chemistry proceedings

MDPI

Proceeding Paper

An Optimised Method to Synthesise N_5O_2 Aminophenols †

Paula Oreiro-Martínez [1,*], Julio Corredoira-Vázquez [1,2], Jesús Sanmartín-Matalobos [1,3] and Matilde Fondo [1]

[1] Departamento de Química Inorgánica, Facultade de Química, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain; julio.corredoira.vazquez@usc.es (J.C.-V.); jesus.sanmartin@usc.es (J.S.-M.); matilde.fondo@usc.es (M.F.)
[2] Phantom-g, CICECO—Aveiro Institute of Materials, Department of Physics, University of Aveiro, 3810-193 Aveiro, Portugal
[3] Institute of Materials (iMATUS), Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain
* Correspondence: paula.oreiro.martinez@rai.usc.es
† Presented at the 27th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-27), 15–30 November 2023; Available online: https://ecsoc-27.sciforum.net/.

Abstract: Aminophenol compounds are usually employed in coordination chemistry due to their versatility to form metal complexes. Heptadentate N_5O_2 aminophenol ligands can lead to the obtention of lanthanoid complexes with pentagonal bypiramidal (pbp) geometry, which are very interesting in the field of molecular magnetism. In this communication we report an optimised method for obtaining two similar N_5O_2 aminophenols named 2-((((6-(((5-hydroxy-2-R-benzyl)(pyridin-2-ylmethyl)amino)methyl)pyridin-2-yl)methyl)(pyridin-2-ylmethyl)amino)methyl)-4-R-phenol (R = methyl or methoxy), which significantly improves the few examples of synthesis of this type of compound reported in literature.

Keywords: aminophenol; N; O donor; heptadentate ligand

Citation: Oreiro-Martínez, P.; Corredoira-Vázquez, J.; Sanmartín-Matalobos, J.; Fondo, M. An Optimised Method to Synthesise N_5O_2 Aminophenols. *Chem. Proc.* **2023**, *14*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s): Name

Published: 15 November 2023

1. Introduction

Aminophenols are di- or polydentate Lewis bases that can coordinate to a variety of metal ions in different ways, which makes them very valuable ligands in coordination chemistry. Besides, some coordination compounds with this kind of ligand also possess interesting biological, luminescent and/or catalytic properties [1–3]. In addition, the number of donor atoms in the aminophenols and their rigidity can be modulated to try to form metal complexes with a predetermined geometry. This is a very attractive field for the development of molecule magnets [4], since, as the theory of Rinehart and Long [5] showed, the magnetic anisotropy of lanthanoid complexes can be modulated by their geometry. In this context, heptadentate N_5O_2 aminophenol ligands can be good candidates for the obtention of lanthanoid complexes of oblate ions with pentagonal bypiramidal (pbp) geometry and, accordingly, increased easy axis anisotropy.

In spite of these advantages, the number of N_5O_2 acyclic aminophenol donors previously described is very scarce [6–9], and the methods of obtaining them are usually very time consuming, leading to several by-products that impurify the target organic derivative, which must be separated by chromatographic techniques. This generally entails long separation times and very low yields, in the best of cases. Therefore, the search for alternative methods of isolating these polydentate Lewis bases, which enhance reaction times and facilitate the separation of the species formed, is a field of interest in coordination chemistry. With these considerations in mind, in this work, we describe an optimised method for obtaining two similar N_5O_2 aminophenols, which significantly improves the few examples of synthesis of this type of compound reported in literature.

2. Materials and Methods

2.1. Materials and General Methods

All chemical reagents were purchased from commercial sources, and used as received without further purification. ^{1}H NMR spectra of H_2L^{Me} and H_2L^{OMe} were recorded on a Varian Inova 400 spectrometer, using $CDCl_3$ as solvent.

2.2. Synthesis

The synthesis of H_2L^R ligands (R = Me or OMe) described herein requires the obtaining of the N_5 precursor 2,6- bis{[(pyrid-2-ylmethyl)amino]methyl}-pyridine from 2-[(tosylamino)methyl]pyridine and 2,6 bis(bromomethyl)pyridine, as detailed in the literature [10].

