*ejpmr, 2015,2(5), 1039-1046.*

**SJIF Impact Factor 2.026**

**EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH**

**www.ejpmr.com**

**Research Article**

**ISSN 3294-3211**

**EJPMR**

# SYNTHESIS, CHARACTERIZATION & ANTIMICROBIAL SCREENING OF 2,5- DICHLORO-1- (N-SUBSTITUTED PHENYL)-1H-PYRROLE-3,4-DICARBALDEHYDES.

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**Article Received on 24/07/2015** **Article Revised on 15/08/2015** **Article Accepted on 06/09/2015**

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## ABSTRACT

The synthesis of Nitrile derivatives by using Ceric Ammonium Nitrate (CAN) catalyst have some attractive features such as simple to operate, fast reaction rate, nontoxic, inexpensive and environmentally friendly catalyst. The pharmacological importance and lack *of* convenient, efficient procedures prompted us to develop a concise, straightforward and economical route for the synthesis of 2,5-dichloro-1-(N-substituted phenyl)-3,4-dicarbonitriles.

**KEY WORDS:** CAN, Vilsmeier Haack Reaction, Nitrile derivatives, Pyrroles.

## INTRODUCTION

Formylation is a key process in organic synthesis, in which the resulting formyl group acts as a 'cross road' intermediate. Formyl group present on pyrrole molecules make them promising precursors for further synthetic transformations. Succinimide is a part of many active molecules possessing activities such as CNS depressant[1], analgesic[2], antitumor[3], cytostatic[4], antispasmodic[7], bacteriostatic[8], nerve conduction blocking[6], muscle relaxant[9], hypotensive[10],antibacterial[11],antifungal[12], anti-convulsant[13] and anti-tubercular activity[14] etc. In view of this literature search & in continuation of our interest on the Vilsmeier- Haack reaction & its synthetic utility, The succinimides were synthesized from succinic acid & substituted aryl amines. The succinimides on diformylation using Vilsmeier-Haack reaction formed 2,5-dichloro-3,4-diformyl (N-substituted phenyl) pyrroles. These dichlorodiformyl pyrroles having formyl groups & chlorine at ortho position to each other may show promising precursors of other novel pyrrole derivatives, heterocyclic schiff's bases

& other fused heterocyclic ring compounds. keeping this view in mind we have carried out functional group inter conversion of these compounds into dicarbonitrile derivatives by treating with CAN in presence of aqueous ammonia at $0^0$C.The resulting dicarbonitriles can also acts as precursors for many bioactive organic molecules. The dicarbonitriles were characterized by spectral & elemental analysis. All the compounds were screened against various microorganisms which showed promising results.]

## MATERIALS AND METHODS

All melting points were determined in open capillary & are uncorrected. I.R. spectra were Recorded on Perkin-Elmier spectrum. $H^1$ NMR were recorded on Bruker DRX 500 MHz.NMR spectrometer with DMSO-d6 as a solvent using TMS as internal references.(chemical shift in δ ppm).

## EXPERIMENTAL WORK

**General procedure for synthesis of 2,5-dichloro-1-(N-substituted phenyl)-3,4-dicarbonitriles.**

A suspension of Vilsmeier-Haack product III (1mmol) in 30% aq. ammonia (5ml) was stirred for 10 min. at RT, which resulted in formation of turbid solution. To this CAN (2mmol) was added with constant stirring at $0^0$c ,after completion of the reaction in 20-30 min, it was extracted with chloroform ethyl acetate mixture (5:3) dried (anhydrous $Na_2SO_4$)and concentrated under reduced pressure to obtain the solid product which was purified by recrystallisation from aq. Ethanol**.**

