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Research Paper

# Synthesis and Characterization of Some New Substituted Piperidine Derivatives

Chemistry

**KEYWORDS :** piperidine-4-one, piperidine, hydrazine hydrochloride, reflux, microwave

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## ABSTRACT

*These findings prompted us to synthesize compounds containing nearly four piperidine are prepared. The piperidine are coupled with three amino acid hydrazides under microwave irradiation. The products obtained are checked for purity and the characterization is done. All these piperidine derivatives are characterized by 1H, 13C NMR and Mass spectral studies.*

## INTRODUCTION

In recent years, there has been a growing interest pertaining to the synthesis of bioactive compounds in the field of organic chemistry. In the present study, a series of piperidines were synthesized by condensation of 4-methyl pentanone, aromatic aldehyde and ammonium acetate by mannich reaction [1-3]. In continuation of earlier studies in piperidines some new derivatives are prepared under microwave irradiation, which gives good yields in shorter reaction times [5-8]. The significance of piperidines as intermediate in the synthesis of a collection of compounds of physiologically active has been reviewed by Prostakov and Gaivoronskaya [9-10]. A recent literature survey revealed that the piperidines moiety have been widely used by the medicinal chemist in the past to explore its biological activities and pharmacological properties viz., antimicrobial, anticancer, antihypertensive, antitubercular activities. Hence, this field has ever growing importance resulting in the development scores of piperidines. Therefore it has been considered worthwhile to synthesize some new series of piperidines by microwave irradiation and conventional methods[11-12]. Piperidines are generally synthesized by one pot cyclocondensation of aryl aldehydes, dicarbonyls, β-ketoesters and ammonium acetate, ammonia, primary amine in refluxing with alcohol leading to low yields with longer reaction times. These compounds were screened for their acute oral to their various biological properties such as antiviral, anti-inflammatory, localanesthetic, antimicrobial activity. Similarly imidazole, pyrazole and oxazole were also exhibiting several activites and the fused bicycles of piperidines with imidazole, pyrazole and oxazole are not available in the literature and hence this prompted us to carry out the system of fused heterocycles with piperidines moiety with other heterocycles. The methods employed have been compared in terms of yields, reaction times[13-16]. All the experimental conditions in MWI method, when compared to conventional, are easy, simple, eco friendly and the reactions are rapid and high yield. The studies undertaken on piperidines have direct relation to the synthesis of drug molecules. However, the biological properties of piperidines are highly dependent on the type and locations of substituent on the heterocyclic ring continue to derive the search for new methodologies[16-17].In recent years green chemistry protocols are incorporated for the synthesis of organic molecules due to their advantages like reduction of waste, improved yields and decreases of reaction time compared with classical methods which required drastic reaction conditions and prolonged reaction time. Therefore, the synthesis of piperidines has been the topic of considerable synthetic effort[18-19].

## MATERIAL AND METHODS

All the chemicals and the reagents used in the study were of synthesis grade purity. Isobutyl methyl ketone, ethylmethyl ketone, banzaldehyde, p-chloro benzaldehyde, ethylchloro acetate, amino acids, hydrazine hydrochloride and ethanol are purchased from Qualigents Fine Chemicals Company. Solvents used were purified by distillation. All substance prepared for studies were purified by crystallization using appropriate solvents and established procedures. Melting points were measured on a sigma melting point apparatus using capillary tubes. Analytical TLC was performed on pre coated sheets of silica gel to monitor the process of the reaction as well as to check the purity. The spots were visualized by using iodine vapour.IR spectra were recorded on FTIR-8300 shimadzu spectrometer. $^{1}$H&$^{13}$C NMR spectra were recorded on Jeol GSX (400 MHz) and DPX 200 (200MHz). Mass spectra were recorded on Jeol-JMS-DX 30hf.

EXPERIMENTAL

**PREPARATION OF 2,6-DIPHENYL PIPERIDINE -4-ONE: 3a-d**

Dry ammonium acetate (38.5g) and ethanol (50ml) was added and the solution was mixed with benzaldehyde (106g) and then ketone was added and boiled in waterbath for 20-30 minutes.The yellow colour solution was formed. After 10 minutes the yellow colour solution turned into a brown colour solution. The solution was removed from the waterbath and the solution remained undisturbed overnight (24hrs). After adding concentrated hydrochloric acid with the above solution a brown precipitate was formed. The precipitate was filtred with suction pump and the precipitate was dried. The dried precipitate was washed with 1:5 (Ethanol:Ether) solution. recrystallization from ethanol and melting point is noted.

