The Synthesis of Sulfenamides Utilizing *N*-Alkylthio-, *N*-Cycloalkylthio-, and *N*-Arylthiolactams

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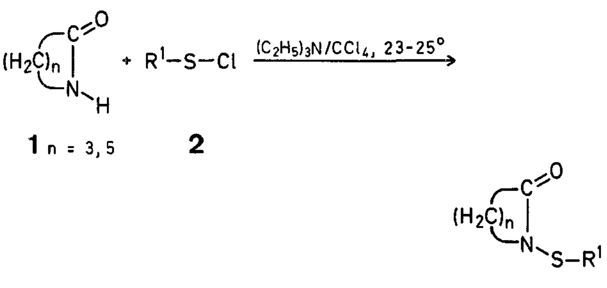
In the past, sulfenamides **5** have been prepared by the reaction of sulfenyl halides with amines[1]. However, this method generally suffered from low yields and side reactions. Over the past twenty years, there have been several improvements[2-12] of the original method. Among these improvements were the use of thiosulfonates[8] and *N*-alkyl- and -arylthioimides[4-7] in place of the sulfenyl halides. The reaction of thiosulfonates with aliphatic amines is quite satisfactory for the synthesis of alkyl sulfenamides, however, it fails with aromatic amines[8]. Other methods also lack generality, and are restricted to the synthesis of either aliphatic[9] or aromatic[10,11,12] sulfenamides. The method involving the use of imides as transfer agents is generally applicable for the preparation of both aliphatic and aromatic sulfenamides. However, the *N*-alkyl- and -arylthioimides which are utilized in this method are somewhat costly, in particular when applied to a large scale.

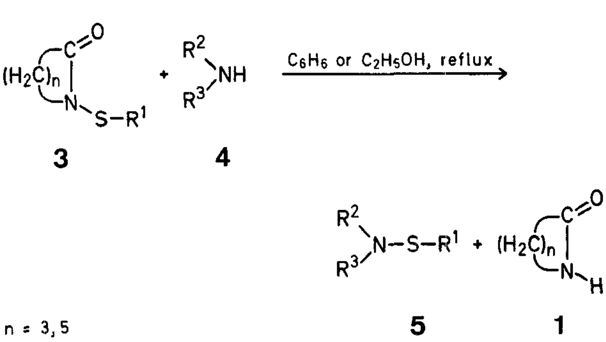
In work on the transfer of nitroxyl-labeled phosphoryl moieties[13-17], imidazoles have been extensively utilized as transfer agents. However, all attempts to adapt this method to the transfer of alkyl, cycloalkyl, or arylthio moieties were unsuccessful because of difficulties encountered in preparing the intermediate *N*-alkyl- or *N*-arylthioimidazolides, although the transfers of some other sulfur moieties using imidazole have been reported[18,19,20].

Recently, the use of *N*-[1-oxyl-2,2,6,6-tetramethyl-4-piperidylphenylphosphono]-2-pyrrolidinone, a *N*-substituted lactam, for the preparation of spin-labeled phosphoroamidates, was reported[17]. Now we have found that this reaction can be successfully applied to the transfer of sulfur moieties, and, thus, represents a versatile new method for the synthesis of sulfenamides in high yields using *N*-alkylthio-, -cycloalkylthio-, and -arylthio-2-pyrrolidinones (**3**, n = 3) and *N*-alkylthio-, -cycloalkylthio-, and -arylthio-2-oxohexamethyleneimines (**3**, n = 5). The intermediates **3** (n = 3, 5) can be prepared in good yields at room temperature by the reaction of the lactams, 2-pyrrolidinone (butanelactam, **1**, n = 3), and 2-oxohexamethyleneimine (caprolactam, **1**, n = 5), with sulfenyl chlorides **2** in the presence of triethylamine (Table 1).



