Synthesis of Substituted 1,2,4-Oxadiazoles from Substituted Acid Chlorides and Amidoximes under Mild Conditions

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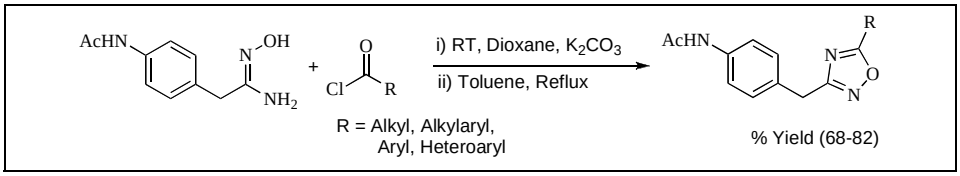

Substituted amidoximes have been synthesized, isolated and converted into substituted oxadiazoles as a novel heterocyclic compounds under mild conditions in good to excellent yield.

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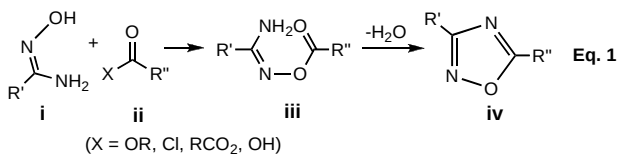
INTRODUCTION

Oxadiazoles have often been described as bio-isosteres for amides and esters [1,2,3]. Due to increased hydrolytic [4] and metabolic stability of the oxadiazole ring, improved pharmacoknetic and *in-vivo* performance is often observed, which make these heterocycles an important structural motif for the pharmaceutical industry. As a consequence of these characteristics, oxadiazoles have impacted numerous drug discovery programs including muscarinic agonists [5], benzodiazepine receptor partial agonists [6], dopamine transporters [7], anti-rhinovirals [8], growth hormone secretogogues [9], 5-HT agonists [10], antispasmodics [11], nematocidal, fungicidal and microbicides [12], analgesics [13], anti-inflammatory agents [14], Fab I inhibitors as antibacterial agents [15], immunosuppressants [16], and also antiplatelet and antithrombotic agents [17] *etc.*



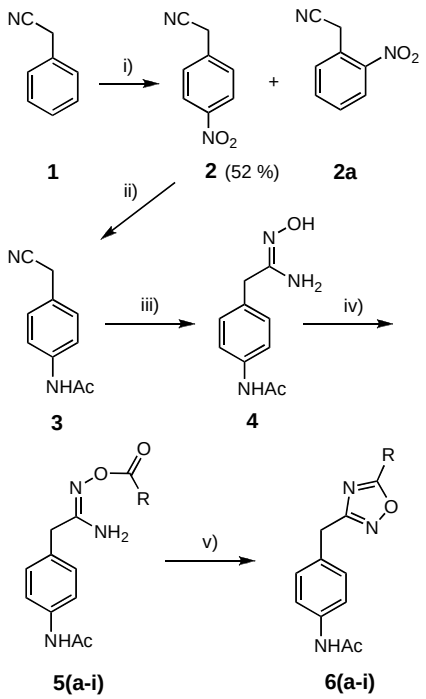
Eq. 1

Several methods have been reported for the synthesis of 1,2,4-oxadiazoles. In general, substituents with varying steric and electronic properties are present at C-3 and C-5 position in 1,2,4-oxadiazole ring, (iv, Eq. 1), which can be synthesized by reacting amidoxime (i) with a suitably activated acid derivative (ii) such as ester [18a,b] or acid chloride [19a,b]or anhydride [20a,b] or orthoester [21] to obtain intermediate (iii) which under different experimental conditions yields compound (iv). In some cases, strong basic conditions like NaH and *n*-BuLi in THF, or NaOEt are utilized [22a,b]. While some methods report drastic conditions such as heating intermediate (iii) well above its melting point for 10 min for cyclization [23], certain reactions are carried out by the heating an intermediate (iii) in 2-methoxyethyl ether at 85 ºC, resulting in a mixture of cyclized and uncyclized products [24].

