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Design, Synthesis, and Characterization of SO_2-Containing Azabicyclo[3.*n*.1]alkanes: Promising Building Blocks for Drug Discovery

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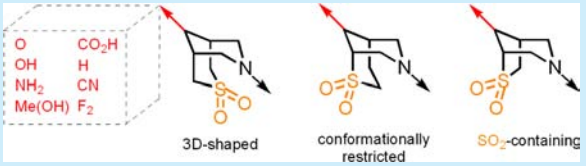
Supporting Information

ABSTRACT: A set of novel SO_2-containing azabicyclo[3.*n*.1]-alkanes has been synthesized by the double-Mannich annulation of of the corresponding monocyclic S-ketones. These compounds have been rationally designed as 3D-shaped, conformationally restricted SO_2-containing building blocks for drug discovery.



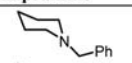
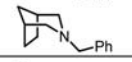
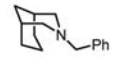
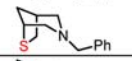
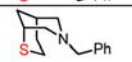
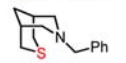
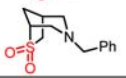
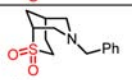
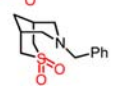
Chemical strategies in drug discovery have been changing rapidly. During the past decade, the terms "scaffold hopping",[1] "escape the flatland,"[2] and "conformational restriction"[3] have been introduced and have already found huge practical applications. It is not surprising, therefore, that currently medicinal chemists look more and more for novel, unique, 3D-shaped, conformationally restricted building blocks.[4,5]

The fragment of piperidine has been playing a role in drug discovery for a long time.[6] Especially popular are 1,4-disubstituted piperidines.[6] Therefore, we recently synthesized their bicyclic conformationally restricted analogues.[7] Subsequently, however, we realized that these structures had high lipophilicity (Table 1, entry 2).[8] Therefore, in this work, we have designed and synthesized novel SO_2-containing building blocks with reduced lipophilicity.

To adjust lipophilicity, we selected the intrinsically hydrophilic SO_2-group that might also interact with a receptor, thereby improving activity/selectivity of the ligand.[9] Recently Li, Rogers-Evans, and Carreira performed a work on SO_2-containing azaspirocylic building blocks.[9a,b]

To synthesize the designed structures, we first attempted the double-Mannich annulation of ketone **1** with reagent **2**[10] to give, after optimization, compound **3** in 64% yield (Scheme 1). The elaborated procedure was scalable, and 90 g of the product was obtained in a single run. Indeed, ketone **3** was previously comprehensively described in the literature by a standard Mannich reaction of **1**, however, with yields of only 38−48%.[11] Oxidation of **3** with H_2O_2 in acetic acid afforded the target core **4** in 58% yield. The developed two-step procedure to novel amino ketone **4** was reproducible and scalable, and we were able to easily obtain 20 g of the product in one synthesis run. Next, we performed the Wolff−Kishner reduction of ketone **4** into compound **5** in 91% yield (Scheme 1). Cleavage of the *N*-Bn

Table 1. Experimental Parameters

Entry		Compound	LogD(7.4)[a]	CL_{int}[b]	Sol(7.4)[c]
0		**Imipramine**	-	164	-
1	**42**		1.7	1	827
	39		2.9	33	695
2	**40**		4.4	21	*n.d.*
	34		2.2	250	752
3	**28**		3.6	66	780
	41		3.0	*n.d.*	734
	35		1.4	17	601
4	**29**		2.1	49	593
	5		1.6	19	891

[a]Experimental *n*-octanol/water distribution coefficient (logD) at pH 7.4. [b]Intrinsic clearance rate CL_{int} (mg/(min·μL)) measured in mouse liver microsomes. [c]Thermodynamic aqueous solubility in 50 mM phosphate buffer (pH 7.4).

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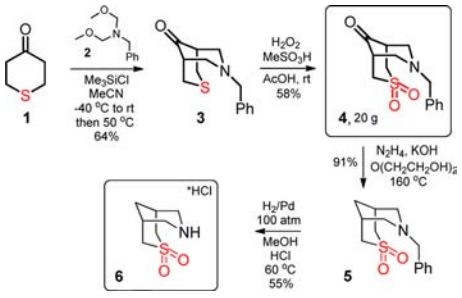
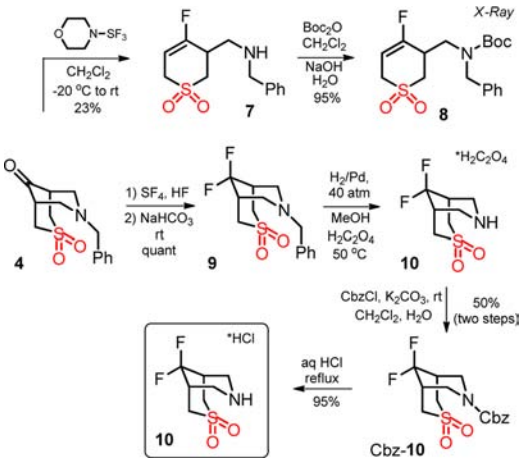
Scheme 1. Synthesis of Ketone 4 and Amine 6



group in **5** by hydrogenation over Pd/C accomplished the synthesis of unique SO_2-amine **6**.

