Synthetic Studies Towards Arylpyrrole Derivatives via Heck-Matsuda Reaction

Cristiane S. Schwalm,[1] Jailton Ferrari[2] and Carlos R. D. Correia[1]*

[1]*Instituto de Química, UNICAMP, P.O. Box 6154, CEP 13083-970, Campinas, SP, Brazil*

[2]*Departamento de Química - CCEN, UFPB, CEP 58051-970, João Pessoa, PB, Brazil*

**roque@iqm.unicamp.br*

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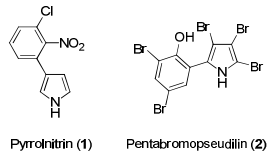
INTRODUCTION

The arylpyrrole unit is a widespread structural motif among biologically active compounds. For example, it is present on the structures of pyrrolnitrin (**1**),[1] a potent antifungal agent, and pentabromopseudilin (**2**),[2] which displays antibiotic, antitumor and lipoxygenase inhibitory activities (Figure 1).



Pyrrolnitrin (**1**) Pentabromopseudilin (**2**)

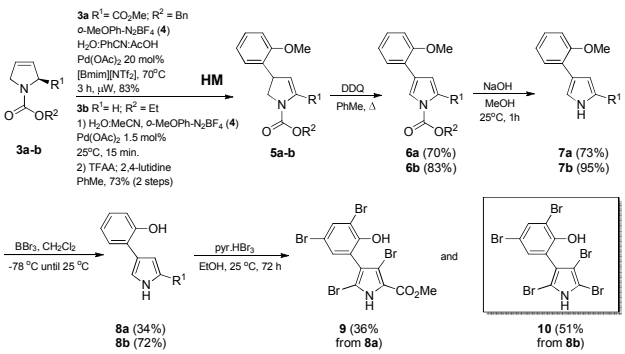
Figure 1. Biologically active arylpyrroles derivatives.

The Heck-Matsuda (HM) reaction employs arenediazonium salts as arylating agents and present several advantages over conventional protocols. It is a phosphine-free and air tolerant process. The more reactive nature of the arylating agent usually implies in shorter reaction times and milder reaction conditions.[3] In this work we present the HM reaction as the key step in the synthesis of both 2 and 3-arylpyrroles, with applications in the synthesis of **2**, isopentabromopseudilin **10** (its 3-aryl analogue) and **9** (a new 3-arylpyrrole derivative).

RESULTS AND DISCUSSION

The *N*-protected 3-pyrrolines **3a-b** were submitted to the HM reaction with the arenediazonium salt **4**, leading to enecarbamates **5a-b** (Scheme 1).

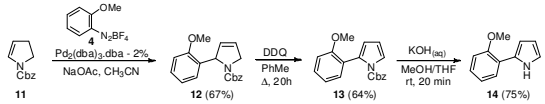
Scheme 1. Synthesis of 3-arylpyrroles derivatives.



Aromatization of **5a-b** employing DDQ afforded the 3-arylpyrroles **6a-b**, which were deprotected under basic conditions and demethylated to afford **8a-b**. Finally, bromination of **8a-b** using pyridinium tribromide completed the total synthesis of isopentabromopseudilin (**10**, with 21% overall yield in 6 steps from **3a**) and its new analogue **9**, with a substituent in the heteroaromatic cycle.

In a similar way, enecarbamate **11** was subjected to the HM reaction with **4**, leading to the Heck adduct **12** (Scheme 2).

Scheme 2. Synthesis of 2-arylpyrrole **14**.



Aromatization of this compound furnished the 2-arylpyrrole **13**, which was deprotected under basic conditions to afford compound **14**, in 32% overall yield in 3 steps from **11** (non-optimized results). Although these steps must be further optimized, this results represent a new formal total synthesis of pentabromopseudilin (**2**), since the conversion of **14** into **2** is already described in the literature.[4]

CONCLUSION

This work illustrates the viability of the Heck-Matsuda reaction as a key step in the synthesis of arylpyrrole derivatives. The versatility of this approach was also demonstrated since both 2 and 3-arylpyrroles could be effectively prepared. Optimization of the synthetic route shown on Scheme 2, as well the development of a total synthesis of **2** are underway.

ACKNOWLEDGEMENTS

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