

Synthetic route to novel asymmetric tetradentate ligands containing both amino and imino groups

Gustavo González-Riopedre,¹ M. Isabel Fernández-García,¹ Ana M. González-Noya,² Rosa Pedrido,² Laura Rodríguez,¹ Marcelino Maneiro^{1,*}

¹ *Departamento de Química Inorgánica, Facultade de Ciencias, Universidade de Santiago de Compostela. Lugo 27002 Spain*

² *Departamento de Química Inorgánica, Facultade de Química, Universidade de Santiago de Compostela, Santiago de Compostela, 15782 Spain*

e-mail: marcelino.maneiro@usc.es

Abstract: The synthesis of the new asymmetric ligand (*E*)-4-bromo-2-(((2-((5-bromo-2-hydroxybenzyl)(methyl)amino)ethyl)imino)methyl)phenol, which was conceived to model the asymmetry in the active site of peroxidase/catalase mimics, is reported. The new synthetic route involves seven steps: 1) Obtention of the phthalimido-acetal; 2) Acetal deprotection; 3) Synthesis of the salicylamine; 4) Obtention of the benzoxacine; 5) Reduction of the benzoxacine with NaBH₃CN; 6) Reduction with hydrazine to form salicylamine; 7) Synthesis of the final ligand by condensation of salicylamine with salicylaldehyde. All organic products were characterised by microanalysis, ¹H NMR, IR and mass spectroscopies.

Keywords: *asymmetry, ligand, Schiff base, synthetic route, amino group*

Introduction

Vast interest has been developed by bioinorganic chemists to devise small molecule models, the properties of which can be compared with different metalloproteins [1]. Biomimetic modeling of metal complexes has denoted a better catalytic behaviour when the complex is able to easily coordinate the substrate molecule, and this is favoured when the catalyst has either a vacancy in the coordination sphere or a labile ligand [2-3]. To achieve this, a careful

design of the ligand is necessary. In this connection, unsymmetrical ligands are also required to imitate many of the active sites of the metalloproteins [4-6].

Tetradentate ONNO Schiff bases are well-known systems for coordination of metal ions, and their synthesis is easily accomplished by condensation of salicylaldehyde and diamines [7]. However, this condensation favours symmetrization processes, and symmetric ligands are systematically obtained even using a mixture of different salicylaldehydes in solution [8]. Consequently, alternative synthetic routes should be explored to achieve unequivocally unsymmetrical ligands.

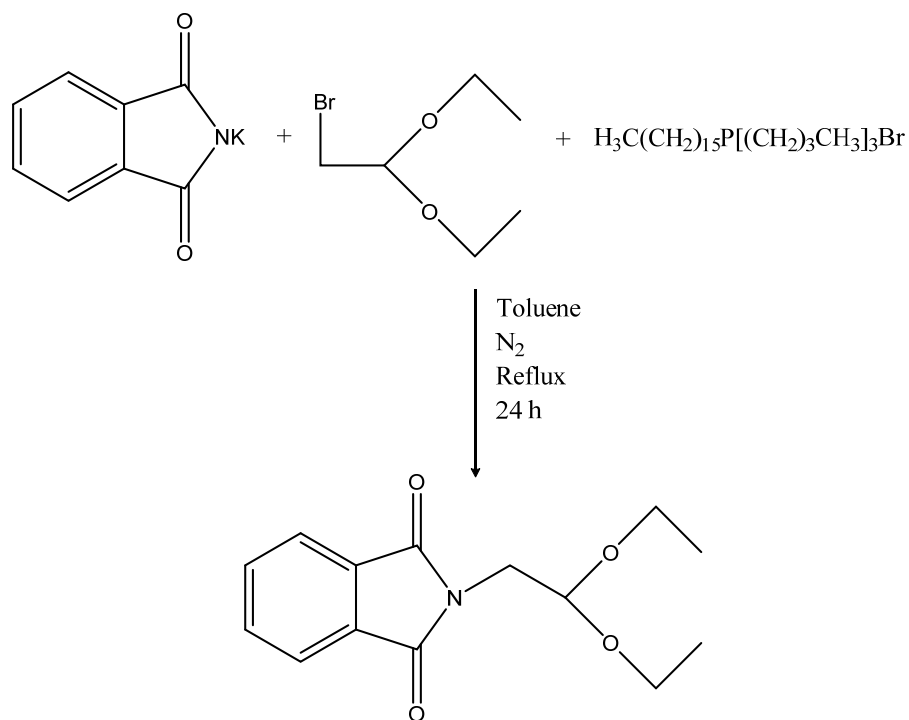
We report here on the synthesis of a new type of unsymmetrical ONNO tetradentate imino-amino *bishydroxy* ligand. The strategy in the design seeks adequate conformations and flexibility to coordinate metal ions in a way that two adjacent positions of the coordination sphere may be vacant or filled with labile ligands. The different hybridization mode for the amino (sp^3) and imino (sp^2) groups may favour the tetracoordination of the organic ligand outside from the equatorial plane of the metal ion. In this case, two of the *cis* positions of a hypothetical first coordination sphere would not be occupied by the ligand and, subsequently, these two *cis* positions would be able to coordinate a suitable substrate molecule for catalysis.

