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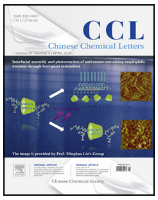

Original article

Sevelamer as an efficient and reusable heterogeneous catalyst for the Knoevenagel reaction in water

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ABSTRACT

A catalyst system of Sevelamer, a phosphate-binding drug, has been prepared and used in the Knoevenagel reaction of aromatic aldehydes in water to produce substituted electrophilic alkenes. The products were obtained in excellent yields. Several novel, related catalytic systems showed promising catalytic properties for aromatic and heterocyclic aldehydes. The Sevelamer catalyst can be recovered using simple filtration and reused numerous times (up to 15 times) in the aqueous Knoevenagel reaction without any significant lowering of activity.

1. Introduction

Functional polymeric catalysts have recently attracted significant attention for organic synthesis because of their ease of recovery, reuse, and simplified product isolation and purification [1,2]. Using polymeric catalysts is an efficient way to achieve economically advantageous and environmentally friendly processes.

The Knoevenagel condensation is a powerful method to construct a carbon–carbon bond and has been widely used in the production of fine chemicals, such as cosmetics, drugs, and other substances [3–5]. Numerous reaction systems have been developed for this reaction, but several disadvantages remain regarding to the use of these catalysts, such as difficulties in catalyst recovery and reuse, longer reaction time, or hash reaction conditions [6–13].

A wide range of heterogeneous catalysts have recently been used in the Knoevenagel condensation [14–22]. However, few of these catalysts are based on functional polymeric catalysts. The polystyrene, polyacrylonitrile and polyacrylonitrile were linked or transformed to catalytically active bases for the Knoevenagel reaction [23–26], but most of these catalysts also suffer from long reaction time, complex preparation, and low-loading functional groups. Therefore, the study of a catalyst for Knoevenagel condensation based on a functional polymeric catalyst is challenging.

Sevelamer, a phosphate-binding drug used to prevent hyperphosphatemia, is a copolymer of epichlorohydrin and allylamine. Sevelamer is an environmentally friendly solid material with excellent mechanical strength and stability. This compound contains abundant amine groups which can be easily transformed into various functions and can also be used as a catalyst.

Recently, we have focused our attention on the use of polymeric bases as recyclable catalysts in organic synthesis [27]. In this paper, we demonstrate that Sevelamer can be used for malononitrile reactions with various aromatic aldehydes in water to provide Knoevenagel condensation products with excellent yields. Water can considerably accelerate this reaction even though the reaction was conducted in a heterogeneous system. The Sevelamer catalyst (S) can be easily recovered and still retains catalytic activity.

2. Experimental

General procedure for Knoevenagel condensation: A 10 mL round-bottomed flask was charged with the carbonyl compound (1 mmol), active methylene compound (1 mmol), S-4 catalyst

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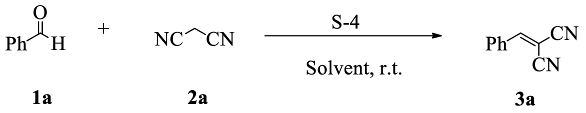
Table 1
The phosphate-binding capacity and acid exchange capacity of Sevelamer-type catalysts.

Cat (S)	Allylamine:epichloro-hydrin	Yield (%)	Phosphate-binding capacity (meq/g)		Acid exchange capacity (mmol/g)
			pH 3.0	pH 7.0	
S-1	1:0.08	94	1.3	1.0	3.5
S-2	1:0.11	98	1.8	1.2	3.4
S-3	1:0.08	92	3.1	2.1	4.4
S-4	1:0.11	94	5.8	4.7	4.6
S-5	1:0.15	96	3.6	2.4	4.3
S-6	1:0.20	98	2.8	1.7	3.2

Table 2
The solvent effects on the reaction of **1a** with **2a** using S-4 catalyst.[a]



Entry	Solvent	Time (h)	Yield (%)[b]
1	CH_2Cl_2	2	85
2	CH_3OH	1	90
3	$CHCl_3$	2	86
4	THF	2	89
5	CH_3CN	2	90
6	DMF	1	92
7	–	8	89
8	H_2O	0.5	91

[a] Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), catalyst (20 mol%), solvent (3 mL), r.t.
[b] Isolated yield.

system (12 mg and 20 mol% of the substrates), and water (3 mL). The resulting reaction suspension was stirred at room temperature. The reaction progress was monitored by thin layer chromatography using *n*-hexane–EtOAc (5:1, v/v) as eluent. Upon completion, the reaction mixture solidified in the round-bottomed flask. The solids were then dissolved in hot ethanol (30 mL). The catalyst was removed by filtration and washed with ethanol. The solid product was obtained after the ethanol was concentrated in vacuo.

