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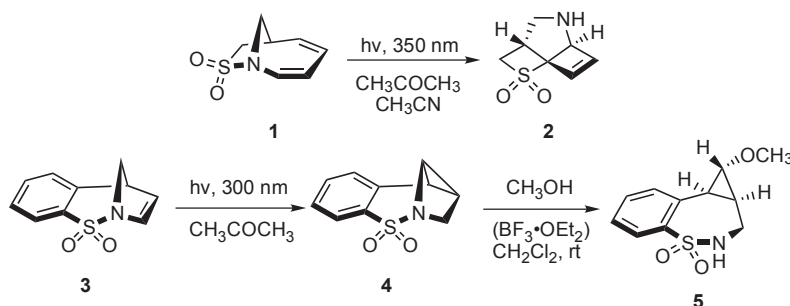
## BROMINATIVE INDOLIZATION OF AN UNSATURATED BRIDGEHEAD SULTAM WITH EXTRUSION OF SULFUR DIOXIDE<sup>‡</sup>

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**Abstract** – The dissolution of an unsaturated bridgehead sultam in liquid bromine at room temperature results in the formation of a pentabromo indole derivative in an unusual desulfonylative process.

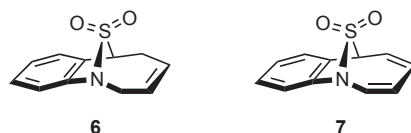
Compound classes with unique and complex architectures often present new insights into organic reactivity. A subgroup typified by this general statement is that consisting of bridgehead sultams, the first examples of which were reported only in 1999.<sup>1</sup> While the means for gaining access to representative prototypes is still limited,<sup>2-5</sup> sufficient information is already available for us to recognize that sulfonamides constructed in this manner can participate in unprecedented chemical transformations. The photoisomerization of **1** with SO<sub>2</sub>-N bond cleavage to give **2**,<sup>6</sup> the unidirectional triplet-sensitized di- $\pi$ -methane isomerization of **3** to **4**,<sup>7</sup> and methanolysis of the latter to deliver **5**<sup>8</sup> constitute recent examples.



Our plan for the acquisition of **7** involved a strategy based on the bromination–dehydrobromination of **6**. After **6** had been secured, it soon became apparent that the addition of bromine across its double bond

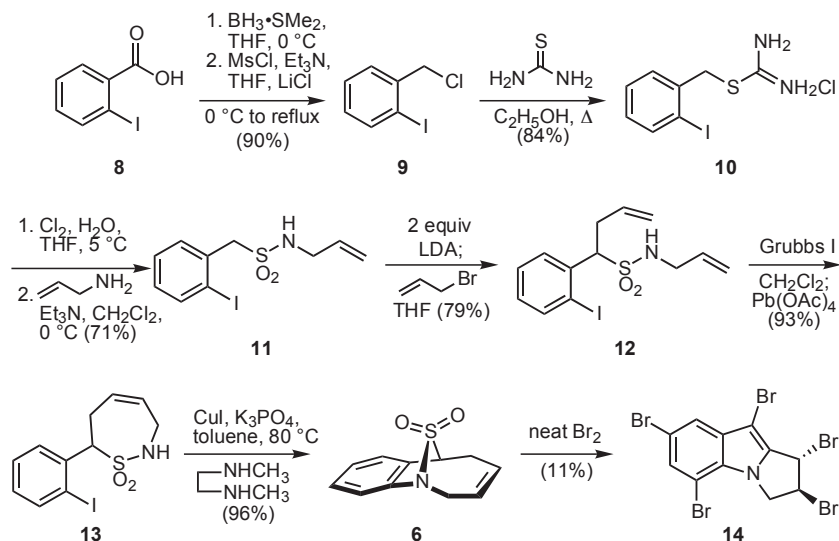
<sup>‡</sup> This paper is dedicated to Professor Steven Weinreb as we celebrate his 65<sup>th</sup> birthday and his many important contributions to the field of heterocyclic chemistry.

was a very sluggish process, presumably as a direct consequence of untoward field and steric effects brought on by the sulfonyl group. To overcome this kinetic retardation, **6** was stirred in neat bromine at room temperature for 30 min. In this communication, we detail the unusual outcome of this reaction, offer verification of the product structure by X-Ray crystallographic analysis, and suggest a possible mechanistic pathway for the desulfonylative polybromination observed.



