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Piperidin-4-one: The Potential Pharmacophore

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Abstract: The piperidin-4-ones have been reported as versatile intermediates. They have been synthesized using a variety of methods, including Mannich reaction and stereoselective synthesis. The piperidin-4-ones have been reported to possess various pharmacological activities, including anticancer and anti HIV activities. The pharmacophore can be suitably modified in order to achieve better receptor interactions and biological activities. The renewed interest in the nucleus has re-established the importance of piperidin-4-ones in medicinal chemistry. The review intends to discuss the current research trends in the synthetic protocols, characterization, stereochemistry and important biological activities of piperidin-4-ones during the last decade.

Keywords: Piperidin-4-one, Mannich reaction, stereochemistry, anticancer, antiviral, antimicrobial.

1. INTRODUCTION

One of the reasons for the widespread use of heterocyclic compounds is that their structures can be subtly manipulated to achieve the required modification in function. Heterocyclic compounds carrying piperidine skeleton are attractive targets of organic synthesis owing to their pharmacological activity and their wide occurrence in nature. Piperidine and its derivatives have high impact on medical filed due to their wide variety of pharmacological actions. Specifically, piperidine based chemical entities, with aryl substituents at carbons 2 and 6 of the piperidone ring, have been well documented. [1]. Piperidin-4-ones **2** (Scheme **1**) belong to the family of heterocyclic and are reported to possess analgesic, anti-malarial, anti-mycobacterial, antipyretic, anticancer, anti HIV and anti-microbial activities [2].

2. CHEMISTRY

Piperidin-4-one nucleus is often generated by Mannich Reaction (Scheme **2, 3 and 4**). Mannich reaction is an organic reaction which consists of amino alkylation of an acidic proton placed next to a carbonyl functional group with formaldehyde/various aldehydes and ammonia or any primary or secondary amine. The final product is a β-amino-carbonyl compound, also known as a Mannich base [3]. This reaction is an example of nucleophilic addition of an amine to a carbonyl group followed by dehydration [4].

The substituted piperidin-4-ones, such as 1, 3-dimethyl-2, 6-diphenyl-4-piperidone, have been found to be versatile intermediates in different types of reactions since they have two reactive sites, carbonyl and keto-methylene groups. This paved the path for the synthesis of some heterocyclic compounds such as tetrahydropyridine, diazepanone, oxazepanone, piperidone, pyridopyrimidone, pyridopyrimidinethione, thiazolopyridine, furanylmethylene and pyridoindole [5].

1 Piperidine **2** Piperidin-4-one

Scheme (1). Structure of piperidine and piperidin-4-one

2.1. Syntheses of Piperidin-4-Ones

Generally, all piperidin-4-ones are synthesized by condensing one mole of various aliphatic/aromatic/hetero-aromatic, substituted/unsubstituted ketones and two moles of different aldehydes with one mole of ammonium acetate, in the presence of ethanol. A number of 4-piperidones with different substituents on the 1, 2, 3, 5 and 6 positions have been synthesized using glacial acetic acid instead of ethanol [6]. A concise route whereby unsaturated alcohols were converted into 3-substituted 4-piperidones was reported, the key step being the formation of the C3-C4 bond via a one-pot tandem oxidation-cyclization-oxidation by Pyridinium Chlorochromate (PCC) [7]. Hu *et al.* prepared a series of heterocycle substituted 1-aryl-4-piperidones **3, 4, 5** (Scheme **2**) via Knoevenagel condensation, of nitrogen containing 5-membered heterocycles and benzaldehyde, followed by reduction or amination [8]. 1,3-Dimethyl-2-phenyl-6-aryl-

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