# Sulfenylation and Selenenylation of Lactams

P. A. Zoretic* and P. Soja[1]

*Department of Chemistry, Southeastern Massachusetts University, North Dartmouth, Massachusetts 02747*

*Received March 2, 1976*

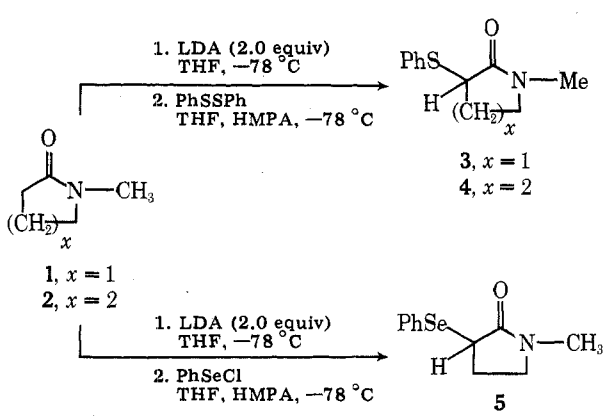
α-Unsubstituted lactams can be monosulfenylated and monoselenenylated or bissulfenylated and bisselenenylated depending on the equivalents of base used to form the lactam anion. Reaction of the lactam and 2 equiv of lithium diisopropylamide (LDA) afforded the monosubstituted products, whereas the utilization of 1 equiv of LDA yielded the bissubstituted lactams.

Sulfenylation and selenenylation reagents have recently been utilized to convert α-lithiated ketones,[2-5] lactones,[3,6] nitriles,[7] and esters[3,8,9] to α-phenylthio or α-phenylseleno carbonyl compounds. The silylation of 1-methyl-2-piperidone and the bissulfenylation of the imino ether, 2-methoxy-3,4,5,6-tetrahydropyridine, have also been reported by Trost and Kunz.[10]

In some related work, we were interested in utilizing an α-phenylthio or an α-phenylseleno moiety in order to carry out further chemical elaborations of a lactam ring system. The model studies reported herein indicate that monosubstitution vs. bissubstitution can be controlled by simply varying the equivalents of base used in the reaction. We have found that α-unsubstituted lactams can be monosulfenylated and monoselenenylated by using 2 equiv of base to form the lactam anion, whereas bissulfenylation and bisselenenylation result if 1 equiv of base is employed.

The reaction of 1-methyl-2-pyrrolidinone **1** (Scheme I) with

**Scheme I**

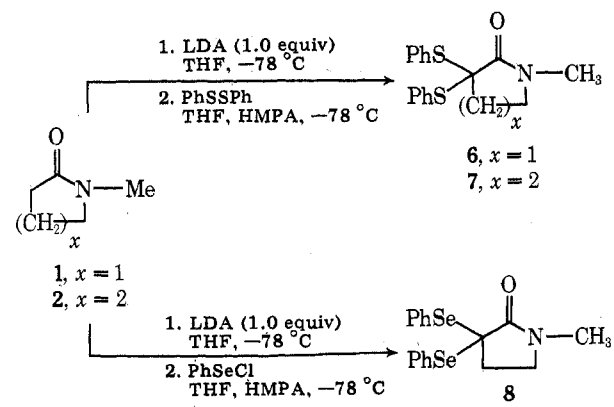



2 equiv of lithium diisopropylamide (LDA) in THF at −78 °C followed by sulfenylation with 1 equiv of phenyl disulfide or selenenylation with 1 equiv of benzeneselenenyl chloride in THF containing 1 equiv of HMPA at −78 °C afforded the monosulfenylated lactam **3** in 60% yield and the monoselenenylated lactam **5** in 55% yield, respectively, as the sole products. A similar sulfenylation of 1-methyl-2-piperidone **2** (Scheme I) afforded the monosulfenylated lactam **4** in 83% yield and a trace amount of the bissulfenylated lactam **7** as detected by TLC.

