Heterocyclic Letters
Vol. 7| No.3|769-773|May-July| 2017
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS OF NEW SUBSTITUTED QUINOLINE DERIVATIVES

Joshi P. P.* and Shirodkar S.G.

P.G. Department of Chemistry, S.B.E.S. College of Science, Aurangabad. 431001
P.G. Department of Chemistry, N.S.B. College, Nanded. 431605
Maharashtra (India)

Abstract :
Substituted aromatic amines on condensation with diethyl malonate yielded N,N'-bis substituted malonamide (1) which on treatment with methane sulfonic acid undergo cyclisation to give substituted 2,4-dihydroxy quinoline (2). Compound (2) on reaction with $POCl_3$ yielded substituted 2,4- dichloro quinoline (3) which on reaction with various cyclic secondary amines afforded a series of new substituted quinoline derivatives . (3a-6c) All the new synthesized compounds were characterized by ^{1}HNMR and IR spectroscopy.

Keywords : Diethyl malonate, 2,4- dihydroxy quinoline, 2,4-dichloro quinoline, $POCl_3$.

Introduction :

In recent years , scientific interest has focused on nitrogen containing heterocycles because of abundant data showing beneficial therapeutic effects in humans for a number of diseases.
Hydroxyquinolines and its derivative have received a great deal of attention in recent times especially as bioactive compounds exhibiting diverse properties such as antiallergin[1-3], CNS depressants[2,3], anti-inflammatory, antibacterial, antiprotozoal and antifungal[4], cardiovascular[5,6], antiulcer[7], radiation therapy potentiators and chemotherapeutic agents[8] only to mention a few. They also widely used as dyes, perfumes and agrochemicals[9]. Besides literature search to date reveals innumerable synthetically prepared derivatives of 2, 4-dihydroxyquinolines, many of them with patents, that stand out as proof of their viability as drugs. These are furano, pyrano, quinolines, and some of the carbazole derivatives.
The marked antimalarial activity of a number of quinoline derivatives having an amino alkyl side chain attached in the fourth position can be readily converted into drug[10-13]. The marked antimalaria activity of a number of quinoline derivatives having an alkylamino side chain attached in the 4-position[13] has led to an investigation of new compounds.

Experimental :

All melting points were determined in open capillary tubes and are uncorrected. The homogeneity of all the compounds were checked by TLC on silica gel coated plates. IR

spectra were obtained in KBr on Perkin-Elmer FTIR Spectrophotometer. ^{1}HNMR spectra were recorded in $CDCl_3$ on varian NMR spectrometer operating at 400 MHz. Chemical Shifts are expressed in δ w.r.t. TMS. Thin Layer Chromatography was performed with E Merck precoated TLC plates, silica gel 60F254 layer thickness 0.25 mm.

Experimental procedure :

Synthesis of N, N'-bis (4-methoxy / ethoxy phenyl) malonamide (1) :

A mixture of 4-methoxyaniline (0.09 mol) was heated with diethyl malonate (0.045 mol) at 170°C for 1.5 hrs. Reaction mixture was cooled to 110°C. Added Toluene (50 ml) at 110°C, slowly cooled to room temperature. White crystalline solid precipitated out. Stirred for 1 hr at room temperature. Filtered and washed with 5 ml Toluene and dried. Yeild = 60 % ; m.p. = 260^0C

Synthesis of 6-methoxy / ethoxy -2, 4-dihydroxyquinoline (2):

A mixture of compound 1 (0.01 mol) and phosphorous pentaoxide (0.0071 mole) heated in methane sulphonic acid (20 ml) to 170°C. The reaction mixture was stirred at 170°C for 2 hrs. The reaction mixture was slowly cooled to room temperature, and was poured over crushed ice. The separated solid was filtered, washed with water. This solid was purified by dissolution in aq. NaOH solution and acidified with dilute HCl solution. Yield =40%; m.p. = 280°C.

