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NOTE

Synthesis of 3,5-disubstituted [1,2,4]-oxadiazoles

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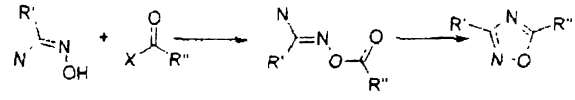
Abstract : Substituted amidoximes have been synthesized, and converted to corresponding oxadiazoles as a novel heterocyclic compounds under mild conditions in good to excellent yield.

Keywords : *O*-Acylation, oxadiazole, heterocycles, cyclodehydration.

Introduction

Heterocyclic moieties are present in numerous compounds of therapeutic importance. The substituted 1,2,4-oxadiazoles have been identified as a metabolically stable analog of ester or amide in pharmacologically active molecules[1,2]. They are key elements with potential biological activities[3-5] such as pesticides[6], anti-peripheral vasomotility[7], CNS stimulant, anti-inflammatory, hypotensive[8], insecticidal[9], bactericidal[10], hypoglycemic[11,12], analgesic, anticonvulsive, antiemetic, diuretic[13], muscle relaxant[14,15], herbicidal[16,17] and antifungal activity[18,19]. As a bioisosteres of esters or amides they are the part of tryptase inhibitors[20], angiotensin II receptor antagonists[21], anti-mycobacterial agents[22], fatty acid oxidation inhibitors[23], serotonin agonists for the treatment of migraine[24]. Several methods have been reported for the synthesis of 1,2,4-oxadiazoles. In general, substituents affecting electronic properties of 1,2,4-oxadiazole ring in eq. (1), present at C-3 and C-5 positions were synthesized by reacting amidoxime **I** with a suitably activated acid derivatives **II** such as ester[25] or acid chloride[26] or anhydride[27] or orthoester[28] to obtain intermediate **III** which on cyclization provided compound **IV**. In some cases, reaction is catalyzed by strong bases such as NaH, *n*-BuLi in THF, or NaOEt etc.[29]. Heating above the melting point[30], or by heating in 2-methoxyethyl ether at 85 °C, resulting a mixture of cyclized and uncyclized products. The above mentioned conditions are rigorous; work up is painstaking and cannot be generalized for the substituents, which are unstable in strong basic condition. As a part of our ongoing research we have developed the methodology for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles which makes the use of mild conditions as depicted in



(I) (II) (III) (IV)

X = OR, Cl, RC(O)O, OH

Eq. (1)

Scheme 1. The methodology developed is simple and provides good to excellent yields with no side products. The reaction goes to completion without uncyclized product even if C-5 substituents is aromatic or heteroaromatic. The hitherto novel compounds synthesized are anticipated to possess various biological activities[5-17].

Results and discussion

The synthesis of 3,5-disubstituted-1,2,4-oxadiazole begins with the nitration[31] of phenylacetonitrile **1** to obtain *o*- and *p*-nitrophenylacetonitrile **2a** and **2** respectively. The pure *p*-nitrophenylacetonitrile **2** was obtained by recrystallization of the isomeric mixture. Nitro group was then reduced with Pd/C under H_2 atmosphere in THF to get *p*-aminophenyl acetonitrile. This amino derivative on treatment with Et_3N and methane sulphonyl chloride in THF afforded *N*-[4-(*N*-hydroxycarbamidoylmethyl)-phenyl]methanesulfonamide **3**.

Compound **3** when treated with $NH_2OH.HCl$ in the presence of $NaHCO_3$ in methanol under reflux, afforded (1*Z*)-*N'*-hydroxy-2-{4-[(methylsulfonyl)amino]-phenyl}ethanimidamide **4** which when reacted with different acid chlorides in the presence of K_2CO_3 in 1,4-dioxan at an ambient temperature, yielded substituted amidoxime compounds **5a-h**.

These compounds were then characterized with the help of IR and ^{1}H NMR spectra. The IR spectra of **5a-h** showed two absorptions bands one at 3535 cm^{-1} and the other in the region of 3440 cm^{-1} which corresponds to asymmetric and symmetric -NH streching vibrations of uncyclized product. Further strong absorption band between 1730–1750 cm^{-1} has been observed due to -O-C(=O)-R. The ^{1}H NMR spectrum of **5a-h** showed a broad singlet at δ 6.2–6.4 ppm for the NH_2 protons, while benzylic protons have showed singlet at 3.2–3.4 ppm.

