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SHORT COMMUNICATIONS

Efficient Synthesis of 1,4-Bis(5-aryl-1,3,4-oxadiazol-2-yl)-2,3,5,6-tetrafluorobenzenes

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Abstract—An efficient acid-catalyzed condensation between substituted benzohydrazides and 2,3,5,6-tetrafluoroterephthalic acid to form 1,4-bis(5-aryl-1,3,4-oxadiazol-2-yl)-2,3,5,6-tetrafluorobenzenes is reported. The products were isolated in 74–87% yield and were characterized by ^{1}H NMR, IR, and mass spectra.

Keywords: 2,3,5,6-tetrafluoroterephthalic acid, substituted benzohydrazides, phosphoryl chloride, cyclization

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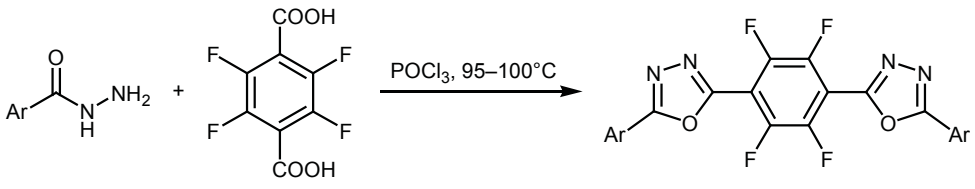
Heterocyclic compounds attract synthetic chemists due to their pharmacological and industrial applications. Among privileged structures, oxadiazole derivatives containing C=N and C–O–C bonds showed various important pharmacological activities such as antimicrobial [1], anticancer [2], antibacterial [3], anticonvulsant [4], antidepressant [5], antifungal [6], analgesic [7], anti-inflammatory [8], antioxidant [9], antitumor [10], etc. The literature survey revealed different methodologies used for the synthesis of oxadiazoles, including Deoxo-Fluor-mediated synthesis [11], visible light-promoted synthesis [12], microwave-assisted solvent-free reaction [13], anodic cyclization [14], cyclizations in the presence of polymer-supported dehydration reagent [15], TsCl and base [16], palladium complex [17], and Al^{3+}K10 clay [18]; the cyclizations were carried out in water [19], in the absence of transition metals [20], and with the system NaOH–DMSO [21].

In view of the aforesaid, we decided to synthesize fluorinated oxadiazoles by a conventional method, condensation of substituted benzohydrazides **1a**–**1l** and 2,3,5,6-tetrafluoroterephthalic acid (**2**) in the presence of a dehydrating and cyclizing agent, phosphoryl chloride (Scheme 1). Initial hydrazides **1a**–**1l** were prepared by hydrazinolysis of the corresponding ethyl esters which were obtained by esterification of substituted benzoic acids. Fluorinated 1,4-bis(5-aryl-1,3,4-oxadiazole-2-yl)benzenes **3a**–**3l** derivatives were isolated in 74–87% yield and were characterized by ^{1}H and ^{13}C NMR, IR, and mass spectra. The ^{1}H NMR spectra of **3a**–**3l** lacked hydrazide NH proton signals at

Scheme 1.



1a–1l **2** **3a–3l**

Ar = Ph (**a**), 4-$O_2NC_6H_4$ (**b**), 3-$O_2NC_6H_4$ (**c**), 4-ClC_6H_4 (**d**), 2-ClC_6H_4 (**e**), 4-$H_2NC_6H_4$ (**f**), 4-$MeOC_6H_4$ (**g**), 4-MeC_6H_4 (**h**), 4-HOC_6H_4 (**i**), 3-HOC_6H_4 (**j**), pyridin-4-yl (**k**), pyridin-3-yl (**l**).

δ 4.67 (NH_2) and 10.09 ppm (NH), and multiplets in the region δ 7.05–9.00 ppm were observed for aromatic protons. The IR spectra of **3a**–**3l** showed a band at 1600 cm^{-1} due to C=N stretching vibrations, which confirmed formation of oxadiazole ring. The band at ~1172 cm^{-1} was assigned to the C–F bonds, and the band at 1081 cm^{-1}, to C–O–C stretching of the oxadiazole ring.

