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Article

A Convenient Preparation of *N*-Alkyl-2,5-dihydroisoxazoles from *O*-Allyl Oximes

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The organoselenium-induced ring-closure reaction of *O*-allyl oximes gave cyclic iminium salts, which reacted with Grignard reagents to produce *N*-alkyl-4-phenylselenoisoxazolidines. 2,5-Dihydroisoxazoles could be obtained in good yields by subsequent selenoxide *syn*-elimination.

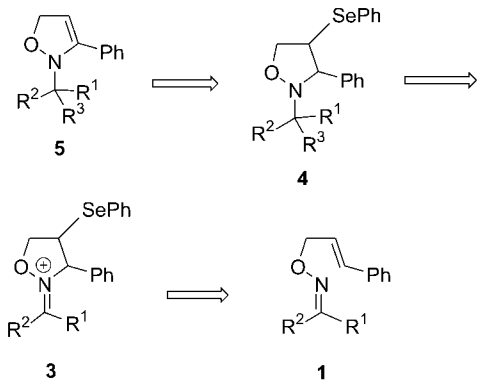
Keywords organoselenium, *O*-allyl oximes, 2,5-dihydroisoxazole, selenoxide *syn*-elimination, intramolecular cyclization

Introduction

2,5-Dihydroisoxazoles are synthetically useful intermediates.[1] Reports concerning the synthesis of 2,5-dihydroisoxazoles include the modification of cyclic compounds[2-4] and intermolecular cyclization reaction.[5,6] However to the best of our knowledge, the synthesis of *N*-alkyl-2,5-dihydroisoxazoles via intramolecular cyclization, especially the synthesis of *N*-tertiary alkyl-2,5-dihydroisoxazole has not been reported. Herein, we wish to report a facile and efficient synthesis of *N*-alkyl-2,5-dihydroisoxazoles via electrophilic selenium-induced intramolecular cyclization followed by deselenenylation reaction of *O*-allyl oximes.

Examination of the general skeleton of 2,5-dihydroisoxazolines **5** showed us a possibility that the C(3)—C(4) double bond might be formed via oxidative-*syn*-selenoxide elimination of intermediate isoxazolidines **4,** which could be obtained by selenium-induced intramolecular cyclization of *O*-allyl oximes **1** followed by the reaction of cyclic iminium salts **3** with Grignard reagents (Scheme 1). Tiecco *et al.*[7] have reported that cyclic iminium salts **3** could react with water and $NaBH_4$ to afford isoxazolidines. However, the addition of Grignard reagents to the cyclic iminium salts **3** has not been reported. Therefore, treatment *O*-allyl oxime **1a** with phenylselenenyl bromide at room temperature for 1.5 h was followed by the reaction of the putative cyclic iminium salt of isoxazolidine **3a** with methyl magnesium iodide under the different conditions (Table 1). The reaction of methyl magnesium iodide (2.0 equiv.) at room temperature for 3 h proceeded smoothly to give 2-(1-phenylethyl)-3-phenyl-4-phenyl-selenoisoxazolidine **4a** in 86% yield (Table 1, entry 7) as a single *trans* stereoisomer, which was confirmed by ^{1}H NMR spectra. The coupling constant ($J_{3,4}$) of 5.6 Hz for **4a** (Table 2, Entry 1) was in agreement with the values for $J_{3,4}$ of *trans*-3-substituted-4-phenylselenoisoxazolidines[7] and *trans*-3,4-substituted isoxazolidines[8] (Scheme 2).

Scheme 1



In order to extend the scope of the method, various *O*-allyl oximes were chosen as substrates to perform selenium-induced intramolecular cyclization and the subsequent treatment of R^3MgX to afford *N*-alkyl-selenoisoxazolidines **4** in good yields. The results are summarized in Table 2.

As can be seen from Table 2, alkyl (Entries 1, 2, 5, 6, 7), aryl (Entry 3) and allyl (Entry 4) magnesium halide can easily react with the cyclic iminium salts to afford *N*-substituted isoxazolidines. *N*-Tertiary alkyl isoxazolidine **4g** (Entry 7) was also conveniently obtained from 3-pentanone oxime by the treatment of phenylselenenyl bromide and the methyl magnesium iodide in 80% yield.

