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Phenol derivatized hexahydropyrimidines prepared from Mannich condensations

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Abstract—Six new phenol derivatized hexahydropyrimidines (1,3-bis-(2-hydroxy-3,5-di(X)benzyl) hexahydropyrimidine and 5,5′-dimethyl-1,3-bis-(2-hydroxy-3,5-di(X)benzyl) hexahydropyrimidine where X = Me, *t*-Bu, and Cl) were synthesized in one-pot in 33–79% yield using Mannich condensations.

1. Introduction

Multicomponent reactions (MCRs) are becoming increasingly important in organic chemistry for building libraries of compounds,[1,2] and the Mannich condensation is a venerable example of an MCR. Hexahydropyrimidines are nitrogen containing heterocycles that have applications in both inorganic and organic chemistry. Hexahydropyrimidines are traditionally synthesized from condensations of alkyl diamines and aldehydes.[3–5] Current interest in the organic chemistry community[6–8] in synthesizing derivatives of these heterocycles focuses on their anti-carcinoma, anti-lymphoma, and anti-biotic properties along with their appearance in alkaloid structures.[9,10] In recent work with inorganic systems, hexahydropyrimidine derivatives have been used as precursors for N-heterocyclic carbenes bound to Rh(I),[11] to prepare tris-μ-oxo Al(III) complexes,[12] and as ligands for biologically relevant metals such as Fe(II), Ni(II), and Zn(II).[13]

2. Results and discussion

The synthesis of the six new hexahydropyrimidine derivatives represents an expansion of our previous work exploring the use of Mannich condensations to prepare new amino-alcohol ligands (Scheme 1).[14] By exchanging the 1,2-diaminoethane (en) starting material (Scheme 1) to 1,3-diaminopropane, we were looking to prepare ligands similar to **2a–c** and **3a–c** that could form larger six-membered rings when bound to metal centers. All of our attempts to prepare diaminodiphenols similar to **2a–c** resulted in product mixtures that were heavily contaminated with hexahydropyrimidine derivatives. Optimization of reaction conditions, where combination of 1 equiv of the diamine, 2 equiv of a 2,4-substituted phenol, and 4 equiv of paraformaldehyde resulted in the formation of the diphenol substituted hexahyropyrimidines **4a–c**[15] and **5a–c**,[16] Chart 1, in excellent yields (with one exception, **4c**) when one considers the product is from six components. Two synthetic protocols were examined. Neat reactions in pressure flasks gave better yields for **4a–c** and refluxing in methanol solutions resulted in better yields for **5a–c**. Purification in all instances consisted of a simple filtration of the product from a methanolic solution of the crude product mixture.

Mechanistically, there are at least three pathways available after two Mannich condensations have occurred (one at each 1° amine) and an additional equivalent of formaldehyde has reacted with one of the two new 2° amines (Scheme 2). The putative iminium intermediate has at least three nucleophiles to react with in the reaction mixture. If the iminium reacts intramolecularly with the phenolic oxygen of the closest phenol (attack by the other phenol would result in an unlikely 10-membered ring), the result is formation of a benzoxazine ring system, path A, Scheme 2.[14] Path A is a favorable

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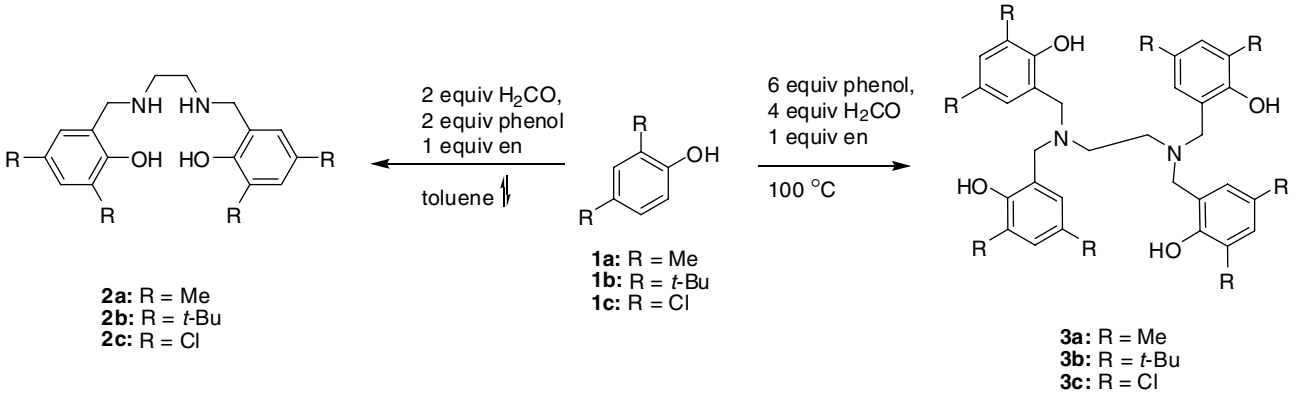
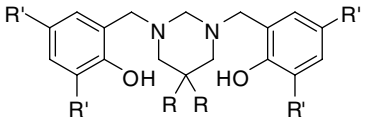


