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Development of Hydrophilic Polyacrylamide Gel-Based Condensing Reagents Comprised of Chlorotriazine

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Hydrophilic polyacrylamide gel-based triazine-type condensing reagents, PAG-Trz-Cl, have been developed. PAG-Trz-ClS were synthesized using a chlorotriazine with an acrylamide moiety, acrylamide, and N,N'-methylenebisacrylamide via both precipitation and solution polymerization. Because PAG-Trz-ClS adequately swell in aqueous media, the amidation between polar carboxylic acids and amines afforded the corresponding amides in good yields.

Key words aqueous solvent; condensation; polyacrylamide; triazine

Introduction

Solid supported reagents, scavengers, and catalysts have been intensively studied because reaction workup and purification procedures can be simplified.1–4 Moreover, toxic, odorous, or hazardous reagents can be safely used when immobilized on polymers. These advantages are useful for automated synthesis, library synthesis, and flow chemistry. However, there are some drawbacks in polymer-supported reagents: (a) an excess amount of monomer is often needed for its introduction into insoluble solid polymers because of low-yield chemical transformations under heterogeneous conditions. (b) A large amount of waste is generated because the weight proportion of the solid carrier relative to the amount of reagent is generally high, i.e., the loading of active reagent on the polymer is limited.

We previously reported the synthesis of immobilized condensing reagents, Poly-O-Trz-Cl, Poly-N-Trz-Cl, ROMP-Trz-Cl, and ROMP(OH)-Trz-Cl,5–7 which are based on the triazine-type condensing reagent, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM).8–10 Because these reagents are prepared by polymerizing the chlorotriazines themselves, their loading is high compared to other polymer-supported condensing reagents.11 However, their physical properties and reactivity can be further improved: condensations using these reagents in aqueous solvents resulted in moderated to poor yields probably owing to their insufficient swelling, which indicates that the synthetic advantages of DMT-MM for amide-forming reactions are not fully exploited in aqueous solvents. Additionally, Poly-N-Trz exhibits a relatively low reactivity due to the electron-donating amino substituents at the triazine ring. We recently found that triazine-based condensing reagents with amido substituents instead of the methoxy group at the triazine ring show a good reactivity compared to DMT-MM.12 Accordingly, we hypothesized that polyacrylamide gel-based reagents synthesized by the polymerization of chlorotriazine via its acrylamide moiety would help overcome the issues mentioned above.13–15 Polyacrylamide gel swells in water and is easily formed by radical polymerization from the inexpensive acrylamide monomer and a crosslinker. Herein, we describe the development of condensing reagents immobilized on water-swelling polyacrylamide.

Results and Discussion

Chlorotriazine with an acrylamide moiety (I) was prepared from 2,4-dichloro-6-methoxy-1,3,5-triazine (DCMT) and N-methylacrylamide in 54% yield (Chart 1).

The precipitation polymerization was performed in 1,4-di-oxane using different mixtures of I (1.0 equiv.), acrylamide monomer (2, p equiv.), and N,N'-methylenebisacrylamide (3, q mol%), in the presence of 2,2'-azobis(isobutyronitrile) (AIBN) as a radical initiator (Table 1). Nine different polymers (polyacrylamide gel-based chlorotriazine (PAG-Trz-Cl)_{p,q}) were obtained in excellent yields (entries 1–9, Condition A)16,17 Additionally, the solution polymerization was carried out in an aqueous solvent (H_{2}O/MeOH) in the presence of sodium dodecyl sulfate (SDS) as surfactant. This afforded three PAG(W)-Trz-Cl_{p,q} in good yields (entries 10–12, Condition B).18 These polymers are nonhygroscopic stable solids, which can be stored in the refrigerator for at least six months. The content of chlorotriazine in the polymers (Loading, mmol/g) were determined by the titration of free chloride anion, which was generated by the formation of triazinylammonium salt using N-methylmorpholine (NMM).7 The percentage of Loading based on the amount of I used for the syntheses were very high (Introduction rate: 75 to 97%), meaning that the chlorotriazine moiety is not affected during the radical polymerization reaction. Because the average molecular mass weight per active unit (MW_{\text{app}}) of PAG-Trz-Cl corresponds to the amount of starting materials used, different polymeric condensing agents can be synthesized depending on the purpose.

