Solid-phase organic synthesis of (*E*)-1-nitroalkenes based on polystyrene-supported selenonitromethane

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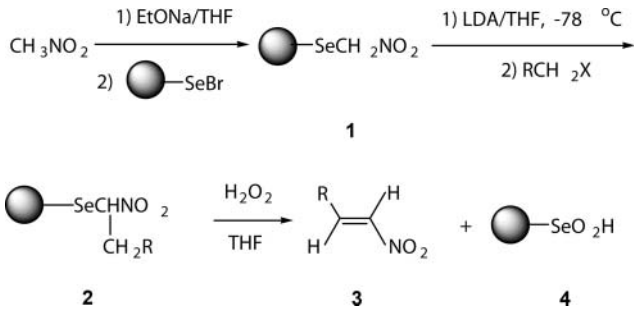
A facile method for solid-phase organic synthesis of (*E*)-1-nitroalkenes from polystyrene-supported selenonitromethane has been developed. Polymer-supported organic reagents are useful for the rapid preparation of small organic molecules.

Keywords: solid-phase organic synthesis, polystyrene-supported selenonitromethane, (*E*)-1-nitroalkenes

Polymer-supported organic reagents have been applied to the rapid preparation of small organic molecules because they can provide attractive and practical methods for combinatorial chemistry and solid-phase organic synthesis (SPOS).[1,2] Organoselenium reagents have been increasingly used as a powerful tool for introducing new functional groups into organic substrates under extremely mild conditions.[3] For example, the phenylseleno group is readily converted to a leaving group giving access to the carbon–carbon double bond *via* oxidation followed by *β*-elimination.[4] Additionally, a selenium-stabilised carbanion has played an important role in organic synthesis because of its easy availability and particularly good nucleophile, which allows the formation of new functionalised carbon–carbon bonds when it is used to react with compounds bearing an electrophilic carbon atom.[3,5] Moreover, the polymeric selenium reagents [6–9] have now been developed for SPOS with a combined advantage of decrease volatility and simplification of product work-up. Nitroalkenes are synthetically important products since they have been used as important reagents as Michael acceptors or dienophiles in the Diels–Alder reactions.[10] Furthermore, nitroalkenes prepared from aromatic aldehydes are especially useful for natural product synthesis.[11,12] For these reasons, various methods have been described for their preparation.[13–21] Although many solution phase methods have been explored for the synthesis of nitroalkenes, to the best of our knowledge, no solid-phase synthetic approaches have been reported. In connection with our interest in solid-phase organoselenium chemistry,[22] we now report the preparation of a novel polymer-bound selenonitromethane reagent and its application for the SPOS synthesis of (*E*)-1-nitroalkenes, as shown in Scheme 1. Compared with reported methods, this method offers significant advantages including decrease volatility and convenient handing of the polymeric selenium reagents, as well as good yields and simplification of product work-up.

In our initial experiment, polymer-supported selenonitromethane (**1**) was prepared by treatment of nitromethane with *n*-butyllithium in THF at 0 °C under nitrogen, followed by treatment with the cross-linked (1%) polystyrene-bound selenium bromide (dark-red resin, Br: 1.20 mmol g^{-1}).[6] However, sodium ethoxide proved to be effective instead of *n*-butyllithium. Thus, the reaction of nitromethane with sodium ethoxide in THF at room temperature in an open vessel, subsequently treated with polystyrene-bound selenium bromide, afforded polystyrene-supported selenonitromethane (**1**) in nearly quantitative yield, monitored by FT-IR showing a typical stretching vibration of the nitro group at 1550 cm^{-1}. In addition, elemental analysis revealed a loading of resin **1** (1.21 mmol N g^{-1}) and all its bromine was found to have been lost, indicating the performed bromine with nitromethyl group exchange has gone to completion. It should be noted, that the nitro-(phenylseleno)-methane[23] is relatively unstable and gradually decomposes to give a fair amount of crystalline diphenyl diselenide after one day even when kept in a freezer under a nitrogen atmosphere. However, this new reagent appeared to be quite stable in air at ambient temperature and could be stored at room temperature for several weeks without diminution of capacity nor the liberation of disagreeable odours.



Scheme 1

Reaction of the lithio derivative of resin **1** with various primary alkyl halides gave the new α-seleno nitroalkane resin **2**, which could not be reliably analysed with FTIR. Hence we carried out next cleavage reaction directly after washing the resin **2** using solvents. Treatment of resin **2** with 30% hydrogen peroxide at room temperature afforded the corresponding (*E*)-1-nitroalkenes **3** in good yields (90–95%) and with good purities (> 95%) (Table 1).

