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Application of the ring-closing metathesis to the formation of 2-aryl-1*H*-pyrrole-3-carboxylates as building blocks for biologically active compounds

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ABSTRACT

Ring-closing metathesis (RCM) is a powerful tool for the preparation of cyclic organic compounds. Yet, one of the major limitations of this method is the difficulty to prepare large quantities of target molecules. Herein we describe a comprehensive study regarding the gram-scale synthesis of 2-aryl-1*H*-pyrrole-3-carboxylates based on the ring-closing metathesis of the corresponding β-amino esters as a key step. This study includes evaluation of solvent and catalyst as well as reaction kinetics on the RCM. After an aromatization step, this methodology allowed for an efficient generation of variously substituted and unprecedented 2-aryl-1*H*-pyrrole-3-carboxylates in good yields and cost-effectiveness. The resulting molecules might serve as key building blocks for the generation of CNS-oriented compound libraries.

1. Introduction

Olefin metathesis has become an efficient tool for the formation of carbon–carbon double bonds. In particular, ring-closing metathesis (RCM) has a large impact on the pharmaceutical industry because this reaction allows formation of medium-to-large size carbocycles and heterocycles from acyclic dienes.[1] One of the first applications of RCM in the synthesis of biologically active compounds concerned the synthesis of Ciluprevir (BILN-2061), a pseudopeptide inhibitor of HCV NS3 protease (Fig. 1).[2] This method stimulated intense generation of Ciluprevir analogs, among which Vaniprevir (MH-7009) is now evaluated in phase III clinical trials.[3] It is worth noting that development of various Hepatitis C inhibitors is currently a subject of intense research in medicinal chemistry.[4] Another eminent example of biologically active compound obtained by RCM process is represented by Tamiflu (oseltamivir phosphate), which behaves as glycosidase inhibitor and is used for the treatment of influenza.[5] RCM was also applied as a central transformation in the synthesis of seven-member heterocyclic ring of SB-462795, a cathepsin K inhibitor, a drug candidate for the treatment of osteoporosis.[6]

Since the first reports of phosphine-containing ruthenium complexes for metathesis reaction,[7] a number of new catalysts have been developed.[8] A major breakthrough was the replacement of the phosphine ligand with a N-heterocyclic carbene (NHC), giving rise to second generation catalysts such as **G-II** (Fig. 2).[9] Such modification increased air and moisture stability of the corresponding complexes. Replacement of the benzylidene moiety with an indenylidene (Fig. 2, **M2** and **M2$_0$**)[8b,10a–d] or 2-isopropoxystyrene derivatives[11] (Fig. 2, **NO$_2$-Grela** and **M5$_1$**) led to new catalyst families with improved stability and activity. However, RCM is a highly substrate depending reaction and despite the wide variety of catalysts, there is no universal one applicable to all kind of dienes.[12] Moreover, cost of the ruthenium complexes constitutes a major limit of the process and studies for determining the proper reaction conditions, which allow for minimal catalyst loading are an important research area with regard to economical issues.

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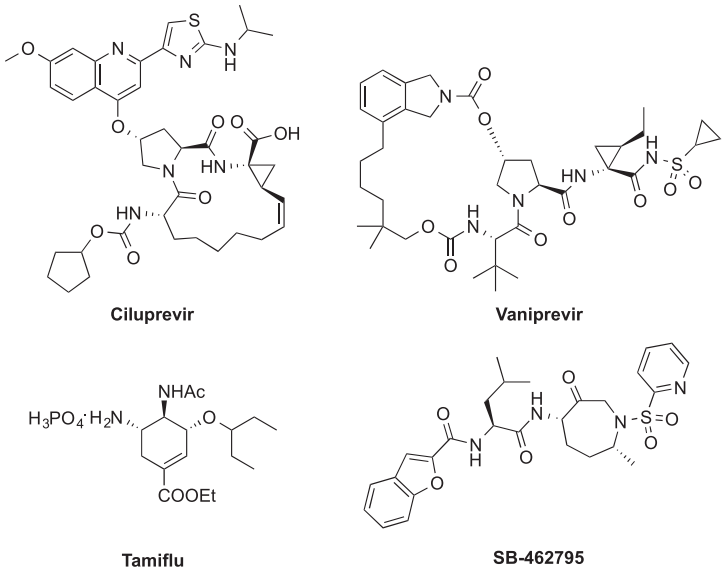


Fig. 1. Selected biologically active compounds obtained *via* RCM method.

