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Simple synthesis of quinolines and dibenzo[*b*,*f*][1,5]diazocines under microwave irradiation

Dai-Il Jung [a,*], Ju-Hyun Song [a], Eon-Jin Lee [a], Yun-Young Kim [a], Do-Hun Lee [a], Yong-Gyun Lee [a], Jung-Tai Hahn [b]

[a] Department of Chemistry, Dong-A University, Saha-Gu, Busan 604 714, Republic of Korea
[b] Department of Beautycare, Young-Dong University, Chungcheongbuk-do 370 701, Republic of Korea

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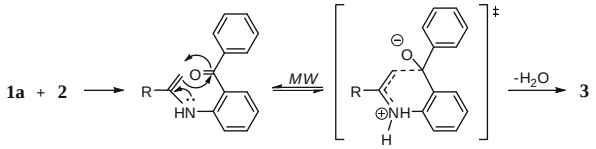
ABSTRACT

Quinolines **3a–f**, **5a–f,** and dibenzo[*b*,*f*][1,5]diazocines **4**, **6** were synthesized in the presence of 0.5 equiv. of diphenyl phosphate (DPP) under microwave irradiation. The obtained yield of 6,12-diphenyl-dibenzo[*b*,*f*][1,5]diazocine **4** was higher when using anhydrous DPP than when using HCl, H_3PO_4, and CH_3COOH.

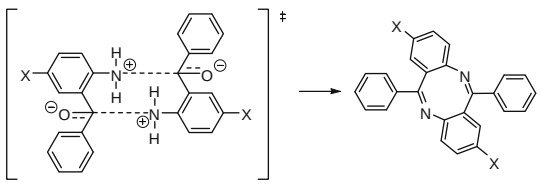
Quinoline-containing natural products have been researched extensively by synthetic and medicinal chemists over the last several decades. The parent bicyclic structure is found in natural products that exhibit a wide spectrum of biological activities; a large number of medicinally important compounds contain 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 (MW)-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 MW irradiation. Herein, we report a new method involving MW 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 **2a–i** with 2-aminobenzophenones **1a–b** under MW irradiation. To explore the scope and limitations of this condensation reaction under the above-mentioned reaction conditions, we generated a mini-library of quinolines. Acetylpyridines, 2-acetylfuran, 2-acetylthiophene, and 2-acetyl-1-methylpyrrole were condensed with **1a–b** under the above-mentioned optimal reaction conditions. The results are summarized in Table 1. Condensation of **2a–f** with **1a** afforded quinolines in good yields (60.0–74.5%); in these reactions, dibenzo[*b*,*f*][1,5]diazocine was isolated as the minor product. However, 6,12-diphenyl-dibenzo[*b*,*f*][1,5]diazocine **4** was the only product formed in low yield when **1a** was reacted with 4-acetylmorpholine **2g**, 3-acetyl-2-oxazolidinone **2h** (an amide), and 4-acetylimidazole **2i** (yield of the product obtained from **2g**, **2h**, and **2i** was 34.0%, 42.0%, and 41.0%, respectively). The effect of MW irradiation on quinoline formation can be explained on the basis of MW activation effects caused by dipole–dipole interactions, mechanistic considerations, and the increase in the polarity of the system during the progress of the reaction (Eq. 1).[9,10]



(1)

6,12-Diphenyl-dibenzo[*b*,*f*][1,5]diazocine **4** is a minor product formed by the self-condensation of **1a** (Eq. 2).



(2)

4 (X = H), **6** (X = Cl)

In order to broaden the scope of the proposed reaction, we carried out reactions of 2-amino-5-chlorobenzophenones **1b** with acetylpyridines **2a–c**. 6-Chloro-4-phenyl-2-pyridine-2-yl-quino-

* Corresponding author. Tel.: +82 51 200 7249; fax: +82 51 200 7259.
E-mail address: dijung@dau.ac.kr (D.-I. Jung).

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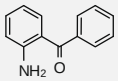
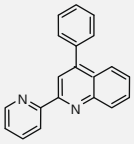
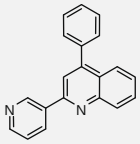
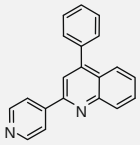
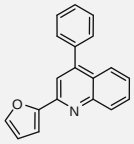
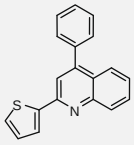
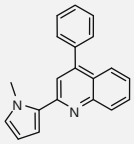
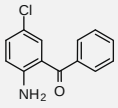
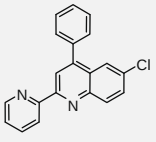
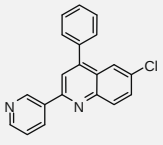
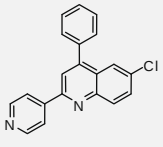
Table 1
Condensation of **1a**–**b** with various heteroaromatic ketones **2a**–**f** under MW irradiation

Entry	2-Aminobenzophenones **1a**–**b**	Heteroaromatic ketones **2a**–**i**	Product	
			Quinolines **3a–f**, **5a–c**	Yield[a] (%)
1	 **1a**	 **2a**	 **3a**	71.0 (63.0[b])
2		 **2b**	 **3b**	74.5 (65.0[b])
3		 **2c**	 **3c**	71.0 (61.5[b])
4		 **2d**	 **3d**	68.0
5		 **2e**	 **3e**	60.0
6		 **2f**	 **3f**	65.2
7	 **1b**	 **2a**	 **5a**	70.0 (59.5[b])
8		 **2b**	 **5b**	72.0
9		 **2c**	 **5c**	66.5

[a] Isolated yields.
[b] Conventional method (oil bath temperature = 110 °C).

