# Chemistry of Sulfonyl Isocyanates and Sulfonyl Isothiocyanates. XI. Cyclizations with Epoxides



J. W. McFarland*, J. J. Beaulieu [1], L. N. Arrey [2], and L. M. Frey [2]

Department of Chemistry, DePauw University,
Greencastle, Indiana 46135

Received March 1, 1988

4-Toluenesulfonyl isocyanate cyclized with 1,2-epoxy-3-phenoxypropane and 2,3-epoxypropyl 4-methoxyphenyl ether, respectively, to give 3-(4-toluenesulfonyl)-5-phenoxymethylene-2-oxazolidone (**I**) and 3-(4-toluenesulfonyl)-5-(4-methoxyphenoxymethylene)-2-oxazolidone (**II**). Compounds **I** and **II** were hydrolyzed in 2 *M* sodium hydroxide solution to the corresponding uncyclized hydroxy amides, **VII** and **VIII**. Compound **I** was remarkably stable toward 6 *M* hydrochloric acid and amines. Styrene oxide, 1,2-epoxybutane, 3-chloro-1,2-epoxypropane, and 1-methoxy-2-methylpropylene oxide reacted with the isocyanate to afford 3-(4-toluenesulfonyl)-4-phenyl-2-oxazolidone (**III**), 3-(4-toluenesulfonyl)-4-ethyl-2-oxazolidone (**IV**), 3-(4-toluenesulfonyl)-5-chloromethyl-2-oxazolidone (**V**), and 3-(4-toluenesulfonyl)-4,4-dimethyl-5-methoxy-2-oxazolidone (**VI**), respectively. The yield of **VI** was constant over a temperature range of 25-90°.

*J. Heterocyclic Chem.*, **25**, 1431 (1988).

Nucleophiles such as amines and alcohols are known to react rapidly with sulfonyl isocyanates and isothiocyanates [3-18]. McFarland and co-workers showed that 2-oxazolidones and 2-oxazolidinethiones could be prepared from sulfonyl isocyanates or sulfonyl isothiocyanates with chloro alcohols [6]. In all cases studied the sulfonyl group added immensely to the reactivity of the isocyanate or isothiocyanate.

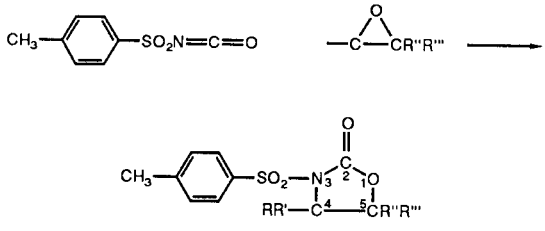
The cycloadditions of ordinary isocyanates with the nucleophiles, epoxides, were studied by Swern and Herweh and their co-workers [19-21]. Very little attention has been given to the cycloaddition of the sulfonyl isocyanates with epoxides. Using a hydrocarbon-soluble catalyst, Herweh and Kauffman studied the reaction of styrene oxide and phenyl glycidyl ether with 4-toluenesulfonyl isocyanate [22]. The authors also studied the effect of the sulfonyl group on the pmr spectra.

In this paper we show the extension of the cyclization reaction of sulfonyl isocyanates to other aromatic-containing epoxides and to purely aliphatic epoxides. In addition to the styrene oxide and phenyl glycidyl ether previously reported [22], 2,3-epoxypropyl 4-methoxyphenyl ether, 1,2-epoxybutane, 3-chloro-1,2-epoxypropane, and 1-methoxy-2-methylpropylene oxide were allowed to react with 4-toluenesulfonyl isocyanate.

It was found that phenyl glycidyl ether with 4-toluenesulfonyl isocyanate gave an almost quantitative yield (88%) of 3-(4-toluenesulfonyl)-5-phenoxymethylene-2-oxazolidone (**I**) [22]. Confirming the findings of Herweh and Kauffman [22], styrene oxide gave a semisolid from which only 44% of the 4-phenyl isomer of oxazolidone was obtained. The oily residue showed from pmr that both isomers (4- and 5-phenyl) were still in the mixture.

