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# Antiinflammatory Property of 3-Aryl-5-(*n*-propyl)-1,2,4-oxadiazoles and Antimicrobial Property of 3-Aryl-5-(*n*-propyl)-4,5-dihydro-1,2,4-oxadiazoles: Their Syntheses and Spectroscopic Studies†

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**Abstract**—The synthesis of six 3-aryl-5-(*n*-propyl)-4,5dihydro-1,2,4-oxadiazoles **3a**–**f** has been achieved in a facile manner by the reaction of an appropriate arylamidoxime **1a**–**f** with butyraldehyde **2**. Oxidation of **3a**–**f** individually using $MnO_2$ in $CH_2Cl_2$ or sodium hypochlorite in THF/$H_2O$ furnished 1,2,4-oxadiazoles **4a**–**f** in good to excellent yields. Compounds **4a**–**f** were also evaluated against inflammation. Except **4e**, all of them reduced inflammation, however, **4c** presented better antiinflammatory activity. A preliminary antimicrobial activity tests of **3a**–**f** showed that these compounds possess activity against some microorganisms. In fact, **3c** and **3f** have been found to be more effective against *Staphylococcus aureus*, *Mycobacterium smegmatis*, and *Candida albicans*.


It is now well known that cyclooxygenase (COX) is involved in the biosynthesis of proinflammatory prostaglandins from arachidonic acid. After their production, prostaglandins are released locally in tissues and cause inflammation. There are two isoforms of COX enzyme, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2).[1] The former is constitutively expressed for carrying on physiological activities in the body, while COX-2 is induced locally by cytokines and mitogens etc. causing overproduction of prostaglandins during the inflammatory and colorectal tumor formation processes.[2] In 1998, it has been suggested that the overexpression of COX-2 and the subsequent enhanced production of prostaglandins might be responsible for the evolution of colon cancer.[3] Therefore, the selective inhibitors of COX-2 are needed to combat the inflammation and also to controle the evolution of cancer in the colon and other parts of the body.

For the last several years, our research has been directed to discover the nonsteroidal antiinflammatory drugs (NSAIDs), more particularly to the selective inhibitors of COX-2, because the importance of this class of drugs is almost impossible to overestimate. The following paragraphs describe the reason for undertaking the synthesis and pharmacological evaluations of the title compounds.

1,2,4-Oxadiazole derivatives possess interesting pharmacological properties.[4,5] Two of our recent publications cite references describing diversified biological activities of 3,5-disubstituted 1,2,4-oxadiazoles.[6,7] Some of the oxadiazoles, synthesized by us, presented analgesic and antiinflammatory properties.[8,9] For example, *N*-[3-aryl-1,2,4-oxadiazol-5-yl-methyl]phthalimides have been found to be analgesic, and one of them viz., *N*-[3-phenyl-1,2,4-oxadiazol-5-yl-methyl]phthalimide exhibited analgesic activity far superior than aspirin.[8] Since 3-aryl-5-isopropyl-1,2,4-oxadiazoles showed antiinflammatory properties,[9] we thought to prepare the title compounds, in order evaluate their response against inflammation and compare their behavior with the known 3-aryl-5-isopropyl-1,2,4-oxadiazoles.[9] This paper therefore describes first the synthesis of 4,5-dihydro-1,2,4-oxadiazoles **3a**–**f** from **1a**–**f** and **2** followed by their oxidation to **4a**–**f** (Scheme 1). Five compounds, viz., **4a**–**d**,**f** have been

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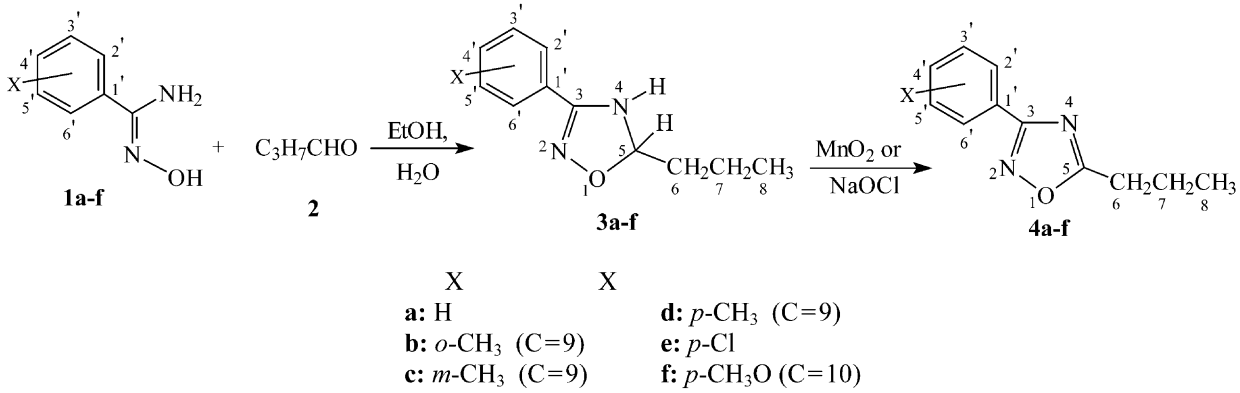



