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Synthesis of lactams and other nitrogen heterocycles by intramolecular cyclizations of carbamates and acyl derivatives of aminosulfones

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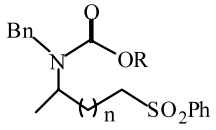
Abstract—The α sulfonyl carbanions obtained by the treatment of the carbamate derivatives of aminosulfones (type **I**) with LHMDS in THF at −78°C, underwent cyclization to give five-, six-, and seven-membered cyclic lactams in excellent yields. Cyclization of the *N*-acyl derivatives of the type **II** led to the formation of substituted dihydropyrrolidines in good yields. The scope and limitations of this cyclization strategy to access functionalized nitrogen containing ring systems have been examined.

The intramolecular cyclization reactions of α-sulfonyl carbanions involving a variety of internal electrophiles have been a valuable tool for the preparation of carbocyclic and heterocyclic ring systems.[1,2] Previous studies in our laboratory have focused on synthetic approaches to lactones, dihydrofurans, dihydropyrans and functionalized cyclic ethers by the intramolecular cyclization reactions of ethoxycarbonyl and acyl derivatives of γ- and δ-hydroxysulfones.[3]

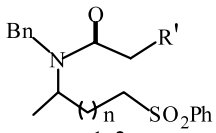
In contrast, the intramolecular cyclization reactions of α-sulfonyl carbanions of aminosulfone derivatives have received very little attention. The preparation of 4*H*-1,4-benzothiazine derivatives and 3-sulfonyl-substituted indole derivatives by an intramolecular cyclization reaction of a sulfonyl carbanion onto an anilide or imidate ester have been reported.[4,5] The stereoselective conjugate addition of amine nucleophiles to vinylsulfones[6] and acetylenic sulfones[7] has been exploited for the preparation of nitrogen heterocycles including hydroxypyrrolidines and hydroxypiperidines.

The cyclization reactions of derivatives of aminosulfones have the potential to give interesting heterocyclic ring systems and hence are valuable for the synthesis of many natural products. Herein, we present the results of our study on the intramolecular cyclization reactions of the sulfonyl carbanions derived from the carbamate and *N*-acyl derivatives of the type **I** and **II**. Our results show that these cyclization reactions are highly effective and give access to useful heterocyclic ring systems. The perception that carbamates and amides are poor electrophiles may be the reason why this class of reactions has not received much attention. During the course of our investigation, a report on the intermolecular reaction of carbamates with the dianion of methyl phenyl sulfone to give amidosulfones was disclosed.[8] A recent paper also described the intermolecular ring opening reaction of protected lactams with sulfonyl carbanions.[9]



n = 1, 2, 3

I



n = 1, 2

II

Intramolecular cyclization reactions of carbamates derivatives of type I

The carbamates of type **I** for our study were readily prepared by the acylation of the corresponding aminosulfones by standard procedures. The γ,δ,ε-aminosulfones in turn were prepared in high yields using a short synthetic sequence from the corresponding readily available hydroxysulfones.[10,11]

As anticipated, the cyclization of the unsubstituted carbamate derivative **1a** did not proceed with 1 or 2

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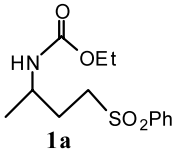
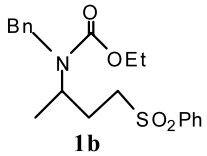
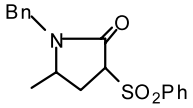
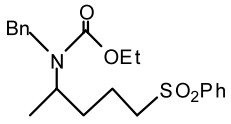
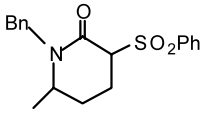
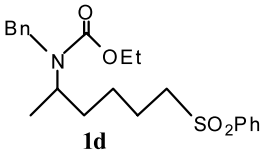
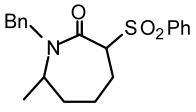
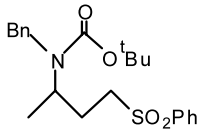
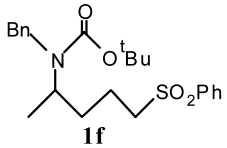
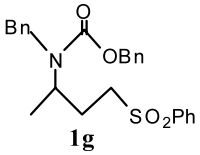
equiv. of base. This can be ascribed to the deprotonation of the acidic N–H of the carbamate, which renders the carbonyl non-electrophilic. In contrast, when the *N*-benzyl protected ethoxycarbonyl derivative **1b** was treated with lithium hexamethyldisilazane (LHMDS, 1.1 equiv.) at −78°C in THF for 6 h (Table 1), the resultant sulfonyl carbanion readily cyclized to give the five-membered lactam **2b** in good yields as a 1:1 mixture of diastereomers.[12]

