



The Baylis–Hillman reaction under high pressure induced by water-freezing

Yujiro Hayashi,* Kotaro Okado, Itaru Ashimine and Mitsuru Shoji

Department of Industrial Chemistry, Faculty of Engineering, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

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Abstract—High pressure (about 200 MPa), which was realized by freezing water in a sealed autoclave, has been successfully applied to the Baylis–Hillman reaction, in which an efficient rate enhancement was observed. © 2002 Elsevier Science Ltd. All rights reserved.

The Baylis–Hillman reaction, the coupling of α,β -unsaturated carbonyl compounds with aldehydes catalyzed by *tert*-amine or phosphine, is an important carbon–carbon bond forming reaction,¹ because the Baylis–Hillman adduct is a valuable synthetic intermediate for natural product synthesis. Though synthetically useful, a problem of the reaction is the low reaction rate, requiring long reaction time. Recently, several methods have been developed to overcome this problem: DBU has been reported to be a better accelerator² than a conventional nucleophilic base like DABCO. LiClO_4 is reported to be an excellent additive,³ while a combination of an acid and a base such as $\text{La}(\text{OTf})_3$ and $\text{N}(\text{CH}_2\text{CH}_2\text{OH})_3$,⁴ or 1,1'-bi-2-naphthol and tributylphosphine⁵ promotes the reaction efficiently. The solvent also has a significant effect on the reaction rate, and it is reported that the reaction proceeds smoothly in a mixture of 1,4-dioxane and water.⁶ Ultrasound⁷ and microwave⁸ are reported to be effective for the Baylis–Hillman reaction. High pressure is a useful method for the acceleration of many organic transformations,⁹ which has been effectively applied to the Baylis–Hillman reaction¹⁰ because of its large negative volume of activation.¹¹ High pressure, however, is regarded as a special technique in organic synthesis, requiring particular apparatus.

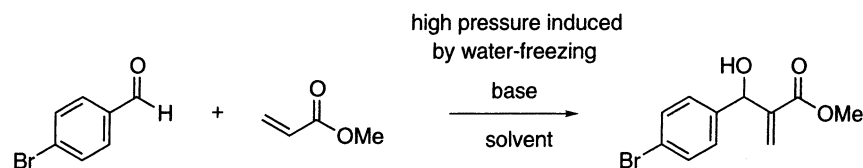
On the other hand, the volume of water increases about 10% on freezing. When water is frozen in a sealed autoclave at -20°C , a high pressure of up to about 200

MPa can be realized. A special advantage of this high pressure induced by water-freezing is that all the apparatus needed to obtain high pressure are an autoclave and a household electric refrigerator.¹² No specialized apparatus is necessary, which makes this high pressure technology easily available to an average laboratory. We have been studying application of this high pressure to accelerate organic reactions, and have already reported that the Michael reaction of alcohols and α,β -unsaturated ester can be accelerated greatly under this pressure in the presence of a catalytic amount of DMAP and LiClO_4 .¹³ In this paper we disclose the successful results achieved by applying high pressure to the Baylis–Hillman reaction.

First of all, we chose the reaction between *p*-bromobenzaldehyde and methyl acrylate as a model reaction and examined the promoter under the pressure induced by water-freezing, with the results summarized in Table 1. 3-Hydroxyquinuclidine (3-HQD)¹⁴ as catalyst is found to be superior to DABCO, DBU² and tributylphosphine.¹⁵ Next, a screening of solvents revealed that MeOH is the most suitable solvent among those examined such as MeOH, CH_2Cl_2 , CH_3CN , toluene, 1,4-dioxane, THF, and a mixture of 1,4-dioxane and water⁶ (Table 2). Under the optimized reaction conditions, the Baylis–Hillman adduct is obtained in 86% yield in 24 h under pressure induced by water-freezing. For a comparison of the pressure effect, the reaction at 1 atm was performed at 0°C and -20°C , and the adduct was obtained in 67 and 65% yield (Table 3, entries 10,11), respectively, indicating the efficiency of the present high pressure induced by water-freezing. As the yields of the reaction at 0°C and -20°C are nearly equal, the temper-