It should be noted that (*E*)-1-nitroalkenes **3a**–**h** are formed exclusively, which was confirmed by the coupling constants (J = 13.4–14.2 Hz) between the two vinyl protons in their ^{1}H NMR spectra. The residual resin, polystyrene-supported phenylseleninic acid **4**, whose IR data was identical to that of the previously reported[24] and showed no residual nitro group absorption indicating the oxidation-elimination was complete.

In summary, a novel and efficient procedure for the traceless solid-phase synthesis of (*E*)-1-nitroalkenes with good yields and purities using polymer-supported selenonitromethane with advantages of decrease volatility and simplification of product work-up has been developed.

Table 1 Yields and purities of (*E*)-1-nitroalkenes (**3a**–**h**)

Entry	RCH_2X	Product	Yield/%[a]	Purity/%[b]
1	$C_6H_5CH_2Cl$	**3a**	95	98
2	4-$CH_3C_6H_4CH_2Br$	**3b**	92	96
3	4-$CH_3OC_6H_4CH_2Br$	**3c**	94	97
4	4-$ClC_6H_4CH_2Br$	**3d**	90	98
5	4-$NO_2C_6H_4CH_2Cl$	**3e**	91	95
6	2-furylmethyl bromide	**3f**	90	96
7	$C_6H_5CH_2CH_2Br$	**3g**	92	98
8	n-$C_6H_{13}CH_2Br$	**3h**	90	97

[a] Isolated yields were based on the functional loading of resin **1** (1.21 mmol N g^{-1}).
[b] Determined by HPLC of crude cleavage product.

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Experimental

Melting points were uncorrected. ^{1}H 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 tetramethylsilane (TMS) as internal standard. FT-IR spectra were taken on a Perkin-Elmer SP One FT-IR spectrophotometer. HPLC analysis was performed on Agilent 1100 automated system having a photodiode array (PDA) detector (λ_{max} = 254 nm used for this study) using a gradient with CH_3CN/H_2O (1 mL min^{-1}) on a RP-18e column (150×4.6 mm). Polystyrene (H 1000, 100–200 mesh, cross-linked with 1% divinylbenzene) for preparation of selenium bromide resin[6] was purchased from Nankai University, and the other starting materials were purchased from commercial suppliers and used without further purification. THF was distilled from sodium-benzophenone immediately prior to use.

Preparation of polystyrene-supported selenonitromethane **1**

A solution of sodium ethoxide (10.0 mmol) in ethanol (15 mL) was added to the stirred solution of nitromethane (10.0 mmol) in THF (10 mL) at room temperature. After 30 min with stirring at room temperature, polystyrene-supported selenium bromide was added (1.0 g, 1.20 mmol Br g^{-1}, the loading of functional Br was analysed by elementary analysis) and the mixture was shaken for 1 h and then diluted with water (5 mL). The resin was collected on a filter and washed successively with H_2O (2×20 mL), THF (3×5 mL) and CH_2Cl_2 (3×5 mL), and then dried under vacuum overnight to afford pale yellow polystyrene-supported selenonitromethane **1** (98.3% yield from selenium bromide resin) with a loading value of 1.21 mmol N g^{-1} (theoretical loading of the resin 1.23 mmol N g^{-1}). IR (KBr): ν = 1550 (NO_2) cm^{-1}.

*Synthesis of (E)-1-nitroalkenes (***3a**–**h***); general procedure*

To a solution of 2.0 mmol of lithium diisopropylamide (LDA) (2.2 mmol of diisopropylamine, 2.0 mmol of n-butyllithium) in anhydrous THF (10 mL) at –78 °C under nitrogen atmosphere was added resin **1** (826 mg, 1.0 mmol). After shaking at –78 °C for 1 h, the primary alkyl halide (3.0 mmol in 5 mL THF) was added dropwise. Then the mixture was warmed up gradually to room temperature and shaken for 4 h. After neutralisation with 1% hydrochloric acid, the resin **2a**–**h** was collected on a filter and washed successively with H_2O (3 × 10 mL), THF (3 × 5 mL) and Et_2O (3 × 5 mL). To a suspension of the swollen resin **2a**–**h** in THF (10 mL) was added 0.5 mL of 30% H_2O_2 (5.8 mmol), and the suspension was shaken at room temperature for 30 min, the residual resin was then collected by filtration and washed with CH_2Cl_2 (3 × 10 mL). The filtrate was washed with saturated $NaHCO_3$ (20 mL) and with water, dried over magnesium sulfate and evaporated to give crude products **3a**–**h** with over 95% purity determined by HPLC, which were further purified by passing the crude product through silica gel chromatographic column [ether/hexane as the eluent: 1/4 (v/v)] affording the pure products for their structures analyses.

