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Simple Synthesis of Dibenzo[*b,f*][1,5]diazocines using Various Catalysts Under Microwave Irradiation.

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ABSTRACT

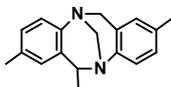
2-Aminobenzophenone, 2-amino-4-chlorobenzophenone, 2-amino-4-bromobenzophenone, 2-amino-2', 5-dichlorobenzophenone and 2-amino-5-chloro-2'-fluorobenzophenone were condensed under optimal reaction conditions. The self-condensation of 2-aminobenzophenones afforded 6,12-diphenyl-dibenzo[*b,f*][1,5]diazocines. The dibenzo[*b,f*][1,5]diazocines were synthesized using an MW-assisted solvent-free method ("green chemistry" conditions).

Keywords: Dibenzo[*b,f*][1,5]diazocines, MW irradiation, green chemistry, benzophenones, self-condensation

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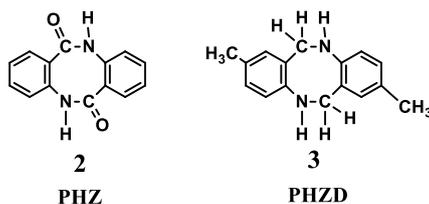
INTRODUCTION

Tröger's base (TB) is a bridged bicyclic molecule originally isolated by Julius Tröger in 1887 while studying the acid-catalyzed condensation of *p*-toluidine and formaldehyde; however, its structure puzzled chemists for decades until it was correctly assigned in 1935.¹



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Dibenzo[*b,f*][1,5]diazocine-6,12-dione also known as PHZD and a derivative of phenhomazine, is an eight-membered cyclic diamine that behaves as a bidentate ligand in the studied complexes and bears resemblance to PHZ with respect to the chromophoric environment.²⁻⁴



PHZ

PHZD

Although dibenzo[*b,f*][1,5]diazocines are well known, their biological activities have not been studied in detail. These compounds are structurally similar to calcium-channel antagonists such as diltiazem that acts as a chemosensitizer against multiple drug resistance.^{5,6}

Recently, considerable attention has been paid to microwave (MW)-assisted organic reactions that do not require any solvent.⁷⁻¹⁰ Thermal reactions are often carried out in solutions using large quantities of reagents and may take several hours for completion. However, MW-assisted reactions proceed to completion within minutes under MW irradiation. Here in, we report a new method involving MW irradiation for synthesizing dibenzo[*b,f*][1,5]diazocines.

EXPERIMENTAL

General procedure for the preparation of dibenzo[*b,f*][1,5]diazocines 4 and 5: Aminobenzophenone (1.0 mmol), and 0.5 equiv of diphenyl phosphate (DPP, 0.5 mmol, Aldrich) were mixed in the absence of any organic solvent and then subjected to microwave irradiation for 3 min using a domestic microwave oven (Samsung, RE-555 TCW). The reaction mixture was work-up following a reported procedure.¹¹ After concentrating the reaction mixture under reduced pressure, the residue was purified by flash column chromatography using silica gel (EtOAc/*n*-hexane = 1:20 v/v) affording the corresponding dibenzo[*b,f*][1,5]diazocines. 6,12-Diphenyldibenzo[*b,f*][1,5]diazocine **4**: 89.4% yield; yellow solid; m.p. 190.5–192.0°C; ¹H NMR (200 MHz, CDCl₃); δ ppm 7.78 (m, 4H), 7.36 (m, 8H), 7.03 (m, 6H); ¹³C NMR (50 MHz, CDCl₃) 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-diphenyldibenzo[*b,f*][1,5]diazocine **5**: 79.8% yield; yellow solid; m.p. 210.5–212.5°C; ¹H NMR (200 MHz, CDCl₃); δ 7.74 (m, 4H), 7.37 (m, 8H), 9.99 (m, 4H); ¹³C NMR (50 MHz, CDCl₃) 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⁺).

