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# Polyguanidine as a Highly Efficient and Reusable Catalyst for Knoevenagel Condensation Reactions in Water

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Polyguanidine is used as a novel and highly efficient catalyst in the Knoevenagel reaction of aldehydes with active methylene compounds in water to afford substituted electrophilic alkenes. This method is applicable for a wide range of aldehydes including aromatic and heterocyclic substrates. The polyguanidine catalyst can be recovered by simple filtration and reused many times for the aqueous Knoevenagel reaction without loss of activity.

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## Introduction

The Knoevenagel condensation is a powerful tool for the construction of carbon-carbon bonds and has been widely applied for the production of fine chemicals such as cosmetics and drugs.<sup>[1]</sup> The Knoevenagel condensation is generally carried out in organic solvents with catalytic bases such as primary or secondary amines and their salts,<sup>[1b,1c]</sup> or amino acids.<sup>[2]</sup> Several Lewis acids can also be used as catalysts in the Knoevenagel reaction.<sup>[3,4]</sup> Recently, a wide range of heterogeneous catalysts such as aluminium oxide,<sup>[5]</sup> alkali-containing MCM-41,<sup>[6]</sup> and zeolites<sup>[7]</sup> have been used in this reaction, as have ionic liquids and functional ionic liquids.<sup>[8]</sup> On the other hand, there have been several reports describing the use of amines immobilised on polymers to catalyse the Knoevenagel reaction. Sotelo has reported that polystyrene-supported 1,1,3,3-tetramethylguanidine was used as a catalyst for the Knoevenagel reaction in acetonitrile and tetrahydrofuran.<sup>[9]</sup> Tamami reported the use of the amino group immobilised on polyacrylamide as a catalyst for the Knoevenagel reaction in water or solvent-free conditions, although the reaction was slower in water.<sup>[10]</sup> However, there still exist some disadvantages with these catalysts, such as difficulties with recovery and reuse, longer reaction times, and complex reaction conditions.

Organosuperbases have attracted much attention due to the ease with which their structures can be modified, the easy reuse of recovered materials, and simple operation based on the acid–base concept.<sup>[11]</sup> They have been widely used for organic reactions because of their stronger affinity to protons or other nucleophiles.<sup>[12]</sup> In addition, they can be anchored on a solid support, solving the problem of recovery and recycling and simplifying the procedure for product isolation and purification.

With increasing concern over environmental issues, one of the fundamental changes and ultimate goals for organic chemistry is to perform reactions in water.<sup>[13]</sup> In comparison with organic solvents, water is not only cheap and safe, but also shows unique properties in promoting reactions and enhancing selectivities.<sup>[14]</sup>

In this paper we report on the use of polyguanidine-type catalysts for the reactions of malononitrile with various aldehydes in water to give the Knoevenagel condensation products in excellent yields. It is notable that water can greatly accelerate this reaction, even though the reactions were carried out in a heterogeneous system. The polyguanidine catalyst can be recovered and still retains high catalytic activity.

# **Results and Discussion**

The polyguanidine-type catalysts (**PG-1–3**) were synthesised according to literature procedures (Scheme 1).<sup>[15]</sup> **PG-1–3** contain different degrees of cross-linking. They are insoluble in common laboratory solvents. We further investigated the catalytic activity of **PG-1–3** with the results shown in Table 1 (Scheme 2). **PG-2** was found to be the best catalyst for the reaction of benzaldehyde **1a** with malononitrile **2a** in water. The amount of 1,6-hexanediamine (**C**) used as the cross-linking agent in **PG-2** was 10 mol-%. With an increase in the proportion of hexanediamine, the catalytic activity of the **PG** decreased. The effects of the molar ratio of **PG-2** on the Knoevenagel reaction were also investigated. It was found that the product **3a** was formed in high yields with catalyst loadings of between 5 and 15 mol-%, however longer reaction times were needed when using less catalyst (entries 2–4).

To examine solvent effects, various solvents were employed in the reaction of **1a** with **2a** in the presence of catalyst **PG-2** (20 mol-%) at room temperature (Table 2). It was found that this reaction proceeded smoothly in organic solvents, but that



Scheme 1. Synthesis of polyguanidine-type catalysts PG-1-3.

