Solid-Phase Synthesis of 2-Alkenamides from Polystyrene-Supported α-Selenocarboxylic Acids

Xiao-Ling Liu (劉曉玲), Xing-Cong Wang (王幸聰) and Shou-Ri Sheng* (盛壽日)
Department of Chemistry, Jiangxi Normal University, Nanchang, 330027, P. R. China

The polystyrene-supported α-selenoacetic acid and α-selenopropionic acid were prepared and used for the synthesis of 2-alkenamides from primary and secondary amines in good yields and high purities.

Keywords: Solid-phase organic synthesis; Polymer-supported α-selenocarboxylic acids; 2-Alkenamides.

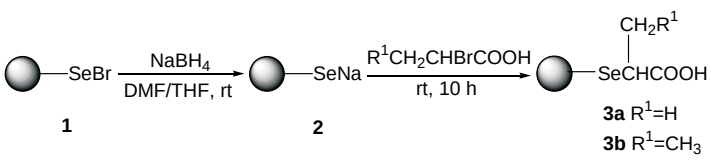
During the last few years, solid-phase methodology has been rapidly and extensively applied to preparation of small organic molecules.[1] The purification of the organic products has been greatly simplified through the use of polymer-supported reagents. 2-Alkenamides, useful monomers for polyamides, have been known to chemists for a long time. In addition, they are widely used as intermediates in organic synthesis. Solution-phase synthetic methods for 2-alkenamides are well documented; however, efforts are being continued for the development of more efficient methods with experimental simplicity. Recently, several solid-phase syntheses of amides have been reported,[2] but to the best of our knowledge, all previous reports for related solid-phase synthesis of 2-alkenamides have paid no attention to the use of the phenylseleno group as leaving group. Polymer-bound selenides have proven to be versatile traceless linkers, which give access to alkenes by oxidation followed by β-elimination.[3] Meanwhile, the use of the selenium reagents immobilized on polymer-resin has provided significant advantages, including decreased volatility and simplification of product work-up. With the successful synthesis of α,β-unsaturated carbonyl compounds[4] from polymer-bound selenium bromide[3a] and (Z)-1,2-disubstituted ethenes using polymer-supported α-selenoaldehydes,[5] we here report a simple and efficient solid-phase synthetic approach to 2-alkenamides based on novel polystyrene-supported α-selenocarboxylic acids.

The polystyrene-supported α-selenocarboxylic acids **3** were prepared by reaction of polystyrene-supported sodium selenide **2**[3a,6] with α-bromocarboxylic acids (Scheme I). The minimum loading of COOH of resin **3** verified by their FT-IR spectra showing a strong carbonyl absorption at 1700-1710 cm^{-1} were determined by acid-base titration[7] to be 1.27 mmol/g (**3a**, R^1 = H) and 1.20 mmol/g (**3b**, R^1 = CH_3), respectively. Resin **3** can be stored at room temperature for a long time without diminution of capacity or the liberation of foul smell.

The acylation of resin **3** would be the key for the success of this protocol. Here, the acylation was investigated starting from α-selenoacetic acid resin **3a** (Scheme II). After considerable experimentation, the acylation of resin **3a** proceeded smoothly simply by adjusting the solvent system used for the reaction; the most dramatic effect was found when anhydrous 1,2-dichloroethane (DCE) was used as the solvent. Treatment of resin **3a** with excess thionyl chloride in DCE under reflux for 10 h gave polystyrene-supported α-selenopropanoyl chloride **4a**. The acylation on solid-phase was complete as also monitored by FT-IR study, which showed a single strong carbonyl absorption at 1768 cm^{-1}. After removing excess thionyl chloride, and without further isolation, it was allowed to react with aniline **5a** in the presence of anhydrous triethylamine to afford α-selenopropanamide resin **6aa** as evidenced by FT-IR with appearance of carbonyl absorption at 1706 cm^{-1} and complete disappearence of peak at 1768 cm^{-1}.