General procedure for the preparation of dibenzo[*b,f*][1,5]diazocines 6: 2-Amino-4-bromobenzophenone (1.0 mmol), and 0.5 equiv of DPP (0.5 mmol, Aldrich) were mixed in the absence of any organic solvent and then subjected to microwave irradiation for 3 min using a domestic microwave oven (Samsung, RE-555 TCW). The reaction mixture was work-up following a reported procedure.¹¹ After concentrating the reaction mixture under reduced pressure, the residue was purified by flash column chromatography using silica gel (EtOAc / *n*-hexane = 1:20 v/v), affording the corresponding (5*z*,11*z*)-3,9-dibromo-6,12-diphenyldibenzo[*b,f*][1,5]diazocine **4**: m.p. 190–192°C; ¹H NMR (200 MHz, CDCl₃); δ 8.1–8.2 (d, 4H), 7.7 (d, 2H), 7.6–7.7 (t, 4H), 7.3–7.4 (d, 2H), 7.3 (t, 4H); ¹³C NMR (50 MHz, CDCl₃); δ 131.8, 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). (5E, 11E)-2,8-dichloro-6,12-bis(2-chlorophenyl)dibenzo[*b,f*][1,5]diazocine **7**: isolated yield: 73.6%; m.p. 202–204°C; R_f : 0.55 (TLC eluent; n-Hexane / EtOAc = 10:1 v/v); ^1H NMR (300 MHz, CDCl_3); δ 7.67 (m, 2H), 7.35 (m, 8H), 7.03 (d, 2H), 6.87 (d, 2H); ^{13}C NMR (75 MHz, CDCl_3); δ 125.22, 127.21, 129.13, 129.80, 129.85, 130.05, 130.30, 131.11, 131.20, 132.15, 138.71, 149.21, 168.56; Anal calcd (%) for $\text{C}_{26}\text{H}_{14}\text{Cl}_4\text{N}_2$: C, 62.93; H, 2.84; Cl, 28.58; N, 5.65. Found (%); C, 62.91; H, 2.85; Cl, 28.55; N, 5.66. (5E,11E)-2,8-dichloro-6,12-bis(2-fluorophenyl)dibenzo[*b,f*][1,5]diazocine **8**: isolated yield: 77.9%; m.p. 212–214°C; R_f : 0.56 (TLC eluent; n-Hexane / EtOAc = 3:1 v/v); ^1H NMR (300 MHz, CDCl_3); δ 7.67 (m, 1H), 7.35 (m, 8H), 7.02 (d, 1H), 6.87 (d, 1H); ^{13}C NMR (75 MHz, CDCl_3); δ 117.58, 122.06, 125.32, 127.21, 129.25, 130.13, 131.02, 131.05, 132.16, 149.22, 164.21, 167.58; Anal calcd (%) for $\text{C}_{26}\text{H}_{14}\text{Cl}_2\text{F}_2\text{N}_2$: C, 67.40; H, 3.05; Cl, 15.30; F, 8.20; N, 6.05. Found (%); C, 67.39; H, 3.06; Cl, 15.29; F, 8.21; N, 6.05.

RESULTS AND DISCUSSION

2-Aminobenzophenone, 2-amino-4-chlorobenzophenone, 2-amino-4-bromobenzophenone, 2-amino-2',5-dichlorobenzophenone and 2-amino-5-chloro-2'-fluorobenzophenone were condensed under the abovementioned optimal reaction conditions. The results are summarized in Table 1.

