WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 12, 1689-1695. Research Article ISSN 2277– 7105

SYNTHESIS AND FORMYLATION OF CYCLIC IMIDES USING VILSMEIER-HAACK REACTION FROM 2,6-DICHLORO-4-TRIFLUOROMETHYL ANILINE AND THEIR ANTIMICROBIAL ACTIVITY

S. S. Rajput[1*] and R. M. Sayyed[2]

[1]Department of Chemistry, SVS's Dadasaheb Rawal College Dondaicha, Dist. Dhule, Maharashtra, India 425408.

[2]Department of Chemistry, PSGVPM's Arts, Commerce and Science College, Shahada, Dist. Nandurbar, Maharashtra, India 425409.

Article Received on
19 Oct 2015,

Revised on 09 Nov 2015,
Accepted on 29 Nov 2015,

***Correspondence for Author**
S. S. Rajput
Department of Chemistry, SVS's Dadasaheb Rawal College Dondaicha, Dist. Dhule, Maharashtra, India 425408.

ABSTRACTS

A simple and efficient method has been developed for the synthesis of five and six membered cyclic imides using succinic anhydride, glutaric anhydride, 2,6-dichloro-4- trifluoromethyl aniline and acetyl chloride in presence of benzene and their formylation using Vilsmeier-Haack reaction. The synthesized compound are screened for their antimicrobial activity.

KEYWORDS: 2,6-Dichloro-4-trifluoromethyl aniline, Succinic anhydride, glutaric anhydride, Vilsmeier-Haack Reagent, cyclic imide.

INTRODUCTION

The importance of creating C-N bonds of aromatic compounds pave the attention of organic chemists over several decades since numerous pharmaceuticals, agrochemicals, polymers and biologically relevant molecules incorporate the aryl nitrogen functionality.[1] Literature survey reveals that N- aryl and N-alkyl imides have attracted much more attention of organic and medicinal chemist, due to their biological activities.[2,5] synthetic utility as intermediates.[6,7] and applications in polymer series.[8]

The Vilsmeier-Haack reaction has emerged as a popular tool for the formylation of a large number of aromatic and heterocyclic compounds.[9,12]

In the present work we anticipated that pyrolidine-2,5-dione and piperidine 2,6 dione could be easily made from three component coupling of the cyclic anhydrides, acetyl chloride and 2,6 dichloro-4-trifluoromethyl aniline which is used as precursors for pesticides such as Fipronil.[13,15]

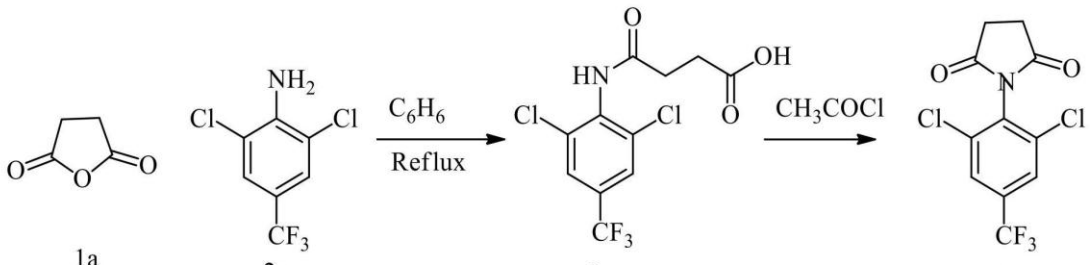
In continuation of our work the resulting five and six membered imides are formylated using Vilsmeier-Haack reaction.[16]

MATERIALS AND METHODS

All reagents are chemically purred, melting point have been determined in open capillary method and are not corrected. IR Spectra were recorded on Perkin-Elmer Spectrum.^{1}HNMR were recorded on Bruker DRX 500 MHz NMR Spectrometer with DMSO-d^{6} solvent and TMS as an internal reference (chemical shift in δ ppm). These two imides and their halo vinyl aldehydes were synthesized according to scheme 1, 2, 3 and 4 respectively.

1. Synthesis of 1-(2, 6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2,5-Dione

Succinic anhydride (0.01mol) was dissolved in 10mL benzene then 2,6-dichloro-4-trifluoromethyl aniline (0.01mol) was added to it vigorously hence 4-((2, 6-dichloro-4-(trifluoromethyl) phenyl) amino)-4-oxobutanoic acid (3a) was formed. This imic acid (3a) was cyclized by using (0.09mol) of fresh acetyl chloride at reflux condition. The solid product (4a) was obtained and recrystallized by methanol.



