SYNLETT
Spotlight 210

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Hantzsch 1,4-Dihydropyridine – An Effective and Convenient Reducing Agent

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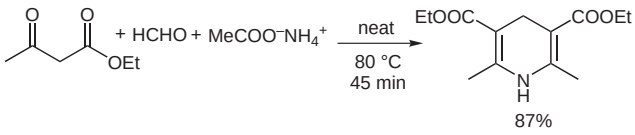
Dedicated to my research advisor Professor David E. Minter

Introduction

Hantzsch 1,4-dihydropyridine [$C_{13}H_{19}NO_4$, CAS: 1149-23-1] is a well-known reducing reagent that has found many applications in organic transformations.[1] In general, chemical hydrogenations of double-bond-containing compounds often involve the use of hydrogen gas with expensive and even toxic organometallic catalysts or stoichiometric amounts of metal hydrides.[2] To circumvent these drawbacks, one of the best alternatives is to apply organoreductants that possess excellent reproducibility.[3] 1,4-Dihydropyridine (DHP) has been used in hydrogen transfer reactions as a synthetic NADH model for the reduction of olefins, carbonyl compounds, and imines. In recent years, synthetic chemists have made many efforts to develop DHP as a widely used reducing agent and have obtained good to excellent results. Along with the conjugate hydride and proton transfer, DHP is usually subsequently oxidized to the Hantzsch pyridine.[4]

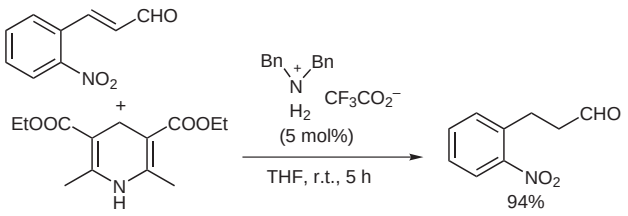
Asymmetric reduction of double-bond-containing compounds by DHP is of particular interest from the viewpoint of NADH models as well as for their synthetic utility.[5] While chiral Hantzsch esters have been employed stoichiometrically,[6] the potential of their simple achiral derivatives as cofactors in catalytic asymmetric reductions has also been explored. In this paper, the applications of DHP as an effective and convenient reducing agent for new synthetic methods and the catalytic asymmetric versions are presented.

The classical method for the synthesis of DHP is a one-pot condensation of formaldehyde, ethyl acetoacetate, and ammonia.[7] Diazomethane crystallizes in yellow needles with green fluorescence, mp 183–185 °C and is commercially available. The title compound can also be easily prepared from a combination of ethyl acetoacetate, formaldehyde, and ammonium acetate under mild and solvent-free conditions.[8]

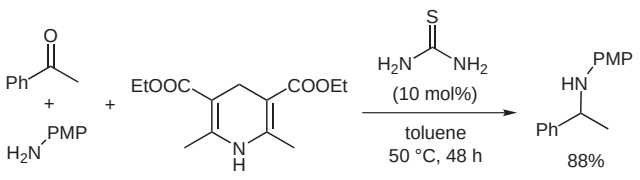


Abstracts

(A) Highly efficient and chemoselective conjugate reduction of α,β-unsaturated aldehydes can be achieved using DHP as a suitable hydride donor.[9] Cyclic as well as acyclic ammonium salts are used for catalysts, and the highest rate and yield are obtained by using dibenzylammonium trifluoroacetate salt.



(B) The direct reductive amination of ketones requires only catalytic amounts of thiourea as hydrogen bond donor and utilizes DHP for transfer hydrogenation.[10] This mild and nonacidic protocol relies on selective imine activation by hydrogen bond formation and allows application to complex or acid-sensitive substrates.



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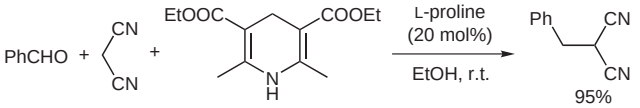
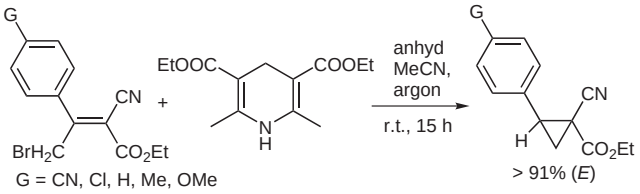
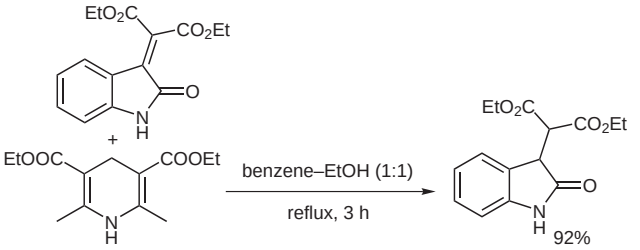
(C) A green approach to the two-carbon homologation of aldehydes using proline-catalyzed direct tandem Knoevenagel and hydrogenation reactions has been carried out in one pot.[11] This reductive methodology covers a broad scope of structurally diverse activated aldehydes and methylenes.



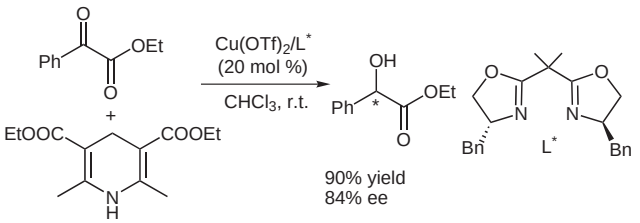
(D) Treatment of allylic and benzylic bromides by DHP gives various types of three-, five-, and seven-membered ring compounds in good yields.[12] It provides a new and high-yielding route to synthesize various cyclopropane, indane, and exopin derivatives under mild conditions.



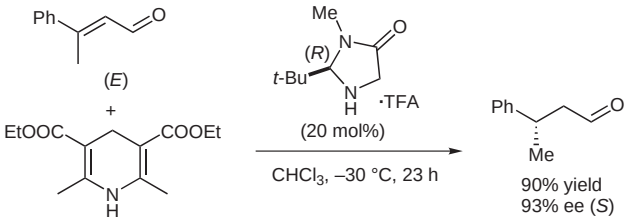
(E) DHP has been observed to be a useful selective reducing agent for the reduction of electron-deficient conjugated carbon–carbon double bonds.[13] The rate of this reaction is observed to be dependent upon the nature of the conjugated substituents and, consequently, the electronic nature of the unsaturated double bond.



(F) The catalytic enantioselective reduction of α-keto esters with DHP as a biomimetic hydrogen donor gives the corresponding α-hydroxy esters in excellent enantioselectivities using Cu(II)-bisoxazoline complex as chiral catalyst.[14]



(G) Organocatalytic hydride reduction allows the enantio- and chemoselective transfer of hydrogen from DHP to α,β-unsaturated aldehydes using imidazolidinone catalysts.[15] In marked contrast to most metal-mediated hydrogenations, isomerically pure *E*- and *Z*-olefin substrates converge to the same *S*-enantiomer products.



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