## Synthesis of Cyclic Sulfonamides through Intramolecular Diels–Alder Reactions

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ABSTRACT



Substituted 2,3,3a,4,5,7a-hexahydrobenzo[*d*]isothiazole 1,1-dioxides and 3,4,4a,5,6,8a-hexahydro-2*H*-benzo[*e*][1,2]thiazine 1,1-dioxides, novel cyclic sulfonamides, were synthesized by the thermal Diels–Alder reaction of triene derivatives of buta-1,3-diene-1-sulfonic acid amide. The stereochemical outcome of the reaction was determined by NMR spectroscopy and X-ray crystallographic analysis. This chemistry has been used for the synthesis of 2-(4-chlorobenzyl)-5-(1*H*-imidazol-4-yl)-2,3,3a,4,5,7a-hexahydrobenzo[*d*]isothiazole 1,1-dioxide, a histamine H<sub>3</sub> receptor antagonist.

The sulfonamide group is ubiquitous in bioorganic and medicinal chemistry, providing a key polar alternative to the amide group for which it is frequently used as a bioisosteric replacement. Through several series of histamine H<sub>3</sub> receptor antagonists,<sup>1-4</sup> we have made particular use of the contrasting properties of sulfonamides, finding that the in vitro profiles were superior to the amide equivalents. As part of this program, we developed methodology for the synthesis of vinyl sulfonamides.5 This also allowed access to the rarely encountered dienes 2, which we hoped would form the basis of conformationally constrained equivalents of our relatively flexible compounds. Growing interest in cyclic sulfonamides is evident in the development of new synthetic approaches utilizing a variety of intramolecular reactions including the cyclization of  $\alpha$ -methylsulfonamidyl radicals<sup>6</sup> and carbanions,<sup>7</sup> radical cyclization based on hypervalent iodine species,<sup>8</sup> the transition metal catalyzed insertion of nitrenes,<sup>9</sup> and ring-closing metathesis.<sup>10</sup> Intramolecular Diels–Alder reactions are an attractive option for constructing rigid cyclic systems, and sulfonamides have been incorporated in the dienophile component as vinyl sulfonamides.<sup>11</sup> However, we have found the inverse electron demand counterpart to be a valuable new route to cyclic sulfonamides, and we report, herein, our findings on the thermal Diels–Alder reactions of trienes **3** and **4**.

1,3-Butadiene sulfonamides **2** were prepared by the basemediated condensation of *N*-Boc-methanesulfonamides **1** with a series of aldehydes (**a** 67%, **b** 69%, **c** 99%, **d** 51%), using the previously reported one-pot version of this reaction.<sup>5</sup> *N*-Alkylation of **2** to give trienes **3** (**a** 69%, **b** 76%, **c** 82%, **d** 59%) and **4** (**a** 29%, **b** 47%, **c** 44%, **d** 27%) was

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<sup>(10) (</sup>a) Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett.* **1999**, *40*, 4761. (b) Brown, R. C. D.; Castro, J. L.; Moriggi, J.-D. *Tetrahedron Lett.* **2000**, *41*, 3681. (c) Long, D. D.; Termin, A. P. *Tetrahedron Lett.* **2000**, *41*, 6743.

<sup>(11)</sup> Plietker, B.; Seng, D.; Frölich, R.; Metz, P. *Tetrahedron* **2000**, *56*, 873. For an example of an intermolecular Diels–Alder reaction involving a vinylsulfonamide see: Abou-Gharbia, M.; Moyer, J. A.; Patel, U.; Webb, M.; Schiehser, G.; Andree, T.; Haskins, J. T. *J. Med. Chem.* **1989**, *32*, 1024.

achieved by reacting the sodium salts with either allyl or homoallyl bromide in tetrahydrofuran at reflux. While generally good yields were obtained in the former case, the lower yields in the latter can be offset against the degree of recovery of the starting diene (Scheme 1). Where studied,



the use of cesium carbonate and dimethylformamide for the alkylation did not afford any improvement.