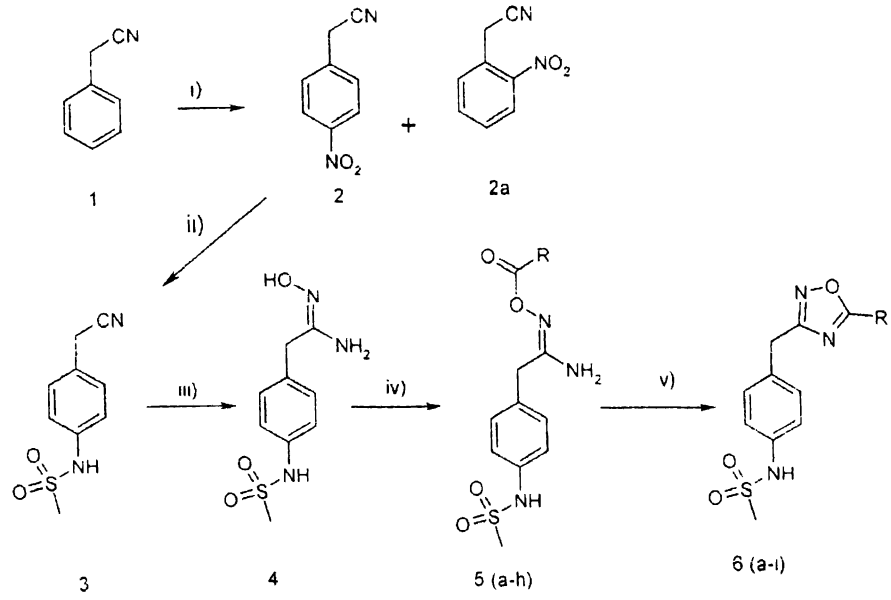
Compounds **5a-h** when refluxed in toluene in presence of molecular sieves for 8–15 h afforded *N*-[4-(5-substituted-1,2,4-oxadiazol-3-ylmethyl)phenyl]methanesulfonamide **6a-h**. IR spectra of these compounds showed single absorption band in the region of 3300–3350 cm^{-1} due to -NH streching vibration and absence of absorption band from the region of 1730–1750 cm^{-1}. ^{1}H NMR spectra showed down field shift of the benzylic -CH_2 protons from 3.2–3.4 to 4.0–4.4 ppm.

In summary, we have synthesized a series of new *N*-[4-(5-substituted-1,2,4-oxadiazol-3-ylmethyl)phenyl]-methanesulfonamide. The methodology developed utilizes neutral conditions i.e. molecular sieves for cyclodehydration therefore acid and base labile substrates can be cyclized in quantitative yield. This method is simple, gives no side product, and easy work up. Not only alkyl but aromatic acid can be reacted to get the cyclized product with no uncyclized product. These advantages make this methodology attractive and useful compared to the present methodologies. The newly synthesized 3,5-disubstituted-1,2,4-oxadiazole compounds are stable and can be explored for various biological implications in drug research.

Table 1. Synthesis of 3,5-disubstituted-1.2.4-oxadiazole

Sr. no.	Entry	R	Yield[a] (%)
1.	**6a**	-CH_3	72
2.	**6b**	-CH_2CH_3	80
3.	**6c**	-Phenyl	85
4.	**6d**	-3-Pyridyl	85
5.	**6e**	-CH_2-phenyl	80
6.	**6f**	-CH_2CH_2-phenyl	75
7.	**6g**	-CH=CH-phenyl	70
8.	**6h**	-^{t}Bu	70
9.	**6i**	-CF_3	75[b]

[a]Isolated yield. [b]Reaction carried at 45 °C.



