Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 04 Dec 2007.

To cite this article: Jaroslaw Spychala (2000): 4-(Cyclic Amidino)phenols - Preparation and Use In A Diamidine Synthesis, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 30:6, 1083-1094

To link to this article: http://dx.doi.org/10.1080/00397910008087126

SYNTHETIC COMMUNICATIONS, 30(6), 1083–1094 (2000)

4-(CYCLIC AMIDINO)PHENOLS - PREPARATION AND USE IN A DIAMIDINE SYNTHESIS

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Abstract: The Pinner synthesis was applied to the preparation of 4-(cyclic amidino)phenols in high yields from readily available 4-hydroxybenzimidic acid methyl ester hydrochloride and diaminoalkanes. An alternative attempt was made to convert 4-(hydroxy)thiobenzamide to 4-(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)phenol. A procedure for the preparation of 3,6-bis(4-hydroxyphenyl)-1,2,4,5-tetrazine is reported here. The syntheses of 2,4-bis[4-(4,5-dihydro-1*H*-imidazol-2-yl)phenoxy]pyrimidine and 2-chloro-4-[4-(4,5-dihydro-1*H*-imidazol-2-yl)-phenoxy]pyrimidine exemplify the use of the title synthetic intermediates.

The formation of (simple amidino)phenols by the Pinner synthesis was already described in the literature.[1] Such products were useful intermediates for the synthesis of certain amidinophenyl esters of biochemical interest. Usually, N-blocked derivatives were used for the coupling reactions. Although these reactions

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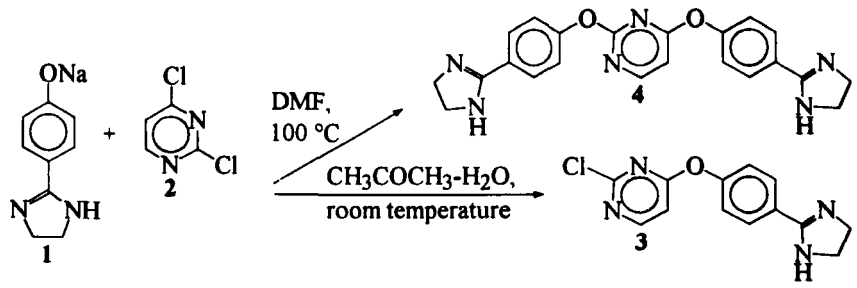
offer a convenient way for the preparation of simple amidine derivatives, the possible applications of 4-(cyclic amidino)phenols have received little attention.

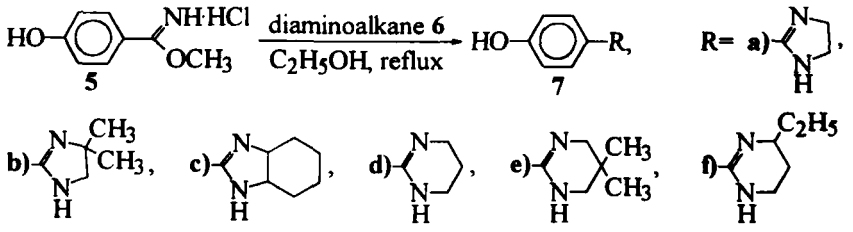
Diamidines continue to attract interest because of their specific biological activities.[2] These compounds can be prepared by several methods, and a convenient synthetic way from readily available 4-(cyclic amidino)phenols is described in this publication. The preparations of 2-chloro-4-[4-(4,5-dihydro-1*H*-imidazol-2-yl)phenoxy]pyrimidine (**3**) and 2,4-bis[4-(4,5-dihydro-1*H*-imidazol-2-yl)phenoxy]-pyrimidine (**4**) are illustrative of the manner in which the diamidines may be prepared. Replacement of the more readily displaced chlorine in 2,4-dichloro-pyrimidine (**2**) [3] was effected with an excess of sodium phenoxylate **1** in acetone-water solution at room temperature to yield the desired monoamidine **3** in 56 %. In an analogous manner, the diamidine **4** was obtained in anhydrous DMF at 100 °C (61 % yield), as shown in Sheme 1.

