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Reactions of Polymer-Supported α-Selenoaldehydes with Grignard Regents. A Facile Solid-Phase Stereoselective Synthesis of (*E*)-1,2-Disubstituted Ethenes

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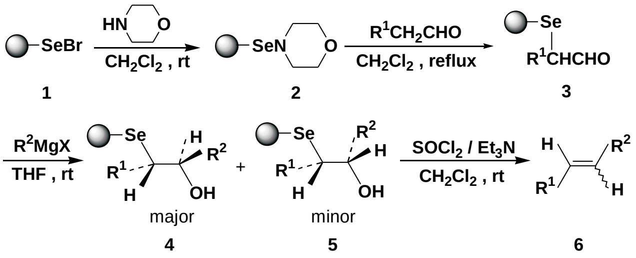
Polymer-supported α-selenoaldehydes easily obtained by reaction of polymer-supported 4-(phenylseleno)morpholine with aldehydes react with Grignard reagents to form polymer-supported β-hydroxyalkyl selenides, which were treated with thionyl chloride/triethylamine leading to (*E*)-1,2-disubstituted ethenes in good yields.

Keywords: Solid-phase organic synthesis; Polymer-supported (4-phenylseleno)morpholine; Polymer-supported α-selenoaldehyde; (*E*)-1,2-Disubstituted ethene.

During the last few years, solid-phase methodology has been rapidly and extensively applied to the preparation of small organic molecules. Polymer-supported reagents have attracted growing interest because they can provide attractive and practical methods for combinatorial chemistry and solid-phase organic synthesis.[1] Organoselenium reagents are now commonly used as a powerful tool for introducing new functional groups into organic substrates under extremely mild conditions.[2] Among them, β-hydroxyalkyl selenides are potentially useful intermediates in organic synthesis.[3] β-Hydroxyalkyl selenides can be regio- and stereoselectively obtained by reacting Grignard reagents with α-selenoaldehydes which are easily prepared from 4-(arylseleno)morpholine formed *in situ* with saturated aldehydes.[4a] Many methods have been developed for the stereoselective synthesis of 1,2-disubstituted ethenes. Among these methods, an important method involves the conversion of β-hydroxyalkyl selenides.[5] However, organic selenium reagents always have a foul smell and are quite toxic, which is often problematic in organic synthesis. Recently, selenium-based approaches for solid-phase chemistry have been reported from different research groups.[6] Our research group has been interested in the applications of organic selenium reagents in organic synthesis for many years. Herein, we wish to report the very simple preparation of polystyrene-supported α-selenoaldehydes and their applications to stereoselective synthesis of (*E*)-1,2-disubstituted ethenes on solid-phase (Scheme I). A distinct advantage of these new polymer-supported selenium reagents is the convenience of handling and totally odorless nature as compared to the non-bound reagents, whose toxicity and foul smell are often problematic.

Scheme I



Simple stirring of polystyrene-supported selenium bromide **1**[6a] with morpholine in CH$_2$Cl$_2$ resulted in nearly quantitative conversion to the polystyrene-supported (4-phenylseleno)morpholine **2** by elemental analysis of nitrogen. Treatment of resin **2** with saturated aldehydes bearing an α-hydrogen gave the corresponding α-phenylselenoaldehyde resins **3** as indicated by FT-IR spectra showing strong carbonyl absorption at 1700-1710 cm^{-1} and no residual Se-N absorption at 1252 cm^{-1}. The minimum degree of functionalization of resins **3** could be calculated from the nitrogen analysis of their corresponding aldoximes and corresponded to 1.02, 1.08 and 1.10 mmol of aldehydes functional group per gram (R^1 = Ph, *n*-Pr and Et, respectively). Resin **3** reacted with Grignard reagents[3g] at room temperature to form polymer-supported β-hydroxyalkyl selenides **4** and **5** showing large hydroxyl absorption at 3430-3440 cm^{-1} and no residual carbonyl absorption in its infrared spectra. The reactions of resin

Table 1. Preparation of (*E*)-1,2-Disubstituted Ethenes[a]

Entry	R^1	R^2	Yield of **6** (%)[b]	*E/Z* ratio[c]
1	C_6H_5	C_6H_5	85 (**6a**)	97/3
2	C_6H_5	4-ClC_6H_4	83 (**6b**)	98/2
3	C_6H_5	4-$CH_3C_6H_4$	84 (**6c**)	94/6
4	C_6H_5	3-$CH_3C_6H_4$	82 (**6d**)	94/6
5	C_6H_5	CH_3	80 (**6e**)	95/5
6	C_6H_5	CH_2=$CHCH_2$	85 (**6f**)	96/4
7	CH_3CH_2	C_6H_5	76 (**6g**)	96/4
8	CH_3CH_2	4-ClC_6H_4	80 (**6h**)	93/7
9	CH_3CH_2	$C_6H_5CH_2$	81 (**6i**)	95/5
10	$CH_3CH_2CH_2$	C_6H_5	78 (**6j**)	94/6
11	$CH_3CH_2CH_2$	$C_6H_5CH_2$	82 (**6k**)	95/5

[a] The products are known and identified by ^{1}H NMR and IR spectra.
[b] Isolated yields based on the minimum loading of aldehyde of polymer-supported α-selenoaldehydes.
[c] The ratio of *E/Z* isomers was determined by ^{1}H NMR (400 MHz).

