

Full Paper

Synthesis of New Unsymmetrical 4,5-Dihydroxy-2-imidazolidinones. Dynamic NMR Spectroscopic Study of the Prototropic Tautomerism in 1-(2-Benzimidazolyl)-3-phenyl-4,5-dihydroxy-2-imidazolidinone

Mehdi Ghandi*, Abolfazl Olyaei and Farshid Salimi

School of Chemistry, University College of Science, University of Tehran, Tehran, Iran

* Author to whom correspondence should be addressed. E-mail: ghandi@khayam.ut.ac.ir; Tel.: (+98)-21-61112250; Fax: (+98)-21-66495291

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Abstract: The acid-catalyzed cyclocondensation in refluxing acetonitrile of aqueous glyoxal with *N*-heteroaryl-*N'*-phenylureas **4a-f** (heteroaryl = 2-thiazolyl, 2-pyrimidinyl, 2-pyrazinyl, 2-pyridinyl, 3-pyridinyl and 2-benzimidazolyl) led to the formation of the corresponding 1-heteroaryl-3-phenyl-4,5-dihydroxy-2-imidazolidinones **5a-f**. All the products were characterized by elemental and spectroscopic analyses. The free-energy barrier ($\Delta G^\ddagger$) for prototropic tautomerism in 1-(2-benzimidazolyl)-3-phenyl-4,5-dihydroxy-2-imidazolidinone (**5f**) was determined by dynamic NMR studies to be 81 ± 2 KJ mol⁻¹.

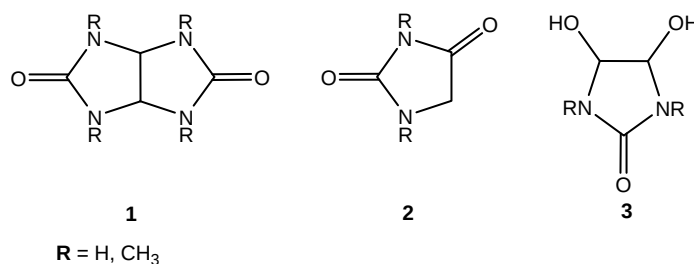
Keywords: Dynamic NMR, *N*-Heteroaryl-*N'*-phenylurea, 2-Imidazolidinone, Glyoxal.

Introduction

Synthesis of imidazolidines through the cyclocondensation of diamines, bisamides and urea derivatives with aqueous glyoxal and other appropriate carbonyl compounds has been the subject of numerous investigations [1-10]. In 1962, Slezak *et al.* reported the acid-catalyzed reaction of urea derivatives with aqueous glyoxal leading to the formation of the corresponding glycolurils **1** (Figure 1) [11]. The formation of hydantoin derivatives **2** (Figure 1) had been found previously to take place

under similar reaction conditions [12]. The additions of *N,N'*-dimethylurea and urea to aqueous glyoxal under both acidic and basic conditions to form 4,5-dihydroxy-2-imidazolidinones derivatives **3** (Figure 1) have been studied by Vail *et al.* [13]. On the basis of NMR spectroscopy, they showed that initially equimolar amounts of the *cis* and *trans* isomers were formed by a non-stereospecific addition, but the resulting equilibrium product mixture contained predominantly the *trans* isomer. In acidic solution, the products would be subject to protonation and subsequent formation of other products. 2-Imidazolidinones are important building blocks in Medicinal Chemistry as central nervous system depressants and enzyme inhibitors [14–16]. They are also used as textile finishing agents [17].

Figure 1. Structures of glycolurils **1**, hydantoins **2** and 4,5-dihydroxy-2-imidazolidinones **3**.

