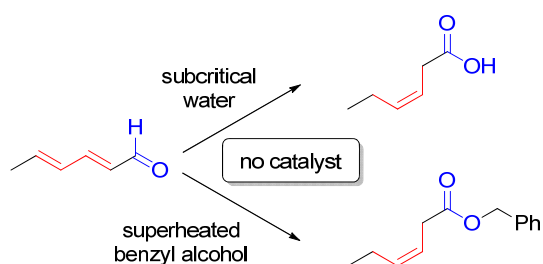


One-step and Non-catalytic Intramolecular Redox Reactions of Conjugated All *E*-Dienals to Non-conjugated *Z*-Enoic Acids in Subcritical Water

Xin Chen, Kana Sumoto, Sotatsu Mitani, Tetsuya Yamagami, Kazuya Yokoyama, Pengyu Wang, Shotaro Hirao, Nagatoshi Nishiwaki, Kazuya Kobiro*

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Keywords: Subcritical water; Non-catalytic reaction; One-step reaction; Intramolecular redox

Highlights

1. Non-conjugated unsaturated acid derivatives are obtained by treating conjugated dienals in superheated fluids in one-step.
2. Simple treatment of all *E*-dienals in superheated fluids produces thermodynamically less-stable *Z* unsaturated acid derivatives.
3. The obtained non-conjugated unsaturated acid is converted to biologically active γ -lactone with a hydroxyl group by hydrogen peroxide in one step.

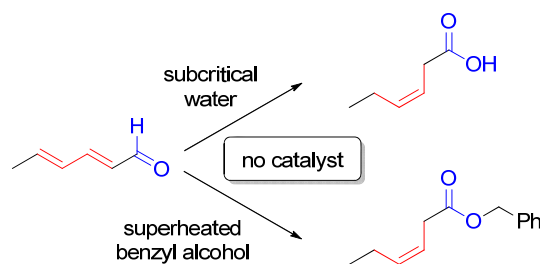
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Abstract

Simple treatment of conjugated all *E*-dienal, (2*E*,4*E*)-hexa-2,4-dienal, in subcritical water afforded an intramolecular redox product, non-conjugated *Z*-enoic acid, (*Z*)-hex-3-enoic acid, in 42% yield without the usage of a metal catalyst in one-step under the conditions of 250 °C, 10 min, and 0.35 g mL⁻¹ water amount. Similar treatment of the dienal in superheated benzyl alcohol produced corresponding ester, benzyl (*Z*)-hex-3-enoate, in 34% yield under the conditions of 300 °C, 30 min, and 0.5 g mL⁻¹ benzyl alcohol amount. The obtained (*Z*)-hex-3-enoic acid was transformed to *cis*-β-hydroxy-γ-ethyl-γ-lactone in 90% yield by hydrogen peroxide at 60 °C for one day under solvent-free conditions.

1. Introduction

Unsaturated acids and their derivatives are important substances to show various bioactivities. For example, naturally occurring unsaturated fatty acids, such as arachidonic, docosahexaenoic, and eicosapentaenoic acids, are quite important bio-precursors that lead to regulating reagents in bodies [1,2]. Almost all naturally occurring fatty acids contain the *Z*-configuration in their double bonds, which is less stable than the *E*-configuration. In addition, simple (*Z*)-alk-3-enoic acids bearing one non-conjugated double bond are important in vivo, some of which are pheromones of certain coleopterous insects or intermediates used in their syntheses [3-5]. Moreover, a brominated (*Z*)-alk-3-enoic acid derivative exhibits cytotoxicity against cultured cells [6]; 3-unsaturated amino acids are known to function as specific enzyme inhibitors and pyridoxal phosphate dependent enzymes [7,8]; and an ester derivative is a potent odorant in Japanese Green Tea [9]. Furthermore, (*Z*)-alk-3-enoic acid derivatives are the possible precursors of γ -lactones with alkyl chains exhibiting pheromone characteristics [10].

