Synthesis of 11a - Aza-5-deoxi-pterocarpans Via Palladium Aza-arylation of Dihydronaphtalen by *Orto*-iodoanilines Derivatives

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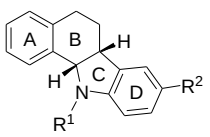
Keywords: *aza-arylation, dihydronaphtalen, o-iodoanilines*

INTRODUCTION

During the course of our studies aiming the discovery of new antineoplasic and antiparasitary compounds, we recently described the synthesis of the aza-dehydropterocarpan **1a** (Figure 1).[1] In order to know more about the structural features required for the observed activities of **1a**, we report in this work the synthesis of compounds **1b-d** and **2a-c**. Our first goal was to modify the substituent at the nitrogen atom in the C-ring (**1b-c**) to see if this moiety is part of the pharmacophore. In analogues **2a-b**, halogen atoms at D-ring were introduced to target diverse set of relevant medicinal proteins due to halogen bond[2]. Trying to understand more about the mechanism of the antineoplasic activity, cell death was evaluated by flow cytometry.



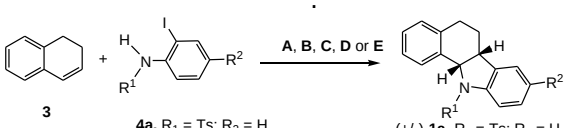
(+/-)- **1**

(+/-)-**1a.** R_1 = Ts; R_2 = H
(+/-)-**1b.** R_1 = Ms; R_2 = H
(+/-)-**1c** R_1 = CbZ; R_2 = H
(+/-)-**1d.** R_1 = Ac; R_2 = H
(+/-)-**1e.** R_1 = Ts; R_2 = Br
(+/-)-**1f.** R_1 = H; R_2 = H
(+/-)-**1g.** R_1 = Ts; R_2 = Cl
(+/-)-**1h.** R_1 = Ts; R_2 = NO_2

Figure 1. Aza-deoxi-pterocarpans **1**

RESULTS AND DISCUSSION

Compounds **1** were prepared by a palladium catalyzed aza-arylation of dihydronaphthalen (**3**) with *o*-iodoaniline derivatives (**4**) in different conditions leading respectively to *N*-tosyl, *N*-mesyl and *N*-CBZ-5-deoxi-aza-pterocarpns **1a**, **1b** and **1c** as shown in Scheme1, with yields ranging from 41 to 85% using acetone as solvent and silver carbonate (3 equiv.). All these reactions were conducted in aproximately 8 hours. When we used PEG400 as solvent, a benign solvent commonly used in green chemistry, compound **1a** was obtained in 1 hour using 1.2 equiv. of silver carbonate under termic conditions or 30 minutes under microwave conditions. In contrast, the aza-arylation of **3** did not work when *N*-acetyl- o-iodoaniline (**4d**) or unprotected *o*-iodoanilin (**4f**) were allowed to react with **3**.



3

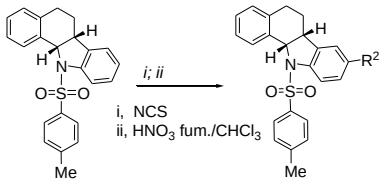
4a. R_1 = Ts; R_2 = H
4b. R_1 = Ms; R_2 = H
4c. R_1 = CbZ; R_2 = H
4d. R_1 = OAc; R_2 = H
4e. R_1 = Ts; R_2 = Br
4f. R_1 = H; R_2 = H

(+/-)-**1a.** R_1 = Ts; R_2 = H (88%)
(+/-)-**1b.** R_1 = Ms; R_2 = H (40%)
(+/-)-**1c** R_1 = CbZ; R_2 = H (67%)
(+/-)-**1d.** R_1 = Ac; R_2 = H (traces)
(+/-)-**1e.** R_1 = Ts; R_2 = Br (75%)
(+/-)-**1f.** R_1 = H; R_2 = H (traces)

A. acetone, 10 mol% $Pd(OAc)_2$, 3 equiv. Ag_2CO_3, 70°C, 8 horas
B. acetone, 10 mol% $Pd(OAc)_2$, 1.5 equiv. Ag_2CO_3, 70°C, 8 horas
C. acetone, 5 mol% $Pd(OAc)_2$, 3.0 equiv. Ag_2CO_3, 70°C, 8 horas
D. PEG400, 10 mol% $Pd(OAc)_2$, 1.2 equiv.Ag_2CO_3, 200°C, 10 min.
E. PEG400, 10 mol% $Pd(OAc)_2$, 1.2 equiv.Ag_2CO_3, 120°C, 10 min. MW

Scheme 1

Compounds **2a** and **2b** were obtained from **1a** by halogenation with NCS or nitration with HNO_3 fum., in chloroform solution. In all cases the reaction was chemoselective for D-ring (Scheme 2).



1a

1g, R^2 = Cl (60%); **1h**, R^2 = NO_2 (50%)

Scheme 2

CONCLUSION

In conclusion, we have developed the Heck aza-arylation of dihydronaphtalen by o-iodoanilines derivatives in good to excellent yields. PEG400 was the best solvent to obtain **1a** under termic and microwave conditions.

ACKNOWLEDGEMENTS

CAPES, CNPq, FAPERJ

REFERENCES

[1]Buarque, C.D.; Militão Gardênia C.G.; Lima, Dayse .J. B.; Costa-Lotufo Letícia V.; Pessoa, Cláudia.; de Moraes, Manoel Odorico, Cunha-Junior, Edézio Ferreira; Torres-Santos, Eduardo Caio; Netto, Chaquip D.; Costa, Paulo R.R.. *Bioorganic & Medicinal Chemistry* **2011**, *19*, 6885.

[2]Wilcken, R.; [2]Zimmermann, M. O.; Lange, A.; Joerger, A.C.and Boeckler , F. M. Principles and Applications of Halogen Bonding in Medicinal Chemistry and Chemical Biology *J. Med. Chem*. 2013, 56, 1363