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Unprecedented Polymer-Supported π-Acid: Synthesis and Its Application as a Promoter to the Monothioacetalization of Acetals

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Abstract: A novel polymer was synthesized by copolymerization of styrene monomer bearing dicyanoketene acetal functionality and ethylene glycol dimethacrylate, and used successfully as a recyclable π-acid catalyst in monothioacetalization of aromatic, aliphatic, acyclic, and cyclic acetals with thiophenol and phenylthiotrimethylsilane.

Since Merrifield's solid phase synthesis of peptides[1a] polymer-supported catalysts, reagents, and substrates have attracted much attentions for many years due to their inherent advantages in synthetic chemistry: simplification of reaction procedures including easy separation of products, application to automation systems leading to the combinatorial chemistry, and recycling of catalysts and reagents.[1b]

Useful polymer-supported acid catalysts so far, are classified to several types from the view point of situations of elements of intrinsic acidity: 1) Lewis acids incorporated coodinately in inorganic and organic polymer matrix such as zeolites,[2a] clays,[2b] silica,[2c] and resins,[2d] 2) Lewis acidic metals introduced covalently in organic[3a] and mixed organic-inorganic polymer matrix,[3b] 3) polymeric protonic (Brønsted) acids such as proton-exchanged zeolites[4a] and clays,[4b] and protonated ion-exchange resins including hydrochloric,[4c] sulfonic,[4d] and carboxylic acid,[4e] 4) organic cation species bound to a polystyrene resin.[5]

In the couse of our investigation on the π-acid property of tetracyanoethylene (TCNE) we have found that certein capto-dative olefins, dicyanoketene acetals (DCKA), in which two geminal cyano groups are substituted with alkoxy groups, work well as a promoter in alcoholysis of epoxides,[6a] tetrahydropyranylation of alcohols,[6b] and monothioacetalization of acetals.[6c] During the modification of the structure of DCKA aiming at novel catalytic activities, we have designed polymer-supported dicyanoketene acetals, which are accessible by polymerization of styrene derivatives bearing dicyanoketene acetal moiety. Reported herein are a synthesis of a unprecedented polymer-supported dicyanoketene acetal, another type of polymer-supported acid, and its use as a recyclable polymeric π-acid catalyst in monothioacetalization of acetals with thiophenol and phenylthiotrimethylsilane.

The preparation of polymeric DCKA (**3** and **4**) is shown in Scheme 1. Condensation of diethyl malonate with an equiv. mole of 4-chloromethyl styrene in the presence of NaH followed by reduction with $LiAlH_4$ gave a diol derivative (**1**) in 46% overall yield for two steps. Condensation of the diol (**1**) with 1.3 mole equiv. of TCNE in the presence of a catalytic amount of Et_2NH in THF produced a monomeric styrene derivative (**2**) in 67% yield, which was ascertained to have the catalytic activities in the reaction of benzaldehyde dimethyl acetal (**5**) with

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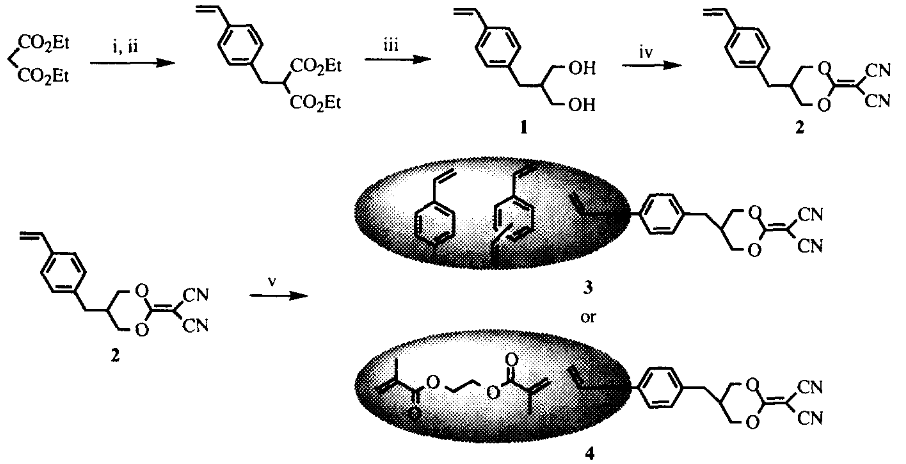
thiophenol (1.5 equiv.) in CH_3CN at 60 C for 3 h to give the corresponding monothioacetal (**6**) in 87% yield. A simple copolymerization of **2** with each one equivalent mole of styrene and divinylbenzene as cross-linking agents produced in 49% yield a polymer-supported DCKA (**3**) as a white powder, which was estimated to be composed of a 2 : 2 : 1 ratio of **2**, styrene, and divinylbenzene from elemental analysis (2.30 mmol/g for loaded DCKA). Another one (**4**) was obtained with ethylene glycol dimethacrylate (EGDMA) as a cross-linking agent according to Dhai's method[7] in 80% yield as a white powder, which was estimated to be composed of a 2 : 1 ratio of **2** and EGDMA from elemental analysis (2.74 mmol/g for loaded DCKA).