The syntheses of both H_2L^R compounds are exemplified by the isolation of H_2L^{Me}, as shown below.

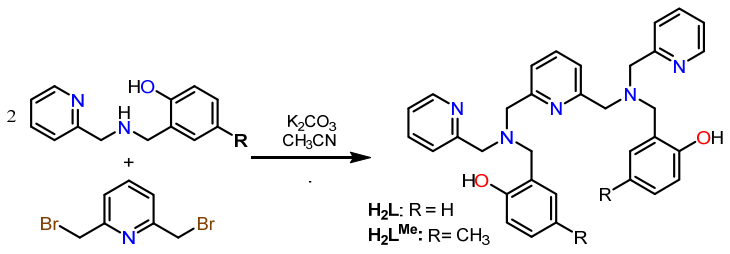
H_2L^{Me}: To a solution of 2,6 bis{[(pyrid-2-ylmethyl)amino]methyl}-pyridine (0.216 g, 0.677 mmol) in toluene (5 mL) and water (10 mL) is added 4-methylphenol (0.195 g, 1.800 mmol) and formaldehyde (135 µL, 1.800 mmol), and the mixture is refluxed for 24 h. Then, it is extracted with dichloromethane (4 × 50 mL), the organic phases are combined, and the solution is dried with anhydrous magnesium sulphate. The magnesium sulphate is removed, and the solution is concentrated to dryness, obtaining a brown oil which is washed with water to remove the excess 4-methylphenol. Yield: 190 mg (50%). MW: 559.70 g/mol. ^{1}H NMR (400MHz, $CDCl_3$, δ in ppm): 2.23 (s, 6H, H18); 3.75 (s, 4H, H11); 3.86 (s, 8H, H4 and H5); 6.78 (d, J = 8.1 Hz, 2H, H14 or H15), 6.85 (s, 2H, H17), 6.96 (d, 2H, J = 8.1 Hz, H14 or H15), 7.12–7.17 (m, 2H, H9), 7.22 (d, J = 7.7 Hz, 2H, H2 or H7); 7.30 (d, J = 7.8 Hz, 2H, H2 or H7); 7.53 (t, J = 7.7 Hz, 1H, H1); 7.61 (t, J = 7.7 Hz, 2H, H8); 8.56 (d, J = 4.6 Hz, 2H, H10); 10.61 (s, 2H, OH).

H_2L^{OMe}: quantity of 2,6 bis{[(pyrid-2-ylmethyl)amino]methyl}-pyridine (0.232 g, 0.727 mmol), 4-methoxyphenol (0.242 g, 1.933 mmol) and formaldehyde (145 µL, 1.933 mmol). Yield: 174 mg (40%). MW: 591.68 g/mol. ^{1}H NMR (400MHz, $CDCl_3$, δ in ppm): 3.73 (s, 6H, H18); 3.76 (s, 4H, H11); 3.87 (s, 8H, H4 and H5); 6.63 (d, J = 3.0 Hz, 2H, H17), 6.73 (dd, J_1= 8.7 Hz, J_2 = 3.0 Hz, 2H, H15), 6.81 (d, 2H, J = 8.7 Hz, H14), 7.12-7.16 (m, 2H, H9), 7.23 (d, J = 7.7 Hz, 2H, H2 or H7); 7.30 (d, J = 7.8 Hz, 2H, H2 or H7); 7.54 (t, J = 7.7 Hz, 1H, H1); 7.59 (t, J = 7.7 Hz, 2H, H8), 8.56 (d, J = 4.9 Hz, 2H, H10); 10.40 (s, 2H, OH).