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 project we have developed methodology for the synthesis of 3,5 disubstituted-1,2,4-oxadiazoles which makes use of milder conditions over

Scheme I



Conditions and reagents :
i) Con. HNO_3/H_2SO_4, 0 °C
ii) Pd/C, H_2, r.t. Acetyl Choride /Et_3N/THF/0 °C
iii)$NH_2OH.HCl/NaHCO_3$/MeOH/reflux
iv) $RCOCl/K_2CO_3$/1-4 Dioxan v) Toulene/Mol.Sieves/Reflux

the reported procedures as depicted in Scheme 1. The methodology developed is simple with good to excellent yields and no side product formation. The reaction goes to completion without uncyclized product even if C'5 substituent is aromatic or heteromatic unlike H. Normand [24] *et al* who had reported the condition wherein mixture of cyclized and uncyclized product formed when the C-5 substituent is aromatic. The hitherto unreported compounds synthesized may possess different biological activities [5-17].

RESULTS AND DISCUSSION

The synthesis of 3,5-disubstituted-1,2,4-oxadiazole begins with the nitration [25] of phenylacetonitrile **1** to obtain *o*- and *p*-nitro- phenylacetonitrile **2a** and **2** respectively. The pure *p*-nitrophenylacetonitrile **2** was obtained by recrystallization of the isomeric mixture. The nitro group was then reduced with Pd/C under H_2 atmosphere in THF to get *p*-aminophenylacetonitrile . This amino derivative on treatment with Et_3N and acetyl chloride in THF afforded *N*-(4-cyanomethylphenyl)-acetamide **3**.

Table 1

Synthesis of 3,5-Disubsituted-1,2,4-Oxadiazole

SN	Entry	R	Yield (%)[a]
1	6a	CH_3	76
2	6b	-CH_2CH_3	72
3	6c	-Ph	82
4	6d	-3-Pyridyl	79
5	6e	-CH_2Ph	75
6	6f	-CH_2CH_2Ph	72
7	6g	-CH=CHPh	71
8	6h	-CH=CH-Furyl	68
9	6i	- ^{t}Bu	73
10	6j	-CF_3	70[b]
11	6k	-H	77[c]

[a] Isolated yield; [b] Reaction carried at 45 °C; [c] Reaction carried at 100 °C.

Compound **3** when treated with $NH_2OH.HCl$ in presence of $NaHCO_3$ in methanol under refluxing condition afforded *N*-[4-(*N*-hydroxycarbamimidoylmethyl)-phenyl]-acetamide **4**. When compound **4** was reacted with different acid chlorides in presence of K_2CO_3 in 1,4-dioxane at an ambient temperature substituted amidoxime compounds **5(a-i)** were obtained. These compounds were then characterized with the help of IR and ^{1}H NMR spectra. The IR spectra of **5(a-i)** showed two absorption 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 **5(a-i)** 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 **5(a-i)** when refluxed in toluene in presence of mol. sieves for 8-15 h afforded *N*-[4-(5-substituted-1,2,4-oxadiazol-3-ylmethyl)-phenyl]-acetamide **6(a-i)**. 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}. Cyclization was also confirmed by the presence of absorption band in the region of 1570-1630 cm^{-1} which is due to imino group and ^{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 and absence of NH_2 protons in the region of 6.2-6.4 ppm.

In summary, we have synthesized a series of new *N*-[4-(5-substituted-1,2,4-oxadiazol-3-ylmethyl)-phenyl]-acetamide. The methodology developed utilizes neutral conditions *i.e*. mol. sieves for cyclodehydration so acid and base labile substrates can be cyclized in quantitative yield. The method is simple, does not produce side products, and the work up is easy. In addition to alkyl acids, aromatic acid can be used as well to obtain the cyclized product without obtaining uncyclized product. These attractive features make this methodology a useful addition to methodologies presently employed. The newly synthesized 3,5-disubstituted-1,2,4-oxadiazole compounds are stable and can be explored for various biological implications in drug research.

EXPERIMENTAL

Melting points were taken on a Precision melting point apparatus (DBK Instruments) and are uncorrected. IR spectra were obtained in potassium bromide (KBr) disks on a Bruker IR spectrophotometer, and ^{1}H NMR spectra were obtained on deuteriochloroform ($CDCl_3$) and or DMSO-d_6 solution on a Varian 200 MHz spectrophotometer. Elemental analyses were performed on Fissons micro CHN analyzer. Mass spectra were recorded on a MicroMass spectrometer by Waters. The yields unless otherwise mentioned are for the pure product.

