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Microwave-Assisted Synthesis of 2-Amino and 2-Azetidinonyl 5-(2-Benzoyl-phenoxymethyl) 1,3,4-Oxadiazoles

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ABSTRACT: *A simple high yielding method for the integration of heterocyclic rings viz. 1,3,4-oxadiazole and azetidin-2-one at the benzophenone nucleus has been developed starting from substituted 2-hydroxybenzophenones, and by using mild conditions, wet solid surface, and microwave irradiation. A comparison of this microwave-accelerated reaction with conventional heating condition is also illustrated.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 15:37–42, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10210

INTRODUCTION

The efficiency of benzophenone derivatives as chemotherapeutic agent is well established and their chemistry has been extensively studied. In the past years, the literature is enriched with progressive finding about the synthesis and pharmacological actions of fused heterocycles. Literature survey revealed that benzophenone derivatives are associated with potent biological activity, such as, inhibition of HIV-1 reverse transcriptase and the growth of HIV-1 in MT-4 cells [1]. These compounds also showed antianaphylactic [2] and antiinflammatory activity [2,3]. Bakana et al. [4] isolated a benzophenone analogue (garcinol) from the stem bark of *Garcinia huillensis* grown in Zaire and used in central-African traditional medicine, and found this to exhibit chemotherapeutical activity against gram-positive and gram-negative cocci, mycobacteria, and fungi [4]. 1,3,4-Oxadiazole is associated with potent pharmacological activity due to the presence of toxophoric —N=C—O— linkage [5]. Considerable evidence has been accumulated to demonstrate the efficacy of 1,3,4-oxadiazole, including its use in herbicides, fungicides, hypnotics sedatives [6], as well as its antibacterial [7], analgesic, antimalarial [8], antiinflammatory [9], hypoglycemic [10], anticonvulsant, diuretic, and antimitotic activity [11]. Besides, considerable work has been carried out both with regard to heterocylic chemistry and pharmacological activity, viz., antiviral, anesthetic, and anticonvulsant activity of the azetidin-2-one ring system [12,13]. Encouraged by these informations it was considered valuable to integrate 1,3,4-oxadiazole-azetidin-2-one moiety in benzophenone framework.

The microwaves enhance chemical reactions in general [14,15] as well as on inorganic solid supports in particular [16,17], they have gained popularity over the usual homogeneous and heterogeneous reactions [18] as they can be carried out rapidly, and provide pure products in quantitative yields without the use of solvents. It was shown that solvent free

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conditions are especially propitious to microwave activation [19], as they provide an opportunity to work with open vessels, thus avoiding the risk of high pressure development and with a possibility of carrying out the reaction on a preparative scale in addition to the associated selectivity and ease of manipulation [15,20]. To develop environmentally benign solventless methods, using montmorillonite K10 clay as solid support and microwave activation, we report herein a solventless synthesis of 2-[3-chloro-4-(3-bromophenyl)azetidin-2-onyl] 5-(2-benzoyl-phenoxymethyl) 1,3,4-oxadiazoles **6a–d**.

