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Robust Synthesis of *N*-Sulfonylazetidine Building Blocks via Ring Contraction of α-Bromo *N*-Sulfonylpyrrolidinones

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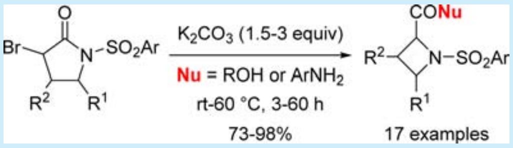
Supporting Information

ABSTRACT: A simple and robust *one-pot* nucleophilic addition−ring contraction of α-bromo *N*-sulfonylpyrrolidinones has been achieved toward α-carbonylated *N*-sulfonylazetidines. In the presence of potassium carbonate, various nucleophiles, such as alcohols, phenols or anilines, have been efficiently incorporated into the azetidine derivatives. Moreover, the α-bromopyrrolidinone precursors could be selectively obtained in good yields by monobromination of cheap and easily available *N*-sulfonyl-2-pyrrolidinone derivatives.



Azetidines have received little interest compared to their three- or five-membered homologues, but a significant reversal has occurred since the 90s, probably due to the isolation of various natural products bearing this motif and to the roles they exhibit in a variety of pharmacologically active compounds (Figure 1).[1]

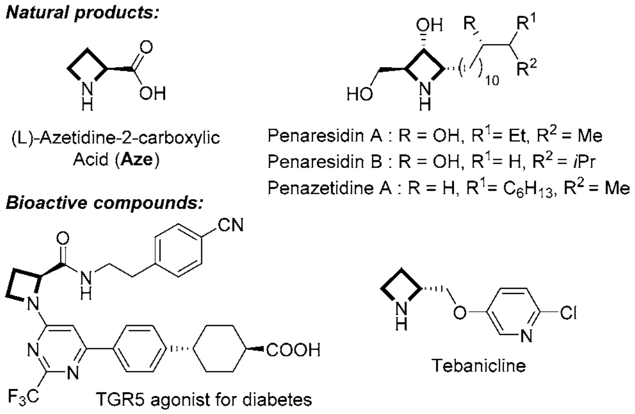


Figure 1. Selected natural products or non-natural bioactive compounds containing the azetidine motif.

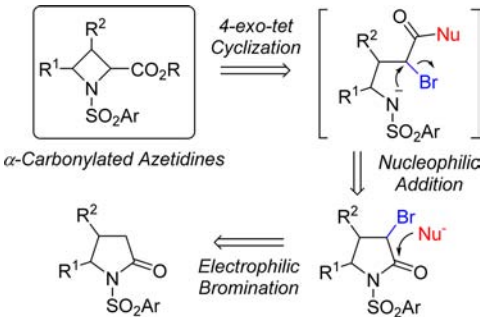
Analogue to proline, the azetidine-2-carboxylic acid (Aze) and its reduced form are often present in bioactive compounds. For example, naturally occurring antibiotic polyoxins[2] and siderophore mugineic acid[3] contain the Aze motif, while sphingosine-type penaresidin derivatives[4] and penazetidine[5] contain its reduced form (Figure 1, top). Aze can also be found in HCV NS3 protease inhibitors,[6] as well as in agonists of Takeda G-protein receptor 5 (TGR5) associated with diabetes, metabolic syndrome, and autoimmune disease (Figure 1, bottom).[7] The corresponding azetidinyl methanol derivatives, such as tebanicline or the improved version,[8] have been, e.g., introduced as neuronal nicotinic acetylcholine receptor (nAChR) selective agonists for treating central nervous system disorders, especially depression.

The incorporation of azetidines, especially Aze derivatives, in numerous drug-like compounds has stimulated a strong synthetic demand for convenient access to such small heterocycles. Few routes have been set up, among which ring closures involving intramolecular alkylation of the amine by nucleophilic substitution remain the most common.[1,9] Nevertheless, reliable routes to such a motif remain elusive.

