

Development of Novel Polymer-type Dehydrocondensing Reagents Comprised of Chlorotriazines

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Experimental Section

General Methods. All solvents and chemicals were obtained from commercial sources and used as received unless otherwise noted. Chemical shifts of ¹H (400 MHz) spectra were recorded in ppm (δ) downfield from TMS as an internal standard. Preparative thin-layer chromatography (TLC) was performed on Merck precoated silica gel plates.

Synthesis of *O,O'*-bis(2-chloro-4-methoxy-1,3,5-triazin-6-yl)tetra(ethylene glycol) (1):

To a solution of cyanuric chloride (17.0 g, 92.2 mmol) in dry THF (50 mL) was added a solution of tetra(ethylene glycol) (8.95 g, 46.1 mmol) and *N,N*-diisopropylethylamine (11.9 g, 92.2 mmol) in THF (6 mL) at 0°C under nitrogen atmosphere. After being stirred for 27 h at 0°C, the reaction mixture was filtered to remove insoluble material, and the filtrate was concentrated. The residue was dissolved in AcOEt and washed with water. The organic layer was dried, concentrated, and then, purified by silica gel column chromatography (hexane : AcOEt = 8 : 2) to give 18.8 g of **1** (83%). Colorless oil. IR (neat) 1541, 1508, 1252, 1054, 804 cm⁻¹; ¹H NMR (CDCl₃) δ: 3.64-3.70 (m, 8H), 3.86-3.88 (m, 4H), 4.65-4.67 (m, 4H). Anal. Calcd for C₁₄H₁₆Cl₄N₆O₅ : C, 34.31; H, 3.29; N, 17.15; Cl, 28.93; Found C, 34.12; H, 3.39; N, 16.96; Cl, 28.72.

Preparation of Polymer A:

To a solution of **1** (3.07 g, 6.26 mmol) in THF (4 mL) was added dropwise a solution of tris(2-aminoethyl)amine **2** (0.61 g, 4.18 mmol) and *N,N*-diisopropylethylamine (3.24 g, 25.1 mmol) in THF (2 mL) at -40°C, and being stirred for 1.5 h at the same temperature. The reaction mixture was allowed to warm to 0°C and stirred for 1.5, followed by 1.5 h at room temperature. The resulting solid material was collected with suction, and washed successively with dry THF, 2-PrOH, water, THF, and Et₂O, and dried *in vacuo* to give 2.18 g of Polymer A (68%). IR (KBr) 3284, 1517, 1336, 1289, 1125, 1057, 807 cm⁻¹.

Determination of the activity of Polymer A by titration of chloride:

To a suspension of Polymer A (26.4 mg) in distilled water (10 mL) was added sodium nitrate (0.50 mmol, 43.6 mg). After being stirred for 10 min at room temperature, the mixture was filtered, and the solid was washed with 5 mL each of distilled water for three times. The resulting solid was suspended in distilled water, and then, treated with NMM (0.31 mmol, 31.2 mg). After being stirred for 1 h at room temperature, sodium nitrate (1.01 mmol, 86.2 mg) was added, and stirred for 2 h. The resulting suspension was diluted with distilled water, and titrated with silver nitrate (0.01 mol/L). The amount of chloride was 0.0769 mmol, which indicated the unit activity to be 2.91 meq/g (0.0769 mmol/26.4 mg)

Typical procedure for the synthesis of *N*-(1-phenylethyl)-3-phenylpropanamide (**3a**) with Polymer A:

A mixture of **3a** (0.155 mmol, 23.3 mg) and **4a** (0.155 mmol, 18.8 mg), and *N*-methylmorpholine (0.47 mmol, 47.1 mg) dissolved in CH₂Cl₂ (3 mL) was added to Polymer A (0.47 mmol, 160 mg) at room temperature, and the mixture was stirred for 19 h at room temperature followed by filtered.

The solid was washed with CH₂Cl₂-acetone (1 : 1), and organic phase was combined, and concentrated. The residue was dissolved in Et₂O, and the resulting solution was washed successively with water, NaHCO₃, water, 1 M HCl, water, and brine. The solution was dried and concentrated to give 32.2 mg of **5a** (82%)

Colorless crystals; mp 50-51°C; IR (KBr) 3260, 1646, 1557 cm⁻¹; ¹H NMR (CDCl₃) δ 1.40 (d, *J* = 6.9 Hz, 3H) 2.46-2.50 (m, 2H), 2.97 (t, *J* = 7.5 Hz, 2H), 5.10 (qd, *J* = 6.9, 7.2 Hz, 1H), 5.51 (br. s, 1H), 7.16-7.32 (m, 10H); LC/MS *m/z* 254 [(M+1)⁺].

