

# A ONE-STEP PRODUCTION OF MONOTERPENE ALCOHOL USING SUPERCRITICAL WATER IN THE ABSENCE OF CATALYST

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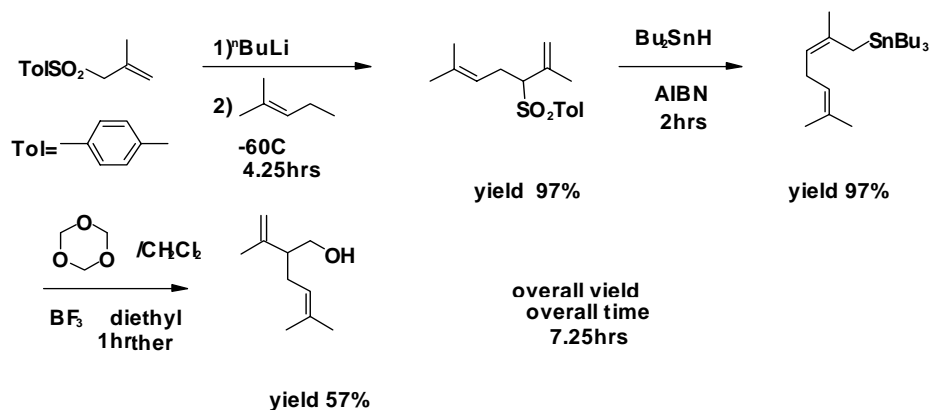
A one-step synthesis of monoterpene alcohols such as lavandulol, linalool and geraniol/nerol from hemiterpene alcohols proceeds efficiently in supercritical water (scH<sub>2</sub>O) without any catalyst. Our device of a microreaction ( $\mu$ -reaction) system achieves the production of lavandulol in 82% selectivity and 59% yield, respectively, even at a short reaction time of 7.7 s at 30 MPa and 375 °C in the near-critical region. The yield was superior to conventional method promoted by organometallic catalysts in which the reaction time of 7.25 hours is needed to obtain 54 % yield. When the reaction was carried out at a lower temperature of 300 °C in hot water, we obtained only 15 % yield even at a reaction time of 38 s. The acidic ability of H<sub>2</sub>O peculiar to supercritical conditions is thus considered to promote the desired pathway alone, and so the scH<sub>2</sub>O  $\mu$ -reaction system could conveniently prevent side reactions such as dehydration and hydrolysis.

## INTRODUCTION

In recent aspects of organic synthesis, the matter of primary interest is accelerating reaction rates as well as improving selectivities via more "green" or environmentally friendly chemical processes. Monoterpene alcohols not only have been known to function as allelochemicals or secondary metabolites which are indispensable for life process [1], but also are valuable compounds for fragrant substance, anti-microbials, fungicide and insecticide in pharmaceutical, cosmetic, and flavor manufacturing industries [2]. However, their practical production has suffered from the disadvantages of complex multistage processes leading to low yields and of using environmentally damaging organic solvents and transition metal catalysts, and of

problems associated with catalyst-product separation.

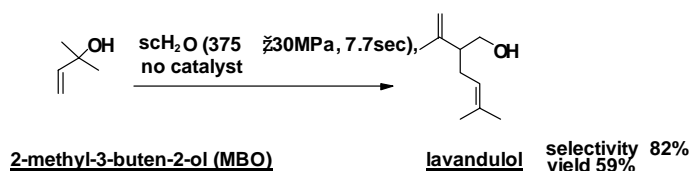
For the efficient production of lavandulol, a one-step synthesis has been attempted to form C<sub>10</sub> unit from C<sub>5</sub> units such as isoprene



Scheme 1. An example of conventional lavandulol synthesis

by use of excess strong acid according to the isoprene rule [3], but the one-step process so far employed has not given the lavandulol in satisfactory yield [4]. On the other hand, as show in Scheme 1, in a batchwise multistep operation in the presence of environmental damaging organotin compounds in organic solvents, the desired lavandulol was synthesized in a better yield of 44 to 53 %, but long reaction times extending to 7 to 11 hrs are required to go up to the reasonable yield. [5].

