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A Novel Heterocyclic Scaffold Formed by Ring Expansion of a Cyclic Sulfone to Sulfonamides

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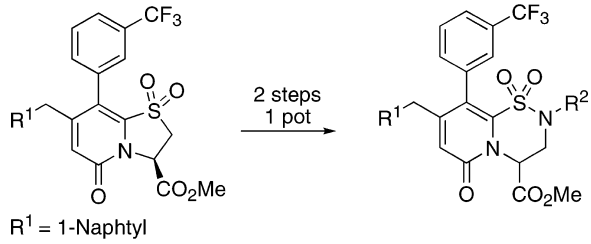
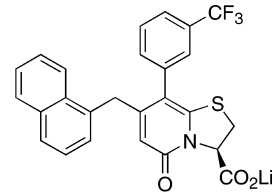
ABSTRACT



A novel heterocyclic scaffold with a peptidomimetic backbone structure has been synthesized. The scaffold is formed by insertion of primary amines into a cyclic sulfone to give the corresponding ring-expanded sulfonamides. By varying the amine component, a series of potentially biologically interesting compounds has been synthesized.

Biologically relevant molecules with ring-fused 2-pyridones as central fragments are found both in nature[1] and as peptide backbone mimetics.[2] We have previously described the synthesis of compound **1** (Figure 1) that inhibits aggregation of an Alzheimer's peptide ($A\beta_{1-40}$) into amyloids.[3] The same compound also inhibits formation of curli, a functional amyloid that is a virulence factor in Gram-negative bacteria.[4]

The central bicyclic 2-pyridone core of **1** has two substituents that can be indepentently varied,[5] and the scaffold can also be further reacted to form ring-fused pyrazoles, giving a rigid tricyclic structure with a peptidomimetic backbone.[6]



1

Figure 1. A known inhibitor of both curli and Alzheimer's amyloid formation.

Now we report the synthesis of a novel scaffold with potential peptidomimetic properties by modification of compound **1**. This scaffold holds an additional substituent introduced through a ring-expanding transformation, converting a cyclic sulfone to sulfonamides.

In the work with analogues of **1**, the corresponding sulfone **4** was prepared (Scheme 1).

(1) (a) Liu, J. S.; Zhu, Y. L.; Yu, C. M.; Zhou, Y. Z.; Han, Y. Y.; Wu, F. W.; Qi, B. F. *Can. J. Chem.* **1986**, *64*, 837–839. (b) Misra, R.; Pandey, R. C.; Silverton, J. V. *J. Am. Chem. Soc.* **1982**, *104*, 4478–4479. (c) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888–3890.

(2) (a) Dragovich, P. S.; Prins, T. J.; Zhou, R.; Johnson, T. O.; Brown, E. L.; Maldonado, F. C.; Fuhrman, S. A.; Zalman, L. S.; Patick, A. K.; Matthews, D. A.; Hou, X.; Meador, J. W.; Ferre, R. A.; Worland, S. T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 733–738. (b) Svensson, A.; Larsson, A.; Emtenäs, H.; Hedenström, M.; Fex, T.; Hultgren, S. J.; Pinkner, J. S.; Almqvist, F.; Kihlberg, J. *ChemBioChem* **2001**, *12*, 915–918. (c) Zhang, X. J.; Schmitt, A. C.; Decicco, C. P. *Tetrahedron Lett.* **2002**, *43*, 9663–9666. (d) Åberg, V.; Sellstedt, M.; Hedenström, M.; Pinkner, J. S.; Hultgren, S. J.; Almqvist, F. *Bioorg. Med. Chem.* **2006**, *14*, 7563–7581.

(3) Åberg, V.; Norman, F.; Chorell, E.; Westermark, A.; Olofsson, A.; Sauer-Eriksson, A. E.; Almqvist, F. *Org. Biomol. Chem.* **2005**, *3*, 2817–2823.

