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Direct benzylation and allylic alkylation in high-temperature water without added catalysts

Tsunehisa Hirashita *, Shō Kuwahara, Sota Okochi, Makoto Tsuji, Shuki Araki

Omohi College, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466-8555, Japan

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ABSTRACT

In high-temperature water a series of benzyl and allylic alcohols reacted with 1,3-dicarbonyl compounds and activated aromatic compounds to give the alkylated products without added catalysts.

The direct reaction of ROH and R′H to generate a new R–R′ bond (Eq. 1) is a desirable process from a view point of Green Chemistry.[1]

$$\mathrm{ROH} + \mathrm{R'H} \rightarrow \mathrm{R\text{-}R'} + \mathrm{H_2O} \qquad (1)$$

There is no need for preparing individual reactive species and water as an only by-product seems to be highly attractive. These type reactions have hitherto been achieved using Lewis acids,[2–5] Brønsted acids,[6] and iodine[7] in organic solvents. Water is undoubtedly a greener solvent than organic solvents. The salient features of water in organic syntheses, exemplified by acceleration of reactions and enhancement of selectivities, have prompted organic chemists to utilize water as an alternative solvent.[8] However, a broad range of catalysts used in organic solvents is often incompatible with water and low solubility of common organic compounds in water makes its practical use highly problematic. Recently, the reactions as shown in Eq. 1 can be realized under aqueous conditions by the aid of alkylbenzenesulfonic acid,[9] which supports the reaction by generating hydrophobic circumstances in water. It is noted that simple Brønsted acids were not effective for the coupling reaction under aqueous conditions.

In order to address the dilemma of water between an environmental benign solvent and usability for performing organic reactions, we focus on high-temperature water as a clean reaction medium.[10] As water is heated, its physical properties are dramatically altered depending on temperature and pressure. For example, increasing the temperature of water increases the ionic product and reduces the dielectric constant; in other words, water itself plays roles as a strong acid/base and becomes miscible with organic compounds.[11] Supercritical water has emerged in chemical process as an environmentally attractive reagent/solvent for destruction of hazardous and toxic materials due to its strong reactive nature.[12] Although some reactions have been documented for regenerating useful resources from organic wastes in near-critical water,[13] organic synthetic reactions at high-temperature water have so far been strictly limited. If the direct coupling reaction shown in Eq. 1 can be realized in high-temperature water without added chemicals, this process would be a clean chemical transformation.[14]

We initiated a reaction of benzhydrol and acetylacetone as test substrates. A mixture of benzhydrol and acetylacetone in water (15 mL) was put in a Teflon container (30 cm^3) supported by a vessel made of SUS 316, and heated in an electric dryer for several hours.[15]

The reaction performed at 170 °C gave no coupling product, whereas small amounts of the corresponding alkylated product **3a** and the deacetylated product **4a** were obtained at 180 °C (Table 1, entries 1 and 2). By prolonging the reaction time at 220 °C, the yield of **4a** increased with keeping the total yield (entries 3 and 4), which indicates that (1) the product **4a** was derived from **3a** via elimination of acetic acid, and (2) acetylacetone was consumed prior to the coupling with benzhydrol. The former possibility was confirmed by the exposure of **3a** under the identical conditions giving **4a** in 60% yield. To reinforce the latter possibility that 1,3-diketone easily undergoes hydrolysis under the present conditions, a larger amount of acetylacetone (600 mol %) was employed in the reaction, resulting in an improvement of the total yields (entries 5 and 6). However, longer reaction time did not give rise the total yield again (entries 7 and 8). The reactions under refluxing at normal pressure as well as the hydrothermal reactions below 170 °C gave no coupling product. Normally, deacetylation of diketones has been performed in basic conditions.[16,17] In the present reactions, both the acid-catalyzed alkylation and the base-promoted deacetylation simultaneously proceeded (Scheme 1).

Next, acyclic and cyclic diketones **2b**–**d** were subjected to the reaction in order to get some insight into this process (Scheme 2). Dibenzoylmethane (**2b**) was treated under hydrothermal conditions to give benzoic acid and acetophenone in 87% and 46% yields, respectively. The reaction of **2b** in the presence of **1a** provided a mixture of **3b** and **4b** as the cases in Table 1.

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* Corresponding author. Tel./fax: +81 52 735 5206.
E-mail address: hirasita@nitech.ac.jp (T. Hirashita).