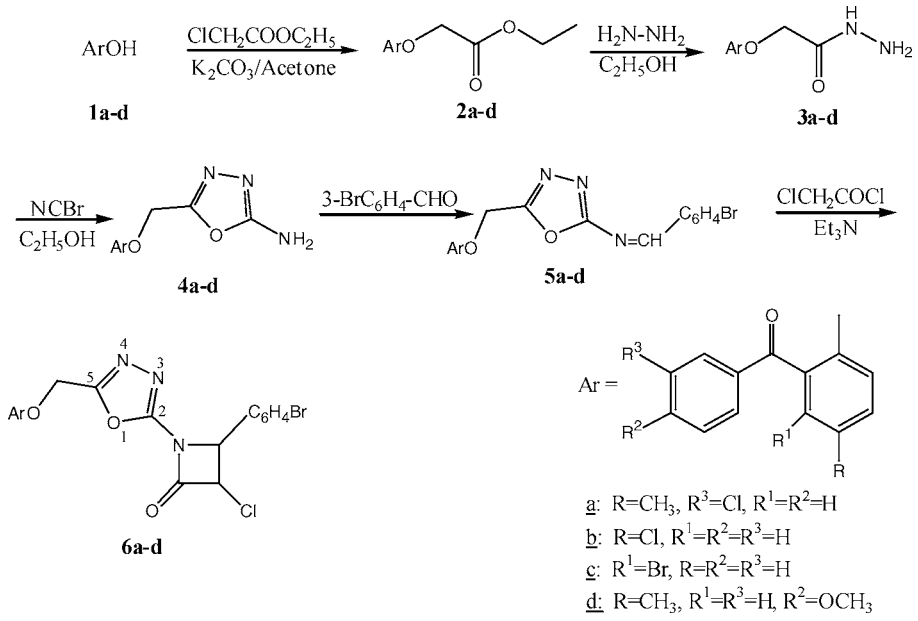
RESULTS AND DISCUSSION

The synthetic route is depicted in Scheme 1. Condensation of substituted 2-hydroxybenzophenones **1a–d** with ethyl chloroacetate yielded substituted ethyl-2-benzoyl-phenoxy acetates **2a–d** [21], which on treatment with 80% hydrazine hydrate in ethanol afforded the respective 2-benzoyl-phenoxy acethydrazides **3a–d**. The cyclization of **3a–d** with cyanogen bromide furnished the corresponding 2-amino 5-(2-benzoyl-phenoxymethyl) 1,3,4-oxadiazoles **4a–d** [22]. Condensation of **4a–d** with 3-bromo benzaldehyde with a drop of glacial acetic acid furnished Schiff bases, 2-(3-bromobenzylidene)amino 5-(2-benzoyl-phenoxymethyl) 1,3,4-oxadiazoles **5a–d**. The azetidin-2-one moiety in the compounds **5a–d** was introduced by the cycloaddition of chloroacetylchloride in the presence of triethylamine to give **6a–d**.

On comparing the synthesis by microwave-assisted method, with that by the conventional method, we observed that the reaction progressed very fast with excellent yield in the former. The reaction remains incomplete in the absence of solid support even after prolonged exposure to microwave radiation. Among various mineral supports examined, such as alumina, montmorillonite K10 clay, silica gel, etc., clay was found to give the best results. Hence the reactions carried out with microwave technique are superior to the reactions using conventional methods in our experiments. The time required for the progress of reactions and the yield of compounds are as shown in Table 1.

EXPERIMENTAL

Melting points were determined with Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded in Nujol on a FT-IR Shimadzu 8300 spectrophotometer and NMR spectra were recorded on a Bruker spectrophotometer in $CDCl_3$ solution. The ^1H NMR and ^{13}C NMR spectra were measured at 300 and 90 MHz, respectively. The chemical shifts are reported as parts per million relative to internal TMS. Elemental analysis results are within 0.4% of the calculated value. Chemicals were purchased from Aldrich Chemical Co. TLC was performed on preactivated (110°C) silica gel plates using ethyl acetate:chloroform (7:2) as eluent and the plates were visualized with UV light.



SCHEME 1

TABLE 1 Time Required (min) and Yield (%) of all Compounds Prepared

	Thermal		*Microwave*	
	Time	*Yield*	*Time*	*Yield*
2a	480	80	8	90
2b	450	79	9	85
2c	480	70	8	78
2d	510	72	9	80
4a	480	74	10	82
4b	450	72	12	80
4c	450	70	12	77
4d	480	71	10	78
5a	360	70	5	80
5b	390	71	8	85
5c	390	71	8	85
5d	360	73	5	86
6a	300	60	8	70
6b	330	62	10	75
6c	330	63	10	74
6d	300	60	9	71

General Procedure for **2a–d**

Thermal Method. A mixture of **1a** (5 g, 0.02 mol) and ethyl chloroacetate (2.4 g, 0.02 mol) in dry acetone (60 ml) and anhydrous potassium carbonate (2.8 g, 0.02 mol) was refluxed for 8 h, then cooled, and the solvent removed under reduced pressure. The residual mass was triturated with ice water to remove potassium carbonate and extracted with ether (3 × 50 ml). The ether layer was then washed with 10% sodium hydroxide solution (3 × 30 ml) followed by water (3 × 30 ml) and then dried over anhydrous sodium sulphate and evaporated to dryness to get crude solid, which on recrystallization with ethanol gave **2a**. Yield 5.39 g (80%).