In summary, a series of 1,4-bis(5-aryl-1,3,4-oxadiazole-2-yl)-2,3,5,6-tetrafluorobenzenes were synthesized by a conventional method from substituted aromatic acid hydrazides and 2,3,5,6-tetrafluoroterephthalic acid in the presence of phosphoryl chloride.

Hydrazides 1a–1l (*general procedure*). A clean and dry 250-mL round-bottom flask was charged with 5 g of the corresponding ethyl ester and 50 mL of ethanol, and 5 g of hydrazine hydrate was added dropwise with stirring at room temperature over a period of 15 min. The mixture was then refluxed for 5 h (TLC) and concentrated, and the solid product was filtered off and recrystallized from methanol.

1,4-Bis(5-aryl-1,3,4-oxadiazole-2-yl)-2,3,5,6-tetrafluorobenzenes 3a–3l (*general procedure*). A mixture of hydrazide **1a**–**1l** (2 mmol) and 2,3,5,6-tetrafluoroterephthalic acid (**2**) (1 mmol) in 5 mL of phosphoryl chloride was refluxed in a 25-mL round-bottom flask until the reaction was complete (TLC). The mixture was cooled to room temperature, poured into 50 mL of ice water with stirring, and neutralized. The solid product was filtered off, washed with water, and recrystallized from ethanol.

2,2′-(2,3,5,6-Tetrafluorobenzene-1,4-diyl)bis-(5-phenyl-1,3,4-oxadiazole) (3a). Yield 83%, mp 231°C. IR spectrum, ν, cm^{-1}: 1610 (C=N), 1081 (C–O–C), 1172 (C–F), 1545 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 7.5 d (2H, *J* = 7.24 Hz), 7.72 d.d (4H, *J* = 7.24, 7.32 Hz), 8.09 d (4H, *J* = 7.32 Hz). Mass spectrum: *m*/*z*: 439 $[M]^+$.

2,2′-(2,3,5,6-Tetrafluorobenzene-1,4-diyl)bis-[5-(4-nitrophenyl)-1,3,4-oxadiazole] (3b). Yield 87%, mp 220°C. IR spectrum, ν, cm^{-1}: 1637 (C=N), 1039 (C–O–C), 1179 (C–F), 1449 (C=C_{arom}).

2,2′-(2,3,5,6-Tetrafluorobenzene-1,4-diyl)bis-[5-(3-nitrophenyl)-1,3,4-oxadiazole] (3c). Yield 85%, mp 251°C. IR spectrum, ν, cm^{-1}: 1614 (C=N), 1060 (C–O–C), 1159 (C–F), 1526 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 7.96 d.d (2H, *J* = 7.88, 8.04 Hz), 8.14 d (2H, *J* = 7.88 Hz), 8.53 d (2H, *J* = 8.04 Hz), 8.82 s (2H).

2,2′-(2,3,5,6-Tetrafluorobenzene-1,4-diyl)bis-[5-(4-chlorophenyl)-1,3,4-oxadiazole] (3d). Yield 83%, mp 120°C. IR spectrum, ν, cm^{-1}: 1643 (C=N), 1075 (C–O–C), 1190 (C–F), 796 (C–Cl), 1597 (C=C_{arom}). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.72 d (4H, *J* = 8.64 Hz), 8.09–8.17 d (4H, *J* = 8.64 Hz). Mass spectrum: *m*/*z*: 506 $[M]^+$.

2,2′-(2,3,5,6-Tetrafluorobenzene-1,4-diyl)bis-[5-(2-chlorophenyl)-1,3,4-oxadiazole] (3e). Yield 74%, mp 148°C. IR spectrum, ν, cm^{-1}: 1648 (C=N), 1066 (C–O–C), 1162 (C–F), 1537 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 7.51 d.d (2H, *J* = 8.24, 8.00 Hz), 7.74 d (2H, *J* = 8.24 Hz), 7.99 d (2H, *J* = 8.00 Hz), 8.21 s (2H).