Scheme 1

Reagents and conditions : (i) Conc. HNO_3/H_2SO_4/0 °C, (ii) (a) H_2/Pd/C, THF/RT, (b) mesyl chloride/Et_3N/0 °C, (iii) $NH_2OH/NaHCO_3$/MeOH/reflux, (iv) $RCOCl/K_2CO_3$/1,4-dioxan, (v) toulene/molecular sieves/reflux.

Experimental

Preparation of (1Z)-N′-hydroxy-2-{4-[(methylsulfonyl)-amino]phenyl}ethaninidamide **(4)** :

To a solution of *p*-nitrophenylacetonitrile **2** (10.0 g, 0.06 mol) in THF (100 ml), was added 10% Pd/C (2.0 g). The resulting heterogeneous reaction mixture was stirred under H_2 atmosphere in a pressure vessel at 100 psi for 4 h. The product *p*-aminophenylacetonitrile (8.2 g, 0.06 mol) was reacted further without isolation with Et_3N (11.0 ml, 0.078 mol, 1.5 eq.) and methanesulfonyl chloride (6.0 ml, 0.07 mol, 1.3 eq.) at 0 °C. The reaction mixture was warmed to room temperature over a period of 2 h. After completion of reaction, the solvent was evaporated under vacuum to obtain pale yellow sticky mass. Solid precipitate obtained upon addition of chilled water, was filtered and dried under vacuum to yield 12.0 g of *N*-(4-cyanomethylphenyl)methanesulfonamide **3**. To a stirred solution of **3** (12.0 g, 0.056 mol, 1.0 eq.) in methanol (60 ml) was added $NH_2OH.HCl$ (38.0 g, 0.51 mol, 9.0 eq.), $NaHCO_3$ (51.24 g, 0.56 mol, 10.0 eq.) and refluxed overnight. The solvent was evaporated under vacuum and ice cold water was added to the crude reaction mass, solid precipitated was filtered and dried under vacuum. It was recrystallized from ethanol to obtain pure (1Z)-*N*′-hydroxy-2-{4-[(methylsulfonyl)-amino]phenyl}ethanimidamide **4** as a off-white solid (9.5 g, 88%).

General procedure for the preparation of (1Z)-*N*′-acetoxy or substituted-acetoxy-2-{4-[(methylsulfonyl)-amino]phenyl}ethanimidamide **5a-h**.

To a stirred solution of (1Z)-*N*′-hydroxy-2-{4-[(methylsulfonyl)amino]phenyl}ethanimidamide **4** (1.0 g, 0.004 mol) in 1,4-dioxan (10.0 ml) was added anhydrous K_2CO_3 (0.9 g, 0.0052 mol, 1.3 eq.). After 15 min, acid chloride (0.0045 mol, 1.1 eq.) was added to the above reaction mixture and stirred at an ambient temperature. After completion of reaction, solvent was evaporated under vacuum and water was added to the crude reaction mass, solid precipitated was filtered and dried. It was then either recrystallized or purified by column chromatography to give details of each compounds are given below.

(1Z)-N′-Acetoxy-2-{4-[(methylsulfonyl)amino]phenyl}-ethanimidamide **(5a)** : White solid, 89% yield, m.p. 158–159 °C; R_f 0.34 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3535, 3442, 3327, 3082, 2967, 1740, 1540 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) : δ 2.0 (3H, s, CH_3), 2.9 (2H, s, CH_3-S(O)$_2$), 3.5 (2H, s, CH_2-Ph), 6.4 (2H, s, NH_2), 7.1–7.3 (2H, d, Ar-H), 7.3–7.4 (2H, d, Ar-H), 9.7 (1H, s, NH). MS : *m/z* 286 [M^{+1}].

(1Z)-N′-Propionyloxy-2-{4-[(methylsulfonyl)-amino]phenyl}ethanimidamide **(5b)** : Off-white solid, 87% yield, m.p. 162–164 °C; R_f 0.32 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3530, 3440, 3325, 3115, 2967, 1740, 1530 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) : δ 1.0–1.1 (3H, t, CH_3), 2.3–2.4 (2H, q, CH_2), 2.9 (3H, s, CH_3-S(O)$_2$), 3.3 (2H, s, CH_2-Ph), 6.0 (2H, s, NH_2), 7.1 (2H, d, Ar-H), 7.3 (2H, d, Ar-H), 9.7 (1H, s, NH). MS : *m/z* 300 [M^{+1}].