Swelling ratios were calculated from the increased weight

| MeO | N | N | Cl | + | O | N | MeH | NaH | 1.2 equiv. | 3.5 h | THF, -20 °C | MeO | Cl | 1 (54%) |
|-----|---|---|---|---|---|---|---|----|-----|------|------|-----------|---|---|------|
| DCMT (1.0 equiv.) | (1.2 equiv.) | | | | | | | | | | | | |

Chart 1. Synthesis of Chlorotriazine with an Acrylamide Moiety

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Table 1. Synthesis and Characterization of PAG-Trz-Cl

| Entry | Polymer name | 2 (p) | 3 (q) | Condition\(^a\) | Yield (%) | Loading\(^b\) (mmol/g) | Introduction rate\(^c\) (%) | MW aver\(^d\) |
|-------|--------------|-------|-------|-----------------|-----------|----------------------|--------------------------|----------|
| 1     | PAG-Trz-Cl\(_{1,1}\) | 1     | 1     | A               | 96        | 2.93                 | 89                       | 341      |
| 2     | PAG-Trz-Cl\(_{3,3}\) | 3     | 1     | A               | 85        | 2.16                 | 97                       | 463      |
| 3     | PAG-Trz-Cl\(_{5,5}\) | 5     | 1     | A               | 87        | 1.52                 | 90                       | 658      |
| 4     | PAG-Trz-Cl\(_{10,1}\) | 10    | 1     | A               | 96        | 0.93                 | 91                       | 1053     |
| 5     | PAG-Trz-Cl\(_{15,1}\) | 15    | 1     | A               | Quant.    | 0.57                 | 75                       | 1754     |
| 6     | PAG-Trz-Cl\(_{3,3}\) | 3     | 3     | A               | 81        | 2.06                 | 92                       | 485      |
| 7     | PAG-Trz-Cl\(_{3,3}\) | 3     | 5     | A               | 92        | 2.00                 | 90                       | 500      |
| 8     | PAG-Trz-Cl\(_{5,5}\) | 5     | 5     | A               | 89        | 1.43                 | 90                       | 699      |
| 9     | PAG-Trz-Cl\(_{10,5}\) | 10    | 5     | A               | 96        | 0.84                 | 86                       | 1186     |
| 10    | PAG(W)-Trz-Cl\(_{10,1}\) | 10    | 1     | B               | 89        | 0.99                 | 94                       | 1015     |
| 11    | PAG(W)-Trz-Cl\(_{10,5}\) | 10    | 3     | B               | 77        | 0.94                 | 93                       | 1067     |
| 12    | PAG(W)-Trz-Cl\(_{10,5}\) | 10    | 5     | B               | 87        | 0.94                 | 96                       | 1062     |

\(^{a}\) Condition A: AIBN (1 mol%), 1,4-dioxane, 80°C, 3 h.  
Condition B: VA-044 (2 mol%), aq. 10% SDS solution/MeOH = 30 : 1, 85°C, 90 s., then room temperature (r.t.), 2 h.  
\(^{b}\) The term “Loading” is defined as below: The content of chlorotriazine in the polymer (mmol/g).  
\(^{c}\) The term “Introduction rate” is defined as below: The percentage of Loading based on the amount of 1 used for the synthesis of the polymer.  
\(^{d}\) The term “MW aver” is defined as below: The average molecular mass weight per active unit in the polymer.

Table 2. Swelling Ratios of PAG-Trz-Cl in H\(_2\)O, MeOH, and H\(_2\)O/MeOH (1 : 1) in the Presence/Absence of NMM

| Polymer                | H\(_2\)O | H\(_2\)O + NMM\(^a\) | H\(_2\)O/MeOH | H\(_2\)O/MeOH + NMM\(^a\) | MeOH | MeOH + NMM\(^a\) |
|------------------------|---------|----------------------|--------------|------------------------|------|------------------|
| PAG-Trz-Cl\(_{1,1}\)   | 116%    | n.d.                 | 130%         | 160%                   | 83%  | 120%             |
| PAG-Trz-Cl\(_{3,3}\)   | 300%    | 800%                 | 226%         | 503%                   | 95%  | 150%             |
| PAG-Trz-Cl\(_{5,5}\)   | 195%    | 700%                 | 180%         | 700%                   | 110% | 170%             |
| PAG(W)-Trz-Cl\(_{10,1}\)| 547%    | 537%                 | 222%         | 242%                   | 32%  | 33%              |
| PAG(W)-Trz-Cl\(_{10,5}\)| 473%    | 796%                 | 207%         | 399%                   | 107% | 114%             |

\(^{a}\) NMM (1.5 equiv to chlorotriazine estimated by Loading (mmol/g)) was added.

