An Efficient Approach to Quinoxaline Derivatives

N. ANSAR
Adamjee Government Science College,
Department of Chemistry, Karachi, Pakistan

(Received 26th November, 2001, revised 5th January, 2002)

Summary: Reaction of 4,6-dimethyl quinoline-2-carboxaldehyde catalysed by potassium cyanide results in the formation of an enediol (**1a**). On oxidation with air 1,2-diketone (**1b**) was obtained which upon condensation with 4-methyl-o-phenylenediamine formed relevant 2,3-dihetaryl-6-methyl quinoxaline (**1c**).

Introduction

The heterocyclic compounds and their derivatives form a very significant class because of their wide spread applications [1a]. The nitrogen containing conjugated heterocyclic compounds are of more importance due to their biological activities being used as antiulcer, antimalarial, tuberculocidal and sedatives, besides their uses in the textile industry, pesticides, stabilizers and inhibitors etc. [1a &b]. This manuscript describes a short and efficient approach to an important class of nitrogen containing conjugated heterocyclic compounds namely methyl substituted quinoxalines. The strategy can be efficiently applied to structural variants of quinoxalines, some of which may exhibit a broad range of medicinal properties.

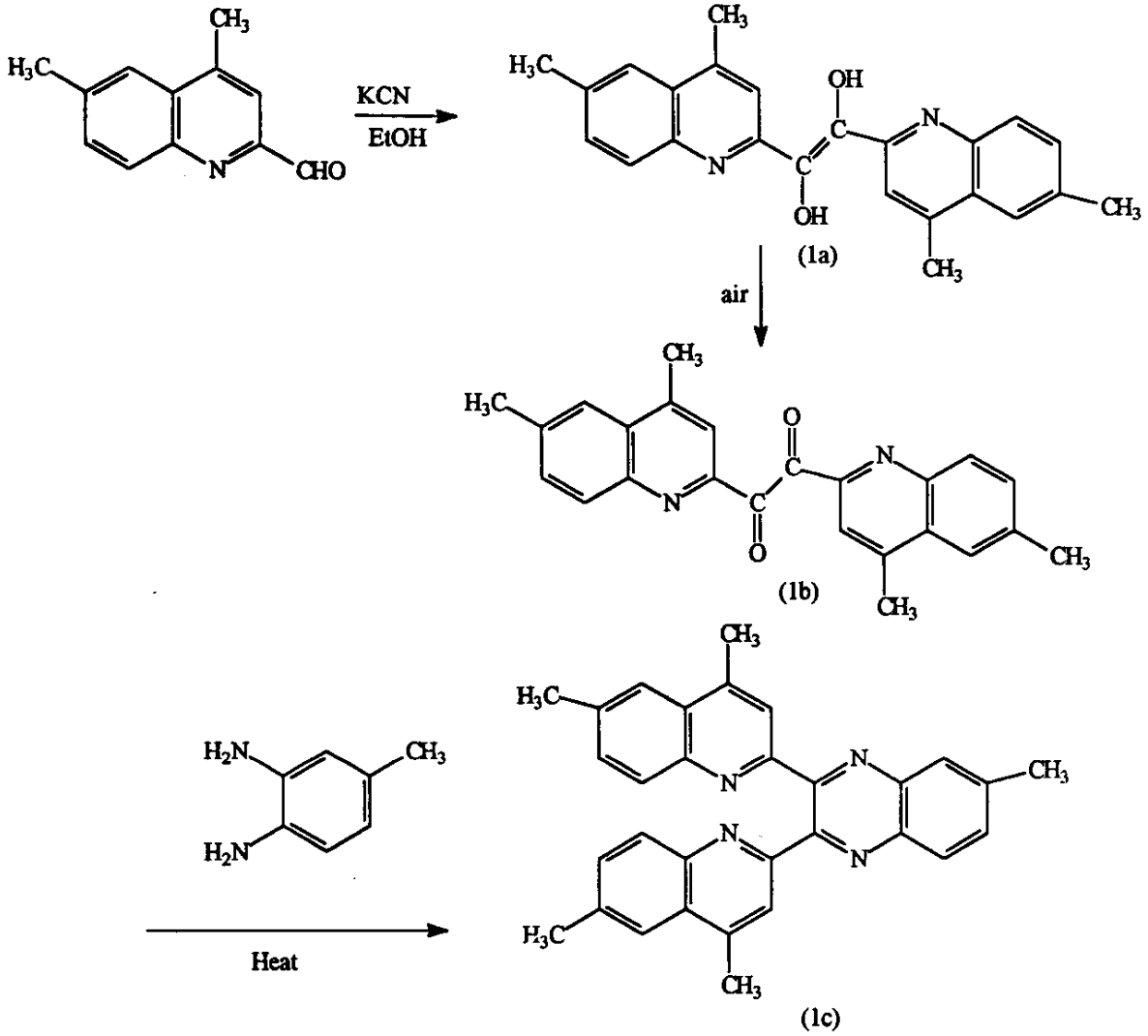
Results and Discussion

Chelated enediols are obtained by the benzoin condensation of different heterocyclic carboxaldehydes having functional group at the 2-position which provides enhanced structural requirement needed for the effective chelation responsible for the stability of the enediol over it's corresponding benzoin tautomer . The predominant formation of trans-enediol has been demonstrsted in

the present work. The *cis*-enediols are not planar and effective chelation will be highly unlikely in the cis-structures [2]. The absence of cis-structure in enediol has been proved with the help of the IR spectrum which shows the absence of C=C stretching vibration between 1660-1600 cm^{-1} which is characteristic for symmetrically substituted C=C bonds [3]. Further evidence was provided by weak absorptions which are characteristic of trans double bond. The UV spectrum of the enediol **1a** reveals chelated structure since the absorption in visible region is due to the presence of the four substituted aromatic rings in the same plane [2]. Enediols of the 2-N-heterocyclic series possess two bands, one with a wave length around 200 nm of high intensity and another with a more variable wave length (300-440nm)at a lower intensity. The synthesized enediol **1a** was then subjected to aerial oxidation providing 1,2-diketone. The carbonyl stretching in IR spectrum was observed at 1700 cm^{-1} which could be attributed to hetaryl groups as observed earlier by Pavia and Bellamy [3,5]. The obtained diketone **1b** was then condensed with 4-methyl-o-phenylenediamine in the presence of glacial acetic acid to afford methyl substituted quinoxaline whose structure was supported by its IR, nmr, mass, uv spectra as well as its elemental analysis.

Experimental

Melting points were measured in open capillaries with an electrothermal IA 9100 digital



melting point apparatus and are uncorrected. Infrared spectra were recorded on a Phillips PU 9714 spectrometer using infrared grade KBr. ^{1}H-NMR spectra were determined on Varian 200 MHz, Gemini, Bruker AC-200 MHz ^{1}H-NMR, FT-NMR and Bruker AM-500MHz FT-NMR in $CDcl_3$ and are reported in ppm using TMS as an internal standard. Mass spectra were obtained with EI MAT 312, Varian MAT 111, Varian MAT 112 and Hewlett Packard GC/MS 5890 spectrometer. For column chromatography silica gel 60 (70-230 mesh) from E-Merck AG was used. Thin layer chromatography (tlc) was performed on Eastman Kodak chromagram 13181 silica gel sheets with fluorescent indicator. The heterocyclic carboxaldehyde was prepared according to the literature procedure using SeO_2 and 2,4,6-trimethyl quonoline as starting material[6]. The SeO_2 was freshly prepared just before use according to the procedure given by Harry Kaplan[7].

1,2-Bis (4,6-Dimethylquinolyl-2)-1,2-ethenediol (1a).