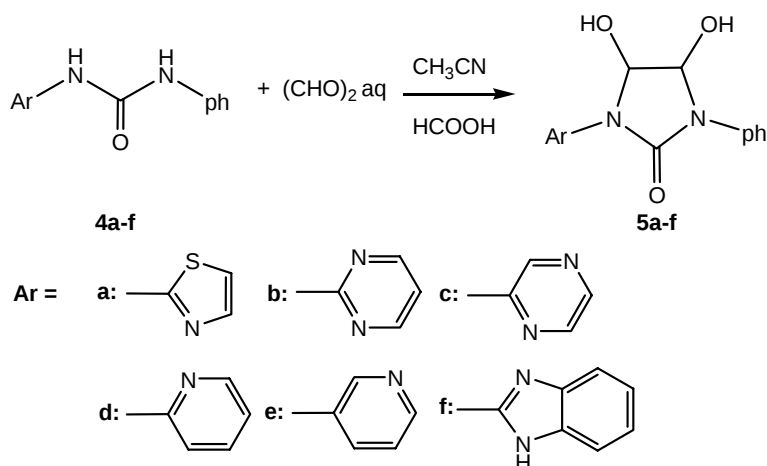


In the present work, we wish to report a facile and convenient synthetic route to some new unsymmetrical 1,3-diarylsubstituted 4,5-dihydroxy-2-imidazolidinones **5a–f** through the reaction of aqueous glyoxal with *N*-heteroaryl-*N'*-phenylureas **4a–f** in the presence of formic acid as catalyst. The dynamic behavior of 1-(2-benzimidazolyl)-3-phenyl-4,5-dihydroxy-2-imidazolidinone (**5f**) was also studied by variable temperature NMR.

Results and Discussion

N-Heteroaryl-*N'*-phenylureas **4a–f** were prepared through the reaction of suitable primary heteroarylamines (2-aminothiazole, 2-aminopyrimidine, 2-aminopyrazine, 2-aminopyridine, 3-aminopyridine and 2-aminobenzimidazole) with phenyl isocyanate [18–21]. In refluxing acetonitrile and in the presence of formic acid as catalyst, treatment of compounds **4a–f** with aqueous glyoxal afforded the corresponding *trans*-1-heteroaryl-3-phenyl-4,5-dihydroxy-2-imidazolidinones **5a–f** (Scheme 1). The products **5a–f** were purified by flash chromatography (FC) and characterized by spectroscopic techniques. Yields, melting points, reaction times and elemental analyses are presented in Table 1.

The mass spectra of compounds **5a–f** exhibited medium intensity parent ions, while the radical cations of *N*-heteroaryl-*N'*-phenylureas **4a–f** and heteroarylisocyanate cations appeared with high intensity. The ^1H -NMR spectra of compounds **5a–f** showed two well-resolved AB quartet spin systems corresponding to two chemically different CH-OH moieties. Based on the lack of coupling between two unequivalent methine protons, it seems likely that the hydroxyl groups are *trans* to each other. The other peaks of the spectra were those arising from the protons of two aromatic moieties. Upon addition of D_2O to the NMR samples, the hydroxyl signals disappeared and the signals of the methine moieties quickly collapsed to two singlets.

Scheme 1. Formic acid catalyzed reaction of *N*-heteroaryl-*N'*-phenylureas **4a-f** with aqueous glyoxal.**Table 1.** Yields, melting points and elemental analyses of compounds **5a-f**.

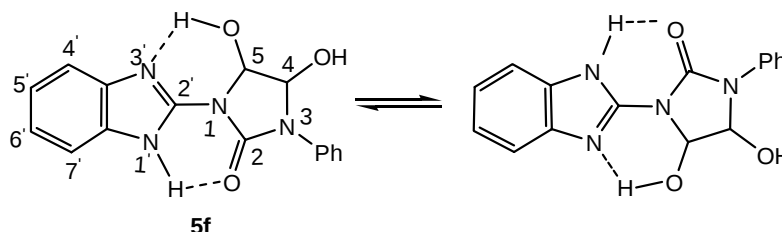
Entry	Ar	Time/h	Mp °C	Yield %	Elemental Analysis (%)		
					Calcd. (Found)		
					C	H	N
5a		3	160-162	70	51.98	3.97	15.16
					(51.76)	(4.02)	(14.96)
5b		10	204-206	90	57.35	4.41	20.58
					(57.17)	(4.45)	(20.43)
5c		8	164-166	80	57.35	4.41	20.58
					(57.23)	(4.38)	(20.51)
5d		0.5	124-126	85	61.99	4.79	15.49
					(61.78)	(4.90)	(15.38)
5e		5	173-175	75	61.99	4.79	15.49
					(61.94)	(4.83)	(15.42)
5f		4	226-228	65	61.93	4.51	18.06
					(61.90)	(4.60)	(17.95)

