# A facile synthesis of 2,5-dihydroisoxazoles via an organoselenium-induced stereoselective cyclisation and deselenylation reaction

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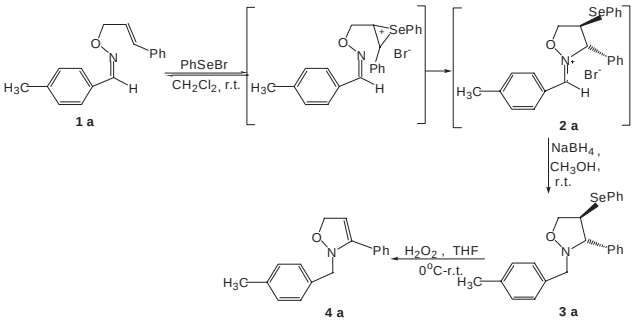
The organoselenium-induced ring-closure reactions of *O*-allyl oximes give cyclic iminium salts that can be reduced *in situ* with $NaBH_4$ to produce *N*-alkyl-4–phenylselenoisoxazolidines; selenoxide *syn*-elimination follows to form 2, 5-dihydroisoxazoles in good yields.

**Keywords**: *O*-allyl oximes, 2,5-dihydroisoxazoles, organoselenium-induced, cyclisation, deselenylation reaction

Isoxazolines are important synthetic intermediates for functionalised building blocks.[1] A number of pharmaceutically active agents contain an optical isoxazoline ring, which plays an important role in their biological activities.[2,3] Reports concerning the syntheses of 2,5-dihydroisoxazoles included the modification of cyclic compounds[4-7] and intercyclisation of two substrates.[8,9] However, to the best of our knowledge, the synthesis of 2,5-dihydroisoxazoles via intracyclisation has not been reported. Herein, we report a facile and efficient synthesis of 2,5-dihydroisoxazoles via an electrophilic selenium-induced intracyclisation and deselenenylation reaction of *O*-allyl oximes.

Firstly, **1a** was treated with phenylselenenyl bromide to produce 4-phenylselenenyl iminium bromide **2a**, which was not isolated from the solvent due to its instability. Then **2a** underwent reduction by $NaBH_4$ to afford the corresponding 2-alkyl-4-phenylselenenyl isoxazolidine **3a** in 80% yield. The isoxazolidine **3a** was then treated with hydrogen peroxide (30%) at 0°C to give product **4a** in 66% overall yield (Scheme 1).




**Scheme 1**

As indicated in Scheme 1, the reaction proceeded through the initial formation of the seleniranium ion intermediate and the cyclic iminium bromide **2a**.[10] Compound **3a** was in fact obtained as a single *trans* stereoisomer which was confirmed by its $^1$H NMR spectrum. The observed coupling ($J_{3,4}$) of 5.6 Hz for **3a** (Table 1, entry 1) was in agreement with the reported values for $J_{3,4}$ of *trans*-3-substituted-4–phenylselenoisoxazolidines[10] and *trans*-3,4-substituted isoxazolidines.[11]

In order to extend this result, various *O*-allyl oximes were chosen as substrates and *N*-alkyl-2,5-dihydroisoxazoles were obtained in moderate to good yields. The results are summarised in Table 1.

In conclusion, a simple and facile method for the synthesis of 2,5-dihydroisoxazoles by oxidation-syn-selenoxide elimination of *N*-alkyl-4–phenylselenoisoxazolidines, which were prepared by organoselenium-induced stereoselective intracyclisation of *O*-allyl oximes, has been developed with the advantages of available starting material, a simple procedure, mild reaction conditions and good yields.

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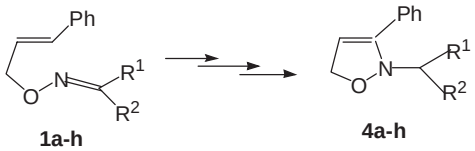
**Table 1** Preparation of 2,5-dihydroisoxazoles




| Entry | $R^1$ | $R^2$ | Product **4**[a] (Yield%)[b] |
|---|---|---|---|
| 1 | *p*-$CH_3C_6H_4$ | H | 4a (66) |
| 2 | $C_6H_5$ | H | 4b (61) |
| 3 | *p*-$ClC_6H_4$ | H | 4c (65) |
| 4 | *p*-$BrC_6H_4$ | H | 4d (62) |
| 5 | *p*-$CH_3OC_6H_4$ | H | 4e (73) |
| 6 | $C_2H_5$ | $C_2H_5$ | 4f (65) |
| 7 | $C_6H_5$ | $CH_3$ | 4g (62) |
| 8 | $(CH_2)_5$ | | 4h (67) |

[a]All products were identified by $^1$H NMR, IR, MS and elemental analysis; [b]Isolated total yield.