3. Results and discussion

Sevelamer-type catalysts (S-1 and S-2) were synthesized according to Method A (see Supporting information, Scheme 1). The yield of Sevelamer-type catalyst, S-1, was 40% with 8 mol% of epichlorohydrin as cross-linking agent. The phosphate-binding capacity of S-1 was determined to be 1.3 meq/g and 1.0 meq/g at pH 3.0 and 7.0, respectively (Table 1) [28,29]. The corresponding acid exchange capacity of S-1 was determined to be 3.5 mmol/g. The yield of catalyst S-2 was 98% with 11 mol% epichlorohydrin as cross-linking agent. The phosphate-binding capacity and the corresponding acid exchange capacity of S-2 were lower than S-1.

Sevelamer-type catalysts (S-3 to S-6) were synthesized according to Method B. The phosphate-binding capacity of S-3 was determined to be 3.1 meq/g and 2.1 meq/g at pH 3.0 and 7.0, respectively. The corresponding acid exchange capacity of S-3 was determined to be 4.4 mmol/g. Compared with S-1, these two main parameters of S-3 were greatly improved. The acid exchange capacity of S-3 to S-5 did not show any apparent difference, although the amounts of cross-linking agent were different. However, the acid exchange capacity of S-6 was lower than S-4.

Table 3
Effects of catalysts Sevelamer on the reaction of **1a** with **2a**.[a]

Entry	S	Cat. Loading (mol%)	Time (min)	Yield of **3a** (%)[b]
1	S-1	20	60	92
2	S-2	20	90	90
3	S-3	20	50	91
4	S-4	30	30	90
5	S-4	20	30	91
6	S-4	10	120	90
7	S-4	5	480	89
8	S-5	20	50	92
9	S-6	20	60	90

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), H_2O (3 mL), room temperature.
[b] Isolated yield.

Based on the highest acid exchange capacity among all catalysts, we selected S-4 as the catalyst to examine the effects of the solvent. Various solvents were employed in the reaction of **1a** with **2a** in the presence of catalyst S-4 (20 mol%) at room temperature (Table 2). The reaction was found to proceed smoothly to completion in the organic solvents (Table 2, entries 1–6). The reaction rate was faster in polar organic solvents, such as CH_3OH, DMF and CH_3CN, than non-polar solvents, such as CH_2Cl_2, $CHCl_3$ and THF. As noted, the reaction time was prolonged to 8 h under solvent-free conditions (Table 2, entry 7). Interestingly, this reaction was finished in water in 0.5 h, and **3a** was found to have a yield of 91% (Table 2, entry 8). The reaction rate was faster in water than in organic solvent or solvent-free conditions.

We further investigated the catalytic activity of the S-1 to S-5 catalysts in the reaction of benzaldehyde (**1a**) with malononitrile (**2a**) in water (Table 3). The reaction was completed in 1 h and 1.5 h when catalyzed by S-1 and S-2, respectively, with the yields afforded above 90% (Table 3, entries 1 and 2). From Table 3, using catalyst S-3 the reaction was faster than S-1, although they all used 8 mol% epichlorohydrin as cross-linking agent (Table 3, entry 3). This result confirms that the catalysts prepared by Method B are better than those from Method A. Also S-4 was found to be the best catalyst among S-3 to S-6. With an increased ratio of epichlorohydrin, the catalytic activity of Sevelamer decreased because the amine, as a functional group, is difficult to act as catalyst in the reactions with increased cross-linking agent. The effects of the molar ratio of S-4 on the Knoevenagel reaction were also investigated. Although the product **3a** was formed in high yields, longer reaction times were needed at catalyst loadings of 10 mol% and 5 mol% (Table 3, entries 6 and 7).