Treatment of resin **6aa** with an excess of 30% hydrogen

Scheme I



Scheme II

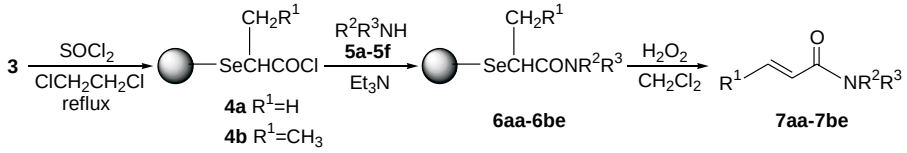


Table 1. Yields and Purities of 2-Alkenamides

R^1 (Resin **3**)	Amine (**5**) R^2, R^3	Product **7**	Yield[a] (%)	Purity[b] (%)
H (**3a**)	C_6H_5, H (**5a**)	**7aa**	88	> 95
H (**3a**)	4-$CH_3C_6H_4$, H (**5b**)	**7ab**	90	> 95
H (**3a**)	4-ClC_6H_4, H (**5c**)	**7ac**	91	> 95
H (**3a**)	$C_6H_5CH_2$, H (**5d**)	**7ad**	91	> 95
H (**3a**)	C_4H_9, H (**5e**)	**7ae**	89	> 95
H (**3a**)	*i*-C_3H_7, *i*-C_3H_7 (**5f**)	**7af**	89	> 95
H (**3a**)	-$(CH_2)_5$- (**5g**)	**7ag**	85	> 95
CH_3 (**3b**)	C_6H_5, H (**5a**)	**7ba**	84	> 95
CH_3 (**3b**)	$C_6H_5CH_2$, H (**5d**)	**7bd**	88	> 95
CH_3 (**3b**)	C_4H_9, H (**5e**)	**7be**	90	> 95

[a] Yields were based on the functional loading of resin **3**.
[b] Determined by ^{1}H NMR (400 MHz).

peroxide at room temperature produced the corresponding N-phenylacrylamide **7aa** in 88% yield and with high purity of crude materials (> 95% by ^{1}H NMR analysis). A summary of these results is given in Table 1. The residual resin, polystyrene-supported phenylseleninic acid, was obtained as a by-product, whose infrared data was identical to the previously reported data[8] and showed no residual carbonyl absorption.

It should be noted that, in the cases of α-selenopropionic acid resin **3b**, (Table 1), the oxidative cleavage of the corresponding resins **6ba-6be** exclusively resulted in the formation of the *E* 2-butenamides **7ba-7be** detected by ^{1}H NMR spectra.

In summary, polystyrene-supported α-selenocarboxylic acids, synthesized from polystyrene beads, have been used for synthesis of 2-alkenamides from primary and secondary amines in good yields and high purity. We are currently applying this method for the derivation of amines from biological sources and for the preparation of small molecule 2-alkenamide libraries.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer using $CDCl_3$ as the solvent and with TMS as internal standard; IR spectra were determined on a Bruker Vector 22 spectrophotometer.

General procedure for the synthesis of polystyrene-supported α-selenocarboxylic acids 3

Under a positive pressure of nitrogen, to polystyrene-supported selenium bromide **1** (1.0 g, 1.45 mmol Br/g, the loading of functional Br was analyzed by elementary analysis) swelled in THF (10 mL) and DMF (2 mL) for 30 min was added $NaBH_4$ (3 mmol). After 6 h of stirring at room temperature, α-bromocarboxylic acid (2 mmol) in 2 mL of THF was added slowly and the stirring was continued for a further 10 h. The resin was collected on a filter and washed successively with saturated $NaHCO_3$ solution (10 mL), H_2O (2 × 20 mL), THF (2 × 5 mL) and CH_2Cl_2 (2 × 5 mL), and then dried under vacuum overnight to afford resin **3**.

General procedure for the preparation of 2-alkenamides 7aa-7be

Resin **3** (1.0 g) was swelled in DCE (10 mL) at room temperature for 30 min and treated with thionyl chloride (5 mmol) under reflux for 10 h. Excess thionyl chloride was then removed in vacuo to afford α-selenocarboxylic acid chloride resin **4**. Without further filtration and washing, to this mixture was added slowly corresponding amine **5** (2.0

mmol) in anhydrous DCE solution and then triethylamine (1.5 mmol). The mixture was stirred at room temperature for 2 h and the amide resin **6** was collected by filtration and washed successively with 3% HCl (10 × 3 mL), H_2O (10 × 3 mL) and THF (5 × 3 mL). The resin **6** was then suspended in CH_2Cl_2 (10 mL) and treated with 1 mL (11.6 mmol) of 30% H_2O_2. After stirring for 30 min at room temperature, the residual resin was collected by filtration. The filtrate was treated with saturated $NaHCO_3$ (20 mL) and washed with water, dried over magnesium sulfate and evaporated to give products **7**.

N-Phenylacrylamide (7aa):[9]

Mp. 102-104 °C (lit. 101-103 °C).^{1}H NMR: δ 8.04 (bs, 1H), 7.10-7.61 (m, 5H), 6.40 (dd, *J* = 17.0, 2.0 Hz, 1H), 6.32 (dd, *J* = 17.0, 10.0 Hz, 1H), 5.70 (dd, *J* = 10.0, 2.0 Hz, 1H). IR: ν_{max} 3442, 3029, 1695, 1601, 962 cm^{-1}.