Involved in the study of metal-catalyzed rearrangements of certain heterocycle derivatives,[10] we needed to develop a rapid, reliable, and scalable synthesis of azetidines. Besides a general synthesis of *N*-aryl azetidines,[11] we also looked for access to Aze derivatives, and we report here the development of a *two-step* sequence allowing the scalable synthesis of substituted α-carbonylated azetidines from cheap or easily available *N*-protected pyrrolidinones (Scheme 1).

Although ring expansion of azetidines to pyrrolidines is known,[12] it looks like the reverse ring contraction has been so far unexplored. We thus reasoned that α-bromo 2-pyrrolidinones,

Scheme 1. Planned Synthesis of α-Carbonylated *N*-Sulfonylazetidine Derivatives



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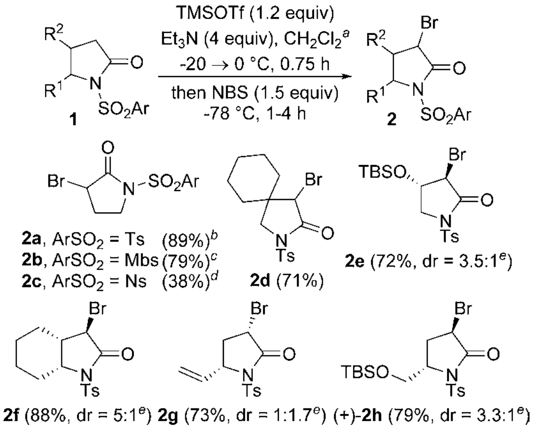
readily obtained by bromination of pyrrolidinones, could be opened by nucleophiles leading to α-bromocarbonyl derivatives bearing a γ-amide anion, which would directly cyclize by displacing the α-bromide via a S_N2 process (Scheme 1). This would lead to the formation of α-carbonylated azetidines through a *one-pot* ring opening–ring closing reaction in the presence of nucleophiles. In order to enhance the electrophilicity of the amide and to get some stabilization of the intermediate anion, we selected *N*-sulfonyl derivatives as starting materials.

Prior to embarking on the azetidine formation by ring contraction, our efforts focused on the selective monobromination of *N*-sulfonylpyrrolidinones **1**, easily available from cheap 2-pyrrolidinone derivatives. With almost no precedent in the literature for such type of compounds,[13] we started with classical conditions using strong bases such as LDA or LiHMDS and *N*-bromosuccinimide (NBS) as electrophilic bromine source. Under such conditions, we always obtained the monobrominated products **2** in good to modest yields (see Supporting Information), but along with significant amount of dibrominated compounds ($\geq$5%). Besides diminishing the yields, this presence greatly complicated the purification step. To tackle this problem, we thought that in situ generated silyl enol ether in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and triethylamine, followed by NBS trapping, would selectively afford the expected α-monobromo sulfonylpyrrolidinones **2**.[14] Indeed, by carefully adjusting reaction time and temperature (see Supporting Information), we were able to form only the monobrominated compounds **2a**–**h** with excellent yields, even on large scale (up to 30 g) starting from various *N*-sulfonylpyrrolidinones **1** (Scheme 2). Moreover, interesting diastereomeric ratios in favor of the trans isomers were obtained for substrates **2e,f,h**. It is worth mentioning that all compounds were crystalline solids and that reported yields were based on a single recrystallization of the crude reaction.

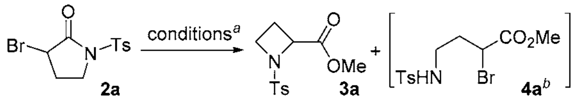
Scheme 2. Synthesis of α-Bromo *N*-Sulfonylpyrrolidinones 2



[a]C = 0,25 M; [b]Reaction run on 0.1 mol; [c]Mbs = *p*-methoxybenzenesulfonyl; [d] Ns = *p*-nitrobenzenesulfonyl; [e] The major diastereoisomer is represented