As depicted in Scheme II, bissulfenylation and bisselenenylation were observed when 1 equiv of LDA was used to form the lactam anion. Utilizing the same reaction conditions as described above, the sulfenylation and selenenylation of **1** afforded the bissulfide **6** (90%) and the bisselenenylide **8** (55%), respectively, as the sole products. A similar sulfenylation of 1-methyl-2-piperidone **2** afforded the bissulfide **7** (64%) and the monosulfide **4** (19%).

When a 1:2:2 ratio of lactam:base:electrophile was employed, it was found that sulfenylation of **1** afforded the bissulfide **6** in 73% yield. An identical sulfenylation of **2** yielded the bissulfide **7** in 76% yield. The results of the sulfenylation and selenenylation of lactams **1** and **2** using different molar ratios of lactam, base, and electrophiles are summarized in Table I.

**Scheme II**




The bissulfenylation and bisselenenylation products can be rationalized by assuming that proton transfer from the monophenylthiolactam or monophenylselenolactam occurs much faster than sulfenylation or selenenylation of the α-lithiated lactam. It should be noted that in the selenenylation of ketones Reich and co-workers[8] reported that no disubstituted products were observed. In these cases, the reaction is probably instantaneous at −78 °C and occurs more rapidly than proton transfer. A similar result has been reported by Trost and Salzman[3] in the sulfenylation of esters.

In the case of the monosulfenylated lactam products, we have demonstrated that desulfenylation[11] of the bissulfide[12] does not occur to afford the monosulfides. In order to substantiate that an unsubstituted lithiated lactam reacts preferentially with phenyl disulfide in the presence of the lithiated monophenylthiolactam, a competition experiment was designed to allow both the unsubstituted and the monosubstituted lithiated anions to compete for the electrophile, phenyl disulfide under normal reaction conditions. A THF solution of 0.05 mol of 3-phenylthio-1-methyl-2-pyrrolidinone and 0.05 mol of 1-methyl-2-pyrrolidinone was allowed to react with 0.15 mol of lithium diisopropylamide and subsequent sulfenylation with 0.05 mol of phenyl disulfide at −78 °C in the presence of 1 equiv of HMPA afforded the monosulfenylated lactam in 60% yield and only a negligible amount of the bissulfenylated product. It thus appears that the role of the excess base is simply to protect the monophenylthiolactam as the anion thus allowing the α-lithiated unsubstituted lactam to preferentially react with the electrophile. In a competition process the unsubstituted lithiated lactam should be a better nucleophile than the lithiated monophenylthiolactam, since the latter anion can be stabilized by dπ–pπ back-bonding with the sulfur atom.

**Table I. Sulfenylation and Selenenylation of Lactams**

| Electrophile | Substrate | Ratio of lactam:base: electrophile | Compd | Mp[a] or bp, °C | Yield, % |
|---|---|---|---|---|---|
| PhSSPh[d] | 1 | 1:2:1 | 3 | 130–133 (0.05 mm) | 60[c] |
| PhSeCl[e] | 1 | 1:2:1 | 5 | 140–142 (0.05 mm) | 55[c] |
| PhSSPh | 2 | 1:2:1 | 4 | 140–147 (0.005 mm) | 83 |
| PhSSPh | 1 | 1:1:1 | 6 | 84–86 | 90[b,c] |
| PhSSPh | 1 | 1:2:2 | 6 | 85–86 | 73[f] |
| PhSSPh | 2 | 1:1:1 | 7 | 138 | 64[b] |
| PhSSPh | 2 | 1:2:2 | 7 | 139 | 76 |
| PhSeCl | 1 | 1:1:1 | 8 | 80–81 | 55[b,c] |

[a] Uncorrected. [b] Yield calculated on the utilization of 0.5 equiv of 1-methyl-2-pyrrolidinone. [c] Isolated by column chromatography using silica gel G. [d] Eastman Kodak Co. [e] Aldrich Chemical Co. [f] From direct recrystallization ($Et_2O$/hexane) of the solid resulting from reaction workup.