Physicochemical data show that the NH proton in benzimidazoles, as in imidazoles, migrates rapidly between the two nitrogen atoms (degenerate tautomerism) (Scheme 2). The imidazole ring with a nonsymmetrical substitution exhibits an $\text{HN}_1\ldots\text{HN}_3$ tautomerism that has been studied both experimentally and theoretically [22].

The ^1H -NMR spectrum of **5f** in DMSO-d_6 at room temperature (25 °C) exhibited two rather sharp doublets at δ 7.48 and 7.50 ppm ($J = 7.07$ and 6.5 Hz), arising from CH-4' and CH-7' protons, each of them exhibiting a further doublet splitting due to the long range coupling with one of the benzimidazolyl hydrogens. Increasing the temperature results in coalescence of the two doublets ($T_C = 384 \pm 1$ K), as shown in Figure 2. Although no extensive line-shape analysis for **5f** was undertaken, the variable temperature spectra allowed us to calculate the free energy barriers $\Delta G^\ddagger$ for the dynamic

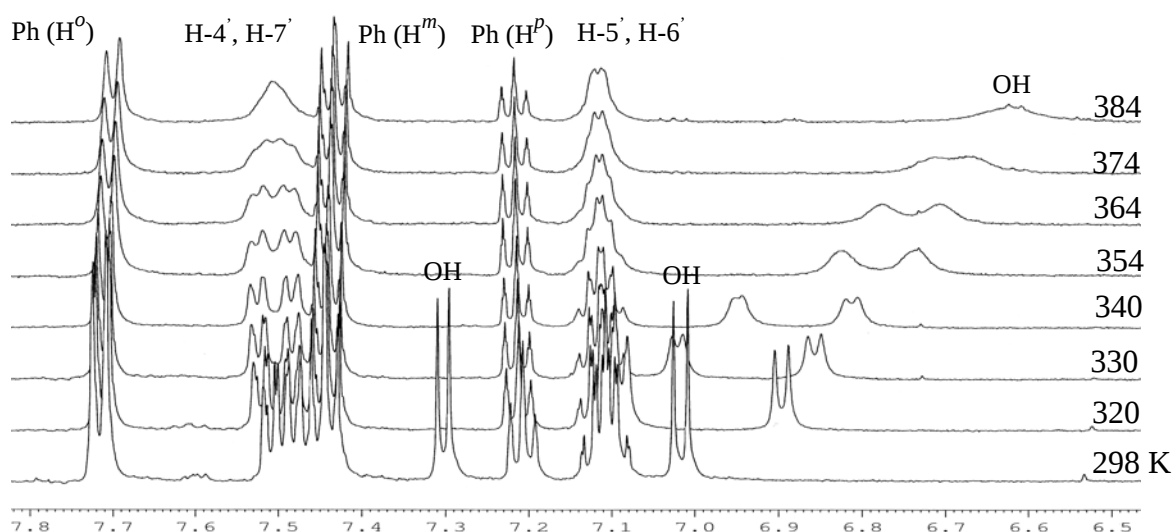
NMR process in **5f** from coalescence of the CH-4' and CH-7' protons. By using the expression, $k = \pi\Delta\nu/\sqrt{2}$, the first-order rate constant (k) for dynamic NMR effect in **5f** was calculated as 31 s^{-1} .

Scheme 2. Degenerate tautomerization of compound **5f**.



Application of the absolute rate theory with a transmission coefficient of 1 gives the free energy of activation ($\Delta G^\ddagger$) as $81 \pm 2\text{ KJ mol}^{-1}$ for compound **5f**, where all known sources of errors are estimated and included [23]. The experimental data available are not suitable for obtaining meaningful values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ even though the errors in $\Delta G^\ddagger$ are not large [24].

