ”	^{18}O Isotope distribution in product
1	1b O_2 , 5 h	2b 1 ($2 \times ^{16}\text{O}$): 3 ($^{16}\text{O} + ^{18}\text{O}$)
2	1b (3 equiv) + 3 air, 3 h	5b 1 ($2 \times ^{16}\text{O}$): 7 ($^{16}\text{O} + ^{18}\text{O}$): 20 ($2 \times ^{18}\text{O}$)
3	1b (3 equiv) + 4 air, 3 h	6b 1 ($2 \times ^{16}\text{O}$): 2 ($^{16}\text{O} + ^{18}\text{O}$): 3 ($2 \times ^{18}\text{O}$)
4	1b + 2b + 3 air, 3 h	5b 1 ($2 \times ^{16}\text{O}$): 8 ($^{16}\text{O} + ^{18}\text{O}$)
5	1b + 2b + 4 air, 3 h	6b 1 ($2 \times ^{16}\text{O}$): 6 ($^{16}\text{O} + ^{18}\text{O}$)

[a] All reactions were performed under standard conditions for the aldehyde oxidation and Passerini reactions.



Scheme 3. General mechanism for aerobic oxidation of aldehydes (see Ref. [5]).

one (minor product) and two (major product) labeled oxygen atoms into the final products was observed (Table 3, entries 2 and 3; **5b** and **6b**, respectively).

The reaction with nonlabeled 1-octanal (**1b**), 1-octanoic acid (**2b**), and ethyl isocyanoacetate (**3**) or pentyl isocyanide (**4**) in H_2^{18}O , gave the Passerini product with one incorporated ^{18}O as the major product (Table 3, entries 4 and 5; **5b** and **6b**, respectively). For comparison, the Passerini reaction products showed no incorporation of ^{18}O upon stirring “on H_2^{18}O ” in the presence of acid. The less reactive ethyl isocyanoacetate (**3**) gave more ^{18}O incorporation in the Passerini reaction product compared to the reaction with pentyl isocyanide (**4**).

In conclusion, we have reported a general approach for “on water” oxidation of aldehydes by using air or molecular oxygen as the oxidant. This method can be extended to perform consecutive organic reactions “on water” with hydrophobic organic compounds, such as the multicomponent Passerini reaction. The reported reactivity significantly advances the use of water as a medium for organic reactions. We are currently investigating the interaction modes between water and organic substrates as well as the scope of the “on water” oxidation of aldehydes in triggering other organic transformations.

Experimental Section

General experimental procedures: All reactions were performed in ultrapure water (Ω 18 MOhm, < 10 ppb total organic content), which was obtained by using the Barnstead EASYpure II UF water

purification system. The use of standard deionized water gave comparable results. The reagents were purchased from Sigma–Aldrich and used as received. In several cases, the aldehydes were purified by distillation, however, the reactivity of the distilled compounds was found to be identical to that of the commercially available chemicals. The reactions were performed in test tubes with the Radleys Carousel Workstation. Alternatively, the reactions could be performed in disposable 20 mL scintillation vials. Complete product characterization is reported in the Supporting Information.

Conditions for aldehyde oxidation: Method A: A suspension of aldehyde (100 μL , ca. 0.6–1 mmol) in pure water (3 mL) was added to a 50 mL glass tube equipped with a magnetic stirrer bar and stirred at room temperature at 1100 rpm for 12 h in the presence of air. The product was quantitatively extracted with CH_2Cl_2 and isolated after solvent evaporation. When CDCl_3 was used instead of CH_2Cl_2 without solvent evaporation, the ^1H NMR analysis of the reaction mixture showed a product distribution identical to that obtained under standard work-up conditions, thus indicating that no volatile organic compounds are formed. Method B: A suspension of aldehyde (100 μL , ca. 0.6–1 mmol) in pure water (3 mL) was added to a 50 mL round-bottomed flask and stirred at room temperature for 2 h in pure molecular oxygen at 1 atm. The product was quantitatively extracted with CH_2Cl_2 and isolated after solvent evaporation. Method C: A suspension of aldehyde (5 mL) in pure water (50 mL) was added to a 500 mL round-bottomed flask and stirred at room temperature for 12 h in the presence of air. The product was quantitatively extracted with CH_2Cl_2 and isolated after solvent evaporation. Generally, most of the product could be collected by simple phase separation of the reaction mixture. The organic solvents were used to ensure quantitative mass balance of organic compounds.

Conditions for the Passerini reaction: Unless reported otherwise, a suspension of aldehyde (0.51 mmol) and isocyanide (0.17 mmol, 3:1 ratio) in water (3 mL) was stirred for 3 h at 40°C in the presence of air in a 50 mL glass reactor. Generally, 2 equiv of the aldehyde was sufficient to achieve high yields of the Passerini product, however, small amounts of hydrolyzed isocyanide were obtained in some cases. For **1i**, 10 equiv of aldehyde was used. The organic products were extracted with CH_2Cl_2 , the solvent was evaporated and the mixture analyzed by ^1H NMR spectroscopy. No by-products were observed in the reactions of aldehydes with isocyanides. Small amounts of recovered starting materials and hydrolysis of the isocyanide were also observed.

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