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Synthesis of Quinolines and Dibenzo[b,f][1,5]Diazocines by MW-Assisted Solvent-Free Method

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Acetylpyridines, 2-acetylfuran, 2-acetylthiophene, acetyimidazoles, acetone and 4-methyl-acetophenone were condensed with 2-amino-4-bromobenzophenone (**1**) under the optimal reaction conditions. Condensation of **2a-j** with **1** afforded quinolines in good yields (60-74.5 %). In these reactions, (5z,11z)-3,9-dibromo-6,12-diphenyl-dibenzo[b,f][1,5]diazocine (**4**) was isolated as the minor product. The self-condensation of **1** afforded **4** as the only product. In order to investigate the effect of DPP on product formation, the synthesis of **4** was carried out under microwave irradiation using different amounts (in equivalents) of DPP. The obtained yield of **4** was higher when using anhydrous DPP than when using HCl, H_3PO_4 and CH_3COOH. The cyclization reaction proceeded very effectively in the presence of DPP, as shown in the two reaction mechanisms for the formation of quinolines and dibenzo[b,f][1,5]diazocine.

Keywords: Quinolines, Dibenzo[b,f][1,5]diazocines, Microwave-assisted solvent-free method, Self condersation.

INTRODUCTION

Quinoline, 1-azanaphthalene, is an aromatic nitrogen compound characterized by a solid-ring structure containing a benzene fused to pyridine at two adjacent carbon atoms. Quinoline-containing natural products have been investigated extensively by synthetic and medicinal chemists over the last several decades. The parent bicyclic structure is found in natural products that exhibit a wide spectrum of biological activities; a large number of medicinally important compounds are available containing quinolone, di- and tetrahydroquinoline and oxo-quinoline moieties[1,2]. Several synthetic routes have already been proposed for quinolines and new methods are being extensively investigated. Quinolines are usually synthesized under harsh heating conditions (heating for 24 h or longer) using large amounts of an acid catalyst and highly toxic solvents[3,4]. Recently, considerable attention has been paid to microwave-assisted organic reactions, which do not require any solvent[5]. Thermal reactions are often carried out in solution using large quantities of the reagents and may take several hours for completion. However, these reactions proceed to completion within minutes under microwave irradiation. Herein, we report a new method involving microwave irradiation for synthesizing quinolines and dibenzo[b,f][1,5]-diazocines. Although dibenzo[b,f][1,5]diazocines are well known, their biological activities have not been studied in detail thus far. These compounds are structurally similar to calcium channel antagonist such as diltiazem, which has been successfully tested as a chemosensitizer against multiple drug resistance (MDR)[6]. We first carried out Friedlander[7,8] condensation of various heteroaromatic ketones with 2-aminobenzophenones under microwave irradiation. To explore the scope and limitations of this condensation reaction under the above-mentioned reaction conditions, we generated a mini-library of quinolines.

EXPERIMENTAL

General procedure for the synthesis of 3a-j and 4: 2-Amino-4-bromobenzophenone (**1**) (1 mmol), heteroaromatic ketone (**2**) (1 mmol) and 0.5 equiv of DPP (0.5 mmol, purchased from Aldrich) were mixed in the absence of any organic solvent and then submitted for 3 min to microwave irradiation inside a domestic microwave oven (Samsung, RE-555 TCW). After the reaction was completed, the reaction mixture was diluted with ethyl acetate and neutralized with aqueous solution of NaOH (10 %). It was extracted with ethyl acetate (three times), washed with water and dried ($MgSO_4$). After the reaction, products were purified by column chromatography (EtOAc/*n*-hexane = 1:20-1:40, v/v) to give the corresponding quinolines.

