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A new one-step synthesis of stable 3-aryl-*trans*-5,6-dihydroxy-5,6-dihydro-1,2,4-oxadiazines

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Abstract—An easy and simple synthesis of 3-aryl-*trans*-5,6-dihydroxy-5,6-dihydro-1,2,4-oxadiazines **4a**–**e** from arylamidoximes **1a**–**e** and glyoxal **2** is described.

The synthesis of 4,5-dihydro-1,2,4-oxadiazoles starting from arylamidoximes and aldehydes is well documented.[1–8] Initially, our intention was to synthesize 3-aryl-5-formyl-4,5-dihydro-1,2,4-oxadiazoles **3** (Scheme 1) employing arylamidoximes **1a**–**e** and glyoxal **2**, because an aldehyde group at C-5 of the heterocyclic ring could easily be transformed to other synthetically and biologically important products. Surprisingly, the above reaction furnished1,2,4-oxadiazines **4a**–**e** instead of the expected products **3a**–**e**.

A literature search revealed that 1,2,4-oxadiazine derivatives possess quite interesting pharmacological properties. For example, 3-phenyl-6-(1,2,3,4-tetrahydro-2-isoquinolyl)methyl-4*H*-5,6-dihydro-1,2,4-oxadiazine has some diuretic and antiphlogistic effect in addition to its definite peripheral vasodilator, coronary flow increasing, and hypotensive action.[9] There are other interesting biological activities of 1,2,4-oxadiazine compounds.[10–13]

Although benzamidoximes have been used to synthesize 1,2,4-oxadiazines, the reagents are different. For example, acid-catalyzed isomerization of 1-aroylaziridine oximes led to the formation of 1,2,4-oxadiazine derivatives.[14] Reaction of benzamidoxime derivatives with ethyl γ-bromoacetate in the presence of an acid catalyst furnished a mixture of geometrical isomers of 3-aryl-5-ethoxycarbonylmethylene-5,6-dihydro-4*H*-1,2,4-oxadiazine derivatives.[15,16] Also, the treatment of N-substituted benzamidoximes with chloroacetyl chloride in the presence of triethylamine gave substituted dihydroxy-Δ^2-1,2,4-oxadiazine-5-ones.[17] To the best of our knowledge, no effort has yet been made to synthesize 3-aryl-5,6-dihydroxy-5,6-dihydro-1,2,4-oxdiazines by the reaction of benzamidoximes with glyoxal **2**. This letter, therefore, reports for the first time a new and very simple synthesis of 3-aryl-*trans*-5,6-dihydroxy-5,6-dihydro-1,2,4-oxadiazines **4a**–**e** starting from benzamidoximes **1a**–**e** and glyoxal **2**. In fact, this constitutes a new, and straightforward method for acquiring the title compounds.

When a mixture of **1** and **2** were stirred at room temperature, gradually the crystals start precipitating after 15 min and the reaction gets completed in about 3 h. None of the pure products showed an aldehydic proton in the ^{1}H NMR spectrum. All compounds have sharp melting points and can be recrystallized from methanol or isopropanol without decomposition. However, longer heating causes slow decomposition and reversal to the starting benzamidoximes. The yields of **4a**,**c**–**e** ranged between 63% and 83% except for **3b**, which could be obtained in 55% yield. The R_f values of all compounds were in the range of 0.27–0.32 in the solvent system EtOAc. The spots could easily be visualized under ultraviolet light.