**Scheme 1.**

found to possess antiinflammatory properties although less than aspirin, but are comparable with 3-aryl-5-isopropyl-1,2,4-oxadiazoles reported earlier.[9]

## Chemistry

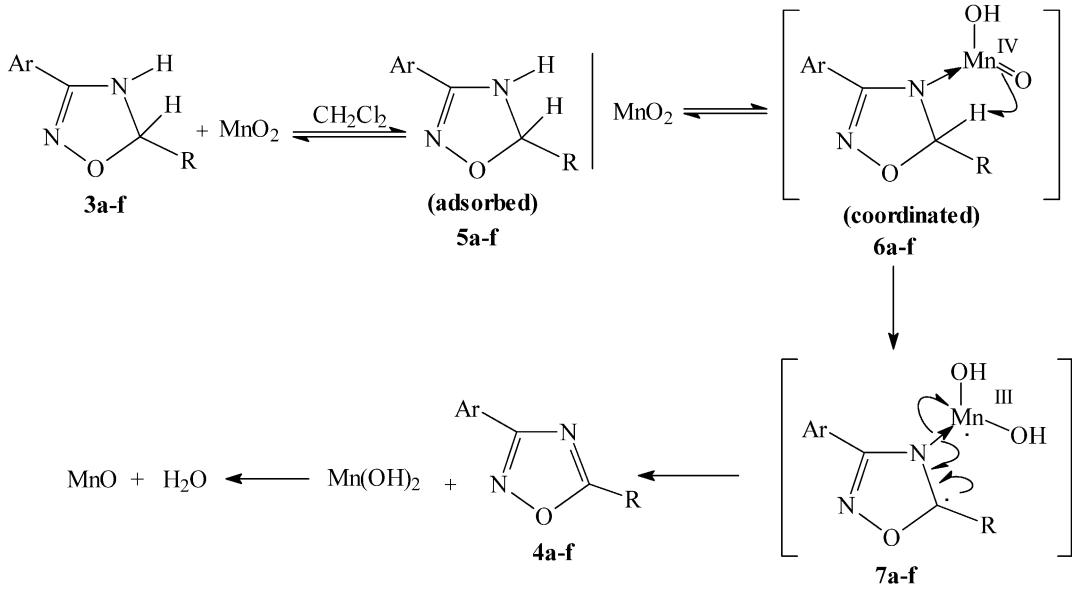
The synthesis of 3-aryl-5-propyl-4,5-dihydro-1,2,4-oxadiazoles **3a–f** has been achieved from arylamidoximes **1a–f** and *n*-butyraldehyde **2** in the presence of a small quantity of an acidic ion-exchange resin (Amberlite IRP-64) as a catalyst. The structures of these products were deduced from infrared and nuclear magnetic resonance spectroscopy.

The synthesis of 3-aryl-5-propyl-1,2,4-oxadiazoles **4a–f** was achieved from **3a–f** in two different oxidative ways: first, with manganese dioxide in methylene chloride and second, with sodium hypochlorite in a mixture of tetrahydrofuran and water. After purification, the compounds gave the expected NMR signals for 1,2,4-oxadiazoles. The infrared spectra also tallied with their structures.

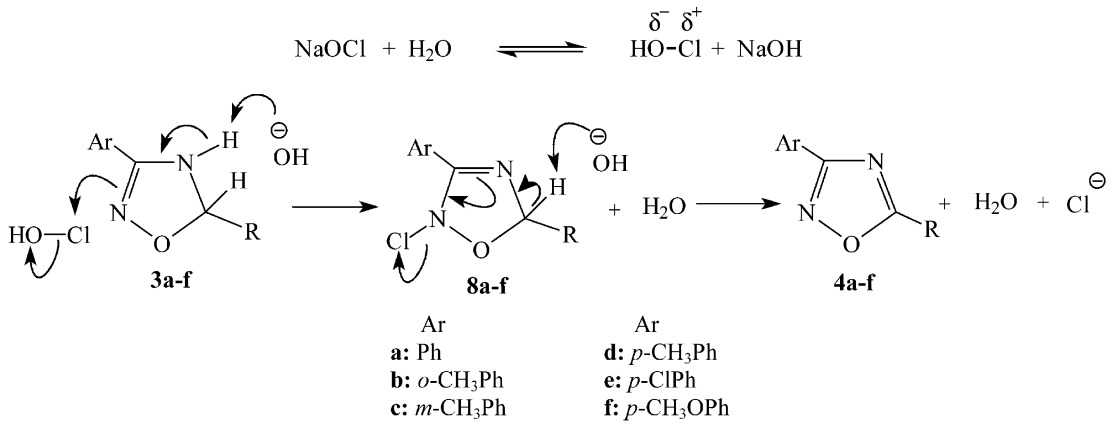
The mechanism of formation of 1,2,4-oxadiazoles from 4,5-dihydro-1,2,4-oxadiazoles with manganese dioxide and with sodium hypochlorite are shown in Schemes 2 and 3. The mechanism of oxidation of benzyl alcohol with manganese dioxide has been studied by Goldman.[10] He concluded that the rate-determining step in the oxidation of benzyl alcohols with activated manganese dioxide involves cleavage of the α-CH bond, and that the assumed adsorption step is reversible. Similar mechanism should be considered for the oxidation of **3a–f** to **4a–f** (Scheme 2).