(Cyclic amidino)phenols (**7**) were obtained from 4-hydroxybenzimidic acid methyl ester hydrochloride (**5**) and diaminoalkane **6** by boiling with ethanol under reflux (Scheme 2).[4] Subsequent aqueous work-up yielded the desired cyclized products **7** as the free bases in high yields (71-95 %). One such compound in this series, 4-(4,5-dihydro-1*H*-imidazol-2-yl)phenol, has previously been obtained by demethylation of 4-(4,5-dihydro-1*H*-imidazol-2-yl)anisole.[5]

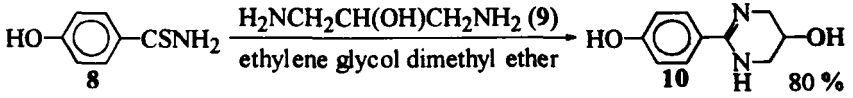
4-(1,4,5,6-Tetrahydro-5-hydroxy-2-pyrimidinyl)phenol has been achieved by a slight modification of the Forsell reaction [6] using monoglyme as solvent (Scheme 3). The starting 4-(hydroxy)thiobenzamide (**8**), obtained here by an improved method, has also been previously described.[7]



Scheme 1



Scheme 2



Scheme 3

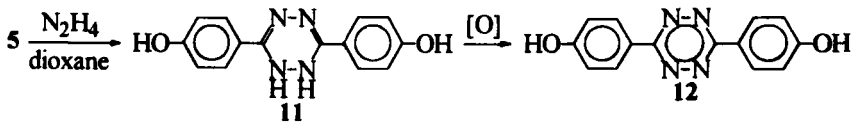
The methyl imidate hydrochloride (**5**) reacted readily with an excess of anhydrous hydrazine under reflux in 1,4-dioxane to give an orange-red dimer **11** in 99 % yield, although observed in the literature reaction with hydrazine at room temperature led to *p*-hydroxybenzamidrazone hydrochloride.[8] 1,2-Dihydro-3,6-bis-(4-hydroxyphenyl)-1,2,4,5-tetrazine (**11**) was oxidized to the intense red *s*-tetra-

zine biphenol **12** with sodium nitrite[9] in 2*N* hydrochloric acid (40 % isolated yield), as illustrated in Scheme 4.

In summary, the procedures presented should make (cyclic amidino)-phenols readily available as important intermediates for organic syntheses, especially for the preparation of novel diamidines. All compounds synthesized were characterized with ^{1}H- and ^{13}C-NMR spectroscopic data. Alternatively, high resolution mass spectra are herein included *in lieu* of CHN-analyses.

EXPERIMENTAL

Melting points are uncorrected and were determined either on a Boetius or Thomas-Hoover melting point apparatuses. NMR spectra were recorded on Varian Gemini (300 MHz) or Jeol JNM-GX (270 MHz) spectrometers. Microanalyses were obtained from Atlantic Microlab Inc. (Norcross, GA). High resolution mass spectra were made in a AMD 402 mass spectrometer, while low resolution spectra in a VG Instruments 70-SE spectrometer. Thin-layer chromatography was performed with Merck silica gel 60 F_{254} plates (0.25 mm thickness), using 18:1, 9:1 $CHCl_3$-CH_3OH; 44:8:1, 11:4:1, or 7:5:2 $CHCl_3$-CH_3OH-NH_4OH as developing solvents. 2,4-Dichloropyrimidine (**2**), 1,3-diamino-2-hydroxypropane (**9**), sodium ethoxide, anhydrous hydrazine, anhydrous ethylene glycol dimethyl ether (monoglyme), and sodium hydroxide volumetric standard, 0.995 *N* solution in water were purchased from Aldrich. Diaminoalkanes **6** (**a**) ethylenediamine, **b**) 1,2-diamino-2-methylpropane, **c**) 1,2-diaminocyclohexane (*cis* and *trans* isomers), **d**) 1,3-diaminopropane, **e**) 2,2-dimethyl-1,3-propanediamine, **f**) (±)-1,3-diaminopentane) were commercially available from Aldrich and distilled from sodium. All final samples were dried in a vacuum oven.



