Pergamon

Tetrahedron Letters 39 (1998) 5321–5322

TETRAHEDRON LETTERS

New Synthesis of 7-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]hept-2-ene. A Key Intermediate in the Synthesis of Epibatidine and Analogs

Lawrence E. Brieaddy, Feng Liang, Philip Abraham, Jeffrey R. Lee, and F. Ivy Carroll*

Chemistry and Life Sciences, Research Triangle Institute, Research Triangle Park, North Carolina 27709, USA

Received 30 April 1998; revised 15 May 1998; accepted 21 May 1998

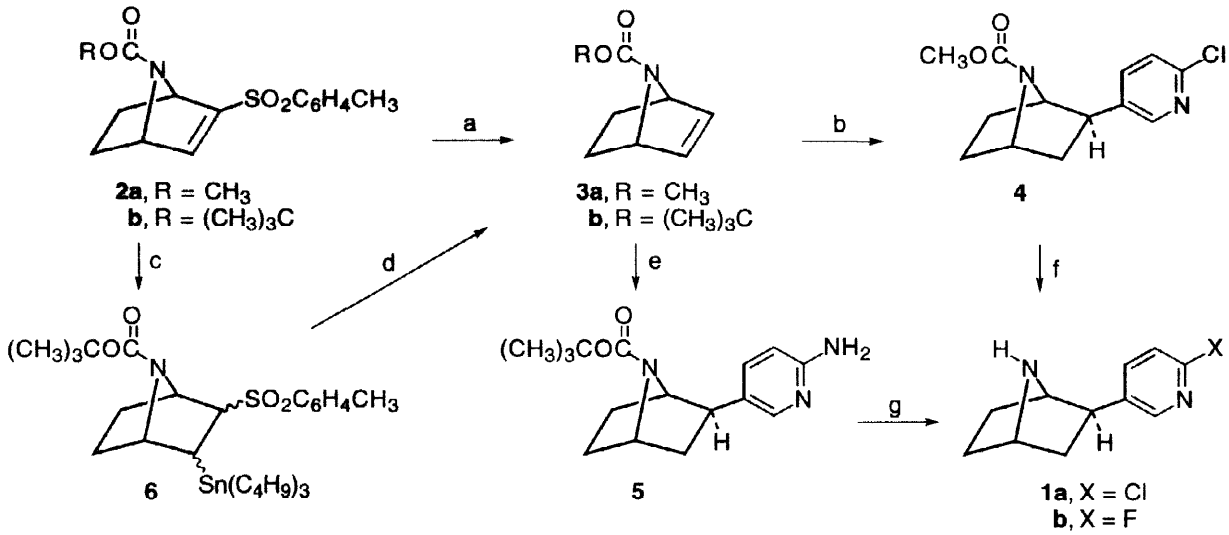
Abstract: A new, high yield, convenient synthesis of 7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]hept-2-ene which involved the addition of tributyltin hydride to 7-(*tert*-butoxycarbonyl)-2-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]-2-ene followed by elimination of the tributyltin and *p*-tolylsulfonyl groups using tetrabutylammonium fluoride was developed.

Epibatidine is an alkaloid isolated from the skin of the Ecuadorian poison frog, *Epipedobates tricolor,* by Daly and coworkers and is shown to have the structure *exo*-2-(6-chloro-3-pyridinyl)-7-azabicyclo-[2.2.1]heptane (**1a**)[1,2]. A review of the total synthesis of **1a**[3-5] shows that the route reported by Clayton and Regan is still the shortest and one of the most efficient syntheses of **1a** (Scheme 1).[6] In their synthesis, the olefin (**2a**) was obtained in two steps from *p*-tolylsulfonylacetylene and N-(methoxycarbonyl)pyrrole. Removal of the p-tolylsulfonyl from **2a** to give **3a** was achieved using sodium amalgam. Palladium-catalyzed reductive addition of 2-chloro-5-iodopyridine to **3a** gave exclusively the desired 2β-substituted compound **4** which yielded **1a** on treatment with hydrogen bromide in acetic acid. We reported the synthesis of the 7-(*tert*-butoxycarbonyl)olefin **3b** and showed that reductive palladium-catalyzed addition using 2-amino-5-iodopyridine afforded exclusively the 7-(*tert*-butoxycarbonyl)-*exo*-2-(2'-amino-5'-pyridinyl)-7-azabicyclo-[2.2.1]heptane (**5**).[7] Epibatidine (**1a**) and the 2'-fluoro analog **1b** were obtained by diazotization of **5** followed by treatment with cuprous chloride in hydrochloric acid or pyridine containing hydrogen fluoride, respectively. The major weakness with the Clayton and Regan[6] route as well as our modified route is that freshly prepared sodium amalgam is needed to convert **2a** and **2b** to the olefins **3a** and **3b**, respectively. Clayton and Evans used 6% sodium amalgam for their conversion, whereas we used 2.5% for the preparation of **3b**. With the 2.5% amalgam, over 2 kg were required to synthesize 10 g of **3b**.