This cyclization strategy could be easily extended to prepare six- and seven-membered lactams in high yields after chromatographic purification (Table 1).[13] The lactams **2b–d** that were isolated as a 1:1 diastereomeric mixture as evidenced by ^{1}H and ^{13}C NMR spectra, were inseparable by chromatographic methods. A higher temperature (0°C for 6 h) was required for efficient cyclization of **1d** to give the seven-membered lactam. Surprisingly, use of this methodology for the

Table 1. Results of the intramolecular cyclization reaction of the carbamate derivatives type **I**[a]

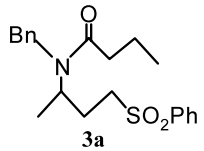
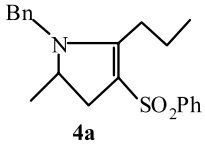
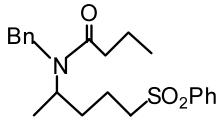
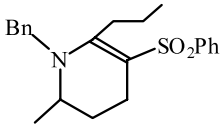
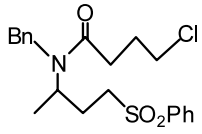
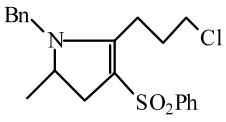
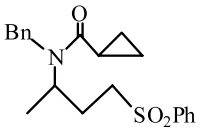
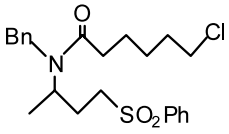
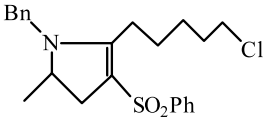
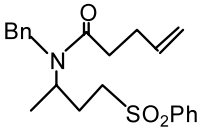
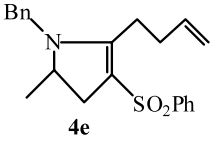
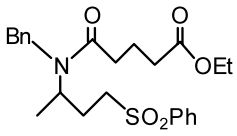
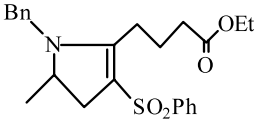
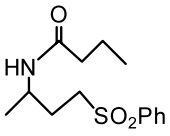
Substrate	Product[b]	Temp.	yield (%)
 **1a**	N. R.	r.t.	
 **1b**	 **2b**	-78°C	71
 **1c**	 **2c**	-78°C	75
 **1d**	 **2d**	0°C	84
 **1e**	**2b**	-78°C r. t.	0 36
 **1f**	**2c**	-78°C r. t.	0 41
 **1g**	**2b**	-78°C	75

a) conditions: 1.1 eq LHMDS, THF, -78 °C, 4-6 h; then glacial acetic acid
b) all products were isolated as a 1:1 mixture of diastereomers

preparation of the corresponding eight-membered lactam systems was unsuccessful under a variety of experimental conditions.