**PREPARATION OF AMIMO ACID HYDRAZIDE**

**Amino acid hydrazides are prepared by the following method:**

Glycine aminoacid (3.75g, 0.05 mole) and ethanol (20 ml) was added with con. hydrochloric acid (5ml),( acid catalyst). This mixture was refluxed for 12 hr to get aminoacid ester. After completion of this reaction, aminoacid ester (4.35g, 0.05 mol) thus obtained was added with hydrazine hydrochloride (3.4g,0.05 mol) and ethanol (50 ml) was refluxed for 15 hrs. The precipitate **(4a-c)** was formed and filetred with suction pump and dried. The dried precipitate (aminoacid hydrazide) was recrystalised from ethanol and the melting point was noted.

**Amino acids used for hydrazide preparation are**

1. Glycine
2. Alanine
3. Phenyl Alanine

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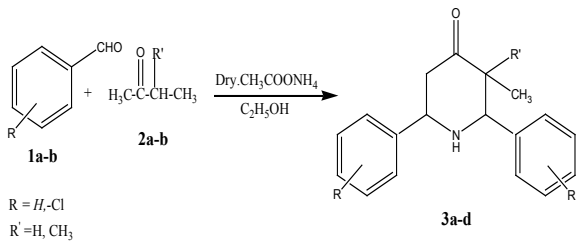
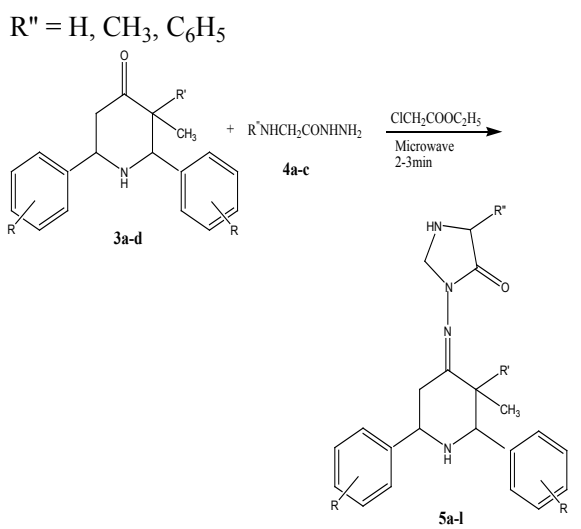
**PREPARATION OF 2,6-DIPHENYL-3-(SUBSTITUTED)-4-PIPERAZO-(1,4 -DIAZO-3-(SUBSTITUTED)-2-KETONE): 5a-l**

Equal mole of substituted amino acid hydrazide (0.8g, 0.01mol) and substituted piperidone (3.17g, 0.01mol) react with ethyl-chloroacetate in the reaction under microwave condition 2-3 minutes. The 2,6-Diphenyl-3-(substituted)-4-piperazo-(1,4- diazo-3-(substituted)-2-ketone) **5a-l** was obtained. The pipridine was recrystalised from ethanol.

**SCHEME-I**




**SCHEME-II**




**CHERACTERIZATION:**

**SYNTHESIS OF 2,6-DIPHENYL-3-DIMETHYL-4-PIPERAZO-(1,4-DIAZO-2-KETONE): 5a**

A mixture of 2,6-diphenyl-3-dimethyl piperidine-4-one **3a** (2.89g, 0.01mol) with glycine hydrazide (0.89g, 0.01mol) is added ethyl chloro acetate in microwave irradiation for 2-3minutes the 2,6-Diphenyl-3-dimethyl-4-piperazo-(1,4-diazo-2-ketone) **5a** was prepared. M.P: 170-173°C.$^{1}$H NMR : : δ 0.805, 1.064(2s,$CH_3$), 2.171, 2.669, 2.703 (3s,$CH_2$), 7.216-7.7281 (m,Ar-H), 7.881 (s'NH), 4.43(s,NH).$^{13}$C NMR : δ16.83, 18.30, 22.06, 22.28, 22.38, 28.47, 45.92, 58.17, 65.21, 122.01, 122.48, 123.07,123.83, 127.10, 127.84, 127.10, 127.84,127.99, 129.22, 130.43, 203.73. Mass : (m/z):371.