Intense research to obtain thermodynamically less-stable *Z* isomers of non-conjugated unsaturated hexenoic acids and their related compounds has led to several methods for

selective hydrogenation using transition metal complexes. Hydrogenation of sorbic acid catalyzed by $\text{Cr}(\text{CO})_6$ [11] or $[\text{Cp}^*\text{Ru}]^+$ [12,13], which fixes two double bonds of sorbic acid to *s-cis* conformation in the metal center, is a typical method. The classical P-2 Ni catalyst is also available through the hydrogenation of unsaturated acid bearing a triple bond [4,5]. Olefin metathesis using the Grubbs' II catalyst is employed to afford cyclic derivatives containing a double bond with the *Z*-configuration followed by ring cleavage [14]. Lithium–ammonia reduction of 2-thiophenecarboxylic acid [15] and the addition of alcohol to ketene intermediate from corresponding acid chloride in situ [16] also appeared in the literature.

In contrast, much attention has been paid to superheated fluids such as subcritical water (sub-CW) [17], supercritical water (SCW) [17], and supercritical alcohols [18,19] from the perspective of green reactions because of their unique properties. For example, extremely strong complexation effect under high pressure produces solvent clusters around the solute molecules, which leads to strong interactions between the solute and solvent molecules. In addition, a major characteristic of superheated fluids is that their inherent high temperatures cause vigorous vibration of the molecules in the system, which leads to high reactivity between them. By employing these remarkable properties, intriguing reactions were reported, such as the Beckmann rearrangement of

cyclohexanone oxime [20], pinacol rearrangement of 2,3-dimethyl-2,3-butanediol [21], and Cannizzaro reaction of formaldehyde [22], acetaldehyde [23,24], and benzaldehyde [25] in SCW without any catalyst. Through the researches, we recently disclosed a series of unique reactions, such as non-catalytic green oxidation of alcohols in SCW without any oxidant to give ketones and hydrogen gas [26], highly selective non-catalytic Oppenauer oxidation of alcohols in SCW [27], the first direct observation of radical species in sub-CW by means of ESR [28], easy permethylation of catechols in SCW [29], and effective aldol reactions in sub-CW [30].

These studies allowed us to delineate the organic transformations of conjugated dienals into non-conjugated unsaturated acids with *Z*-form by thermal intramolecular rearrangement in superheated fluids. We now present an example of metal-free, non-catalytic, and simple preparation of (*Z*)-alk-3-enoic acid from (*2E,4E*)-alka-2,4-dienal in sub-CW.

2. Material and methods

General information.

(*2E,4E*)-Hexa-2,4-dienal and (*2E,4E*)-hexa-2,4-dienol were purchased from Alfa Aesar. Cinnamaldehyde, acetophenone, benzaldehyde, 3-methylbut-2-enal, *m*-xylene, 2,4-dinitrophenylhydrazine, and benzyl alcohol were purchased from Nacalai Tesque Inc. (*2E,4E*)-1,5-Diphenylpenta-2,4-dien-1-one, (*3E,5E*)-6-methylhepta-3,5-dien-2-one and silica gel (Wakogel C-200) were purchased from Wako Pure Chemical Industries Co. Ltd. (*2E,4E*)-Deca-2,4-dienal, *n*-decane, *n*-dodecane, and *n*-tridecane were obtained from Tokyo Chemical Industry Co. Ltd. They were used as received without further purification. NMR spectra were obtained using Varian UNITY INOVA spectrometer and Bruker AVANCE III 400N (400 MHz). GC-MS analyses were performed on a Shimadzu QP5050 with DB-1 column. GC analyses were performed on a Shimadzu GC-17A and DB-1 or CBP-5 column. Recoveries of reactants (percentage of reactant recovered to that loaded in the reaction) and yields of products were determined by internal standard methods on GC. *n*-Decane, *n*-dodecane, and *n*-tridecane were used as the internal standards. Products were identified by comparing the ¹H NMR and/or GC-MS spectra with those of authentic samples. Microwave heating was performed using Anton Paar

Monowave 300 microwave Synthesis Reactor.

General procedure for reactions in subcritical water.