3. Results and Discussion

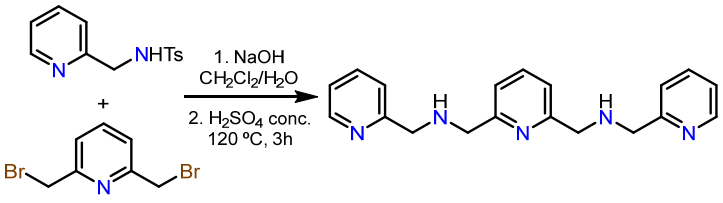
3.1. Synthesis of the Aminophenols

The method described herein for the isolation of the N_5O_2 acyclic aminophenols completely differs from the previously reported one [6-9] not only in the purification method but also in the reactants employed. Thus, in the reported method the precursor R-2-(((pyridin-2-ylmethyl)amino)-methyl)phenol is initially synthesised, and then it reacts with 2,6-bis(bromomethyl)pyridine, as shown in Scheme 1, followed by columm chromatography for purifying the product.



Scheme 1. Synthesis of N_5O_2 aminophenols by reported methods [6–9].

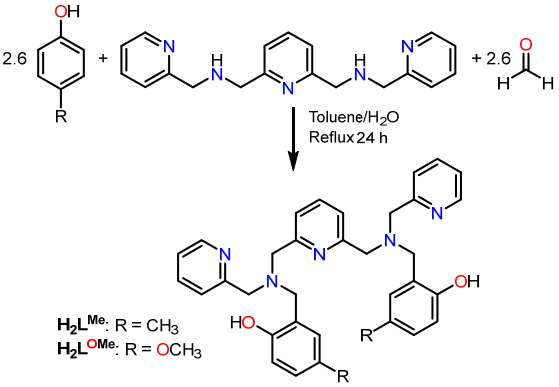
In our case study, the precursor is the N_5 (2,6-bis{[(pyrid-2-ylmethyl)amino]methyl}-pyridine) amine, which was isolated as described in the literature [10] (Scheme 2) from commercially available reagents.



Scheme 2. Synthesis of 2,6 bis{[(pyrid-2-ylmethyl)amino]methyl}-pyridine [10].

The reaction of this precursor with formaldehyde and 4-methylphenol or 4-methoxyphenol, lead to the isolation of $\mathbf{H_2L^{Me}}$ or $\mathbf{H_2L^{OMe}}$, respectively (Scheme 3).

In this synthesis, a significant excess of R-phenol and formaldehyde is necessary for the correct addition of the R-phenol onto the amine nitrogen atoms. After the reflux time has elapsed, the mixture is extracted with CH_2Cl_2, and the organic phase is dried and concentrated to dryness. The aminophenol is the only product formed in this reaction, but it is contaminated with the excess of R-phenol. This latter is removed by washing with water, thus obtaining two pure different brown products.



Scheme 3. Synthesis of H_2L^R (R = Me or OMe) by a new method reported herein.

3.2. Characterisation of the Aminophenols

Both compounds were characterised by 1H NMR spectroscopy in $CDCl_3$ (Figures 1 and 2).

From these spectra, it is noticeable:

- The presence of two singlets in the region 3.5-4 ppm that integrate by 12 protons in total, which indicate the existence of six CH_2 groups, and that agree with the addition of the phenolic arms at the N_5 precursor.
- The presence of nine signals in the aromatic region, which globally integrate by 17 protons, in agreement with the five aromatic rings and, therefore, with the correct addition of the R-phenol to the N_5 precursor.
- The presence of a singlet at 10 ppm (2H), and a second singlet at 2.3 ppm (6H) for H_2L^{Me} and at 3.73 for H_2L^{OMe} (6H), assigned to the hydroxyl and CH_3 groups, respectively, which also indicate the successful binding of the R-fenol to the precursor.

These NMR spectra also confirm that this way of synthesis leads to H_2L^R ligands with high purity, as there are no additional signals. Thus, it is noteworthy that no peak corresponding to free R-phenol is observed, which shows that water washing is a very efficient method to separate the ligand and excess R-phenol, and much faster and less polluting than the column chromatography carried out in the synthesis of this ligand previously described.