**SYNTHESIS OF 2,6-DIPHENYL-3-DIMETHYL-4-PIPERAZO-(1,4-DIAZO-3-METHYL-2-KETONE): 5b**

A mixture of 2,6-diphenyl-3-dimethyl piperidine-4-one **3a**(2.89g, 0.01mol) with Alanine hydrazide (1.03g, 0.01mol) is added ethyl chloro acetate by the usual workup afforded 2,6-Diphenyl-3-dimethyl-4-piperazo-(1,4-diazo-3-methyl-2-ketone) **5b** was prepared. M.P:145-150°C. $^{1}$H MNR : δ 0.770, 1.039, 1.286 (3s,$CH_3$), 2.379, 2.631 (2s,$CH_2$), 4.625 (s,NH), 7.206-7.981 (m,Ar-H), 8.691 (s,NH). 13C MNR : δ 17.71, 22.39, 25.83, 39.85, 40.80, 55.42, 57.16, 61.29, 65.14, 127.05, 127.38, 127.56, 128.58, 128.85, 129.04, 129.26, 129.39, 130.05,133.01, 133.50, 133.95, 203.39. Mass : (m/z):387.

**SYNTHESIS OF 2,6-DIPHENYL-3-DIMETHYL-4-PIPERAZO-(1,4-DIAZO-3-PHENYL-2-KETONE): 5c**

A mixture of 2,6-diphenyl-3-dimethyl piperidine-4-one **3a** (2.89g, 0.01mol) with phenyl Alanine hydrazide (1.81g, 0.01mol) is added ethyl chloro acetate by the usual workup afforded 2,6-Diphenyl-3-dimethyl-4-piperazo-(1,4-diazo-3-phenyl-2-ketone) **5c** was prepared. M.P:160°C. $^{1}$H NMR: δ 0.956, 1.054 (2s,$CH_3$), 2.004, 2.391 (2s,$CH_2$), 3.758 (s,CH), 4.634 (s,NH), 7.194-7.741 (m,Ar-H), 7.977(s,NH). $^{13}$C NMR : δ 20.33, 21.97, 39.58, 40.08, 41.17, 45.87, 55.32, 57.36, 127.00, 127.48, 127.81, 128.70, 128.83, 128.90, 129.04, 129.22, 129.30, 129.44, 129.66, 129.76, 130.15, 131.43, 133.58, 133.83, 134.06, 203.47. Mass : (m/z):463.

**SYNTHESIS OF 2,6-DIPHENYL-3-METHYL-4-PIPERAZO-(1,4-DIAZO-2-KETONE): 5d**

A mixture of 2,6-diphenyl-3-methyl piperidine-4-one **3b** (2.61g, 0.01mol) with Glycine hydrazide (0.89g, 0.01mol) is added ethyl chloro acetate by the usual workup afforded 2,6-Diphenyl-3-methyl-4-piperazo-(1,4-diazo-2-ketone) **5d** was prepared. M.P:154°C. $^{1}$ H NMR :δ 0.871(s,$CH_3$), 2.971, 2.565, 2.613(3s,$CH_2$), 7.162-7.813(m,Ar-H), 4.051(s,NH), 8.916(CS,NH). $^{13}$C NMR: δ14.17 ,22.59 ,22.83, 26.03, 26.21, 45.87, 65.14, 127.50, 127.83, 127.56, 127.94, 128.31, 128.56, 128.92, 129.32, 129.56, 133.63, 202.14. Mass : (m/z):345.

**SYNTHESIS OF 2,6-DIPHENYL-3-METHYL-4-PIPERAZO-(1,4-DIAZO-3-METHYL-2-KETONE):5e**

A mixture of 2,6-diphenyl-3-methyl piperidine-4-one **3b** (2.61g, 0.01mol) with Alanine hydrazide (1.03g, 0.01mol) is added ethyl chloro acetate by the usual workup afforded 2,6-Diphenyl-3-methyl-4-piperazo-(1,4-diazo-3-methyl-2-ketone) **5e** was prepared. M.P: 132°C. $^{1}$H NMR : . δ 0.789(2s,$CH_3$) , 2.171(s-CH), 2.669,2.703(d,$CH_2$), 3.593(s,$CH_2$),7.126-7.818(m,Ar-H), 4.473(s,NH),7.881(s,NH). $^{13}$C NMR : δ15.86, 16.92, 23.51, 23.89, 26.56, 26.82, 27.92, 127.02, 127.63, 128.35, 128.69, 128.92, 129.12, 129.45, 130.12, 135.95, 136.12, 136.92, 205.12. Mass : (m/z):359.

