Solid-phase organic synthesis of 1-(*E*)-phenylethenyl-4-substituted-1,2,3-triazoles from polystyrene-supported (2-azido-1-phenyl)ethyl selenide

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A facile method for solid-phase organic synthesis of 1-(*E*)-phenylethenyl-4-substituted-1,2,3-triazoles from polystyrene-supported (2-azido-1-phenyl)ethyl selenide and substituted ethynes has been developed. The advantages of this method include straightforward operation, high yield and purity of the products, as well as lack of odour and good stability of the polymeric reagent.

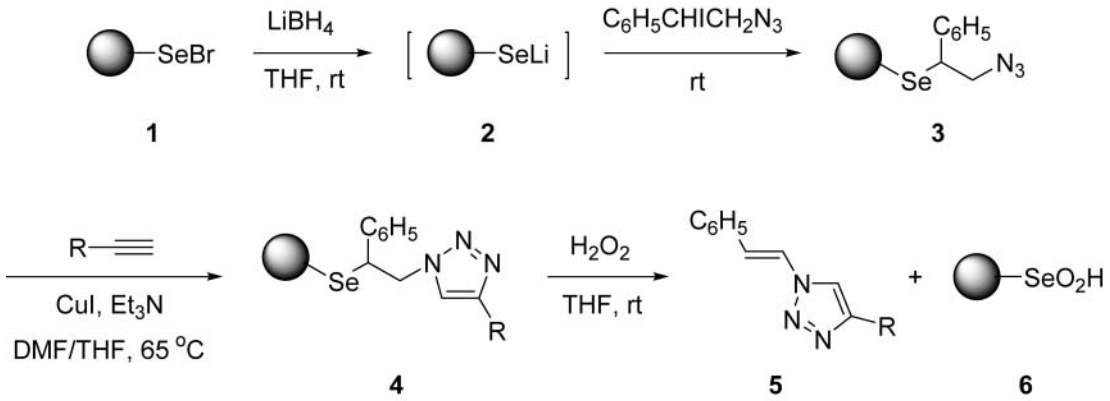
Keywords: Solid-phase organic synthesis, polystyrene-supported (2-azido-1-phenyl)ethyl selenide, 1-(*E*)-phenylethenyl-4-substituted-1,2,3-triazoles, cycloaddition, oxidation-elimination

Solid-phase organic synthesis (SPOS) has gained widespread acceptance in combinatorial chemistry for the high-speed synthesis of structurally diverse compounds for use in drug discovery programmes. Synthesis on a solid support shows a number of advantages over solution chemistry. The most salient one is the possibility of applying excesses of reagents and removing them without involving time-consuming separation techniques.[1] Organoselenium reagents have been increasingly used as powerful tools for introducing new functional groups into organic substrates under extremely mild conditions.[2] For example, the phenylseleno group is readily converted into a leaving group giving access to a carbon–carbon double bond by oxidation followed by β-elimination.[3] Moreover, the polymeric selenium reagents[4–7] have been now developed for SPOS with the combined advantage of a decrease in volatility and a simplification of product work-up.

1,2,3-Triazoles are most useful heterocycles[8] and have been widely used in many research fields such as materials and chemical and biological sciences.[9] Because of their importance, the synthesis of 1,2,3-triazoles from various azides and alkynes has been widely studied in the solution phase.[10–12] Nevertheless, among them, little attention has been paid to the preparation of 1-phenylethenyl-4-substituted-1,2,3-triazoles.[13–15] To our knowledge, only a few papers have reported the solid-phase synthesis of 1,2,3-triazoles using a selenium linker up to now.[16–18] Furthermore, there are no reported examples involving the SPOS of phenylethenyl-4-substituted-1,2,3-triazoles. Therefore, the development of a versatile SPOS procedure for the synthesis of functionalised 1,2,3-triazoles containing the phenylethenyl moiety is timely. In continuation of our interest in solid-phase organoselenium chemistry,[19] we now describe a new simple and efficient traceless solid-phase synthetic approach to 1-(*E*)-phenylethenyl-4-substituted-1,2,3-triazoles based on a novel polystyrene-supported (2-azido-1-phenyl)ethyl selenide reagent (Scheme 1).

