

# 2-Bromoethynyl aryl sulfones as versatile dienophiles: a formal synthesis of epibatidine

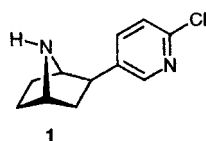
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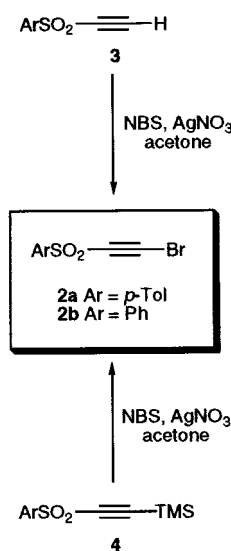
A facile synthesis of 2-bromoethynyl aryl sulfones has been developed; the reactivity of these versatile dienophiles in [4 + 2] cycloaddition reactions as well as application in a formal synthesis of epibatidine is described.

Epibatidine (**1**), a novel alkaloid isolated from Ecuadorian



poison dart frog, *Epibedobates tricolor*, by Daly and co-workers,<sup>1</sup> has been shown to be a highly potent, non-opioid analgesic and nicotinic acetylcholine receptor agonist.<sup>2</sup> Its scarcity in nature (less than 1 mg was isolated from 750 frogs), remarkable biological activity, and uncommon 7-azabicyclo[2.2.1]heptane ring system makes it an attractive target for synthetic chemists.<sup>3</sup> Previous work in our laboratories has shown that methyl 3-bromopropiolate acting as a novel dienophile, readily underwent a [4 + 2] cycloaddition reaction with *N*-acyl pyrroles to give *N*-acyl-3-bromo-2-methoxycarbonyl-7-azabicyclo[2.2.1]hepta-2,5-dienes in good yields.<sup>4</sup> Elaboration of the cycloaddition adducts led to a short and facile synthesis of epibatidine.<sup>5</sup> Inspired by this result, we became interested in exploring the [4 + 2] cycloaddition reaction of other ethynyl bromides. Herein we wish to report the preparation of 2-bromoethynyl aryl sulfones (**2**) and their application in [4 + 2] cycloaddition reactions.

2-Bromoethynyl aryl sulfone (**2**) was prepared by the bromination of ethynyl aryl sulfone (**3**) using a similar procedure to that described for the propiolate esters (Scheme 1).<sup>6</sup> Thus a



Scheme 1

Table 1 [4 + 2] Cycloaddition reaction of dienes with 2-bromoethynyl *p*-tolyl sulfone (**2a**)

Entry	Diene ( <b>5</b> )	Product ( <b>6</b> ) <sup>a</sup>	Yield (%) <sup>b</sup>
a			57
b			74
c			94
d			66
e			70
f			78

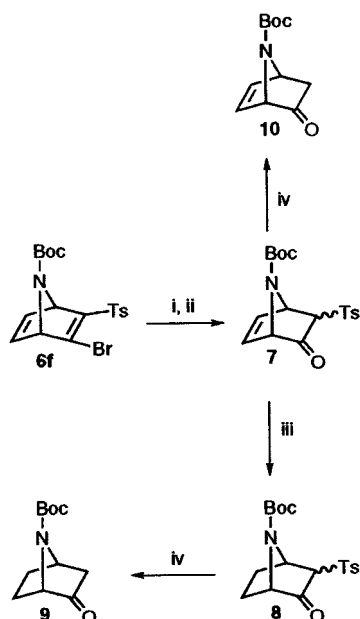
<sup>a</sup> Reaction conditions: 90 °C, toluene, 24 h. <sup>b</sup> Isolated yields.

solution of ethynyl aryl sulfone (**3**) in acetone was allowed to react with an equivalent of *N*-bromosuccinimide (NBS) in the presence of AgNO<sub>3</sub> as catalyst (10%), which gave 2-bromoethynyl aryl sulfone **2** in high yield (>95%) within 30 min. Alternatively, since ethynyl aryl sulfones **3** are usually obtained by removal of the trimethylsilyl moiety of 2-trimethylsilyl-ethynyl sulfone **4**,<sup>7</sup> we examined the direct conversion of **4** into **2**. A stirred solution of **4** in acetone with NBS in the presence of AgNO<sub>3</sub> as a catalyst at room temperature for 30 min, afforded the same product **2** in high yield. Without the presence of AgNO<sub>3</sub>, the reaction did not take place.

