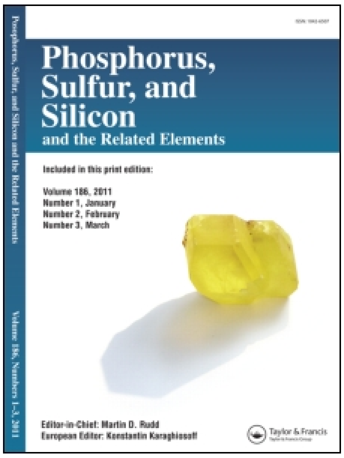

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Fang Wang[a]; Liming Hu[b]; Xiaopeng Li[b]; Xuemei Xu[b]; Hongguang Du[a]
[a] College of Science Beijing University of Chemical Technology, Beijing, China [b] College of Life Sciences and Bioengineering, Beijing University of Technology, Beijing, China

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# Synthesis of O,O-Dialkyl 2-Oxo-2-(4-(Selenomorpho-Linosulfonyl)Phenylamino)Ethylphosphonate

**Fang Wang,[1] Liming Hu,[2] Xiaopeng Li,[2] Xuemei Xu,[2]
and Hongguang Du[3]**
[1]College of Science Beijing University of Chemical Technology, Beijing
100029, China
[2]College of Life Sciences and Bioengineering, Beijing University of
Technology, Beijing 100022, China
[3]College of Science Beijing University of Chemical Technology, Beijing
100029, China

*A series of O,O-dialkyl 2-oxo-2-(4-(seleomorpholinosulfonyl)phenylamino)ethylphosphonate were synthesized by reactions of 2-chloro-N-(4-(seleomorpholino sulfonyl)phenyl)acetamide with dialkylphosphite in the presence of sodium hydride. The structure of all new compounds has been confirmed by* $^1H$ *NMR,* $^{31}P$ *NMR, IR, Mass spectroscopy and elemental analyses.*

**Keywords** Dialkyl phosphite; selenomorpholine; phosphonate; synthesis

## INTRODUCTION

Since selenium was found to be an active center of glutathione peroxidase(GSH-Px), which can catalyze and decompose liquid hydroperoxide or hydrogen peroxide, the study of selenium biological activity has developed rapidly.[1–2] Selenoorganic compound, such as Ebselen, with the function against biological damage caused in vivo by reactive hydroperoxides,[3–7] which increased a striking interest in developing new seleoorganic compound for therapy. These compounds have been potentially used in a variety of fields varying from medicinal to agriculture application.[8–10] In our pervious work, many selenoorganic compounds were synthesized and exhibited excellent pharmacological effect.[11–13] Recently, the antibiotic activity and plant systemic activity of selenomor pholine derivatives were studied in our

Address correspondence to Liming Hu, College of Life Sciences and Bioengineering, Beijing University of Technology, Beijing 100022, China. E-mail: huliming@bjut.edu.cn

Lab.[14–15] In this work, we present the synthesis of O,O-dialkyl 2-oxo-2-(4-(seleomorpholinosulfonyl)-phenyl-amino)ethylphosphonate.