Scheme 4

2-Chloro-4-[4-(4,5-dihydro-1*H*-imidazol-2-yl)phenoxy]pyrimidine **(3)**, 4-(4,5-dihydro-1*H*-imidazol-2-yl)phenol (**7a**, 1g, 0.0062 mole), was added to acetone (30 cm^3), water (30 cm^3), and 0.995 *N* water sodium hydroxide solution (6.5 cm^3). Undissolved material was removed by filtration, and the reaction mixture containing 2,4-dichloropyrimidine (**2**, 0.411 g, 0.0028 mole) was stirred at room temperature for 2 hours until the reaction was complete by TLC ($CHCl_3$ and $CHCl_3$:CH_3OH:NH_4OH= 44:8:1). The solvents were evaporated under vacuum and the residue extracted with methylene chloride. The product was collected upon concentration (0.427g, 56%). An analytical sample was recrystallized from methanol: m.p.> 300 °C (dec.), *anal.* calc. for $C_{13}H_{11}ClN_4O$: C, 56.84; H, 4.04; N, 20.40, found: C, 56.91; H, 4.07; N, 20.29, *^{1}H-NMR* (DMSO-d_6), δ, 3.62 (s, 4H), 6.87 (br.s, 1H), 7.16 (d, 1H, J= 5.86 Hz), 7.31 (d, 2H, J= 8.79 Hz), 7.92 (d, 2H, J= 8.79 Hz), 8.63 (d, 1H, J= 5.86 Hz), *^{13}C-NMR* (DMSO-d_6), δ, 49.6, 107.6, 121.1, 128.7, 128.8, 153.0, 159.0, 161.5, 162.8, 169.8. *MS*, EI, m/z, 276, 274, 247, 245 (base peak), 237, 209, 157, 40.

2,4-Bis[4-(4,5-dihydro-1*H*-imidazol-2-yl)phenoxy]pyrimidine **(4)**, this compound was obtained by reaction of 2,4-dichloropyrimidine (**2**, 0.411 g, 0.0028 mole) and sodium 4-(4,5-dihydro-1*H*-imidazol-2-yl)phenoxylate **1**, prepared from 4-(4,5-di-

hydro-1*H*-imidazol-2-yl)phenol (**7a**, 1g, 0.0062 mole) and sodium ethoxide (0.410 g, 0.0061 mole) in anhydrous dimethylformamide (10 cm^3). The reaction mixture was then heated in an oil bath at 100 °C for 7 hours, evaporated to dryness, and the residue was extracted for one day with chloroform in a Soxhlet apparatus. The extract was concentrated and crystals separated after addition of diethyl ether. The solid was filtered, washed with ether and water, to afford homogeneous product **4** (TLC, $CHCl_3$:CH_3OH:NH_4OH=11:4:1): m.p. 170-2°C, yield 0.680 g (61 %), *^{1}H-NMR* (DMSO-d_6), δ, 3.62 (s, 4H), 3.63 (s, 4H), 5.80 (br.s, 2H), 6.88 (d, 1H, J= 5.37 Hz), 7.22 (d, 2H, J= 8.79 Hz), 7.30 (d, 2H, J= 8.78 Hz), 7.82 (d, 2H, J= 8.79 Hz), 7.88 (d, 2H, J= 8.79 Hz), 8.48 (d, 1H, J= 5.37 Hz), *^{13}C-NMR* (DMSO-d_6), δ, 49.7, 49.8, 103.5, 121.2, 121.3, 127.4, 128.1, 128.4, 128.7, 153.2, 153.9, 161.1, 162.9, 163.0, 164.0, 170.6, *MS*, CI (isobutane), m/z, 401 $(M+H)^+$, 400 (M^+), 399 $(M.-H)^+$, 133 (base peak). Dipropanoate salt of **4**, m.p.< 100 °C (semisolid), ***anal.*** calc. for $C_{22}H_{20}N_6O_2 \cdot 2CH_3CH_2COOH$: C, 61.30; H, 5.88; N, 15.32, found: C, 59.53; H, 5.75; N, 15.94, *^{1}H-NMR* (DMSO-d_6), δ, 0.99 (t, 6H, J= 7.57 Hz), 2.18 (q, 4H, J= 7.49 Hz), 3.67 (s, 8H), 6.89 (d, 1H, J= 5.37 Hz), 7.24 (d, 2H, 8.30 Hz), 7.31 (d, 2H, J= 8.30 Hz), 7.85 (d, 2H, J= 8.30 Hz), 7.90 (d, 2H, J= 8.30 Hz), 8.49 (d, 1H, J= 5.37 Hz), *^{13}C-NMR* (DMSO-d_6), δ, 9.2, 27.2, 48.7, 48.9, 103.5, 121.2, 121.3, 126.3, 127.1, 128.6, 128.8, 153.5, 154.3, 161.2, 163.0, 163.2, 163.9, 170.4, 175.3. *MS*, EI, m/z, 400 (M^+), 399, 341, 237, 162, 161, 133.