(1Z)-N′-Benzoyloxy-2-{4-[(methylsulfonyl)-amino]phenyl}ethanimidamide **(5c)** : Buff colored solid, 91% yield, m.p. 185–186 °C; R_f 0.38 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3540, 3465, 3330, 3120, 2980, 1745, 1553 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) : δ 2.95 (3H, s, CH_3), 3.4 (2H, s, CH_2-Ph), 6.6 (2H, s, NH_2), 7.1 (2H, d, Ar-H), 7.3 (2H, d, Ar-H), 7.5 (3H, m, Ar-H), 8.0–8.2 (2H, d, Ar-H), 9.7 (1H, s, NH). MS : *m/z* 348 [M^{+1}].

(1Z)-N′-[(3-Pyridinoyloxy)]-2-{4-[(methyl-sulfonyl)amino]phenyl}ethanimidamide **(5d)** : White solid, 89% yield, m.p. 185–186 °C; R_f 0.32 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3530, 3440, 3335, 3080, 2980, 1745, 1677, 1530 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) : δ 2.95 (3H, s, CH_3), 3.4 (2H, s, CH_2-Ph), 6.7 (2H, s, NH_2), 7.1 (2H, d, Ar-H), 7.3 (2H, d, Ar-H), 7.5–7.6 (1H, m, py-H), 8.4 (1H, dd, py-H), 8.8 (1H, dd, py-H), 9.2 (1H, s, py-H), 9.7 (1H. s, NH). MS : *m/z* 349 [M^{+1}].

(1Z)-N′-[Phenylacetoxy)]-2-{4-[methylsulfonyl)amino]-phenyl}ethanimidamide **(5e)** : Pale yellow solid, 90% yield, m.p. 165–166 °C; R_f 0.45 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3533, 3440, 3335, 3125, 2967, 1740, 1550 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) : δ 2.95 (3H, s, CH_3), 3.3 (2H, s, CH_2-Ph), 3.7 (2H, s, -(O=C-CH_2-Ph)), 6.45 (2H, s, NH_2), 7.2 (d, Ar-H), 7.3 (2H, d, Ar-H), 7.3–7.5 (5H, m, Ar-H), 9.7 (1H, s, NH). MS : *m/z* 363 [M^{+1}].

(1Z)-N′-Phenylpropionyloxy-2-{4-[(methylsulfonyl)-amino]phenyl}ethanimidamide **(5f)** : Off-white solid, 84% yield, m.p. 165–166 °C; R_f 0.55 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3533, 3337, 3125, 2970, 1745, 1545 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) : δ 2.6–2.7 (2H, d, CH_2), 2.7–2.8 (2H, s, CH_2), 2.95 (3H, s, CH_3), 3.3 (2H, s, CH_2-Ph), 6.4 (2H, s, NH_2), 7.1–7.2 (2H, d, Ar-H), 7.2–7.3 (2H, d, Ar-H), 7.3–7.4 (5H, m, Ar-H), 7.5–7.6 (2H, d, Ar-H), 9.7 (1H, s, NH). MS : *m/z* 376 [M^{+1}].

(1Z)-N′-Phenylacryloyloxy-2-{4-[(methylsulfonyl)-amino]phenyl}ethanimidamide **(5g)** : White solid, 83% yield, m.p. 175–176 °C; R_f 0.52 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3535, 3443, 3330, 3105, 2975, 1740,

1540 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) : δ 2.95 (3H, s, CH_3), 3.4 (2H, s, CH_2-Ph), 6.5 (2H, s, NH_2), 6.6-6.7 (1H, d, =CH), 7.1-7.3 (2H, d, Ar-H), 7.3-7.4 (2H, d, Ar-H), 7.5 (3H, m, Ar-H), 7.6 (2H, m, Ar-H), 7.7 (1H, d, =CH), 9.7 (1H, s, NH). MS : *m/z* 374 [M^{+1}].