7-Bromo-4-phenyl-2-(pyridine-2-yl)quinolone (3a): m.p.: 140-142 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ7.9 (d, 2H), 7.9 (s, 1H), 7.8-7.9 (d, 1H), 7.6-7.7 (t, 2H), 7.1-7.5 (m, 6H), 6.9-7.0 (t, 1H); ^{13}C NMR ($CDCl_3$, 50MHz) δ155.3, 151.1, 150.3, 149.2, 145.3, 139.8, 137.2, 131.0, 130.6, 129.8, 129.2,

127.4, 124.0, 123.6, 121.4, 118.6, 102.6; MS (MOLDI-TOP), *m/z* 361 (Anal. calcd. (%) for C, 66.50; H, 3.63; Br, 22.12; N, 7.75 Found (%); C, 66.53; H, 3.64; Br, 22.11; N, 7.72).

7-Bromo-4-phenyl-2-(pyridine-3-yl)quinolone (3b): m.p.: 151-152 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ7.9 (s, 1H), 7.8-7.9 (d, 1H), 7.6-7.7 (d, 1H), 7.5-7.6 (d, 1H), 7.4-7.5 (d, 1H), 7.3 (s, 1H), 7.0 (t, 1H), 6.9-7.0 (m, 6H); ^{13}C NMR ($CDCl_3$, 50MHz) δ154.5, 150.7, 149.5, 148.9, 144.4, 139.8, 134.6, 134.5, 131.0, 129.2,127.4, 121.2, 101.0; MS (MOLDI-TOP), *m/z* 361 (Anal. calcd. (%) for C, 66.50; H, 3.63; Br, 22.12; N, 7.75 Found (%); C, 66.51; H, 3.62; Br, 30.10; N, 5.77).

7-Bromo-4-phenyl-2-(pyridine-4-yl)quinolone (3c): m.p.: 139-140 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ8.3 (d, 2H), 7.7 (d, 2H), 7.6-7.7 (d, 1H), 7.5 (d, 1H), 7.4 (s, 1H), 7.3-7.4 (t, 1H), 6.9-7.0 (m, 5H); ^{13}C NMR ($CDCl_3$, 50MHz) δ157.4, 150.3, 149.8, 145.7, 145.3, 139.8, 131.0, 130.6, 129.8, 129.2, 127.4, 124.0, 121.4, 118.6, 102.6; MS (MOLDI-TOP), *m/z* 361 (Anal. calcd. (%) for C, 66.50; H, 3.63; Br, 22.12; N, 7.75 Found (%); C, 66.46; H, 3.65; Br, 22.11; N, 7.78).

7-Bromo-2-(furan-2-yl)-4-phenylquinolone (3d): m.p.: 122-125 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ8.3 (s, 1H), 7.7 (d, 1H), 7.7 (d, 1H), 7.6-7.7 (m, 5H), 7.2-7.5 (m, 5H), 6.6 (t, 1H); ^{13}C NMR ($CDCl_3$, 50MHz) δ158.8, 157.7, 150.3, 145.3, 142.9, 139.8, 131.0, 130.6, 129.8, 129.2, 127.4, 124.0, 118.6, 112.0, 107.1, 102.6; MS (MOLDI-TOP), *m/z* 349 (Anal. calcd. (%) for C, 65.16; H, 3.45; Br, 22.82; N, 4.00. Found (%); C, 65.11; H, 3.47; Br, 22.83; N, 4.02).

7-Bromo-2-(furan-3-yl)-4-phenylquinolone (3e): m.p.: 126-127 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ8.0 (s, 1H), 7.7-7.9 (d, 2H), 7.5-7.9 (d, 2H), 7.5-7.6 (m, 4H), 7.2-7.5 (m, 4H), 6.2 (d, 1H); ^{13}C NMR ($CDCl_3$, 50MHz) δ157.4, 150.3, 145.3, 144.1, 139.8, 138.5, 131.0, 130.6, 129.8, 129.3, 129.2, 127.4, 124.0, 118.6, 108.8, 102.6; MS (MOLDI-TOP), *m/z* 349 (Anal. calcd. (%) for C, 65.16; H, 3.45; Br, 22.82; N, 4.00. Found (%); C, 65.16; H, 3.45; Br, 22.82; N, 4.00).