We then screened various conditions to efficiently produce *N*-sulfonylazetidines with the unsubstituted α-bromo *N*-tosylpyrrolidinone **2a** as the model (Table 1). Rewardingly, the reaction with sodium methoxide (1.3 equiv) in methanol at 60 °C provided *N*-tosyl azetidine **3a** in high yield (Table 1, entry 1), along with traces of the linear intermediate **4a**. Increasing the amount of base did not improve the yield (Table 1, entry 2), but the reaction performed in acetonitrile with an excess of MeONa gave complete conversion within 2 h at 80 °C, leading to **3a** in 90% yield (Table 1, entry 3). Interestingly, less basic conditions, i.e., excess of potassium carbonate in acetonitrile–methanol, quantitatively gave **3a** (Table 1, entry 5), the sodium or cesium analogues being either not or too reactive (Table 1, entries 4 and 6 vs 5). As suspected, the reaction performed at room temperature was slightly less effective, providing some remaining intermediate (Table 1, entry 7). Decreasing the nucleophile amount (5 equiv MeOH) did not significantly affect the yield, but a longer reaction time was needed (Table 1, entry 8 vs 5). Various other mild bases, such as triethylamine, 4-(dimethylamino)-pyridine, pyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene were also examined, but only the latter afforded complete conversion along with excellent yield, even at room temperature (Table 1, entry 9). Nevertheless, we selected as best conditions the use of K_2CO_3, as base, since the azetidine **3a** can be obtained pure by simple filtration (Table 1, entry 5 vs 9). Control experiment confirmed that the presence of base was essential for such transformation (Table 1, entry 10).

Table 1. Screening of Reaction Conditions for the Formation of α-Methyl *N*-Tosylazetidine Carboxylate 3a from 2a

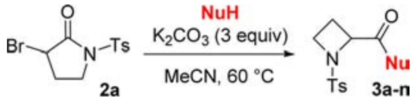


entry	base (equiv)	solvent	temp (°C)	time (h)	yield (%)
1	MeONa (1.3)	MeOH	60	16	85[b]
2	MeONa (2)	MeOH	60	16	85[b]
3	MeONa (3)	MeCN	80	2	90
4	Na_2CO_3 (3)	MeCN/MeOH (9:1)	60	16	c
5	**K_2CO_3 (3)**	**MeCN/MeOH (9:1)**	**60**	**3**	**97**
6	Cs_2CO_3 (3)	MeCN/MeOH (9:1)	60	3	74[b]
7	K_2CO_3 (3)	MeCN/MeOH (9:1)	rt	4	88[b]
8	K_2CO_3 (3)	MeCN/MeOH (20:1)	60	16	95
9	DBU[d] (1.5)	MeCN/MeOH (9:1)	rt	2	96
10		MeCN/MeOH (9:1)	60	16	c

[a]C = 0.2 mol/L. [b]Intermediate **4a** was observed as trace (<5%) on the crude ^1H NMR spectrum. [c]No conversion. [d]1,8-Diazabicyclo[5.4.0]-undec-7-ene.

With these conditions in hand, we then examined the scale-up of the reaction and the possibility of using other nucleophiles (Table 2). Performed on a multigram scale (>15 g of **2a**) with 10 equiv of methanol, the reaction smoothly proceeded without loss of yield (Table 2, entry 1 vs Table 1, entry 5). Interestingly, various other primary alcohols, such as pentyl, benzyl, allyl, or propargyl alcohols reacted very well, leading to the corresponding α-azetidinyl esters **3b**–**h** in good to excellent yields (Table 2, entries 2–7). Phenol was also well tolerated as nucleophile in the ring contraction (Table 2, entry 8). However, more hindered alcohols, such as isopropanol, were less effective in promoting the ring contraction, and only low conversion was achieved even after 24 h (Table 2, entry 9). Amines or thiols were then screened as potential nucleophiles. With benzyl amine only a small amount of the expected *N*-tosylazetidine **3j** was formed along with degradation products (Table 2, entry 10). Interestingly, switching to aniline derivatives restored high yields despite increased reaction times (Table 2, entries 11–13). With benzyl

