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Research Article

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Thermal Cyclization of enaminoimine hydrochlorides of 2,5-dichloro-3,4-diformyl(N-substituted phenyl)pyrroles

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ABSTRACT

Pyrroles possess wide spectrum of biological activities and are calcium & sodium channel blockers. Formyl group present on Pyrrole molecules make them promising precursors for further synthetic transformations. In view of this literature search and in continuation of our interest on the Vilsmeier-Haack Reaction and its synthetic utility[14]. We have synthesized 2,5-dichloro-3,4-diformyl(N-substituted phenyl)pyrroles. These compounds were obtained from N-substituted succinimides upon reaction with V-H reagent. The succinimides in turn were synthesized from succinic acid and substituted aryl amines. The dichloro diformyl compounds obtained after V-H reactions are having formyl groups & chlorine at suitable proximity hence may show promise as precursors for still other novel pyrrole derivatives, heterocyclic Schiff bases & other fused five, six and seven member cyclic rings. By keeping this view in mind we treated dichloroaldehydes with 4.4 equivalents of arylamines in ethanolic HCl at 0^{o}C temp which formed the corresponding enaminoimine hydrochlorides in very good yields. These on thermal cyclization at 200-210 ^{o} C for 8-10 min in preheated oil bath formed symmetrical polycyclic compounds. These compounds are expected to show cytotoxic activities. All the resultant compounds are characterized by Spectral & elemental analysis.

Keywords: Thermal cyclisation, Pyrroles, Vilsmeier-Haack Reaction, Schiff bases, Enaminoimine hydrochlorides, Dichlorodialdehydes .

INTRODUCTION

Pyrroles is one of the most important five-member aza heterocyclic because of its occurrence as a synthon in many bioactive natural products, synthetic pharmaceuticals and various kinds of functional *N*-materials with interconvertable properties[1-3]. The existence of pyrrole was first interpreted by Runge in 1934, when he first time noticed the formation of a new substance during the destructive distillation of coal tar and bone oil. Pyrroles have displayed considerable pharmaceutical properties like remarkable biological and pharmaceutical properties such as anti-inflammatory [4], anti-fungal [5], anti-oxidation [6], anti-bacterial [7], and anti- tumour [8]. Therefore, it has wide range of biological properties.

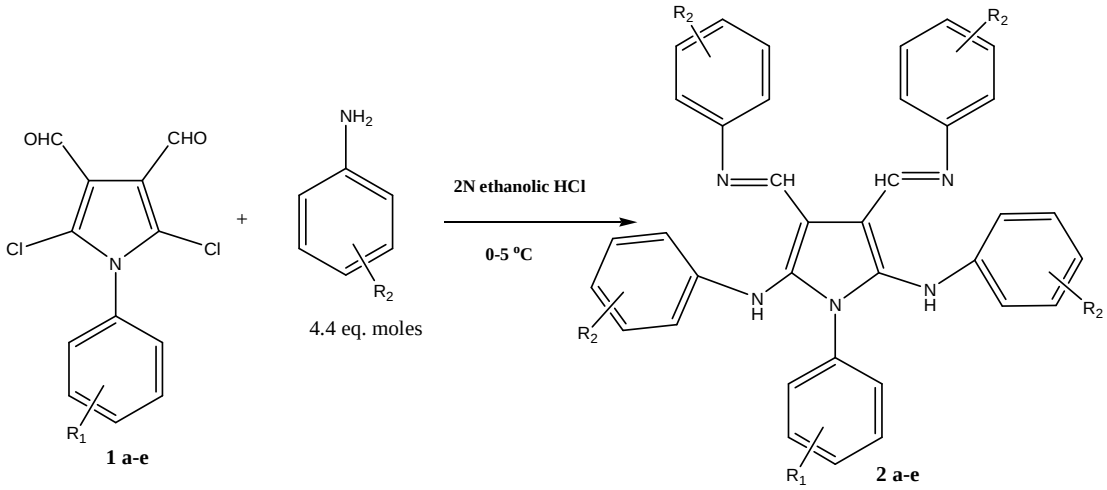
EXPERIMENTAL SECTION

Melting Points of compounds were recorded by one open end capillary tube methods which are uncorrected. ^{1}H-NMR spectra were recorded on 399 MHz Gemini 2000(Varian, Oxford using DMSO as solvent. unless otherwise stated; down field from the internal standard TMS as the internal standard, IR spectra were recorded on a Perkin-Elmier spectrophotometer FT-IR 1725X. Analytical TLC; Thin-layer charomatography (TLC) was performed on precoated on merck silica gel 60 F254 plates. The elemental analysis was performed on the Vario EL III-C,H,N,O elemental Analyzer (Elementar Analy sensensysteme GmbH, Hanau- Germany). Reagents and solvents were used without purification: Loba Chem Pvt. Ltd.

