Studies Towards new Ribavirin Nucleoside Analogs

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Keywords: type 3 keywords here (*Arial* 10)

INTRODUCTION

Hepatitis C is a viral infection that commits about 3-4 million people per year worldwide. Its treatment consists mainly in the administration of interferon α and Ribavirin. However the collateral effects associated with this treatment, specifically attributed to the Ribavirin, precludes the treatment in some patients, which make the search for new drugs a very important issue.

The discovery of a high active Ribavirin analog denominated SR91, figure 1, towards inhibition of IMP-DH prompted us to further investigate and pursuit in the direction of synthesizing new derivatives guided by a *in silico* docking study.

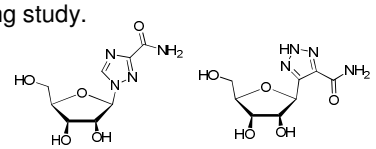


Figure 1

In these studies the structures **2** and **3,** figure 2 emerged as potential candidates and their synthesis was studied.

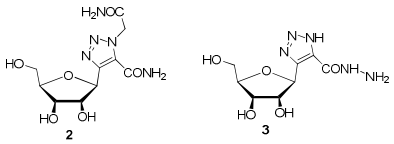


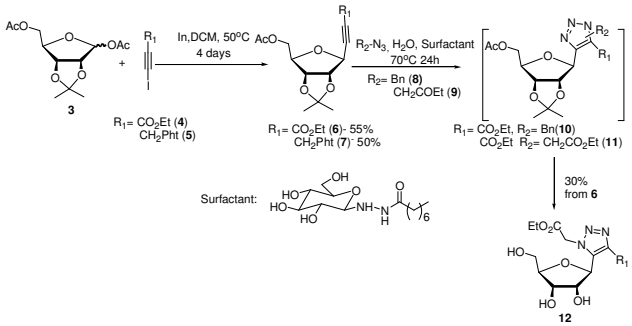
Figure 2

The methodology used was based on the indium mediated alkynylation of sugar acetates. The triazole ring was constructed through a micellar catalyzed Huisgen cycloaddition developed by Uziel and col.[1]

RESULTS AND DISCUSSION

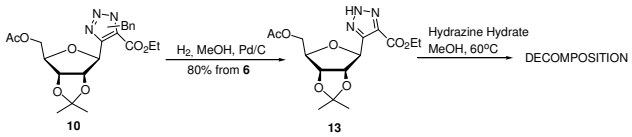
The Indium mediated coupling between iodoacetylenes **4** and **5** and ribose derivative **3** was achieved with 55 and 50% yield for products **6** and **7,** respectively. In these reactions only the β-anomer was detected in the NMR analysis.

The ribosylacetylenes were then reacted with organic azides under micellar catalysis. In this system the ribosylacetylene **7** did not show any product when reacted with azide **8**, mainly because of its insolubiity in the aqueous reaction media. Ribosyl acetylene **7** reacted with azides **8** and **9**. The reaction between **7** and **9** led to the isolation of a pure fraction containing triazole **12** as the only regioisomer in a 30% overall yield for 3 steps. The regioselectivity could not be determined due to the complexity of the reaction media profile due to the presence of partially protected regioisomers, scheme 1.



scheme1

In the case of triazole **10** after debenzylation of the mixture of regioisomers (85:15 in favor of the 1,4 regioisomer) led to the product **13** in 80% overall yield from **6**. The ribosyl triazole **13** was then essayed in a hydrazinolysis reaction obtain the corresponding acylhydrazine. However this hydrazinolysis reaction proved difficult due to the decomposition of the substrate and further investigations are needed concerning this step, scheme 2.



Scheme 2

CONCLUSION

In the present work important advances towards new C-nucleosides analogues of Ribavirin were obtained, bases on a indium mediated propargilation of ribosyl acetate. The micellar catalysis proved a very promising in controlling the regiochemistry of the cycloaddition.

ACKNOWLEDGEMENTS

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico

FAPERJ

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