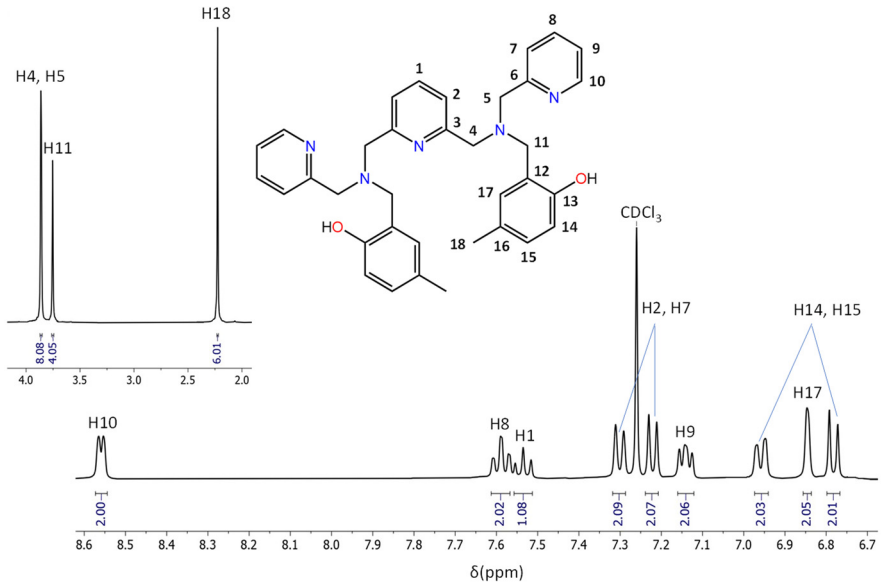


Figure 1. ^{1}H NMR spectrum of H_2L^{Me} in $CDCl_3$ between 6.7 and 8.6 ppm. Inset: spectrum between 2.0 and 4.0 ppm.

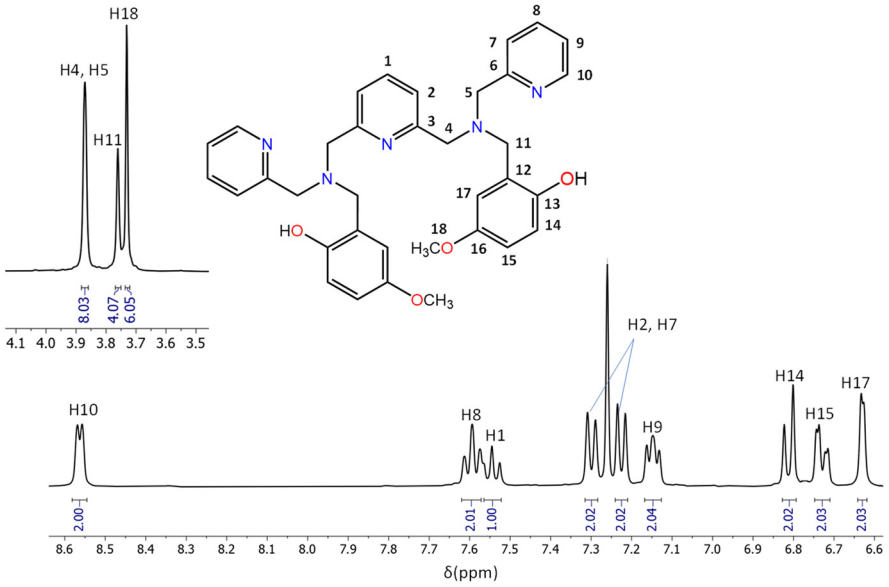


Figure 2. ^{1}H NMR spectrum of H_2L^{OMe} in $CDCl_3$ between 6.6 and 8.6 ppm. Inset: spectrum between 3.5 and 4.1 ppm.

4. Conclusions

This work reports an alternative and optimised method to synthesise N_5O_2 aminophenols, avoiding chromatography to purify the final product.

