IJPSR (2017), Vol. 8, Issue 5 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 31 October, 2016; received in revised form, 31 January, 2016; accepted, 20 April, 2016; published 01 May, 2017

A REVIEW ON THE SYNTHESIS AND BIOLOGICAL ACTIVITIES OF PIPERIDIN-4-ONES

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Keywords:

Piperidine-4-ones, Synthesis of derivatives, biological activities

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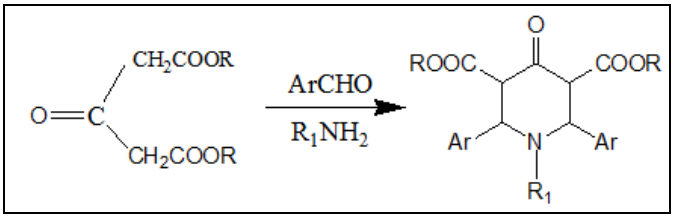
ABSTRACT: Piperidine is a key structural motif in various alkaloids and a variety of compounds studied in medicinal chemistry. Though many methods have been developed for their construction, there is still need for noval approaches. Among the wide variety of heterocyclic compounds; piperidin-4-ones exhibit various biological activities. Synthesis and biological applications of piperidin-4-ones derivatives are outlined in this paper.

INTRODUCTION: Piperidine is a family of heterocyclic organic compound derived from pyridine through hydrogenation. Piperidine ring is a very important molecular fragment in natural and pharmaceutically active compounds. Piperidine derivatives show many biological activities like analgesic, antihypersensitive, central nervous system depressant antiviral, bactericidal etc. [1-5] Watson *et al.*, asserted that during a recent 10year period, there were thousands of piperidine compounds mentioned in clinical and preclinical studies [6].

Synthesis of piperidine-4-ones: Substituted 4-piperidones were synthesized by Mannich condensation reaction between substituted aromatic aldehydes, ethylmethylketone and ammonium acetate in ethanol medium. The formation of β-amino carbonyl compounds (Mannich bases) from the reaction of an active methylene compound with formaldehyde and an amine was first recognized by Mannich [7]. Baliah and his coworker's [8-13] developed an elegant method of synthesis of 2, 6-diphenylpiperidine-4-ones based on the earlier work of Petrenko-Kritschenko *et al.,* [14-17]. The earlier reaction involved the condensation of an ester of acetone dicarboxylic acid with an aromatic aldehyde and ammonia or a primary amine, leading to the formation of 2,6-diaryl-4oxopiperidine-3,5-di-carboxylate or their N-substituted derivatives (**Scheme 1**)



R= Me, ET, R_1= H, Me, Et, Ph, $PhCH_2$

SCHEME: 1

The reaction was later extended to aliphatic aldehydes and several amines by Mannich *et al.,* [18-21]. The importance of the further work by Baliah *et al* lies not only in the simplicity of their procedure but also in the use of acetone and other aliphatic ketones in the place of esters of acetonedicarboxylic acid.

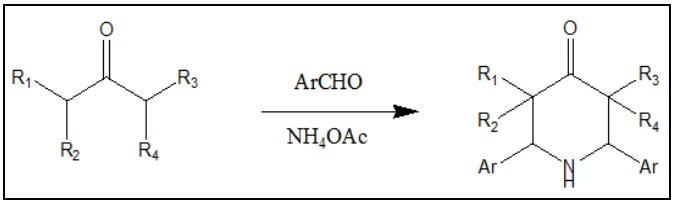
QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.8(5).1967-71

