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Cation−n Control of Regiochemistry of Intramolecular Schmidt Reactions en Route to Bridged Bicyclic Lactams

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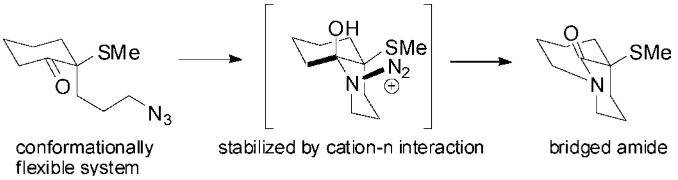
ABSTRACT



The regiochemistry of the intramolecular Schmidt reaction of 2-azidoalkylketones is controlled by placing a thioether substituent at the position adjacent to the ketone to provide access to a family of unsubstituted medium bridged twisted amides. This outcome is ascribed to the presence of stabilizing through-space interactions between the diazonium cation and the n electrons on heteroatom and does not require a locked conformation of the ketone.

Bridged lactams, in which the amide bond deviates considerably from planarity, display properties divergent from traditional amides and are of interest from structural and reactivity perspectives.[1,2] The importance of distorted amides in cis/trans isomerization of peptide bonds has also been established.[3] However, the synthesis of bridged amides is complicated by hyperreactivity of such amide bonds and their tendency to undergo rapid hydrolysis.[4]

Recently, we have reported the utility of an intramolecular Schmidt reaction to the problem of one-carbon bridged lactam synthesis.[5] Although intramolecular Schmidt reactions of α-substituted ketones almost always afford fused lactams by migration of the bond proximal to the azide (Figure 1a, path a),[6,7] it proved possible to reverse the regiochemistry of the reaction to afford bridged isomers (Figure 1a, path b) by a combination of two effects: (1) axial orientation of the azide-containing tether and (2) favoring a specific orientation of the N_2^+ leaving group by engineering a stabilizing

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(1) For twisted amide reviews, see: (a) Hall, H. K.; Elshekeil, A. *Chem. Rev.* **1983**, *83*, 549. (b) Lease, T. G.; Shea, K. J. *Advances in Theoretically Interesting Molecules*; JAI Press Inc., 1992; Vol. 2, p 79. (c) Greenberg, A. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; Wiley-Interscience, 2000; p 47. (d) Clayden, J.; Moran, W. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7118.

(2) For selected examples see: (a) Kirby, A. J.; Komarov, I. V.; Feeder, N. *J. Chem. Soc., Perkin Trans. 2* **2001**, 522. (b) Bashore, C. G.; Samardjiev, I. J.; Bordner, J.; Coe, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 3268. (c) Lei, Y.; Wrobleski, A. D.; Golden, J. E.; Powell, D. R.; Aubé, J. *J. Am. Chem. Soc.* **2005**, *127*, 4552. (d) Tani, K.; Stoltz, B. M. *Nature* **2006**, *441*, 731. (e) Ribelin, T. P.; Judd, A. S.; Akritopoulou-Zanze, I.; Henry, R. F.; Cross, J. L.; Whittern, D. N.; Djuric, S. W. *Org. Lett.* **2007**, *9*, 5119. (f) Williams, R. M.; Lee, B. H.; Miller, M. M.; Anderson, O. P. *J. Am. Chem. Soc.* **1989**, *111*, 1073. (g) Lease, T. G.; Shea, K. J. *J. Am. Chem. Soc.* **1993**, *115*, 2248. For ab initio studies, see: (h) Greenberg, A.; Venanzi, C. A. *J. Am. Chem. Soc.* **1993**, *115*, 6951. (i) Greenberg, A.; Moore, D. T.; DuBois, T. D. *J. Am. Chem. Soc.* **1996**, *118*, 8658.