Scheme I

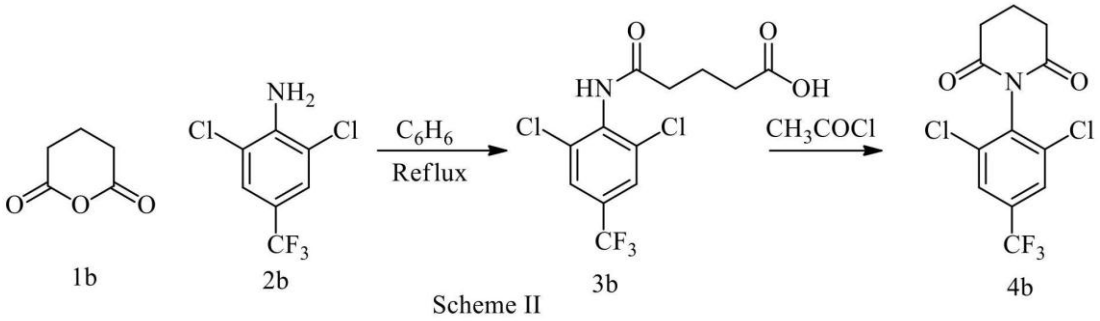
1-(2,6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2, 5-Dione (4a): Yield 90%, m.p.165-167^{0}C.

IR (KBr) cm^{-1}: 2900-3000 cm^{-1} (CH_2), 1650-1700 cm^{-1} (C=C), 1470-1500 cm^{-1} (ArC=C), 1200-1220 cm^{-1} (C-N).

^{1}HNMR (500 MHz, DMSO-d^{6} δ ppm): 2.1-2.5 (t, 4H), 7.5-8 (s, 2H, Ar-H).

2. Synthesis of 1-(2, 6-Dichloro-4-triflouromethyl-phenyl)-piperidine-2, 6-Dione

Glutaric anhydride (0.01mol) was dissolved in 10 ml benzene then 2,6 Dichloro-4-trifluoromethyl aniline (0.01mol) was added to it, 5-((2, 6-dichloro-4-(trifluoromethyl) phenyl) amino)-5-oxopentanoic acid (3a) was formed, this acid was cyclized by using of acetyl chloride (0.09mol) at reflux condition. The solid product (4b) was obtained and recrystallized by methanol. Similar procedure was here used as mentioned for scheme I.



Scheme II

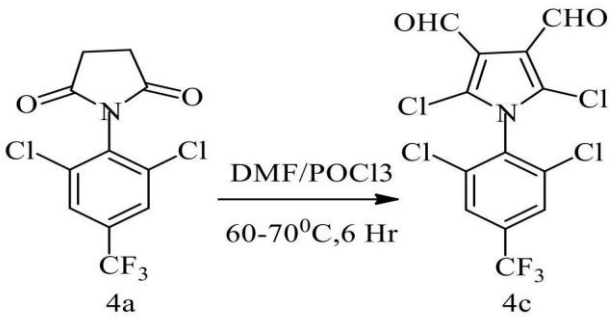
1-(2, 6-Dichloro-4-triflouromethyl-phenyl)-piperidine-2, 6-Dione (4b): Yield 85%, m.p 68-70^{0}C.

IR (KBr) cm^{-1}:3000-3100 cm^{-1} (CH_2), 1650-1700 cm^{-1} (C=O), 1400-1500 cm^{-1} (ArC=C).

^{1}HNMR (500 MHz, DMSO- d^6 δ ppm): 7.5-8.0 (S, 2H, Ar-H), 2.1-2.5(t, 4H), 0.9-1.5 (m, 2H).

3. Synthesis of 2, 5-Dichloro-1-(2, 6-dichloro-4-triflouromrthyl-phenyl)-1H-pyrrole-3, 4-dicarbaldehyde

Formylation of cyclic imide (4a) was accomplished by Vilsmeier-Haack reaction, freshly DMF (0.09mol) was placed at 0-5 ^{0}C temperature then drop wise addition of $POCl_3$ (0.06mol) to cooled DMF with constant stirring by magnetic stirrer, after the complete addition, tiny aliquots of imide was transferred to it, this mixture was placed to heating at 60-70 ^{0}C temperature for next six hours, after simultaneous six hours heating it was kept overnight then this mixture was slowly transferred to crushed ice with constant stirring, cleared yellow solution was obtained, this cleared yellow solution was neutralized by 50% NaOH with monitoring by pH paper, as soon as solution was neutralized precipitate getting formed, this solid precipitate was recrystallized by ethanol.



4a 4c

Scheme III

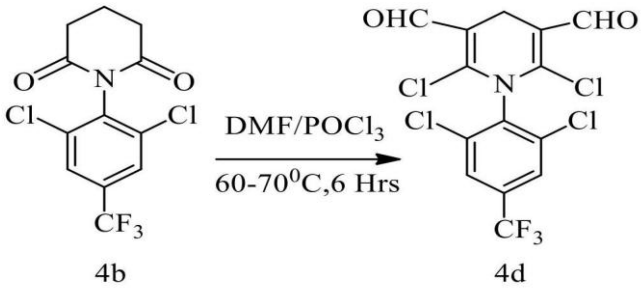
2,5-Dichloro-1-(2,6-dichloro-4-triflouromrthyl-phenyl)-1H-pyrrole-3,4-dicarbaldehyde(4c): Yield 82%, m.p.68-70 ^{0}C.