Because BOC and Cbz protecting groups are widely used in synthesis, the effect of the alkoxy group on the carbamate on this class of cyclizations was investigated.[14] The intramolecular cyclization reactions of the α sulfonyl carbanions of BOC-protected aminosulfones **1e** and **1f** did not proceed at −78°C even after several hours and the starting material was recovered at the end of the reaction. Low yields of the cyclized product could be achieved by warming the reaction mixture to room temperature and stirring for several hours. The inhibition of the cyclization can be attributed to steric factors associated with the BOC protecting group.[8] As predicted, the cyclization of Cbz-protected aminosulfone **1g** was similar to that of **1b** and readily occurred at −78°C to give **2b** in good yield.

Table 2. Results of the intramolecular cyclization of *N*-acylaminosulfones, type **II**[a]

Substrate	Product	yield (%)
 **3a**	 **4a**	74
 **3b**	 **4b**	20 - 30
 **3c**	 **4c** (20)	 **4g** (43)
 **3d**	 **4d**	68
 **3e**	 **4e**	67
 **3f**	 **4f**	63
 **3g**	N.R.	

a) conditions: 2.1 eq LHMDS, THF, -78 °C, 4-6 h; then glacial acetic acid

Intramolecular cyclization reactions of *N*-acyl derivatives of type II

The intramolecular cyclization reactions of *N*-acyl derivatives of aminosulfones were then examined. A priori, it was tough to predict whether efficient ring closure of the α sulfonyl carbanion onto the amide carbonyl could be realized in these systems for two reasons. First, amide carbonyls are known to be poor electrophiles. Secondly, in these substrates, the protons next to the carbonyl of the amide and the α sulfonyl protons are of comparable acidity raising the question of selective deprotonation to generate the required α sulfonyl carbanion.[15] Irreversible generation of the amide enolate would prohibit the desired cyclization.

N-Acylaminosulfone **3a** was prepared by treating the corresponding aminosulfone with butanoyl chloride in the presence of Et_3N in CH_2Cl_2 at room temperature for 24 h. The cyclization of this substrate was then examined. The amidosulfone **3a** was treated with LHMDS (2.1 equiv.) at −78°C in THF for 6 h and the reaction was quenched with acetic acid prior to work-up. The product that was isolated in 74% yield after column chromatography was the dihydropyrrolidine derivative **4a**.[16] The cyclization does occur with 1.1 equiv. of base but the yields were somewhat lower (30–40%). Our initial success prompted us to examine the scope and limitations of intramolecular cyclization reactions of functionalized amidosulfones.

Our results show that the amidosulfone cyclization to give five-membered pyrrolidine systems is quite facile and proceeds in high yields, even in the presence of other functional groups elsewhere in the molecule (Table 2). As anticipated, the cyclization of the unsubstituted amidosulfone **3g** was not successful using a similar experimental protocol as well as at higher temperatures (rt, 24 h). This can be ascribed to the deprotonation of the N–H proton of the amide, rendering it unreactive. In the case of the 4-chlorobutyrate derivative **3c**, the cyclization pathway to give **4c** was minor. The major product **4g** is formed by a competing intramolecular displacement reaction of the amide enolate on the chloride to give the cyclopropane ring system. In contrast, the cyclization of **3d**, having a chlorohexanoyl side chain, proceeds to give dihydropyrrolidine **4d**, with no interference from the chloro substituent. It is interesting to note that the ester group of **3f** does not inhibit the cyclization. However, we were unsuccessful in using this methodology to access dihydropiperidine systems in high yields. The cyclization of *N*-acyl derivative **3b** was inefficient and led to the recovery of starting material with low yields of the product **4b**.

Based on our results, we suggest the following mechanistic scenario for the intramolecular cyclization reactions of these amidosulfones. The initial deprotonation may occur α to the amide and/or α to the sulfone (Scheme 1). In any case, proton exchange leads to a sulfonyl carbanion that undergoes ring closure on the amide carbonyl. Upon work up with mild acid, the intermediate undergoes dehydration to give the dihydropyrrolidine derivative.[3b–d] The formation of the cyclopropane ring system in the case of **3c** supports the fact that deprotonation α to the amide can occur in these systems.

