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Synthesis, Characterization and Antimicrobial study of piperidine-2,6-diones derivatives

A. P. Rajput* and Deepak V. Nagarale[1]

** Art's, Science and Commerce College, Bodwad, Jalgaon. India.*
[1]P.G. Research Centre JET's Z.B. Patil College, Dhule, North Maharashtra University, Jalgaon. India

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ABSTRACT

*The piperidine ring is a structural feature of many alkaloids and drug [1] candidates and there were thousands of piperidine compounds mentioned in clinical and preclinical studies[2]. The piperidine ring system is one of the commonest structural sub units in natural compounds. Several substituted piperidines display important biological properties like antiviral activity. We have used a simple and highly efficient method for the synthesis of 1-(4-chlorophenyl) piperidine-2,6-diones. The reaction was optimized by using various solvents with some modifications in reaction conditions. The synthesized compounds are a precursor for dichlorodialdehydes 1, 4-DHP. Characterization of all synthesized piperidine-dione derivatives was done by analytical technique such as FTIR, ^{1}H-NMR. The resulting compounds possess symmetrical structures [3**]** and have high yields. All the compounds were screened for antimicrobial activities.*

Keywords*:* Piperidine dione; Vilsmeier Haack reactions; Piperidines; Zinc Chloride; Green Chemistry

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INTRODUCTION

The piperidine shows structural feature of many alkaloid. Piperidone compounds are mentioned in clinical and preclinical studies [4]. Piperidones are somewhat less important, but often they serve a role as superior intermediates former to their change to piperidines. Most of reviews were updating progress in the syntheses of piperidones derivatives [5-7]. There after some methodologies are used to convert piperidones to piperidines. The synthesis of these useful heterocycles[8] and annulation reactions[9] is also mentioned in the literatures.

The piperidone ring system is one of the general structural sub units in natural compounds. Several substituted piperidines display important biological properties like antiviral activity[10]. Some piperidine derivatives are used as neuroleptic agents[11]. A novel optically active [12] and diastereoselective application to 2,4-disubstituted piperidines involving the radical cyclization of 7-substituted 6-aza-8-bromooct-2-enoates have been recently reported. Stereoselective syntheses of several differently functionalized piperidines have been recently reported [13-17]. Due to the importance of the piperdine chemistry, one pot simple procedures for the formation of piperidines are highly desirable[18]. The piperidine structural moiety appears frequently in natural products and synthetic compounds that possess potent biological activity. The reaction has also gone very well in MeOH, Ethanol and DCM in the presence of $ZnCl_2$ under reflux conditions in the synthesis of benzimidazoles from o-phenylenediamine and β –ketoesters [19]. The synthesized compounds are used as starting material for Vilsmeier Haack reactions [20-22].

MATERIALS AND METHODS

Melting Points of compounds were taken in open air capillary tube and are uncorrected. ^{1}H-NMR spectra were recorded on 399 MHz Gemini 2000(Varian, Oxford using DMSO as solvent. IR spectra were recorded on a Perkin-Elmier spectrophotometer FT-IR 1725X. Analytical TLC; Thin-layer charomatography(TLC) was performed on

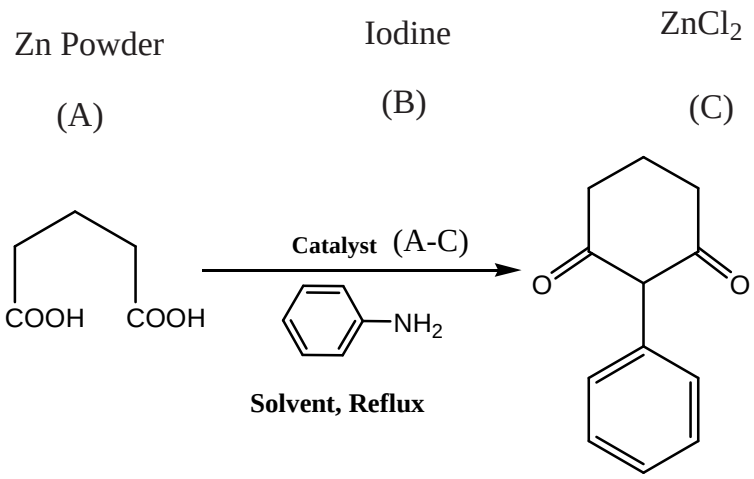
precoated on merk silica gel 60 F254 plates. The elemental analysis was performed on the Vario EL III-C,H,N,O elemental Analyzer-GmbH, Hanau-Germany. Reagents and solvents were used without purification purched from Loba Chem Pvt. Ltd and used as such.

