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A facile solid-phase synthesis of vinyl ethers using a selenium traceless linker

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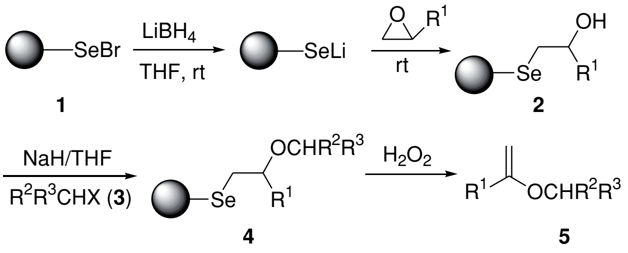
A simple, efficient and environmentally friendly procedure for the solid-phase synthesis of vinyl ethers in good yields and purities by reaction of polystyrene-supported 2-hydroxyalkyl selenide with primary or secondary organic halides and subsequent oxidation–elimination with a traceless linker strategy is described.

Keywords: solid-phase organic synthesis, selenium traceless linker, vinyl ether, oxidation–elimination

Vinyl ethers are valuable intermediates that can be used in a wide array of chemical transformations[1] as well as for the formation vinyl polymer materials[2] containing oxygen which are expected to degrade easily in nature. Practically, vinyl ethers are prepared by the reaction of acetylene with alcohols that was developed by Reppe.[3] However, this reaction must be carried out under severe conditions at high pressure and temperature in the presence of KOH as a catalyst. Several other methods have been reported for the preparation of vinyl and alkenyl ethers: for instance, mercury-catalysed transvinylation of alcohols with vinyl ethers,[4] elimination of the alcohol moiety or hydrogen bromide from acetals or α-bromo ethers, respectively,[5,6] isomerisation of allyl ethers,[7] carbometalation of alkynic ethers[8] and ester methylenation promoted by metal-complexes.[9] Recently, iridium complex-promoted coupling of vinyl acetate with alcohols[10] has also been reported. However, most of these methods have drawbacks such as harsh reaction conditions, laborious manipulation and low overall yields, or in some cases, the reactions conditions are unsuitable for sensitive substrates, toxic compounds are used or some reagents are not readily available. Organoselenium reagents are now commonly used as powerful tools for introducing new functional groups into organic substrates under extremely mild conditions.[11] For example, the phenylseleno group is readily converted into a leaving group giving access to carbon-carbon double bonds *via* oxidation followed by β-elimination. However, organoselenium reagents always have a foul smell and are toxic, which is a problem in organic synthesis. Recently, the use of the selenium reagents immobilised on a polymer-resin has provided significant advantages, including decreased volatility and simplification of reaction work-up.[12] In connection with our interest in solid-phase organoselenium chemistry,[13] here, we report a convenient and efficient solid-phase synthetic approach to vinyl ethers based on a novel polymer-supported 2-hydroxyalkyl selenide **2** (Scheme 1).



Scheme 1

The resin **2a–2c** was easily prepared in a few steps from cross-linked (1%) polystyrene by reaction of polystyrene-supported lithium selenide [12a] with three different epoxides. The IR spectra of resin **2a–2c** showed a large hydroxyl absorption near 3600 cm^{-1} and 3380 cm^{-1}, and bands at 1065 cm^{-1} (C–O). Resin **2** can be stored at room temperature for several months or even a year without diminution of capacity or the liberation of disagreeable odours. With the resin **2** in hand, the *O*-alkylation reaction was investigated starting from 2-hydroxy-2-phenylethyl selenide resin (**2a**) with allyl bromide (**3a**) in THF in the presence of sodium hydride, and **2a** was easily *O*-alkylated using a standard solution-phase method[14] to afford polystyrene-supported 2-(allyloxy)-2-phenylethylselenide (**4a**), which was characterised by its IR spectrum featuring a C=C stretch at 1640 cm^{-1}, a C–O–C stretch at 1060 cm^{-1}, and almost complete disappearance of the hydroxyl absorption.

