

Synthesis of Thiourea Derivatives on Soluble Polymeric Support

YANG, Gui-Chun* (杨桂春) CHEN, Zu-Xing(陈祖兴) ZHANG, Zhao-Jun(张照军)

Faculty of Chemistry and Material Science, Hubei University, Wuhan, Hubei 430062, China

A modified poly(ethylene glycol) (PEG) has been developed as the soluble polymeric supports for liquid phase synthesis of novel thiourea derivatives. In each step of the sequence, the PEG-bound products were precipitated in cold Et₂O and the unreacted materials and by-products were removed by simple filtration. The progress of reaction, purity of the isolation and the structure of the PEG-bound products were easily monitored by TLC, IR and ¹H NMR spectra. Representative thiourea derivatives were obtained in moderate yields with excellent purity from this modified PEG-bound product by the cleavage with 50% TFA/H₂O.

Keywords poly(ethylene glycol) (PEG), soluble polymeric supports, synthesis, thiourea derivatives

Introduction

Combinatorial chemistry has recently emerged as a powerful tool that can generate large and diversified molecular libraries. The synthesis on the insoluble polymeric supports offers significant advantages over many conventional solution phase routes,^{1,2} with the benefits of easing of isolation and purification of products, minimization of side-reactions and the ability to use an excess of reagents to drive a reaction to complete. However, in the insoluble nature of the insoluble polymer supports under heterogenous condition, there are some problems such as lowered reactivities, taking a great deal of development time and effort to work up synthetic conditions on insoluble polymer supports. Such deficiencies have promoted the evaluation of soluble polymers as supports for organic chemistry. The use of soluble polymers as supports has the potential to combine the best aspect of both solid phase chemistry and conventional solution phase

chemistry, facilitates compound characterization, allows for isolation and purification of polymers/compounds through precipitation and filtration, and it has currently attracted people's much attention in organic chemistry.^{3,4} PEGs are widely used as soluble polymeric supports. They are readily functionalized with different spacers and linkers, soluble in many organic solvents, but can be precipitated selectively after reactions, while the product remained bounds to the support and the unreacted materials and the by-products were removed by simple filtration. As a consequence, the synthesis and the immobilization of several organic molecules on PEG supports have been reported over last years.³⁻⁸ The extension to the field of combinatorial chemistry is particularly attractive, since biological evaluation can be carried out directly on the PEG anchored molecules.³ Recently some highly loaded PEGs have been synthesized.⁹ The thiourea derivatives have been found to possess widespread pharmacological activity¹⁰ and been synthesized with conventional solution phase reactions,¹¹ nevertheless, high temperature was required or there was difficulty in purification of the product. The synthesis of thiourea derivatives has been unreported on soluble polymeric supports up to now. In this paper the new synthetic way of novel thiourea derivatives with modified PEG as soluble polymeric support under homogenous solution condition, as shown in Scheme 1, is reported.