Figure 2. Variable-temperature 500 MHz ^1H -NMR spectra of the aromatic region of **5f** in DMSO-d_6 .



The ^{13}C -NMR spectra of **5f** also show 14 and 11 peaks at 298 and 384 K, respectively. This clearly indicates that the tautomers are interconverting fast at 384 K on the NMR time scale. No conversion occurred when we examined reaction of **4a-f** with glyoxal in the presence of sodium hydroxide in different solvents. On the other hand, reaction of compounds **5a-f** with sodium hydroxide regenerated the starting materials **4a-f**. Imidazolidinones **5a-f** are stable materials and can be stored at room temperature for extended periods.

Conclusions

In summary, the reaction between *N*-heteroaryl-*N'*-phenylureas **4a-f** with aqueous glyoxal in acetonitrile under reflux conditions provides a simple one-pot entry into the synthesis of 1-heteroaryl-

3-phenyl-4,5-dihydroxy-2-imidazolidinones **5a-f**. Since scaling up of this easy method seems plausible, utilization of the procedure in industrial applications such as the preparation of textile finishing agents is conceivable. The free-energy barrier ($\Delta G^\ddagger$) for prototropic tautomerism in 1-(2-benzimidazolyl)-3-phenyl-4,5-dihydroxy-2-imidazolidinone (**5f**) was found to be 81 ± 2 KJ mol⁻¹.

Experimental

General

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The ¹H- and ¹³C-NMR spectra were recorded in DMSO-*d*₆ on a DRX-500 AVANCE spectrometer at 298 K. Chemical shifts (δ) are reported in ppm and are referenced to the NMR solvent peak. Mass spectra of the products were obtained with a HP (Agilent Technologies) 5937 Mass Selective Detector. Elemental analyses were carried out with a Thermo Finnigan (FLASH 1112 SERIES EA) CHNS-O analyzer. Flash chromatography (FC) was carried out using silica gel 60 (63-200 mesh). Progress of the reactions was monitored by TLC using precoated sheets of silica gel Merck 60 F₂₅₄ on aluminium.

General procedure for the synthesis of 1-heteroaryl-3-phenyl-4,5-dihydroxy-2-imidazolidinones **5a-f**.

A stirring solution of *N*-heteroaryl-*N'*-phenylurea **4a-f** (1 mmol), glyoxal (0.14 g of 40% aqueous solution, 1 mmol) and formic acid (0.005 g of 98% aqueous solution, 0.1 mmol) in acetonitrile (30 mL) was refluxed for the time given in Table 1. The solvent was then removed under reduced pressure and the crude material was purified by flash chromatography on silica gel, eluting with a 4:1 THF/hexane mixture to give a white crystalline product.

1-(2-Thiazolyl)-3-phenyl-4,5-dihydroxy-2-imidazolidinone (5a): Yield: 70%; m.p. 160-162 °C (from acetonitrile); IR (KBr): 3323 (OH), 3058, 2943, 1730 (C=O), 1596, 1487, 1402, 1280, 1139 cm⁻¹; ¹H-NMR δ : 5.34 (d, 1H, *J* = 8.5 Hz, CH), 5.62 (d, 1H, *J* = 7.1 Hz, CH), 7.00 (d, 1H, *J* = 8.5 Hz, OH), 7.27 (d, 1H, *J* = 7.1 Hz, OH), 7.30 (d, 1H, *J* = 3.4 Hz, thiazole H-4), 7.50 (d, 1H, *J* = 3.4 Hz, thiazole H-5), 7.19, 7.42 and 7.68 (3m, 5H, Ar-H); ¹H-NMR (DMSO-*d*₆ + D₂O) δ : 5.33 (s, 1H, CH), 5.61 (s, 1H, CH), 7.26 (d, 1H, *J* = 3.4 Hz, thiazole H-4), 7.48 (d, 1H, *J* = 3.4 Hz, thiazole H-5), 7.18, 7.41 and 7.64 (3m, 5H, Ar-H); ¹³C-NMR δ : 84.18, 86.35, 114.58, 121.21, 125.23, 129.77, 138.41, 138.60, 152.72, 158.13 ppm; MS (EI): *m/z* 277 (M⁺); Anal. Calcd for C₁₂H₁₁N₃O₃S: C, 51.98; H, 3.97; N, 15.16. Found: C, 51.76; H, 4.02; N, 14.96.