(2*E*,4*E*)-Hexa-2,4-dienal and reverse osmosis water, in which the dissolved oxygen was removed by N₂ gas bubbling for 30 min, were introduced into an SUS 316 batch-type reactor (10 mL volume). To remove the oxygen in the reactor, the reactor was purged with N₂ for 10 min and sealed with a screw cap, which was equipped with a thermocouple for measuring the inner reactor temperature. The reactor was then placed in a molten salt bath, which was maintained at an appropriate temperature and heated for an appropriate time. A period of approximately 20–30 s was required to raise the inner temperature of the reactor to 200–350 °C. The reaction was quenched by placing the reactor into an ice-water bath. The screw cap was opened after the reactor cooled completely. Microwave heating was done in a glass reaction vessel. A period of approximately 3.5 min was required to raise the temperature of the reactor to 220 °C and approximately 4.5 min was required to cool the temperature to 60 °C. The reaction mixture was extracted with ethyl ether three times. The organic phase was separated from the water phase, and the solvent was evaporated in vacuo to produce crude products. These crude products were purified by using silica gel chromatography (Wako

C-200, ether and hexane) and GPC (JAI gel 1H and 2H, chloroform) when necessary.

Reaction of 2a with hydrogen peroxide.

A mixture of 34 mg (0.30 mmol) of (*Z*)-hex-3-enoic acid and 150 μ L of 30% H₂O₂ solution (1.47 mmol) was heated at 60 °C for 1 day with vigorous stirring. The solvent was removed under reduced pressure to afford 35.4 mg (0.27 mmol, 90%) of *cis*- β -hydroxy- γ -ethyl- γ -lactone as a single product.

3. Results and discussion

(*2E,4E*)-Hexa-2,4-dienal (**1a**) was treated in sub-CW under different conditions of reaction temperature, reaction time, and water amount (Scheme 1 and Table 1). When the reaction was performed under the conditions of 250 °C, 10 min, and 0.10 g/mL water amount, the reaction proceeded smoothly to afford mainly (*Z*)-hex-3-enoic acid (**2a**, 29%) and a by-product 2-methylcyclopent-2-enone (**3a**, 1%) with 19% recovery of dienal **1a** (entry 4). It is quite noteworthy that the *Z* isomer of **2a** was easily obtained simply by starting from all *E* dienal without using any metal catalyst. Interestingly, the diene moiety of **1a** was reduced to monoene and the aldehyde moiety was oxidized to carboxylic acid in one step, which is an example of intramolecular redox reactions. For intermolecular redox reactions of aldehydes, the conventional Cannizzaro reaction is well known to simultaneously give a reduction product of alcohol and an oxidation product of acid under strongly basic conditions. However, when the Cannizzaro reaction is performed under sub-CW and SCW conditions, the reaction proceeds even without a catalyst [22-25]. For intramolecular redox reaction of conjugated enals, unique catalytic intramolecular redox reactions of enals affording saturated acids as well as lactones were reported [31]. However, our reaction is, to the best of our knowledge, the first

example of non-catalytic intramolecular Cannizzaro reaction of dienals affording non-conjugated unsaturated acids **2a**. When the reaction was performed at a low temperature (200 °C), only a small amount of **2a** with a trace amount of **3a** was obtained (entry 1). The yield of **2a** increased with temperature up to 250 °C, while a higher temperature (350 °C) did not yield the product (entries 1, 5, 8, and 9). These results indicate that the reaction has high activation energy and that the products are not stable at high temperatures. Prolonged heating caused isomerization to yield a conjugated acid with higher stability, (*E*)-hex-2-enoic acid (**4a**), and γ -ethyl- γ -lactone (**5a**), which should be derived from the cyclization of **2a** or **4a** under the reaction conditions (entry 7). It is noteworthy that no product was produced in the absence of water (entry 3), indicating water plays a critical role in the reaction. In addition, water amount dependence was observed for the formation of **2a** (entries 3-6) at the fixed temperature (250 °C) and in fixed reaction time (10 min), suggesting solubility of **1a** to water is improved till 0.35 g mL⁻¹ water amount. The best result was achieved under the conditions of 250 °C, 10 min, and 0.35 g/mL water amount to afford **2a** in 42% yield with a trace amount of **3a** (1%) (entry 5). Microwave heating instead of molten salt bath resulted in similar yield of **2a** (entry 2).