The intramolecular Diels-Alder reactions of compounds **3** and **4** were performed at 145 °C in toluene, in a sealed screw-cap vessel under argon (Scheme 2).<sup>12</sup> Under these



conditions, the [4.3.0] products 5 and 6 and the [4.4.0]products 7 and 8 were obtained in good yields (Table 1). Lower temperatures, such as toluene at reflux, were not adequate, although the effects of elevated pressures have not been investigated. The two products in each case differed in the geometry about the newly formed ring junction, with the *cis*-fused compounds 5 and 7 predominating. For some product mixtures, such as 7c and 8c, separation of the individual components was possible by flash column chromatography,<sup>12</sup> and for others, such as 5c and 6c, enrichment in the major component was achieved by recrystallization. The relative stereochemistries of 5c, 6c, and 7c were confirmed by X-ray crystallography (Figure 1)<sup>13</sup> and the measurement of nuclear Overhauser effects using <sup>1</sup>H NMR spectroscopy. <sup>1</sup>H NMR spectroscopy thence became an invaluable tool in analyzing the other product mixtures.

The amide equivalent of this reaction has been the subject of several reports,<sup>14</sup> and from the results disclosed here a similarity between the two systems is apparent. Selectivity for *cis*-fused products was generally higher for the sulfon-

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 Table 1.
 Thermal Intramolecular Diels-Alder Reactions of

 Trienes 3a-d and 4a-d
 Alder Reactions of

triene	$\mathbb{R}^1$	<b>R</b> <sup>2</sup>	product (ratio) <sup>a,b</sup>	yield (%) <sup>c</sup>
3a	Н	4-Cl-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>5a</b> , <b>6a</b> (6:1)	76
3b	Me	4-Cl-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	5b, 6b (6:1)	71
3c	Ph	4-Cl-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>5c</b> , <b>6c</b> (3:1)	92
3d	Ph	<i>n</i> -Bu	5d, 6d (3:1)	87
4a	Н	4-Cl-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	7a, 8a (5:1)	66
4b	Me	4-Cl-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	7b, 8b (6:1)	74
<b>4</b> c	Ph	4-Cl-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	7c, 8c (4:1)	92
<b>4d</b>	Ph	<i>n</i> -Bu	7d, 8d (4:1)	80

<sup>*a*</sup> Ratio estimated from integral values of discernible peaks of common protons in the <sup>1</sup>H NMR spectrum. The crude reaction mixtures were used for this analysis. <sup>*b*</sup> Compounds **5**, **7**, and **8**c were characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy techniques, including 2D correlation experiments for peak assignment. Satisfactory data from microanalysis and mass spectrometery were also obtained. <sup>*c*</sup> Combined yields (**5** and **6** or **7** and **8**) after flash column chromatography.

amides, although an exact comparison of substituent effects and reaction conditions is not possible at present. Within the limits of experimental measurement and the scope of this study, it seems that the nature of the substituents  $R^1$  and  $R^2$ were not determinants in the stereoselectivity. From examples in the amide series, it could be suggested that a monosubstituted sulfonamide nitrogen ( $R^2 = H$ ) might be deleterious to cyclization.<sup>14b</sup> However, the stereoelectronic demands of sulfonamides and amides differ. The exploration of these and the other steric and stereoelectronic factors<sup>14a</sup> that contribute to the stereoselectivity of the reaction will be the concern of future studies.

With a practical route to the novel cyclic sulfonamides in hand, we applied our findings to the synthesis of the imidazole analogue **9**, a racemic mixture of *cis*- and *trans*-fused products. Compound **9** was conceived as a conforma-



Figure 1. X-ray crystallographic structures of the *cis*-fused compounds **5c** and **7c**, rendered in Chem3D. For the purposes of clarity, only protons attached to stereogenic centers are shown.

tionally restricted variant of existing histamine H<sub>3</sub> receptor antagonists,<sup>2,3</sup> and affinity levels in the micromolar range