## REACTION SCHEME

**(IVa), 5-dichloro-1-phenyl-1H- pyrrole-3,4-dicarbonitrile.**

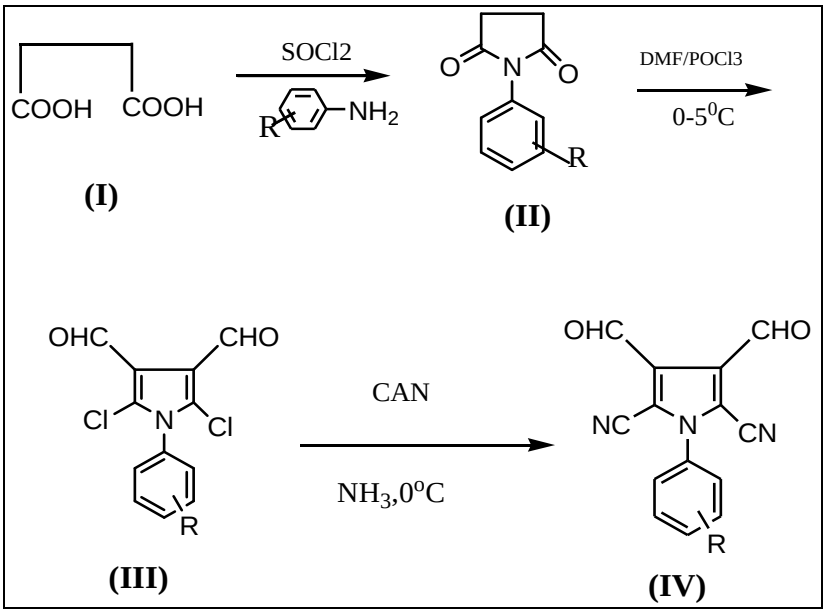
Molecular formula:- $C_{12}H_5N_3Cl_2$ Physical nature is white , Yield: 85 %

M.P : 140-145$^0$C Mol. Wt 262

IR (KBr)cm$^{-1}$ 2249 (-CN), 1519 (Ar-C=C-), 1209 (C-N), 788(C-Cl).

$H^1$NMR (300MHz, DMSO-$d_6$,δppm,) 7.40-7 (m,4H,Ar)

$C^{13}$NMR 117(-CN), 119 (C-Cl), 121-129 (Ar-H)




**R = a=-H, b=2-Cl,c=4-Cl,d=3-Cl,e=3-$OCH_3$,f=4-$CH_3$**

**Elemental Analysis**

Calculated for $C_{12}H_5N_3Cl_2$ : C-54.96, H-1.90, N-16.03. Found, C-54.80, H-1.80, N-16.00.

**(IVb) 2,5-dichloro-1-(2-chlorophenyl)-1H- pyrrole-3,4-dicarbonitrile.**

Molecular Formula : $C_{12}H_4N_3Cl_3$

Physical nature whitish Yield(%) 87 % M.P: 115-120$^0$C Mol Wt :- 296.5

IR (KBr)cm$^{-1}$ 2245 (-CN), 1512 (Ar-C=C-), 1200 (-C-N), 785 (-C-Cl).

H$^1$NMR (300MHz,DMSO-$d_6$,δppm) 7.50-7 (m,4H,Ar)

C$^{13}$NMR 118 (-CN), 120 (C-Cl), 121-130 (Ar-H), 134 (Ar-Cl).

**Elemental Analysis**

Calculated for $C_{12}H_4N_3Cl_3$ : C-48.56, H-1.34, N-14.16. Found, C-48.50, H-1.30, N-14.10.

**(IVc) 2,5-dichloro-1-(4-chlorophenyl)-1H- pyrrole-3,4-dicarbonitrile.**

Molecular Formula: $C_{12}H_4N_3Cl_3$

Physical nature whitish Yield(%) :- 88 %

M.P.:180-184$^0$C Mol. Wt. :- 296.5

IR (KBr)cm$^{-1}$ 2235 (-CN), 1500 (Ar-C=C-), 1200 (-C-N), 781 (-C-Cl).

H$^1$NMR (300MHz, DMSO-$d_6$,δppm) 7.54-7 (m,4H,Ar)

C$^{13}$NMR**:** 118 (-CN), 119 (C-Cl), 121-129 (Ar-H), 134 (Ar-Cl).

**Elemental Analysis**

Calculated for $C_{12}H_4N_3Cl_3$ : C-54.96, H-1.90, N-16.03. Found, C-54.90, H-1.80, N-16.00.