**SYNTHESIS OF 2,6-DIPHENYL-3-DIMETHYL-4-PIPERAZO-(1,4-DIAZO-3-PHENYL-2-KETONE): 5f**

A mixture of 2,6-diphenyl-3-methyl piperidine-4-one **3b** (2.61g, 0.01mol) with phenyl Alanine hydrazide (1.81g, 0.01mol) is added ethyl chloro acetate by the usual workup afforded 2,6-Diphenyl-3-dimethyl-4-piperazo-(1,4-diazo-3-phenyl-2-ketone) **5f** was prepared. M.P: 86°C. $^{1}$H NMR : δ 0.893(s,$CH_3$), 1.620,1.731(2s,$CH_2$), 2.913(s-CH), 7.207-7.708(m,Ar-H), 7.923(s,NH), 4.523(s,NH). $^{13}$C NMR: δ 16.92, 22.19, 23.56, 23.92, 45.78, 129.12, 129.73, 129.94, 130.17, 130.45, 130.86, 130.99, 132.19, 132.25, 132.79, 133.09, 133.25, 133.46, 133.53, 133.82, 202.69. Mass : (m/z):435.

**SYNTHESIS OF 2,6-(4--CHLOROPHENYL-3-DIMETHYL-4-PIPERAZO-(1,4-DIAZO-2-KETONE):5g**

A mixture of 2,6-(4-Chlorophenyl)-3-dimethyl piperidine-4-one **3c** (3.59g, 0.01mol) with glycine hydrazide (0.89g, 0.01mol) is added ethyl chloro acetate by the usual workup afforded 2,6-(4--Chlorophenyl-3-dimethyl-4-piperazo-(1,4-diazo-2-ketone) **5g** was prepared. M.P: 168-170°C.$^{1}$H NMR :δ 0.806, 1.065(2s,$CH_3$), 2.172, 2.668, 2.704 (3s,$CH_2$), 7.215-7.728 (m,Ar-H), 7.882 (s'NH), 4.432(s,NH).$^{13}$C NMR : δ16.84, 18.32, 22.07, 22.38, 22.39, 28.48, 45.93, 58.18, 65.23, 122.02, 122.49, 123.06,123.84, 127.12, 127.85, 127.11, 127.85,127.98, 129.23, 130.44, 203.74. Mass : (m/z):439,441($M^{2+}$-Cl).

**SYNTHESIS OF 2,6-(4-CHLOROPHENYL-3-DIMETHYL-4-PIPERAZO-(1,4-DIAZO-3-METHYL-2-KETONE): 5h**

A mixture of 2,6-(4-Chlorophenyl)-3-dimethyl piperidine-4-one **3c** (3.59g, 0.01mol) with Alanine hydrazide (1.03g, 0.01mol) is added ethyl chloro acetate by the usual workup afforded 2,6-(4-Chlorophenyl-3-dimethyl-4-piperazo-(1,4-diazo-3-methyl-2-ketone) **5h** was prepared. M.P:150-155°C. $^{1}$H MNR : δ 0.780, 1.038, 1.287 (3s,$CH_3$), 2.377, 2.632 (2s,$CH_2$), 4.626 (s,NH), 7.205-7.982 (m,Ar-H), 8.694 (s,NH). $^{13}$C MNR : δ 17.72, 22.38, 25.84, 39.86, 40.81, 55.44, 57.15, 61.38, 65.16, 127.04, 127.39, 127.54, 128.57, 128.86, 129.06, 129.36, 129.36, 130.08,133.02, 133.50,

133.96, 203.38 Mass : (m/z):455,457($M^{2+}$-Cl).

