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MICROWAVE MEDIATED SYNTHESIS OF SOME DIARYL PIPERIDINE-4-ONE DERIVATIVES

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ABSTRACT

A series of Diaryl piperidine-4-one Derivatives were synthesized by using microwave irradiation. The synthesis involves microwave irradiation of Ammonium acetate with montmorillonite K – 10 in a dry condition. Freshly distilled aromatic aldehyde, and ketone was added to the above mixture and then heated until colour of the solution turned yellow and left at room temperature overnight. The reaction was completed in 6-12 hrs with 40-50% yields and was environmentally friendly with easy to workup. The synthesized compounds were evaluated and its M.P's were determined.

Keywords: Di aryl piperidine-4-one Derivatives, Proline, Montmorillonite K – 10, Anti neoplastic agent, Thiouroperoxides.

INTRODUCTION

Search for new compounds is one of the most challenging tasks of current medicinal chemistry. Many of the currently available drugs are toxic produce recurrence. Therefore there is a clear need for discovery of new structures with potent activities, which could lead to the development of new drugs for management of various infections. Di aryl piperidine-4-one Derivatives has been proven to be attractive compounds because of their outstanding biological activities. In view of above observations, the synthesis of these compounds are of considerable interest. In the present paper, we wish to report a simple, single step microwave mediated synthesis of some Di aryl piperidine-4-one Derivatives (Hall HK, 1957).

2,6-diphenyl-4-piperidinone

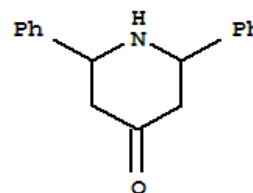
Molecular Formula: C₁₇H₁₇NO

Molecular Weight : 251.328 g/mol

M.P : 240°C

Density : 0.8

Refractive index : 2.2



• HCl

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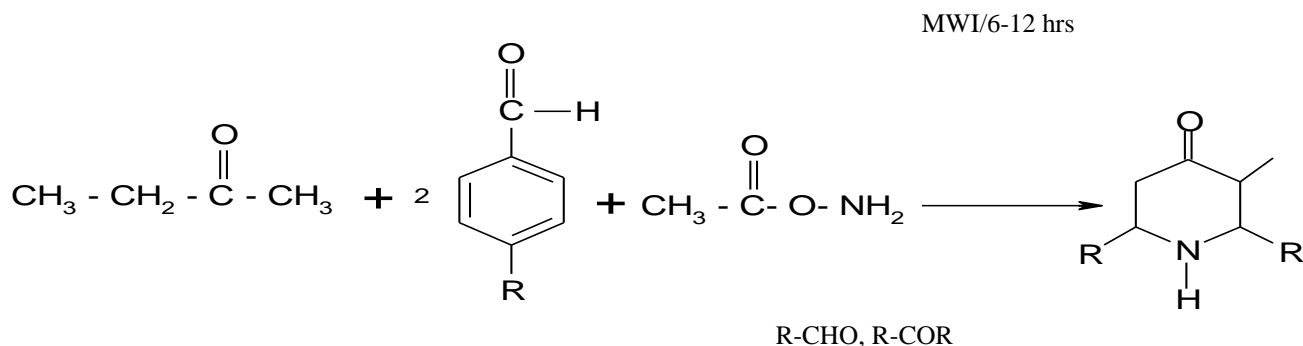
Synonym Name(s) 2,6-diphenyl-piperidin-4-one (or) 2,6-diphenyl-4-piperidone (or) 2,6-diphenylpiperidin-4-one

Experimental

General Procedure for the synthesis of 2, 6-diarylpiperidin-4-ones

To a mixture of ammonium acetate, 3 (1 mmol) montmorillonite K – 10 (100 mg) in a dry condition add freshly distilled aromatic aldehyde, 2 (2 mmol) and ketone, 1 (1 mmol) was added and then heated until colour of the solution turned yellow and left at room temperature

overnight. After the completion of the reaction (monitored by TLC); the reaction mixture was dissolved in ether (10 ml), treated with aqueous hydrochloric acid [20 ml; 1:1 (v/v)]. The hydrochloride salt of the piperidine- 4-one was filtered and washed with ether. The base was liberated from an alcoholic solution of the hydrochloride by adding a slight excess of aqueous ammonia and diluted with water at 0°C. The piperidin-4-ones were crystallized from ethanol or ethanol–ethyl acetate mixture (Karsten Eller *et al.*, 2002; Pandeya *et al.*, 2005).



Methodology

Synthesis of proline catalysed 3-substituted-2,6-diarylpiperidin-4-ones

Ammonia (0.4 ml, 25 %, 4.8 mmol) and (L)-proline (0.17 g, 1.4 mmol) were dissolved in ethanol (2 ml). Freshly distilled aromatic aldehyde (9.6 mmol) and ketone (4.8 mmol) were added to this solution and the mixture kept at room temperature until the mixture became a viscous liquids. Then the reaction mixture was dissolved in ether (10 ml) and treated with aqueous hydrochloric acid [20 ml; 1:1 (v/v)]. The hydrochloride salt of the piperidin-4-one was filtered and washed with ether. The base was liberated from an alcoholic solution of the hydrochloride by adding a slight excess of aqueous ammonia and diluted with water at 0°C. The piperidin-4-ones were crystallized from ethanol or ethanol–ethyl acetate mixture (Sharma PC and Jain S, 2008).

