Stereoselective Generation of E- and Z-Disubstituted Amide Enolates. Reductive Enolate Formation from Bicyclic Thioglycolate Lactams

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The formation of enolates is a process that is fundamental to a multitude of chemical transformations. In many cases, the stereochemistry of an enolate (E or Z) is an integral part of stereoselective reactions (e.g., syn/anti control in aldol reactions). For monosubstituted ester and ketone enolates, stereochemistry can often be influenced by judicious choice of solvent, base, and temperature.[1] For monosubstituted tertiary amide enolates, minimization of A-1,3 interactions usually favors Z-enolate formation.[2] Stereocontrol in disubstituted enolates is a more difficult task and must often be evaluated on a case-by-case basis. Highest levels of stereocontrol are usually associated with cyclic frameworks,[3] including metal chelates,[4] while control based on differential steric environments is less reliable.[5,6] We have initiated a project to develop stereoselective quaternary carbon forming reactions based on enolate transformations. The goal is to develop a general method that does not rely on specific enolate features such as chelating functionality or a large steric difference between enolate substituents. In this communication, we report a method for controlling enolate geometry in disubstituted amide enolates where the E/Z selectivity is dependent only on the geometry and stereochemistry of the enolate precursor.

Our design utilizes a two-electron reduction of α,α-dialkylated bicyclic thioglycolate lactams to provide disubstituted amide enolates (Figure 1).[7] Assuming that (a) two alkyl groups (R_1 and R_2) are installed stereoselectively at the α-position, (b) the O−C−C−S dihedral angle is held as close to 90° as possible by the bicyclic system, and (c) significant bond rotation does not occur about the carbonyl-carbon/α-carbon bond during the two-electron reduction process, the E/Z stereochemistry of the enolate should be controlled by the relative positions of R_1 and R_2 in the starting lactam. Importantly, this should afford kinetic E/Z stereocontrol that is independent of the relative stabilities of the two enolates

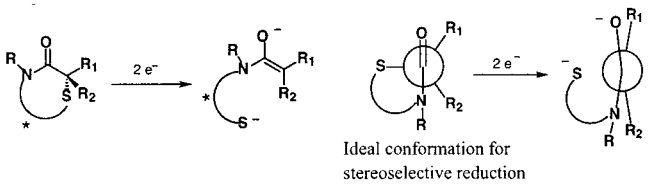
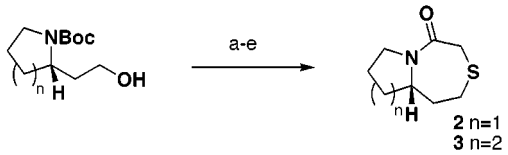


Figure 1. Model for stereoselective enolate generation.

Scheme 1. Synthesis of 5,7- and 6,7-Bicyclic Lactams

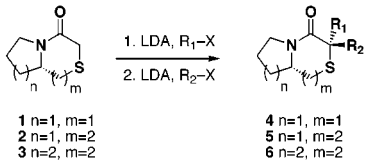


[a] MsCl, NEt_3, CH_2Cl_2. [b] MeO_2CCH_2SH, NaH, DMF. [c] LiOH, THF/H_2O. [d] TFA (or HCl/Et_2O). [e] EDC-HOBT (or 2-chloro-1-methylpyridnium iodide), NEt_3, CH_2Cl_2. 53% yield (5 steps) for **2**. 46% yield (5 steps) for **3**.

and does not depend on a large difference in size of the two alkyl groups. Significantly, switching the position of R_1 and R_2 by inverting the order of their installation should lead to a reversal of enolate geometry. In many regards, our model resembles the preferred transition state for deprotonation adjacent to a carbonyl group, with sulfur transposed for hydrogen. The significant difference is that deprotonation is a concerted (two-electron) process whereas the reductive process undoubtedly involves two separate one-electron-transfer steps and thus bond rotation is a potential competing process in the intermediate radical anion resulting from C−S bond scission.

