Synthesis of Substituted 1,3-Propanesultams from *N*-Substituted 2-Amino Alcohols

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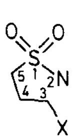
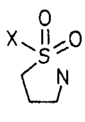
Substituted 1,3-propanesultams (isothiazolidine 1,1-dioxides) **3a–c** have been prepared via butyllithium-mediated cyclization of the *N,O*-dimesylates **2a–c** of *N*-substituted 2-amino alcohols **1a–c**.

Aliphatic 1,3-propanesultams (isothiazolidine 1,1-dioxides) have previously been prepared by thermal or base-catalyzed cyclization of halo- or tosyloxyalkanesulfonamides[1] (type **A**), halosulfonylalkylamines[2] (type **B**), or alkylhaloalkanesulfonamides[3] (type **C**). Such methods tend to be lengthy, and to be limited in their ability to place substituents on the ring carbon atoms.



A



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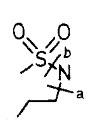
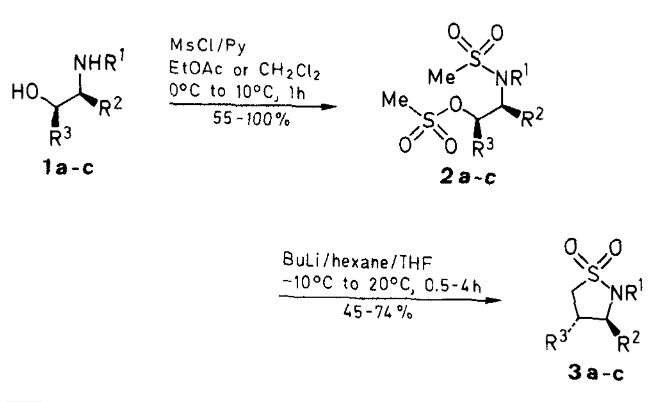


C

In what is perhaps the most versatile of the cyclization methods with respect to the inclusion of ring substituents, type **C** substrates have been prepared by the photochemical formation of bond a. Alkyl substituents were placed at N and C-4, and optionally at C-5, but no stereochemical control of the substituents was possible.[3]

We describe here a conceptually simple, facile synthesis of aliphatic 1,3-propanesultams from 2-amino alcohols which is characterized by brevity and by versatility with respect to the position and stereochemical control of substituents. In this method a substrate of type **C** is prepared by formation of bond b.

We have found that *N,O*-dimesylates **2** of *N*-substituted 2-amino alcohols **1** react with butyllithium to give sultams **3** in good yield (Scheme). Although the hydrogens α to both sulfonyl groups are acidic enough to be deprotonated by butyllithium,[4] only the anion derived from the *N*-mesylate can react in the favored intramolecular sense to productively displace the *O*-mesylate.



1–3	R^1	R^2	R^3	Yield (%)	
				2	**3**
a	Bn	H	H	95	74
b	–(CH_2)$_3$–		H	54	81
c	Me	Me	Ph	100	45

Scheme

Three representative 2-amino alcohols have been converted via their dimesylates to the corresponding sultams. 2-(Benzylamino)ethanol (**1a**) readily gave the dimesylate **2a** (95%) which was cyclized with a slight excess (105 mol%) of butyllithium in tetrahydrofuran/hexane to sultam **3a**[5] (74%). (*S*)-(+)-2-pyrrolidinemethanol (L-prolinol, **1b**) gave **3b** (81%) via **2b** (54%). (1*R*,2*S*)-(−)-Ephedrine (**1c**) gave **3c** (45%) via **2c** (100%).

A wide variety of *N*-substituted 2-amino alcohols are commercially available or can be readily prepared. Reaction of 2-amino alcohols with halides,[6] or with aldehydes or ketones followed by catalytic[7] or sodium borohydride[8] reduction leads to *N*-substituted α-amino alcohols as does reaction of substituted amines with oxiranes.[9] Reduction of amino acids or their esters is a convenient source of chiral 2-amino alcohols from which chiral sultams can be prepared.