3 with Grigard reagents are known to lead predominately to the major diastereoisomers **4**, as predicated by “Cram’s rule”.[7] These new polymer-supported selenium reagents are remarkably stable and may be stored for several months at ambient temperature without any deterioration. With treatment of β-hydroxyalkyl selenide resins with *p*-toluenesulfonic acid or perchloric acid[5a] the yields of products **6** were poor. When methanesulfonyl chloride,[5a] and trifluoroacetic anhydride/triethylamine[5c] were adopted, the yields are 50-60%. After some screening, we found that (*E*)-1,2-disubstituted ethenes were obtained in better yields (Table 1) when thionyl chloride[5b] was used in the presence of triethylamine at room temperature. Under the described conditions, the conversion was highly stereoselective (> 90%) and occurred formally by *trans*-elimination of the “hydroxyl” and “selenyl” moieties.[8]

In conclusion, we have prepared several new polystyrene-supported selenium reagents and developed a SPOS route to synthesize (*E*)-1,2-disubstituted ethenes. Although an excess amount of reagents was required, higher yields were achieved as compared to those of the corresponding solution-phase synthesis. Furthermore, the procedure replaces the time-consuming isolation and purification steps in the corresponding solution-phase reaction.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer using $CDCl_3$ as the solvent and with TMS as internal standard; IR spectra were determined on a Bruker Vector 22 spectrophotometer.

Preparation of polystyrene-supported 4-(phenylseleno)-morpholine (2)

Polystyrene-supported selenium bromide (1.0 g, 1.18 mmol/g, Br), prepared from 1% cross-linked polystyrene beads,[6a] was swelled in CH_2Cl_2 (10 mL) for 30 min, and morpholine (2.40 mmol) was added. The mixture was stirred at room temperature for 30 min and filtered. After washing successively with H_2O, CH_2Cl_2 (2 × 3 mL of each) and then drying in vacuum, the resin **2** containing 1.12 mmol N/g was obtained as yellow beads. IR (KBr): 3058, 3024, 2920, 2849, 1600, 1584, 1492, 1449, 1275, 1252, 1108, 1067, 903, 755, 696 cm^{-1}; Anal Calcd for resin **2**: N, 1.64%. Found: N, 1.57%.

General procedure for preparation of polystyrene-supported α-selenoaldehyde resin (3)

Resin **2** (1.0 g, 1.12 mmol) was swelled with CH_2Cl_2 (10 mL) for 30 min, aldehyde (1.15 mmol) was added, and the suspension was refluxed for 5 h, then cooled and filtered. The resin **3** was washed with CH_2Cl_2 (4 × 3 mL) and dried under vacuum. The minimum capacity of this resin was calculated from the nitrogen elemental analysis of its corresponding aldoxime according to the method described in the literature.[9]

General method for synthesis of polystyrene-supported β-hydroxyalkyl selenides resin

Resin **3** (1.0 g) preswollen in THF (10 mL) was treated with Grignard reagent (2.0 mmol) in THF. Stirring continued at 0 °C for 1 h, then at room temperature for 5 h under a nitrogen atmosphere, and then quenched with aqueous NH_4Cl and filtered. This new β-hydroxyalkyl selenides resin was washed successively with H_2O, THF, methanol, CH_2Cl_2, ether (2 × 3 mL of each), and then dried under vacuum.

General procedure for preparation of (*E*)-1,2-disubstituted ethenes (6)

To a suspension of β-hydroxyalkyl selenides resin (1.0 g) swollen in CH_2Cl_2 (10 mL) and containing triethylamine (7 mmol) was added thionyl chloride (2 mmol) at room temperature and stirred for 4 h. After the resin was filtered off and washed with CH_2Cl_2, the filtrate was washed with brine, dried over Na_2SO_4, and evaporated to give the crude product, which was purified by preparative TLC on silica gel.

(*E*)-Stilbene (6a)[10]

mp 121.5-123 °C (*lit*. 122-123 °C); ^{1}H-NMR δ 7.12 (s, 2H), 7.18-7.21 (m, 2H), 7.36-7.43 (m, 4H), 7.48-7.55 (m, 4H); IR ν_{max} (KBr) 3019, 1579, 1468, 1072, 962, 910, 765, 693 cm^{-1}.