Supercritical water (scH<sub>2</sub>O) should be a useful replacement for organic solvents, because water is the most environmentally acceptable, naturally abundant, and inexpensive solvent, and its physicochemical properties can be changed widely with pressure and temperature [6]. However, the ion product (K<sub>w</sub>) for scH<sub>2</sub>O is much lower than liquid water under certain conditions [7], and there have been few research works on the use of scH<sub>2</sub>O as catalyst for acid-or base-catalyzed organic syntheses [8]. Contrary to the conventional wisdom that acid or base-catalyzed reactions will not take place in scH<sub>2</sub>O, Ikushima et al. [9-13] demonstrated the possibility of scH<sub>2</sub>O participating in acid or base-catalyzed organic synthesis at the same time as catalyst as well as medium. This new conception originated from our finding on the significant reduction of the strength of hydrogen bonding in H<sub>2</sub>O peculiarly near the critical point base on *in situ* IR [12], Raman [14] measurements as well as an *ab initio* first principle dynamic study [15]. In this report, we thus substantiated that the new-generation one-step synthesis of lavandulol from 2-methyl-3-buten-2-ol as shown in Scheme 2 can be successfully created by our microreaction system [12,13].



Scheme 2. One-step production of lavandulol using scH<sub>2</sub>O.

## I - EXPERIMENTALS

The scH<sub>2</sub>O microreaction ( $\mu$ -reaction) system can heat up very quickly an ambient substrate solution to the supercritical state and then can quench rapidly to sufficiently low temperatures after the reaction. That is, as shown in Figure 1, pressurized ambient water at relatively faster flow rates of 3.0 to 10.0 mL min<sup>-1</sup> was heated up to around 500 °C in a heating bath, and then the scH<sub>2</sub>O solution was sent to the entrance of a quick-heating part (union tee made of Hastelloy C-276) through a 1/16 in. Hastelloy C-276 tube. A stream of ambient substrate prenol or 2-methyl-3-butene-2-ol (MBO) aqueous solution (0.15 mol kg<sup>-1</sup>) passing through a 1/16 in. Hastelloy C-276 tube was struck against the high-speed flow of the scH<sub>2</sub>O

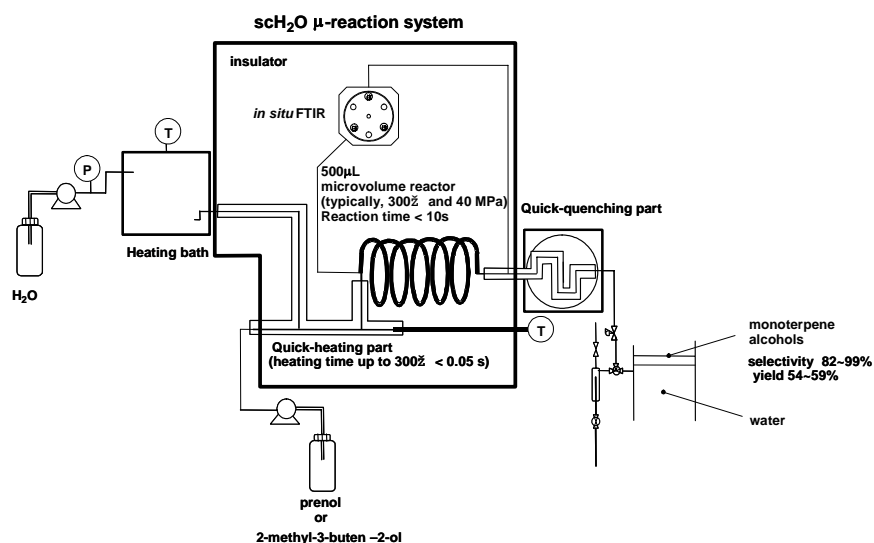


Figure 1. A schematic diagram of microreaction system equipped with high-pressure and high-temperature FTIR.

in the union tee, and was realized to be raised up to the supercritical temperature of 375 within 0.05 s, and the mixture was then introduced into a 500  $\mu\text{L}$  microreactor (300  $\mu\text{m}$  i.d.) made of Hastelloy C-276, in which the reaction times were adjusted to be shorter than several seconds in order to investigate the extent of ability drawn from the real acidity or basicity of  $\text{scH}_2\text{O}$  itself at such short residence times. After the reaction, the solution was quenched rapidly to room temperature because of the prevention of pyrolysis and hydrolysis. As a result, the fluctuations in temperature were controlled to within  $\pm 0.1$  allowed for the experimental error. This  $\text{scH}_2\text{O}$   $\mu$ -reaction system also permitted observation of IR spectral changes *in situ* by high pressure and high temperature FTIR. Further detailed analysis of the reaction mixture at the end of reaction was performed by GC-MS.