4,4′-[(2,3,5,6-Tetrafluorobenzene-1,4-diyl)bis-(1,3,4-oxadiazole-5,2-diyl)]dianiline (3f). Yield 82%, mp 191°C. IR spectrum, ν, cm^{-1}: 1597 (C=N), 1063 (C–O–C), 1108 (C–F), 3327 (NH_2), 1488 (C=C_{arom}). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.51 s (4H, NH_2), 7.4 d (4H, *J* = 7.28 Hz), 7.96 d (4H, *J* = 7.28 Hz).

2,2′-(2,3,5,6-Tetrafluorobenzene-1,4-diyl)bis-[5-(4-methoxyphenyl)-1,3,4-oxadiazole] (3g). Yield 81%, mp 151°C. IR spectrum, ν, cm^{-1}: 1645 (C=N), 1124 (C–O–C), 1164 (C–F), 1523 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 3.89 s (6H, OCH_3), 7.01 d (4H, *J* = 7.2 Hz), 7.04 d (4H, *J* = 7.2 Hz).

2,2′-(2,3,5,6-Tetrafluorobenzene-1,4-diyl)bis-[5-(4-methylphenyl)-1,3,4-oxadiazole] (3h). Yield 81%, mp 210°C. IR spectrum, ν, cm^{-1}: 1615 (C=N), 1172 (C–O–C), 1175 (C–F), 1487 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 2.51 s (6H, CH_3), 7.4 d (4H, *J* = 7.28 Hz), 7.96 d (4H, *J* = 7.28 Hz).

4,4′-[(2,3,5,6-Tetrafluorobenzene-1,4-diyl)bis-(1,3,4-oxadiazole-5,2-diyl)]diphenol (3i). Yield 76%, mp 262°C. IR spectrum, ν, cm^{-1}: 1601 (C=N), 1063 (C–O–C), 1124 (C–F), 3441 (O-H), 1488 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 7.47 d (4H, *J* = 8.44 Hz), 8.02 s (2H, OH), 8.04 d (4H, *J* = 8.44 Hz).

3,3′-[(2,3,5,6-Tetrafluorobenzene-1,4-diyl)bis-(1,3,4-oxadiazole-5,2-diyl)]diphenol (3j). Yield 74%, mp 230°C. IR spectrum, ν, cm^{-1}: 1645 (C=N), 1039 (C–O–C), 1119 (C–F), 3454 (O–H),1548 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 7.13 s (2H, OH), 7.29 s (2H), 7.43 d (2H, *J* = 6.8 Hz), 7.60 d.d (2H, *J* = 6.8, 8.92 Hz), 7.73 d (2H, *J* = 8.92 Hz).

4,4′-[(2,3,5,6-Tetrafluorobenzene-1,4-diyl)bis-(1,3,4-oxadiazole-5,2-diyl)]dipyridine (3k). Yield 82%, mp 222°C. IR spectrum, ν, cm^{-1}: 1612 (C=N),

1040 (C–O–C), 974 (C–F), 1468 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 7.4 d (4H, J = 8.00 Hz), 8.4 d (4H, J = 8.00 Hz).

3,3′-[(2,3,5,6-Tetrafluorobenzene-1,4-diyl)bis-(1,3,4-oxadiazole-5,2-diyl)]dipyridine (3l). Yield 81%, mp 225°C. IR spectrum, ν, cm^{-1}: 1637 (C=N), 1077 (C–O–C), 1173 (C–F), 1492 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 7.76 d.d (2H, J = 7.28, 6.00 Hz), 8.44 d (2H, J = 7.28 Hz), 8.8 d (2H, J = 6.00 Hz), 9.22 s (2H).

All starting materials and reagents were of analytical grade and were used without further purification. The melting points were measured on a DBK precision melting point apparatus and are uncorrected. The IR spectra were recorded from KBr disks on a Bruker IR spectrometer. The ^{1}H NMR spectra were obtained in $CDCl_3$ (unless otherwise stated) on a Bruker Avance-II spectrometer at 400 MHz. The mass spectra were recorded on a Waters ZQ-4000 spectrometer. The yields refer to the isolated compounds.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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