General procedure for the preparation of 4-(cyclic amidino)phenols **7**

4-Hydroxybenzimidic acid methyl ester hydrochloride[1] (**5**, 3.7526, 0.02 mole), and

one molecular equivalent of a diaminoalkane **6** in ethanol (20 cm^3) were heated under reflux with stirring for 18 hours. The material resulting from evaporation of the solvent was treated with a solution of potassium hydrogencarbonate (2 g, 0.02 mole) in water. The precipitate was then filtered, washed with cold water, and dried *in vacuo*. After solidification had occured, the crude **7b** and **7f** were purified by crystallization from boiling water. In most cases, compounds **7** were obtained as chromatographically pure solids.

4-(4,5-Dihydro-1*H*-imidazol-2-yl)phenol (**7a**), m.p. 290-2 °C (lit.[5] it begins to char at 290 °C and has m.p. *ca.* 300 °C), yield 90 %, *^{1}H-NMR* [10] (DMSO-d_6, TMS), δ, 3.68 (s, 4H), 6.80 (d, 2H, J= 8.30 Hz), 7.70 (d, 2H, J= 8.30 Hz), *^{13}C-NMR* (DMSO-d_6, TMS), δ, 47.4, 115.4, 117.4, 129.5, 161.6, 163.9, *HR MS*, EI, m/z, calc. for $C_9H_{10}N_2O$: 162.07932, found: 162.07995, -3.9 ppm.

4-(4,5-Dihydro-4,4-dimethyl-1*H*-imidazol-2-yl)phenol (**7b**), m.p. 295-6 °C (dec.), yield 75 %, *^{1}H-NMR* (CD_3OH, TMS), δ, 1.46 (s, 6H), 3.66 (s, 2H), 6.59 (d, 2H, J= 8.79 Hz), 7.51 (d, 2H, J= 9.07 Hz), *^{13}C-NMR* (CD_3OD, TMS), δ, 27.9, 58.1, 61.8, 106.3, 120.9, 131.5, 164.9, 176.9, *HR MS*, EI, m/z, calc. for $C_{11}H_{14}N_2O$: 190.11061, found: 190.11174, -5.9 ppm.

4-(4,5,6,7,8,9-Hexahydro-1*H*-benzimidazol-2-yl)phenol, mixture of *cis* and *trans* isomers (**7c**), m.p. 335-7 °C (dec.), yield 88 %, *^{1}H-NMR* (CD_3OH, DCl/D_2O), δ, 1.30-2.00 (m, 6H), 2.20-2.40 (m, 2H), 3.55 (m, 2H), 6.99 (d, 2H, J= 8.79 Hz), 7.89 (d, 2H, J= 8.79 Hz), *^{13}C-NMR* (CD_3OD), δ, 24.8, 29.7, 66.0, 114.0, 117.4, 132.1, 165.1, 168.5, *HR MS*, EI, m/z, calc. for $C_{13}H_{16}N_2O$: 216.12627, found: 216.12559, 3.1 ppm.