Based on the optimal reaction conditions, various aldehydes were reacted with malononitrile in the presence of S-4 (20 mol%) in water (Table 4). Both electron-rich and electron-deficient aromatic aldehydes worked well and produced high product yields. Electron-deficient aldehydes, however, needed less time

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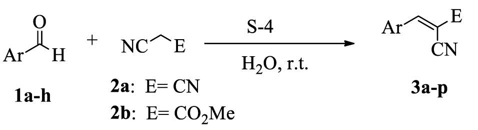
Table 4
Reaction of aldehydes (**1a-h**) with **2a-b** in water catalyzed by S-4.[a]



Entry	Ar	2	Time (min)	Product	Yield (%)[b]
1	**1a** Ph	**2a**	30	**3a**	91
2	**1b** *p*-ClPh	**2a**	30	**3b**	94
3	**1c** *o*-ClPh	**2a**	40	**3c**	90
4	**1d** *p*-NO_2Ph	**2a**	20	**3d**	91
5	**1e** *p*-MeOPh	**2a**	60	**3e**	91
6	**1f** *p*-OHPh	**2a**	60	**3f**	92
7	**1g** 2-furaldehyde	**2a**	30	**3g**	92
8	**1h** 2-thienaldehyde	**2a**	30	**3h**	94
9	**1a** Ph	**2b**	50	**3i**	90
10	**1b** *p*-ClPh	**2b**	50	**3j**	91
11	**1c** *o*-ClPh	**2b**	50	**3k**	90
12	**1d** *p*-NO_2Ph	**2b**	40	**3l**	93
14	**1e** *p*-MeOPh	**2b**	90	**3m**	90
14	**1f** *p*-OHPh	**2b**	90	**3n**	91
15	**1g** 2-furaldehyde	**2b**	50	**3o**	93
16	**1h** 2-thienaldehyde	**2b**	50	**3p**	92

[a] Reaction conditions: aldehyde (1 mmol), **2** (1 mmol), S-4 (20 mol%) in H_2O (3 mL), room temperature.
[b] Isolated yield.

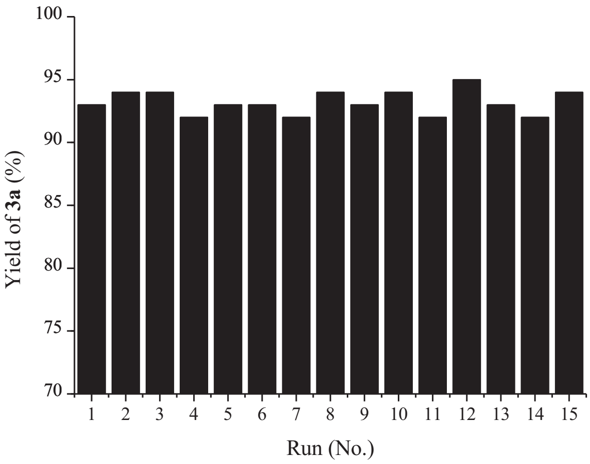
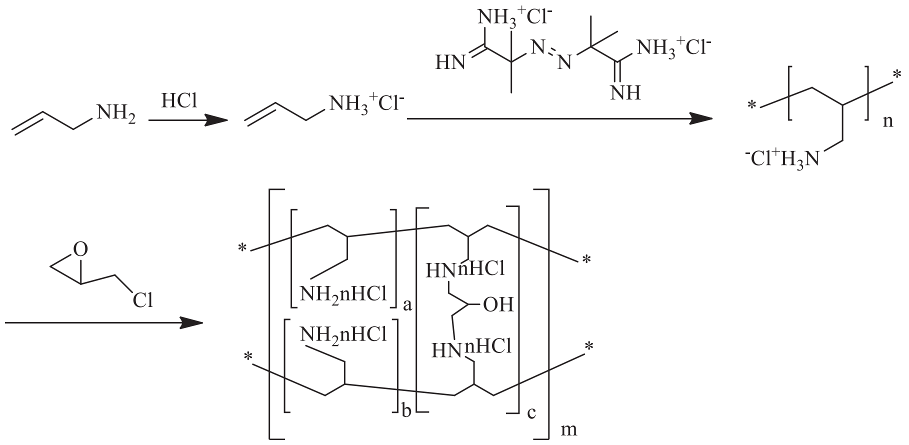