R^1 = alkyl, cycloalkyl, aryl

Alternatively, the intermediates **3** (n = 3, 5) can be prepared by the reaction of an *N*-trimethylsilyllactam[20] with a sulfenyl halide **2**. However, in this method an additional step is required. The reactions of compounds **3** (n = 3, 5), with both aliphatic and aromatic primary and secondary amines **4** (Table 2) proceed readily to form sulfenamides **5**, and, offer some advantages over the previously used methods.



n = 3, 5

R^2, R^3 = H, C_6H_5, or

R^2R^3 = $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$, $-\underset{CH_3}{CH}-(CH_2)_4-$

Thus, the use of either caprolactam or 2-pyrrolidinone, which are produced on a large scale industrially, as a source of sulfur-transfer reagents represents a significant cost reduction of starting materials compared to the imides which have been used in the past[4-7]. Furthermore, the transfer of the alkylthio, cycloalkylthio, and arylthio group using the corresponding lactam derivative **3** (n = 3, 5), gives, in addition

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Table 1. Preparation of *N*-Substituted Lactams **3** (n = 3, 5) from Sulfenyl Chlorides **2** and the Lactams **1** (n = 3, 5)

Product **3** R^1	n	Yield [%][a, b]	m.p. or b.p./torr	n_D^{25}	Molecular formula[c]	Molecular Weight	^{1}H-N.M.R. (CDCl$_3$) δ [ppm]
C_6H_5	3	77	118–120°/0.05	1.5956	$C_{10}H_{11}NOS$ (193.3)	202	1.7–2.55 (m, 4H); 3.2–3.6 (t, 2H); 7.0–7.25 (m, 5H)
C_6H_5	5	71, 82[d]	68–69° 68–70°[d]	—	$C_{12}H_{15}NOS$ (221.3)	217	1.55–1.95 (m, 6H); 2.55–2.95 (m, 2H); 3.75–4.05 (m, 2H); 7.05–7.2 (m, 5H)
cyclo-C_6H_{11}	3	71	108°/0.05	1.4989	$C_{10}H_{17}NOS$ (199.3)	196	1.0–3.4 (m, 15H); 2.45–2.75 (t, 2H)
cyclo-C_6H_{11}	5	73	102–105°/0.01	1.5385	$C_{12}H_{21}NOS$ (227.4)	222	1.05–2.3 (m, 17H); 2.45–3.00 (m, 2H); 3.70–4.00 (m, 2H)
n-C_4H_9	3	81	71–73°/0.04	1.5044	$C_8H_{15}NOS$ (185.3)	183	0.75–1.1 (t, 3H); 1.1–2.65 (m, 8H); 2.65–2.95 (t, 2H); 3.45–3.8 (t, 2H)
n-C_4H_9	5	83	82°/0.10	1.5361	$C_{10}H_{19}NOS$ (201.3)	203	0.80–1.1 (t, 3H); 1.1–2.70 (m, 12H); 2.5–2.9 (m, 2H); 3.75–4.1 (m, 2H)

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[a] Yields of pure isolated products.

[b] Reaction in carbon tetrachloride, 2h, ambient temperature.

[c] The microanalyses were in satisfactory agreement with the calculated values C, ±0.30; H, ±0.30; N, ±0.30.

[d] Yield of **3** (n = 5) from the reaction of *N*-trimethylsilylcaprolactam with benzenesulfenyl chloride. *N*-Trimethylsilylcaprolactam was prepared by the method of Harpp et al.[20] in 76% yield [b.p. 55–56°/0.05 torr; n_D^{25} = 1.3817; ^{1}H-N.M.R. (CDCl$_3$): δ = 0.3 (s, 9H); 1.5–1.85 (m, 6H); 2.4–2.6 (m, 2H); 3.1–3.4 ppm (m, 2H); molecular formula: $C_9H_{19}NOSi$ (185.2); M.W. found: 183].

