Liquid-phase synthesis of ethyl (*Z*)-2-(thiocyanatomethyl)alk-2-enoates from PEG-bound α-phenylselenopropionate

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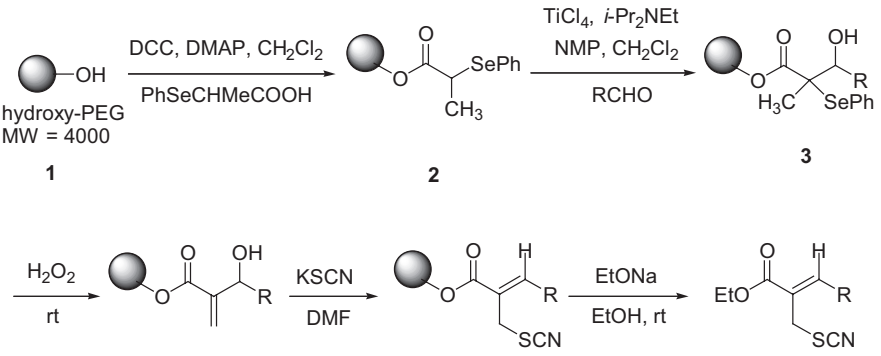
Aldolisation of novel PEG-bound α-phenylselenopropionate with aldehydes, followed by oxidation–elimination with 30% hydrogen peroxide and then treatment with potassium thiocyanate formed PEG-bound 2-(thiocyanatomethyl)alk-2-enoates. Subsequent cleavage from the PEG efficiently afforded ethyl (*Z*)-2-(thiocyanatomethyl)alk-2-enoates in good yields and high purities.

Keywords: liquid-phase organic synthesis, PEG-supported α-selenopropionate, ethyl (*Z*)-2-(thiocyanatomethyl)alk-2-enoates

Recently, much attention has been focused on liquid-phase organic synthesis (LPOS) because it combines the advantages of the classical homogeneous solution methodology (high reactivity and simple analytical procedures) with those of solid-phase organic synthesis (SPOS) (easy isolation and purification of the final products and high stability of the system polymer-supported molecule).[1] Polyethylene glycol (PEG), as a inexpensive polymer, is an ideal support for liquid-phase combinatorial synthesis since it can be functionalised with different spacers or reactive groups and are also commercially available, inexpensive, non-toxic, highly resistant to drastic physical and chemical conditions, and soluble in a wide variety of solvents such as CH_2Cl_2, THF, CH_3OH and H_2O at room temperature, and can be precipitated from a solution by addition of diethyl ether, *tert*-butyl methyl ether, propan-2-ol or hexane.[2] Furthermore, the PEG-bound intermediate products can be adequately characterised by using routine analytical techniques like TLC, IR and ^{1}H NMR.[3] Thiocyanates, as useful substrates, can be easily converted into various sulfur containing molecules[4] such as thiols, thiophenoils, and disulfides which serve as important synthetic intermediates in agricultural and pharmaceutical chemistry.[5] Although some synthetic methods have been developed for preparation thiocyanates,[3b,6] in view of their significance in organic synthesis, it is still necessary to develop a more efficient alternative method with operational simplicity.

The Baylis–Hillman reaction is well known as a powerful carbon–carbon bond-forming methods in organic synthesis.[7] Nucleophilic displacement of Baylis–Hillman acetates is one of the most straightforward reactions for stereoselective synthesis of trisubstituted alkenes in organic chemistry. On the other hand, organoselenium reagents are commonly used as a powerful tool for introducing new functional groups into organic substrates under extremely mild conditions.[8] For example, the phenylseleno group is readily converted to a leaving group giving access to carbon–carbon double bond *via* oxidation followed by β-elimination. Recently, several research groups[9] and our group[10] have developed selenium-based approaches for solid-phase synthesis with a combined advantage of decrease volatility and simplification of product work-up. However, to our knowledge, organic selenium compounds attached to soluble polymer supports have not been reported. As part of an ongoing research program focused on the use of organoselenium reagents in organic synthesis, we report here a new method for the synthesis of ethyl (*Z*)-2-(thiocyanatomethyl)alk-2-enoates based on PEG-bound α-phenylselenopropionate (Scheme 1).