Microwave Irradiation Method. In a typical procedure, a mixture of **1a** (1 g, 4 mmol) and ethyl chloroacetate (0.48 g, 4 mmol) was thoroughly mixed with clay (1:3 w/w) in the solid state, using a vortex mixer, and subjected to microwave irradiation operating at 40% power for 8 min. After conventional work-up, this was followed by recrystallization with ethanol. A white solid of **2a** was obtained.

2a: mp 60–62°C; IR (Nujol): 1670 (C═O), 1735 cm^{-1} (ester, C═O); ^{1}H NMR ($CDCl_3$): δ 1.2 (t, J = 7 Hz, 3H, CH_3 of ester), 2.3 (s, 3H, CH_3), 4.2 (q, J = 6 Hz, 2H, CH_2 of ester), 4.45 (s, 2H, CH_2), 7.2–7.6 (m, 7H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 13.6 (q), 20.9 (q), 59.5 (t), 75.6 (t), 113.7 (d), 123.3 (s), 128.2 (d), 129.61 (d), 129.7 (s), 130.5 (d), 131.8 (d), 132.6 (d), 133.5 (s), 139.2 (s), 133.9 (d), 160.6 (s), 171.0 (s), 187.0 (s), Anal. Calcd for $C_{18}H_{17}O_4Cl$ (332.5): C, 64.96; H, 5.11; Cl, 10.67%. Found: C, 64.94; H, 5.07; Cl, 10.64%.

2b: mp 65–67°C; IR (Nujol): 1672 (C═O), 1738 cm^{-1} (ester, C═O); ^{1}H NMR ($CDCl_3$): δ 1.21 (t, J = 7 Hz, 3H, CH_3 of ester), 4.23 (q, J = 6 Hz, 2H, CH_2 of ester), 4.5 (s, 2H, CH_2), 7.2–7.75 (m, 8H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 13.62 (q), 59.52 (t), 75.61 (t), 115.2 (d), 124.8 (s), 125.8 (s), 128.22 (d), 130.1 (d), 131.5 (d), 132.21 (d), 133.6 (d), 137.8 (s), 161.7 (s), 171.8 (s), 187.03 (s). Anal. Calcd for $C_{17}H_{15}ClO_4$ (318.5): C, 64.05; H, 4.70; Cl, 11.14%. Found: C, 64.02; H, 4.67; Cl, 11.11%.

2c: mp 69–71°C; IR (Nujol): 1672 (C═O), 1736 cm^{-1} (ester, C═O); ^{1}H NMR ($CDCl_3$): δ 1.2 (t, J = 7 Hz, 3H, CH_3 of ester), 4.22 (q, J = 6 Hz, 2H, CH_2 of ester), 4.45 (s, 2H, CH_2), 7.22–7.8 (m, 8H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 13.61 (q), 59.51 (t), 75.61 (t), 117.1 (d), 122.4 (s), 123.8 (d), 127.8 (s), 128.21 (d), 130.1 (d), 132.2 (d), 133.3 (d), 137.8 (s), 165.8 (s), 171.0 (s), 187.03 (s). Anal. Calcd for $C_{17}H_{15}BrO_4$ (363): C, 56.19; H, 4.13; Br, 22.03%. Found: C, 56.17; H, 4.10; Br, 22.0%.

2d: mp 58–60°C; IR (Nujol): 1660 (C═O), 1730 cm^{-1} (ester, C═O); ^{1}H NMR ($CDCl_3$): δ 1.2 (t, J = 7 Hz, 3H, CH_3 of ester), 2.25 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 4.2 (q, J = 6 Hz, 2H, CH_2 of ester), 4.42 (s, 2H, CH_2), 7.0–7.6 (m, 7H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 13.63 (q), 20.92 (q), 56.0 (q), 59.53 (t), 75.6 (t), 113.71 (d), 113.8 (d), 123.32 (s), 129.7 (s), 130.1 (s), 131.1 (d), 131.81 (d), 133.91 (d), 160.62 (s), 165.7 (s), 171.02 (s), 187.04 (s). Anal. Calcd for $C_{19}H_{20}O_5$(328): C, 69.51; H, 6.09%. Found: C, 69.49; H, 6.05%.