Initially, 4,5-dihydro-1,2,4-oxadiazole is adsorbed at the surface of manganese didoxide (shown in **5a–f**) followed by the proton transfer from N-4 to one of the oxygen atoms of $MnO_2$ with the formation of a coordinated bond between N-4 and Mn (**6a–f**). Abstraction of a hydrogen radical from C-5 generates a diradical species which loses $Mn(OH)_2$ from **7a–f** to give **4a–f**.

The literature records the oxidation of 4,5-dihydro-1,2,4-oxadiazoles to 1,2,4-oxadiazoles using sodium hypochlorite, but no mechanism of such oxidation has been reported.[11] Therefore, we suggest a probable mechanism of transformation of 4,5-dihydro-1,24-oxadiazoles to oxadiazoles with sodium hypochlorite (Scheme




**Scheme 2.**




**Scheme 3.**

3). The first step is the removal of proton from N-4 which leads to the formation of 3-aryl-2-chloro-2,5-dihydro-1,2,4-oxadiazoles **8a–f**. Subsequent elimination of HCl by the hydroxide ion from this intermediate furnishes **4a–f**.

### Antiinflammatory activity

For the last many years, there has been a great interest to develop new non-steroidal antiinflammatory drugs (NSAIDs) which could specifically inhibit cyclooxygenase-2 (COX-2), the enzyme responsible for the production of prostaglandins and other mediators which are directly associated with inflammation process. Some selective inhibitors for COX-2 have already been found,[12–14] and the research in this direction continues with a view to discover new drugs for inhibiting this enzyme. The aim is to have drugs with better efficacy, less toxicity and less side effects.

5-Methyl-3-phenyl-1,2,4-oxadiazole was examined in 1972 for antiinflammatory properties, which showed similar effect as that of phenylbutazone[15] in terms of activity. Later on, other oxadiazoles have been examined by us for analgesic and/or antiinflammatory activities with promising results.[8,9] Since, 3-aryl-5-alkyl-1,2,4-oxadiazoles possess an aromatic ring at position 3 and an alkyl group at C-5, they become liposoluble. It is supposed that such property should possibly lead to anaesthetic or hypoanalgesic properties in living beings, because this lipophylic property is essential for a drug to cross the hematoencephalic barrier and to reach the central nervous system, exercising its effects, such as, sedation.

## Results

### Preliminary antiinflammatory and toxicity tests of 3-aryl-5-propyl-1,2,4-oxadiazoles 4a–f

Preliminary antiinflammatory activity tests have been performed for compounds **4a–f**. All of them except compound **4e** exhibited antiinflammatory properties when compared with acetylsalicylic acid. Oxadiazoles **4a** and **4f** were 50% less effective than aspirin while **4b** and **4d** were ~70% less effective. Compound **4c** gave significant results and is comparable with aspirin (Table 1). Heterocycle **4e** did not cause any inflammation reduction.

A comparative analysis of the antiinflammatory test results of compounds **4a–d,f** and aspirin is shown in Figure 1.

The acute toxicity test in mice produced an interesting phenomenon. The animals demonstrated a sign of nervous system excitation (piloerection, cardiac acceleration, psychomotor agitation with repeated shivering), and soon after a light sedation. These phenomenon were exacerbated with the gradual increase in dose administration. Meanwhile, no animal of any group died after

**Table 1.** Antiinflammatory test results of compounds **4a–d,f** and acetylsalicylic acid (Aspirin)[a]

| Compd | Average difference in paw weights (g) (standard deviation) | Edema reduction (%) |
|---|---|---|
| ASA | 0.06392 ± 0.00449 | 35.17 |
| **4a** | 0.08160 ± 0.00609 | 17.24 |
| **4b** | 0.08666 ± 0.01096 | 12.17 |
| **4c** | 0.07240 ± 0.00427 | 26.57 |
| **4d** | 0.08516 ± 0.00874 | 9.73 |
| **4f** | 0.08008 ± 0.00827 | 18.78 |

[a]Compound **4e** did not show any antiinflammatory activity.

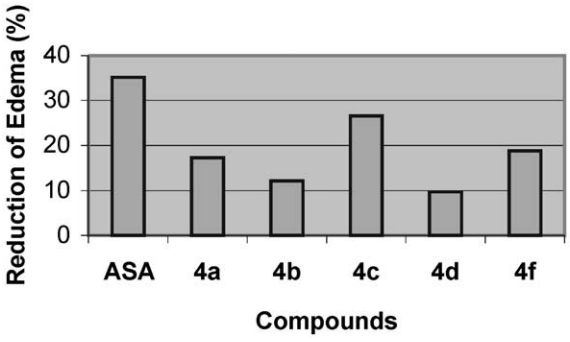



**Figure 1.** Comparative analyses of the antiinflammatory activity of compounds **4a–d,f** and acetyl salicylic acid (ASA).