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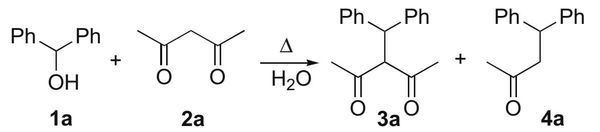
Table 1
Hydrothermal reaction of benzhydrol and acetylacetone[a]

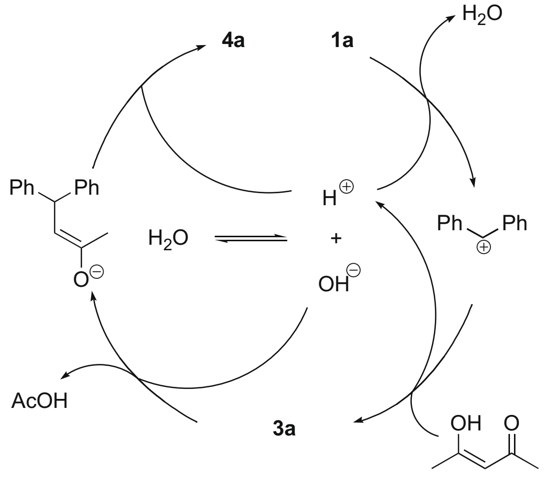


Entry	Conditions			Yields (%)		
	2a (mol %)	*T* (°C)	*t* (h)	**3a**	**4a**	**1a** (recovery)
1	200	170	12	0	0	91
2	200	180	6	3	1	72
3	200	220	6	15	5	58
4	200	220	48	0	19	45
5	600	220	2	16	3	73
6	600	220	6	31	26	29
7	600	220	12	13	49	27
8	600	220	24	0	68	28

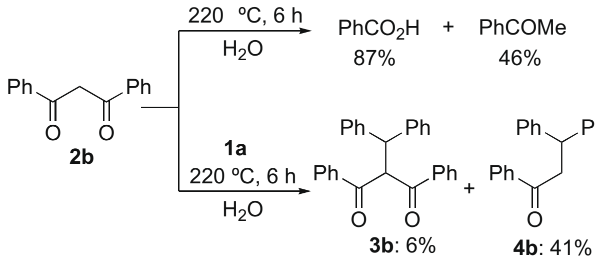
[a] All reactions were performed with benzhydrol (1.0 mmol) and acetylacetone in ion-exchanged water (15 mL).

The reaction of cyclic diketone **2c** performed with 1 mmol scale in water (15 mL) gave linear δ-keto carboxylate **5c** in 12% yield after the esterification with $TMSCHN_2$ (Scheme 3). When cyclic diketone **2d** carrying a phenyl group was employed, the yield was slightly improved to afford the corresponding methyl carboxylate **5d** in 28% yield. With 10-times lower concentration (0.1 mmol scale), the yield was increased up to 45%. In the reactions of cyclic diketones **2c** and **2d**, unexpected diketo esters **6c** and **6d** were isolated. On the basis of ^{13}C NMR analysis, **6d** was found to be a 1:1 mixture of the diastereomers. The most plausible reaction mechanism for the formation of **6c** and **6d** is depicted in Scheme 4. The aldol condensation of **2** generates **A**,[18] which is followed by hydrolysis leading to the formation of **6** according to the sequence mentioned above.[19]

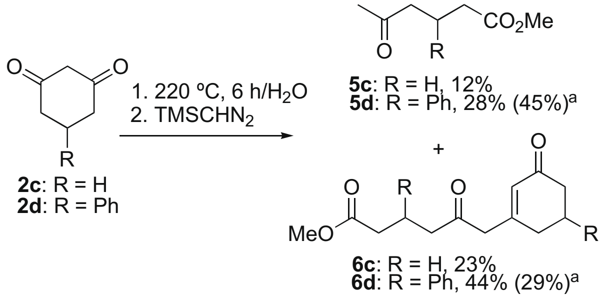
As active methylene compounds including a 1,3-diketone moiety prove to be highly sensitive under the present conditions, we turned our attention to aromatic electrophilic substitution in high-temperature water (Table 2).



Scheme 1. Proposed mechanism for the acid- and base-catalyzed reactions under hydrothermal conditions.