General Procedure for **3a–d**

In a typical procedure, 80% hydrazine hydrate (0.3 g, 6 mmol) was added in drops to **2a** (2 g, 6 mmol) in methanol (10 ml), and stirred for 1 h at room temperature. A white solid separated, which on recrystallization with ethanol gave **3a**. Yield 1.43 g (75%).

3a: mp 177–180°C; IR (Nujol): 1620 (C═O), 1655 (amide, C═O), 3110–3215 cm^{-1} (NH—NH_2); ^{1}H NMR ($CDCl_3$): δ 2.3 (s, 3H, CH_3), 3.7 (bs, 2H, NH_2), 4.5 (s, 2H, CH_2), 7.1–7.6 (m, 7H, Ar—H), 9.25 (bs, 1H, CONH); ^{13}C NMR ($CDCl_3$): δ 20.91 (q), 78.0 (t), 113.7 (d), 123.3 (s), 128.21 (d), 129.62 (d), 129.7 (s), 130.5 (d), 131.8 (d), 132.6 (d), 133.51 (s), 133.9 (d), 139.2 (d), 160.6 (s), 170.3 (s), 187.0 (s). Anal. Calcd for $C_{16}H_{15}ClN_2O_3$ (318.5): C, 60.28; H, 4.70; Cl, 11.14; N, 8.79%. Found: C, 60.24; H, 4.67; Cl, 11.10; N, 8.75%.

3b: mp 181–183°C; IR (Nujol): 1630 (C═O), 1668 (amide, C═O), 3120–3223 cm^{-1} (NH—NH_2); ^{1}H NMR ($CDCl_3$): δ 3.72 (bs, 2H, NH_2), 4.55 (s, 2H, CH_2), 7.15–7.75 (m, 8H, Ar—H), 9.35 (bs, 1H, CONH); ^{13}C NMR ($CDCl_3$): δ 78.01 (t), 115.2 (d), 124.8 (s), 125.8 (s), 128.21 (d), 130.1 (d), 131.51 (d), 132.62 (d), 133.61 (d), 137.81 (s), 161.7 (s), 170.31 (s), 187.03 (s). Anal.

Calcd for $C_{15}H_{13}ClN_2O_3$(304.5): C, 59.11; H, 4.26; Cl, 11.65; N, 9.19%. Found: C, 59.12; H, 4.24; Cl, 11.67; N, 9.17%.

3c: mp 182–185°C; IR (Nujol): 1625 (C=O), 1670 (amide, C=O), 3115–3220 cm^{-1} (NH—NH_2); ^1H NMR ($CDCl_3$): δ 3.72 (bs, 2H, NH_2), 4.6 (s, 2H, CH_2), 7.15–7.76 (m, 8H, Ar—H), 9.35 (bs, 1H, CONH); ^{13}C NMR ($CDCl_3$): δ 78.01 (t), 117.1 (d), 122.4 (s), 123.8 (d), 127.8 (s), 128.2 (d), 130.1 (d), 132.2 (d), 133.3 (d), 137.8 (s), 165.8 (s), 170.3 (s), 187.03 (s). Anal. Calcd for $C_{15}H_{13}BrN_2O_3$ (349): C, 51.57; H, 3.72; Br, 23.92; N, 8.02%. Found: C, 51.54; H, 3.70; Br, 23.89; N, 8.0%.

3d: mp 175–177°C; IR (Nujol): 1610 (C=O), 1645 (amide, C=O), 3100–3205 cm^{-1} (NH—NH_2); ^1H NMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 3.5 (bs, 2H, NH_2), 3.9 (s, 3H, OCH_3), 4.55 (s, 2H, CH_2), 7.2–7.9 (m, 7H, Ar—H), 9.4 (bs, 1H, CONH); ^{13}C NMR ($CDCl_3$): δ 20.92 (q), 56.0 (q), 78.02 (t), 113.72 (d), 113.82 (d), 129.6 (d), 129.72 (s), 130.1 (s), 131.1 (d), 131.8 (d), 133.9 (d), 160.62 (s), 165.7 (s), 170.3 (s), 187.04 (s). Anal. Calcd for $C_{17}H_{18}N_2O_4$ (314): C, 64.96; H, 5.73; N, 8.91%. Found: C, 64.94; H, 5.70; N, 8.89%.