## RESULTS AND DISCUSSION

### Synthesis of O,O-dialkyl 2-oxo-2-(4-(selenomorpholinosulfonyl) phenylamino) Ethyl Phosphonate

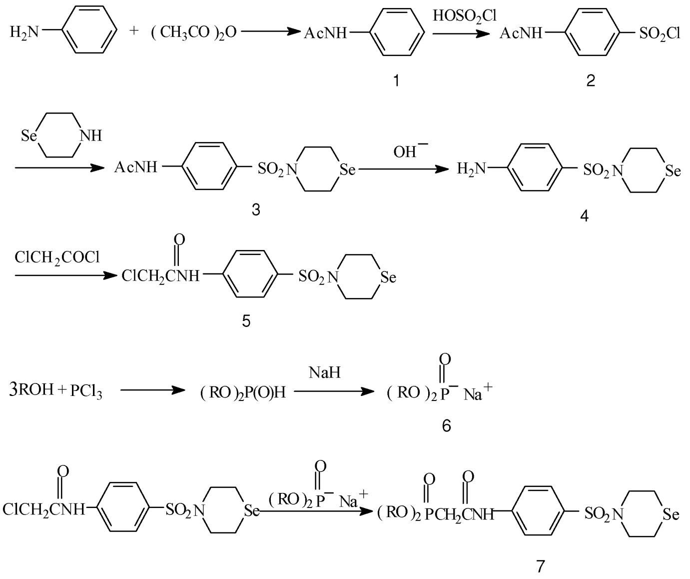
A general synthesis of the title compounds **7** is described by a multistep route outlined in Scheme 1. The synthesis of selenomorpholine started from selenium and utilized a synthetic sequence previously reported from our laboratory.[16] Acylation of aniline followed by sulfonation with sulfuric chloride gave 4-acetamidobenzene-1-sulfonyl chloride **2**, which was coupled to selenomorpholine to give **3**. Ac-deprotection with aqueous sodium hydroxide followed by reaction with 2-chlorlacetyl chloride afforded the desired 2-chloro-N-(4-(selenomorpholinosulfonyl)-phenyl)acetamide **5**, which reacted with dialkyl phosphite in the presence of sodium hydride to give title compounds **7**.

The structure of **7** was confirmed by $^1$H NMR, $^{31}$P NMR, IR, Mass spectroscopy and elemental analyses. In the $^1$H NMR spectra of compound **7**, the proton in PCH appeared as a doublet in the range of $\delta$ 3.0–3.2 ppm ($^2J_{\mathrm{PH}}$=20.4–21.4Hz). The chemical shift of labile proton in the NH of compound **7** is 9.5–10.0 ppm, which can disappear slowly when deuterated. The $^{31}$P NMR spectra of **7** revealed a singlet at the range of $\delta$19.1–22.6 ppm. The IR spectra of compound **7** showed the existence of the group P=O(1233–1281cm$^{-1}$) and C=O(1685–1699cm$^{-1}$).

The EI-MS spectra of **7** demonstrated the molecular ion peak (M$^+$). Other ions were consistent with their structures and can be clearly assigned. Because there are two major isotopes of selenium (approximate ratio 2:1), the fragmental ion abundance ratio which contain two isotopes of selenium is 2:1.

## EXPERIMENTAL

The melting points were determined on a hot stage apparatus and uncorrected, Elemental analyses were performed on a CHN Carlo Erba element analyzer. $^1$H NMR spectra were recorded with a Varian XL-200 spectrometer, TMS was used as an internal standard for $^1$H NMR and 85% $H_3PO_4$ was used as an external standard for $^{31}$P NMR. The IR spectra were measured by a NICOLET AVATAR360 instrument. Mass spectra were recorded with a HP-5988A spectrometer.



R= $-CH_3$, $-C_2H_5$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)CH_2CH_3$, $-CH_2Ph$,

**SCHEME 1**

The reagents and solvents were available commercially and purified according to conventional methods; column chromatography was performed on silica gel (10–40 $\mu$, Hai Yang Chemical Factory of Qingdao). Unless other noted, all solvents were dried over $Na_2SO_4$ or $MgSO_4$, and the solvent was removed in a rotary evaporator under reduce pressure, chromatography was performed on silica gel.

N-phenylacetamide **1**,[17] 4-acetamidobenzene-1-sulfonyl chloride **2**[18] and dialkylphos- phate **6**[19] have been prepared following literature methods.

## N-(4-(Selenomorpholinosulfonyl)phenyl)acetamide (3)

To a stirred solution of selenomorpholine (3.0 g, 20 mmol) and dry pyridine (10 mL) at room temperature under a nitrogen atmosphere, 4-acetamidobenzene-1-sulfonyl chloride (5.2 g, 22 mmol) was added over a period of 0.5 h, and was heated at 100°C for 1 h. The resulting mixture was quenched with ice and water. A light yellow precipitate was produced. The crude product was filtered and washed with water and purified by recrystallization in ethanol as a white solid (m.p. 89–91°C, yield, 74%).