## II-RESULTS AND DISCUSSION

### II-I The one-step production from prenil

We attempted the GC-MS analysis of the reaction mixture obtained by our  $\mu$ -reaction system at a reaction (residence) time of 38.0 s in  $\text{scH}_2\text{O}$  at 375 and 30 MPa. As a result, as shown in Figure 2, the monoterpene alcohol mixture, including predominantly lavandulol, linalool,  $\alpha$ -terpineol and geraniol/nerol was confirmed by a direct comparison with each authentic sample. Hence we have first demonstrated a new one-step dimerization process for the formation of monoterpene alcohols from hemiterpene alcohol such as prenil using only  $\text{H}_2\text{O}$  in the absence of any catalyst. The monoterpene alcohols were formed in a high conversion around 90 % at a higher temperature of 375 in  $\text{scH}_2\text{O}$ , but in a low yield below 20 %. This low yield seems to be due to the isomerization of prenil to MBO and the subsequent dehydration of MBO to isoprene from the GC-MS results. Moreover, the monoterpene alcohol formed by the dimerization would be further dehydrated to isoprene. That is, such unwanted side reactions easily occurred with the desired dimerization to the monoterpene alcohols from prenil during the relatively longer reaction time of 38 s, leading to the low selectivity in monoterpene alcohol. The monoterpene alcohols were substantiated to be successfully synthesized peculiar to the  $\text{scH}_2\text{O}$  state, but be thermally unstable at such higher temperatures, and so in order to prevent the side reactions from occurring, shorter reaction (residence) times in  $\text{scH}_2\text{O}$  should be preferable for producing the monoterpene alcohols in more satisfactory yield.

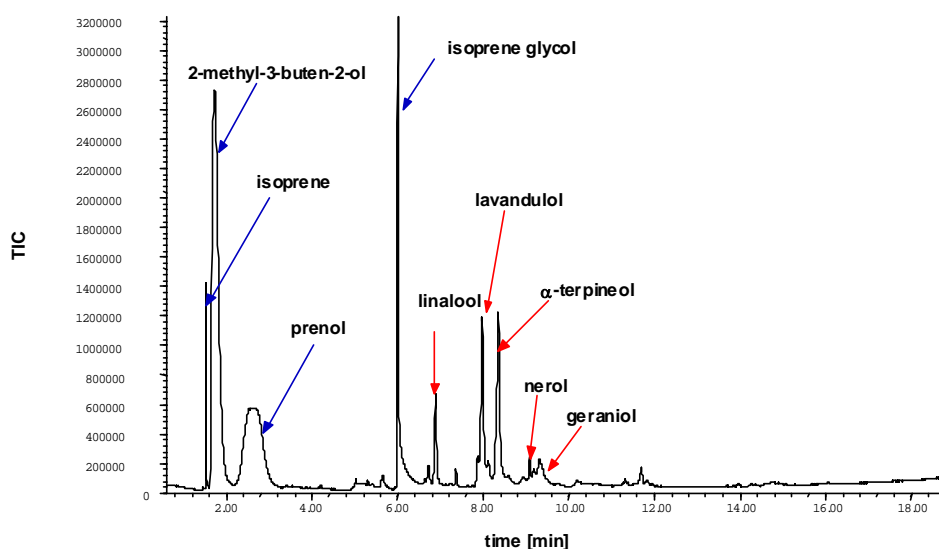


Figure 2. TIC spectrum of prenil solution treated with hot water at 215  $\pm$ 30MPa for a period of 38sec

