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Facile Method for Solid-Phase Synthesis of Vinyl Sulfones Using Polystyrene-Supported Selenomethyl Aryl Sulfone

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Abstract: Treatment of novel polystyrene-supported selenomethyl aryl sulfone with LDA followed by alkylation and oxidation elimination efficiently afforded vinyl sulfones in good yields and purities.

Keywords: Polystyrene-supported selenomethyl aryl sulfone, solid-phase synthesis, vinyl sulfone

Solid-phase synthesis has gained widespread acceptance in combinatorial chemistry related to drug discovery in order to accelerate lead generation and lead optimization.[1] Synthesis on a polymer support shows a number of advantages as compared to solution chemistry. The most salient one is the possibility of applying excesses of reagents and removing them without involving time-consuming separation techniques. Vinyl sulfones have

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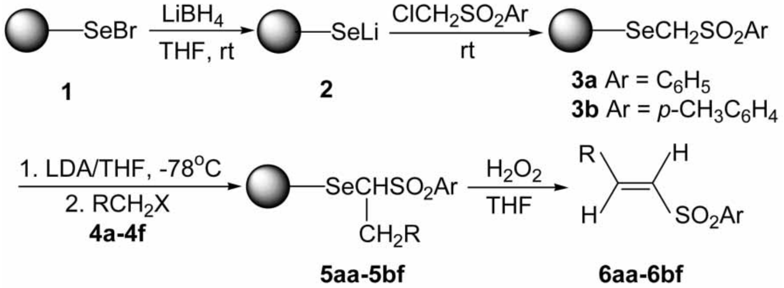
now become generally accepted useful intermediates in organic synthesis, e.g., serving efficiently as both Michael acceptors and π partners in cycloaddition reaction. Many methods for preparing vinyl sufones have been developed.[2] Among these methods, the ionic and radical addition of selenosulfonate to alkenes and alkynes is an important procedure.[3] However, organic selenium reagents typically have a foul smell and are quite toxic, which is often problematic in organic synthesis. Recently, polymer-bound selenides have proven to be versatile traceless linkers, which give access to alkenes by oxidation elimination.[4] Furthermore, the use of polymeric selenium reagents has significant advantages, including decreased volatility, convenience of handing, and simplification of product workup. In our previous communication, we used polymer-supported β-selenopropionic acid to prepare acrylamides;[5] we here wish to report a facile synthetic approach to vinyl sulfones from polystyrene-supported selenomethyl aryl sulfone **3** (Scheme 1).

The resin **3a**–**3b** was easily prepared in a few steps from crosslinked (1%) polystyrene by reaction of polystyrene-supported lithium selenide **2**[4a] with chloromethyl phenyl sulfone and chloromethyl *p*-tolyl sulfone, respectively. The formation of **3** could be monitored by FT-IR. There were two strong characteristic sulfone stretches at 1317 and 1145 cm^{-1}, with a loading of 1.28 mmol/g (**3a**, $\mathrm{Ar} = \mathrm{C_6H_5}$) and a loading of 1.25 mmol/g (**3b**, $\mathrm{Ar} = p\text{-}\mathrm{CH_3C_6H_4}$), as determined by elemental analysis. Resin **3** can be stored at room temperature for long time without diminution of capacity or the liberation of disagreeable odors.

As illustrated, reaction of the lithio derivative of resin **3** with representative primary alkyl halides **4** furnished the α-selenylated alkyl aryl sulfone resin **5**, which could not be reliably analyzed with FT-IR. Hence we carried out the next cleavage reaction directly after washing the resin **5** with solvents. Treatment of resin **5** with 30% hydrogen peroxide at 0°C and then at room temperature afforded the corresponding vinyl sulfones **6** in good yields (86–93%) and with good purities of crude materials (92–96%). The results are summarized in Table 1. It should be noted that *trans*-1-alkenylsulfones



Scheme 1.

Table 1. Yields and purities of vinyl sulfones (**6aa**–**6bf**)

Resin	RCH_2X (**4**)	Product	Yield[a] (%)	Purity[b] (%)
3a	$C_6H_5CH_2Br$ (**4a**)	**6aa**	90	92
3a	$NCCH_2Cl$ (**4b**)	**6ab**	86	95
3a	CH_3OCOCH_2Br (**4c**)	**6ac**	91	92
3a	CH_3CH_2Br (**4d**)	**6ad**	93	96
3a	CH_3I (**4e**)	**6ae**	93	96
3b	$C_6H_5CH_2Br$ (**4a**)	**6ba**	90	94
3b	$NCCH_2Cl$ (**4b**)	**6bb**	87	95
3b	$CH_3(CH_2)_3Br$ (**4f**)	**6bf**	91	93

[a] Yields were based on the functional loading of resin **3**.