## 4-(Selenomorpholinosulfonyl)benzeneamine (4)

A solution of N-(4-(selenomorpholinosulfonyl)phenyl)acetamide (1.75 g, 5 mmol) and 10% sodium hydroxide solution (20 mL) was refluxed under stirring for 1h and then allowed to cool to room temperature. The reaction mixture was neutralized with 6M hydrochloric acid solution to pH 8. The reaction mixture was cooled, and the precipitate was filtered off and washed with hot water. The crude product was purified by recrystallization in ethanol to provide compound **4** (1.35 g). White crystal, m.p.201–202°C; yield 88%. $^1$HNMR ($\delta$,ppm,$CDCl_3$) 2.71 (t,4H $SeCH_2$,$^3J_{HH}$ =4.8Hz), 3.43 (t,4H,$NCH_2$,$^3J_{HH}$ =4.8Hz), 4.17 (s,2H,NH), 6.64 (d,2H,Ar—H), 7.45 (d,2H,Ar—H),MS(M/z,%) 306 ($M^+$,4.2).

## 2-Chloro-N-(4-(selenomorpholinosulfonyl)phenyl) Acetamide (5)

A mixture of 4-(selenomorpholinosulfonyl)benzeneamine (3.06 g, 10 mmol) in chloroform (20 mL) and triethylamine (1.2 g, 12 mmol) was treated with 2-chloroacetyl chloride (1.13 g, 10 mmol) in chloroform (5 mL) and stirred for 1 h under 2°C, and standing for overnight at room temperature. The reaction mixture was washed with water. The organic layer was separated and dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the crude product was purified by recrystallization in ethanol to provide compound **5** as a white solid (2.7 g, 71%).

## O,O-Dialkyl 2-oxo-2-(4-(selenomorpholinosulfonyl) phenylamino) Ethylphosphonate (7a–g)

### *General procedure*

A solution of dialkyl phosphite (5 mmol) in dry petroleum ether (20 mL) was treated with 60% sodium hydroxide (0.22 g, 5.5 mmol). The reaction mixture was stirred at room temperature for1 h and concentrated under reduced pressure till half volume. Then the mixture was cooled under ice bathe to 5°C, a solution of 2-chloro-N-(4-(selenomorpholinosulfonyl)phenyl)acetamide (1.91 g, 5.5 mmol)) in acetonitrile (20 mL) was added dropwise and the reaction was allowed to proceed at 70°C for 3 h. Then the reaction mixture was cooled to room temperature and washed with water and extracted with chloroform. The combined organic extracts were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 15% acetone in petroleum ether) to provide title compounds **7**.

### O,O-Dimethyl- 2-oxo-2-(4-(selenomorpholinosulfonyl) phenylamino) ethylphos- phonate(7a)

Light yellow solid, yield, 42%, m.p. 60–62°C. $^1$H NMR ($\delta$,ppm): 2.69–2.77 (m,4H,SeCH$_2$), 3.09 (d,2H,PCH$_2$,$^2J_{PH}$ =20.4Hz), 3.52–3.57 (m, 4H,NCH$_2$), 3.77 (d,6H,OCH$_3$,$^3J_{PH}$=10.7Hz), 7.44–7.78 (m,4H,Ph), 9.53 (s,1H, NH) . IR (cm$^{-1}$): 1697 ($\nu_{C=O}$), 1253 ($\nu_{P=O}$), 1159 ($\nu_{S=O}$), 1027 ($\nu_{P-O-C}$) MS (M/z,%): 456 (M$^+$, 0.43), 306 (2.07), 242 (8.31), 151 (6.32), 123 (8.74), 109 (15.95), 78 (23.51), 63 (25.72), 42 (100). $^{31}$PNMR($\delta$,ppm): 22.15. Anal. Calcd. for $C_{14}H_{21}N_2O_6PSSe$ (456): C, 36.90; H, 4.65; N 6.15; found, C, 36.72; H, 4.71; N, 6.19.

