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Facile Stereoselective Synthesis of (*E*)-1-Arylseleno-Substituted 1,3-Enynes and Their Applications in Synthesis of (*E*)-Enediynes

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Abstract: (*E*)-1-Iodo-2-arylselenoethylenes **1** underwent the Sonogashira coupling reactions with terminal alkynes **2** to afford (*E*)-1-arylseleno-substituted 1,3-enynes **3** in high yields. (*E*)-1-Arylseleno-substituted 1,3-enynes **3** were coupled with alkynylmagnesium bromides **4** in the presence of a catalytic amount of $NiCl_2(PPh_3)_2$ to give stereoselectively (*E*)-enediynes **5** in good yields.

Keywords: (*E*)-1-Arylseleno-substituted 1,3-enyne, (*E*)-enediyne, nickel catalysis, Sonogashira coupling, stereoselective synthesis

INTRODUCTION

Enyne systems have attracted much attention from synthetic organic chemists because enynes show interesting chemical and biological reactivities.[1] Conjugated enynes are also important synthetic intermediates because the conjugated enyne moiety can be readily converted in a stereospecific manner into the corresponding diene system.[2] Recently, Hara et al. described the formation of highly substituted enynes using a coupling reaction between alkenylzirconium compounds and alkynyl halides.[3] Cadierno et al. reported the stereoselective synthesis of chiral terminal (*E*)-1,3-enynes derived from the optically active aldehydes.[4]

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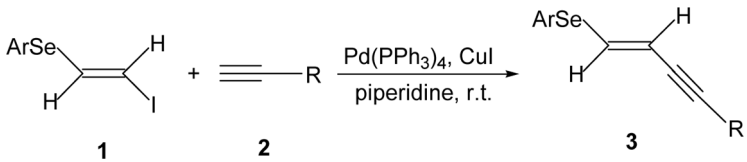
The stereocontrolled synthesis of 1,3-enynes containing metal or heteroatom functional groups has also attracted considerable interest in organic synthesis because many useful functional group transformations can be achieved by introduction and removal of metal or heteroatom functions. The stereoselective synthesis of 1,3-enynylsulfides,[5] 1,3-enynyltellurides,[6] 1,3-enynylsulfones,[7] 1,3-enynylsilanes,[8] 1,3-enynylstannanes,[9] and fluoro or CF_3-substituted 1,3-enynes[10] has already been described in the literature. The synthesis of (*E*)-2-arylseleno-substituted 1,3-enynes has also been reported[11]; however, report on the synthesis of (*E*)-1-arylseleno-substituted 1,3-enynes is rare. Sonogashira coupling is a reliable and convenient reaction for constructing enyne unit and has often been used for the preparation of such compounds.[12] Herein, we report that (*E*)-1-arylseleno-substituted 1,3-enynes could be conveniently synthesized via Sonogashira coupling reactions of (*E*)-1-iodo-2-arylselenoethylenes with terminal alkynes (Scheme 1).

RESULTS AND DISCUSSION

(*E*)-1-Iodo-2-arylselenoethylenes **1** were easily prepared by the hydrozirconation of arylselenoacetylenes, followed by the reaction with iodine according to a literature procedure.[13] (*E*)-1-Iodo-2-arylselenoethylenes **1** are difunctional group reagents in which two synthetically versatile groups are linked to the olefinic carbon atoms and can be considered both as vinylic selenides and as vinylic iodides. We carried out the Sonogashira coupling reactions of (*E*)-1-iodo-2-arylselenoethylenes **1** with terminal alkynes **2**; the experimental results are summarized in Table 1. As shown in Table 1, the Sonogashira coupling reactions proceeded smoothly in piperidine at room temperature in the presence of catalytic amounts of $Pd(PPh_3)_4$ and CuI to afford stereoselectively desired (*E*)-1-arylseleno-substituted 1,3-enynes **3** in high yields. It is well documented that the Sonogashira coupling reaction of vinylic iodides with terminal alkynes in the presence of a palladium and CuI cocatalyst occurs with retention of configuration.[12] The *E*-configuration of the



Scheme 1. Synthesis of (*E*)-1-arylseleno-substituted 1,3-enynes.