The procedures reported here allow the facile (2 step) preparation of 1,3-propanesultams variously substituted at N, C-3, and C-4 including chiral and/or bicyclic sultams from readily available *N*-substituted 2-amino alcohols. Although the enantiomeric purity of the chiral 1,3-propanesultams was not determined, racemization is highly unlikely in this sequence, and the purified analytical samples showed no evidence of diastereoisomerism.

All starting materials and reagents were obtained from Aldrich Chemical Co. except for BuLi in hexane which was obtained from Foote Mineral Co. Reagent quality solvents were used without further purification. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet 5PC FT-IR spectrophotometer. Optical rotations were measured using a Perkin-Elmer 141 polarimeter. ^1H- and ^{13}C-NMR spectra were obtained using Bruker WM-300 or AM-500 instruments. Elemental analyses were performed by the Analytical and Environmental Research group, Syntex Research.

2-[Benzyl(methylsulfonyl)amino]ethyl Methanesulfonate (2a); Typical Procedure:

To a solution of 2-(benzylamino)ethanol (**1a**; 5 g, 33.1 mmol) in dry EtOAc (50 mL) is added Et_3N (8.36 g, 82.7 mmol). The solution is cooled in an ice bath and methanesulfonyl chloride (7.95 g, 69.4 mmol) in EtOAc (30 mL) is added dropwise over 20 min. After 1 h the resulting suspension is filtered through a "C" sintered funnel and washed in to the funnel with ice cold EtOAc (50 mL). The filtrate is washed with H_2O (25 mL), 5% HCl (25 mL), H_2O (25 mL), brine (25 mL), and dried ($MgSO_4$). Filtration and evaporation of solvent gives an oil which solidifies and is used in the next reaction without further purification; yield: 9.63 g (95%). An analytical sample is prepared by recrystallization (*i*-PrOAc); mp 74–75 °C;

$C_{11}H_{17}NO_5S_2$	calc.	C 42.98	H 5.57	N 4.55	S 20.86
(307.4)	*found*	43.36	5.59	4.54	20.85

IR (KBr): ν = 1351, 1323, 1178, 1152, 1139 cm^{-1}.

^{1}H-NMR (CDCl$_3$/TMS): δ = 2.93, 2.96 (s, s, 3 H each, SO$_2$CH$_3$), 3.54 (t, 2 H, J = 5.6 Hz, NCH$_2$), 4.21 (t, 2 H, J = 5.6 Hz, OCH$_2$), 4.47 (s, 2 H, NCH$_2$Ph), 7.31–7.40 (s, 5 H$_{arom}$).

^{13}C-NMR (CDCl$_3$/TMS): δ = 37.34, 39.41 (q, q, SO$_2$CH$_3$), 45.89 (d, NCH$_2$), 51.90 (d, NCH$_2$Ph), 67.07 (d, OCH$_2$), 128.36, 128.51, 128.96, 135.32 (d, d, d, s, C$_{arom}$).

2-(Methylsulfonyloxymethyl)-1-methylsulfonylpyrrolidine (**2b**):

Yield: 54.4 %; mp 75.2–77 °C (i-PrOAc); $[\alpha]_D^{25}$ −48.4° (c = 0.892, CHCl$_3$).

C$_7$H$_{15}$NO$_5$S$_2$	calc.	C 32.67	H 5.87	N 5.44	S 24.92
(257.3)	found	32.75	5.84	5.44	25.02

IR (KBr): ν = 1356, 1346, 1334, 1317, 1172, 1142 cm^{-1}.

^{1}H-NMR (CDCl$_3$/TMS): δ = 1.92 (br m, 1 H, CH$_2$), 2.04 (br m, 3 H, CH$_2$), 2.86, 3.03 (s, s, 3 H each, SO$_2$CH$_3$, 3.32 (br m, 1 H, NCH$_2$), 3.44 (br m, 1 H, NCH$_2$), 3.94 (br m, 1 H, NCH), 4.25 (m, 2 H, OCH$_2$).