(*E*)-1-Phenyl-2-(*p*-chlorophenyl)ethene (6b)[10]

mp 127-128 °C (*lit*. 126-127 °C); ^{1}H-NMR δ 7.10 (s, 2H), 7.26-7.48 (m, 9H); IR ν_{max} (KBr) 3025, 1585, 1465, 945, 815, 699 cm^{-1}.

(*E*)-1-Phenyl-2-(*p*-methylphenyl)ethene (6c)[10]

mp 116-117 °C (*lit*. 116-117 °C); ^{1}H-NMR δ 2.35 (s, 3H), 7.04 (s, 2H), 7.10-7.60 (m, 9H); IR ν_{max} (KBr) 3025, 2977, 1595, 1468, 941, 820, 705 cm^{-1}.

(*E*)-1-Phenyl-2-(*m*-methylphenyl)ethene (6d)[10]

mp 46-47 °C (*lit*. 47-48 °C); ^{1}H-NMR δ 2.32 (s, 3H), 7.01 (s, 2H), 7.08-7.65 (m, 9H); IR ν_{max} (KBr) 3029, 2970, 1594, 1466, 950, 818, 705 cm^{-1}.

(*E*)-1-Phenyl-1-propylene (6e)[11]

Colorless oil; ^{1}H-NMR δ 1.87 (d, J = 1.5 Hz, 3H), 6.21-6.27 (m, 1H), 6.42 (d, J = 16.9 Hz, 1H), 7.0-7.35 (m, 5H); IR ν_{max} (film) 3028, 2972, 1600, 1495, 1445, 956, 728 cm^{-1}.

(*E*)-1-Phenyl-1,4-pentadiene (6f)[12]

Colorless oil; ^{1}H-NMR δ 2.95-2.98 (m, 2H), 5.05-5.09 (m, 2H), 5.87-5.92 (m, 1H), 6.21-6.26 (m, 1H), 6.43 (d, J = 15.9 Hz, 1H), 7.20-7.37 (m, 5H); IR ν_{max} (film) 3026, 2978, 1600, 1496, 1449, 965, 913, 742 cm^{-1}.

(*E*)-1-Phenyl-1-butene (6g)[13]

Colorless oil; ^{1}H-NMR δ 1.07 (t, J = 7.2 Hz, 3H), 2.21-2.24 (m, 2H), 6.24-6.30 (m, 1H), 6.40 (d, J = 15.9 Hz, 1H), 7.18-7.35 (m, 5H); IR ν_{max} (film) 3024, 2964, 1652, 1598, 1494, 1377, 963, 909, 738 cm^{-1}.

(*E*)-1-(*p*-Chlorophenyl)-1-butene (6h)[13]

Colorless oil; ^{1}H-NMR δ 0.89 (t, J = 7.2 Hz, 3H), 2.19-2.21 (m, 2H), 6.20-6.24 (m, 1H), 6.29 (d, J = 15.6 Hz, 1H), 7.12-7.30 (m, 4H); IR ν_{max} (film) 3025, 2964, 1652, 1593, 1490, 1461, 965, 801, 734 cm^{-1}.

(*E*)-1-Phenyl-2-pentene (6i)[14]

Colorless oil; ^{1}H-NMR δ 1.01 (t, J = 7.4 Hz, 3H), 2.01-2.06 (m, 2H), 3.33 (d, J = 4.0 Hz, 2H), 5.55-5.57 (m, 2H), 7.17-7.30 (m, 5H); IR ν_{max} (film) 3027, 2963, 1603, 1494, 1453, 1378, 967, 909, 734 cm^{-1}.

(*E*)-1-Phenyl-1-pentene (6j)[13]

Colorless oil; ^{1}H-NMR δ 0.97 (t, J = 7.3 Hz, 3H), 1.45-1.54 (m, 2H), 2.16-2.22 (m, 2H), 6.19-6.26 (m, 1H), 6.40 (d, J = 15.8 Hz, 1H), 7.16-7.35 (m, 5H); IR ν_{max} (film) 3025, 2958, 1653, 1598, 1449, 1378, 963, 738 cm^{-1}.

(*E*)-1-Phenyl-2-hexene (6k)[15]

Colorless oil; ^{1}H-NMR δ 0.92 (t, J = 7.4 Hz, 3H), 1.35-1.42 (m, 2H), 1.98-2.03 (m, 2H), 3.34 (d, J = 6.1 Hz, 2H), 5.48-5.59 (m, 2H), 7.16-7.30 (m, 5H); IR ν_{max} (film) 3027, 2959, 1653, 1603, 1494, 1378, 965, 744 cm^{-1}.

