Solid-phase synthesis of acrylamides with polymer-bound 2-sulfonylpropanoic acid

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A novel polystyrene-bound 2-sulfonylpropanoic acid has been developed and applied to convenient, traceless synthesis of acrylamides in good yield and purity.

Keywords: solid-phase organic synthesis, polystyrene-bound 2-sulfonylpropanoic acid, acrylamides.

Solid-phase organic synthesis (SPOS) is of current interest[1] because of several advantages over solution-phase synthesis such as easy manipulation and purification of the organic products which is greatly simplified through the use of polymer-bound reagents. Acrylamides are useful monomers for polyacrylamides, and they are widely used as intermediates in organic synthesis. Solution-phase synthetic methods for them are well documented. However, efforts are continuing for the development of more efficient synthetic methods with experimental simplicity. Recently, several solid-phase synthesis of amides have already been reported;[2] but to our knowledge, there have been no reports on the preparation of acrylamides using a traceless sulfone linker strategy.[3] Herein, we report the extension of this sulfone-based chemistry to a convenient, traceless solid-phase synthesis of acrylamides employing a novel polystyrene-bound 2-sulfonylpropanoic acid (Scheme 1).

Polystyrene-bound 2-sulfonylpropanoic acid **2** can be prepared by reaction of a THF-swollen suspension of polystyrene/1% divinylbenzene lithiophenylsulfinate **1** with a loading of 1.05 mmol /g as determined by titration[3f] with α-bromopropanoic acid at a reflux temperature. This transformation could be monitored by FT-IR [polymer-bound lithiophenylsulfinate **1** (1200, 1028, 980 cm^{-1}) → polymer-supported 2-sulfonylpropanoic acid **2** (1725, 1380, 1325, 1152, 1084 cm^{-1})]. The minimum loading of the COOH of the resin **2** was determined by acid-base titration[4] to be 0.90 mmol COOH/g.

With the resin **2** in hand, the preparation of polymer-bound 2-sulfonylpropanoyl chloride **3**, the key for the success of this protocol was investigated. After considerable experimentation, the acylation of resin **2** was obtained smoothly 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 **2** with excess thionyl chloride and DMF in DCE under reflux yielded polymer **3**. The acylation of the solid-phase was as also monitored by FT–IR study, which showed a single strong carbonyl absorption at 1770 cm^{-1}. After removing excess thionyl chloride, and without further isolation, the product was treated with the corresponding primary or secondary amines in the presence of anhydrous triethylamine to afford the 2-sulfonylpropanamide resins **4** as evidenced by FT–IR with appearance of carbonyl absorption at 1650–1660 cm^{-1} and complete disappearence of a peak at 1725 cm^{-1}.

As illustrated, treatment of the resin **4** with potassium *tert*-butoxide at 0°C in THF released the corresponding acrylamides **5** in good yield (85–96%) and with a high purity of the crude material (93–96%). The residual resin with no residual carbonyl absorption indicated that the sulfinate elimination of resin **4** was complete. A summary of these results is given in Table 1. It should be pointed that the reaction of **4** with potassium *tert*-butoxide at room temperature or at a higher temperature in THF gave a lower yield of **5**.

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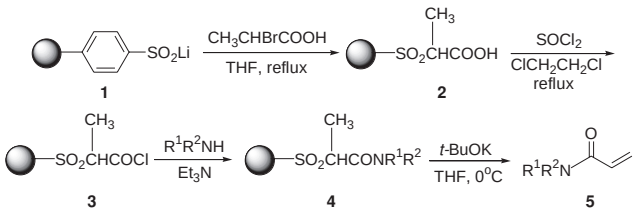

Scheme 1

Table 1 Yields and purities of acrylamides

Product	R^1	R^2	Yield [a]/%	Purity [b]/%
5a	C_6H_5	H	95	94
5b	4-$CH_3C_6H_4$	H	96	95
5c	4-$CH_3OC_6H_4$	H	93	93
5d	4-ClC_6H_4	H	94	93
5e	$C_6H_5CH_2$	H	90	94
5f	C_4H_9	H	85	95
5g	*i*-C_3H_7	*i*-C_3H_7	88	96

[a]Yields were based on the functional loading of resin **2** (0.90 mmol COOH/g).
[b]Purities of crude products were determined by HPLC.

In conclusion, we have developed a route to acrylamides in good yields and high purity via a traceless solid-phase sulfone linker strategy. Although excess reagents are required, simple work-up procedures take the place of the time-consuming isolation and purification steps in the solution-phase synthesis.

Experimental

Melting points were uncorrected. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance (400 MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as internal standard. Mass spectra (EI, 70eV) were recorded on a HP5989B mass spectrometer. FT–IR spectra were taken on a Perkin-Elmer SP One FT-IR spectrophotometer. Polystyrene for the preparation of polystyrene-supported 2-sulfonylpropanoic acid prepared according to the reported method[3f, 3e] was purchased from Aldrich (200 mesh, cross-linked with 1% divinylbenzene).

Procedure for the preparation of polystyrene-bound 2-sulfonylpropanoic acid **2**: Polymer **1** (1.0 g, 1.05 mmol) was swollen in THF (10 ml) and α-bromopropanoic acid (2.5 mmol) was added under reflux under nitrogen for 24 h. The resin was collected by filtration using a medium sintered glass fritted Buchner funnel, washed successively with THF/H_2O (2:1, 3×10 ml), THF (2×5 ml), CH_2Cl_2 (2×5 ml) and ether(2×5 ml), and then dried under vacuum overnight to afford polymer-bound 2-sulfonylpropanoic acid **2** as yellow beads. The resin **2** was found to contain a loading of 0.90 mmol of functional COOH/g by treating 0.5 g of resin **2** with an excess of BuLi in benzene and back-titrating with 0.1 *N* H_2SO_4. FT-IR (KBr): 3168, 2985, 2942, 1725, 1380, 1325, 1221, 1152, 960, 870, 780 cm^{-1}.