7-Bromo-4-phenyl-2-(thiophen-2-yl)quinolone (3f): m.p.: 143-144 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ8.6 (d, 1H), 7.7 (d, 1H), 7.6-7.7 (m, 6H), 7.6 (m, 3H), 7.3 (t, 1H); ^{13}C NMR ($CDCl_3$, 50MHz) δ158.8, 150.3, 145.3, 142.4, 139.8, 131.0, 130.6, 129.8, 128.6, 128.0, 127.6, 124.0, 118.6, 102.6; MS (MOLDI-TOP), *m/z* 366.3 (Anal. calcd. (%) for C, 62.30; H, 3.30; Br, 21.82; N, 3.82; S, 8.75. Found (%); C, 62.30; H, 3.33; Br, 21.79; N, 3.81; S, 8.76).

7-Bromo-2(1*H*-imidazol-1-yl)-4-phenylquinoline (3g): m.p.: 135-137 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ7.7 (s, 1H), 7.6 (d, 1H), 7.5-7.6 (m, 3H), 7.3-7.5 (m, 5H), 6.9 (d, 2H); ^{13}C NMR ($CDCl_3$, 50MHz) δ159.4, 150.0, 146.0, 143.5, 134.5, 131.0, 130.6, 129.8, 129.2, 127.8, 127.4, 124.0,121.2, 111.4; MS (MOLDI-TOP), *m/z* 349 (Anal. calcd. (%) for C, 61.73; H, 3.43; Br, 22.82; N, 12.00. Found (%); C, 61.72; H, 3.40; Br, 22.83; N, 12.03).

7-Bromo-4-phenyl-2-(pyrazin-2-yl)quinolone (3h): m.p.: 160-161 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ8.2 (t, 3H), 7.9 (d, 1H), 7.7 (t, 1H), 7.5-7.7 (m, 4H), 7.1-7.3 (m, 3H); ^{13}C NMR ($CDCl_3$, 50MHz) δ151.1, 150.3, 146.6, 145.3, 144.7, 144.4, 142.3, 139.8, 131.6, 129.8, 129.2, 127.4, 124.0, 118.6, 102.6; MS (MOLDI-TOP), *m/z* 361 (Anal. calcd. (%) for C, 63.00; H, 3.34; Br, 22.06; N, 11.6. Found (%); C, 62.98; H, 3.32; Br, 22.09; N, 11.61).

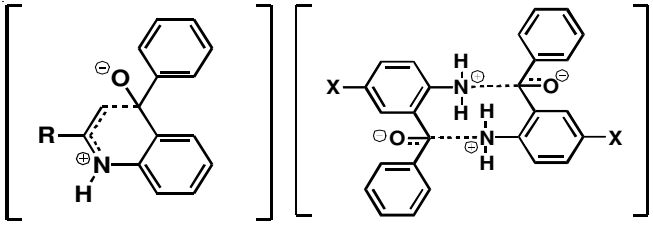
7-Bromo-4-phenyl-2-*p*-tolylquinolone (3i): m.p.: 144-145 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ8.1 (m, 3H), 7.6 (t, 1H), 7.5 (m, 3H), 7.4 (s, 1H), 7.3-7.4 (m, 2H), 6.6 (d, 2H), 2.4 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ157.4, 150.3, 145.3, 139.8, 136.0, 131.0, 130.6, 130.3, 129.8, 129.5, 129.2, 127.4, 124.0, 1233, 118.6, 102.6, 21.3; MS (MOLDI-TOP), *m/z* 374.2 (Anal. calcd. (%) for C, 70.60; H, 4.31; Br, 21.35; N, 3.74. Found (%); C, 70.65; H, 4.29; Br, 21.34; N, 3.72).