GENERAL PROCEDURE

Synthesis of Schiff's bases of 2,5-dichloro-3,4-diformyl(N-substituted)-4-hydropyrroles.

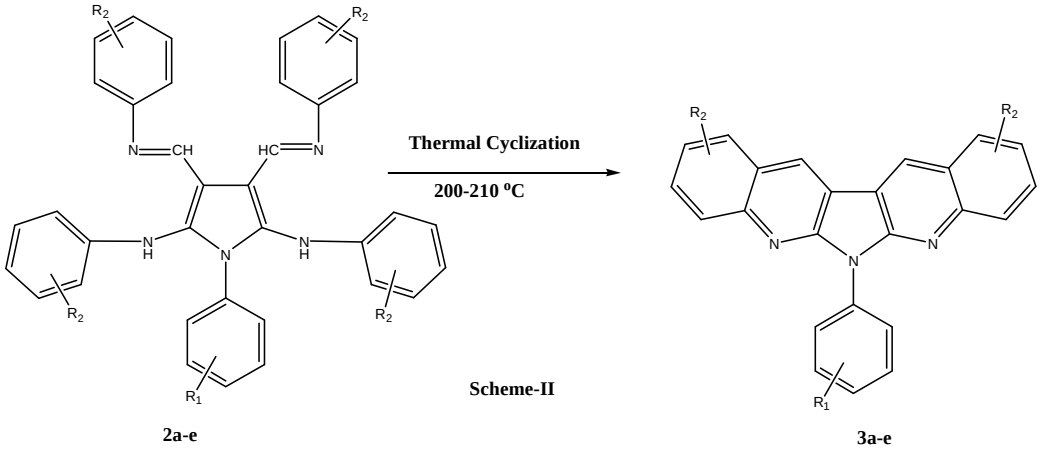
The dichlorodialdehydes **1a-e** were synthesized by Vilsmeier-Haack reactions on succinamids [9-12] which upon reaction with 4.4 equivalent of various aryl amines in 2 N ethanolic HCl at 0°C which produced the corresponding *3,4-bis (N-phenylimino)alkyl)-N²,N⁵,1-tris1-tris(N-phenyl)-1-H-Pyrrole-2,5-diamine* hydrochlorides **2a-e** in very good yields.



Scheme-I: Formation of Schiff's bases

Synthesis of 2-(2-subsituted phyenyl)quinoline derivatives.

The resulted compounds **2a-e** were thermally cyclised at 200-210°C produced *2-(2-subsituted phyenyl)quinolines* **3a-e** as the major isolable product. The desired diqunolines **3a-e** was synthesized by heating **2a-e (Scheme-II).**



Scheme-II

Scheme-II: Thermal Cyclization of Schiff's bases

Table: 1- Schiff's base of 2,5-dichloro-3,4-diformyl(N-substituted phenyl)pyrroles

Compounds	Reagents	Primary Amines	Yield's (%)	Melting Point (°C)
2a	2,5-dichloro-3,4-diformyl(4-methylphenyl)pyrrole	p-anisidine	92	122
2b	2,5-dichloro-3,4-diformyl(4-methoxylphenyl)pyrrole	p-toludene	90	168
2c	2,5-dichloro-3,4-diformyl(4-chlorophenyl pyrroles	p-toludene	94	190
2d	2,5-dichloro-3,4-diformyl(4-chlorophenyl)pyrrole	p-anisidine	94	104
2e	2,5-dichloro-3,4-diformyl(4-methoxyphenyl)pyrrole	p-chloroaniline	88	108

RESULTS AND DISCUSSION

Experimental procedure for thermal cyclization of 2a-e:

In this type of thermal reaction [13] stating material the Schiff's base hydrochlorides **2a-e** were taken in hard glass test tube and heated at 200-210 °C for 8 to 10 min in a preheated oil bath. In the upper cooler part of the test tube, arylamine hydrochloride was condensed. The product was formed at the bottom. After cooling the residue was washed with ice cold water and dissolved in ethylacetate. The organic layer was washed well with water, dried over

anhydrous Na_2SO_4 and the solvent was removed under vacuum rotary evaporator. The crude products **3a-e** thus obtained were purified by recrystallisation with aq ethanol.

Table 2: Cyclization of 3,4-bis (*N*-phenylimino)alkyl)-N^2,N^5,1-tris1-tris(N-phenyl)-1-H-Pyrrole-2,5-diamine hydrochlorides

Compounds	Yield's [c](%)	Melting Point (^oC)
3a	90	112
3b	88	180
3c	94	108
3d	94	110
3e	86	142

ANALYTICAL AND SPECTRAL DATA FOR THE SYNTHESIZED COMPOUNDS

Scheme-I:

Synthesis of Schiff's base of 2,5-dichloro-3,4-diformyl(N-substituted phenyl)pyrroles.