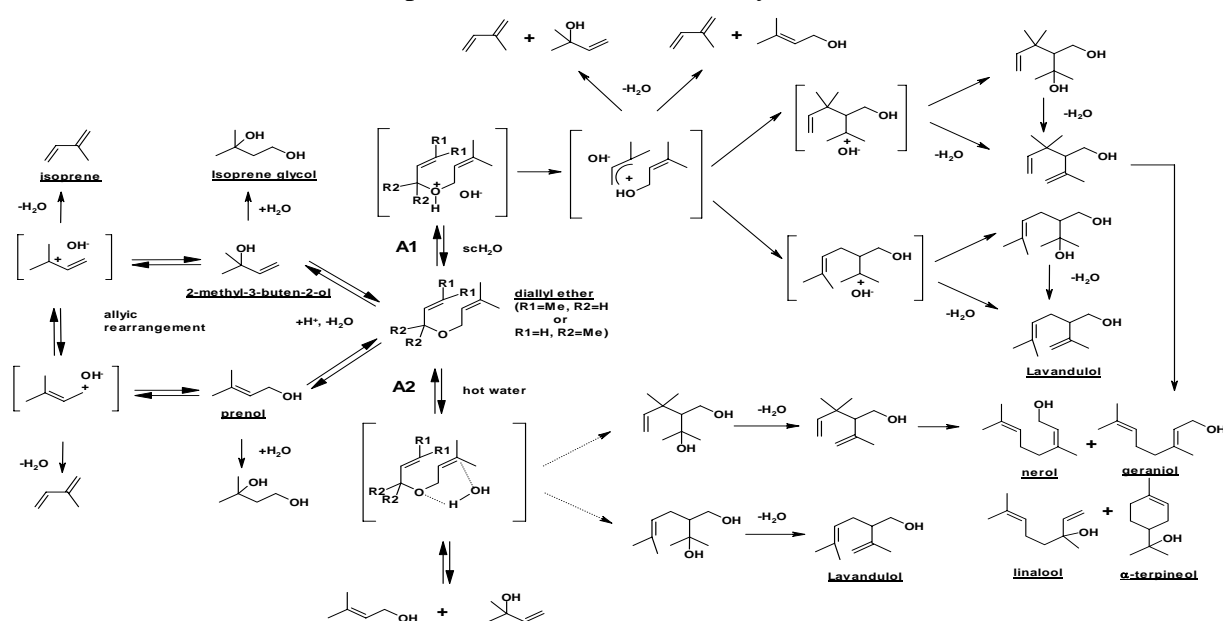
Table 1. Comparison of preparation of monoterpene alcohol from prenol by various methods

entry		T	P	$\tau$	conv.	selectivity	yield
			MPa	sec			
1	0.27m <i>p</i> -toluene sulfonic acid	145	0.1	12,600	99	5	5
2	0.35m ZnCl <sub>2</sub> /dichloroethane	25	0.1	3,600	85	14	12
3	hot water <i>in situ</i> IR	150	30	38	37	1	0.4
4	hot water <i>in situ</i> IR	215	30	38	81	18	15
5	hot water $\mu$ -reaction	215	40	30	96	16	15
6	MeOH+H <sub>2</sub> O (1:1) $\mu$ -reaction	375	40	7.7	92	0	0*
7	scH <sub>2</sub> O $\mu$ -reaction	375	40	5.1	98	40	39
8	scH <sub>2</sub> O $\mu$ -reaction	425	40	4.1	99	47	46
9	scH <sub>2</sub> O $\mu$ -reaction	450	40	3.6	99	55	54**

\* Diallyl ether (diprenyl ether+2,2-dimethyl-3-butenyl prenol ether) was generated in a 69% yield.

\*\*This consisted of linalool: geraniol: nerol: lavandulol:  $\alpha$ -terpineol= 9: 10: 1: 24: 10

We thus attempted the selective dimerization of monoterpene alcohols from prenol using the scH<sub>2</sub>O  $\mu$ -reaction system ranging in shorter reaction times around several seconds at higher temperature above the critical temperature. Table 1 compares the production of monoterpene alcohols from prenol by several methods. The total yield of the monoterpene alcohol product was found to be increased with increasing temperature at 40 MPa in scH<sub>2</sub>O (Table 1, entry 7 to 9). The monoterpene alcohol mixture was maximally obtained in 55% selectivity and in high conversion of 99% (entry 9) when the reaction was performed at a reaction time shorter than 5 s at 450 °C and 40 MPa in scH<sub>2</sub>O with the  $\mu$ -reaction process, in which the composition of linalool, geraniol, nerol, and lavandulol was 9, 10, 1, 24, and 10%, respectively. Its yield was greatly superior to those promoted by *p*-toluene sulfonic acid or ZnCl<sub>2</sub>/dichloroethane catalyst (entry 1, 2). We obtained only 16% selectivity regardless of the high conversion above 90% achieved at a reaction time of 30 s at 215 °C and 40 MPa (entry 5), in which isoprene, as the dehydration product of MBO and/or monoterpene alcohols, was predominantly formed. When the prenol solution was heated up to hot water or scH<sub>2</sub>O region at a slower rate in a batchwise operation, one cannot see any reactivities below 200 °C, but the



Scheme 3. Postulated two acid-catalyzed routes (A1 or A2 mechanism) for preparation of monoterpene alcohols from prenol or 2-methyl-3-buten-2-ol in scH<sub>2</sub>O and hot water.

introduction of the  $\mu$ -reaction system in the same region of hot water reaction led to an increase in the yield. Hence, the low yield would result from the side reaction such as dehydration occurring during a long elapse of time.