2,3-Epoxypropyl 4-methoxyphenyl ether gave 90% of sulfonyl oxazolidone **II**. The assignment of structure as the 5-isomer is in analogy to that of **I**. There is no reason to believe that a 4-methoxy group would change the position on the oxazolidone ring. 1,2-Epoxybutane likewise gave a good yield (76%) of product which we believe to be 3-(4-toluenesulfonyl)-4-ethyl-2-oxazolidone (**IV**). The pmr and ir spectra are consistent with the structure and also

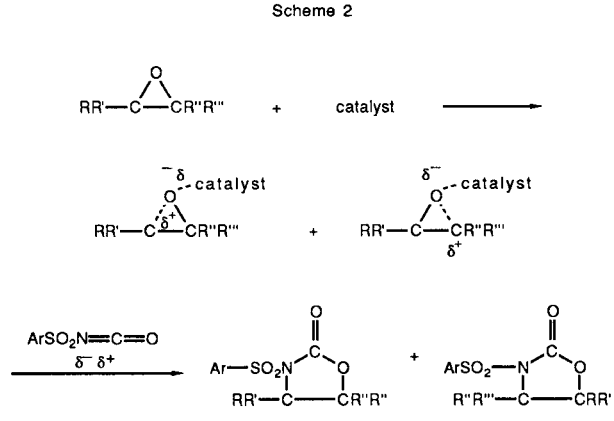
Scheme 1




Oxazolidone

| | |
|---|---|
| I | R = H, R' = H, R" = H, R"' = -$CH_2OC_6H_5$ |
| II | R = H, R' = H, R" = H, R"' = -$CH_2OC_6H_4OCH_3$-4 |
| III | R = H, R' = $C_6H_5$, R" = H, R"' = H |
| IV | R = H, R' = $C_2H_5$, R" = H, R"' = H |
| V | R = H, R' = H, R" = H, R"' = $CH_2Cl$ |
| VI | R = $CH_3$, R' = $CH_3$, R" = H, R"' = $OCH_3$ |

Scheme 2



reasonable if the mechanism postulated in Scheme 2 is valid.

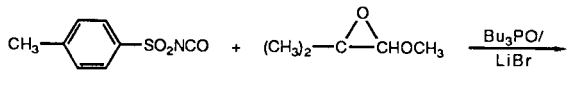
3-Chloro-1,2-epoxypropane (glycidyl chloride) afforded 98% of the 5-chloromethyl isomer of the sulfonyl oxazolidone **V**. From the sharpness of the melting point it is probably only one isomer. The trisubstituted epoxide, 1-methoxy-2-methylpropylene oxide, reacted with 4-toluenesulfonyl isocyanate to give quantitative yields of substituted oxazolidone **VI**. The assignment of structure is again based on the postulation of a positive or partially-positive intermediate. The predominant product depends upon which carbon atom on the epoxide would better accommodate a partially-positive charge. In the preparations of **I**, **II**, and **V** the phenoxymethyl, 4-methoxyphenoxymethyl, and chloromethyl groups would predictably destabilize a positive carbon. In the preparations of **III**, **IV**, and **VI**, however, the phenyl, ethyl, and methyl groups should be stabilizing and thus give rise to 4-isomers of the oxazolidones.

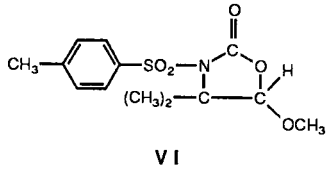
A brief study of the effect of catalyst, solvent, and temperature on the yields of products was carried out. The substitution of triphenylphosphine oxide for tributylphosphine oxide gave no essential difference in product yield of either **I** or **VI**. Using the Lewis acid, boron trifluoride etherate, in either benzene or methylene chloride in attempted synthesis of **VI** gave black intractable oils.

The yields of crude **VI** in hydrocarbon or tetrahydrofuran solvent did not change within the temperature range 25-90°.

Table 1

Effect of Temperature on Reaction Product




**VI**

| Solvent | Reaction Time (hours) | Temperature (°C) | Yield (%) | mp °C |
|---|---|---|---|---|
| Toluene | 6 | 90 | 100 | 87-89 |
| Benzene | 6 | 80 | 100 | 88-90 |
| Benzene | 6 | 60 | 99 | 87-89 |
| Benzene | 6 | 40 | 100 | 88-90 |
| Benzene | 6 | 25 | 100 | 86-89.5 |
| Tetrahydrofuran | 6 | 67 | 99 | 87-89 |

Oxazolidones **I** and **II** were cleaved to the corresponding hydroxy sulfonamides by heating with 2*M* aqueous sodium hydroxide solution [6]. Compound **I** showed remarkable resistance toward cleavage by aniline, benzylamine, or 6*M* hydrochloric acid solution.

