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ONE-POT SYNTHESIS OF 2-IMINO-1,3-OXASELENOLANES BY REACTION OF ISOSELENOCYANATES WITH 2-BROMOETHANOL

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Abstract – One-pot synthesis of 2-imino-1,3-oxaselenolanes has been achieved by reactions of isoselenocyanates with 2-bromoethanol in good to excellent yields. The structure of the 2-imino-1,3-oxaselenolanes was confirmed by spectroscopic and X-ray analysis. The thermal rearrangement of 2-imino-1,3-oxaselenolanes to 1,3-selenazolidin-2-one is observed for the first time.

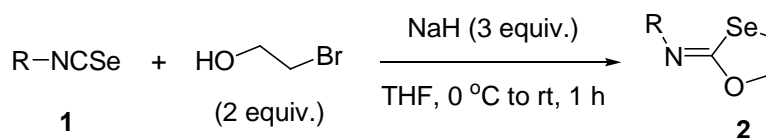
INTRODUCTION

In recent years, interest in the synthesis of compounds containing selenium has increased because of their interesting reactivities¹ and their potential biological activity. The biological and medicinal properties of selenium and organoselenium compounds are increasingly appreciated, mainly due to their antioxidant, antitumor, antimicrobial, and antiviral properties.² The 1,3-selenolanes have been found to have anticancer activity.³ From the result of the investigation of structure-biological activity relationships, 1,3-selenolane skeleton bearing specific substituent groups has been indicated to influence strongly the activity. Therefore the preparation of many kinds of 1,3-selenolane derivatives has been desired for the development of potential agents. On the other hand, there are some drawbacks of the syntheses of selenium heterocycles as they often involve the use of toxic selenium reagents, which are difficult to handle and to store. In this context, isoselenocyanates have been emerged as a powerful tool for the synthesis of selenium-containing heterocycles, since they are easy to prepare and store and are safe to handle.⁴ Our group has shown the utility of isoselenocyanates as building blocks for the synthesis of selenium heterocycles.⁵ Recently we have reported the synthesis of 2-imino-1,3-oxaselenolanes *via* iodocyclization reaction of *O*-allylselenocarbamates,⁶ whereas Kambe et al. reported the synthesis of

2-imino-1,3-selenolanes *via* intramolecular cycloaddition reaction of selenolates to carbon-carbon triple bonds.⁷ By way of contrast, no report on the synthesis of 2-imino-1,3-oxaselenolanes by the reaction of 2-bromoethanol with isoselenocyanates in the literature. Herein, we report the one-pot synthesis of 2-imino-1,3-oxaselenolanes and their rearrangement to 1,3-selenazolidin-2-one.

RESULTS AND DISCUSSION

The starting alkyl and aryl isoselenocyanates (**1**) for our approach were prepared by reactions of *N*-substituted formamides with an excess of triphosgene, selenium and triethylamine according to the previous literature.⁸ First, the reaction of isoselenocyanates (R = *p*-CH₃-C₆H₄) **1a** with 2-bromoethanol using 1.1 equiv. of NaH in THF was examined, to our delight the reaction took place readily at room temperature and the cyclization product **2a** was obtained in 52% yield after work-up of the reaction mixture. To improve the yield of reaction, different conditions were then screened. As shown in Scheme 1, 2.0 equiv. of 2-bromoethanol was a suitable for the cyclization reaction, furthermore the reaction was influenced by the amount of base used and the best result was obtained when 3.0 equiv. of NaH was used (92%, Table 1). The structure of **2a** was elucidated by studies of IR, ¹H-, ¹³C-, ⁷⁷Se-NMR, correlation spectroscopy (COSY), hetero-nuclear multiple quantum coherence (HMQC), hetero-nuclear multiple-bond connectivity (HMBC), MS, elemental analysis and X-ray analysis.