Experimental

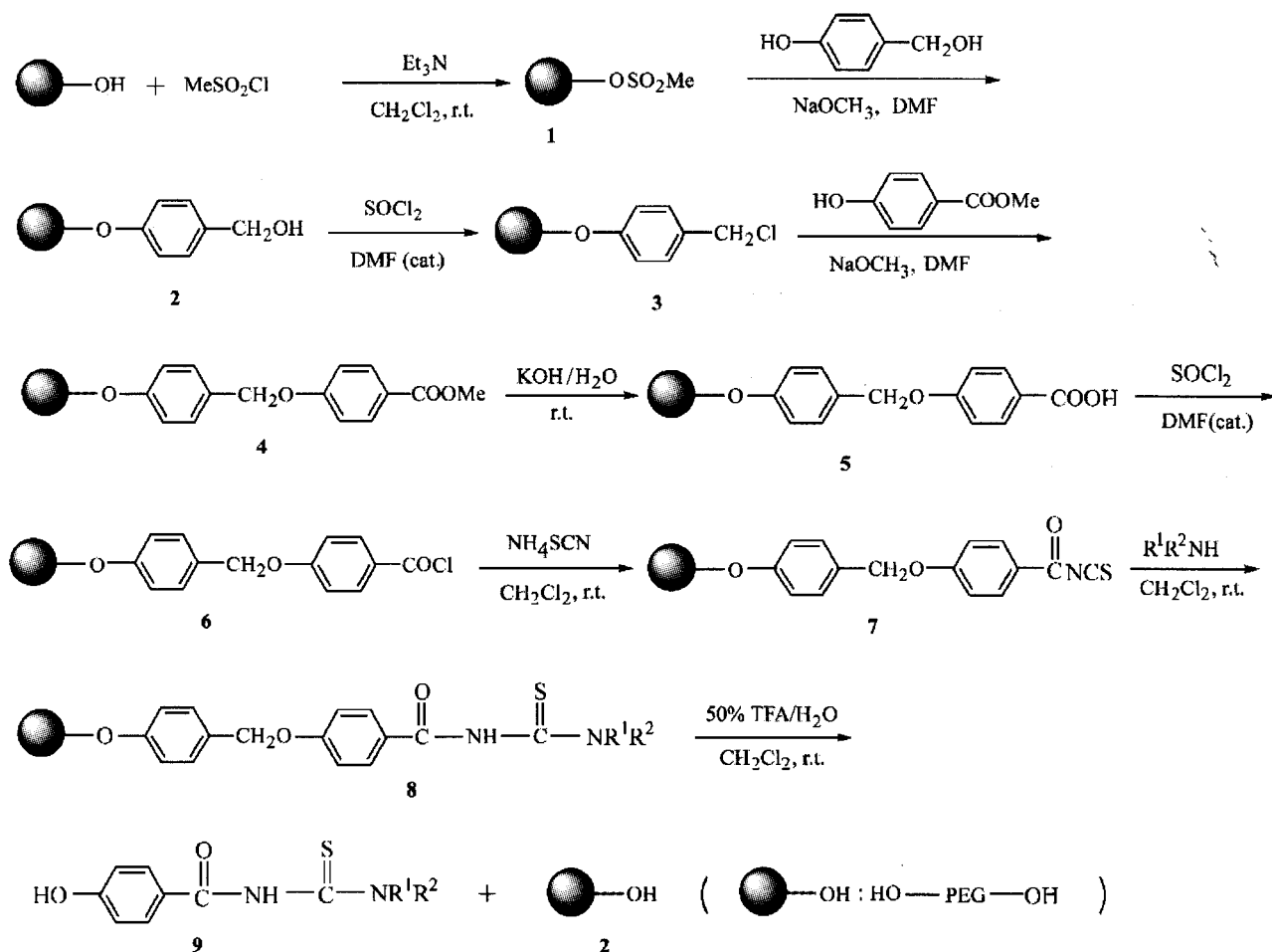
Thiourea derivatives were synthesized according to Scheme 1. All organic solvents were dried by standard methods.¹² All PEG samples were melted at 80 °C in

* E-mail: ygc33@163.net

Received March 5, 2001; revised August 16, 2001; accepted September 13, 2001.

Project supported by the Education Department of Hubei Province, China (No. 2001A01017).

Scheme 1



	9	a	b	c	d	e	f	g	h
R ¹									
R ²	H	H	H	H		H	H	H	—

vacuum for 30 min before use to remove traces of moisture. After reaction, products were purified by evaporation of the reaction solvent in vacuum and addition of the residue dissolved in a little CH_2Cl_2 to Et_2O , which was stirred and cooled at $0\text{ }^\circ\text{C}$. After stirring 20–30 min at $0\text{ }^\circ\text{C}$, the obtained suspension was filtered and the solid was repeatedly washed with Et_2O . Melting points were determined on a electrothermal melting point apparatus and were uncorrected. Elemental analyses were obtained on a PE 2400CHN analyzer, IR spectra were recorded

on an IR-Spectrum One (PE). ^1H NMR spectra were recorded on a JNM-FX 90Q (JEOL) spectrometer. Chemical shifts were reported in the δ using TMS as the internal standard.

Preparation of 1

To a solution of PEG-4000 (8.00 g) and triethylamine (2.80 mL, 20 mmol) in CH_2Cl_2 (100 mL), methanesulfonyl chloride (1.58 mL, 20 mmol) was

added dropwise under nitrogen atmosphere at 0 °C within 30 min and the reaction mixture was stirred for 18 h at r.t. The mixture was concentrated under vacuum until slightly viscous and purified by precipitation in Et₂O to give **1** (7.6 g) in 95% yield. ¹H NMR (CDCl₃) δ: 3.00 (s, 3H, OS₂CH₃), 3.50–3.70 (m, PEGO-CH₂CH₂O), 4.20–4.40 (m, 2H, CH₂OSO₂CH₃); IR (KBr) ν: 1170 (OSO₂) cm⁻¹.