(3) (a) Shao, H.; Jiang, X.; Gantzel, P.; Goodman, M. *Chem. Biol.* **1994**, *1*, 231. (b) Fischer, G.; Schmid, F. X. *Molecular Chaperones and Folding Catalysts: Regulation, Cellular Functions and Mechanisms*; Bakau, B., Ed.; CRC, 1999; p 461. (c) Schmid, F. X. *Protein Folding in the Cell*; 2002; Vol. 59, p 243. (d) Fischer, G. *Chem. Soc. Rev.* **2000**, *29*, 119.

(4) (a) Somayaji, V.; Brown, R. S. *J. Org. Chem.* **1986**, *51*, 2676. (b) Brown, R. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*; Greenberg, A., Breneman, C. M., Liebman, J. F., Ed.; Wiley-Interscience, 2000; p 85. (c) Mujika, J. I.; Mercero, J. M.; Lopez, X. *J. Am. Chem. Soc.* **2005**, *127*, 4445. (d) Szostak, M.; Yao, L.; Aubé, J. *J. Org. Chem.* **2009**, *74*, 1869.

(5) Yao, L.; Aubé, J. *J. Am. Chem. Soc.* **2007**, *129*, 2766.

(6) For reviews, see: (a) Nyfeler, E.; Renaud, P. *Chimia* **2006**, *60*, 276. (b) Lang, S.; Murphy, J. A. *Chem. Soc. Rev.* **2006**, *35*, 146. (c) Grecian, S.; Aubé, J. *Organic Azides: Syntheses and Applications*; Bräse, S., Banert, K., Eds.; John Wiley and Sons: New York, 2009.

10.1021/ol901771b CCC: $40.75

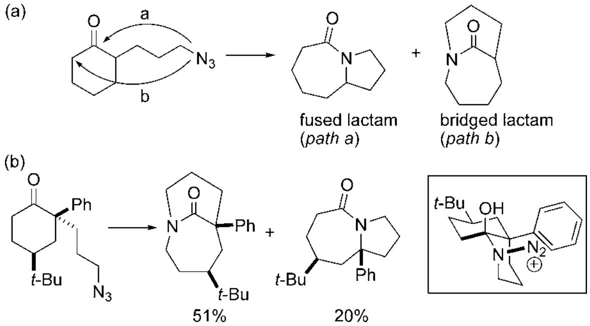
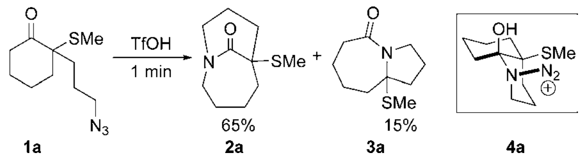


Figure 1. (a) Regiochemical options for the intramolecular Schmidt reaction of α-substituted ketones. (b) Formation of bridged amides and proposed intermediate leading to the major isomer.[5]

cation−π interaction[8] into the key azidohydrin intermediate (Figure 1b).

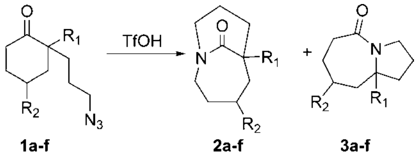
Herein, we report that the presence of an α-heteroatomic group can also direct the regiochemistry of the intramolecular Schmidt reaction toward path b (Figure 1). This stabilization obviates the necessity for the locked conformation of the reactive azidohydrin intermediate, significantly expanding the utility of Schmidt reaction in the synthesis of one-carbon bridged lactams. In addition, we provide explicit experimental confirmation that the regiochemistry of these reactions depends on whether the azide-containing tether occupies an axial or equatorial position.

Scheme 1



The first example of an intramolecular Schmidt reaction to afford a bridged bicyclic lactam without relying on the locked conformation of cyclohexanone was encountered when a thiomethyl was placed in the α position to the ketone (Scheme 1).[4d] We orginally proposed that the mechanism of intramolecular Schmidt reactions involves formation of chairlike azidohydrins followed by the selective migration of the C−C bond antiperiplanar to the leaving diazonium group.[9b] In this scenario, a bridged lactam can be obtained only when the azide-containing chain occupies a pseudoaxial orientation (see Supporting Information for details of this published argument). Accordingly, we hypothesize that lactam **2a** is formed from the azidohydrin **4a** (Scheme 1, box) in which a stabilizing electrostatic 1,3-diaxial interaction between the cation and thiomethyl groups becomes possible.

