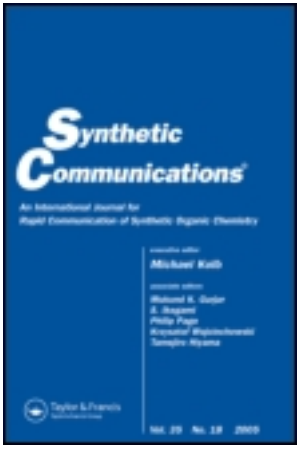

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Ian W.J. Still [a] , L. James [a] & P. Martyn [a]
[a] Department of Chemistry, University of Toronto at Mississauga, 3359 Mississauga Road North, Mississauga, Ontario, Canada, L5L 1C6
Published online: 20 Aug 2006.

To cite this article: Ian W.J. Still , L. James & P. Martyn (1998) The Generation of (Samarium) Thiolates from Aryl Thiocyanates and Their Reaction with Epoxides: A Route to β-Hydroxy Sulfides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:5, 913-923, DOI: 10.1080/00032719808006491

To link to this article: http://dx.doi.org/10.1080/00032719808006491

SYNTHETIC COMMUNICATIONS, 28(5), 913-923 (1998)

THE GENERATION OF (SAMARIUM) THIOLATES FROM ARYL THIOCYANATES AND THEIR REACTION WITH EPOXIDES: A ROUTE TO β-HYDROXY SULFIDES

Ian W.J. Still* and L. James P. Martyn

Department of Chemistry, University of Toronto at Mississauga,
3359 Mississauga Road North, Mississauga, Ontario, Canada L5L 1C6

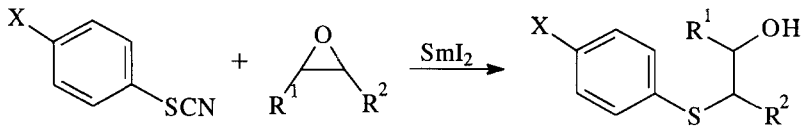
ABSTRACT: This investigation describes the reduction of an aryl thiocyanate with samarium(II) iodide, followed by reaction with various epoxides, to produce β-hydroxy sulfides. This method of ring opening of epoxides provides a substantial improvement in reaction time and convenience over existing methods while maintaining good regioselectivity and excellent yield.

As part of our continuing investigation of the synthetic potential of aryl thiocyanates,[1-3] as well as the samarium(III) thiolates which are easily generated from them by treatment with SmI_2,[4,5] we have chosen to examine the reactions of the samarium thiolates with a series of epoxides. The conversion of epoxides to β-hydroxy sulfides by reaction with thiols or thiolates has been the subject of a number of earlier investigations, including the reaction of thiols with epoxides catalyzed by Sm(III) species.[6,7] Interest in the nucleophilic ring-opening of epoxides continues unabated[8] and the use of various lanthanide and other, less-common organometallic reagents as Lewis acid catalysts is a relatively recent but growing area of interest.[9-12]

*To whom correspondence should be addressed.

In our study the reactions were carried out by sequential addition of the aryl thiocyanate and the relevant epoxide to a preformed solution of SmI_2.[13] The results which we obtained are presented below.

Two reports have recently described the preparation of samarium(III) thiolates from the corresponding thiol[14] or thiolate,[15] although in neither case were the synthetic applications of these species explored. Our own previous investigations[4] and, independently, those of Zhou and coworkers[16] have shown that SmI_2 can be used as an efficient method of reductively cleaving the S-CN bond in thiocyanates and that the (samarium) thiolates so formed react efficiently with various alkylating and acylating reagents. We decided to examine the use of epoxides in this context as representing another important class of electrophilic reagents.