## Experimental Section

**3,3-Diphenylthio-1-methyl-2-pyrrolidinone (6). General Procedure.** A 250-ml three-neck flask fitted with a nitrogen inlet tube, addition funnel, serum cap, and a magnetic stirring bar was flamed and deaerated with nitrogen. A solution of diisopropylamine (4.1 g, 0.040 mol) in 50 ml of THF was added under $N_2$ and the reaction vessel cooled to 0 °C. A hexane solution of 2.1 M *n*-butyllithium (19.2 ml, 0.040 mol) was added with a hypodermic syringe and allowed to stir at 0 °C for approximately 10 min. The reaction mixture was then cooled with a dry ice–acetone bath to −78 °C and 1-methyl-2-pyrrolidinone (4.0 g, 0.04 mol) dissolved in THF (25 ml) was added dropwise over a 15-min period. The reaction mixture was allowed to stir at −78 °C for 35 min. Phenyl disulfide (8.8 g, 0.040 mol) dissolved in THF (20 ml) containing HMPA (7.2 g, 0.040 mol) was than added dropwise over a 20-min period and the reaction mixture was stirred for an additional 35 min at −78 °C. The reaction mixture was allowed to warm to −20 °C over a 30-min period, and then to room temperature. The reaction mixture was poured into 400 ml of $H_2O$ and extracted with 3 × 350 ml of ether. The ethereal extracts were combined and washed consecutively with a 10% NaOH solution (150 ml), $H_2O$ (150 ml), 10% HCl (150 ml), and $H_2O$ (150 ml). The ether solution was then dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator, affording 8 g of a semisolid. The crude product was chromatographed on silica gel G. Elution with ether afforded 5.7 g (90%)[13] of 3,3-diphenylthio-1-methyl-2-pyrrolidinone (6): mp 84–86 °C ($Et_2O$/MeOH); NMR ($CCl_4$) δ 2.16 (2 H, t), 2.67 (3 H, s), 2.90 (2 H, t), and 7.25 and 7.55 (10 H, multiplet).

Anal. Calcd for $C_{17}H_{17}NOS_2$: C, 64.71; H, 5.44; N, 4.44. Found: C, 64.81; H, 5.48; N, 4.40.

**3,3-Diphenylseleno-1-methyl-2-pyrrolidinone (8).** Following the general procedure a reaction was carried out with diisopropylamine (4.1 g, 0.040 mol), 2.1 M *n*-butyllithium (19.2 ml, 0.040 mol), 1-methyl-2-pyrrolidinone (4.0 g, 0.040 mol), benzeneselenenyl chloride (7.7 g, 0.040 mol), and HMPA (7.2 g, 0.040 mol). Processing the reaction afforded a semisolid (7.9 g). The semisolid was chromatographed on silica gel G, and elution with ether afforded 4.5 g (55%)[13] of 3,3-diphenylseleno-1-methyl-2-pyrrolidinone (8): mp 80–81 °C; NMR ($CDCl_3$) δ 7.21–7.95 (m, 10 H), 2.73 (s), and 2.22–2.29 (m) [7 H].

Anal. Calcd for $C_{17}H_{17}NOSe_2$: C, 49.87; H, 4.19; N, 3.42. Found: C, 49.85; H, 4.20; N, 3.34.

**3,3-Diphenylthio-1-methyl-2-piperidone (7).** Following the general procedure a reaction was carried out with diisopropylamine (3.57 g, 0.0353 mol), 2.5 M *n*-butyllithium (14.1 ml, 0.0353 mol), 1-methyl-2-piperidone (4.0 g, 0.0353 mol), HMPA (6.3 g, 0.0353 mol), and phenyl disulfide (7.7 g, 0.0353 mol). Processing the reaction afforded a semisolid. A 20% ether–hexanes solution was added to the semisolid and filtration afforded 3.7 g (64%)[13] of 3,3-diphenylthio-1-methyl-2-piperidone (7): mp 138 °C; NMR ($CDCl_3$) δ 7.27–7.90 (m, 10 H), 2.78 (s) and 2.70–2.98 (m) [5 H], and 2.30 (t, distorted, 2 H).

Anal. Calcd for $C_{18}H_{19}NOS_2$: C, 65.62; H, 5.81; N, 4.25. Found: C, 65.63; H, 5.78; N, 4.39.