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Scheme 2

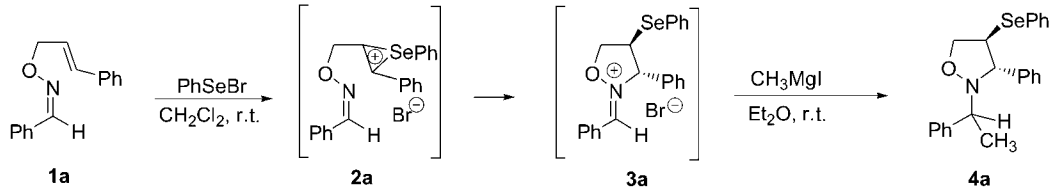
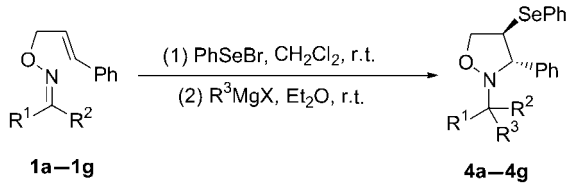


Table 1 Reaction of MeMgI with **3a** under different reaction conditions

Entry	Solvent	Temp./℃	Time/h	Yield[a] /% of **5a**
1	CH_2Cl_2-THF (*V*/*V*=2/1)	0	1.0	21
2	CH_2Cl_2-Et_2O (*V*/*V*=2/1)	0	2.0	46
3	CH_2Cl_2-Et_2O (*V*/*V*=2/1)	0	3.0	64
4	CH_2Cl_2-Et_2O (*V*/*V*=2/1)	0	4.0	67
5	CH_2Cl_2-THF (*V*/*V*=2/1)	r.t.	1.0	43
6	CH_2Cl_2-Et_2O (*V*/*V*=2/1)	r.t.	2.0	70
7	CH_2Cl_2-Et_2O (*V*/*V*=2/1)	r.t.	3.0	86
8	CH_2Cl_2-Et_2O (*V*/*V*=2/1)	r.t.	4.0	84

[a] Isolated yield.

Table 2 Preparation of *N*-alkyl-selenoisoxazolidines



Entry	R^1	R^2	R^3	Product [a]	Yield [b]/%
1	C_6H_5	H	CH_3	**4a**	86
2	C_6H_5	H	C_2H_5	**4b**	84
3	C_6H_5	H	C_6H_5	**4c**	80
4	*p*-$CH_3C_6H_4$	H	$CH_2CH=CH_2$	**4d**	78
5	*p*-ClC_6H_4	H	CH_3	**4e**	82
6	*p*-ClC_6H_4	H	C_2H_5	**4f**	82
7	C_2H_5	C_2H_5	CH_3	**4g**	80

[a] All products were identified by ^{1}H NMR, IR, MS and elemental analysis; [b] isolated yield.

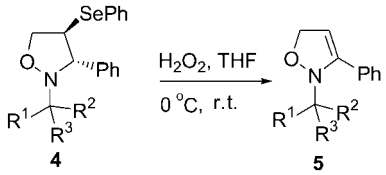
Then, some oxidative-*syn*-selenoxide eliminations of the compounds **4** were carried out with hydrogen peroxide (30%) at 0 ℃, which afforded 2,5-dihydroisoxazoles **5** in good yields. The results are summarized in Table 3.

In conclusion, we have developed a facile and efficient method for the synthesis of *N*-alkyl-2,5-dihydroisoxazoles via electrophilic selenium-induced intramolecular cyclization and the reaction of Grignard reagents with cyclic iminium salts followed by deselenenylation reaction. The method presents advantages such as use easily available starting material, mild reaction conditions, simple procedure and good yields.

Experimental

^{1}H NMR (400 MHz) spectra were recorded on a Bruker Advance (400 MHz) spectrometer using $CDCl_3$ as the solvent and TMS as the internal standard. Mass spectra (EI, 70 eV) were recorded on an HP5989B mass spectrometer. Infrared spectra were recorded on a Shimadzu IR-408 spectrometer. Elemental analyses were performed on a Flash EA1112 instrument. Dichloromethane was dried with calcium hydride. THF and Et_2O were distilled from sodium/benzophenone immediately prior to use.

Table 3 Preparation of 2,5-dihydroisoxazoles



4 **5**

Entry	R^1	R^2	R^3	Product[a]	Yield[b]/%
1	C_6H_5	H	CH_3	**5a**	76
2	C_6H_5	H	C_6H_5	**5c**	83
3	*p*-ClC_6H_4	H	CH_3	**5e**	80
4	*p*-ClC_6H_4	H	C_2H_5	**5f**	80
5	C_2H_4	C_2H_5	CH_3	**5g**	70

[a] All products were identified by ^{1}H NMR, IR, MS and elemental analysis; [b] isolated yield.