^{13}C-NMR (CDCl$_3$/TMS): δ = 24.35 (CH$_2$), 28.64 (CH$_2$), 35.18, 37.14 (2 SO$_2$CH$_3$), 49.14 (NCH$_2$), 57.84 (NCH), 71.05 (OCH$_2$).

(1R,2S)-α-[1-(Methyl[methylsulfonyl]amino)ethyl]benzyl Methansulfonate (**2c**):

Yield 100 % (unstable material used directly in the next step).

HRMS: m/z, C$_{12}$H$_{19}$NO$_5$S$_2$ calc.: 321.0705; found: 321.0709.

^{1}H-NMR (CDCl$_3$/TMS): δ = 1.38 (d, 3 H, J = 6.7 Hz, CH$_3$), 2.33 (s, 3 H, NCH$_3$), 2.67, 2.78 (s, s, 3 H each, SO$_2$CH$_3$), 4.40 (dq, 1 H, J = 7.0, 7.0 Hz, CCHN), 5.45 (d, 1 H, J = 7.6 Hz, OCHPh), 7.40 (m, 5 H$_{arom}$).

^{13}C-NMR (CDCl$_3$/TMS): δ = 14.10 (CH$_3$), 29.38 (NCH$_3$), 38.18, 39.09 (2 SO$_2$CH$_3$), 56.58 (NCH), 85.48 (OCH), 127.16, 129.07, 129.65, 136.17 (C$_{arom}$).

MS (70 eV): m/z = 321 (M$^+$, 0.07), 226 (4), 136 (100).

2-Benzylisothiazolidine 1,1-Dioxide (3a); Typical Procedure:

A solution of methanesulfonate **2a**; (1.00 g, 3.25 mmol) in dry THF (10 mL) is cooled to −10 °C under N$_2$. BuLi (1.59 M in hexane, 2.15 mL, 3.42 mmol) is added dropwise over 15 min. The reaction is allowed to warm to r. t. over 2.5 h. H$_2$O (10 mL) is added and the aqeous phase is extracted with Et$_2$O (2 × 10 mL). The combined extracts are washed with H$_2$O (5 mL), brine (5 mL) and dried (MgSO$_4$). Filtration and evaporation of the solvent gives a colorless oil which is chromatographed on a silica gel column (8.9 cm × 2.2 cm; 230–400 mesh). Elution with hexanes/EtOAc (7 : 3) gives **3a** as a colorless oil[5]; yield: 0.51 g (74 %). Bulb-to-bulb distillation gives an analytical sample.

C$_{10}$H$_{13}$NO$_2$S	calc.	C 56.84	H 6.20	N 6.62	S 15.17
(211.3)	found	56.65	6.16	6.58	15.36

IR (neat): ν = 1304, 1137 cm^{-1}.

^{1}H-NMR (CDCl$_3$/TMS): δ = 2.30 (m, 2 H, J = 7.7, 6.8 Hz, CH$_2$), 3.11 (t, 2 H, J = 6.8 Hz, CH$_2$SO$_2$), 3.20 (t, 2 H, J = 7.7 Hz, NCH$_2$), 4.17 (s, 2 H, NCH$_2$Ph), 7.23–7.37 (m, 5 H$_{arom}$).

^{13}C-NMR (CDCl$_3$/TMS): δ = 18.40 (CH$_2$), 45.93, 46.40, 48.04 (CH$_2$X), 127.78, 128.38, 128.58, 135.62 (C$_{arom}$).

MS (70 eV): m/z = 211 (M$^+$, 8), 146 (24), 118 (16), 91 (100).

(3aS)-2,3,3a,4,5,6-Hexahydropyrrolo[1,2-b]isothiazole 1,1-Dioxide (**3b**):

Yield: 81 %; Recrystallization from t-BuOMe gives an analytical sample; mp 42–43 °C; $[\alpha]_D^{25}$ +5.8° (c = 1.28, CHCl$_3$).

