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RESEARCH ARTICLE

Thermal Condensation of Enaminoimine Hydrochlorides of 2,6-Dichloro-3,5-diformyl (*N*-Substituted Phenyl)pyridines

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Abstract: 1,4-Dihydropyridines are calcium and sodium channel blockers and also possess wide spectrum of biological activities and are most promising precursors for further synthetic transformations. The dichloro diformyl compounds obtained after V-H reactions are having formyl groups and chlorine at suitable closeness hence may show promising precursors for still other novel qunoline synthesis. By keeping this view in mind we treated 2,6-dichloro-3,5-diformyl(*N*-substituted phenyl)pyridine with 4.4 equivalents of arylamines in ethanolic HCl at 0 ^{o}C which formed the corresponding enaminoimine hydrochlorides in good yields. These on thermal reaction at 200-210 ^{o}C for 8-10 min in preheated oil bath formed symmetrical polycyclic diqunoline type of compounds. These compounds were screened for antimicrobial activities. The resultant symmetrical compounds are expected to show some cytotoxic activities. All the resultant compounds were characterized by spectral and elemental analysis.

Keywords: Thermal reaction, Pyridines, Vilsmeier-Haack Reaction, Schiff bases, Enaminoimine hydrochlorides, Quinolines

Introduction

In drug discovery quinolone ring system has been frequently studied and is an attractive synthetic target in organic synthesis[1]. It was found in most of natural product structures as the core structural moiety of many antibacterial agents. Quinoxalines and quinolines are two important groups of aza-polycyclic compounds which have many biological and pharmaceutical properties. For example, quinoxalines have been used as antibacterial[2] antimycobacterial[3]. Quinolines have been also used as antimalarial, antiasthmatic, antihypertensive, antibacterial and tyrosine kinase inhibiting agents[4,5]. The condensation of 1,2-diamines with 1,2-diketones has been used as a useful synthetic route towards quinoxalines. For this transformation some catalysts[6,7] such as, $Zr(DS)_4$, $Yb(OTf)_3$, oxalic

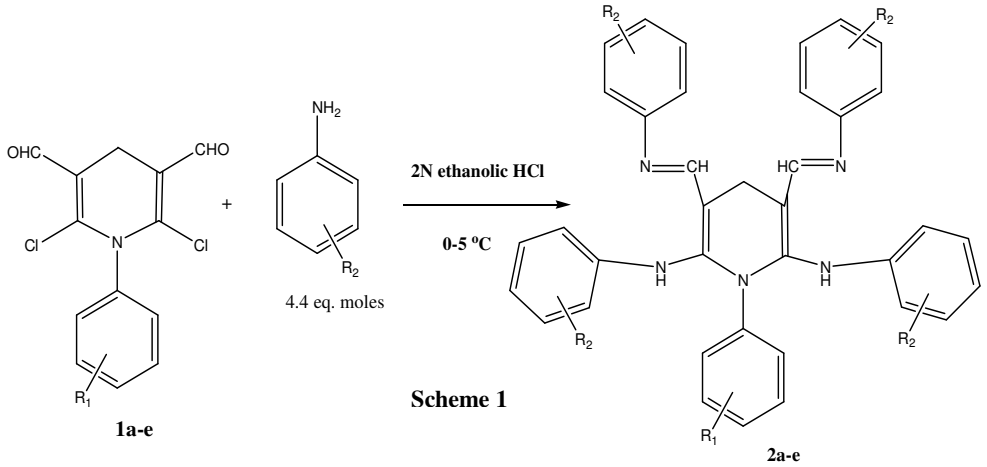
acid[8], $(NH_4)_6Mo_7O_{24}4H_2O$, iodine[9] in DMSO[10], Zn[*L*-proline][11] and sulfamic acid/MeOH[12] have been reported in various literatures. In this paper quinolines have been synthesized by thermal catalyzed intramolecular condensation with removal of primary amine molecule. Many of the reported procedures for the synthesis of quinoxalines and quinolines shows some disadvantages such as, the use of high cost catalysts, the need for anhydrous conditions, long reaction times, low yields, difficult experimental arrangement as well as workup procedures. In this work we have used simple, convenient, less time consuming and high yielding advantages method for the synthesis of qunoline derivatives[13].

Experimental

Melting Points of compounds were recorded by one open end capillary tube methods which are uncorrected (Table 1). ^{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 Analysensensysteme GmbH, Hanau- Germany). Reagents and solvents were used without purification: Loba Chem Pvt. Ltd.