### O,O-Diethyl- 2-oxo-2-(4-(selenomorpholinosulfonyl) phenylamino) ethylphosphonate (7b)

Light yellow solid, yield, 48%, m.p. 74–77°C. $^1$H NMR($\delta$,ppm): 1.38 (t,6H,CH$_3$,$^3J_{HH}$=6.8Hz), 2.72 (m,4H, SeCH$_2$), 3.08 (d,2H,PCH$_2$, $^2J_{PH}$=21.4Hz), 3.45 (m,4H,NCH$_2$), 4.12–4.26 (m, 4H, OCH$_2$), 7.53–7.64 (m,4H,Ph), 9.66 (s, 1H,NH). IR (cm$^{-1}$): 1696 ($\nu_{C=O}$), 1233 ($\nu_{P=O}$), 1160 ($\nu_{S=O}$), 1026 ($\nu_{P—O—C}$). MS(M/z,%): 484 (M$^+$, 0.21), 335 (1.49), 272 (7.77), 179 (5.23), 150 (19.51), 108 (15.97), 92 (17.85), 63 (20.92), 42 (100$^{31}$PNMR($\delta$,ppm): 22.64. Anal. Calcd. for $C_{16}H_{25}N_2O_6PSSe$ (484): C, 39.76; H, 5.21; N 5.80; found, C, 39.48; H, 5.29; N, 6.01.

### O,O-Di(n-propyl)-2-oxo-2-(4-(selenomorpholinosulfonyl) phenylamino) ethylphos- phonate (7c)

Light yellow solid, yield, 56%, m.p. 88-91°C. $^1$H NMR ($\delta$,ppm): 0.99 (t,6H,CH$_3$,$^3J_{HH}$=7.2Hz), 1.73 (m,4H, CH$_2$CH$_3$,$^3J_{HH}$=6.8Hz), 2.71 (m,4H, SeCH$_2$,$^3J_{HH}$=5.3Hz), 3.15 (d,2H,PCH$_2$,$^2J_{PH}$=21.4Hz), 3.41 (m,4H,NCH$_2$,$^3J_{HH}$=4.9Hz), 4.05–4.15 (m,4H,OCH$_2$,$^3J_{HH}$=6.8Hz), 7.46–7.61 (m,4H,Ph), 9.66 (s, 1H,NH). IR (cm$^{-1}$): 1698 ($\nu_{C=O}$), 1233 ($\nu_{P=O}$), 1161 ($\nu_{S=O}$), 1007 ($\nu_{P-O-C}$). MS (M/z,%): 512 (M$^+$, 0.24), 362 (1.37), 298 (6.32), 207 (16.63), 179 (6.17), 150 (17.05), 106 (20.45), 63 (26.37), 42 (100). $^{31}$PNMR($\delta$,ppm): 22.23. Anal. Calcd. for $C_{18}H_{29}N_2O_6PSSe$ (512): C, 42.28; H, 5.72; N 5.48; found, C, 42.41; H, 5.74; N, 5.56.

### O,O-Di(iso-propyl)- 2-oxo-2-(4-(selenomorpholinosulfonyl) phenylamino) ethylphos- phonate (7d)

Light yellow solid, yield, 39%, m.p. 67–69°C. $^1$H NMR ($\delta$,ppm): 1.36 (dd,12H,CH$_3$,$^3J_{HH}$=6.0Hz,$^4J_{PH}$=1.94Hz,) 2.69–2.75 (m,4H, SeCH$_2$), 3.03 (d,2H,PCH$_2$,$^2J_{PH}$=21.4Hz), 3.41-3.47 (m,4H,NCH$_2$), 4.69-4.80

(m,2H,OCH), 7.52–7.64 (m,4H,Ph), 9.74 (s,1H,NH). IR (cm$^{-1}$): 1696 ($\nu_{C=O}$), 1234 ($\nu_{P=O}$), 1160 ($\nu_{S=O}$), 1000 ($\nu_{P—O—C}$). MS(M/z,%): 512 (M$^+$, 0.13), 362 (2.38), 298 (8.39), 179 (4.32), 150 (20.39), 106 (22.81), 63 (28.74), 42 (100). $^{31}$PNMR($\delta$,ppm): 20.15. Anal. Calcd. for $C_{18}H_{29}N_2O_6PSSe$ (512): C, 42.28; H, 5.72; N 5.48; found, C, 42.43; H, 5.68; N, 5.51.