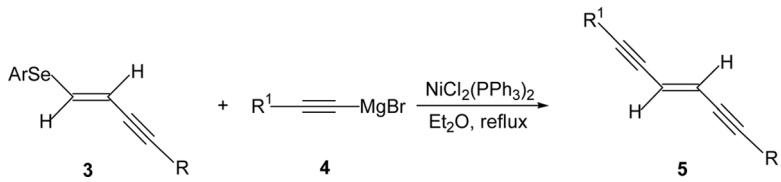
Table 1. Synthesis of (*E*)-1-arylseleno-substituted 1,3-enynes **3a–g**[a]

Entry	Ar	R	Product	Yield[b] (%)
1	Ph	*n*-C_4H_9	**3a**	88
2	Ph	*n*-C_6H_{13}	**3b**	87
3	Ph	Me_3Si	**3c**	85
4	Ph	$MeOCH_2$	**3d**	90
5	Ph	Ph	**3e**	89
6	4-ClC_6H_4	Me_3Si	**3f**	86
7	4-MeC_6H_4	Me_3Si	**3g**	88

[a]The reactions were performed with 1.0 mmol of **1**, 1.5 mmol of **2**, 0.05 mmol of $Pd(PPh_3)_4$, and 0.1 mmol of CuI in 3 mL of piperidine at room temperature.
[b]Isolated yield based on **1** used.

compounds **3a–g** has been proved by their ^{1}H NMR spectra, which show a doublet at $\delta = 5.64$–5.80 with a coupling constant of 15.6–16.0 Hz.

Enediyne compounds have recently received considerable attention because they can be used not only to study on the mechanism for their function in antitumor antibiotics[14–16] such as dynemicin, neocarzinostatin, and esperamicin but also are utilized in syntheses of oligoenynes and oligoenediynes as well as π-conjugated polymers for electronic and photonic applications.[17] Very recently, they have been widely used as important synthetic intermediates in organic synthesis.[18] It is well known that vinylic selenides can couple with Grignard reagents in the presence of a catalytic amount of nickel-phosphine complexes to afford the corresponding unsaturated hydrocarbons with loss of selenium-containing groups.[19] We carried out the cross-coupling reactions of (*E*)-1-arylseleno-substituted 1,3-enynes **3** with alkynylmagnesium bromides **4** in ether in the presence of a catalytic amount of $NiCl_2(PPh_3)_2$ to afford the selenium-free (*E*)-enediynes **5** (Scheme 2). The typical results are summarized in Table 2. As shown in Table 2, the cross-coupling reactions of (*E*)-1-arylseleno-substituted 1,3-enynes **3** with alkynylmagnesium bromides **4** proceeded smoothly under mild



Scheme 2. Synthesis of (*E*)-enediynes.

Table 2. Synthesis of (*E*)-enediynes **5a–e**[a]

Entry	Ar	R	R^1	Product	Yield[b] (%)
1	Ph	*n*-C_4H_9	Me_3Si	**5a**	72
2	Ph	*n*-C_6H_{13}	*n*-C_4H_9	**5b**	75
3	4-MeC_6H_4	Me_3Si	Me_3Si	**5c**	81
4	4-MeC_6H_4	Me_3Si	*n*-C_6H_{13}	**5d**	76
5	Ph	Ph	*n*-C_6H_{13}	**5e**	69

[a]The reactions were performed with 1.0 mmol of **3**, 2.5 mmol of **4**, and 0.03 mmol of $NiCl_2(PPh_3)_2$ in 12 mL of Et_2O at reflux temperature.
[b]Isolated yield based on **3** used.

conditions to give the corresponding (*E*)-enediynes **5** in good yields. The *E*-configuration of the compounds **5a**, **5d**, and **5e** has been proved by their ^1H NMR spectra, which show two doublets at $\delta = 5.88$–6.12 with a coupling constant of 16.0 Hz. Because arylseleno-substituted compounds are toxic and give off a bad smell, we tried to combine the Sonogashira coupling and Ni-catalyzed coupling reactions into a one-pot reaction to synthesize (*E*)-enediynes **5**, but this was unsuccessful.

EXPERIMENTAL

General

IR spectra were obtained on a Perkin-Elmer 683 instrument as neat films. ^1H NMR spectra were recorded on a Bruker AC-400 (400-MHz) spectrometer with TMS as an internal standard using $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded on a Bruker AC-400 (100-MHz) spectrometer using $CDCl_3$ as solvent. Mass spectra were determined on a Finnigan 8230 mass spectrometer. Microanalyses were measured using a Yanaco MT-3 CHN microelemental analyzer. Piperidine was dried over potassium hydroxide (KOH) and distilled before use. Diethyl ether was distilled from sodium benzophenone ketyl prior to use.

