

NOTES

Aldol Addition of Dimethylsilyl Enolate in the Presence of Polyisocyanate with Alkali Metal Salt Catalyst

Shin-ichi YAMAMOTO, Yusuke AIZAWA, and Osamu MORIYA[†]

Department of Applied Chemistry, National Defense Academy,
1-10-20 Hashirimizu, Yokosuka 239-8686, Japan

(Received July 20, 2004; Accepted October 4, 2004; Published January 15, 2005)

KEY WORDS Polyisocyanate / Aldol Addition / Solid Solvent / Reaction Environment / [DOI 10.1295/polymj.37.47]

The polymers containing the aprotic polar solvent structures such as DMF, DMAc, and DMSO have been employed as the additives for several nucleophilic substitution reactions.^{1–6} These polymers, called “solid co-solvent”, have been used with alkali metal bases and alkylhalide nucleophiles in two phases reaction system of organic solvent and water. In the works, the main role of the solid solvents is regarded as an effective phase-transfer agent. In addition, it has been pointed that the solid solvent provides a good reaction environment to enhance the substitution reactions by the effects of the polar solvent structure and hydrophobic main chain. Such previous findings suggest that the polymeric solvents possess the possibility to be utilized as the solvent itself and enable a solvent-free reaction. The use of the solid solvents is preferable in the view of environmental problem and, further, the solid solvents are reusable. Consequently, the reaction system utilizing the solid solvents is thought to be an interesting ecological methodology.

On the basis of the consideration mentioned above, we reported recently the effects of the solid poly(*N,N*-dimethylacrylamide), as the analog of DMF, on the alkali metal salt catalyzed aldol addition of dimethylsilyl (DMS) enolate to aldehyde.⁷ In the work, the solvent structure in the polyacrylamide gel was demonstrated to be effective for holding an alkali metal salt and provide the reaction environment to give the corresponding aldol products in good yields. The results were comparable with those obtained in DMF solution by the use of analogous catalysts, which was reported previously by Hosomi *et al.*⁸ In the examinations using the several kinds of the polyacrylamide gels, the derivative of Wang resin (PDMA), which was assumed to contain more flexible polyacrylamide chain, was found to be more suitable than the traditional cross-linked gel (PDMAG) for

the aldol reaction (Scheme 1). In line with the obtained information, several polymeric solid solvents derived from Wang resin have been newly prepared and applied to the efficient aldol reaction catalyzed by alkali metal salts. In this work, we employ polybutylisocyanate (PBI) as the solid solvent, which has been prepared from Wang resin bounded pyrrolidine derivative according to the procedure reported by Okamoto *et al.* (Scheme 2)¹⁷ The polyisocyanate PBI is also consisted of amide groups as the main chain and, further, assumed to be a kind of asymmetric polymer. Therefore, the use of PBI is expected to show several characteristics such as the effective holding of alkali metal salts and the possibility of stereoselective reaction.