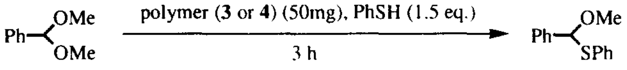


Scheme 1. i: 1.1 eq. NaH, DMF, r.t., 1 h; ii: 0.3 eq. NaI, 1.0 eq. 4-chloromethylstyrene, 50 °C, 2 h; iii: 3.0 eq. $LiAlH_4$, Et_2O, reflux, 2 h (46 % for 2 steps); iv: 0.2 eq. Et_2NH, 1.3 eq. TCNE, THF, r.t., 2 h (67%); v: (synthesis of **3**), 0.05 eq. AIBN, 1.0 eq. styrene, 1.0 eq. divinylbenzene,Toluene,100 °C, 22 h (49%); (synthesis of **4**), 0.05 eq. AIBN, 1.0 eq. EGDMA, Toluene, 100 °C, 2 h (80%)

The polymeric DCKAs (**3** and **4**) were evaluated as catalysts in monothioacetalization of benzaldehyde dimethyl acetal (**5**) with thiophenol. The polymer (**3** or **4**) (50 mg) was added to a solution of the dimethyl acetal (**5**) (50 mg, 0.33 mmol) and thiophenol (PhSH) (0.50 mmol) in a solvent (1.0 ml). The mixture was stirred at 60 C and the reaction was monitored by TLC. The reaction displayed a noticeable solvent dependence listed in Table 1. Although the polymeric DCKA (**3**) showed little catalytic activity, another one (**4**) accelerated remarkably the monothioacetalization reaction in acetonitrile, which was the solvent of choice for providing a high yield (83%) of a monothioacetal (**6**). Solvents, CH_2Cl_2, Et_2O, C_6H_6, $CH_3C_6H_5$, and DMSO were poor to sluggish and DMF was moderate for the reaction. The product could be easily isolated by filtration of the catalyst followed by the usual work-up. After washing the recovered polymer successively with water and ethyl acetate followed by drying at room temperature in vacuo for 4 h, the catalysts (**3** and **4**) could be reused without loss of the activities (entry 1, 2 and 8).

Next, efficiency of the catalyst (**4**) was investigated in the monothioacetalization of several aliphatic acetals including a methoxymethyl (MOM) (**10**), tetrahydropyranyl (THP) (**11**), and tetrahydrofuranyl (THF) ethers (**12**) using PhSH as well as phenylthiotrimethylsilane (TMS-SPh) as a nucleophile, and the results are summarized in Table 2. Typical dimethyl acetals of decyl aldehyde (**7**), 2-octanone (**8**), and cyclohexanone (**9**)

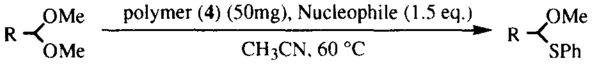
Table 1. Solvent effect and the reusing of polymeric DCKA (**3** and **4**) in the monothioacetalization of benzaldehyde dimethyl acetal