Preparation of *N*-[4-(*N*-Hydroxycarbaimidoyl-ethyl)-phenyl]-acetamide (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 shaker flask at a pressure of 100 psi. for 4 h. The product *p*-amino-phenyl-acetonitrile (8.2 g, 0.06 mol) was reacted further without isolation with Et_3N (11.0 ml, 0.078 mol, 1.3 eq.) and acetyl chloride (5.3 ml, 0.07 mol, 1.1eq.) at 0 °C. The reaction mixture was warmed to r.t. over a period of 2 h. After completion of reaction, the solvent was evaporated under *vacuum* to obtain a pale yellow sticky mass. Solid precipitate obtained upon addition of chilled water, was collected by filtration and dried under *vacuum* to yield 11.0 g of *N*-(4-cyanomethyl-phenyl)-acetamide **3**. To a stirred solution of **3** (11.0 g, 0.061 mol, 1.0 eq.) in methanol (60 ml) was added $NH_2OH.HCl$ (38.0 g, 0.55 mol, 9.0 eq.), $NaHCO_3$ (51.24 g, 0.61 mol, 10.0 eq.) and refluxed overnight. The solvent was evapo-

rated under *vacuum* and ice cold water was added to the crude reaction mass. The solid that precipitated was collected by filtration and dried under *vacuum* and recrystallized from ethanol to obtain pure *N*-[4-(*N*-Hydroxycarbaimidoylmethyl)-phenyl]-acetamide **4** as a white solid (9.0 g, 85 %).

General procedure for the preparation of *O*-[alkyl or aryl substituted carbonyl]-4-acetamidophenyl methylamidoxime 5(a-i). To a stirred solution of *N*-[4-(*N*-hydroxycarbaimidoyl-methyl)-phenyl]-acetamide **4** (1.0 g, 0.005 mol) in 1,4-dioxan (10.0 ml) was added anhydrous K_2CO_3 (0.9 g, 0.0065 mol, 1.3 eq.). After 15 min, acid chloride (0.0055 mol, 1.1 eq.) was added to the above reaction mixture and stirred at r.t. After completion of the reaction, the solvent was removed under *vacuum* and water was added to the crude reaction mass. The solid that precipitated was collected by filtration, dried then either recrystallized or purified by column chromatography to give compounds **5(a-i)**. The yield, R_f value, mp and other details of each compound are given below.

***O*-Acetyl-(4-acetamidophenyl)-methylamidoxime (5a).** This compound was prepared using general procedure in 80 % yield, as white solid, mp 138-139 ºC; R_f = 0.27 ($CHCl_3$:MeOH ; 9:1); IR (KBr): 3538, 3442, 3125, 2967, 1741, 1670, 1615 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 3.5 (s, 2H, CH_2-Ph), 4.7 (s, 2H, NH_2), 7.2-7.3 (d, 2H, Ar-H), 7.4 (s, 1H, NH), 7.5-7.6 (d, 2H, Ar-H). ms: m/z 250 [M^+].

Anal. Calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 58.18; H, 6.37; N, 17.34.

***O*-Propionyl-(4-acetamidophenyl)-methylamidoxime (5b)**. This compound was prepared using general procedure in 78 % yield, as off-white solid, mp 150-51ºC; R_f = 0.25 ($CHCl_3$: MeOH; 9:1); IR (KBr): 3546, 3437, 3065, 2926, 1748, 1665, 1600 cm^{-1}; ^1H NMR (200 MHz, DMSO d_6): δ 1.0-1.1 (t, 3H, CH_3), 2.0 (s, 3H, O=C-CH_3), 2.3-2.4 (q, 2H, CH_2), 3.3 (s, 2H, CH_2Ph), 6.4 (s, 2H, NH_2), 7.2-7.3 (d, 2H, Ar-H), 7.4-7.6 (d, 2H, Ar-H), 9.9 (s, 1H, NH). ms: m/z 264.30 [M^+]. *Anal*. Calcd. For $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.65; H, 6.87; N, 16.50.

