Category

Innovative Drug Discovery and Development

Key words

Prins reaction

Friedel–Crafts acylation

piperidine

schizophrenia

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Chemistry and Pharmacology of CNS Depressants Related to 4-(4-Hydroxy-4-phenylpiperidino)butyrophenone. Part I — Synthesis and Screening Data in Mice

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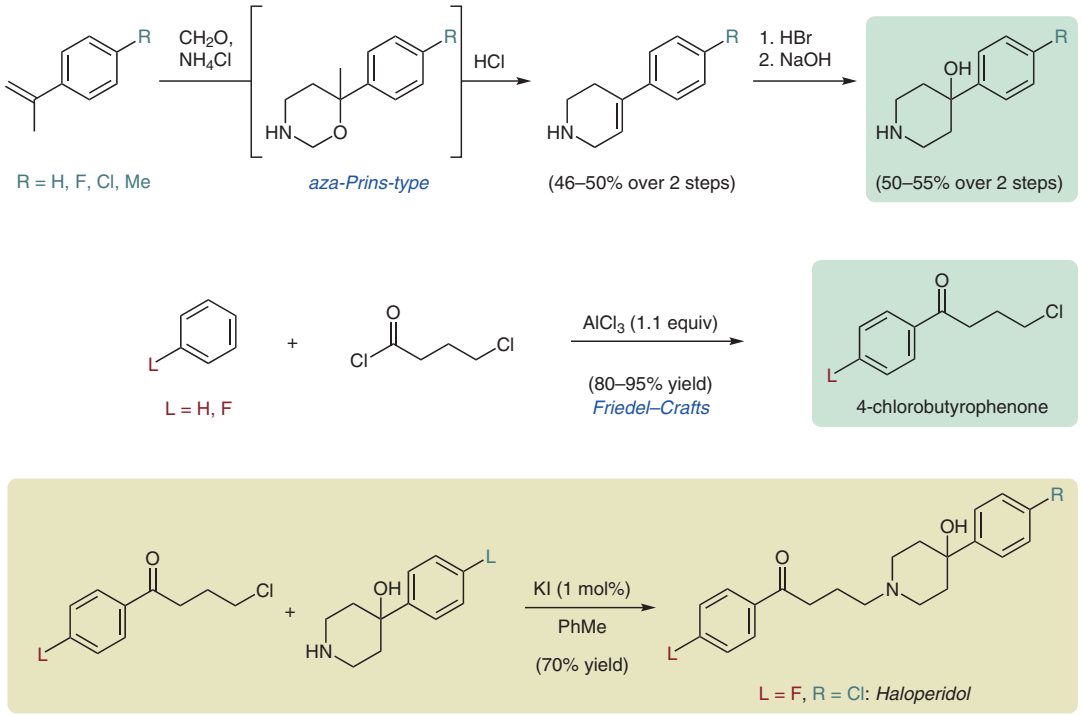
Discovery of Haloperidol



Significance: Schizophrenia is a condition marked by positive and negative symptoms such as hallucinations and cognitive disruption. The global prevalence has been estimated to reach up to one percent of all people across their lifetime; as such, pharmacological and non-pharmacological interventions have been investigated for decades. The discovery of Haloperidol by Janssen and co-workers in 1959 invigorated efforts to discover molecules with antipsychotic effects, efforts that continue to this day.

Comment: Haloperidol was discovered in the course of screening hundreds of Brønsted basic ketones. Its synthesis follows a convergent approach that unites the piperidine (Brønsted base) and butyrophenone (ketone) fragments via a substitution reaction. The substituted piperidines are formed in an aza-Prins-type reaction of α-methylstyrenes (*J. Am. Chem. Soc.* **1955**, *77*, 5698), forming 4-phenyl-tetrahydropiperidine intermediates that undergo hydrobromination and hydrolysis. Friedel–Crafts acylation affords the requisite 4-chlorobutyrophenones. The desired combination of potency and duration were observed when L = F and R = Cl (Haloperidol).

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