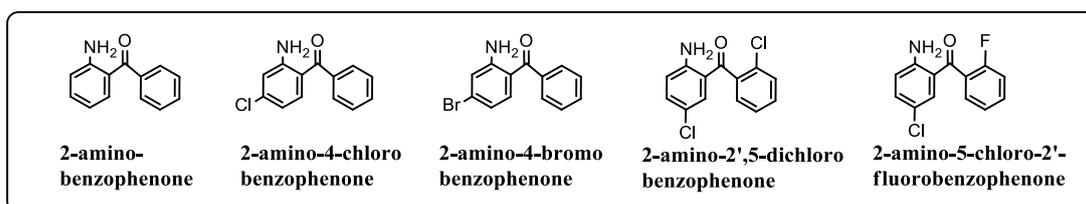
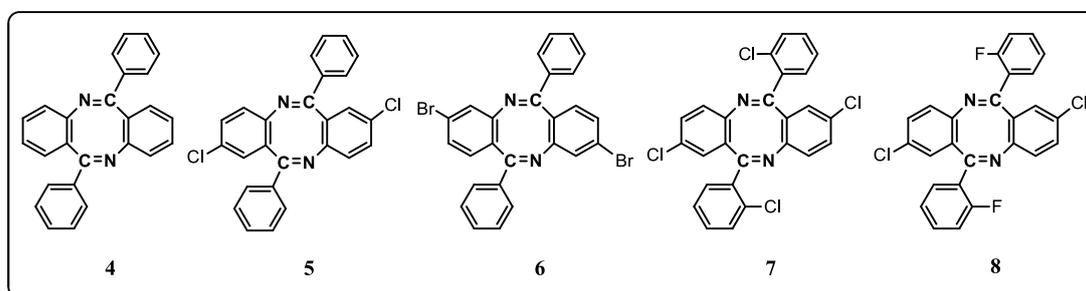
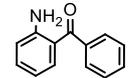
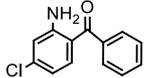
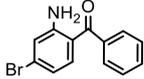
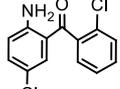
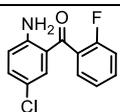
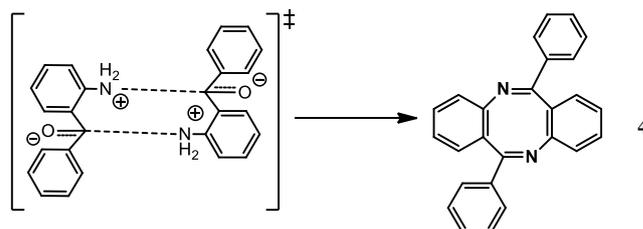


Table 1: 6,12-Diphenyldibenzo[*b,f*][1,5]diazocines by self-condensation

Entry	Benzophenone	6,12-Diphenyldibenzo[<i>b,f</i>][1,5]diazocine	Yield* (%)
1		4	89.4
2		5	79.8
3		6	84.7
4		7	73.6
5		8	77.9

* Isolated yields

The products 6,12-diphenyldibenzo[*b,f*][1,5]diazocines (**4–8**) were obtained by the self-condensation (Q) of 2-aminobenzophenones.



The self-condensation of 2-aminobenzophenone afforded compound **4** as the only product. To investigate the effect of DPP on product formation, the synthesis of compound **4** was carried out under MW irradiation using different equivalents of DPP (Table 2).

Table 2: Synthesis of compound 4 using various catalysts under MW irradiation

Entry	2-Aminobenzophenone (mmol)	Catalyst	Yield of 4* (%)
1	1.0	DPP	89.4
2	1.0	HCl	61.6
3	1.0	H ₃ PO ₄	45.7
4	1.0	CH ₃ COOH	18.9
5	1.0	H ₂ SO ₄	0

* Isolated yields

The isolated yields of compound **4**, **7**, and **8** were higher when using anhydrous DPP than HCl, H₃PO₄, CH₃COOH, and H₂SO₄ (Tables 3 and 4). The self-condensation reaction proceeded efficiently in the presence of DPP, as shown in the reaction mechanism for the formation of dibenzo[*b,f*][1,5]diazocines.

Table 3: Synthesis of compound 7 using various catalysts under MW irradiation

Entry	2-Amino-2',5-dichlorobenzophenone (mmol)	Reaction time (min)	Catalyst	Yield of 7* (%)
1	1.0	5	DPP	73.6
2	1.0	5	HCl	38.2
3	1.0	5	H ₃ PO ₄	29.5
4	1.0	5	CH ₃ COOH	22.3
5	1.0	5	H ₂ SO ₄	0

*Isolated yield

Table 4: Synthesis of compound 8 using various catalysts under MW irradiation

Entry	2-Amino-5-chloro-2'-fluorobenzophenone (mmol)	Reaction time (min)	Catalyst	Yield of 8* (%)
1	1.0	5	DPP	77.9
2	1.0	5	HCl	43.6
3	1.0	5	H ₃ PO ₄	33.2
4	1.0	5	CH ₃ COOH	19.8
5	1.0	5	H ₂ SO ₄	0

*Isolated yield

In summary, dibenzo[b,f][1,5]diazocine derivatives were synthesized using an MW-assisted solvent-free method ("green chemistry" conditions). The yields of products obtained using the proposed method are significantly higher than those obtained by conventional thermal reactions; further, this method does not require hazardous solvents and excess amounts of expensive acidic catalysts. Moreover, this method is economical, environmentally benign, and afforded the desired products within a short time.

ACKNOWLEDGEMENT

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