1) *3,4-bis((E)-(4-methoxyphenylimino)methyl)-N^2,N^5-bis(4-methoxyphenyl)-1-p-tolyl-1H-pyrrole-2,5-diamine* (2a) m. p. 122^{o}C

FT-IR: 1574.36, 1551.81, 1416.29, 1496.88, 1629.30, 1222.22, 819.16, 1059.88, 3571.65, 1016.59.

2) *3,4-bis((E)-(p-tolylimino)methyl)-1-(4-methoxyphenyl)- N^2,N^5-dip-tolyl-1H-pyrrole-2,5-diamine*(2b) m. p. 168^{o}C

FT-IR: 1557.67, 1418.97, 1496.84, 1574.61, 1602.91, 1222.20, 839.02, 1016.27, 1660.03, 3001.52.

3) *3,4-bis((E)-(p-tolylimino)methyl)-1-(4-chlorophenyl)- N^2,N^5-dip-tolyl-1H-pyrrole-2,5-diamine*(2c) m. p. 190^{o}C

FT-IR: 812.06 , 727.19, 1109.11, 1203.62, 1620.26, 1510.31, 1549.96, 1442, 1390.

4) *3,4-bis((E)-(4-methoxyphenylimino)methyl)-1-(4-chlorophenyl)- N^2,N^5-bis(4-methoxyphenyl)-1H-pyrrole-2,5-diamine*(2d) m. p. 104^{o}C

FT-IR: 1621.43, 1554.47, 1201.95, 813.56, 1081.53, 3444.14.

5) *3,4-bis((E)-(4-chlorophenylimino)methyl)- N^2,N^5-bis(4-chlorophenyl)-1-(4-methoxyphenyl)-1H-pyrrole-2,5-diamine*(2e), m. p. 108^{o}C

FT-IR: 1551.83, 1574.83,1496.75, 1647.18, 1222.46, 838.58, 1016.11, 4358.49.

Scheme-II: Cyclization of *3,4-bis (N-phenylimino)alkyl)-N^2,N^5,1-tris1-tris(N-phenyl)-1-H-Pyrrole-2,5-diamine hydrochlorides*.

1) *3, 8 dimethoxy- 12(p-tolyl)-pyrrole[2,3-b-4,5,9]diquinoline*(3a), m.p. 112 ^{o}C ;

FT-IR.: 1510 cm^{-1}, 1589.40, 1107.18, 1629.90, 1246.06 cm^{-1}.

^{1}H NMR (DMSO-d6) δ: (3a) 4.93(S, 3 H),3.62 (S,6 H),6.71 (S,2H),6.75 (S,2 H),7.32 (S,2 H),7.28 (S,2 H),7.24 (S,2 H),7.30 (S,2 H)

Elemental analysis for Molecular Formula $C_{27}H_{21}N_3O$:

Calculated- C(80.37%) H(5.25%) N(10.41%) O(3.97%)

Observed: C(80.49%) H(5.17%) N(10.52%) O(3.82.%)

2) *3, 8 dimethaoxy- 12(p-tolyl)- pyrrole [2,3-b-4,5,9]diquinoline* (3b), m.p. 180^{o}C ;

FT-IR.: 1546,1581,1097,1629,1647,1311 cm^{-1};

^{1}H NMR (DMSO-d6) δ : 3.73 (S,6 H),3.62 (S,3 H)

6.76 (S, 2 H),7.33 (S, 2 H),7.31(S, 2 H),7.29 (S, 2 H),7.23 (S, 2 H),7.26 (S, 2 H)

Elemental analysis for Molecular Formula $C_{27}H_{21}N_3O_2$:

Calculated- C(77.31%) H(5.05%) N(10.02%) O(7.63%)

Observed: C(77.40%) H(5.08%) N(10.08%) O(7.44%)

3) *3, 8 dimethyl- 12(p-chlorophenyl)- pyrrole [2,3-b-4,5,9]diquinoline* (3c), m.p. 108 ^{o}C ;

FT-IR.: 1504,1546, 1201,1253,883.43 cm-1

^{1}H NMR (DMSO-d6) δ: 3.62 (S, 6 H),3. 73 (S, 2 H),7.25(S, 2H),7.29 (S, 2H),7.31 (S, 2 H),7.40 (S, 2 H),6.66(S, 2 H),7.23(S, 2 H)

Elemental analysis for Molecular Formula $C_{26}H_{18}ClN_3$:

Calculated- C(76.56%) H(4.45%) Cl(8.69%) N(10.30%)

Observed: C(76.48%) H(4.54%) Cl(8.75),N(10.23%)

4) *3, 8 dimethaoxy- 12(p-chlorophenyl)- pyrrole [2,3-b-4,5,9]diquinoline* (3d), m.p.110^{o}C.