Table 2
Synthesis of **4** using various catalysts under MW irradiation

Entry	**1a** (mmol)	**2a** (mmol)	Catalyst	Yield of **4**[a] (%)
1	1.0	1.0	DPP	13.2
2	1.0	—	DPP	89.4
3	1.0	—	HCl	61.6
4	1.0	—	H_3PO_4	45.7
5	1.0	—	CH_3COOH	18.9

[a] Isolated yields.

line **5a**, 6-chloro-4-phenyl-2-pyridine-3-yl-quinoline **5b**, and 6-chloro-4-phenyl-2-pyridine-4-yl-quinoline **5c** were isolated as the major products in good yields from **2a**, **2b**, and **2c**, respectively. In this case, 2,8-dichloro-6,12-diphenyl-dibenzo[*b*,*f*][1,5]diazocine **6** was obtained as the minor product in low yield (entry 7: 8.9%; entry 8: 9.4%; and entry 9: 9.4%). Therefore, it is important to ensure that the chloro functionality is unaffected under the present reaction conditions.

The self-condensation of **1a** 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 MW irradiation using different amounts (in equivalents) of DPP (Table 2). 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. In summary, we have employed a MW-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.

Acknowledgment

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11. *General procedure for the synthesis of* **3a–f** *and* **5a–c**: 2-aminobenzophenone **1** (1.0 mmol), heteroaromatic ketone **2** (1.0 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 10% NaOH. 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.
4-Phenyl-2-pyridine-2-yl-quinoline (**3a**): yield 71.0%; pale yellow solid; mp 138.3–140.2 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.70 (d, J = 7.4 Hz, 2H), 8.53 (s, 1H), 8.26 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 1.5 Hz, 1H), 7.55 (m, 6H), 7.46 (t, J = 1.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.3, 155.6, 149.2, 149.1, 148.5, 136.9, 130.2, 129.6, 129.4, 128.4, 128.3, 126.8, 125.8, 124.0, 121.8, 119.2; FT-IR (KBr) cm^{-1}; 1357, 1489, 1590, 2986, 3053; GC/MS *m/z* 282 (M$^+$). *4-Phenyl-2-pyridine-3-yl-quinoline* (**3b**): yield 74.5%; pale yellow solid; mp 152.0–154.0 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.70 (d, J = 3.7 Hz, 1H), 8.53 (d, J = 7.9 Hz, 1H), 8.24 (d, J = 8.7 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.82 (s, 1H), 7.78 (t, J = 6.9 Hz, 1H), 7.53 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.2, 150.2, 149.6, 148.8, 140.0, 135.0, 130.1, 129.8, 129.5, 128.7, 128.6, 126.8, 125.9, 125.8, 123.7, 118.9; FT-IR (KBr) cm^{-1}; 1355, 1475, 1590, 2986, 3054 GC/MS *m/z* 282 (M$^+$). *4-Phenyl-2-pyridine-4-yl-quinoline* (**3c**): yield 71.0%; pale yellow solid; mp 138.0–138.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.78 (s, 2H), 8.26 (d, J = 8.9 Hz, 1H), 8.10 (d, J = 6.2 Hz, 2H), 7.93 (d, J = 8.4 Hz, 1H), 7.84 (s, 1H), 7.78 (t, J = 6.9 Hz, 1H), 7.54 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.0, 150.4, 149.8, 148.8, 146.6, 137.9, 130.3, 129.9, 129.5, 128.7, 127.2, 125.7, 121.7, 118.8; FT-IR (KBr) cm^{-1}; 1357, 1485, 1593, 2985, 3050; GC/MS *m/z* 282 (M$^+$). *2-Furan-2-yl-4-phenylquinoline* (**3d**): yield 68.0%; brown solid; mp 90.0–92.0 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.21 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.76 (s, 1H), 7.69 (t, J = 6.9 Hz, 1H), 7.61 (s, 1H), 7.45 (m, 6H), 7.23 (d, J = 3.4 Hz, 1H), 6.57 (t, J = 1.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.6, 148.9, 148.5, 148.4, 143.9, 137.9, 129.6, 129.4, 128.9, 128.5, 128.3, 125.6, 125.5, 117.6, 112.1, 110.1; FT-IR (KBr) cm^{-1}; 1353, 1480, 1595, 2989, 3048; GC/MS *m/z* 271 (M$^+$). *4-Phenyl-2-thiophen-2-yl-quinoline* (**3e**): yield 60.0%; pale yellow solid; mp 80.4–83.8 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.26 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.77 (s, 1H), 7.72 (m, 2H), 7.56 (m, 7H), 7.15 (dd, J = 3.8, 4.