The mechanism of formation of **4a**–**e** from **1a**–**e** and **2** occurs in steps. First, the oxygen atom of the benzamidoxime molecule attacks the aldehydic carbon

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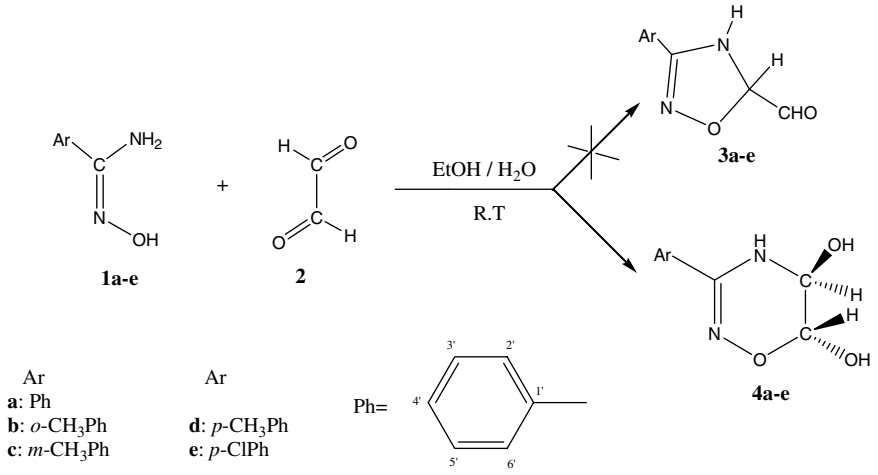


Scheme 1.

atom (Scheme 2), because this atom is more nucleophilic than amidic nitrogen atom. The better nucleophilicity of the oxygen atom compared to amidic nitrogen atom has been dealt with earlier.[3,18] The hemiacetal **5a**–**e** formed is in equilibrium with **6a**–**e**, which in turn closes the ring as shown. Finally, **7a**–**e** equilibrates to **4a**–**e** just by a proton transfer.

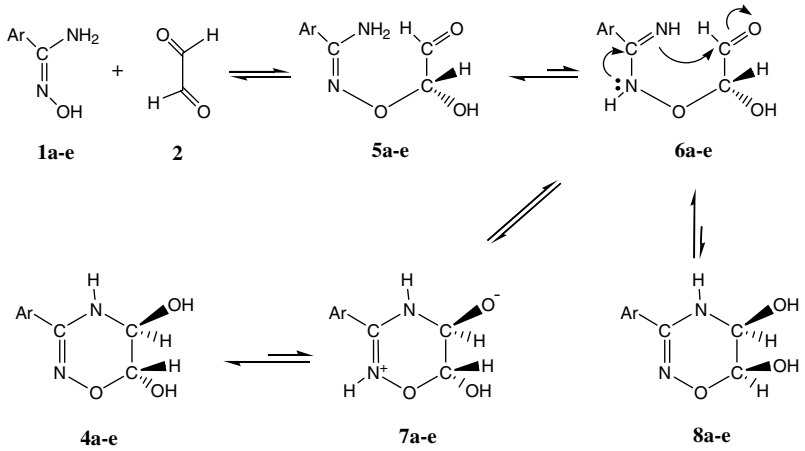
Oxadiazine derivatives **4a**–**e**, prepared by us, are crystalline and stable compounds. The remarkable stability of **4a**–**e** is due to three reasons: (1) The hemi-acetal function at C-6 and the hemi-aminal group at C-5 belong to a six-membered ring; (2) Carbons 5 and 6 are attached to electron-withdrawing groups; (3) The two hydroxyls at C-5 and C-6 are trans to each other.

The preferential formation of racemic (5*S*,6*R* and 5*R*,6*S*)-1,2,4-oxadiazines needs comment. The generation of the other enantiomeric pair (5*R*,6*R* and 5*S*,6*S*) is less likely because of the unfavorable interaction of the two –OH groups on the same side. This is what we found when the crude sample was examined by the ^{1}H NMR spectroscopy, showing additional proton signals corresponding to presumably another enantiomeric pair (5*R*,6*R* and 5*S*,6*S*), but the quantity of this enantiomeric pair is less than 10%, and no effort was made to isolate them.

