Development of novel polymer-type dehydrocondensing reagents comprised of chlorotriazines†

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A novel immobilized dehydrocondensing reagent comprised of a triazine-type dehydrocondensing reagent itself in a polymerized form was synthesized by copolymerization between tetra(ethylene glycol) bis(dichlorotriazinyl) ether and tris(2-aminoethyl)amine.

Because of both the research and industrial importance of amides and esters, development of useful dehydrocondensing reagents has received much attention. In spite of many studies on dehydrocondensing reagents, reports of developing a solid-supported reagent of this type that is practically useful are limited.[1] For example, for the preparation of reported polymer-supported reagents carrying EEDQ, DCC, TBTU, or DMC, inefficient chemical transformations on the insoluble polymer under heterogeneous conditions were required.[2,3] On the contrary, a polymer-supported EDC (P-EDC), in which EDC is connected *via* its dimethylamino group can be prepared relatively easily. However, the reaction introducing EDC to a polymer requires an excess amount of expensive EDC under drastic conditions.[4,5] On the other hand, the weight proportion of the solid carrier relative to the amount of solid-supported reagent is generally high, which is inevitably linked to the generation of a large amount of waste, this being a serious problem common to solid-supported reagents. For instance, the molecular weight per unit reactivity of the P-EDC reaches about 1250, which is greatly increased compared to that of EDC hydrochloride, of which the original molecular weight is 192. Therefore, the development of practically useful solid-supported dehydrocondensing reagents without these disadvantages has been desired.

In the course of our research on the triazine-type dehydrocondensing reagent,[6] we have succeeded in the first development of a quite novel polymer type of dehydrocondensing reagent comprised of chlorotriazines, which can solve the aforementioned problems. Thus, the polymer reagent is eco-friendly, and has excellent cost efficiency as well as good reactivity.

As examples of an immobilized reagent of triazine derivatives, reagents in which cyanuric chloride is supported on the Wang resin or MeO-PEG-OH have been reported.[7–9] The mean molecular weight per a unit reactivity of these reagents reached up to 5000. Furthermore, a large excess (5 equiv) of cyanuric chloride is sometimes required to connect the triazino group into insoluble polymers because of the inefficiency of heterogeneous conditions. Although these reagents were prepared utilizing the high reactivity of cyanuric chloride toward nucleophilic substitution, the idea did not go beyond the conventional concept of supporting a reagent on an existing polymer, therefore, the disadvantage of the increase in molecular weight has not been improved, which remains a problem to be solved for practical use. Changing our way of thinking, we speculated that the immobilization of a chlorotriazino group could be achieved without great increase in molecular weight, when a cyanuric chloride derivative itself could be converted to a polymer by direct polymerization by efficiently exploiting the reactivity of all chlorine atoms of the cyanuric acid.[10,11]

On the basis of the reactivity of cyanuric chloride, in which the three chlorine atoms show different reactivity toward nucleophilic substitution,[12] we designed polymer A as illustrated in Scheme 1. At first, tetra(ethylene glycol) was allowed to react with cyanuric chloride (2 equiv) in THF at 0 °C for 27 h, giving a *O,O′*-bis(dichlorotriazino) compound **1** in a yield of 83%. A copolymerization was conducted by reacting **1** with the cross-linking reagent, tris(2-aminoethyl)amine **2** bearing three primary amino groups, at −40 °C to room temperature for 4 h, giving polymer A in a yield of 68%.[13] The polymer thus obtained was insoluble in any common solvents, and could be simply purified by filtration, followed by washing with water and organic solvents. The condensing reactivity of polymer A was determined by measuring the amount of free chloride ions released from the polymer by the substitution reaction with NMM to form its active form (polymer A_{ac}).[14] As a result, the amount of chloride loaded on polymer A was 2.91 meq g^{-1}, and the molecular weight per a unit of the condensing activity was 344, indicating that polymer A was high loading compared to conventional polymer-supported dehydrocondensing reagents.[2,4]

