

## A Facile One-Pot Method for Synthesis of 2,4-Dichloroquinoline Derivatives

Azizian, Javad\*; Kefayati, Hassan; Mehrdad, Morteza;  
Jadidi, Khosrow and Sarrafi, Yaghob

Department of Chemistry, Faculty of Sciences, Shahid Beheshti University, Tehran, I. R. Iran.

**ABSTRACT:** A facile one-pot method with good yield for the synthesis of 2,4-dichloroquinoline and some related new derivatives by condensation of the appropriate primary aromatic amine with malonic acid in presence of excess phosphorus oxychloride is described.

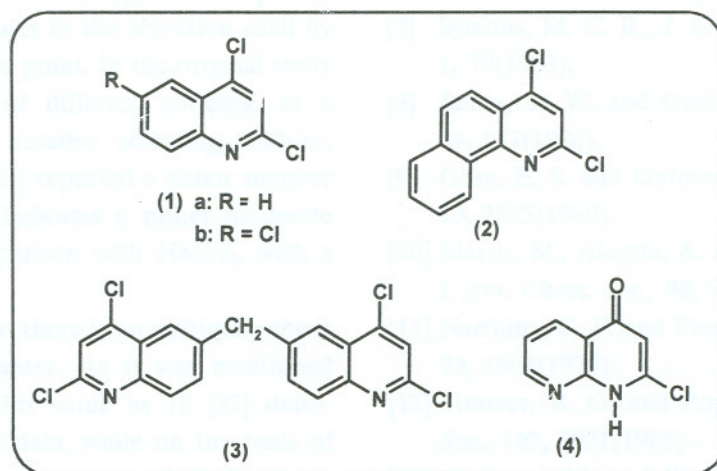
**KEY WORDS:** 2,4-Dichloro-7,8-benzoquinoline; 2,4-dichloroquinoline; 2,4,6-trichloroquinoline; Bis(2,4-dichloroquinoline)methane; 2-chloro-1,8-naphtyridine-4-one

2,4-Dichloroquinolines are used for the synthesis of 2,4-disubstituted quinolines like 4-amino-4-alkylaminoquinoline and 5-triazolquinoline which shows biological activity [1-4]. Reaction of quinoline N-oxide with chlorinating agent [1,5] and reaction of 2,4-dihydroxyquinoline with chlorinating agent like  $\text{POCl}_3$ ,  $\text{PCl}_5$  or  $\text{PCl}$  [6-9] are used to prepare the

2,4-dichloroquinolines.

In the present work a facile method with good yield for synthesis of 2,4-dichloroquinoline and some derivatives is described (Scheme).

The desired reaction occurs by refluxing a variety of commercially available primary aromatic amines and diamines (one mole) with malonic acid (two



Scheme

\* To whom correspondence should be addressed.

moles) and an excess of phosphorus oxychloride. In this manner a number of 2,4-dichloroquinoline derivatives, bis (2,4-dichloroquinoline) methane (3) and an unexpected product, 2-chloro-1,8-naphthyridine-4-one (4) were obtained in good yields.

#### EXPERIMENTAL

Melting points were measured on the Electrothermal 9100 apparatus and are uncorrected. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyser. IR spectra were measured on a Bomem FT-IR-MB100 spectrophotometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were measured with a Bruker DRX-300 Avance spectrometer. Mass spectra were recorded on a Hewlett-Packard 5973 mass spectrometer operating at 70 eV.

#### Preparation of 2,4-dichloroquinoline

##### General procedure

Malonic acid (3.43 g, 0.033 mol) is dissolved in phosphorus oxychloride (10 mL) and aromatic amine (0.016 mol) was added slowly, mixture was stirred for a few minutes, and phosphorus oxychloride (10 mol) was added again. The mixture was gently refluxed 3 h, allowed to cool and then poured into ice water. After neutralisation with concentrated aqueous NaOH, the crude product was filtered off and recrystallized in petroleum ether.

