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An efficient and green synthesis of novel benzoxazole under ultrasound irradiation

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ABSTRACT

Ultrasound as green process and an alternative energy source was investigated for the environmentally benign synthesis of novel benzoxazoles from different azo-linked salicylic acid derivatives and 2-amino-4-chlorophenol in short reaction time and high yield. These benzoxazole compounds have been characterized by elemental analysis, FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy.

1. Introduction

Oxazole containing ring systems occur in many natural products and it is well known that benzoxazole derivatives act as diverse medicinal mediators, such as antimicrobial [1], Alzheimer's disease [2], Rho kinase [3], antitumor [4], anti-inflammatory, fungicides, adrenergic antagonists, anti-hypertensive, anti-ulcer, leukotriene A4 hydrolase [5] and fatty acid amide hydrolase [6]. In recent times it has been observed that oxazole containing compounds are investigated thoroughly for cancer and anti-HIV-1 agents [7,8], leukemia, and potent selective 5-HT1A serotonin receptor ligands [9] and some other noticeable activities [10–13].

2-Substituted benzoxazoles are generally prepared by condensation of *o*-aminophenol and carboxylic acids [14] or derivatives of acyl halides and bromoanilines [15]. *N*-benzoylo-chloroaniline is transformed to 2-phenylbenzoxazole by potassium amide in liquid nitrogen [16]. Benzoxazoles can be prepared from *o*-chlorocarboxylic acid esters and o-aminophenol in good yields [17].

On the other hand, in comparison with conventional thermal heating, ultrasound irradiation have some important advantages: improved yields, substantial decreases of reaction time, increased selectivity, lower costs and simplicity in handling and processing and high purity of the compounds. At the same time, in many cases, reactions under ultrasound irradiation could be considered environmentally friendly processes, using small amounts of solvents and being less energy consumer [18]. So ultrasonic irradiation provides minimal side reactions [19].

2. Material and methods

2.1. Apparatus and analysis

For the ultrasound reactions, ultrasound apparatus astra 3D (9.5 dm^3, 45 kHz frequency, input power with heating, 305 W, number of transducers, 2) from TECNO-GAZ and EUROSONIC 4D ultrasound cleaner with a frequency of 50 kHz and an output power of 200 W were used. Chemicals were purchased from Merck and Fluka and used as purchased. Melting points were measured on an Electro-thermal 9100 apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Bruker DRX 500Avance spectrometer in DMSO-d_6 as solvent and with TMS as internal standard. FT-IR spectra were recorded on a Shimadzu FT-IR-8400S spectrometer. Elemental analyses were recorded on a Carlo-Erba EA1110CNNO-S analyzer.

2.2. General procedure for the synthesis of benzoxazole

A mixture of azo-linked salicylic acids (1 mmol: 0.29 g of acid **1a**, 0.24 g of acid **1b**, 0.32 g of acid **1c**, 0.32 g of acid **1d**, 0.33 g of acid **1e**, 0.34 g of acid **1f**, 0.27 g of acid **1g**, 0.30 g of acid **1h**, 0.28 g of acid **1i**, 0.28 g of acid **1j**), 2-amino-4-chlorophenol (1 mmol: 1.14 g) and 10 mL EtOH were placed into Pyrex-glass open vessel and irradiated in a water bath under silent condition by ultrasound (45 kHz) at room temperature for the required reaction times (10–30 min). The progress of the reaction was monitored by Thin Layer Chromatography (TLC) (EtOAc: petroleum ether 1:2). Then the reaction mixture was filtered to separate the

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product and recrystallized from EtOH. The pure products were collected in 90–96% yields.

*2.2.1. (E)-4-(2-(4-nitrophenyl)diazenyl)-2-(5-chlorobenzo[d]oxazol-2-yl)phenol **3a***

brown solid, mp 273–275 °C, IR (KBr, cm^{-1}) ν_{max} 3486, 1703, 1616, 1527, 1343 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H; 6.69 (dd, J = 8.4 Hz, J = 2 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.69 (s, 1H), 8.1 (d, J = 8.4 Hz, 1H), 8.43 (d, J = 8.4 Hz, 1H), 8.66 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C; 106.4, 110.7, 119.8, 120.4, 120.4, 122.9, 124.0, 125.3, 129.0, 131.9, 138.8, 145.9, 147.4, 150.5, 158.7, 159.9, 172.7 ppm. Anal. Calcd. for $C_{19}H_{11}ClN_4O_4$: C, 57.81; H, 2.81; N, 14.19. Found: C, 57.73; H, 2.89; N, 14.08.