General Procedure for **4a–d**

Thermal Method. A mixture of **3a** (1.5 g, 4.7 mmol) and cyanogen bromide (0.73 g, 0.070 mol) in ethanol (20 ml) was refluxed for 8 h. The cooled reaction mixture was neutralized with sodium bicarbonate solution and poured onto crushed ice. The solid product was isolated, and on recrystallization with DMF gave **4a**. Yield 0.39 g (74%).

Microwave Irradiation Method. A mixture of **3a** (1.5 g, 4.7 mmol) and cyanogen bromide (0.73 g, 0.070 mol) was thoroughly mixed with clay (1:3 w/w) in the solid state, using a vortex mixer. The mixture was transferred into a tube and sealed (to prevent gases affecting the inside of the oven). The tube was subjected to microwave irradiation operating at 60% power for 10 min, and after conventional work-up, was followed by recrystallization with DMF. A white solid of **4a** was obtained.

4a: mp 120–122°C; IR (Nujol): 1160 (C—O—C linkage), 1625 (C=O), 1670 (C=N), 3110 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$): 2.2 (s, 3H, CH_3), 3.33 (bs, 2H, NH_2), 5.0 (s, 2H, CH_2), 7.3–7.9 (m, 7H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 20.9 (q), 72.0 (t), 113.7 (d), 123.3 (s), 128.2 (d), 129.6 (d), 129.7 (s), 130.5 (d), 131.8 (d), 132.61 (d), 133.5 (s), 139.2 (s), 133.9 (d), 157.17 (s), 160.6 (s), 163.21 (s), 187.0 (s). Anal. Calcd for $C_{17}H_{14}ClN_3O_3$(343.5): C, 59.38; H, 4.07; Cl, 10.33; N, 12.22%. Found: C, 59.36; H, 4.09; Cl, 10.30; N, 12.19%.

4b: mp 124–126°C; IR (Nujol): 1170 (C—O—C linkage), 1640 (C=O), 1680 (C=N), 3115 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$): δ 3.36 (bs, 2H, NH_2), 5.12 (s, 2H, CH_2), 7.35–7.9 (m, 8H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 72.01 (t), 113.71 (d), 123.32 (s), 128.22 (d), 129.71 (s), 130.12 (d), 131.81 (d), 132.2 (d), 133.91 (d), 137.8 (s), 157.51 (s), 160.6 (s), 163.6 (s), 187.03 (s). Anal. Calcd for $C_{16}H_{12}ClN_3O_3$ (329.5): C, 58.27; H, 3.64; Cl, 10.77; N, 12.74%. Found: C, 58.29; H, 3.62; Cl, 10.79; N, 12.76%.

4c: mp 129–131°C; IR (Nujol): 1175 (C—O—C linkage), 1645 (C=O), 1685 (C=N), 3120 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$): δ 3.35 (bs, 2H, NH_2), 5.11 (s, 2H, CH_2), 7.35–7.9 (m, 8H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 72.01 (t), 112.8 (d), 123.8 (d), 125.7 (s), 126.7 (s), 130.11 (d), 132.82 (d), 135.22 (d), 137.98 (s), 157.32 (s), 163.4 (s), 165.6 (s), 187.03 (s). Anal. Calcd for $C_{16}H_{12}BrN_3O_3$ (374): C, 51.33; H, 3.20; Br, 21.39; N, 11.22%. Found: C, 51.30; H, 3.22; Br, 21.37; N, 11.25%.