3-(4-Toluenesulfonyl)-4,4-dimethyl-5-methoxy-2-oxazolidone **(VI)** gave 4-toluenesulfonamide when heated with aqueous sodium hydroxide solution or with aqueous-alcohol sodium hydroxide solution. Heating with aniline gave starting material and an oil.

## EXPERIMENTAL

4-Toluenesulfonyl isocyanate, the epoxides, lithium bromide, tributylphosphine oxide, and triphenylphosphine oxide were purchased from the Aldrich Chemical Co. and used without further purification. The ir spectra, using potassium bromide pellets, were recorded on a Nicolet 5DXB Fourier Transform Spectrometer and the pmr spectra on a Varian EM360L NMR Spectrometer using deuteriochloroform solvent containing 1% TMS. Melting points were obtained on a Mel-Temp apparatus and are uncorrected. Elemental analyses were by the Midwest Microlab, Inc., Indianapolis, Indiana.

3-(4-Toluenesulfonyl)-5-phenoxymethylene-2-Oxazolidone (**I**).

The reaction was carried out by modification of the procedure of Herweh and Kauffman [22]. 4-Toluenesulfonyl isocyanate (12.23 g, 0.067 mole) and 1,2-epoxy-3-phenoxypropane (10.07 g, 0.067 mole) were added to 50 ml of dried (over sodium) toluene. Lithium bromide (0.1 g) and tributylphosphine oxide (0.35 g) were added. The mixture was heated under reflux for 6 hours under nitrogen. Upon cooling a white solid precipitate appeared and was collected by suction filtration, 20.7 g (88%), mp 152-154°. Recrystallization from benzene gave crystals, mp 155-156.5°, lit 156.5-157.5° [22]; pmr (deuteriochloroform): δ 2.40 (s, 3H), 4.05 (m, 4H), 4.71 (m, 1H), 6.9 (m, 5H), 7.35 (d, 2H), 2.90, (d, 2H) ; ir (potassium bromide): 1781 (vs C=O) $cm^{-1}$.

*Anal.* Calcd. for $C_{17}H_{17}NO_5S$: C, 58.79; H, 4.94; N, 4.05; S, 9.24. Found: C, 59.15; H, 5.03; N, 4.28; S, 9.34.

The same results were obtained when triphenylphosphine oxide was substituted for tributylphosphine oxide.

3-(4-Toluenesulfonyl)-5-(4-methoxyphenoxymethylene)-2-oxazolidone (**II**).

The procedure was similar to that used in producing **I**. 4-Toluenesulfonyl isocyanate (11.75 g, 0.060 mole), 2,3-epoxypropyl 4-methoxyphenyl ether (12.19, g, 0.068 mole), 0.1 g of lithium bromide and 0.36 g of tributylphosphine oxide in 50 ml of dry toluene were heated under reflux under nitrogen for 6 hours. Removal of solvent *in vacuo* afforded 20.2 g (90%), of white crystals, mp 152-156°. Recrystallization from benzene gave fine crystals of **II**, mp 162-163°; pmr δ 2.40 (s, 3H), 3.65 (s, 3H), 4.04 (t, 2H), 4.2 (t, 2H), 4.6 (m, 1H), 6.8 (s, 4H), 7.4 (d, 2H), 7.95 (d, 2H); ir (potassium bromide): 1778 (vs C=O) $cm^{-1}$.

*Anal.* Calcd. for $C_{18}H_{19}NO_6S$: C, 57.28; H, 5.04; N, 3.71, S, 8.49. Found: C, 57.56; H, 5.34; N, 3.87; S, 8.32.

*N*-(4-Toluenesulfonyl)-4-phenyl-2-oxazolidone (**III**).