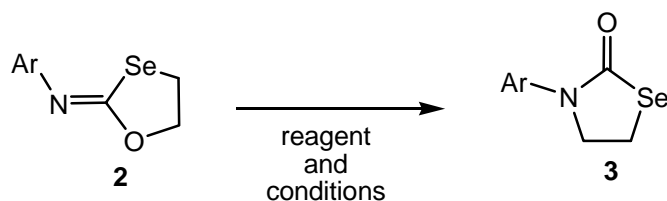
Scheme 1

Table 1. Reaction of isoselenocyanates with 2-bromoethanol

Product (2)	Yield (%) ^a	⁷⁷ Se NMR (δ)	Product (2)	Yield (%) ^a	⁷⁷ Se NMR (δ)
	92	285.6		79	291.3
	93	286.9		78	269.0
	96	290.6		45	255.2

a: Isolated yield.

al.¹⁴ This prompted us to examine its use of indium as a catalyst in the thermal rearrangement reaction. No rearrangement reaction was observed when the In metal (1 equiv.) was used in the reaction and the 2-(4-methylphenyl)imino-1,3-oxaselenolane (**2a**) was recovered in quantitative (entry 3). When the reaction of 1,3-oxaselenolane **2** with ethyl bromoacetate (2.0 equiv.) in the presence of indium metal (2.2 equiv.) using THF as the solvent produced the rearranged product **3a** in 27 % yield (entry 4). Toluene was found to be good solvent for the rearrangement reaction (entry 5) and best results were obtained when the reaction time was shortened to 9 h (Table 2, entries 6 and 7). To the best of our knowledge there is no report on the rearrangement of 2-imino-1,3-oxaselenolane in the literature. In the present reaction indium as well as ethyl bromoacetate is needed for the rearrangement reaction.



Scheme 2

Table 2. Reaction of 1,3-oxaselenolanes **2** with indium and ethyl bromoacetate

Entry	Ar	In (equiv.)	BrCH ₂ CO ₂ Et (equiv.)	Solvent	Temp.	Time	Yield (%) ^a
1	<i>p</i> -MeC ₆ H ₄	—	—	THF	reflux	16 h	0 (3a)
2	<i>p</i> -MeC ₆ H ₄	—	—	Toluene	100 °C	4 days	0 (3a)
3	<i>p</i> -MeC ₆ H ₄	1.0	—	THF	reflux	26 h	0 (3a)
4	<i>p</i> -MeC ₆ H ₄	2.2	2.0	THF	reflux	24 h	27 (3a) ^b
5	<i>p</i> -MeC ₆ H ₄	2.2	2.0	Toluene	100 °C	24 h	26 (3a)
6	<i>p</i> -MeC ₆ H ₄	2.2	2.0	Toluene	100 °C	9 h	30 (3a)
7	C ₆ H ₅	2.2	2.0	Toluene	100 °C	9 h	37 (3b)

^aIsolated yield. ^bReaction results are not consistent.

In conclusion, we have demonstrated one-pot synthesis of 2-imino-1,3-oxaselenolane (**2**) by reactions of the isoselenocyanates (**1**) with 2-bromoethanol. The rearrangement of 2-imino-1,3-oxaselenolanes (**2**) to 1,3-selenazolidin-2-one (**3**) is observed for the first time. Further expansion of current strategies is in progress.

EXPERIMENTAL

General

The chemical shifts of ^{77}Se NMR were expressed in ppm deshielded with respect to neat Me_2Se in CDCl_3 . $^2J(^{77}\text{Se}-^1\text{H})$ values are the satellites of the ^1H NMR spectra. Melting points were measured by a Yanagimoto micromelting point apparatus (uncorrected).

General procedure for the synthesis of 2-(4-methylphenyl)imino-1,3-oxaselenolane (2a) To a stirred solution of NaH (60%, 59.5 mg, 1.49 mmol) in dry THF (1.5 mL) was added 4-methylphenyl isoselenocyanate (98.1 mg, 0.50 mmol) at 0 °C. After 10 min 2-bromoethanol (95%, 74.5 μL , 1.00 mmol) was added and stirring was continued for 1 h at rt. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with Et_2O , washed with water and brine. The combined organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel with $\text{Et}_2\text{O} / n\text{-hexane}$ (1/1) as the eluent to give **2a** (110.5 mg, yield 92%) mp (n-Hexane/EtOAc) 95 °C; IR (KBr): 1646, 1503 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 2.33 (3H, s, CH_3) 3.43 (2H, t, $J = 6.4$ Hz, $^2J(^{77}\text{Se}-^1\text{H}) = 26.1$ Hz, CH_2), 4.50 (2H, t, $J = 6.4$ Hz, CH_2), 6.85 (2H, d, $J = 8.2$ Hz, Ar), 7.12 (2H, d, $J = 8.2$ Hz, Ar); ^{13}C NMR (100 MHz, CDCl_3): δ 20.9 (q), 26.6 (t), 71.1 (t), 120.6 (d), 129.8 (d), 134.0 (s), 148.0 (s), 162.2 (s); ^{77}Se NMR (95 MHz, CDCl_3): δ 285.2; MS (EI): $m/z = 241$ [M^+]; Anal. Calcd for $\text{C}_{10}\text{H}_{11}\text{NOSe}$: C, 50.01; H, 4.62; N, 5.83. Found: C, 49.65; H, 4.64; N, 5.79.