The filtrate was evaporated on a rotary evaporator and distillation of the resulting oil afforded 1.4 g (19%) of 3-phenylthio-1-methyl-2-piperidone (4), bp 120–135 °C (0.01 mm); the NMR and TLC analyses were consistent when compared with those of authentic 4.

**3-Phenylseleno-1-methyl-2-pyrrolidinone (5).** Following the general procedure a reaction was carried out with diisopropylamine (8.2 g, 0.081 mol), 2.1 M *n*-butyllithium (38.5 ml, 0.081 mol), 1-methyl-2-pyrrolidinone (4.0 g, 0.040 mol), benzeneselenenyl chloride (7.7 g, 0.040 mol), and HMPA (7.2 g, 0.040 mol). Processing the reaction yielded 8.8 g of an oil. The oil was chromatographed on silica gel G, and elution with ether and 2% MeOH–ether afforded 5.6 g (55%) of 3-phenylseleno-1-methyl-2-pyrrolidinone (5): bp 140–142 °C (0.05 mm); ir (neat) lactam band 1690 $cm^{-1}$; NMR ($CDCl_3$) δ 7.20–7.87 (m, 5 H), 3.75–3.99 (m, 1 H), 2.84–3.28 (m, 2 H), 2.72 (s, 3 H), and 1.90–2.62 (m, 2 H).

Anal. Calcd for $C_{11}H_{13}NOSe$: C, 51.92; H, 5.16; N, 5.51. Found: C, 51.79; H, 5.10; N, 5.42.

**3-Phenylthio-1-methyl-2-pyrrolidinone (3).** Following the general procedure a reaction was carried out with diisopropylamine (8.2 g, 0.081 mol), 2.1 M *n*-butyllithium (38.5 ml, 0.081 mol), 1-methyl-2-pyrrolidinone (4.0 g, 0.040 mol), phenyl disulfide (8.8 g, 0.040 mol), and HMPA (7.2 g, 0.040 mol). Processing the reaction afforded 6.7 g of an oil. The oil was chromatographed on silica gel G, and elution with ether yielded 5.0 g (60%) of 3-phenylthio-1-methyl-2-pyrrolidinone (3): bp 130–133 °C (0.05 mm); ir (neat) lactam band 1690 $cm^{-1}$; NMR ($CCl_4$) δ 7.10–7.70 (m, 5 H), 3.60–3.85 (m, 1 H), 2.98–3.30 (m, 2 H), 2.70 (s, 3 H), and 1.70–2.60 (m, 2 H).

Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; N, 6.76. Found: C, 63.21; H, 6.32; N, 6.73.

**3-Phenylthio-1-methyl-2-piperidone (4).** Following the general procedure a reaction was carried out with diisopropylamine (7.15 g, 0.070 mol), 2.1 M *n*-butyllithium (33.6 ml, 0.070 mol), 1-methyl-2-piperidone (4.0 g, 0.0353 mol), phenyl disulfide (7.7 g, 0.0353 mol), and HMPA (6.3 g, 0.0353 mol). Processing of the reaction afforded 7.1 g of an oil. The oil was chromatographed on silica gel G, and elution with ether–hexanes yielded 6.5 g (83%) of 3-phenylthio-1-methyl-2-piperidone (4): bp 140–147 °C (0.005 mm); ir (neat) lactam band 1635 $cm^{-1}$; NMR ($CCl_4$) δ 7.06–7.60 (m, 5 H), 3.70 (t, 1 H), 3.20 (t, 2 H), 2.83 (s, 3 H), and 1.53–2.20 (m, 4 H).

Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.32. Found: C, 65.38; H, 6.69; N, 6.43.

**3,3-Diphenylthio-1-methyl-2-piperidone (7). Using a 1:2:2 Ratio.** Following the general procedure a reaction was carried out with diisopropylamine (7.15 g, 0.070 mol), 2.45 M *n*-butyllithium (28.8 ml, 0.070 mol), 1-methyl-2-piperidone (4.0 g, 0.0353 mol), phenyl disulfide (15.4 g, 0.070 mol), and HMPA (12.7 g, 0.070 mol) dissolved in 30 ml of dry THF. Processing of the reaction afforded 15 g of a light yellow solid. Recrystallization of the solid from ether–hexanes solution yielded 8.8 g (76%) of 3,3-diphenylthio-1-methyl-2-piperidone (7): mp 139 °C; the NMR and TLC analyses were consistent when compared with those of authentic 7.