## O,O-Di(n-butyl)- 2-oxo-2-(4-(selenomorpholinosulfonyl) phenylamino) ethylphosphonate (7e)

Light yellow solid, yield, 69%, m.p. 97–99°C. $^1$H NMR ($\delta$,ppm): 0.93 (t,6H,CH$_3$,$^3J_{HH}$=6.8Hz), 1.31–1.49 (m,4H, CH$_2$CH$_3$,$^3J_{HH}$=7.2Hz), 1.61–1.76 (m, 4H,OCH$_2$ CH$_2$,$^3J_{HH}$=7.0Hz), 2.69–2.74 (m,4H,SeCH$_2$, $^3J_{HH}$=4.9Hz), 3.06 (d, 2H,PCH$_2$,$^2J_{PH}$=21.4Hz), 3.42–3.47 (m,4H, NCH$_2$, $^3J_{HH}$=4.9Hz), 4.05-4.16 (m,4H,OCH$_2$,$^3J_{HH}$=6.8Hz), 7.47–7.73 (m,4H,Ph), 9.58 (s,1H,NH). IR (cm$^{-1}$): 1699 ($\nu_{C=O}$), 1281 ($\nu_{P=O}$), 1159 ($\nu_{S=O}$), 1026 ($\nu_{P—O—C}$). MS (M/z,%): 540 (M$^+$, 0.11), 390 (2.41), 235 (10.37), 207 (10.91), 193 (14.36), 150 (35.75), 136 (2.95), 63 (27.14), 57 (100). $^{31}$PNMR ($\delta$,ppm): 22.30. Anal. Calcd. for $C_{20}H_{33}N_2O_6PSSe$ (540): C, 44.53; H, 6.17; N 5.19; found, C, 44.38; H, 6.14; N, 5.21.

## O,O-Di(iso-butyl)-2-oxo-2-(4-(selenomorpholinosulfonyl) phenylamino) ethylphosphonate (7f )

Light yellow solid, yield, 47%, m.p.83–86°C. $^1$H NMR ($\delta$,ppm): 0.93 (d,6H,CH$_3$,$^3J_{HH}$=6.8Hz), 1.34 (d,6H,CH$_3$,$^3J_{HH}$=6.6Hz), 1.61–1.74 (m,2H, CH), 2.69 (m,4H,SeCH$_2$,$^3J_{HH}$=5.8Hz), 3.00 (d,2H, PCH$_2$,$^2J_{PH}$=20.4Hz), 3.46 (m,4H, NCH$_2$,$^3J_{HH}$= 5.4Hz), 4.49–4.55 (m,4H,OCH$_2$,$^3J_{HH}$=5.8Hz), 7.57–7.68 (m,4H, Ph), 9.55 (s, 1H,NH). IR (cm$^{-1}$): 1695 ($\nu_{C=O}$), 1233 ($\nu_{P=O}$), 1160 ($\nu_{S=O}$), 997 ($\nu_{P—O—C}$). MS (M/z,%): 540 (M$^+$,0.27), 390 (4.64), 333 (7.30), 242 (33.90), 207 (30.24), 150 (1.79), 42 (100). $^{31}$PNMR ($\delta$,ppm): 20.75. Anal. Calcd. for $C_{20}H_{33}N_2O_6PSSe$ (540): C, 44.53; H, 6.17; N 5.19; found, C, 44.69; H, 6.23; N, 5.18.

## O,O-Di(benzyl)- 2-Oxo-2-(4-(Selenomorpholinosulfonyl) phenylamino) ethylphosphonate (7g )

Light yellow solid, yield, 45%, m.p.103–106°C. $^1$H NMR ($\delta$,ppm): 2.68–2.74 (m,4H,SeCH$_2$), 3.14 (d,2H,PCH$_2$,$^2J_{PH}$=21.4Hz), 3.38–3.43 (m, 4H,NCH$_2$), 4.98–5.07 (m,4H,OCH$_2$), 7.32–7.68 (m,14H,Ph), 10.04 (s,1H,NH). IR (cm$^{-1}$): 1685 ($\nu_{C=O}$), 1236 ($\nu_{P=O}$), 1162 ($\nu_{S=O}$), 1012 ($\nu_{P-O-C}$). MS (M/z,%)608: C, ,0.14, 458 (1.37), 390 (4.64), 305 (4.23), 275 (7.82), 170 (2.56), 150 (4.37), 91 (100), 77 (53,4), 63 (27.6). $^{31}$PNMR ($\delta$,ppm): 19.06. Anal. Calcd. for $C_{26}H_{29}N_2O_4PSSe$ (608): C, 62.18; H, 5.03; N4.51; found, C, 62.31; H, 5.09; N, 4.46.

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