(1Z)-N'-Pivaloyloxy-2-{4-[(methylsulfonyl)amino]-phenyl}ethanimidamide **(5h)** : White solid, 85% yield, m.p. 174-175 °C; R_f 0.47 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3535, 3430, 3325, 3120, 2975, 1747, 1540 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) : δ 1.3 (9H, s, ^{t}butyl), 3.0 (3H, s, CH_3), 3.5 (2H, s, CH_2-Ph), 6.4 (2H, s, NH_2), 7.2-7.3 (2H, d, Ar-H), 7.4-7.6 (2H, d, Ar-H), 6.7 (1H, s, NH). MS : *m/z* 328 [M^{+1}].

General procedure for the preparation of *N*-[4-(5-substituted-1,2,4-oxadiazol-3-ylmethyl)phenyl]-methanesulfonamide **(6a-h)** :

To a solution of **5a** (0.001 mol) in toluene (10.0 ml) and *N,N*-dimethylformamide (2.0 ml) was added freshly dried molecular sieves 4 Å and refluxed for 6-15 h. After completion, reaction mixture was cooled to room temperature and filtered. Filtrate was evaporated under vacuum to obtain crude cyclized product, was then purified either by recrystallization or by column chromatography using $CHCl_3$: MeOH (9 : 1) to afford pure solid compounds **6a-h**. The yield, R_f value, m.p. and other details of each product are given below.

N-[4-(5-Methyl-1,2,4-oxadiazol-3-ylmethyl)phenyl]-methanesulfonamide **(6a)** : White solid, 75% yield, m.p. 123-124 °C; R_f 0.43 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3310, 3100, 2950, 1575 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) : δ 2.6 (3H, s, CH_3), 3.0 (3H, s, CH_3), 4.0 (2H, s, CH_2), 6.4 (1H, s, NH), 7.1-7.2 (2H, d, Ar-H), 7.3-7.4 (2H, s, Ar-H). MS : *m/z* 282 [M^{+1}].

N-[4-(5-Ethyl-1,2,4-oxadiazol-3-ylmethyl)phenyl]-methanesulfonamide **(6b)** : White solid, 80% yield, m.p. 90-91 °C; R_f 0.45 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3330, 3100, 2950, 1580 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) : δ 1.3-1.4 (3H, t, CH_3), 2.8-3.0 (2H, q, CH_2), 3.0 (3H, s, CH_3), 4.0 (2H, s, CH_2-Ph), 6.6 (1H, s, NH), 7.1-7.3 (1H, d, Ar-H), 7.3-7.4 (2H, d, Ar-H). MS : *m/z* 246 [M^{+1}].

N-[4-(5-Phenyl-1,2,4-oxadiazol-3-ylmethyl)-phenyl]-methatlesulfonamide **(6c)** : Pale yellow solid, 85% yield, m.p. 170-171 °C; R_f 0.58 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3311, 3100, 2970, 1585 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) : δ 3.0 (3H, s, CH_3), 4.1 (2H, s, CH_2-Ph), 6.6 (2H, s, NH_2), 7.2 (2H, d, Ar-H), 7.4 (2H, s, Ar-H), 7.5-7.6 (3H, m, Ar-H), 8.1 (2H, d, Ar-H). MS : *m/z* 330 [M^{+1}].

N-[4-(5-Pyridyl-1,2,4-oxadiazol-3-ylmethyl)-phenyl]methanesulfonamide **(6d)** : Pale yellow solid, 85% yield, m.p. 170-171 °C; R_f 0.45 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3315, 3100, 2940, 1500 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) : δ 3.0 (3H, s, CH_3), 4.1 (2H, s, CH_2-Ph), 7.0 (2H, d, Ar-H), 7.2 (2H, d, Ar-H), 7.6 (1H, dd, py-H), 8.4 (1H, dd, py-H), 8.9 (1H, d, py-H), 9.2 (1H, s, py-H). MS : *m/z* 331 [M^{+1}].