A solution of 4-toluenesulfonyl isocyanate (4.93 g, 0.025 mole), 0.1 g of lithium bromide, and 0.35 g of tributylphosphine oxide in 50 ml of dry toluene was heated to reflux under nitrogen and a solution of 3.00 g (0.025 mole) of styrene oxide in 10 ml of dry toluene added during 2 hours [22]. The solution was heated an additional 6 hours. Removal of toluene and cooling produced a yellow oil which partially crystallized. Trituration with diethyl ether gave 3.58 g (44%) of white crystals, mp 139-144°; pmr (deuteriochloroform): δ 2.35 (s, 3H), 4.25 (dd, 1H), 4.72 (t, 1H), 5.53 (dd, 1H), 7.1 (d, 2H), 7.25 (m, 5H), 7.58 (d, 2H); ir (potassium bromide): 1772 (vs C=O) $cm^{-1}$.

*Anal.* Calcd. for $C_{16}H_{15}NO_4S$: C, 60.55; H, 4.76; N, 4.41; S, 10.10. Found: C, 60.64; H, 4.86; N, 4.31; S, 10.37.

*N*-(4-Toluenesulfonyl-4-ethyl-2-oxazolidone (**IV**).

A solution of 14.9 g (0.083 mole) of 4-toluenesulfonyl isocyanate and 17.1 g (0.236 mole) of 1,2-epoxybutane in 40 ml of sodium-dried benzene was prepared. Catalyst (0.1 g of lithium bromide and 0.35 g of tributylphosphine oxide) was added and the mixture heated under reflux for 6 hours under nitrogen. After removal of solvent under vacuum a white precipitate (16.9 g, 77%) was obtained, mp 92-98°. Recrystallization from benzene-petroleum ether gave product, mp 108-109°; pmr (deuteriochloroform): δ 1.0 (t, 3H), 1.75 (m, 2H), 2.4 (s, 3H), 3.65 (m, 1H), 4.3 (d, 2H), 7.35 (d, 2H), 7.95 (d, 2H); ir (potassium bromide): 1775 (vs C=O) $cm^{-1}$.

*Anal.* Calcd. for $C_{12}H_{15}NO_4S$: C, 53.55; H, 5.57; N, 5.21; S, 11.91. Found: C, 53.31; H, 5.50; N, 5.37; S, 11.68.

3-(4-Toluenesulfonyl-5-chloromethyl-2-oxazolidine (**V**).

The procedure was as above using 7.86 g (0.04 mole) of 4-toluenesulfonyl isocyanate, 3.89 g (0.042 mole) of 3-chloro-1,2-epoxypropane, 0.1 g of lithium bromide, and 0.35 g of tributylphosphine oxide in 50 ml of dry toluene. The solution was heated under reflux for 16 hours and solvent removed *in vacuo*. The resultant slightly yellow oil slowly crystallized upon standing. Trituration with petroleum ether gave 11.4 g (98%) of white crystals, mp 96-99°. Recrystallization from benzene afforded analytically pure product, mp 99-100°; pmr (deuteriochloroform): δ 2.50 (s, 3H), 3.71 (d, 2H), 4.18 (m, 2H), 4.85 (m, 1H), 7.35 (d, 2H), 7.97 (d, 2H); ir (potassium bromide): 1786 (vs C=O) $cm^{-1}$.

*Anal.* Calcd. for $C_{11}H_{12}ClNO_4S$: C, 45.60; H, 4.17; N, 4.83; S, 11.07; Cl, 12.24. Found C, 45.89; H, 4.34; N, 5.09; S, 10.95; Cl, 12.02.

3-(4-Toluenesulfonyl-4,4-dimethyl-5-methoxy-2-oxazolidone (**VI**).

4-Toluenesulfonyl isocyanate (10.0 g, 0.051 mole), 0.1 g of lithium bromide and 0.35 g of tributylphosphine oxide were added to 50 ml of dry benzene under nitrogen. While warming a solution of 5.70 g (0.056 mole) of (±)-1-methoxy-2-methylpropylene oxide in 15 ml of dry benzene was added. The mixture was heated 6 hours under reflux and concentrated *in vacuo*. The resultant oil crystallized to 15.2 g (100%) of white crystals, mp 88-90°. Recrystallization from benzene-petroleum ether gave product, mp 92-94°; pmr (deuteriochloroform): δ 1.33 (s, 6H), 2.40 (s, 3H), 3.58 (s, 3H), 5.1 (s, 1H), 7.30 (d, 2H), 7.95 (d, 2H); ir (potassium bromide): 1768 (vs C=O) $cm^{-1}$.