Compounds **4a**–**e** exhibit absorption at 3330 (sometimes split bands) for OH groups in their infrared spectra (KBr), bands between 1488 and 1606 cm^{-1} (C=C, ar). No carbonyl group absorptions have been noticed. The NMR spectra agree with the structures proposed. The spectroscopic data are given the references and note's section.[19]

The stereochemistry of one of these compounds **4a** was confirmed by X-ray crystallography. The molecular structure is shown in Figure 1. Analysis of the X-ray data revealed that five of the six atoms of the heterocyclic ring, that is, O(1), N(2), C(3), N(4), and C(5) are coplanar, and C(6) is out of plane making an angle of 107.1° for N(4)–C(5)–C(6). That the two OH groups are trans can be confirmed by the torsion angle of −167.1° for the atoms O(2)–C(5)–C(6)–O(3). The other interesting point is that the phenyl ring is not coplanar with the 1,2,4-oxadiazine ring.

The phenyl ring is about 38° off the plane of the heterocyclic ring. The other fact, which arouses interest is that



Scheme 2.

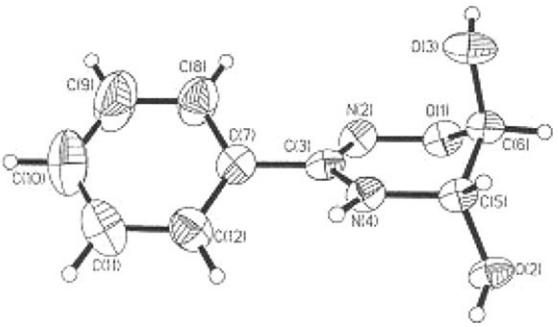


Figure 1. Thermal ellipsoid diagram of structure **4a**.

the molecules are linked into sheets normal to the *c*-axis by a series of hydrogen bonds. Each possible donor participates: O(2) is linked to N(2) of an adjacent molecule, O(3) is linked to O(2) of another molecule, and N(4) forms a weaker bifurcated hydrogen bond to O(3) and O(1) of other molecules. Each oxygen atom and each nitrogen atom thus forms three bonds or hydrogen bonds in a flat or flat pyramidal arrangement (Fig. 2). The compound crystallizes in a cell that contains both enantiomers; the space group has glide planes (normal to all three axes), which requires a racemic mixture.

In order to get more insight about the stability of *cis*- and *trans*-5,6-dihydroxy-Δ^2-1,2,4-oxadiazines, we determined the total energy of each isomer, that is, **4a** and **8a**. The ab initio Hartree–Fock self-consistent field (HF-SCF) molecular orbital calculations were carried out employing Gaussian 94 program[20] and the basis set of HF/6-31G. It turned out that 3-phenyl-*trans*-5,6-dihydroxy-5,6-dihydro-1,2,4-oxadiazine **4a** is more stable than 3-phenyl-*cis*-5,6-dihydroxy-5,6-dihydro-1,2,4-oxadiazine **8a** by ~8.05 kcal/mol. This explains the formation of trans-isomers **4a**–**e** preferentially.

In a typical experiment, a 40% aqueous solution of glyoxal **2** (0.32 mL, 2.2 mmol) was added to benzamidoxime **1a** (0.27 g, 2.0 mmol) dissolved in a mixture of 95% ethanol (1.0 mL) and water (2.0 mL) and the solution stirred at room temperature for an

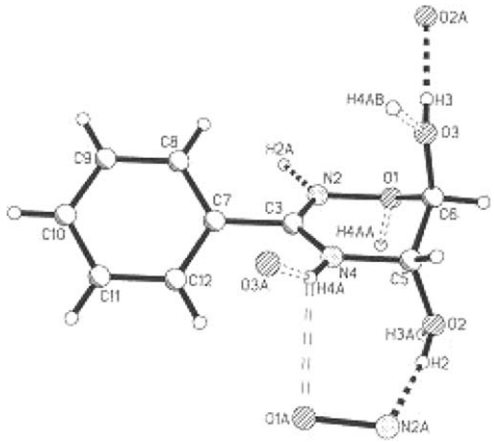


Figure 2. Compound **4a** depicting hydrogen bonding with other molecules of the same compound.