N-[4-(5-Benzyl-1,2,4-oxadiazol-3-ylmethyl)phenyl]-methanesulfonamide **(6e)** : Off-white solid, 80% yield, m.p. 82-83 °C; R_f 0.60 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3307, 3080, 2958, 1585 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) : δ 3.0 (3H, s, CH_3), 4.1 (2H, s, CH_2-Ph), 4.3 (2H, s, CH_2-Ph), 6.8 (1H, s, NH), 7.2 (2H, d, Ar-H), 7.3 (2H, d, Ar-H), 7.3-7.5 (5H, m, Ar-H). MS : *m/z* 344 [M^{+1}].

N-[4-(5-Phenylethyl-1,2,4-oxadiazol-3-ylmethyl)-phenyl]methanesulfonamide **(6f)** : Off-white solid, 75% yield, m.p. 100-101 °C; R_f 0.68 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3310, 3110, 2960, 1596 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) : δ 2.9 (2H, d, CH_2), 3.1 (3H, s, CH_3), 3.3 (2H, d, CH_2), 4.1 (2H, s, CH_2-Ph), 6.5 (1H, s, NH), 7.1-7.2 (2H, d, Ar-H), 7.2-7.3 (2H, d, Ar-H), 7.4-7.5 (3H, m, Ar-H), 7.5-7.6 (2H, m, Ar-H). MS : *m/z* 358 [M^{+1}].

N-[4-(5-((E-Styryl)-1,2,4-oxadiazol-3-ylmethyl)-phenyl]methanesulfonamide **(6g)** : White solid, 70% yield, m.p. 162-163 °C; R_f 0.64 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3310, 3105, 2969, 1572 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) : δ 3.0 (3H, s, CH_3), 4.1 (2H, s, CH_2-Ph), 6.4 (1H, s, NH), 6.9-7.0 (1H, d, CH=CH), 7.2-7.3 (2H, d, Ar-H), 7.3-7.4 (2H, d, Ar-H), 7.4-7.5 (3H, m, Ar-H), 7.6 (2H, m, Ar-H), 7.7-7.9 (1H, d, CH=CH). MS : *m/z* 356 [M^{+1}].

N-[4-(5-tert-Butyl-1,2,4-oxadiazol-3-ylmethyl)-phenyl]methanesulfonamide **(6h)** : White solid, 70% yield, m.p. 134-135 °C; R_f 0.55 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3317, 3090, 2980, 1575 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) : δ 1.4 (9H, s, $(CH_3)_3$), 3.0 (3H, s, CH_3), 4.0 (2H, s, CH_2-Ph), 6.6 (1H, s, NH), 7.2 (2H, d, Ar-R), 7.3 (2H, d, Ar-H). MS : *m/z* 311 [M^{+1}].

N-[4-(5-Trifluoromethyl-1,2,4-oxadiazol-3-ylethyl)-phenyl]methanesulfonamide **(6i)** : To a solution of compound **4** (0.3 g, 0.0012 mol) and Et_3N (0.24 ml, 0.0014 mol, 1.2 eq.) in dry CH_2Cl_2 (15.0 ml) was added trifluoroacetic anhydride (0.6 ml, 0.0036 mol, 3.0 eq.) and heated to reflux for 5 h. After completion of reaction, organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to get crude compound which after tritu-

rating in diethyl ether afforded white solid in 75% yield, m.p. 114-115 °C; R_f 0.45 ($CHCl_3$: MeOH; 9 : 1); IR (KBr) : 3300, 3120, 2960, 1570 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) : δ 3.4 (3H, s, CH_3), 4.2 (2H, s, CH_2-Ph), 6.4 (1H, s, NH), 7.3-7.4 (2H, d, Ar-H), 7.5 (2H, d, Ar-H). MS : *m/z* 322 [M^{+1}].

