

Synthesis of Substituted Glycerol Selenide Ethers under Microwave Irradiation

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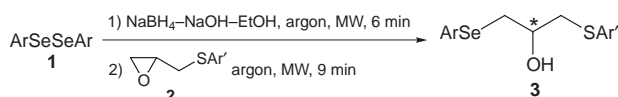
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Substituted glycerol selenide ethers are rapidly obtained in high yields and good regioselectivities by reducing dialkyl diselenides with sodium tetrahydroborate in a basic environment followed by reaction with glycidyl sulfide ether under microwave irradiation conditions.

Selenides have been known as versatile reagents in organic chemistry for a long time. Many methods involving diselenides have been developed into standard procedures to introduce new functional groups under mild conditions. Diselenides have provided useful methods for the generation of double bonds, for addition to double bonds,² as well as for cyclization of unsaturated systems. Glycerol ethers, substituted glycerol sulfide ethers and their derivatives have been studied widely as cardiovascular agents since they are antioxidants which can protect cells and extracellular regions from attack by free radicals that are involved in the cytotoxic injury of tissues. The opening of the oxirane ring by various nucleophiles is an important tool in organic chemistry,⁷ in particular, in the fields of pharmaceutical and natural products chemistry, and can be performed by several methods:¹¹ using Lewis acids, such as boron trifluoride etherate, lanthanide chlorides, lithium perchlorate, cobalt(II) chloride or Co₂(CO)₈, neutral alumina, quaternary onium salts, organic and inorganic bases and Ce(OTf)₄. The reaction of epoxides with organoselenium reagents has already been reported. However, many of these reactions suffer from lack of generality, poor regioselectivity and require low temperatures (–78 °C).¹⁴ Our work involves the synthesis of chiral substituted glycerol selenide ethers *via* the reaction of glycidyl sulfide ethers with alkyl diselenides.

In recent years interest has been shown in the study of microwave assisted organic reaction, and some important reviews have been published.¹⁸ Microwave irradiation has also been applied to several organic reactions. However, few practical applications have been devised for the synthesis of organoselenium compounds. Recently, we have reported the synthesis of dibenzyl diselenide, diaryl diselenides, aromatic ethers and chiral glycerol sulfide ethers²⁶ under phase-transfer catalysis and microwave irradiation conditions.



Scheme 1

We have now found that substituted glycerol selenide ethers can be obtained from glycidyl sulfide ethers and dialkyl diselenides using microwave irradiation. A comparative study on the reaction of glycidyl sulfide ethers with dialkyl diselenides shows that this method offers the possibility to considerably decrease the reaction time compared to that required when using conventional conductive

heating. This method is simple, rapid, highly regioselective and affords good yields. The reactions are shown in Scheme 1 and results are summarized in Table 1.

Using the synthesis reaction of 1-phenylthio-3-phenylselenopropan-2-ol as an example, we investigated the effects of various solvents on the reaction. When absolute ethanol was used as solvent, the yield of **3a** is high (85.6%), whereas the yield is only 74.8 and 30.4%, respectively, when the reaction is carried out in DMF or

Table 1 Preparation of 1-alkylthio-3-alkylselenopropan-2-ol compounds **3a–m**

	Product ^{a-c}	Yield ^d (%)
3a		85.6
3b		84
3c		78
3d		83
3e		81
3f		82
3g		83
3h		87
3i		84
3j		73
3k		76
3l		77
3m		86

^aMol ratio (ArSe)₂: glycidyl sulfide ether: NaBH₄: NaOH = 4:8:16:7.5. ^bIrradiation conditions: power, 750 W; time, 15 min.

^cAbsolute ethanol used as solvent. ^dIsolated yield.

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Table 5 Comparison of times and yields in synthesis of compounds **3a–m** using microwave and conventional heating at reflux^{a,b}

Product	Conventional heating		Microwave heating			t_c/t_{mw}
	t/h	Yield(%)	Power/W	t/min	Yield(%)	
3a	9	84	750	15	85.6	36
3b	11	78	750	15	84	44
3c	10	76	750	15	78	40
3d	12	82	750	15	83	48
3e	11	80	750	15	81	44
3f	11	80	750	15	82	44
3g	10	81	750	15	83	40
3h	12	85	750	15	87	48
3i	12	82	750	15	84	48
3j	13	72	750	15	73	52
3k	13	75	750	15	76	52
3l	10	74	750	15	77	40
3m	10	86	750	15	86	40

^aMol ratio (ArSe)₂: glycidyl sulfide ether: NaBH₄:NaOH = 4:8:16:7.5. ^bResults are the mean of two experiments.

MeCN. No reaction occurs when C₆H₆, CH₂Cl₂ or PhCH₃ are used as solvents, since they cannot stabilize alkyl selenide ions. We have also investigated the effects of irradiation power and time on the reactions. It was found that the highest yield of compound **3a** is obtained at a power level of 750 W for 15 min continuous irradiation. In conclusion, we have investigated the one-pot synthesis of substituted glycerol selenide ethers.

The impact of the microwave irradiation and conventional heating for the synthesis of compounds **3a–m** has been compared and results are summarized in Table 5. The results showed that the synthesis of compounds **3a–m** under microwave irradiation were 40–52 times faster than under conventional reflux.

This ratio between the reaction time using conventional reflux and microwave irradiation (t_c/t_{mw}), under the same conditions, quantifies the microwave heating effect.

Experimental

Chromatographic Optical Resolution of Compounds 3a–m by HPLC on a Chiralcel OD Column.—The optical resolution of thirteen racemic substituted glycerol selenide ethers was examined by HPLC using the tris(phenylcarbamate) and tris(3,5-dimethylphenylcarbamate) of cellulose as the chiral stationary phase. The results showed that eight substituted glycerol selenide ethers were completely separated into enantiomers on chiralcel OD when hexane–propan-2-ol was used as eluent. The separation factor is 1.15–1.30.

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Techniques used: IR, ¹H NMR, MS, elemental analysis, HPLC

References: 26

Table 2: Effect of solvent on the synthesis of **3a**

Table 3: Effect of microwave irradiation power on the synthesis of **3a**

Table 4: Effect of microwave irradiation time on the synthesis of **3a**

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