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (5).1967-71

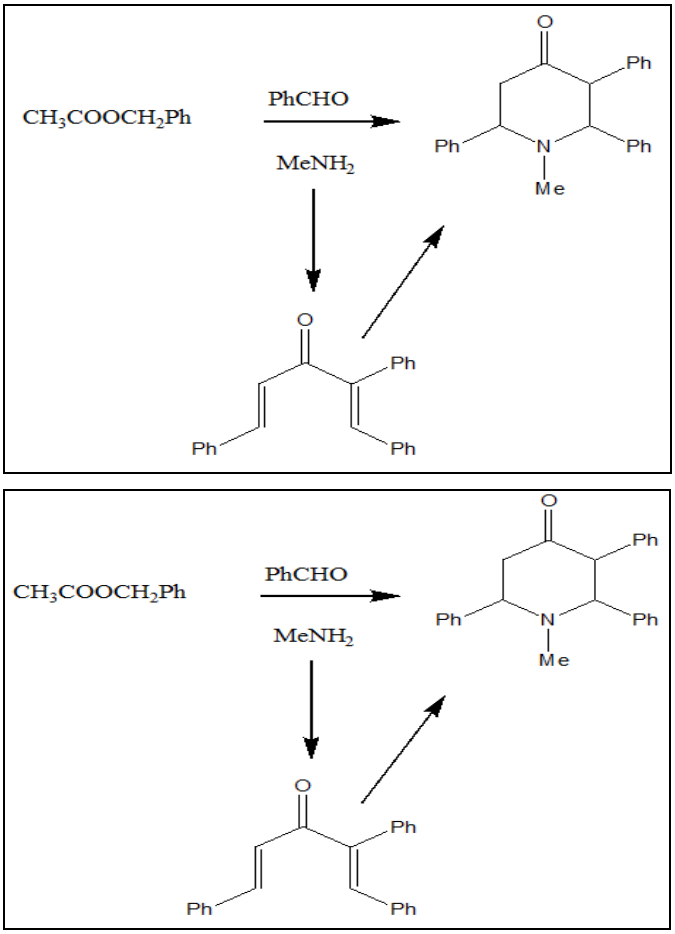
The yields were also very high, with practically no side reactions of any consequences [8]. A large number of piperidine-4-ones (**Scheme 2**) have thus been synthesized by employing various aldehydes and ammonium acetate or amines with aliphatic ketones containing α-hydrogen atoms on both sides of the carbonyl group [22-27].



R_1= R_2 = R_3= R_4= H, Me, Et, Ph, R_1= R_2 = R_3= H, R_4= Me, Et, Pr, Bu

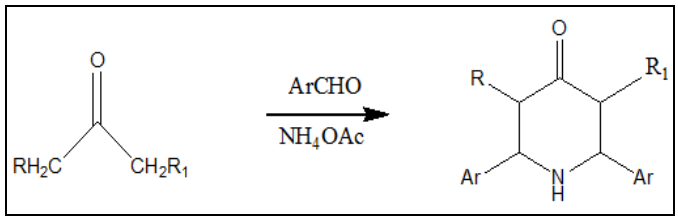
SCHEME: 2

Only aromatic aldehydes undergo this modified reaction.3-alkyl-pipeidin-4-ones (**Scheme 3**) have been obtained by employing alkyl methyl ketones with varying chain length [4]. The cyclocondensation of benzyl methyl ketone with benzaldehyde and methylamine gave 2, 3, 6-triphenylpiperidine-4-one **(Scheme 3)**.



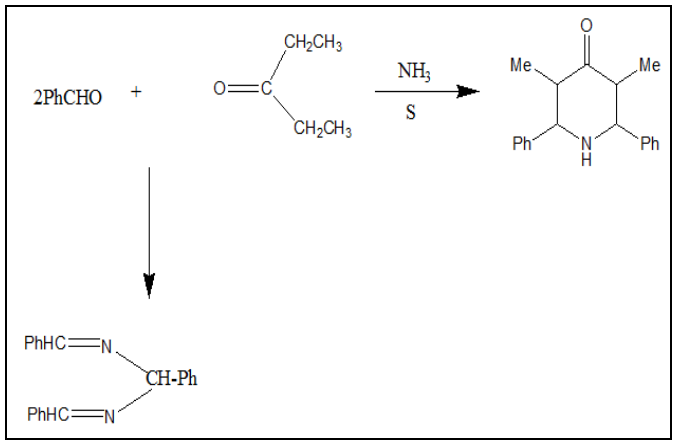
SCHEME: 3

3, 5 –Disubstitued piperidine-4-ones **(Scheme 4)** were formed when both symmetric and unsymmetrical aliphatic ketones were employed [8, 28, 29].