Scheme 1. Synthesis of amino-alcohol ligands using the Mannich condensation.

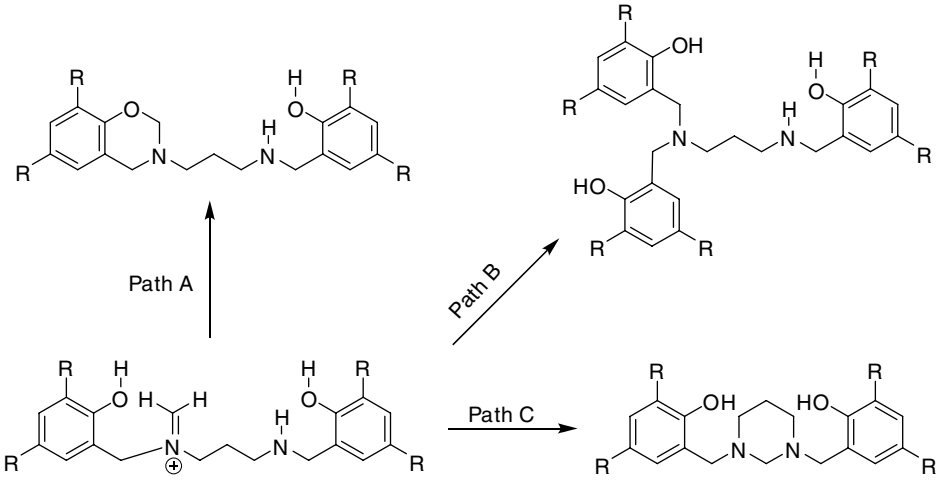


4a: R = H, R' = Me, 76%
4b: R = H, R' = *t*-Bu, 70%
4c: R = H, R' = Cl, 34%
5a: R = Me, R' = Me, 79%
5b: R = Me, R' = *t*-Bu, 61%
5c: R = Me, R' = Cl, 65%

Chart 1. Hexahydropyrimidine complexes prepared in listed yields.

six-*endo-trig* ring closure.[17] We observed occasional formation of five-membered imidazolidines ring systems when using 1,2-diaminoethane as the starting material (a disfavored five-*endo-trig* ring closure), but six-membered benzoxazine rings were the more common outcome when extra equivalents of formaldehyde were present in the absence additional equivalents of phenol.[14] If the iminium intermediate reacts intermolecularly with a second equivalent of phenol, then the resulting complex will be similar to **3a**–**c** where the amine has two phenol derivatives attached to it, path B, Scheme 2. Path B was the predominant pathway when there is an ethyl chain between the two amine groups.[14] Finally, if there is an intramolecular reaction with the iminium and the other amine of the diamine (also a favored six-*endo-trig* ring closure), then a hexahydropyrimidine will be the result, path C, Scheme 2. In this work, the formation of six-membered hexahydropyrimidine rings (path C) are greatly favored over paths A and B, even when extra equivalents of phenol are present. Thus far, we have been unable to prepare diamino-tetraphenols similar to **3a**–**c** using 1,3-diaminopropane or 2,2′-dimethyl-1,3-diaminopropane as a starting material. The lack of tetraphenol formation using 2,2′-dimethyl-1,3-diaminopropane is less surprising as the *gem* dimethyl substituents could invoke the Thorpe–Ingold effect and increase the rate of formation of **5a**–**c** over other possible reactions, Scheme 2.

All of the new compounds have been completely characterized by ^{1}H and ^{13}C NMR, FTIR, melting point, and elemental analysis and all results are consistent with the proposed formulations. None of the compounds are water soluble, and only **4c** was soluble in a 1 M NaOH(aq) solution. Using MeOH, **4a** and **5a** are soluble, while all six compounds are soluble in CH_2Cl_2. Adding the two methyl groups to the 5-position of the hexahydropyrimidine ring only make a difference of the solubility of **4c** compared to the insolubility of **5c** in 1 M NaOH(aq) solution.



