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Promotion of one-pot Robinson annelation achieved by gradual pressure and temperature manipulation under supercritical conditions

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Abstract—The one-pot Robinson annelation from 2-methyl-cyclohexane-1,3-dione with 3-buten-2-one can be achieved in high yield (95%) and high selectivity (95%) by pressure and temperature manipulation using supercritical carbon dioxide in the presence of MgO catalyst, whose method could be applied for various ketones to synthesize fused polycyclic compounds.
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From the view point of green sustainable chemistry, the utilization of carbon dioxide (CO_2), especially supercritical CO_2 (scCO_2) has become of much interest as a suitable medium in recent years, because scCO_2 is considered as an environmentally benign and cheap organic reaction medium. ScCO_2 has also several advantages favorable for chemical reaction such as the mild critical point ($Tc = 304.2$ K, $Pc = 7.38$ MPa) and easily tunable physicochemical properties.[1]

Robinson annelation[2] of cyclohexanones, or cyclohexane-1,3-diones with methyl vinyl ketone and its homologues is an important process for the formation of cyclic structure in the synthesis of many natural products, such as steroid series,[2d] which is the Michael reaction, followed by the aldol condensation and then the dehydration (Scheme 1). Though the Robinson annelation has been widely used in organic synthesis, the long reaction time are usually required to achieve conventional yields.[3a,b,c] Thus, to overcome these serious defects, one-pot Robinson annelation has been developed, but the yields still remain low.[3d]

Recently, we found to successfully accelerate the reaction such as CO_2 fixation by using scCO_2,[4] and to control the ratio of aldol to enal product of the aldol condensation by pressure manipulation in the presence of heterogeneous MgO catalyst,[5a,b] which is especially of great advantage to catalyst/product separation.[5] In this work, we demonstrate that the Robinson annelation can produce the fused polycyclic compounds such as 8a-methyl-3,4,8,8a-tetrahydro-2H,7H-naphthalene-1,6-dione **5a** in a high yield under supercritical conditions in the presence of MgO catalyst. This is the great achievement of one-pot synthesis effected by simple manipulation of only pressure and temperature.

The Robinson annelation of 2-methylcyclohexan-1,3-dione **2a** with 3-buten-2-one **1a** was conducted in batchwise operation under various conditions in the presence of MgO catalyst, and the results of preliminary screening were shown in Table 1.[6,7] The reaction at various pressures at a constant temperature of 100 °C produced **5a** as one of minor products (run 1–4), whereas 2-methyl-2-(3-oxo-butyl)-cyclohexane-1,3-dione **3a** as a main product, which is the product by the Michael reaction between **1a** and **2a**. Especially, at the near-critical pressure of 10 MPa, the yield of the product **3a** attained up to maximally 78% in excellent selectivity of 92%, but the yield of **5a** was very low (run 2). Accordingly the Michael reaction from **2a** to **3a** would be suitable for the reaction condition of 10 MPa at 100 °C, but the yield of **5a** was not improved by only pressure manipulation. The reaction at a higher temperature of 180 °C was further investigated at several
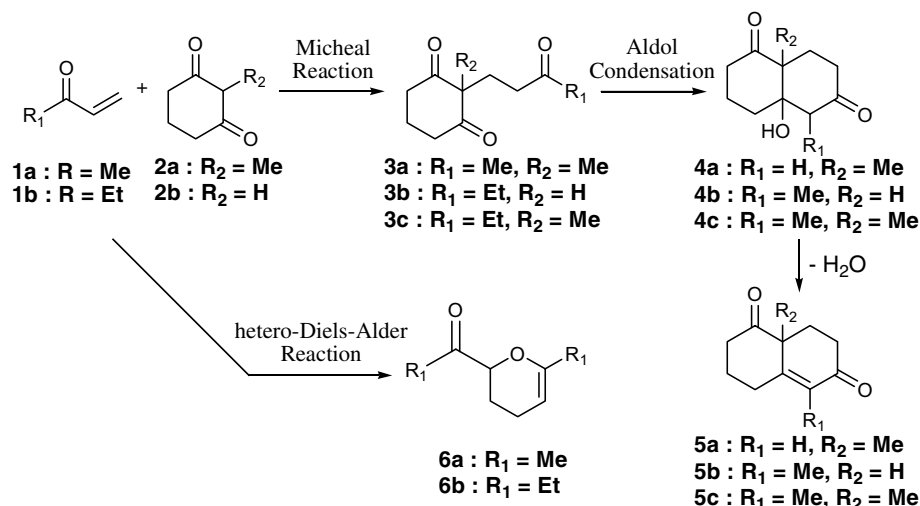
Scheme 1. Robinson annelation and hetero-Diels–Alder reaction.