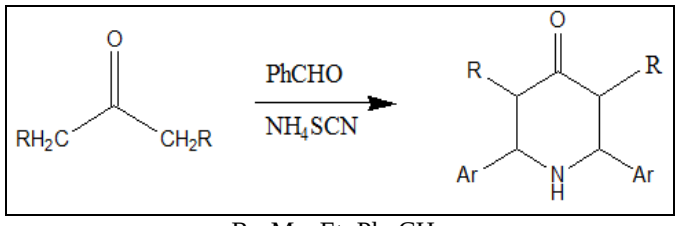
SCHEME: 4

When ammonia passed into a mixture of benzaldehyde and diethyl ketone containing a little sulphur, a vigorous exothermic reaction occurred leading to the formation of 2, 6-diphenyl-3, 5-dimethylpiperidine-4-one (**Scheme 5**) in good yield [30].



SCHEME: 5

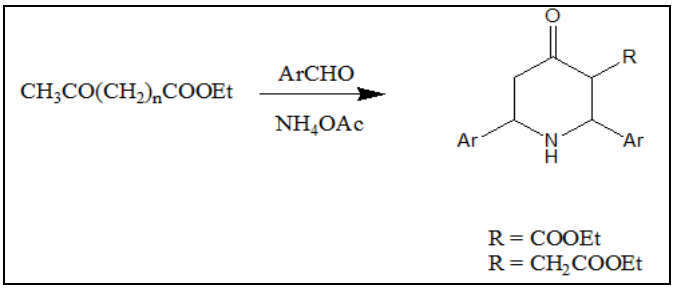
In the absence of sulfur the piperidin -4-ones was not formed, only the imine formed and the diethyl ketone remained unchanged [30]. In similar experiments, butane-2-one, heptanes-4-one, and dibenzyl ketone were employed. These ketones do not give piperidine-4-ones in the presence of sulfur but give them in the presence of NH_4SCN [30] **(Scheme 6)**

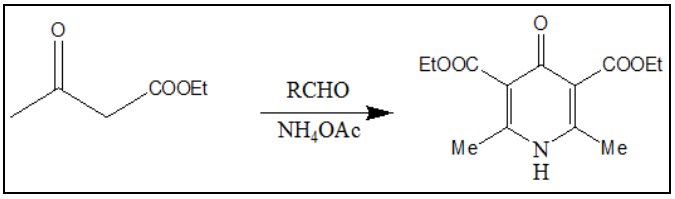


R= Me, Et, Ph, CH_2

SCHEME: 6

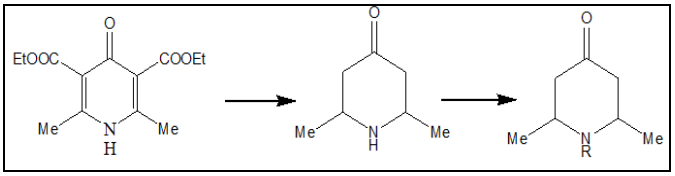
Ethyl acetoacetate and ethyllevulinate have also been employed as the ketone component for the synthesis of piperidine-4-ones (**Scheme 7a**) [13, 31-34]. With ethyl acetoacetate, aromatic aldehyde gave piperidine-4-ones while with aliphatic aldehydes, 1,4-dihydropyridines has been obtained. **(Scheme 7b)**. Treatment of ethyl acetoacetate with benzaldehyde and aniline in absolute ethanol in presence of malonic acid gave ethyl1,2,6-triphenyl-4-oxo-piperidine-3-carboxylate [18, 35]. Hydrolysis of the ester with 10% HCl in acetone gave 1,2,6-triphenylpiperidine-4-one.





SCHEME: 7a AND 8b

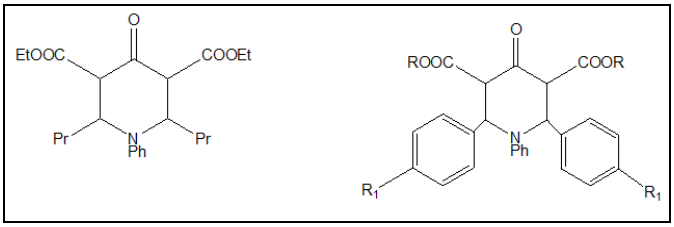
A number of piperidin 4-ones have been obtained from acetonedicarboxylic acid and its esters [36-38] (**Scheme 8**). The 2, 6 dimethylpiperidine -4-ones obtained from the ester was subsequently converted to keto the N-methyl and N-ethyl derivatives by treatement with methyl and ethyl p-toluene sulfonates[38]



R= Me, Et

Acetonedicarboxilic acid and its esters gave two geometric isomers of piperidine-4-ones[14].