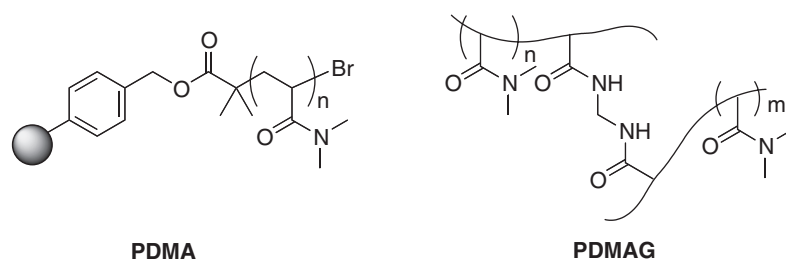
EXPERIMENTAL

General

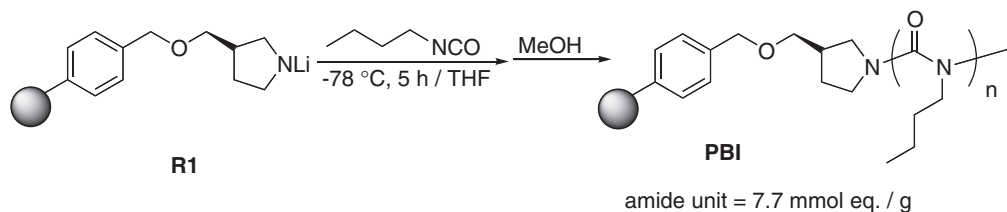
¹H and ¹³C NMR spectra were recorded on either a Bruker DMX-500 or a JEOL AL-300 spectrometer, using tetramethylsilane (TMS) as an internal standard in chloroform-*d* (CDCl₃). IR spectra were recorded on a Jasco FT/IR-230 spectrometer. The number-average molecular weight (*M_n*) and polydispersity (*M_w*/*M_n*) were estimated on a Tosoh HPLC-8220 system with refractive index (RI) and ultraviolet (UV, λ = 254 nm) detectors and a consecutive column (TSKgel Super HM-H) by using a calibration curve of polystyrene standards. As an eluent, chloroform (CHCl₃) was used at 40 °C, the flow rate of which was adjusted to be 0.6 mL/min. Optical rotation was measured by a Jasco P-1030 polarimeter.

Unless stated otherwise, all the chemicals and reagents were obtained commercially and used without further purification. Wang resin (100–200 mesh, 2% DVB, loading of OH group: 0.88 mmol equiv/g) was

[†]To whom correspondence should be addressed (E-mail: moriyaos@nda.ac.jp).



Scheme 1.



Scheme 2.

used as received from Novabiochem. Butylisocyanate and aldehydes were distilled over CaH_2 . THF and toluene were distilled from sodium-benzophenone ketyl before use. Dimethylsilyl enolates, **1a**,⁸ **1b**,⁸ **1c**,⁹ and **1d**,⁹ and pyrrolidine functionalized Wang resin (**R1**)¹⁰ were prepared according to the previous reports.

Preparation of **PBI**

R1 having 0.73 mmol equiv/g of pyrrolidine unit (1.40 g, 1 mmol) in toluene (1 mL) was fed in the round bottom flask equipped three ways stopped cock. The toluene solution of *t*-BuLi (1.46 M, 0.68 mL, 1 mmol) was added to the above suspension under argon atmosphere and the mixture was stirred for 10 min at room temperature. The reaction mixture was diluted with THF (100 mL), and cooled at -78°C . Butylisocyanate (11 mL, 100 mmol) was added to the THF solution in the flask *via* syringe. After the reaction was continued for 5 h, the resulting mixture was added to MeOH (5 mL), and stirred for 1 h at -78°C . After filtration, the residue was suspended in CHCl_3 (200 mL) to dissolve unsupported polymer. The insoluble resin, collected by filtration, was washed with DMF and MeOH, and dried *in vacuo*: Yield = 6.20 g (amide unit was 7.70 mmol equiv/g). IR (KBr): 2960, 1700 (C=O), 1348, 1084 (C–O) cm^{-1} . M_n and M_w/M_n were estimated by size exclusion chromatography (SEC) using polystyrene standards after the cleavage of polyisocyanate from **PBI** by trifluoroacetic acid in CHCl_3 (v/v = 1/5), which was conducted for 30 min at room temperature. The specific rotation of the polyisocyanate was measured in CHCl_3 at 20°C : $[\alpha]_{365}^{25} = -5^\circ$, $M_n = 20200$, $M_w/M_n = 1.56$. $^1\text{H NMR}$ (CDCl_3) δ 0.87–0.92 (m,

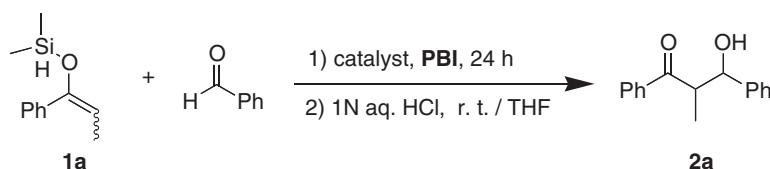
$-\text{CH}_3$), 1.30 (br, $-\text{CH}_2-\text{C}$), 1.59 (br, $-\text{CH}_2-\text{C}$), 3.20–3.32 (m, $-\text{CH}_2-\text{N}$), 3.68–3.87 (m, $-\text{CH}_2-\text{N}$, $>\text{CH}$) ppm. $^{13}\text{C NMR}$ (CDCl_3) δ 14.1, 20.4, 30.4, 41.2, 47.3, 55.9, 157.9 ppm.