Table 2. Screening of Nucleophiles in the Ring Contraction of α-Bromo *N*-Tosylpyrrolidinone 2a



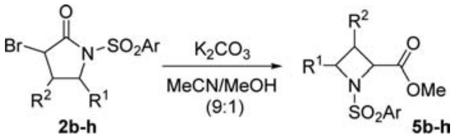
entry	nucleophile (10 equiv)	azetidine	time (h)	yield (%)
1	methanol	**3a**	5	96[a]
2	pentanol	**3b**	7	92
3	benzyl alcohol	**3c**	4	93
4	allyl alcohol	**3d**	4	96
5	propargyl alcohol	**3e**	4	82
6		**3f**	3	80
7		**3g**	36[b]	73
8	phenol	**3h**	2	81
9	isopropyl alcohol	**3i**	24	30[c]
10	benzyl amine	**3j**	4	10[c,d]
11	aniline	**3k**	16	75
12	*p*MeO-aniline	**3l**	16	90
13	*p*F-aniline	**3m**	16	77
14	benzyl thiol	**3n**	16	-[e]

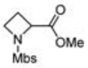
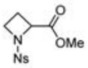
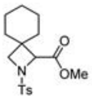
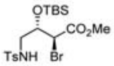
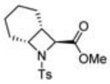
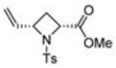
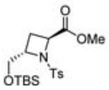
[a] Performed on 0.05 mol. [b] Reaction run at room temperature to avoid degradation. [c] Estimated yield by ^{1}H NMR spectroscopy. [d] Degradation occurs leading to unidentified byproducts. [e] Only debrominated *N*-tosylpyrrolidinone was isolated (85%).

thiol as nucleophile, only dehalogenation of the starting α-bromo pyrrolidinone was observed (Table 2, entry 14).[15]

The reaction scope was then briefly explored by submitting various substituted α-bromo *N*-sulfonylpyrrolidinones **2b**−**h** (see Scheme 2) to our selected best conditions with methanol as nucleophile (Table 3). Other sulfonyl groups, such as *p*-methoxybenzenesulfonyl or nosyl, which are more easily removable than the tosyl group,[16] were perfectly compatible with our conditions, as showed by the quantitative formation of the azetidines **5b** and **5c**, respectively, from substrate **2b** and **2c** at 60 °C using 3 equiv of K_2CO_3 (Table 3, entries 1 and 2). The ring substitution (R^1 and R^2, Scheme 1) was then evaluated with compounds **2d**−**h**. Despite high steric bulk, the formation of the 2-azaspiro[3.5]nonane derivative **5d** from compound **2d** was very efficient (Table 3, entry 3). However, the ring contraction of pure *trans*-**2e** did not afford the expected azetidine at 60 °C due to degradation, while the open intermediate **4e** could be isolated at room temperature using a lower amount of K_2CO_3 (Table 3, entry 4 vs 5). In contrast, under the same milder conditions, the bicyclic pure *trans*-**2f** gave the expected azetidine **5f** in high yields (Table 3, entry 6). Keeping these mild reaction conditions avoiding degradation, the azetidines **5g** and the homochiral *trans*-**5h** were obtained in high yields from, respectively, the inseparable mixture of *trans*- and *cis*-**2g** and the homochiral pyrrolidinone derivative *trans*-**2h**, synthesized in few steps from L-pyroglutamic acid (Table 3, entries 7 and 8). It is worth noting that erosion (from 1:0 to 2:1 or 7.3:1) or improvement (from 1:1.7 to 1:3.7) in diastereomeric ratios compared to the starting materials was observed depending on the starting pyrrolidinones.