General procedure

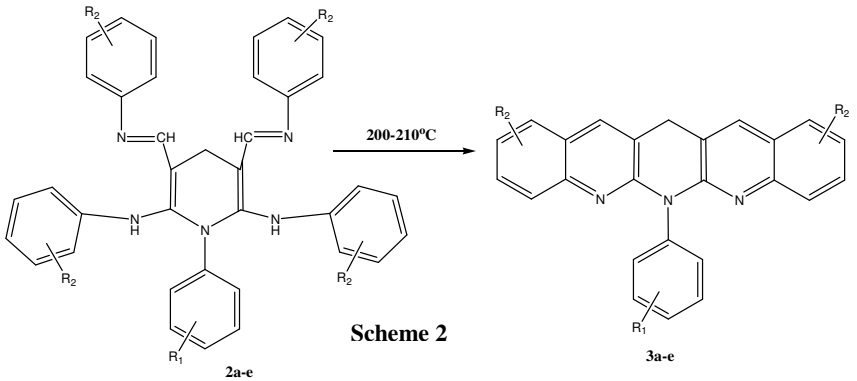
The dichlorodialdehydes **(1a-e)** were synthesized by Vilsmeier-Haack reactions on glutariamides[14-17]. The synthesized synthone **1a-e** were subjected to reaction with 4.4 equivalent of various primary amines in 2N ethanolic HCl at 0 ^oC produced the corresponding 3,4-bis (*N*-phenylimino)alkyl)-N^2,N^5,1-tris1-tris(*N*-phenyl)-1-*H*-Pyrrole-2,5-diamine hydrochlorides (**2a-e)** in very good yields (Scheme 1).



Scheme 1

Scheme 1. Synthesis of Schiff bases of 2,6-dichloro-3,5-diformyl(*N*-substituted)-1,4-dihydropyridine

The resulted compounds 3,4-bis(*N*-phenylimino)alkyl)-N^2,N^5,1-tris1-tris(*N*-phenyl)-1-*H*-pyrrole-2,5-diamine hydrochlorides **(2a-e)** were thermally cyclised at 200-210 ^oC to form 2-(2-subsituted phyenyl)quinoline (**3a-e)** as the major isolable products. The desired diquinoline **3a-e** were synthesize (Scheme 2) by heating **2a-e**.



Scheme 2. Synthesis of 2-(2-subsituted phyenyl)quinoline derivatives by thermal condensation

Table 1. Physical data Schiff base of **1a-e**

Compounds	Reagents	Primary Amines[b]	Yield[c] %	Melting Point, °C
2a	2,6-Dichloro-3,5-diformyl(4-methylphenyl) 1,4-DHP	*p*-Anisidine	92	180
2b	2,6-Dichloro-3,5-diformyl(4-methoxyphenyl) 1,4-DHP	*p*-Toluidene	90	176
2c	2,6-Dichloro-3,5-diformyl(4-chloropheny) 1,4-DHP	*p*-Toluidene	94	146
2d	2,6-Dichloro-3,5-diformyl(4-chloropheny) 1,4-DHP	*p*-Anisidine	94	166
2e	2,6-Dichloro-3,5-diformyl(4-methoxyphenyl) 1,4-DHP	*p*-Chloroaniline	88	130

[c] Isolated yield, [b] Primary amine(a-e)

Results and Discussion

*Experimental procedure for thermal condensation of **2a-e***

In this type of thermal reaction[18] the synthesized 3,4-bis (*N*-phenylimino)alkyl)-N^2,N^5,1-tris1-tris(*N*-phenyl)-1-*H*-pyrrole-2,5-diimine hydrochloride **2a-e** was taken in hard glass test tube. It was then heated at 200-210 °C for 8 to 10 min in a preheated oil bath. The completion of reaction was tested on TLC plate. After completion of reaction time it was observed that cooler part of the test tube was found to condense primary aryl amine hydrochloride. The compound at the bottom was the product. 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 product **3a-e** thus obtained was purified by recrystallization with 50% ethanol (Table 2).

Table 2. Physical data of condensation products **3a-e**

Compounds	Yield[c] %	Melting point °C
3a	90	198
3b	88	180
3c	94	165
3d	94	140
3e	86	124

[c] Isolated yield

Selected spectroscopic data

Analytical and spectral data for the synthesized compounds

3, 9 Dimethoxy-13(*p*-tolyl)pyridine[2,3-b-4,5,9]diquinoline**(3a):** M.p. 180 ^{o}C; FT-IR.: 1510.30, 1589.40, 1107.18, 1629.90,1246.06 cm^{-1}; ^{1}H NMR (DMSO-d6) δ: (3a) 3.967 (S,6 H);, 3,990(S, 2 H);, 7.126(S,2H);, 7.156(S,2H);, 8.32(S,2 H);, 8.34(S,2 H);, 7.68,(S,2 H);, 7.69 (S, 2 H);, 2.586, (S,3H).

