Abstract

The goal of this research was to synthesize the natural product epibatidine, a non-opiate analgesic and nicotinic acetylcholine agonist originally isolated from Epipedobates tricolor. A synthetic pathway utilizing a Diels-Alder cycloaddition of a 3-pyridyl substituted pyrrole and tosylacetylene was conceived based upon the original mass spectral fragmentation pathway of epibatidine determined by Daly. Although this pathway had been previously attempted using 1-(triisopropyl)-3-[5-(2-chloropyridyl)]pyrrole in the key Diels-Alder step, the lack of cycloadduct suggested that a pyrrole with a more electron withdrawing protecting group was required for this step. Therefore, synthesis of 1-(phenylsulfonyl)-3-[5-(2-chloropyridyl)]pyrrole via a palladium catalyzed cross-coupling reaction of 1-(phenylsulfonyl)-3-pyrroline and 2-chloro-5-iodopyridine was set as a synthetic goal and accomplished. The 1-(phenylsulfonyl)-3-pyrroline could be obtained by reduction of 1-(phenylsulfonyl)pyrrole with sodium cyanoborohydride in trifluoroacetic acid.

The key Diels-Alder reaction required further investigation to determine the extent to which 1-(phenylsulfonyl)pyrrole would undergo cycloaddition with dienophiles such as tosylacetylene and dimethyl acetylenedicarboxylate. A solid foundation had been established for this reaction under thermal conditions, but the use of microwave irradiation to afford the cycloaddition had not been previously investigated. It was found that this reaction occurs readily upon microwave irradiation, although not to the extent that the original thermal reactions did. Since it has always been assumed that strongly electron withdrawing substituents on the pyrrole nitrogen serve to decrease the aromaticity of this heterocycle, an even more electron withdrawing pyrrole, 1-(4-nitrophenylsulfonyl)pyrrole was synthesized and reacted under Diels-Alder conditions with dimethyl acetylenedicarboxylate, although no conclusion could be drawn on which diene is more reactive.

The stumbling block of this research has been the Diels-Alder reaction of 1-(phenylsulfonyl)pyrrole with tosylacetylene. Although a product was isolated from the reaction, it was determined this product was not to be the desired cycloadduct and has remained unknown following limited characterization. The Diels-Alder reaction of 1-(phenylsulfonyl)-3-[5-(2-chloropyridyl)]pyrrole was attempted with tosylacetylene but the desired cycloadduct could not be found.