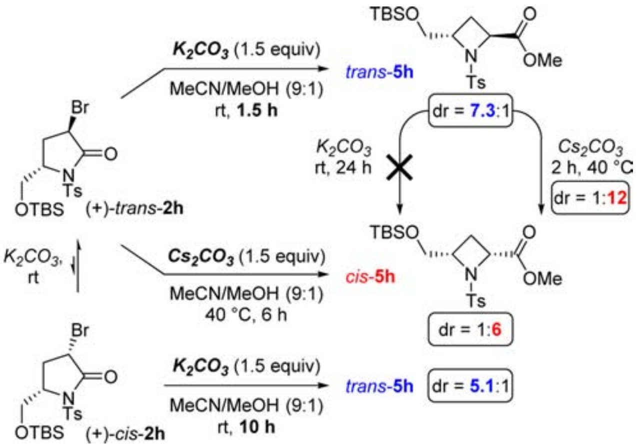
Table 3. Synthesis of Various α-Methylester *N*-Sulfonylazetidines 5



entry	pyrroli-dinone	K_2CO_3 equiv	temp (°C)	time (h)	azetidine		yield, dr[a]
1	**2b**	3	60	3		**5b**	98
2	**2c**	3	60	3		**5c**	98
3	**2d**	3	60	3		**5d**	95
4	*trans*-**2e**	3	60	3		**4e**	19[b]
5	*trans*-**2e**	1.5	rt	3			71 1:0
6	*trans*-**2f**	1.5	rt	60		**5f**	87 2:1
7	**2g**[c]	1.5	rt	4		**5g**	88 1:3.7
8	*trans*-**2h**	1.5	rt	2		**5h**	96 7.3:1

[a] Isolated yield in % and diastereomeric ratio of trans and cis products. [b] Degradation occurs leading to unidentified byproducts. [c] Reaction run of an inseparable 1:1.7 mixture of trans and cis stereoisomers.

Scheme 3. Diastereoselectivity Studies on the Rearrangement of Enantiopure *trans*-2h and *cis*-2h



To better understand the stereochemical outcome of the reaction, we studied the effect of the base used in the rearrangement of **2h** (Scheme 3). Starting from a mixture of the two diastereomers, enriched in cis isomer (trans/cis = 1:1.6), we observed the slow epimerization (compared to the ring contraction) of the α-bromo sulfonylpyrrolidinone in favor of the trans-product in the presence of K_2CO_3 at room temperature *without* nucleophile (trans/cis = 3.1:1 after 4 h of stirring). However, under the same conditions, the azetidine product **5h** did not epimerize even after a prolonged contact time. We then independently engaged the pure *trans*-**2h** or *cis*-**2h** diastereomers in the ring contraction reaction with an excess of methanol. As expected for a S_N2 process, the *trans*-**2h** afforded the *trans*-**5h** in an excellent 7.3:1 diastereomeric ratio (dr) with 1.5 equiv of K_2CO_3 in *only 1.5 h*. In contrast, the pure *cis*-**2h** furnished the *trans*-azetidine as the major isomer (5.1:1), but *after 10 h* of reaction. This result revealed that the ring contraction is much faster for the substrate *trans*-**2h** and that the cis isomer evolved after epimerization to its trans isomer. Surprisingly, with cesium carbonate at 40 °C for 6 h, the *trans*-**2h** afforded the *cis*-**5h** with a 1:6 dr. Suspecting product epimerization, we performed a control experiment that effectively demonstrated that the azetidine *trans*-**5h** (7.3:1 dr) isomerized in such conditions, giving the more stable *cis*-**5h** in a 1:12 ratio. It is worth noting that in all reactions quantitative conversion in favor of azetidines **5h** was observed by ^1H NMR monitoring.

In conclusion, we have developed a short and very efficient *three-step* sequence toward the formation of α-carbonylated *N*-sulfonylazetidines from cheap 2-pyrrolidinones. As a key step, the highly efficient one-pot nucleophilic addition−ring contraction reaction tolerated various alcohols or anilines as nucleophiles. Starting from substituted α-bromo *N*-sulfonylpyrrolidinones, both diasteroisomers can be obtained in an excellent ratio depending on the base used in the ring contraction. Further investigations to apply these azetidine building blocks in total synthesis are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete experimental procedures, characterization data, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Dejaegher, Y.; Kuz'menok, N. M.; Zvonok, A. M.; De Kimpe, N. *Chem. Rev.* **2002**, *102*, 29. (b) Couty, F.; Evano, G.; Prim, D. *Mini-Rev. Org. Chem.* **2004**, *1*, 133. (c) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988.