[b] Purities of crude products were determined by HPLC.

are formed exclusively except for compound **6e**. The residual resin, polystyrene-supported phenylseleninic acid, was obtained as a by-product whose infrared data was identical to the previously reported data[6] and showed no residual $-SO_2-$ absorption, which indicated the oxidative cleavage was complete.

In conclusion, we have developed a facile methodology for the solid-phase construction of vinyl sulfones in good yields and purities employing a selenium-based traceless linker strategy. Although an excess amount of reagents is required, simple workup procedures take the place of the time-consuming isolation and purification steps in the solution-phase synthesis.

EXPERIMENTAL

Melting points were not corrected. ^1H NMR spectra were recorded on a Bruker Avance 400 M Hz spectrometer in $CDCl_3$ with TMS as internal standard. FT-IR spectra were taken on a Perkin Elmer One instrument. Mass spectra (EI, 70 eV) were recorded on a HP5989B mass spectrometer. THF was newly distilled from sodium/benzophenone before use. Polystyrene (100/200 mesh, crosslinked with 1% divinylbenzene) for the preparation of polystyrene-supported selenium bromide according to the procedure described by Nicolaou,[4a] chloromethyl phenyl sulfone, and chloromethyl *p*-tolyl sulfone were purchased from Aldrich.

Procedure for the Synthesis of Polystyrene-Supported Selenomethyl Aryl Sulfone 3

Under a nitrogen atmosphere, $LiBH_4$ (3 mmol) was added to polystyrene-supported selenium bromide **1** (1.0 g, 1.50 mmol Br/g, the loading of functional Br was analyzed by elementary analysis) swelled in THF (10 mL) for 30 min. After 1 h with stirring at room temperature, chloromethyl aryl sulfone (3 mmol) in 2 mL of THF was added slowly and the mixture was stirred for 10 h. The resin **3** was collected by filtration, washed successively with H_2O (2 × 20 mL), THF (2 × 5 mL) and CH_2Cl_2 (2 × 5 mL), and then dried in a vacuum. **3a**: 1.28 mmol S/g, IR ν (KBr): 3022, 2921, 1600, 1495, 1448, 1317, 1303, 1145, 1070, 810, 751, 696, 579, 526; **3b**: 1.25 mmol S/g, IR ν (KBr): 3023, 2920, 1600, 1496, 1445, 1317, 1300, 1145, 1074, 821, 754, 700, 578, 530.

General Procedure for the Preparation of Vinyl Sulfones 6aa–6bf

Resin **3** (1.0 mmol) was swelled in THF (10 mL) at room temperature for 30 min. After cooling to 78°C, a solution of LDA (0.6 mL, 2.0 M) was added under nitrogen and the mixture was stirring at the same temperature for 30 min. Then, a solution of primary alkyl halide **4a**–**4f** (1.5 mmol) in THF (2 mL) was added and the mixture was warmed up gradually to room temperature and kept standing for 5 h. After neutralization with 1% hydrochloric acid, the resin **5aa**–**5bf** was collected on a filter and washed successively with H_2O (3 × 15 mL), THF (3 × 5 mL), and Et_2O (3 × 5 mL), suspended in THF (10 mL), and treated with 1.0 mL (11.6 mmol) of 30% H_2O_2. After stirring for 20 min at 0°C, and then for 20 min at room temperature, the residual resin was collected by filtration and washed CH_2Cl_2 (4 × 5 mL). The filtrate was washed with water (2 × 30 mL), dried over magnesium sulfate, and concentrated to give crude products, which were purified by preparative TLC on silica gel or crystallization, affording the final products **6aa**–**6bf** for ^1H NMR analysis.

(*E*)-2-(Phenylsulfonyl)styrene (**6aa**)[2j]

White crystals; mp 75–76°C (lit. 76°C). ^1H NMR: δ 6.88 (d, $J = 15.3$ Hz, 1H), 7.38–7.42 (m, 3H), 7.46–7.50 (m, 2H), 7.52–7.56 (m, 2H), 7.58–7.62 (m, 1H), 7.70 (d, $J = 15.2$ Hz, 1H), 7.87–7.96 (m, 2H). IR: ν_{max} 3060, 2925, 1615, 1577, 1494, 1447, 1308, 1145, 1085, 972, 856, 818, 746, 688 cm^{-1}.