Table 2. Preparation of Sulfenamides **5** from Amines **4** and *N*-Substituted Lactams **3** (n = 3, 5)

Lactam **3** R^1	n	Amine **4** R^2	R^3	Yield [%][a]	Reaction conditions solvent/time	m.p. or b.p./torr (Lit. m.p. or b.p./torr)	n_D^{25}	Molecular formula[b]	Molecular weight	^{1}H-N.M.R. (CDCl$_3$) δ [ppm]
C_6H_5	3	C_6H_5	H	78 84	C_2H_5OH/2h C_6H_6/2h	57° (57–59°)[6]	—	$C_{12}H_{11}NS$ (201.3)	199	1.0–1.2 (s, 1H); 7.1–7.65 (m, 10H)
C_6H_5	3	—$(CH_2)_2$—O—$(CH_2)_2$—		90	C_6H_6/2h	30–31° (31–33°)[6]	—	$C_{10}H_{13}NOS$ (195.3)	190	2.55–3.0 (t, 4H); 3.25–3.75 (t, 4H); 6.9–7.45 (m, 5H)
C_6H_5	3	—$(CH_2)_5$—		71 94	C_2H_5OH/8h C_6H_6/2h	70°/0.01	1.5554	$C_{11}H_{15}NS$ (193.3)	190	1.1–2.1 (m, 6H); 2.75–3.35 (t, 4H); 7.05–7.55 (m, 5H)
C_6H_5	5	C_6H_5	H	82 82	C_2H_5OH/2h C_6H_6/2h	57° (57–59°)[6]	—	$C_{12}H_{11}NS$ (201.3)	198 200	1.0–1.2 (s, 1H); 7.1–7.65 (m, 10H)
C_6H_5	5	—$(CH_2)_2$—O—$(CH_2)_2$—		89	C_6H_6/2h	30–31° (31–33°)[6]	—	$C_{10}H_{13}NOS$ (195.3)	191	2.55–3.0 (t, 4H); 3.25–3.75 (t, 4H); 6.9–7.45 (m, 5H)
C_6H_5	5	—$(CH_2)_5$—		92	C_6H_6/2h	70°/0.01	1.5556	$C_{11}H_{15}NS$ (193.3)	196	1.1–2.1 (m, 6H); 2.75–3.35 (t, 4H); 7.05–7.55 (m, 5H)
cyclo-C_6H_{11}	3	—$(CH_2)_5$—		84	C_2H_5OH/16h	71–73°/0.3 (83–88°/0.5)[5]	1.5102[c]	$C_{11}H_{21}NS$ (199.4)	202	1.1–2.2 (m, 17H); 2.7–3.1 (m, 4H)
cyclo-C_6H_{11}	3	—$CH(CH_3)$—$(CH_2)_4$—		59	C_2H_5OH/24h	76–77°/0.5 (106°/1.5)[5]	1.5097	$C_{12}H_{23}NS$ (213.4)	211	1.1–1.3 (d, 3H); 1.3–2.15 (m, 17H); 2.5–3.45 (m, 3H)
cyclo-C_6H_{11}	3	—$(CH_2)_2$—O—$(CH_2)_2$—		80	C_2H_5OH/16h	82–83°/0.4 (76–77°/0.005)[22]	1.5090	$C_{10}H_{19}NOS$ (201.3)	195	0.95–2.2 (m, 11H); 2.65–3.15 (t, 4H); 3.45–3.90 (t, 4H)
cyclo-C_6H_{11}	5	—$(CH_2)_5$—		82	C_2H_5OH/16h	71–73°/0.3 (83–88°/0.5)[5]	1.5095	$C_{11}H_{21}NS$ (199.4)	190	1.1–2.2 (m, 17H); 2.7–3.1 (m, 4H)
cyclo-C_6H_{11}	5	—$CH(CH_3)$—$(CH_2)_4$—		56	C_2H_5OH/24h	76–77°/0.05 (106°/1.5)[5]	1.5103	$C_{12}H_{23}NS$ (213.4)	208	1.1–1.3 (d, 3H); 1.3–2.15 (m, 17H); 2.5–3.45 (m, 3H)
cyclo-C_6H_{11}	5	—$(CH_2)_2$—O—$(CH_2)_2$—		79	C_2H_5OH/16h	82–83°/0.4 (76–78°/0.005)[22]	1.5093	$C_{10}H_{19}NOS$ (201.3)	194	0.95–2.2 (m, 11H); 2.65–3.15 (t, 4H); 3.45–3.90 (t, 4H)
n-C_4H_9	3	—$(CH_2)_5$—		86 72	C_2H_5OH/24h C_6H_6/24h	48–49°/0.2 (43–44°/0 15)[6]	1.4843	$C_9H_{19}NS$ (173.3)	171	0.75–1.1 (t, 3H); 1.15–1.85 (m, 10H); 2.25–2.8 (m, 2H); 2.8–3.1 (t, 4H)
n-C_4H_9	5	—$(CH_2)_5$—		87	C_2H_5OH/24h	48–49°/0.2 (43–44°/0.15)[6]	1.4845	$C_9H_{19}NS$ (173.3)	169	0.75–1.1 (t, 3H); 1.15–1.85 (m, 10H); 2.25–2.8 (m, 2H); 2.8–3.1 (t, 4H)

