An Efficient Synthetic Route for New 1,3,4-Oxadiazoles Having Sulphonamido Pharmacophore

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In recent days, active research has been initiated on sulfonamido pharmacophore containing heterocycles. Sulfonamides are an important class of biologically active compounds. Indeed, the antibacterial sulfonamides[1] continue to play an important role in chemotherapy alone or in the combination with other drugs.[2] The hypoglycemic sulfonamides are extensively used in the treatment of diabetes.[3] Sulfonamides like Sotalol,[4] Soterenol and Oryzalin have displayed antihypertensive, bronchodilator[5] andherbicidal[6] activities, respectively. Recently attention is paid on the synthesis of sulfonamides possessing heteroaryl moieties[7] and Sulphamethizole, Sulfamoxazole and Sulfafenazole are explored as clinical agents.

Additionally 1,3,4-oxadiazole derivatives are gaining importance in the heterocyclic family because of their broad-spectrum of biological activities such as antimicrobial,[8] antimycobacte-rial,[9] antiviral,[10] anticonvulsant,[11] insecticidal [12] and anti-inflammatory properties.[13] The well established antihypertensive drugs like Tiodazosin[15] and Nesapidil[16] as well as antibiotics such as furamizole[17] possess oxadiazole nucleus.

Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles. The commonly used synthetic route for 1,3,4-oxadiazoles include reaction of acid hydrazides (or hydrazine) with acid chlorides,[18,19]/carboxylic acids.[20]/direct cyclization of diacylhydrazines using variety of dehydrating agents such as thionyl chlorides,[21] phosphorous pentaoxide,[22] phosphorous oxychloride,[23] triflic anhydride[24] and polyphosphoric acid.[25] Recently, solid-phase synthesis of these compounds were also reported.[26-28] However, these methods often require long reaction times and high temperature.

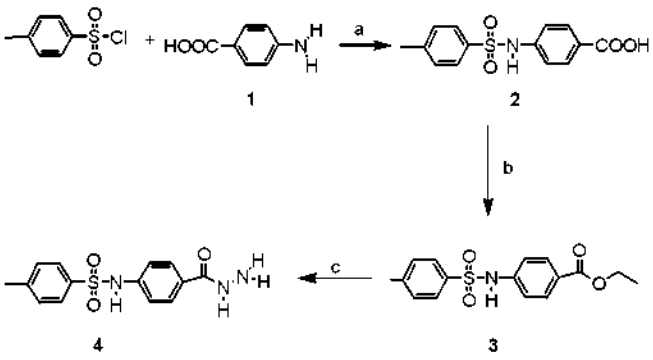
Considering the biological significance of the oxadiazoles and need to develop an efficient route for the oxadiazoles here in the present work an attempt has been made to provide one pot method for obtaining new oxadiazoles bearing sulphonamido phenyl pharmacophore. Therefore here we report an efficient synthesis of *N*-{4-[4-acetyl-5-(4-substituted-phenyl)-4,5-dihydro-[1,3,4]oxadi-azole-2-yl]-phenyl}-4-methyl-benzenesulfonmide using 4-aminobenzoic acid as starting material.

4-Aminobenzoic acid (**1**) was converted to 4-(toluene-4-sulfonylamino)benzoic acid (**2**) by subjecting to *p*-toluenesulfonyl chloride. Esterification of (**2**) with ethanol in an acetic medium afforded ester (**3**). Treatment of (**3**) with hydrazine hydrate furnished the corresponding hydrazide (**4**) in good yield. Compounds (**5**) were prepared by the reaction of compound (**4**) with aromatic aldehydes and acetic anhydride in one pot.

Using this method we obtained excellent yields of the new oxadiazoles (**5**). The reaction sequence is outlined in Scheme 1 and 2.

