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THE PREPARATION AND ALKYLATION OF β-SULTAM MONO- AND DIANIONS

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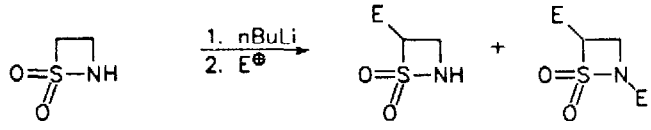
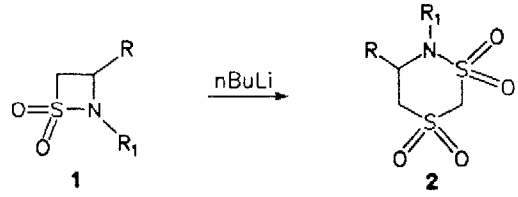
Abstract: *The reaction of 2-unsubstituted 1,2-thiazetidine-1,1-dioxides with n-butyllithium affords dianions which react with a variety of electrophiles. Selective mono- and dialkylation is readily accomplished.*

In the preceding paper we disclosed methodology for the preparation of 4-carbomethoxy β-sultams, valuable intermediates for further elaboration into β-sultam analogs of β-lactam antibiotics.[1] This synthon was developed to address the lack of synthetic methods for introducing the sidechains at **C4** known to impart bioactivity in analogous β-lactams. We wish to report that useful sidechains may also be incorporated *via* electrophilic addition to β-sultam mono- and dianions as shown in **Schemes 1** and **2.**

Scheme 1



It has been reported that the anions generated from 2,3-disubstituted β-sultams **1** suffer facile dimerization to yield exclusively **2,4,1-dithiazine 2,2,4,4-tetroxides 2.**[2] We reasoned that such



1 **2**

dimerisation would not occur if the sultam bond were rendered less electrophilic by a nitrogen-borne negative charge. Table 1 summarizes the reaction of the ethanesultam dianion with a representative array of electrophiles. Selective monoalkylation or 2,4-dialkylation can be achieved through the proper choice of conditions. A modest excess of electrophile and a low temperature quench yields monoalkylated products. A severalfold excess of electrophile followed by prolonged reaction at room temperature results in further alkylation of the relatively

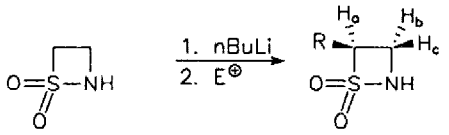


Table 1

Compound	Electrophile	R	Yield
3	$(CH_3)_3SiCl$	$(CH_3)_3Si$	31% (48% bis)
4	Et_3SiCl	Et_3Si	70%
8	methyl iodide	CH_3	60%
9	acetaldehyde	CH_2OHCH_3	46%
	propyl nitrate		0%
	$tBu(CH_3)_2SiCl$		0%

non-nucleophilic sulfonamide. A typical procedure is described below.

Ethanesultam[3] was dissolved in THF (0.10-0.15M) under an argon atmosphere and chilled to -78°. The nBuLi (2.1 eq.) was added dropwise and the solution aged for 1.5 hours at -78°. Two eq. of acetaldehyde was added in one portion. After 5 minutes, three eq. HOAc (slightly diluted with THF) was added and the mixture was partitioned between EtOAc and pH7 phosphate buffer. After the usual extractive workup, the combined organics were dried over Na_2SO_4, concentrated in vacuo *and subjected to flash chromatography (40→75% Et_2O/CH_2Cl_2, stepwise gradient elution) to afford 4-(1-hydroxyethyl)-1,2-thiazetidine-1,1-dioxide in 46% yield.[4]*