Fig. 1. Recycling of catalyst S-4 in the aqueous reaction of **1a** with **2a**. Reaction conditions are same as in Table 2.

and produced relatively higher yields than their electron-rich counterparts (entries 1–6, Table 4). Heterocyclic aldehydes also afforded high yields (entries 7 and 8, Table 4). The treatment of aldehydes with methyl cyanoacetate also produced Knoevenagel products with high yields under similar reaction conditions. Compared with malononitrile, the reactions of methyl cyanoacetate with the same aromatic aldehydes required more time (entries 9–16, Table 4).

Finally, the recovery and reuse of the catalytic systems has been investigated (Fig. 1). Once product **3a** was dissolved in hot ethanol and filtered from the reaction mixture, S-4 was directly used for another cycle. As shown in Fig. 1, the catalyst S-4 substantially demonstrated the ability to retain its catalytic activity even after fifteen cycles and all reactions were completed in 0.5 h.



Scheme 1. Synthesis of Sevelamer-type catalysts S-1 to S-6.

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4. Conclusion

In conclusion, a catalyst system of Sevelamer as phoshate-binding drug was prepared and employed as an effective catalyst for the Knoevenagel condensation of aromatic aldehydes in water. Water was not only employed as a reaction medium, but also played a role in accelerating the Knoevenagel condensation. The green and mild reaction conditions, short to medium reaction times, excellent yields, and operational simplicity are among the attractive features of this catalytic system. The catalysts can be easily recovered by simple filtration and display no loss of activity when recycled.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2014.03.002.