Table 1. Synthesis of Bridged and Fused Lactams



entry	azide	R_1	R_2	2:3 ratio[a]	yield (%)[b]
1	**1a**	SMe	H	80:20	80
2	**1b**	SMe, trans	t-Bu	86:14	74
3	**1c**	SMe, cis	t-Bu	>5:95	75
4	**1d**	H[c]	H	>5:95	85
5	**1e**	Ph[d]	H	>5:95	96
6	**1f**	4-(MeO)C_6H_4, trans[d]	t-Bu	87:13	75

[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] Combined yield, see Supporting Information for full experimantal details. [c] Ref 9, TFA instead of TfOH. [d] Ref 5, $MeAlCl_2$ instead of TfOH.

Control experiments demonstrated that the axial orientation of the azide-containing side-chain is required for the formation of bridged lactams (Table 1, entries 2 and 3) and that the use of thiomethyl is crucial to the outcome of the reaction (entries 1, 4, and 5). The selectivity observed with the conformationally locked azide **1b** equals the highest selectivity for a bridged isomer obtained in the previous study (cf. entries 2 and 6). Thus, it appears that the α-thiomethyl effect is comparable to those arising from cation−π interactions as previously reported.[5] However, a significant remarkable advantage is that the thiomethyl-containing substrate does not require an additional conformational constraint (entries 1 and 6), allowing for the synthesis of otherwise unsubstituted bridged lactams.

The proposed reactive intermediates are shown in Scheme 2. The fact that the trans isomer **1b** leads primarily to the bridged product while the cis isomer **1c** affords only fused product provides the first experimental support for the original hypothesis of the intramolecular Schmidt reaction requiring the azidoalkyl chain in the axial orientation to give

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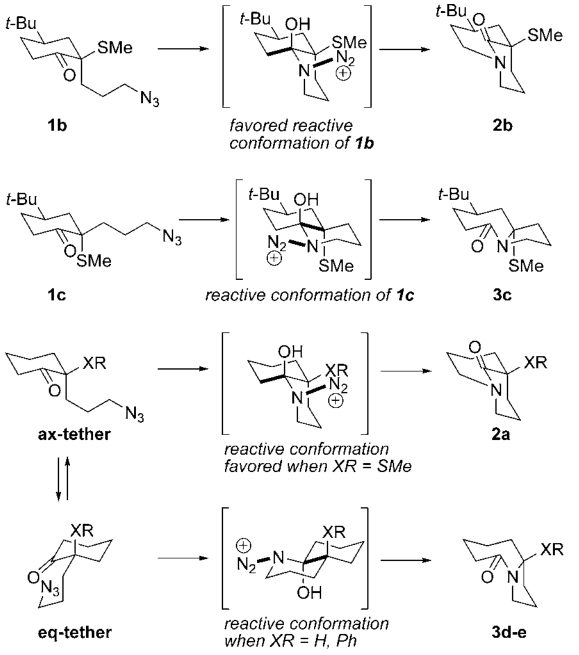
(7) For selected examples from the recent literature, see: (a) Frankowski, K. J.; Golden, J. E.; Zeng, Y. B.; Lei, Y.; Aubé, J. *J. Am. Chem. Soc.* **2008**, *130*, 6018. (b) Iyengar, R.; Schildknegt, K.; Morton, M.; Aubé, J. *J. Org. Chem.* **2005**, *70*, 10645. (c) Wrobleski, A.; Sahasrabudhe, K.; Aubé, J. *J. Am. Chem. Soc.* **2004**, *126*, 5475. (d) Lertpibulpanyaa, D.; Marsden, S. P. *Org. Biomol. Chem.* **2006**, *4*, 3498. (e) Zhao, Y. M.; Gu, P.; Zhang, H. J.; Zhang, Q. W.; Fan, C. A.; Tu, Y. Q.; Zhang, F. M. *J. Org. Chem.* **2009**, *74*, 3211.