**1a:** White needles, yield 75%, m.p. 67°C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) 7.4( $\text{H}_3$ , s), 7.6( $\text{H}_6$ , ddd), 7.75( $\text{H}_7$ , ddd), 7.98( $\text{H}_8$ , br), 8.15( $\text{H}_5$ , dd);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) 149.5, 147.8, 144.2, 131.4, 128.8, 127.7, 124.9, 124.0, 121.7; MS (m/z, %) 197( $\text{M}^+$ , 100), 199( $\text{M}^+ + 2$ , 65), 201 ( $\text{M}^+ + 4$ , 10) 162(80), 127(30); Anal. Calcd for  $\text{C}_9\text{H}_5\text{Cl}_2\text{N}$ : C, 54.58; H, 2.54; N, 7.07. Found: C, 54.3; H, 2.4; N, 7.3.

**1b:** light yellow needles, yield 58%, m.p. 123°C,  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ ), 7.6( $\text{H}_3$ , s), 7.75( $\text{H}_7$ , dd), 7.98( $\text{H}_8$ , d), 8.19( $\text{H}_5$ , d),  $^{13}\text{C}$  NMR (75MHz,  $\text{CDCl}_3$ ), 149.7, 147.5, 144.0, 142.6, 134.1, 128.9, 127.9, 123.2, 122.1; MS (m/z, %), 231( $\text{M}^+$ , 60), 233( $\text{M}^+ + 2$ , 60), 196(40), 161(5). Anal. Calcd for  $\text{C}_9\text{H}_4\text{Cl}_2\text{N}$ : C, 46.49; H, 1.73; N, 6.02. Found: C, 46.3; H, 1.6; N, 5.9.

**2:** white needles, yield 70%, m.p. 133°C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ), 7.6( $\text{H}_3$ , s), 7.75(2H, m), 7.9(3H,

m), 8.0( $\text{H}_5$ , d),  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ), 148.8, 147.1, 143.9, 133.9, 130.1, 128.3, 128.0, 127.8, 127.6, 125.1, 123.1, 122.3, 120.3; MS(m/z, %), 247( $\text{M}^+$ , 100), 249( $\text{M}^+ + 2$ , 60), 251( $\text{M}^+ + 4$ , 10), 212(30), 177(40), Anal. Calcd for  $\text{C}_{13}\text{H}_7\text{Cl}_2\text{N}$ : C, 62.93; H, 2.84; N, 5.65. Found: C, 62.6; H, 2.9; N, 5.5.

**3:** light yellow powder, yield 67%, m.p. 174°C;  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ ), 7.5( $\text{H}_3$ , s), 7.65( $\text{H}_7$ , dd), 7.98( $\text{H}_8$ , d), 8.05( $\text{H}_5$ , br);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ), 40.0, 122.2, 123.5, 125.3, 129.4, 132.9, 139.9, 143.9, 147.1, 149.6, MS(m/z, %), 406( $\text{M}^+$ , 70), 408( $\text{M}^+ + 2$ , 100), 371(30), 336(25), 301(15). Anal. Calcd for  $\text{C}_{19}\text{H}_{10}\text{Cl}_2\text{N}_2$ : C, 55.92; H, 2.47; N, 6.86. Found: C, 55.7; H, 2.5; N, 6.7.

**4:** white needles, yield 67%, m.p. 144°C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ), 7.3( $\text{H}_3$ , NH, dd), 7.7( $\text{H}_7$ , br), 7.9( $\text{H}_6$ , ddd), 9.1( $\text{H}_5$ , br);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ), 103.0(C=O), 116.8, 126.2, 128.2, 138.5, 150.8, 157.1, 159.1, MS (m/z, %), 180( $\text{M}^+$ , 60), 182( $\text{M}^+ + 2$ , 20), 152(60), 145(40). Anal. Calcd for  $\text{C}_8\text{H}_5\text{ClN}_2\text{O}$ : C, 53.21, H, 2.79; N, 15.51. Found: C, 53.4; H, 2.6; N, 15.3.

Received: 26<sup>th</sup>, December 1998 ; Accepted: 14<sup>th</sup>, August 2000

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