Synthesis of Compounds Derivatives of Carbazol with Potencial anticancer Activity

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Palavras Chave: *tosyl-carbazole, aza-arylation reaction, anticancer activity*

Introduction

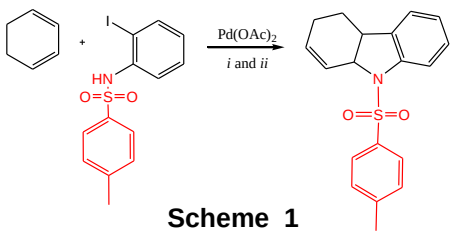
Carbazole is a tricyclic molecule of natural origin that was first described in 1872. Ninety years later, a strong interest by chemists and biologists for carbazoles began, mainly due to their promising pharmacological activities.[1] More recently, a variety of synthetic procedures using commercially available raw materials have been developed in good yields in order to obtain substituted carbazoles in the ring A and C.[2]

Some examples of synthesis of substituted carbazoles involve Fischer-Borsche cyclization, which consist in a condensation between ciclohexanones with phenylhydrazines giving arylhydrazones, leading to the corresponding carbazoles. Another reaction for the formation of C-C bonds involves cross-coupling reactions.[3]

Although there are many methods for the synthesis of carbazoles, few of these undergo by tosylated intermediates. Many of these analogues containing sulfonamide has not been tested in certain cancer cell lines. A structural analogue of carbazole, 9-tosyl-carbazole (2) possesses interesting structural requirements for the treatment of cancer and inflammation, since, besides having the basic carbazole skeleton, also shows the sulfonamide group which is the pharmacophoric group of numerous substances with such biological action.

Results and Discussion

In order to investigate the aza-arylation methodology between cyclohexadiene and tosyl-iodoaniline to obtain tosyl-carbazoles and carbazoles, we studied two different conditions.

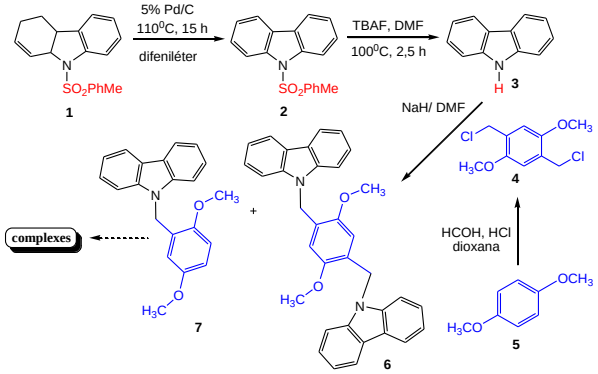


Scheme 1

Table 01. Conditions for the synthesis of **1**

Cond.	Solv.	Cat.	t (h)	T (ºC)	Yield
i	Acetone	1.2 equiv. Ag_2CO_3	25	100	20
ii	PEG400	2 equiv. Ag_2CO_3	25	100	41%

In order to continue carbazole's synthesis to obtain cupper complexes based on carbazole framework, we followed with steps that consisted in the aromatization of ring C using Pd/C and removing the tosyl group to afford 3, which is further reacted with 4, previously prepared from 1,4- dimethoxybenzene (5). A mixture of mono e di substitution products 6 and 7 were formed and this reaction is under optimization. Compounds 1 and 2 are being evaluated as antileukemic activity (HL-60 and K562 cell lines).



Scheme 2

Conclusion

Through two-step synthesis it was possible to obtain (2), which is being tested for its potential anti-cancer activity. We've also extend the methodology to obtain carbazoles by the aza-arylation of cyclohexadiene and tosyl-iodoaniline. The next step is to get the respective complexes and evaluate their pharmacological activity as well as a catalyst for organic reactions.

Acknowledgement

CNPq, PUC-Rio, IPPN-UFRJ.

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