(8) For reviews, see: (a) Dougherty, D. A. *Science* **1996**, *271*, 163. (b) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303. (c) Yamada, S. *Org. Biomol. Chem.* **2007**, *5*, 2903. For selected examples, see: (d) Katz, C. E.; Aubé, J. *J. Am. Chem. Soc.* **2003**, *125*, 13948. (e) Katz, C. E.; Ribelin, T.; Withrow, D.; Basseri, Y.; Manukyan, A. K.; Bermudez, A.; Nuera, C. G.; Day, V. W.; Powell, D. R.; Poutsma, J. L.; Aubé, J. *J. Org. Chem.* **2008**, *73*, 3318. (f) Monje, P.; Paleo, M. R.; Garcia-Rio, L.; Sardina, F. J. *J. Org. Chem.* **2008**, *73*, 7394. (g) Ishihara, K.; Fushimi, N.; Akakura, M. *Acc. Chem. Res.* **2007**, *40*, 1049.

(9) (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965. (b) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449. (c) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W. K.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183. (d) Smith, B. T.; Gracias, V.; Aubé, J. *J. Org. Chem.* **2000**, *65*, 3771. For examples of Schmidt reaction involving 4-C tether, see: (e) Gracias, V.; Zeng, Y.; Desai, P.; Aubé, J. *Org. Lett.* **2003**, *5*, 4999. (f) Smith, B. T.; Wendt, J. A.; Aubé, J. *Org. Lett.* **2002**, *4*, 2577. (g) Ref 7c. For examples of Schmidt reaction involving 8- and larger rings, see: ref 9b.

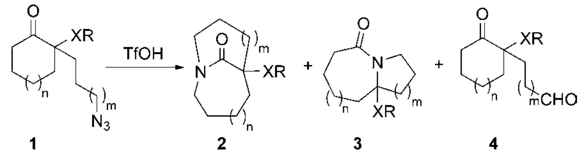
Scheme 2



the bridged lactam.[9b] Moreover, since azides **1b** and **1c** are isomeric, the results cannot be solely explained by electronic migratory aptitude considerations. We propose that the bridged isomer **2b** is formed due to stabilizing cation−n interaction favoring the orientation of diazonium cation in pseudoaxial position in the azidohydrin intermediate. The effect of the α substituent is shown in the bottom part of Scheme 2. All of the cyclohexyl-containing substrates lacking a *tert*-butyl group are expected to exist in a ground-state equilibrium between **eq-tether** and **ax-tether**, presumably favoring the former; however, the 2-SMe substrate **1a** stands apart from the others in that the predominant product from the ring expansion reaction arises from the **ax-tether** intermediate.

We also probed the effect of varying heteroatom substituents and ring sizes on the outcome of the reaction (Table 2). Thiophenyl and methoxy groups allowed for the synthesis of bridged lactams, albeit in lower yield. Sulfur substitution with either an electron-withdrawing group (entry 2) or a less polarizable methoxy group (entry 3) led to diminished amounts of bridged lactams. The low amounts of bridged lactam with azide **1h** were surprising since a methoxy group proved to be a very effective cation−n stabilizing group in another type of ring expansion reaction.[10] Interestingly, these reactions were very dependent on the acid used for rearrangement suggesting that cation coordination likely has a profound effect on the product distribution (see Supporting Information for details). Sulfonyl was also found to be an efficient directing group (entry 4). However, since in this case the interaction takes place between cation and oxygen, a cation$-\pi$ component cannot be excluded. It is not possible to completely discard a role for migratory aptitude based on our results. However, the enhanced bridged/fused ratio where XR = SMe over analogues containing better electron-withdrawing groups seems to be more consistent with the proposed attractive nonbonding effect being responsible.