N-(*p*-Methylphenyl)acrylamide (7ab):[10]

Mp. 138-139 °C (lit. 138-139 °C).^{1}H NMR: δ 7.70 (bs, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.44 (dd, *J* = 17.1, 1.9 Hz, 1H), 6.28 (dd, *J* = 17.1, 10.0 Hz, 1H), 5.72 (dd, *J* = 10.0, 1.9 Hz, 1H), 2.30 (s, 3H). IR: ν_{max} 3445, 3031, 1695, 1600, 1507, 1377, 960, 822 cm^{-1}.

N-(*p*-Chlorophenyl)acrylamide (7ac):[11]

Mp. 100-101 °C (lit. 101-103 °C).^{1}H NMR: δ 9.89 (bs, 1H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.41-6.27 (m, 2H), 5.70 (dd, *J* = 8.6, 3.6 Hz, 1H). IR: ν_{max} 3441, 3032, 1690, 1600, 1455, 969, 820 cm^{-1}.

N-Benzylacrylamide (7ad):[9]

Mp. 58-59 °C (lit. 58-59 °C).^{1}H NMR: δ 7.31-7.25 (m, 5H), 6.36-6.15 (m, 2H), 5.98-5.86 (m, 1H), 5.64 (dd, *J* = 1.7, 1.1 Hz, 1H), 4.50 (d, *J* = 5.8, 2.1 Hz, 2H). IR: ν_{max} 3454, 3030, 1685, 1630, 1506, 975 cm^{-1}.

N-(n-Butyl)acrylamide (7ae):[9]

Oil. ^{1}H NMR: δ 6.30-5.98 (m, 2H), 5.80-5.90 (m, 1H), 5.60 (dd, *J* = 10.1, 1.0 Hz, 1H), 3.33 (q, *J* = 6.0 Hz, 2H), 1.52-1.35 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H). IR: ν_{max} 3456, 2951, 1675, 1630, 1512, 1455, 915 cm^{-1}.

N,N-Diisopropylacylamide (7af):[12]

Oil. ^{1}H NMR: δ 6.24-5.08 (m, 2H), 5.60 (dd, *J* = 10.0, 1.1 Hz, 1H), 3.68 (m 2H), 1.30 (d, *J* = 7.1 Hz, 12H). IR: ν_{max} 3455, 2965, 1638, 1512, 1445, 1374, 1045, 915 cm^{-1}.

N-Acrylpiperidine (7ag):[12]

Oil. ^{1}H NMR: δ 6.25-6.10 (m, 2H), 5.65 (dd, *J* = 10.0, 1.0 Hz, 1H), 3.15 (t, *J* = 5.7 Hz, 4H), 1.62-1.75 (m, 4H), 1.22-1.11 (m, 2H). IR: ν_{max} 3459, 2920, 1680, 1629, 1510, 975 cm^{-1}.

N-Phenyl-2-butenamide (7ba):[9]

Mp. 110-111 °C (lit. 112-114 °C). ^{1}H NMR: δ 8.04 (bs, 1H), 7.11-7.60 (m, 5H), 6.92 (dq, *J* = 15.3, 1.7 Hz, 1H), 5.92 (dq, *J* = 15.3, 1.7 Hz, 1H), 1.85 (dd, *J* = 1.7, 6.7 Hz, 3H). IR: ν_{max} 3442, 3029, 1696, 1600, 961 cm^{-1}.

N-Benzyl-2-butenamide (7bd):[9]

Mp. 116-117 °C (lit. 116-117 C). ^{1}H NMR: δ 7.31-7.25 (m, 5H), 6.85 (dq, *J* = 16.5, 6.8 Hz, 1H), 5.91-5.80 (m, 1H), 5.80 (dq, *J* = 16.5, 1.6 Hz, 1H), 4.50 (d, *J* = 5.8 Hz, 2H), 1.83 (dd, *J* = 1.6, 6.8 Hz, 3H). IR: ν_{max} 3454, 3035, 1684, 1650, 1506, 965 cm^{-1}.

N-Butyl-2-butenamide (7be):[9]

Oil. ^{1}H NMR: δ 6.80 (dq, *J* = 16.5, 7.0 Hz, 1H), 5.92-5.85 (m, 1H), 5.76 (dq, *J* = 16.5, 1.5 Hz, 1H), 3.36-3.30 (m, 2H), 1.82 (dd, *J* = 1.5, 7.0 Hz, 3H), 1.52-1.35 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H). IR: ν_{max} 3456, 2951, 1675, 1630, 1512, 1455, 915 cm^{-1}.

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