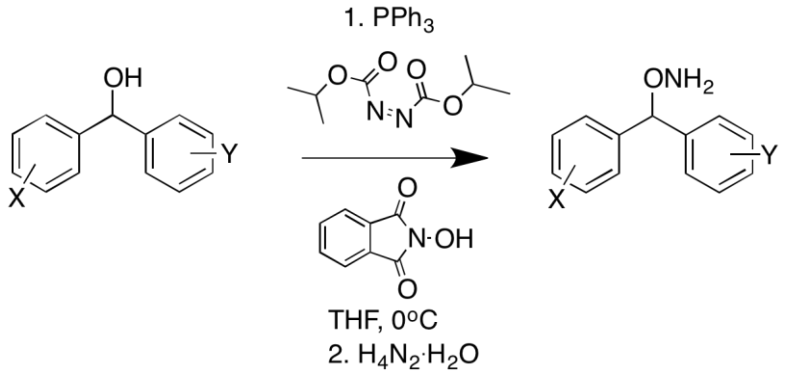
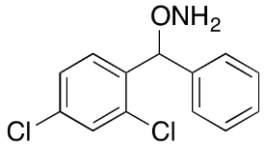
Synthesis of Hydroxylamines as Indoleamine-2, 3-dioxygenase Inhibitors

Indoleamine-2, 3-dioxygenase (IDO) is an enzyme that has been found in high levels in cancer patients and linked to a decline in T cells. Research suggests that inhibiting the function of this enzyme could improve the effectiveness of chemotherapy by promoting a more robust immune response to the developing tumor.

O-Hydroxylamines have been found to be inhibitors of IDO; specifically, compounds containing multiple phenyl rings and electron withdrawing groups seem to be the most effective. Hydroxylamines can be synthesized via the Mitsunobu reaction, which involves the substitution of primary and secondary alcohols with a nucleophile in the presence of triphenylphosphine and diisopropyl azodicarboxylate. In a second step, hydrazine monohydrate is added in order to reveal the critical hydroxylamine moiety.



The product is then recrystallized as an HCl salt for testing on isolated IDO by our biological collaborators at Lankenau Institute of Medical Research. The effectiveness of a compound in inhibiting the function of an enzyme is measured using the half maximal inhibitory concentration (IC_{50}). The current lead compound synthesized by the Malachowski group has an IC_{50} of 0.186 μM. The goal is to synthesize a more potent compound, preferably with an IC_{50} less than 100 nM.



Lead compound