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# Reactions of resorcinol derivatives with 1-methyl-3-phenylimidazol-2-one as a new method for the synthesis of 5-arylimidazolidin-2-ones

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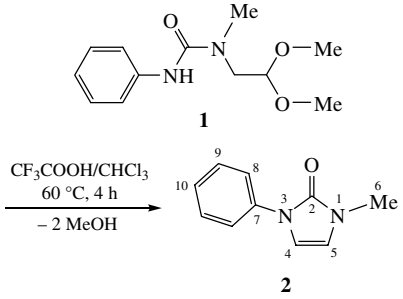
**Substituted imidazolidin-2-ones have been synthesised by the interaction of imidazol-2-one with 2-methylresorcinol and pyrogallol in a chloroform solution in the presence of trifluoroacetic acid.**

Imidazol-2-ones and imidazolidin-2-ones are important biologically active compounds. Imidazol-2-ones are *in vivo* antioxidants,[1] which can be formed under physiological conditions by the interaction of angeotensin I with ascorbate.[2] Imidazol-2-one is a structural basis of the nucleotide antibiotic Nikkomycin X. Imidazol-2-ones play a role in intraocular pressure regulation,[3] they also exhibit anticonvulsant activity.[4] The derivatives of imidazolidin-2-ones are used as proteingenase modulators.[5]

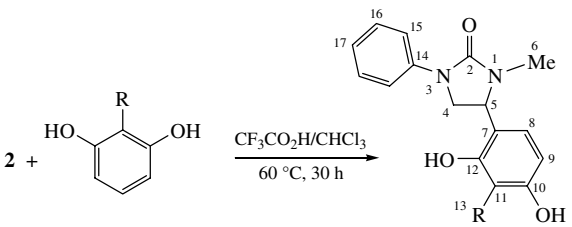
The general method of the synthesis of imidazolidin-2-one derivatives is the interaction of functionalised α-aminocarbonyl compounds with isocyanates.[6–8] Thus, the first stage of the reaction is the formation of appropriate ureas, which are cyclised under acid catalysis conditions. The synthesis of imidazolidin-2-one derivatives can be performed by the condensation of ethylenediamine with phosgene,[9] bis(trichloromethyl) carbonate,[10] diethyl carbonate,[11] di(*tret*-butyl) carbonate[12] and 1,1′-carbonyldiimidazole.[13] 1-Methyl-3-phenylimidazol-2-one **2** was synthesised by the cyclization of acetal **1** in an acid medium[8] (Scheme 1).




**Scheme 1**

We found that the interaction of compound **2** with 2-methylresorcinol or pyrogallol in a chloroform solution in the presence of trifluoroacetic acid results in the formation of imidazolidin-2-ones **3**, **4** (Scheme 2). Note that trimethoxybenzene and dimethoxybenzene did not react with compound **2** under these conditions.

The structures of the compounds obtained were confirmed by $^1$H and $^{13}$C NMR spectroscopy, elemental analysis and mass spectrometry.† The HSQC and HMBC experiment was carried out to elucidate the structure of **3**. The presence of a cross-peak between protons of the MeN group and the C(5) carbon atom and the absence of a cross-peak with the carbon C(4) of the




**Scheme 2**

methyl group in the HMBC spectrum indicates the addition of 2-methylresorcinol to the C(5) carbon atom of a heterocyclic ring. One-dimensional DPFGSE-NOE experiments with compound **3** exhibited a twice larger NOE cross-peak intensity for the C(5)H group proton (2%) compared to that of the C(8)H group (1%) and practically complete absence of NOE for CH(3)N group protons (NOE < 0.01%) after saturation of H(6) revealed the addition of 2-methylresorcinol fragment to the 5-position of the heterocyclic ring.

According to the X-ray data,‡ compound **4** forms triclinic crystals in spatial group $P\bar{1}$. In the symmetrically independent part of a crystal cell, there are two independent molecules of imidazolidinone **4** and two molecules of water. The configuration of the C(5) atom for molecules A and B in the asymmetrical part of a crystal cell is identical. Five-membered heterocyclic rings in both molecules are flat to within 0.025(3) and 0.087(3) Å, respectively. The torsion angles of phenyl substituents in compound **4** equal –9.7(4), 16.2(4)° and –19.9(4), –30.4 (3)° for molecules A and B, respectively.

The molecules of compound **4** in a crystal are stabilised by a system of intra- and intermolecular O–H···O hydrogen bonds.

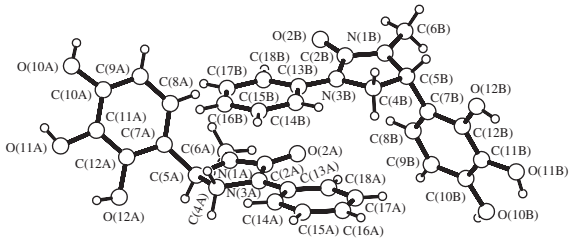



**Figure 1** Molecular structure of compound **4**.

Thus, the interaction of resorcinol derivatives with imidazolone **2** is a new convenient method for the synthesis of 5-aryl-imidazolidin-2-one derivatives.