(2) Emmer, G. *Tetrahedron* **1992**, *48*, 7165.

(3) Seo, G.; Akimoto, Y.; Hamashima, H.; Masuda, K.; Shiojima, K.; Sakuma, C.; Sasatsu, M.; Arai, T. *Microbios* **2000**, *101*, 105.

(4) Alvi, K. A.; Jaspars, M.; Crews, P. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2447.

(5) Kobayashi, J.; Cheng, J.-F.; Ishibashi, M.; Wälchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1135.

(6) Bondada, L.; Rondla, R.; Pradere, U.; Liu, P.; Li, C.; Bobeck, D.; McBrayer, T.; Tharnish, P.; Courcambeck, J.; Halfon, P.; Whitaker, T.; Amblard, F.; Coats, S. J.; Schinazi, R. F. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6325.

(7) Phillips, D.; Gao, W.; Yang, Y.; Zhang, G.; Lerario, I. K.; Lau, T. L.; Jiang, J.; Wang, X.; Nguyen, D. G.; Bhat, B. G.; Trotter, C.; Sullivan, H.; Welzel, G.; Landry, J.; Chen, Y.; Joseph, S. B.; Li, C.; Gordon, W. P.; Richmond, W.; Johnson, K.; Bretz, A.; Bursulaya, B.; Pan, S.; McNamara, P.; Seidel, H. M. *J. Med. Chem.* **2014**, *57*, 3263.

(8) (a) Zhang, H.-K.; Yu, L.-F.; Eaton, J. B.; Whiteaker, P.; Onajole, O. K.; Hanania, T.; Brunner, D.; Lukas, R. J.; Kozikowski, A. P. *J. Med. Chem.* **2013**, *56*, 5495. (b) Yu, L.-F.; Eaton, J. B.; Fedolak, A.; Zhang, H.-K.; Hanania, T.; Brunner, D.; Lukas, R. J.; Kozikowski, A. P. *J. Med. Chem.* **2012**, *55*, 9998.

(9) For a review on Aze synthesis, see: Couty, F.; Evano, G. *Org. Prep. Proc. Int.* **2006**, *38*, 427.

(10) Kern, N.; Hoffmann, M.; Blanc, A.; Weibel, J.-M.; Pale, P. *Org. Lett.* **2013**, *15*, 836.

(11) Kern, N.; Hoffmann, M.; Weibel, J.-M.; Pale, P.; Blanc, A. *Tetrahedron* **2014**, *70*, 5519.

(12) For a review, see: Couty, F.; Evano, G. *Synlett* **2009**, 3053.

(13) For the sole known example, although performed on acyclic compounds, see: Otaka, A.; Mitsuyama, E.; Kinoshita, T.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2000**, *65*, 4888.

(14) King, A. O.; Anderson, R. K.; Shuman, R. F.; Karady, S.; Abramson, N. L.; Douglas, A. W. *J. Org. Chem.* **1993**, *58*, 3384.

(15) For dehalogenation of α-halogeno ketones, see: Fuji, K.; Node, M.; Kawabata, T.; Fujimoto, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1043.

(16) For deprotection of α-carbonylated *N*-tosyl azetidines, see: (a) Burtoloso, A. C. B.; Correia, C. R. D. *Tetrahedron* **2008**, *64*, 9928. (b) Burtoloso, A. C. B.; Correia, C. R. D. *Tetrahedron Lett.* **2004**, *45*, 3355. For other related deprotections, see: (c) Ohshita, K.; Ishiyama, H.; Takahashi, Y.; Ito, J.; Mikami, Y.; Kobayashi, J. I. *Bioorg. Med. Chem.* **2007**, *15*, 4910. (d) Takikawa, H.; Maeda, T.; Mori, K. *Tetrahedron Lett.* **1995**, *36*, 7689.