*Anal.* Calcd. for $C_{13}H_{17}NO_5S$: C, 52.17; H, 5.68; N, 4.68; S, 10.70. Found: C, 52.04; H, 5.82; N, 4.56; S, 10.47.

Using the same procedure as above, the respective % yields of crude product were 100, 100, 99, 100, and 100 for temperatures of 90° (toluene), 80°, 60°, 40°, and 25° (the latter four in benzene). Melting points were not significantly different (See Table 1).

Changing the catalyst from tributylphosphine oxide/lithium bromide to triphenylphosphine oxide/lithium bromide at 80° in benzene gave essentially the same results. Using boron trifluoride etherate as catalyst in either benzene or methylene chloride at 25° gave black intractable oils.

Hydrolysis of **I**.

Oxazolidone **I** (1.74 g, 0.005 mole) was heated under reflux with 50 ml of 2*M* aqueous sodium hydroxide solution for 3 hours. Acidification with concentrated sulfuric acid precipitated a gum. Decantation of the aqueous solution, followed by washing with water and drying under vacuum gave product which slowly solidified, 1.60 g (99%), mp 60-68° (with small amount not melting). Solution in chloroform, filtration, and concentration of filtrate gave solid **VII**, mp 64-66°; pmr (deuteriochloroform): δ 2.34 (s, 3H), 3.15 (m, 2H), 3.85 (m, 3H), 4.4 (broad, 2H), 6.7-7.3 (5H), 7.2 (d, 2H), 7.68 (d, 2H); ir (potassium bromide): 3482 (OH), 3249 (N-H), 3000, 2924, 1596, 1496, 1323 ($SO_2$), 1157 ($SO_2$) $cm^{-1}$.

*Anal.* Calcd. for $C_{16}H_{19}NO_4S$: C, 59.80; H, 5.96; N, 4.36; S, 9.98. Found: C, 58.97; H, 6.23; N, 4.51; S, 10.26.

Hydrolysis of **II**.

Oxazolidone **II** (1.89 g, 0.005 mole) was heated under reflux with 50 ml of 2*M* sodium hydroxide solution for 5 hours. Work-up as above gave 1.20 g (69%) of pure **VIII**, mp 65-67°; pmr (deuteriochloroform): δ 2.34 (s, 3H), 3.15 (m, 2H), 3.65 (s, 3H), 3.8 (m, 4H), 4.8 (m, 1H), 6.73 (s, 4H), 7.2 (d, 2H), 7.67 (d, 2H); ir (potassium bromide): 3455 (OH), 3262 (N-H), 1596, 1516, 1317, 1157 $cm^{-1}$.

*Anal.* Calcd. for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99; S, 9.12. Found: C, 58.08; H, 6.25; N, 4.20; S, 8.89.

Attempted Reaction of **I** with Aniline.

Compound **I** (1.74 g, 0.005 mole) and 0.52 g (0.0055 mole) of aniline in 50 ml of dry benzene was heated under reflux for 4.5 hours. The white precipitate was collected by suction filtration and amounted to 1.43 g, mp 154-155°, mmp with **I**, 154-155°. Evaporation of the solvent to 25 ml gave another 0.15 g of **I**, mp 154-155°, total recovery of **I**, 1.58 g (91%).

Heating under reflux with toluene gave a similar result.

Heating **I** and benzylamine in toluene at 110° for 8 hours gave 80% recovery of **I**.

Heating **I** with 6*M* hydrochloric acid solution at reflux for 15 hours resulted in 86% recovery of **I**.

Reaction of 3-(4-Toluenesulfonyl)-4,4-dimethyl-5-methoxy-2-oxazolidone (**VI**) with Bases.

(a) With Sodium Hydroxide.

A mixture of 1.0 g (0.0033 mole) of **VI** and 50 ml of 2*M* aqueous sodium hydroxide solution was heated under reflux for 6 hours. Neutralization with cold 6*M* sulfuric acid gave a precipitate, mostly melting at 140-143° but some higher melting. Solution in acetone, filtration, and removal of solvent gave 0.44 g of crystals, mp 140-142°, mmp with 4-toluenesulfonamide, 140-142°; ir: 3362 (N-H), 1529 (arom), 1320 ($SO_2$), 1164 ($SO_2$) $cm^{-1}$.