**3,3-Diphenylthio-1-methyl-2-pyrrolidinone (6). Using a 1:2:2 Ratio.** Following the general procedure a reaction was carried out with diisopropylamine (8.2 g, 0.081 mol), 2.1 M *n*-butyllithium (38.5 ml, 0.081 mol), 1-methyl-2-pyrrolidinone (4.0 g, 0.040 mol) phenyl disulfide (17.6 g, 0.081 mol), and HMPA (14.5 g, 0.081 mol) dissolved in 30 ml of dry THF. Processing the reaction afforded 13 g of a solid. Recrystallation of the solid from an ether–hexane solution yielded 9.2 g (73%) of 3,3-diphenylthio-1-methyl-2-pyrrolidinone )6): mp 85–86 °C; the NMR and TLC analyses were consistent when compared with those of authentic 6.

**Registry No.**—**1**, 872-50-4; **2**, 931-20-4; **3**, 59953-50-3; **4**, 59953-51-4; **5**, 59953-52-5; **6**, 59953-53-6; **7**, 59953-54-7; **8**, 59953-55-8; PhSSPh, 882-33-7; PhSeCl, 5707-04-0.

## References and Notes


(1) Undergraduate research participant.
(2) D. Seebach and M. Teschner, *Tetrahedron Lett.*, 5113 (1973).
(3) B. M. Trost and T. N. Salzman, *J. Am. Chem. Soc.*, **95**, 6840 (1973).
(4) H. J. Reich, J. M. Renga, and I. L. Reich, *J. Org. Chem.*, **39**, 2133 (1974).
(5) P. A. Grieco and J. J. Reap, *Tetrahedron Lett.*, 1097 (1974).
(6) P. A. Grieco and M. Miyashita, *J. Org. Chem.*, **39**, 120 (1974).
(7) D. N. Brattesani and C. H. Heathcock, *Tetrahedron Lett.*, 2279 (1974).
(8) H. J. Reich, I. L. Reich, and J. M. Renga, *J. Am. Chem. Soc.*, **95**, 5813 (1973); H. J. Reich, J. M. Renga, and I. Reich, *ibid.*, **97**, 5434 (1975).
(9) K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Am. Chem. Soc.*, **95**, 6137 (1973).
(10) B. M. Trost and R. A. Hunz, *J. Org. Chem.*, **39**, 2475 (1974).
(11) M. Oki, W. Funakoshi, and A. Nakamura, *Bull. Chem. Soc. Jpn.*, **44**, 828–832 (1971).
(12) The reaction of the bissulfide **6** with 1 equiv of LDA and lithium thiophenoxide, respectively, under identical reaction conditions as described for effecting monosulfenylation, afforded only unreacted **6**.
(13) See footnote *b*, Table I.


# Carbon-13 Nuclear Magnetic Resonance Study of Pyridine $N$-Oxide

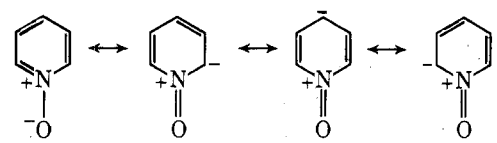

F. A. L. Anet* and Issa Yavari

*Contribution No. 3647 from the Department of Chemistry, University of California, Los Angeles, California 90024*


*Received May 25, 1976*


Carbon-13 chemical shifts and one-bond carbon–hydrogen coupling constants of pyridine $N$-oxide and of model compounds in a variety of neutral and acidic solvents are reported and discussed. Large shieldings (relative to pyridine) and solvent effects are observed for the $\alpha$- and $\gamma$-carbon chemical shifts in pyridine $N$-oxide. The observed variations in $^1J_{CH}$'s indicate that there are appreciable contributions, other than the Fermi contact contribution, to the coupling constants. The $\alpha$-carbon resonances are appreciably broadened (except in pyridine itself) as a result of $^{14}N$–$^{13}C$ coupling.


