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α-Iodocycloalkenones: Synthesis of (±)-Epibatidine

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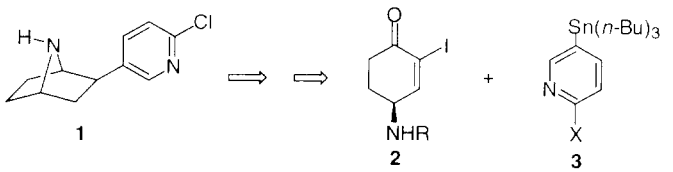
Abstract: A synthesis of the non-opiate analgesic alkaloid epibatidine was achieved in 13 steps and 13% overall yield starting from 1,3-cyclohexadiene using in a key step a modified Stille coupling reaction on an α-iodocyclohexenone.

Epibatidine (**1**), a unique alkaloid isolated from Ecuadorian poison frog *Epipedobates tricolor* by Daly and co-workers,[1] is a highly potent, non-opioid analgesic and nicotinic acetylcholine receptor agonist.[2] Its low abundance in nature (< 1 mg from 750 frogs) and remarkable biological activity makes it an attractive subject for total synthesis. More than twenty papers featuring the synthesis or approaches to the synthesis of epibatidine and analogues have been published.[3]

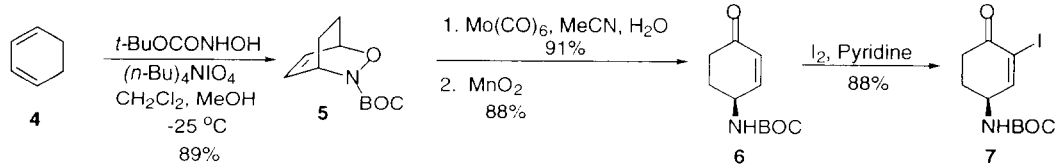
In this communication, we report a total synthesis of racemic epibatidine (**1**) which is unique among the approaches to the target in that it involves a modified Stille coupling reaction between α-iodoenone **2** and the pyridylstannane **3** to introduce the pyridyl subunit on the central six-carbon skeleton (Scheme 1).[4]

Scheme 1



The synthesis of the requisite α-iodo enone is outlined in Scheme 2. An *in situ* generated nitroso reagent underwent cycloaddition with 1,3-cyclohexadiene (**4**) to afford the adduct **5**.[5] Reductive cleavage of N-O bond was achieved by using $Mo(CO)_6$ in wet acetonitrile.[6] The resulting allylic alcohol was oxidized with activated MnO_2 to give enone **6** (mp 113-114 °C); α-iodination of the latter was carried out using a method developed in our laboratory to obtain **7** (mp 142-142.5 °C).[7]

Scheme 2



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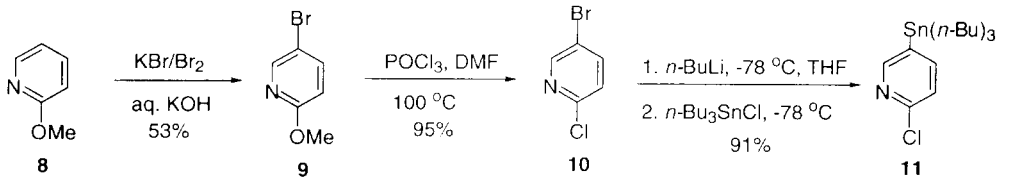
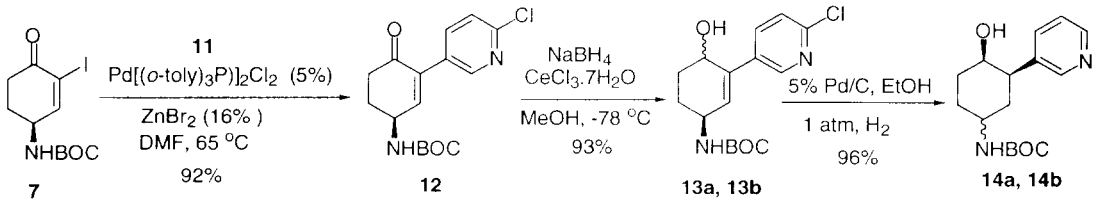
The preparation of pyridylstannane **11** required for the key coupling step is shown in Scheme 3. Bromination of 2-methoxypyridine (**8**) in the presence of KBr gave 2-methoxy-5-bromo pyridine (**9**)[8] which was transformed to 2-chloro-5-bromo pyridine (**10**) under Vilsmeier conditions.[9] The preparation of pyridylstannane **11** was completed by generating the pyridyllithium by lithium/halogen exchange and treatment with tributylstannyl chloride.