Table 2. Effect of Substituents and Ring Sizes on Synthesis of Bridged and Fused Lactams



					yield (%)		
entry	azide	XR	*n*	*m*	**2**	**3**	**4**
1	**1a**	SMe	1	1	65	15	-
2	**1g**	SPh	1	1	35	32	-
3	**1h**	OMe	1	1	23	52[a]	-
4	**1i**	SO_2Me	1	1	48	13[a]	-
5	**1j**	SMe	0	1	-	43	-
6	**1k**	SMe	2	1	62	11[a]	20
7	**1l**	SMe	3	1	-	-	30
8	**1m**	SMe	1	2	-	-	53

[a] Combined yield of elimination products;[11] see Supporting Information for full details.

Examination of different ring sizes revealed that bridged lactams are formed efficiently for six- and seven-membered rings in which the azide is separated from the ring by a three-carbon tether. Extending the ring size or the tether length decelerated the reaction, and decomposition of azide to aldehyde was the only reaction pathway observed (entries 7 and 8). As determined earlier for intramolecular Schmidt reactions,[9] substitution with an electron-withdrawing substitutent slows down the rate of migration. This is likely why the Schmidt reaction of the eight-membered ketone (entry 7) or the 4-carbon tether (entry 8) is not observed in the current case.[9d−g]

Thiomethyl is a valuable synthetic handle,[12] and we used it to obtain a family of structurally related bridged amides (Scheme 3). Noteworthy is the chemoselective oxidation of thiomethyl in the presence of sensitive twisted amide functionalities (**5**, **6**, **8**), reductive thiomethyl removal proceeding with generation of a bridgehead radical (**7**), and isolation of the bridged amide **9** containing also a bridgehead olefin in the same functionality.

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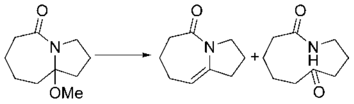
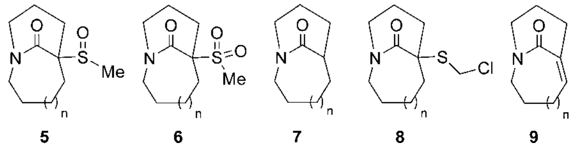
(10) Ribelin, T.; Katz, C. E.; English, D. G.; Smith, S.; Manukyan, A. K.; Day, V. W.; Neuenswander, B.; Poutsma, J. L.; Aubé, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6233.

(11) From **3b**, *N*-acyl iminium ion is formed, followed by deprotonation or hydrolysis in ca. 1:1 ratio. Similar reactions are observed with **3i** and **3k**. An analogous ring opening has been observed earlier: Forsee, J. E.; Aubé, J. *J. Org. Chem.* **1999**, *64*, 4381



(12) Block, E. *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Sulphur Analogues*; Patai, S., Ed.; Wiley: New York, 1980; p 539.

Scheme 3[a]



[a] Conditions: **5** ($n = 2$), *m*CPBA (1.0 equiv), 72%. **6** ($n = 1$), *m*CPBA (2.0 equiv), 67%. **7** ($n = 2$), Raney Ni, 86%. **8** ($n = 2$), NCS, 58%. **9** ($n = 2$), i. *m*CPBA (1.0 equiv), ii. 110 °C, 72 h, 36%.

Overall, we have demonstrated that the regiochemistry of the intramolecular Schmidt reaction is amenable to control by the addition of certain heteroatom-containing groups and propose that this phenomenon is due to electrostatic cation−n interactions. The significant features of this chemistry include (1) participation of intermediates subjected to nonbonding through-space interactions and (2) efficient synthesis of previously unattainable bridged amides lacking a conformational control feature like a *tert*-butyl group. This laboratory is currently enagaged in extending the concept of cation−n stabilization in synthesis and the study of the unusual properties of medium-bridged twisted amides.

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

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