Typical procedure for the conversion of benzaldehyde *O*-(3-phenylallyl)oxime 1a into 2-(1-phenylethyl)-3-phenyl-4-phenylselenoisoxazolidine (4a)

To a solution of *O*-allyl oxime **1a** (1 mmol) in dry dichloromethane (3 mL) was added dropwise a solution of phenylselenenyl bromide (1.1 mmol) in dry dichloromethane (3 mL) at room temperature and the mixture was stirred for 1.5 h. Then, methyl magnesium iodide (2.0 mmol) in diethyl ether (3 mL) was added and the solution was stirred at room temperature for 3 h. The reaction mixture was poured into saturated aqueous ammonium chloride solution (10 mL) and extracted with dichloromethane (5 mL×3). The organic extracts were combined, washed with water and dried over $MgSO_4$. After evaporation of solvent, the oily residue was purified by preparative chromatography on silica gel with ethyl acetate and light petroleum (1/9, *V*/*V*) as eluent to give 351 mg of **4a** in 86% yield. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (dt, J=6.4, 1.6 Hz, 2H), 7.28—7.01 (m, 13H), 4.42 (dd, 1H, J=7.6, 9.2 Hz), 4.14 (dd, J=7.6, 9.2 Hz, 1H), 4.07 (q, J=6.4 Hz, 1H), 3.97 (d, J=5.6 Hz, 1H), 3.84 (dt, J=7.6, 5.6 Hz, 1H), 1.45 (d, J=6.4 Hz, 3H); IR (neat) ν: 3060, 3028, 2974, 2931, 2866, 1601, 1578, 1493, 1476, 1453, 1438, 1370, 1069, 1023, 759, 740, 697 cm^{-1}; MS *m/z* (%): 408 (M^+), 306, 273, 117, 105 (100), 79, 77. Anal. calcd for $C_{23}H_{23}NOSe$: C 67.64, H 5.68, N 3.43; found C 67.43, H 5.60, N 3.51.

2-(1-Phenylpropyl)-3-phenyl-4-phenylselenoisoxazolidine (4b)

Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (d, J=7.2 Hz, 2H), 7.26—7.02 (m, 13H), 4.41 (dd, J=7.6, 8.8 Hz, 1H), 4.14 (dd, J=7.6, 8.8 Hz, 1H), 3.94 (d, J=5.6 Hz, 1H), 3.86—3.80 (m, 2H), 2.24—2.11 (m, 1H), 1.80—1.66 (m, 1H), 0.67 (t, J=7.2 Hz, 3H); IR (neat) ν: 3059, 3027, 2971, 2931, 2872, 1601, 1578, 1513, 1493, 1476, 1453, 1438, 1379, 1118, 1074, 1022, 738, 697 cm^{-1}; MS *m/z* (%): 422 (M^+), 394, 306, 239, 157, 119, 117, 91 (100), 77. Anal. calcd for $C_{24}H_{25}NOSe$: C 68.24, H 5.97, N 3.32; found C 68.41, H 5.86, N 3.41.

2-Benzhydryl-3-phenyl-4-phenylselenoisoxazolidine (4c)

Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43—7.05 (m, 20H), 5.03 (s, 1H), 4.38 (dd, J=7.2, 8.8 Hz, 1H), 4.08 (dd, J=7.2, 8.8 Hz, 1H), 4.02 (d, J=6.4 Hz, 1H), 3.86 (dt, J=6.4, 7.2Hz, 1H); IR (neat) *v:* 3061, 3028, 2974, 2929, 2865, 1601, 1579, 1493, 1477, 1453, 1381, 1115, 1075, 1028, 741, 698 cm^{-1}; MS *m/z* (%): 470 (M^+), 273, 157, 168, 165, 117, 167 (100), 91, 77. Anal. calcd for $C_{28}H_{25}NOSe$: C 71.47, H 5.36, N 3.00; found C 71.68, H 5.45, N 2.88.