Scheme 1.

Reactions of (2*E*,4*E*)-hexa-2,4-dienal (**1a**) and (2*E*,4*E*)-deca-2,4-dienal (**1b**) in sub-CW.

Table 1

Reaction of (*E,E*)-dienal **1a** in sub-CW.

When the present reaction was applied to (2*E*,4*E*)-deca-2,4-dienal (**1b**) with a long alkyl chain under similar reaction conditions of 250 °C, 30 min, and 0.35 g/mL water amount, corresponding (*Z*)-dec-3-enoic acid (**2b**), which is a precursor of a γ -lactone derivative exhibiting pheromone character [11], was nicely obtained in 20% yield. For conjugated ketone derivatives such as (2*E*,4*E*)-1,5-diphenylpenta-2,4-dien-1-one (**6**) and (3*E*,5*E*)-6-methylhepta-3,5-dien-2-one (**10**), however, a remarkable difference in reaction behavior was observed to continuously produce retro-aldol products cinnamaldehyde (**7**), acetophenone (**8**), benzaldehyde (**9**), and 3-methylbut-2-enal (**11**) in addition to a cyclization product, m-xylene (**12**). Judging from these results, the aldehyde group is indispensable for the intramolecular redox reactions and the cyclization. The formation of **12** can be explained by thermal electrocyclic reaction of a 6π electron system of enol generated by tautomerism of **10** followed by dehydration [32,33].

Scheme 2.

Reaction of dienones in sub-CW.

Concerning the formation of cyclopentenones, Miller et al. reported the reaction of dienal derivatives via Nazarov-type cyclization or hetero $[\pi 4a+\pi 2a]$ concerted bond formation [34]. However, the critical differences between their and our reactions are the configuration of double bonds in the reactants and the use of catalysts. The researchers specifically used 2*Z*,4*E*-isomer as a substrate in dichloromethane in the presence of strong Lewis acids as catalysts, while we used 2*E*,4*E*-isomer and only water without any catalyst. Similar cyclization was reported for the congested dienal with plural sterically bulky groups via a ketene intermediate as a special case [35]; however, non-substituted simple dienal **1a** was used in our reaction.

As plausible reaction pathways, we propose two possibilities via ketene intermediate (pathway A) and *gem*-diol intermediate (pathway B), both of which include [1,5]hydrogen shift as the key step (Scheme 3). Thermal reactions yielding *Z*-configuration of double bonds employ [1,5]hydrogen shift as a well-established methodology. Interesting applications of [1,5]hydrogen shift recently appeared as a key

process for the activation of C-H bonds, although the reactions required acid catalysts [36,37]. Intermediate **I** can be produced via Michael addition of water followed by the *E/Z* isomerization of a double bond and dehydration. Further hydration of intermediate **I** would afford *gem*-diol intermediate **II** (Scheme 3). Theoretical considerations by DFT calculations suggested a plausible reaction pathway via [1,5]hydrogen shift leading to a ketene intermediate **III** (Scheme 4). The activation energy from the intermediate **I** to the transition state **TS-1** is calculated to be 26.3 kcal/mol. Once the ketene intermediate **III** is generated, water can be easily added to produce carboxylic acid **2a**. As an additional possibility, we supposed the reaction pathway via *gem*-diol intermediate **II** because aldehyde intermediate **I** can be easily hydrated in high-pressure water to produce intermediate **II** (Scheme 3). Similar DFT calculation indicates that the pathway leading to the transition state **TS-2** from the *gem*-diol intermediate **II** requires slightly higher activation energy of 30.8 kcal/mol (Scheme 4). The resulting intermediate **IV** would get tautomerism to produce non-conjugated acid **2a**. Thus, high-density water molecules of sub-CW seem not to participate in the key step of the reaction, while sub-CW can play several important roles at once required for the reaction; such as i) a green reaction medium (solvent), ii) an effective heat-transferring material tolerating quite drastic atmosphere, and iii) an indispensable reactant affording the acid.