*2.2.2. (E)-4-(2-phenyldiazenyl)-2-(5-chlorobenzo[d]oxazol-2-yl) phenol **3b***

cream solid, mp 253 °C, IR (KBr, cm^{-1}) ν_{max} 3362, 1696, 1621 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H; 7.16 (dd, J = 8 Hz, J = 1.6 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.49–7.52 (m, 4H), 7.62 (s, 1H), 8.0–8.03 (m, 3H), 8.6 (s, 1H), 8.99 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C; 106.8, 110.6, 119.3, 121.1, 120.4, 122.3, 124.6, 128.8, 129.2, 130.2, 131.9, 138.8, 146.2, 147.3, 154.5, 158.8, 173.9 ppm. Anal. Calcd. for $C_{19}H_{12}ClN_3O_2$: C, 65.24; H, 3.46; N, 12.01. Found: C, 65.31; H, 3.52; N, 11.92.

*2.2.3. (E)-4-(2-(2-chloro-4-nitrophenyl)diazenyl)-2-(5-chlorobenzo [d]oxazol-2-yl)phenol **3c***

light Brown solid, mp 243–245 °C, IR (KBr, cm^{-1}) ν_{max} 3369, 1684, 1611, 1519 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H; 7.16 (d, J = 8. 4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.62 (s. 1H), 7.96 (d, J = 5.6 Hz, 1H), 8.04 (s, 1H), 8.11 (d, J = 7.2 Hz, 1H), 8.24 (dd, J = 6.8 Hz, J = 2.4 Hz, 1H), 8.56 (s, 1H), 8.91 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C; 117.2, 122.3, 106.9, 110.7, 119.2, 120.1, 120.4, 124.4, 127.6, 129.9, 130.7, 131.7, 138.8, 146.2, 147.4, 152.6, 158.8, 160.2, 173.97 ppm. Anal. Calcd. for $C_{19}H_{10}Cl_2N_4O_4$: C, 53.17; H, 2.35; N, 13.05. Found: C, 53.10; H, 2.42; N, 12.94.

*2.2.4. (E)-4-(2-(4-chloro-2-nitrophenyl)diazenyl)-2-(5-chlorobenzo [d]oxazol-2-yl)phenol **3d***

light brown solid, mp 236–238 °C, IR (KBr, cm^{-1}) ν_{max} 3476, 1664, 1606, 1572, 1523, 1347 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H; 7.16 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8 Hz, 1H), 7.62 (s, 1H), 7.89 (dd, J = 8.4 Hz, J = 2 Hz, 1H), 7.98 (s, 1H), 8.02 (d, J = 5.6 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.88 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C; 106.9, 110.7, 119.2, 120.1, 120.4, 121.8, 122.1, 128.8, 129.3, 130.7, 135.1, 135.5, 138.8, 142.7, 145.6, 146.2, 149.6, 158.8, 173.97 ppm. Anal. Calcd. for $C_{19}H_{10}Cl_2N_4O_4$: C, 53.17; H, 2.35; N, 13.05. Found: C, 53.09; H, 2.29; N, 12.95.

*2.2.5. (E)-4-(2-(2,4-dinitrophenyl)diazenyl)-2-(5-chlorobenzo[d] oxazol-2-yl)phenol **3e***

Brown solid, mp 189–191 °C, IR (KBr, cm^{-1}) ν_{max} 3298, 1632, 1605, 1585, 1525, 1348 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H; 7.16 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8 Hz, 1H), 7.62 (s, 1H), 8.02 (d, J = 7.2 Hz, 1H), 8.63–8.70 (m, 2H), 8.82 (s,1H), 8.84–8.85 (m, 1H), 8.98 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C; 106.8, 110.7, 119.2, 120.1, 120.4, 123.9, 128.7, 128.8, 129.3, 130.6, 130.9, 138.8, 142.4, 146.2, 148.8, 149.1, 152.6, 158.8, 173.97 ppm. Anal. Calcd. for $C_{19}H_{10}ClN_5O_6$: C, 51.89; H, 2.29;N, 15.93. Found: C, 51.72; H, 2.32; N, 15.85.

*2.2.6. (E)-4-(2-(2,4,5-trichlorophenyl)diazenyl)-2-(5-chlorobenzo[d] oxazol-2-yl)phenol **3f***

Brown solid, mp 278–280 °C, IR (KBr, cm^{-1}) ν_{max} 1411, 1690, 1610, 1572 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H; 7.16 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.59–7.97 (m, 2H), 8.56 (s, 1H), 8.93 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C; 106.9, 110.7, 119.2, 120.1, 120.4, 124.5, 125.7, 128.8, 131.3, 131.7, 132.3, 135.7, 136.0, 138.8, 146.2, 146.7, 156.2, 158.8, 173.97 ppm. Anal. Calcd. for $C_{19}H_9Cl_4N_3O_2$: C, 50.36; H, 2.00; N, 9.27. Found: C, 50.28; H, 1.92; N, 9.19.

