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 Beheshty University, Tehran, I. R. Iran.

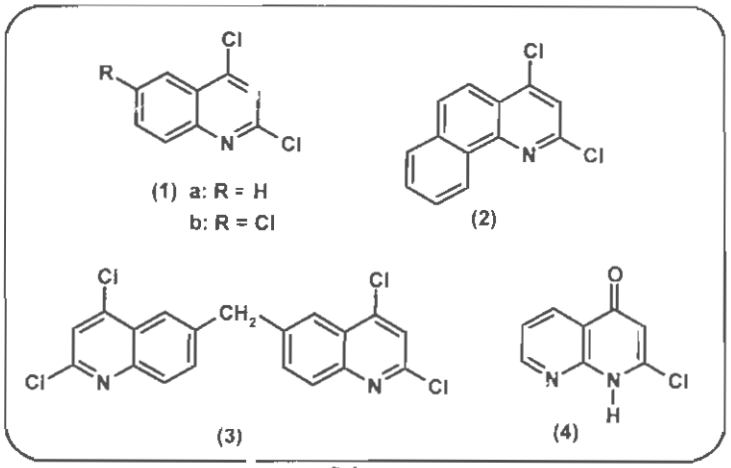
ABSTRACT: *A facile one-pot method with good yield for the synthesis of 2,4-dichloroquinoline and some related new derivatives by condensation of the appropriate primary aromatic amine with malonic acid in presence of excess phosphorus oxychloride is described.*

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-alkyl-aminoquinoline 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 $POCl_3$, PCl_5 or 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.*

1021-9986/2001/1/20 2/$/2.20

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-naphtyridine-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. ^1H and ^{13}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; ^1H NMR (300 MHz, $CDCl_3$) 7.4(H_3 , s), 7.6(H_6 , ddd), 7.75(H_7 , ddd), 7.98(H_8 , br), 8.15(H_5 , dd); ^{13}C NMR (75 MHz, $CDCl_3$) 149.5, 147.8, 144.2, 131.4, 128.8, 127.7, 124.9, 124.0, 121.7; MS (m/z, %) 197(M^+, 100), 199(M^++2, 65), 201 (M^++4, 10) 162(80), 127(30); Anal. Calcd for $C_9H_5Cl_2N$: 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, ^1H-NMR (300 MHz, $CDCl_3$), 7.6(H_3 , s), 7.75(H_7 , dd), 7.98(H_8 , d), 8.19(H_5 , d), ^{13}C NMR (75MHz, $CDCl_3$), 149.7, 147.5, 144.0, 142.6, 134.1, 128.9, 127.9, 123.2, 122.1; MS (m/z, %), 231(M^+, 60), 233(M^++2, 60), 196(40), 161(5). Anal. Calcd for $C_9H_4Cl_3N$: 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; ^1H NMR (300 MHz, $CDCl_3$), 7.6(H_3 , s), 7.75(2H, m), 7.9(3H, m), 8.0(H_5 , d), ^{13}C NMR (75 MHz, $CDCl_3$), 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(M^+, 100), 249(M^++2, 60), 251(M^++4, 10), 212(30), 177(40), Anal. Calcd for $C_{13}H_7Cl_2N$: 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; ^1H-NMR (300 MHz, $CDCl_3$), 7.5(H_3 , s), 7.65(H_7 , dd), 7.98(H_8 , d), 8.05(H_3 , br); ^{13}C NMR (75 MHz, $CDCl_3$), 40.0, 122.2, 123.5, 125.3, 129.4, 132.9, 139.9, 143.9, 147.1, 149.6, MS(m/z, %), 406(M^+, 70), 408(M^++2, 100), 371(30), 336(25), 301(15). Anal. Calcd for $C_{19}H_{10}Cl_2N_2$: 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; ^1H NMR (300 MHz, $CDCl_3$), 7.3(H_3 , NH, dd), 7.7(H_7 , br), 7.9(H_6, ddd), 9.1(H_5, br); ^{13}C NMR (75 MHz, $CDCl_3$), 103.0(C=O), 116.8, 126.2, 128.2, 138.5, 150.8, 157.1, 159.1, MS (m/z, %), 180(M^+, 60), 182(M^++2, 20), 152(60), 145(40). Anal. Calcd for $C_8H_5ClN_2O$: C, 53.21, H, 2.79; N, 15.51. Found: C, 53.4; H, 2.6; N, 15.3.

Received: 26th, December 1998 ; Accepted: 14th, August 2000

REFERENCES

[1] Lutz, R. E., Condington, J. F., Rowlett, R. J. Jr., Deinet, A. J. and Bailey, P. S., *J. Am. Chem. Soc.*, **68**, 1810(1946).

[2] Ernst, M., Wolfgang, S., Gunter, O., Barbara, H., Hans, L. and Gerhand, K., *Eup. J. Med. Chem.*, **25**, 137(1990).

[3] Oda, K., *J. Pharm. Soc. Japan*, **64**, 6(1994).

[4] Werner, H., Catherine, J. and Synes, J., *Can. Pat. Appl.*, 2,133,620(1995); *C. A.* **123**(1005) 313786z.

[5] Baumgarten, K., *Ber*, **60**, 823(1926).

[6] Koller, G., *Ber*, **60**, 1108(1927).

[7] Shah, V. R., Bose, J. L. and Shah, R. C., *J. Sci. Ind. Res.*, **19B**, 176(1960).

[8] Osorne, A. G., Buley, J. M., Clarke, H., Dakin, R. C. H. and Price, P. I., *J. Chem. Soc. Perkin Trans. 1*, 2747(1993).

[9] Baker, R. H., Lappin, G. R. and Rieghi, B., *J. Am. Chem. Soc.*, **68**, 1284(1946).