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Communications

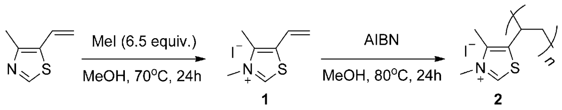
Poly(3,4-dimethyl-5-vinylthiazolium)/DBU-Catalyzed Thioesterification of Aldehydes with Thiols**

Junyong Chung, Ue Ryung Seo, Supill Chun, and Young Keun Chung*[a]

Poly(3,4-dimethyl-5-vinylthiazolium) was synthesized from 3,4-dimethyl-5-vinylthiazole through free radical polymerization and was examined as polymer precatalysts in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for the thioesterification of aldehydes with thiols. The poly(5-vinylthiazolium)/DBU had excellent catalytic activity and could be reused 10 times without a considerable loss of activity.

Recently, organocatalysts related to green chemistry have attracted much attention.[1] One of the advantages of organocatalysts is that the catalytic reaction does not require a metal catalyst. However, most organic syntheses need a large amount of an organic catalyst and are performed in a homogeneous medium; hence, recovery and reuse of the catalyst is often not feasible. To overcome these obstacles, the heterogenization of organocatalysts over organic polymers and mesoporous materials was recently reported.[2] However, most of these heterogeneous catalysts suffer from relatively low yields and poor recyclability, presumably as a result of the poor stability or degradation of the catalysts under the reaction conditions. We recently developed a highly efficient, recyclable polymer-based organocatalytic system, that is, poly(4-vinylimidazolium),[3] that shows high catalytic activity for benzoin condensation and cycloaddition of CO_2 to epoxides. These polymeric catalysts were successfully recovered and reused over several cycles without any loss of performance. Our interest in poly(vinylimidazolium)s led us to study poly(vinylthiazolium)s. Thiazoles have been widely studied in materials science;[4] however, to the best of our knowledge, there is no report on the synthesis and chemistry of poly(vinylthiazolium)s. Therefore, we decided to study the polymerization of 4-methyl-5-vinylthiazole, because it is commercially available and its polymerization to poly(4-methyl-5-vinylthiazole) has not yet been reported. We also studied the use of poly(vinylthiazolium) as a precatalyst for the thioesterification of aldehydes with thiols, because direct thioesterification of aldehydes has received little attention relative to direct aldehyde-to-ester conversions.[5] Thioesters are widespread in biochemistry[6] and are versatile building blocks for the construction of various natural products.[7] Many useful synthetic routes have been developed.[8] However, only a few studies on N-heterocyclic carbene (NHC)-catalyzed thioesterification have been reported.[9] Herein, we communicate the synthesis of poly(vinylthiazolium) from 3,4-dimethyl-5-vinylthiazolium and its use as a precatalyst for thioesterification of aldehyde and alkyl thiols. In 1989, Tsuda et al. reported thiazolium salt polymers.[10] According to their report, *N*-methyl-4-vinylphenylthiazolium iodide could not be not polymerized by radical initiators. Therefore, 4-vinylphenylthiazole was polymerized, and the resultant polythiazole was quaternized by using methyl iodide. The degree of quaternization was calculated by elemental analysis of iodine.

We synthesized poly(vinylthiazolium) from 3,4-dimethyl-5-vinylthiazol-3-ium by using a radical initiator, that is, 2,2′-azobisisobutyronitrile (AIBN) (Scheme 1). 3,4-Dimethyl-5-vinylthiazol-3-ium (**1**) was prepared by reaction of 4-methyl-5-vinylthiazole, which is commercially available, with methyl iodide. The reaction of 4-methyl-5-vinylthiazole with methyl iodide afforded 3,4-dimethyl-5-vinylthiazol-3-ium in 87 % yield. Polymerization of **1** in the presence of AIBN afforded poly(3,4-dimethyl-5-vinylthiazol-3-ium) (**2**), which is the organocatalyst precursor, in various yields depending on the reaction conditions (see the Supporting Information). Broad ^1H NMR signals are observed for this compound, as expected for a high molecular weight polymer. The polymer was slightly soluble in DMSO, DMF, and water at room temperature but insoluble in other polar solvents, including chloroform, dichloromethane, and acetone. The weight-average molecular weight (*Mw*) of **2** is approximately 42 700, as determined by light-scattering experiments.[11]



Scheme 1. Synthesis of poly(vinylthiazolium).