Molecular modeling calculations (MM2) using a Monte Carlo conformational search (Macromodel) were used to identify suitable candidates for this stereoselective reduction process. Several classes of bicyclic thioglycolate lactams were analyzed for desirable O−C−C−S dihedral angles both at the ground state and as a weighed average of all stable conformations within 2 kcal/mol of the ground state. From these calculations, the 5,6-, 5,7- and 6,7-bicyclic lactams **1**−**3** were identified as candidates for study (see Table 1). Of these, the 5,7- and 6,7-bicyclic lactams **2** and **3** appear to be reasonable candidates (O−C−C−S dihedral angles of 120−150°), while the 5,6-bicyclic lactam **1** has an

Table 1. Alkylation of Bicyclic Lactams



lactam	R_1−X	yield	de[a]	R_2−X	product	yield	de[b]
1	*n*-PrI	84%	88%	MeI	**4a**	94%	72%
1	MeI	88%	81%	*n*-PrI	**4b**	88%	72%
1	allyl-Br	88%	85%	MeI	**4c**	91%	79%
1	MeI			allyl-Br	**4d**	86%	78%
2	*n*-PrI	76%	88%	MeI	**5a**	90%	90%
2	MeI	86%	93%	*n*-PrI	**5b**	72%	86%
2	allyl-Br	88%	85%	MeI	**5c**	85%	95%
2	MeI			allyl-Br	**5d**	96%	87%
2	BnBr	96%	>95%	MeI	**5e**	88%	>99%
2	MeI			BnBr	**5f**	91%	>99%
2	*n*-PrI			EtI	**5g**	75%	88%
2	EtI	80%	87%	*n*-PrI	**5h**	76%	94%
3	*n*-PrI	95%	68%	MeI	**6b**	81%	50%[a,c]
3	MeI	95%	87%	*n*-PrI	**6a**	81%	62%[a,c]
3	BnBr	80%	>95%	MeI	**6f**	89%	66%[a,e]
3	MeI			BnBr	**6f**	69%[d]	10%

[a] Determined by integration of ^1H and/or ^{13}C NMR resonances. [b] Determined by capillary gas chromatography on a Chirasil Dex column. Unless otherwise noted, diastereomers were not separable. [c] Alkylation selectivity is reversed for these substrates. These substrates were readily separable by flash chromatography. [d] Lactam **6e** was isolated in 31% yield and lactam **6f** was isolated in 38% yield.

(1) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959. (c) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *24*, 495. (d) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650.

(2) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233.

(3) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503.

(4) (a) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825, 2829. (b) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828.

(5) Vedejs, E.; Kruger, A. W.; Lee, N.; Sakata, S. T.; Stec, M.; Suna, E *J. Am. Chem. Soc.* **2000**, *122*, 4602.

(6) For a stereoselective enolization of tiglate oxazolidinone imides, see: Hosoawa, S.; Sekiguchi, K.; Enemoto, M.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6429.

(7) Kamata, S.; Uyeo, S.; Haga, N.; Nagata, W. *Synth. Commun.* **1973**, *3*, 265.

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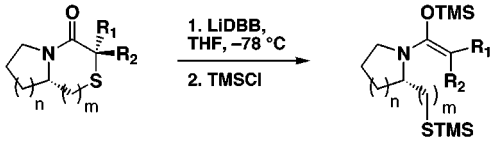
Table 2. Reductive Enolization of Bicyclic Thioglycolate Lactams



series	*n*	*m*	lactam	R_1	R_2	O−C−C−S dihedral[a]	Z/E ratio[b]	lactam	R_1	R_2	O−C−C−S dihedral[a]	Z/E ratio[b]
1	1	1	**4a**	*n*-Pr	Me	174	47:53	**4b**	Me	*n*-Pr	182	64:36
2	1	1	**4c**	Allyl	Me	175	44:56	**4d**	Me	Allyl	178	68:32
3	1	2	**5a**	*n*-Pr	Me	141	87:13	**5b**	Me	*n*-Pr	128	20:80
4	1	2	**5c**	Allyl	Me	140	87:13	**5d**	Me	Allyl	138	26:74
5	1	2	**5e**	Bn	Me	145	92:8	**5f**	Me	Bn	149	12:88
6	1	2	**5g**	*n*-Pr	Et	139	80:20	**5h**	Et	*n*-Pr	137	12:88
7	2	2	**6a**	*n*-Pr	Me	140	83:17	**6b**	Me	*n*-Pr	133	37:63
8	2	2	**6e**	Bn	Me	143	92:8	**6f**	Me	Bn	139	53:47

[a] Weighted average (calculated at −78 °C) of all conformations within 2 kcal/mol of the ground state as determined by Monte Carlo calculations. [b] Determined by integration of ^{13}C resonances.

unfavorable dihedral angle (175−180°) and thus was expected to serve as a control.