1-(2-Pyrimidinyl)-3-phenyl-4,5-dihydroxy-2-imidazolidinone (5b): Yield: 90%; m.p. 204-206 °C (from acetonitrile); IR (KBr): 3261 (OH), 3085, 2858, 1730 (C=O), 1569, 1456, 1380, 1299, 1060 cm⁻¹; ¹H-NMR δ : 5.22 (d, 1H, *J* = 7.9 Hz, CH), 5.68 (d, 1H, *J* = 6.3 Hz, CH), 6.82 (d, 1H, *J* = 6.3 Hz, OH), 6.84 (d, 1H, *J* = 7.9 Hz, OH), 7.22 (t, 1H, *J* = 4.8 Hz, pyrimidine H-5), 7.16 and 7.39-7.68 (2m, 5H, Ar-H), 8.72 (d, 2H, *J* = 4.8 Hz, pyrimidine H-4, H-6); ¹H-NMR (DMSO-*d*₆ + D₂O) δ : 5.22 (s, 1H, CH),

5.67 (s, 1H, CH), 7.21 (t, 1H, $J = 4.8$ Hz, pyrimidine H-5), 7.17 and 7.38-7.63 (2m, 5H, Ar-H), 8.69 (d, 2H, $J = 4.8$ Hz, pyrimidine H-4, H-6); ^{13}C -NMR δ : 63.83, 84.80, 117.43, 121.63, 124.92, 129.61, 139.17, 151.46, 157.88, 159.14 ppm; MS (EI): m/z 272 (M^+); Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}_3$: C, 57.35; H, 4.41; N, 20.58. Found: C, 57.17; H, 4.45; N, 20.43.

1-(2-Pyrazinyl)-3-phenyl-4,5-dihydroxy-2-imidazolidinone (5c): Yield: 80%; m.p. 164-166 °C (from 1:1 THF-hexane); IR (KBr): 3400 (OH), 3066, 1708 (C=O), 1591, 1427, 1271, 1207, 1080 cm^{-1} ; ^1H -NMR δ : 5.31 (d, 1H, $J = 8.3$ Hz, CH), 5.72 (d, 1H, $J = 6.8$ Hz, CH), 6.91 (d, 1H, $J = 8.3$ Hz, OH), 6.93 (d, 1H, $J = 6.8$ Hz, OH), 7.17-7.69 (m, 5H, Ar-H), 8.37-9.45 (m, 3H, pyrazine H-3, H-5, H-6); ^1H -NMR ($\text{DMSO-d}_6 + \text{D}_2\text{O}$) δ : 5.30 (s, 1H, CH), 5.71 (s, 1H, CH), 7.18-7.65 (m, 5H, Ar-H), 8.35-9.40 (m, 3H, pyrazine H-3, H-5, H-6); ^{13}C -NMR δ : 82.52, 85.74, 121.69, 125.23, 129.70, 136.63, 138.67, 139.70, 143.03, 148.71, 153.17 ppm; MS (EI): m/z 272 (M^+); Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}_3$: C, 57.35; H, 4.41; N, 20.58. Found: C, 57.23; H, 4.38; N, 20.51.