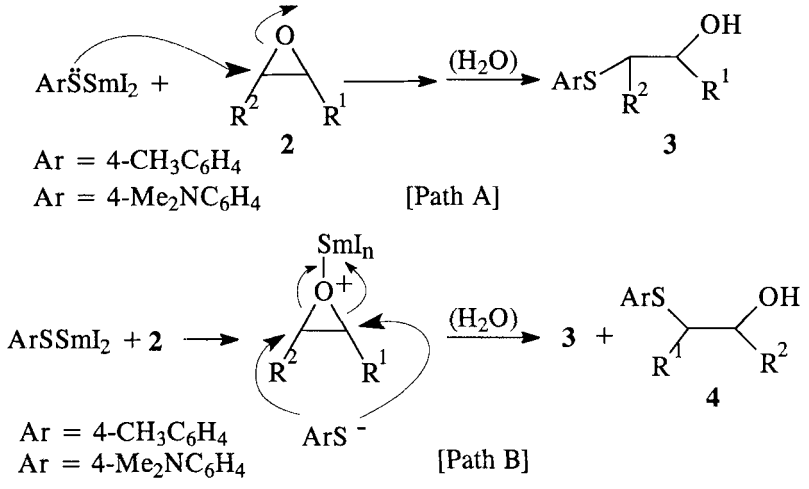
1a, X = CH_3
b, X = $N(CH_3)_2$ **2** **3**

Results and Discussion

At the outset of this work it appeared that two extreme mechanistic pathways were plausible: direct nucleophilic (S_N2) ring-opening of the epoxide (Path A) or Sm(II/III) catalyzed opening of the epoxide and subsequent reaction at (the most favored) carbocation-like site by the thiolate species (Path B). These possibilities are summarized in Scheme 1.

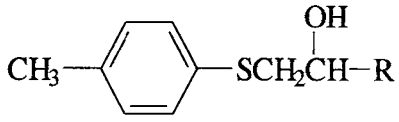
To explore this question we first examined a series of simple aliphatic primary epoxides, 1-butene oxide, 1-hexene oxide and 1,5-hexadiene monoepoxide,

Scheme 1

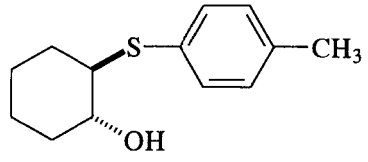


with **1a** in the presence of SmI_2. The results obtained are presented in Table 1. As can be seen, the only β-hydroxy sulfide isolated in all cases (entries 1-3) resulted from an apparent S_N2-like opening at the less hindered site, to give products (**5a-c**) of structural type **3** (R^1 = alkyl, R^2 = H). It is noteworthy that, in entry 3, the presence of a double bond has no deleterious effect upon the reaction. When a symmetrical epoxide such as cyclohexene oxide (entries 4 and 6) was allowed to react with samarium thiolate the expected product (**6a,b**), was formed in excellent yield. Although a mixture of *cis/trans* isomers, this consisted mainly (84%) of the *trans* isomer **6a**, as shown by comparison of our ^1H NMR data with those obtained by Vougioukas and Kagan.[6] While not conclusive, this result is again indicative of a preferred Path A type of reaction. (Norbornene epoxide was also used but the yields were very disappointing in this case, perhaps due to steric factors.)

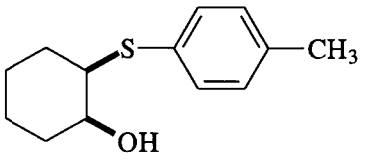
In sharp contrast to the foregoing results, the reaction of **1a** or **1b** with styrene oxide in the presence of SmI_2 gave very good yields of the β-hydroxy sulfides **7a** and **7b**, resulting from preferred attack by the thiolate species at the more hindered site



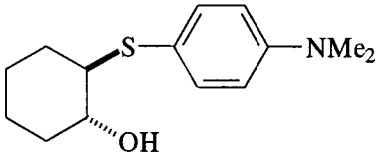
5a, R = CH_2CH_3
b, R = $(CH_2)_3CH_3$
c, R = $CH_2CH_2CH{=}CH_2$



