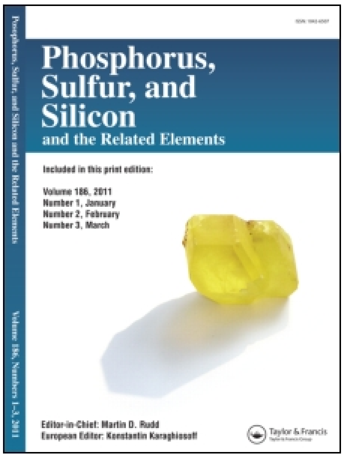

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SYNTHESIS OF 2-ETHOXY CARBONYL PHENYLSELENO AMINOMETHYLENE PHOSPHONATE

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SYNTHESIS OF 2-ETHOXY CARBONYL PHENYLSELENO AMINOMETHYLENE PHOSPHONATE

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A number of 2-ethoxycarbonyl phenylseleno aminomethylene phosphonates have been synthesized by the Mannich-type reaction of 1,2-benzisoselenazol-3(2H)-one, formaldehyde and dialkylphosphite with anhydrous ethanol as the solvent. The structures are supported by elemental analysis, ^{1}H, ^{31}PNMR, Mass and IR spectra. It was found that ethanol participates in the reaction and leads to the opening of 1,2-benzisoselenazol-3(2H)-one to form title compounds.

Keywords: 1,2-benzisoselenazol-3(2H)-one; dialkylphosphite; Mannich-type reaction; C-N bond cleavage

INTRODUCTION

In previous papers[1-3], a number of amino acid ester derivatives of benzisoselenazolone were synthesized from O-chloroselenobenzoyl chloride and an amino acid ester. It was found that these compounds possess anti-lipid peroxidation activity. In order to investigate the reaction further in an attempt to look for compounds with better anti-lipid peroxidation activity, we found that derivatives of benzisoselenazolone containing phosphorus have not been reported. Thus, it was interesting for us to explore their synthesis.

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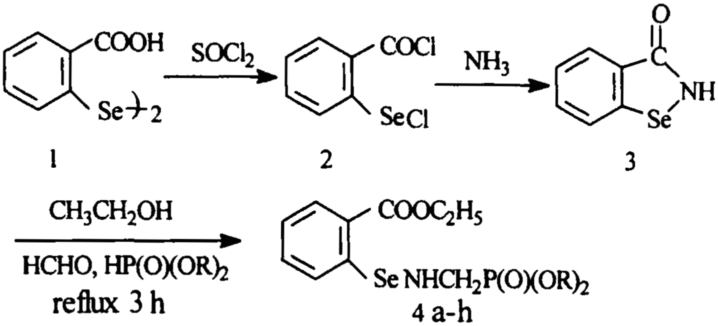
A series of new N-methylene phosphonate benzisoselenazolones should be produced by a Mannich-type reaction of benzisoselenazolone, formaldehyde and dialkyl phosphite in ethanol according to our synthetic approach. Unfortunately, the target materials were not formed. The ring of the benzisoselenazolone was opened in the procedure, as shown in the scheme.



R: 4a, CH_3; 4b, CH_2CH_3; 4c, $CH_2CH_2CH_3$; 4d, $CH(CH_3)_2$; 4e, $CH_2CH_2CH_2CH_3$; 4f, $CH_2CH(CH_3)_2$; 4g, CH_2Ph; 4h, Ph

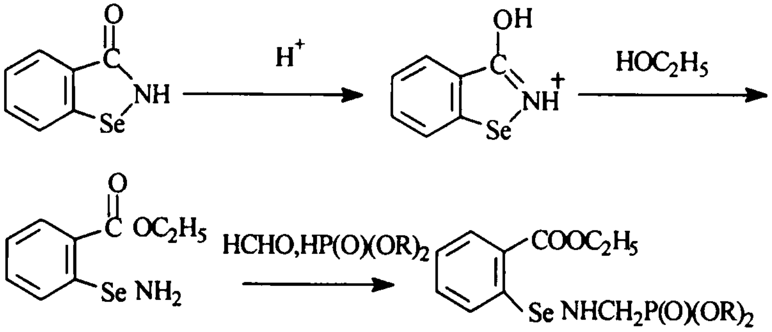
RESULTS AND DISCUSSION

First, treatment of bis(o-carboxyphenyl)diselenide **1** with thionyl chloride in DMF at reflux temperature for 3h afforded o-chloroselenobenzoyl chloride **2**. Then, benzisoselenazolone **3** was obtained by the reaction of **2** with ammonia in toluene. Finally, benzisoselenazolone was treated with formaldehyde and a series of dialkyl phosphites in ethanol to give **4**.