Synthesis of 2, 4-Dichloro-6-Methoxy / ethoxy quinoline (3) :

6-Methoxy-2, 4-dihydroxyquinoline (**2**, 0.0279) was refluxed in $POCl_3$ (20 ml) till the starting material was consumed (3 hrs). Excess $POCl_3$ was distilled off and the residue was treated with chilled water, basified with a solution of $NaHCO_3$ and extracted with chloroform. The chloroform extract was passed through a short column of neutral alumina using PE 60-80°C/ $CHCl_3$ to obtain colorless solid. Yield = 70%; m.p. = 92°C.

Synthesis of 2-Chloro-6-Methoxy / ethoxy-4-morpholin-4-yl-quinoline (3a) :

2, 4-Dichloro-6-Methoxyquinoline (**3**, 0.001 mol) dissolved in toluene (20 ml) at room temperature. Triethylamine (0.003 mol) was added into the reaction mixture followed by addition of morpholine (0.001 mol). The reaction mixture was heated to 50-55°C in water bath. Stirred the reaction mixture for 12 hrs. The progress of reaction was monitored by TLC. After the completion of reaction it was cooled to room temperature and washed with 20 ml dilute HCl solution and separated the two layers. The aqueous layer was basified using liq. Ammonia and solid separated was filtered and washed with water.

Same procedure as above was followed in the synthesis of Synthesis of 2-Chloro-6-Methoxy-4-piperidin-1-yl-quinoline **(3b) ,** Synthesis of 2-Chloro-6-Methoxy -4-(1*H*-imidazol-1-yl) quinoline **(3c)** and 2-chloro-6-ethoxy-4-morpholinoquinoline (**4a**), 2-chloro-6-ethoxy-4-(piperidin-1-yl) quinoline **(4b) and** Synthesis of 2-Chloro-6-ethoxy -4-(1*H*-imidazol-1-yl) quinoline **(4c)**

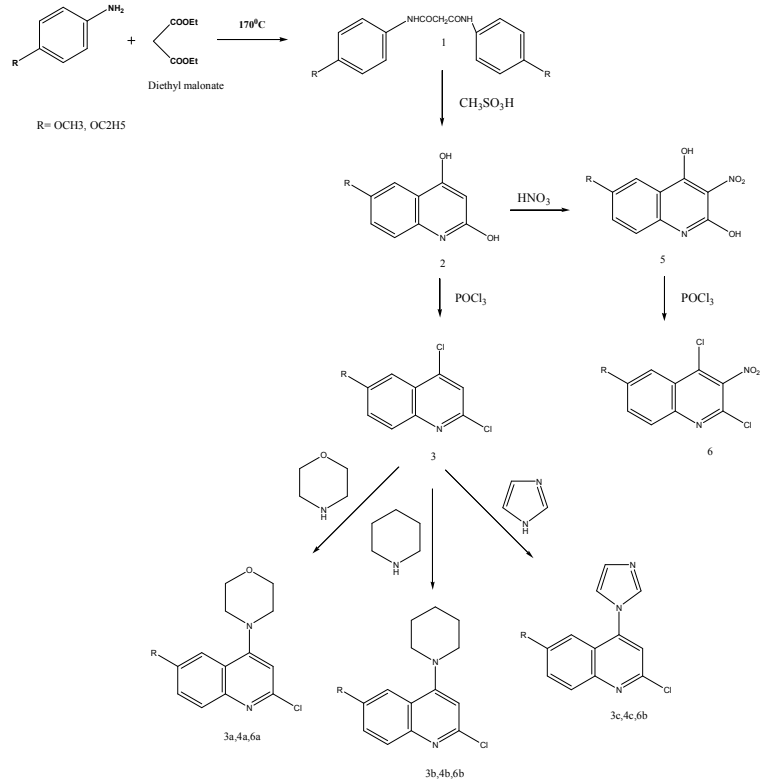
Synthesis of 6-Methoxy-3-nitro-2, 4-dihydroxyquinoline (5) :

The 6-Methoxy-2, 4-dihydroxyquinoline (**2**, 0.0279 mol) was taken in acetic acid (35 ml) at room temperature. To the suspension, fuming nitric acid (0.055 mol) was added slowly at 15°C and temperature was slowly raised to 40-45°C. Yellow colored solid precipitated out after stirring for 2 hrs at 40-45°C. The reaction mass was poured into ice cold water and the yellow colored solid precipitated was filtered and washed with water. Yield =60%; m.p. = 200°C.