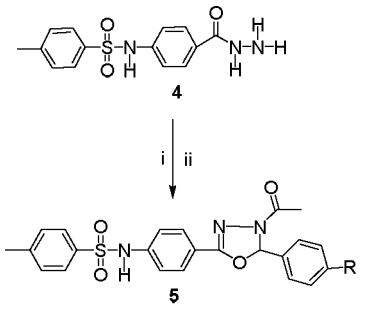
This method offers several advantages including short reaction time, nontedious workup, high yields and there is no need to isolate azomethine.

The new compounds and intermediates have been characterized by elemental analyses IR, ^{1}H NMR and mass analyses. Spectra data of (**5a**) as one of the representative products (**5a-e**) has been presented below. MS (*m/z*, % abandance): 466 (M^++1, 89.45). IR 3116 cm^{-1} (NH str.), 1627 cm^{-1} ($COCH_3$ str.), 1564 cm^{-1} (C=N str.), 1343 and 1293 cm^{-1} (SO_2 str.), 1255 cm^{-1} (C-O-C str.), ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.31 (s, 3H, CH_3), 2.49 (s, 3H, $COCH_3$), 3.73 (s, 3H, OCH_3), 6.92 (d, 2H,



a) Pyridine, acetone, reflux, b) EtOH, H^+ reflux, c) $NH_2NH_2{\cdot}H_2O$, rt.

Scheme 1



i) RCHO, CH_3CN/AcOH, reflux, ii) $(CH_3CO)_2O$, reflux.

Scheme 2

Table 1. Physical data of 1,3,4-oxadiazoles (5a-e, Scheme 2).

Products	R	Yield (%)[a]	Mp (°C)
5a	OCH_3	75	208 - 210
5b	Cl	81	150 - 152
5c	F	71	110 - 112
5d	Br	75	164 - 166
5e	H	78	126 - 128

[a]Yield of isolated product based on acid hydrazide (4).

Ar-H, J = 8.0 Hz), 7.04 (s, 1H, oxadiazole), 7.19 (d, 2H, Ar-H, J = 8.2 Hz), 7.34 (d, 2H, Ar-H, J = 8 Hz), 7.45 (d, 2H, Ar-H, J = 8 Hz), 7.67 (d, 2H, Ar-H, J = 8 Hz), 7.76 (d, 2H, Ar-H, J = 8 Hz), 10.69 (br s, 1H, NH, D_2O exchangeable).

Experimental Section

General procedures. All chemicals were obtained from commercial sources and used without any further purification. The melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a FT-IR (JASCO FT-IR 4100) Japan. The ^{1}H NMR was measured on Bruker DRX-300, 300 MHz FT NMR with low and high temperature in DMSO using TMS as internal reference. The coupling constant J are in Hz. Mass spectra were recorded on a Jeol SX 102/DA-600 mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 CHN analyzer.

Synthesis of 4-(toluene-4-sulfonylamino)-benzoic acid (2). 4-Aminobenzoic acid (0.01 mol, 1.37 g), *p*-toluenesulfonyl chloride (0.01 mol, 1.9 g) and pyridine (0.01 mole, 0.8 mL) were dissolved in dry acetone (25 mL). The reaction solution was refluxed for 4 h. The reaction was monitored by TLC. After completion of the reaction the solvent was removed under vacuum. The solid mass was poured in ice cold water. It was acidified using dilute hydrochloric acid. The solid obtained was filtered, washed with water and crystallized from aqueous ethanol. Yield 87%, mp 230 °C, IR (cm^{-1}) 3239, 1693, 1337, 1291. ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3H, CH_3), 7.16 (d, 2H, Ar-H), 7.33 (d, 2H, Ar-H), 7.68 (d, 2H, Ar-H), 7.76 (d, 2H, Ar-H), 10.82 (s, 1H, COOH, D_2O exchangeable). MS (*m/z*): 292 (M^++1).