4-(1,4,5,6-Tetrahydro-2-pyrimidinyl)phenol (**7d**), m.p.> 300 °C, yield 89 %, *^{1}H-NMR* (DMSO-d_6, TMS), δ, 1.89 (quintet, 2H, J= 5.86 Hz), 3.41 (t, 4H, J= 5.86 Hz), 5.14 (br.s, 2H), 6.75 (d, 2H, J= 8.79 Hz), 7.54 (d, 2H, J= 8.79 Hz), *^{13}C-NMR* (CD_3OD), δ, 20.0, 40.2, 113.3, 120.3, 129.7, 161.4, 174.2. *HR MS*, EI, m/z, calc. for $C_{10}H_{12}N_2O$: 176.09497, found: 176.09539, -2.4 ppm.

4-(1,4,5,6-Tetrahydro-5,5-dimethyl-2-pyrimidinyl)phenol (**7e**), m.p.>310°C, yield 95%, *^{1}H-NMR* (DMSO-d_6), δ, 1.00 (s, 6H), 3.12 (s, 4H), 5.88 (br.s, 2H), 6.73 (d, 2H, J= 8.79 Hz), 7.59 (d, 2H, J= 8.79 Hz), *^{13}C-NMR* (DMSO-d_6), δ, 23.5, 25.5, 49.7, 114.1, 116.7, 129.2, 157.5, 167.0, *HR MS*, EI, m/z, calc. for $C_{12}H_{16}N_2O$: 204.12627, found: 204.12704, -3.8 ppm.

(±)-4-(4-Ethyl-1,4,5,6-tetrahydro-2-pyrimidinyl)phenol (**7f**), m.p.> 300 °C, yield 71 %, *^{1}H-NMR* (CD_3OD, TMS), δ, 1.05 (t, 3H, J= 7.55 Hz), 1.63 (m, 1H), 1.75-1.93 (m, 2H), 2.04-2.18 (m, 1H), 3.40-3.60 (m, 3H), 6.62 (d, 2H, J= 8.79 Hz), 7.37 (d, 2H, J= 8.79 Hz), *^{13}C-NMR* (CD_3OD, TMS), δ, 24.7, 28.7, 38.7, 52.6, 112.9, 120.5, 129.9, 161.6, 175.0, *HR MS*, EI, m/z, calc. for $C_{12}H_{16}N_2O$: 204.12627, found: 204.12794, -8.2 ppm.

4-(Hydroxy)thiobenzamide (**8**), this starting compound was herein obtained by appropriate modifications of literature methods.[6,7] An improved procedure utilizes commercially available 20 % ammonium sulfide solution in water (10 cm^3), pyridine (5 cm^3), and 4-hydroxybenzonitrile (1.4533g, 0.0122 mole). The solution was allowed to stand at room temperature to complete the reaction. The tightly stoppered reaction flask was occasionally shaken. The isolation was effected by

evaporation to dryness and recrystallization from boiling water (50 cm^3): m.p. 191-2 °C (lit.[7] 185-6 °C), yield 83 %, *^{1}H-NMR* (DMSO-d_6), δ, 6.77 (d, 2H, J= 8.78 Hz), 7.88 (d, 2H, J= 9.16 Hz), 9.23 (s, 1H), 9.55 (s, 1H), 10.12 (br.s, 1H), *^{13}C-NMR* (DMSO-d_6), δ, 114.4, 129.7, 129.8, 160.7, 198.7, *HR MS*, EI, m/z, calc. for C_7H_7NOS: 153.02484, found: 153.02630, -9.5 ppm.