As shown in Scheme 1, esterification of commercially available difunctional PEG (MW = 4,000) with α-phenylselenopropanoic acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in anhydrous CH_2Cl_2 at room temperature for 24 h readily gave rise to the corresponding PEG bound α-phenylselenopropionate ester **2**. The conversion of terminal hydroxyl groups on PEG was determined by ^{1}H NMR analysis to be quantitative. The PEG-bound ester **2** showed complete disappearance of the hydroxyl OH stretching vibration and the appearance of a strong C=O stretching vibration at 1728 cm^{-1}. The PEG-bound ester **2** can be stored at room temperature for long time without diminution of capacity or the liberation of disagreeable odors. As illustrated, reaction of the PEG-bound ester **2** with $TiCl_4$ Followed by *i*-Pr_2NEt and NMP in CH_2Cl_2 at 0°C generate the titanium enolate (following Crimmins' procedure) [11] to which are added different aldehydes furnished the corresponding PEG-bound intermediate **3** in excellent yields. Without further isolation of **3**, we carried out the next step of oxidation–elimination reaction directly with 30% hydrogen peroxide at



Scheme 1

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0°C and then at room temperature to obtain the corresponding PEG-bound Baylis–Hillman products **4**, which exhibited a broad hydroxyl absorption in 3300–3400 cm^{-1} region, an intense carbonyl absorption at 1709–1722 cm^{-1}, C=C olefin absorption at 1625–1630 cm^{-1} in its FT–IR spectra and was found to have lost all its selenium by elemental analysis, indicating the oxidation–elimination was complete.

Then the reaction conditions of PEG-bound B-H adducts **4** with potassium thiocyanate were firstly optimised. When dichloromethane, tetrahydrofuran, and acetonitrile were used as solvent, the reaction proceeded slowly and gave a poor yield; fairly good yield of PEG-bound 2-(thiocyanatomethyl)alk-2-enoates **5** showing characteristic absorption at 2120–2250 cm^{-1} (CN) in FT–IR spectra was obtained in anhydrous *N,N*-dimethylformamide (DMF) while the best result was found in DMF at 80°C for 2–3 h with addition of ammonium hydrogen carbonate to the reaction mixture. After precipitation by addition of diethyl ether to the mixture and separated by simple filtration, the PEG-bound products **5** were cleaved with 0.1 $moll^{-1}$ EtONa/EtOH solution at room temperature for approximately 8 h to afford target compounds **6** in good yields and purities (Table 1).

As seen from Table 1, the present method was effective for substrates possessing either aryl (entries 1–7) or alkyl substituents (entries 8–9). Besides good yields, the present process also exhibited high stereoselectivity. The exclusive (*Z*)-stereoselectivity of target products **6** was assigned by comparing the chemical shifts in ^{1}H NMR with reported relevant values of trisubstituted alkenes[12] and no *E* isomers were observed from the spectra. In some cases, a trace amount of the PEG residue might contaminate the final products **6**, which could be easily purified by passing the crude product through a pad of silica gel (ethyl acetate–hexane as the eluent, 2 : 8).

In summary, a novel and efficient procedure for the liquid-phase synthesis of ethyl (*Z*)-2-(thiocyanatomethyl)alk-2-enoates in good yields and purities using PEG-bound α-phenylselenopropionate reagent with advantages of decrease volatility and simplification of product work-up has been developed.

Experimental

All reactions were conducted under a nitrogen atmosphere. NMP and DMF were refluxed with calcium hydride and distilled under reduced pressure prior to use. Dichloromethane was dried by distillation from phosphorous pentoxide prior to use. α-Phenylselenopropanoic acid[13] was prepared according to the literature procedures. PEG 4000 and other reagents were purchased from commercial sources. Melting points were determined on X_4 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance (400 MHz) spectrometer. FT–IR spectra were taken on a Perkin-Elmer SP One FT–IR spectrophotometer. Mass spectra (EI, 70eV) were recorded on a HP5989B mass spectrometer. Microanalyses were performed with a PE 2400 elemental analyser. HPLC analysis was carried out on an Agilent 1100 (column, ODS 5 μm 250 × 4 mm, gradient elution with CH_3CN/H_2O, UV absorption detector at 254 nm).

Preparation of PEG-bound α-phenylselenopropionate **2**

To a stirred solution of PEG (5.0 g, 2.5 mmol) in CH_2Cl_2 (20 ml) were added α-phenylselenopropanoic acid (1.72 g, 7.5 mmol), DCC (2.06 g, 10 mmol) and DMAP (0.305 g, 2.5 mmol). After the mixture was stirred at room temperature for 24 h, the precipitate was removed by filtration and the polymer was precipitated by addition of diethyl ether (200 ml) to the filtrate. For completion of the precipitation, the suspension was left at 0°C for another 30 min. The precipitate was collected and washed with diethyl ether (3 × 30 ml of each), and dried in *vacuo* to afford 5.15 g (98%) of the PEG bound ester **2** as a pale yellow solid**:** ^{1}H NMR ($CDCl_3$) δ: 7.61–7.59 (m, 2H), 7.31–7.29 (m, 3H), 4.18 (t, *J* = 4.98 Hz, 2H, PEG-OCH_2CH_2OCO), 4.08 (q, *J* = 6.8 Hz, 1H), 3.46–3.81 (m, PEG CH_2), 1.54 (d, *J* = 6.8 Hz, 3H); IR (KBr) ν: 2886, 1728, 1644, 1455, 1350, 1252, 1146, 950, 849 cm^{-1}.

