Efficient EDA Addition and Ring-Expansion Reaction of Isatins Catalyzed by a DBU/Rh(II) Metal-Organo System: On Route to the Synthesis of Viridicatin Alkaloids

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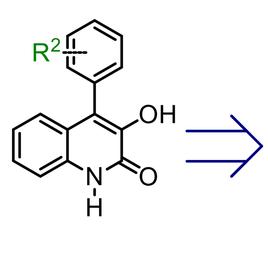
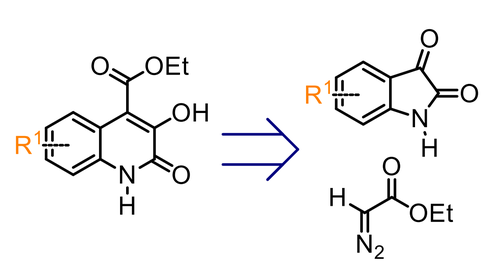
Introduction

4-Arylquinolin-2(1*H*)-ones[1] are an invaluable class of heterocyclic compounds that displays a broad range of biological activities. They have been reported to be maxi-K channel openers for the treatment of male erectile dysfunction, neuroprotectors [2] and to have notable antitumoral properties such as the ones reported for Zanestra™ in phase II clinical trials for Neurofibromatosis Type I, amongst others. An important sub-group of this family of heterocycles are the 3-hydroxy-4-arylquinolin-2(1*H*)-ones, that include several natural products like viridicatin [3] **1**, viridicatol **2** and 3-*O*-methyl viridicatin **3,** which were shown to be very promising compounds with inhibitory activity against the human immunodeficiency virus replication (**3**) induced by tumour necrosis or as promising lead compounds for the development of new anti-inflammatory agents.

***Key-step:* Suzukĩ-Miyaurą coupling of the 3-hydroxy-4-bromoquinolin-2(1H)-ones core**



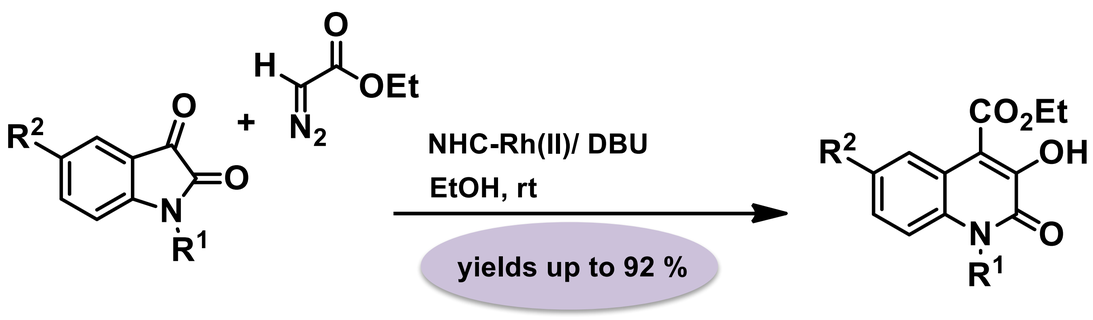
***Key-step:* Eistert ring-expansion reaction of isatin with EDA**



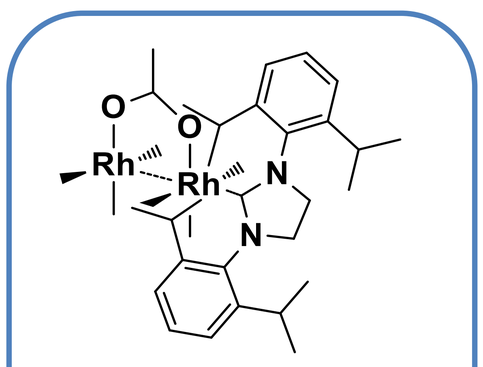
Fourth Step | Second and Third Step | First Step

Results

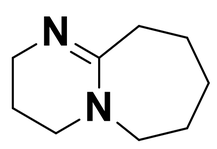
First Step :New one-pot **NHC-dirhodium(II)/DBU** catalyzed Eistert Ring Expansion reaction of isatins with ethyl diazoacetate