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† The $^1$H and $^{13}$C NMR spectra were recorded on an Avance 600 instrument with working frequencies of 600.13 ($^1$H) and 150.90 ($^{13}$C) MHz. The IR spectra were recorded on a Vector 22 (Bruker) spectrometer. Mass spectra were measured on a MAT-212 (Finnigan) instrument.

*1-Methyl-1-(2,2-dimethoxyethyl)-3-phenylurea* **1**. A solution of 3.0 g (25.2 mmol) of phenylisocyanate in 3 ml of benzene was added dropwise to a solution of 3.0 g (25.2 mmol) of *N*-methylaminoacetaldehyde dimethyl acetal in 6 ml of benzene. The reaction mixture was stirred for 1 h at 30 °C; the solvent was removed, and the residue was crystallised from benzene. Yield, 65%; mp 66–68 °C. $^1$H NMR ([$^2H_6$]acetone) $\delta$: 3.04 (s, 3H), 3.41 (s, 6H), 3.43 (d, 2H, $^3J_{HH}$ 5.30 Hz), 4.55 (t, 1H, $^3J_{HH}$ 5.30 Hz), 6.93 (m, 1H), 7.21 (m, 2H), 7.48 (m, 2H), 7.86 (s, 1H). Found (%): C, 60.07; H, 7.82; N, 11.38. Calc. for $C_{12}H_{18}N_2O_3$ (%): C, 60.49; H, 7.61; N, 11.76.

*1-Methyl-3-phenylimidazol-2-one* **2**. A mixture of 4 g (16.8 mmol) of 1-(2,2-dimethoxyethyl)-1-methyl-3-phenylurea **1**, 2.1 g (18.4 mmol) of trifluoroacetic acid in 25 ml of chloroform was heated at 60 °C for 4 h. The solvent was removed, and the dry residue was washed with 50 ml of diethyl ether. Yield, 90%; mp 117 °C. $^1$H NMR ($CDCl_3$) $\delta$: 3.28 (s, 3H), 6.29 (d, 1H, $^3J$ 2.93 Hz), 6.54 (d, 1H, $^3J$ 2.93 Hz), 7.21 (t, 1H, $^3J$ 7.33 Hz), 7.38 (t, 2H, $^3J$ 7.92 Hz), 7.59 (d, 2H, $^3J$ 8.21 Hz). $^{13}$C NMR ($CD_3OD$) $\delta$: 29.40 [C(6), $^1J_{CH}$ 139.13 Hz], 109.83 [C(5), $^1J_{CH}$ 197.92 Hz], 113.29 [C(4), $^1J_{CH}$ 196.61 Hz], 121.78 [C(8), $^1J_{CH}$ 159.77 Hz], 125.94 [C(10), $^1J_{CH}$ 159.22 Hz], 128.91 [C(9), $^1J_{CH}$ 158.66 Hz], 137.17 [C(7)], 152.20 [C(2)]. Found (%): C, 68.60; H, 5.93; N, 15.78. Calc. for $C_{10}H_{10}N_2O$ (%): C, 68.95; H, 5.79; N, 16.08.

*5-(2,4-Dihydroxy-3-methylphenyl)-1-methyl-3-phenylimidazolidin-2-one* **3**. A mixture of 2-methylresorcinol (0.39 g, 3.1 mmol), trifluoroacetic acid (0.35 g, 3.1 mmol), compound **2** (0.54 g, 3.1 mmol) and chloroform (3 ml) was heated at 60 °C for 30 h. The solvent was removed; the crystal product was recrystallised from benzene. Yield, 81%; mp 158–159 °C. $^1$H NMR ($CD_3OD$) $\delta$: 2.09 [s, 3H, C(13)H], 2.69 [s, 3H, C(6)H], 3.62, 4.93 [dd, 2H, C(4)H, $^2J_{HH}$ 7.01 Hz, $^3J_{HH}$ 9.12 Hz], 4.16 [t, 1H, C(5)H, $^3J_{HH}$ 9.12 Hz], 6.40 [d, 1H, C(9)H, $^3J_{HH}$ 8.41 Hz], 6.83 [d, 1H, C(8)H, $^3J_{HH}$ 8.41 Hz], 7.01 [m, 1H, C(17)H], 7.27 [m, 2H, C(16)H], 7.51 [m, 2H, C(15)H]. $^{13}$C NMR ($CD_3OD$) $\delta$: 8.57 [C(13), $^1J_{CH}$ 127.39 Hz], 29.29 [C(6), $^1J_{CH}$ 134.66 Hz], 51.75 [C(4), $^1J_{CH}$ 149.68 Hz], 55.54 [C(5), $^1J_{CH}$ 140.96 Hz], 108.13 [C(9), $^1J_{CH}$ 158.40 Hz], 113.08 [C(11)], 118.29 [C(7)], 119.02 [C(15), $^1J_{CH}$ 158.40 Hz], 123.39 [C(17), $^1J_{CH}$ 156.94 Hz], 125.50 [C(8), $^1J_{CH}$ 156.94 Hz], 129.5 [C(16), $^1J_{CH}$ 156.94 Hz], 141.58 [C(14)], 157.06, 155.18 [C(10), C(12)], 160.09 [C(2)]. IR ($\nu$/cm$^{-1}$): 3330, 1680, 1600. Found (%): C, 68.07; H, 6.35; N, 9.38. Calc. for $C_{17}H_{18}N_2O$ (%): C, 68.44; H, 6.08; N, 9.39. MS (EI), *m*/*z*: 298.