**Table 2.** Acute toxicity test results of compounds **4a–f**

| Compd | Dose (mg/kg) | Number of dead/batch. after 72 h | DL-50 |
|---|---|---|---|
| **4a** | 125 | 0/5 | |
| | 250 | 0/5 | |
| | 500 | 0/5 | n.f. |
| | 1000 | 0/5 | |
| **4b** | 125 | 0/5 | |
| | 250 | 0/5 | |
| | 500 | 0/5 | n.f. |
| | 1000 | 0/5 | |
| **4c** | 125 | 0/5 | |
| | 250 | 0/5 | |
| | 500 | 0/5 | n.f. |
| | 1000 | 0/5 | |
| **4d** | 125 | 0/5 | |
| | 250 | 0/5 | |
| | 500 | 0/5 | n.f. |
| | 1000 | 0/5 | |
| **4e** | 125 | 4/5 | |
| | 250 | 4/5 | |
| | 500 | 5/5 | — |
| | 1000 | 5/5 | |
| **4f** | 125 | 0/5 | |
| | 250 | 0/5 | |
| | 500 | 0/5 | n.f. |
| | 1000 | 0/5 | |

n.f.: Not found., DL-50: lethal dose for 50% of the animals.

48 h with the dose tested (125–1000 mg/kg of body weight) except in the case of **4e**, where more than 50% of the animals died (see Table 2).

## Experimental determination of antiinflammatory activity

All compounds were evaluated for their antiinflammatory activity following the procedure developed by Levy.[16] The inflammation was introduced by administering (0.1%) carrageenin in aqueous saline (0.9% NaCl) solution on the hind paws of the white male Swiss albino mice of specie *Mus muscullus* having approximate weight of 30.00 g each. After 30 min, the synthesized compounds were administered intraperitoneally in one dose of 250 mg/kg of the animal's weight to one group of five animals. Simultaneously, for positive and negative controls, acetyl salicylic acid and vegetable oil were injected intraperitoneally. The animals were sacrificed 4 h after the drug administration, and the antiinflammatory activity determined by amputation of the hind paws of the region, which were weighed and the difference was obtained from the control groups.

## Preliminary antimicrobial evaluation of compounds 3a–f

It is common in countries with tropical climate and precarious socio-economic conditions to have higher incidence of diseases caused by microorganisms, especially bacteria and fungi. The climate in conjunction with sub-normal life conditions in certain regions cause the microorganisms to proliferate. The indiscriminate use of antibiotics has been increasing resulting in the resistance of many bacteria. For example, *Staphylococcus aureus* is responsible for hospital infections in many patients. For this reason, we became interested to test 3-aryl-4,5-dihydro-1,2,4-oxadiazoles **3a–f** against bacteria and fungi. In fact, many heterocycles have been found to be effective against these microorganisms, the literature, however, doesn't contain much information about 4,5-dihydro-1,2,4-oxadiazoles. The closer example is a 4,5-dihydro-1,3-oxazole connected to a isoxazole ring through an ether bridge.[17] This compound inhibits rhinovirus.

A preliminary antimicrobial activity tests of compounds **3a–f** against *Mycobacterium smegmatis*, *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Enterobacter aerogenes*, *Saccharomyces cerevisae and Candida albicans*, were carried out. However, only two of them, viz., **3c** and **3f** gave interesting results as shown in Tables 3 and 4. Two different technicques, viz., the procedure of dilution in agar,[18] and the disc method,[19] have been used to evaluate the antimicrobial activity. The disc test involved the culture medium of Mueller–Hinton[20] with D-glucose, 2 g/L, 13 mm of disc diameter, and the concentration of the compounds were 1.2 mg/disc.

Although, **3c** and **3f** are more efficient, **3c** has presented much better activity against *Mycobacterium smegmatis*, and needs exploration in the future for acid-resistant bacteria specially the ones which cause tuberculosis and leprosy.

## Conclusion

We have achieved the syntheses of six 3-aryl-5-(*n*-propyl)-4,5-dihydro-1,2,4-oxadiazoles **3a–f**, five of which **3b–f** are new. Oxidation of **3a–f** either with manganese dioxide or with sodium hypochlorite furnished 3-aryl-5-(*n*-propyl)-1,2,4-oxadiazoles **4a–f**. The mechanism of oxidation of **3a–f** to **4a–f** by both methods has been suggested by us. Oxadiazoles **4a–d**,**f** have been found to possess antiinflammatory activity. Also, 4,5-dihydro-

**Table 3.** Antimicrobial activity of 3-aryl-5-(*n*-propyl)-4,5-dihydro-1,2,4-oxadiazoles **3c–f**[a] using the dilution susceptibility test technique

| Microorganisms | Minimum inhibitory concentration (MIC) in mg/L or in ppm | | | |
|---|---|---|---|---|
| | **3c** | **3d** | **3e** | **3f** |
| *Staphylococcus aureus* | >100≤200 | >400 | >400 | >100≤200 |
| *Bacillus subtilis* | >200≤300 | >400 | >400 | >200≤300 |
| *Escherichia coli* | >400 | >400 | >400 | >400 |
| *Enterobacter aerogenes* | >300≤400 | >400 | >400 | >400 |
| *Candida albicans* | >200≤300 | >400 | >400 | >200≤300 |

[a]Compounds **3a** and **3b** did not show any reasonable antimicrobial activity.

