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Selective Synthesis of Heterocyclic Compounds through the Intramolecular Substitution of Phenylselenonyl Group by Nitrogen or Carbonyl Oxygen in Amides

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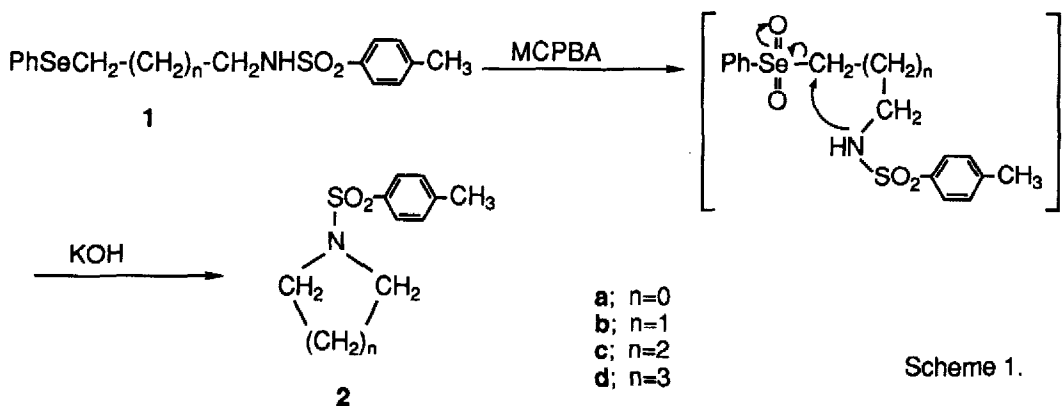
Key words; Selenone, Nitrogen heterocycle, Oxazoline, Dihydrooxazine

Abstract: *Nitrogen heterocycles were produced by the oxidation of N-[ω-(phenylseleno)alkyl]-p-toluenesulfonamides through the intramolecular substitution of the resultant phenylselenonyl group by the nitrogen atom. By the oxidation of the corresponding benzamides, on the other hand, cyclization by nitrogen or carbonyl oxygen proceeded depending on the number of carbon atoms between the nucleophile (amide) and the leaving group (selenonyl group).*

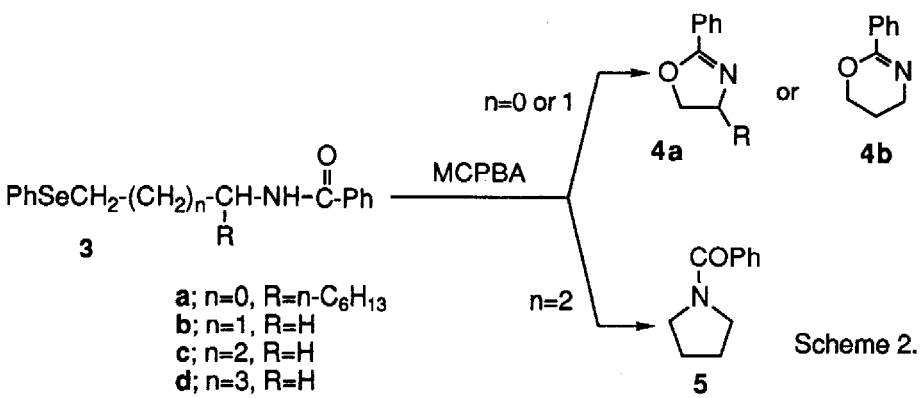
The selenonyl group has been recognized as an excellent leaving group [1-3] and many substitution reactions have been reported using various kinds of nucleophiles. Among these substitution reactions, the intramolecular ones are particularly interesting leading to the cyclic compounds. Several examples of the cyclization by carbon and oxygen nucleophiles have been reported in the literature.[1,3] However, little has been known about the cyclization by nitrogen atom to afford nitrogen heterocycles[4] which are very important in organic synthesis. We report herein that the oxidation of *N*-[ω-(phenylseleno)alkyl]-*p*-toluene-



Scheme 1.

sulfonamides affords nitrogen heterocycles through the intramolecular substitution of the resultant selenonyl group by nitrogen atom in sulfonamides. By the oxidation of the corresponding benzamide, on the other hand, cyclization by nitrogen or carbonyl oxygen proceeds selectively to afford pyrrolidine or oxazoline (dihydrooxazine) derivatives depending on the number of carbon atoms between the nucleophile (amide) and the leaving group (selenonyl group). As compared to the similar procedures using other leaving groups,[5] our procedure can be carried out under mild conditions and may be useful in the preparation of various heterocyclic compounds.