Synthesis of 4-(toluene-4-sulfonylamino)-benzoic acid ethyl ester (3). 4-(Toluene-4-sulfonylamino)benzoic acid (0.01 mol, 2.91 g) was dissolve in ethanol (50 mL). To this solution con-centrated sulphuric acid (2 mL) was added. Then the reaction mixture was refluxed for 7 h. The completion of the reaction was confirmed by TLC. Then the content of the reaction mass was poured in ice cold water. Thus obtained solid washed by saturated sodium hydrogen carbonate solution and, finally by water. It was crystallized from alcohol. Yield 80%, mp 191 °C, IR (cm^{-1}) 3215, 1691, 1337, 1291, 1238. ^{1}H NMR (DMSO-d_6) δ 1.25 (t, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.21 (q, 2H, CH_2), 7.18 (d, 2H, Ar-H), 7.33 (d, 2H, Ar-H), 7.67 (d, 2H, Ar-H), 7.78 (d, 2H, Ar-H), 10.75 (s, 1H, NH, D_2O exchangeable). MS (*m/z*): 320 (M^++1).

Synthesis of *N*-(4-hydrazinocarbonylphen-yl)-4-methyl-benzenesulfonamide (4). 4-(Toluene-4-sulfonylamino)benzoic acid ethyl ester (0.01 mol, 3.19 g) was dissolved in (25 mL) hydrazine hydrate. The reaction mixture was stirred at room temperature for 6 h. The content of the flask was then poured in ice cold water. The obtained solid was filtered, dried and crystallized by methanol. Yield 90%, mp 236 °C, IR (cm^{-1}) 3322, 3152, 2940, 1342, 1235, 854. ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3H, CH_3), 4.41 (s, 2H, NH_2), 7.09 (d, 4H, Ar-H), 7.32 (d, 4H, Ar-H), 9.56 (s, 1H, CONH, D_2O exchangeable), 10.54 (s, 1H, NH, D_2O exchangeable). MS (*m/z*): 306 (M^++1).

General procedure for the synthesis of *N*-{4-[4-acetyl-5-(4-substituted-phenyl)-4,5-dihydro-[1,3,4]-oxadiazol-2-yl]-phenyl}-4-methyl-benzenesulfonamide (5a-e). A mixture of compound (**4**) (0.002 mol, 0.61 g) and aryl aldehydes (0.002 mol, 0.272 g) was dissolved in acetonitrile (25 mL). To this solution few drops of glacial acetic acid were added and it was then refluxed for 6 h. The progress of reaction was monitored by TLC. After formation of azomethines acetic anhydride (5 mL) was added and then reaction mixture was further refluxed for 3 h. Reaction was monitored by TLC. After completion of the reaction it was poured on crushed ice and stirred vigorously until the oil became solid. The obtained solid was filtered, dried and crystallized from ethanol.

***N*-{4-[4-Acetyl-5-(4-methoxy-phenyl)-4,5-dihydro-[1,3,4] oxadiazol-2-yl]-phenyl}-4-methyl-benzenesulfonamide (5a).** Yield 75%, mp 208 - 210 °C, IR (cm^{-1}) 3116, 1627, 1514, 1343, 1293, 1255. ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3H, CH_3), 2.49 (s, 3H, $COCH_3$), 3.73 (s, 3H, OCH_3), 6.92 (d, 2H, Ar-H), 7.04 (s, 1H, oxadiazole), 7.19 (d, 2H, Ar-H), 7.34 (d, 2H, Ar-H), 7.45 (d, 2H, Ar-H), 7.67 (d, 2H, Ar-H), 7.76 (d, 2H, Ar-H), 10.69 (br s, 1H, NH, D_2O exchangeable). MS (*m/z*): 466 (M^++1). Anal. Calcd. for $C_{24}H_{23}N_3O_5S$ (465.53): Found C 61.62, H 4.98, N 8.78.