We next challenged fluorination of ketone **4** with Morph-DAST. Unexpectedly, along with many unidentified products, compound **7** was isolated in 23% yield (Scheme 2). To the best of

Scheme 2. Synthesis of Amine 10·HCl and Unexpected Product 7



our knowledge, this is a novel type of DAST-like mediated rearrangements.[12] The structure of **7** was proven by X-ray crystallographic analysis of the *N*-Boc derivative **8** (Figure 1).

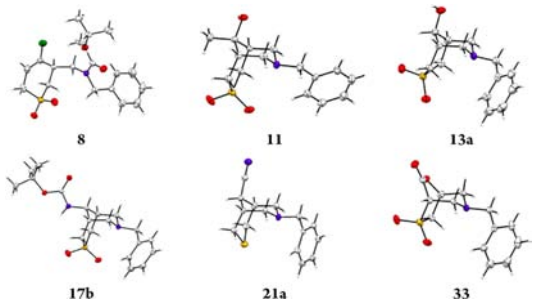
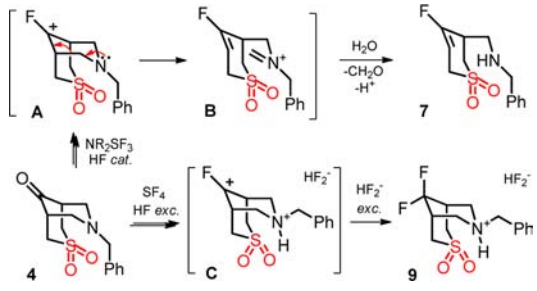


Figure 1. X-ray structure of amines **8**, **11**, **13a**, **17b**, **21a**, and **33**.[15]

Fluorination of **4** with SF_4/HF,[13] however, provided the desired bicycle **9** quantitatively. Standard cleavage of the *N*-Bn group in **9** by hydrogenation over Pd/C as the catalyst afforded the crude fluorinated amine **10**·$H_2C_2O_4$ (ca. 80% purity). We next converted it into the corresponding derivative Cbz-**10** that was easily purified by standard column chromatography. Subsequent acidic hydrolysis of the carbamate group afforded the pure fluorinated amine **10**·HCl.[14]

Proposed mechanism for the formation of compound **7** is depicted in Scheme 3. Presumably, the strained nature of bicyclic

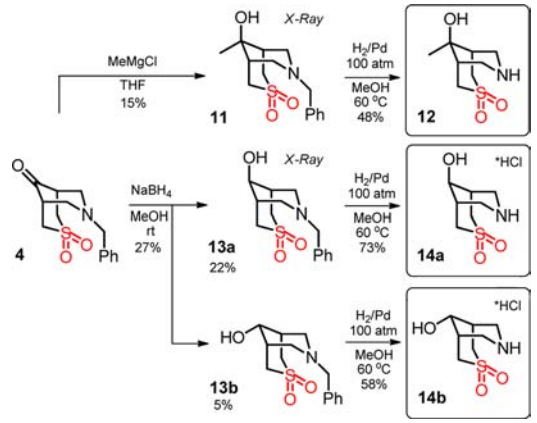
Scheme 3. Proposed Mechanism for the Formation of 7 and 9



skeleton in **A** drives this reaction toward the less strained monocycle **B**. An excess of HF (SF_4/HF), however, protonates the N atom in **A** (**C**), thus preventing the above rearrangement. Additionally, an excess of HF_2^- anion quenches the formed intermediate **C** rapidly.

Next, we intended to synthesize diverse SO_2-containing amino alcohols. After addition of MeMgCl to ketone **4**, we isolated **11** as the single isomer, however, in 15% yield (Scheme 4). Despite the

Scheme 4. Synthesis of Amino Alcohols 12, 14a, and 14b



low yield, the procedure was reproducible and allowed us to obtain gram quantities of alcohol **11** (1.3 g). Reduction of ketone **4** with $NaBH_4$ gave two isomers **13a**/**13b** that were easily separated by column chromatography. Stereochemistry of **11** and **13a** was proven by X-ray crystallographic analysis (Figure 1). Pd-catalyzed hydrogenative cleavage of the *N*-Bn group in **11**, **13a**, and **13b** afforded the needed amino alcohols **12**, **14a**, and **14b**, respectively.