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[a] Yields of pure isolated products.

[b] The microanalyses were in satisfactory agreement with the calculated values C, ±0.30; H, ±0.30; N, ±0.30.

[c] Lit.[5] n_D^{20}: 1.4894.

to the desired sulfenamide, a water-soluble lactam **1** ($n=3$, 5) as a by-product which can, therefore, be readily removed during the workup of the reaction mixture with water.

The reaction is performed in either a polar (ethanol) or non-polar (benzene) solvent, generally at reflux (see experimental). The transfer of the arylthio moiety occurs equally well in either benzene or ethanol in ~ 2 h, while the transfer of an alkylthio or cycloalkylthio group is more difficult and is somewhat facilitated by the polar solvent and longer reaction times of up to 24 h. The reaction of **3** ($n=3$, 5) with the sterically hindered amine, 2-methylpiperidine, results in lower yields as compared to the unhindered amines.

In conclusion, we feel that the preparation of alkyl-, cycloalkyl-, and arylsulfenamides by this method, because of its economy, simplicity, and in view of the stability and ease of preparation of the intermediates **3** ($n=3$, 5), may become a method of choice.

Materials:
All reagents were of the finest quality commercially available. The sulfenyl chlorides were prepared by the reaction of chlorine with the corresponding thiol[21], and were used immediately after distillation, in the case of aromatic sulfenyl chlorides, or without further purification in the case of aliphatic sulfenyl chlorides. 2-Pyrrolidinone was obtained from the General Aniline and Film Corporation of New York, New York. The caprolactam, amines, and thiols were obtained from the Aldrich Chemical Co. of Milwaukee, Wisconsin. The carbon tetrachloride was a certified A.C.S. grade from the Mallinckrodt Company of St. Louis, Missouri. The benzene was distilled from and stored over sodium. The ethanol was the absolute grade from the U.S. Industrial Chemicals Co. of New York, New York.

Analytical Procedures:
All melting points and boiling points are uncorrected. The I.R. analyses were recorded on a Perkin-Elmer Infracord Spectrophotometer, Model 137. ^{1}H-N.M.R. analyses were performed on a Varian T-60 Spectrometer using TMS as an internal standard in $CDCl_3$. Microanalyses were obtained on a F & M Scientific Corporation Carbon, Hydrogen, and Nitrogen Analyzer, Model 185. Molecular weights were determined isopiestically in benzene on a Hitachi Perkin-Elmer Model 115 Molecular Weight apparatus.

***N*-Substituted Lactams 3 ($n=3$, 5); General Procedure:**
A solution of freshly prepared sulfenyl chloride[21] **2** (0.05 mol), in carbon tetrachloride (20 ml) is added dropwise with stirring, at room temperature under anhydrous conditions, to a solution of the lactam **1** (0.05 mol), and triethylamine (0.055 mol) in carbon tetrachloride (30 ml). The formation of triethylamine hydrochloride is accompanied by a fading of the orange coloration of the reaction mixture. The reaction is slightly exothermic. After the addition of the sulfenyl chloride, the reaction mixture is stirred at ambient temperature for 3 h, and then filtered to remove triethylamine hydrochloride. The filter cake is washed with carbon tetrachloride (2×10 ml), then dried in an oven at 55–60°/40 torr (99–100% yield). The filtrate is poured into water (50 ml), and the aqueous phase is extracted with carbon tetrachloride (2×10 ml). The combined carbon tetrachloride extracts are dried over anhydrous magnesium sulfate, then filtered. The filtrate is concentrated on a rotating evaporator at 23–25°/12–15 torr to give the crude product. The product is purified by distillation using a mechanical pump to give compounds **3** ($n=3$, 5) (Table 1).