The route to **6** began with 2-iodobenzoic acid (**8**) where reduction to the alcohol was followed by generation of chloride (**9**) either directly by reaction with thionyl chloride or preferably *in situ* via the mesylate and lithium chloride (Scheme 1).<sup>9</sup> Introduction of the sulfur atom involved the intermediacy of isothiuronium salt (**10**), the aqueous chlorination of which afforded the sulfonyl chloride,<sup>10</sup> which was reacted directly with allylamine. Subsequent regioselective C-allylation of the benzylic position in **11** was brought about by way of the dianion intermediate to give **12**, which was directed into ring-closing metathesis by exposure to the first generation Grubbs catalyst.<sup>11</sup> The otherwise annoying ruthenium by-products were effectively removed by overnight stirring with lead tetraacetate.<sup>12</sup> The notable efficiency associated with the production of sultam (**13**) was foreshadowed by other research groups working with related sulfonamides of comparable ring size.<sup>13</sup> The second-stage cyclization that leads from **13** to **6** consisted of an intramolecular Ullmann-Goldberg reaction.<sup>14</sup> After screening a number of copper-based

### Scheme 1



promoters, we settled on the combination of copper(I) iodide, potassium phosphate, and *N,N'*-dimethylethylenediamine in hot toluene. Under these conditions, the desired conversion was achieved cleanly and in near-quantitative yield.

At this point, the dibromination of **6** with ensuing twofold debromination was projected to be a viable route to **7**. However, the admixture of **6** with stoichiometric amounts of bromine in  $\text{CH}_2\text{Cl}_2$  or  $\text{CHCl}_3$  failed to give any indication of dibromide formation after several days. As a consequence, this reaction was undertaken again, this time in neat bromine as the reaction medium. After 30 min, a new product identified by X-ray crystallography (Figure 1) as the highly functionalized indole (**14**)<sup>16</sup> had formed in modest yield with loss of the sulfonyl group. From among the several mechanistic options capable of rationalizing this unusual chemical transformation, we offer the route depicted in Scheme 2 with but one comment. Recourse to neat bromine as a reaction solvent has good synthetic value and can be depended upon to deliver dibromides effectively as exemplified in Scheme 3. The selected reactants (**3**) and (**16**) do not benefit from an aromatization driving force comparable to that available to **6**, as well as from the expulsion of a small, neutral molecule.

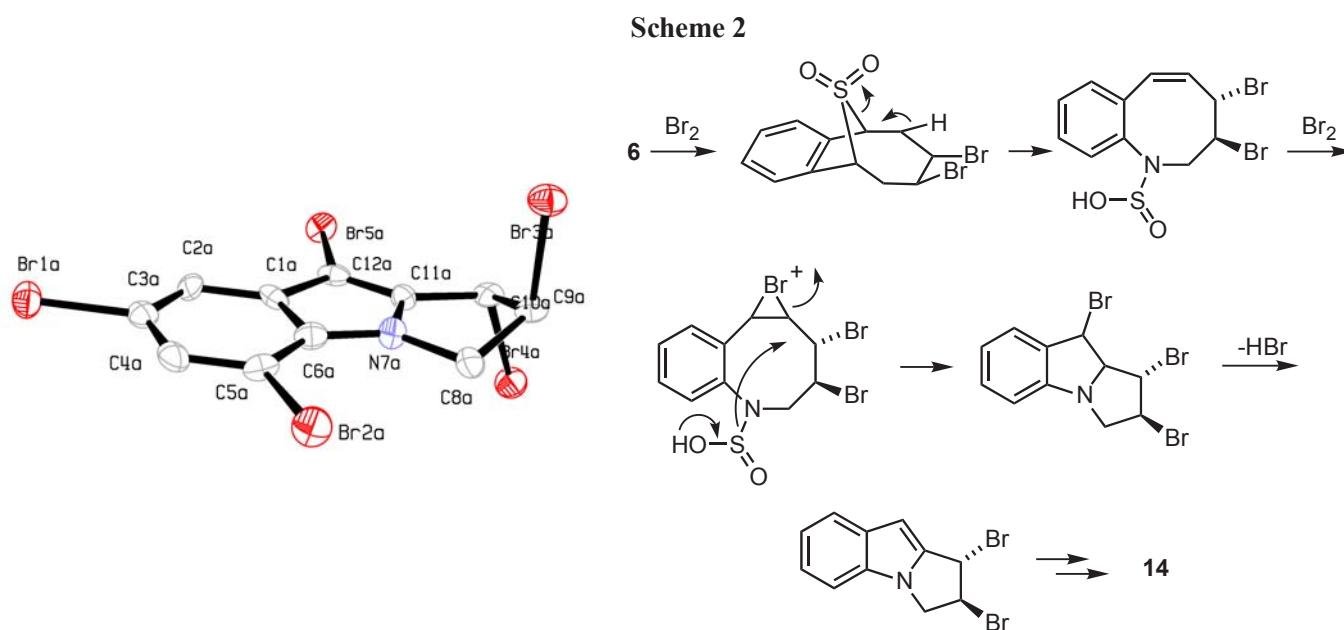
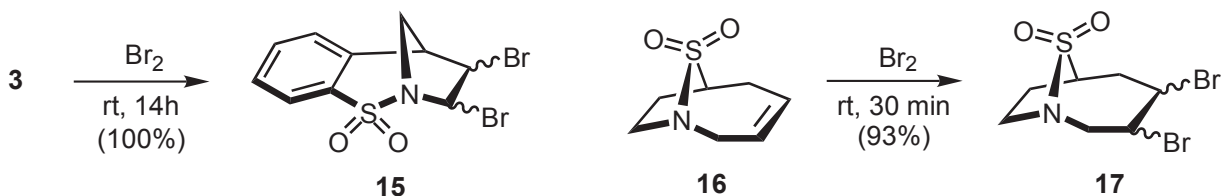
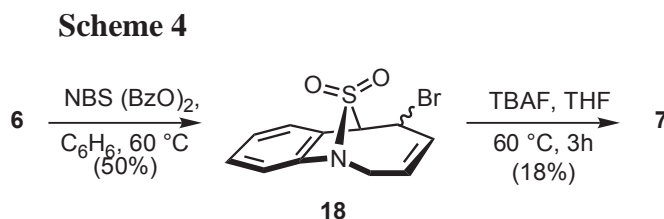


