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COMMUNICATIONS

Published on Web 02/16/2007

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

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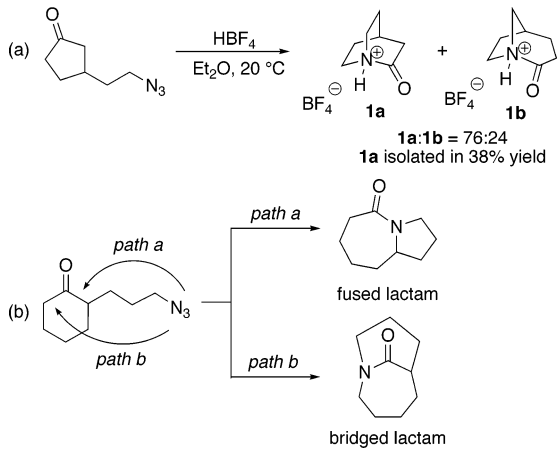
Bridged bicyclic lactams that incorporate the lactam nitrogen at a bridgehead position have been of interest for many years because they incorporate a "twisted amide" unable to achieve standard planar geometry.[1] Although much of the work devoted to these compounds has focused on the hyperreactivity of the amide bond toward hydrolysis, recent work by us[2] and others[3] suggests that there is still much to be learned about the reactivity of these interesting structures. Not surprisingly, the tendency of these compounds to undergo rapid hydrolysis has complicated their synthesis. Although standard methods for amide bond formation have been used, such routes often proceed in poor yields or are accompanied by difficulty in product isolation.[1] In this paper, we describe a solution to the problem of bridged bicyclic lactam synthesis that utilizes the acid-promoted reaction of an alkyl azide and a ketone[4] in which the regiochemistry is controlled by a through-space interaction of an aryl group with a cationic leaving group in a key reaction intermediate.

The utility of the intramolecular Schmidt reaction to the problem of bridged lactam was recently reported by Stoltz and Tani (Scheme 1a).[5] Using 3-(azidoethyl)cyclopentanone, it proved possible to form a mixture of two lactams from which the desired quinuclidone **1a** was isolated by recrystallization. This sequence is noteworthy because it permitted the isolation and characterization of the iconic bridged lactam **1a** for the first time and also demonstrated the loss of N_2 as a powerful driving force for the formation of this unstable ring system.

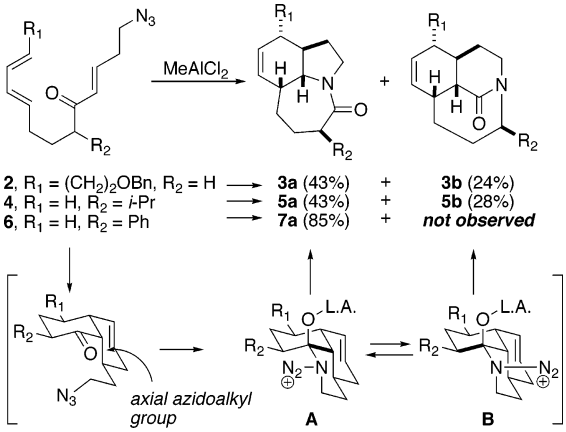
The placement of the azide-containing side chain at a carbon nonadjacent to the ketone means that *only* bridged lactams are possible in this reaction. For the analogous α-substituted ketones, however, two regiochemical outcomes can be envisioned (Scheme 1b). Such reactions almost always afford fused lactam by formal insertion of the azide into the proximal C−C bond of the reactive ketone (path a).[4] We set out to obtain a new class of bridged lactams[2] that would be formed by the regiochemical alternative ring expansion via path b.

The first example of an intramolecular Schmidt reaction to afford such a bridged bicyclic lactam was encountered unexpectedly (Scheme 2).[6,7] Thus, triene **2** underwent an intramolecular Diels−Alder reaction to afford a ketone that further reacted to give a mixture of the expected fused lactam **3a** and a bridged isomer **3b**. We propose that the regiochemistry of the Schmidt reaction involves the selective migration of the C−C bond antiperiplanar to the leaving N_2^+ substituent. In this scenario, chairlike cyclohexanones can only afford a bridged lactam when the azide-containing side chain occupies a pseudoaxial orientation (see the Supporting Information for details of this published argument[4]). Once this condition is satisfied, then antiperiplanar migration of the C−C bond anti to the equatorial N_2^+ group in **A** would afford the fused isomers, whereas the axially disposed leaving group in **B** is necessary for the formation of the bridged isomers.