## Experimental

$^1$H NMR (400 MHz) was recorded on a Bruker Avance (400 MHz) spectrometer using $CDCl_3$ as the solvent and TMS as the internal standard. Mass spectra (EI, 70 eV) were recorded on a HP5989B mass spectrometer. Infrared spectra were recorded on a Bruker Vector22 infrared spectrometer. Elemental analyses were performed on a Flash EA1112 instrument. Dichloromethane was dried with calcium hydride and THF was distilled from sodium/ benzophenone immediately prior to use.

*Typical procedure for the synthesis of 2-(4-methylbenzyl)-3-phenyl-4-phenylselenoisoxazolidine* (**3a)**: To a solution of O-allyl oxime **1a** (1 mmol) in dry dichloromethane (3 ml) was added dropwise the solution of phenylselenenyl bromide **(**1.1 mmol) in dry dichloromethane (2 ml) at room temperature and the mixture was stirred for 1.5 h. Then, $NaBH_4$ (1.5 mmol) in methanol (1 ml) was added and the solution was stirred at room temperature for 1h. The reaction mixture was poured into water (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 subjected to preparative TLC on silica gel with ethyl acetate and light petroleum (1:9) as eluent to give 327mg of 2-(4-methylbenzyl)-3-phenyl-4-phenylselenoisoxazolidine **3a** (80%). oil; $^1$H NMR (400 MHz, $CDCl_3$) δ7.45–7.16 (m, 12H); 7.09 (d, 2H, *J* =7.6 Hz ); 4.47 (dd, 1H, *J* =8.0 and 8.8 Hz ); 4.09 (dd, 1H, *J* =5.6 and 8.8 Hz ); 3.93 (d, 1H, *J* =14.0 Hz ); 3.87 (dt, 1H, *J* =5.6, 8.0Hz ); 3.74 (d, 1H, *J* =5.6 Hz ); 3.71 (d, 1H, *J* =14.0 Hz ); 2.31 (s, 3H); MS (*m*/*e*) 410–407 ($M^+$), 316, 271, 252, 225, 210, 146, 117, 105 (100), 91, 77; IR (neat) 3060, 2923, 2852, 1601, 1578, 1514, 1438, 1377, 1021, 807, 766, 734, 691 $cm^{-1}$. Anal. calcd. for $C_{23}H_{23}NOSe$: C, 67.64; H, 5.68; N, 3.43. Found: C, 67.85; H, 5.64; N, 3.48.

*Typical Procedure for the synthesis of* 2-(4-methylbenzyl)-3-phenyl-2,5-dihydro- isoxazole (**4a)**: To a solution of the isoxazolidine **3a** (0.5 mmol) in THF (5 ml) was added 30% hydrogen peroxide (3.5 mmol)

in 30 min at 0°C. The solution was warmed to room temperature and stirred 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 the solvent, the oily residue was subjected to preparative TLC on silica gel with ethyl acetate and light petroleum (1:9) to afford 82.8mg of **4a** (66% overall yield). oil; $^1$H NMR (400 MHz, $CDCl_3$) δ7. 62–7.15 (m, 10H); 4.68 (s, 2H); 4.18 (s, 2H); 2.38 (s, 3H); MS (*m*/*e*) 251 ($M^+$), 146, 117, 105 (100), 91, 77; IR (neat) 3060, 2923, 2852, 1674, 1578, 1438, 1021, 766, 734, 691 cm$^{-1}$. Anal. calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.52; H, 6.87; N, 5.50.

*2-Benzyl-3-phenyl-2,5-dihydroisoxazole* (**4b**): oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7. 60–7.12 (m, 11H); 4.72 (s, 2H); 4.21 (s, 2H); MS (*m*/*e*) 237 ($M^+$), 117, 91 (100), 77, 65, 51; IR (neat) 3059, 3029, 2926, 2850, 1672, 1577, 1547, 1493, 1475, 1438, 1069, 1021, 735, 694cm$^{-1}$; Anal. calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.71; H, 6.34; N, 5.86.

