

## Abstract

**Thesis:** Synthesis of Substituted 2-Amino-3-Cyano-4H-Chromenes

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The Knoevenagel reaction is defined by the condensation of an aldehyde or ketone with a carbon nucleophile produced by the deprotonation of a methylene species whose acidity is dramatically increased by bonds to strongly electron withdrawing groups. Previously, our group developed an effective one-pot method for the preparation of 4H-chromenes using sodium borohydride reduction of the cyclized intermediates formed by the Knoevenagel condensation of malononitrile with salicylaldehydes in aqueous ethanol. In this study we outline the extension of these strategies to include 2'-hydroxyphenylketones as the starting material. Many of these compounds are also unique and were prepared by Friedel-Crafts acylation of phenols with acyl chlorides and/or Fries Rearrangement of the corresponding phenyl ester.

The objective of this project has been to expand the application of the methods optimized in our lab for the simple and efficient formation of carbon-carbon bonds via the selective reduction of the alkylidene portion of the Knoevenagel reaction products. These methods have allowed for the production of several important classes of natural product-like compounds. Specifically, in this investigation, we have adapted these methods to the production of various 4-alkyl and 4-aryl substituted 3-amino-2-cyano-4H-chromenes. These types of molecules exhibit diverse pharmacological activity and have been shown to be potentially useful for the treatment of various diseases. A subset of the synthesized compounds will be submitted to Eli Lilly through their PD<sup>2</sup> program.

Further variation of substrates included the reaction of salicylaldehydes with ethyl cyanoacetate or cyanoacetamide which provided products unreported in the literature. Reactions with cyanoacetates gave the expected 3-carboethoxy(ester) functionalized 4H-chromene compounds. Products from cyanoacetamide were found to occur in open rather than cyclized forms.