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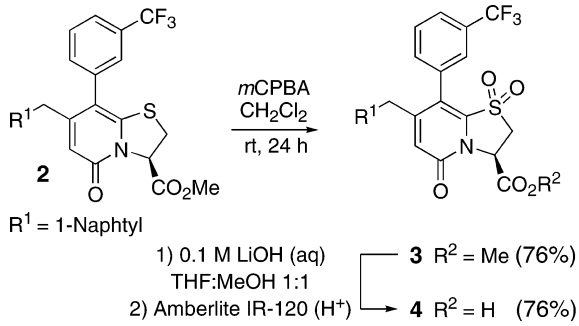
Scheme 1. Oxidation of **1**



It was curiously noticed that, unlike **2**, the stereocenter of **3** was completely epimerized during basic hydrolysis of the methyl ester. This could suggest reversible elimination of the sulfone under basic conditions, and indeed, in the presence of benzyl amine with sodium methoxide as base, the conjugate addition product **5** was formed (Figure 2).

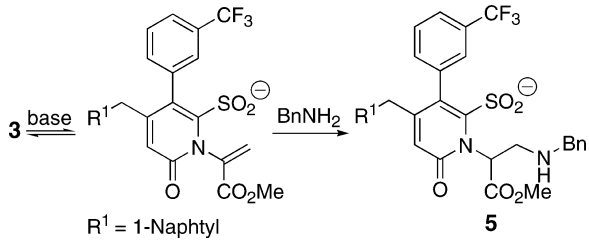


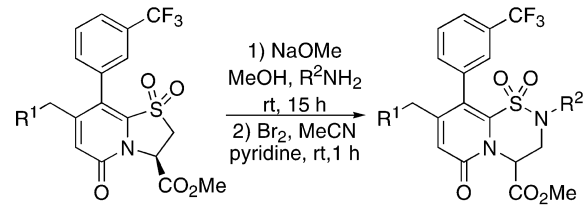
Figure 2. Proposed intermediates formed from compound **3** under basic conditions in presence of benzyl amine.

Although somewhat unstable, with loss of sulfur dioxide as primary decomposition product, the conjugate acid of **5** could be isolated in 53% yield.

Sulfonamides are common structural features in drugs,[7] and compound **5** was immediately recognized as a potential precursor to a cyclic sulfonamide. Oxidative coupling of sulfinic acids and amines using potassium ferricyanide has been reported.[8] However, **5** was unaffected by these conditions. Sodium sulfinates form sulfonbromides when reacted with bromine,[9] and when **5** was treated with bromine and pyridine, ring closure to a novel heterocyclic scaffold occurred (Table 1).

Effectively this two-step one-pot reaction expands a cyclic sulfone to its sulfonamide analogue by insertion of a primary

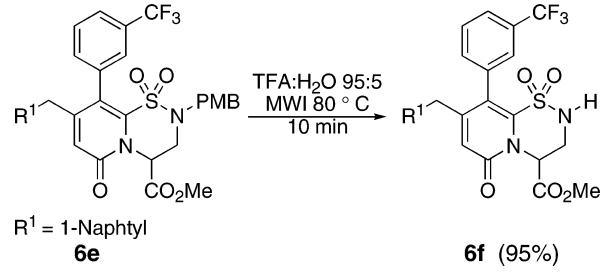
Table 1. Ring Expansion of Compound **3** To Form Sulfonamides



entry	R^2	product	yield (%)
1	Bn	**6a**	74
2	Me	**6b**	65
3	iPr	**6c**	42
4	CH_2CH_2OH	**6d**	61
5	PMB	**6e**	71

amine. To the best of our knowledge this is a transformation not earlier described. It was beneficial to use methanol as solvent in the first step, as significant decomposition occurred in nonprotic solvents. However, a change of solvent in the next step was necessary to avoid oxidation of the sulfinate to the corresponding sulfate. A variety of primary alkyl amines reacted well, while anilines and ammonia did not give any of the expected product and instead decomposition of **3** was observed. The unsubstituted sulfonamide could though conveniently be obtained by acidic cleavage of the PMB group in compound **6e** under microwave conditions. (Scheme 2).