(*E*)-3-(Phenylsulfonyl)acrylonitrile (**6ab**)

Colorless oil. ^1H NMR: δ 6.55 (d, $J = 15.6$ Hz, 1H), 7.23 (d, $J = 15.6$ Hz, 1H), 7.61–7.65 (m, 2H), 7.73–7.76 (m, 1H), 7.89–7.95 (m, 2H). MS (*m/e*): 195 ($M^+ + 2$, 0.39), 194 ($M^+ + 1$, 1.90), 193 (M^+, 3.98), 141, 129, 127, 126, 125, 102, 97, 93, 77, 65, 51. IR: ν_{max} 3061, 2228, 1585, 1447, 1315, 1151, 1084, 936, 837, 755, 721, 686, 610 cm^{-1}.

Methyl (*E*)-3-(phenylsulfonyl)acrylate (**6ac**)

Colorless oil. ^{1}H NMR: δ 3.80 (s, 3H), 6.86 (d, $J = 15.2$ Hz, 1H), 7.36 (d, $J = 15.2$ Hz, 1H), 7.58–7.63 (m, 2H), 7.69–7.73 (m, 1H), 7.89–7.94 (m, 2H). MS (m/e): 228 ($M^+ + 2$, 0.26), 227 ($M^+ + 1$, 1.30), 226 (M^+, 1.60), 195, 161, 150, 141, 131, 127, 126, 125, 118, 103, 97, 77, 51. IR: ν_{max} 3065, 2955, 1723, 1615, 1550, 1448, 1435, 1305, 1238, 1170, 1151, 1086, 970, 821, 756, 738, 698, 680 cm^{-1}.

(*E*)-1-(Phenylsulfonyl)propene (**6ad**)[7]

White crystals; mp 67–68°C (lit. 67–68°C). ^{1}H NMR: δ 2.01 (dd, $J = 7.0$, 1.7 Hz, 3H), 6.33 (dq, $J = 15.0$, 1.7 Hz, 1H), 6.90 (dq, $J = 15.0$, 7.0 Hz, 1H), 7.48–7.52 (m, 2H), 7.59–7.63 (m, 1H), 7.74–7.84 (m, 2H). IR: ν_{max} 3062, 2955, 1620, 1550, 1448, 1375, 1320, 1160, 1080, 971, 820, 756, 738, 695 cm^{-1}.

Phenylsulphonylethene (**6ae**)[7]

White crystals; mp 65–66°C (lit. 67–68°C). 5.72 (dd, $J = 10.1$, 2.1 Hz, 1H), 6.32 (dd, $J = 17.0$, 10.1 Hz, 1H), 6.41 (dd, $J = 16.9$, 2.1 Hz, 1H), 7.63–7.66 (m, 2H), 7.75–7.77 (m, 1H), 7.83–7.90 (m, 2H). IR: ν_{max} 3060, 2955, 1615, 1550, 1448, 1320, 1160, 1080, 991, 910, 756, 695 cm^{-1}.

(*E*)-2-(*p*-Toluenesulfonyl)styrene (**6ba**)[3a]

White crystals; mp 121–122°C (lit. 121–122°C).^{1}H NMR: δ 2.45 (s, 3H), 6.86 (d, $J = 15.2$ Hz, 1H), 7.35 (d, $J = 8.0$ Hz, 2H), 7.36–7.41 (m, 3H), 7.46–7.51 (m, 2H), 7.65 (d, $J = 15.4$ Hz, 1H), 7.82 (d, $J = 8.1$ Hz, 2H). IR: ν_{max} 3061, 2925, 1613, 1597, 1450, 1316, 1305, 1145, 1085, 973, 860, 746, 665, 635 cm^{-1}.

(*E*)-3-(*p*-Toluenesulfonyl)acrylonitrile (**6bb**)[3a]

White crystals; mp 132–133°C (lit. 132–134°C).^{1}H NMR: δ 2.50 (s, 3H), 6.51 (d, $J = 15.7$ Hz, 1H), 7.22 (d, $J = 15.7$ Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 2H), 7.79 (d, $J = 8.1$ Hz, 2H). IR: ν_{max} 3068, 2231, 1597, 1323, 1150, 1086, 955, 836, 802, 666, 585 cm^{-1}.

(*E*)-1-(*p*-Toluenesulfonyl)pentene (**6bf**)[2d]

Colorless oil. ^{1}H NMR: δ 0.92 (t, $J = 7.0$ Hz, 3H), 1.43–1.54 (m, 2H), 1.92–1.98 (m, 2H), 2.51 (s, 3H), 6.32 (dt, $J = 15.1$, 1.6 Hz,1H), 6.94 (dt, $J = 15.1$, 6.9 Hz, 1H), 7.41 (d, $J = 8.1$ Hz, 2H), 7.78 (d, $J = 8.1$ Hz, 2H). IR: $\nu_{\max}$ 3064, 2926, 2875, 1625, 1596, 1378, 1321, 1155, 1085, 976, 835, 800, 668 cm^{-1}.

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