Results and discussion

The asymmetrical ligand (*E*)-4-bromo-2-(((2-((5-bromo-2-hydroxybenzyl)(methyl)amino)ethyl)imino)methyl)phenol has been successfully obtained by means of a seven-step synthetic route.

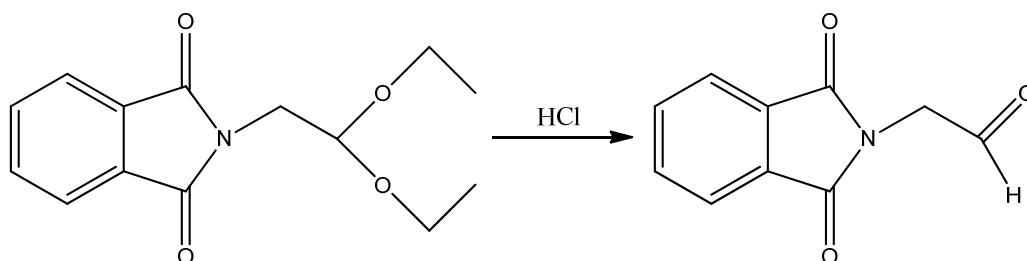
1) *Obtention of phthalimido-acetal*. Phthalimido-acetal was obtained as shown in Scheme 1, through a Gabriel synthesis, using 0.5 g (2.65 mmol) of potassium phthalimide, 0.41 mL (2.65 mmol) of bromoacetal and 1.387 g (2.65 mmol) of hexadecyltributylfosfonium bromide, using toluene as solvent.

Yield 70 %; $C_{14}H_{17}NO_4$ (263.29): calcd. C 63.8, H 6.4, N 5.3; exp. C 64.6, H 6.5, N 5.3. 1H NMR (300 MHz, $CDCl_3$): δ 7.8-7.6 (m, 4H), 4.79 (t, 1H), 3.75 (d, 2H), 3.62-3.42 (m, 4H), 1.06 (t, 6H). ES-MS: m/z 264. IR: $\nu(C-O-C)$ 2800, $\nu(C=O)$ 1721 cm^{-1} .



Scheme 1

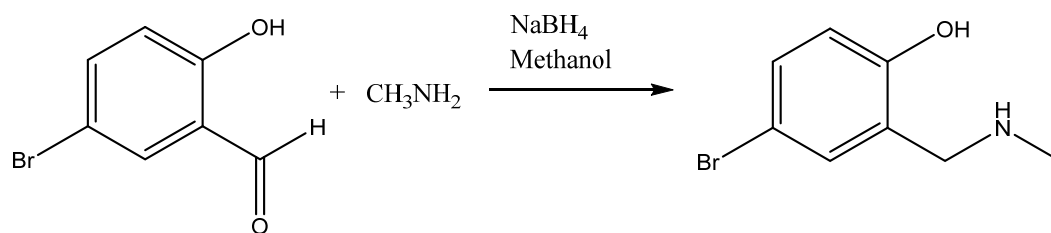
2) *Acetal deprotection*. The reaction is depicted in Scheme 2.



Scheme 2

Yield 80 %; C₁₀H₇NO₃ (189.17): calcd. C 63.4, H 3.7, N 7.4; exp. C 62.4, H 3.4, N 7.5. ¹H NMR (300 MHz, CDCl₃): δ 9.62 (s, 1H), 7.85-7.65 (m, 4H), 4.45 (s, 2H). ES-MS: m/z 190. IR: ν(C=O) 1721 cm⁻¹.

