Pergamon

Tetrahedron Letters 39 (1998) 1021–1022

TETRAHEDRON LETTERS

# β-Metallation of Bridged Alkenyl Sulfones: Access to a Key Intermediate for Epibatidine Total Synthesis

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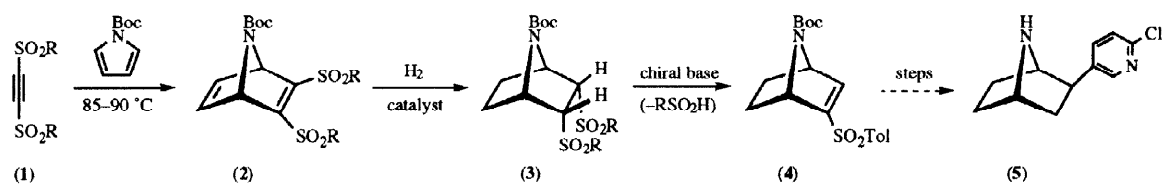
Received 21 October 1997; revised 20 November 1997; accepted 21 November 1997

**Abstract:** Efficient β-metallation of certain bridged alkenyl sulfones has been demonstrated. The reaction allows the synthesis of a *bis*-sulfone as a key intermediate for epibatidine synthesis.



The alkaloid epibatidine **5**, possessed of both the unique 7-azabicyclo[2.2.1]heptane skeleton and intriguing analgesic properties, has been the subject of intense synthetic interest over the past few years.[1] We recently described a concise stereoselective synthesis of this compound in racemic form, by a route involving the Michael addition of a metallated pyridine to the key alkenyl sulfone **4**.[2] We conceived that this route would be amenable to a novel asymmetric variant whereby the alkenyl sulfone **4** would be accessed via chiral base mediated asymmetric elimination from a symmetrical *bis*-sulfone **3**.[3]

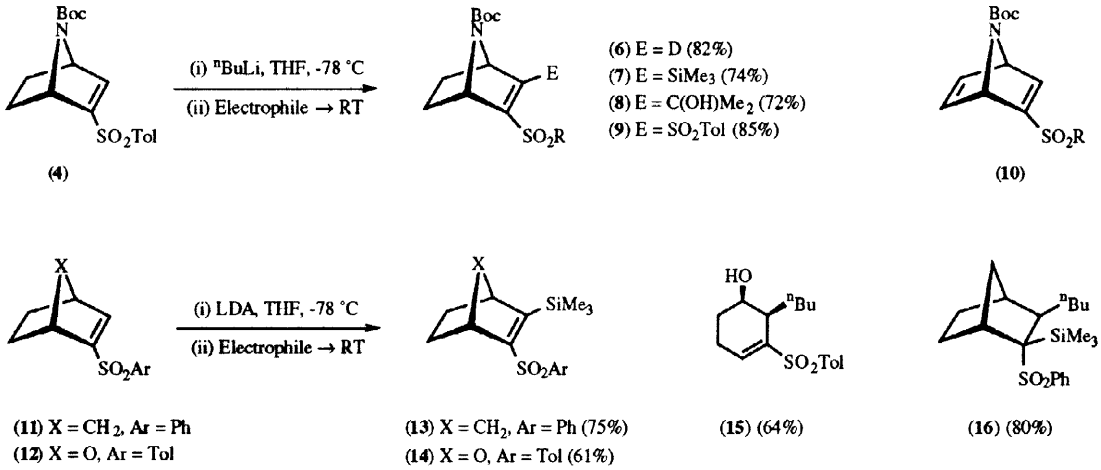



This in turn would be available via cycloaddition of alkyne **1** with *N*-Boc pyrrole to give **2**, followed by exhaustive hydrogenation.[4] However, this plan soon ran into difficulties because the high reactivity of the *bis*-arylsulfonylalkyne **1** (R = *p*-Tol), precluded its use on a meaningful scale,[5] whilst the alternative alkyne **1** (R = $^{t}$Bu)[6] gave a cycloadduct **2** with an alkenyl sulfone highly resistant to hydrogenation (presumably for steric reasons). This type of difficulty has been noted previously; the use of chlorinated alkenyl *bis*-sulfones, as described by De Lucchi and co-workers, providing one solution.[7]

Herein we demonstrate an alternative solution to the problem, which relies on the β-metallation of alkenyl sulfones, such as **4** (themselves very readily available by cycloadditions of ethynyl tolyl sulfone) to allow the introduction of several different substituents, including the sulfonyl group required for conversion into **3**. Although this mode of sulfone metallation has previously been noted as an unwanted pathway competing with organometallic addition to certain alkenyl sulfones,[8] this reaction has not been demonstrated to be synthetically useful, and indeed, we expected that predominant metallation of the aromatic nucleus could be a problem.[9]

0040-4039/98/$19.00 
*PII:* S0040-4039(97)10692-X

Therefore, we were delighted to find that treatment of alkenyl sulfone **4** with $^{n}$BuLi at -78 °C resulted in clean metallation at the β-position, as evidenced by the recovery of fully deuterated material **6** on quenching the reaction mixture with $D_2O$. As shown, use of $Me_3SiCl$, acetone or *p*-Tol$SO_2F$ as the electrophile resulted in efficient formation of **7**, **8** and **9** respectively; preparation of **9** by this route solving our problem in accessing *bis*-sulfone **3** through cycloaddition of **1** (see accompanying paper).




Attempts to carry out analogous reaction sequences using the unsaturated analogue **10** were not successful, whilst reactions involving attempted metallation of the carbocyclic **11**, and oxacyclic **12**, analogues (using $Me_3SiCl$ as the electrophile), led instead to the addition products **15** and **16** respectively. However, by changing the base from $^{n}$BuLi to LDA both of these systems could be metallated in the desired fashion, to give acceptable yields of the silylated products **13** and **14**. Further exploration of this mode of metallation, along with applications to target synthesis are underway.

**Acknowledgements**

We are grateful to the Engineering and Physical Sciences Research Council (EPSRC) and Glaxo Wellcome for support of C. D. J. under the CASE scheme.

**References and Footnotes**

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3. See accompanying paper for preliminary results of the enantioselective elimination reaction.
4. The apparent alternative, involving the use of an alkenyl *bis*-sulfone is not viable because these compounds do not undergo cycloaddition with pyrrole partners.
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