SYNTHESIS OF COMPOUND 4

The Mannich-type reaction of trivalent phosphorus is a facile method for the preparation of phosphonate compounds[4,5], Benzisoselenazolone was allowed to react with dialkyl phosphites and formaldehyde to produce **4a-h** in 36%-69% yields.

In order to explain the result of ring opening of benzisoselenazolone, a series of experiments were carried out. It was found that a complicate mixture was gained when used aprotic solvent, such as THF or acetonitrile. It was also found that **3** is stable in ethanol from 30°C to 80°C, but when a mineral acid, such as phosphorous acid, was added to the mixture of **3** and ethanol at 80°C, the ring of benzisoselenazolone was opened and a new substance, 2-ethoxycarbonyl phenylselenoamine, was produced. We suggest a possible mechanism:



The structure of 4 were confirmed by ^{1}HNMR, ^{31}PNMR, IR, MS spectroscopy and elemental analysis. In the ^{1}HNMR spectra of compound **4**, the proton in PCH appeared as a doublet in the range of δ 4.82–5.32ppm ($^2J_{PH}$ = 7.8–17.0Hz). The chemical shift of the labile proton in the NH of compound **4** is 8.14–8.38 ppm, which didn't disappear when deuterated. This suggestes a strong intramolecular hydrogen bond; the ^{31}PNMR spectra of **4** revealed a singlet at the range of δ 15.7–24.8ppm.

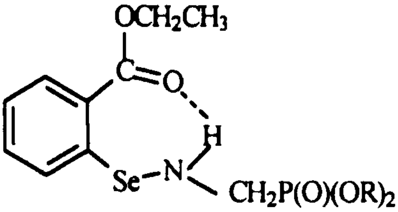
The IR spectra of compound **4** showed the existence of the group P=O(1230–1250cm^{-1}). The presence of the intramolecular hydrogen bond structure is consistent with the observed IR data for **4**, where the absorption band for the C=O stretching appears at 1659–1665 cm^{-1} instead of the more typical range of 1715–1730 cm^{-1} for conjugated ester C=O groups.

The EI-MS spectra of **4** demonstrated the molecular ion peak (M^+). Other ions were consistent with their structures and can be clearly assigned. Because there are two major isotops of Selenium (approximately

2:1), the ion abundance ratio which contain two isotopes of selenium is about 2:1. For example, ion abundance ratios of compound **4c** are:

M/e	abundance
423:421(M^+)	2.35:1.18
394:392	13.54:6.89
377:375	8.98:4.25
349:347	16.44:8.15
265:263	21.39:10.26
258:256	4.02:2.05
184:182	20.82:10.47

Compound **4** gives the fragmentary ion peaks of mass 28,29,45 and 73. We can therefore conclude that the structure of compound **4** is:



EXPERIMENTAL

Elemental analysis was performed with a CHN Carlo Erba elementary analyzer. ^{1}HNMR spectra were recorded with a Varian XL200 spectrometer, TMS was used as an internal standard for ^{1}HNMR, and 85% H_3PO_4 was used as an external standard for ^{31}PNMR. The IR spectra were measured by using a SP3–100 instrument, Mass spectra were recorded with a HP-5988A spectrometer.

The reagents and solvents were available commerially and purified according to conventional methods; colunm chromatography was performed on silica gel G(10–40 μ, Hai Yang Chemical Factory of Qingdao).

O-Chloroseleno benzoyl chloride **2**[6], benzisoselenazol-3(2H)-one **3**[7] and dialkylphosphite[8] have been prepared following literature methods.

Dialkyl 2-ethoxycarbonyl phenylselenoaminophosphates 4a-h

General procedure

A mixture of **3** (2.0g, 10.1mmol), formaldehyde (1.68g, 36%, 20.2mmol), 5mL ethanol was added to a four-necked flask equipped with a reflux condenser and a thermometer, nitrogen gas was passed to the reaction mixture to prevent from oxidation. To the stirred solution was dropped 10.1mmol of dialkylphosphite slowly at ambient temperature. The stirring was kept for 1h, the solution was heated under reflux at 80°C for 3h, the solution was removed under vacuum to yield crude products. Compound **4** were further purified by VLC[9].