(12) The preparation of 2-(4-chlorobenzyl)-6-phenyl-3,4,4a,5,6,8ahexahydro- $2\hat{H}$ -benzo[e][1,2]thiazine 1,1-dioxide (7c and 8c) is given as an illustration of the general procedure for the intramolecular Diels-Alder reactions. A solution of 4c (393 mg, 1.01 mmol) in dry toluene (5 mL), in a screw-cap vessel with a septum, was degassed in vacuo three times and sealed under an atmosphere of argon. The solution was heated at 145 °C, with stirring, for 60 h. The mixture was adsorbed onto silica gel and purifed by column chromatography (silica, 20% EtOAc/hexane). Thus, in addition to a mixture of 7c and 8c (207 mg, 53%, 7c:8c = 10:1), 7c was isolated as a colorless oil (90 mg, 23%) and **8c** as a colorless solid (63 mg, 16%). **7c** <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  7.35–7.23 (9H, m, Ar), 6.21 (1H, d, *J* 9.9 Hz, H-7), 6.06 (1H, m, H-8), 4.44 (1H, d, J 14.4 Hz, NCHH'Ar), 4.27 (1H, d, J 14.7 Hz, NCHH'Ar), 3.86 (1H, m, H-8a), 3.52 (2H, m, H-3, 6), 2.94 (1H, dt, J 14.1, 3.3 Hz, H-3'), 2.57 (2H, m, H-4a, 5), 2.09 (1H, m, H-4), 1.75 (1H, m, H-5), 1.47 (1H, d, J 14.7, H-4'); <sup>13</sup>C NMR (75 MHz; CDCl<sub>3</sub>) δ 145.1, 140.3 (C-7), 135.4, 134.4, 130.4, 129.5, 129.3, 128.4, 127.3, 118.3 (C-8), 58.7 (C-8a), 50.2 (NCH2Ar), 44.8 (C-3), 43.9 (C-6), 35.4 (C-4a), 32.6 (C-5), 28.3 (C-4). 8c <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>) δ 7.35-7.25 (9H, m, Ar), 6.25 (1H, d, J 10.2 Hz, H-8), 6.13 (1H, m, H-7), 4.41 (1H, d, J 14.4 Hz, NCHH'Ar), 4.22 (1H, d, J 14.7 Hz, NCHH'Ar), 3.61 (1H, m, H-6), 3.54 (1H, ddd, J 10.8, 4.2, 2.4 Hz, H-8a), 3.36 (1H, dt, J 13.2, 3.0 Hz, H-3), 2.98 (1H, ddd, J 13.8, 4.2, 2.4 Hz, H-3'), 2.36 (1H, m, H-4a), 1.94 (1H, dt, J 13.0, 6.5 Hz, H-5), 1.77 (1H, dt, J 13.0, 1.5 Hz, H-5'), 1.52 (1H, m, H-4), 1.39 (1H, m, H-4'); <sup>13</sup>C NMR (75 MHz; CDCI<sub>3</sub>) δ 143.7, 135.1, 134.9 (C-7), 134.1, 130.2, 129.2, 129.0, 128.8, 127.0, 119.2 (C-8), 63.8 (C-8a), 50.3 (NCH<sub>2</sub>Ar), 48.1 (C-3), 40.3 (C-6), 36.6 (C-5), 32.4 (C-4a), 30.0 (C-4).

(13) See Supporting Information for full details of the X-ray crystal structures of compounds 5c (with 6c) and 7c.

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were measured in two standard in vitro assays (Figure 2).<sup>15</sup> A further discussion of the chemistry reported here and its use in the histamine  $H_3$  area will appear in due course.



**Figure 2.** Histamine H<sub>3</sub> antagonist with affinities from the guinea pig isolated ileum assay ( $pK_B$ ) and a radioligand binding assay using guinea pig cerebral cortex membranes ( $pK_i$ ).<sup>15</sup>

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**Supporting Information Available:** Details, data, and illustrations for the X-ray crystal structures of compounds **5c** (with **6c**) and **7c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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<sup>(15)</sup> For a discussion of these assays refer to ref 1 and other papers cited therein.