In conclusion, it is clear that cyclization reactions of carbamates and amidosulfones is a promising class of reactions which deserves much greater attention. The cyclizations of the carbamate derivatives of the type **I**, provide easy access to a variety of lactam systems in good yields. Particularly exciting is the fact that functionalized amidosulfones of the type **II**, undergo intramolecular cyclization to give dihydropyrrolidines in good yields. The extension of this chemistry as well as specific applications to natural products synthesis is under investigation in our laboratory.

Acknowledgements

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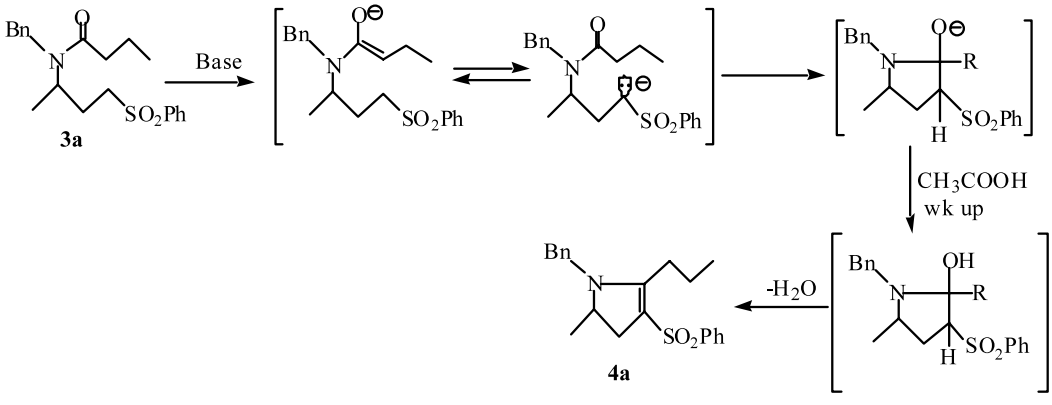

Scheme 1.