**(IVd) 2,5-dichloro-1-(3-chloro phenyl)-1H-pyrrole-3,4-dicarbonitrile.**

Molecular Formula:$C_{12}H_4N_3Cl_3$

Physical nature whitish Yield(%) : 87 %

M.P: 160-165$^0$C, Mol Wt :- 296.5

IR (KBr)cm$^{-1}$ 2240 (-CN), 1523 (Ar-C=C-), 1215 (C-N), 785 (C-Cl).

H$^1$NMR (300MHz, DMSO-$d_6$,δppm) 7.45-7 (m,4H,Ar)

C$^{13}$NMR 117 (-CN), 119 (C-Cl), 121-129 (Ar-H), 135 (Ar-Cl).

**Elemental Analysis**

Calculated for $C_{12}H_4N_3Cl_3$ , C-54.96, H-1.90, N-16.03. Found, C-54.90, H-1.85, N-16.00.

**(IVe) 2,5-dichloro-1-(3-methoxyphenyl)-1H-pyrrole-3,4-dicarbonitrile.**

Molecular Formula: $C_{13}H_7ON_3Cl_2$

Physical nature whitish Yield(%) :- 90 %

M.P**:** 95-100$^0$C , Mol. Wight **:** 292

IR (KBr) cm$^{-1}$ 2235 (-CN), 1500 (Ar-C=C-), 1200 (-C-N), 781 (-C-Cl), 1300 (-$OCH_3$).

H$^1$NMR (300MHz,DMSO-$d_6$,δppm) 7.54-7 (m,4H,Ar-H), 3.83 (s,3H,$OCH_3$).

C$^{13}$NMR **:** 117 (-CN), 119 (C-Cl), 121-129 (Ar-H), 55.9 (-$OCH_3$) **.**

**Elemental Analysis**

Calculated for: $C_{13}H_7ON_3Cl_2$ , C-54.96, H-1.90, N-16.03. Found, C-53.99, H-.69, N-15.99.

**(IVf) 2,5-dichloro-1-(4-methyl phenyl)-1H-pyrrole-3,4-dicarbonitrile**

Molecular Formula: $C_{13}H_7N_3Cl_2$

Physical nature whitish Yield(%) :- 75 % , M.P. 210-215$^o$C Mol. Weight : 276

IR (KBr)cm$^{-1}$ 2235 (-CN), 1500 (Ar-C=C-), 1200 (-C-N), 781 (-C-Cl).

H$^1$NMR (300MHz, DMSO-$d_6$,δppm) 7.54-7 (m,4H,Ar) C$^{13}$NMR 116 (-CN),119 (C-Cl), 121-129(Ar-H),

**Elemental Analysis**

Calculated for $C_{13}H_7N_3Cl_2$ **:**, C-56.52, H-2.53, N-15.21. Found, C-56.40, H-2.45, N-15.10.

**Table-1 shows physical data of compound**

| Compounds | R group | Molecular Formula | M.P. ($^{O}$C) | Yield (%) |
|---|---|---|---|---|
| Iva | -H | $C_{12}H_5N_3Cl_2$ | 140-145 | 85 |
| IVb | -2-Cl | $C_{12}H_4N_3Cl_3$ | 115-120 | 87 |
| IVc | 4-Cl | $C_{12}H_4N_3Cl_3$ | 180-182 | 88 |
| IVd | 3-Cl | $C_{12}H_4N_3Cl_3$ | 160-165 | 87 |
| IVe | 3-$OCH_3$ | $C_{13}H_7ON_3Cl_2$ | 95-100 | 90 |
| IVf | 4-$CH_3$ | $C_{13}H_7N_3Cl_2$ | 210-215 | 75 |

**BIOLOGICAL TESTING OF COMPOUNDS.**

Heterocyclic Nitrile compounds IV(a-f) were evaluated for antibacterial against Escherichia coli (Ec), pseudomona S. aeruginosa (PA), staphylococcus aureus (SA), Bacillus subtillis (BS), And antifungal against candida albicans (CA), Asperginu S niger (AN).