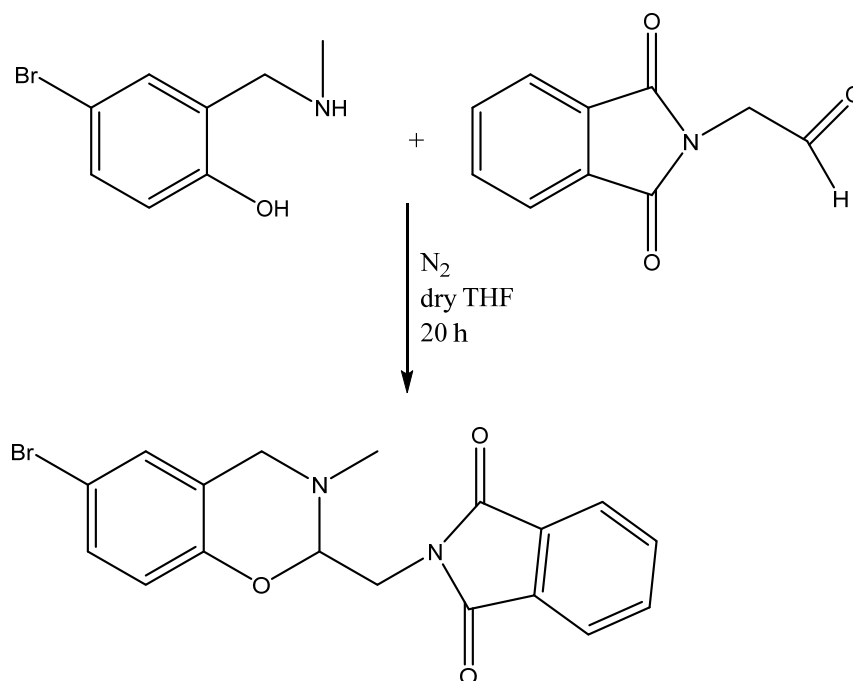
3) *Synthesis of the salicylamine*. Salicylamine was obtained as shown in Scheme 3 through a condensation of 9.3 g (46.7 mmol) of salicylaldehyde with 3.96 mL (46.7 mmol) of methylamine, and subsequent reduction “*in situ*” with NaBH₄ (0.901 g, 23.3 mmol).



Scheme 3

Yield 35 %; $\text{C}_8\text{H}_{10}\text{BrNO}$ (263.29): calcd. C 44.4, H 4.6, N 6.5; exp. C 44.2, H 4.4, N 6.5. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.19-6.63 (m, 3H), 4.8-4.2 (a, 1H), 3.86 (s, 2H), 2.40 (s, 3H). ES-MS: m/z 264. IR: $\nu(\text{O-H})$ 3014, $\nu(\text{N-H})$ 2736 cm^{-1} .

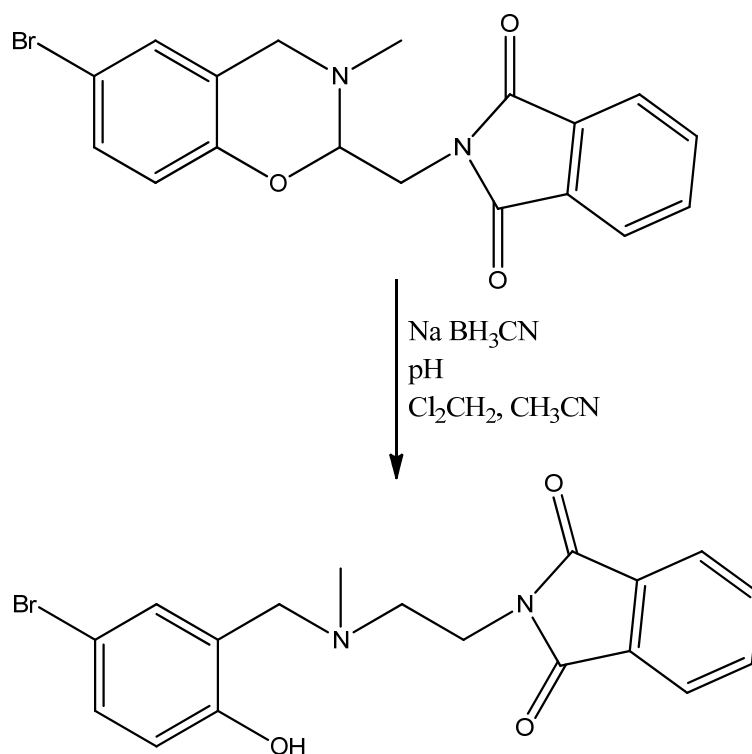
4) *Obtention of benzoxacine*. The reaction is depicted in Scheme 4.