Preparation of ethyl (Z)-2-(thiocyanatomethyl)alk-2-enoates (**6a–6i**); *general procedure*

To a stirred solution of PEG-bound ester **2** (1.0 mmol) in CH_2Cl_2 (10 ml) at 0°C, was added $TiCl_4$ (0.12 ml, 1.05 mmol) and the mixture was stirred for 20 min. *i*-Pr_2NEt (0.19 ml, 1.1 mmol) was added and the mixture was stirred for 40 min before adding NMP (0.1 ml). The mixture was stirred for 10 min and the appropriate aldehyde (1.2 mmol) was added. After 30 min, NH_4Cl was added and the reaction mixture was warmed to 0°C and 30% aqueous hydrogen peroxide (1.0 ml, 11.6 mmol) were added. After 30 min, the ice bath was removed and the mixture was stirred at room temperature for 1–2 h. After completion of the reaction, the reaction mixture was cooled and the diethyl ether (100 ml) was added to allow the precipitation of PEG-bound B-H adducts **4**, which were collected by filtration and washed with diethyl ether (3 × 30 ml of each). To a solution of PEG-bound B-H adducts **4** (1.0 mmol) in anhydrous DMF (10 ml) was added KSCN (194 mg, 2.0 mmol) and NH_4HCO_3 (79 mg, 1.0 mmol) and the reaction mixture was stirred at 80°C for 2–3 h. Then the PEG-bound intermediate **5** was precipitated by addition of diethyl ether (100 ml) to the mixture. For completion of the precipitation, the suspension was left at 0°C for another 30 min. The white precipitate was collected, washed several times with diethyl ether (2 × 10 ml) and dried *in vacuo*. The PEG-bound intermediate **5** was treated with 0.1 mol/l EtONa in EtOH (10 ml), the obtained mixture was stirred at room temperature for 8 h, then Et_2O (60 ml) was added to the mixture and the organic phase was separated. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated to afford crude products **6a**–**6i**, which were further purified by passing the crude product through a pad of silica gel (ethyl acetate–hexane as the eluent, 2 : 8), if necessary.

Ethyl (Z)-3-Phenyl-2-(thiocyanatomethyl)acrylate (**6a**): Colourless oil (Lit.[6d] colourless oil); ^{1}H NMR: δ = 7.96 (s, 1H), 7.50–7.46 (m, 2H), 7.39–7.36 (m, 3H), 4.25 (q, *J* = 6.8 Hz, 2H), 4.06 (s, 2H), 1.38 (t, *J* = 6.8 Hz, 3H); IR (film): ν = 2985, 2116, 1708, 1630, 1495, 1369, 1245, 1065, 1028, 910 cm^{-1}.

Ethyl (Z)-3-(4-Methoxyphenyl)-2-(thiocyanatomethyl)acrylate (**6b**): Colourless oil; ^{1}H NMR: δ = 7.78 (d, *J* = 8.8 Hz, 2H), 7.70 (s, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 4.25 (q, *J* = 6.8 Hz, 2H), 4.04 (s, 2H), 3.84 (s, 3H), 1.41 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.6, 140.8, 130.3, 129.3, 124.6, 116.2, 114.5, 113.8, 60.1, 55.2, 45.5, 14.1; IR (film): ν = 2986, 2124, 1710, 1630, 1498, 1375, 1242, 1068, 1030, 910, 824 cm^{-1}; EIMS: *m/z* (%) = 277 (M^+); Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.70; H, 5.52; N, 5.12.

Ethyl (Z)-3-(4-Fluorophenyl)-2-(thiocyanatomethyl)acrylate (**6c**): Colourless oil (Lit.[6d] colourless oil); ^{1}H NMR: δ = 7.74 (s, 1H), 7.53-7.40 (m, 2H), 7.04 (t, *J* = 8.1 Hz, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.66 (s, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); IR (film): ν = 2985, 2120, 1712, 1632, 1501, 1370, 1244, 1065, 1033, 914, 822, 765 cm^{-1}.