Same procedure as above was followed in the synthesis of 2, 4-Dichloro-6-Mehoxy-3-nitroquinoline (**6**) and Synthesis of 2-Chloro-6-Methoxy-4-morpholin-4-yl-3-nitroquinoline

(**6a**), 2-Chloro-6-Methoxy-3-nitro-4-piperidin-1-ylquinoline (**6b**) and 2-Chloro-6-Methoxy-4-(1H-imidazol-1-yl)-3-nitroquinoline (**6c**)

Scheme :



Scheme

Result and discussion :

The importance of quinoline having substitution at 4-position in the field of pharmacological as well as pharmaceutical composition led us to synthesize new quinoline derivatives.

Accordingly we outline here the synthesis of 2-chloro-6- methoxy/ethoxy-4-substituted quinoline derivatives.

The 4-methoxyaniline was reacted with diethylmalonate at high temperature with the molar ratio of 2:1 without using any solvent. The condensation takes place with the removal of ethanol. Continuous removal of ethanol drives the reaction towards completion. On cooling, resulted into hard cake, therefore toluene was added at 110°C and then slowly cooled to room temperature, the precipitated solid, filtered and washed with toluene. The quantitative yield of N, N'-bis substituted malonamide (1) was obtained.

The 6-methoxy-2, 4-dihydroxyquinoline (2) was prepared by cyclizing the compound (1) in methane sulfonic acid at high temperature. The compound obtained by pouring into ice cold water, which was purified by dissolving in aq. NaOH and acidification with dil.HCl.

The compound (2) was converted to the corresponding dichloro derivative (3) by reacting with $POCl_3$. After the reaction the excess of $POCl_3$ was distilled off under reduced pressure and the residue was extracted with $CHCl_3$. The removal of chloroform gave the compound (3), which was purified by passing through a column of neutral alumina using pet. ether-$CHCl_3$ as eluent. The compound (3) was then reacted with cyclic secondary amines in ethanol like morpholine; piperidine and imidazole to yield the corresponding product. 3a-6c.

The nitration of compound (2) using fuming nitric acid in glacial acetic acid gave the 6-methoxy-3-nitro-2, 4-dihydroxyquinoline (5). Different conditions employed for nitration, but reaction at 40-45°C gave the best result.

The compound (5) was converted to the corresponding quinoline derivatives by the above procedure.

The synthesized compounds were confirmed by spectral data. The ^{1}HNMR spectra showed a triplet for four protons at δ 3.55-3.68 due to 2X–CH_2 group of H^2 & H^6 protons of morpholine and four proton triplet at δ 3.72-3.75 also 2X–CH_2 group of H^3 and H^5 protons of morpholine ring. A singlet at δ 3.80 is due to 3H of –OCH_3 group. The multiple at δ 7.35-7.83 is due to aromatic protons. Similarly a triplet at δ 1.59-1.76 is due to 6H (2X-CH_2 group of H^3, H^5 and H^5 protons of piperidine ring and a four proton triplet at δ 3.17-3.23 due to 2x-CH_2 of H_2 and H^6 protons of piperidine ring. This is supported by IR spectrum. Absorption band in the region 1248-1300 cm-1 is due to (–OCH_3) group. Similarly absorption band in the region 1450-1600 cm^{-1} is due to (Ar-H) group, band at 848 cm^{-1} is due to (Cl) and band at 1480 cm^{-1} showed the presence of NO_2 group.

Analytical and physical data of new synthesized quinoline derivatives :