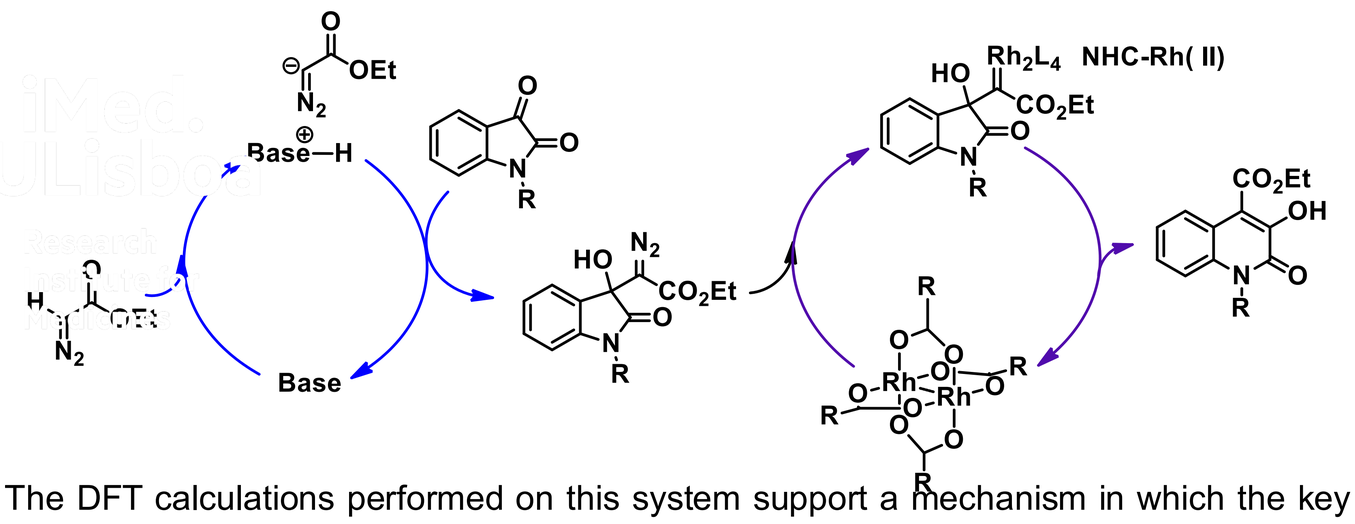
Entry	R^1	R^2	Yield (%)
1	H	H	63
4	H	Cl	92
6	CH_3	H	75
9	CH_3	Cl	81
11	CH_2Ph	H	73
13	CH_2Ph	Cl	87



NHC-dirhodium(II)