Elemental analysis for molecular formula $C_{28}H_{23}O_2N_3$: Calculated C(77.58%) H(5.35%) N(9.69%) O(7.38%) Observed: C(77.90%) H(5.10%) N(9.85%) O(7.15.%)

3, 9 Dimethyl-13(p-tolyl)pyridine[2,3-b-4,5,9]diquinoline **(3b):** M.p. 176 ^{o}C; FT-IR.: 1546.96,1581.68,1097.53,1629.90,1647.26,1311.64 cm^{-1}; ^{1}H NMR (DMSO-d6) δ: 2.68 (S, 6 H),7.26 (S, 2H),7.08(S, 2H),7.05 (S, 2H),7.03 (S, 2H),6.55(S, 2H),6.70 (S, 2H),3.64 (S, 2H),2.95(S, 3 H).

Elemental analysis for molecular formula $C_{28}H_{23}N_3O$: Calculated C(80.55%) H(5.55%) N(10.06%) O(3.83%) Observed C(80.90%) H(5.33%) N(10.15%) O(3.62%).

3, 9 Dimethyl-13(p-chlorophenyl)pyridine[2,3-b-4,5,9]diquinoline **(3c):** M.p. 146 ^{o}C ; FT-IR.: 1504.53,1546.96, 1201.69,1253.77,883.43 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 $C_{27}H_{20}ClN_3$: Calculated C(76.86%) H(4.78%) Cl(8.40%) N(9.96%) Observed C(77.05%) H(4.71%) Cl(8.35),N(9.89%)

3, 9 Dimethaoxy-13(p-chlorophenyl)pyridine[2,3-b-4,5,9]diquinoline **(3d):** M.p.166 ^{o}C. FT-IR.: 1494.88,1545.03,1590.03,1058.96,713.69 cm^{-1}; ^{1}H NMR (DMSO-d6) δ: 3.59 (S, 6 H),3.61 (S, 2H),6.97(S, 2 H),7.22 (S, 2 H),7.51 (S, 2H),7.84(S, 2H),7.02, (S, 2 H),6.46(S, 2 H).

Elemental analysis for molecular formula $C_{27}H_{20}ClN_3O_2$: Calculated C(71.44%) H(4.44%) Cl(7.81%) N(9.26%) O(7.05%) Observed C(71.30%) H(4.55%) Cl(7.40%) N(9.16),O(7.65%).

Antimicrobial study

In the antibacterial study inhibition outcome was observed (Table 3 & Figure 1) in the course of the development of the bacterium in nutrient agar-agar medium[19]. Activities showed as zone of inhibition measured as diameter in millimetres in disk diffusion method[20]. Test solutions were prepared by Agar-100 mg, sample compound 1 g, distilled water 10 mL thus, the final concentration of test obtained was 10 mg/mL[20].

Table 3. Antimicrobial activity of compounds **3a-e**

Compound	*Escherichia Coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Bacillus subtills*	*Candida albicans*	*Asperagillus niger*
3a	8.11	9.34	11.23	10.33	8.44	10.11
3b	10.12	7.88	9.45	10.08	9.77	12.33
3c	10.67	9.13	10.87	11.28	-	-
3d	11.34	8.23	11.87	11.45	-	-
3e	11.06	8.88	9.96	-	-	-
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

NA =Not applicable

The compounds **3b**, **3c** and **3e** showed moderate to good antibacterial activity against *E. coil, S. aureus* and *B. subtills* while compounds **3a** and **3b** showed good antifungal activity against *C. albicans* and *A. niger.*

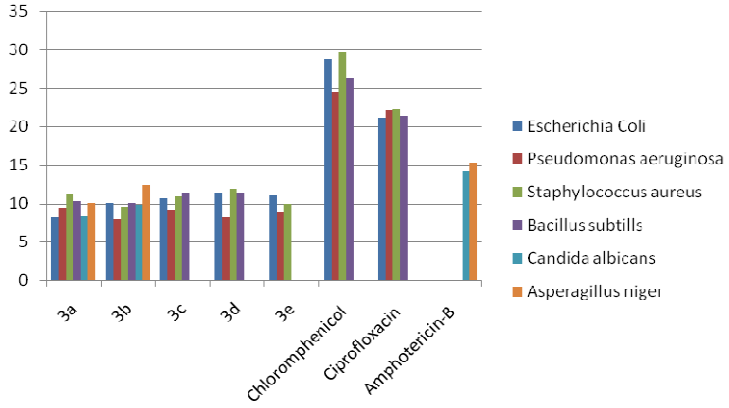


Figure 1. Comparative analysis of microbial activity

Conclusion

We have explained the advantages of a novel methodology for the synthesis of quinolones, as well as their anti microbial applications. The main purpose of this research is to provide good yielding method for syntheses leading to quinolones and study their relevant biological activities. We have synthesized various Schiff bases obtained from easily accessible starting materials catalysed by 2N ethanolic HCl. The thermal condensation has mild reaction condition and operational simplicity. High yields and rapid formation of the products. The majority of compounds showed moderate to good antibacterial as well as antifungal activities against test organisms.

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