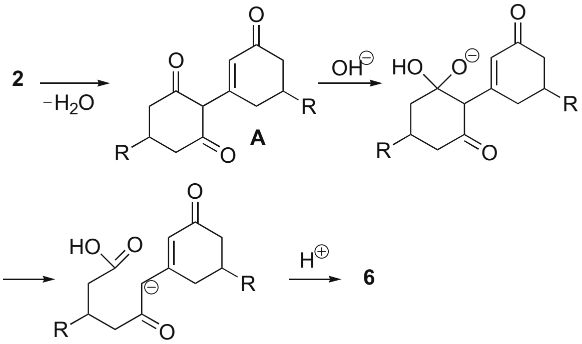


Scheme 2. Carbon–carbon bond coupling and cleavage of **2b** under hydrothermal conditions.



[a] Under diluted conditions.

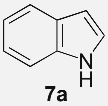
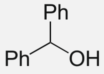
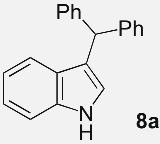
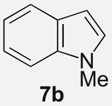
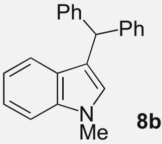
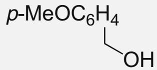
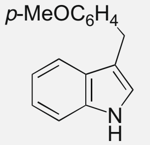
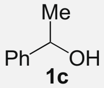
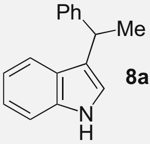
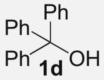
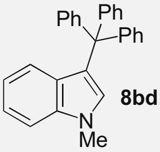
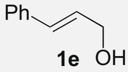
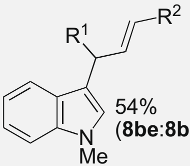
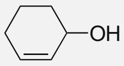
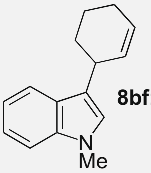
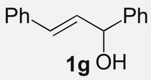
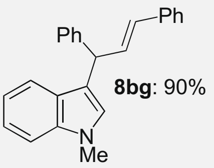
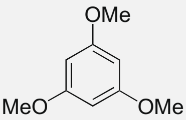
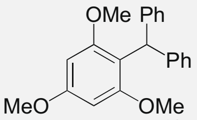
Scheme 3. Carbon–carbon bond coupling and cleavage of cyclic diketones **2c** and **2d** under hydrothermal conditions.



Scheme 4. Proposed mechanism for the formation of **6**.

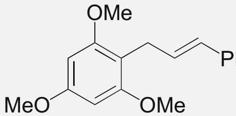
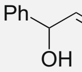
The reaction of indole (**7a**) and benzyl alcohol at 220 °C did not occur and the starting materials remained intact. However, the reaction of **1a** with **7a** under hydrothermal conditions gave the alkylated product **8aa** quantitatively (Table 2, entry 1). 1-Methylindole (**7b**) afforded the corresponding product **8ba** in high yield at 220 °C (entry 2). The reaction of 4-methoxybenzyl alcohol (**1b**) with **7a** under reflux conditions resulted in a recovery of **1b** and **7a**, whereas under hydrothermal conditions, **8ab** was obtained in a moderate yield along with 4,4′-dimethoxydiphenylmethane (17%) as a major by-product (entry 3). 1-Phenylethanol (**1c**) afforded the alkylated product **8ac** in 52% yield under hydrothermal conditions (entry 4). The reaction of triphenylmethanol (**1d**) with **7b** under refluxing resulted in a quantitative recovery of **1d**, whereas under hydrothermal conditions the corresponding alkylated product **8bd** was obtained in high yield (entry 5). The reaction of cinnamyl alcohol (**1e**) gave a mixture of regioisomers **8be** and **8be′** in a moderate yield (entry 6). Cyclic alcohol **1f** afforded **8bf** (entry 7). However, the alkylation failed with crotyl alcohol, but-3-en-2-ol and 2-methylbut-3-en-2-ol. 1,3-Diphenylpropen-1-ol (**1g**) proved to be susceptible to heating under aqueous conditions; just refluxing of **1g** with **7b** for 15 h reached a high level of conversion into the corresponding alkylated product **8bg** in 82% yield. In contrast, the reaction of **1g** and **7b** in toluene at 100 °C gave no coupling product. The reaction performed in water at 220 °C gave the better yield (entry 8).[20] Next, 1,3,5-trimethoxybenzene (**7c**) was submitted to the hydrothermal reaction. The reaction of **1a**

Table 2
Electrophilic substitution reaction under hydrothermal conditions[a]