2-Phenylimino-1,3-oxaselenolane (2b) mp (n-Hexane/EtOAc) 91 °C; IR (KBr): 1651, 1590 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 3.44 (2H, t, $J = 6.4$ Hz, $^2J(^{77}\text{Se}-^1\text{H}) = 24.7$ Hz, CH_2), 4.51 (2H, t, $J = 6.4$ Hz, CH_2), 6.97 (2H, dd, $J = 7.8, 7.8$ Hz, Ar), 7.15 (1H, t, $J = 7.8$ Hz, Ar), 7.33 (2H, t, $J = 7.8$ Hz, Ar); ^{13}C NMR (100 MHz, CDCl_3): δ 26.6 ($^1J(^{77}\text{Se}-^{13}\text{C}) = 54.6$ Hz, t), 71.0 (t), 120.6 (d), 124.3 (d), 129.0 (d), 150.3 (s), 162.4 (s); ^{77}Se NMR (95 MHz, CDCl_3): δ 286.9; MS (EI): $m/z = 227$ [M^+]; Anal. Calcd for $\text{C}_9\text{H}_9\text{NOSe}$: C, 47.80; H, 4.01; N, 6.19. Found: C, 47.46; H, 3.83; N, 6.17.

2-(4-Chlorophenyl)imino-1,3-oxaselenolane (2c) mp (n-Hexane/EtOAc) 97 °C; IR (KBr): 1645, 1589, 841 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 3.44 (2H, t, $J = 6.4$ Hz, $^2J(^{77}\text{Se}-^1\text{H}) = 24.6$ Hz, CH_2), 4.50 (2H, t, $J = 6.4$ Hz, CH_2), 6.88 (2H, d, $J = 8.7$ Hz, Ar), 7.27 (2H, d, $J = 8.7$ Hz, Ar); ^{13}C NMR (100 MHz, CDCl_3): δ 26.8 ($^1J(^{77}\text{Se}-^{13}\text{C}) = 53.6$ Hz, t), 71.3 (t), 122.2 (d), 129.2 (d), 129.7 (s), 148.9 (s), 163.1 (s); ^{77}Se NMR (95 MHz, CDCl_3): δ 290.6; MS (EI): $m/z = 261$ [M^+]; Anal. Calcd for $\text{C}_9\text{H}_8\text{ClNOSe}$: C, 41.48; H, 3.09; N, 5.38. Found: C, 41.29; H, 3.16; N, 5.31.

2-(2-Naphthyl)imino-1,3-oxaselenolane (2d) mp (n-Hexane/EtOAc) 106 °C; IR (KBr): 1653, 1619 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 3.45 (2H, t, $J = 6.4$ Hz, $^2J(^{77}\text{Se}-^1\text{H}) = 25.7$ Hz, CH_2), 4.55 (2H, t, $J = 6.4$ Hz, CH_2), 7.16 (1H, dd, $J = 1.9, 8.7$ Hz, Ar), 7.34 (1H, s, Ar), 7.38-7.48 (2H, m, Ar), 7.75-7.83 (3H, m, Ar); ^{13}C NMR (100 MHz, CDCl_3): δ 26.7 (t), 71.3 (t), 116.7 (d), 121.9 (d), 124.9 (d), 126.2 (d), 127.5 (d), 127.7 (d), 129.2 (d), 131.0 (s), 134.1 (s), 148.4 (s), 162.8 (s); ^{77}Se NMR (95 MHz, CDCl_3): δ 291.3; MS (EI): $m/z = 277$ [M^+]; Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{NOSe}$: C, 56.53; H, 4.01; N, 5.07. Found: C, 56.09; H, 4.00;

N, 5.12.