***O*-Benzoyl-(4-acetamidophenyl)-methylamidoxme (5c).** This compound was prepared using general procedure in 86 % yield, as buff colored solid, mp 180-81ºC; R_f = 0.35 ($CHCl_3$:MeOH; 9:1); IR (KBr): 3520, 3330, 3180, 2960, 1735, 1675, 1607 cm^{-1}; ^1H NMR (200 MHz, DMSO d_6): δ 2.0 (s, 3H, O=C-CH_3), 3.4 (s, 2H, CH_2-Ph), 6.6 (s, 2H, NH_2), 7.2-7.3 (d, 2H, Ar-H), 7.4-7.6 (d, 2H, Ar-H), 7.6-7.7 (m, 3H, Ar-H), 8.0-8.2 (d, 2H, Ar-H), 9.9 (s, 1H, NH). ms: m/z 312 [M+]. *Anal*. Calcd. For $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.96; H, 5.87; N, 13.96.

***O*-Pyridyl-(4-acetamidophenyl)-methylamidoxime (5d).** This compound was prepared using general procedure in 83 % yield, as white solid, mp 198-99 ºC; R_f = 0.24 ($CHCl_3$:MeOH; 9:1); IR (KBr): 3475, 3320, 3115, 2990, 1725, 1677, 1600 cm^{-1}; ^1H NMR (200 MHz, DMSO d_6): δ 2.0 (s, 3H, O=C-CH_3), 3.4 (s, 2H, CH_2-Ph), 6.7 (s, 2H, NH_2), 7.2-7.3 (d, 2H, Ar-H), 7.4-7.5 (d, 2H, Ar-H), 7.5-7.6 (m, 1H, Py-H), 8.4 (dd, 1H, Py-H), 8.8 (dd, 1H, Py-H), 9.2 (s, 1H, Py-H), 9.9 (s, 1H, NH). ms: m/z 313 [M+]. *Anal*. Calcd. For $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61.90; H, 5.52; N, 18.48.

***O*-Phenylacetyl-(4-acetamidophenyl)-methylamidoxime (5e).** This compound was prepared using general procedure in 80 % yield as pale yellow solid; mp 161-162 °C ; R_f = 0.28 ($CHCl_3$:MeOH ; 9:1); IR (KBr) : 3446, 3342, 3058, 2967, 1715, 1658, 1595; ^1H NMR (200 MHz, DMSO d_6): δ 2.0 (s, 3H, O=C-CH_3), 3.2 (s, 2H, CH_2-Ph), 3.7 (s, 2H, CH_2-Ph), 6.5 (s, 2H, NH_2), 7.2-7.3 (d, 2H, Ar-H), 7.3-7.4 (m, 5H, Ar-H), 7.4-7.5 (d, 2H, Ar-H), 9.9 (s, 1H, NH). ms: m/z 326 [M+]. *Anal*. Calcd. For $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.83; H, 6.34; N, 13.35.

***O*-Phenylpropionyl-(4-acetamidophenyl)-methyl-amidoxime (5f).** This compound was prepared using the general procedure in 78 % yield as pale yellow solid, mp 163-64 ºC; R_f = 0.41 ($CHCl_3$:MeOH; 9:1); IR (KBr): 3527, 3417, 3071, 2935, 1728, 1668, 1607 cm^{-1}; ^1H NMR (200 MHz, DMSO d_6): δ 2.1 (*s*, 3H, O=C-CH_3), 2.6-2.7 (t, 2H, CH_2), 2.8-2.9 (t, 2H, CH_2), 3.3 (s, 2H, CH_2Ph), 6.4 (s, 2H, NH_2), 7.2-7.3 (d, 2H, Ar-H), 7.3-7.5 (m, 5H, Ar-H), 7.5-7.6 (d, 2H, Ar-H), 9.9 (s, 1H, NH). ms: m/z 340 [M+]. *Anal*. Calcd. For $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 67.60; H, 6.55; N, 12.80.

***O*-3-Phenyl-acryloyl-(4-acetamidophenyl)-methyl-amidoxime (5g).** This compound was prepared using the general procedure in 83 % yield as white solid, mp 180-81 ºC; R_f = 0.36 ($CHCl_3$:MeOH; 9:1). IR (KBr): 3547, 3433, 3095, 2967, 1742, 1673, 1617cm^{-1}; ^1H NMR (200 MHz, DMSO d_6): δ 2.0 (s, 3H, O=C-CH_3), 3.3 (s, 2H, CH_2-Ph), 6.5 (s, 2H, NH_2), 6.7 (d, 1H, CH), 7.2-7.3 (d, 2H, Ar-H), 7.3-7.5 (m, 5H, Ar-H) 7.5 (d, 2H, Ar-H), 7.8 (d, 1H, CH), 9.9 (s, 1H, NH). ms: m/z 338 [M+]. *Anal*. Calcd. For $C_{19}H_2N_3O_3$: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.99; H, 6.05; N, 12.89.