**SYNTHESIS OF 2,6-(4-CHLOROPHENYL-3-DIMETHYL-4-PIPERAZO-(1,4-DIAZO-3-PHENYL-2-KETONE): 5i**

A mixture of 2,6-(4-Chlorophenyl)-3-dimethyl piperidine-4-one **3c** (3.59g, 0.01mol) with phenyl Alanine hydrazide (1.81g, 0.01mol) is added ethyl chloro acetate by the usual workup afforded 2,6-(4-Chlorophenyl-3-dimethyl-4-piperazo-(1,4-diazo-3-phenyl-2-ketone **5i** was prepared. M.P:196°C. $^1$H NMR: δ 0.956, 1.055 (2s,$CH_3$), 2.014, 2.392 (2s,$CH_2$), 3.757 (s,CH), 4.636 (s,NH), 7.196-7.742 (m,Ar-H), 7.978(s,NH). $^{13}$C NMR : δ 20.34, 21.98, 39.56, 40.05, 41.18, 45.89, 55.33, 57.37, 127.01, 127.49, 127.82, 128.71, 128.84, 128.92, 129.05, 129.24, 129.31, 129.45, 129.67, 129.76, 130.16, 131.44, 133.59, 133.83, 134.08, 203.48. Mass : (m/z):531,533($M^{2+}$-Cl).

**SYNTHESIS OF 2,6-(4-CHLOROPHENYL-3-METHYL-4-PIPERAZO-(1,4-DIAZO--2-KETONE): 5J**

A mixture of 2,6-(4-Chlorophenyl)-3-methyl piperidine-4-one **3d** (3.31g, 0.01mol) with Glycine hydrazide (0.89g, 0.01mol) is added ethyl chloro acetate by the usual workup afforded 2,6-(4-Chlorophenyl-3-methyl-4-piperazo-(1,4-diazo--2-ketone) **5j** was prepared. M.P:160°C. $^1$ H NMR : δ 0.892(s,$CH_3$), 2.854, 2.956, 3.152 (3s,$CH_2$), 7.252-7.416(2d,Ar-H), 4.312(s,NH), 8.892(S,NH). $^{13}$C NMR: δ14.18 ,22.60 ,22.73, 26.04, 26.31, 45.77, 65.24, 127.60, 127.73, 127.46, 127.84, 128.41, 128.66, 128.81, 129.43, 129.67, 133.73, 202.15. Mass : (m/z): 413,415($M^{2+}$-Cl).

**SYNTHESIS OF 2,6-(4-CHLOROPHENYL-3-METHYL-4-PIPERAZO-(1,4-DIAZO-3-METHYL-2-KETONE): 5k**

A mixture of 2,6-(4-Chlorophenyl)-3-methyl piperidine-4-one **3d** (3.31g, 0.01mol) with Alanine hydrazide (1.03g, 0.01mol) is added ethyl chloro acetate by the usual workup afforded 2,6-(4-Chlorophenyl-3-methyl-4-piperazo-(1,4-diazo-3-methyl-2-ketone) **5k** was prepared. M.P: 120°C. $^1$H NMR : . δ 0.799 (2s,$CH_3$) , 2.281(s-CH), 2.568,2.802(d,$CH_2$), 3.483(s,$CH_2$),7.225-7.819(m,Ar-H), 4.475(s,NH),7.982(s,NH). $^{13}$C NMR : δ15.76, 16.82, 23.52, 23.88, 26.66, 26.83, 27.94, 127.05, 127.73, 128.45, 128.68, 128.93, 129.22, 129.46, 130.32, 135.75, 136.22, 136.82, 205.14.Mass : (m/z):427,429 ($M^{2+}$-Cl).

**SYNTHESIS OF 2,6-(4-CHLOROPHENYL-3-METHYL-4-PIPERAZO-(1,4-DIAZO-3-PHENYL-2-KETONE) : 5l**

A mixture of 2,6-(4-Chlorophenyl)-3-methyl piperidine-4-one **3d** (3.39g, 0.01mol) with phenyl Alanine hydrazide (1.81g, 0.01mol) is added ethyl chloro acetate by the usual workup afforded 2,6-(4-Chlorophenyl-3-methyl-4-piperazo-(1,4-diazo-3-phenyl-2-ketone) **5l** was prepared. M.P: 178°C. $^1$H NMR :δ 0.882(s,$CH_3$), 1.721,1.732(2s,$CH_2$), 2.915(s-CH), 7.308-7.609(m,Ar-H), 7.824(s,NH), 4.643(s,NH). $^{13}$C NMR: δ 16.93, 22.18, 23.56, 23.93, 45.68, 129.13, 129.63, 129.95, 130.18, 130.25, 130.87, 130.98, 132.17, 132.35, 132.78, 133.06, 133.26, 133.26, 133.54, 133.83, 202.68. Mass : (m/z):503,505 ($M^{2+}$-Cl).

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