6a



6b



6c

$ArSCHCH_2OH$ (Ar on S, C_6H_5 on CH)

7a, Ar = 4-$CH_3C_6H_4$
b, Ar = 4-$Me_2NC_6H_4$

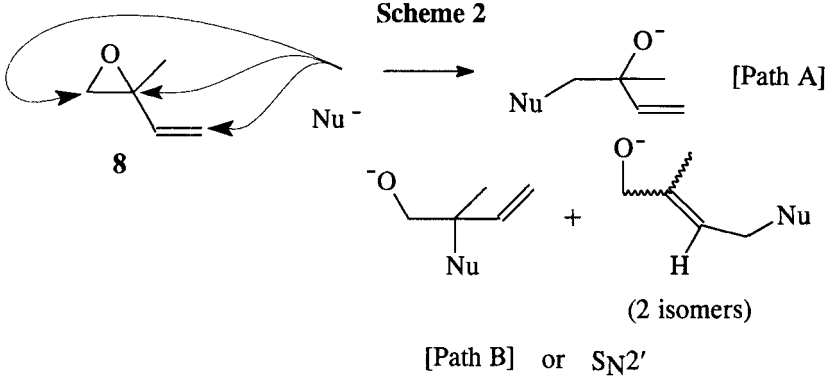
(at least 95% preference, Table 1, entries 5 and 7). This is a clear indication of a change in mechanism and strongly supports the possibility of a Path B mechanistic pathway, with the presence of the phenyl ring accounting for the intermediacy of a relatively stable carbocation-like species.

The reaction of nucleophilic species with (mono)epoxides derived from a conjugated diene may involve attack at the primary position, the tertiary allylic position, or attack at the (allylic) alkene terminus (Scheme 2). We thus decided to investigate the reaction of the samarium thiolate from **1a** with isoprene monoepoxide, **8**. Four possible products, including the two geometrical isomers arising from *quasi* S_N2' attack, may be expected. We have found that all four

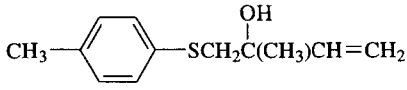
Table 1. Result of the Reactions of Expoxides (2) with the Samarium Thiolates from (1a,b).

Entry	(Sm) Thiolate from	R^1	R^2	Reaction time (h)	Product	Isolated Yield (%)
1	**1a**	$-CH_2CH_3$	H	20	**5a**	83
2	**1a**	$-(CH_2)_3CH_3$	H	20	**5b**	60
3	**1a**	$-(CH_2)_2CH{=}CH_2$	H	23	**5c**	69
4	**1a**	$-(CH_2)_4-$		1	**(6a/b)**	90
5	**1a**	H	$-C_6H_5$	1	**7a**	81
6	**1b**	$-(CH_2)_4-$		2	**6c**	92
7	**1b**	H	$-C_6H_5$	(1 min)	**7b**	82

Scheme 2



products, **9-12**, were formed, in a total overall yield of 79%, in the ratio 5:60:24:11. The product (**9**) of apparent S_N2 attack on the epoxide is by far the least favored and the combination of **10** and **11** accounts for 84% of the total. The *Z*-alkene (**10**) is formed in major amount, as established by NOE measurements. The lack of stereospecificity involved in the formation of **10** and **11**, argues strongly for an initial, Lewis acid-catalyzed type of ring-opening in **8**, preferential attack at the more accessible allylic site being attributed to steric hindrance.