4d: mp 135–137°C; IR (Nujol): 1180 (C—O—C linkage), 1650 (C=O), 1688 (C=N), 3124 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$): δ 2.3 (s, 3H, CH_3), 3.37 (bs, 2H, NH_2), 3.75 (s, 3H, OCH_3), 5.2 (s, 2H, CH_2), 7.37–7.95 (m, 7H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 20.92 (q), 56.0 (q), 72.02 (t), 113.72 (d), 113.8 (d), 123.31 (s), 129.72 (s), 130.1 (s), 131.1 (d), 131.82 (d), 133.9 (d), 157.6 (s), 160.61 (s), 163.8 (s), 165.7 (s), 187.04 (s). Anal. Calcd for $C_{18}H_{17}N_3O_4$(339): C, 63.71; H, 5.01; N, 12.38%. Found: C, 63.68; H, 5.04; N, 12.36%.

General Procedure for **5a–d**

Thermal Method. A mixture of **4a** (0.5 g, 1.42 mmol), 3-bromo benzaldehyde (0.26 g, 1.42 mmol), and a drop of glacial acetic acid were refluxed in methanol (30 ml) for about 6 h. The solvent was distilled off at reduced pressure and the solid mass thus obtained was recrystallized from a chloroform:benzene mixture to afford **5a**. Yield 0.364 g (70%).

Microwave Irradiation Method. A mixture of **4a** (0.5 g, 1.42 mmol), 3-bromo benzaldehyde (0.26 g, 1.42 mmol), and a drop of glacial acetic acid was thoroughly mixed with clay (1:3 w/w) in the solid state, using a vortex mixer, and subjected to microwave irradiation operating at 50% power for 5 min. After conventional work-up, this was followed by recrystallization with DMF. A white solid of **5a** was obtained.

5a: mp 150–152°C; IR (Nujol): 1130 (C—O—C linkage), 1580 (—N=CH), 1600 (C=N), 1665 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 5.12 (s, 2H, CH_2), 6.8–7.8 (m, 11H, Ar—H), 8.1 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$): δ 20.9 (q), 72.0 (t), 113.7 (d), 123.2 (s), 123.3 (s), 128.0 (d), 128.2 (d), 129.6 (d), 129.7 (s),

130.5 (d), 130.8 (d), 131.8 (d), 132.3 (d), 132.6 (d), 133.41 (d), 133.5 (s), 133.91 (d), 134.1 (d), 139.2 (s), 157.20 (s), 160.6 (s), 163.26 (s), 163.7 (d), 187.0 (s). Anal. Calcd for $C_{24}H_{17}BrCl\,N_3O_3$ (510.5): C, 56.47; H, 3.33; Br, 15.67; Cl, 6.95; N, 8.22%. Found: C, 56.45; H, 3.35; Br, 15.69; Cl, 6.93; N, 8.24%.

5b: mp 157–159°C; IR (Nujol): 1135 (C—O—C linkage), 1590 (—N=CH), 1610 (C=N), 1670 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 5.15 (s, 2H, CH_2), 6.85–7.85 (m, 12H, Ar—H), 8.12 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$): δ 72.02 (t), 115.2 (d), 123.21 (s), 124.8 (s), 125.8 (s), 128.02 (d), 128.2 (d), 130.1 (d), 130.8 (d), 131.5 (d), 132.2 (d), 132.3 (d), 133.43 (s), 133.6 (d), 134.13 (d), 137.8 (s), 157.55 (s), 161.7 (s), 163.66 (s), 163.7 (d), 187.02 (s). Anal. Calcd for $C_{23}H_{15}BrCl\,N_3O_3$ (496.5): C, 55.58; H, 3.02; Br, 16.11; Cl, 7.15; N, 8.45%. Found: C, 55.55; H, 3.05; Br, 16.14; Cl, 7.17; N, 8.48%.

5c: mp 160–162°C; IR (Nujol): 1140 (C—O—C linkage), 1586 (—N=CH), 1605 (C=N), 1668 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 5.13 (s, 2H, CH_2), 6.82–7.85 (m, 12H, Ar—H), 8.12 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$): δ 72.01 (t), 112.8 (d), 123.21 (s), 123.8 (d), 125.7 (s), 126.7 (s), 128.01 (d), 128.2 (d), 130.1 (d), 130.8 (d), 132.21 (d), 132.31 (d), 133.42 (s), 134.12 (d), 135.4 (d), 137.8 (s), 157.38 (s), 163.7 (d), 163.48 (s), 165.8 (s), 187.01 (s). Anal. Calcd for $C_{23}H_{15}Br_2N_3O_3$ (541): C, 51.01; H, 2.77; Br, 29.57; N, 7.76%. Found: C, 51.04; H, 2.75; Br, 29.59; N, 7.74%.