General Procedure for the Synthesis of (*E*)-1-Arylseleno-Substituted 1,3-Enynes 3a–g

(*E*)-1-Iodo-2-arylselenoethylene **1** (1.0 mmol), $Pd(PPh_3)_4$ (0.05 mmol), piperidine (3 mL), and CuI (0.1 mmol) were added to a flask under argon,

and the resulting mixture was stirred at room temperature for 5 min. Terminal alkyne **2** (1.5 mmol) was added to this solution, and the reaction mixture was stirred at room temperature for 3 h, quenched with sat. NH_4Cl aq. solution (10 mL) at 0 °C, and extracted with Et_2O (2×25 mL). The ethereal solution was washed with water (2×10 mL) and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel eluting with light petroleum ether (bp 30–60 °C).

Data

(*E*)-1-Phenylseleno-1-octen-3-yne (**3a**)

Oil, bp 78 °C (0.35 torr). IR (film): ν (cm^{-1}) 3058, 2957, 2931, 2871, 2212, 1708, 1578, 1477, 930, 736, 690; ^{1}H NMR ($CDCl_3$): δ 7.52–7.50 (m, 2H), 7.32–7.30 (m, 3H), 6.99 (d, $J = 15.6$ Hz, 1H), 5.80 (d, $J = 15.6$ Hz, 1H), 2.31–2.26 (m, 2H), 1.52–1.37 (m, 4H), 0.91 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 133.3, 131.8, 129.4, 128.8, 127.9, 114.0, 91.6, 78.9, 30.7, 22.0, 19.2, 13.6; MS (EI): m/z 264 (M^+, 17), 263 (54), 142 (100), 129 (56), 115 (70), 91 (63), 77 (74). Anal. calc. for $C_{14}H_{16}Se$: C, 63.88; H, 6.13. Found: C, 63.59; H, 6.16%.

(*E*)-1-Phenylseleno-1-decen-3-yne (**3b**)

Oil, bp 82 °C (0.3 torr). IR (film): ν (cm^{-1}) 3059, 2955, 2930, 2857, 2211, 1712, 1578, 1477, 930, 736, 690; ^{1}H NMR ($CDCl_3$): δ 7.52–7.50 (m, 2H), 7.32–7.30 (m, 3H), 6.99 (d, $J = 16.0$ Hz, 1H), 5.80 (d, $J = 16.0$ Hz, 1H), 2.30–2.25 (m, 2H), 1.53–1.47 (m, 2H), 1.39–1.25 (m, 6H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 133.3, 131.8, 129.4, 128.8, 127.8, 114.0, 91.7, 78.9, 31.3, 28.6, 28.5, 22.5, 19.5, 14.1; MS (EI): m/z 292 (M^+, 13), 291 (51), 142 (100), 129 (57), 115 (75), 91 (85), 77 (84). Anal. calc. for $C_{16}H_{20}Se$: C, 65.97; H, 6.92. Found: C, 65.74; H, 6.78%.

(*E*)-1-Phenylseleno-4-(trimethylsilyl)-1-buten-3-yne (**3c**)

Oil, bp 89 °C (0.5 torr). IR (film): ν (cm^{-1}) 3059, 2958, 2142, 1712, 1578, 1250, 844, 690; ^{1}H NMR ($CDCl_3$): δ 7.54–7.52 (m, 2H), 7.34–7.32 (m, 3H), 7.21 (d, $J = 16.0$ Hz, 1H), 5.71 (d, $J = 16.0$ Hz, 1H), 0.16 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 136.4, 134.1, 129.6, 128.3, 127.8, 111.7, 103.3, 95.2, −0.12; MS (EI): m/z 280 (M^+, 5.8), 250 (55), 78 (44), 73 (100). Anal. calc. for $C_{13}H_{16}SiSe$: C, 55.90; H, 5.77. Found: C, 55.62; H, 5.79%.

(*E*)-1-Phenylseleno-5-methoxy-1-penten-3-yne (**3d**)

Oil, bp 73 °C (0.4 torr). IR (film): ν (cm^{-1}) 3057, 2929, 2204, 1713, 1578, 1094, 930, 739, 690; ^1H NMR ($CDCl_3$): δ 7.55–7.51 (m, 2H), 7.35–7.32 (m, 3H), 7.16 (d, $J = 15.6$ Hz, 1H), 5.76 (d, $J = 15.6$ Hz, 1H), 4.18 (s, 2H), 3.37 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 135.3, 133.8, 129.6, 128.2, 128.1, 111.5, 85.7, 84.7, 60.4, 57.6; MS (EI): m/z 252 (M^+, 16), 251 (57), 220 (78), 142 (93), 129 (82), 115 (72), 95 (100), 77 (84), 51 (77). Anal. Calc. for $C_{12}H_{12}OSe$: C, 57.38; H, 4.81. Found: C, 57.19; H, 4.56%.