Preparation of **2**

NaOCH₃ (1.08 g, 20 mmol) and *p*-hydroxybenzyl alcohol (3.04 g, 20 mmol) were added to a solution of **1** (7.6 g) in DMF (80 mL). The mixture was stirred for 18 h at 50 °C, then distilled to remove DMF until slightly viscous. The residue was dissolved in H₂O and further neutralized with dilute aqueous solution of hydrochloric acid until pH = 7. Then the whole mixture was extracted with CH₂Cl₂. The organic phase was washed with H₂O, dried with over MgSO₄, filtered and concentrated under vacuum until slightly viscous. Purification by precipitation in cold Et₂O gave **2** (6.84 g, 90%). ¹H NMR (CDCl₃) δ: 3.40–3.80 (s, PEGO-CH₂CH₂O), 3.90–4.05 (m, 2H, CH₂OAr), 4.40 (s, 1H, ArCH₂OH), 5.85–6.05 (m, 2H, ArCH₂-OH), 6.50–7.10 (m, 4H, ArH); IR (KBr) ν: 3410 (OH), 1580, 1510 (Ar) cm⁻¹.

Preparation of **3**

Four drops of DMF were added to a solution of **2** (6.84 g) in thionyl chloride (80 mL). The mixture was refluxed for 6 h, then the excess amount of thionyl chloride was removed under vacuum to give **3** (6.5 g, 95%). IR (KBr) ν: 1785 (COCl), 1580, 1510 (Ar) cm⁻¹.

Preparation of **4**

NaOCH₃ (0.81 g, 15 mmol) and methyl *p*-hydroxybenzoate (2.28 g, 15 mmol) were added to a solution of **3** (6.5 g) in DMF (60 mL). The mixture was stirred for 18 h at 50 °C, distilled to remove DMF until slightly viscous. The residue was dissolved in H₂O and further neutralized with dilute solution of hydrochloric acid until pH = 7. The mixture was extracted with

CH₂Cl₂. The organic phase was washed with H₂O, dried with over MgSO₄, filtered and concentrated under vacuum until slightly viscous. Purification by precipitation in cold Et₂O gave **4** (5.72 g, 88%). ¹H NMR (CDCl₃) δ: 3.30 (s, 1H, COOCH₃), 3.40–3.80 (m, PEGO-CH₂CH₂O), 3.90–4.00 (m, 2H, CH₂OAr), 4.90–5.15 (m, 2H, ArCH₂OAr), 6.70–7.60 (m, 8H, ArH); IR (KBr) ν: 1715 (COO), 1580, 1510 (Ar) cm⁻¹.

Preparation of **5**

Compound **4** (5.72 g) was added to solution of KOH (6.5 g, 144 mmol) in H₂O (60 mL). The mixture was stirred for 18 h at r.t., acidified with dilute hydrochloric acid to pH = 4, extracted with CH₂Cl₂. The organic phase was washed with H₂O, dried with over MgSO₄, filtered and concentrated under vacuum until slightly viscous, purified by precipitation in cold Et₂O to give **5** (4.86 g, 85%). ¹H NMR (CDCl₃) δ: 3.40–3.80 (m, PEG-OCH₂CH₂O), 3.90–4.00 (m, 2H, CH₂OAr), 4.90–5.15 (m, 2H, ArCH₂OAr), 6.70–7.60 (m, 8H, ArH), 10.80 (s, 1H, COOH); IR (KBr) ν: 1680 (COO), 1580, 1510 (Ar) cm⁻¹.

Preparation of **6**

Four drops of DMF were added to a solution of **5** (4.86 g) in thionyl chloride (60 mL). The mixture was refluxed for 6 h. Then the excess amount of thionyl chloride was removed under vacuum to give **6** (4.47 g, 92%). IR (KBr) ν: 1785 (COCl), 1580, 1510 (Ar) cm⁻¹.

Preparation of **7**

Ammonium thiocyanate powder (0.76 g, 10 mmol) was added to solution of **6** (4.47 g) in CH₂Cl₂ (10 mL). The mixture was stirred at r.t. for 18 h, filtered to remove excessive ammonium thiocyanate and resulting ammonium chloride. The filtrate was concentrated under vacuum until slightly viscous, filtered the precipitation by adding cold Et₂O to give **7** (4.02 g, 95%). IR (KBr) ν: 2073 (NCS), 1690 (COO), 1660 (CONCS) cm⁻¹.

Typical procedure for preparation of 8a

p-Aminoacetophenone (0.14 g, 1.0 mmol) was added to a solution of **7** (0.50 g) in CH₂Cl₂ (20 mL). The mixture was stirred at r. t. for 2 h, concentrated under vacuum until slightly viscous, purification by precipitation in cold Et₂O to give **8a** (0.43 g, 85%). ¹H NMR (CDCl₃) δ: 2.60 (s, 3H, ArCOCH₃), 3.50—3.70 (m, PEG-OCH₂CH₂O), 3.90—4.00 (m, 2H, CH₂OAr), 4.90—5.15 (m, 2H, ArCH₂OAr), 6.70—8.10 (m, 12H, ArH), 9.98 (s, 1H, CSNH), 12.45 (s, 1H, OCNH); IR (KBr) ν: 3259, 3201 (NH), 1715 (CO), 1668 (CONH), 1580, 1515 (Ar), 1175 (CS) cm⁻¹.