2-(1-*p*-Tolyl-but-3-enyl)-3-phenyl-4-phenylselenoisoxazolidine (4d)

Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (d, 2H, J=7.2 Hz), 7.27—6.92 (m, 12H), 5.54 (ddt, J=17.6, 10.8, 7.2 Hz, 1H), 4.89 (t, J=17.6, 10.8 Hz, 2H), 4.42 (dd, J=7.6, 8.8 Hz, 1H), 4.15 (dd, J=7.6, 8.8 Hz, 1H), 3.97 (d, J=5.6 Hz, 2H), 3.83 (dt, J=5.6, 7.6Hz, 1H), 2.96—2.83 (m, 1H), 2.60—2.47 (m, 1H), 2.22 (s, 3H); IR (neat) ν: 3060, 3028, 2927, 2922, 2860, 1640, 1601, 1578, 1513, 1494, 1476, 1453, 1437, 1329, 1180, 1071, 1022, 912, 809, 737, 696 cm^{-1}; MS *m/z* (%): 448 (M^+), 410, 409, 408, 406, 405, 404, 306, 273, 158, 145 (100), 130, 117, 105, 9, 77. Anal. calcd for $C_{26}H_{27}NOSe$: C 69.63, H 6.07, N 3.12; found C 69.87, H 5.99, N 3.23.

2-[1-(4-Chlorophenyl)ethyl]-3-phenyl-4-phenylselenoisoxazolidine (4e)

Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (d, J=8.0 Hz, 2H), 7.26—7.06 (m, 12H), 4.41 (dd, J=7.2, 8.8 Hz, 1H), 4.10 (dd, J=7.2, 8.8 Hz, 1H), 4.01 (q, J=6.4 Hz, 1H), 3.89 (d, J=5.6 Hz, 1H), 3.82 (dt, J=5.6, 7.2 Hz, 1H), 1.40 (d, J=6.4 Hz, 3H); IR (neat) ν: 3061, 3030, 2976, 2932, 2867, 1601, 1578, 1493, 1477, 1454, 1437, 1371, 1091, 1014, 908, 833, 733, 698 cm^{-1}; MS *m/z* (%): 443 (M^+), 306, 259, 184, 157, 141, 139 (100), 117, 103, 91, 77. Anal. calcd for $C_{23}H_{22}ClNOSe$: C 62.38, H 5.01, N 3.16; found C 62.53, H 5.12, N 3.05.

2-[1-(4-Chlorophenyl)propyl]-3-phenyl-4-phenylselenoisoxazolidine (4f)

Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (d, 2H, J=8.0 Hz), 7.32—7.01 (m, 12H), 4.42 (dd, J=7.2, 9.2 Hz, 1H), 4.12 (dd, J=7.2, 9.2 Hz, 1H), 3.87—3.77 (m, 3H), 2.19—2.11 (m, 1H), 1.71—1.62 (m, 1H), 0.66 (t, J=7.2 Hz, 3H); IR (neat) ν: 3060, 3029, 2967, 2933, 2874, 1597, 1578, 1491, 1477, 1455, 1437, 1379, 1337, 1175, 1090, 1015, 839, 813, 739, 697 cm^{-1}; MS *m/z* (%): 457 (M^+), 430, 428, 306, 273, 153, 125, 117 (100), 103, 91, 77. Anal. calcd for $C_{24}H_{24}ClNOSe$: C 63.09, H 5.29, N 3.07; found C 63.31, H 5.40 N 2.95.

2-(1-Ethyl-1-methylpropyl)-3-phenyl-4-phenylselenoisoxazolidine (4g)

Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43—7.25 (m, 10H), 4.26 (dd, J=6.0, 9.2 Hz, 1H), 4.11 (d, J=6.8 Hz,

1H), 3.91 (dd, J=6.0, 9.2 Hz, 1H), 3.68 (dt, J=6.0, 6.8 Hz, 1H), 1.76—1.64 (m, 1H), 1.47—1.35 (m, 1H), 1.20—1.07 (m, 2H), 0.86 (s, 3H), 0.82 (t, J=7.2 Hz, 3H), 0.66 (t, J=7.2 Hz, 3H); IR (neat) *v*: 3060, 3028, 2964, 2931, 2876, 1601, 1578, 1493, 1476, 1453, 1438, 1379, 1069, 1023, 739, 697 cm^{-1}; MS *m/z* (%): 388 (M^+), 362, 361, 360 (100), 359, 358, 357, 356, 306, 273, 184, 117, 91, 77, 70, 43. Anal. calcd for $C_{21}H_{27}NOSe$: C 64.94, H 7.01, N 3.61; found C, 65.17, H 7.09, N 3.50.