(*E*)-1-Phenylseleno-4-phenyl-1-buten-3-yne (**3e**)

Oil, bp 118 °C (0.6 torr). IR (film): ν (cm^{-1}) 3057, 2196, 1706, 1597, 1565, 1488, 928, 688; ^1H NMR ($CDCl_3$): δ 7.58–7.21 (m, 11H), 5.71 (d, $J = 15.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 134.6, 133.8, 131.6, 131.4, 129.6, 128.4, 128.3, 128.2, 128.1, 112.2, 90.2, 87.9; MS (EI): m/z 284 (M^+, 74), 228 (82), 204 (78), 169 (100), 126 (66), 77 (44). Anal. calc. for $C_{16}H_{12}Se$: C, 67.85; H, 4.27. Found: C, 67.59; H, 4.08%.

(*E*)-1-[(4-Chlorophenyl)seleno]-4-(trimethylsilyl)-1-buten-3-yne (**3f**)

Oil, bp 85 °C (0.35 torr). IR (film): ν (cm^{-1}) 2958, 2110, 1556, 1473, 1254, 1089, 930, 842, 760; ^1H NMR ($CDCl_3$): δ 7.45 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 8.4$ Hz, 2H), 7.14 (d, $J = 15.6$ Hz, 1H), 5.73 (d, $J = 15.6$ Hz, 1H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 135.5, 135.4, 134.9, 130.0, 126.2, 112.6, 103.1, 95.8, 0.01; MS (EI): m/z 316 (M^+, ^{37}Cl, 15), 314 (M^+, ^{35}Cl, 31), 191 (100), 189 (53), 156 (47), 73 (36). Anal. calc. for $C_{13}H_{15}ClSiSe$: C, 49.76; H, 4.82. Found: C, 49.54; H, 4.89%.

(*E*)-1-[(4-Methylphenyl)seleno]-4-(trimethylsilyl)-1-buten-3-yne (**3g**)

Oil, bp 82 °C (0.4 torr). IR (film): ν (cm^{-1}) 2960, 2163, 1563, 1489, 1251, 927, 843, 803, 760; ^1H NMR ($CDCl_3$): δ 7.42 (d, $J = 8.4$ Hz, 2H), 7.19 (d, $J = 15.6$ Hz, 1H), 7.13 (d, $J = 8.4$ Hz, 2H), 5.64 (d, $J = 15.6$ Hz, 1H), 2.34 (s, 3H), 0.16 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 138.8, 137.1, 134.7, 130.5, 123.9, 111.1, 103.6, 95.1, 21.3, 0.04; MS (EI): m/z 294 (M^+, 14), 263 (35), 91 (43), 73 (100). Anal. calc. for $C_{14}H_{18}SiSe$: C, 57.32; H, 6.18. Found: C, 57.50; H, 6.31%.

General Procedure for the Synthesis of (*E*)-Enediynes 5a–e

To a mixture of (*E*)-1-arylseleno-substituted 1,3-enyne **3** (1.0 mmol) and $NiCl_2(PPh_3)_2$ (0.03 mmol) in diethyl ether (8 mL), alkynylmagnesium bromide **4** (2.5 mmol) in diethyl ether (4 mL) was added under argon at room temperature with stirring. The resulting mixture was heated to reflux for 10 h. The mixture was treated with sat. NH_4Cl aq. solution (15 mL) at 0 °C and extracted with diethyl ether (2×20 mL). The ethereal solution was washed with water (2×20 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave an oil, which was purified by preparative thin-layer chromatography (TLC) on silica gel eluting with light petroleum ether (bp 30–60 °C).