Table 1. Physical properties of compounds of compounds **4a**–**e**

Compound	Crude yield (%)	Cryst. solvent	Mp (°C)	R_f[a] value
4a	83	Isopropanol	161–162	0.28
4b	55	Not recrystallized[b]	141–143	0.32
4c	63.4	Isopropanol	151–152	0.31
4d	77.2	MeOH and EtOH	145–146	0.27
4e	82.3	MeOH	155–156	0.29

[a] Solvent: Ethyl acetate. The spots were visualized under ultraviolet light.

[b] The compound was extracted with ethyl acetate. Solvent evaporation left crystals, which were collected and washed with cold ethyl acetate. No effort was made to recrystallize due to the fear of decomposition.

hour. Another batch of glyoxal solution (0.16 mL, 1.1 mmol) was again added to the solution and continued stirring for an additional hour. Repetition of third addition and agitation for 2 h more indicated the completion of the reaction as verified by TLC (AcOEt/$CHCl_3$, 1:1) and revelation under UV light. Normally, the product precipitates during the reaction. Filtration and drying the crystals under vacuum yielded 0.39 g (83%) of **4a** as a racemic mixture. The other compounds were obtained in a similar manner. Table 1 provides the details of compounds **4a**–**e**.

Selected bond lengths (Å): O(1)–C(6) 1.413(3), O(1)–N(2) 1.442(3), N(2)–C(3) 1.295(3), C(3)–N(4) 1.350(3), C(5)–C(6) 1.515(3), C(5)–O(2) 1.415(3), C(6)–O(3) 1.394(3). Intramolecular angles (°): C(6)–O(1)–N(2) 114.54(19), C(3)–N(2)–O(1) 115.00(2), N(2)–C(3)–N(4) 125.7(3), N(3)–N(4)–C(5) 121.4(2), O(2)–C(5)–N(4) 113.0(2), O(2)–C(5)–C(6) 108.10(2), O(3)–C(6)–O(1), 112.7(1) O(1)–C(6)–C(5) 106.6(2). Selected torsion angles (°): O(1)–N(2)–C(3)–N(4) −0.2(4), N(4)–C(5)–C(6)–O(1) −52.0(3), N(4)–C(3)–C(7)–C(12) −38.3(4).

A referee pointed out that a mixture of the products including 3-*n*-hexyl-4,5-dihydro-1,2,4-oxadiazole-5-ylcarboxaldehyde might be formed if *n*-hexylamidoxime is allowed to react with glyoxal **2.** He further asked our comments about this. The following paragraph gives our view.

The referee's suggestion is really interesting and we agree with him. In fact, it would be worthwhile to examine such a reaction. Even other amidoximes containing saturated hydrocarbon-chains at C-3 should be investigated. Since the literature does not report anything like this, we shall undertake this kind of research project at a latter date because we do not have anybody to start this work at this moment.