Entry	NuH	Alcohol	Products and yield
1	 **7a**	 **1a**	 **8aa**: 99%
2	 **7b**	**1a**	 **8ba**: 98%
3[b]	**7a**	 **1b**	 **8ab**: 44%
4	**7a**	 **1c**	 **8ac**: 52%
5	**7b**	 **1d**	 **8bd**: 87%
6	**7b**	 **1e**	 54% (**8be**:**8be'** = 52:48) **8be**: R^1 = H, R^2 = Ph **8be'**: R^1 = Ph, R^2 = H
7	**7b**	 **1f**	 **8bf**: 61%
8	**7b**	 **1g**	 **8bg**: 90%
9	 **7c**	**1a**	 **8ca**: >99%

(*continued on next page*)

Table 2 (*continued*)

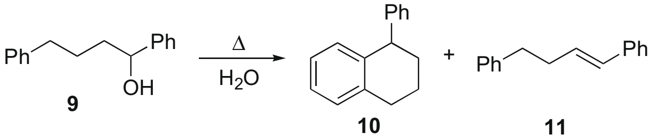
Entry	NuH	Alcohol	Products and yield
10	**7c**	**1e**	 **8ce**: 66%
11	**7c**	 **1e'**	**8ce: 77%**

[a] All reactions were performed with NuH **7** (1.2 mmol) and alcohol **1** (1.0 mmol) in ion exchanged water (15 mL) at 220 °C for 6 h.

[b] 4,4′-Dimethoxydiphenylmethane (17%) was also obtained.

Table 3

Intramolecular reaction of **9** under hydrothermal conditions[a]



Entry	Conditions		Yields (%)		
	T (°C)	*t* (h)	**10**[b]	**11**[b]	**9** (recovery)
1	rfx	18	0	0	96
2	150	6	0	0	98
3	160	6	0	0	98
4	170	6	4	Trace	95
5	170	48	61	16	0
6	180	6	19	6	51
7	220	6	57	20	0

[a] All reactions were performed with **9** (1.0 mmol) in ion-exchanged water (15 mL).

[b] NMR yields estimated from a mixture of **10** and **11**.

gave **8ca** in a quantitative yield (entry 9). The regioisomeric alcohols **1e** and **1e**′ gave coinciding results (entries 10 and 11). *p*-Dimethoxybenzene was found to be inactive at 220 °C.

The aromatic compounds that can be applied in this alkylation are limited to electron-rich aromatics, indicating that the transient intermediates are not electrophilic and/or stable enough under the conditions to promote the alkylation. We anticipated that an intramolecular reaction would open the possibility of using non-activated aromatic units as a substrate. Thus, alcohol **9** was subjected to the hydrothermal reaction with altering temperature and the results are compiled in Table 3. The reactions under refluxing and the thermal reactions below 170 °C, **9** remained intact (entries 1–3). A small amount of cyclization product **10** was obtained at 170 °C for 6 h and prolonging the time allowed to consume **9** affording **10** in 61% yield along with a dehydrated product **11** (entries 4 and 5). Reactions at higher temperature gave better yields in a shorter time (entries 6 and 7). The above results show that a non-activated aromatic has a potential for the hydrothermal alkylation and the cationic intermediate was practically generated from benzylic alcohols even at 170 °C.

In summary, the direct coupling of alcohols and aromatic compounds in high-temperature water has been achieved. Water under hydrothermal conditions would open opportunities for alcohols as an alkylating agent without added chemicals.[21]

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19. The formation of the dimeric acid from 1,3-cyclohexanedione in the presence of sodium bicarbonate was documented: Conrow, K. *J. Org. Chem.* **1966**, *31*, 1050–1053.
20. The reaction of **1g** with **7a** under reflux conditions gave the corresponding product in 63% yield. However, the reaction performed at 220 °C resulted in a formation of a complicated mixture.
21. *General experimental procedure:* All reactions were carried out in ion-exchanged water (<0.08 mS/cm), which was obtained by an ORGANO PURE LITE PRB-002A. The autoclave was purchased from Shikokurika Co., Ltd. Representative procedure for reaction screening (Table 2, entry 2): A mixture of benzhydrol (0.18 g, 1.0 mmol), 1-methylindole (0.15 mL, 1.2 mmol), and ion-exchanged water (15 mL) was introduced into an autoclave with a volume filling factor of 50%. The autoclave was heated at 220 °C in an electric drier for 6 h. After the reactor was cooled down to room temperature, the product was extracted with ether. The organic solution was washed with brine and concentrated under reduced pressure giving a crude product (321 mg), from which excess 1-methylindole was removed by distillation (150 °C, 20 mmHg) to afford 3-(1,1-diphenylmethyl)-1-methylindole (**8ba**, 291 mg, 98%).