As a model reaction for thioesterification, we initially examined the reaction of benzaldehyde with 1-pentanthiol in the presence of **2** (10 mol %), an oxidant (1.2 equiv.), and DBU (10 mol %) in DMSO at room temperature for 24 h (Table 1). The use of oxidants such as phenazine, MnO_2, and O_2 afforded the corresponding thioester in yields of 90, 38, and 7 %, respectively (Table 1, entries 1–3). However, *tert*-butyl hydroperoxide, 2-iodobenzoic acid, potassium persulfate, diethyl azodicarboxylate, 4-phenyl-1,2,4-triazole-3,5-dione, and (diacetoxyiodo)benzene as oxidants gave only a trace amount of the corresponding thioester (not shown in Table 1). The use of azobenzene as an oxidant resulted in a considerable amount of

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[a] *J. Chung, U. R. Seo, S. Chun, Prof. Dr. Y. K. Chung*
Department of Chemistry
Seoul National University
Seoul 151-747 (Korea)
E-mail: ykchung@snu.ac.kr

[**] *DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.*

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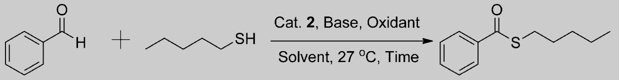
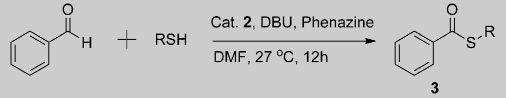
Table 1. Optimization of the reaction conditions.[a]

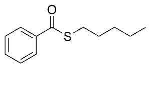


Entry	Cat. 2 [mol %]	Base [mol %]	Oxidant	Solvent	t [h]	Yield [%]
1	10	DBU (10)	phenazine	DMSO	24	90
2	10	DBU (10)	azobenzene	DMSO	24	91
3	10	DBU (10)	MnO_2	DMSO	24	38
4	10	DBU (10)	O_2	DMSO	24	7
5	10	Et_3N (10)	phenazine	DMSO	24	69
6	10	DBU (10)	phenazine	DMF	24	92
7	7	DBU (7)	phenazine	DMF	24	93
8	5	DBU (5)	phenazine	DMF	24	97
9	3	DBU (3)	phenazine	DMF	24	86
10	5	DBU (5)	phenazine	DMF	12	95
11	5	DBU (5)	phenazine	DMF	9	92
12	4	DBU (4)	phenazine	DMF	12	97
13[b]	4	DBU (4)	phenazine	DMF	12	11
14[c]	4	DBU (4)	phenazine	DMF	12	50

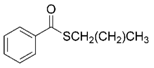
[a] Conditions: benzaldehyde (1 mmol), 1-pentanethiol (1.1 equiv.), oxidant (1.2 equiv.), solvent (1 mL). [b] Azobenzene was used. [c] **1** was used.

Table 2. Thioesterification of benzaldehyde with thiols.[a]

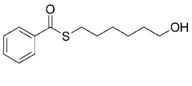




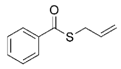
3aa, 97%[b]



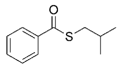
3ab, 96%



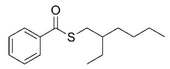
3ac[c], 80%



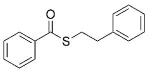
3ad[d], 83%



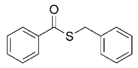
3ae, 89%



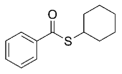
3af, 76%



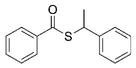
3ag, 88%



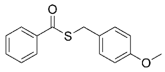
3ah, 90%



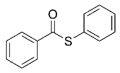
3ai, 87%



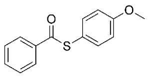
3aj, 98%



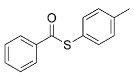
3ak, 90%



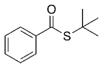
3al[e], 79% (15%)[f]



3am[e], 56% (25%)[f]



3an[e], 51% (28%)[f]



3ao[e], 74% (23%)[f]