*2-(4-Chlorobenzyl)-3-phenyl-2,5-dihydroisoxazole* (**4c**): oil; $^1$H NMR (400 MHz, $CDCl_3$) δ7. 37–7.16 (m, 10H); 4.70 (s, 2H); 4.16 (s, 2H); MS (*m*/*e*) 272 ($M^+$), 146, 127, 125 (100), 117, 105, 91, 77; IR (neat) 3059, 2926, 2848, 1675, 1578, 1485, 1445, 1069, 1016, 797, 763, 737, 693 cm$^{-1}$. Anal. calcd for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; N, 5.15. Found: C, 70.98; H, 5.25; N, 5.10.

*2-(4-Bromobenzyl)-3-phenyl-2,5-dihydroisoxazole* (**4d**): oil; $^1$H NMR (400 MHz, $CDCl_3$) δ7. 55–7.20 (m, 10H); 4.71 (s, 2H); 4.15 (s, 2H); MS (*m*/*e*) 316 ($M^+$), 171, 169, 146, 117 (100), 105, 91, 90, 77; IR (neat) 3057, 2925, 2849, 1673, 1580, 1484, 1441, 1069, 1014, 797, 764, 736, 693 cm$^{-1}$. Anal. calcd for $C_{16}H_{14}BrNO$: C, 60.78; H, 4.46; N, 4.43. Found: C, 60.55; H, 4.41; N, 4.48.

*2-(4-Methoxylbenzyl)-3-phenyl-2,5-dihydroisoxazole* (**4e**): oil; $^1$H NMR (400 MHz, $CDCl_3$) δ7. 60–7.01 (m, 10H); 4.62 (s, 2H); 4.14 (s, 2H); 3.87 (s, 3H); MS (*m*/*e*) 267 ($M^+$), 121, 117 (100), 105, 91, 77; IR (neat) 3062, 2924, 2866, 1677, 1579, 1495, 1455, 1267, 1023, 736, 691 cm$^{-1}$. Anal. calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.62; H, 6.37; N, 5.29.

*2-(1-Ethyl-propyl)-3-phenyl-2,5-dihydroisoxazole* (**4f**): oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.52–7.15 (m, 6H); 4.76 (d, 1H, *J* = 8.8 Hz); 4.67 (d, 1H, *J* = 8.8 Hz); 2.52 (m, 1H), 1.71–1.35 (m, 4H), 0.85 (t, 6H, *J* = 7.6 Hz); MS (*m*/*e*) 217 ($M^+$) 202, 188, 117 (100), 91, 77; IR (neat) 3058, 2932, 2871, 1669, 1576, 1492, 1476, 1454, 1433, 1377, 1066, 1021, 739, 693 cm$^{-1}$. Anal. calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.68; H, 8.85; N, 6.38.

*2-(1-Phenylethyl)-3-phenyl-2,5-dihydroisoxazole* (**4g**): oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.55–6.96 (m, 11H), 4.71 (d, 1H, *J* = 8.8 Hz); 4.58 (d, 1H, *J* = 8.8 Hz); 4.29 (q, 1H, *J* = 6.8 Hz); 1.63 (d, 3H, *J* = 6.8 Hz); MS (*m*/*e*) 251 ($M^+$), 174, 146, 105 (100), 91, 77; IR (neat) 3060, 3028, 2930, 1675, 1597, 1577, 1492, 1475, 1452, 1372, 1070, 1021, 909, 740, 697 cm$^{-1}$; Anal. calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.60; H, 6.78; N, 5.61.

*2-Cyclohexyl-3-phenyl-2,5-dihydroisoxazole* (**4h**): oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.51–7.13 (m, 6H); 4.75 (d, 1H, *J* = 8.8 Hz); 4.67 (d, 1H, *J* = 8.8 Hz); 2.60 (m, 1H), 2.14–1.12 (m, 10H); MS (*m*/*e*) 229 ($M^+$), 201, 186, 117 (100), 91, 77; IR (neat) 3060, 2932, 1668, 1577, 1493, 1475, 1434, 1068, 1022, 738, 693 cm$^{-1}$. Anal. calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.31; H, 8.38; N, 6.17.

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