**Table 4.** Antimicrobial activity of 3-aryl-5-(*n*-propyl)-4,5-dihydro-1,2,4-oxadiazoles **3b–f** using diffusion test procedures

| Microorganisms | Zone diam (nearest whole mm) | | | | | |
|---|---|---|---|---|---|---|
| | **3a** | **3b** | **3c** | **3d** | **3e** | **3f** |
| *S. aureus* | — | — | — | — | — | — |
| *B. subtilis* | — | — | — | — | — | — |
| *E. coli* | — | — | — | — | — | — |
| *E. aerogenes* | — | — | — | — | — | — |
| *M. smegmatis* | 3 | 2 | 6 | 3 | 1 | 4 |
| *S. cerevisae* | 3 | 1 | 8 | 2 | 3 | 1 |

1,2,4-oxadiazoles **3a–e** have shown to possess reasonable microbial activity against *Mycobacterium smegtatis*, *Monila sitophila*, *Candida albicans*, and *Staphylococcus aureus*.

## Experimental

Melting points were determined on an Electrothermal digital melting point apparatus (model 9100) and are uncorrected. Infrared spectra were recorded with a Brucker model IFS66 FT-IR spectrophotometer using potassium bromide pellets for solid samples and neat material for liquid samples. NMR spectra were measured with a Varian Unity Plus instrument (300 $MH_2$) using $CDCl_3$ as solvent, and $Me_4Si$ as an internal reference. Silica gel coated plates with fluorescent indicator ($PF_{254}$) were used for thin-layer chromatography (TLC), and the spots were detected under ultraviolet light. The solvent system for TLC plates was chloroform for compounds **4a–f** and chloroform–ethyl acetate (8:2) for **3a–f**.

### General procedure

**3-Aryl-5-(*n*-propyl)-4,5-dihydro-1,2,4-oxadiazoles 3a–f.** Initially, the preparation of **3a–f** was carried out according to the method reported earlier.[21] The reaction was performed with an appropriate arylamidoxime and freshly distilled butyraldehyde at room temperature. It took between 5 and 8 days for the reaction to complete.

When the reaction of an arylamidoxime with butyraldehyde was done in the presence of Amberlite IRP-64 (–$CO_2H$ form) following the published methodology, the reaction time was reduced from 5–8 days to 3 days.[9] The details of each 4,5-dihidro-1,24-oxadiazole is given below. The compounds were crystallized from chloroform–*n*-hexane or ethanol–water.

**5-(*n*-Propyl)-3-phenyl-4,5-dihydro-1,2,4-oxadiazole (3a).** (89%, 75.6–76.0 °C, $R_f$ 0.69, lit.[22] mp 74.0 °C). UV$\lambda_{max}$ (EtOH), 291.2 and 228.2 nm. IR (KBr) 3202 (NH), 1598 (C=N), 861(NO), 1131 $cm^{-1}$ (C–O). $^1H$ NMR ($CDCl_3$) δ 0.98 (t, 3H, $J=7.35$ Hz, $CH_3$), 1.43–1.56 (m, 2H, $CH_2$), 1.66–1.86 (m, 2H, $CH_2$), 4.77 (b, 1H, NH), 5.67 (4 line signal, 1H, $J=5.10$ Hz, $J=9.30$ Hz, CH), 7.35–7.48 (m, 3H, H-3′, H-4′ and H-5′), 7.65–7.72 (m, 2H, H-2′ and H-6′); $^{13}C$ NMR ($CDCl_3$) δ 13.88 (C-8), 17,12 (C-7), 38.10 (C-6), 92.89 (C-5), 125.63 (C-1′), 126.39 (C-2′ and C-6′), 128.64 (C-3′ and C-5′), 130.74 (C-4′), 155.99 (C-3). Anal. calcd for $C_{11}H_{14}N_2O$. C, 69.47; H, 7.37; N, 14.72. Found C, 69.29; H, 7.13; N, 14.48.

**5-(*n*-Propyl)-3-(*o*-tolyl)-4,5-dihydro-1,2,4-oxadiazole (3b).** (59%, 65.8–66.4 °C, $R_f$ 0.70). UV$\lambda_{max}$ (EtOH), 274.4 and 226.4 nm. IR (KBr) 3201 (N–H), 1608 (Ar–H), 1588 (C=N), 830 (N–O), 1105 $cm^{-1}$ (C–O). $^1H$ NMR ($CDCl_3$) δ 1.02 (t, 3H, $J=7.35$ Hz, $CH_3$), 1.44–1.62 (m, 2H, $CH_2$), 1.68–1.90 (m, 2H, $CH_2$), 2.55 (s, 3H, Ar–$CH_3$), 4.50 (b, 1H, N–H), 5.67 (m, 1H, C–H), 7.20–7.39 (m, 3H, H-3′, H-4′, H-5′), 7.51 (dd, 1H, $J=7.65$ Hz, $J=2.70$ Hz, H-6′); $^{13}C$ NMR ($CDCl_3$) δ 13.93 (C-8), 17.18 (C-7), 21.45 (C-9), 38.14 (C-6), 92.03 (C-5), 125.03 (C-1′), 125.80 (C-5′), 128.41 (C-6′), 130.16 (C-3′), 131.26 (C-4′), 137.96 (C-2′) 156.08 (C-3). Anal. calcd for $C_{12}H_{16}N_2O$. C, 70.57; H, 7.89; N, 13.71. Found C, 70.46; H, 7.67; N, 13.47.