Table 1. Robinson annelation of 2-methylcyclohexan-1,3-dione 2a with 3-buten-2-one 1a in the presence of MgO catalyst[a]

Run	Subst.	Subst.	Pressure /MPa	Temp/°C	Recov. of 1/%[a]	Yield of 6/%	Yield of 3/%	Select. of 3/%	Yield of 5/%	Select. of 5/%
1			0	100	15	17	46	54	22	26
2			10	100	15	5	78	92	2	2
3			20	100	11	13	68	77	8	9
4			25	100	12	18	58	67	12	13
5			0	180	16	0	1	28	1	26
6	1a	2a	10	180	16	10	13	16	44	53
7			20	180	12	8	21	24	57	64
8			25	180	16	24	11	13	47	57
9[b]			10 (first)	100						
			20 (second)	180	0	2	3	3	95(82)[d]	95
10[b,c]			10 (first)	100						
			20 (second)	180	0	2	4	4	94	94
11[b,e]	1a	2b	10 (first)	35						
			20 (second)	180	0	0	6[c]	6	94[e] (79)[d]	94[e]
12[b]	1b	2b	10 (first)	100						
			20 (second)	180	1	5	3	3	91	92
13	1a	2a	0	35	—	—	—	—	49[f]	—
14	1b	2a	0	Reflux	—	—	—	—	74[g]	—

[a] The reaction time is 2 h.
[b] The reaction times are 2 h at first stage and 2 h at second stage.
[c] The catalyst was reused.
[d] Isolated yield.
[e] Pressure dependences were also examined and the reaction conditions were adjusted, and 4b was formed instead of 5b.
[f] Ref. 3b. The reaction time to synthesize 5a was 89 h at 35 °C in DMSO catalyzed by L-proline.
[g] Ref. 3c. The reaction time to synthesize 5c was 4 h (methanol reflux) + 16 h (benzene reflux).

pressures (run 5–8), leading to the better yield of 5a than that at 100 °C and the maximum yield of 57% at 20 MPa (run 7). The supercritical reaction condition at 20 MPa and 180 °C would be favorable for the aldol condensation followed by the dehydration to give 5a.[8]

To further improve the yield of 5a, we thus attempted the reaction at a lower pressure of 10 MPa at 100 °C, to begin with, and then subsequently at a higher pressure of 20 MPa and a high temperature of 180 °C (run 9). Consequently, as shown in Table 1, this one-pot reaction method by varying pressure and temperature provides a much better yield (95%, 82% isolated yield) and

selectivity (95%) of 5a compared to a 49% (run 13) yield of 5a synthesized step by step in organic solvents.[3b,c] Furthermore, this reaction by this method can be achieved in good yield within 4 h (2+2 h), whereas those in organic solvents were more than 20 h.[3a,b,c] In addition, the MgO heterogeneous catalyst can be separated easily by only filtration and can be reused (run 10). We also applied this pressure–temperature-variable method to another cyclic ketone 2b as shown in Scheme 1.[9] This method can give good conversions of 2b into 5b (run 11), and of 2b into 5c (run 12). So this suitable manipulation of only pressure and temperature under supercritical conditions has enabled to Robinson annelation

in one-pot, which consists of some elemental reactions of the Michael reaction and the aldol condensation and dehydration.

To elucidate what is responsible for the effect of one-pot Robinson annelation by the pressure and temperature manipulation, the pressure dependence of selectivities at 100 and 180 °C was investigated, and the results were shown in Figures 1 and 2. One can see the interesting pressure dependence at each temperature. In the case of 100 °C (Fig. 1), the selectivities of **5a**, and by-product **6a** decrease with increasing pressure up to 10 MPa, whereas the selectivity of **3a** increases, reaching maximum selectivity of 95% at 10 MPa near the critical pressure.

It is considered that in the near critical density $(0.189 \, g \, cm^{-3})$ at 10 MPa, the local concentration of **2a** with **1a** would be large than that at lower pressure,[10] and the product **3a** would be less soluble into CO_2 phase as compared to **1a** and **2a**, resulting promotion of the Michael reaction of **2a** with **1a**. On the other hand, at the higher pressure than 10 MPa, the aldol condensation from **3a** to **5a** was accelerated under supercritical condition in the presence of MgO catalyst,[5] giving the

increasing yield of **5a** with decreasing the yield of **3a**. However, the by-product **6a**, which is formed by the hetero-Diels–Alder cycloaddition (Scheme 1),[11] is known to proceed favorably under supercritical and pressurized condition,[12] and this formation of **6a** interferes the Michael reaction of **1a** and **2a**, leading to the decrease in selectivity of **3a** at higher pressures above 10 MPa.