***O*-3-Furan-2-yl-acryloyl-(4-acetamidophenyl)-methyl-amidoxime (5h).** This compound was prepared using general procedure in 79 % yield as white solid, mp 190-91 ºC. R_f = 0.38 ($CHCl_3$:MeOH; 9:1). IR (KBr): 3519, 3428, 3067, 2973, 1729, 1679, 1627 cm^{-1}; ^1H NMR (200 MHz, DMSO d_6): δ 2.2 (s, 3H, O=C-CH_3), 3.6 (s, 2H, CH_2-Ph), 4.9 (s, 2H, NH_2), 6.4 (d, 1H, CH), 6.6 (m, 1H, CH), 6.8 (d, 1H, CH), 7.2-7.3 (d, 2H, Ar-H), 7.3-7.4 (d, 2H, Ar-H), 7.4-7.5 (s, 1H, CH), 7.6 (d, 1H, CH), 9.9 (s, 1H, NH). ms: m/z 328 [M+]. *Anal*. Calcd. For $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23; N, 12.84. Found: C, 62.75; H, 5.60; N, 13.30.

***O*-Pivaloyl-(4-acetamidophenyl)-methylamidoxime (5i).** This compound was prepared using general procedure in 81 % yield as white solid, mp 146-47 ºC. R_f = 0.43 ($CHCl_3$:MeOH; 9:1). IR (KBr): 3522, 3413, 3079, 2981, 1737, 1681, 1621 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.3 (s, 9H, ^{t}butyl), 2.2 (s, 3H, O=C-CH_3), 3.5 (s, 2H, CH_2-Ph), 4.8 (s, 2H, NH_2), 7.2-7.3 (d, 2H, Ar-H), 7.4-7.6 (d, 2H, Ar-H), 7.7 (s, 1H, NH). ms: m/z 292 [M+]. *Anal*. Calcd. For $C_{15}H_{21}N_3O_3$: C, 61.84; H, 7.27; N, 14.42. Found: C, 62.20; H, 7.63; N, 14.87.

General procedure for the preparation of *N*-[4-(5-substituted-1,2,4-oxadiazol-3-ylmethyl)-phenyl]-acetamide 6 (a-i). To a solution of **5 (a-i)** (0.001 mol) in toluene (10.0 ml) and *N*,*N*-dimethylformamide (2.0 ml) was added freshly dried mol. sieves 4Å and refluxed for 6-15 h. After completion of reaction, the reaction mixture was cooled to r.t. and filtered. The filtrate was evaporated under *vacuum* to obtain crude cyclized product that was then purified either by recrystallization or by column chromatography using $CHCl_3$:MeOH (9:1) to afford pure solid compounds **6 (a-i)**. The yield, R_f value, mp and other details of each product are given below.

***N*-[4-(5-Methyl-1,2,4-oxadiazol-3-ylmethyl)-phenyl]-acetamide (6a).** This compound was prepared using the general procedure in 76 % yield as white powder, mp 148-149 ºC; R_f = 0.37 ($CHCl_3$:MeOH; 9:1); IR (KBr): 3315, 3085, 2975, 1690, 1607 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 4.0 (s, 2H, CH_2-Ph), 7.2 (s, 1H, NH), 7.2-7.3 (d, 2H, Ar-H), 7.4-7.5 (s, 2H, Ar-H). ms: m/z 232 [M+]. *Anal*. Calcd for $C_{12}H_{13}N_3O_2$:

C, 62.33; H, 5.67; N, 18.17. Found: C, 62.58; H, 5.99; N, 18.54.