**5-(*n*-Propyl)-3-(*m*-tolyl)-4,5-dihydro-1,2,4-oxadiazole (3c).** (85%, 67.0–67.5 °C, $R_f$ 0.77). UV$\lambda_{max}$ (EtOH), 282.2 and 232.2 nm. IR (KBr) 3204 (N–H), 1606 (C=N), 857 (N–O), 1106 (C–O). $^1H$ NMR ($CDCl_3$) δ 0.94 (t, 3H, $J=7.35$ Hz, $CH_3$), 1.42–1.60 (m, 2H, $CH_2$), 1.64–1.90 (m, 2H, $CH_2$), 2.35 (s, 3H, Ar–$CH_3$), 5.60 (dd, 1H, $J=4.95$ Hz, $J=9.00$ Hz, C–H), 7.21–7.34 (m, 2H, H-4′ and H-5′) 7.42–7.60 (m, 2H, H-2′ and H-6′); $^{13}C$ NMR ($CDCl_3$) δ 13.87 (C-8), 17.09 (C-7), 21.21 (C-9), 38.10 (C-6), 92.80 (C-5), 123.47 (C-6′), 125.47 (C-1′), 126.97 (C-2′), 128.51 (C-5′), 131.49 (C-4′), 138.42 (C-3′) 156.10 (C-3). Anal. calcd for $C_{12}H_{16}N_2O$ C, 70.57, H, 7.89, N, 13.71. Found C, 70.59, H, 8.14, N, 13.73%.

**5-(*n*-Propyl)-3-(*p*-tolyl)-4,5-dihydro-1,2,4-oxadiazole (3d).** (87%, 82 °C, $R_f$ 0.67). UV$\lambda_{max}$ (EtOH) 288.8 and 235.8 nm. IR (KBr) 3222 (N–H), 1599 (either Ar–H or C=N), 865 (N–O), 1106 (C–O). $^1H$ NMR ($CDCl_3$) δ 0.96 (t, 3H, $J=7.35$ Hz, $CH_3$), 1.40–1.58 (m, 2H, $CH_2$), 1.64–1.86 (m, 2H, $CH_2$), 2.37 (s, 3H, Ar–$CH_3$), 4.86 (b, 1H, N–H), 5.63 (dd, 1H, $J=4.80$ Hz, $J=9.30$ Hz, H-5), 7.17 (d, 2H, $J=8.25$ Hz, H-3′ and H-5′), 7.55 (d, 2H, $J=8.25$ Hz, H-2′ and H-6′); $^{13}C$ NMR ($CDCl_3$) δ 14.16 (C-8), 17.44 (C-7), 21.73 (C-9), 38.35 (C-6), 93.02 (C-5), 122.93 (C-1′), 126.67 (C-2′ and C-6′), 129.64 (C-3′ and C-5′), 141.45 (C-4′), 156.26 (C-3). Anal. calcd for $C_{12}H_{16}N_2O$. C, 70.57; H, 7.89; N, 13.71. Found C, 70.59; H, 7.91; N, 13.71.

**3-(*p*-Chlorophenyl)-5-(*n*-propyl)-4,5-dihydro-1,2,4-oxadiazole (3e).** (85%, 113 °C, $R_f$ 0.70). UV$\lambda_{max}$ (EtOH) 298.2 and 238.8 nm. IR (KBr) 3215 (N–H), 1599 (C=N), 870.5 (N–O), 1089 (C–O). $^1H$ NMR ($CDCl_3$) δ 0.99 (t, 3H, $J=7.35$ Hz, $CH_3$), 1.46–1.54 (m, 2H, $CH_2$), 1.71–1.76 (m, 2H, $CH_2$), 4.58 (b, 1H, N–H), 5.68 (4 lines, 1H, C–H), 7.39 (d, 2H, $J=8.85$ Hz, H-3′ and H-5′), 7.63 (d, 2H, $J=8.85$ Hz, H-2′ and H-6′). $^{13}C$ NMR ($CDCl_3$) δ 13.91 (C-8), 17.19 (C-7), 38.11 (C-6), 93.15 (C-5), 124.27 (C-1′), 127.74 (C-2′ and C-6′), 129.03 (C-3′ and C-5′), 136.83 (C-4′), 155.18 (C-3). Anal. calcd for $C_{11}H_{13}N_2OCl$. C, 58.79; H, 5.83; N, 12.46. Found C, 59.00; H, 5.59; N, 12.03%.

**3-(*p*-Anisyl)-5-(*n*-propyl)-4,5-dihydro-1,2,4-oxadiazole (3f).** (85%, 105–106 °C, $R_f$ 0.81). UV$\lambda_{max}$ (EtOH), 246.0

and 282.0 nm. IR (KBr) 3240 (N–H), 1614 (C=N), 831 (N–O), 1179 (C–O). $^1$H NMR ($CDCl_3$) δ 0.98 (t, 3H, $J=7.20$ Hz, $CH_3$), 1.42–1.57 (m, 2H, $CH_2$), 1.65–1.90 (m, 2H, $CH_2$), 3.83 (s, 3H, $OCH_3$), 4.56 (b, 1H, N–H), 5.63 (dd, 1H, $J=4.95$ Hz, $J=9.45$ Hz, H–5), 6.90 (d, 2H, $J=9.00$ Hz, H-2′ and H-6′) 7.62 (d, 2H, $J=9.00$ Hz, H-3′ and H-5′); $^{13}$C NMR ($CDCl_3$) δ 13.90 (C-8), 17.21 (C-7), 38.07 (C-6), 55.33 (C-10), 92.58 (C-5), 114.06 (C-3′ and C-5′), 118.04 (C-1′), 128.00 (C-2′ and C-6′), 155.71 (C-3), 161.52 (C-4′). Anal. calcd for $C_{12}H_{16}N_2O_2$. C, 65.43; H, 7.32; N, 12.72. Found C, 65.80; H, 7.25; N, 12.74.