Using 50 ml of 2*M* sodium hydroxide and 50 ml of ethanol resulted in a 57% yield of *p*-toluenesulfonamide, mp 138-140°.

(b) With Aniline.

A mixture of 1.0 g (0.0033 mole) of **VI**, 0.50 g (0.0054 mole) of aniline, and 10 ml of dry toluene was heated under reflux for 6 hours. Removal of solvent and trituration with diethyl ether afforded 0.44 g (44% recovery) of crystals which were determined from ir and pmr to be starting material. The residue was an oil which was not further investigated.

Acknowledgements.

We are grateful to Mr. Wilbert B. McCluer, The Dow Chemical Company Foundation, and The Charles A. Dana Foundation for partial support of this work.

REFERENCES AND NOTES

[1] Dow Chemical Foundation Scholar, Summer, 1987; McCluer Scholar 1987-88.

[2] Charles A. Dana Intern, Summer, 1987.

[3] J. W. McFarland, *Int. J. Sulfur Chem.*, **B,7**, 319 (1972).

[4] J. W. McFarland, *Sulfur Rep.*, **1**, #4 (1981).

[5] J. W. McFarland and R. W. Houser, *J. Org. Chem.*, **33**, 340 (1968).

[6] J. W. McFarland, C. E. Hayes, E. B. Blair, and K. R. Stuhlmacher, *J. Heterocyclic Chem.*, **17**, 271 (1980).

[7] J. W. McFarland, T. H. Kozel, K. R. Stuhlmacher, and T. S. Chevalier, *J. Heterocyclic Chem.*, **17**, 273 (1980).

[8] T. Kodama, Y. Kodama, S. Shinohara, T. Uehara, and S. Hisada, Japanese Patent 68 09,053 (April 12, 1968); *Chem. Abstr.*, **70**, 3555r (1969).

[9] N. B. Dessai, J. Jayaraman, N. N. Naik, V. Ramanathan, K. Artz, and W. Jenny, Swiss Patent 561,265 (April 30, 1975); *Chem. Abstr.*, **83**, 81218r (1975).

[10] H. Dietrich, U. S. Patent 3,687,934 (August 29, 1972); *Chem. Abstr.*, **78**, 16071r (1973).

[11] Z. Zrzozouski, *Acta. Pol. Pharm.*, **31**, 293 (1974); *Chem. Abstr.*, **82**,

72862y (1975).

[12] H. Kiefer and B. Giese, German Patent 2,034,530 (February 3, 1972); *Chem. Abstr.*, **76**, 140276p (1972).

[13] L. D. Spicer, J. M. Pensack, and R. D. Wilbur, U. S. Patent 4,005,140 (January 25, 1977); *Chem. Abstr.*, **87**, 22872j (1977).

[14] W. Wymek, Z. Ryznershi, A. Cygankiewicz, and R. Zimon, *Pol. J. Pharmacol. Pharm.*, **26**, 479 (1974); *Chem. Abstr.*, **82**, 57600t (1975).

[15] J. Philippe, German Patent 2,239,311 (February 22, 1973); *Chem. Abstr.*, **78**, 12472t (1973).

[16] H. Egg, *Monatsch. Chem.*, **103**, 1391 (1972); *Chem. Abstr.*, **78**, 57979r (1973).

[17] C. M. Schneider, R. P. Owne, G. A. Miller, W. D. Wier, and E. E. Kilbourne, German Patent 2,325,036 (January 3, 1974); *Chem. Abstr.*, **80**, 95531n (1974).

[18] R. Miess and H. Eilingsfeld, German Patent 2,150,686 (April 19, 1973); *Chem. Abstr.*, **79**, 32096h (1973).

[19] M. E. Dyer and D. Swern, *Chem. Rev.*, **67**, 197 (1967).

[20] J. E. Herweh, T. A. Foglia, and D. Swern, *J. Org. Chem.*, **33**, 4029 (1968).

[21] J. E. Herweh, *J. Heterocyclic Chem.*, **5**, 809 (1968).

[22] J. E. Herweh and W. J. Kauffman, *J. Heterocyclic Chem.*, **8**, 983 (1971); *Tetrahedron Letters*, 809 (1971).