4,6-Dimethyl quinoline-2-carboxaldehyde (1.85g, 10 mmol) was dissolved in 6mL 50% aqueous ethanol in a 100 ml round bottom flask. To it was added an aqueous solution of potassium cyanide (0.13g, 2.0 mmol). The colour of the solution at once changed to a dark brown along with the precipitation of a solid. It was stirred for two minutes and then heated on water bath using water condenser for half an hour. The reaction mixture was cooled, the resulting precipitate filtered and successively washed with water, little methanol and diethyl ether. It was then crystallized from pyridine to obtain 1a (1.23g , 66%), mp 284-86 °C.

IR (KBr): 3590-3160, 3100-2990, 2990-2860, 1580, 1540, 1460, 1440, 1430, 1205, 1190, 1130, 840, 810cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.54 (s, 2 x CH_3, 6H), 2.79 (s, 2xCH_3, 6H), 7.42-811 (m, aromatic, 8H). UV ($CHCl_3$) : λ_{max} 242.0, 437.6nm, MS: *m/z* (relative intensity) 372 (M+2, 11), 371 (M+1, 69), 370 (M^+, 87), 34 (6), 325(142), 311(6), 187(47), 186(95), 158(100), 157(98), 156(72), 129(20), 115(22). Anal: Calcd for $C_{24}H_{22}N_2O_2$, C;77.81, H;5.98, N;7.56; found; C; 77.84, H;5.96, N; 7.75.

1-2-Bis (4-6-dimethyl quinolyl-2) 1, 2-ethanedione (1b).

1, 2-Bis (4,6-dimethylquinolyl-2) 1, 2-ethenediol (3.7g, 10.0 mmol) was dissolved in dioxane and heated in an electrical bath and then air was passed through the solution till the dark brown colour changed to light yellow. After cooling, water was added till precipitation. The crude product was then crystallized from dioxane (2.47g, 67%), mp 280-81 °C. IR (KBr): 3100-3000; 3000-2800, 1700, 1625, 1590, 1500,1440, 1360, 1205, 1165, 1135, 825, 720, 695, cm^{-1}. ^{1}H NMR ($CDCl_3$): δ2.54(s,' 2x-CH_3, 6H) 2.79(s, 2x-CH_3, 6H), 7.42-8.11 (m, aromatic, 8H). UV ($CHCl_3$): λ_{max} 261.7, 314.4nm. MS: *m/z* (relative intensity) 369 (M+2, 21), 368 (M^+,75) 340(45), 311(86), 297(61), 184(5), 156(100), 141(23), 129(38), 116(20). Anal calcd. for $C_{24}H_{20}N_2O_2$ C; 78.24, H; 5.47, N 7.60 found C; 78.09, H 5.51, N; 7.37.

2,3-Bis(4,6-dimethyl quinolyl-2)-6-methyl quinoxaline (1c)

4-Methyl 1,2-phenylcnediamine (0.24g, 2.0 mmol) was taken in a 100mL round bottom flask. To it was added 2.0 mL glacial acetic acid followed by 1b (0.736g, 2.0 mmol) and refluxed for one hour. The solution was cooled, poured into 100mL of water and added 20% aqueous NaOH solution. The precipitate thus obtained was filtered. It was dissolved in ethanol, heated with activated charcoal and filtered. Water was added to obtain the required product which crystallised from petroleum ether as light yellow crystals (0.545g, 74%), mp 130-31 °C.

IR (KBr): 3070-2980, 2980-2780, 1585, 1585, 1540, 1480, 1425, 1365, 112, 1075, 1030, 875, 815 cm^{-1}. ^{1}H NMR($CDCl_3$) δ2.50(s, 2xCH_3, 6H) 2.64(s, CH_3, 3H) 2.72(s, 2xCH_3, 6H), 7.28-8.16 (m, aromatic, 11H). UV($CHCl_3$): λ_{max} 259.2, 342.4nm. MS: *m/z* (relative intensity) 456(M+2) (17), 455(M+1)(74), 454(M^+)(100), 453(M-1)(95), 439(76), 423(7), 287(12), 227(48), 182(7), 156(10), 129(6), 118(10). Anal; Calcd for $C_{31}H_{26}N_4$, C; 81.91, H; 5.76 N; 12.32; found; C; 81.81, H; 5.61, N; 12.20

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