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One-Pot Microwave-Assisted Synthesis of 2,4-Dichloroquinolines

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In this paper, a fast one-pot microwave-assisted conversion of aromatic amines to 2,4-dichloroquinolines in presence of $POCl_3$, malonic acid ($CH_2(COOH)_2$) and under microwave irradiation (600 W, 50 s) in good yields was reported. The products were characterized by FT-IR, GC/MS and NMR spectroscopy results.

Key Words: Microwave irradiation, One-pot synthesis, Aromatic amines, 2,4-Dichloroquinoline compounds.

INTRODUCTION

The synthesis of the important compounds of quinoline derivatives with many applications in chemistry and medicinal area has been observed in the literatures[1-13]. Microwave-assisted synthesis has been utilized as a powerful and effective technique to promote a group of chemical reactions[14-19]. Several methods for synthesizing the quinoline derivatives have been reported in the literatures[1,2]. It has long been known that condensation of an aromatic primary amine with malonic acid in the presence of phosphorous oxychloride ($POCl_3$) affords the 4-hydroxy-2-quinolone and finally make the 2,4-dichloroquinoline[3-6]. Zigler and Gelfert[7] have subsequently reported a facile synthesis and the procedure had been extended to the preparation of further derivatives by Shah *et al.*[8]. In literature, few methods for synthesis of 2,4-dichloroquinolines have been reported[1-8]. An important feature in the synthesis of quinoline derivatives is the possibility of the formation of isomeric products from reactions commencing with *m*-substituted or 3,4-disubstituted anilines. However, only a few isolated studies of orientation effects in synthesis leading to 2,4-dichloroquinolines are available[8-11].

With regard to the useful application of microwaves in organic synthesis and the popularization of using industrial microwaves, the reactions mentioned above can be carried out on an industrial scale[20]. Good purification allows excellent products recovery.

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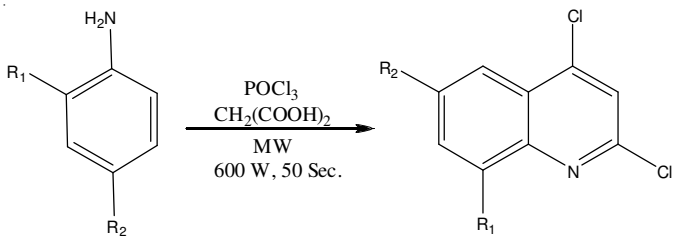
In this study, a fast method for one-pot microwave-assisted synthesis of 2,4-dichloroquinolines from anilines and *o*- or *p*-toluidine in presence of $POCl_3$ and malonic acid and under microwave irradiation (600 W, 50 s) was reported. This conversion was characterized by FT-IR, GC/MS and NMR. There were no noticable by-products and only final products have been considered.

EXPERIMENTAL

The simple synthesized imides (**2**, **4**, **6** and **8**), are known compounds and their physical data, infrared and ^1H NMR spectra were essentially identical with those of authentic samples[3,4]. The FT-IR spectra was recorded as KBr pellets on a Shimadzu FT-IR 8000 spectrometer. ^1H NMR spectra was determined on a 300 MHz Brüker spectrometer in $CDCl_3$ solvent.

Synthesis: A malonic acid (4.15 g, 0.04 mol) dissolved in 25 mL phosphorus oxichloride and then aniline (4.6 g, 0.05 mol) was slowly added. The tube was sealed by a $CaCl_2$ trap and then exposed to microwave oven. After 50 s irradiation at 600 W, the solution was cooled to room temperature and then poured into iced water (200 mL). The solution made slightly alkaline with dilute aqueous sodium hydroxide. After neutralization the initial product (6.1 g, 61 %) was filtered off. The condition of MW-irradiation was shown in Table-1. The final product was recrystallized by ethanol-water solvent with the aid of charcoal. The melting point of the product (2,4-dichloroquinoline, **2**) was 64-66 °C (lit. m.p. 66-67 °C) (**Scheme-I**).



$R_1=R_2=H$: **1** **2**
$R_1=CH_3$, $R_2=H$: **3** **4**
$R_1=H$, $R_2=CH_3$: **5** **6**
$R_1=R_2=CH_3$: **7** **8**

Scheme-I

RESULTS AND DISCUSSION

The reaction described here represents a simple and fast procedure to synthesize 2,4-dichloroquinoline derivatives **2**, **4**, **6** and **8** from aromatic amines **1**, **3**, **5** and **7**. Comparison of this procedure with other methods[1-12] confirms the ease and rapidity of this method for the synthesis of 2,4-dichloroquinoline from aniline derivatives.

TABLE-1
ANALYTICAL DATA OF MICROWAVE ASSISTED SYNTHESIZED 2,4-DICHLOROQUINOLINES

No.	m.f.	m.p. (ºC)	IR (cm^{-1})*	^{1}H NMR (δ ppm)*	^{13}C NMR (δ ppm)*	Mass (m/z)*	Elemental analysis (%)			MW		Final yield (%)
								Exp.	Calcd.	Time (s)	Power (W)	
2	$C_9H_5Cl_2N$	64-66	3170m, 3060m, 1600s, 1488s, 1638m, under 900s, 650-720s	7.73 (s, 1H), 7.77 (m, 1H), 7.93 (m, 1H), 8.2 (d, 1H), 8.5 (d, 1H)	121.5, 124, 125, 127.7, 128, 133, 143.4, 147.5, 151	197 (M), 199 (M+2), 201 (M+4), 161, 163, 99.	C H N	5398 2.53 7.01	54.58 2.54 7.07	50	600	67
4	$C_{10}H_7Cl_2N$	111-114	3155m, 3066m, 2980s, 2888m, 1600s, 1498s, 1643m, 800-900s, 620-750s	2.7 (s, 3H), 7.70 (s, 1H), 7.8 (m, 1H), 7.9 (m, 1H), 8.5 (m, 1H)	18, 122.5, 123.1, 125, 127.1, 133.4, 137.2, 145.3, 150.1, 157.1	211 (M), 213 (M+2), 215 (M+4), 196, 176, 178, 180, 105	C H N	56.90 3.22 6.40	56.63 3.33 6.60	50	600	68
6	$C_{10}H_7Cl_2N$	91-93	3158m, 3065m, 2983s, 2876m, 1600s, 1478s, 1650m, 800-900s, 620-750s	2.41 (s, 3H), 7.69 (s, 1H), 7.66 (d, 1H), 7.87 (d, 1H), 8.2 (s, 1H)	23.2, 122.1, 123.4, 124.4, 129.9, 135.5, 137.9, 143.0, 145.9, 148.8	(Similar to 2) 211 (M), 213 (M+2), 215 (M+4), 196, 176, 178, 180, 105	C H N	56.50 3.33 6.51	56.63 3.33 6.60	50	600	77
8	$C_{11}H_9Cl_2N$	103-106	3170m-3020m, 2993s, 2866m, 1600s, 1493s, 1658m, 800-900s, 710-760s	2.0 (s, 3H), 2.21 (s, 3H), 7.60 (s, 1H), 7.9 (s, 1H), 8.11 (s, 1H)	18.1, 23.0, 121.1, 122.0, 125.3, 134.9, 135.95, 137.2, 144.0, 148.4, 154.9	225 (M), 227 (M+2), 229 (M+4), 210, 195, 194, 192, 190, 112	C H N	58.11 3.98 6.18	58.43 4.01 6.19	50	600	60

*See reference no. 14.

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