Table 1. Effects of catalysts PG on the reaction of 1a with 2a<sup>A</sup>

Entry	PG	A:B:C	Cat. loading	Time [min]	Yield of $3a$
				[]	[, 0]
1	PG-2	1:0.8:0.2	20	10	94
2	PG-2		15	30	95
3	PG-2		10	4 h	93
4	PG-2		5	10 h	92
5	PG-1	1:0.6:0.4	20	15	88
6	PG-3	1:0.5:0.5	20	30	89

<sup>A</sup>Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), catalyst,  $H_2O$  (3 mL), room temperature.

<sup>B</sup>The catalyst loading is calculated by molecular weight of one guanidine unit.

<sup>C</sup>Isolated yield.



Scheme 2. The reaction of 1a with 2a in water catalysed by PG.

reaction times over 60 min were required, except with  $CH_3OH$ and DMF (entries 4 and 5). In addition, the reaction time was prolonged to 6 h under solvent-free conditions (entry 6). It is interesting to note that this reaction was completed in only 10 min in water, with the yield of **3a** reaching 94 % (entry 7). It is clear that the reaction rate is faster in water than in organic nonpolar solvents or solvent-free conditions. Since polyguanidine swells considerably in polar solvents, the guanidine functional group is better able to catalyse the condensation reactions in water than in other non-polar solvents. Any highly polar or polar protic organic solvent is just as good as water, however these solvents have toxicity problems compared with water.

Based on these results, various aldehydes were allowed to react with active methylene compounds in the presence of **PG-2** (20 mol-%) in water (Scheme 3, Table 3). Both electron-rich and electron-deficient aromatic aldehydes worked well, giving high yields of the products. Electron-deficient aldehydes needed shorter reaction times and gave somewhat higher yields than their electron-rich counterparts (entries 1–6, Table 3). Heterocyclic aldehydes, such as furfural and thiophene-2carboxaldehyde, also gave high yields (entries 9–10, Table 3). However, aliphatic aldehydes afforded complex mixtures including aldol products and Michael addition products (entries 7–8, Table 3).

 Table 2.
 Solvent effects on the reaction of 1a with 2a<sup>A</sup>

Entry	Solvent	Reaction time [min]	Yield of $3a [\%]^{B}$	
1	CH <sub>2</sub> Cl <sub>2</sub>	90	86	
2	THF	90	88	
3	CH <sub>3</sub> CN	90	91	
4	CH <sub>3</sub> OH	10	90	
5	DMF	15	92	
6	_	6 h	93	
7	$H_2O$	10	94	

<sup>A</sup>Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), **PG-2** (20 mol-%), solvent (3 mL), room temperature.

<sup>B</sup>Isolated yield.



#### Scheme 3.

Compared with malononitrile, the reactions of ethyl cyanoacetate with the same aromatic aldehydes needed more time (entries 11–20, Table 3). Because the electron-withdrawing ability of the CN group is stronger than that of the carbonyl or carboxylic group, the methylene group of malononitrile is more activated than ethyl cyanoacetate in its reaction with aromatic aldehydes.

Furthermore, this method failed to give the desired olefinic products from aldehydes and diethyl malonate. No further improvement was observed in the reaction of benzaldehyde (1a) with diethyl malonate either by increasing the amount of **PG-2** (stoichiometric ratio) or by raising the reaction temperature.

In addition, the recyclability of the catalyst PG-2 was examined (Fig. 1). Once product **3a** was removed from the reaction mixture (it dissolved in hot ethanol), PG-2 was directly used for another cycle. It was found, as seen in Fig. 1, that the catalyst showed no substantial reduction in activity even after the tenth run. All reactions were completed in 10 min and afforded **3a** in yields of 90–94 %.