Synthesis of diverse SO_2-containing monoprotected diamines was challenged next (Scheme 5). Reaction of ketone **4** with hydroxylamine smoothly afforded oxime **15**. Reduction of **15** with AlH_3 produced two *N*-Bn-protected isomeric amines **16a**/**16b** that were separated by column chromatography. Boc protection of the primary amino group (**17a**/**17b**) followed by cleavage of the *N*-Bn group gave diamines **18a**/**18b** with the free secondary amino function. Stereochemistry of the synthesized compounds was proven by X-ray crystallographic analysis of isomer **17b** (Figure 1). On the other hand, Schmidt reaction of ketone **4** easily gave amide **19** that was subsequently reduced into the *N*-Bn-protected diamine **20**.

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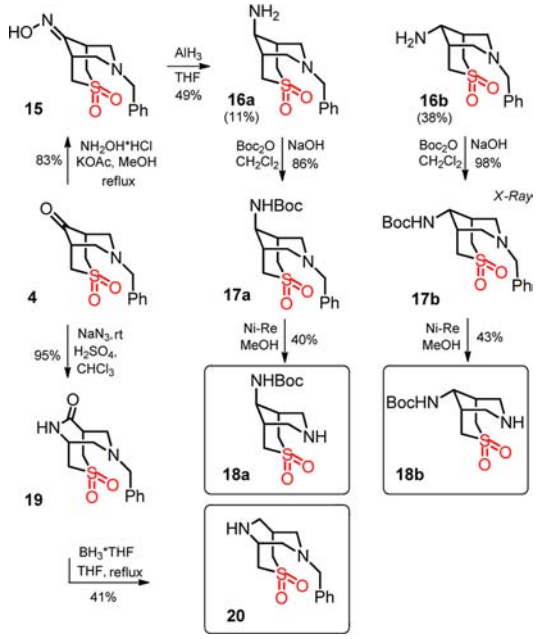
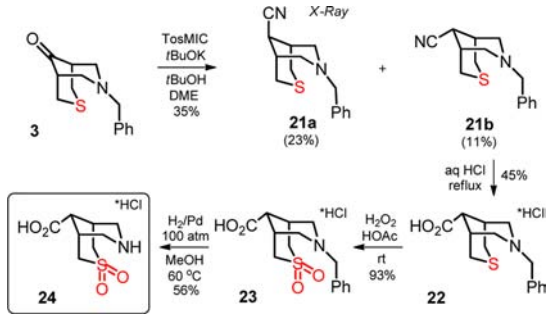
Scheme 5. Synthesis of Monoprotected Diamines 18a, 18b, and 20



Preparation of the corresponding SO_2-containing amino acid was further performed (Scheme 6). Although reaction of ketone

Scheme 6. Synthesis of Amino Acid 24

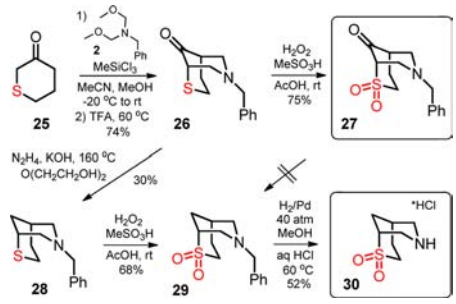


4 with TosMIC gave a complex mixture, we managed to realize the corresponding transformation with ketone **3**; two isomeric products were synthesized, **21a** (23%, 3.0 g, X-ray, Figure 1) and **21b** (12%, 1.6 g). Again, in spite of the low synthesis yield, the procedure allowed us to obtain gram quantities of products. Hydrolysis of the isomer **21b** provided *N*-Bn-amino acid **22** in 45% yield. Oxidation of the S atom with H_2O_2 in acetic acid gave *N*-Bn-amino acid **23**. Finally, cleavage of the *N*-Bn group by Pd-catalyzed hydrogenation afforded the needed SO_2-amino acid **24**.

Having demonstrated the key transformations of ketone **4** toward several attractive SO_2-containing building blocks, we decided to also elaborate the synthesis of its closest analogues and to perform the representative transformations with them.