In the present study we have synthesized piperidine -2, 6-dionones derivatives by green method which is alternative to conventional [23].

CONVENTIONAL GENERAL PROCEDURE

In a round bottom flask Glutaric acid (0.01mol) was taken then, $SOCl_2$ was added (0.02 mol). The reaction mixture was wormed for 2 hour. Then Primary amine (0.01mol) was added to round bottom flask. The reaction mixture was then refluxed for 1 hour. After completion of reaction (checked by TLC), the reaction mixture was poured in cooled water and washed the solid product with 1:1 HCl to remove unreacted amine. The solid product was then filtered and recrystallised by using aqueous ethanol.

Table: 1 Catalyst used for optimization



Scheme-I

Table 2: Optimization of reaction parameters[a]

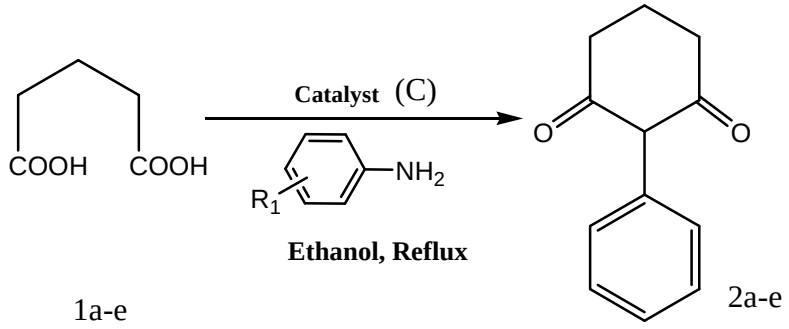
Entry	**Catalyst**	**Solvent**	**Time (Hour)**	**Temperature** (^oC)	**Yield**[b](%)
1.	A	Ethanol	4	70	-
2.	A	CH_2Cl_2	5	70	Trace
3.	A	H_2O	5	70	Trace
4.	B	Ethanol	5	70	10
5.	B	CH_2Cl_2	5	70	15
6.	B	H_2O	5	70	-
7.	C	H_2O	5	80	40
8.	C	Ethanol	5	70	70
9.	C	Ethanol	4	80	88
10.	**C**	**Ethanol**	**1**	**90**	**92**

[a]Reaction conditions: Glutaric acid (0.01mol), Primary amine (0.01 mol),under reflux. [b]Isolated yield

In conventional reactions corrosive reagents and solvents were used. The procedure for these reactions was really simple and required no toxic organic solvent atmosphere. We established the conversion which could be done by reaction of mixture of Glutaric acid (0.01mol) and $ZnCl_2$ in ethanol, after 1 hour the Primary amine (0.01 mol) was added gradually. Reaction was monitored by TLC. The reaction period was optimized up to 1 hour. The resulting compounds were washed with 50% HCl to eliminate the unreacted primary amine and washed with water to reduce acidic nature of product. Finally the product was primary purified by recrystalization method with 1:1 ethanol and can be further used as precursor for dihydropyridines.[24]

RESULTS AND DISCUSSION

Table 3: Substrate study for 1-(n-substituted phenyl)piperidine-2,6-dione synthesis[a]



Scheme-II

Compounds	Catalyst	Primary Amines[b]	Yield[c] (%)
2a	C	3-nitroaniline	88
2b	C	2-nitro, 4- chloro aniline	88
2c	C	α-napthylamine	90
2d	C	2-aminoazobenzene	92
2e	C	Aniline	92

[a]Reaction conditions: Glutaric acid (0.01mol), [b]Primary amine(a-e) (0.01 mol),under reflux. [c]Isolated yield

In this study we have explored the substrate scope and its importance of the $ZnCl_2$ catalyst in various condensation reactions using primary amines (Table -3 Scheme). According to the above experimental part, we are exposure a practical piperidine-diones synthesis using a mild catalyst hydrated $ZnCl_2$, which is conserved simple and always resulted in to 82-94% yields. The results of these reactions are shown in Table 3.