Synthesis of HCl catalysed 3-substituted-2,6-diarylpiperidin-4-ones

Ammonia (0.4 ml, 25 %, 4.8 mmol) and (L)-proline (0.17 g, 1.4 mmol) were dissolved in ethanol (2 ml). Freshly distilled aromatic aldehyde (9.6 mmol) and ketone (4.8 mmol) were added to this solution and the mixture of 4 ml of aq HCl kept at room temperature until the mixture became a viscous liquid. Then the reaction mixture was dissolved in ether (10 ml) and treated with aqueous hydrochloric acid [20 ml; 1:1 (v/v)]. The hydrochloride salt of the piperidin-4-one was filtered and washed with ether. The base was liberated from an alcoholic solution of the hydrochloride by adding a slight excess of aqueous ammonia and diluted with water at 0°C. The piperidin-4-ones were crystallized from ethanol or ethanol–ethyl acetate mixture (Singh *et al.*, 2007).

Table 1. The reactions catalyzed with Proline and HCL

Compound	Substrates	Catalyst	Time	R _f	% yield	M.P
2,6(P- Chlorophenyl) Piperidinone	p- chloro benzaldehyde, amoniumacetate	Proline	8 hr	0.4	40%	140 ⁰ c
2,6(P- dimetyl amino phenyl) Piperidinone	p- dimethyl amino benzaldehyde, amonium acetate	Proline	9 hr	0.58	45%	210 ⁰ c
2,6(P- Chlorophenyl) Piperidinone	p- chloro benzaldehyde, ammonium acetate	Hcl	12 hr	0.44	43%	140 ⁰ c
2,6(P- dimetyl amino phenyl) Piperidinone	p- dimethyl amino benzaldehyde, amoniumacetate	Hcl	14 hr	0.63	47%	205 ⁰ c

The reactions catalyzed with Proline took less time when compared to HCL in experimental conditions.

RESULTS AND DISCUSSION

Formation of Thiosemicarbazone at 4th position increases – anti thyroid activity by inhibiting thiouperoxides. Incorporation of hydroxyl group 1th-position increases – Anti bacterial, anti fungal activity. Introduction of N- hydroxyl urea- Anti neoplastic agent cicloproe broad spectrum anti fungal activity. when substations on aryl ring of 2,6- Pepperdine with electron with drawing group increases activity. If aromatic ring replaced by alkyl groups decreases activity due to decreased electron density. Methyl group at 3rd- position is responsible for formation of H bond with membrane of organism. Introduction of benzoxyl group at 1st- position increases specificity against streptococcus. When N at 1st- position replaced by S causes apoptosis of cell by DNA alkylation.

Uses

1. Currently diarylpiperidin-4-ones are employed in manufacture of wide verities of compounds.
2. They exhibit analgesic activity which is determined by tail immersion method using albino mice. When electron withdrawing group is present it may exhibit more activity.
3. Analgesic activity is exhibited by blocking neurokinin receptors in CNS.
4. They also exhibit local anesthetic activity by blocking nerve transmission.
5. They exhibit anti fungal activity, which is compared against amphotercin B.
6. The antifungal activity of the compounds was tested against *C. albicans* and *A. niger*.
7. Diarylpiperidin-4-ones also exhibit Anti-hypertensive activity properties by acting at coronary artery fatty

tissue.

8. 2-Acetylpyridine thiosemicarbazones. 2. N4,N4-Disubstituted derivatives as potential Anti malarial agents.
9. cis-2,6-dimethyl-.alpha.,.alpha.-diaryl-1-piperidinebutanols exhibit Anti arrhythmic activity.
10. The same is true for certain derivatives: *N*-formylpiperidine is a polar aprotic solvent with better hydrocarbon solubility than other amide solvents, and 2,2,6,6 tetramethylpiperidine is highly sterically hindered base, useful because of its low nucleophilicity and high solubility in organic solvents.
11. A significant industrial application of piperidine is for the production of dipiperidiny dithiuram tetrasulfide, which is used as a rubber vulcanization accelerator (Sharma PC and Jain S, 2008; Organic Synthesis, 1941 & 1929).

CONCLUSION

A simple, solvent free, solid based synthesis of piperidine derivatives has been formulated for the construction of above stated piperidine derivatives from ammonium acetate with montmorillonite K – 10. in the presence of freshly distilled aromatic aldehyde, and ketone in a dry condition .The derivatives of piperidine compounds obtained during this synthesis were prone to produce more potent analgesic , anti hypertensive ,anesthetic ,anti malarial activity than basic parent molecule . In view of above observations, the synthesis of these compounds are of considerable interest .in the present paper ,we reported a simple, one step microwave mediated synthesis of some Diaryl piperidine-4-one Derivatives.

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