As showed in Scheme 1, polystyrene-supported selenenyl bromide (**1**) [4] (dark-red resin, Br: 1.25 mmol g^{-1}) was chosen as the starting material in our initial experiments. Polymeric selenium resin **1** as prepared from polystyrene by lithiation and quenching with MeSeSeMe, followed by treatment with bromine. Reaction of a THF-swollen suspension of resin **1** with $LiBH_4$, followed by treatment with (2-azido-1-iodoethyl)-benzene[20] to afford polymer-supported (2-azido-1-phenyl)ethyl selenide (**3**) proceeded readily in excellent yield (>95%, determined by elemental analysis of the nitrogen: azide loading of 1.12 mmol g^{-1}), which was amenable to FTIR monitoring for the appearance of the characteristic azido band at 2092 cm^{-1}. It should be noted, that the non-supported 2-azido-1-phenyl-1-(phenylseleno)ethane[21] is relatively unstable and gradually decomposes to give a fair amount of crystalline diphenyl diselenide after several days 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 or the liberation of disagreeable and toxic odours.

With resin **3** in hand, [3 + 2] cycloaddition reaction of **3** with various terminal alkynes, the key for the success of this protocol was then investigated. It has been reported that the copper-catalysed alkyne–azide cycloaddition (CuAAC) is a reliable means for the synthesis of 1,4-disubstituted-1,2,3-triazoles exclusively.[9–12] Based on these results, phenylacetylene was



Scheme 1

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chosen for the template reaction with **3**. To optimise reaction conditions, several solvents such as THF, MeCN, DMF, DMSO, *t*-BuOH, CH_2Cl_2, and their co-solvents were tested in the same standard reaction in the presence of catalyst ($CuSO_4$/sodium ascorbate or CuI). After a considerable number of experiments, the 1,3-dipolar cycloaddition of **3** with phenylacetylene was conducted smoothly in DMF/THF (1/2) in the presence of triethylamine and 10 mol% of CuI at 65 °C for 6 h, leading to the polymer-supported (1-phenyl-2-triazolyl)ethyl selenide (**4a**). This transformation seemed to be quantitative, since no characteristic azido absorption at 2092 cm^{-1} could be detected in the FTIR spectrum of **4a** after completing this cycloaddition reaction. In the progress of this transformation, it was found that the signal of the azido group (2092 cm^{-1}) has been distinctly shrunk after 5 h of reaction time, nearly 90% conversion of the azido group depending on the transformation of its IR absorption signal, and another 1h of reaction time led to an almost complete disappearance of the characteristic azido absorption.

Subsequently, treatment of resin **4a** with 30% hydrogen peroxide at room temperature afforded the corresponding 1-phenylethenyl-4-phenyl-1,2,3-triazole (**5a**).[14,15] Without further purification, the crude product **5a** was obtained in high purity (97%, indicated by HPLC analysis) after removal of excess cleavage reagent and evaporation of residual solvent. Then passing the crude product through a flash silica gel column chromatography eluted with ethyl acetate/hexane afforded the pure target molecule **5a** in 90% yield based on the loading of resin **3** (Table 1, entry 1). The residual resin, polystyrene-supported phenylseleninic acid (**6**), whose IR data were identical to those previously reported[22] showed no residual triazolyl group. This was confirmed by nitrogen elemental analysis of resin **6**, indicating that the oxidation-elimination was complete.