Table 4: Physical Data

Compounds	R	Molecular Formula	Yield (%)	Melting Point(^{O}C)
2a	3-nitro	$C_{11}H_{10}O_4N$	87	130-134
2b	2-nitro,4-chloro	$C_{11}H_{09}O_2N$	88	117-119
2c	α-napthylamine	$C_{15}H_{13}O_2N$	94	156-158
2d	4-amino azo	$C_{16}H_{15}O_2N_2$	92	146-148

Analytical and spectral data for the synthesized compounds

1) *1-(3-nitrophenyl)piperidine-2,6-dione* ***(2a)****, m.p. 130-134 ^oC*

FT-IR.: 1633.62, 1465.72, 1570.78, 2910 cm-1; ^{1}H NMR (DMSO-d6) δ: 6.98 (s, 1H). 6.95 (s, 1H). 6.55 (s, 1H), 6.48 (s, 1H).6.45 (s, 1H). 6.04 (s, 1H), 4.04 (t, 4H) 2.48 (t, 2H) GC-MS:234 M.W.,206,90,76,55. Elemental analysis for Molecular Formula $C_{11}H_{10}O_4N$: Calculated-C(61.80%) H(4.75%) N(6.01%) O(27.44%) Observed: C(61.68%) H(4.85%) N(6.15%) O(27.32%)

2) *1-(4-chloro-2-nitrophenyl)piperidine-2,6-dione* ***(2b)****, m.p. 117-119 ^oC*

FT-IR.: 640.12,1634.66,1344.06,1509.32,3304.87cm^{-1}; ^{1}H NMR (DMSO-d6) δ: 7.903 (s, 1H). 7.66 (d, 1H). 7.72 (d, 1H), 2.43 (t, 4H), 1.84 (t, 2H). GC-MS:298 M.W.,227,110,90,75. Elemental analysis for Molecular Formula $C_{11}H_9O_2N$: Calculated- C(53.85%) H(3.77%) Cl(13.25%) N(5.23%) O(23.91%) Observed: C(53.90%) H(3.72%) Cl(13.11%) N(5.30%) O(23.97%)

3) *1-(naphthalen-4-yl)piperidine-2,6-dione* ***(2c)****, m.p. 156-158 ^oC*

FT-IR.: 1621.43,1554.47, 3045.97 cm^{-1};, ^{1}H NMR (DMSO-d6) δ: 2.30 (t, 1H). 2.32 (t, 1H), 1.87(t,2H). 7.30 (dd, 1H), 7.49 (t, 1H), 7.49 (dd, 1H), 7.71 (dd, 1H), 7.58 (t, 1H), 7.50 (t, 1H), 7.90 (dd, 1H). GC-MS:239M.W,236,127,77, Elemental analysis for Molecular Formula $C_{15}H_{13}O_2N$: Calculated- C(75.30%) H(5.48%) N(5.85%) O(13.37%) Observed: C(75.37%) H(5.41%) N(5.80%) O(13.42%)

4) *1-{4-[(Z)-phenyldiazenyl]phenyl}piperidine-2,6-dione* ***(2d)****, m.p. 146-148 ^oC*

FT-IR.: 1648.22,1490.84,1574.61,3061.52 cm^{-1}; ^{1}H NMR (DMSO-d6) δ: 7.38 (s,1H), 7.33 (s,1H), 7.29 (s,1H), 7.25 (s,1H), 7.08 (s,1H), 7.06 (s,1H), 6.97 (s,1H). 6.95 (s, 1H). 5.20 (s, 1H), 3.73(t,2H), 3.65 (t,2H), 2.28 (t,2H).
GC-MS:289 M.W.316,234,85,68, Elemental analysis for Molecular Formula $C_{16}H_{15}O_2N_2$: Calculated- C(69.61%) H(5.15%) N(14.33%) O(10.91%) Observed: C(69.52%) H(5.08%) N(14.56%) O(10.84%)

Antimicrobial Study:

Antimicrobial activities of any therapeutic agent are understood by its extent of development inhibition of microorganisms as well as bacterial assets [26]. The antibacterial study of a synthesized compounds convey as its inhibition outcome in the course of the growth of the bacterium in nutrient agar medium. The antimicrobial activities expressed as zone diameter in millimetres in disk diffusion method [25], which is measured by a scale mm. Test solutions were prepared by Agar-100mg, sample compound- 1gm, distilled water-10 ml Thus, the final concentration of test obtained was 10 mg/ml[25].

