

Application of High Pressure Induced by Water-freezing to the Michael Reaction of Alcohols with α,β -Enones

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High pressure (about 200 MPa), which was realized by freezing water in a sealed autoclave, has been successfully applied to a high-yield Michael reaction of alcohols and α,β -unsaturated ketones in the presence of a catalytic amount of DMAP and LiClO₄. Only a moderate yield was obtained under atmospheric pressure.

Pressure is one of the important factors affecting the rate of organic reactions, especially many reactions with a large, negative volume of activation.¹ High pressure technology has become an indispensable tool in organic synthesis, though specialized, expensive apparatus is necessary to carry out reactions under high pressure. Hence the development of more convenient techniques for performing high pressure reactions is desirable.

The volume of water increases about 10% on freezing. When water is frozen in a sealed autoclave, a high pressure of up to about 200 MPa can be realized. Recently, this pressure has been elegantly utilized for the inactivation of microorganisms by Hayakawa et al.² This paper describes the first application of the pressure induced by water-freezing to accelerate organic reactions.

The Michael reaction of alcohols and α,β -enones under basic conditions is one of the hardest synthetic transformations to achieve efficiently, because the product β -alkoxy ketones easily revert to the starting materials via the retro Michael reaction. To overcome this, a large excess of Michael donor is generally employed.³ There are, however, successful examples of this reaction under strong basic conditions employing the reactive Michael acceptor⁴ and non-basic conditions using Pd(II) catalyst.⁵ As the Michael reaction is known to be accelerated by the high pressure owing to the large negative volume of activation⁶ and the product β -alkoxy ketones are useful intermediates for natural product synthesis, the pressure induced by water-freezing was first applied to this reaction.

The reaction of benzyl alcohol (BnOH) with 2-cyclohexen-1-one was selected as a model. It was performed as follows: To a 1 mL Teflon tube⁷ was added BnOH, 2-cyclohexen-1-one, base and additive (*vide infra*), and the tube was capped with exclusion of air. This tube was placed in an autoclave (capacity about 100 mL),⁸ and equipped with a pressure monitor.⁹ The autoclave was completely filled with water, sealed tightly, and left in a household electric refrigerator at $-20\text{ }^\circ\text{C}$.¹⁰ It was found that the internal pressure reached about 200 MPa after 12 h. After a given time, the autoclave was taken out of the refrigerator, and the Teflon tube was removed from the autoclave. Volatile organic materials were removed under reduced pressure, after which purification by column chromatography on Florisil afforded the Michael product.¹¹

First, the use of bases such as DMAP,¹² DBU,¹² DABCO,¹²

tetramethylguanidine and NaOMe¹³ was investigated. Among the bases examined, DMAP gave the best result but the yield was not satisfactory ($\sim 30\%$).¹⁴ To improve the yield, various metal salts¹⁵ were screened as additives. Lithium salts, especially LiClO₄ (52%) and LiBF₄ (53%), were found to give good results. Further investigation of the reaction conditions including molar ratio of the reagents and reaction time revealed that the reaction of 2-cyclohexen-1-one with 3 equiv of BnOH in the presence of 10 mol% of each DMAP and LiClO₄¹⁶ under the pressure induced by water-freezing for 85 h¹⁷ gave the desired Michael adduct nearly quantitatively (97%, Table 1, entry 1).

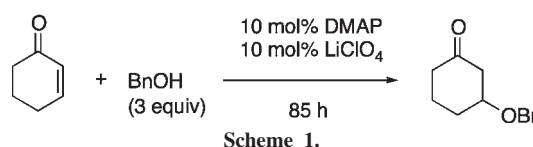


Table 1. The effect of pressure and temperature on yield^a

Entry	Pressure/atm	Temp./ $^\circ\text{C}$	Yield/% ^b
1	2000	-20	97
2	1	-20	55
3	1	20	56
4	1	50	18


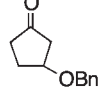

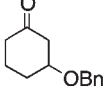

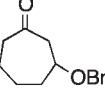

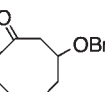
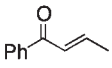
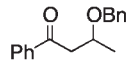
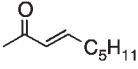
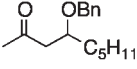
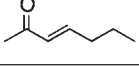
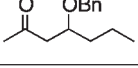
^aReaction conditions: molar ratio; 2-cyclohexen-1-one : BnOH : DMAP : LiClO₄ = 1 : 3 : 0.1 : 0.1. ^bIsolated yield.

To confirm the effect of pressure, the same reaction was performed at atmospheric pressure at -20 , 20 , and $50\text{ }^\circ\text{C}$ without changing the other reaction parameters. The results are shown in Table 1. Under atmospheric pressure, the product was isolated in about 55% yield both at -20 and $20\text{ }^\circ\text{C}$. This yield did not increase further with longer reaction times. On the other hand, the yield decreased at higher temperature because of the side reactions ($50\text{ }^\circ\text{C}$). When the purified Michael product and 2 equiv of BnOH were treated with 10 mol% of DMAP and LiClO₄ for 85 h at $20\text{ }^\circ\text{C}$, the Michael product was recovered in 70% yield along with 2-cyclohexen-1-one in 25%. This result clearly indicates that the present Michael reaction is an equilibrium, and that high pressure shifts this equilibrium towards the formation of the Michael adduct, giving the product in good yield.