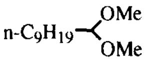
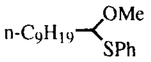
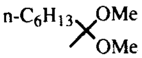
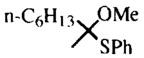
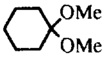
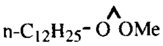
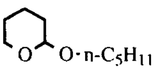
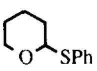
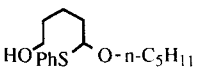
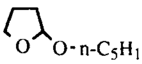
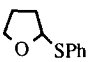
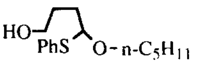
5 (50 mg) **6**

Entry	Solvent	Polymer	T / °C	Yield (%)		
				1st.	2nd.	3rd.
1	CH_3CN	**3**	60	21	25	—
2	CH_3CN	**4**	60	83	88	87
3	CH_2Cl_2	**4**	reflux	10	—	—
4	Et_2O	**4**	reflux	32	—	—
5	Benzene	**4**	60	29	—	—
6	Toluene	**4**	60	35	—	—
7	DMSO	**4**	60	42	—	—
8	DMF	**4**	60	61	58	60

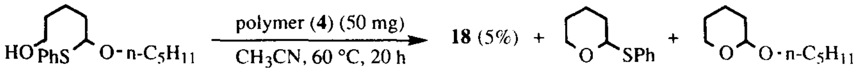
Table 2. Monothioacetalization of acetals catalyzed by polymeric DCKA (**4**)



50 mg

Entry	Substrate	Nucleophile	Time (h)	Product / Yield (%)			
1	 **7**	PhSH	6	 **13**	73 [a]		
2		PhSH	20		75		
3		TMS-SPh	7		50 [b]		
4		TMS-SPh	20		61		
5		TMS-SPh	40		86		
6	 **8**	PhSH	2	 **14**	64		
7		TMS-SPh	5		69		
8	 **9**	PhSH	6	 **15**	29		36
9		TMS-SPh	7		80		
10	 **10**	PhSH	31	no reaction			
11		TMS-SPh	31	no reaction			
12	 **11**	PhSH	12	 **16**	73	 **18**	
13		TMS-SPh	19		6 [c]		35
14		TMS-SPh	40		48 [d]		14
15	 **12**	PhSH	12	 **17**	86	 **19**	
16		TMS-SPh	40		75		18

[a] 14% of the starting material was recovered. [b] 40% of the starting material was recovered. [c] 31% of the starting material was recovered. [d] 21% of the starting material was recovered.



18 (50 mg) **16** (71%) **11** (11%)

underwent smoothly substitution reactions under the conditions at 60 ℃ within two days to give the corresponding monothioacetal (**13**), (**14**), and (**15**), respectively, although the ketone acetals (**8**, **9**) reacted more rapidly than that of the aldehyde (**7**) (entry 3, 4, 5, 7, 9). Unexpectedly, no reaction was observed with dodecyl-MOM ether (**10**) (entry 10 and 11). Mixed acetals, THP (**11**) and THF ethers (**12**) derived from n-pentanol, underwent regioselective thiolysis depending on the amount of the catalyst and the reaction time especially when TMS-SPh was used as a nucleophile to afford selectively endo- (**18**) or exo-cyclic C-O bond cleaved products (**16**) (entry 12~16). The fact that a smaller amount of the catalyst and shorter period of the reaction time led to the linear monothioacetals (**18**) selectively (entry 13) indicated that the endocyclic C-O bond of the THP ether (**11**) appears to be cleaved more rapidly than the exocyclic one, leading initially to **18** which is transformed to cyclic monothioacetal (**16**) with elimination of n-pentanol under the reaction conditions. Thus, the intermediate linear monothioacetal (**18**) (50 mg, 0.177 mmol) was warmed at 60 ℃ for 20 h with the polymer catalyst (**4**) (50 mg) to produce 71% yield of the cyclic monothioacetal (**16**).

In conclusion, we synthesized a novel polymer-supported DCKA (**4**), which was found to be a unprecedented and recyclable polymeric π-acid and successfully promoted mild monothioacetalization reaction of acetals. Further application of this polymer-supported catalyst to the nucleophilic substitution reaction of acetals using such carbon-nucleophiles as TMS-CN and TMS-enol ethers is currently under investigation.

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