International Journal of Pharmaceutical Chemistry
ISSN: 2249-734X (Online)
Journal DOI: 10.7439/ijpc
CODEN: IJPCH3 (American Chemical Society)
Research Article

A Novel Synthesis of N-substituted Glutarimides using ZnCl2 Catalyst: A green approach

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Abstract

The glutarimides containing piperidine ring is a structural feature of many alkaloids and starting material for drug synthesis. Many piperidine type of compounds are mentioned in clinical and preclinical analysis. 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 optimised and used a simple $ZnCl_2$ catalysed and highly efficient method for the synthesis of 1-(4-chlorophenyl) piperidine-2,6-diones(Glutarimides) using ethanol solvent. The synthesized compounds are used as precursor for 2,6-dichlorodialdehydes 1, 4-DHP[1-2]. All the synthesized glutarimides are characterized by analytical and modern spectral methods such as FTIR, ^{1}H-NMR, GC-MS. The resulting compounds possess symmetrical structures and have high yields.

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

1. Introduction

The piperidine ring (Glutarimides)[3] is a ubiquitous structural feature of many alkaloid natural products and drug candidates. Watson et al. asserted that during recent 10-years of period thousands of piperidine compounds are mentioned in clinical and preclinical studies [4] as these show potent biological activities. Piperidines and its derivatives are also the important drug intermediates, such as antidepressant and rennin inhibitor[5]. Piperidones are somewhat less prominent, but often they serve a role as advanced intermediates prior to their conversion to piperidines. Reviews updating progress in the stereoselective syntheses of substituted piperidines have appeared recently [6-8].The piperidine ring is a structural characteristic of many drugs and alkaloids candidates. There are lots off piperidine compounds mentioned in preclinical and clinical studies [9]. The piperidine ring system is one of the general structural sub units in natural compounds. Several substituted piperidines exhibit important biological properties like antiviral active nature [10], antidepressant effects [11], cytotoxic activity [12], and antimalarial activity [13]**,** some piperidine derivatives are used as neuroleptic agents [14]. The purpose of this study is to find out approach for the synthesis of piperidone and piperidine heterocycles, using $ZnCl_2$ as a catalyst. This type of work is also reported by Mahajan et al for the synthesis of benzimidazoles from a P-phenylene diamines and β-lactoesters[15] Methodologies are selected on the basis of diversity and stereocontrol, keeping in view providing the reader with a variety of options for the synthesis of these useful heterocycles[16]and annulation reaction[17-18].

2. Experimental

Melting Points were recorded by open end capillary tube method and are uncorrected. 1H-NMR (399MHz): Gemini 2000 (Varian, Oxford); solvent DMSO, unless otherwise stated; ppm (δ) downfield from the internal standard TMS as the internal standard; IR spectra: IR spectra were recorded on a Perkin-Elmer spectrophotometer FT-IR 1725X. Analytical TLC: Thin-layer chromatography (TLC) was performed on precoated Merck silica gel 60 F254 plates. The elemental analysis was performed on the Vario EL III- C, H, N, O Elemental Analyzer (Elementar Analysensysteme GmbH, Hanau-Germany). Reagents and solvents were used without purification: Loba Chem Ltd. In our study we have synthesized piperidine -2, 6-dionones by conventional as well as modified procedures.

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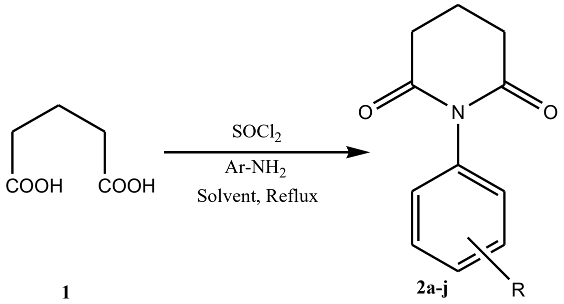
2.1 Conventional general procedure

In a round bottom flask Glutaric acid (0.01mol) was taken then, 0.04 mol of thionyl Chloride was added. The reaction mixture was warmed for 2 hr. Then Primary amine (0.01mol) was added to R.B. The reaction mixture was then refluxed for 1 hr. 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 1^{o} amine. The solid product was then filtered and recrystallised by using aqueous ethanol.



1 2a-j

Scheme-1: Conventional synthesis using Thionyl Chloride as reagent

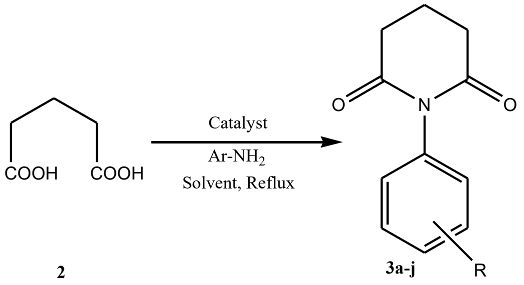
2.2 Modified procedure

To the Glutaric acid (1.33 gm, 0.01mol) was taken in ethanol (10 ml) to it $ZnCl_2$ (0.050 gm 0.005 mol) was added. The resultant mixture was warmed for 1 hr. Then primary amine (0.01 mol) was then added in R.B. and the reaction mixture was refluxed for 1 hr. After completion of reaction (monitored by TLC), the reaction mixture was poured in ice 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 50% ethanol. In this modified method corrosive thionyl chloride was replaced by $ZnCl_2$. In our study we have used Zn powder (**A**), Iodine (**B**), and $ZnCl_2$(**C**) as catalyst for optimisation.