Scheme 3.

Plausible reaction pathways from **1a** to **2a**.

Scheme 4.

Activation energies of the reactions via a ketene intermediate (pathway A) and a *gem*-diol intermediate (pathway B). (Numbers are relative energies in kcal/mol calculated by DFT B3LYP/6-31G* plus zero-point vibrational energy)

According to the reaction pathway proposed in Scheme 3, the reaction in superheated alcohol instead of sub-CW should afford a corresponding ester instead of the acid. The reaction of **1a** in high-temperature benzyl alcohol (300 °C, 30 min, and 0.2 g/mL alcohol amount) actually yielded corresponding ester, benzyl (*Z*)-hex-3-enoate (**13**), in 31% yield as expected, concomitant with benzyl (*E*)-hex-2-enoate (**14**) in 4% and (*2E,4E*)-hexa-2,4-dienol (**15**) in 5% yield (Scheme 5 and Table 2). Alcohol **15** should be produced by Meerwein–Ponndorf–Verley (MPV) reduction of aldehyde **1a** in the presence of a large excess amount of benzyl alcohol because the reaction conditions were the variant of representative non-catalytic MPV reduction [19]. Thus, it is truly

noteworthy that the ester was obtained as a main product from aldehyde directly even though under MPV reduction conditions.

Scheme 5.

Reaction of (*E,E*)-dienal **1a** in superheated benzyl alcohol.

Table 2

Reaction of **1a** in superheated benzyl alcohol.

The bifunctionality of the unsaturated acid prompted us to further study chemical transformation. A C=C bond of an alkene is generally oxidized by peracid such as *m*CPBA or by a combination of hydrogen peroxide and acid. Thus, intramolecular oxidation appears to be possible when unsaturated acids are treated with hydrogen peroxide under solvent-free conditions; however, oleic acid, a typical unsaturated acid, is intact upon heating with hydrogen peroxide at 60 °C. In contrast, β,γ -unsaturated acid **2a** efficiently reacted under the same conditions to afford *cis*- β -hydroxy- γ -ethyl- γ -lactone (**16**) [38] in 90% yield (Scheme 6). It is considered that intramolecular oxidation readily proceeds, leading to epoxide **18** when **2a** is converted to peracid **17** by hydrogen peroxide. The successive ring expansion is caused by

participation of the carboxyl group to form a lactone framework, although an additional pathway via diol **19** is possible. This reaction does not require a solvent or a reagent other than hydrogen peroxide and furnishes *cis*- γ -lactone **16** as a single isomer, which is promising for application to organic syntheses.

Scheme 6.

Tandem intramolecular oxidation-ring expansion affording *cis*- γ -lactone **16**.

4. Conclusions

In summary, the organic one-step transformation of conjugated dienals into non-conjugated unsaturated acid derivatives was achieved in superheated fluids. It is of importance that thermodynamically less-stable *Z* isomers of unsaturated acid derivatives were produced mainly by simple treatment of all *E*-dienals in superheated fluids. In addition, the obtained non-conjugated unsaturated acid was converted to the biologically active γ -lactone with a hydroxyl group by hydrogen peroxide in one step.