Figure 1. ORTEP diagram of **14**.

### Scheme 3



Finally, a by-pass route to bridged sultam (**7**)<sup>16</sup> was successfully realized by the allylic bromination of **6** with NBS to give **18** predominantly, followed by exposure of this intermediate to TBAF (Scheme 4). The yields in this sequence have not yet been optimized.



## ACKNOWLEDGEMENT

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## REFERENCES AND NOTES

1. L. A. Paquette and S. M. Leit, *J. Am. Chem. Soc.*, 1999, **121**, 8126.
2. R. Grigg and M. York, *Tetrahedron Lett.*, 2000, **41**, 7255.
3. J. D. Schloss, S. M. Leit, and L. A. Paquette, *J. Org. Chem.*, 2000, **65**, 7119.
4. P. Dauben and R. H. Dodd, *Org. Lett.*, 2000, **2**, 2327.
5. P. Evans, T. McCabe, B. S. Morgan, and S. Reau, *Org. Lett.*, 2005, **7**, 43.
6. L. A. Paquette, W. R. S. Barton, and J. C. Gallucci, *Org. Lett.*, 2004, **6**, 1313.
7. R. D. Dura and L. A. Paquette, *J. Org. Chem.*, 2006, **71**, 2456.
8. R. D. Dura, unpublished results from this laboratory.
9. M. A. Ciufolini and M. E. Browne, *Tetrahedron Lett.*, 1987, **28**, 171.
10. S. D. Wyrick, I. H. Hall, and A. Dubey, *J. Pharm. Sci.*, 1984, **73**, 374.
11. (a) R. H. Grubbs, S. J. Miller, and G. C. Fu, *Acc. Chem. Res.*, 1995, **28**, 446. (b) R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4113.
12. L. A. Paquette, J. D. Schloss, I. Efremov, F. Fabris, F. Gallou, J. Mendez-Andino, and J. Yang, *Org. Lett.*, 2000, **2**, 1259.
13. (a) S. Karsch, D. Freitag, P. Schwab, and P. Metz, *Synthesis*, 2004, 1696. (b) S. Hanessian, H. Sailes, and E. Therrien, *Tetrahedron*, 2002, **59**, 7047. (c) J. Wanner, A. M. Harned, D. A. Probst, R. E. Robinson, T. A. Klein, K. A. Snelgrove, and P. R. Hanson, *Tetrahedron*, 2000, **56**, 9781. (d) J. U. Jun, M. S. Hrmenez, J. M. Dougherty, and P. R. Hanson, *Tetrahedron*, 2003, **59**, 8901. (e) A. M. Harned, S. Mukherjee, D. L. Flynn, and R. R. Hanson, *Org. Lett.*, 2003, **5**, 15. (f) S. S. Salim, R. K. Bellingham, B. Satcharoen, and R. C. D. Brown, *Org. Lett.*, 2003, **5**, 3403.
14. (a) W. Deng, L. Liu, C. Zhang, M. Liu, and Q. X. Guo, *Tetrahedron Lett.*, 2005, **46**, 7295. (b) K. Kung, U. Scholz, and D. Ganzer, *Syn. Lett.*, 2003, 2428. (c) D. Steinhubel, M. Palucki, D. Askin, and U. Dolling, *Tetrahedron Lett.*, 2004, **45**, 3305. (d) H. He and Y.-J. Wu, *Tetrahedron Lett.*, 2003, **44**, 3385.
15. The N-CH<sub>2</sub>- absorptions appearing at  $\delta$  4.40 and 3.95 in **6** remain relatively unchanged in bromide (**18**) ( $\delta$  4.50 and 3.98). In contrast, the C-CH<sub>2</sub>-C signals that are positioned at  $\delta$  2.94 and 2.63 in **6** are reduced in area to 1H and shifted downfield to  $\delta$  5.31.
16. For **7**: mp 142 °C (decomp.); for **14**: mp 159 °C (decomp.).