Typical procedure for preparation of 9a

TFA/H₂O (50%, 0.2 mL) was added to a solution of **8a** (0.43 g) in H₂O (10 mL). The mixture was stirred for 2 h at r. t. to give slightly yellow solid crude **9a**. Washing the solid with deionized water and drying it under vacuum at 50 °C to afford pure **9a**. All the other compounds (**9b**—**9h**) were prepared similarly, yields based on **7**.

9a Yellow crystal, 40 mg, yield 51%, m. p. 195—196.5 °C (H₂O); ¹H NMR (CD₃COCD₃) δ: 2.55 (s, 3H, CH₃), 6.70—8.10 (m, 8H, ArH), 9.45 (s, 1H, OH), 10.17 (s, 1H, CSNH), 13.19 (s, 1H, OCNH); IR (KBr) ν: 3310 (OH), 3295, 3200 (NH), 1654, 1152 (CO), 1152 (CS) cm⁻¹; Anal. calcd for C₁₆H₁₄N₂O₃S: C 61.15, H 4.46, N 8.92; found C 61.34, H 4.56, N 8.83.

9b Yellow crystal, 31 mg, yield 39.5%, m. p. 195—196 °C (H₂O); ¹H NMR (CD₃COCD₃) δ: 6.90—8.22 (m, 8H, ArH), 8.85 (s, 1H, OH), 9.34 (s, 1H, CSNH), 13.41 (s, 1H, OCNH); IR (KBr) ν: 3468 (OH), 3336, 3275 (NH), 1671 (CO), 1550, 1315 (NO₂), 1175 (CS) cm⁻¹; Anal. calcd for C₁₄-H₁₁N₃O₄S: C 53.00, H 3.47, N 13.25; found C 53.13, H 3.42, N 13.22.

9c White crystal, 34 mg, yield 45.1%, m. p. 165—167 °C (H₂O); ¹H NMR (CD₃COCD₃) δ: 3.57 (s, 3H, OCH₃), 6.90—8.10 (m, 8H, ArH), 9.55 (s, 1H, OH), 10.80 (s, 1H, CSNH), 12.27 (s, 1H, OCNH); IR (KBr) ν: 3414 (OH), 3401, 3255 (NH), 1678 (CO), 1177 (CS) cm⁻¹; Anal.

calcd for C₁₅H₁₄N₂O₃S: C 59.60, H 4.46, N 9.27; found C 59.74, H 4.55, N 9.38.

9d Pale yellow crystal, 33 mg, yield 43.3%, m. p. 206—208 °C (H₂O); ¹H NMR (CD₃COCD₃) δ: 6.72—8.04 (m, 8H, ArH), 9.32 (s, 1H, OH), 11.13 (s, 1H, CSNH), 12.69 (s, 1H, OCNH); IR (KBr) ν: 3398 (OH), 3322, 3208 (NH), 1664 (CO), 1154 (CS) cm⁻¹; Anal. calcd for C₁₄H₁₁-ClN₂O₂S: C 54.81, H 3.59, N 9.14; found C 54.85, H 3.51, N 9.02.

9e White crystal, 33 mg, yield 48.0%, m. p. 218—219 °C (H₂O); ¹H NMR (CD₃COCD₃) δ: 6.62—7.86 (m, 14H, ArH), 9.36 (s, 1H, OH), 12.71 (s, 1H, OCNH); IR (KBr) ν: 3450 (OH), 3273 (NH), 1660 (CO), 1179 (CS) cm⁻¹; Anal. calcd for C₂₀H₁₆N₂O₂S: C 68.96, H 4.58, N 8.04; found C 68.77, H 4.71, N 8.17.

9f Pale yellow crystal, 35 mg, yield 43.5%, m. p. 215—216 °C (H₂O); ¹H NMR (CD₃COCD₃) δ: 6.84—8.23 (m, 11H, ArH), 8.85 (s, 1H, OH), 9.36 (s, 1H, CSNH), 12.77 (s, 1H, OCNH); IR (KBr) ν: 3407 (OH), 3388, 3190 (NH), 1672 (CO), 1174 (CS) cm⁻¹; Anal. calcd for C₁₈H₁₄-N₂O₂S: C 67.08, H 4.35, N 8.70; found C 67.02, H 4.39, N 8.65.