In conclusion, polyguanidine was employed as a novel and efficient catalyst for the Knoevenagel condensation of aromatic aldehydes with active methylene compounds in water. Furthermore, the attractive features of this procedure are the green and

Entry	Aldehyde	2 (E)	Time [min]	Product	Yield [%] <sup>B</sup>
1	la CHO	2a CN	10	3a CN CN	94
2	1b CHO	2a	10	3b CN CN	93
3	1c CHO	2a	15	3c CI CN CN	92
4	1d O <sub>2</sub> N CHO	2a	8	3d $CN$ $CN$ $CN$	90
5	1e MeO	2a	20	3e CN MeO CN	93
6	1f CHO	2a	15	3f CN HO CN	94
7	1g CHO	2a	40	3g CN CN	_
8	1h Y <sup>CHO</sup>	2a	40	3h CN	_
9	1i CHO	2a	15	3i CN CN	91
10	1j CHO	2a	15	3j CN S CN	93
11	la	<b>2b</b> CO <sub>2</sub> Me	15	3k CN	92
12	1b	2b	15	3I CN CN	92
13	10	2b	20	$3m$ $Cl$ $CO_2Me$ $CN$	90
14	1d	2b	13	3n O <sub>2</sub> N CN	93
15	1e	2b	30	30 CO <sub>2</sub> Me	92
16	1f	2b	25	3p CO <sub>2</sub> Me	93

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(Continued)

Entry	Aldehyde	2 (E)	Time [min]		Product	Yield [%] <sup>E</sup>
17	1g	2b	60	3q	CO <sub>2</sub> Me CN	-
18	1h	2b	60	3r	CN CN	-
19	1i	2b	15	3s	CO <sub>2</sub> Me O CN	91
20	1j	2b	60	3t	CO <sub>2</sub> Me S CN	94

Table 3. (Continued)

<sup>A</sup>Reaction conditions: aldehyde (1 mmol), active methylene compound (1 mmol), **PG-2** (20 mol-%) in H<sub>2</sub>O (3 mL), room temperature. <sup>B</sup>Isolated yield.



**Fig. 1.** Recycling of catalyst **PG-2** in the aqueous reaction of **1a** with **2a**. Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), solvent (3 mL), **PG-2** (20 mol-%), room temperature. The yield of **3a** is the isolated yield.

mild reaction conditions, medium to short reaction times, excellent yields, and operational simplicity. The catalysts can be recycled more than ten times without obvious loss of catalytic activity. Thus, we believe that this simple and green procedure will be a practical method to cater for the needs of academia as well as chemical industries. The scope and synthetic application of the polyguanidine catalyst is under investigation.

# Experimental

#### Typical Procedure for Preparation of Catalyst PG-2

To a solution of hexamethylenediamine (2.32 g, 0.02 mol) in isopropanol was added hexamethylenedicyanamide (16.60 g, 0.1 mol) and hexamethylenediamine dihydrobromide (22.08 g, 0.08 mol). The mixture was heated at reflux for 6 h. After the reaction, the isopropanol was removed by distillation under reduced pressure, leaving a colourless, transparent, gel-like mass. The crude product was solidified by being heated at  $130^{\circ}$ C for 3 h, resulting in 41 g of a water-insoluble resinous product. The product was then soaked in 100 g of an aqueous solution of NaOH (10%) at room temperature for 24 h, then the product was filtered and repeatedly washed with hot water ( $60^{\circ}$ C) until pH was neutral. The product was dried in a vacuum drying oven at  $60^{\circ}$ C for 24 h to give catalyst **PG-2**.

# General Procedure for the Knoevenagel Condensation

A 10 mL round bottomed flask was charged with the carbonyl compound (1 mmol), active methylene compound (1 mmol), **PG-2** (14 mg, 20 mol-%), and water (3 mL). The reaction mixture was stirred at room temperature for the time shown in Table 3. Progress of the reaction was monitored by TLC, using *n*-hexane–EtOAc (5:1) as eluent. After completion of the reaction, the reaction mixture often solidified in the round bottomed flask. The solids were dissolved in hot ethanol (30 mL). The catalyst was removed by filtration and washed with hot ethanol. The solid product was obtained after solvents were removed under vacuum. The product **3a** was purified through recrystallisation from ethanol. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  = 7.91 (d, *J* = 7.8 Hz, 2H), 7.80 (s, 1H), 7.65 (t, *J* = 7.3 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  = 159.9, 134.6, 130.9, 130.7, 129.6, 113.7, 112.5, 82.9.

## **Supplementary Material**

Experimental procedures, characterisation data and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra are available on the Journal's website.

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