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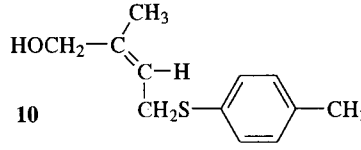

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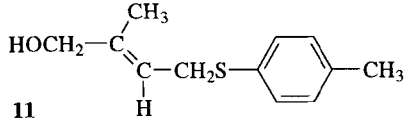
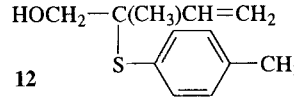


11



12

Our results have demonstrated that the samarium thiolates derived from aryl thiocyanates by reduction with SmI_2 react rapidly and efficiently with epoxides, with good regioselectivity, under very mild reaction conditions. No additional Lewis acid catalyst is required in this simple, 'one-pot' process, which provides a convenient route to β-hydroxy sulfides. When combined with our method for mild, selective thiocyanation of aromatic substrates[1] these reactions may be carried out without the necessity to prepare and purify the foul-smelling parent thiols.

Experimental Section

The epoxides used in this study were available commercially and were used without further purification. 4-Methyl-1-thiocyanatobenzene (**1a**) and N,N-dimethyl-4-thiocyanatoaniline (**1b**) were prepared by the procedures we had reported previously.[1,5] Samarium(II) iodide was generated in situ from 1,2-diiodoethane (washed in diethyl ether solution immediately before use with

$Na_2S_2O_3$ soln., then water) and samarium -40 mesh (obtained from Sigma-Aldrich), according to the literature procedure.[13]

THF was dried by refluxing over sodium metal with benzophenone and dichloromethane was redistilled prior to use. All reactions were run in oven- or flame-dried glassware, under argon. Reaction mixtures were quenched with aqueous ammonium chloride and the products were extracted from THF/water mixture using CH_2Cl_2 (minimum of 100 mL to achieve phase separation), followed by evaporation and flash chromatography on SiO_2 gel (E. Merck; 40-60 μ), eluting with CH_2Cl_2. R_f values are noted for each product, along with NMR, IR, and MS data.

^1H NMR and ^{13}C NMR spectra were run at 200 MHz and 125 MHz respectively, in $CDCl_3$ unless otherwise stated. Infrared spectra were run as KBr pellets or liquid films. Mass spectra were run under electron impact conditions at 70 eV. Based on 27 measurements of the mass to charge ratio of the molecular ion of cholesterol at 10,000 (10% valley) resolving power, the standard error deviation is 2.85 ppm: the 96% confidence limit for high resolution measurements would thus be ± 5.7 ppm.

Representative Procedure

trans-2-(4′-N,N-Dimethylaminophenylthio)cyclohexanol (6c). Samarium mesh (1.00 g, 6.64 mmol) was placed in dry THF(60 mL). 1,2-Diiodoethane (1.44 g, 5.10 mmol) was injected. The solution was stirred for 1.5 h under an argon atmosphere until it turned deep blue. N,N-Dimethyl-4-thiocyanatoaniline (0.40 g, 2.21 mmol) **1b** was added and the solution was stirred for an additional 1.5 h. (The blue color was initially lost but was regained by the end of this time.) Cyclohexene oxide (0.54 g, 5.5 mmol) was injected and the mixture was stirred for 2 h. The product was purified by column chromatography to give **6c** as a yellow liquid (92%) which later crystallized as a pale yellow solid, mp 67-70°C. ^1H NMR: δ 7.37 (d, J = 9.1 Hz, 2H), 6.64 (d, J = 9.1 Hz, 2H), 3.21 (m, 1H), 3.21 (s, 1H), 2.97 (s, 6H),

2.48 (m, 1H), 2.07 (m, 2H), 1.68 (m, 2H), 1.20 (m, 4H); ^{13}C NMR: δ 151.7, 137.2, 115.6, 112.5, 71.3, 56.9, 40.3, 33.7, 32.2, 26.3, 24.4; FTIR (KBr): ν 3430 cm^{-1}; MS: m/z (%), 251(81), 153(100), 152(62); HRMS calcd for $C_{14}H_{21}NOS$ 251.1344, found 251.1351.