In this report, we describe a high yield synthesis of **3b** which can be easily upscaled to provide large amounts of the compound (Scheme 1). The addition of tributyltin hydride to **2b** in benzene containing 2,2'-azabisisobutyronitrile (AIBN) gave 78–91% of **6** depending on the scale (0.04 to 0.07 mol). Treatment of **6** with tetrabutylammonium fluoride in tetrahydrofuran provides 93–98% of **3b** that was identical to material prepared using sodium amalgam. To our knowledge, this is a new method for the desulfonation of sulfonyl olefins to free olefins. Attempts to convert **6** to **3b** using tetrabutylammonium iodide in tetrahydrofuran or sodium methoxide in methanol were unsuccessful. In addition, all attempts to convert **2b** directly to **3b** using zinc in acetic acid,[8] sodium dithionite in various solvents,[9] and methylene chloride and silica gel[10] were unsuccessful.

The ready availability of **3b** has allowed the synthesis of gram amounts of epibatidine as well as the synthesis of a number of analogs. The results from these studies will be reported in due course.

0040-4039/98/$19.00
PII: S0040-4039(98)01077-6



Reagents: (a) Na/Hg, Na_2HPO_4, EtOAc:*t*-BuOH (1:1); (b) 2-chloro-5-iodopyridine; $(C_6H_5)_2Pd(OAc)_2$; DMF, piperidine; HCO_2H; 70 °C, 6.5 h; (c) $(C_4H_9)_3SnH$, AIBN, benzene; (d) $(C_4H_9)_4NF$, THF; (e) 2-amino-5-iodopyridine; $Pd(OAc)_2$; *n*-Bu_4^+N Cl^-; $K^+HCO_2^-$; DMF; 100 °C, 12 h; (f) HBr-HOAc, RT, 22 h; (g) $NaNO_2$, HCl, CuCl (**1a**) or $NaNO_2$, Py•HF (**1b**)

Scheme 1

References and Notes

1. Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, 114, 3475–3478.
2. Badio, B.; Daly, J. W. *Mol. Pharmacol.* **1994**, 45, 563–569.
3. Broka, C. A. *Med. Chem. Res.* **1994**, 4, 449–460.
4. Chen, Z.; Trudell, M. L. *Chem. Rev.* **1996**, 96, 1179–1193.
5. Szantay, C.; Kardos-Balogh, Z.; Szantay, C., Jr. In *The Alkaloids*; Academic Press: 1995; Vol. 46; pp. 95–125.
6. Clayton, S. C.; Regan, A. C. *Tetrahedron Lett.* **1993**, 34, 7493–7496.
7. Liang, F.; Navarro, H. A.; Abraham, P.; Kotian, P.; Ding, Y.-S.; Fowler, J.; Volkow, N.; Kuhar, M. J.; Carroll, F. I. *J. Med. Chem.* **1997**, 40, 2293–2295.
8. Bordwell, F. G.; McKellin, W. H. *J. Am. Chem. Soc.* **1951**, 73, 2251–2253.
9. Bremner, J.; Julia, M.; Launay, M.; Stacino, J.-P. *Tetrahedron Lett.* **1982**, 23, 3265–3266.
10. Ochiai, M.; Ukita, T.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1983**, 619–620.