Table 1 The yields and purities of ethyl (*Z*)-2-thiocyanatomethylalk-2-enoates 6

Entry	R	Product **6**	Yield/%[a]	Purity/%[b]
1	C_6H_5	**6a**	85	94
2	4-$CH_3OC_6H_4$	**6b**	86	94
3	4-FC_6H_4	**6c**	86	95
4	2-BrC_6H_4	**6d**	83	92
5	4-NCC_6H_4	**6e**	80	90
6	4-$NO_2C_6H_4$	**6f**	80	91
7	2-furyl	**6g**	82	93
8	(*E*)-CH_3CH=CH	**6h**	85	95
9	$CH_3CH_2CH_2$	**6i**	87	96

[a]Isolated yield based on loading of original HO-PEG-OH. [b]Determined by HPLC analysis of the crude products before purification

Ethyl (Z)-3-(2-Bromophenyl)-2-(thiocyanatomethyl)acrylate (**6d**): White solid; m.p. 80–82°C; ^{1}H NMR: δ = 7.73 (s, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.40–7.24 (m, 3H), 4.27 (q, *J* = 7.0 Hz, 2H), 3.54 (s, 2H), 1.36 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 167.5, 139.8, 134.7, 133.3, 131.5, 130.2, 127.8, 123.8, 123.4, 114.5, 60.1, 45.6, 14.2; IR (KBr): ν = 2978, 2230, 1706, 1628, 1475, 1240, 1106, 1025, 788 cm^{-1}; EIMS: *m/z* (%) = 326 (M^+); Anal. Calcd for $C_{13}H_{12}BrNO_2S$: C, 47.87; H, 3.71; N, 4.29. Found: C, 47.92; H, 3.76; N, 4.34.

Ethyl (Z)-3-(4-Cyanophenyl)-2-(thiocyanatomethyl)acrylate (**6e**): Light yellow solid; m.p. 128–130°C (Lit.[6d] m.p. 129–131°C); ^{1}H NMR: δ = 7.72 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.54 (s, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 167.2, 139.5, 139.1, 132.1, 130.5, 130.0, 118.4, 112.5, 112.1, 60.9, 45.5, 14.1; IR (KBr): ν = 2968, 2245, 2123, 1710, 1634, 1595, 1375, 1260, 1025, 834, 778 cm^{-1}.

Ethyl (Z)-3-(4-Nitrophenyl)-2-(thiocyanatomethyl)acrylate (**6f**): Brown oil (Lit.[6d] brown oil); ^{1}H NMR: δ = 8.15 (d, *J* = 8.4 Hz, 2H), 7.72 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.47 (s, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); IR (film): ν = 2926, 2123, 1712, 1632, 1599, 1521, 1347, 1235, 1158, 1109, 851 cm^{-1}.

Ethyl (Z)-3-(2-Furyl)-2-(thiocyanatomethyl)acrylate (**6g**): Light yellow solid; m.p. 161–163°C (Lit.[6d] m.p. 159–162°C); ^{1}H NMR: δ = 7.50 (d, *J* = 7.4 Hz, 2H), 6.72 (d, *J* = 3.1 Hz, 1H), 6.38 (d, *J* = 2.3 Hz, 1H), 4.27 (q, *J* = 7.0 Hz, 2H), 3.57 (s, 2H), 1.33 (t, *J* = 7.0 Hz, 3H); IR (KBr): ν = 2926, 2125, 1705, 1631, 1595, 1368, 1240, 1105, 765 cm^{-1}.

Ethyl (2Z, 4E)-2-(Thiocyanatomethyl)hexa-2,4-dienoate (**6h**): White solid; m.p. 87–89°C (Lit.[6d] m.p. 83–87°C); ^{1}H NMR: δ = 7.25–7.18 (m, 1H), 6.50–6.35 (m, 1H), 6.12–5.99 (m, 1H), 4.26 (q, *J* = 7.0 Hz, 2H), 3.24 (s, 2H), 1.80 (t, *J* = 6.5 Hz, 3H), 1.35 (t, *J* = 7.0 Hz, 3H); IR (KBr): ν = 2962, 2120, 1715, 1630, 1615, 1370, 1238, 1158, 725, 620 cm^{-1}.

Ethyl (Z)-2-(Thiocyanatomethyl)hexa-2-enoate (**6i**): Colourless oil; ^{1}H NMR: δ = 6.75 (t, *J* = 7.5 Hz, 1H), 4.20 (q, *J* = 6.8 Hz, 2H), 3.13 (s, 2H), 2.30-2.12 (m, 2H), 1.24–1.17 (m, 5H), 0.97 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.2, 148.2, 129.8, 116.2, 60.3, 49.5, 27.2, 19.2, 14.3, 13.2; IR (film): ν = 2965, 2120, 1716, 1617, 1459, 1368, 1235, 1148, 724, 621 cm^{-1}; EIMS: *m/z* (%) = 213 (M^+); Anal. Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57. Found: C, 56.37; H, 7.15; N, 6.62.

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