*5-(2,3,4-Trihydroxyphenyl)-1-methyl-3-phenylimidazolidin-2-one* **4**. Compound **4** was obtained from **2** and pyrogallol by analogous procedure. Yield, 81%; mp 150–151 °C. $^1$H NMR ($CD_3OD$) $\delta$: 2.67 [s, 3H, C(6)H], 3.61 [dd, 2H, C(4)H, $^1J$ 8.88 Hz, $^2J$ 6.79 Hz], 4.07 [t, 1H, C(5)H, $^1J$ 9.40 Hz], 4.87 [dd, C(4)H, $^1J$ 9.66 Hz, $^2J$ 7.05 Hz], 6.41 [d, 1H, C(9)H, $^1J$ 8.36 Hz], 6.51 [d, 1H, C(8)H, $^1J$ 8.36 Hz], 6.97 [t, 1H, C(17)H, $^1J$ 7.31 Hz], 7.25 [t, 2H, C(16)H, $^1J$ 8.09 Hz], 7.48 [d, 2H, C(15)H, $^1J$ 7.84 Hz]. $^{13}$C NMR ($CD_3OD$) $\delta$: 29.57 [C(6), $^1J_{CH}$ 137.84 Hz], 51.86 [C(4), $^1J_{CH}$ 145.95 Hz], 55.39 [C(5), $^1J_{CH}$ 145.40 Hz], 108.34 [C(9), $^1J_{CH}$ 161.43 Hz], 118.40 [C(8), $^1J_{CH}$ 158.66 Hz], 118.49 [C(7)], 119.29 [C(15), $^1J_{CH}$ 159.22 Hz], 123.70 [C(17), $^1J_{CH}$ 160.32 Hz], 129.84 [C(16), $^1J_{CH}$ 158.66 Hz], 141.85 [C(14)], 134.49 [C(11)], 147.23, 146.18 [C(10), C(12)], 160.30 [C(2)]. IR ($\nu$/cm$^{-1}$): 3337, 1692, 1653. Found (%): C, 63.50; H, 5.89; N, 9.01. Calc. for $C_{16}H_{16}N_2O_4$ (%): C, 63.99; H, 5.37; N, 9.33.

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‡ *X-ray crystallography of* **4**: $C_{16}H_{16}N_2O_4 \cdot H_2O$, $M$ = 318.32, triclinic, space group $P\bar{1}$, $a$ = 10.663(3), $b$ = 11.0674(18) and $c$ = 14.8613(13) Å, $\alpha$ = 81.88(1), $\beta$ = 75.28(2) and $\gamma$ = 65.64(2)°, $V$ = 1543.9(5) Å$^3$, $Z$ = 4 (two independent molecules and two solvent water molecules), $d_{calc}$ = = 1.37 g cm$^{-3}$. Cell parameters and intensities of 6268 independent reflections (3909 with $I \geq 2\sigma$) were measured on an Enraf-Nonius CAD-4 diffractometer in the $\omega/2\theta$-scan mode, $\theta \leq 74.20°$, using CuK$\alpha$ radiation with a graphite monochromator. The intensity falling was not observed at three control measurements. Absorption correction was not applied [$\mu$(CuK$\alpha$) = 8.59 cm$^{-1}$]. The structure was solved by a direct method using the SIR program[14] and refined by the full matrix least-squares using the SHELX-97 program package. All non-hydrogen atoms were refined anisotropically. The positions of the hydrogen atoms were idealised. The final divergence factors are $R$ = 0.047, $R_w$ = 0.104 based on 3909 reflections with $F^2 \geq 2\sigma^2$. All calculations were performed on a PC using the WinGX program.[15] Cell parameters, data collection and data reduction were performed on an Alpha Station 200 computer using MoLEN.[16] Figures of molecules were performed with the program PLATON.[17]

CCDC 643328 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2008.