Solvent-Free Robinson Annelation Reaction

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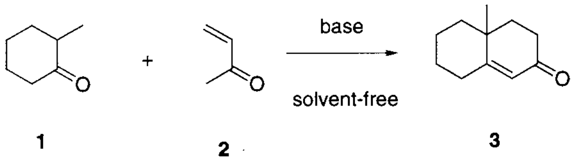
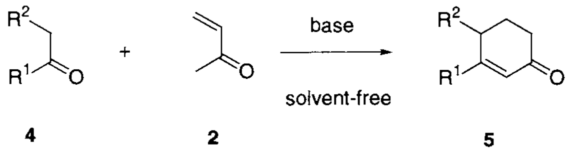
Solvent-free Robinson annelation reaction proceeded at room temperature to give corresponding cyclohexenones.

Base-catalyzed annelation reaction of cyclic ketones with α,β-unsaturated ketones which gives cyclohexenones in 15–20% yield had been reported by Robinson.[1] This reaction is known as Robinson annelation reaction.[2–4] An acid-catalyzed Robinson annelation reaction which proceeds by heating in solution for a long time has also been known.[5] We found that solvent-free Robinson annelation reaction proceeds efficiently at room temperature. We now report ecologically and economically valuable solvent-free annelation reactions.





For example, 2-methylcyclohexanone **1** (2.24 g, 20 mmol), methyl vinyl ketone **2** (4.50 g, 40 mmol), and sodium methoxide (1.2 g, 24 mmol) were well mixed with agate mortar and pestle and the mixture was kept at room temperature for 3 h. The reaction product was mixed with 3M HCl (20 mL), extracted with ether, and the dried ether solution was evaporated. Distillation of the residue *in vacuo* gave 4,4a,5,6,7,8-hexahydro-4a-methyl-2(3*H*)-naphthalenone **3**[1] as colorless oil (1.05 g, 25% yield).[6] The reaction can also be carried out by using potassium hydroxide, sodium ethoxide, sodium *t*-butoxide, and potassium *t*-butoxide instead of sodium methoxide (Table 1). The solvent-free Robinson annelation reaction in one-pot process has some advantages. Namely, procedure is much simpler and yield of product is higher than that of solution reaction. In order to isolate the product without using solvent, the reaction mixture was neutralized by addition of *p*-toluenesulfonic acid and distilled *in vacuo*. However, this method gave only decomposed material.

We also found that the reaction of acyclic ketone **4** and

Table 1. Yield of **3** by solvent-free Robinson annelation reaction[a]

Entry	Base	Yield / % **3**
1	CH_3ONa	25
2	KOH	25
3	CH_3CH_2ONa	16
4	$(CH_3)_3CONa$	18
5	$(CH_3)_3COK$	13

[a] **1**, **2**, and base were well mixed by agate mortar and pestle and the mixture was kept at room temperature for 3 h.

Table 2. Yield of **5** in the absence of solvent[a] and in MeOH[b]

Entry	4	R^1	R^2	Yield / % **5** in the absence of solvent	in MeOH
1	**a**	C_6H_5	H	c	c
2	**b**	C_6H_5	CH_3	27	17
3	**c**	C_6H_5	CH_2CH_3	12	8
4	**d**	C_6H_5	C_6H_5	45	29
5	**e**	p-CH_3-C_6H_4	C_6H_5	15	5
6	**f**	p-Br-C_6H_4	C_6H_5	15	8
7	**g**	CH_3	H	c	c
8	**h**	CH_3	CO_2CH_3	21	28

[a] **4**, **2**, and sodium methoxide were well mixed by agate mortar and pestle and the mixture was kept at room temperature for 3 h. [b] Reactions were carried out by refluxing for 12 h. [c] No reaction occurred .

methyl vinyl ketone **2** with base in the absence of solvent gives corresponding cyclohexenones **5**. For example, benzyl phenyl ketone **4d** (2.0 g, 10 mmol), methyl vinyl ketone **2** (2.1 g, 30 mmol), and sodium methoxide (0.6 g, 12 mmol) were well mixed with agate mortar and pestle and the mixture was kept at room temperature for 3 h. The reaction product was mixed with 3M HCl (20 mL), extracted with ether, and the dried ether solution was evaporated. Distillation of the residue *in vacuo* gave 3,4-diphenyl-2-cyclohexen-1-one **5d** as colorless crystals (1.13 g, 45% yield). When the reaction was carried out in methyl alcohol (60 mL) by heating for 12 h, 3,4-diphenyl-2-cyclohexen-1-one **5d** was obtained in 29% yield. The reaction of benzyl phenyl ketone **4d** and methyl vinyl ketone **2** with sodium methoxide proceeded more efficiently in the absence of solvent than in solution. By a similar procedure using **4b–c**, **4e–f**, and **4h** in the absence of solvent and in methyl alcohol, cyclohexenones **5b–c**, **5e–f**, and **5h** were obtained in the yield indicated in Table 2. In most cases, the reaction of acyclic ketone **4** and methyl vinyl ketone **2** with sodium methoxide proceeded more efficiently in the absence of solvent than in solution. In the case of **4a** and **4g**, reaction occurred neither in the absence of solvent nor in methyl alcohol (Table 2).

Various organic reactions have been found to proceed efficiently in the solid state.[7] Although various simple organic reactions have been established to proceed in the absence of solvent,[7] it is interesting to know the two-step reaction such as Robinson condensation proceeds efficiently in the absence of solvent and in one-pot.

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References and Notes

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6 A typical procedure follows: Commercially available 2-methylcyclohexanone **1**, methyl vinyl ketone **2**, and acyclic ketone **3** were used for annelation reactions. IR spectra were measured with an IR spectrometer, JASCO FT/IR-350. ^{1}H NMR spectra were recorded in $CDCl_3$ on a JEOL JNM-LA300 (300 MHz) spectrometer. 2-Methylcyclohexanone **1** (2.21 g, 20 mmol), methyl vinyl ketone **2** (4.50 g, 40 mmol), and sodium methoxide (1.2 g, 24 mmol) were well mixed with agate mortar and pestle and the mixture was kept at room temperature for 3 h. The reaction product was combined with 3M HCl (20 mL), extracted with ether (20 mL × 4), and the ether solution was washed with water and dried over $MgSO_4$. The dried ether solution was evaporated. Distillation of the residue *in vacuo* (150–170 °C / 25 mmHg) gave 4,4a,5,6,7,8-hexahydro-4a-methyl-2(3*H*)-naphthalenone **3**[1] as colorless oil (1.05 g, 25% yield). IR (Neat) ν_{max} 1698 cm^{-1}; ^{1}H NMR δ 1.25 (s, 3H), 1.25–2.50 (m, 12H), 5.73 (s, 1H). Similar treatment of **1** and **2** with other base, and **4** and **2** with sodium methoxide gave **3** and **5** in the yields shown in Table 1 and 2, respectively.

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