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Microwave-Assisted Catalyst-Free and Solvent-Free Method for the Synthesis of Quinoxalines

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Abstract: A green and efficient procedure for the synthesis of quinoxalines is reported starting from benzil and 1,2-diaminobenzene. The reactions were carried out under catalyst-free, solvent-free, and microwave-irradiation conditions, affording the corresponding quinoxalines. This method had many dramatic advantages, such as the short reaction time (2–6 min), high yields (71–98%), and environmental friendliness, as well as convenient operation.

Keywords: Benzil, catalyst-free, 1,2-diaminobenzene, microwave irradiation, quinoxaline, solvent-free

In today's world, synthetic chemists in both academia and industry are constantly challenged to consider more environmentally benign methods for generation of the desired target molecules. It is known that microwave irradiation has been utilized as one of the most convenient and efficient ways to promote organic reactions.[1] In particular, the use of microwave energy to directly heat chemical reactions has become an increasingly popular technique in the scientific community. Therefore, in recent years the combination of these several prominent green

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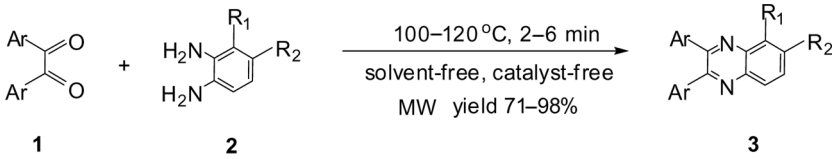
chemistry principles—microwaves, lack of solvent, and lack of catalyst–has become very popular and received substantial interest because of the work of chemists[2] who demonstrated that a great variety of synthetic organic transformations can be carried out very efficiently and rapidly under these environmentally benign conditions.

Quinoxaline derivatives are an important class of benzoheterocycles, which have a wide range of pharmacologically active compounds that have anticancer,[3] antimicrobial,[4] and antibacterial[5] activities. Some quinoxaline derivatives serve as DNA photo-cleavers,[6] antagonists of the 5-HT3 receptor,[7] inhibitors of HCV NS5B RNA-dependent RNA polymerase,[8] and fluorescent dyes.[9] Furthermore, they also serve as useful rigid subunits in macrocyclic receptors for molecular recognition[10] and chemically controllable switches,[11] and they constitute the building blocks of some organic semiconductors.[12]

Numerous synthetic routes have been developed for the synthesis of quinoxaline derivatives involve involving condensation of 1,2-diamines with α-diketones,[13] 1,4-addition of 1,2-diamines to diazenylbutenes,[14] and cyclization–oxidation of phenacyl bromides and o-phenylenediamines through solid-phase synthesis.[15] 2,3-Disubstituted quinoxalines have also been prepared via the Suzuki–Miyaura coupling reaction,[16] condensation of o-phenylenediamines with 1,2-dicarbonyl compounds under microwave irradiation,[17] and iodine-catalyzed cyclocondensation of 1,2-dicarbonyl compounds with substituted o-phenylenediamines.[18] Also, α-hydroxy ketones react with o-phenylenediamines in the presence of transition metals such as Mn, Pd, Ru, Cu, Pb, and Bi to give quinoxalines.[19,20] The most common method is the condensation of an aryl 1,2-diamine with a 1,2-dicarbonyl compound by heating it in a solvent for 2–12 h. The yields of products are 34–85%. Improved methods have been reported for the synthesis of quinoxaline derivatives including the use of $RuCl_2(PPh_3)_3$-2,2′,6,6′-tetramethylpiperidine N-oxyl (TEMPO),[19a] MnO_2,[19b] $POCl_3$,[19c] cerium ammonium nitrate,[19d] SA/MeOH,[19e] $CuSO_4 \cdot 5H_2O$,[19f] Montmorillonite K-10,[19g] $HClO_4 \cdot SiO_2$,[19h] $H_6P_2W_{18}O6_2 \cdot 24H_2O$,[19i] $KHSO_4$,[19j] Ni-nanoparticles,[19k] Zn[(l)proline],[19l] and *p*-toluenesulfonic acid[19m] as catalyst. However, most of the existing methodologies sufer from disadvantages such as use of volatile organic solvents, critical product isolation procedures, expensive and detrimental metal precursors, and harsh reaction conditions, which limit their environmental friendliness.

Continuing our interest in the synthesis of organic compounds by microwave irradiation,[21] we report herein a novel method to synthesize differently substituted quinoxalines from benzils and 1,2-diaminobenzenes under catalyst-free, solvent-free, and microwave-irradiation conditions (Scheme 1).



1 2 3

Scheme 1. Ar=C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4, funyl; R_1=H, CH_3; R_2=H, CH_3, OCH_3, NO_2.