Compound 4a

Yield: 57%, Oily liquid

IR(KBr, cm^{-1}) 3324(NH), 1658(C=O), 1237(P=O)

$C_{12}H_{18}NO_5PSe$	calc.	C 39.32	H 4.96	N 3.83
366.21	found	39.57	4.87	3.76

^{1}HNMR(δ, ppm) 1.23 (t, 3H, $OCH_2\underline{CH_3}$, $^3J_{HH}$=7.0Hz), 3.74 (q, 2H, $O\underline{CH_2}CH_3$, $^3J_{HH}$=7.0Hz), 3.82 (d, 6H, OCH_3, $^3J_{PH}$=13.1Hz), 5.10 (d, 2H, PCH, $^2J_{PH}$=17.0Hz), 7.36–7.82(m, 4H, Ar-H), 8.14(w, 1H, NH)

MS(M/e,%): 367(4.2), 338(12.6), 322(18.4), 294(46.2), 184(100) ^{31}PNMR(δ, ppm): 20.5

Compound 4b

Yield: 68%, Oily liquid

IR(KBr, cm^{-1}) 3300(NH), 1660(C=O), 1234(P=O)

$C_{14}H_{22}NO_5PSe$	calc.	C 42.62	H 5.64	N 3.55
394.16	found	42.37	5.57	3.43

^{1}HNMR(δ, ppm) 1.25 (t, 3H, $OCH_2\underline{CH}_3$, $^3J_{HH}$=6.8Hz), 1.39 (t, 6H, $POCH_2\underline{CH}_3$, $^3J_{HH}$=7.0Hz), 3.72 (q, 2H, $O\underline{CH}_2CH_3$, $^3J_{HH}$=7.2Hz), 4.20 (m, 4H, $POCH_2$), 4.90 (d, 2H, PCH, $^2J_{PH}$=9.8Hz), 7.34–7.82(m, 4H, Ar-H), 8.19(w, 1H, NH)

MS(M/e,%): 395(2.6), 366(15.7), 349(9.4), 321(30.4), 265(14.4), 184(23.3), 77(13.2), 65(26.1), 59(100)

^{31}PNMR(δ, ppm): 16.6

Compound 4c

Yield: 73%, Oily liquid

IR(KBr, cm^{-1}) 3298(NH), 1659(C=O), 1234(P=O)

$C_{16}H_{26}NO_5PSe$	calc.	C 45.50	H 6.21	N 3.32
422.32	found	45.78	6.27	3.41

^{1}HNMR(δ, ppm) 0.95 (t, 6H, $CH_2CH_2\underline{CH}_3$, $^3J_{HH}$=7.2Hz), 1.22 (t, 3H, $OCH_2\underline{CH}_3$, $^3J_{HH}$=7.2Hz), 1.71 (m, 4H, $CH_2\underline{CH}_2CH_3$, $^3J_{HH}$=6.4Hz), 3.71 (q, 2H, $O\underline{CH}_2CH_3$, $^3J_{HH}$=7.2Hz), 4.06 (m, 4H, $O\underline{CH}_2CH_2CH_3$), 4.82 (d, 2H, PCH, $^2J_{PH}$=7.8Hz), 7.24–7.78(m, 4H, Ar-H), 8.19(w, 1H, NH)

MS(M/e,%): 423(2.4), 394(13.5), 377(9.0), 349(16.5), 265(21.4), 184(20.8), 99(23), 59(97.1), 43(100),

^{31}PNMR(δ, ppm): 18.4

Compound 4d

Yield: 54%, Oily liquid

IR(KBr, cm^{-1}) 3294(NH), 1661(C=O), 1234(P=O)

$C_{16}H_{26}NO_5PSe$	calc.	C 45.50	H 6.21	N 3.32
422.32	found	45.64	6.33	3.27

^{1}HNMR(δ, ppm) 1.23 (t, 3H, $OCH_2\underline{CH}_3$, $^3J_{HH}$=7.0Hz), 1.30 (d, 6H, $OCH(\underline{CH}_3)_2$, $^3J_{HH}$=6.2Hz), 1.38 (d, 6H, $OCH(\underline{CH}_3)_2$, $^3J_{HH}$=6.0Hz), 3.71 (q, 2H, $O\underline{CH}_2CH_3$, $^3J_{HH}$=7.2Hz), 4.79 (m, 2H, $O\underline{CH}(CH_3)_2$), 4.91 (d, 2H, PCH, $^2J_{PH}$=13.0Hz), 7.29–7.84(m, 4H, Ar-H), 8.38(w, 1H, NH)

MS(M/e,%): 394(0.6), 377(0.7), 349(0.5), 305(1.2), 263(3.7), 184(100), 156(67.1), 76(14.3), 59(8.8), 43(40.1)

^{31}PNMR(δ, ppm): 15.7

Compound 4e

Yield: 65%, Oily liquid

IR(KBr, cm^{-1}) 3291(NH), 1663(C=O), 1235(P=O)