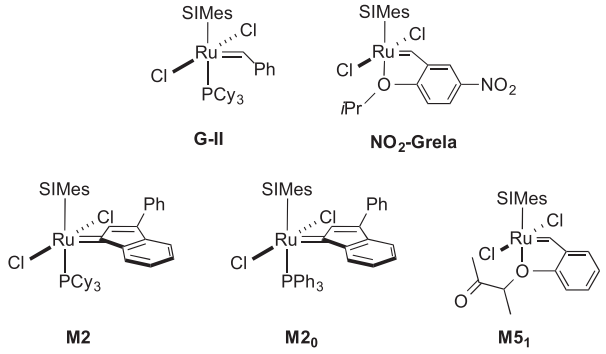
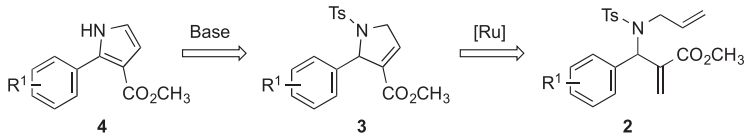


Fig. 2. Structure of catalysts used in this study.

cyclization of homopropargyl azides, although highly efficient, needed either 24 h reaction time or the use of toxic mercury as catalyst.[20]

During our recent study on the synthesis of 1*H*-pyrrolo[3,2-*c*] quinolines as 5-HT_6 receptor antagonists,[21] we found that RCM could be an efficient pathway to obtain pyrroles. We thus decided to optimize a method for the generation of 2-aryl-1*H*-pyrrole-3-carboxylates **4** involving RCM of **2** followed by base-induced aromatization (Scheme 1). These scaffolds should represent key intermediates for the synthesis of biologically active compounds targeted on CNS receptors. This approach has already proven its efficiency in the preparation of aromatic and heteroaromatic structures.[22]

Taking into account our interest in olefin metathesis[23] as well as economic limitations of this process, we wished to find optimal reaction conditions to obtain differently substituted pyrroline derivatives **3** in a gram-scale, in satisfactory yields, using a reduced



Scheme 1. Retrosynthetic approach for the formation of pyrrole derivatives **4**.

The pyrrole scaffold has focused a special attention as a privileged structure in medicinal chemistry, since several pyrrole-containing compounds displayed antipsychotic, anxiolytic, anticancer and antibacterial activity.[13] Among them, 2-arylpyrrole core was present in a series of 5-phenyl pyrrole-3-carboxamides and 2,5-disubstitued phenyl-1-*H*-pyrroles were classified as dopamine D_2 receptor ligands[14] and D_3 receptor antagonists,[15] respectively. Furthermore, compound TAK-438 (Venoprazan), displaying high H^+/K^+-ATP-ase inhibitory activity is currently evaluated in phase III clinical trials for its efficacy in digestive disorders.[16] Moreover, 2-arylpyrrole derivatives behaved as potent progesterone receptor modulators.[17]

The synthetic procedures described for 2-arylpyrroles generally consist in C2 arylation of the heterocyclic core involving palladium catalyzed coupling[18] or cyclization of *N*-allylimine under oxidative conditions.[19] Nevertheless, these methods required either harsh conditions or prolonged reaction times. The metal-catalyzed catalyst loading. Herein we report a comparative study of selected metathesis catalysts, as well as the influence of solvent and reaction kinetics on RCM.

2. Results and discussion

Compound **2a** bearing a nitro-substituent in the C2 position of the phenyl ring was selected as a model substrate for the preliminary RCM experiments. Indeed, this substrate has already been used for the synthesis of pyrroloquinoline scaffolds, using the NO_2 moiety as an extra functional group for further transformations.[23d] In addition, the RCM of **2a** was found challenging since the nitro-substituent was suspected to poison the ruthenium catalyst. At that time, RCM of **2a** to yield **3a** was performed in dichloromethane, either at room temperature, in the presence of 10 mol % of **G-II** for 12 h, or at 100 °C with 4 mol % of **G-II** under microwave activation in