General Procedure of Aldol Addition of Dimethylsilyl Enolate with Aldehyde

LiBr (5.2 mg, 0.06 mmol) was added to a solution of **PBI** (0.09 g, 0.63 mmol equiv of amide unit) in methanol (5 mL). The suspension was stirred for 15 min, and then methanol was evaporated under reduced pressure. The residual solid was dried *in vacuo* (ca. 0.5 Torr) at 60°C for 2 h. After cooling, dimethylsilyl enolate (**1**, 1.00 mmol) and aldehyde (0.50 mmol) were added to the mixture of LiBr and **PBI** under argon atmosphere and heated at 40°C or 60°C for 24 h. After the reaction, the mixture was diluted with dichloromethane (10 mL) and the insoluble solid was filtrated off. The filtrate was concentrated by a rotary evaporator and the residue was treated with aq 1 N HCl (1 mL) in THF (5 mL) at room temperature for 30 min. The aliquot solution was extracted with ether (30 mL) and the organic layer was washed with brine. After drying with anhydrous MgSO_4 , the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to obtain the aldol product (**2**). Spectroscopic data of the products (**2a**,¹¹ **2b**,¹¹ **2c**,¹² **2d**,¹³ **2e**,¹⁴ **2f**,¹⁵ **2g**,¹¹ and **2h**,¹⁶) are consistent with those reported in the previous literature.¹¹

RESULTS AND DISCUSSION

The solid solvent **PBI** was thought to be an asymmetric polymer, because the polybutylisocyanate was prepared by the use of optical active pyrrolidine



Scheme 3.

Table I. Aldol additions of **1a** with benzaldehyde in the Presence of **PBI**^a

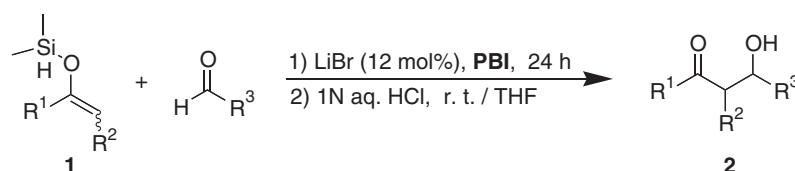
Entry	Catalyst	[Amide unit] /[Catalyst]	[1a]/ [benzaldehyde]	Temp. (°C)	Yield (%)	<i>syn:anti</i> ^b
1	LiBr (25)	0	2	40	13	51:49
2	LiBr (25)	10	2	40	98	65:35
3	—	— ^c	2	40	10	59:41
4	LiBr (12)	10	2	40	98	63:37
5	LiBr (5)	10	2	40	15	65:35
6	LiBr (5)	20	2	40	20	62:38
7	LiBr (12)	10	1	40	36	57:43
8	LiBr (12)	10	2	20	31	64:36
9	LiBr (12)	10	2	40	32	59:41
10	LiBr (12)	10	2	40	28	57:43
11	MgCl ₂ (12)	10	2	40	73	37:63
12	MgCl ₂ (12)	0	2	40	42	61:39
13	CaCl ₂ (12)	10	2	40	13	56:44
14	ZnBr ₂ (12)	10	2	40	92	56:44
15	ZnBr ₂ (12)	0	2	40	94	52:48

^aConditions: 0.5 mmol of benzaldehyde for 24 h. ^bDetermined by ¹H NMR. ^c0.63 mmol equiv of amide unit ([amide unit]/[benzaldehyde] = 1.25).

group bounded on Wang resin modified Okamoto *et al.*'s procedure (Scheme 2).¹⁷ The polyisocyanate chain incorporated into the resin under anionic conditions was analyzed after the cleavage by trifluoroacetic acid. The M_n and M_w/M_n were estimated by size exclusion chromatography (SEC) using polystyrene standards to be 20200 and 1.56, respectively. The content of amide unit, 7.70 mmol equiv/g, was determined by the weight increased after the polymerization. The specific rotation of polyisocyanate after cleavage from **PBI** was -5° , which was lower than that of the analogous polymer initiated from soluble pyrrolidine derivatives reported as $+416^\circ$ in the previous paper.¹⁷ Such difference might be caused by the steric effect of the supported resin, but the exact reasons have not been clarified yet. Thus, the conformation of polyisocyanate chain has been still ambiguous and seems not to be taken up as a proper reason for the discussion concerning the stereoselectivity of the aldol reaction in this work.