We examined dehydrocondensation of various carboxylic acids **3** with amines **4** using 2–3 equiv of polymer A in the presence of NMM in CH_2Cl_2 (Table 1). The active species for the dehydrocondensation are considered to be polymer A_{ac}, which will be formed *in situ* during the reaction.[6,15] Treatment of a mixture of 3-phenylpropionic acid **3a**, DL-1-phenylethylamine **4a**, and NMM (2 equiv) in CH_2Cl_2 with polymer A (2 equiv) at room temperature for 18 h afforded **5a** in 70% (Run 1). The yield of **5a** was increased to 82% when 3 equiv of polymer A and NMM were used (Run 2). The polymer chain was found to be stable under the reaction conditions, with no decomposed compounds derived from the polymer reagent being detected. Thus, the desired amide **5** could be simply obtained in pure form by filtering the reaction mixture, followed by washing the filtrate with water. When the reaction mixture was treated with an anion-exchange resin for 30 minutes, the amide **5** could be more simply obtained at a good

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† Electronic supplementary information (ESI) available: details of preparation of polymer A. See http://www.rsc.org/suppdata/cc/b5/b501917f/

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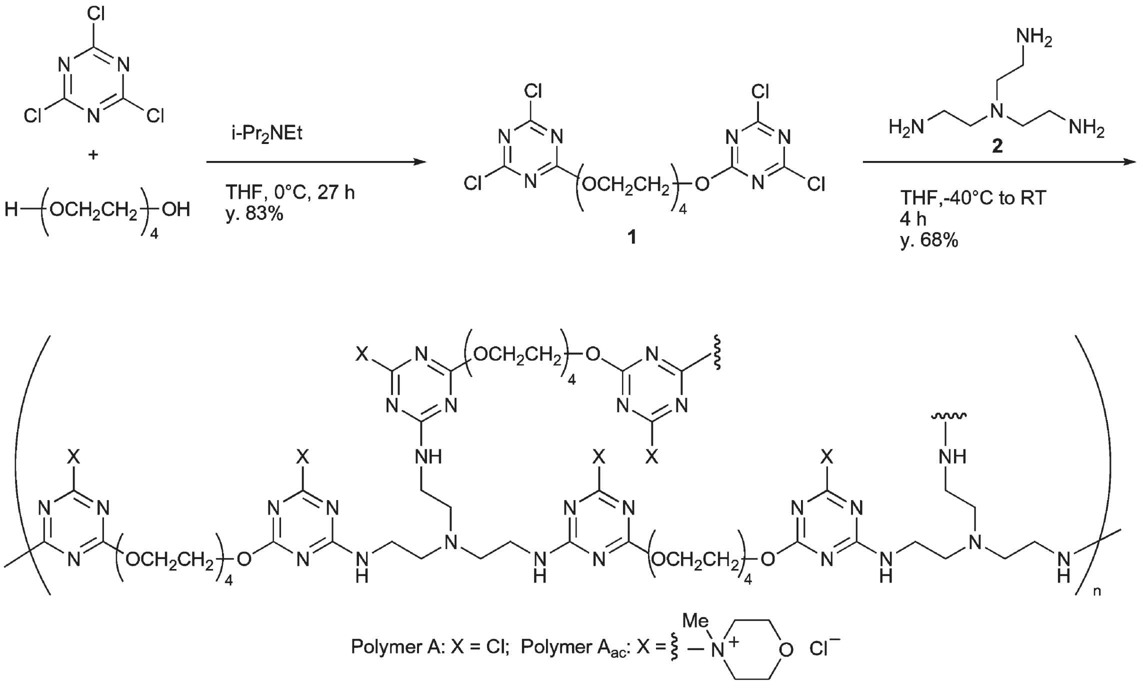

Scheme 1 Synthesis of polymer A and polymer A$_{ac}$.

Table 1 Condensation of carboxylic acids with amines in CH_2Cl_2 by the method of *in situ* generation of polymer A$_{ac}$