5d: mp 153–155°C; IR (Nujol): 1142 (C—O—C linkage), 1588 (—N=CH), 1612 (C=N), 1672 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 2.21 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 5.21 (s, 2H, CH_2), 6.85–7.86 (m, 11H, Ar—H), 8.13 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$): δ 20.91 (q), 56.02 (q), 72.02 (t), 113.71 (d), 113.8 (d), 123.22 (s), 123.3 (s), 128.03 (d), 129.72 (s), 130.1 (s), 130.8 (d), 131.1 (d), 131.82 (d), 132.32 (d), 133.44 (s), 133.93 (d), 134.14 (d), 157.65 (s), 160.62 (s), 163.7 (d), 163.84 (s), 165.7 (s), 187.04 (s). Anal. Calcd for $C_{25}H_{20}BrN_3O_4$(506): C, 59.28; H, 3.95; Br, 15.81; N, 8.3%. Found: C, 59.26; H, 3.92; Br, 15.83; N, 8.32%.

General Procedure for **6a–d**

Thermal Method. To a stirred solution of compound **5a** (0.51 g, 1 mmol) and triethylamine (0.12 g, 1.2 mmol) in 1,4 dioxane (10 ml), chloroacetylchloride (0.135 g, 1.2 mmol) was added drop wise at 0–5°C. The reaction mixture was stirred for about 1 h and the precipitated amine hydrochloride was filtered off. The filtrate was refluxed for about 5 h and the separated solid was crystallized from methanol to give **6a**. Yield 0.35 g (60%).

Microwave Irradiation Method. To a stirred solution of compound **5a** (0.51 g, 1 mmol) and triethyl amine (0.12 g, 1.2 mmol) in 1,4 dioxane (20 ml), chloroacetylchloride (0.135 g, 1.2 mmol) was added drop wise at 0–5°C. The reaction mixture was stirred for about 1 h and the precipitated amine hydrochloride was filtered off. From reaction mixture, solvent was removed under reduced pressure and the solid was thoroughly mixed with clay (1:3 w/w) in the solid state, using a vortex mixer. Finally, it was subjected to microwave irradiation operating at 50% power for 8 min. After conventional work-up, this was followed by recrystallization with DMF. A white solid of **6a** was obtained.

6a: mp 203–205°C; IR (Nujol): 1135 (C—O—C linkage), 1605 (C=N), 1668 (C=O), 1748 (β-lactam C=O); ^{1}H NMR ($CDCl_3$): δ 2.22 (s, 3H, CH_3), 4.83 (d, J = 7 Hz, 1H, N=CH), 5.2 (s, 2H, CH_2), 5.4 (d, J = 7 Hz, 1H, CHCl), 6.71–7.82 (m, 11H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 20.9 (q), 62.0 (d), 62.1 (d), 72.0 (t), 113.7 (d), 122.9 (s), 123.3 (s), 126.11 (d), 128.21 (d), 129.6 (d), 129.7 (s), 129.8 (d), 130.4 (d), 130.5 (d), 131.8 (d), 132.6 (d), 133.5 (s), 133.9 (d), 139.2 (s), 144.8 (s), 157.22 (s), 160.6 (s), 161.4 (s), 163.29 (s), 187.0 (s). Anal. Calcd for $C_{26}H_{18}BrCl_2\,N_3O_4$ (587): C, 53.15; H, 3.06; Br, 13.62; Cl, 12.09; N, 7.15%. Found: C, 53.17; H, 3.04; Br, 13.65; Cl, 12.06; N, 7.12%.