(E)-1-Nitro-2-phenylethylene (**3a**): Pale yellow solid (commercial), m.p. 57–58 °C (lit.[25] 56–58 °C); ^{1}H NMR: δ 8.00 (d, *J* = 13.6 Hz, 1H), 7.64–7.46 (m, 6H); ^{13}C NMR: δ 138.8, 136.8, 131.7, 129.7, 129.1, 128.8; IR (KBr): ν_{max} = 1640, 1526, 1336 cm^{-1}.

(*E*)*-1-(4-Methylphenyl)-2-nitroethylene* (**3b**): Pale yellow solid (commercial), m.p. 102–103 °C (lit.[25] m.p. 102–104 °C); ^{1}H NMR: δ 7.99 (d, *J* = 13.8 Hz, 1H), 7.57 (d, *J* = 13.8 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR: δ 142.8, 138.9, 135.9, 129.9, 128.7, 126.9, 21.4; IR (KBr): ν_{max} = 1645, 1523, 1320 cm^{-1}.

(E)-1-(4-Methoxyphenyl)-2-nitroethylene (**3c**): Pale yellow solid (commercial), m.p. 88–89 °C (lit.[25] 86–88 °C); ^{1}H NMR: δ 7.88 (d, *J* = 14.2 Hz, 1H), 7.48–7.42 (m, 3H), 6.90 (d, *J* = 8.6 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR: δ 162.0, 138.7, 134.6, 130.8, 128.4, 114.6, 55.2; IR (KBr): ν_{max} = 1649, 1520, 1320 cm^{-1}.

(E)-1-(4-Chlorophenyl)-2-nitroethylene (**3d**): Pale yellow solid (commercial), m.p. 113–115 °C (lit.[25] m.p. 112–116 °C); ^{1}H NMR: δ 7.87 (d, *J* = 14.0 Hz, 1H), 7.65 (d, *J* = 14.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR: δ 138.3, 137.6, 137.4, 130.2, 129.7, 128.5; IR (KBr): ν_{max} = 1642, 1522, 1322 cm^{-1}.

(E)-2-Nitro-1-(4-nitrophenyl)ethylene (**3e**): Yellow solid, m.p. 204–205 °C (lit.[25] 204–206 °C); ^{1}H NMR: δ 8.06 (d, *J* = 8.4 Hz, 2 H), 7.85 (d, *J* = 14.0 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 14.0 Hz, 1H); ^{13}C NMR: δ 148.2, 139.6, 132.4, 129.5, 128.4, 123.5; IR (KBr): ν_{max} = 1652, 1525, 1335 cm^{-1}.

(E)-2-(2-Nitrovinyl)furan (**3f**): Pale yellow solid, m.p. 70–72 °C (lit.[25] m.p. 69–71 °C); ^{1}H NMR: δ 7.80 (d, *J* = 13.4 Hz, 1H), 7.60 (s, 1H), 7.55 (d, *J* = 13.4 Hz, 1H), 6.90 (d, *J* = 3.4 Hz, 1H), 6.59–6.57 (m, 1H); ^{13}C NMR: δ 146.5, 146.3, 134.5, 125.1, 119.6, 113.0; IR (KBr): ν_{max} = 1650, 1520, 1320 cm^{-1}.

(E)-3-Phenyl-1-nitroprop-1-ene (**3g**): Yellow oil (lit.[18] yellow oil); ^{1}H NMR: δ 7.47–7.04 (m, 6H), 6.86 (d, *J* = 13.5 Hz, 1H), 3.50 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR: δ 141.0, 140.3, 135.6, 128.8, 128.6, 127.3, 34.5; IR (film): ν_{max} = 1644, 1560, 1356 cm^{-1}.

(E)-1-Nitronon-1-ene (**3h**): Pale yellow oil (lit.[18] pale yellow oil); ^{1}H NMR: δ 7.26 (dt, *J* = 13.6, 6.4 Hz, 1H), 6.96 (d, *J* = 13.6 Hz, 1H), 2.30–2.22 (m, 2H), 1.55–1.06 (m, 10H), 0.88 (t, *J* = 6.8, 3H); ^{13}C NMR: δ 1428, 139.6, 31.5, 28.9, 28.6, 28.4, 27.6, 22.6, 13.9); IR (film): ν_{max} = 1645, 1530, 1358 cm^{-1}.

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