Scheme 4

Yield 65 %; $\text{C}_{18}\text{H}_{15}\text{BrN}_2\text{O}_3$ (387.22): calcd. C 55.9, H 3.9, N 7.2; exp. C 55.0, H 4.2, N 7.4. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.90-7.71 (m, 4H), 7.26-6.64 (m, 3H), 5.14 (t, 1H), 4.08-3.95 (m, 4H), 2.51 (s, 3H). IR: $\nu(\text{C=O})$ 1719 cm^{-1} .

5) *Reduction of the benzoxazine with NaBH₃CN.* The reaction is depicted in Scheme 5.

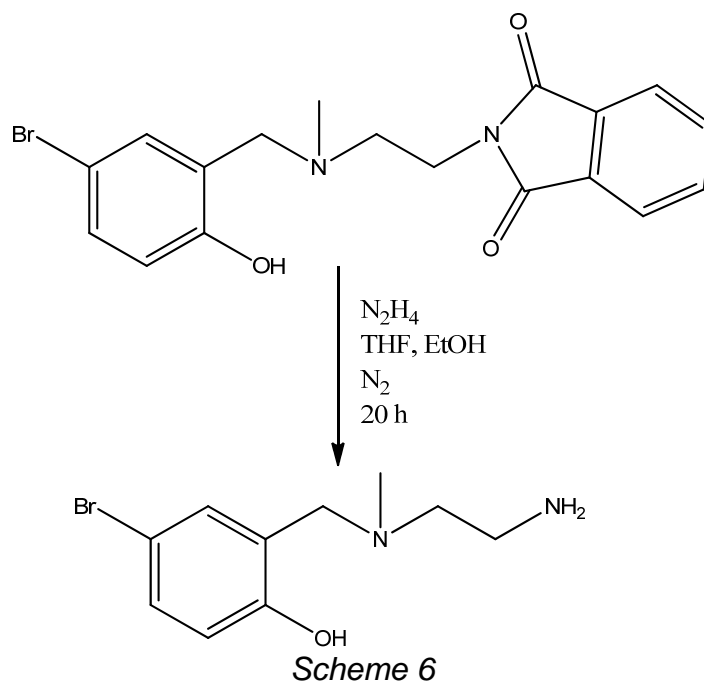


Scheme 5

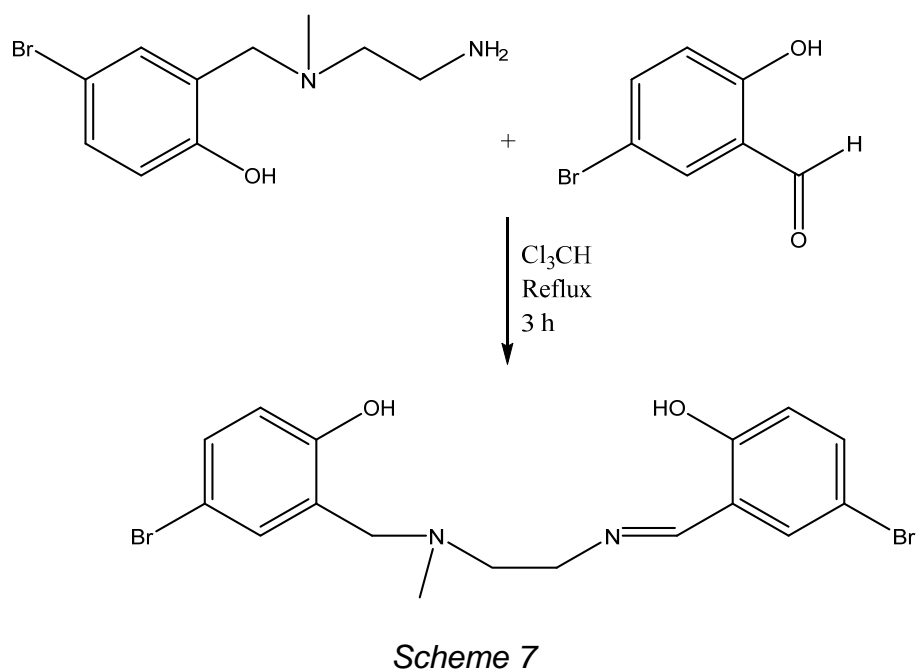
Yield 70 %; C₁₈H₁₇BrNO₃ (389.24): calcd. C 55.5, H 4.4, N 7.2; exp. C 55.6, H 4.9, N 7.6. ¹H NMR (300 MHz, DMSO): δ 7.89-7.80 (m, 4H), 7.19 (d, 2H), 6.49 (d, 1H), 3.77 (t, 2H), 3.60 (s, 2H), 2.70 (s, 2H), 2.30 (s, 3H). IR: ν(C=O) 1709 cm⁻¹.