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* Corresponding author. Tel.: (+81)3-5228-8318; fax: (+81)3-5261-4631; e-mail: hayashi@ci.kagu.tus.ac.jp

Table 1. The effect of a base on the Baylis–Hillman reaction^a

Entry	Base	Yield (%) ^b
1	3-HQD	86
2	DABCO	61
3	DBU	7
4	DMAP	15
5	PBu ₃	5

^a Reactions were conducted on 0.6 mmol scale using 1.2/1.0/0.1 ratio of *p*-bromobenzaldehyde/methyl acrylate/base under water-freezing induced pressure conditions (200 MPa, –20°C) for 24 h using MeOH as solvent.

^b Isolated yield.

Table 2. The effect of a solvent on the Baylis–Hillman reaction^a

Entry	Solvent	Yield (%) ^b
1	MeOH	86
2	CH ₂ Cl ₂	70
3	CH ₃ CN	67
4	Toluene	46
5	THF	56
6	1,4-Dioxane	64
7	1,4-Dioxane–H ₂ O ^c	<5
8	Neat	67

^a Reactions were conducted on 0.6 mmol scale using 1.2/1.0/0.1 ratio of *p*-bromobenzaldehyde/methyl acrylate/3-HQD under water-freezing induced pressure conditions (200 MPa, –20°C) for 24 h.

^b Isolated yield.

^c 1,4-dioxane:H₂O = 1:1

ature effect is small in the present reaction. Thus, the good yield under high pressure induced by water-freezing would mostly be owing to high pressure.

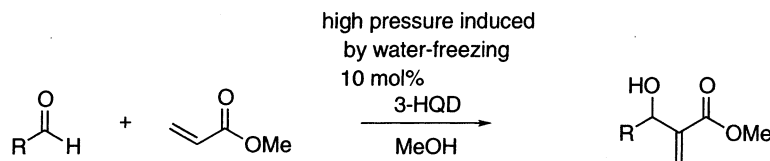
The reaction was performed as follows (Table 3, entry 9): To a 0.5 mL Teflon tube was added *p*-bromobenzaldehyde (123 mg, 0.67 mmol), methyl acrylate (50 μL, 0.56 mmol), 3-HQD (7.1 mg, 0.056 mmol) and MeOH (350 μL), and the tube was capped with exclusion of air. This tube was placed in an autoclave with inner capacity of about 100 mL. The autoclave was completely filled with water, sealed tightly, and left in a household electric refrigerator at –20°C. The inner pressure reached about 200 MPa after 12 h. Twenty four hours after setting the autoclave in the refrigerator, the autoclave was taken out, and the Teflon tube was removed from the autoclave. After removal of volatile organic materials under reduced pressure, purification was performed by column chromatography (AcOEt: hexane = 1:10–1:3) to afford the Baylis–Hillman adduct (129 mg, 0.48 mmol) in 86% yield.

Next, the generality of the reaction was examined. The results with various aldehydes both under the high

pressure induced by water-freezing and under normal pressure for comparison of the pressure effect are summarized in Table 3. As highly electron-deficient aldehydes such as *m*- and *p*-nitrobenzaldehydes react with methyl acrylate smoothly even at 1 atm, it is not necessary to use high pressure (entries 18, 19). As for the other aldehydes, effective rate acceleration was observed. Reaction of benzaldehyde and electron-deficient aldehydes such as *o*-, *p*-chlorobenzaldehyde, *p*-fluoro, and *p*-bromobenzaldehyde, proceeds smoothly under high pressure, providing adducts in 72–86% yield, while 28–67% yields are obtained under normal pressure at rt (entries 1–11). Though the reaction of an electron-rich aldehyde like *p*-anisaldehyde is slow, requiring long reaction time (104 h) even under high pressure conditions, much higher yield (62%) was obtained compared with the yield under 1 atm (8%) (entries 12, 13). α,β -Unsaturated aldehyde like cinnamaldehyde, and furylaldehyde can react much faster under high pressure conditions (entries 14–17). High pressure is not effective, however, toward aliphatic aldehydes: The Baylis–Hillman adduct of butanal was obtained in 16% yield in 20 h under 1 atm, while 7% is the yield under the high pressure (entries 20, 21).