[a] Conditions: benzaldehyde (1 mmol), thiol (1.1 equiv.), **2** (4 mol %), DBU (4 mol %), phenazine (1.2 equiv.), DMF (1 mL). [b] Yield of isolated product. [c] Selectivity of thioesterification and esterification (98:2) [d] Conditions: **2** (7 mol %), DBU (7 mol %). [e] Conditions: **2** (10 mol %), DBU (10 mol %), 40 °C, 24 h. [f] **2** (4 mol %) was used.

product; however, purification of the product was difficult, because its polarity is similar to that of azobenzene. Replacement of DBU with triethylamine in the presence of poly(4-methyl-5-vinylthiazolium) and phenazine led to a lower yield (69 %; Table 1, entry 5), whereas changing the reaction solvent from DMSO to DMF gave a better yield (92 %; Table 1, entry 6). The amount of catalyst used also influenced the yield of the reaction (Table 1, entries 6–9). The yield of the product was slightly dependent on the reaction time (Table 1, entries 9–11). The optimum reaction conditions were determined as follows: **2** (4 mol %), DBU (4 mol %), phenazine (1.2 equiv.), DMF (1 mL), room temperature, 12 h. Moreover, the catalytic activity of **2** was higher than that of **1** (50 %; Table 1, entry 14). Several years ago, Murata and Kageyama reported the use of 3-butyl-4-methylthiazolium bromide as a catalyst for the reaction of benzaldehydes with azobenzene in dichloromethane containing octanethiol and Et_3N.[9a] They isolated the corresponding *S*-octyl thiobenzoates with concomitant formation of hydrazide derivatives

Using the optimized reaction conditions, the catalytic activity of **2** was investigated for the reaction of benzaldehyde with a variety of thiols (Table 2). Various alkyl thiols containing hydroxy, alkene, and aryl groups afforded high to excellent yields of the corresponding thioesters (see compounds **3 ab**, **3 ac**, **3 ag**, **3 ah**, and **3 ak**). In the case of allyl thiol, the yield was highly sensitive to the amount of **2**; 4 mol % **2** generated a yield of 32 %, whereas 7 mol % **2** generated a yield of 83 %. For 6-mercaptohexan-1-ol (**3 ac**), two reaction products could be produced because of the presence of two potential reaction sites.[12] However, excellent thia selectivity over oxa selectivity (98:2) was observed. Secondary alkyl thiols (see compounds **3 ai** and **3 aj**) also gave excellent yields of the thioester products. For aryl thiols and *tert*-butyl thiol (see compounds **3 al**–**3 ao**), poor yields (15–28 %) were obtained in the presence of 4 mol % **2**. However, the yields dramatically increased to 51–79 % in the presence of 10 mol % **2** at 40 °C. Therefore, the catalytic system is quite effective for the reaction of benzaldehyde with alkyl and aryl thiols

We next investigated the reaction of various aldehydes with 1-pentanthiol (Table 3). Most aryl aldehydes were good substrates at room temperature; however, aryl aldehydes with halo or nitro substituents did not provide high yields at room temperature. Therefore, for these substrates, we altered the reaction temperature and determined that the optimal temperature was 90 °C (see the Supporting Information). Aromatic as well as aliphatic aldehydes reacted with 1-pentathiol with the use of this procedure. A wide range of aromatic aldehydes bearing both electron-donating and electron-withdrawing groups were used, regardless of the position of their substituents, and they gave the corresponding thioesters in high yields (see compounds **3 ba**, **3 fa**, **3 ha**–**3 ma**, and **3 pa**) except nitrobenzaldehydes **3 ga** and **3 na**. In particular, 2-chloro-5-nitrobenzaldehyde (**3 na**), which has two electron-withdrawing substituents on the aromatic ring, gave a poor yield (30 %). Cyclohexane carbaldehyde (**3 oa**), which is an example of an unactivated aldehyde, gave a good yield of thioester (85 %). Heteroaro-