*2.2.7. (E)-4-(2-(2,4-dimethylphenyl)diazenyl)-2-(5-chlorobenzo[d] oxazol-2-yl)phenol **3g***

light Brown solid, mp 210–212 °C, IR (KBr, cm^{-1}) ν_{max} 3269, 1635, 1611, 1458, 1370 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H; 2.29 (s, 3H), 2.65 (s, 3H), 7.15 (t, J = 8.8 Hz, 2H), 7.15 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H) 7.54 (t, J = 8.4 Hz, 2H), 7.62 (s, 1H), 7.98 (dd, J = 8.0 Hz, J = 2.4 Hz, 1H), 8.54 (s, 1H), 8.96 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C; 18.7, 20.7, 106.4, 110.7, 119.2, 120.1, 120.4, 125.6, 128.1, 128.3, 128.8, 130.8, 132.1, 137.1, 137.9, 138.8, 146.0, 146.3, 152.4, 158.9, 173.97 ppm. Anal. Calcd. for C_{12}-$H_{16}ClN_3O_2$: C, 66.76; H, 4.27; N, 11.12. Found: C, 66.69; H, 4.33; N, 11.05.

*2.2.8. (E)-4-(2-(2-nitrophenyl)diazenyl)-2-(5-chlorobenzo[d]oxazol-2-yl)phenol **3h***

Brown solid, mp 285–287 °C, IR (KBr, cm^{-1}) ν_{max} 3407, 1705, 1668, 1614, 1543, 1528, 1351 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H; 7.6 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.62 (s, 1H), 8.02 (d, J = 6.8 Hz, 1H), 8.13 (d, J = 7.6 Hz, 1H), 8.4 (s, 1H), 8.63 (s, 1H), 8.76 (d, J = 8.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C; 112.3, 118.8, 120.1, 125.3, 128.3, 128.5, 128.7, 129.3, 129.8, 130.8, 131.0, 132.6, 136.3, 141.7, 147.0, 147.2, 154.4, 155.2, 170.07 ppm. Anal. Calcd. for $C_{19}H_{11}ClN_4O_4$: C, 57.81; H, 2.81; N, 14.19. Found: C, 57.76; H, 2.76; N, 14.22.

*2.2.9. (E)-4-(2-mesityldiazenyl)-2-(5-chlorobenzo[d]oxazol-2-yl) phenol **3i***

Brown solid, mp 206–208 °C, IR (KBr, cm^{-1}) ν_{max} 3264, 1662, 1616, 1545, 1373 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H; 2.31 (s, 3H), 2.41 (s, 6H), 7.07 (s, 2H), 7.16 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.62 (s, 1H), 7.96 (d, J = 6.0 Hz, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.86 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C; 19.27, 19.48, 110.4, 118.9, 120.1, 128.6, 129.6, 129.9, 130.55, 130.8, 131.1, 132.3, 140.1, 140.0, 147.1, 151.3, 152.1, 154.1, 169.07 ppm. Anal. Calcd. for $C_{22}H_{18}ClN_3O_2$: C, 67.43; H, 4.63; N, 10.72. Found: C, 67.50; H, 4.69; N, 10.65.

*2.2.10. (E)-4-(2-(2-chlorophenyl)diazenyl)-2-(5-chlorobenzo[d] oxazol-2-yl)phenol **3j***

brown solid, mp 239–241 °C, IR (KBr, cm^{-1}) ν_{max} 3417, 1688, 1611, 1575 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ_H; 7.16 (t, J = 8.4 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.49–7.54 (m, 3H), 7.62 (s, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.96 (d, J = 6.4 Hz, 1H), 8.56 (s, 1H), 8.87 (d, J = 2.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C; 110.4, 118.9, 120.1, 125.4, 126.8, 127.5, 128.7, 129.3, 129.6, 129.9, 130.7, 130.8, 130.9, 132.3, 147.4, 153.1, 153.6, 154.5, 169.77 ppm. Anal. Calcd. for $C_{19}H_{11}Cl_2N_3O_2$: C, 59.39; H, 2.89; N, 10.94. Found: C, 59.43; H, 2.94; N, 11.00.