To examine the scope of the methodology, a series of 1-phenylethenyl-4-substituted-1,2,3-triazoles (**5a**–**i**) were prepared from different terminal alkynes with resin **3** under the optimised conditions. As seen from Table 1, both aromatic and aliphatic alkynes underwent the reaction smoothly to afford the corresponding products **5a–i** in good to high yields (83–91%) with excellent purities (95–98%). Note that all target compounds were formed with complete (*E*) stereoselectivities, which were confirmed by the coupling constants of the olefinic protons in their ^{1}H NMR spectra. For instance, in the ^{1}H NMR spectrum of 1-*(E)*-phenylethenyl-4-(2-nitrophenoxymethyl)-1,2,3-triazole (**5e**), the coupling constants (J = 14.8 Hz) between the two olefinic protons at δ = 7.76 and 7.22 ppm were observed, which indicated the exclusive production of the *E*-isomer. In addition, the ^{1}H NMR spectrum of **5e** exhibited a distinct singlet at δ = 8.05 ppm for the triazolyl C_5–H proton, and its IR spectrum displayed C=C olefin absorption at 1658 cm^{-1}, and a characteristic band at 1521 cm^{-1}, indicating the presence of a nitro group.

Table 1 Yields and purities of target molecules (**5a**–**h**)

Entry	R	Product	Yield/%[a]	Purity/%[b]
1	C_6H_5	**5a**	90	97
2	4-$CH_3CH_2C_6H_4$	**5b**	91	98
3	2-$CH_3C_6H_4OCH_2$	**5c**	87	97
4	2-$ClC_6H_4OCH_2$	**5d**	86	95
5	2-$NO_2C_6H_4OCH_2$	**5e**	85	97
6	4-$NO_2C_6H_4OCH_2$	**5f**	86	96
7	2-Naphthoxymethyl	**5g**	84	97
8	*n*-C_4H_9	**5h**	83	95

[a] Overall isolated yields based on polystyrene-supported (2-azido-1-phenyl)ethyl selenide **3** (azide loading: 1.12 mmol g^{-1}).
[b] Determined by HPLC of crude cleavage product (λ = 254 nm).

In summary, a facile protocol for the solid-phase synthesis of 1-(*E*)-phenylethenyl-4-substituted-1,2,3-triazoles has been developed based on a traceless selenium linker. Simple work-up, mild reaction conditions and good to high yields make this methodology attractive and suitable for combinatorial library production.

Experimental

Melting points are 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 FTIR spectrophotometer. Microanalyses were performed with a Carlo Erba 1106 Elemental Analyzer. High performance liquid chromatography (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), and chromatographic peak areas were used to calculate the purities of crude products. Polystyrene (H 1000, 100–200 mesh, cross-linked with 1% divinylbenzene) 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.

Synthesis of polystyrene-supported (2-azido-1-phenyl)ethyl selenide (**3**)

According to the reported procedure,[4] polystyrene-supported selenium bromide **1** (loading: 1.25 mmol Br g^{-1}, analysed by elemental analysis) was prepared from polystyrene by lithiation and quenching with MeSeSeMe, followed by treatment with bromine. To **1** (1.0 g), swelled in THF (10 mL) for 30 min, was added $NaBH_4$ (3 mmol) under nitrogen. After 1 h with stirring at room temperature, a solution of 2-azido-1-phenyl-1-(phenylseleno)ethane (3 mmol) in THF (2 mL) was added slowly and the mixture was stirred for 5 h. The resin was collected on a filter and washed successively with H_2O, CH_3OH, CH_2Cl_2 (2×10 mL of each), and then dried under reduced pressure overnight to afford pale yellow polystyrene-supported (2-azido-1-phenyl)ethyl selenide (**3**) (97.3% yield from selenium bromide resin) with an azide loading value of 1.12 mmol g^{-1} (theoretical azide loading of the resin 1.15 mmol g^{-1}). IR (KBr): $\nu_{N=N=N}$ = 2092 cm^{-1}.

Synthesis of 1-(E)-phenylethenyl-4-substituted-1,2,3-triazoles (**5a**–**h**)**;** *general procedure*

To a suspension of the resin **3** (893 mg, 1.0 mmol) pre-swollen in DMF/THF (1:2, 15 mL) was added alkyne (3.0 mmol), CuI (191 mg, 10 mol%) and Et_3N (0.5 mol) and the resulting reaction mixture was heated to 65 °C and shaken for 6 h under an N_2 atmosphere. The resin **4a–h** was then collected by filtration and washed successively with pyridine, CH_2Cl_2, THF and Et_2O (2 × 10 mL of each). Subsequently, the washed resin **4a–h** was suspended in THF (10 mL) and 30% hydrogen peroxide (0.5 mL, 5.8 mmol) was added; 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 **5a**–**h** with over 95% purity determined by HPLC, which was further purified by flash silica gel column chromatography eluted with ethyl acetate/hexane to provide pure product **5a–h** for their structural analysis.