References

1. Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon Press: Oxford, 1993.
2. (a) Jin, C. Y.; Jacobs, H. K.; Gopalan, A. S. *Tetrahedron Lett*. **2000**, *41*, 9753; (b) Marco, J. L.; Ingate, S. T.; Jaime, C.; Beá, I. *Tetrahedron* **2000**, *56*, 2523; (c) de Vicente, J.; Arrayás, R. G.; Carretero, J. C. *Tetrahedron Lett*. **1999**, *40*, 6083; (d) Carretero, J. C.; Arrayás, R. G. *J. Org. Chem*. **1998**, *63*, 2993; (e) Suh, Y. G.; Koo, B. A.; Kim, E. N.; Chio, N. S. *Tetrahedron Lett*. **1995**, *36*, 2089; (f) Cohen, T.; Tong, S. *Tetrahedron* **1997**, *53*, 9487; (g) Ihara, M.; Suzuki, S.; Tokunaga, Y.; Takeshita, H.; Fukumoto, K. *Chem. Commun*. **1996**, 1801; (h) Grimm, E. L.; Levac, S.; Trimble, L. A. *Tetrahedron Lett*. **1994**, *35*, 6847; (i) Jones, D. N.; Maybury, M. W. J.; Swallow, S.; Tomkinson, N. C. O. *Tetrahedron Lett*. **1993**, *34*, 8553.
3. (a) Jin, C. Y.; Jacobs, H. K.; Cervantes-Lee, F.; Gopalan, A. S. *Tetrahedron* **2002**, *58*, 3737; (b) Jin, C. Y.; Ramirez, R. D.; Gopalan, A. S. *Tetrahedron Lett*. **2001**, *42*, 4747; (c) Gonzales, S. S.; Jacobs, H. K.; Juarros, L. E.; Gopalan, A. S. *Tetrahedron Lett*. **1996**, *37*, 6827; (d) Jacobs, H. K.; Gopalan, A. S. *J. Org. Chem*. **1994**, *59*, 2014; (e) Jacobs, H. K.; Mueller, B. H.; Gopalan, A. S. *Tetrahedron* **1992**, *48*, 8891.
4. Babudri, F.; Florio, S.; Vitrani, A. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1899.
5. Wojciechowski, K.; Makosza, M. *Synthesis* **1986**, 651.
6. (a) Iradier, F.; Arrayás, R. G.; Carretero, J. C. *Org. Lett*. **2001**, *3*, 2957; (b) Enders, D.; Müller, S. F.; Raabe, G. *Angew. Chem., Int. Ed*. **1999**, *38*, 195; (c) Carretero, J. C.; Arrayás, R. *J. Org. Chem*. **1998**, *63*, 2993; (d) Alonso, D. A.; Costa, A.; Mancheño, B.; Najera, C. *Tetrahedron* **1997**, *53*, 4791; (e) Carretero, J. C.; Arrayás, R. G.; Storch de Gracia, I. *Tetrahedron Lett*. **1996**, *37*, 3379; (f) Carretero, J. C.; Arrayás, R. *J. Org. Chem*. **1995**, *60*, 2993; (g) de Blas, J.; Carretero, J. C.; Domínguez, E. *Tetrahedron Lett*. **1994**, *35*, 2993.
7. Back, T.; Nakajima, K. *J. Org. Chem*. **2000**, *65*, 4543 and references cited therein.
8. White, J.; Blakemore, P.; Milicevic, S. *Org. Lett*. **2002**, *10*, 1803.
9. Arias, L. A.; Arbelo, D.; Alzerreca, A.; Prieto, J. A. *J. Hetercycl. Chem*. **2001**, *38*, 29.
10. For the preparation of hydroxysulfones, see: Gopalan, A. S.; Jacobs, H. K. *Tetrahedron Lett*. **1990**, *31*, 5575.
11. The aminosulfones were readily prepared by conversion of the hydroxysulfone into the corresponding mesylate followed by reaction with excess benzylamine at 75°C. The benzyl protecting group could be removed by reaction with Pd-black in 4.4% formic acid in methanol.
12. Spectral data for **2b** (1:1 mixture of diastereomers): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02–7.52 (m, 5H), 7.27–7.17 (m, 5H), 4.95 (d, $J=15.0$ Hz, 0.5H), 4.80 (d, $J=15.0$ Hz, 0.5H), 4.18–3.93 (m, 2H), 3.73–3.45 (m, 1H), 3.69 (q, $J=6.6$ Hz, 0.5H), 3.5 (q, $J=6.2$ Hz, 0.5H), 2.86 (ddd, $J=3.7$, 7.3, 14.6 Hz, 0.5H), 2.58 (ddd, $J=4.0$, 8.4, 16.5 Hz, 0.5H), 2.29 (ddd, $J=5.5$, 6.4, 13.7 Hz, 0.5H), 2.0 (ddd, $J=7.0$, 9.0, 15.9 Hz, 0.5H), 1.22 and 1.13 (d, $J=6.2$ Hz, 3H); anal. calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.40; H, 5.99; N, 4.50%.
13. Spectroscopic and elemental analysis of all compounds are in agreement with the assigned structures.
14. Bodanszky, M. *Principles of Peptide Chemistry*; Springer-Verlag: New York, 1984.
15. (a) Bordwell, F. G.; Fried, H. E. *J. Org. Chem*. **1981**, *46*, 4331; (b) Bordwell, F. G. *Acc. Chem. Res*. **1988**, *21*, 456.
16. Spectral data for **4a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.90–7.45 (m, 5H), 7.32–7.11 (m, 5H) 4.31 (dd, $J=16.3$, 49.3 Hz, 2H), 3.71–3.53 (m, 1H), 3.02–2.87 (m, 2H), 2.54–2.26 (m, 2H), 1.61–1.43 (m, 2H), 1.08 (d, $J=6.2$ Hz, 3H), 0.99 (t, $J=7.3$ Hz, 3H); anal. calcd for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94. Found: C, 70.60; H, 6.75; N, 4.21%.