RESULTS AND DISCUSSION

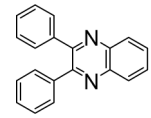
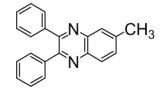
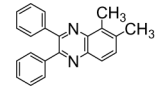
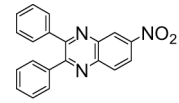
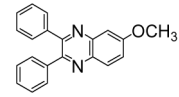
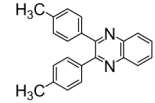
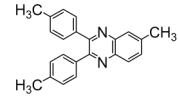
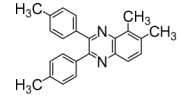
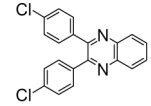
When a mixture of benzil **1** (Ar=C_6H_5) and 1,2-diaminobenzene **2** were irradiated at 100°C in catalyst-free and solvent-free conditions, the reaction was completed after 4 min. The crude product was purified by recrystallization from 95% ethanol to afford product **3a** with excellent yield (96%). Subsequently, to examine the efficiency and applicability of this protocol, the reaction was extended to other substituted benzils **1** (Ar=4-$CH_3C_6H_4$, 4-ClC_6H_4, furyl) and substituted 1,2-diaminobenzenes **2** (R_1=H, CH_3; R_2=H, CH_3, OCH_3, Br, NO_2) under catalyst-free, catalyst-free, and microwave-irradiation conditions. To our delight, these actions proceeded smoothly to afford a series of quinoxaline derivatives **3** in excellent yields (entries 2–16 of Table 1). The results showed that the scope of the reaction is quite broad in regard to the benzils **1** and 1,2-diaminobenzenes **2**. The structures of these compounds are established by infrared (IR), ^{1}H NMR, ^{13}C NMR, and mass spectrometry (MS).

In conclusion, we have developed a novel, efficient method for synthesis of quinoxalines of potential synthetic and pharmacological interest. Catalyst-free, solvent-free, and microwave-irradiation conditions, the short reaction time, excellent yields of the products, environmental friendliness, and convenient workup are the advantages of this method.

EXPERIMENTAL

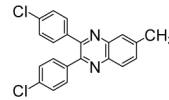
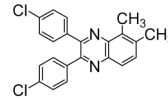
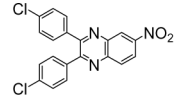
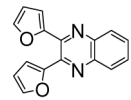
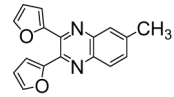
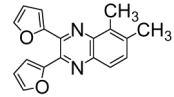
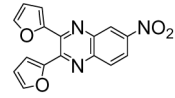
The reactions under microwaves were performed in a CEM Discover monomode microwave reactor. Melting points were determined with a WRS-1B digital melting-point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were measured on a Burke 400-MHz spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a Nicolet Avatar 360 FT-IR instrument. MS spectra were recorded on a LCQ Advantage instrument. Elemental analyses were determined using a Perkin-Elmer 240C elemental analyzer. All the reagents are commercially available.

Table 1. Synthesis of quinoxalines **3a–p** under catalyst-free, solvent-free, and microwave-irradiation conditions

Entry	Ar	R_1, R_2	Temp. (°C)	Time (min)	Products	Yield[a] (%)
1	C_6H_5	R_1=R_2=H	100	4	 **3a**	96
2	C_6H_5	R_1=H R_2=CH_3	100	4	 **3b**	93
3	C_6H_5	R_1=R_2=CH_3	100	3	 **3c**	97
4	C_6H_5	R_1=H R_2=NO_2	120	3.5	 **3d**	98
5	C_6H_5	R_1=H R_2=OCH_3	110	4	 **3e**	71
6	4-$CH_3C_6H_4$	R_1=R_2=H	120	3	 **3f**	97
7	4-$CH_3C_6H_4$	R_1=H R_2=CH_3	120	4	 **3g**	95
8	4-$CH_3C_6H_4$	R_1=R_2=CH_3	120	3	 **3h**	95
9	4-ClC_6H_4	R_1=R_2=H	120	3	 **3i**	93

(*Continued*)

Table 1. Continued

Entry	Ar	R_1, R_2	Temp. (°C)	Time (min)	Products	Yield[a] (%)
10	4-ClC_6H_4	R_1=H R_2=CH_3	120	6	 **3j**	97
11	4-ClC_6H_4	R_1=R_2=CH_3	120	5	 **3k**	97
12	4-ClC^6H^4	R^1=H R^2=NO^2	120	3	 **3l**	94
13	Furyl	R_1=R_2=H	120	3	 **3m**	98
14	Furyl	R^1=H R^2=CH^3	120	3	 **3n**	96
15	Furyl	R_1=R_2=CH_3	120	2	 **3o**	90
16	Furyl	R_1=H R_2=NO_2	120	3	 **3p**	98

[a]Yields of the isolated product.