1-(4′-Methylphenylthio)-2-butanol (5a). (Pale yellow oil, yield = 83%; R_f = 0.47.) ^{1}H NMR: δ 7.30 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 3.58 (m, 1H), 3.11 (dd, *J* = 13.6, 3.4 Hz, 1H), 2.79 (dd, *J* = 13.7, 8.7 Hz, 1H), 2.50 (d, *J* = 3.0 Hz, 1H), 2.30 (s, 3H), 1.55 (m, 2H), 0.93 (t, *J* = 7.9 Hz, 3H); ^{13}C NMR: δ 136.7, 131.9, 130.7, 129.8, 70.8, 42.3, 29.0, 21.0, 10.0; FTIR (film): ν 3402 cm^{-1}; MS: m/z (%), 196(81), 138(100), 123(39), 91(56); HRMS calcd for $C_{11}H_{16}OS$ 196.0922, found 196.0928.

1-(4′-Methylphenylthio)-2-hexanol (5b). (Pale yellow oil, yield = 60%; R_f = 0.52.) ^{1}H NMR: δ 7.30 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 3.61 (m, 1H), 3.12 (dd, *J* = 13.6, 3.4 Hz, 1H), 2.78 (dd, *J* = 12.9, 9.0 Hz, 1H), 2.44 (d, *J* = 3.0 Hz, 1H), 2.30 (s, 3H), 1.53 (m, 2H), 1.28 (m, 4H), 0.88 (t, *J* = 7.9 Hz, 3H); ^{13}C NMR: δ 136.8, 132.4, 130.8, 129.8, 69.3, 43.0, 35.8, 27.8, 22.7, 21.0, 14.0; FTIR (film): ν 3402 cm^{-1}; MS: m/z (%), 224(33), 138(100), 124(20), 91(43); HRMS calcd for $C_{13}H_{20}OS$ 224.1235, found 224.1234.

1-(4′-Methylphenylthio)-5-hexen-2-ol (5c). (Pale yellow oil, yield = 69%; R_f = 0.35.) ^{1}H NMR: δ 7.30 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 5.80 (m, 1H), 5.00 (m, 2H), 3.67 (m, 1H), 3.11 (dd, *J* = 13.6, 3.4 Hz, 1H), 2.79 (dd, *J* = 13.7, 9.1 Hz, 1H), 2.48 (d, *J* = 3.0 Hz, 1H), 2.32 (s, 3H), 2.18 (m, 2H), 1.62 (m, 2H); ^{13}C NMR: δ 138.1, 136.9, 131.3, 130.8, 129.8, 114.9, 68.8, 43.0, 35.2, 30.0, 21.1; FTIR (film): ν 3404 cm^{-1}; MS: m/z (%), 222(53), 138(100), 124(78), 91(77); HRMS calcd for $C_{13}H_{18}OS$ 222.1078, found 222.1075.

2-(4′-Methylphenylthio)cyclohexanol (6a/b). (Pale yellow oil, total yield = 90%; *cis*/*trans* = 16:84; R_f = 0.32, 0.26 respectively.) ^{1}H NMR: δ 7.38 (d, *J* = 7.9 Hz,

2H), 7.12 (d, J = 8.3 Hz, 2H), (*cis*) 3.75 (m, 1H), (*trans*) 3.28 (m, 1H), (*cis*) 3.26 (m, 1H), (*trans*) 3.03 (d, J = 1.1 Hz, 1H), (*trans*) 2.68 (m, 1H), (*cis*) 2.52 (d, J = 3.4 Hz, 1H), 2.33 (s, 3H), (*trans*) 2.10 (m, 2H), (*cis*) 1.78 (m, 4H), (*trans*) 1.69 (m, 2H), (*cis*) 1.40 (m, 4H), (*trans*) 1.28 (m, 4H); ^{13}C NMR (**6a**): δ 138.1, 134.5, 129.7, 71.9, 56.7, 33.8, 32.6, 26.2, 24.3, 21.1 (C-1′ was not detected); FTIR (film): ν 3406 cm^{-1}; MS: m/z (%), 222(48), 124(100), 91(43); HRMS calcd for $C_{13}H_{18}OS$ 222.1078, found 222.1075.