7-Bromo-2-methylyl- 4-phenylquinolone (3j): m.p.: 122-123 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ7.7 (d, 1H), 7.6 (d, 1H), 7.4-7.5 (m, 3H), 6.9-7.0 (t, 1H), 6.9 (s, 1H), 2.0 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ160.0, 148.3, 145.0, 130.4, 129.5, 129.3, 127.4, 123.8, 120.9, 119.7; MS (MOLDI-TOP), *m/z* 298 (Anal. calcd. For C, 64.45; H, 4.06; Br, 26.80; N, 4.70 Found; C, 64.43; H, 4.08; Br, 26.80; N, 4.70).

General procedure for the preparation of dibenzo-[b,f][1,5]diazocines (4): 2-Amino-4-bromobenzophenone (1.0 mmol) and 0.5 equivalents of DPP (0.5 mmol, purchased from Aldrich) were mixed in the absence of any organic solvent and then submitted for 3 min to microwave irradiation inside a domestic microwave oven (Samsung, RE-555 TCW). The work-up procedure is same as reported earlier[10]. After concentration under reduced pressure, the residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:20, v/v) to give the corresponding (5z,11z)-3,9-dibromo-6,12-diphenyl-dibenzo[b,f][1,5]diazocine (**4**). m.p.: 190-192 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ8.1-8.2 (d, 4H), 7.7 (d, 2H), 7.6-7.7 (t, 4H), 7.3-7.4 (d, 2H), 7.3 (t, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ131.8, 131.6, 131.2, 130.7, 129.2, 128.7, 128.2, 127.5, 123.1; MS (MOLDI-TOP), *m/z* 513.9 (Anal. calcd. (%) for C, 66.49; H, 3.12; Br, 30.96; N, 5.43. Found (%); C, 66.48; H, 3.10; Br, 30.99; N, 5.43).

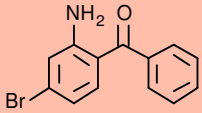
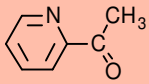
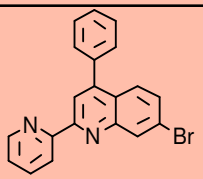
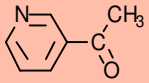
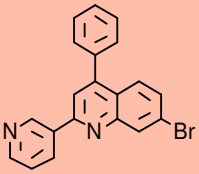
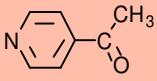
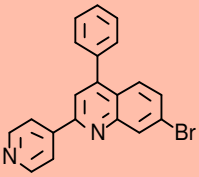
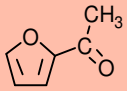
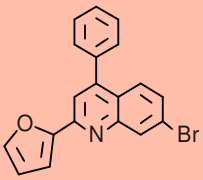
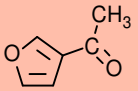
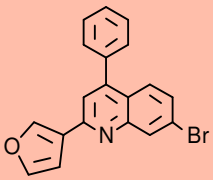
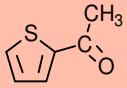
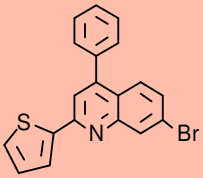
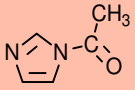
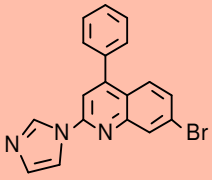
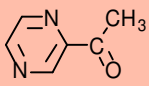
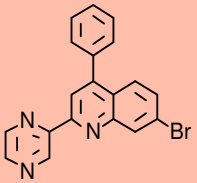
RESULTS AND DISCUSSION