Acknowledgements

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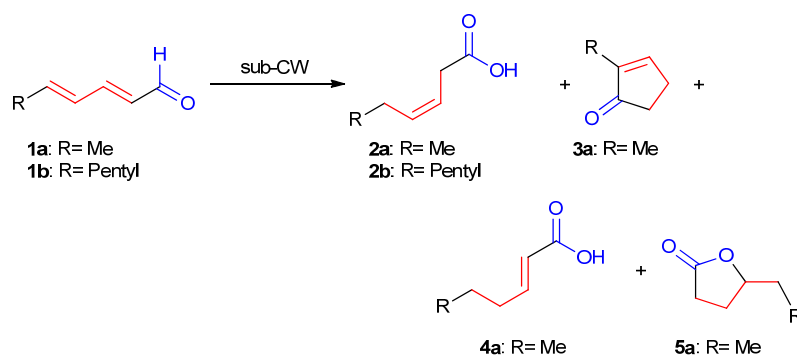
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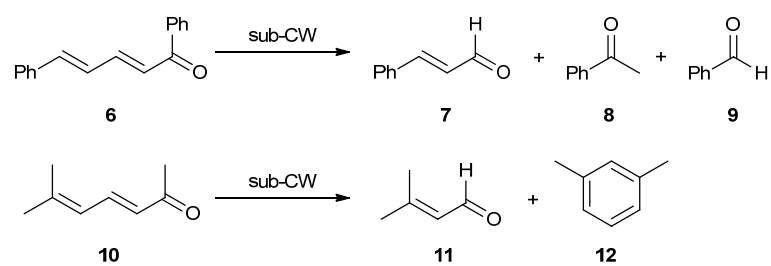
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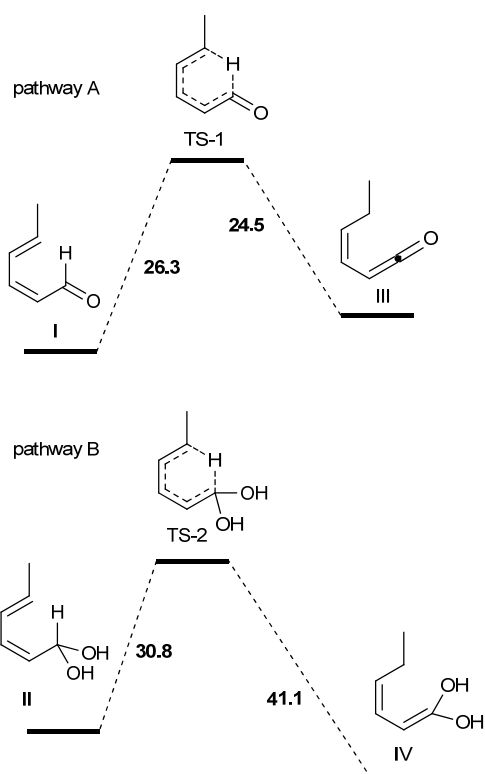


Scheme 1. Reactions of (2*E*,4*E*)-hexa-2,4-dienal (**1a**) and (2*E*,4*E*)-deca-2,4-dienal (**1b**)

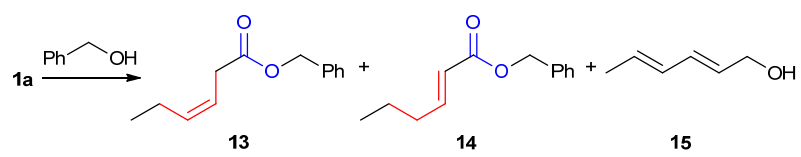
in sub-CW.



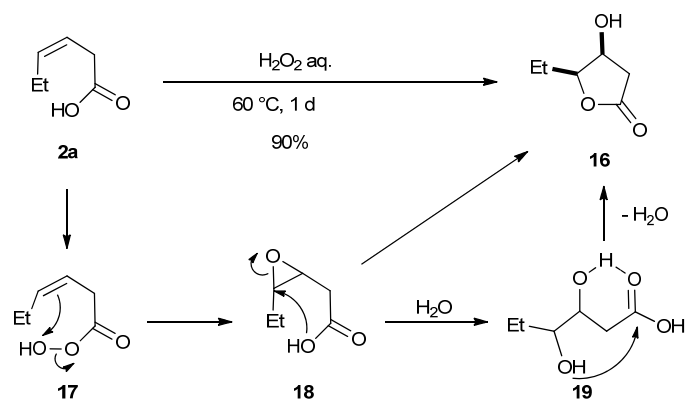
Scheme 2. Reaction of dienones in sub-CW.