Scheme 2. Potential products derived from putative iminium intermediate (lower left corner) with three available nucleophiles.

The new compounds prepared in this study will most likely be useful as ligands in bioinorganic chemistry. The ability of the hexahydropyrimidine framework to support μ-O cores[12] and the presence of two phenols, which are easily deprotonated may make these compounds a versatile 'organic chip' for modeling the structure and function of metallo-enzymes and protein active-sites. The electronic and steric properties of these compounds are easily varied and all can be synthesized in multi-gram quantities from commercially available starting materials. We are currently investigating the binding of these complexes to biologically relevant metal centers.

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15. *Representative experimental procedure for* **4a–c**. In a 120 mL pressure flask equipped with a magnetic stir bar, 1.67 mL (0.020 mol, 1 equiv) of 1,3-diaminopropane, 2.52 g (0.080 mol, 4 equiv) of 95% paraformaldehyde, and (0.040 mol, 2 equiv) of a 2,4-disubstituted phenol (**1a–c**) were combined and allowed to react at 90 °C for 18 h. The resulting mixture was then sonicated with methanol (~100 mL) for 30 min. A white solid precipitate formed from the brown oil was collected by vacuum filtration. Compound **4a**. Yield: 5.504 g, 76.3%. IR: 3008, 2957, 2937, 2911, 2825, 2729, 1767, 1613 cm^{-1}. ^1H NMR ($CDCl_3$) δ 10.24 (s, 2H, Ph–O*H*), 6.86 (s, 2H, Ph–*H*), 6.65 (s, 2H, Ph–*H*), 3.73 (s, 4H, Ph–CH_2–N), 3.43 (s, 2H, N–CH_2–N), 2.71 (s, 4H, N–CH_2–CH$_2$–CH_2–N), 2.21 (s, 12H, Ph–CH_3), 1.78 (s, 2H, N–CH$_2$–CH_2–CH$_2$–N). ^{13}C NMR ($CDCl_3$) δ 153.58, 130.96, 127.97, 127.07, 124.93, 119.89, 73.47, 57.94, 51.30, 21.77, 20.59, 15.85. Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.43; H, 8.93; N, 7.78. Mp 113.2–114.5 °C. Compound **4b**. Yield: 6.252 g, 69.5%. IR: 2955, 2901, 2866, 2805, 2719, 2678, 1775, 1607 cm^{-1}. ^1H NMR ($CDCl_3$) δ 10.43 (s, 2H, Ph–O*H*), 7.235 (d, 2H, Ph–*H*, $J = 2.4$ Hz), 6.871 (d, 2H, Ph–*H*, $J = 2.0$ Hz), 3.77 (s, 4H, Ph–CH_2–N), 3.48 (s, 2H, N–CH_2–N), 2.72 (s, 4H, N–CH_2–CH$_2$–CH_2–N), 1.78 (s, 2H, N–CH$_2$–CH_2–CH$_2$–N), 1.43 (s, 18H, Ph–C(CH_3)$_3$), 1.29 (s, 18H, Ph–C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$) δ 154.39, 140.92, 135.97, 123.85, 123.39, 120.40, 73.42, 58.48, 50.88, 35.09, 34.36, 31.89, 29.81, 21.35. Anal. Calcd for $C_{34}H_{54}N_2O_2$: C, 78.11; H, 10.41; N, 5.36. Found: C, 77.72; H, 10.48; N, 5.32. Mp 174.5–175.4 °C. Compound **4c**. Yield: 2.934 g, 33.7%. IR: 3078, 2952, 2932, 2834, 2749, 1722, 1604 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.273 (d, 2H, Ph–*H*, $J = 2.0$ Hz), 6.915 (d, 2H, Ph–*H*, $J = 2.4$ Hz), 3.81 (s, 4H, Ph–CH_2–N), 3.47 (s, 2H, N–CH_2–N), 2.80 (s, 4H, N–CH_2–CH$_2$–CH_2–N), 1.85 (s, 2H, N–CH$_2$–CH_2–CH$_2$–N). ^{13}C NMR ($CDCl_3$) δ 152.47, 129.36, 127.22, 124.12, 122.76, 121.11, 72.41, 57.17, 51.22, 21.18. Anal. Calcd for $C_{18}H_{18}Cl_4N_2O_2$: C, 49.57; H, 4.16; N, 6.42. Found: C, 49.28; H, 3.95; N, 6.05. Mp 113.2–114.5 °C.