Table 3. Screening of Reaction Conditions

| Entry | Polymer (equiv) | NMM (equiv) | Time (h) | Yield (%)\(^d\) |
|-------|-----------------|-------------|----------|-----------------|
| 1     | PAG-Trz-Cl\(_{1,1}\) (2.0) | 3.0         | 3        | 68              |
| 2     | PAG-Trz-Cl\(_{1,1}\) (2.0) | 3.0         | 6        | 84              |
| 3     | PAG-Trz-Cl\(_{1,1}\) (2.0) | 3.0         | 24       | 93              |
| 4\(^b\) | PAG-Trz-Cl\(_{1,1}\) (2.0) | 3.0         | 24       | 95              |
| 5     | PAG-Trz-Cl\(_{1,1}\) (4.0) | 6.0         | 0.5      | 85              |
| 6     | PAG-Trz-Cl\(_{1,1}\) (4.0) | 6.0         | 3        | 93              |
| 7\(^c\) | PAG-Trz-Cl\(_{1,1}\) (4.0) | 6.0         | 0.5      | 88              |
| 8\(^d\) | PAG-Trz-Cl\(_{1,1}\) (4.0) | 6.0         | 0.5      | 86              |
| 9     | PAG-Trz-Cl\(_{1,1}\) (4.0) | 3.0         | 24       | 90              |
| 10    | PAG-Trz-Cl\(_{1,1}\) (4.0) | 3.0         | 3        | 91              |
| 11    | PAG-Trz-Cl\(_{1,1}\) (2.0) | 3.0         | 24       | 93              |
| 12    | PAG-Trz-Cl\(_{1,1}\) (4.0) | 6.0         | 3        | 95              |
| 13    | PAG(W)-Trz-Cl\(_{10,1}\) (2.0) | 3.0         | 24       | 98              |
| 14    | PAG(W)-Trz-Cl\(_{10,5}\) (2.0) | 3.0         | 24       | 94\(^e\) |

\(^{a}\) NMR yield.  
\(^{b}\) The reaction was conducted in a 1.0 M solution of 4a.  
\(^{c}\) 2-(2-Aminoethoxy)ethanol 5a (2.0 equiv) was used.  
\(^{d}\) 3-Phenylpropionic acid 4a (2.0 equiv) and 5a (1.0 equiv) were used.  
\(^{e}\) Isolated yield.
of the polymer after swelling and the initial weight (dry polymer)\(^7\) (Table 2). The swelling of all the PAG-Trz-Cl measured in \(\text{H}_2\text{O}\) and \(\text{MeOH}\) was better than ROMP(OH)-Trz-Cl (in \(\text{H}_2\text{O}: 0\%\), in \(\text{MeOH}: 60\%)\(^7\). Good swelling ratios were also observed in a \(\text{H}_2\text{O}/\text{MeOH}\) mixture (1:1), which can solubilize both the highly polar carboxylic acid and amine starting materials and the relatively less polar amide product (\textit{vide infra}). Especially in the case of PAG-Trz-Cl\(_{3-3}\), and PAG-Trz-Cl\(_{3-5}\) synthesized in 1,4-dioxane, swelling ratios were dramatically increased when 1.5 equiv. of NMM were added, due to the formation of polar triazinylammonium salts, which are the actual reactive species during the condensation.\(^8\) PAG(W)-Trz-Cl\(_{10-1}\) and PAG(W)-Trz-Cl\(_{10-5}\) prepared in water (Condition B) showed a remarkable swelling ratio in water compared to that of PAG-Trz-Cls synthesized in 1,4-dioxane (Condition A).

The condensation between 3-phenylpropionic acid \(4\text{a}\) and 2-(2-aminoethoxy)ethanol \(5\text{a}\) was conducted in MeOH/H\(_2\)O (1:1). Shortly after the reaction started, the swollen polymers did not allow for the magnetic stirrer to move, thus, the reaction proceeded with no stirring. As shown in Table 3, the 3h reaction with 2.0 equiv. of PAG-Trz-Cl\(_{3-1}\) and 3.0 equiv. of NMM yielded amide \(6\text{aa}\) (68\%, entry 1). When increasing the reaction time to 24h, the yield increased to 93\% (entries 2,3). A higher concentration of starting materials did not improve the reaction rate (entry 4). The use of 4.0 equiv. of PAG-Trz-Cl\(_{3-1}\) and 6.0 equiv. of NMM shortened the reaction time to 3h (entries 5 and 6). An excess of amine slightly enhanced the reaction rate (entry 7). The reaction of 1.0 equiv. of amine and 2.0 equiv. of carboxylic acid provided the product in 86\% yield (entry 8). Moreover, other PAG-Trz-Cls also showed