General procedure for preparation of acrylamides **5**: Resin **2** (1.0 g) was swollen in DCE (10 ml) at room temperature for 30 min, and treated with thionyl chloride (10 mmol) and 1–2 drops of DMF under reflux for 8 h. The reaction mixture was concentrated under reduced pressure to remove excess thionyl chloride to afford 2-sulfonylpropanoyl chloride resin **3**. Without further filtration and

washing, the corresponding amine (2 mmol) in anhydrous THF (10 ml) solution was slowly added to the mixture, and followed with triethylamine (1.5 mmol). The mixture was stirred at room temperature for 2 h and the 2-sulfonyl propanamide resin **4** was collected by filtration and washed successively with 3 % HCl (3×10 ml), H_2O (3×10 ml) and THF (3×5 ml). After drying in a vacuum, the resin **4** was swollen in THF (10 ml) and treated with potassium *tert*-butoxide (0.12 g, 1.0 mmol) at 0°C for 2 h under dry nitrogen. The residual resin was collected by filtration and washed with ether (5×5 ml), and the filtrate was washed with water (3×10 ml), then the organic layer was separated, dried with anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under a reduced pressure to give the crude acrylamides (**5a**–**5g**) products, which were further purified by silica gel chromatographic column (petroleum ether/ethyl acetate = 2/1) affording the pure products for ^{1}H NMR analysis.

N-Phenylacrylamide **(5a)**: [5] Colourless crystals; m.p. 102–104°C (lit.101–103°C).^{1}H NMR: δ 8.04 (bs, 1H), 7.10–7.61 (m, 5H), 6.41 (dd, *J* = 16.8, 2.0 Hz, 1H), 6.31 (dd, *J* = 17.0, 10.0 Hz, 1H), 5.70 (dd, *J* = 10.0, 2.0 Hz, 1H). IR:ν_{max} 3444, 3030, 1698, 1600, 962 cm^{-1}

N-(p-Methylphenyl)acrylamide **(5b)**: [6] Colourless crystals; m.p. 138–139°C (lit.138–139°C).^{1}H NMR: δ 7.71 (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, 2.0 Hz, 1H), 2.30 (s, 3H). IR: ν_{max} 3445, 3031, 1695, 1600, 1507, 1377, 960, 822 cm^{-1}

N-(p-Methoxyphenyl)acrylamide **(5c)**: Colourless crystals; m.p. 98–100°C. ^{1}H NMR: δ 7.90 (bs, 1H), 7.50 (d, *J* = 9.0 Hz, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 6.41 (dd, *J* = 17.1, 2.0 Hz, 1H), 6.26 (dd, *J* = 17.1, 9.9 Hz, 1H), 5.70 (dd, *J* = 9.9, 2.0 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR: 165.4, 138.0, 130.6, 128.6, 127.8, 127.5, 126.6, 43.6. MS: *m/z* 177 (M^+, 100), 123 (80.3), 122 (27.6), 108 (46.4), 55 (53.0). *Anal. Calcd* for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.85; H, 6.33; N, 7.95. IR:ν_{max} 3440, 3030, 1698, 1600, 1505, 1385, 962, 820 cm^{-1}

N-(p-Chlorophenyl)acrylamide **(5d)**: [7] Colourless crystals; m.p. 100–101°C (lit.101–103°C).^{1}H NMR: δ 9.88 (bs, 1H), 7.70 (d, *J* = 8.8 Hz 2H), 7.23 (d, *J* = 8.8 Hz 2H), 6.38–6.42 (m, 2H), 5.70 (dd, *J* = 8.7, 3.6 Hz, 1H). IR: ν_{max} 3440, 3030, 1695, 1600, 1456, 700, 820 cm^{-1}

N-Benzylacrylamide **(5e)**: [5] Colourless crystals; m.p. 58–59°C (lit.58–59°C).^{1}H NMR: δ 7.30–7.25 (m, 5H), 6.36–6.14 (m, 2H), 5.98–5.95 (m, 1H), 5.63 (dd, *J* = 1.7, 1.0 Hz, 1H), 4.51 (d, *J* = 5.8, 2.0 Hz, 2H). IR: ν_{max} 3454, 3030, 1685, 1630, 1506, 975 cm^{-1}

N-(n-Butyl)acrylamide **(5f)**: [5] Colourless oil.^{1}H NMR: δ 6.30–5.97 (m, 2H), 5.75–5.82 (m, 1H), 5.60 (dd, *J* = 10.0, 1.0 Hz, 1H), 3.35 (q, *J* = 6.0 Hz, 2H), 1.52–1.34 (m, 4H), 0.94 (t, *J* = 7.0 Hz, 3H). IR: ν_{max} 3455, 2950, 1675, 1633, 1512, 1455, 915 cm^{-1}

N, N-Diisopropylacylamide **(5g)**: [8] Colourless oil. ^{1}H NMR: δ 5.97 (d, *J* = 10.1 Hz, 2H), 5.60 (dd, *J* = 10.1, 1.1 Hz, 1H), 3.64–3.70 (m, 2H), 1.30 (d, *J* = 7.1 Hz, 12H). IR: ν_{max} 3457, 2966, 1640, 1512, 1445, 1375, 1044, 916 cm^{-1}

We are grateful to the Natural Science Foundation of Jiangxi Province (No.0420017) for financial support.

Received 22 June 2004; accepted 26 July 2004
Paper 04/2595

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