In fact, after extensive optimization, we were able to synthesize *S*-ketone **26** from **25** (Scheme 7). Under the reaction conditions used to prepare ketone **3**, only a complex mixture was obtained. Replacing Me_3SiCl with $MeSiCl_3$, however, led to a mixture of products (according to LC−MS: ketone, ketal, dimers) that after prolonged acidic hydrolysis gave the needed ketone **26** in 74% yield. Oxidation of **26** with H_2O_2 provided SO_2-ketone **27**. Unfortunately, Wolff−Kishner reduction of ketone **27** was

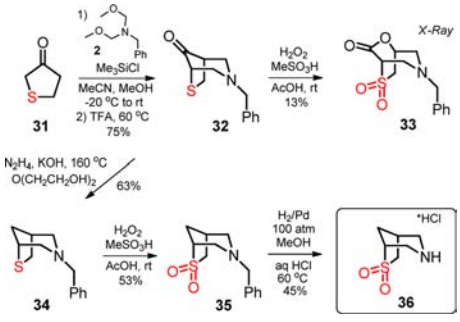
Scheme 7. Synthesis of Ketone 27 and Amine 30



ineffective; therefore, we first synthesized *S*-ketone **28** followed by its oxidation with H_2O_2 (**29**). Cleavage of the *N*-Bn group gave the target SO_2-amine **30**, an isomer of **6**.

Reaction of ketone **31** with reagent **2** under the conditions used to synthesize **3** afforded ketal that after prolonged hydrolysis with TFA gave ketone **32** in a good yield of 75% (Scheme 8). Very unexpectedly, however, oxidation of ketone **32**

Scheme 8. Synthesis of Amine 36



with H_2O_2 afforded the SO_2-containing Baeyer−Villiger rearrangement product **33** (X-ray, Figure 1). Presumably, in strict contrast to ketone **26**, the strained bicyclic skeleton in **32** facilitated the additional Baeyer−Villiger oxidation toward the less strained bicyclic ester **33**. Therefore, to synthesize the corresponding SO_2-core, we first performed Wolff−Kishner reduction of **32** (amine **34**) followed by oxidation with H_2O_2 toward the needed compound **35**. Cleavage of *N*-Bn group gave the target SO_2-amine **36**, a homologue of **6**.

Indeed, we believe that apart from the synthesized amines **30** and **36**, ketones **26**, **27**, and **32** can also be used to perform a transformation similar to those already realized with ketone **4** (diamines, amino acids, amino alcohols, etc.).

After the synthesis of the target SO_2-containing building blocks, we determined their physicochemical characteristics. We first measured the experimental logD (pH = 7.4) values of the *N*-Bn-protected C-, S-, and SO_2-amines and compared data with the parent piperidine derivative **42** (Table 1). Several conclusions can be made from these experiments: (a) conformationally restricted derivatives of piperidine compounds **39** and **40** (entry 2) were significantly more lipophilic than **42** (entry 1); (b) incorporation of the S atom, **34**, **28**, **41**, slightly reduced lipophilicity (entry 3); and (c) replacing the C atom with an SO_2-fragment led to conformationally restricted cores **5**, **29**, and **35** without any significant change in lipophilicity compared with **42** (entry 4). Moreover, compounds **5** and **35** were even less lipophilic than the parent **42**.

Next, metabolic stability of the compounds in mouse liver microsomes (CL_{int}) was measured: (a) more lipophilic

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compounds **39** and **40** were less stable than **42** (entries 1 and 2); (b) incorporation of the S atom (**34**, **28**, and **41**) drastically reduced the metabolic stability (entry 3); but (c) SO_2-derivatives **5** and **35** (and to some extent **29**, entry 4) were stable. Finally, water solubility of the compounds at pH 7.4 was studied: (a) more lipophilic compound **39** had lower solubility than the model **42** (entries 1 and 2); (b) incorporation of the S atom slightly improved the solubility; (c) the SO_2-group significantly increased solubility of **5** (even more soluble than **42**) but decreased that of **29** and **35**. To rationalize these data, one must keep in mind that the SO_2 group has a dual effect on the solubility at pH 7.4: (a) it decreases basicity of the N atom (↓ solubility) but simultaneously (b) increases intrinsic hydrophilicity (↑ solubility). In compounds **29** and **34**, the SO_2-group is distanced from the N atom by three single bonds, while in **5** it is distanced by four. As a result, in **5**, effect b is larger than effect a, while in **29** and **34** it is smaller.

In summary, we have designed and synthesized the novel SO_2-containing conformationally restricted analogues of piperidine. All syntheses commenced from cheap available starting materials and allowed preparation of the target compounds in gram quantities. All SO_2-compounds were chemically and metabolically stable in vitro and possessed appropriate lipophilicity and water solubility. Especially attractive is the core **5**; it is less lipophilic and more soluble than the parent model **42**.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, copies of NMR spectra, and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): The authors are employees of "Enamine, Ltd." The compounds described in this work are commercially already available at Enamine Ltd.

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