FT-IR.: 1494,1545,1590,1058,713 cm^{-1};

^{1}H NMR (DMSO-d6) δ: 3.96 (S, 6 H),8.32(S, 2 H),7.99 (S, 2 H),7.69 (S, 2 H),7.15 (S, 2 H),7.68 (S, 2 H)

Elemental analysis for Molecular Formula $C_{26}H_{18}ClN_3O_2$:

Calculated- C(70.99%) H(4.12%) Cl(8.06%) N(9.55%) O(7.27%)

Observed: C(70.89%) H(4.22%) Cl(8.13%) N(9.61),O(7.28%)

Antimicrobial Study:

Antimicrobial activities of compounds we come to know the extent of development inhibition of microorganisms [16]. The antibacterial study is inhibition outcome in the course of the development of the bacterium in nutrient agar-agar medium. Activities showed as zone of inhibition diameter in millimetres in disk diffusion method [15], 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[15].

Table 3: Antimicrobial Activity of Compounds 3a-e

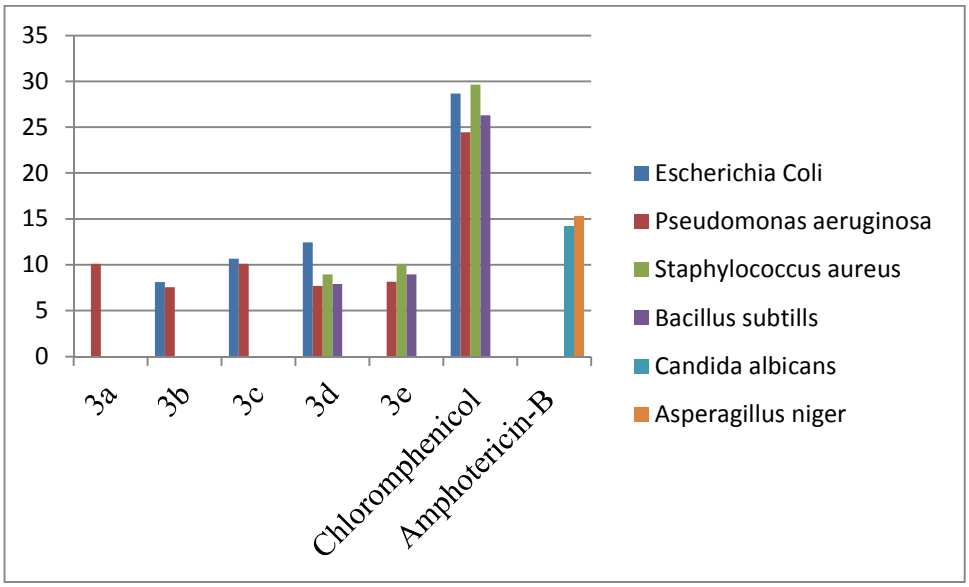
Compound	*Escherichia Coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Bacillus subtills*	*Candida albicans*	*Asperagillus niger*
3a	-	10.12	-	-	-	-
3b	08.12	7.55	-	-	-	-
3c	10.67	10.12	-	-	-	-
3d	12.45	7.69	8.96	7.89	-	-
3e	-	8.14	10.12	8.95	-	-
Chloromphenicol	28.67	24.44	29.63	26.30	NA	NA
Amphotericin-B	NA	NA	NA	NA	14.23	15.34

"-" means no zone of inhibition

Compounds **3-a-e** were evaluated for antimicrobial activity agents *Escherichia Coli, Pseudomonas aeruginosa , Staphylococcus aureus , Bacillus subtills* and antifungal activity against *Candida albicans, Asperagillus niger*. The results were obtained in the form of clearing zone and were noted after the period of incubation (37 ^{o}C for 24 hr). The zone of inhibition was measured in mm and data is presented in **table-3**

The compounds **3b**, **3c** and **3d** showed moderate antimicrobial activity against *E.coli*, **3a** and **3c** showed moderate antimicrobial activity *p.aeruginosa*, **3e** showed antimicrobial activity against both *S. aureus* and *Bacillus subtills.* None of the compound showed antifungal activity against the *Candida albicans* and *Asperagillus niger*.

Table 4: Comparative graph of antimicrobial activity of Compounds 3a-e



CONCLUSION

In conclusion we have used a simple method for the synthesis of various 2,5-diamine hydrochlorides bisubstituted quinolines obtained from easily accessible starting materials catalysed by 2N ethanolic HCl. The used thermal cyclization procedure has mild reaction condition and operational simplicity. High yields and rapid formation of the products are the main advantages this procedure. Few compounds showed moderate to good antimicrobial activity.

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