$C_{18}H_{30}NO_5PSe$	calc.	C 48.00	H 6.71	N 3.11
450.38	found	47.92	6.67	3.04

^{1}HNMR(δ, ppm) 0.93 (t, 6H, $CH_2CH_2CH_2\underline{CH}_3$, $^3J_{HH}$=7.2Hz), 1.22 (t, 3H, $OCH_2\underline{CH}_3$, $^3J_{HH}$=7.0Hz), 1.40 (m, 4H, $CH_2CH_2\underline{CH}_2CH_3$, $^3J_{HH}$=7.4Hz), 1.68 (m, 4H, $CH_2\underline{CH}_2CH_2CH_3$, $^3J_{HH}$=6.6Hz), 3.72 (t, 2H, $O\underline{CH}_2CH_3$, $^3J_{HH}$=7.0Hz), 4.13 (m, 4H, $O\underline{CH}_2CH_2CH_2CH_3$), 4.91 (d, 2H, PCH, $^2J_{PH}$=9.4Hz), 7.28–7.79(m, 4H, Ar-H), 8.27(w, 1H, NH)

MS(M/e,%): 405(0.7), 377(1.25), 321(1.61), 213(13.5), 211(6.73), 184(33.8), 156(22.4), 57(14.4), 41(100),

^{31}PNMR(δ, ppm): 16.8

Compound 4f

Yield: 43%, Oily liquid

IR(KBr, cm^{-1}) 3296(NH), 1665(C=O), 1234(P=O)

$C_{18}H_{30}NO_5PSe$	calc.	C 48.00	H 6.71	N 3.11
450.38	found	47.69	6.85	3.24

^{1}HNMR(δ, ppm) 0.93 (d, 12H, $CH(\underline{CH}_3)_2$, $^3J_{HH}$=6.4Hz), 1.24 (t, 3H, $OCH_2\underline{CH}_3$, $^3J_{HH}$=6.6Hz), 1.98 (m, 2H, $\underline{CH}(CH_3)_2$), 3.73 (t, 2H, $O\underline{CH}_2CH_3$, $^3J_{HH}$=7.2Hz), 3.90 (m, 4H, $PO\underline{CH}_2CH(CH_3)_2$), 4.91 (d, 2H, PCH, $^2J_{PH}$=9.4Hz), 7.28–7.79(m, 4H, Ar-H), 8.32(w, 1H, NH)

MS(M/e,%): 451(2.2), 422(7.9), 405(5.1), 377(3.5), 321(3.6), 265(18.8), 184(17.5), 156(5.8), 57(87.2), 43(100),

^{31}PNMR(δ, ppm): 17.5

Compound 4g

Yield: 56%, m.p. 56°C

IR(KBr, cm^{-1}) 3308(NH), 1659(C=O), 1225(P=O)

$C_{24}H_{26}NO_5PSe$	calc.	C 55.61	H 5.05	N 2.70
518.41	found	55.46	5.13	2.68

^{1}HNMR(δ, ppm) 1.24 (t, 3H, $OCH_2\underline{CH}_3$, $^3J_{HH}$=7.4Hz), 3.66 (q, 2H, $O\underline{CH}_2CH_3$, $^3J_{HH}$=7.0Hz), 4.32 (d, 4H, $PO\underline{CH}_2Ph$), 5.26 (d, 2H, PCH, $^2J_{PH}$=14.5Hz), 7.01–7.84(m, 14H, Ar-H), 8.29(w, 1H, NH)

MS(M/e,%): 490(1.4), 474(4.6), 442(14.3), 412(10.6), 365(23.7), 184(28.7), 91(100), 77(13.7), 65(32.2)

^{31}PNMR(δ, ppm): 21.3

Compound 4h

Yield: 42%, m.p. 97°C

IR(KBr, cm^{-1}) 3319(NH), 1647(C=O), 1238(P=O)

$C_{22}H_{22}NO_5PSe$	calc.	C 55.88	H 4.52	N 2.86
490.35	found	55.97	4.46	2.78

^{1}HNMR(δ, ppm) 1.26(t, 3H, $OCH_2\underline{CH}_3$, $^3J_{HH}$=7.6Hz), 3.70 (q, 2H, $O\underline{CH}_2CH_3$, $^3J_{HH}$=6.8Hz), 5.32 (d, 2H, PCH, $^2J_{PH}$=16.5Hz), 7.15–7.88(m, 14H, Ar-H), 8.37(w, 1H, NH)

MS(M/e,%): 491(1.9), 462(5.6), 385(4.5), 308(10.7), 184(100), 156(78.0), 77(43.4), 63(23.6)

^{31}PNMR(δ, ppm): 24.8

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