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ORIGINAL ARTICLE

Synthesis of amine-phenol ligands in water – a simple demonstration of a hydrophobic effect

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The synthesis in water of a series of tetradentate amine-phenol ligands derived from formaldehyde, 2,4-disubstituted phenols and amines is presented. These molecules, which are used in catalyst development, include 4,6-di-alkyl-2-bis(2-methoxyethyl)aminomethylphenols and 4,6-di-tert-amyl-2-bis(3-(dimethylamino)propyl)aminomethylphenols. Yields were generally greater than reactions performed in methanol and near quantitative for hydrophobic phenols.

Keywords: Amine-phenol; Mannich condensation; water; hydrophobic; ligand

Introduction

Most homogeneous catalytic systems are developed via a judicious choice of suitable metal center and ligand (1). One important class of ligands are salens, used most famously in Jacobsen's manganese-based epoxidation catalysts (2). Recently, cleaner, more benign routes to these ligands have been reported (3). Therefore, we wondered if other ligands could also be prepared in a more green fashion. In this paper, we report the high yielding syntheses of tetradentate amine-phenol ligands in water (Figure 1). These ligands are usually prepared in methanol solutions or mixtures (4), but we describe herein increased yields and better reproducibility for these reactions when water is used as the reaction medium. In fact, as aqueous formaldehyde is one of the reagents, no added solvent is required beyond what is present in the reagent solution. These and related ligands are currently the subject of intense study because, in combination with a range of metals, they are active catalysts for alkene polymerization (5), and initiators in the ring opening polymerization of lactones (6). The latter is of particular interest to green chemists because these materials can be biosourced and yield biodegradable polymers.

Results and discussion

Water has enormous potential as a reaction medium instead of conventional organic solvents, and many

reactions have been studied in this solvent (7), including Mannich-type reactions using a surfactant to facilitate the acid catalyzed process (8). Therefore, we decided that water could potentially be used in the preparation of amine-phenol ligands, which are easily prepared via Mannich condensation reactions. It should be noted that although many Mannich condensations are performed under 'aqueous' conditions, as aqueous formaldehyde is usually employed, it is common to use either a co-solvent or a surfactant to facilitate the reaction. Beyond the three reactive components in these condensations, no auxiliaries are required to obtain near quantitative yields of the desired products **2a**, **2b**, **4a** and **4b**.

In catalyst development, these amine-phenol ligands are of interest to researchers as they are highly modifiable in both the types of amine used in their synthesis and the substitution about the phenol ring. If yields for their synthesis are high, a library of ligands can readily be prepared, thereby making the effect of varying the donor groups and steric demand on subsequent catalytic activities of their metal complexes easily studied. 4,6-Di-alkyl-2-bis(2-methoxyethyl)aminomethylphenols **2a–d** and 4,6-Di-tert-amyl-2-bis(3-(dimethylamino)propyl)aminomethylphenol **3a** were obtained in moderate to high yields using water as the reaction medium (see Scheme 1 and Experimental details). The products are pale colored, hydrophobic oils and can easily be isolated as a separate phase from the aqueous mixture. The formaldehyde and amine reagents are miscible in the aqueous phase, however,