As expected, oxidation-elimination of resin **4a** was very rapid and efficient with excess of 30% hydrogen peroxide at room temperature to afford 1-phenyl-1-(3-propenoxy)ethene

Table 1 Yields and purities of vinyl ethers

Entry	R^1 (**2**)	R^{2}R^{3}CHX (**3**)	Product	Yield/%[a]	Conversion/%[b]
1	C_6H_5 (2a)	CH_2=$CHCH_2Br$ (3a)	5a	88	95
2	C_6H_5 (2a)	CH_3CH_2Br (3b)	5b	84	94
3	C_6H_5 (2a)	CH_3I (3c)	5c	90	94
4	C_6H_5 (2a)	Propargyl bromide (3d)	5d	78	88
5	C_6H_5 (2a)	$(CH_3)_2CHBr$ (3e)	5e	74	85
6	C_6H_5 (2a)	3-Cyclohexenyl bromide (3f)	5f	85	95
7	C_6H_5 (2a)	$C_6H_5CH_2Cl$ (3g)	5g	88	92
8	$C_6H_5OCH_2$ (2b)	CH_2=$CHCH_2Br$ (3a)	5h	87	93
9	$C_6H_5OCH_2$ (2b)	CH_3CH_2Br (3b)	5i	86	90
10	*p*-$CH_3C_6H_4OCH_2$ (2c)	CH_3CH_2Br (3b)	5j	85	92

[a] Overall yield based on polymer-supported selenium bromide (1.18 mmol Br/g).
[b] Determined by HPLC of crude cleavage product.

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(**5a**) in 88% yield and high purity of crude material (95 % by HPLC analysis). The residual resin, polystyrene-supported phenylseleninic acid, was obtained as a by-product, whose IR data were identical to the previously reported data.[15] The polystyrene-supported phenylseleninic acid could be converted into polymer-supported selenium lithium for reuse by treatment with KI/$Na_2S_2O_3$[16] followed by $LiBH_4$. For example, 1-phenyl-1-(3-propenoxy)ethene (**5a**) was obtained in 82% yield under the same reaction conditions using the recovered selenium lithium resin (second run), and in 75% yield after second recycle (*i.e.* third run). It was shown that recycling 2–3 times led to a gradual deterioration of activity of the resin.

To evaluate the scope of this transformation, a variety of primary and secondary organic halides were subjected to the reaction conditions to afford the corresponding vinyl ethers in 74-90% yield and good purities shown in Table 1. However, it is worth noting that the yields of vinyl ethers **5d** and **5e** (Entries **4** and **5**, Table 1) were relatively low under the same reaction conditions, which may result from the corresponding *O*-prop-2-ynylation and *O*-isopropylation being effected in poorer yields than the other *O*-alkylations. In particular, secondary halide (**3e**) may easily undergo elimination rather than substitution under the basic conditions. Further study on the reaction of resin **2a** with a tertiary halide such as *t*-butyl chloride was examined. However, only a 25% isolated yield of 1-butoxy-1-phenylethene (**5k**) was obtained. Obviously, *t*-butyl chloride would tend to mainly undergo elimination rather than substitution under the reaction conditions. Additionally an attempt to prepare aryl vinyl ether, using phenyl bromide instead of primary or secondary halides was made but no reaction was observed in a similar procedure to the above.

In summary, a convenient, efficient, and environmentally friendly route for the solid-phase synthesis of vinyl ethers by the alkylation of polymer-supported 2-hydroxyalkyl selenide with primary or secondary organic halides and subsequent oxidation-elimination has been developed. A simple workup procedure replaces the time-consuming isolation and purification steps in the corresponding solution-phase synthesis. This methodology is applicable for the construction of libraries of vinyl ethers.

Experimental

^{1}H NMR (400 MHz) spectra were recorded on a Bruker Avance (400 MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as internal standard. 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. Styrene oxide was commercially available and the other two epoxides were prepared according to the literature procedure.[17] THF was distilled under N_2 from sodium/benzophenone immediately prior to use. Organic halides were obtained from commercial suppliers and used without further purification.

Preparation of vinyl ethers; general procedure

Under a nitrogen atmosphere, to polystyrene-supported selenium bromide **1** (1.0 g, 1.18 mmol Br/g, the loading of functional Br was analysed by elementary analysis) swelled in THF (10 ml) for 30 min was added $LiBH_4$ (2.5 mmol). After 1 h with stirring at room temperature, a solution of the epoxide (2.5 mmol) in THF (2 ml) was added over 10 min and the mixture was stirred for 12 h. The resin **2** was collected by filtration and washed successively with H_2O (2 × 20 ml), THF (2 × 5 ml) and CH_2Cl_2 (2 × 5 ml) and then dried under reduced pressure. To resin **2** (1.0 mmol) swelled in THF (10 ml) at room temperature for 30 min was added sodium hydride (0.04 g, 60% dispersion, 1.5 mmol). After 1 h with stirring at room temperature, a solution of the organic halide (2.0 mmol) in dry THF (4 ml) was then added over 15 min. The mixture was refluxed for 2 h and then cooled gradually to room temperature and filtered. The resin **4** was 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). The washed resin **4** was preswollen with THF (15 ml), followed by the treatment with 30% hydrogen peroxide (1 ml, 11.6 mmol). The reaction suspension was stirred at room temperature for 30 min, and then the resin was filtered off and rinsed with ether (5 × 5 ml). The organic phase was washed with saturated $NaHCO_3$ solution (10 ml), brine (10 ml) and twice with water (2 × 10 ml), dried over magnesium sulfate and concentrated to give the crude products, which were purified by flash silica gel column chromatography (CH_2Cl_2/hexane, 10:90) to afford the final products **5** for ^{1}H NMR analysis.