No conditions were found for the direct alkylation of the ethanesultam dianion by propyl nitrate. It was speculated that under strongly basic conditions nitroethanesultam **6** isomerized to the *aci* nitro form which suffered redox degradation analogous to the Nef reaction. It was expected that under the same conditions 4-(trimethylsilyl)ethanesultam **3** would afford a tertiary nitro group incapable of isomerization and degradation. An unexpected result observed during the preparation of **3** was overalkylation to 4,4-bis(trimethylsilyl)ethanesultam **5**, a process which occurred even with an insufficiency of silyl chloride. Selective monoalkylation was achieved only *via* use of the more sterically demanding triethylsilyl chloride. Reaction of the corresponding dianion with excess propyl nitrate afforded 4-nitroethanesultam **6** directly. This unusually facile silyl cleavage may be a consequence of a 1,3-silatropic rearrangement, affording a readily hydrolyzed silyl nitronate. Although the labile sultam **6** could be isolated using flash chromatography,[5] efforts to elaborate **6** into a 4-amino-β-sultam *via* catalytic hydrogenation or chemical reduction were unsuccessful. Other sources of electrophilic nitrogen were investigated but none furnished the desired products upon reaction with β-sultam anions or dianions.[6] These results are in accord with previous reports that unacylated α-aminosulfonamides are unstable.[7]

Scheme 2

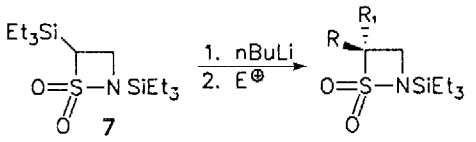
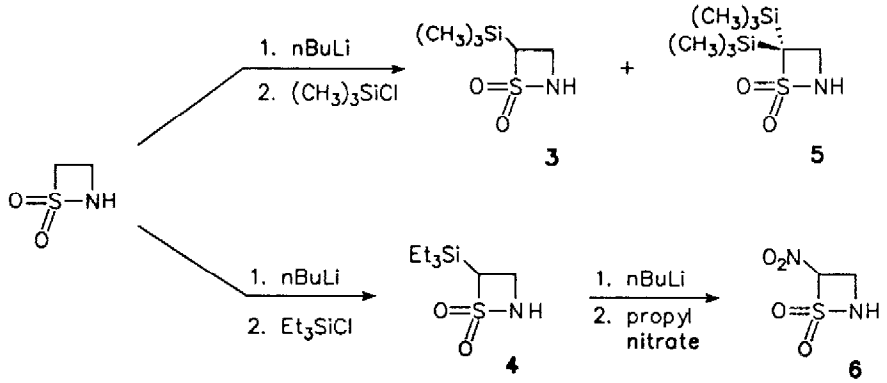


Table 2

Compound	R	Electrophile	R_1	Yield
10	Et_3Si	methyl iodide	CH_3	100%
11	H	propyl nitrate	NO_2	78%

Surprisingly, 2,4-bis(triethylsilyl)ethanesultam **7** yields a stable anion upon treatment with nBuLi and, as shown in Table 2, has been alkylated in greater yield than the monosilyl ethanesultam. Whereas nucleophilic attack on **4** and its derivatives produces a primary amide anion which can initiate a process of ring-opening polymerization, **7** and its derivatives yield a hindered secondary amide anion which is more likely to act as base than as nucleophile. The disadvantages of anions derived from sultam **7** are increased consumption of silylating reagent, lessened nucleophilicity and increased steric bulk of the anion, and the subsequent need to deprotect the sultam nitrogen.

The disparate behavior of anions derived from **7** and **1** encouraged an inquiry into the characteristics of the anion derived from N-(triethylsilyl)ethanesultam. However, all efforts to silylate the ethanesultam nitrogen were unsuccessful. We speculate that silylation of the relatively non-nucleophilic anion is sufficiently slow that self condensation becomes a competitive process. In contrast, the 4-triethylsilylethanesultam anion, the initial product of dianion silylation, enjoys the protection of steric shielding and so is further alkylated to afford sultam **7**.