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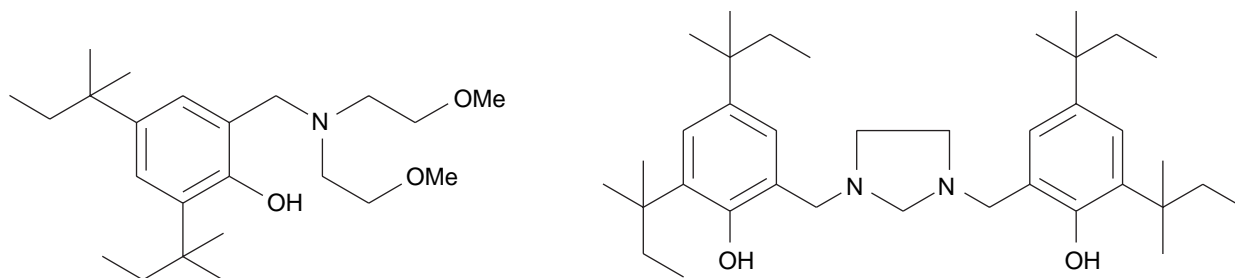
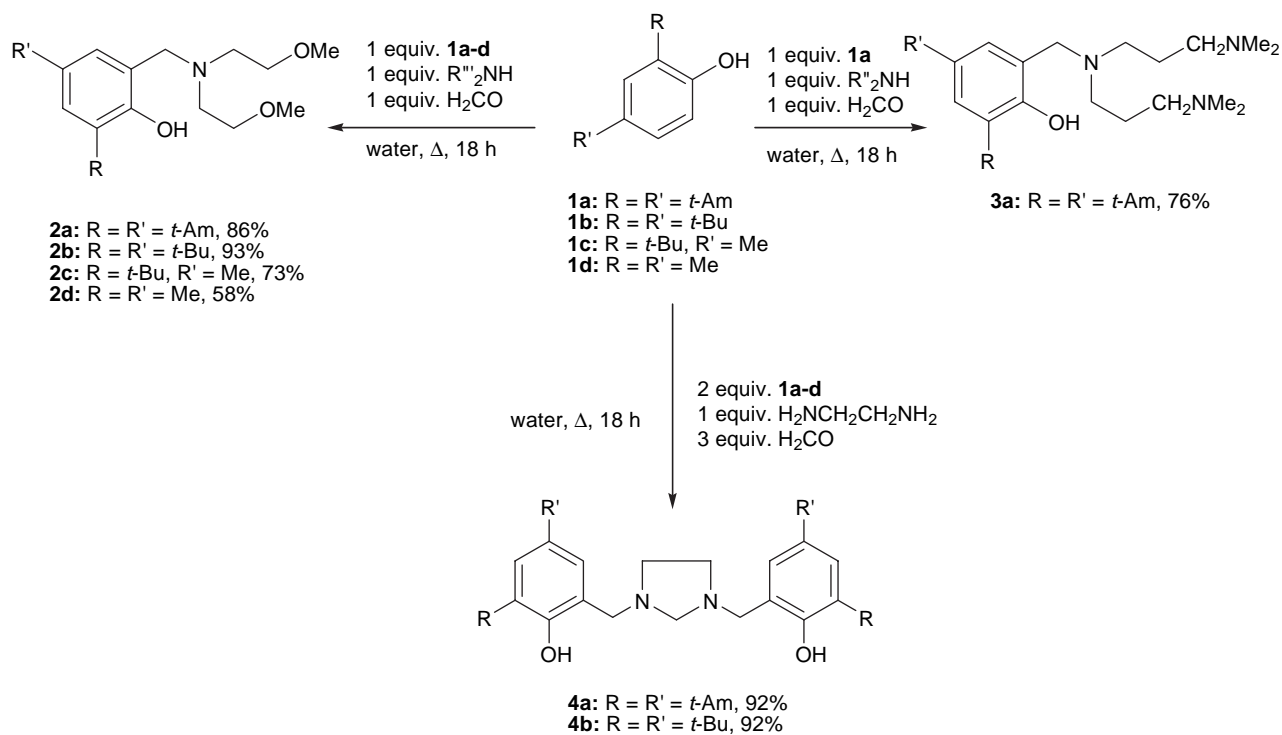


Figure 1. Examples of tert-amyl substituted amine-phenol ligands.

the phenols were generally insoluble, but with rapid stirring of the reaction mixture an emulsion forms, and the reaction can occur at the aqueous-organic interface. Recently, it has been discovered that in some cases, when reactants and products are insoluble in water, the reactions occur in a suspension or 'on water' (9). Although, we did not see the rate enhancements observed by Sharpless et al. (9), the yields of these Mannich condensation reactions improve with an increase in the hydrophobicity of the phenol. For example, yields of **2a,b** using di-tert-butyl (**1a**) and di-tert-amyl phenol (**1b**) were significantly higher than those using dimethyl phenol (**1d**) as the reagent (Scheme 1). The syntheses of **2a–d** have been performed three times and the yields reported are reproducible. To confirm the assumption that **1d** was significantly more water-soluble than **1a** and **1b**, and that this may be the origin of the lower yields of **2d**, a

simple NMR experiment was performed. For each phenol, two NMR samples of the same concentration (0.20 M) were prepared, one in CDCl_3 and one in D_2O . Identical ^1H NMR experiments were performed on each sample and the spectra processed using the same parameters. Comparison of the alkyl-substituted phenol's signals intensities in the CDCl_3 sample with the D_2O sample allowed a quick and crude assessment of the phenol's hydrophobicity. For example, **1a** did not show any resonances in the D_2O sample indicating that it was completely immiscible within the sensitivity limits of the NMR experiment, whereas the intensity of signals from **1b** in D_2O was approximately 1% of those observed in the CDCl_3 sample. This means that **1b** shows a slight but significant solubility in water. Similarly, by inspecting the spectra for **1c** and **1d**, an increase in relative intensity of the phenol signals in D_2O was observed (**1c** 5% and **1d** 10% of the intensity



Scheme 1.

compared with the equal molarity CDCl_3 samples). Therefore, **1d** was the least hydrophobic phenol, and this is perhaps the origin of the lower yield of **2d** compared with **2a–c**. Currently, further investigations into the solubility effects of the substituted phenols on the ligand yields in water are being conducted. For example, more accurate values and temperature effects for their solubility in water may perhaps be obtained using a water-soluble external ^1H NMR standard.