N-Phenethyl-3-phenylpropanamide (5b)

Colorless crystals; 94.5-95.5°C; IR(KBr): 3299, 1635, 1544 cm⁻¹; ¹H NMR (CDCl₃) δ: 2.42 (t, *J* = 7.7 Hz, 2H), 2.74 (t, *J* = 6.9 Hz, 2H), 2.94 (t, *J* = 7.7 Hz, 2H), 3.48 (td, *J* = 6.9, 6.0 Hz, 2H), 5.31 (br, s, 1H), 7.07-7.10 (m, 5H). HRMS calcd for C₁₇H₁₉NO (M⁺) 253.1467, found 253.1477.

N-Phenethyl-(4-methoxyphenyl)acetamide (5c)

Colorless crystals; mp 98-98.5°C; IR (KBr): 3286, 1643, 1544, 1241, 1037 cm⁻¹; ¹H NMR (CDCl₃) δ: 2.71 (t, *J* = 6.8 Hz, 2H), 3.45 (td, *J* = 6.8, 6.1 Hz, 2H), 3.46 (s, 2H), 5.39 (br s, 1H), 6.82-6.87 (m, 2H), 7.02-7.10 (m, 4H), 7.18-7.26 (m, 3H); MS *m/z* 269 (M⁺).

N-Phenethylcinnamamide (5d)

Colorless needles; mp 126-127°C; IR (KBr): 3299, 1650, 1614, 1544 cm⁻¹; ¹H NMR (CDCl₃) δ: 2.89 (t, *J* = 6.9 Hz, 2H), 3.66 (td, *J* = 6.9, 6.0 Hz, 2H), 5.73 (br s, 1H), 7.21-7.37 (m, 8H), 7.45-7.50 (m, 2H), 7.62 (d, *J* = 15.6 Hz, 1H); MS *m/z* 251 (M⁺).

N, N-Diethyl-3-phenylpropanamide (5e):^a

Colorless oil; IR (neat) 1641 cm⁻¹; ¹H NMR (CDCl₃) δ 1.10 (t, *J* = 7.1 Hz, 3 H), 1.11 (t, *J* = 7.1 Hz, 3 H), 2.59 (t, *J* = 7.9 Hz, 2 H), 2.99 (t, *J* = 7.9 Hz, 2 H), 3.22 (q, *J* = 7.1 Hz, 2 H), 3.38 (q, *J* = 7.1 Hz, 2 H), 7.17-7.31 (m, 5 H); MS *m/z* 205 (M⁺).

Z-Gly-Phe-OMe (5f):^b

Colorless oil; IR (neat): 1731, 1673, 1531 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ: 2.86-3.01 (m, 2H), 3.56 (s, 3H), 3.51-3.64 (m, 2H), 4.42-4.48 (m, 1H), 4.99 (s, 2H), 7.16-7.38 (m, 11H), 8.28 (d, *J* = 8.0 Hz, 1H); ESI-MS *m/z* = 371 (M+1)⁺.

N-(2-Hydroxyethyl)-3-phenylpropanamide (5g):^c

Colorless needles; mp 72.5–73.5 °C (AcOEt/hexane); IR (KBr) 3293, 1646, 1556 cm⁻¹; ¹H NMR (CDCl₃) δ 2.36 (br s, 1H), 2.50 (t, *J* = 7.6 Hz, 2 H), 2.98 (t, *J* = 7.6 Hz, 2 H), 3.33-3.39 (m, 2 H), 3.63 (d, *J* = 5.0 Hz, 2 H), 5.58 (br s, 1H), 5.72 (dd, *J* = 17.6, 0.9 Hz, 1 H), 7.18-7.24 (m, 3H), 7.27-7.32 (m, 2 H); Anal. Calcd for C₁₁H₁₅NO₂: C, 68.37; H, 7.82. Found C, 68.19; H, 7.82.

References:

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