4-(1,4,5,6-Tetrahydro-5-hydroxy-2-pyrimidinyl)phenol (**10**), to a solution of 1,3-diamino-2-hydroxypropane (**9**, 0.9013g, 0.01 mole) in ethylene glycol dimethyl ether (10 cm^3), 4-(hydroxy)thiobenzamide (**8**, 1.5322g, 0.01 mole) was added. The mixture was heated with stirring for 18 hours. After cooling, the solid was filtered, washed with ethylene glycol dimethyl ether, and crystallized from boiling water. An analytically pure sample was recrystallized from methanol: m.p. 294-5 °C (dec.), yield 80%, *^{1}H-NMR* (CD_3COOD, TMS), δ, 3.67 (d, 4H, J= 2.75 Hz), 4.54 (t, 1H, J= 2.75 Hz), 7.01 (d, 2H, J= 8.86 Hz), 7.65 (d, 2H, J= 8.86 Hz), *^{13}C-NMR* (CD_3COOD), δ, 46.1, 59.1, 117.2, 119.9, 130.3, 160.8, 163.1, *HR MS*, EI, m/z, calc. for $C_{10}H_{12}N_2O_2$: 192.08987, found: 192.09076, -4.6 ppm. Mono-hydrochloride salt of **10**, m.p. 197-8 °C, *^{1}H-NMR* (DMSO-d_6), δ, 3.33 (d, 2H, J= 14.83 Hz), 3.50 (d; 2H, J= 14.83 Hz), 4.20 (m, 1H), 5.62 (d, 1H, J= 3.30 Hz), 6.97 (d, 2H, J= 8.79 Hz), 7.65 (d, 2H, J= 8.79 Hz), 9.77 (s, 2H), 10.69 (s, 1H).

1,2-Dihydro-3,6-bis(4-hydroxyphenyl)-1,2,4,5-tetrazine (**11**), the imidate **5** was obtained by reaction of 4-hydroxybenzonitrile (25g, 0.2098 mole), and methanol (200 cm^3) saturated with hydrogen chloride at below 0 °C. After standing at room temperature for 3 days, dry diethyl ether (250 cm^3) was added, the precipitated white crystals were collected by filtration, washed with ether, and dried in a

vacuum oven at 40 °C until free of solvent and excess hydrogen chloride. 4-Hydroxybenzimidic acid methyl ester hydrochloride required no further purification and was used in the next step. To a mixture of anhydrous hydrazine (15 cm^3) in 1,4-dioxane (150 cm^3) the above imidate was gradually added, and the mixture was refluxed overnight with stirring. The yellow mixture was cooled in the refrigerator, filtered, and the residue washed successively with water. The dihydrotetrazine was partially oxidized to the red tetrazine on heating with methanol, but was more stable when dry. Recrystallization from dry dioxane afforded an analytical orange-red sample: m.p. 286-9 °C (dec.), the total yield was practically that calculated (based on starting 4-hydroxybenzonitrile), *^{1}H-NMR* (pyridine-d_5), δ, 6.78 (s, 2H), 7.20 (d, 2H, J= 8.79 Hz), 7.27 (d, 2H, J= 8.79 Hz), 8.16 (d, 2H, J= 8.79 Hz), 8.36 (d, 2H, J= 8.79 Hz), 9.51 (s, 2H), *^{13}C-NMR* (pyridine-d_5), δ, 116.4, 116.5, 128.5, 130.8, 155.0, 160.4, 160.9, *HR MS*, EI, m/z, calc. for $C_{14}H_{12}N_4O_2$: 268.09604, found: 268.09773.

3,6-Bis(4-hydroxyphenyl)-1,2,4,5-tetrazine (**12**), the dihydrotetrazine **8** (22.3g, 0.0831 mole) was oxidized to the red tetrazine **12** by addition of sodium nitrite (30g, 0.4348 mole), and cold 2*N* hydrochloric acid (300 cm^3). The heterogeneous mixture was overnight mechanically stirred at room temperature. The crude product was filtered, washed with water, dried, and extracted with acetone in a Soxhlet device to afford chromatographically pure **12** ($CHCl_3$:CH_3OH:NH_4OH= 44:8:1) in 40 % isolated yield: m.p. 300-301 °C, *^{1}H-NMR* (DMSO-d_6, TMS), δ, 7.04 (d, 4H, J= 8.79 Hz), 8.36 (d, 4H, J= 8.06 Hz), 10.35 (br.s, 2H), *^{13}C-NMR*

(DMSO-d_6, TMS), δ, 116.3, 122.6, 129.2, 161.5, 162.6, *HR MS*, EI, m/z, calc. for $C_{14}H_{10}N_4O_2$: 266.08038, found: 266.08239, -7.5 ppm.

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Received in the UK 17 May 1999