Table: 1 Catalyst used for optimization

Zn Powder	Iodine	$ZnCl_2$
(A)	(B)	(C)

SCHEME USED FOR OPTIMIZATION



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Scheme-2

Table 2: Optimization of reaction parameters^{a}

Entry	**Catalyst**	**Solvent**	**Time**	**Temperature**	**Yield^{b}**(%)
1.	A	Ethanol	4 hr	70^{o}C	Trace
2.	A	2N Ethanolic HCl	4 hr	70^{o}C	5
3.	A(activated)	Ethanol	5 hr	70^{o}C	15
4.	A	Ethanol + K_2CO_3	5 hr	70^{o}C	15
5.	A	CH_2Cl_2	5 hr	70^{o}C	-
6.	A	H_2O	5 hr	70^{o}C	-
7.	**B**	Ethanol	5 hr	70^{o}C	**10**
8.	**B**	CH_2Cl_2	5 hr	70^{o}C	**15**
9.	**B**	H_2O	5 hr	70^{o}C	**-**
10.	**C**	Ethanol	5 hr	70^{o}C	**70**
11.	**C**	H_2O	5 hr	80 ^{o}C	**40**
12.	**C**	Ethanol	4 hr	80 ^{o}C	**88**
13.	**C**	Ethanol	1 hr	90 ^{o}C	**92**

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

The novelty of these reactions is that no corrosive reagents and solvents are used. The experimental procedure for these reactions is really simple and required no toxic organic solvent or inert atmosphere. We have established the transformations which could be accomplished by reacting mixture of Glutaric acid (0.01mol) and Zinc Chloride in ethanol, after 1 hr the Primary amine (0.01 mol) is added slowly. Reaction is monitored by TLC. The reaction time is optimized at 1 hr. The resulting product is washed with 1:1 HCl to remove the unreacted amine and washed with water to remove the acid part. Finally the product was recrystalized with 50% alchohol(ethanol).

3. Results and discussion

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

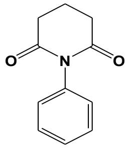
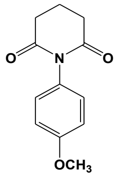
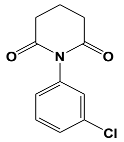
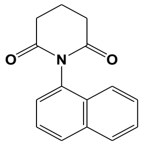
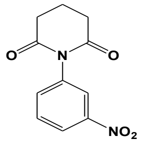
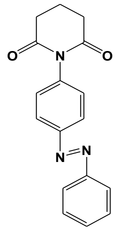
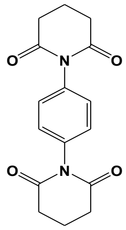
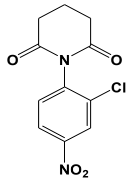
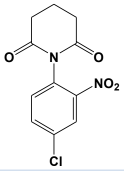
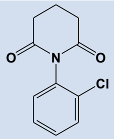
Compounds	Catalyst	Primary Amines[b]	Yield [c] (%)	Products
3a	C	Aniline	92	
3b	C	P-Anisidine	90	
3c	C	3-Chloroaniline	90	
3d	C	α-Napthylamine[C]	94	
3e	C	3-Nitroaniline	88	
3f	C	2-aminoazobenzene	92	
3g	C	P- phenyline diamine	86	
3h	C	2-Chloro,4-Nitro aniline	82	

Table 3. Continue………………

3i	C	2-Nitro, 4- Chloro aniline	88	
3j	C	2-Chloroaniline	92	

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

In this study we have explored the substrate scope and importance of the Zinc chloride catalyst in various condensation reactions using primary amines (Table -3 Scheme). According to the above experimental section, we are reporting here the practical piperidine-diones synthesis using a mild catalyst hydrated $ZnCl_2$, which can be preserved in a simple manner and every time yields resulted in the range of 82-94%. We have also synthesized novel compounds **3d, 3f, 3g, 3h** and **3i.** The results of these reactions are shown in Table 4.

Table 4: Physical Data

Compounds	R	Molecular Formula	Yield (%)	Melting Point(^{O}C)
4d	α-napthylamine	$C_{15}H_{13}O_2N$	94	156-158
4e	3-NO_2	$C_{11}H_{10}O_4N$	88	130-134
4f	-N=N-Ar	$C_{16}H_{15}O_2N_2$	92	146-148
4i	2-NO_2,4-Cl	$C_{11}H_{09}O_2N$	88	117-119

3.2 Spectral data

1) 1-(3-nitrophenyl)piperidine-2,6-dione (4e), Colour: yellow m.p. 130-134 °C ; 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 (4i), Colour: yellow m.p. 117-119 °C ;
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 (4d), Colour: brown m.p. 156-158 °C ; 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 (4f), Colour: Purple m.p. 146-148 °C ;
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%)

4. Conclusion

In conclusion, we have modified, optimized and developed an highly efficient $ZnCl_2$ catalyzed, green method for the synthesis of 1-(*N*-substituted phenyl) piperidine-2,6-diones (Glutarimides) by using ethanol as the solvent for refluxing. The procedure has mild reaction conditions, operational simplicity, and application of a nontoxic and water soluble catalytic system. High yield and rapid formation of the products are the outstanding advantages of this method.

Acknowledgements

The authors are thankful to The Principal, JET's Z.B. Patil College, Dhule for providing the laboratory facilities for this work

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