

An Efficient Synthetic Pathway to Chloroethylpyrroles

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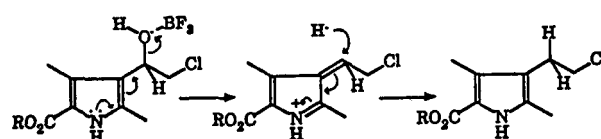
For the preparation of protoporphyrins or chlorophylls the chloroethylpyrroles are the key intermediate to the vinyl substitution and many researchers used the 3-(2-methoxycarbonyl)ethylpyrroles as the starting materials which can be prepared by way of Johnson-Kleinspohn pyrrole synthesis¹ or $Ti(NO_3)_3$ treatment to the 3-acetylpyrroles (1)². T. Wollmann and B. Franck³ recently investigated a new pathway to 3-(2-methoxycarbonyl)ethylpyrroles from the easily made 3-acetylpyrroles (1) using the chloroacetylpyrroles (2) as an intermediate, but synthesis of the chloroethylpyrroles from the acetylpyrroles have not been known yet.

Usually the chloroethylpyrroles are made from the 3-(2-methoxycarbonyl)ethylpyrroles as the starting material. For the preparation of the 3-(2-methoxycarbonyl)ethylpyrroles, however you need methyl 3-acetyl-4-oxopentanoate which is derived from the reaction of the 2,4-pentanedione with methyl chloroacetate, which gave pyrroles with somewhat lengthy procedures and low yield.

Furthermore the 3-(2-methoxycarbonyl)ethylpyrroles need to be treated with BH_3 followed by $SOCl_2$ to give the desired chloroethylpyrroles⁴.

Now we found a new novel synthetic pathway to chloroethylpyrroles (3) and the 3-(2-chloro-1-hydroxyethyl)pyrroles from the easy-prepared acetyl compounds (1).

Because the conversion of the aromatic acetyl compounds to the alkyl aromatics by BH_3 or $NaBH_4$ and BF_3 etherate is well known⁵ we treated the chloroacetylpyrroles (2) with BH_3 in THF aiming the desired chloroethylpyrroles (3). Unfortunately, the reaction gave us the mixture of 3-(2-chloro-1-hydroxyethyl)pyrroles (4) and 3-(2-chlorovinyl)pyrroles. $NaBH_4/BF_3$ etherate was also tried but the same result was



Scheme 1

occurred. Without BF_3 etherate, however the chloroacetylpyrroles (2) with $NaBH_4$ in THF were transformed quantitatively into the 3-(2-chloro-1-hydroxyethyl)pyrroles only.

From this result we used BF_3 etherate along with BH_3 in THF and obtained the desired chloroethylpyrroles (3) quantitatively. $NaBH_4$ was also used along with the excess of BF_3 etherate give the same result. This new excellent procedure to chloroethylpyrroles can shorten the synthetic pathway to porphyrins with high yield. In addition the hydroxy compounds (4) were easily converted into chlorovinylpyrroles (5) over 90% yield, which are the useful key intermediates in bipyrrole synthesis⁶, by treatment with 10% HCl in THF at 50 °C for 30 min. Chlorovinylpyrroles were converted to the desired chloroethylpyrroles by hydrogenation on the 10% Pd-C/THF. On the obtaining the chloroethylpyrroles, we postulate that the hydroxy group in the chlorohydroxyethyl intermediates was promoted by BF_3 to give the pyrrolinium ion which was reduced by the hydride ion to give rise to the desired chloroethylpyrroles (Scheme 1). Without BF_3 etherate the hydroxy intermediates are not further promoted easily and the mixtures of the chlorohydroxyethylpyrroles and chlorovinylpyrroles are obtained.

Representative Procedure. Benzyl 3-Chloroethyl-2,4-dimethylpyrrole-5-carboxylate (3)¹: Benzyl 3-Chloroacetyl-2,4-dimethylpyrrole-5-carboxylate (2)³ (1g, 3.27 mmol) was dissolved in dry THF (10 ml) under nitrogen atmosphere and BF_3 etherate (0.5 ml) was added. BH_3/THF (10 ml) was transferred by the syringe to the reaction mixture slowly at 0 °C and was stirred at room temperature for 2 hr followed by quenching with methanol. The solvent was removed in vacuo to give solid which was chromatographed on silica gel with dichloromethane and evaporation of the solvent gave the desired product in 95% yield. mp = 119-120 °C (Lit.¹, mp = 118-119 °C)

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