Scheme 2. Cleavage of the PMB Group in **6e**



With the unsubstituted sulfonamide **6f** in hand, coupling to form an *N*-arylated species was attempted. Copper(I)-catalyzed coupling of sulfonamides with aryl halides has proven successful.[10] However, attempted reaction of **6f** with iodobenzene did not produce any coupling product. The attention was then turned to Chan-Lam couplings.[11] Although

(4) Cegelski, L.; Pinkner J. S.; Hammer N.; Cusumano C. K.; Hung C. S.; Chorell E. ; Åberg V.; Garofalo C.; Walker J. N.; Seed P. C.; Almqvist F.; Chapman M. R.; Hultgren S. J. *Nat. Chem. Biol.* **2009**, DOI:10.1038/nchembio.242.

(5) Emtenas, H.; Alderin, L.; Almqvist, F. *J. Org. Chem.* **2001**, *66*, 6756–6761.

(6) Sellstedt, M.; Almqvist, F. *Org. Lett.* **2008**, *10*, 4005–4007.

(7) Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003**, *10*, 925–953.

(8) Farrar, W. V. *J. Chem. Soc.* **1965**, 856–858.

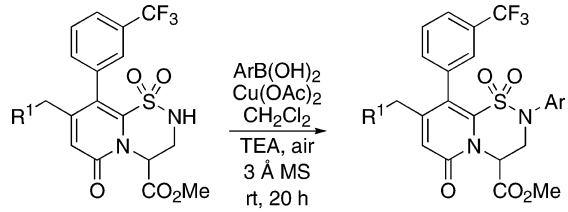
(9) Cristol, S. J.; Harrington, J. K.; Singer, M. S. *J. Am. Chem. Soc.* **1966**, *88*, 1529–1532.

(10) Deng, W.; Liu, L.; Zhang, C.; Liu, M.; Guo, Q. X. *Tetrahedron Lett.* **2005**, *46*, 7295–7298.

(11) (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936. (b) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415–3418.

electron-deficient aryls reacted poorly, we were pleased to find that both electron-rich and electron-neutral aryls could be coupled (Table 2).

Table 2. Chan-Lam N-Arylations



R^1 = 1-Naphtyl

6f **6g-h**

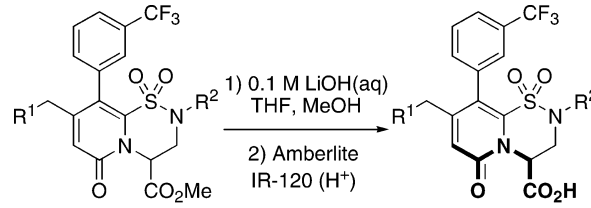
entry	Ar	product	yield (%)
1	Ph	**6g**	53
2	pMeOPh	**6h**	37
3	mNO_2Ph	**6i**	trace

Finally, the methyl esters **6a**−**h** were hydrolyzed to their corresponding carboxylic acids, revealing a scaffold with a C-terminal peptidomimetic backbone (Table 3).

The obtained compounds will initially be biologically tested as racemates. However, resolution using chiral chromatography appears quite straightforward as indicated by analytical separation of the enatiomers of **7a** and **7b**. Further, enantio-enrichment by co-precipitation of **7a** with (*S*)-1-phenylethylamine was possible, giving an enantiomeric excess of about 60% of each enantiomer in the mother liquor and precipitate, respectively (see Supporting Information).

In conclusion, we report a novel heterocyclic scaffold with structural peptidomimetic properties. The scaffold is prepared by a two-step one-pot ring-expanding reaction between a cyclic sulfone and primary amines. Compared to our previously prepared compounds this scaffold holds an additional easily variable substitiuent, allowing access to diverse molecular libraries.

Table 3. Hydrolysis of Methyl Esters **6a**−**h**



R^1 = 1-Naphtyl

6a-h **7a-h**

entry	R^2	product	yield (%)
1	Bn	**7a**	96
2	Me	**7b**	96
3	iPr	**7c**	91
4	CH_2CH_2OH	**7d**	88
5	PMB	**7e**	89
6	H	**7f**	84
7	Ph	**7g**	88
8	pMeOPh	**7h**	96

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Supporting Information Available: Experimental procedures and spectroscopic data of all new compounds and chromatograms of chiral chromatography of coumpounds **7a** and **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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