General Procedure for Synthesize of Quinoxalines Under Catalyst-Free, Solvent-Free, and Microwave-Irradiation Conditions

Benzils **1** (1 mmol) and 1,2-diaminobenzenes **2** (1 mmol) were mixed and sealed with a cap containing a septum. The loaded vial was then placed into the cavity of the microwave reactor and heated at 100–130°C for 2–6 min (as indicated by thin-layer chromatography, TLC). After completion of the reaction, the reaction mixture was then allowed to cool to room temperature, resulting in the precipitation of

the solid product. The product was were filtered off and dried. The crude products were recrystallized from 95% ethanol to afford the pure product **3a–p**.

Data

Compound **3a**

Mp 126.2–126.8°C (126–127°C).[19h] ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.21$–8.23 (m, 2H), 7.82–7.80 (m, 2H), 7.56–7.54 (m, 4H), 7.40–7.35 (m, 6H). MS m/z (%): $(M + H)^+ = 283.6$ (100).

Compound **3b**

Mp 115.1°C (116–117°C).[19h] ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.09$ (d, 1H, $J = 8.8$ Hz), 7.98 (s, 1H), 7.64–7.62 (m, 1H), 7.54 (t, 4H, $J = 7.6$ Hz), 7.40–7.35 (m, 6H), 2.65 (s, 3H). MS m/z (%): $(M + H)^+ = 297.6$ (100).

Compound **3c**

Mp 150.7–150.9°C. IR (KBr): 3058, 2919, 1636, 1341, 1094, 967, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.96$ (d, 1H, $J = 8.4$ Hz), 7.62 (t, 3H, $J = 8.8$ Hz), 7.55 (t, 2H, $J = 7.6$ Hz), 7.40–7.35 (m, 6H), 2.83 (s, 3H), 2.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 151.6$, 140.2 139.6, 137.7, 134.6, 132.9, 130.1, 129.8, 128.5, 128.1, 125.9, 20.5, 12.9. MS m/z (%): $(M + H)^+ = 311.7$ (100). Anal. calcd. for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03; found: C, 84.81; H, 5.87; N, 8.97.

Compound **3d**

Mp 188.9°C (187°C).[22] ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 9.11$ (s, 1H), 8.58–8.55 (m, 1H), 8.33 (d, 1H, $J = 9.2$ Hz), 7.60–7.58 (m, 4H), 7.47–7.38 (m, 6H). MS m/z (%): $(M + H)^+ = 328.6$ (100).

Compound **3e**

Mp 156.4–156.5°C (155–156°C).[23] ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.09$ (d, 1H, $J = 9.2$ Hz), 7.51–7.54 (m, 5H), 7.44–7.49 (m, 1H), 7.34–7.40 (m, 6H), 4.02 (s, 3H). MS: m/e $(M + H)^+ = 313.7$ (100).

Compound **3f**

Mp 149.4–149.7°C. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.19$–8.17 (m, 2H), 7.80–7.75 (m, 2H), 7.46 (d, 4H, $J = 7.6$ Hz), 7.18 (d, 4H, $J = 7.6$ Hz). MS m/z (%): $(M + H)^+ = 311.5$ (100). Anal. calcd. for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03; found: C, 84.80; H, 5.87; N, 8.96.

Compound **3g**

Mp 130.2–130.6°C (137°C).[19d] ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.07$ (d, 1H, $J = 8.4$ Hz), 7.97 (s, 1H), 7.60 (d, 1H, $J = 8.0$ Hz), 7.43 (t, 4H, $J = 7.6$ Hz), 7.16 (d, 4H, $J = 7.6$ Hz), 2.63 (s, 3H), 2.39 (s, 6H). MS m/z (%): $(M + H)^+ = 325.4$ (100).

Compound **3h**

Mp 173.4–73.6°C. IR (KBr): 3022, 2920, 1609, 1512, 1340, 1089, 823, 797 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.00$ (d, 1H, $J = 8.4$ Hz), 7.59 (d, 1H, $J = 8.8$ Hz), 7.52–7.46 (m, 4H), 7.19–7.16 (m, 4H), 2.81 (s, 3H), 2.57 (s, 3H), 2.39 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 151.6$, 140.1, 139.4, 138.5, 137.5, 136.8, 134.5, 132.6, 130.0, 129.7, 128.9, 125.7, 21.3, 20.5, 12.9. MS m/z (%): $(M + H)^+ = 339.4$ (100). Anal. calcd. for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28; found: C, 84.85; H, 6.57; N, 8.22.