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References

1. M. K. Khan and Ullah-Zia, *Letters in Organic Chemistry,* 2005, **1,** 50.
2. F. Watjen and R. Baker, *J. Med. Chem.,* 1989, **32,** 2282.
3. J. P. Joseph and L. Y. Harry, U.S. Pat. 3, 141, 022 (1961) (*Chem. Abstr.,* 1964, **61,** 8317).
4. B. Hokfelt and A. Jonsson, *J. Med. Chem.,* 1962, **5,** 247.
5. P. S. Ansel, U.S. Pat. 2, 883, 391 (1959) (*Chem. Abstr.,* 1959, **53,** 16157).
6. K. Hiroshi, H. Isaq and O. Shigeki, *Zassokenkyn,* 1969, **8,** 46 *(Chem. Abstr.,* 1970, **73,** 108544).
7. C. Derappe, R. Rips, O. Albert and M. Aurousseau, *Chim. Ther.,* 1968, **3,** 181 (*Chem. Abstr.,* 1968, **69,** 106626).
8. A. A. Deshmukh and P. B. Sattur, *Indian Chem. Expt. Biol.,* 1976, **4,** 166.
9. A. K. Sen Gupta, M. Garg and U. J. Chandra, *J. Indian Chem. Soc.,* 1979, **56,** 1230.
10. I. Chiyomaru, K. Takita and H. Ito, Kumiai Chem. Ind. Co. Ltd., Jap. Pat. 72, 07, 549 (1972) (*Chem. Abstr.,* 1972, **77,** 549).
11. J. B. O. Neal, H. Rosen, P. B. Russel, A. C. Adams and A. Blumenthal, *J. Med. Pharm. Chem.,* 1962, **5,** 617 (*Chem. Abstr.,* 1962, **57,** 9168).
12. F. Kurzer, *Org. Compd. Sulphur, Selenium. Tellurium,* 1974, **4,** 417.
13. J. Thomas, Ger. Pat. 2, 403, 357 (1974) (*Chem. Abstr.,* 1974, **81,** 36153).
14. H. L. Yale and K. J. Losee, *J. Med. Chem.,* 1966, **9,** 478.
15. S. Turner, Reckitt and Colman Products Ltd., Ger. Pat. 2, 727, 146 (1978) (*Chem. Abstr.,* 1978, **88,** 105357).
16. Hodogaya Chemical Co. Ltd., Jap. Pat. 80, 27, 024 (1980) (*Chem. Abstr.,* 1980, **93,** 232719).
17. Hakko Chem. Ind. Co. Ltd., Brit. Pat. 1, 266, 542 (1972) (*Chem. Abstr.,* 1972, **77,** 5474).
18. H. Singh and L. D. S. Yadav, *Agric. Biol. Chem.,* 1976, **40,** 759.
19. T. Misato, K. Ko, K. Konno and E. Taniyama, Inst. Phys. Chem. Res., Jap. Pat. 772, 508 (1977) (*Chem. Abstr.,* 1977, **87,** 147054).
20. T. Palmer James, *Biol. Med. Chem. Lett.,* 2006, **16,** 3434.
21. Meyar Emerson, *Synthesis,* 2003, 899.
22. M. H. Gezginci, *J. Med. Chem.,* 2001, **44,** 1560.
23. Elzein Elfaith, *Biol. Med. Chem. Lett.,* 2004, **14,** 6017.
24. (a) J. L. LaMattina and C. J. Mularski, *J. Org. Chem.,* 1984, **49,** 4800; (b) K. D. Amarsinghe and M. B. Maier, *Tetrahedron Lett.,* 2006, **47,** 3629.
25. B. Kaboudin and Navaee Kian, *Heterocycles,* 2003, **60,** 2287.
26. (a) W Steglich and T. VanRee, *Synth. Coummun.,* 1982, **12,** 457; (b) S. Chiou and H. J. Shine, *J. Heterocyclic Chem.,* 1989, **26,** 125.
27. (a) F. Tieman and P. Kruger, *Chem. Ber.,* 1884, **17,** 1685; (b) J. A. Claisse and M. W. Foxton, *J. Chem. Soc., Perkin Trans. 1,* 1973, 2241.
28. (a) L. A. Kayukova and K. D. Praliev, *Chem. Heterocycl. Compd. (NY),* 1999, **35,** 630; (b) D. Korbonits, *Heterocycles,* 1994, **37,** 2051.
29. R. M. Srivastava and F. J. S. Oliverira, *Synth. Commun.,* 1999, **29,** 1437.
30. H. Normand and A. L. Hannah, *Tetrahedron Lett.,* 1999, **40,** 8547.
31. "Vogel's Text Book of Practical Organic Chemistry", 5th ed., 2004, 857.