Sr. No.	M.F.	Name of the Compound	Colour	Yield %	M.P. ^{0}C
1.	$C_{14}H_{15}ClN_2O_2$	2-Chloro-6-methoxy-4-morpholini quinoline	Colourless	50	168
2.	$C_{15}H_{17}ClN_2O$	2-Chloro-6-methoxy-H-(piperidine-1-yl) quinoline	Colourless	45	188
3.	$C_{13}H_{10}ClN_3O$	2-Chloro-4-(1H-imidazole-1-yl)-6-methoxy quinoline	Colourless	55	182
4.	$C_{15}H17ClN_2O_2$	2-chloro-6-ethoxy-4-morpholinoquinoline	Colourless	50	177
5.	$C_{16}H_{19}ClN_2O$	2-chloro-6-ethoxy-4-(piperidin-1-yl)quinoline	Colourless	50	162
6.	$C_{14}H_{12}ClN_3O$	2-chloro-6-ethoxy-4-(1*H*-imidazol-1-yl)quinoline	Colourless	45	158
7.	$C_{13}H_{10}ClN_3O$	4-(2-Chloro-6-methoxy-3-nitroquinolin-4-yl) morpholine	Yellow	48	195
8.	$C_{15}H_{16}ClN_3O_3$	2-Chloro-6-methoxy-3-nitro-4-(piperidin-1-yl) Quinoline	Yellow	35	212
9.	$C_{13}H_9ClN_4O_3$	2-Chloro-4-(1H-imidazole-1-yl)-6-methoxy-3-nitroquinoline	Yellow	52	218

Spectral data :

1. 2-Chloro-6-methoxy -4-morpholiniquinoline

NMR ($CDCl_3$) : δ 2.72-2.92 (4H, t, H^2, H^6 of Morpholine ring), δ 3.55-3.68 (4H, t, H^3, H^5 of Morpholine ring), δ 7.35-7.82 (3H, m, Ar-H), δ 3.82 (3H, s, -OCH3).

IR (KBr) cm^{-1} : 848 (Cl) , 1210 (C-O-C), 1248 (OCH_3) , 1450-1600 (Ar-H)

2. 2-Chloro-6-methoxy-H-(piperidine-1-yl)quinoline

NMR ($CDCl_3$) : δ 1.59-1.76 (6H, t, H^3, H^5, H^6 of Piperidine ring), δ 3.17-3.23 (4H, t, H^2, H^6 of Piperidine ring), δ 7.37-7.83 (3H, m, Ar-H), δ 3.81 (3H, s, -OCH3).
IR (KBr) cm^{-1} : 880 (Cl) , 1222 (C-O-C), 1300 (OCH_3) , 1455-1600 (Ar-H)

3. **4-(2-Chloro-6-methoxy-3-nitroquinolin-4-yl)morpholine**

NMR ($CDCl_3$) : δ 3.65-3.68 (4H, t, H^2, H^6 of Morpholine ring), δ 3.72-3.78 (4H, t, H^3, H^5 of Morpholine ring), δ 7.25-8.12 (3H, m, Ar-H), δ 3.81 (3H, s, -OCH3).
IR (KBr) cm^{-1} : 850 (Cl) , 1210 (C-O-C), 1250 (OCH_3) , 1455-1610 (Ar-H) , 1480 ($-NO_2$)

References :

i. T. Stortz ., Organic process research and development, 8, 663-668 (2004).
ii. G. C Wright, J. E. Gray., Journal of Medicinal chemistry, 18,727, (1975).
iii. B. Chandrashekhar, A. S. R. Prasad, S. Eswaraiah and A. Venkteshvaralu . Organic process research and development, 6 , 242-245, (2002).
iv. G. H. Patel, C. M. Mehta . J. Sc. Industri., Res. 1913, Nov. (1960).
v. G.C. Wright, Joseph E. Cray., J. Medicinal Chemistry, 17, 2, (1974).
vi. T. Kappe and B. Schnell., J. Heterocyclic Chem., 33, 663, (1996).
vii. P. Roschger, W. Fiala and W. Stadbarner., J. Heterocyclic Chem., 29, 225, (1992).
viii. A. Omori, N. Sonoda, S. Tsutsuni., Bulletin of Chem. Society of Japan vol.43,1135-1138, (1970).
ix. B. J. Buchmann, C. S. Hamilton., J. Am. Soc., 1537, (1942).
x. T. Singh, G. R. Stain, H. J. Biel., J. Medicinal Chem., 12, 787, (1969).
xi. N.D. Heindel, I. Bechara, J. C. Ohnmacht., J. Med. Chem. 12, 797, (1969).
xii. A. K. Sen; J. Indian Chem. Soc. 44, 597, (1967)
xiii. H. Andersag, S. Breitner and H. Jung; German patent 683, 792,(1939).

Received on June 5, 2017.