***N*-[4-(5-Ethyl-1,2,4-oxadiazol-3-ylmethyl)-phenyl]-acetamide (6b).** This compound was obtained as white solid in 72 % yield, mp 90-91 ºC; R_f = 0.38 ($CHCl_3$:MeOH; 9:1). IR (KBr): 3330, 3062, 2990, 1675, 1595 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.3-1.4 (t, 3H, CH_3), 2.2 (s, 3H, CH_3), 2.8-3.0(q, 2H, CH_2), 4.0(s, 2H, CH_2-Ph), 7.2 (s, 1H, NH), 7.2-7.4 (d, 2H, Ar-H), 7.4-7.6 (s, 2H, Ar-H). ms: m/z 246 [M+]. *Anal* Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.99; H, 6.53; N, 17.55.

***N*-[4-(5-Phenyl-1,2,4-oxadiazol-3-ylmethyl)-phenyl]-acetamide (6c).** This compound was obtained as white solid in 82 % yield, mp 137-138 ºC; R_f = 0.45 ($CHCl_3$:MeOH; 9:1). IR (KBr): 3321, 3081, 2979, 1685, 1615 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 2.0 (s, 3H, CH_3), 4.1(s, 2H, CH_2-Ph), 7.2-7.3 (d, 2H, Ar-H), 7.4-7.6 (s, 2H, Ar-H). 7.6-7.7(m, 3H, Ar-H), 8.0-8.1(d, 2H, Ar-H), 9.9(s, 1H, NH). ms: m/z 294 [M+]. *Anal* Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33; Found: C, 69.98; H, 5.52; N, 14.75.

***N*-[4-(5-Pyridyl-1,2,4-oxadiazol-3-ylmethyl)-pheyl]-acetamide (6d).** This compound was prepared using general procedure in 79 % yield, as buff colored solid , mp 169-170 ºC; R_f= 0.36 ($CHCl_3$:MeOH; 9:1) IR (KBr): 3329, 3070, 2971, 1689, 1610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 4.1 (s, 2H, CH_2-Ph), 7.2 (s, 1H, NH), 7.3-7.4 (d, 2H, Ar-H), 7.4-7.5 (s, 2H, Ar-H). 7.5-7.6 (m, 3H, py-H), 8.4-8.5 (dd, 1H, py-H), 8.8 (dd, 1H, py-H), 9.4 (s, 1H, py-H). ms: m/z 295 [M+]. *Anal* Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04; Found: C, 65.68; H, 5.17; N, 19.44.

***N*-[4-(5-Benzyl-1,2,4-oxadiazol-3-ylmethyl)-phenyl]-acetamide (6e).** This compound was prepared using general procedure in 75 % yield, as pale yellow solid, mp 82-83 ºC; R_f = 0.41 ($CHCl_3$:MeOH; 9:1); IR (KBr): 3333, 3091, 2981, 1667, 1586 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 4.0 (s, 2H, CH_2-Ph), 4.2 (s, 2H, CH_2-Ph), 7.2 (s, 1H, NH), 7.2-7.3 (d, 2H, Ar-H), 7.3-7.4 (m, 5H, Ar-H). 7.4-7.5 (d, 2H, Ar-H). ms: m/z 308 [M+]. *Anal* Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67; Found: C, 70.71; H, 5.83; N, 14.14.

***N*-[4-(5-Phenylethyl-1,2,4-oxadiazol-3-ylmethyl)-phenyl]-acetamide (6f).** This compound was prepared using the general procedure in 72 % yield as white solid, mp 84-85 ºC; R_f = 0.53 ($CHCl_3$:MeOH; 9:1); IR (KBr): 3346, 3082, 2971, 1673, 1616 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.1 (s, 3H, CH_3), 2.7-2.8 (t, 2H, CH_2), 2.9-3.0 (t, 2H, CH_2), 4.0 (s, 2H, CH_2-Ph), 7.2 (s, 1H, NH), 7.2-7.3 (d, 2H, Ar-H), 7.3-7.4 (m, 5H, Ar-H), 7.4-7.6 (d, 2H, Ar-H) ms: m/z 322 [M+]. *Anal* Calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.07; Found: C, 71.38; H, 6.31; N, 13.44.

***N*-[4-(5-((*E*-Styryl)-1,2,4-oxadiazol-3-ylmethyl)-phenyl]-acetamide (6g).** This compound was obtained as white solid in 71 % yield, mp 156-57 ºC; R_f = 0.56 ($CHCl_3$:MeOH; 9:1); IR (KBr): 3332, 3070, 2969, 1668, 1612 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 4.1(s, 2H, CH_2-Ph), 6.95-7.05(d, 2H, CH), 7.2-7.3 (d, 2H, Ar-H), 7.3-7.4 (m, 5H, Ar-H). 7.4-7.6(d, 2H, Ar-H); ms: m/z 320 [M+]. *Anal* Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.84; H, 5.51; N, 13.59.

