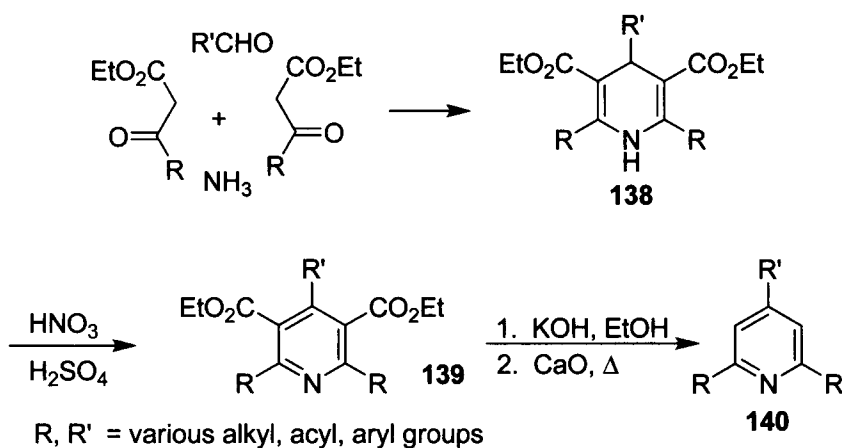


Hantzsch (dihydro)pyridine synthesis

The Hantzsch pyridine synthesis⁸⁶ is the condensation of two equivalents of a β -dicarbonyl compound such as ethylacetoacetate, one equivalent of an aldehyde, and one equivalent of a nitrogen donor such as ammonia (or ammonium acetate) in refluxing alcohol or acetic acid. The immediate result from this three-component coupling, 1,4-dihydropyridine **138**, is then oxidized, driven by aromatization, to substituted pyridine **139**. Saponification and decarboxylation of the 3,5-ester substituents then leads to symmetric 2,4,6-tri-substituted pyridine **140**.



Several research laboratories investigated the mechanism of the Hantzsch dihydropyridine synthesis.⁸⁷⁻⁹⁰ A comprehensive discussion on the mechanism is reported recently.^{85g}

The Hantzsch chemistry was used to construct model systems of NADH coenzyme to understand the mechanistic details of this biological reducing agent. Later on, the 1,4-dihydropyridines were identified to pose various biological activities such as vasodilator, bronchodilator, antitumor, hepato-protective, and gero-protective activity. Some of them are well-known calcium channel blockers and commercialized as cardiovascular and antihypertensive agents such as nifedipine (**141**), amlodipine (Norvasc, **142**) or nimodipine. Amlodipine (**142**) was one of the most prescribed medicines for hypertension and one of the biggest selling drugs worldwide. Improvements and modifications of the Hantzsch pyridine synthesis have also been reported in the past several decades. Herein we only give several recent literature examples.