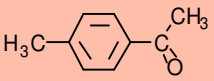
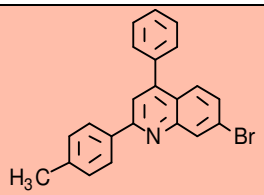
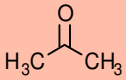
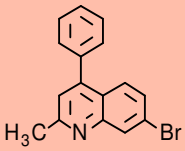
Acetylpyridines, 2-acetylfuran, 2-acetylthiophene, acetyimidazoles, acetone and 4-methyl-acetophenone were condensed with 2-amino-4-bromobenzophenone (**1**) under the above mentioned optimal reaction conditions. The results are summarized in Table-1. Condensation of **2a**-**j** with **1** afforded quinolines in good yields (60.0-74.5 %); in these reactions, (5z,11z)-3,9-dibromo-6,12-diphenyl-dibenzo[b,f][1,5] diazocine (**4**) was isolated as the minor product. The effect of microwave irradiation on quinoline formation can be explained on the basis of microwave activation effects caused by dipole-dipole interactions, mechanistic considerations and the increase in the polarity of the system (**P**) during the progress of the reaction[9,10]. 6,12-Diphenyl-dibenzo[b,f][1,5]diazocine (**4**) is a minor product formed by the self-condensation (**Q**) of **1**.



P **Q**

TABLE-1
CONDENSATION OF **1** WITH VARIOUS HETEROAROMATIC KETONES **2a-j** UNDER MW IRRADIATION

Entry	2-Amino-4-bromo-Benzophenone (**1**)	Heteroaromatic Ketone **2a-j**		Product: Quinolines **3a-j** / Dimer **4**[b]	Yield (%)[a]
1			**a**		71
				4	13.2
2			**b**		74.3
				4	15.1
3			**c**		66.5
				4	9.4
4			**d**		77.0
				4	11.4
5			**e**		78.5
				4	8.9
6			**f**		72.5
				4	15.8
7			**g**		78.1
				4	10.4
8			**h**		75.1
				4	10.2

9		i		4	77.7
					9.3
10		j		4	74.6
					8.2

[a] Isolated yield.

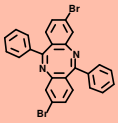
[b] Product **4** 

TABLE-2
SYNTHESIS OF 4 USING VARIOUS CATALYSTS UNDER MICROWAVE IRRADIATION

Entry	**1** (mol)	**2a** (mol)	Catalyst	Yield of **4**[a] (%)
1	1.0	1.0	DPP	12.2
2	1.0	-	DPP	84.7
3	1.0	-	HCl	65.3
4	1.0	-	H_3PO_4	43.2
5	1.0	-	CH_3COOH	16.5

[a]Isolated yields.

In order to broaden the scope of the proposed reaction, we carried out reactions of 2-amino-4-bromobenzophenones with acetylpyridines (**2a**-**c**). 7-Bromo-4-phenyl-2-(pyridine-2-yl)quinoline (**3a**), 7-bromo-4-phenyl-2-(pyridine-3-yl)quinolone (**3b**) and 7-bromo-4-phenyl-2-(pyridine-4-yl) quinolone (**3c**) were isolated as the major products in good yields from **2a**, **2b** and **2c**, respectively. In this case, (5z,11z)-3,9-dibromo-6,12-diphenyl-dibenzo[b,f][1,5]diazocine(**4**) was obtained as the minor product in low yield (entry **4**: 11.4 %; entry **5**: 8.9 %; and entry **6**: 15.8 %). Therefore, it is important to ensure that the bromo functionality is unaffected under the present reaction conditions

The self-condensation of **1** afforded **4** as the only product. In order to investigate the effect of DPP on product formation, the synthesis of **4** was carried out under microwave irradiation using different amounts (in equivalents) of DPP. The obtained yield of **4** was higher when using anhydrous DPP than when using HCl, H_3PO_4 and CH_3COOH (Table-2). The cyclization reaction proceeded effectively in the presence of DPP, as shown in the two reaction mechanisms for the formation of quinolines and dibenzo[b,f][1,5]diazocine.

In summary, we have employed a microwave-assisted solvent-free method ('green chemistry' conditions) to synthesize quinoline and dibenzo[b,f][1,5]diazocine derivatives. The yields obtained with the proposed synthesis method are markedly higher than those obtained in conventional thermal reactions; further, this method does not require hazardous solvents and excess amounts of expensive acidic catalysts. In addition, this method is economical, environmentally benign and affords the desired product within a short time.

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