The residual resin, polystyrene-supported phenylselenimie acid, was then treated successively with KI/$Na_2S_2O_3$ and $LiBH_4$,[16] followed by the corresponding epoxide to afford resin **2** for recycling.

1-Phenyl-1-(3-propenoxy)ethene (**5a**): Colourless oil. (Lit.[9b] Oil). ^{1}H NMR: δ = 6.88–6.45 (m, 2 H), 7.01–6.84 (m, 3 H), 5.81–6.27 (m, 1H), 5.60–5.14 (m, 2H), 4.65 (d, *J* = 3.1 Hz, 1H), 4.40–4.11 (m, 2H), 4.16 (d, *J* = 3.1 Hz, 1H). IR (film) 3056, 2974, 2850, 1645, 1622, 1595, 1495, 1242, 1100, 1044, 991, 912, 812 cm^{-1}.

1-Ethoxy-1-phenylethene (**5b**): Colourless oil. (Lit.[9d] Oil). ^{1}H NMR: δ = 7.68–7.56 (m, 2 H), 7.19–7.07 (m, 3 H), 4.60 (d, *J* = 2.1 Hz, 1H), 4.20 (d, *J* = 2.1 Hz, 1H), 3.74 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). IR (film) 3056, 2975, 2852, 1632, 1592, 1495, 1378, 1244, 1096, 1045, 990, 813 cm^{-1}.

1-Methoxy-1-phenylethene (**5c**): Colourless oil. (Lit.[9b] Oil). ^{1}H NMR: δ = 7.65–7.52 (m, 2 H), 7.18–7.04 (m, 3 H), 4.58 (d, *J* = 2.0 Hz, 1H), 4.21 (d, *J* = 2.0 Hz, 1H), 3.71 (s, 3H). IR (film) 3057, 2974, 2855, 1634, 1593, 1495, 1380, 1243, 1094, 1045, 988, 812 cm^{-1}.

1-Phenyl-1-(3-propynyloxy)ethene (**5d**): Colourless oil. ^{1}H NMR: δ = 6.92–6.57 (m, 2 H), 7.04–7.02 (m, 3 H), 4.68 (d, *J* = 3.0 Hz, 1H), 4.22 (d, *J* = 3.0 Hz, 1H), 4.16 (dd, *J* = 15.6, 2.4 Hz, 1H), 3.90 (dd, *J* = 15.6, 2.4 Hz, 1H), 2.41 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR: δ = 158.7, 136.7, 132.1, 129.2, 126.8, 126.0, 80.1, 74.5, 56.7. IR (film) 3280, 3059, 2972, 2851, 2212, 1636, 1595, 1495, 1354, 1245, 1102, 1044, 990, 910, 665 cm^{-1}. EI-MS: *m/z* 158.2 [M$^+$]. Anal. Calcd for $C_{11}H_{10}O$: C, 83.5; H, 6.4. Found: C, 83.6; H, 6.4.

1-Isopropoxy-1-phenylethene (**5e**): Colourless oil. (Lit.[9b] Oil). ^{1}H NMR: δ = 7.48–7.21 (m, 2 H), 7.10–7.01 (m, 3 H), 4.56 (d, *J* = 2.1 Hz, 1H), 4.25–4.32 (m, 1H), 4.03 (d, *J* = 2.1 Hz, 1H), 1.32 (d, *J* = 7.2 Hz, 6H). IR (film) 3058, 2976, 2845, 1635, 1558, 1495, 1384, 1375, 1240, 1101, 1042, 989, 810 cm^{-1}.