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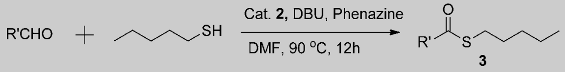
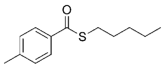
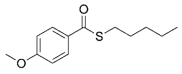
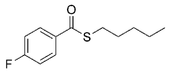
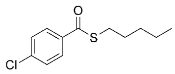
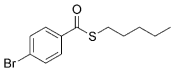
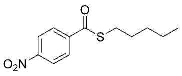
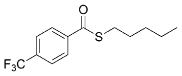
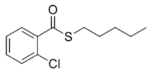
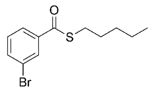
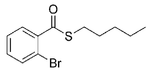
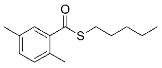
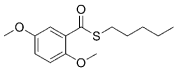
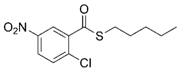
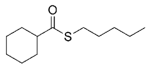
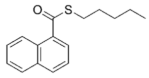
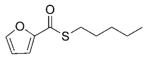
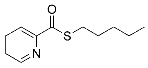
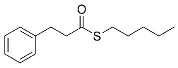
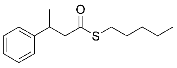
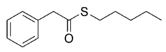
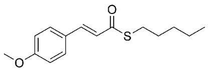
Table 3. Thioesterification of aldehydes with 1-pentanethiol.[a]

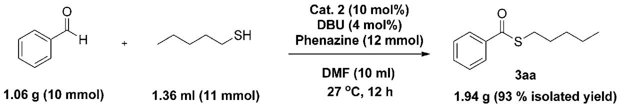


 **3ba**, 98%[b] (93%)[c]	 **3ca**, 75%	 **3da**, 89%
 **3ea**, 86%	 **3fa**, 84%	 **3ga**, 48%
 **3ha**, 88%	 **3ia**, 82%	 **3ja**, 78%
 **3ka**, 85%	 **3la**, 86% (89%)[c]	 **3ma**, 89% (71%)[c]
 **3na**, 30%	 **3oa**, 85% (24%)[c]	 **3pa**, 89% (70%)[c]
 **3qa**, 77%	 **3ra**, 69%	 **3sa**, 86%
 **3ta**, 88%	 **3ua**[d], 43%	 **3va**[d], 47%

[a] Conditions: aldehyde (1 mmol), 1-pentanethiol (1.1 equiv.), **2** (4 mol%), DBU (4 mol%), phenazine (1.2 equiv.), DMF (1 mL). [b] Yield of isolated product. [c] At room temperature. [d] Conditions: **2** (10 mol%), DBU (10 mol%), 24 h.

matic aldehydes such as furan-2-carbaldehyde (**3 qa**) and picolinaldehyde (**3 ra**) also gave high yields (77 and 69%, respectively). Alkyl aldehydes with phenyl groups (see compounds **3 sa** and **3 ta**) were good substrates (86 and 88% yield, respectively). However, for 2-phenylacetaldehyde (**3 ua**) and 3-(4-methoxyphenyl)acrylaldehyde (**3 va**), a longer reaction time (24 h) was needed to give moderate yields (43 and 47%, respectively).

Finally, it is worth noting that the reaction may be scaled up [Eq. (1)]. In the reaction of 1.06 g of benzaldehyde (10 mmol) with pentane thiol (11 mmol), 1.94 g (93% yield) of **3 aa** was isolated.



(1)

The reusability of **2** was also examined (Figure 1). For the recycling test, 10 mol% **2** was used. As the reaction progressed, **2** started to decompose through loss of a hydrogen atom of the C–H bond. However, this problem could be easily overcome by adding hydriodic acid to the reaction mixture. The addition of hydriodic acid led to precipitation of **2** and the phenazine salt. Given that **2** and the phenazine salt have different solubilities in ethyl acetate, **2** was easily recovered from the reaction mixture. Recovered **2** was successfully reused without loss of performance over 10 cycles (each time, 83–95% yield) and 73% of **2** was recovered after recycling 10 times.

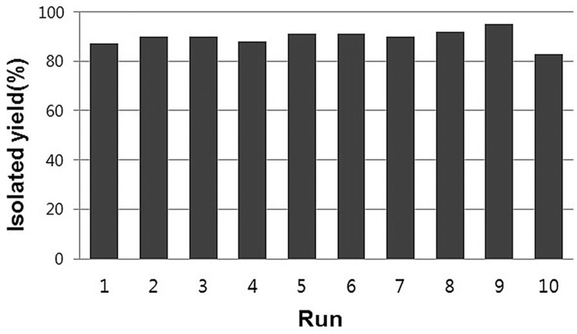


Figure 1. Recycling of poly(vinylthiazolium) in the thioesterification of benzaldehyde with pentane thiol.

