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Reactions of 1,2- & 1,4-dihydropyridines

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Abstract: This review provides a comprehensive compilation of available literature concerning the reactions of 1,2- & 1,4-dihydropyridines, which have opened new frontiers in the area of synthetic and medicinal chemistry. These reactions mainly include cycloaddition, 1,3-Dipolar cycloaddition, alkoxy halogenation, diamination, hydroxyamination, oxidation, hydroxylation, photooxygenation reaction, nucleophilic addition, cyclization, electrophilic substitution, multicomponent reactions (MCRs) and rearrangement reactions. 1,4-Dihydropyridine has also been used in hydrogen transfer reactions as a synthetic NADH model for the reduction of several important molecules in excellent yields.

Keywords: 1,2- 1,4-Dihydropyridines, aromatization, cycloaddition, diamination, oxidation, oxyselenation, photodimerisation, rearrangement.

1. INTRODUCTION

Over the years many outstanding discoveries have been made in the field of drug design and development with multifaceted drugs having great potential. 1,2- & 1,4-Dihydropyridines are such privileged structures which have revolutionized the pharmaceutical industry. It is a well explored scaffold which binds to multiple receptors, possesses a wide variety of biological features and also has its basis in biologically active natural products. Hantzsch in 1881 described dialkyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates (Hantzsch 1,4-DHP; Fig. **1**) which now have been recognized as vital drugs in the treatment of angina and hypertension [1a]. Various 1,4-dihydropyridines with cardiovascular properties (some of them are Amlodipine, Felodipine, Isradipine, Lacidipine, Nicardipine, Nifedipine, Nimodipine and Nitrendipine) have been discovered and it was found that these molecules act by inhibiting the entry of Ca^{2+} into the cells of cardiac and vascular muscle through the voltage-dependent calcium channels. Subsequently, the 1,4-dihydropyridine nucleus has served as scaffold for second and third generation drugs of this class and also as a scaffold or "privileged" structure for molecules active at a diverse collection of ion channels and pharmacological receptors. With the wide-ranging pharmacological activities of natural alkaloids and azasugars, their chemical synthesis is of great interest, many of which are accomplished starting from dihydropyridines. 1,4-Dihydropyridine derivatives are often regarded as models of the natural reduced nicotinamine adenine dinucleotide (NADH) coenzyme (Fig. **1**) which transfers an electron or a hydride ion to the substrate, thus acting as a redox reagent for biological reactions. 1,4-Dihydropyridines have been used for the reduction of the aldehyde and ketones, asymmetric reduction and reduction of the other biologically important heterocyclic compounds. The chemistry of dihydropyridines was earlier reviewed in 1972 and 1982 [1]. In this review article various types of reactions of 1,2- & 1,4-dihydropyridines have been discussed in detail.

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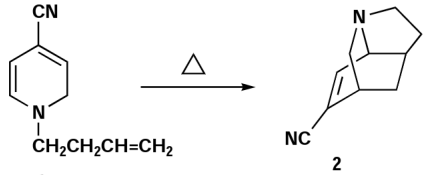
2. REACTIONS OF 1,2- & 1,4-DIHYDROPYRIDINES

2.1. Cycloaddition Reaction

A number of dihydropyridines undergo cycloaddition reaction e.g. [4+2] and [2+2] cycloaddition reactions.

2.1.1. [4+2] Cycloaddition Reactions (Diels-Alder Type Reactions)

The 1,2-dihydropyridine ring system behaves like diene component in the Diels-Alder reaction [2]. *N*-alkenyl-1,2-dihydropyridine **1** (in which both diene and dienophile are present), derived from *N*-alkenylpyridinium salts [3] or by heating the dihydropyridine dimer in toluene [4], undergo an intramolecular Diels-Alder reaction to give tricyclic amine **2** (Scheme **1**).



Scheme 1. Intramolecular [4+2] cycloaddition reactions of *N*-alkenyl-1,2-dihydropyridine **1**.

1,2-Dihydropyridines **3** & **4a-c** react with dienophile such as *N*-phenylmaleimide **5** and 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione **6** to give the Diels-Alder adducts **7** and **8**, respectively [5a]. F. W. Fowler [5b] observed that when a mixture of 1,2- and 1,4-dihydropyridines was treated with maleic anhydride **9**, only 1,2-dihydropyridines yielded the Diels-Alder adducts **10**, whereas the 1,4-dihydropyridines did not showed any reactivity with maleic anhydride **9** (Scheme **2**).

The ability of 1,2-dihydropyridines to undergo Diels-Alder reaction with dienophile such as methyl vinyl ketone **11** has been utilized in the synthesis of polyfunctional isoquinuclidine as a key intermediate in the synthesis of aspidosperma- and iboga-type alkaloids [6]. For example, the Diels-Alder reaction of *N*-benzyl-3-carboxamido-1,6-dihydropyridine **12a** and *N*-benzyl-3-cyano-1,6-dihydropyridine **12b** with methyl vinyl ketone **11b** yielded isoquinuclidines **13a** and **13b**, respectively, which can be converted

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