We have extended the approach described above for the synthesis of mono-phenol ligands to other ligands that can be made via similar Mannich condensations. For example, we have prepared 1,4-bis(2-hydroxy-3,5-di-alkyl-benzyl)-imidazolidine compounds **4a,b** in over 90% yield in water (Scheme 1), and this compares favorably with the 65% yield reported for the synthesis of **4b** in dilute methanol solutions (**4d**). In contrast to the monophenol compounds, **4a,b** are solids and can be separated from the reaction mixture by filtration, and purified by recrystallization from suitable solvents including methanol and THF. Care must be taken to use the correct relative stoichiometries in this reaction as alternative products, such as a diaminotetraphenol or a diamine-bis(phenol), can form (*5c,6j,10*). The syntheses of **4a,b** are also of interest as they proceed via a disfavored five-*endo*-trig ring closure (*11*). The coordination of this recently discovered more rigid ligand-set has so far been limited to ytterbium (**4d**), but given the large, inflexible bite angle between the two phenol donors it is likely to show diverse chemistry with other lanthanides and larger transition metals, e.g., zirconium and hafnium. Related hexahydropyrimidine containing ligands have recently been reported and prepared via a solventless approach using 95% paraformaldehyde and 1,3-diaminopropane (*11*).

The facile syntheses described here represent atom economic routes to a diverse set of ligands – under the correct conditions water is the only by-product. They are easily characterized by NMR spectroscopy and particularly if reaction times could be reduced – possibly by implementing a microwave-assisted approach – they could be used to prepare libraries of ligands for combinatorial approaches in catalyst discovery. Within our group, these ligands will be studied further in coordination chemistry experiments, and act as a starting point for the development of new initiators in the ring-opening polymerization of lactones and catalysts in the copolymerization of carbon dioxide with epoxides.

Experimental Section

Typical procedure for the synthesis of amine-phenol-bis(ether) ligands (**2a**)

Water (40 ml), 1 equivalent of 2,4-di-*tert*-amylphenol (28.8 g, 123 mmol) and 1 equivalent of 37% formaldehyde (10 ml) were added, respectively, to a 500-ml round-bottom flask equipped with a condenser. 1 equivalent bis(2-methoxyethyl)amine (16.38 g, 123 mmol) was added dropwise. (Note: slow initial addition of the amine is crucial as the reaction is exothermic.) The mixture was heated at reflux for 18 h. Upon cooling to room temperature, a separate organic layer formed which was isolated and dried under high vacuum to remove any unreacted organic components and water. Yield 39.9 g (85.5%). Characterization for **2a**: ^1H NMR (CDCl_3 , 500 MHz, 298 K) δ 10.38 (s, 1H, OH); 7.08 (d, $^4J_{\text{HH}} = 2.4$ Hz, 1H, ArH); 6.78 (d, $^4J_{\text{HH}} = 2.4$ Hz, 1H, ArH); 3.85 (s, 2H, CH_2N); 3.55 (t, 4H, $^3J_{\text{HH}} = 5.0$ Hz, $\text{N}(\text{CH}_2\text{CH}_2)$); 3.34 (s, 6H, OCH_3); 2.82 (t, 4H, $^3J_{\text{HH}} = 5.0$ Hz, $\text{N}(\text{CH}_2\text{CH}_2)$); 1.93 (m, 2H, CH_2CH_3); 1.60 (m, 2H, CH_2CH_3); 1.39 (s, 6H, $\text{C}(\text{CH}_3)_2$); 1.26 (s, 6H, $\text{C}(\text{CH}_3)_2$); 0.67 (m, 6H, CH_2CH_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 500 MHz, 298 K) δ 154.5, 138.9, 134.3, 125.4, 124.6, 121.8, 70.8, 60.0, 59.2, 53.8, 38.8, 37.6, 33.2, 29.0, 28.1, 9.9, 9.61; MS (MALDI, matrix: anthracene) m/z 379 (M^+ , 100%), 336, ($\text{M}-3\text{Me}$, 20%), 334 ($\text{M}-\text{CH}_2\text{OCH}_3$, 44%); Anal. Calcd for $\text{C}_{23}\text{H}_{41}\text{NO}_3$: C, 72.78; H, 10.89; N, 3.69. Found: C, 73.32; H, 10.94; N, 3.82. Characterization data for **2b–d** was in agreement with literature values (**4b,c**).