9g Yellow crystal, 29 mg, yield 42.0%, m. p. 114—115 °C (H₂O); ¹H NMR (CD₃COCD₃) δ: 0.99 (t, *J* = 6 Hz, 3H, CH₃), 1.02—2.01 (m, 8H, C(CH₂)₄), 3.60—3.70 (m, 2H, NCH₂), 6.70—8.04 (m, 4H, ArH), 9.28 (s, 1H, OH), 9.65 (s, 1H, CSNH), 10.89 (s, 1H, OCNH); IR (KBr) ν: 3387 (OH), 3310, 3285 (NH), 1672 (CO), 1177 (CS) cm⁻¹; Anal. calcd for C₁₄H₂₀N₂O₂S: C 60.00, H 7.14, N 10.00; found C 59.43, H 7.27, N 9.81.

9h Yellow crystal, 28 mg, yield 40.5%, m. p. 163—164 °C (H₂O); ¹H NMR (CD₃COCD₃) δ: 1.26—2.09 (m, 6H, 3CH₂), 3.47 (t, *J* = 4.5 Hz, 4H, 2NCH₂), 6.70—7.35 (m, 4H, Ar), 9.36 (s, 1H, OH), 10.91 (s, 1H, OCNH); IR (KBr) ν: 3400 (OH), 3225 (NH), 1664 (CO), 1168 (CS) cm⁻¹; Anal. calcd for C₁₃H₁₆N₂O₂S: C 59.09, H 6.06, N 10.60; found C 59.95, H 6.17, N 10.51.

Results and discussion

When choosing a polymer as soluble polymeric sup-

ports for homogeneous solution synthesis, a compromise must be made between loading capacity and solubility. In this paper, PEG ($M_w = 4000$) with two hydroxy groups was employed that corresponds to approximately 0.5 mmol of free OH for each gram of the polymer with the advantages of higher loading capacities and readily separation.

All of the polymeric supported intermediates were readily isolated using a general procedure of polymer precipitation with cold Et_2O , the unreacted materials and the by-products were removed by simple filtration. PEG could act both as support and phase-transfer catalyst in the synthesis of thiourea derivatives.^{13,14} It was worthy of note that, in contrast to the various restriction on the analysis of reaction development in solid phase synthesis, liquid phase synthesis allows routine analytical methods such as IR, NMR spectra and TLC to monitor the situation of reaction and the purity of isolated products without cleaving the support.

Conclusion

In summary, a modified PEG has been developed for the soluble polymer supported solution phase synthesis of thiourea derivatives. Modified PEGs were used as soluble polymeric supports, as well as acting as phase-transfer in some steps. In each step of the sequence, the PEG-bound intermediates were purified by precipitation fol-

lowed by simple filtration. The structure of PEG-bound product was readily analyzed by ^1H NMR and IR spectra without detaching the material from the supports.

References

- 1 Greswell, M. W.; Bolton, G. L.; Hodges, J. C.; Meppen, M. *Tetrahedron* **1998**, *54*, 3983.
- 2 Richard, C. D. B. *J. Chem. Soc., Perkin. Trans. I* **1998**, 3293.
- 3 Paul, W. J.; Kim, D. J. *Chem. Commun.* **1999**, 1917.
- 4 Gravert, D. J.; Kim, D. J. *Chem. Review* **1997**, *97*, 489.
- 5 Reggelin, M.; Brenig, V.; Zur, C. *Org. Lett.* **1999**, *1*, 1185.
- 6 Yeh, C. M.; Sun, C. M. *Tetrahedron* **1999**, *40*, 7247.
- 7 Chi, Y. C.; Sun, C. M. *Synlett* **2000**, *5*, 591.
- 8 Rita, A.; Maurizio, B.; Mauro, C. *Chem. Eur. J.* **2000**, *6*, 133.
- 9 Maurizio, B.; Rita, A. *J. Org. Chem.* **1998**, *63*, 8628.
- 10 Schroeder, D. C. *Chem. Review* **1995**, *95*, 181.
- 11 Zhang, Y.; Wang, T. *Synth. Commun.* **1997**, *27*, 751.
- 12 Li, S. W.; Fang, Y. S. *Dictionary of Practical Organic Chemistry*, Shanghai Science Press, Shanghai, **1981**, pp. 540—550.
- 13 Berengere, S.; Ferderic, L.; Rene, L. *Tetrahedron Lett.* **2000**, *41*, 6371.
- 14 Berengere, S.; Ferderic, L. *Tetrahedron Lett.* **1998**, *39*, 821.

(E0103051 SONG, J. P.; HUANG, W. Q.)