Scheme 1



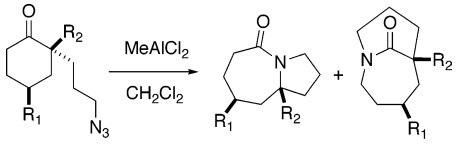
Scheme 2



We first attempted to affect this equilibrium by disfavoring isomer **A** through the placement of a bulky group at R_2. To this end, the isopropyl-containing isomer **4** was synthesized and submitted to Lewis acid treatment. In this case, essentially the same ratio of bridged/fused adducts was obtained. Conversely, the analogue bearing a phenyl group at the same position gave a dramatically different result. In this case, fused isomer **7a** was formed exclusively in 85% yield, making this reaction the most efficient example of this sequence observed to date. Although the phenyl and isopropyl have similar *A* values,[8] we wondered if apparently exclusive intermediacy of **A** might be explained by an attractive through-space interaction between the positively charged leaving group and the phenyl group. Although commonly invoked in small-molecule/protein binding interactions,[9] such cation−π interactions have only occasionally been proposed in stereoselective synthesis.[10] In one case, we proposed such an interaction as a controlling feature of certain asymmetric Schmidt reactions.[11]

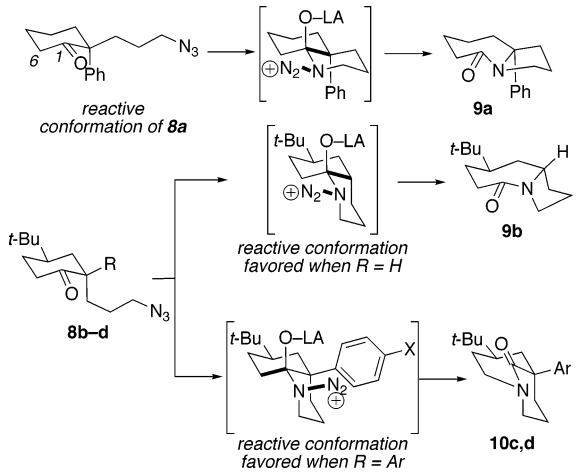
10.1021/ja068919r CCC: $37.00

Table 1. Synthesis of Fused and Bridged Lactams



				yield (%)	
entry	**8–10**	R_1	R_2	**9**	**10**
1	**a**	H	Ph	96	0
2	**b**	*t*-Bu	H	57	17
3	**c**	*t*-Bu	Ph	20	51
4	**d**	*t*-Bu	*p*-(MeO)C_6H_4	10	65

Scheme 3



Accordingly, we hypothesized that an appropriately situated aromatic group might be able to stabilize isomer **B** and provide a direct route to bridged isomers.

Control experiments demonstrated that neither placement of a phenyl group at the α carbon (entry 1) nor the axial orientation of the side chain (entry 2) alone is sufficient to steer the reaction toward fused lactam product (although the small amounts of **10b** observed are consistent with the results seen in Scheme 2[12]). *However, the combination of an axial azide-containing tether and an aromatic group in a 1,3-diaxial relationship with the leaving N_2^+ group in the intermediate azidohydrin diverts the reaction so that bridged product predominates.* The fact that the ratio of bridged to fused isomers increases with a more electron-rich aromatic group provides strong support that a 1,3 cation$-\pi$ effect is in play (cf. entries 3 and 4).

The relevant intermediates are shown in Scheme 3. Our hypothesis is supported by several observations. First, the fact that **8a** affords only fused product **9a** rules out any effect arising from differences in intrinsic migration aptitudes. In this case, the thermodynamically favored conformation of **8a** affords a reactive intermediate that can only lead to **9a**. Interestingly, the alternative conformation bearing an axial side chain, that could in principle lead to bridged isomer, does not appear to react in this example (although it very likely exists in the ground state). The effect of phenyl group placement in compounds **8b**−**d** is depicted in the bottom part of Scheme 3.

Overall, these results indicate an important role for stereoelectronic effects in controlling the regiochemistry of this reaction. The fact that the vast majority of 2-azidoalkyl ketones undergo rearrangement to afford fused lactams may reflect both the conformation of the reactive intermediate azidohydrin and the stability of normal vs twisted lactams. In particular, the observation of a small amount of twisted amide from compound **8b** indicates that appropriately constrained compounds can lead to bridged isomers, if only as minor products. However, the observation of through-space control of these intramolecular Schmidt reactions is especially provocative. This laboratory will carry out further investigations of this interesting effect in this chemistry and in other contexts as well.

Acknowledgment. We thank the National Institutes of Health Institute of General Medical Sciences (GM-49093) for financial support, and Christopher Katz and Michal Szostak for experimental assistance.

Supporting Information Available: Additional discussion of the effect of the orientation of the C-2 substituent on regiochemistry, experimental details, and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Interestingly, this same reaction when carried out using $TiCl_4$ provided compound **9b** as a single product in 92% yield, suggesting that the regiochemistry of the reaction is Lewis acid-dependent. Further work to examine this point is in progress.

JA068919R