References

[1] J. Lu, P.H. Toy, Organic polymer supports for synthesis and for reagent and catalyst immobilization, Chem. Rev. 109 (2009) 815–838.
[2] B. Clapham, T.S. Reger, K.D. Janda, Polymer-supported catalysis in synthetic organic chemistry, Tetrahedron 57 (2001) 4637–4662.
[3] G. Jones, The Knoevenagel condensation, Org. React. 15 (1967) 204–599.
[4] L.F. Tietze, Domino reactions in organic synthesis, Chem. Rev. 96 (1996) 115–136.
[5] F. Freeman, Properties and reactions of ylidenemalononitriles, Chem. Rev. 80 (1980) 329–350.
[6] F. Bigi, L. Chesini, R. Maggi, G. Sartori, Montmorillonite KSF as an inorganic, water stable, and reusable catalyst for the Knoevenagel synthesis of coumarin-3-carboxylic acids, J. Org. Chem. 64 (1999) 1033–1035.
[7] G. Cardillo, S. Fabbroni, L. Gentilucci, M. Gianotti, A. Tolomelli, A straightforward method for the synthesis of alkylidene and arylidene malonates through proline-catalyzed Knoevenagel condensation, Synth. Commun. 33 (2003) 1587–1594.
[8] B.M. Choudary, M.L. Kantam, V. Neeraja, et al., Layered double hydroxide fluoride: a novel solid base catalyst for C–C bond formation, Green Chem. 3 (2001) 257–260.
[9] M.B. Deshmukh, S.S. Patil, S.D. Jadhav, P.B. Pawar, Green approach for Knoevenagel condensation of aromatic aldehydes with active methylene group, Synth. Commun. 42 (2012) 1177–1183.
[10] P.S. Rao, R.V. Venkataratnam, Zinc chloride as a new catalyst for Knoevenagel condensation, Tetrahedron Lett. 32 (1991) 5821–5822.
[11] G.W. Wang, B.L. Wang, Facile synthesis of Z/E-3-arylmethylidene-2,3-dihydroindol-2-one under solvent-free conditions, Chin. J. Org. Chem. 24 (2004) 85–87.
[12] L. Rand, J.V. Swisher, C.J. Cronin, Reactions catalyzed by potassiumfluoride. III. The Knoevenagel reaction, J. Org. Chem. 27 (1962) 3505–3507.
[13] A.K. Mitra, A. De, N. Karchaudhuri, Solvent-free microwave enhanced Knoevenagel condensation of ethyl cyanoacetate with aldehydes, Synth. Commun. 29 (1999) 2731–2739.
[14] M.L. Kantam, B.M. Choudary, C.V. Reddy, K.K. Rao, F. Figueras, Aldol and Knoevenagel condensations catalysed by modified Mg–Al hydrotalcite: a solid base as catalyst useful in synthetic organic chemistry, Chem. Commun. (1998) 1033–1034.
[15] C. Xu, J.K. Bartley, D.I. Enache, D.W. Knight, G.J. Hutchings, High surface area MgO as a highly effective heterogeneous base catalyst for Michael addition and Knoevenagel condensation reactions, Synthesis (2005) 3468–3476.
[16] T.I. Reddy, R.S. Varma, Rare-earth (RE) exchanged NaY zeolite promoted Knoevenagel condensation, Tetrahedron Lett. 38 (1997) 1721–1724.
[17] H.M.S. Kumar, B.V.S. Reddy, E.J. Reddy, J.S. Yadav, SiO_2 catalysed expedient synthesis of [E]-3-alkenoic acids in dry media, Tetrahedron Lett. 40 (1999) 2401–2404.
[18] S. Wada, H. Suzuki, Calcite and fluorite as catalyst for the Knövenagel condensation of malononitrile and methyl cyanoacetate under solvent-free conditions, Tetrahedron Lett. 44 (2003) 399–401.
[19] Q.L. Wang, Y.D. Ma, B. Zuo, Knoevenagel condensation catalyzed by USY zeolite, Synth. Commun. 27 (1997) 4107–4110.
[20] S. Sebti, A. Smahi, A. Solhy, Natural phosphate doped with potassium fluoride and modified with sodium nitrate: efficient catalysts for the Knoevenagel condensation, Tetrahedron Lett. 43 (2002) 1813–1815.
[21] F.T. Boullet, A. Foucaud, Knoevenagel condensation catalysed by aluminium oxide, Tetrahedron Lett. 23 (1982) 4927–4928.
[22] G.W. Li, J. Xiao, W.Q. Zhang, Highly efficient Knoevenagel condensation reactions catalyzed by a proline-functionalized polyacrylonitrile fiber, Chin. Chem. Lett. 24 (2013) 52–54.
[23] A. Coelho, A. Crespo, F. Fernandez, et al., Synthetic applications of polystyrene-supported 1,1,3,3-tetramethylguanidine, Comb. Chem. High Throughput Screen. 11 (2008) 843–847.
[24] G.W. Li, J. Xiao, W.Q. Zhang, Knoevenagel condensation catalyzed by a tertiary-amine functionalized polyacrylonitrile fiber, Green Chem. 13 (2011) 1828–1836.
[25] B. Tamami, A. Fadavi, Amino group immobilized on polyacrylamide: an efficient heterogeneous catalyst for the Knoevenagel reaction in solvent-free and aqueous media, Catal. Commun. 6 (2005) 747–751.
[26] K.P. Boroujeni, M. Jafarinasab, Polystyrene-supported chloroaluminate ionic liquid as a new heterogeneous Lewis acid catalyst for Knoevenagel condensation, Chin. Chem. Lett. 23 (2012) 1067–1070.
[27] X.L. Zhao, K.F. Yang, X.G. Liu, et al., Polyguanidine as a highly efficient and reusable catalyst for Knoevenagel condensation reactions in water, Aust. J. Chem. 66 (2013) 500–504.
[28] J.R. Mazzeo, R.M. Peters, M.R. Hanus, X. Chen, K.A. Norton, A phosphate binding assay for sevelamer hydrochloride by ion chromatography, J. Pharm. Biomed. Anal. 19 (1999) 911–915.
[29] R.A. Swearingen, E. Zhorov, A. Cohen, T. Sybertz, E.F. Barry, Determination of the binding parameter constants of Renagel capsules and tablets at pH 7 by high performance capillary electrophoresis, J. Pharm. Biomed. Anal. 35 (2004) 753–760.

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