### 3-Aryl-5-propyl-1,2,4-oxadiazoles 4a–f

Two methods have been used for the oxidation of 4,5-dihydro-1,2,4-oxadiazoles **3a**–**f** to **4a**–**f**. These are given below.

**Procedure A.** To a solution of 3-phenyl-5-propyl-4,5-dihydro-1,2,4-oxadiazole **3a** (2.63 mmol) in 250 mL of dichloromethane was added manganese dioxide (10 mmol) and the contents stirred for 2 h at room temperature. TLC plate (chloroform–hexane, 4:1) revealed the completion of the reaction. Filtration and solvent evaporation yielded the desired compound **4a** in almost quantitative yield. Quick chromatography over silica gel gave chromatographically pure product. Similarly, other 4,5-dihydro-1,2,4-oxadiazoles **3b**–**f** were transformed to 1,2,4-oxadiazoles **4b**–**f**. The details of each compound are given below.

**Procedure B.** An aqueous solution (5%) of sodium hypochlorite (3.9 mL) was added to 3-phenyl-5-propyl-4,5-dihydro-1,2,4-oxadiazole **3a** (3.63 mmol) dissolved in tetrahydrofuran (5–10 mL) and the contents were stirred overnight at room temperature. Next morning, an additional 1.5 mL solution of sodium hypochlorite was added to the mixture and left stirring for a few hours. The completion of the reaction was monitored by TLC. Evaporation of tetrahydrofuran, neutralization of the contents with a saturated solution of sodium bicarbonate followed by extraction with chloroform, drying and solvent evaporation gave **4a** in a somewhat comparable yield reported above in procedure A, although this method provided somewhat lesser yield. A quick chromatography over silica gel furnished pure oxadiazoles.

**3-(Phenyl)-5-(*n*-propyl)-1,2,4-oxadiazole (4a).** (90%, colorless oil, $R_f$ 0.50): UV$\lambda_{max}$ (EtOH) 241.0, 276.4 and 284.4 nm. IR (Nujol) 1596 (C=N), 1572 (C=C), 910 (N–O), 1200 cm$^{-1}$ (C–O). $^1$H NMR ($CDCl_3$) δ 1.05 (t, 3H, $J=7.5$ Hz, $CH_3$). 1.92 (m, 2H, $CH_2$). 2.93 (t, 2H, $J=7.35$ Hz. $CH_2$). 7.45–7.51 (m, 3H, Ar–H). 8.06–8.12 (m, 2H, Ar–H); $^{13}$C NMR ($CDCl_3$) δ 13.60 (C-8), 20.18 (C-7), 28.44 (C-6), 126.91 (C-1′) 127.34 (C-2′ and C-6′), 128.77 (C-3′ and C-5′), 131.02 (C-4′), 168.20 (C-3), 179.85 (C-5). Anal. calcd for $C_{11}H_{12}N_2O$. C, 70.2; H, 6.32; N, 14.74. Found C, 69.89; H, 6.19; N, 14.66.

**5-(*n*-Propyl)-3-(*o*-tolyl)-1,2,4-oxadiazole (4b).** (74%, colorless liquid, $R_f$ 0,46): UV$\lambda_{max}$ (EtOH) 2.39, 276.4 and 284.4 nm IR Nujol 1605 (C=C), 1592 (C=N), 1571 (C=C), 906 (N–O), 1201 cm$^{-1}$ (C–O). $^1$H NMR ($CDCl_3$) δ 1.07 (t, 3H, $J=7.35$ Hz, $CH_3$), 1.92 (m, 2H, $CH_2$), 2.62 (s, 3H, Ar–$CH_3$), 2.93 (t, 2H, $J=7.50$ Hz, $CH_2$), 7.26–7.42 (m, 3H, Ar–H), 7.95–8.05 (dd, 1H $J=7.50$ Hz, $J=1.80$ Hz, Ar–H); $^{13}$C NMR ($CDCl_3$) δ 13. 66 (C-8), 20.23 (C-7), 22.07 (C-9), 28.38 (C-6), 125.94 (C-5′), 126.27 (C-1′), 130.02 (C-3′), 130.44 (C-6′), 131.33 (C-4′), 138.16 (C-2′), 168.84 (C-3), 178.80 (C-5). Anal. calcd for $C_{12}H_{14}N_2O.0.5H_2O$. C, 68.22; H, 7.15. Found C, 68.11; H, 7.45.