At first, the aldol reaction of benzaldehyde with two equiv of DMS enolate (**1a**), prepared from ethyl phenyl ketone, in the presence of LiBr catalyst was examined without any solvent (Table I). In the absence of **PBI**, the aldol reaction proceeded unsatisfactory to afford the corresponding product (**2a**) in only

13% yield (Table I, entry 1). Whereas, the use of **PBI**, loaded the alkali metal salt catalyst before the reaction, was obviously improved the yield of **2a**. The adduct **2a** was obtained almost quantitatively, when 25 mol % of LiBr to the aldehyde was employed and the molar ratio of [amide unit] to [LiBr] was adjusted to be 10 (Table I, entry 2). From the examinations on the required amount of the catalyst, 12 mol % of LiBr was found to be also effective for the reaction (Table I, entry 4). In comparison with the previous results using **PDMA** and **PDMAG**, where 25 mol % of LiBr was required to give a satisfactory result.⁷ While, in the use of **PDMA**, **PDMAG**, and **PBI**, the ratio of [amide]/[LiBr] = 10 was preferable for the efficient reaction. These results indicated that the coordination abilities of **PDMA** and **PBI** were nearly equal. Therefore it was speculated **PBI** had the sufficient space to progress the reaction effectively owing to rigid polymer backbone. In addition, **PBI** and **PDMA** had the flexible polymer chains compared to the cross-linked **PDMAG**. This seemed to be one of the advantages for the effective solid solvents. Since the free polymeric amide units should trap the metal catalyst more effectively and provide the space for the substrates more readily than those in the rigid structure. As the result, it was indicated **PBI** was more appropriate sol-



Scheme 4.

Table II. Aldol additions of DMS enolates with aldehydes in the Presence of **PBI**^a

Entry	Enolate	R ¹	R ²	R ³	Temp. (°C)	Product	Yield (%)	syn:anti ^b
1	1a	Ph	Me	Naph	40	2b	35	59:41
2	1a	Ph	Me	Pr	60	2c	43	55:45
3	1a	Ph	Me	cyclohexyl	60	2d	29	52:48
4	1a	Ph	Me	<i>t</i> -Bu	60	2e	trace	—
5	1b	<i>t</i> -Bu	Me	Ph	40	2f	45	73:27
6	1c	(CH ₂) ₄		Ph	40	2g	46	66:34
7	1d	Ph	H	Ph	40	2h	37	—

^a1.0 mmol of enolate, 0.5 mmol of aldehyde 12 mol % of LiBr for 24 h, [amide unit]/[LiBr] = 10.

^bDetermined by ¹H NMR.

id solvent for the reaction. However, the use of 5 mol % of the catalyst resulted in the drastic decrease of the yield such as 15% even in the presence of **PBI**. In the aldol reaction, two equiv of benzaldehyde was required to obtain **2a** in a good yield. As shown in the case using one equiv of aldehyde to DMS enolate, the yield of **2a** decreased to 36% (Table I, entry 7).

Several metal halides were employed as the catalysts for the reaction to obtain the information about the activities, which related with **PBI**. The effects of anion species on the reaction were demonstrated by the facts that the yields of **2a** decreased in order of LiBr ≫ LiCl > LiI (Table I, entries 4, 9, and 10). Further, alkaline earth metal salts were used for the reaction as the catalysts. The combination of magnesium chloride (MgCl₂) with **PBI** was also effective to obtain **2a** in the good yield such as 73% (Table I, entry 11). The yield of **2a** decreased to 42% without **PBI** (Table I, entry 12). While, calcium chloride (CaCl₂), which was reported to be an effective catalyst for the analogous aldol reaction in DMF, hardly catalyzed the reaction under the conditions mentioned here (Table I, entry 13).⁸ In addition, the catalytic activity of other kind of catalyst, zinc bromide (ZnBr₂), was examined. The reaction proceeded to give **2a** in the excellent yield over 92%. However, no enhancement of the reaction brought by the presence of **PBI** was observed in the use of ZnBr₂ (Table I, entries 14 and 15). ZnBr₂ has been known to act as a Lewis acid in various reactions and should accelerate such aldol reaction.¹⁸ On the other hand, in the case of alkali metal salts and alkaline earth metal salts, anion species seemed to activate DMS enolate. Therefore, the