1-(E)-Phenylethenyl-4-phenyl-1,2,3-triazole (**5a**): Pale yellow solid, m.p. 95–96 °C (lit.[14] 96–98 °C); ^{1}H NMR: δ = 7.79–7.77 (m, 2H), 7.72 (s, 1H), 7.42–7.32 (m, 8H), 5.80 (s, 1H), 5.48 (s, 1H); ^{13}C NMR: δ = 146.6, 142.0, 133.7, 129.2, 128.9, 128.0, 127.8, 127.4, 126.4, 124.8, 118.8, 108.4; IR (film): ν = 3061, 1644, 1021, 898, 763 cm^{-1}. Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 17.00. Found: C, 77.56 H, 5.42; N, 17.11%.

1-(E)-Phenylethenyl-4-(4-ethylphenyl)-1,2,3-triazole (**5b**): Pale yellow viscous oil; ^{1}H NMR: δ = 7.90 (s, 1H), 7.71–7.68 (m, 2H), 7.41–7.29 (m, 5H), 7.19–7.12 (m, 2H), 5.78 (s, 1H), 5.47 (s, 1H), 2.60 (q, J = 7.2 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR: δ = 147.7, 144.6, 143.1, 134.7, 129.9, 128.9, 128.4, 127.7, 127.4, 125.8, 119.5, 109.3, 28.7, 15.5; IR (KBr): ν = 3028, 2964, 1642, 1017, 896, 839, 772 cm^{-1}. Anal. Calcd for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26. Found: C, 78.41; H, 6.36; N, 15.38%.

1-(E)-Phenylethenyl-4-(2-methylphenoxymethyl)-1,2,3-triazole (**5c**): Pale yellow solid, m.p. 129–130 °C; ^{1}H NMR: δ = 7.90 (s, 1H), 7.77 (d, *J* = 14.4 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.41–7.32 (m, 3H), 7.19–7.13 (m, 3H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 14.4 Hz, 1H), 5.28 (s, 2H), 2.04 (s, 3H); ^{13}C NMR: δ = 156.4, 145.2, 133.5, 130.8, 129.0, 128.9, 127.0, 126.9, 126.8, 123.0, 122.1, 121.1, 120.0, 111.5, 62.2, 16.3; IR (KBr): ν = 3096, 2927, 1655, 1383, 1021, 950, 752 cm^{-1}. Anal. Calcd for $C_{18}H_{17}ON_3$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.35; H, 5.98; N, 14.30%.

1-(E)-Phenylethenyl-4-(2-chlorophenoxymethyl)-1,2,3-triazole (**5d**): Pale yellow solid, m.p. 106–108 °C; ^{1}H NMR: δ = 7.98 (s, 1H), 7.76 (d, *J* = 15.2 Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.41–7.32 (m, 4H), 7.26–7.19 (m, 2H), 7.15 (d, *J* = 15.2 Hz, 1H), 6.92–6.89 (m, 1H), 5.34 (s, 2H); ^{13}C NMR: δ = 153.7, 144.4, 133.5, 130.4, 129.0, 128.9, 127.9, 126.8, 123.2, 122.9, 122.2, 120.3, 116.2, 114.3, 63.4; IR (KBr): ν = 3086, 1654, 1242, 1018, 969, 750 cm^{-1}. Anal. Calcd for $C_{17}H_{14}ClON_3$: C, 65.49; H, 4.53; N, 13.48. Found: C, 65.60; H, 4.63; N, 13.57%.