| Entry | Carboxylic acid | Amine | Polymer | Method | Amide | Yield (%) |
|-------|-----------------|-------|---------|--------|-------|-----------|
| 1     | \(\text{PhCOOH} 4\text{b}\) | \(\text{H}_2\text{NN} 5\text{a}\) | PAG-Trz-Cl\(_{3-1}\) | Y      | \(\text{PhCOOH} 6\text{ba}\) | 94        |
| 2     | \(\text{CbzHN} 4\text{c}\) | \(\text{H}_2\text{NN}_\text{Me} 5\text{b}\) | PAG-Trz-Cl\(_{3-5}\) | Y      | \(\text{CbzHN} 6\text{cb}\) | 80        |
| 3     | \(\text{CbzHN} 4\text{c}\) | \(\text{H}_2\text{NN}_\text{Me} 5\text{c}\) | PAG-Trz-Cl\(_{3-5}\) | X      | \(\text{CbzHN} 6\text{cc}\) | 90        |
| 4     | \(\text{CbzHN} 4\text{d}\) | \(\text{H}_2\text{NN} 5\text{b}\) | PAG-Trz-Cl\(_{3-5}\) | X      | \(\text{CbzHN} 6\text{db}\) | 63\%      |
| 5     | \(\text{PhCOOH} 4\text{a}\) | \(\text{H}_2\text{NN} 5\text{d}\) | PAG-Trz-Cl\(_{3-1}\) | Y      | \(\text{PhCOOH} 6\text{ad}\) | 87        |
| 6     | \(\text{4a}\) | \(\text{5d}\) | PAG(W)-Trz-Cl\(_{10-1}\) | X      | \(\text{6ad}\) | 87        |
| 7     | \(\text{2-HNPh} 4\text{e}\) | \(\text{H}_2\text{NN} 5\text{e}\) | PAG-Trz-Cl\(_{3-5}\) | X      | \(\text{6ee}\) | 81        |
| 8     | \(\text{4e}\) | \(\text{5a}\) | PAG-Trz-Cl\(_{3-1}\) | X      | \(\text{6ea}\) | 46        |

\(\text{a}\) Method X: polymer (2.0 equiv), NMM (3.0 equiv), 24h. Method Y: polymer (4.0 equiv), NMM (6.0 equiv), 3h. \(\text{b}\) Reaction time was 4h. \(\text{c}\) The reaction was conducted in MeOH/H\(_2\)O (1:2).
good reactivities (entries 9–14).

Amidation between several carboxylic acids and amines was evaluated under the conditions described in Table 3, entry 3 as the “method X,” or entry 6 as the “method Y” (Table 4). Benzoic acid 4b gave the product 6ba in 94% yield (entry 1). The couplings of Cbz-glycine 4e and alanine ester 5b or leucine ester 5c afforded the corresponding dipeptides 6cb and 6cc in good yields (entries 2 and 3). Cbz-serine with no protecting group at the hydroxy group (4d) provided the dipeptide 6db in 63% yield without racemization (entry 4, See Supplementary materials, Figure S1). It is worth noting that the reaction of highly polar sugar derivatives, 5d and 4e, with two reagents yielded the corresponding amides 6ad, 6ee, 87 and 81% yields, respectively (entries 5–7). Coupling between 4e and 5a as polar substrates proceeded to give 6ea in 46% yield (entry 8). Since polymer can be simply removed by filtration, the product can be purified depending on its physical property; for example, the less-polar amide 6aa was purified by liquid phase partition, the polar amide 6ad by silica gel chromatography, and the highly polar amide 6ea by passing through an ion exchange resin. Polymers with high loading and moderate swelling ratio such as PAG(W)-Trz-Cl 10-1. This is because the volume of PAG-Trz-Cl3-1 in the reaction mixture is smaller than that of PAG(W)-Trz-Cl10-1.

Conclusion

We developed polyacrylamide gel-based condensing reagents, PAG-Trz-Cl, which can be used for reactions in aqueous media. The reagents are bench-stable solids, which were easily synthesized from inexpensive materials via radical polymerization. The loading and their physical properties can be modified by changing the amount of the chlorotriazine–acrylamide molecule 1, acrylamide monomer 2, and N,N'-methylenebisacrylamide 3. The condensation between highly polar carboxylic acids and amines using PAG-Trz-Cl afforded the corresponding amides in good yields and the accompanying waste was readily removed by simple filtration.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Materials

The online version of this article contains supplementary materials (detailed experimental procedure, physical data, and NMR spectra of isolated products).

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