2-(4′-Methylphenylthio)-2-phenylethanol (7a). (Pale yellow oil, yield = 81%; R_f = 0.36.) ^{1}H NMR: δ 7.30 (m, 7H), 7.04 (d, J = 7.9 Hz, 2H), 4.25 (t, J = 6.8 Hz, 1H), 3.90 (td, J = 6.8, 1.9 Hz, 2H), 2.31 (s, 3H), 2.08 (t, J = 6.8 Hz, 1H); ^{13}C NMR: δ 139.0, 137.9, 133.2, 129.8, 129.7, 128.6, 128.3, 127.7, 65.1, 56.5, 21.1; FTIR (film): ν 3396 cm^{-1}; MS: m/z (%), 244(40), 213(76), 124(95), 91(100), 77(46); HRMS calcd for $C_{15}H_{16}OS$ 244.0922, found 244.0931.

2-(4′-N,N-Dimethylaminophenylthio)-2-phenylethanol (7b). (Yellow oil, which slowly crystallized to a pale yellow solid, mp 38-40°C, yield = 82%; R_f = 0.22.) ^{1}H NMR: δ 7.25 (m, 7H), 6.58 (d, J = 9.1 Hz, 2H), 4.09 (t, J = 6.4 Hz, 1H), 3.87 (t, J = 6.4 Hz, 2H), 2.94 (s, 6H), 2.12 (t, J = 6.4 Hz, 1H); ^{13}C NMR: δ 150.5, 139.3, 136.4, 128.5, 128.1, 127.5, 117.0, 112.4, 64.3, 57.2, 40.3; FTIR (film): ν 3400 cm^{-1}; MS: m/z (%), 273(42), 152(100), 120(14), 91(24); HRMS calcd for $C_{16}H_{19}NOS$ 273.1187, found 273.1174.

Z- and E-4-(4′-Methylphenylthio)-2-methyl-2-buten-1-ol (10,11). (Yellow oils, total yield = 66%.) ^{1}H NMR (**10**, R_f = 0.19): δ 7.29 (d, J = 8.3 Hz, 2H), 7.08 (d, J = 7.9 Hz, 2H), 5.58 (tq, J = 7.5, 1.5 Hz, 1H), 4.00 (d, J = 4.9 Hz, 2H), 3.52 (d, J = 7.6 Hz, 2H), 2.30 (s, 3H), 1.78 (s, 3H), 1.36 (t, J = 5.7 Hz, 1H); (**11**, R_f = 0.25): δ 7.30 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 5.44 (t, J = 8.4 Hz, 1H), 3.90 (d, J = 5.7 Hz, 2H), 3.50 (dd, J = 8.3, 0.8 Hz, 2H), 2.33 (s, 3H), 1.78 (s, 3H), 0.72 (t, J = 6.4 Hz, 1H); ^{13}C NMR (**10**): δ 138.6, 136.5, 131.0, 129.6, 129.5, 120.8, 68.2,

32.3, 21.0, 13.5; ^{13}C NMR (**11**): δ 138.6, 137.3, 132.3, 131.7, 129.6, 123.0, 61.1, 32.9, 21.2, 21.0; FTIR (film) (Z-isomer): ν 3369, 1636 cm^{-1}; (E-isomer): ν 3409, 1643 cm^{-1}; MS (**10**): m/z (%), 208(30), 124(100), 91(51), 84(50); HRMS (**10**) calcd for $C_{12}H_{16}OS$ 208.0922, found 208.0930; MS (**11**): m/z (%), 208(31), 124(100), 91(55), 84(50); HRMS (**11**) calcd for $C_{12}H_{16}OS$ 208.0922, found 208.0919.

Acknowledgement. This work was supported by the Natural Sciences and Engineering Research Council (Canada). We are also very grateful for support from GlaxoWellcome (U.K.) and Du Pont Agricultural Products.

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(Received in the USA 01 September 1997)