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

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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. Azapterocarpons 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).

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

The imines type 12 were obtained by Kurth methodology2 (75%) and employed in 1,3-IDC preliminary experiments. The metallo-azomethine ylides, generated by reaction of imine with DBU in combination with LiBr,2 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.

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REFERENCES