Lactam **1** was prepared in two steps from prolinol following the procedure of Ishibashi.[8] Lactams **2** and **3** were prepared from *N*-Boc-2-(2-pyrrolidine)ethanol and *N*-Boc-2-(2-piperidine)ethanol, respectively, by displacement of the corresponding mesylates with methyl thioglycolate followed by a straightforward lactamization protocol (Scheme 1). Sequential alkylation of lactams **1**−**3** was performed in THF with LDA (1.1 equiv) in the presence of LiCl (5 equiv).[9] Excellent yields and good to excellent diastereoselectivities were obtained for the alkylations of 5,6- and 5,7-bicyclic lactams (Table 1). The expected stereochemical outcome of these alkylations, wherein the electrophile approaches from the exo-face of the bicyclic system,[3] was confirmed through NOE studies. Alkylation of the 6,7-bicyclic lactam **3** was not only less selective but the facial selectivity in the second alkylation reaction was reversed relative to that of the 5,7-bicyclic system.

Reduction of the thioglycolate lactams was best accomplished by titrating with lithium di-*tert*-butylbiphenylide (LiDBB) in THF at −78 °C. The resulting enolate dianions were trapped as the silyl ketene aminals by addition of trimethylsilyl chloride followed by warming the reaction slowly to 23 °C over 0.5 h.[10] The silyl ketene aminals were isolated by removal of solvent in vacuo and trituration into C_6D_6 and the E/Z ratio of the products was determined by ^{13}C NMR.[11] The stereochemistry for the silyl ketene aminals derived from **5e**−**h** (Table 2, Series 5−6) was definitively assigned by observation of NOE enhancements. Assignments for the remaining products were made by analogy and by comparison of the ^{13}C NMR shifts for the ketene aminal carbons among related series.

Reduction and trapping of amides **4a**−**d** proceeded with low levels of E/Z selectivity, consistent with the large O−C−C−S dihedral angle in these substrates (Series 1−2, Table 2). In contrast, reduction of lactam **5a** afforded the *Z*-2-methylpentanamide enolate with 87:13 selectivity. *Importantly, reduction of the stereoisomeric lactam (***5b***) produced the E-enolate, also with good levels of stereocontrol (80:20 E/Z).* A similar trend was observed for all 5,7-bicyclic lactams studied (Series 3−6, Table 2). Reduction of the 6,7-bicyclic lactams **6a** and **6e** produced *Z*-enolates cleanly. However, *E*-enolate selectivity was reduced for reduction of diatstereomers **6b** and **6f**. Overall, the results are in accord with our proposed model and indicate that bond rotation in the intermediate radical anions is at most a minor competing factor in the reductive enolization process. The reasons for reduced selectivity with lactams **6b** and **6f** are unclear, but may reflect a higher degree of flexibility in the 6,7-bicyclic ring system.

In conclusion, we have developed a method for stereoselective generation of disubstituted amide enolates wherein the E/Z selectivity is determined by the stereochemistry and geometry of the starting bicyclic lactams. The method affords both *E*- and *Z*-amide enolates without relying on a steric difference between the two substituents. The high levels of alkylation selectivity of the 5,7-bicyclic system and the excellent levels of stereocontrol for enolate generation appear to earmark it for future development. In this regard, it is important to note that the reduction generates an enolate structure that is reminiscent of prolinol amide enolates[2] and may serve as a template for subsequent stereoselective transformations.[12] We expect that this new enolate preparation will find use in numerous reactions including alkylations and aldol reactions.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0058280

(8) Ishibashi, H.; Uegaki, M.; Sakai, M. *Synlett* **1997**, 915.

(9) For the use of LiCl in alkylations of amide enolates, see: Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

(10) Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1978**, *43*, 881.

(11) Generally the reduction of the amides was complete and ≤5% of enolate quenching was observed. Reduction of **5d** produced a byproduct (ca. 30%) that could not be fully characterized.

(12) For example, reduction of **5e** with LiDBB followed by addition of allyl bromide (3 equiv) and stirring at −78 °C for 3 h affords the corresponding C,S-dialkylated product in 96% yield and 90:10 diastereoselectivity. Complete studies on this alkylation reaction will be reported in due course.