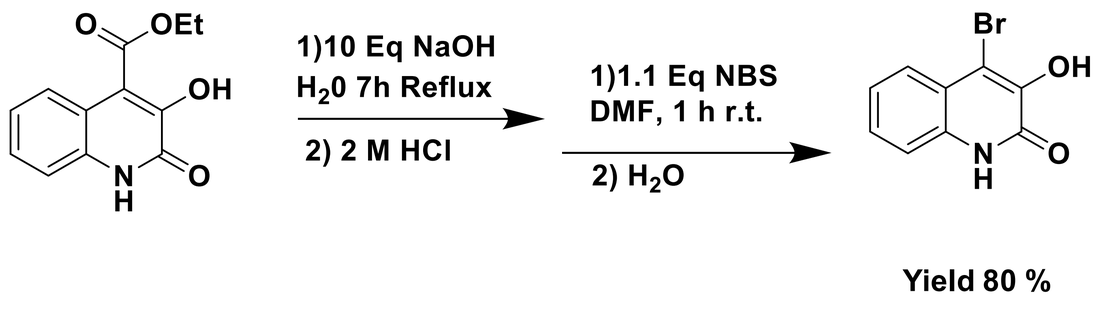


DBU



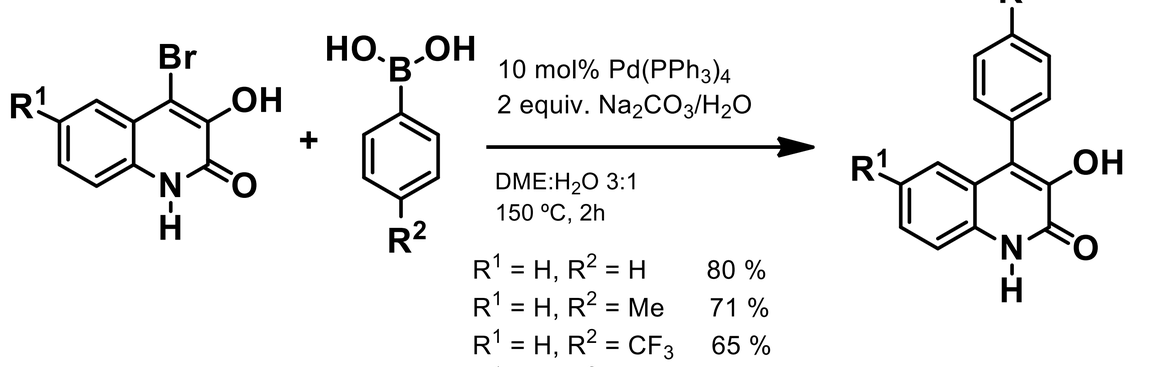
The DFT calculations performed on this system support a mechanism in which the key step is the metallocarbene formation between the 3-hidroxyindole-diazo intermediateand the dirhodium(II) complex.

Second and third hydrolysis and decarboxylation of 3-hydroxy-4-ethylesterquinolin-2(1*H*)-ones and synthesis of 3-hydroxy-4-bromoquinolin-2(1*H*)-ones



Yield 80 %

Fourth Step Synthesis of viridicatin alkaloid derivatives based on the Suzuki-Miyaura coupling reaction of aryl-boronic acids with 3-hydroxy-4-bromoquinolin-2(1*H*)-ones.



R^1 = H, R^2 = H 80 %
R^1 = H, R^2 = Me 71 %
R^1 = H, R^2 = CF_3 65 %
R^1 = H, R^2 = F 71 %

Conclusions

In summary, herein is disclosed an efficient synthesis of viridicatin alkaloids based on *a* Suzuki-Miyaura coupling reaction of aryl-boronic acids with 3-hydroxy-4-bromoquinolin-2(1*H*)-ones prepared from 3-hydroxy-4-ethylesterquinolin-2(1*H*)-ones. The 3-hydroxy-4-ethylesterquinolin-2(1*H*)-one was simply prepared by a regioselective ring expansion reaction of isatins with ethyl diazo acetate catalysed by dirhodium(II) complexes. The reaction mechanism was studied by DFT calculations that highlighted the metallocarbene formation between the 3-hidroxyindole-diazo intermediate and the dirhodium(II) complex as the key step of the mechanism. The discovered compatibility of the NHC-dirhodium(II) complex and DBU, enabled the implementation of an one-pot addition of ethyl diazo acetate to isatin followed by the NHC-dirhodium(II) catalyzed ring expansion reaction, to prepared the 3-hydroxy-4-ethylesterquinolin-2(1*H*)-one in yields up to 92 %. Finally, the 3-hydroxy-4-bromoquinolin-2(1*H*)-one core was simply coupled with aryl-boronic acid afforded the expected vidicatin alkaloids in up to 80 % yield.

Acknowledgments: We thank the Fundação para a Ciência e Tecnolgia for financial support (PEst-OE/SAU/UI4013/2011; PTDC/QUIQUI/099389/2008; SFRH/BD/78301/2011).

References: [1] For preparation of 4-Arylquinolin-2(1H)-ones, see:(a) Borhade, S. *et al*. *Can. J. Chem.***2011**, *89*, 1355;(b) Wang, Z. *et al*. , *J. Comb. Chem.***2007**, *9*, 811;(c) Kappe, C. O. *J. Org. Chem.***2005**, *70*, 3864. [2] Boy, K. M.; Guernon et al. *Bioorg. Med. Chem. Lett.***2004**, *14*, 5089; [3] (a) Cunningham, K. G. et al. ,*Biochem. J.***1953**, *53*, 328;(b) Bracken, A. *Biochem. J.***1954**, *57*, 587;(c) Luckner, M.;. *Tetrahedron Lett.***1962**, *3*, 1035.