Typical procedure for the synthesis of tris(amine)-phenol ligands (**3a**)

Water (40 ml), 1 equivalent of 2,4-di-*tert*-amylphenol (28.8 g, 123 mmol) and 1 equivalent of 37% formaldehyde (10 ml) were added to a 500-ml round-bottom flask equipped with a condenser. 1 equivalent 3,3'-iminobis(*N,N*-dimethyl-propylamine) (23.0 g, 123 mmol) was added dropwise to the stirred solution. (Note: slow initial addition of the amine is crucial as the reaction is exothermic.) The mixture was heated at reflux for 18 h. Upon cooling to room temperature, a separate organic layer formed which was isolated and dried under high vacuum to remove any unreacted organic components and water. Yield 40.7 g (76.3%). Characterization for **3a**: ^1H NMR (CDCl_3 , 500 MHz, 298 K) δ 10.93 (s, 1H, OH); 7.07 (d, $^4J_{\text{HH}} = 2.3$ Hz, 1H, ArH); 6.75 (d, $^4J_{\text{HH}} = 2.3$ Hz, 1H, ArH); 3.73 (s, 2H, ArCH_2N); 2.55 (t, $^3J_{\text{HH}} = 5.0$ Hz, 4H, $\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2)$); 2.27 (m, 4H, $\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2)$); 2.18 (s, 12H, $\text{N}(\text{CH}_3)_2$); 1.90 (m, 2H, CH_2CH_3); 1.71 (m, 4H, $\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2)_2$); 1.59

(m, 2H, CH₂CH₃); 1.38 (s, 6 H, C(CH₃)); 1.25 (s, 6H, C(CH₃)); 0.67 (m, 6H, CH₂CH₃); ¹³C{¹H} NMR (CDCl₃, 500 MHz, 298 K): δ 154.5, 138.8, 134.1, 125.2, 124.4, 121.6, 59.6, 58.1, 51.8, 45.9, 38.7, 37.6, 33.2, 28.0, 24.9, 27.8, 24.9, 9.9, 9.8, 9.4; MS (MALDI, matrix: anthracene) *m/z* 433 (M⁺, 100%), 348 (M-CH₂CH₂CH₂NMe₂, 13%); Anal. Calcd for C₂₇H₅₁N₃O: C, 74.77; H, 11.85; N, 9.69. Found: C, 75.68; H, 11.77; N, 9.88.

Typical procedure for the synthesis of imidazolidine-bridged bis(phenol) ligands (4a)

Water (40 ml), 2 equivalent of 2,4-di-*tert*-amylphenol (19.2 g, 82 mmol) and 3 equivalent of 37% formaldehyde (10 ml) were added, respectively, to a 500-ml round-bottom flask equipped with a condenser. 1 equivalent ethylenediamine (2.5 g, 41 mmol) was added dropwise to the stirred solution. (Note: slow initial addition of the amine is crucial as the reaction is exothermic. Ethylenediamine is a corrosive lachrymator with a flashpoint of 34°C.) The mixture was heated at reflux for 18 h. After cooling to room temperature, a precipitate formed and was isolated by filtration. Analytically pure **4a** could be obtained by growing colorless crystals from a saturated methanol solution. Yield 21.4 g (92.3%). Characterization for **4a**: ¹H NMR (CDCl₃, 500 MHz, 298 K) δ 8.90 (br, 2H, OH), 7.10 (d, ⁴J_{HH} = 2.0 Hz, 2H, ArH), 6.84 (d, ⁴J_{HH} = 2.0 Hz, 2H, ArH), 4.03 (s, 2H, imidazolidine ring, NCH₂N), 3.64 (s, 4H, ArCH₂), 3.00 (t, ³J_{HH} = 5.0 Hz, 2H, NC₂H₄N), 2.65 (t, ³J_{HH} = 5.0 Hz, 2H, NC₂H₄N), 1.88 (m, 4H, CH₂CH₃), 1.53 (m, 4H, CH₂CH₃), 1.35 (s, 12H, C(CH₃)), 1.23 (s, 12H, C(CH₃)), 0.65 (m, 12H, CH₂CH₃); ¹³C{¹H} NMR (CDCl₃, 500 MHz, 298 K): δ 152.6, 138.6, 134.1, 125.5, 121.1, 117.6, 80.9, 56.7, 48.8, 47.4, 38.2, 36.9, 32.7, 28.4, 27.5, 9.5, 9.1; MS (MALDI, matrix: anthracene) *m/z* 564 (M⁺, 100%), 522 (M-Et-Me, 48%), 331 (M-di-*t*-amyl-phenol, 6%), 317 (M-di-*t*-amyl-phenol-CH₂, 47%), 247 (di-*t*-amyl-phenol + CH₂, 32%); Anal. Calcd for C₃₇H₆₀N₂O₂: C, 78.67; H, 10.71; N, 4.96. Found: C, 78.83; H, 10.81; N, 5.00. Characterization data for **4b** was in agreement with literature values (4d).

Conclusions

In summary, we have reported the synthesis of a series of amine-phenol ligands in water. Yields for these compounds are generally improved compared to routes using volatile organic compound (VOC) solvents. This approach could potentially be extended to other related ligand syntheses and to other Mannich condensation reactions.

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