Scheme 3



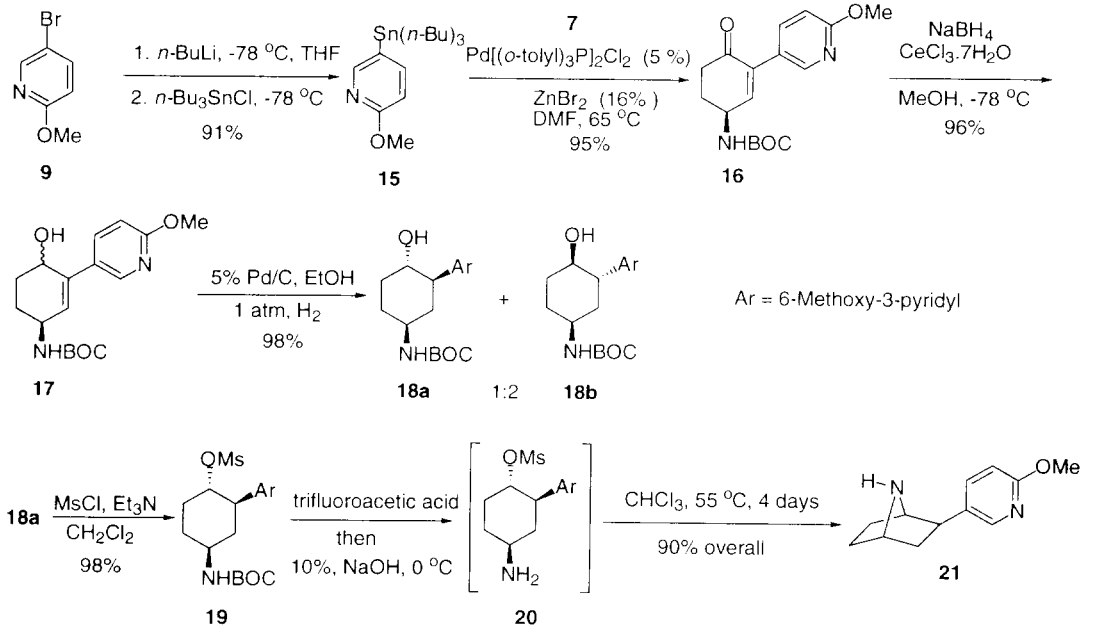
The crucial Stille coupling is shown in Scheme 4. Iodoenone **7** underwent coupling with pyridylstannane **11** in the presence of $Pd[(o\text{-tolyl})_3P]_2Cl_2$ as a catalyst, to give the α-functionalized enone **12** (mp 143-144 °C) in excellent yield.[10] Under Lüche conditions, **12** gave diastereomeric allylic alcohols **13a** and **13b** (1:2) as an inseparable mixture.[11] Although the diastereomeric ratio remained unchanged,[12] concomitant reduction of the chloro substituent was observed, producing **14a** and **14b**, under a variety of hydrogenation conditions. This dechlorination dilemma has been reported in several previous syntheses of epibatidine.[3b, 3e]

Scheme 4



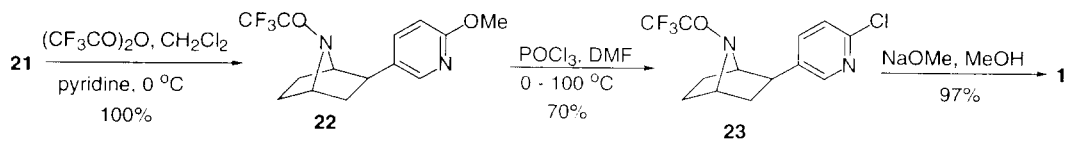
Adopting a strategy to install the chloro substituent at a later stage of the synthesis, α-iodoenone **7** and 2-methoxy-5(tri-*n*-butyl)stannylpyridine (**15**) were coupled using modified Stille conditions. The resulting coupled product **16** (mp 129-130 °C), was converted to the fully reduced ring system as described earlier. The diastereomeric alcohols **18a** and **18b** were separated, the desired, and unfortunately minor, isomer **18a** was converted to the mesylate **19** and removal of the BOC group set the stage for intramolecular cyclization. The aminomesylate **20** was heated in $CHCl_3$ to obtain the fully assembled 7-azabicyclo[2.2.1] system **21** (Scheme 5).[3f]

Scheme 5



Conversion of intermediate **21** to epibatidine was achieved in 3 steps (Scheme 6). First apical nitrogen was protected as trifluoroacetamide **22**, which gave **23** under Vilsmeier conditions. Removal of trifluoroacetamide under basic conditions gave epibatidine (**1**)[13] (mp 50 °C, lit.[3] 50-51 °C).

Scheme 6



In conclusion, a convenient and relatively short process has been developed for the total synthesis of epibatidine from cyclohexadiene (13 steps and 13% overall yield). The route provides an illustration of the utility of transition-metal catalyzed coupling strategies involving α-iodocycloalkenones.[14]

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10. Instead of 5% of $Pd[(o\text{-tolyl})_3P]_2Cl_2$, 5% of $Pd(PhCN)_2Cl_2$ and 10% of $P(o\text{-tolyl})_3$ could be used without any sacrifice in yield.

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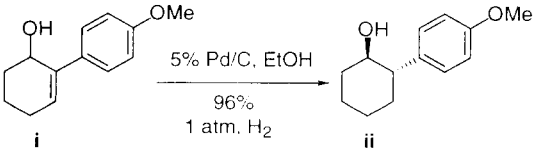
12. In a model study allylic alcohol **i** gave only single diastereomeric alcohol **ii** upon catalytic hydrogenation:



i ii

13. (±)-**1**: ^{13}C NMR ($CDCl_3$) δ 30.1, 31.2, 40.3, 44.5, 56.4, 62.7, 123.9, 137.6, 141.0, 148.8, 148.9 (lit.[3f] 29.8, 31.2, 40.1, 44.4, 56.6, 62.8, 124.0, 137.7, 140.6, 148.8, 149.0).

14. See for examples Johnson, C. R. ; Braun, M. P. *J. Amer. Chem. Soc.* **115**, 11014 (1993); Miller, M. M.; C. R. Johnson, C. R. *J. Org. Chem.* **62**, 1582 (1997); Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1993**, *115*, 7021; Brosius A. D.; Overman L. E. *J. Org. Chem.* **1997**, *62*, 440. Commins, D. L.; Joseph, S. P.; Chen, X.*Tetrahedron Lett.* **1995**, *36*, 9141. For a pioneering contribution is this area see Negishi, E.; Owczarczyk, Z. R.; Swanson, R. D. *Tetrahedron Lett.* **1991**, *32*, 4453.