One can also see an interesting solvent effect in Table 1. When the reaction was carried out under the same operating conditions with entry 7 in an equimolar solution of water and methanol used in the place of pure water solution, the formation of monoterpene alcohols was not confirmed at all, whereas the conversion of entry 7 went up to 82%. In the presence of methanol, diallyl ether was found to be synthesized in a 69% yield of by the dyhydration between two prenil molecules. We thus recognize that its own acidic ability peculiar to scH<sub>2</sub>O state can promote the dimerization of prenil to monoterpene alcohols, but the presence of methanol in the high-temperature water medium completely suppresses the scH<sub>2</sub>O acidic ability bringing about the desired dimerization, and thereby leading to profound repression of the subsequent protonation of diallyl ether. The postulated mechanism is described in Scheme 3.

## II-II The one-step production from MBO

We demonstrated the formation of MBO by allylic rearrangement as well as of monoterpene alcohols by dimerization from prenil even in the absence of acid catalyst in scH<sub>2</sub>O. It has further become apparent by the GC-MS measurement that the subsequent dehydration of MBO formed from prenil to isoprene would be responsible for the low selectivity to monoterpene alcohols. Therefore, the application of MBO instead of prenil as starting material could be expected to contribute to the repression of side reactions including the dehydration, resulting in the improvement in selectivity.

Table 2 compares the selectivity and yield for the monoterpene alcohol synthesis from MBO in hot water and scH<sub>2</sub>O using the  $\mu$ -reaction system. The use of MBO substrate in hot water and scH<sub>2</sub>O has enabled the selective production of lavandulol, especially in a high selectivity of 82% and a yield of 59% in scH<sub>2</sub>O, which is one component of the monoterpene alcohols, although prenil substrate led to the formation of a mixture of monoterpene alcohols in a remarkably lower selectivity under the same scH<sub>2</sub>O conditions as shown in Table 1. Figure 4 shows the product distribution on lavandulol synthesis in scH<sub>2</sub>O, hot water, and by the conventional method. The one-step production of lavandulol was achieved in a 59% yield at a shorter reaction time of 7.7 s in scH<sub>2</sub>O even without catalyst, whereas in the conventional method consisting of three main steps in the presence of environmental damaging organotin compounds in organic solvents (Scheme 1), a satisfactory yield of 54% was obtained; however, a long reaction time extending to several hours is required to reach it. It can be also seen in Fig 4 that not only MBO is converted in scH<sub>2</sub>O more efficiently than in hot water, but that the allylic rearrangement to prenil from MBO is depressed significantly in scH<sub>2</sub>O, leading to the increase in selectivity of lavandulol. Hence, scH<sub>2</sub>O medium, though the reaction at a shorter reaction time around several seconds is a prerequisite, was found to be more favorable for the lavandulol production compared with hot water region.

Table 2. Production of lavandulol from 2-methyl-3-buten-2-ol in scH<sub>2</sub>O and hot water

entry		T	P	$\tau$	conv.	selectivity	yield
			MPa	sec			
1	hot water <i>in situ</i> IR	300	30	38	67	52	35
2	scH <sub>2</sub> O $\mu$ -reaction	375	30	7.7	72	82	59

## CONCLUSION

The present results demonstrate that  $\text{scH}_2\text{O}$  itself shows its real ability as an acid for remarkably accelerating the dimerization of hemiterpene alcohols such as prenol and MBO to monoterpene alcohols, especially lavandulol, only if one can suppress side reactions like dehydration disturbing the formation of the desired monoterpene alcohols. We are sure that our new approach not only can realize the one-step manufacture of monoterpene alcohols in high yield and high selectivity, even without catalyst in  $\text{scH}_2\text{O}$ , but can be useful for a wide range of acid-catalyzed organic syntheses, thus rendering newly potential applications in environmentally friendly and economically favorable synthesis of various fine chemicals

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