1-(3-Cyclohexenyloxy)-1-phenylethene (**5f**): Colourless oil. ^{1}H NMR: δ = 7.77–7.73 (m, 2 H), 7.15–7.06 (m, 3 H), 5.94 (dd, *J* = 10, 2.4 Hz, 1H), 5.70 (dt, *J* = 10, 2.8 Hz, 1 H), 4.75 (d, *J* = 2.4 Hz, 1 H), 4.56 (bs, 1 H), 4.20 (d, *J* = 2.4 Hz, 1 H), 1.88–1.60 (m, 5 H), 1.36–1.31 (m, 1 H). ^{13}C NMR: δ = 158.9, 137.7, 131.3, 128.5, 128.3, 126.8, 126.0, 83.3, 70.4, 28.3, 25.3, 19.4. IR (film) 3059, 2972, 2851, 1643, 1620, 1590, 1496, 1241, 1101, 1042, 978, 910, 810 cm^{-1}. EI-MS: *m/z* 200.3 [M$^+$]. Anal. Calcd for $C_{14}H_{16}O$: C, 84.0; H, 8.05. Found: C, 83.9; H, 8.15.

1-Benzyloxy-1-phenylethene (**5g**): Colourless oil. (Lit.[9b] Oil). ^{1}H NMR: δ = 7.60–7.01 (m, 10 H), 4.81 (s, 2H), 4.52 (d, *J* = 3.2 Hz, 1H), 4.12 (d, *J* = 3.2 Hz, 1H). IR (film) 3059, 2975, 2844, 1632, 1559, 1494, 1445, 1241, 1100, 1039, 985, 812 cm^{-1}.

1-Phenoxymethyl-1-(3-propenoxy) ethene (**5h**): Colourless oil. ^{1}H NMR: δ = 6.95–6.86 (m, 2 H), 7.27–7.20 (m, 3 H), 5.94–5.84 (m, 1H), 5.25 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.15 (d, *J* = 10.4 Hz, 1H), 4.12 (s, 2H), 4.09 (d, *J* = 4.8 Hz, 2H), 3.15–3.26 (m, 2H). ^{13}C NMR: δ = 158.6, 134.7, 132.6, 129.2, 127.0, 121.0, 117.5, 114.6, 71.4, 29.3.IR (film) 3060, 2923, 2856, 1622, 1600, 1495, 1244, 1096, 1079, 925, 814, 737, 691 cm^{-1}. EI-MS: *m/z* 190.2 [M$^+$]. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.8; H, 7.4. Found: C, 75.8; H, 7.5.

1-Ethoxy-1-phenoxymethylethene (**5i**): Colourless oil. ^{1}H NMR: δ = 7.52–7.19 (m, 2 H), 6.86–7.00 (m, 3 H), 4.08 (d, *J* = 4.8 Hz, 2H), 3.59 (q, *J* = 7.1 Hz, 2H), 3.26 (dd, *J* = 12.8, 6.0 Hz, 1H), 3.23 (dd, *J* = 12.8, 6.0 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR: δ = 158.6, 132.5, 129.4, 126.9, 121.0, 114.6, 65.9, 29.5, 15.2. IR (film): ν = 3059, 2975, 2872, 1625, 1600, 1495, 1383, 1243, 1094, 1045, 882, 813, 691 cm^{-1}. EI-MS: *m/z* 178.2 [M$^+$]. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.1; H, 7.9. Found: C, 74.1; H, 8.0.

1-Ethoxy-1-(p-methylphenoxymethyl) ethene (**5j**): Colourless oil. ^{1}H NMR: δ = 7.52 (d, *J* = 8.8 Hz, 2 H), 6.77 (d, *J* = 8.8 Hz, 2 H), 4.06 (d, *J* = 3.2 Hz, 2H), 3.60 (q, *J* = 7.2 Hz, 2H), 3.24 (dd, *J* = 12.8, 6.0 Hz, 1H), 3.17 (dd, *J* = 12.8, 6.0 Hz, 1H), 2.31 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR: δ = 156.7, 132.6, 129.2, 127.2, 121.1, 114.5, 70.0, 29.6, 20.5, 15.3; IR (film) 3057, 2975, 2871, 1624, 1600, 1494, 1385, 1244, 1095, 1045, 880, 812, 690 cm^{-1}. EI-MS: *m/z* 192.2

[M^+]. Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.0; H, 8.4. Found: C, 75.0; H, 8.4.

1-Butoxy-1-phenylethene (**5k**): Colourless oil. (Lit.^{9b} Oil). ^{1}H NMR: δ = 7.44–7.19 (m, 2 H), 7.12–6.95 (m, 3 H), 4.65 (d, J = 2.0 Hz, 1H), 4.28 (d, J = 2.0 Hz, 1H), 1.34 (s, 9H). IR (film) 3058, 2976, 2845, 1635, 1558, 1500, 1390, 1365, 1240, 1101, 1042, 990, 810 cm^{-1}.

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