References and Notes

1. M.J. Szymonifka and J.V. Heck, *Tetrahedron Lett.*, preceding paper.
2. E. Meyle and H.H. Otto, *J. Chem Soc., Chem. Commun.*, **1984**, 1084.
3. A. Le Berre and J. Petit, *Tetrahedron Lett.*, **1972**, 213.
4. All compounds were obtained as racemic/diastereomeric mixtures; only one isomer is presented in the diagrams. Satisfactory spectroscopic data were obtained for all compounds. ^{1}H-NMR data (200 MHz, δ,$CDCl_3$ unless noted elsewise) for all new compounds: **3.** ($CDCl_3/CD_3OD$) 4.08 (dd, $J_{Ha,Hb}$=9.0 Hz, $J_{Ha,Hc}$=6.0 Hz, C<u>H</u>SO_2); 3.36 (dd, $J_{Ha,Hb}$=9.0 Hz, $J_{Hb,Hc}$=6.0 Hz, C<u>H</u>$_2$N); 3.06 (t, $J_{Ha,Hc}$=$J_{Hb,Hc}$=6.0 Hz, C<u>H</u>$_2$N); 0.17 (s, Si(C<u>H</u>$_3$)$_3$. **4.** 5.18 (bs, N<u>H</u>); 4.24 (dd, $J_{Ha,Hb}$=9.0 Hz, $J_{Ha,Hc}$=6.0 Hz, C<u>H</u>SO_2); 3.40 and 3.20 (m, C<u>H</u>$_2$N); 1.0 and 0.78 (m, $SiEt_3$). **5.** 5.32 (bs, N<u>H</u>); 3.26 (d, J=4 Hz, C<u>H</u>$_2$N); 0.30 (s, Si(C<u>H</u>$_3$)$_3$. **6.** (CD_3CN/CD_3OD) 6.96 (dd, $J_{Ha,Hb}$=7.2 Hz, $J_{Ha,Hc}$=4.0 Hz, C<u>H</u>SO_2); 3.95 (m, C<u>H</u>$_2$N). (CD_3OD) 6.97 (dd, $J_{Ha,Hb}$=7.2 Hz, $J_{Ha,Hc}$=4.0 Hz, C<u>H</u>SO_2); 3.80 and 3.66 (m, C<u>H</u>$_2$N). IR:(CH_2Cl_2) 1360, 1570 cm^{-1}. **7.** 4.20 (dd, $J_{Ha,Hb}$=9.5 Hz, $J_{Ha,Hc}$=6.0 Hz, C<u>H</u>SO_2); 3.34 (dd, $J_{Ha,Hb}$=9.5 Hz, $J_{Hb,Hc}$=6.0 Hz, C<u>H</u>$_2$N); 3.13 (t, $J_{Ha,Hc}$=$J_{Hb,Hc}$=6.0 Hz, C<u>H</u>$_2$N); 1.0 and 0.78 (m, $SiEt_3$). **8.** 5.36 (bs, N<u>H</u>); 4.62 (m, $J_{Ha,Hb}$=8.0 Hz, $J_{Ha,Hc}$=6.10 Hz, $J_{Ha,Me}$=8.0 Hz, C<u>H</u>SO_2); 3.54 (m, $J_{Ha,Hb}$=8.0 Hz, $J_{Hb,Hc}$=6.1 Hz, C<u>H</u>$_2$N); 2.96 (dd, $J_{Ha,Hc}$=$J_{Hb,Hc}$=6.1 Hz, C<u>H</u>$_2$N); 1.63 (d, J=8 Hz, C<u>H</u>$_3$). **9.** Diastereomer A: 5.28 (bs, N<u>H</u> and O<u>H</u>); 4.52 (m, C<u>H</u>OH and C<u>H</u>SO_2); 3.52 and 3.42 (m, C<u>H</u>$_2$N); 1.24 (d, J=7 Hz, C<u>H</u>$_3$). Diastereomer B: 5.35 (bs, N<u>H</u> and O<u>H</u>); 4.53 (m, C<u>H</u>SO_2); 4.53 and 4.26 (m, C<u>H</u>OH); 3.44 and 3.24 (m, C<u>H</u>$_2$N); 1.38 (d, J=7 Hz, C<u>H</u>$_3$). **10.** 3.33 and 2.77 (d, J=5.0 Hz, C<u>H</u>$_2$N); 1.62 (s, C<u>H</u>$_3$), 1.0 and 0.80 (m, $SiEt_3$). **11.** (DMSO-*d6*) 7.40 (m, C<u>H</u>SO_2); 3.70 (m, C<u>H</u>$_2$N); 0.9 and 0.7 (m, $SiEt_3$). (CD_3CN) 6.90 (m, C<u>H</u>SO_2); 3.95 (m, C<u>H</u>$_2$N); 1.1 and 0.95 (m, $SiEt_3$). IR:(CH_2Cl_2) 1365,1570 cm^{-1}.
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