In conclusion, we developed a polymer-based organocatalytic system (see compound **2**) by polymerization of 3,4-dimethyl-5-vinylthiazolium; this system showed high catalytic activity for the thioesterification of aldehydes with thiols. Precatalyst **2** showed higher catalytic activity than its monomeric analogue (see compound **1**) and could be reused 10 times without a considerable loss of activity. Thus, precatalyst **2** has great potential, and further investigation of the applicability of polymer-based thiazolium system **2** for other reactions are ongoing in our laboratory.

Experimental Section

Synthesis of monomer 1

A Schlenk flask was charged with 4-methyl-5-vinythiazole (0.12 g, 1 mmol), MeI (0.2 mL, 6.5 mmol), and MeOH (8 mL). The mixture was stirred at 70 °C for 24 h, and the solvent was then evaporated. The mixture was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH = 10:1).

Synthesis of polymer precatalyst 2

In a typical experiment, a 10 mL Schlenk flask was flame-dried and charged with **1** (3 mmol), AIBN (0.012 mmol), and MeOH (3 mL).

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The Schlenk tube was subjected to three freeze–pump–thaw cycles and was placed in a thermostatted oil bath previously maintained at 80 °C. The polymerization reaction was quenched after 24 h by sudden cooling with liquid nitrogen. Resulting poly(3,4-dimethyl-5-vinylthiazolium) salt **2** was isolated by precipitation in acetone solution. After the precipitate was dried, **2** was obtained as a light-green powder.

General procedure for the thioesterification of benzaldehyde with thiols

Reactions were performed in a tube-type Schlenk flask equipped with a stirring bar and capped with a rubber cap. The flask was charged sequentially with catalyst **2** (10 mg, 0.04 mmol, 4 mol %), DBU (6 mg, 0.04 mmol, 4 mol %), benzaldehyde (0.11 g, 1 mmol), phenazine (0.22 g, 1.2 mmol), thiol (1.1 mmol), and DMF (1 mL). The mixture was stirred at room temperature for 12 h. The mixture was added to acetone (30 mL), the catalyst was filtered off, and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (silica gel, hexane/EtOAc) afforded the thioester.

General procedure for the thioesterification of aldehydes with 1-pentanethiol

Reactions were performed in a tube-type Schlenk flask equipped with a stirring bar and capped with a rubber cap. The flask was charged sequentially with catalyst **2** (10 mg, 0.04 mmol, 4 mol %), DBU (6 mg,0.04 mmol, 4 mol %), 1-pentanethiol (0.11 g, 1.1 mmol), phenazine (0.22 g, 1.2 mmol), aldehyde (1 mmol), and DMF (1 mL). The mixture was stirred at 90 °C for 12 h. The mixture was added to acetone, the catalyst was filtered off, and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (silica gel, hexane/EtOAc) afforded the thioester.

Recycling test

A Schlenk tube was charged with benzaldehyde (106 mg, 1 mmol), pentanethiol (116 mg, 1.1 mmol), phenazine (220 mg, 1.2 mmol), catalyst (26 mg, 0.1 mmol, 10 mol %), DBU (15 mg, 0.1 mmol, 10 mol %), and DMF (1 mL). After stirring for 12 h at room temperature, hydriodic acid (1.5 mmol) was added to the mixture, and the resulting solution was stirred for 1 h. After evaporation of DMF under reduced pressure, MeOH (180 mL) was added to the residue. The solution was filtered and EtOAc (20 mL) was added to precipitate **2**. Recovered **2** was reused in the next experiment. The filtrate containing the phenazine salt and the product was concentrated under reduced pressure, and the residue was redissolved in EtOAc. The resulting solution was filtered over a pad of Celite, and the resulting filtrate was concentrated and purified by flash column chromatography to give the product. The catalytic performance of poly(NHC) was well maintained over the 10 recycling steps with yields of 83–95 %, and 73 % of **2** was recovered after recycling 10 times (starting from 26 mg of **2**, 19 mg of **2** was recovered after 10 cycles).

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Keywords: polymer precatalysts · polymerization · radicals · sustainable chemistry · thioesterification

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