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METAL ION-CATALYSED REDUCTION OF INDOLIC IMIDES, A FACILE β-CARBOLINE SYNTHESIS

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Abstract: A novel procedure for the synthesis of β-carbolines by metal catalysed reduction of imides with sodium borohydride is described.

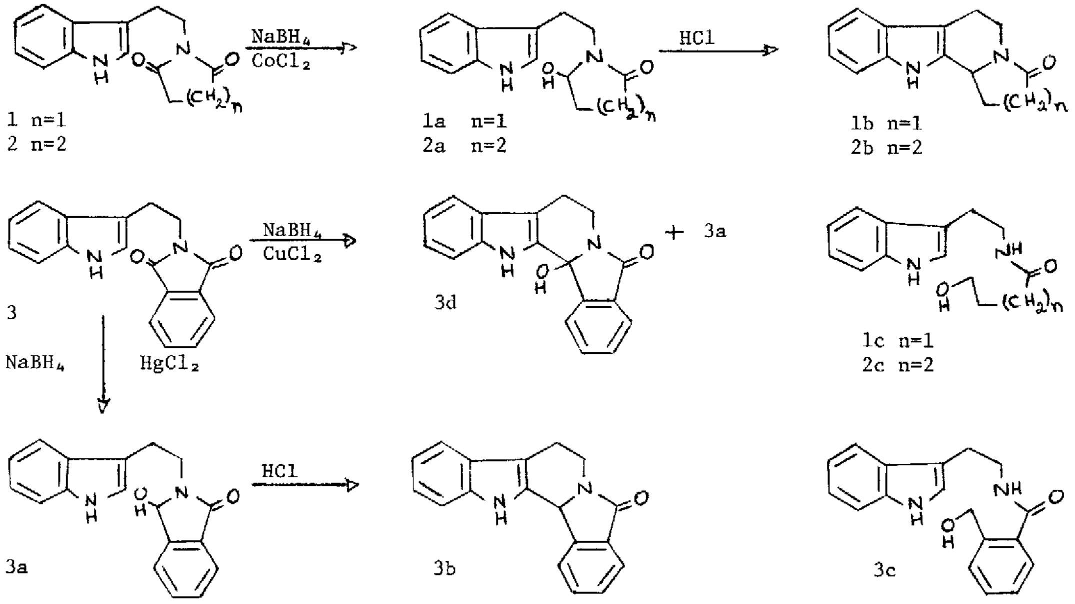
Our previous efforts to develop new organic reactions[1-4] led us to report new syntheses of β-carboline systems from N-imidotryptamines[5-7]. We now report the clean conversion of N-imidotryptamines to the corresponding α-hydroxy lactams in the presence of various metal halides, HCl being unnecessary in this step. The α-hydroxy lactams could then be cyclised to the corresponding β-carbolines in the presence of acid.

N-Succinimidotryptamine (1) when treated with $NaBH_4$ (5 equiv.), and $CoCl_2$ (1 equiv.), in EtOH at 0°C for two hours was cleanly converted to (1a) in 95% yield with trace formation of the cleaved alcohol (1c). The hydroxylactam (1a) was convertible to the β-carboline (1b) on treatment with conc. HCl at 30°C in quantitative yield. When the reaction was conducted in the absence of $CoCl_2$ only 60% conversion to (1a) was achieved after two hours. Similar catalytic action of metals was observed with $NiCl_2$, $CrCl_3$, $FeCl_3$, $SnCl_2$, $SrCl_2$, $MnCl_2$ and $CeCl_2$. Interestingly $CuCl_2$ was found to be most effective in preventing the formation of the over-reduced amide alcohol (1c), the hydroxylactam (1a) being the only product observable even after several hours. The presence of $CdCl_2$ retarded the reactions.

Similarly N-glutarimidotryptamine (2) on reaction with $NaBH_4$ (5 equiv.) and $CoCl_2$ (1 equiv.) at 0° in EtOH afforded the hydroxylactam (2a) which cyclised to the β-carboline (2b) on treatment with conc HCl (5 mts.) in over 95% overall yield.

N-Phthalimidotryptamine (3) when treated with $NaBH_4$ (5 equiv.) and $HgCl_2$ (1 equiv.) in EtOH at 0°C was converted to (3a) and traces of (3c) within 5-10 minutes. On stirring for 30 minutes with conc. HCl at 30°C, the hydroxylactam (3a) afforded the β-carboline (3b) in quantitative yield. Similar catalysis was observed with $CrCl_3$, $SnCl_2$, $MnCl_2$, and $CeCl_2$, while in the presence of $CuCl_2$, $FeCl_3$ and $NiCl_2$ the new product (3d) was also formed.

The catalysis is attributed to complexation of the metal ions with the imide nitrogen or carbonyl oxygen which makes the imide carbonyl groups more electrophilic for attack by hydride ion. The undesired over-reduction[8], which is facilitated by longer reaction times and higher $NaBH_4$ concentrations, is effectively avoided under these conditions. This new procedure makes the presence of HCl in the reduction step, as stipulated previously[6,9], quite unnecessary, and offers an attractive high yield route to β-carbolines.



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