Synthesis of Azapterocarpan Analogues by Intramolecular 1,3-dipolar Cycloaddition

Júlio C. F. Barcellos,[(a)]; Ayres G.Dias,[(b)]; Paulo R. R.Costa[(a)]**

[a] *Laboratório de Química Bioorgânica, NPPN, Universidade Federal do Rio de Janeiro. Cidade Universitária, 21941-590, Rio de Janeiro, Brasil.* [b]*Departamento de Química Orgânica, Instituto de Química, Universidade do Estado do Rio de Janeiro, R. São Francisco Xavier, 524, Maracanã, 20550-900, Rio de Janeiro, Brasil*

**E-mail :* ayres.dias@gmail.com ; prrcosta2011@gmail.com

Keywords: aza pterocarpan, Intramolecular 1,3-dipolar cycloaddition,antiparasitic drugs, anticancer

INTRODUCTION

As part of a program directed at the discovery of new anticancer and antiparasitic drugs, our laboratory synthesized very promising new aza-pterocarpan analogues type **1**, through a palladium catalyzed aza-arylation reaction (Figure 1).[1] Now we are concentrating our efforts in the synthesis of analogues of **1**, type **2**-**4**, through intramolecular 1,3 dipolar cycloaddition, (1,3-IDC)**.**

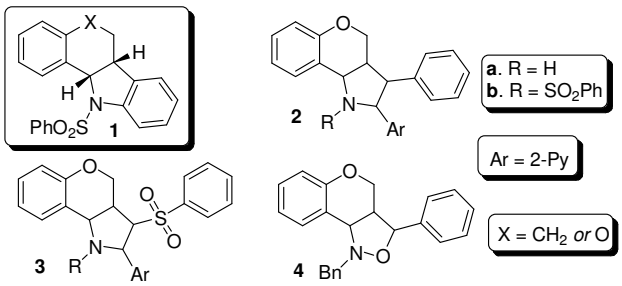
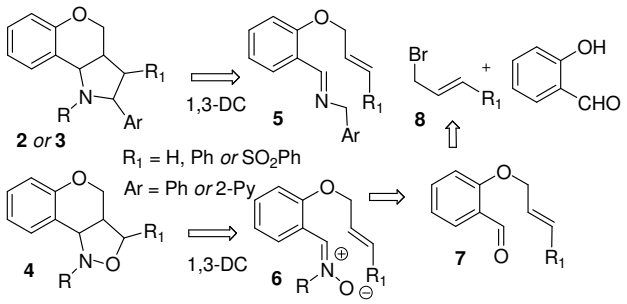


Figure 1. Azapterocarpans **1** and analogues.

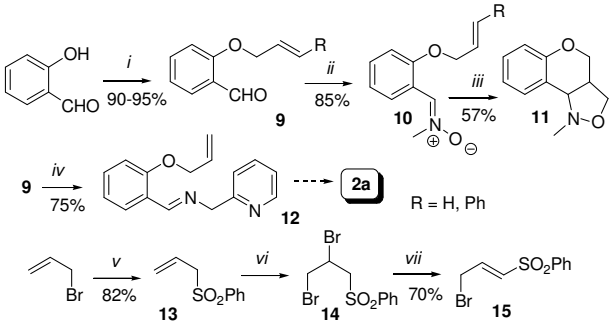
RESULTS AND DISCUSSION

The strategies chosen to prepare the aza-analogues type **2**-**4** are shown in Scheme 1. In both cases the key step is an 1,3-IDC. The preliminary results obtained are shown in Scheme 2.



Scheme 1. Synthetic strategy to analogues type **2**-**4**.

Salicylaldehyde was *O*-alkylated with allylic bromides, leading to **9** in excellent yield. These compounds were transformed into the corresponding *N*-methylnitrones **10** and a thermal condensation leads a prototype **11** in 57% yields (non-optimized).



i. Bromide, Acetone, K_2CO_3, 60 °C, 2-6h; *ii.* $NH_2OH.HCl$; TEA,CH_2Cl_2, Na_2SO_4, 4h,r.t.; *iii.* Toluene, ref., 6h; *iv.* DIPEA, 2-$PyCH_2NH_2$, MS 4ºA, 3d, r.t.; *v.* $PhSO_2Na$, DMF, 12h, r.t.; *vi.* Br_2, CCl_4; *vii.* TEA, r.t.

Scheme 2. Studies toward the synthesis of **2**-**4**.

The imines type **12** were obtained by Kurth methodology[2] (75%) and employed in 1,3-IDC preliminary experiments. The metallo-azomethine ylides, generated by reaction of imine with DBU in combination with LiBr,[3] were studied in thermal and microwave-assisted experiments to obtained **2a**. The allylic sulphone **15** was most conveniently obtained from *S*-alkylation/bromination of allyl bromide followed by dehydrobromination using TEA, Scheme 2. This bromide will be use in 1,3 IDC reactions to prepare **3** analogues. Work is now in progress to establish the relative configuration in **11** and accomplish others 1,3-DC reactions.

CONCLUSION

The 1,3-IDC reaction is a rapid and practical approach to Aza-pterocarpan and analogues skeletons.

ACKNOWLEDGEMENTS

FAPERJ, CNPq, CAPES.

REFERENCES

[1] Djenne, B.C. PhD Thesis, NPPN-UFRJ, December 2010, Costa, P.R.R. *et all J. Braz. Chem. Soc.* **2009**, *20*,1916.
[2] Kurth, M.J. *et all*, *J. Org. Chem. Soc.* **1998**, *63*, 3081
[3] Grigg, R. *et all*, *Tetrahedron*. **1995**, *51*, 273.