Data

(*E*)-1-(Trimethylsilyl)-6-butyl-3-hexen-1,5-diyne (**5a**)

Oil, bp 65 °C (0.6 torr). IR (film): ν (cm^{-1}) 3033, 2960, 2162, 2118, 1250, 1073, 937, 844; ^1H NMR ($CDCl_3$): δ 6.02 (d, $J = 16.0$ Hz, 1H), 5.89 (d, $J = 16.0$ Hz, 1H), 2.36–2.31 (m, 2H), 1.54–1.37 (m, 4H), 0.92 (t, $J = 7.2$ Hz, 3H), 0.20 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 122.8, 119.3, 103.4, 98.9, 96.8, 79.0, 30.6, 22.0, 19.4, 13.6, −0.17; MS (EI): m/z 204 (M^+, 9.4), 190 (100), 73 (68). Anal. calc. for $C_{13}H_{20}Si$: C, 76.39; H, 9.86. Found: C, 76.25; H, 9.69%.

(*E*)-1-Hexyl-6-butyl-3-hexen-1,5-diyne (**5b**)

Oil, bp 58 °C (0.45 torr). IR (film): ν (cm^{-1}) 3031, 2960, 2163, 2118, 1252, 1073, 935, 844; ^1H NMR ($CDCl_3$): δ 5.88 (s, 2H), 2.34–2.29 (m, 4H), 1.55–1.24 (m, 12H), 0.93–0.87 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 120.3, 120.2, 95.0, 94.9, 79.1, 31.3, 30.7, 28.6, 22.5, 22.0, 19.6, 19.3, 14.0, 13.6; MS (EI): m/z 216 (M^+, 4.5), 146 (52), 132 (95), 118 (98), 115 (80), 91 (100). Anal. calc. for $C_{16}H_{24}$: C, 88.82; H, 11.18. Found: C, 88.55; H, 11.27%.

(*E*)-1,6-Bis(trimethylsilyl)-3-hexen-1,5-diyne (**5c**)

White solid, mp 71–72 °C (lit.[20] mp 72 °C). IR (film): ν (cm^{-1}) 2955, 2174, 2127, 1251, 1093, 933, 843; ^1H NMR ($CDCl_3$): δ 6.01 (s, 2H),

0.20 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 121.7, 102.9, 100.7, −0.24; MS (EI): m/z 220 (M^+, 11), 207 (75), 205 (69), 191 (43), 155 (38), 73 (100). Anal. calc. for $C_{12}H_{20}Si_2$: C, 65.37; H, 9.14. Found: C, 65.56; H, 9.27%.

(*E*)-1-(Trimethylsilyl)-6-hexyl-3-hexen-1,5-diyne (**5d**)

Oil, bp 71 °C (0.5 torr). IR (film): ν (cm^{-1}) 3033, 2959, 2162, 2118, 1250, 1073, 937, 844; ^{1}H NMR ($CDCl_3$): δ 6.01 (d, $J = 16.0$ Hz, 1H), 5.88 (d, $J = 16.0$ Hz, 1H), 2.35–2.30 (m, 2H), 1.54–1.26 (m, 8H), 0.89 (t, $J = 7.2$ Hz, 3H), 0.19 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 122.8, 119.3, 103.4, 98.9, 96.8, 79.0, 31.3, 28.6, 28.5, 22.5, 19.7, 14.0, − 0.18; MS (EI): m/z 232 (M^+, 8.5), 217 (35), 73 (100). Anal. calc. for C_{15} H_{24} Si: C, 77.51; H, 10.41. Found: C, 77.27; H, 10.20%.

(*E*)-1-Hexyl-6-phenyl-3-hexen-1,5-diyne (**5e**)

Oil, bp 68 °C (0.35 torr). IR (film): ν (cm^{-1}) 3032, 2927, 2856, 2214, 1261, 1023, 934, 754; ^{1}H NMR ($CDCl_3$): δ 7.46–7.41 (m, 2H), 7.38–7.33 (m, 3H), 6.12 (d, $J = 16.0$ Hz, 1H), 6.06 (d, $J = 16.0$ Hz, 1H), 2.38–2.33 (m, 2H), 1.56–1.25 (m, 8H), 0.90 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 132.5, 131.5, 129.2, 128.4, 121.7, 119.4, 96.6, 93.4, 88.1, 79.2, 31.3, 29.7, 28.5, 22.5, 19.7, 14.1; MS (EI): m/z 236 (M^+, 34), 202 (100), 178 (33), 165 (45). Anal. calc. for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.18; H, 8.29%.

CONCLUSION

In conclusion, we have developed an efficient and stereoselective method for the synthesis of (*E*)-1-arylseleno-substituted 1,3-enynes and (*E*)-enediynes. The present method has the advantages of readily available starting materials, straightforward and simple procedures, mild reaction conditions, and good yields.

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