The generality of the reaction was further examined with electron-deficient alkenes and the results are summarized in Table 4.¹⁶ As the reaction of *t*-butyl acrylate is slow probably owing to the steric hindrance, an amount of solvent was reduced to 150 μL instead of 350 μL, and better yield is obtained under high pressure conditions compared with the reaction under normal pressure (entries 3, 4). As the self-condensation product of methyl vinyl ketone, 3-methyleneheptane-2,6-dione,¹⁷ was formed in a substantial amount when 1.2 equivalent of benzaldehyde was used in the reaction of methyl vinyl ketone, 3 equivalents of aldehyde was employed, providing the Baylis–Hillman adduct in 54% yield under high pressure conditions, much higher than the low yield under normal pressure (entries 5, 6).

In summary, some Baylis–Hillman reactions can be accelerated by high pressure induced by water-freezing.

Table 3. The Baylis–Hillman reaction of various aldehydes with methyl acrylate^a

Entry	RCHO	Pressure (Mpa)	Temp. (°C)	Time (h)	Yield (%) ^b
1	Benzaldehyde	200	−20	24	78
2	Benzaldehyde	0.1	23	24	40
3	<i>o</i> -Chlorobenzaldehyde	200	−20	24	72
4	<i>o</i> -Chlorobenzaldehyde	0.1	23	24	49
5	<i>p</i> -Chlorobenzaldehyde	200	−20	24	78
6	<i>p</i> -Chlorobenzaldehyde	0.1	23	24	47
7	<i>p</i> -Fluorobenzaldehyde	200	−20	24	84
8	<i>p</i> -Fluorobenzaldehyde	0.1	23	24	28
9	<i>p</i> -Bromobenzaldehyde	200	−20	24	86
10	<i>p</i> -Bromobenzaldehyde	0.1	23	24	67
11	<i>p</i> -Bromobenzaldehyde	0.1	−20	24	65
12	<i>p</i> -Anisaldehyde	200	−20	104	62
13	<i>p</i> -Anisaldehyde	0.1	23	104	8
14	Cinnamaldehyde	200	−20	20	37
15	Cinnamaldehyde	0.1	23	20	22
16	Furylaldehyde	200	−20	20	89
17	Furylaldehyde	0.1	23	20	62
18	<i>m</i> -Nitrobenzaldehyde	0.1	23	12	80
19	<i>p</i> -Nitrobenzaldehyde	0.1	23	12	77
20	Butanal	200	−20	20	7
21	Butanal	0.1	23	20	16

^a Reactions were conducted on 0.6 mmol scale using 1.2/1.0/0.1 molar ratio of aldehyde /methyl acrylate/3-HQD.

^b Isolated yield.

Table 4. The Baylis–Hillman reaction of various electron deficient alkenes with benzaldehyde under high pressure and normal pressure

Entry	Alkene	Pressure (Mpa)	Time (h)	Yield (%) ^a
1	Methyl acrylate ^b	200	24	78
2	Methyl acrylate ^b	0.1	24	40
3	<i>t</i> -Butyl acrylate ^{b,c}	200	52	71
4	<i>t</i> -Butyl acrylate ^{b,c}	0.1	52	52
5	Methyl vinyl ketone ^d	200	14	54
6	Methyl vinyl ketone ^d	0.1	14	10

^a Isolated yield.

^b Reactions were conducted on 0.6 mmol scale using 1.2/1.0/0.1 ratio of benzaldehyde/alkene/3-HQD.

^c MeOH (150 μ L) was used instead of 350 μ L.

^d Reactions were conducted on 0.6 mmol scale using 3.0/1.0/0.1 ratio of benzaldehyde/alkene/3-HQD.

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