The result were obtained in the form of clearing zone and were noted after the period of incubation ($37^{0c}$ for 24 hrs). The zone of inhibition was measured in mm and data is presented in table 2. **Media used**

For bacteria : Nutrient agar ( Hi-media)

For yeast : MGYP

Inoculums size : Bacteria : 1 x 10 bacteria per ml. Yeast : 1 x 10 cells per ml

- concentration of compound

(Prepared in ethanol) 100 µ gm 1 disc

- ❖ method used

( disc method, disc size 6mm)

"__" means no zone of inhibition.

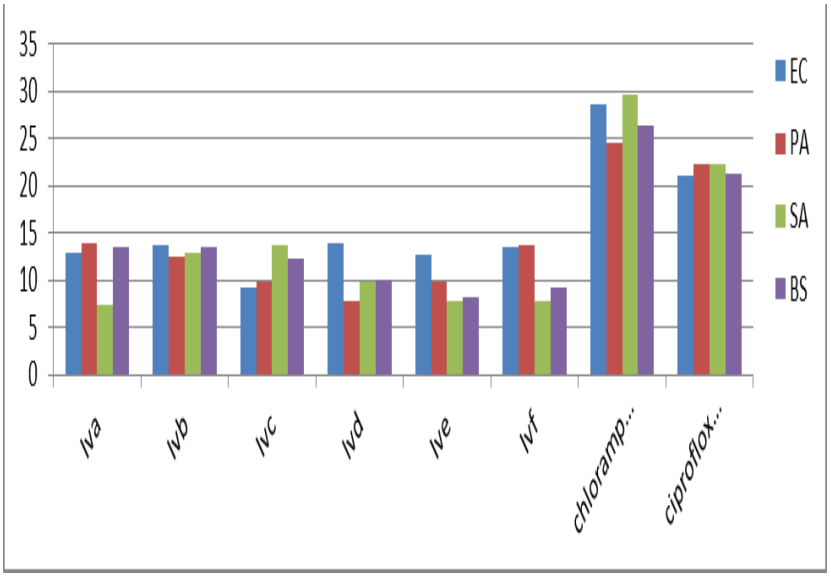
**CULTURE USED**

| Type | Culture name | Culture code |
|---|---|---|
| ES | Escherichia coli | NCIM 1209 |
| PA | Pseudomonas aeruginosa | NCIM 2036 |
| SA | Staphylococcus aureus | NCIM 2079 |
| BS | Bacillus subtilis | NICM 2250 |
| AN | Aspergillus niger | NICM 545 |

**Table-2 Antimicrobial activity of compounds**

| Sr. No. | Compounds | EC | PA | SA | BS | CA | AN |
|---|---|---|---|---|---|---|---|
| 1 | Iva | 12.97 | 13.90 | 7.47 | 13.50 | - | - |
| 2 | IVb | 13.60 | 12.54 | 12.97 | 13.56 | - | - |
| 3 | IVc | 9.23 | 9.88 | 13.66 | 12.36 | - | - |
| 4 | IVd | 13.90 | 7.77 | 9.83 | 10.12 | - | - |
| 5 | IVe | 12.60 | 9.78 | 7.76 | 8.15 | - | - |
| 6 | IVf | 13.50 | 13.60 | 7.78 | 9.23 | - | - |
| 7 | Chloramphenicol | 28.67 | 24.44 | 29.63 | 26.30 | NA | - |
| 8 | Ciprofloxacin | 21.11 | 22.23 | 22.23 | 21.34 | NA | - |

(Zone of inhibition in mm)




**Graph -1: Comparative antimicrobial activity of compounds (Iva-f)**

**ACKNOWLEDGEMENTS**

The authors are gratefully acknowledged to Principal, P. G. Research Centre, Department of Chemistry JET's Z. B. Patil College, Dhule (MS) India, for providing the necessary facilities utilized to carry out the research project successfully. Furthermore the authors would like to extend their special thanks to university of Pune, Department of Chemistry for NMR data and Principal, R.C. Patel Pharmacy College Shirpur, for microbial analysis of compounds.

