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Efficient Synthesis of (+)-N-BOC-*exo*-2-(methoxycarbonyl)-7-Azabicyclo[2.2.1]heptane, A Versatile Intermediate for the Synthesis of Epibatidine and Epiboxidine

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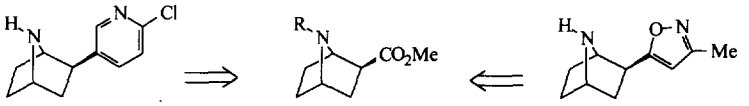
Abstract: N-BOC-*exo*-2-(methoxycarbonyl)-7-azabicyclo[2.2.1]heptane, an important intermediate for the synthesis of epibatidine and its analogs was efficiently synthesized from N-BOC-*exo*-2-(methoxycarbonyl)-7-azabicyclo[2.2.1]hepta-2,5-diene (**5**) *via* hydrogenation followed by reductive dehalogenation or *via* hydrodehalogenation followed by epimerization. The diene **5** was obtained by Diels-Alder reaction.

The alkaloid epibatidine (**1**) was first isolated from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*, by Daly and workers[1], and has been recognized as the most potent non-opioid analgesic.[1-3] The unique 7-azabicyclo[2.2.1]heptane ring system and remarkable biological profile has stimulated significant interest in the total synthesis of epibatidine around the world. This has been reviewed by Chen and Trudell.[4] Recently epiboxidine (**2**), an isoxazole containing isostere of epibatidine has been synthesized and shown to be 10-fold less potent than epibatidine, but 20-fold less toxic than epibatidine.[5]

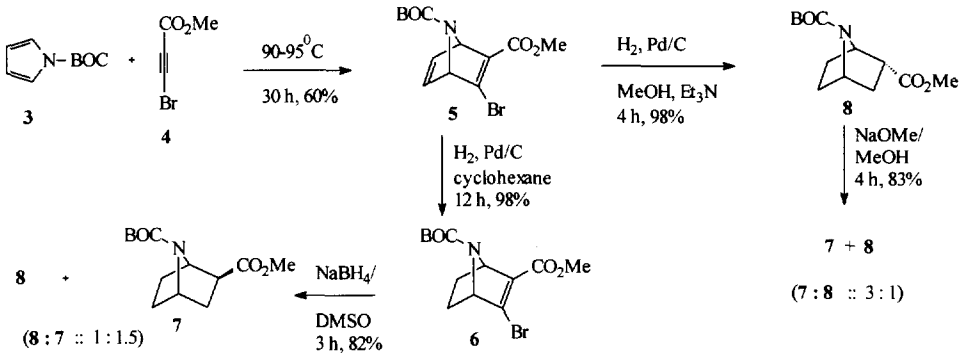


1 **2**

The N-protected *exo*-2-(methoxycarbonyl)-7-azabicyclo[2.2.1]heptane is an important intermediate for the synthesis of epibatidine[6] and epiboxidine.[5] The N-protected *exo*-2-(methoxycarbonyl)-7-azabicyclo[2.2.1]heptane has been previously synthesized from tropinone by ring contraction[6] or from L-glutamic acid and levulinic acid.[7] In this communication, we report an efficient synthesis of (+)-N-BOC- *exo*-2-(methoxycarbonyl)-7-azabicyclo[2.2.1]heptane.

As shown in Scheme 1, 5 equiv of N-BOC-pyrrole (**3**)[8] was reacted with methyl-3-bromopropiolate (**4**)[9] at 90-95^{0}C for 30 h to give [4+2] cycloadduct **5** in 60% yield.[10] Hydrodehalogenation of **5** was next attempted with Pd/C and H_2 in cyclohexane as solvent. This reaction was very selective and only the unsubstituted double bond was hydrogenated. Longer reaction times (48 h) led to only 22-25% of the hydrodehalogenated product **8**. The reaction of **5**, however, was much faster when hydrodehalogenation was conducted in the presence of 1.1 equiv of triethyl amine base and methanol as solvent.[11] Although the reaction was complete in about 4 h; only the *endo* ester (**8**) was produced (>95%).

Scheme 1



Thus alkene **6** was obtained by stirring diene **5** in cyclohexane with 10%Pd/C (10 wt.%) at atmospheric pressure under H_2 for 12 h in quantitative yield. The alkene **6** was then reductively dehalogenated with 2 equiv of sodium borohydride in dimethyl sulfoxide at room temperature under dry N_2 in 82% yield.[12] A mixture of *exo/endo* esters was obtained. It is interesting to note that *exo/endo* ratio of the two esters was 1.5:1 (**7:8**) as determined by ^{1}H NMR data.[7] Alternatively, the *endo* ester (**8**) was epimerized to the *exo* ester (**7**) with 2.5 equiv of sodium methoxide in methanol in 83% yield by refluxing for 4 h. The ratio of the *exo/endo* ester was 3:1 (**7:8**). The *exo* ester (**7**) was relatively more polar compared to the *endo* ester (**8**) and was easily separated by column chromatography (15:1; petroleum ether/EtOAc).

In summary, a facile and practical synthesis of N-BOC-*exo*-2-(methoxycarbonyl)-7-azabicyclo[2.2.1]heptane (**7**) was developed from readily available materials using mild and readily controlled reactions. Compound **7** can be utilized to prepare epibatidine, epiboxidine and other analogs.

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