Typical procedure for the synthesis of 2-(1-phenylethyl)-3-phenyl-2,5-dihydroisoxazol (5a)

To a solution of the isoxazolidines **4a** (0.5 mmol) in THF (5 mL) was added a solution of 30% hydrogen peroxide (3.5 mmol) in 30 min at 0 ℃. The solution was warmed to room temperature and stired for another 30 min. The reaction mixtures were washed with brine (15 mL) and extracted with dichloromethane (10 mL× 3). The organic extracts were combined and dried over $MgSO_4$. After evaporating solvent, the oily residue was purified by preparative chromatography on silica gel with ethyl acetate and light petroleum (1∶9) to afford 95.4 mg of **5a** in 76% yield. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55—6.96 (m, 11H), 4.71 (d, J=8.8 Hz, 1H), 4.58 (d, J=8.8 Hz, 1H), 4.29 (q, J=6.8 Hz, 1H), 1.63 (d, J=6.8 Hz, 3H); IR (neat) *v*: 3060, 3028, 2930, 1675, 1597, 1577, 1492, 1475, 1452, 1372, 1070, 1021, 733, 697 cm^{-1}; MS *m/z* (%): 251 (M^+), 174, 146, 105 (100), 91, 77. Anal. calcd for $C_{17}H_{17}NO$: C 81.24, H 6.82, N 5.57; found C 81.52, H, 6.93, N 5.65.

2-Benzhydryl-3-phenyl-2,5-dihydroisoxazole (5c)

Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.4—7.1 (m, 16H), 5.42 (s, 1H), 4.48 (s, 2H); IR (neat) *v*: 3060, 3027, 2930, 2866, 1678, 1600, 1579, 1493, 1478, 1453, 1381, 1075, 1028, 743, 698 cm^{-1}; MS *m/z* (%): 313 (M^+), 167 (100), 146, 91, 77. Anal. calcd for $C_{22}H_{19}NO$: C 84.31, H 6.11, N 4.47; found: C 84.09, H 6.18, N 4.35.

2-[1-(4-Chlorophenyl)ethyl]-3-phenyl-2,5-dihydroisoxazole (5e)

Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.5—6.9 (m, 10H), 4.71 (d, J=9.2 Hz, 1H), 4.60 (d, J=9.2 Hz, 1H); 4.26 (q, J=6.8 Hz, 1H), 1.60 (d, 3H, J=6.8 Hz, 3H); IR (neat) *v*: 3059, 2930, 2850, 1674, 1596, 1577, 1491, 1476, 1091, 733, 698 cm^{-1}; MS *m/z* (%): 286 (M^+), 146, 141, 139 (100), 103, 91, 77. Anal. calcd for $C_{17}H_{16}ClNO$: C 71.45, H 5.64, N 4.90; found C 71.65, H 5.74, N 5.03.

2-[1-(4-Chlorophenyl)propyl]-3-phenyl-2,5-dihydroisoxazole (5f)

Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.6—6.8 (m, 10H); 4.74 (d, J=8.8 Hz, 1H), 4.62 (d, J=8.8 Hz, 1H), 4.27 (t, J=7.6 Hz, 1H), 2.26—2.20 (m, 1H), 1.90—1.83 (m, 1H), 0.96 (t, J=7.2 Hz, 3H); IR (neat) *v*: 3059, 2924, 2852, 1672, 1577, 1491, 1475, 1438, 1090, 1015, 736, 690 cm^{-1}; MS *m/z* (%): 300 (M^+), 153 (100), 155, 146, 117, 91, 77. Anal. calcd for $C_{18}H_{18}ClNO$: C 72.11, H 6.05, N 4.67; found C 72.32, H 6.13, N 4.57.

2-(1-Ethyl-1-methylpropyl)-3-phenyl-2,5-dihydroisoxazole (5g)

Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.5—7.15 (m, 6H), 4.75 (d, J=8.8 Hz, 1H), 4.66 (d, J=8.8 Hz, 1H), 1.73—1.32 (m, 4H), 1.08 (s, 3H), 0.86 (t, 6H, J=7.6 Hz); IR (neat) *v*: 3059, 2932, 2874, 1668, 1578, 1491, 1475, 1455, 1438, 1379, 1069, 1022, 739, 693 cm^{-1}; MS *m/z* (%): 231 (M^+), 205 (100), 146, 117, 91, 77, 70, 43. Anal. calcd for $C_{15}H_{21}NO$: C 77.88, H 9.15, N 6.05; found C 77.61, H 9.04, N 6.18.

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