Though salicylaldehyde and substituted salicyl-aldehydes were reported to react with ketones and ammonia to form piperidine-4-ones [37, 38, 39]. Baliah *et al*., have established [40] with IR, NMR and Mass spectral data that the products are substituted benzopyrans and not piperidine-4-ones.



R= Et, R_1= H, R_2 = Et, R= Me, Et, R= H, Me, MeO

SCHEME: 8

Stereoselective synthesis of piperidine-4-ones: Reviews updating progress in the stereo selective synthesis of substituted piperidines have appeared recently [41]. 2,3 –dihydro-4-pyridones were utilized in the synthesis of numerous alkaloids due to the variety of stereo controlled functionalizations that were possible [42]. 2-substitued –N-acyl-2,3dihydro-4-pyridones were prepared in an enantiomerically pure state by the stereoselctive addition of organomettailc reagents and metallenolates to chiral 1acylpyridinium salts [43].

Intra molecular Processes: The intramolecular Mannich reaction is a powerful tool for the rapid, efficient, highly stereo selective assembly of polysubstitued piperidones. Sulfinyl amines served as asymmetric precursors to δ-amino-β ketoesters[44]. Treatement with excess trifluroacetic acid removed the sulfinyl group and the released chiral amine salt was then reacted with an aldehyde or ketone giving polysubstitued piperidone. The Major isomer shown to have the C-2 and C-6 substituents in a cis –orientation with the C-2 and C-3 substituents trans. For aldehydes, nearly exclusive formation of the 2,6-cis-disubstitued piperidone was consistent with transition state. Decarboxylation was effected with 48% HBr in methanol. Some erosion of chirality was noted and was attributed to a retro-Mannich reaction. Disubstitued -4-piperidones serve as an important buiding block for piperidine alkaloid synthesis.

Biological activities: 2, 6 –Disubstitued pieridin-4-ones are considered as an important framework and also precursors of many biologically active natural alkaloids [45]. Introduction of benzimidazole nuclei exert a very important role in drug discovery and also exhibit anti bacterial and anti tubercular activities. Mainly, against both sensitive and drug resistant Gram-positive bacterias [46 a-d].

Introduction of Chloroacetyl [47a], Morpholinoacetyl [47b], N-methylipiperazinoacetyl [47c] or benzazoylethoxy [47 d-f] moiety at nitrogen ring displayed enhanced antibacterial and antifungal activities.

Piperidone derivatives are found to act as potentional inhibitors of human placenta aromatase *in vitro* [48]. 3,5 –Bis (arylidene) piperidin- 4-ones behave as cytotoxic and anti cancer agents [49, 50]. 2, 2, 6, 6-Tetra methyl piperidin -4-one hydrochloride has been used as spin trap in several EPR studies [51, 52]. 2-Arylpiperidin- 4-ones used as a key intermediate for the synthesis of tachykinin antagonist and indolizidine alkaloids [53]. Earlier reports have been indicated that biological activity is significant in substitution at 2nd or 6th position of piperdin-4-one.The arylthiopiperidin-4-ones exhibit significant antibacterial activity against *Staphylococcus aureus, Vibrio cholerae, Salmonella typhi,* and *Escherichia coli* and antifungal activity against *Candida albicans* and *Aspergillus niger* [54].

CONCLUSION: As shown in the present review, a wide variety of synthetic strategies are being used for the preparation of pharmaceutically active piperidones with a range of potential applications. Due to the demand for improved selectivity and reduction of side effect of drugs in pharmaceutical research are to be designed even in the future.

ACKNOWLEDGEMENT: The authors are thankful to the Management, Secretary, Principal and Head of Science Department of SNR sons college, Coimbatore for the facilities provided and moral support.

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How to cite this article:
Greeshma KP and Muthulingam S: A review on the synthesis and biological activities of piperidin-4-ones. Int J Pharm Sci Res 2017; 8(5): 1967-71.doi: 10.13040/IJPSR.0975-8232.8(5).1967-71.