**CONCLUSION**

We have synthesized various Nitrile derivatives by using Ceric Ammonium Nitrate (CAN), it is a simple to operate, fast reaction rate, nontoxic, inexpensive and environmentally friendly catalyst. The compounds were shows good to mild Anti microbial activity. All compounds are characterized by IR, NMR, etc. analytical methods.

**REFERENCES**


1. Lucka-Sabstel,Barbara Zeic, Alfred and Obinskagolanta,Arch Immunol Thre Exp, 25 (1977) 285, Chem.Abstr.87, 5291t.
2. Saainivaara Laila and Mattila, K,J.,Psycopharmacologia, 1974; 35: 221.
3. Dahibon, J.R. and Karlen, B.L. Ger.Pat.1, 670, 019. 17 Oct. 1974.Chem. Abstr. 1975; 82: 139969.
4. Gventher Weitzel and FriendhelmSchneider.J.PhysChem, 336, 107, (1964), Chem.Abstr. 1964; 61: 488b.
5. Crasspeter,E; Dickinson Roger P;Halliwell Geoffrey and Kemp John E.G. Eur. J.Med.Chem.Chim Ther, 1977; 12, 173.
6. Sandberg Rune and Domegji Karl Erik, Acta Pharmsues, 1979; 16, 386.
7. Dahlbon,J.R. and Karlen, B.L; Swedpat 323374,4 May 1970,Chem.Abstr, 1972; 77, 114424.
8. Chaivarell,S. and Mazzeop, Farmaco (poria) Ed Sci 18, 750, (1875), Chem Abstr. 1964; 60: 2929.
9. Hromatka and Skopalik,C; Mnchem. Soc, 75, 2261 (1953), Chem Abstr, 1954; 48: 10571.
10. Rice, L.M. and Grogan, C.H.,J.Am. Chem.Soc., 1953; 75: 2261.
11. Akira-Fujinami, Toshiaki,Ozati et al.Arg.Biol. Chem. 1972; 36(2): 318.
12. Pandey,V.K; Lohani, H.C. and Agrawal Akhilesh. Indian Drugs, 1984; 21(4): 135.
13. Micheal Orider and Edward Margrian.J. Med. Chem. 1977; 20(3): 405.
14. Rangnekar,V.M.; Lokhande, S.R. and Khadase,G.Ind.J.Chem, 1983; 22(b): 1070.
15. Eisner,U.,Kuthan,J.Chem.Rev.1972; 72, 1.
16. Ouintela,J.M.;Peinador,C.;Botana,L.;Estevez,M.;Reiguera,R.Bioorg.Med.Chem.1997; 5: 1543
17. Monna,F. *et al* .Eur.J.Med.Chem.1999; 34: 245
18. Ueno,K *et al* .15 Apr 1999 Int.Appl.WO 99 180 77 ;ref.Chem.Abstr.1999,130,311813b.
19. Elderfied,R.C.;King,T.P.J.Am.Chem.Soc.1954; 76: 5439
20. Monem,W.R.A.Chem.Pap. 2004; 58(4): 276.
21. Hosni,H.M.;Abdulla,M.M.Acta Pharm. 2008; 58: 175.
22. Zhang, N.;Wu, B.; Boschelli, D.H.; Goals, J. M.; Boschnelli, Bioorg. Med. Chem. Lett. 2009; 5071
23. Chioua, M.; *et al* , J. Bioorg. Med. Chem. Lett. 2009; 19: 4566.
24. Loge, *et al* M.;Meijer,L;Besson,T.Eur.J.Med.Chem. 2001469.
25. (a)Yang,Z.;Jingliang,J.;Robert,A.J.Org.Chem. 2006; 71:4516,

(b) Surendra,K.;Srilakshmi,K.and Rama Rao,K.Tetrahedron Lett. 2005; 46: 4111

(c)Ravi,V.;Ramu,E.;Sreelatha,N.;Srinivas,R.A.Synlett. 2006; 1009.

26. Nair,V.;Panicker,S.B.;Nair,L.G.;George,T.G. and Augustine,A.Synlett. 2003; 156.