C$_6$H$_{11}$NO$_2$S	calc.	C 44.69	H 6.87	N 8.68	S 19.88
(161.2)	found	44.85	6.92	8.72	19.74

IR (KBr): ν = 1322, 1315, 1146 cm^{-1}.

^{1}H-NMR (CDCl$_3$/TMS): δ = 1.48–1.59 (m, 1 H, H-4), 1.81–1.94 (m, 1 H, H-5), 2.00–2.13 (m, 2 H, H-3, H-4), 2.44–2.57 (m, 1 H, H-3), 2.85–2.95 (m, 1 H, H-2), 3.14–3.23 (m, 2 H, H-6, H-2), 3.50–3.56 (m, 1 H, H-6), 3.90–3.98 (m, 1 H, H-3a).

^{13}C-NMR (CDCl$_3$/TMS): δ = 25.65 (t, C-5), 26.83 (t, C-3), 32.25 (t, C-4), 46.02 (t, C-2), 48.26 (t, C-6), 61.85 (d, C-3a).

(3S,4S)-2,3-Dimethyl-4-phenylisothiazolidine 1,1-Dioxide (**3c**):

Yield: 45.3 %; Recrystallization from i-PrOAc gives an analytical sample; mp 146–148.5 °C; $[\alpha]_D^{25}$ −13.8° (c = 1.74, CHCl$_3$).

C$_{11}$H$_{15}$NO$_2$S	calc.	C 58.63	H 6.71	N 6.21	S 14.23
(225.3)	found	58.74	6.73	6.22	14.14

IR (KBr): ν = 1303, 1293, 1137 cm^{-1}.

^{1}H-NMR (CDCl$_3$/TMS): δ = 1.16 (d, 3 H, J = 5.8 Hz, CH$_3$), 2.67 (s, 3 H, NCH$_3$), 3.23 (m, 3 H, CH$_2$SO$_2$, PhCH), 3.59 (m, 1 H, NCH), 7.25–7.37 (m, 5 H$_{arom}$).

^{13}C-NMR (CDCl$_3$/TMS): δ = 17.00 (q, CH$_3$), 28.55 (d, CHPh), 46.77 (q, NCH$_3$), 53.50 (t, CH$_2$SO$_2$), 62.69 (d, NCH), 127.86, 128.11, 129.17, 137.83 (C$_{arom}$).

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(1) Helberger, H.; Manecke, G.; Fischer, H. M. *Liebigs Ann. Chem.* **1949**, *562*, 23.
Bliss, A. D.; Cline, W. K.; Sweeting, O. J. *J. Org. Chem.* **1964**, *29*, 2412.
Helferich, B.; Doss, S. H. *Liebigs Ann. Chem.* **1972**, *756*, 170.

(2) Feichtinger, H. *Chem. Ber.* **1963**, *96*, 3068.
Dirscherl, W.; Weingarten, F. W.; Otto, K. *Liebigs Ann. Chem.* **1954**, *588*, 200.

(3) Kobayashi, M.; Okahara, M.; Komori, S.; Agawa, T. *Synthesis* **1973**, 667.

(4) Kaiser, E. M.; Knutson, P. L. A. *J. Org. Chem.* **1975**, *40*, 1342.

(5) Matsuyama, H.; Izuoka, A.; Kobayashi, M. *Heterocycles* **1985**, *23*, 1897.

(6) Surrey, A. R. *US Patent* 2732402 (1956), Sterling Drug Inc.; *C. A.* **1957**, *51*, 2032.

(7) Cope, A. C.; Hancock, E. M. *J. Am. Chem. Soc.* **1942**, *64*, 1503.

(8) Saavedra, J. E. *J. Org. Chem.* **1985**, *50*, 2271.

(9) Burfield, D. R.; Gan, S.-N.; Smithers, R. H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 666.