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19. IR spectra of **4a**–**e** in KBr. Compound **4a**: *v* 2500–3500 (broad), 1617, 1553, 1448, 1057, 1039, 769.9 cm^{-1}. Compound **4b**: *v* 3357 (broad), 2917.7, 1599, 1522, 1487, 1058, 752 cm^{-1}. Compound **4c**: *v* 3342 (broad), 3313 (broad), 1600, 1575, 1524, 1458, 1057, 1030, 791 cm^{-1}. Compound **4d**: *v* 3381 and 3263 (broad), 2948, 1607, 1559, 1535, 1072, 906, 824 cm^{-1}. Compound **4e**: *v* 3372–3262 (broad), 1606, 1558, 1526, 1488, 1067, 836 cm^{-1}. ^1H NMR (DMSO-d_6) data, **4a**: δ 7.76 (1H, d, $J = 4.8$ Hz, NH), 7.66 (2H, m, Ar H), 7.41 (3H, m, Ar H), 6.70 (H, d, $J = 4.2$ Hz, –OH), 5.07 (1H, d, $J = 3.0$ Hz, –OH), 4.54 (1H, br d, $J = 4.2$ Hz, H-6), 3.96 (1H, m, H-5). Signals at δ 7.76, 6.70, and 5.07 ppm disappeared when D_2O was added to the solution containing **4a** and spectrum taken again; **4b**: δ 7.63 (1H, d, $J = 4.8$ Hz, N–H), 7.34–7.28 (1H, 2dd, $J = 6.3$ Hz, $J = 1.8$ Hz, Ar–H), 7.78–7.17 (3H, m, Ar–H), 6.63 (1H, d, $J = 3.9$ Hz, –OH), 5.78 (1H, d, $J = 6.3$ Hz, –OH), 4.96 (1H, dd, $J = 3.9$ Hz, $J = 1.2$ Hz, H-6), 4.52 (1H, ddd, $J = 4.8$ Hz, $J = 1.5$ Hz, $J = 1.5$ Hz, H-5) 2.35 (3H, s, Ar–CH_3); **4c**: δ 7.78 (1H, d, $J = 5.1$ Hz, NH), 7.44 (2H, m, Ar H), 7.32–7.23 (2H, m, Ar–H), 6.61 (1H, d, $J = 2.1$ Hz, –OH), 5.76 (1H, d, $J = 6.0$ Hz, –OH), 4.97 (1H, dd, $J = 4.5$ Hz, $J = 1.5$ Hz, H-6), 4.57 (1H, m, H-5), 2.33 (3H, s, Ar–CH_3); **4d**: 7.78 (1H, d, $J = 4.8$ Hz, NH), 7.54 (2H, d, $J = 8.0$ Hz, Ar–H), 7.21 (2H, d, $J = 8.0$ Hz, Ar–H0), 6.63 (1H, d, $J = 4.2$ Hz, –OH), 5.77 (1H, d, $J = 6.3$ Hz, –OH), 4.96 (1H, dd, $J = 4.2$ Hz, $J = 1.2$ Hz, H-6), 4.57 (1H, m, H-5), 2.32 (3H, s, Ar–CH_3); **4e**: δ 7.95 (1H, d, $J = 4.8$ Hz, NH), 7.67 (2H, d, $J = 8.7$ Hz, Ar–H), 7.49 (2H, d, $J = 8.7$ Hz, Ar–H), 6.70 (1H, d, $J = 4.8$ Hz, –OH), 5.85 (1H, d, $J = 6.0$ Hz, –OH), 4.99 (1H, dd, $J = 3.9$ Hz, $J = 1.2$ Hz, H-6), 4.59 (1H, t, $J = 4.8$ Hz, H-5). ^{13}C NMR of compounds **4a**–**e** (DMSO-d_6), **4a**: δ 72.09 (C-5), 89.65 (C-6), 125.57 (C-2′ and C-6′), 127.95 (C-3′ and C-5′), 129.34 (C-4′), 132.66 (C-1′), 149.02 (C-3). Compound **4b**: δ 19.22 (C of CH_3), 72.29 (C-5), 89.55 (C-6), 125.36 (C-5′), 128.86 (C-3′), 129.00 (C-4′), 130.07 (C-6′), 133.55 (C-1′), 136.71 (C-2′), 151.11 (C-3). Compound **4c**: δ 21.07 (C of CH_3), 72.13 (C-5), 89.67 (C-6), 122.90 (C-6′), 126.36 (C-2′), 128.16 (C-5′), 130.23 (C-4′), 132.73 (C-1′), 137.37 (C-3′), 149.20 (C-3). Compound **4d**: δ 21.03 (C of CH_3), 72.32 (C-5), 89.83 (C-6), 125.83 (C-2′ and C-6′), 129.05 (C-3′ and C-5′), 129.99 (C-1′), 139.54 (C-4′), 149.46 (C-3). Compound **4e**: δ 71.98 (C-5), 89.65 (C-6), 127.47 (C-2′ and C-6′), 128.38 (C-3′ and C-5′), 131.56 (C-1′), 134.33 (C-4′), 148.23 (C-3).
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