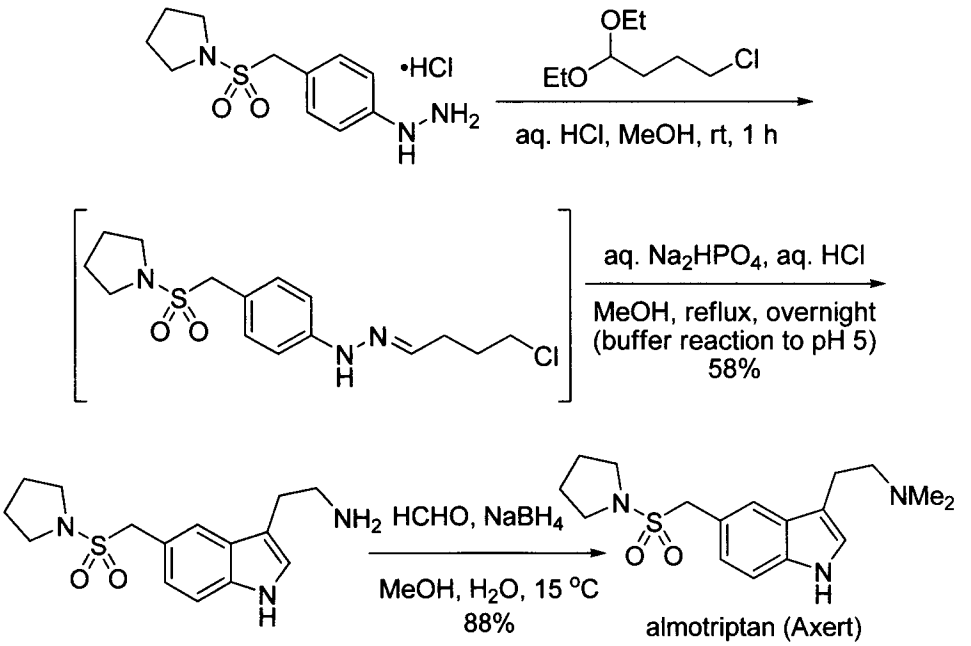
The Grandberg modification of the Fischer indole reaction is another example of understanding the reaction mechanism of the Fischer indole synthesis.[16] It takes advantage of the fact that one molecule of ammonia is released in the Fischer indole synthesis. When an alkyl halide is present, ammonia attacks it in an S_N2 fashion to give a primary amine. For instance, the Grandberg modification was applied in a synthesis of almotriptan (Axert), Almirall's triptan for the treatment of migraine.[17] As shown below, the hydrazine was treated with 4-chlorobutanal diethyl acetal in aqueous HCl and the resulting hydrazone precipitated out and was isolated by filtration. Treatment of the crude hydrazone with aqueous HCl buffered with Na_2HPO_4 to pH 5 promoted the Grandberg modification of the Fischer indole synthesis whereby the alkyl chloride underwent aminolysis under the reaction conditions to afford the tryptamine in 58% yield. Reductive alkylation of the indoloethylamine with formaldehyde in the presence of $NaBH_4$ then provided almotriptan.



3.3.2 Mori–Ban Indole Synthesis

The Mori–Ban indole synthesis[18] is referred to the intramolecular version of the Heck reaction applied to synthesis indoles. The cyclization of *o*-halo-*N*-allylanilines to indoles is a general and efficient methodology. For example,[18a] the conversion to 3-methylindole can be performed at lower temperature, shorter reaction time, and with less catalyst.