6) *Reduction with hydrazine to form salicylamine.* The corresponding salicylamine is obtained by hydrazinolysis (depicted in Scheme 6), which involves the rupture of the imide group in the N-alkyl-1,2-benzenedicarboxylic acid molecule.

Yield 45 %; C₁₀H₁₅BrN₂O (389.24): calcd. C 46.3, H 5.8, N 10.8; exp. C 47.3, H 5.6, N 10.1. ¹H NMR (300 MHz, DMSO): δ 7.21-6.62 (m, 3H), 4.1-3.7 (a, 2H), 3.59 (s, 2H), 2.84 (t, 2H), 2.49 (t, 2H), 2.23 (s, 3H). ES-MS: m/z 390. IR: ν(O-H) 3473, ν(N-H) 3280 cm⁻¹.



7) *Synthesis of the final ligand by condensation of salicylamine with salicylaldehyde.* The final ligand is obtained by condensation of 0.105 g (0.405 mmol) of the amine with 0.0814 g (0.0405 mmol) of 5-bromo-2-hydroxybenzaldehyde in chloroform. The reaction is depicted in Scheme 7.



Yield 85 %; $C_{17}H_{18}Br_2N_2O_2$ (442.14): calcd. C 46.1, H 4.1, N 6.3; exp. C 46.4, H 4.1, N 6.3. 1H NMR (300 MHz, DMSO): δ 8.22 (s, 1H), 7.34-6.60 (m, 6H), 3.71

(t, 2H), 3.65 (s, 2H), 2.78 (t, 2H), 2.29 (s, 3H). ES-MS: m/z 443. IR: $\nu(\text{C}=\text{N})$ 1634 cm^{-1} .

Conclusion

The proposed synthetic route afforded the desired asymmetric product with a reasonable yield. The final ligand and all the organic intermediates have been successfully characterised. This synthetic strategy may be used to obtain a new family of organic ligands suitable for coordination of different metal ions. The variety of this novel family of ligands may be envisioned by the chance of replacing the methylamine used in the third step of the synthetic route by different amines or aminoacids.

Acknowledgements

Financial support from the Spanish Ministerio de Ciencia e Innovación (CTQ2010-19191) and Xunta de Galicia (10PXIB262132PR) is acknowledged.

References

- [1] Simmons, T. R.; Berggren, G.; Bacchi, M.; Fontecave, M.; Artero, V. *Coord. Chem. Rev.* **2014**, *270*, 127-150.
- [2] Vázquez-Fernández, A.; Bermejo, M. R.; Fernández-García, M. I.; González-Riopedre, G.; Rodríguez-Doutón, M. J.; Maneiro, M. *J. Inorg. Biochem.* **2011**, *105*, 1538-1547.
- [3] González-Riopedre, G.; Fernández-García, M.I.; González-Noya, A. M.; Vázquez-Fernández, M. A.; Bermejo, M. R.; Maneiro, M. *Phys. Chem. Chem. Phys.* **2011**, *13*, 18069-18077.
- [4] Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051-1069.
- [5] Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97-102.
- [6] Rondelez, Y.; Rager, M. N.; Duprat, A.; Reinaud, O. *J. Am. Chem. Soc.* **2002**, *124*, 1334-1340.
- [7] Alexander, V. *Chem. Rev.* **1995**, *95*, 273-342.
- [8] Lopez-Torres, E.; Mendiola, M. A. *Inorg. Chim. Acta* **2010**, *363*, 1275-1283.