***N*-{4-[4-Acetyl-5-(4-chloro-phenyl)-4,5-dihydro-[1,3,4] oxadiazol-2-yl]-phenyl}-4-methyl-benzenesulfonamide (5b).** Yield 81%, mp 150 - 152 °C, IR (cm^{-1}) 3066, 1669, 1509, 1411, 1221. ^{1}H NMR (DMSO-d_6) δ 2.27 (s, 3H, CH_3), 2.42 (s, 3H, $COCH_3$), 7.12 (d, 2H, Ar-H), 7.24 (s, 1H, oxadiazole), 7.33 (d, 2H, Ar-H), 7.46 (d, 2H, Ar-H), 7.52 (d, 2H, Ar-H), 7.76 (d, 2H, Ar-H), 7.85 (d, 2H, Ar-H), 9.99 (br s, 1H, NH, D_2O exchangeable). MS (*m/z*): 470 (M^++1). Anal. Calcd. for $C_{23}H_{20}ClN_3O_4S$ (469.95): Found C 58.53, H 4.19, N 8.84.

***N*-{4-[4-Acetyl-5-(4-fluro-phenyl)-4,5-dihydro-[1,3,4]oxadiazol-2-yl]-phenyl}-4-methyl-benzenesulfonamide (5c).** Yield 71%, mp 110 - 112 °C, IR (cm^{-1}) 3070, 1713, 1510, 1411, 1265. ^{1}H NMR (DMSO-d_6) δ 2.27 (s, 3H, CH_3), 2.42 (s, 3H, $COCH_3$), 7.23 (s, 1H, oxaidazole), 7.33 (d, 2H, Ar-H), 7.47 (d, 2H, Ar-H), 7.76 (d, 2H, Ar-H), 7.83 (d, 2H, Ar-H), 7.94 (d, 2H, Ar-H), 8.04 (d, 2H, Ar-H), 9.97 (br s, 1H, NH, D_2O exchangeable). MS (*m/z*): 454 (M^++1). Anal. Calcd. for $C_{23}H_{20}FN_3O_4S$ (453.50): Found C 60.75, H 4.31, N 9.17.

***N*-{4-[4-Acetyl-5-(4-bromo-phenyl)-4,5-dihydro-[1,3,4] oxadiazol-2-yl]-phenyl}-4-methyl-benzenesulfonamide (5d).** Yield 75%, mp 164 - 166 °C, IR (cm^{-1}) 3051, 1713, 1509, 1455, 1265. ^{1}H NMR (DMSO-d_6) δ 2.27 (s, 3H, CH_3), 2.42 (s, 3H, $COCH_3$), 7.15 (d, 2H, Ar-H), 7.23 (s, 1H, oxadiazole), 7.15 (d, 2H, Ar-H), 7.45 (d, 2H, Ar-H), 7.55 (d, 2H, Ar-H), 7.64 (d, 2H, Ar-H), 8.83 (d, 2H, Ar-H), 7.94 (d, 2H, Ar-H), 9.98 (br s, NH, 1H, D_2O exchangeable). MS (*m/z*): 515 (M^++1). Anal.

Calcd. for $C_{23}H_{20}BrN_3O_4S$ (514.40): Found C 53.50, H 3.82, N 8.12.

***N*-{4-[4-Acetyl-5-phenyl-4,5-dihydro-[1,3,4] oxadiazol-2-yl]-phenyl}-4-methyl-benzenesulfonamide (5e).** Yield 78%, mp 126 - 128 °C, IR (cm^{-1}) 3036, 1712, 1493, 1456, 1264. ^1H NMR (DMSO-d_6) δ 2.28 (s, 3H, CH_3), 2.42 (s, 3H, $COCH_3$), 7.22 (s, 1H, oxadiazole), 7.33 (d, 2H, Ar-H), 7.45 (d, 2H, Ar-H), 7.55 (d, 2H, Ar-H), 7.67 (d, 2H, Ar-H), 7.83 (d, 2H, Ar-H), 7.94 (d, 2H, Ar-H), 10.70 (br s, 1H, NH, D_2O exchangeable). MS (*m/z*): 436 (M^++1). Anal. Calcd. for $C_{23}H_{21}N_3O_4S$ (435.51): Found C 63.16, H 4.61, N 9.35.

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