Simple and efficient synthesis of novel porphyrin-phosphoramidates

Leandro F. Pedrosa[ab]*, Marcos C. Souza[a], Vitor F. Ferreira[a] and José A. S. Cavaleiro[b]

[a] *Universidade Federal Fluminense, Departamento de Química Orgânica, 24020-150, Niterói, RJ.*

[b] *University of Aveiro, Department of Chemistry and QOPNA, 3810-193, Aveiro, Portugal.*

**e-mail corresponding author*: leandropedrosa@globo.com

Keywords: phosphoramidate, porphyrin, singlet oxygen.

INTRODUCTION

Medicinal formulations which include the use of porphyrin derivatives as photosensitisers are already being considered in several countries for the photodynamic therapy (PDT) of malignant tumors and also for the treatment of age-related macular degeneration.[1]

Organophosphorus compounds also have a prominent place in medicine, being used as anticancer drugs, antivirals, antifungals, inhibitors of bone resorption among other applications. Porphyrin phosphonates, in particular, display interesting binding properties, where the P=O group plays a significant role as a strong hydrogen bond acceptor.[2]

Phosphoramidates possess a great biological activity and have been used in several prodrug strategies. Therefore, the synthesis of porphyrins containing phosphoramidate moieties may lead to new compounds with interesting biological properties or with adequate properties to be used as photosensitisers in photodynamic therapy.[3]

RESULTS AND DISCUSSION

The synthesis of the new porphyrin-phosphoramidate conjugates can be performed by nucleophilic aromatic substitution of the *p*-fluorine atom in *meso*-tetrakis(pentafluorophenyl)porphyrin (**1**) by aminoalkylphosphoramidates **2a-e**.[3] The starting porphyrin **1** is easily prepared from pentafluorobenzaldehyde and pyrrole under microwave irradiation[4] while the aminoalkyl phosphoramidates **2a-e** are obtained by selective monophosphorylation of aliphatic diamines.[5] In this work, we were able to synthesize selectively the monosubstituted porphyrins **3a-e** or the tetrasubstituted derivatives **4a-e** by selecting the appropriate porphyrin / phosphoramidate ratio (Figure 1). All compounds were characterized by 1H, 19F and 31P NMR spectroscopy and confirmed by mass spectrometry. The new porphyrin derivatives show high photostability and some of them are better singlet oxygen generators than **Tetra-Py$^+$-Me**, a well known good singlet oxygen producer.

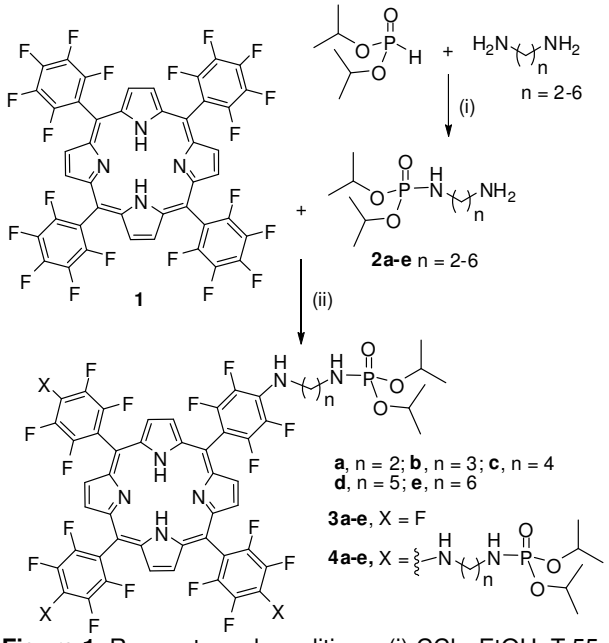

Figure 1. Reagents and conditions: (i) CCl_4, EtOH, T 55-65 ºC, 10-25 min. (ii) toluene, reflux, 8-72h.

CONCLUSION

Ten new porphyrin-phosphoramidates is described. The compounds were obtained in satisfactory yields by nucleophilic aromatic substitution of the fluorine atoms in *para*-position of the pentafluorophenyl groups of *meso*-tetrakis(pentafluorophenyl)porphyrin (**1**) with aminoalkylphosphoramidates (**2a-e**). The compound **4c** showed to be the better singlet oxygen generator being more efficient than **Tetra-Py$^+$-Me** considered a good singlet oxygen producer. Further studies on the properties of these new porphyrin derivatives are currently under investigation in our laboratories.

ACKNOWLEDGEMENTS

UFF, UA, CNPq, CAPES and FCT.

REFERENCES

[1] Cavaleiro, J. A. S.; et al., in *Handbook of Porphyrin Science*, **2010**, Vol 2. Ch. 9, pp. 194-294.
[2] Bhosale, S. V.; et al., *Eur. J. Org. Chem.* **2009**,*24*, 4128.
[3] Pedrosa, L. F.; et al., *Aust. J. Chem.* **2011**, *in press*.
[4] De Paula, R.; et al., *J. Heterocycl. Chem.* **2008**, *45*, 453.
[5] Souza, M. C.; et al., *Phosphorus, Sulfur, and Silicon* **2006**, *181*, 1885.