IR (KBr) cm^{-1}: 1700-1740 cm^{-1} (CHO), 1200-1210cm^{-1} (C-N), 1470-1500 cm^{-1}(ArC=C).

^{1}HMNR (500MHz DMSO-d$_6$δ ppm): 9.5-10.11 (S, 2H, 2-CHO), 7.5-8.2 (S, 2H, Ar-H).

4. Synthesis of 2,6-dichloro-1-(2, 6-dichloro-4-triflouromethyl-phenyl)-1, 4-dihydro-pyridine-3, 5-dicarbaldehyde

Formylation of cyclic imide (4b) was accomplished by Vilsmeier-Haack reaction, in similar way as mentioned for scheme III.



4b 4d

SchemeIV

2,6-Dichloro-1-(2,6-dichloro-4-triflouromethyl-phenyl)-1,4-dihydro-pyridine-3,5- dicarbaldehyde (4d): Yield 80%,m.p.75-77 ^{0}C.

IR(KBr) cm^{-1}:1700-1740 cm^{-1} (CHO),2950-3100 cm^{-1} (CH$_2$), 1210-1230 cm^{-1} (C-N), 1470- 1500 cm^{-1} (ArC=C).

^{1}HNMR (500-mhz DMSO-d$_6$, δ ppm):9.5-10.10 (S, 2H, 2-CHO), 7.5-8.2 (S, 2H, Ar-H) 2.32- 3.1 (S, 2H).

RESULT

Biological activity of synthesized imides and halo vinyl aldehydes

The synthesized compounds 4a-d were screened in-vitro antimicrobial activity against bacteria and fungi, Staphylococcus aurreus, Bacillus sabtilis, Escherichia coli, Pseudomonas aeruginosa and Candida albicans, Aspergilus niger. Stock solution (1000 microgram per ml) of each compound prepared in DMSO. Assay carried out by taking concentration 100 microgram per disk.

Hi-media antibiotics disk: Ciprofloxacin (10 microgram/disk, Amphotericin-B (100 units/disk) moistened with DMSO are used as standard. Microbiological media used for bacteria is nutrient agar (Hi-media), microbial media used for fungi, mould (Aspergillus Niger) is potato dextrose agar (Hi-media), and for yeast (Candida Albicans) is MGYP (All ingredients of Hi-media).

Sr.No.	Sample code	S.aureus	B.Sabtilis	E.coli	P.aeruginosa	C.albicans	A.niger
1	4a	-	-	-	-	-	-
2	4b	8.45	-	-	8.43	-	-
3	4c	-	-	-	7.35	-	-
4	4d	-	-	-	-	-	-
5	Ciprofloxacin	16.06	16.29	20.05	19.20	NA	NA
6	Amphotericin	NA	NA	NA	NA	12.87	8.93

DISCUSSION

The synthesized compounds were expected to be biologically active compounds, they were screened in-vitro antimicrobial activity, therefore it was confirmed that they possess antimicrobial activity against some bacteria and fungi. These synthesized compounds (4a-d) have been characterized by ^{1}HNMR and IR spectroscopy. The ^{1}HNMR spectrum of halovinyl aldehyde 4c and 4d showed the signals at 9.5-10.11δ (S, 2H-2-CHO), 9.5-10.10 δ(S, 2H-2-CHO) respectively and these signals were disappeared from cyclic imides hence it was confirmed that preparation of these two halo vinyl aldehyde from cyclic imides was successfully done. These two cyclic imides 4a and 4b also analyzed by ^{1}HNMR and IR spectroscopy, the ^{1}HNMR spectrum of these imides exhibited the signals at 2.1-2.5 δ (t 4H), 0.9-1.5 (m 2H) respectively. The IR spectrum of these two cyclic imides showed peaks at 1470-1500 cm^{-1} and 1400-1500 cm^{-1} (N-C=O). These peaks were disappeared from starting substrates such as cyclic anhydrides and 2,6-dichloro-4-trifluoromethyl aniline hence it was known that preparation of these cyclic imides compounds have been successfully achieved.

CONCLUSION

A method for synthesis of compounds (4a-d) has been developed. All these compounds were characterized by their spectral analysis. Compound 4b showed moderate activity against S. aureus and P. aeroginosa. Similarly compound 4c exhibited moderate activity against P. aeruginosa. The synthesized compounds may be used for preparation of heterocyclic system.

ACKNOWLEDGEMENTS

We wish to acknowledge financial support provided by UGC-MANF, New Delhi (award letter: F1-17.1/2013-14 MUS-MAH-25825/ (SA-III/Website) dated 06-Feb-2014) for this research work. The authors are also thankful to Dr Ulhas Patil, Department of microbiology, R.C. Patel ASC College, Shirpur for providing us biological activity of samples.

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