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A Novel Synthesis of Compounds Containing a Fused Pyrrole Ring from Cyclic Ketones and *N*-BOC-L-Phenylalaninal

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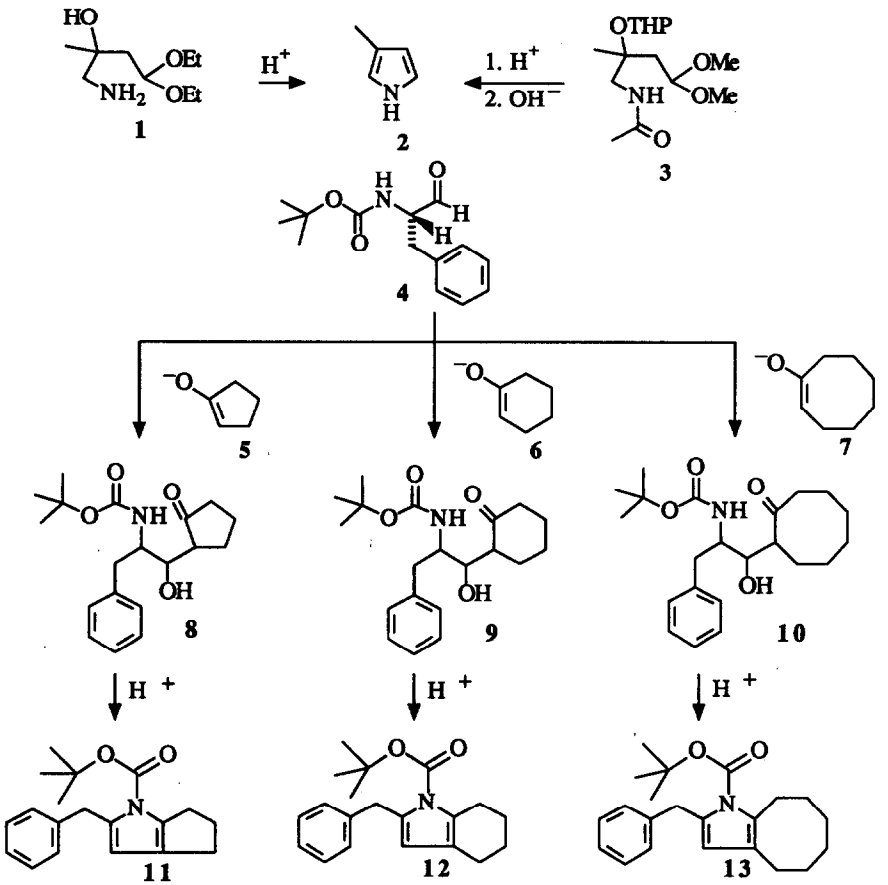
Key Words: Pyrrole synthesis, N-BOC-L-Phenylalaninal.

Abstract: A synthesis of fused pyrrole-containing compounds from N-Boc-L-phenylalaninal and cyclic ketones is described.

The importance of compounds containing pyrrole rings in natural products chemistry has led to the development of a variety of methods for their synthesis.[1] These include the cyclization of 4-amino or 4-imino carbonyl compounds, which are often prepared by the reduction of 4-nitro[2] or 4-*aci*-nitro[3] carbonyl compounds. The 4-amino acetal **1**, prepared by opening of an epoxide with ammonia, cyclized and dehydrated to 3-methylpyrrole (**2**) in aqueous citric acid.[4] Alternatively, intermediate **3** has been prepared by conversion of β-ketobutyraldehyde dimethylacetal to the cyanohydrin and protection of the alcohol as the THP ether, followed by reduction of the nitrile and acetylation of the resulting amine.[5] Compound **3** has also been converted to 3-methylpyrrole (**2**) by treatment with *p*-toluenesulfonic acid in refluxing acetone, followed by hydrolysis of the resulting *N*-acylpyrrole under basic conditions.[5] The disadvantage of these pyrrole syntheses is that they involve multistep procedures which are tedious and compromise the overall yields. We have therefore sought alternative methods for the preparation of 3-hydroxy-4-aminocarbonyl derivatives that would cyclize to pyrroles under acidic conditions. This led to an investigation of the reaction of enolates **5-7** derived from cyclic ketones with BOC-L-phenylalaninal (**4**)[6,7] to afford intermediates **8-10**,[8] which were expected to form products **11-13** containing fused pyrrole rings under acidic conditions. We now report that this strategy has in fact provided high yields of the desired substances in two steps.

The *N*-BOC-L-phenylalaninal (**4**) used in these studies was prepared by lithium aluminum hydride reduction of *N*-(*tert*-butoxycarbonyl)-L-phenylalanine *N*-methoxy-*N*-methylamide[6] at -50 °C in ether.[7] For the synthesis of *N*-BOC-2-benzyl-4,5,6,7-tetrahydro-1*H*-indole (**12**), lithium diisopropylamide (11 mmol) was added to a stirred solution of cyclohexanone (10 mmol) in tetrahydrofuran (30 mL) at -78 °C, and the reaction was allowed to proceed for 1.5 h. A solution of *N*-BOC-L-phenylalaninal (5 mmol) which had been cooled on a dry ice-acetone bath was added dropwise with a syringe at a rate to maintain the temperature of the reaction mixture at -78 °C, and stirring was continued for an additional 5 min. The reaction mixture was then quenched with water (25 mL), ether (400 mL) was added, and the solution was washed with water (4 x 100 mL), once with brine (100 mL), dried with magnesium sulfate, and evaporated to afford aldol **9** as a mixture of diastereomers in 70% yield. The diastereomeric mixture **9** (1 mmol) was dissolved in methylene chloride (10 mL) at room temperature, 2 drops of conc. hydrochloric acid were added, and the solution was stirred at room temperature until TLC indicated that the starting material had disappeared (about 1 h). The solution was diluted with methylene chloride (20 mL), washed with aq sodium bicarbonate (10 mL) and water (10 mL), dried with magnesium sulfate, and evaporated. The residue was purified on a silica gel column, eluting with hexane-chloroform (3:1), to give the product **12** in 90% yield as a yellow oil.[9] Fused pyrroles **11** and **13** were prepared by similar procedures.

Although we have not yet studied the scope of this method, it appears to have potential for application to the synthesis of a wide variety of pyrroles because of the ready availability of many amino acids and ketones.



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9. IR (film) 2931, 1733, 1368, 1325, 1133, 1084 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.12-7.34 (m, 5 H), 5.50 (s, 1 H), 4.15 (s, 2 H), 2.78 (m, 2 H), 2.35 (m, 2 H), 1.71 (m, 4 H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 140.0, 133.0, 129.9, 128.7, 128.1, 125.8, 120.2, 112.6, 83.0, 35.7, 27.9, 25.6, 23.7, 23.1, 22.8; CIMS *m/e* (relative intensity) 312 (34), 310 (90), 286 (20), 270 (63), 254 (73), 242 (59), 226 (100). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09; N, 4.50. Found: C, 76.79; H, 8.32; N, 4.43.

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