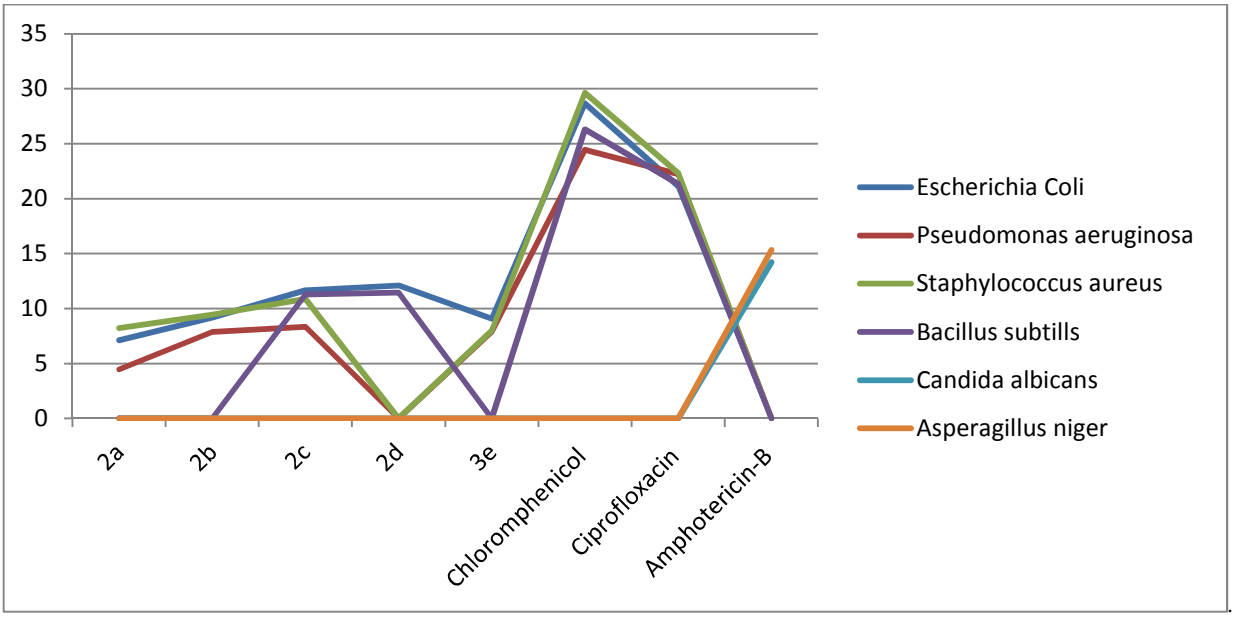
Table 5: Antimicrobial Activity of Compounds 2a-e

compound	*Escherichia Coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Bacillus subtills*	*Candida albicans*	*Asperagillus niger*
2a	7.11	4.45	8.23	-	-	-
2b	9.17	7.88	9.45	-	-	-
2c	11.67	8.33	10.87	11.28	-	-
2d	12.08	-	-	11.45	-	-
2e	09.06	7.89	7.98	-	-	-
Chloromphenicol	28.67	24.44	29.63	26.30	NA	NA
Ciprofloxacin	21.11	22.23	22.33	21.34	NA	NA
Amphotericin-B	NA	NA	NA	NA	14.23	15.34

"-" means no zone of inhibition

The compound **2c** and **2d** shown good antimicrobial activity agents ***Escherichia Coli*** and ***Bacillus subtills*** compound **3c** showed antibacterial activity agent ***Staphylococcus aureus***. The entire compound failed to show antifungal activity against ***Candida albicans*** as well as ***Asperagillus niger.***

Table 6: Comparative line graph of antimicrobial activity of compounds 3a-e.



CONCLUSION

In conclusion we have developed an efficient $ZnCl_2$ catalyzed, green method for the synthesis of various piperidine-2, 6-dione derivatives by refluxing in ethanol. The procedure has mild reaction conditions, operational simplicity, and application of a nontoxic and water soluble catalytic system. High yield and fast development of the products are the excellent advantages of this method. All compounds are tested for antimicrobial activities most of the compounds are found to have good antibacterial activity.

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