16. *Representative experimental procedure for* **5a–c**. In a 50 mL round bottom flask equipped with a magnetic stir bar, 1.20 mL (0.010 mol, 1 equiv) of 2,2-dimethyl-1,3-diaminopropane, 1.26 g (0.040 mol, 4 equiv) of 95% paraformaldehyde, and (0.020 mol, 2 equiv) of a 2,4-disubstituted phenol (**1a–c**) were combined with 15 mL of methanol. The reaction was allowed to reflux for three days and the resultant white solid was collected by vacuum filtration and washed with cold methanol. Compound **5a**. Yield: 3.022 g, 78.7%. IR: 3007, 2985, 2915, 2797, 2673, 1743, 1613 cm^{-1}. ^1H NMR ($CDCl_3$) δ 10.03 (s, 2H, Ph–O*H*), 6.87 (s, 2H, Ph–*H*), 6.61 (s, 2H, Ph–*H*), 3.57 (s, 4H, Ph–CH_2–N), 2.21 (s, 16H, Ph–CH_3, N–CH_2–C–CH_2–N), 1.57 (s, 2H, N–CH_2–N), 1.03 (s, 6H, N–CH$_2$–C(CH_3)$_2$–CH$_2$–N) ^{13}C NMR ($CDCl_3$) δ 153.50, 131.02, 127.83, 126.89, 125.15, 119.73, 75.23, 64.08, 59.11, 31.26, 25.88, 20.59, 15.90. Anal. Calcd for $C_{24}H_{34}N_2O_2$: C, 75.35; H, 8.96; N, 7.32. Found: C, 74.92; H, 8.99; N, 7.19. Mp 131.1–131.8 °C. Compound **5b**. Yield: 3.942 g, 60.9%. IR: 2997, 2954, 2901, 2866, 2805, 2724, 2673, 1770, 1606 cm^{-1}. ^1H NMR ($CDCl_3$) δ 10.33 (s, 2H, Ph–O*H*), 7.24 (d, 2H, Ph–*H*, $J = 2.4$ Hz), 6.82 (d, 2H, Ph–*H*, $J = 2.4$ Hz), 3.64 (s, 4H, Ph–CH_2–N), 2.23 (b, 2H, N–CH_2–N), 1.56 (s, 4H, N–CH_2–CH$_2$–CH_2–N), 1.43 (s, 18H, Ph–C(CH_3)$_3$), 1.29 (s, 18H, Ph–C(CH_3)$_3$), 1.00 (s, 6H, N–CH$_2$–C(CH_3)$_2$–CH$_2$–N). ^{13}C NMR ($CDCl_3$) δ 154.21, 140.75, 136.07, 123.68, 123.38, 120.14, 75.56, 63.61, 59.66, 35.12, 34.35, 31.91, 31.29, 29.74, 25.71. Anal. Calcd for $C_{36}H_{58}N_2O_2$: C, 78.49; H, 10.61; N, 5.09. Found: C, 78.45; H, 10.94; N, 4.93. Mp 240.3–241.5 °C. Compound **5c**. Yield: 4.640 g, 64.7%. IR: 3084, 2975, 2906, 2828, 2595, 1728, 1598 cm^{-1}. ^1H NMR ($CDCl_3$) δ 10.82 (s, 2H, Ph–O*H*), 7.28 (d, 2H, Ph–*H*, $J = 2.0$ Hz), 6.87 (d, 2H, Ph–*H*, $J = 2.8$ Hz), 3.65 (s, 4H, Ph–CH_2–N), 3.18 (s, 2H, N–CH_2–N), 2.32 (s, 4H, N–CH_2–CH$_2$–CH_2–N), 1.07 (s, 6H, N–CH$_2$–C(CH_3)$_2$–CH$_2$–N). ^{13}C NMR ($CDCl_3$) δ 152.40, 129.41, 127.03, 123.93, 122.65, 122.16, 74.30, 63.92, 58.45, 31.40, 25.90. Anal. Calcd for $C_{20}H_{22}Cl_4N_2O_2$: C, 51.75; H, 4.78; N, 6.03. Found: C, 51.49; H, 4.79; N, 5.76. Mp 193.3–194.0 °C.
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