2-Bromoethynyl *p*-tolyl sulfone (**2a**), as expected, was found to readily undergo a [4 + 2] cycloaddition reaction with a variety of diene derivatives **5**, including alkane-1,3-diene, cycloalkane-1,3-diene, furan and *N*-acyl pyrrole derivatives. The reaction of this substituted acetylene derivative **2a** with dienes **5** in toluene at 90 °C afforded the corresponding cycloaddition adducts **6** in good to excellent yields ranging from 57 to 94% (Table 1).

Further elaboration of the cycloaddition adducts was found to be quite facile. Treatment of adduct **6f** with 1.1 equivalents of diethylamine in the presence of three equivalents of triethylamine in acetonitrile (room temperature), followed by hydrolysis with 10% HCl (room temperature), afforded the ketone **7** in 86% yield (Scheme 2). Hydrogenation of the carbon-carbon double bond of **7** over 10% Pd/C (H<sub>2</sub>, 1 atm)

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**Scheme 2** Reagents and conditions: i,  $\text{Et}_2\text{NH}$ ,  $\text{Et}_3\text{N}$ ; ii, 10% HCl; iii,  $\text{H}_2$ , 10% Pd/C, MeOH; iv, Al(Hg), MeOH.

gave **8** in almost quantitative yield. Removal of the sulfonyl moiety of **8** was readily achieved by treatment with Al-Hg, which afforded the ketone **9** in 60% yield.<sup>8</sup> In addition, compound **7** was also desulfonated in a similar fashion to give the *N*-Boc-7-azabicyclo[2.2.1]hept-5-en-2-one (**10**). Based on this sequence of reactions 2-bromoethynyl *p*-tolyl sulfone (**2a**) can be considered as a synthetic equivalent to ketene in [4 + 2] cycloaddition reactions.

As we and others have previously reported, the facile synthesis of epibatidine (**1**) has been achieved from the ketone **9**.<sup>3c,6-9</sup> Therefore the cycloaddition of **2a** with *N*-Boc-pyrrole (**5f**) and subsequent transformations of the adduct **6f** into the ketone **9** represents a new formal synthesis of epibatidine (**1**).

## Experimental

### Preparation of **2a** from **4a**

To a magnetically stirred solution of **4a** (5.0 g, 20 mmol) in acetone (150 mL) was added silver nitrate (0.34 g, 2.0 mmol) followed by the addition of *N*-bromosuccinimide (NBS) (3.8 g, 22 mmol) in one portion. The mixture was stirred at

room temperature for 30 min. The resulting precipitate was filtered and washed with a small amount of  $\text{CCl}_4$ . Silica gel (10 g) was added to the filtrate to absorb the crude product. The solvent was removed under reduced pressure and the residue was subjected to column chromatography ( $\text{SiO}_2$ , EtOAc-hexane, 1:5). This afforded **2a** (5.0 g, 96%) as a light yellow solid, mp 99–101 °C;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 2.45 (s, 3H), 7.36 (d,  $J = 8.4$  Hz, 2H), 7.86 (d,  $J = 8.4$  Hz, 2H); IR (neat) $\nu_{\text{max}}$  2165, 1603, 1341, 1162  $\text{cm}^{-1}$ ;  $m/z$  (CI,  $\text{CH}_4$ ) 261 [ $\text{M}^+(\text{Br}) + 1$ , 100%], 259 [ $\text{M}^+(\text{Br}) + 1$ , 98]. Calcd. for  $\text{C}_9\text{H}_7\text{BrO}_2\text{S}$ : C, 41.72; H, 2.72. Found: C, 41.46; H, 2.80%.

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