Pyridine $N$-oxide (I) is interesting in that its N–O moiety can act both as an electron donor and electron acceptor.[1] The difference (2.0 D) in dipole moments of I (4.2 D) and of pyridine (2.2 D) is smaller than that (4.8 D) between trimethylamine $N$-oxide (5.4 D) and trimethylamine (0.6 D), reflecting the contributions of resonance structures Ia, Ib, and Ic.[2]



I Ia Ib Ic

In view of the structural relationship of I to furoxans, whose $^{13}C$ NMR features have been recently reported,[3] we have undertaken a study of I and related model compounds. Previous investigations of the $^1H$[4] and $^{14}N$[5] NMR spectra of I exist, but the only $^{13}C$ NMR data on this compound concerns lanthanide-induced chemical shifts.[6] The $^{13}C$ NMR spectra of 3-hydroxypyridine $N$-oxide and some of its derivatives as anions in water have been measured;[7] however, the compounds and the conditions are rather special.

The $^{13}C$ chemical shifts of I, pyridine, and $N$-methylpyridinium iodide (II) in various solvents were measured and are listed in Table I. The solvents chosen were carbon tetrachloride, a nonpolar aprotic solvent; dimethyl sulfoxide, a polar aprotic solvent; chloroform a weakly interacting "aprotic" solvent; 95% ethanol, a neutral protic solvent; hexafluoro-2-propanol (HFP), a weakly acidic protic solvent ($pK_a = 9.3$);[8] trifluoroacetic acid (TFA), a strongly acidic protic solvent ($H_0 = -3$);[9] and finally, 98% $H_2SO_4$, a very strongly acidic protic solvent ($H_0 = -12$).[9] Chemical shifts were measured with respect to internal tetramethylsilane, with the exception of solutions in TFA and sulfuric acid, where an external reference had to be used. Although no correction was made for differences in magnetic susceptibilities, the error introduced thereby is expected to be less than 1 ppm.[10]

Since I has a $pK_a$ in water of 1.9,[11] it is expected to be extensively protonated in trifluoroacetic acid, and essentially completely protonated in 98% sulfuric acid. Hydrogen bonding of I should take place in ethanol and in HFP, and to a smaller extent in chloroform.[12]

An examination of Table I shows that the $\gamma$-carbon resonance of I in carbon tetrachloride occurs at an unusually high field as compared to the same signal in pyridine or pyridinium salts. Since the chemical shift of a $^{13}C$ atom is known to depend in part on the excess electronic charge[13] at that atom, the high-field shift of the $\gamma$ carbon implies a high electron density at this position, in agreement with a significant contribution of Ib to the resonance hybrid of I. The $\alpha$-carbon signal in I occurs at about 11 ppm to higher field of the corresponding carbon resonance in pyridine in contrast to the $\alpha$ carbons of saturated tertiary amine $N$-oxides, which are deshielded by about 15 ppm compared to the same carbons in the parent amines.[14]

The $\gamma$-carbon chemical shift of I is sensitive to the polarity of the solvent and especially to the presence of a hydrogen-bond donor in the solvent. In HFP, which is the strongest hydrogen-bonding solvent that does not protonate I, the $\gamma$ carbon is shifted by 9.4 ppm to lower field as compared to its position in carbon tetrachloride, but the $\alpha$ and $\beta$ carbons are deshielded by only 2.0 and 2.8 ppm, respectively. The small effect of hydrogen bonding on the $\alpha$ carbons may result from a cancellation of a downfield shift due to a reduced electron density and an upfield shift due to a higher excitation energy[15] and/or a change in the bond order to the $\alpha$-carbon atoms.[16,17]

The $^{13}C$ chemical shifts of protonated pyridine $N$-oxide (III) in sulfuric acid are similar to those of protonated pyridine (IV) or of pyridine methiodide (II) in the same solvent. In III, the electron donor effect of the N–O moiety is greatly reduced and the ring carbon chemical shifts are expectedly close to those in II and IV.

III IV