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.6, 148.7, 148.4, 148.1, 137.9, 129.4, 129.3, 129.2, 128.6, 128.4, 128.2, 127.8, 127.7, 125.7, 125.6, 125.4, 117.6; FT-IR (KBr) cm^{-1}; 1359, 1486, 1590, 2988, 3057; GC/MS *m/z* 287 (M$^+$). *2-(1-Methyl-1H-pyrrol-2-yl)-4-phenylquinoline* (**3f**): yield 65.2%; brown oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.10 (d, J = 8.09 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.67 (d, J = 6.1 Hz, 1H), 7.64 (s, 1H), 7.55 (m, 5H), 7.43 (dd, J = 1.0, 8.1 Hz, 1H), 6.83 (m, 2H), 6.23 (dd, J = 2.5, 3.8 Hz, 1H), 4.25 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 151.8, 148.2, 138.4, 129.5, 129.2, 128.5, 128.2, 127.6, 125.5, 124.7, 120.3, 120.2, 112.3, 107.9, 107.7, 37.7; FT-IR (KBr) cm^{-1}; 1350, 1493, 1587, 2980, 3043; GC/MS *m/z* 285 (M$^+$). *6-Chloro-4-phenyl-2-pyridine-2-yl-quinoline* (**5a**): yield 70.0%; pale yellow solid; mp 171.5–173.0 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.67 (d, J = 10.7 Hz, 1H), 8.54 (s, 1H), 8.18 (d, J = 8.9 Hz, 1H), 7.88 (m, 2H), 7.65 (d, J = 8.9 Hz, 1H), 7.55 (m, 5H), 7.37 (t, J = 5.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.8, 149.3, 149.1, 148.5, 146.8, 137.7, 137.0, 132.7, 131.8, 130.3, 129.5, 128.7, 124.7, 124.2, 121.9, 120.0, 119.9; FT-IR (KBr) cm^{-1}; 1356, 1487, 1588, 2980, 3051; GC/MS *m/z* 314 (M$^+$). *6-Chloro-4-phenyl-2-pyridine-3-yl-quinoline* (**5b**): yield 72.0%; pale yellow solid; mp 191.5–192.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.37 (d, J = 1.9 Hz, 1H), 8.71 (dd, J = 1.6, 4.8 Hz, 1H), 8.51 (d, J = 6.0 Hz, 1H), 8.17 (d, J = 8.9 Hz, 1H), 7.88 (d, J = 2.3 Hz, 1H), 7.83 (s, 1H), 7.68 (dd, J = 2.4, 8.9 Hz, 1H), 7.50 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.4, 150.4, 150.3, 148.7, 147.2, 137.3, 135.0, 134.7, 132.8, 131.8, 130.3, 129.4, 128.9, 126.7, 124.6, 123.7, 119.6; FT-IR (KBr) cm^{-1}; 1359, 1483, 1585, 2991, 3055; GC/MS *m/z* 314 (M$^+$). *6-Chloro-4-phenyl-2-pyridine-4-yl-quinoline* (**5c**): yield 66.5%; pale yellow solid; mp 188.0–192.0 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.79 (d, J = 6.0 Hz, 2H), 8.18 (d, J = 8.9 Hz, 1H), 8.07 (dd, J = 1.4, 4.5 Hz, 2H), 7.87 (m, 2H), 7.69 (dd, J = 2.4, 8.9 Hz, 1H), 7.53 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.4, 150.6, 150.5, 149.1, 147.5, 146.1, 137.3, 133.2, 131.9, 131.8, 130.9, 130.8, 129.4, 128.9, 127.1, 124.6, 124.5, 121.6, 121.4, 119.5; FT-IR (KBr) cm^{-1}; 1357, 1485, 1593, 2988, 3052; GC/MS *m/z* 314 (M$^+$).
General procedure for the preparation of dibenzo[b,f][1,5]diazocines (**4**, **6**): Aminobenzophenone (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 that given in Ref. 11. 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 dibenzo[*b*,*f*][1,5]diazocines.
6,12-Diphenyl-dibenzo[b,f][1,5]diazocine (**4**): yield 89.4%; yellow solid; mp 190.5–192.0 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78 (m, 4H), 7.36 (m, 8H), 7.03 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.5, 151.8, 138.8, 131.0, 129.6, 129.4, 128.2, 127.5, 126.9, 123.3, 120.9; FT-IR (KBr) cm^{-1}; 1355, 1492, 1585, 2983, 3056; GC/MS *m/z* 358 (M$^+$). *2,8-Dichloro-6,12-diphenyl-dibenzo[b,f][1,5]diazocine* (**6**): yield 79.8%; yellow solid; mp 210.0–212.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74 (m, 4H), 7.37 (m, 8H), 6.99 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.7, 150.1, 137.1, 131.2, 130.0, 129.3, 128.4, 128.0, 127.1, 122.4; FT-IR (KBr) cm^{-1}; 1357, 1490, 1583, 2989, 3051; GC/MS *m/z* 428 (M$^+$).