Next, the present method was applied to other α,β -unsaturated ketones, the results being summarized in Table 2. Though 2-cyclopenten-1-one gave a poor result, other cyclic enones such as 2-cyclohepten-1-one and 2-cycloocten-1-one were found to react effectively to afford the Michael products in good yields. Not only cyclic enones, but also acyclic enones are suitable acceptors. Moreover the latter are found to react much faster than the former. 1-Phenyl-2-buten-1-one, 3-nonen-2-one and 3-hepten-2-one gave the Michael products in good yields after 13 h. In contrast to these successful results, α -substituted α,β -unsaturated ketones such as 3-methyl-3-penten-2-one and

carvone, and α,β -unsaturated esters such as *tert*-butyl crotonate and dibenzyl fumarate did not react with BnOH under the present high pressure conditions.

Table 2. Michael reaction of α,β -enone and BnOH under the pressure induced by water-freezing^a

α,β -Enone	Product	Time / h	Yield / % ^b
		85	20
		85	97
		85	90
		85	88
		13	99
		13	91
		13	86

^aReaction conditions: molar ratio; α,β -enone : BnOH : DMAP : LiClO₄ = 1 : 3 : 0.1 : 0.1. ^bIsolated yield.

The generality of this reaction with respect to the Michael donor, alcohol, was examined as summarized in Table 3. The lower yield observed for 4-methoxybenzyl alcohol is due to the high viscosity of the reaction media at -20°C with this alcohol which melts at 24°C . Though 1-phenyl-1-ethanol did not react with 2-cyclohexen-1-one, probably owing to steric effects, other alcohols such as MeOH, EtOH, and allyl alcohol were found to be good Michael donors, reacting with 2-cyclohexen-1-one to afford the products in good yields. As BnOH and allyl alcohol, which are both masked water equivalents,¹⁸ are good Michael donors, their reactions are equivalent to hydroxylation of water to α,β -unsaturated carbonyl compounds, water itself being a poor Michael donor.

Table 3. The Michael reaction of various alcohols and of water with 2-cyclohexen-1-one under the pressure induced by water-freezing^a

Alcohols	Yield/% ^b	Alcohols	Yield/% ^b
PhCH ₂ OH	97	CH ₂ = CHCH ₂ OH	72
MeOH	93	<i>p</i> -CH ₃ OPhCH ₂ OH	57
EtOH	86	H ₂ O	3–10

^aReaction conditions: molar ratio; 2-cyclohexen-1-one : alcohol : DMAP : LiClO₄ = 1 : 3 : 0.1 : 0.1, reaction time is 85 h. ^bIsolated yield.

In summary, we have successfully applied the high pressure induced by water-freezing to the Michael addition of alcohols to α,β -unsaturated ketones. The combined use of a catalytic amount of DMAP and LiClO₄ is a key to the success of this reaction. The

pressure induced by water-freezing has several noteworthy features: Only an autoclave and a household electric refrigerator are required to achieve the high pressure, no specialized or expensive apparatus is needed, which makes this high pressure technology easily available to the average laboratory. Scale-up would be easy compared to the usual high pressure technology. Further studies of the application of the pressure induced by water-freezing to organic synthesis are under way.

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This paper is dedicated to Professor T. Mukaiyama on the occasion of his 75th birthday.

References and Notes

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- G. Jenner, *New J. Chem.*, **23**, 525 (1999), and see reviews in Reference 1.
- The Teflon tube is made by Hikari Koatu Kiki Co. Ltd. Hiroshima, Japan.
- The autoclave is made by Atlas Co. Ltd. Tokyo, Japan and its size is as follows; 78 mm outside diameter, 340 mm height, 25 mm inside diameter, and 200 mm depth.
- KH78, Naganokeiki Co. Ltd., Tokyo, Japan.
- Occasional stirring is not necessary.
- When the Michael product, 3-benzyloxycyclohexan-1-one, was purified by column chromatography on silica gel, the retro Michael reaction proceeded in part with a concomitant decrease in yield.
- DMAP = 4-(*N,N*-dimethylamino)pyridine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane.
- In the case of NaOMe, MeOH was used as the Michael donor instead of BnOH.
- Reaction conditions are as follows; molar ratio; 2-cyclohexen-1-one : BnOH : DMAP = 1 : 1.7 : 0.1, reaction time is 15 h.
- The amount of additive is 10 mol%. The yields for the other additives examined are as follows; LiCl 41%, LiBr 41%, LiI 43%, LiOH·H₂O 25%, LiNO₂ 39%, NaCl 33%, NaI 29%, KCl 14%, K₂CO₃ 41%, MgCl₂ 0%, NH₄Cl 16%, BaOH·8H₂O 34%, Yb(OSO₂CF₃)₃ 25%, Sc(OSO₂CF₃)₃ 18%.
- Without DMAP, the reaction did not proceed at all even in the presence of LiClO₄.
- The yields for other reaction times are as follows; 61% (15 h), 79% (35 h).
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