1-(E)-Phenylethenyl-4-(2-nitrophenoxymethyl)-1,2,3-triazole (**5e**): Pale yellow solid, m.p. 134–135 °C; ^{1}H NMR: δ = 8.04 (s, 1H), 7.87 (dd, *J* = 8.0, 1.2Hz, 1H), 7.76 (d, *J* = 14.8 Hz, 1H), 7.58–7.54 (m, 1H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.41–7.30 (m, 4H), 7.22 (d, *J* = 14.8 Hz, 1H), 7.10–7.06 (m, 1H), 5.42 (s, 2H); ^{13}C NMR: δ = 151.4, 143.6, 140.2, 134.3, 133.4, 129.0, 128.8, 126.8, 125.7, 122.8, 122.4, 121.2, 120.7, 115.4, 63.7; IR (KBr): ν = 3071, 2957, 1658, 1251, 1044, 957, 862, 775, 693 cm^{-1}. Anal. Calcd for $C_{17}H_{14}O_3N_4$: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.46; H, 4.49; N, 17.48%.

1-(E)-Phenylethenyl-4-(4-nitrophenoxymethyl)-1,2,3-triazole (**5f**): Pale yellow solid, m.p. 149–150 °C; ^{1}H NMR: δ = 8.22–8.19 (m, 2H), 7.99 (s, 1H), 7.77 (d, *J* = 14.8 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.42–7.33 (m, 3H), 7.22 (d, *J* = 14.8 Hz, 1H), 7.11–7.07 (m, 2H), 5.36 (s, 2H); ^{13}C NMR: δ = 163.0, 143.1, 141.9, 133.3, 129.0, 128.8, 126.8, 126.0, 122.7, 122.6, 120.6, 114.9, 62.3; IR (KBr): ν = 3080, 2930, 1655, 1509, 1018, 951, 868, 751 cm^{-1}. Anal. Calcd for $C_{17}H_{14}O_3N_4$: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.23; H, 4.49; N, 17.49%.

1-(E)-Phenylethenyl-4-(2-naphthoxymethyl)-1,2,3-triazole (**5g**): White solid, m.p. 158–160 °C; ^{1}H NMR: δ = 7.97 (s, 1H), 7.97–7.74 (m, 4H), 7.48–7.44 (m, 3H), 7.40–7.34 (m, 5H), 7.23–7.20 (m, 1H), 7.19 (d, *J* = 14.8 Hz, 1H), 5.40 (s, 2H); ^{13}C NMR: δ = 156.1, 144.6, 134.4, 133.5, 129.7, 129.2, 129.1, 128.9, 127.7, 126.9, 126.8, 126.6, 124.0, 122.9, 122.1, 120.1, 118.7, 107.3, 62.0; IR (KBr): ν = 3055, 2917, 1658, 1390, 1043, 951, 837, 749 cm^{-1}. Anal. Calcd for $C_{21}H_{17}ON_3$: C, 77.04; H, 5.23; N, 12.84. Found: C, 76.91; H, 5.35; N, 12.94%.

1-(E)-Phenylethenyl-4-(n-butyl)-1,2,3-triazole (**5h**): Colourless solid, m.p. 90–91 °C (lit.[14] m.p. 92–93 °C); ^{1}H NMR: δ = 7.98 (s, 1H), 7.75 (d, *J* = 14.8 Hz, 1H), 7.42–7.38 (m, 2H), 7.34–7.27 (m, 3H), 7.15 (d, *J* = 14.8 Hz, 1H), 2.70 (t, *J* = 7.2 Hz, 2H), 1.68–1.60 (m, 2H), 1.41–1.39 (m, 2H), 0.98 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR: δ = 147.2, 135.9, 133.9, 128.7, 128.1, 126.9, 125.7, 118.8, 32.3, 26.0, 22.6, 14.1; IR (KBr): ν = 3050, 2923, 1655, 1040, 950, 835, 750, 695 cm^{-1}. Anal. Calcd for $C_{14}H_{17}N_3$: C, 73.98; H, 7.54; N, 18.49. Found: C, 73.85; H, 7.61; N, 18.59%.

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