Run[a]	Carboxylic acid	Amine	Polymer A (eq)	NMM (eq)	Time (h)	Product	Yield (%)
1	$Ph(CH_2)_2COOH$ (**3a**)	$PhCHMeNH_2$ (**4a**)	2.0	2.0	18	$Ph(CH_2)_2CONHCHMePh$ (**5a**)	70
2	**3a**	**4a**	3.0	3.0	19	**5a**	82
3	**3a**	$Ph(CH_2)_2NH_2$ (**4b**)	3.0	3.0	19	$Ph(CH_2)_2CONH(CH_2)_2Ph$ (**5b**)	97
4[b]	**3a**	**4b**	2.0	2.0	20	**5b**	85
5	*p*-MeO-$C_6H_4CH_2COOH$ (**3b**)	**4b**	3.0	3.0	19	*p*-MeO-$C_6H_4CH_2CONH(CH_2)_2Ph$ (**5c**)	quant
6	$PhCH{=}CHCOOH$ (**3c**)	**4b**	3.0	3.0	19	$PhCH{=}CHCONH(CH_2)_2Ph$ (**5d**)	97
7[b]	**3a**	Et_2NH (**4c**)	2.5	2.5	20	$Ph(CH_2)_2CONEt_2$ (**5e**)	83
8[c]	Z-Gly-OH (**3e**)	H-Phe-OMe (**4d**)	2.5	4.0	20	Z-Gly-Phe-OMe (**5f**)	81
9[b]	**3a**	$HO(CH_2)_2NH_2$ (**4e**)	2.5	2.5	20	$Ph(CH_2)_2CONH(CH_2)_2OH$ (**5g**)	87

[a] The produced amide was isolated by filtration of the reaction mixture, followed by washing the filtrate with water. [b] The reaction mixture was treated with Amberlite IRA-400 OH for 0.5 h, and then filtered. The resulting filtrate was concentrated. [c] The reaction mixture was treated with Amberlite IRA-400 OH for 3 h.

purity by concentrating the filtrate without washing with water (Runs 4, 7–9). α,β-Unsaturated carboxylic acid **3c** as well as aliphatic carboxylic acids **3a** and **3b** was found to condense with primary amines **4a** and **4b**, or secondary amine **4c**, giving the corresponding amides in good yields under the same conditions. When polar compounds are used for the reaction, the isolation procedure sometimes becomes troublesome. Condensations of amino acid derivatives **3e** and **4d**, or hydroxyethylamine **4e**, could be readily performed, and the desired products were isolated by the simple procedures of filtration and concentration. In particular, it was notable that a selective reaction occurred at the amino group, producing the corresponding amide in the case of the reaction of **4e**.

As described above, we succeeded in the development of a quite novel and practical polymer type dehydrocondensing reagent by ingeniously exploiting the reactivity of chlorotriazines. The polymer is easy to prepare, because the polymerization proceeds with high efficiency in a homogeneous medium, and only a stoichiometric amount of the chlorotriazine derivatives is needed. Because no carrier is used, the amount of waste arising from the polymer A can be greatly reduced. Furthermore, cyanuric chloride and ethylene glycols used as starting material are inexpensive, affording an excellent cost efficiency. In addition, a dehydrocondensation can be performed by a very simple procedure, mixing a carboxylic acid and an amine together with the polymer. As we have already established a method for regenerating CDMT from HO-DMT, the latter of which is produced as a co-product of DMT-MM,[16] we are also investigating the recycling of the polymer after it has been used for a condensing reaction.

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3 Abbreviations used in this report are as follows: DCC: 1,3-dicyclohexylcarbodiimide; EEDQ: 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline; TBTU: *N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene-*N*-methylmethanaminium tetrafluoroborate *N*-oxide; DMC: 1,3-dimethyl-2-imidazolidinone; EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; MeO-PEG-OH: poly(ethylene glycol) monomethyl ether; DMT-MM: 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride; CDMT: 2-chloro-4,6-dimethoxy-1,3,5-triazine; NMM: *N*-methylmorpholine; HO-DMT: 2-hydroxy-4,6-dimethoxytriazine.

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10 Although melamine-type polymers comprised of triazine are well known,[11] the polymers of this type used as a dehydrocondensing reagent have not been reported, to the best of our knowledge.

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13 The yield was determined based on the theoretical structure of polymer A as illustrated in Scheme 1.

14 The amount of chloride ion was determined by titration with $AgNO_3$. See ESI.

15 We found that the condensation of **3a** and **4a** proceeded by a monomeric model of polymer A_{ac}, 4-(4-ethylamino-6-methoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (AMT-MM), which was prepared from 4-chloro-2-ethylamino-6-methoxy-1,3,5-triazine (AMT) by treatment with NMM.

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