In a typical procedure, *meta*-chloroperbenzoic acid (MCPBA) (5 mmol) was added to a solution of *N*-[4-(phenylseleno)butyl]-*p*-toluenesulfonamide (1 mmol) and potassium hydroxide (7.5 mmol) in 2-propanol (40 ml) and the resulting solution was stirred at ambient temperature for 1 h. After the usual workup, evaporation of the solvent afforded almost pure *N*-tosylpyrrolidine (**2c**) which was further purified by column chromatography (1 mmol; 100%) (Scheme 1). The yield of **2c** was somewhat unsatisfactory in the reaction without the base (59%). When the amount of MCPBA was reduced to 1 equiv., almost no cyclization occurred (**2c**; 4%). This suggests that the cyclization proceeds through the intermediate selenone. Typical results are summarized in Table 1 for the formation of three- to six-membered nitrogen heterocycles. Alcohols are suitable solvent for this reaction, presumably due to the fact that the oxidation to selenones, especially the step from selenoxides to selenones, is facile in alcohols.[3] Olefins, which would be formed by the selenoxide elimination, were not detected among the products. Either ethanol or 2-propanol may be used as solvent. In the cyclization to **2c**, 2-propanol gave better results (Entries 3 and 4). The use of methanol as solvent is not recommended, as considerable amount of methyl *meta*-chlorobenzoate was produced by the esterification of *meta*-chlorobenzoic acid.



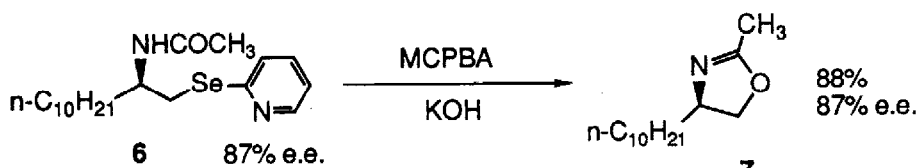
Scheme 2.

When a benzoylamino group was employed as a nucleophile, two types of cyclization were observed (Scheme 2). When the number of carbon atoms between the amide and the selenonyl group was 2 or 3 (**3a** or **3b**), cyclization by carbonyl oxygen[6] proceeded exclusively to afford oxazoline or dihydrooxazine derivatives in excellent yields. This cyclization by oxygen atom was very fast and methoxy substituted linear amide was not detected in the products even by the use of methanol as solvent (*vide infra*). When the number of carbon atoms was increased to 4 (**3c** in Scheme 2), cyclization by oxygen atom was not possible and pyrrolidine (**5**) was produced selectively. As compared to a nitrogen atom in sulfonamide, the one in benzamide seems to be less reactive in the intramolecular substitution reaction. Substitution of the selenonyl

Table 1. Yields of various nitrogen heterocycles[a]

Entry	Starting selenide	MCPBA (mmol)	KOH (mmol)	Solvent (ml)	Product	Yield(%)[b]
1	**1a**	2.4	4	EtOH (20)	**2a**	92
2	**1b**	2.4	4	EtOH (20)	**2b**	100
3	**1c**	5	7.5	EtOH (40)	**2c**	84
4	**1c**	5	7.5	i-PrOH (40)	**2c**	100
5	**1d**	5	7.5	i-PrOH (40)	**2d**	95
6	**3a**	2	0	MeOH (20)	**4a**	84
7	**3b**	2	0	MeOH (20)	**4b**	90
8	**3c**	5	7.5	EtOH (20)	**5**	89[c]
9	**3c**	5	7.5	i-PrOH (40)	**5**	83

[a] Carried out using selenide (1 mmol) at room temperature for 0.5-1 h. [b] Isolated yield by column chromatography. [c] N-(4-Ethoxybutyl)benzamide (6%) was formed.



6 87% e.e. **7**

Scheme 3.

moiety by ethoxy group was observed in the oxidation of **3c** in ethanol as solvent (Entry 8 in Table 1; compare to Entry 3). Moreover, cyclization to six-membered ring did not proceed by the oxidation of **3d** even in 2-propanol as solvent.[7]

By the application of the present procedure to optically active amide bearing 2-pyridylseleno group on β carbon atom (**6**),[8] we succeeded in the preparation of optically active oxazoline (**7**)[9] (Scheme 3). The absolute configuration of the asymmetric carbon in **6** was proved to be *R*,[8] and was kept intact during the cyclization. Thus, the produced oxazoline (**7**) contains asymmetric carbon of *R* configuration. As

various kinds of (2*R*)-2-(acylamino)alkyl 2-pyridyl selenides can be prepared from commercially available (*R*)-1,2-epoxyalkanes,[8] this procedure may be utilized in the preparation of optically active oxazolines with opposite configuration to those prepared from natural amino acids.

Acknowledgement

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4. There is a short statement in ref. 2b that aziridines are produced by the reaction of primary amines with vinyl selenones.
5. See for example; "Comprehensive Heterocyclic Chemistry," Eds. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, Vols. 2, 3, 4, 6, and 7.
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7. The identified products are N-[[5-(1-methylethyl)oxy]pentyl]benzamide (*ca.* 15%) and 5-(benzoylamino)-1-pentanol (*ca.* 10%), the mechanism of the formation of the latter compound has not yet been clarified. The rests of them seem to remain as the selenone.
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9. To confirm the optical purity, **7** was hydrolized to 2-amino-1-dodecanol (4N HCl/MeOH, reflux, 2 h) whose hydroxy group was then protected as trimethylsilyl ether. The amine was then converted to the amide of (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid. The diastereomeric excess of the amide was found to be 87% by the integrals of 200 MHz ^{1}H NMR spectrum, indicating that enantiomeric excess of **7** is 87%.

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