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REFERENCES

1. For recent reviews on SPOS, see: (a) Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed.* **1996**, *35*, 17. (b) Hermkens, P. H. H.; Ottenhijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643. (c) Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293. (d) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549. (e) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091. (f) Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137.
2. Paulmier, C., Ed.; Selenium Reagents and Intermediates in Organic Synthesis; Pergamon Press: Oxford, 1986.
3. (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697. (b) Dumont, W.; Bayet, P.; Krief, A. *Angew. Chem., Int. Ed.* **1974**, *13*, 804. (c) Seebac, D.; Beck, A. K. *Angew. Chem., Int. Ed.* **1974**, *13*, 805. (d) Dumont, W.; Krief, A. *Angew. Chem., Int. Ed.* **1975**, *14*, 350. (e) Van Ende, D.; Dumont, W.; Krief, A. *Angew. Chem., Int. Ed.* **1975**, *14*, 700. (f) Van Ende, D.; Krief, A. *Tetrahedron Lett.* **1975**, *16*, 457. (g) Lémion, A. M.; Krief, A. *Tetrahedron Lett.* **1976**, *17*, 3227. (h) Sevrin, M.; Dumont, W.; Hevesi, L.; Krief, A. *Tetrahedron Lett.* **1976**, *17*, 2647.
4. (a) Lerouge, P.; Paulmier, C. *Bull. Soc. Chim. Fr.* **1985**, 1219; Related α-Selenenylating Aldehydes, see: (b) Reich, H. J.; Renga, J. M. *J. Org. Chem.* **1975**, *40*, 3313. (c) Jefson, M.; Meinwald, J. *Tetrahedron Lett.* **1981**, *22*, 3561.
5. (a) Rémion, J.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1976**, *17*, 1385. (b) Rémion, J.; Krief, A. *Tetrahedron Lett.*

1976, *17*, 3743. (c) Reich, H. J.; Chow, F. *Chem. Commun*. **1975**, 790.

6. (a) Nicolaou, K. C.; Pastor, J.; Barluenga, S.; Winssinger, N. *Chem. Commun*. **1998**, 1947. (b) Ruhland, T.; Andersen, K.; Pedersen, H. *J. Org. Chem.* **1998**, *63*, 9204. (c) Yanda, K.; Fujita, T.; Yanada, R. *Synlett* **1998**, 971. (d) Fujita, K.; Watanabe, K.; Oishi, A.; Ikeda, Y.; Taguchi, Y. *Synlett* **1999**, 1760. (e) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q.; Kim, S.; Kessabi, J. *Org. Lett.* **1999**, *1,* 807. (f) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q. *Angew. Chem., Int. Ed.* **2000**, *39*, 734. (g) Nicolaou, K. C.; Cao, G.-Q.; Pfefferkorn, J. A. *Angew*. *Chem., Int. Ed.* **2000**, *39*, 739. (h) Nicolaou, K. C.; Winssinger, N.; Hughes, R.; Smethurst, C.; Cho, S. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 1084. (i) Nicolaou, K. C.; Mitchell, H. J.; Fylaktakidou, K. C.; Suzuki, H.; Rodriguez, R. M. *Angew. Chem., Int. Ed*. **2000**, *39*, 1089. (j) Nicolaou, K. C.; Roecker, A. J.; Pfefferkorn, J. A.; Cao, G.-Q. *J. Am. Chem. Soc*. **2000**, *122*, 2966. (k) Fujita, K.; Taka, H.; Oishi, A.; Ikeda, Y.; Aguchi, Y.; Fujie, K.; Saeki, T.; Sakuma, M. *Synlett* **2000**, 1509. (l) Uehlin, L.; Wirth, T. *Chimia* **2001**, *55*, 65. (m) Uehlin, L.; Wirth, T. *Org. Lett.* **2001**, *3*, 2931.
7. (a) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc*. **1952**, *74*, 5828. (b) Cram, D. J.; Greene, F. D. *J. Am. Chem. Soc*. **1953**, *75*, 6005.
8. Schmid, G. H.; Garratt, D. G. *Tetrahedron Lett*. **1975**, *16*, 3991.
9. Farrall, M. J.; Fréchet, J. M. J. *J. Org. Chem.* **1976**, *41*, 3877.
10. Zhu, L.-S.; Huang, X. *Synth. Commun.* **1997**, *27*, 39.
11. Wilmhurst, J. R. *Aust. J. Chem.* **1965**, *8*, 1759.
12. Vincent, S.; Armand, L. *Bull. Soc. Chim. Fr.* **1971**, 3057.
13. Schlosser, M.; Müeller, G.; Christmann, K. F. *Angew*. *Chem., Int. Ed.* **1966**, *5*, 667.
14. Nakai, T.; Shiono, H.; Okawara, M. *Chem. Lett.* **1975**, 249.
15. Klages, A. *Ber.* **1907**, *40*, 1768.