amide units in **PBI**, which should coordinate the cation species and contribute to the formation of anion species, might be effective in those cases. In the utilization of the Lewis acid catalyst, the coordination by **PBI** is essentially useless to activate it. The results observed in the use of ZnBr₂ seem to be explained by the above speculation, which is based on our thinking about the role of the solid solvent **PBI**.

The reaction system of LiBr and **PBI** was applied to the aldol reaction using various DMS enolates and aldehydes. The results of these solvent-free reactions were listed in Table II. The enolate **1b** and **1c** having cyclic and bulky *tert*-butyl substituent as R¹, respectively, reacted with benzaldehyde to give the corresponding aldol products **2f** and **2g** in the moderate yields around 45% (Table II, entries 5 and 6). In the case of **1d** having phenyl group as R¹ and no alkyl substituent as R², the yield of the aldol **2h** was 37% (Table II, entry 7). The reactions using alkylaldehydes with **1a** hardly gave the products. Therefore, the reaction temperature was raised from 40 to 60 °C to obtain **2c** in 43% yield (Table II, entry 2). However, the reactions of **1a** with cyclohexylaldehyde and pivalaldehyde provided the corresponding aldols **2d** or **2e** in the lower yields such as 29% and trace (Table II, entries 3 and 4). These reactions might be affected by a steric hindrance, which should be an important factor especially in the polymeric environment. In the use of **PBI**, the site, holding the catalyst, assumed to be surrounded by the polyisocyanate chain. This basically makes the access of the bulky aldehydes to the site, where the enolate and the catalyst were also assembled, difficult in comparison with the

less-bulky aldehyde. However, more detailed experiments using various substrates are required to clarify the critical factor on the steric problems, which relate to the configuration of polyisocyanate chain containing the alkali metal salt.

The stereoselectivity has been important in the investigation on the recent aldol reaction. However, the stereoselective aldol reaction was essentially difficult in the use of **PBI** with the alkali metal salt catalysts. All the aldols **2** obtained in this work showed only moderate *syn*-diastereoselectivity. Essentially, there were two considerable reasons to explain the results. One was the primarily doubt on the asymmetric polyisocyanate chain, which showed the low specific rotation as mentioned above. The other seemed to be main one that the aldol reaction does not progress through complete penta-coordinate silicate transition state, which has been reported previously,¹⁹ and Lewis acidity of lithium cation on **PBI** is not strong enough to form the cyclic transition state. Meanwhile, in the use of trimethylsilyl (TMS) enolate, no corresponding product was obtained. This result might be caused by the decrement of Lewis acidity of silicon atom and/or the steric hindrance due to three methyl groups. Consequently, the role of **PBI** is thought to hold on cation species and form free anion species, which should activate DMS enolate. In other words, the relationship between **PBI** and the substrates might be neglect at least in a stereo determining step.

SUMMARY

In this report, we prepared the new solid solvent, **PBI**, and investigated its' effects on the aldol reaction using alkali metal salt as a catalyst. The results demonstrated that **PBI** was an effective matrix for the solvent-free aldol reaction. The structure containing amide units as the main chain in **PBI** was shown to be more favorable to hold alkali metal cation and afford free anion specie compared to polyacrylamide, since the use of **PBI** enable to decrease the required amount of the catalyst. The analogous aldol reaction using the metal salt catalysts has been reported to proceed quantitatively in the use of the liquid solvents such as DMF and DMAc. Consequently, the use of the solid solvents may not be favorable to pursue

the efficiency of the reaction, but these like **PBI** could be collected readily after the reaction by a simple filtration and reused. Especially, in the consideration of an environmental problem, the combination of the low toxic metal catalyst such as alkali metal salt with the solid solvent seems to be a useful reaction system. The continuous investigations on the usages of designed solid polymer solvents are progressed and the results will be presented in near future.

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