6b: mp 209–211°C; IR (Nujol): 1138 (C—O—C linkage), 1612 (C=N), 1672 (C=O), 1750 (β-lactam C=O); ^{1}H NMR ($CDCl_3$): δ 4.86 (d, J = 7 Hz, 1H, N—CH), 5.21 (s, 2H, CH_2), 5.41 (d, J = 7 Hz, 1H, CHCl), 6.75–7.86 (m, 12H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 62.01 (d), 62.11 (d), 72.02 (t), 115.2 (d), 122.91 (s), 124.8 (s), 125.81 (s), 126.12 (d), 128.21 (d), 129.81 (d), 130.1 (d), 130.4 (d), 130.5 (d), 131.5 (d), 132.2 (d), 133.6 (d), 137.8 (s), 144.61 (s), 157.58 (s), 161.41 (s), 161.7 (s), 163.69 (s), 187.01 (s). Anal. Calcd for $C_{25}H_{16}BrCl_2\,N_3O_4$ (573): C, 52.35; H, 2.79; Br, 13.96; Cl, 12.39; N, 7.32%. Found: C, 52.37; H, 2.77; Br, 13.94; Cl, 12.40; N, 7.35%.

6c: mp 212–214°C; IR (Nujol): 1144 (C—O—C linkage), 1608 (C=N), 1670 (C=O), 1748 (β-lactam C=O); ^{1}H NMR ($CDCl_3$): δ 4.88 (d, J = 7 Hz, 1H, N—CH), 5.21 (s, 2H, CH_2), 5.41 (d, J = 7 Hz, 1H, CHCl), 6.72–7.86 (m, 12H, Ar—H); ^{13}C NMR ($CDCl_3$): δ 62.01 (d), 62.11 (d), 72.01 (t), 112.8 (d), 122.91 (s), 123.8 (d), 125.7 (s), 126.12 (d), 126.7 (s), 128.23 (d), 129.8 (d), 130.1 (d), 130.4 (d), 130.5 (d), 132.2 (d), 135.4 (d), 137.8 (s), 144.8 (s), 157.4 (s), 161.4 (s), 163.6 (s), 165.8 (s), 187.02 (s). Anal. Calcd for $C_{25}H_{16}Br_2ClN_3O_4$ (617.5): C, 48.58; H, 2.59; Br, 25.91; Cl, 5.74; N, 6.80%. Found: C, 48.56; H, 2.57; Br, 25.93; Cl, 5.77; N, 6.83%.

6d: mp 217–219°C; IR (Nujol): 1145 (C—O—C linkage), 1610 (C=N), 1675 (C=O), 1752 (β-lactam

C=O); ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.9 (d, J = 7 Hz, 1H, N–CH), 5.22 (s, 2H, CH_2), 5.42 (d, J = 7 Hz, 1H, CHCl), 6.8–7.88 (m, 11H, Ar–H); ^{13}C NMR ($CDCl_3$): δ 20.92 (q), 56.01 (q), 62.02 (d), 62.12 (d), 72.03 (t), 113.7 (d), 113.8 (d), 122.92 (s), 123.33 (s), 126.13 (d), 129.7 (s), 129.8 (d), 130.1 (s), 130.4 (d), 130.5 (d), 131.1 (d), 131.82 (d), 133.93 (d), 144.6 (s), 157.41 (s), 160.63 (s), 161.42 (s), 163.66 (s), 165.7 (s), 187.04 (s). Anal. Calcd for $C_{27}H_{21}BrClN_3O_5$ (582.5): C, 55.62; H, 3.60; Br, 13.73; Cl, 6.09; N, 7.21%. Found: C, 55.60; H, 3.62; Br, 13.72; Cl, 6.07; N, 7.19%.

CONCLUSION

In conclusion, we have developed a highly efficient microwave-induced procedure for the preparation of various substituted 2-amino 5-(2-benzoyl-phenoxymethyl) 1,3,4-oxadiazoles and their azetidin-2-one derivatives, that occurs remarkably fast, under mild conditions, using inexpensive reagents, and a household microwave oven as the irradiation source. The eco-friendly advantages of these solvent-free protocols can be found in instances where catalytic amounts of supported agents are used, since they provide reduction of solvents, thus preventing pollution "at source." The reaction rate enhancements achieved in these methods may be ascribed to nonthermal effects. The rationalization of microwave effects and mechanistic considerations possibly involve the intermediacy of polar transition states which couple to microwaves more readily.

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