**5-Ethyl-3-(*m*-tolyl)-1,2,4-oxadiazole (4c).** (81%, colorless liquid, $R_f$ 0.62): UV$\lambda_{max}$ (EtOH), 242.0, 281.0 and 291.6 nm. IR (Nujol) 1593 (C=N), 1572 (C=C), 904 (N–O), 1281 cm$^{-1}$ (C–O). $^1$H NMR ($CDCl_3$) δ 1.05 (t, 3H, $J=7.35$ Hz, $CH_3$), 1.82–1.98 (m, 2H, $CH_2$), 2.41 (s, 3H, Ar–$CH_3$), 2.92 (t, 2H, $J=7.50$ Hz, $CH_2$), 7.27–7.40 (m, 2H, H–4′ and H-5′), 7.85–7.92 (m, 2H, H-2′ and H-6′); $^{13}$C NMR ($CDCl_3$) δ 13. 59 (C-8), 20.20 (C-7), 21.27 (C-9), 28.44 (C-6), 124.45 (C-6′), 126.764 (C-1′), 127.90 (C-5′), 128.69 (C-2′), 131.79 (C-4′), 138.56 (C-3′), 168.30 (C-3), 179.76 (C-5). Anal. calcd for $C_{12}H_{14}N_2O$. C, 71.26; H, 6.98; N, 13.85. Found C, 71.19; H, 7.19; N, 13.44.

**5-(*n*-Propyl)-3-(*p*-tolyl)-1,2,4-oxadiazole (4d).** (95%, colorless oil, $R_f$ 0.56): UV$\lambda_{max}$ (EtOH) 247.0, 279.0 and 288.0 nm. IR (Nujol) 1598 (C=N), 1577 (C=C), 913 (N–O), 1210 cm$^{-1}$ (C–O). $^1$H NMR ($CDCl_3$) δ 1.06 (t, 3H, $J=7.5$ Hz, $CH_3$), 1.82–1.98 (m, 2H, $CH_2$), 2.41 (s,3H, Ar–$CH_3$), 2.91 (t, 2H, $J=7.5$ Hz, $CH_2$), 7.28 (d, 2H, $J=8.40$ Hz, H-3′ and H-5′) 7.96 (d, 2H, $J=8.40$ Hz, H-2′ and H-6′). $^{13}$C NMR ($CDCl_3$) δ 13.60 (C-8), 20.19 (C-7), 21.51 (C-9), 28.44 (C-6), 124.07 (C-1′), 127.26 (C-2′ and C-6′), 129.48 (C-3′ and C-5′), 141.31 (C-4′) 168.19 (C-3), 179.67 (C-5). Anal. calcd for $C_{12}H_{14}N_2O$. C, 71.26; H, 6.98; N, 13.85. Found C, 71.38; H, 7.26; N, 13.48.

**3-(*p*-Chlorophenyl)-5-(*n*-Propyl)-1,2,4-oxadiazole (4e).** (86%, 56.8–57.1 °C, $R_f$ 0.54): UV$\lambda_{max}$ (EtOH) 247.6, 272.2 and 286.6 nm. IR (Nujol) 1592 (C=N), 1570 (C=C), 909 (N–O), 1119 cm$^{-1}$ (C–O). $^1$H NMR ($CDCl_3$) δ 1.06 (t, 3H, $J=7.50$ Hz, $CH_3$), 1.84–1.98 (m, 2H, $CH_2$), 2.92 (t, 2H, $J=7.35$ Hz, $CH_2$), 7.45 (d, 2H, $J=8.70$, H-3′ and H-5′), 8.02 (d, 2H, $J=8.70$ Hz, H-2′ and H-6′); $^{13}$C NMR ($CDCl_3$) δ 13.62 (C-8), 20.17 (C-7), 28.43 (C-6), 125.44 (C-1′), 128.67 (C-2′ and C-6′), 129.12 (C-3′ and C-5′), 137.16 (C-4′), 167.43 (C-3), 180.10 (C-5). Anal. calcd for $C_{11}H_{11}N_2OCl$. C, 59.38; H, 4.94; N, 12.58. Found C, 59.53; H, 4.89; N, 12.32.

**3-(*p*-Anisyl)-5-(*n*-propyl)-1,2,4-oxadiazole (4f).** (85%, colorless liquid, $R_f$ 0.63): UV$\lambda_{max}$ 237.0 and 261.0 nm. IR (Nujol) 1594 (C=N), 1568 (C=C), 911 (N–O), 1119 cm$^{-1}$ (C–O). $^1$H NMR ($CDCl_3$) δ 1.05 (t, 3H, $J=7.50$ Hz, $CH_3$), 1.83–1.96 (m, 2H, $CH_2$), 2.90 (t, 2H, $J=7.50$ Hz, $CH_2$), 3.85 (s, 3H, $OCH_3$), 6.98 (d, 2H, $J=9.00$ Hz, H-3′ and H-5′), 8.00 (d, 2H, $J=9.00$ Hz, H-2′ and H-6′); $^{13}$C NMR ($CDCl_3$) δ 13.88 (C-8), 20.46 (C-7), 28.71 (C-6), 55.59 (C-10), 114.44 (C-3′ and C-5′), 119.67 (C-1′), 129.21 (C-2′ and C-6′), 162.06 (C-4′), 168.17 (C-3), 179.84 (C-5). Anal. calcd for $C_{12}H_{14}N_2O_2$. C, 66.05; H, 6.42; N, 12.84. Found C, 66.12; H, 6.24; N, 12.81.

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