Povarov reaction for the synthesis of 2-(2-pyridyl)quinoline

Luiz C. A. Barbosa [a,b*], **Carmindo R. Borel**[b], **Sergio A. Fernandes**[b], **Célia R. A. Maltha**[b]

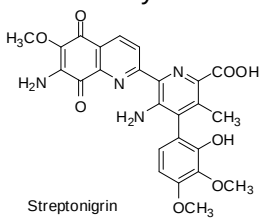
[a] *Department of Chemistry, Federal University of Minas Gerais, Av. Pres. Antônio Carlos 6627, Campus Pampulha, CEP 31270-901, Belo Horizonte, MG, Brazil.*
[a] *Department of Chemistry, Federal University of Viçosa. Av. P.H. Rolfs, CEP 36570-000, Viçosa, MG, Brazil*

* Tel.:(31)34093396; e-mail:lcab@ufmg.br

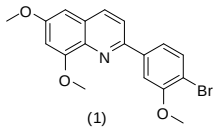
Keywords: Povarov reaction, multicomponent reactions, pyridylquinoline, streptonigrin

INTRODUCTION

Antitumor antibiotic streptonigrin **(1)** is an highly functionalized quinolinequinone which has attracted considerable attention from synthetic organic chemistry and biochemists, due to its antitumor activity[1,2]. Thus, considerable efforts have been made to obtain analogues of streptonigrin, with the ultimate goal to obtain a molecule with promising anticancer activity and attenuated toxicity[3].



Streptonigrin



(1)

Multicomponent reactions (MCRs) continue to attract attention as they can result in a substantial increase in molecular complexity and provide opportunities for high levels of convergence in synthesis[4]. The use of MCRs has therefore been frequently adopted by the pharmaceutical industry for the development of combinatorial libraries and the identification of lead compounds.

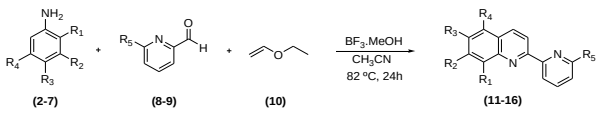
In this work we investigate the synthesis of 2-pyridylquinolines via MCR cascade process known as the Povarov reaction. The aim was to develop an efficient protocol for the preparation 2-pyridylquinolines that constitutes the core structure of streptonigrin, and then apply this methodology to prepare several analogues for biological evaluation.

RESULTS AND DISCUSSION

In order to optimize the reactions conditions we first used 3-bromo-4-methoxy benzaldehyde as a model compound since the pyridinecarbaldehydes are expensive. This aldehyde was then reacted with 2,4-dimethoxy aniline and ethyl vinyl ether using BF_3.MeOH as a catalyst. For this optimization step the following conditions were used: catalyst load from 20 to 100 mol%; the temperature was 82 ºC or 100 ºC; and the solvents tested included acetonitrile, ethanol, dimethylsul- foxide, nitromethane, 1,2-dimethoxyethane, 2,2,2-trifluoroethanol. The requi- red product (**1**) was obtained in variable yields (27-81%), and the best results involved the use of acetonitrile as solvent, 30 mol% of BF_3.MeOH, at 82 ºC and 24 hours.

These conditions were then employed for the preparation of several 2-pyridinylquinolines (**11-16**) employing three methoxylated anilines (**2-7**; 1 mmol), 2-pyridinecarbaldehyde (**8**; 1mmol) or 6-bromo-2-pyridinecarbaldehyde (**9**; 1mmol) and ethyl vinyl ether (**10**; 1,5 mmol) (Table 1). The yields of the required products ranged from 52% to 72%, showing the potential of this one pot methodology for the synthesis of complex 2-piridinylquinolines.

Tab 1. Povarov reactions with 2-pyridinecarbaldehydes, ethyl vinyl ether and various anilines.



(2-7) (8-9) (10) (11-16)

Compound	Substituents					Yield
	R^1	R^2	R^3	R^4	R^5	(%)
11	H	OMe	OMe	OMe	Br	63
12	OMe	H	H	OMe	Br	52
13	H	OMe	OMe	H	Br	56
14	H	OMe	OMe	OMe	H	66
15	OMe	H	H	OMe	H	72
16	H	OMe	OMe	H	H	68

In all cases, the pure products were isolated and fully characterized by spectroscopic IR, MS and NMR analyses.

In summary, we have developed an efficient three-component cascade reaction for the production of 2-pyridylquinolines using BF_3.MeOH as a catalyst. To the best of our knowledge, although the Povarov reaction has largely been investigated no detail study on use of this methodology for the preparation of 2-pyridylquinolines has been reported. The compounds obtained could be further modified and used for the design of new substances endowed with activity anticancer.

ACKNOWLEDGEMENTS

We are grateful to CNPq, CAPES and FAPEMIG

REFERENCES

1. HARTLEY, D. L.; SPEEDIE M. K. *Biochem. J.* ***1984****, 220, 309-319.*
2. DONOHOE, T.J.; JONES, C.; BARBOSA, L.C.A.. *J. Am. Chem. Soc.* ***2011****, 133, 16413-16421.*
3. XIAO-HUA, C.; XIAO-YING, X.; HUA, L.; LIN-FENG, C., LIU-ZHU, G. *J. Am. Chem. Soc.* ***2006****, 128, 14802-14803.*
4. TEJEDOR, D.; TELLADO, F.G.Chem. Soc. Rev. ***2007***, 36, 484-491..