***N*-[4-(5-((*E*-Furan-2-yl-vinyl)-1,2,4-oxadiazol-3-yl-methyl)-phenyl]-acetamide (6h).** This compound was obtained as white solid in 68 % yield, mp 180-81 ºC; R_f = 0.48, ($CHCl_3$:MeOH; 9:1); IR (KBr): 3341, 3090, 2988, 1688, 1622 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.2(s, 3H, CH_3), 4.0-4.1(s, 2H, CH_2-Ph), 6.5(m, 1H, CH), 6.7(d, 1H, CH), 6.8-6.9(d, 2H, CH), 7.2(s, 1H, NH), 7.3-7.4 (d, 2H, Ar-H). 7.4-7.5 (d, 2H, Ar-H), 7.5(d, 1H CH). ms: m/z 310. *Anal*. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 66.38; H, 5.27; N, 14.00.

***N*-[4-(5-*tert*-Butyl-1,2,4-oxadiazol-3-ylmethyl)-phenyl]-acetamide (6i).** This compound was prepared using general procedure in 73 % yield as white solid, mp 110-111 ºC; R_f = 0.52, ($CHCl_3$:MeOH; 9:1); IR (KBr): 3331, 3083, 2993, 1692, 1611 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.4 (s, 9H, $(CH_3)_3$), 2.1 (s, 3H, CH_3), 4.0 (s, 2H, CH_2-Ph), 7.2 (s, 1H, NH), 7.2-7.3 (d, 2H, Ar-H), 7.4-7.5 (d, 2H, Ar-H). ms: m/z 274 [M+]. *Anal* Calcd for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 66.28; H, 7.40; N, 15.79.

***N*-[4-(5-Trifluoromethyl-1,2,4-oxadiazol-3-ylethyl)-phenyl]-acetamide (6j).** To a solution of compound **4** (0.3 g, 0.0014 mol) and Et_3N (0.24 ml, 0.0017 mol, 1.2 eq.) in dry CH_2Cl_2 (15.0 ml) was added trifluoroacetic anhydride (0.6 ml, 0.0042 mol, 3.0 eq.) and heated to reflux for 6 h. After completion of reaction, organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to get crude compound which after triturating in diethyl ether afforded white solid in 70 % yield, mp 120-121 ºC; R_f = 0.42, ($CHCl_3$:MeOH; 9:1); IR (KBr): 3325, 3075, 2975, 1671, 1604 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 4.2 (s, 2H, CH_2-Ph), 7.2 (s, 1H, NH), 7.2-7.3 (d, 2H, Ar-H), 7.5-7.6 (d, 2H, Ar-H). ms: m/z 286 [M+]. *Anal*. Calcd for $C_{12}H_{10}F_3N_3O_2$: C, 50.53; H, 3.53; N 14.73. Found: C, 50.89; H, 3.90; N, 15.20.

***N*-[4-(1,2,4-Oxadiazol-3-yl-methyl)-phenyl)]-acetamide (6k).** A solution of compound **4** (0.3 g, 0.0014 mmole) in dimethyl-formamide-dimethylacetal (3.0 ml) was heated at 100 °C for 4-6 h. Reaction mixture was brought to r.t. and poured onto crushed ice under vigorous stirring. The precipitate was separated by filtration, dried and purified by column chromatography over silica gel using $CHCl_3$-MeOH (9:1) as mobile phase to obtain white solid in 77 % yield, mp 130-131 ºC; R_f = 0.32 ($CHCl_3$:MeOH; 9:1); IR (KBr): 3330, 3060, 2969, 1670, 1614 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.2 (s, 3H, CH_3), 4.1 (s, 2H, CH_2-Ph), 7.2 (s, 1H, NH), 7.3 (d, 2H, Ar-H), 7.5 (d, 2H, Ar-H), 8.6 (s, 1H, Oxadiazole-H). ms: m/z 218 [M^+]. *Anal* Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 61.18; H, 5.46; N, 19.80.

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