2-Benzylimino-1,3-oxaselenolane (2e) Yellow oil; IR (KBr): 1666, 1560 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 3.42 (2H, t, $J = 6.4$ Hz, $^2J(^{77}\text{Se}-^1\text{H}) = 23.4$ Hz, CH_2), 4.30 (2H, s, CH_2), 4.32 (2H, t, $J = 6.4$ Hz, CH_2), 7.20-7.35 (5H, m, Ar); ^{13}C NMR (100 MHz, CDCl_3): δ 27.1 ($^1J(^{77}\text{Se}-^{13}\text{C}) = 47.9$ Hz, t), 60.8 (t), 70.1 (t), 126.8 (d), 127.5 (d), 128.2 (d), 139.0 (s), 160.8 (s); ^{77}Se NMR (95 MHz, CDCl_3): δ 269.0; MS (EI): $m/z = 241$ [M^+]; Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{Se}$: C, 50.10; H, 4.62; N, 5.83. Found: C, 49.63; H, 4.97; N, 5.76.

2-Cyclohexylimino-1,3-oxaselenolane (2f) Colorless oil; IR (KBr): 1669, 1544 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.16-1.47 (5H, m, ring CH_2), 1.57-1.65 (1H, m, ringCH), 1.70-1.80 (4H, m, ring CH_2), 2.46-2.54 (1H, m, ringCH), 3.42 (2H, t, $J = 6.4$ Hz, $^2J(^{77}\text{Se}-^1\text{H}) = 25.7$ Hz, CH_2), 4.29 (2H, t, $J = 6.4$ Hz, CH_2); ^{13}C NMR (100 MHz, CDCl_3): δ 24.6 (t), 25.5 (t), 26.5 (t), 33.7 (t), 67.2 (d), 69.5 (t), 157.0 (s); ^{77}Se NMR (95 MHz, CDCl_3): δ 255.2; MS (EI): $m/z = 233$ [M^+]; Anal. Calcd for $\text{C}_9\text{H}_{15}\text{NOSe}$: C, 46.56; H, 6.51; N, 6.03. Found: C, 46.50; H, 6.56; N, 5.87.

General procedure for the synthesis of 3-(4-Methylphenyl)-1,3-selenazolidin-2-one (3a) To a stirred solution of 2-(4-methylphenyl)imino-1,3-oxaselenolane (**2a**) (48.6 mg, 0.20 mmol) in toluene (2 mL) was added indium (51.2 mg, 0.44 mmol) and ethyl bromoacetate (44.3 μL , 0.40 mmol) at rt and stirring was continued for 9 h at 100 $^\circ\text{C}$. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and filtered through bed of celite, extracted with CH_2Cl_2 . The combined organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel with EtOAc / *n*-hexane (1/10) as the eluent to give **3a** (14.4 mg, yield 30%) mp (n-Hexane/EtOAc) 97 $^\circ\text{C}$; IR (KBr): 1667, 1544 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 2.33 (3H, s, CH_3), 3.44 (2H, t, $J = 6.9$ Hz, $^2J(^{77}\text{Se}-^1\text{H}) = 25.7$ Hz, CH_2), 4.09 (2H, t, $J = 6.9$ Hz, CH_2), 7.17 (2H, d, $J = 8.2$ Hz, Ar), 7.22 (2H, d, $J = 8.2$ Hz, Ar); ^{13}C NMR (100 MHz, CDCl_3): δ 20.7 (t), 20.9 (q), 52.7 (t), 123.2 (d), 129.6 (t), 135.9 (s), 136.8 (s), 168.9 (s); ^{77}Se NMR (95 MHz, CDCl_3): δ 323.2; MS (EI): $m/z = 241$ [M^+]; Anal. Calcd for $\text{C}_{10}\text{H}_{11}\text{NOSe}$: C, 50.01; H, 4.62; N, 5.83. Found: C, 50.05; H, 4.69; N, 5.76.

3-Phenyl-1,3-selenazolidin-2-one (3b) mp (n-Hexane/EtOAc) 72 $^\circ\text{C}$; IR (KBr): 1662 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 3.45 (2H, t, $J = 6.8$ Hz, $^2J(^{77}\text{Se}-^1\text{H}) = 26.6$ Hz, CH_2), 4.13 (2H, t, $J = 6.4$ Hz, CH_2), 7.18-7.2 (1H, m, Ar), 7.33-7.40 (4H, m, Ar); ^{13}C NMR (100 MHz, CDCl_3): δ 20.7 (t), 52.4 (t), 123.1 (d), 125.9 (d), 129.1 (d), 139.4 (s), 169.0 (s); ^{77}Se NMR (95 MHz, CDCl_3): δ 326.4; MS (EI): $m/z = 227$ [M^+]; Anal. Calcd for $\text{C}_9\text{H}_9\text{NOSe}$: C, 47.80; H, 4.01; N, 6.19. Found: C, 48.15; H, 4.26; N, 5.97.

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