Compound **3i**

Mp 174.9°C (187–188°C).[24] ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.21$–8.18 (m, 2H), 7.94 (d, 1H, $J = 8.4$ Hz), 7.84–7.81 (m, 2H), 7.54 (s, 1H), 7.50 (d, 3H, $J = 8.4$ Hz), 7.37 (d, 3H, $J = 8.0$ Hz). MS m/z (%): $(M)^+ = 351.6$ (100).

Compound **3j**

Mp 170.6–172.5°C (180°C).[19l] ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.08$ (d, 1H, $J = 8.4$ Hz), 7.97–7.93 (m, 2H), 7.65 (d, 1H, $J = 8.4$ Hz), 7.54–7.47 (m, 4H), 7.36 (d, 3H, $J = 8.4$ Hz), 2.65 (s, 3H). MS m/z (%): $(M)^+ = 365.6$ (100).

Compound **3k**

Mp 184.8–184.9°C. IR (KBr): 3052, 1661, 1586, 1091, 836, 732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.01$ (d, 1H, $J = 8.4$ Hz), 7.94 (d, 2H,

$J = 8.4$ Hz), 7.65 (d, 1H, $J = 8.8$ Hz), 7.55–7.31 (m, 6H), 2.81 (s, 3H), 2.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 150.1$, 141.8, 140.3, 139.6, 138.3, 137.6, 135.1, 134.6, 133.4, 131.4, 131.2, 129.5, 128.6, 125.8, 20.5, 12.9. MS m/z (%): $(M)^+ = 379.7$ (100). Anal. calcd. for $C_{22}H_{16}Cl_2N_2$: C, 69.67; H, 4.25; N, 7.39; found: C, 69.41; H, 4.27; N, 7.34.

Compound **3l**

Mp 163.7–164.4°C (176°C).[19l] ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 9.07$ (s, 1H), 8.58–8.55 (m, 1H), 8.30 (d, 1H, $J = 9.2$ Hz), 7.56–7.52 (m, 4H), 7.41 (d, 4H, $J = 8.0$ Hz). MS m/z (%): $(M)^+ = 396.5$ (100).

Compound **3m**

Mp 133.9–134.1°C (131–132°C).[25] ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.18$–8.16 (m, 2H), 7.79–7.76 (m, 2H), 7.65 (s, 2H), 6.69 (d, 2H, $J = 3.2$ Hz), 6.60–6.58 (m, 2H). MS m/z (%): $(M + H)^+ = 263.7$ (100).

Compound **3n**

Mp 116–116.2°C (119–120°C).[26] ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.06$ (d, 2H, $J = 8.4$ Hz), 7.96 (s, 1H), 7.64–7.60 (m, 3H), 7.67 (d, 2H, $J = 3.2$ Hz),), 6.58 (s, 2H), 2.62 (s, 3H). MS m/z (%): $(M + H)^+ = 277.5$ (100).

Compound **3o**

Mp 125–125.1°C. IR (KBr): 3111, 2920, 1591, 1560, 1492, 1328, 1147, 1008, 879, 759 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.91$ (d, 1H, $J = 8.8$ Hz), 7.63 (s, 1H), 7.59 (d, 2H, $J = 9.2$ Hz), 6.82 (s, 1H, $J = 3.2$ Hz), 6.60 (d, 2H, $J = 3.2$ Hz), 6.56 (t, 1H, $J = 4.8$ Hz), 2.78 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) $\delta = 151.9$, 151.2, 143.9, 143.6, 141.1, 139.7, 139.3, 138.3, 134.5, 133.3, 125.9, 112.3, 111.8, 20.5, 12.9. MS m/z (%): $(M + H)^+ = 291.6$ (100). Anal. calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65; found: C, 74.19; H, 4.88; N, 9.58.

Compound **3p**

Mp 169.2–169.4°C. IR (KBr): 3094, 1566, 1522, 1241, 1059, 826, 741 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 9.03$ (d, 1H, $J = 2.4$ Hz), 8.52–8.50 (m,

1H), 8.25 (d, 2H, $J = 9.2$ Hz), 7.69 (d, 1H, $J = 6.0$ Hz), 6.91 (d, 1H, $J = 3.2$ Hz), 8.86 (d, 1H, $J = 3.2$ Hz), 6.65–6.63 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) $\delta = 150.2$, 148.0, 145.4, 144. 8, 144.2, 143.0, 139.2, 130.4, 125.3, 123.6, 115.3, 114.4, 112.3. MS m/z (%): $(M + H)^+ = 308.3$ (100). $C_{16}H_9N_3O_4$: C, 62.54; H, 2.95; N, 13.68; found: C, 65.31; H, 2.97; N, 13.58.

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