Author Contributions: Conceptualization, M.F., P.O.-M. and J.C.-V.; methodology, P.O.-M. and J.C.-V.; investigation, M.F., P.O.-M. and J.C.-V.; writing—original draft preparation, P.O.-M., M.F.; supervision, M.F., J.S.-M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: P. Oreiro-Martínez acknowledges Fundación Segundo Gil Dávila for her predoctoral fellowship and J. Corredoira-Vázquez acknowledges Xunta de Galicia for his postdoctoral fellowship (ED481B-2022-068).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Çesme, M. 2-Aminophenol-based ligands and Cu(II) complexes: Synthesis, characterization, X-ray structure, thermal and electrochemical properties, and in vitro biological evaluation, ADMET study and molecular docking simulation. *J. Mol. Struct*. **2023**, *1271*, 134073. https://doi.org/10.1016/j.molstruc.2022.134073.
2. Nakai, H.; Nonaka, K.; Goto, T.; Seo, J.; Matsumoto, T.; Ogo, S. A macrocyclic tetraamine bearing four phenol groups: A new class of heptadentate ligands to provide an oxygen-sensitive luminescent Tb(III) complex with an extendable phenol pendant arm. *Dalton Trans.* **2015**, *44*, 10923–10927. https://doi.org/10.1039/c5dt00816f.
3. Liu, J.; Lorraine, S.C.; Dolinar, B.S.; Hoover, J.M. Aerobic oxidation reactivity of well-defined cobalt(II) and cobalt(III) aminophenol complexes. *Inorg. Chem.* **2022**, *61*, 6008–6016. https://doi.org/10.1021/acs.inorgchem.1c03686.
4. Corredoira-Vázquez, J.; Oreiro-Martínez, P.; Nieto-Pastoriza, D.; García-Deibe, A.M.; Sanmartín-Matalobos, J.; Fondo, M. Dy_4, Dy_5 and Ho_2 complexes o fan N_3O_2 aminophenol donor: A Dy_3-μ_3-peroxide single molecule magnet. *Int. J. Mol. Sci.* **2023**, *24*, 9061. https://doi.org/10.3390/ijms24109061.
5. Rinehart, J.D.; Long, J.R. Exploiting single-ion anisotropy in the desing of f-elements in single-molecule magnets. *Chem. Sci.* **2011**, *2*, 2018–2085. https://doi.org/10.1039/C1SC00513H.
6. You, X.; Wei, Z.; Wang, H.; Li, D.; Liu, J.; Xu, B.; Liu, X. Synthesis of two copper clusters and their catalysis towards the oxidation of benzene into phenol. *RSC Adv.* **2014**, *4*, 61790–61798. https://doi.org/10.1039/C4RA12832J.
7. You, X.; Wei, Z.; Xu, B.; Liu, X. A heptadentate ligand possessing two phenol groups: Its diverse coordination chemistry and the catalytic behaviors of its transition complexes towards benzene oxidation. *Polyhedron* **2014**, *81*, 743–748. https://doi.org/10.1016/j.poly.2014.07.038.
8. Xu, S.-M.; An, Z.-W.; Zhang, W.; Zhang, Y.-Q.; Yao, M.-X. Ligand field and anion-driven structures and magnetic properties of dysprosium complexes. *CrystEngComm* **2021,** *23*, 2825–2834. https://doi.org/10.1039/d1ce00115a.
9. Meng, X.; Wang, M.: Gou, X.; Lan, W.; Jia, K.; Wang, Y.-X.; Zhang, Y.-Q.; Shi, W.; Cheng, P. Two C_{2v} symmetry dysprosium(III) single-molecule magnets with effective energy barriers over 600 K. *Inorg. Chem. Front.* **2021**, *8*, 2349–2355. https://doi.org/10.1039/d1qi00145k.
10. Darbre, T.; Dubs, C.; Rusanov, E.; Stoeckli-Evans, H. Syntheses of Zinc Complexes with Multidentate Nitrogen Ligands: New Catalysts for Aldol Reactions. *Eur. J. Inorg. Chem.* **2002**, 2002, 3284–3291. https://doi.org/10.1002/1099-0682(200212)2002:12<3284::AID-EJIC3284>3.0.CO;2-6.