1-(2-Pyridinyl)-3-phenyl-4,5-dihydroxy-2-imidazolidinone (5d): Yield: 85%; m.p. 124-126 °C (from 1:1 THF-hexane); IR (KBr): 3290 (OH), 3066, 2962, 1724 (C=O), 1595, 1483, 1311, 1176, 1047 cm^{-1} ; ^1H -NMR δ : 5.25 (d, 1H, $J = 8.0$ Hz, CH), 5.80 (d, 1H, $J = 6.4$ Hz, CH), 6.71 (d, 1H, $J = 6.4$ Hz, OH), 6.83 (d, 1H, $J = 8.0$ Hz, OH), 7.11-8.39 (m, 9H, Ar-H); ^1H -NMR ($\text{DMSO-d}_6 + \text{D}_2\text{O}$) δ : 5.24 (s, 1H, CH), 5.79 (s, 1H, CH), 7.10-8.38 (m, 9H, Ar-H); ^{13}C -NMR δ : 82.78, 85.14, 113.96, 119.63, 121.42, 124.83, 129.62, 138.86, 139.10, 148.55, 151.90, 153.53 ppm; MS (EI): m/z 271 (M^+); Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_3$: C, 61.99; H, 4.79; N 15.49. Found: C, 61.78; H, 4.90; N, 15.38.

1-(3-Pyridinyl)-3-phenyl-4,5-dihydroxy-2-imidazolidinone (5e): Yield: 75%; m.p. 173-175 °C (from acetonitrile); IR (KBr): 3336 (OH), 3043, 2916, 1695 (C=O), 1581, 1490, 1413, 1271, 1070 cm^{-1} ; ^1H -NMR δ : 5.29 (d, 1H, $J = 8.3$ Hz, CH), 5.34 (d, 1H, $J = 8.1$ Hz, CH), 6.88 (d, 1H, $J = 8.3$ Hz, OH), 6.96 (d, 1H, $J = 8.1$ Hz, OH), 7.13-8.90 (m, 9H, Ar-H); ^1H -NMR ($\text{DMSO-d}_6 + \text{D}_2\text{O}$) δ : 5.28 (s, 1H, CH), 5.33 (s, 1H, CH), 7.14-8.88 (m, 9H, Ar-H); ^{13}C -NMR δ : 84.84, 85.61, 121.20, 124.42, 124.70, 127.69, 129.61, 136.08, 139.09, 142.15, 145.18, 153.84 ppm; MS (EI): m/z 271 (M^+); Anal. Calcd. for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_3$: C, 61.99; H, 4.79; N, 15.49. Found: C, 61.94; H, 4.83; N, 15.42.

1-(2-Benzimidazolyl)-3-phenyl-4,5-dihydroxy-2-imidazolidinone (5f): Yield: 65%; m.p. 226-228 °C (from acetonitrile); IR (KBr): 3498, 3400, 3288, 3041, 2960, 1722 (C=O), 1627, 1568, 1498, 1460, 1271, 1147 cm^{-1} ; ^1H -NMR δ : 5.35 (d, 1H, $J = 8.5$ Hz, CH), 5.65 (d, 1H, $J = 6.9$ Hz, CH), 7.02 (d, 1H, $J = 8.5$ Hz, OH), 7.32 (d, 1H, $J = 6.9$ Hz, OH), 7.20, 7.44 and 7.72 (3m, 5H, Ar-H), 7.10 and 7.50 (2m, 4H, benzimidazole-H), 12.05 (s, 1H, NH); ^1H -NMR ($\text{DMSO-d}_6 + \text{D}_2\text{O}$) δ : 5.35 (s, 1H, CH), 5.65 (s, 1H, CH), 7.21, 7.43 and 7.66 (3m, 5H, Ar-H), 7.12 and 7.49 (2m, 4H, benzimidazole-H); ^{13}C -NMR (298 K) δ : 83.61, 86.40, 112.25, 117.73, 121.41, 121.58, 122.03, 125.26, 129.78, 134.08, 138.52, 141.62, 146.36, 152.97; ^{13}C NMR (384 K) δ : 84.16, 86.81, 112.55, 115.23, 121.80, 122.29, 125.44, 129.55, 138.74, 146.83, 153.42 ppm; MS (EI): m/z 310 (M^+); Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}_3$: C, 61.93; H, 4.51; N, 18.06. Found: C, 61.90; H, 4.60; N, 17.95.

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Sample Availability: Samples of compounds **5a-f** are available from the authors.