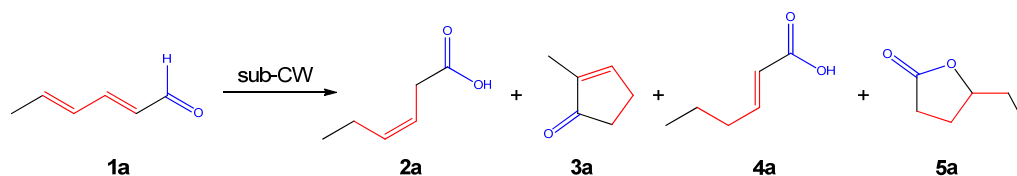
Scheme 4. Activation energies of the reactions via a ketene intermediate (pathway A) and a *gem*-diol intermediate (pathway B). (Numbers are relative energies in kcal/mol calculated by DFT B3LYP/6-31G* plus zero-point vibrational energy)



Scheme 5. Reaction of (*E,E*)-dienal **1a** in superheated benzyl alcohol.



Scheme 6. Tandem intramolecular oxidation-ring expansion affording *cis*- γ -lactone **16**.

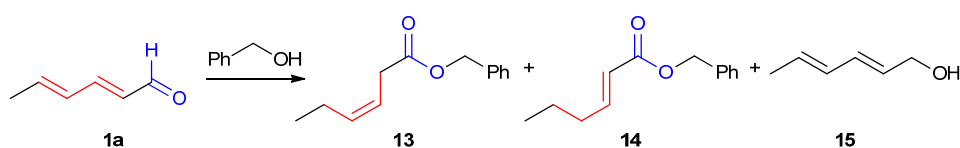
Table 1Reaction of (*E,E*)-dienal **1a** in sub-CW.^a

Entry	Temperature (°C)	Water amount (g mL ⁻¹) ^b	Time (min)	Recovery of 1a (%)	Yield (%)			
					2a	3a	4a	5a
1	200	0.35	10	58 (3)	3 (0.9)	1 (0.1)	—	—
2 ^c	220	0.35	30	7 (2)	37 (3)	3 (0.1)	—	—
3	250	0	10	43 (2)	—	—	—	—
4	250	0.10	10	19 (3)	29 (0.2)	1 (0.2)	—	—
5	250	0.35	10	11 (3)	42 (0.5)	1 (0.6)	—	—
6	250	0.40	10	8 (0.8)	36 (3)	1 (0.3)	—	—
7	250	0.35	30	—	32 (2)	2 (0.2)	10 (0.7)	3 (0.3)
8	300	0.35	10	—	5 (0.9)	—	2 (0.4)	—
9	350	0.35	10	—	—	—	—	—

^a 100 mg (1.04 mmol) of **1a** was reacted. Mean value is given for a minimum of three runs.

Standard deviation is shown in parentheses.

^b Water amount was defined as the weight of water (g)/reactor volume (mL).^c Microwave heating.

Table 2Reaction of **1a** in superheated benzyl alcohol.^a

Entry	Alcohol amount (g mL ⁻¹) ^b	Recovery of 1a (%)	Yield (%)		
			13	14	15
1 ^c	0.15	80 (4)	2 (0.2)	—	—
2 ^d	0.15	25 (7)	18 (1)	—	—
3	0.15	—	32 (0.3)	4 (2)	4 (0.1)
4	0.2	—	31 (2)	4 (0.2)	5 (1)
5	0.3	—	31 (4)	4 (0.2)	8 (2)
6	0.4	—	32 (1)	5 (1)	9 (1)
7	0.5	—	34 (1)	4 (0.6)	13 (0.5)

^a 100 mg (1.04 mmol) of **1a** was reacted at 300 °C. Mean value is given for a minimum of three runs. Standard deviation is shown in parentheses. Reaction time was 30 min.

^b Alcohol amount was defined as the weight of benzyl alcohol (g)/reactor volume (mL).

^c Reaction temperature at 200 °C.

^d Reaction temperature at 250 °C.