In the case of 180 °C (Fig. 2), the selectivity of **5a** was improved and was much higher than **3a**, with maximum selectivity of 65% at 20 MPa (density is $0.281 \, g \, cm^{-3}$). However, the both selectivities of **3a** and **5a** were decreased with increasing pressure above 20 MPa, because of formation of the by-product **6a**, which interferes the production of **3a** and **5a**. Therefore, acceleration only the Robinson annelation in one-pot to obtain **5a** in good yield and good selectivity can be achieved by the simply gradual pressure and temperature manipulation, and this method would be apply for other reactions.

In conclusion, we demonstrated that the gradual pressure and temperature manipulation under supercritical conditions is available for the one-pot Robinson annelation in high yield. By adjusting the pressure and temperature, **5a** was obtained in very high yield of 95%. Furthermore, under supercritical condition, this reaction was found to be much faster compared to that in conventional organic solvent. [3a,b,c]

Figure 1. Pressure dependence of the selectivity of each product (**3a**, **5a**, and **6a**) under scCO$_2$ at 100 °C.

Figure 2. Pressure dependence of the selectivity of each product (**3a**, **5a**, and **6a**) under scCO$_2$ at 180 °C.

Acknowledgements

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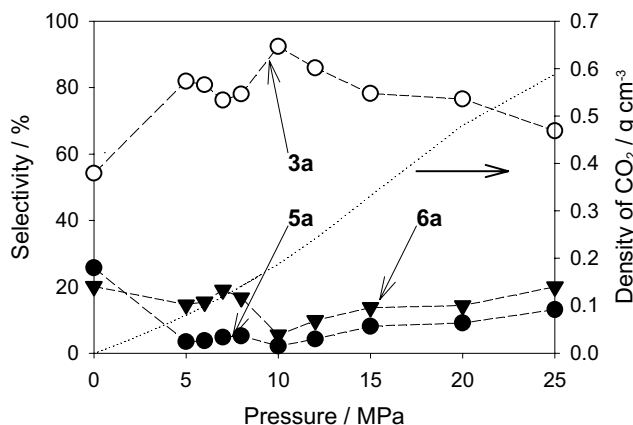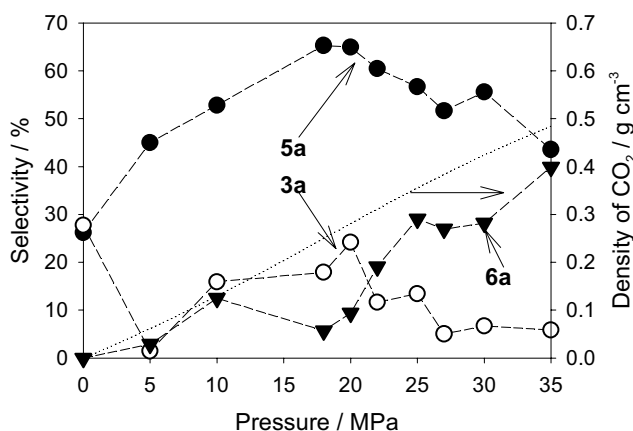
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6. MgO (JRC-MGO-4 100A) was purchased from The Catalysis Society of Japan, and its physical properties are as follows: particle size: ca. 14 nm, BET surface area; $120 \, m^2 \, g^{-1}$.

7. The typical experiment procedure is as follows: 2-Methyl-cyclohexa-1,3-none (0.13 g, 1.0 mmol) or 3-buten-2-one (0.1 mL, 1.2 mmol), and MgO (50 mg) were charged into a $25 \, cm^3$ stainless steel reactor at room temperature. The reactor was heated to 100 °C within 15 min using oil bath and CO_2 was subsequently charged into the reactor using a high-pressure liquid pump and compressed to the desired pressure. The reactions were started by stirring the mixture, continued for 2 h. Then the reactor was moved into an another oil bath, and was heated to 180 °C within 15 min, and CO_2 was further introduced at the desired pressure. After the reaction for 2 h, the reactor was cooled to 0 °C with ice quickly and the pressure was released slowly. The MgO was removed by filtration, and the products and yields were determined by GC–MS/MS (Varian CP3800/1200L) with decane as an internal reference. Isolated yields were obtained after purification using silica-gel chromatography.

8. We examined the reaction of **3a** at 180 °C for 2 h, obtaining **5a** with the yield of 97%.

9. We have also examined the reaction of other cyclic ketones, such as 2-methyl-cyclopentan-1,3-dione, and obtained polycyclic compounds with the yields of 71% under the same condition in the case of **2a**.

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