Sulfenamides 5; General Procedure:
A solution of **3** ($n=3$, 5; 5.0 mmol), and an amine **4** (5.5 mmol) in either benzene or ethanol (25 ml), is stirred vigorously and brought to boil. After 2–24 h (Table 2), the resulting amber colored solution is cooled to ambient temperature, then poured into water (20 ml). In the case of benzene as the solvent, the water layer is separated and extracted with benzene (2×10 ml). In the case of ethanol as solvent, there is no phase separation. Instead, the solution is extracted with ether (3×10 ml). The combined organic layers in either case are dried over anhydrous magnesium sulfate, and filtered. The filtrate is concentrated on a rotating evaporator at 23–25°/12–15 torr to give the crude sulfenamides **5**. The solid products are then recrystallized from hexane, and liquids are purified by distillation (Table 2).

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[1] N. Kharasch, S. J. Potempa, H. L. Wehrmeister, *Chem. Rev.* **39**, 269 (1946).

[2] E. E. Reid, *Organic Chemistry of Bivalent Sulfur*, Vol. 1, Chemical Publishing Co., Inc., New York, 1958, p. 279.

[3] E. Riesz, *Bull. Soc. Chem. Fr.* **1966**, 1449.

[4] T. Mukaiyama, S. Kobayashi, T. Kumamoto, *Tetrahedron Lett.* **1970**, 5115.

[5] K. Boustany, *Chimia* **1970**, 396.

[6] D. N. Harpp, T. G. Back, *Tetrahedron Lett.* **1971**, 4953.

[7] D. N. Harpp, T. G. Back, *Tetrahedron Lett.* **1972**, 1481.

[8] J. E. Dunbar, J. H. Rogers, *J. Org. Chem.* **31**, 2842 (1966).

[9] T. Saegusa, Y. Ito, T. Shimizu, *J. Org. Chem.* **35**, 2979 (1970).

[10] D. J. Abbott, C. J. M. Stirling, *J. Chem. Soc.* [C], **1969**, 818.

[11] M. D. Bentley, I. B. Douglass, J. A. Lacadie, D. C. Weaver, *J. Chem. Soc. Chem. Commun.* **1971**, 1625.

[12] R. H. Cragg, J. P. N. Husband, G. C. H. Jones, A. F. Weston, *J. Organometal. Chem.* **44**, C37 (1972).

[13] G. Sosnovsky, M. Konieczny, *Synthesis* **1975**, 671.

[14] G. Sosnovsky, M. Konieczny, *Synthesis* **1976**, 537.

[15] G. Sosnovsky, M. Konieczny, *Z. Naturforsch.* [b] **32**, 82 (1977).

[16] G. Sosnovsky, M. Konieczny, *Z. Naturforsch.* [b] **32**, 321 (1977).

[17] G. Sosnovsky, M. Konieczny, *Synthesis* **1977**, 618.

[18] H. A. Staab, W. Rohr, *Newer Methods of Preparative Organic Chemistry*, W. Foerst, Ed., Vol. 5, Verlag Chemie, Weinheim/Bergstr., Academic Press, New York, 1968, 94–97, and references therein.

[19] F. Fehér, B. Degen, *Angew. Chem.* **79**, 690 (1967); *Angew. Chem. Int. Ed. Engl.* **6**, 703 (1967).

[20] D. N. Harpp, K. Steliou, T. H. Chan, *J. Am. Chem. Soc.* **100**, 1222 (1978).

[21] M. Behforouz, J. E. Kerwood, *J. Org. Chem.* **34**, 51 (1969).

[22] E. Müller, E. W. Schmidt, *Chem. Ber.* **96**, 3059 (1963).