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Diversity-oriented approach to spirocycles with indole moiety via Fischer indole cyclization, olefin metathesis and Suzuki–Miyaura cross-coupling reactions

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ABSTRACT

A range of aryl substituted spirocycles containing the indole moiety have been assembled through Claisen rearrangement, Fischer indole cyclization, ring-closing metathesis and the Suzuki–Miyaura cross-coupling reactions. Some of these molecules contain either a spirocyclic system or an indeno[1,2-*b*] indole framework, which is present in diverse bioactive targets. Here, we have used simple and readily available starting materials to generate a library of spirocycles with an indole unit in their structures.

1. Introduction

Indole is a unique heterocycle and functionalized indoles have been referred as privileged structures because they are a feature in a large number of bioactive molecules.[1] The construction and derivatization of compounds containing an indole moiety has drawn a considerable amount of attention of synthetic organic chemists. Over the last decade, several efforts have been directed to develop simple and efficient methodologies[2] for the synthesis of indole-based compounds. More specifically, the indeno[1,2-*b*]indole framework **1** (Fig. 1) has gained importance in the realm of biological as well as pharmacologically active substances.[3] The structures of some important bioactive molecules containing the indole moiety are shown in Fig. 1.[4]

Spirocycles have drawn a considerable amount of attention of the synthetic as well as material chemists due to the challenges involved in the creation of a quaternary centre.[5] A variety of complex molecules such as fredericamycin, fenestrindane alicyclic [5.5.5.5]fenestrane contain a spiro linkage as a structural unit.[6] Even though numerous methods[7] are available in the literature to construct spirocycles, most of them have limitations due to functional-group tolerence[5k] and group diversity.

In view of the importance of spirocycles as well as indoles, we envisioned a novel synthetic approach to spirocycles with an indole moiety through Claisen rearrangement (CR), Fischer indole cyclization (FIC), ring-closing metathesis (RCM)[8,9] and Suzuki–Miyaura (SM) cross-coupling reactions. Furthermore, incorporation of the SM cross-coupling reaction during the construction of spirocyclic systems is rather scarce.[10]

Our interest in spirocycles containing an indole moiety encompasses to prepare a range of intricate spirocycles with an indole unit and further enhance the indole library via the SM cross-coupling reaction.[11]

2. Results and discussion

To begin with, we generated the di-allyl derivative **8** by treating 6-bromo-2-naphthol **7** with allyl bromide followed by a microwave irradiated (MWI) CR. The di-allylated compound **8** was then subjected to the RCM sequence in the presence of Grubbs' second generation catalyst (Fig. 2) to deliver the known spiro compound **9** (Scheme 1).[12]

Next, the tricyclic spiro derivative **9** was subjected to SM cross-coupling with phenylboronic acid to furnish the desired cross-coupling product **10a** in 96% yield (Scheme 2, Fig. 3). The scope of the cross-coupling reaction was further extended by using other arylboronic acids to deliver the desired products **10b–f** in good to excellent yields (Fig. 3). The new compounds were fully

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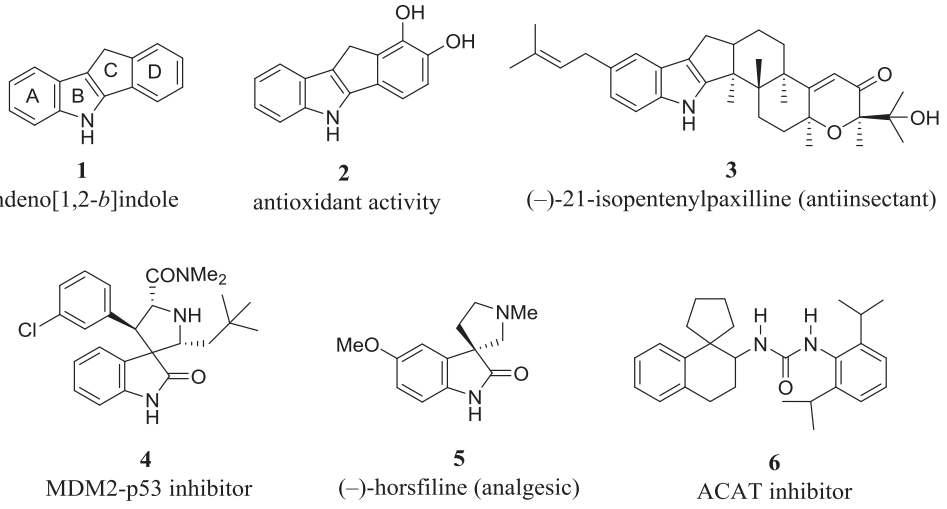


Fig. 1. Some biologically important compounds.

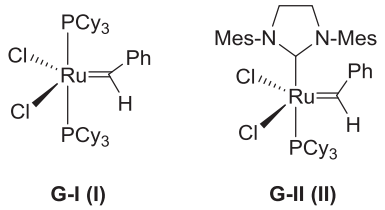
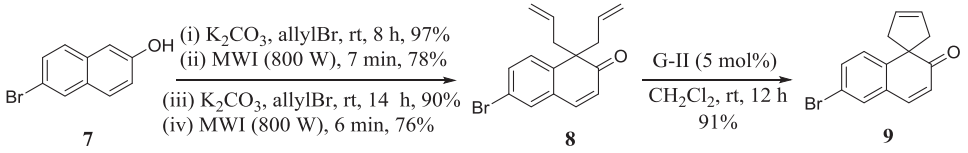


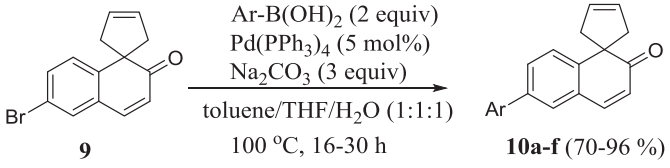
Fig. 2. Ru-catalysts [G-(I-II)] used in our study.

characterized by ^{1}H, ^{13}C NMR spectroscopy and further supported by high-resolution mass spectrometric (HRMS) data.

To further expand the substrate scope to spirocycles, we have also selected 5-bromo-1-indanone **11** as a starting material. The allylation of the indanone **11** under NaH/allyl bromide conditions furnished the di-allyl ketone **12** in 70% yield. This compound was then subjected to the RCM sequence with the aid of Grubbs' first generation catalyst (Fig. 2) to generate the required spirocyclic framework **13** in excellent yield (Scheme 3).[12]



Scheme 1. Design and synthesis of building block **9**.



Scheme 2. The SM cross-coupling of compound **9**.

Having the bromo derivative **13** in hand, the SM cross-coupling reaction with phenylboronic acid using $Pd(PPh_3)_4$, Na_2CO_3 in a THF/toluene/water solvent mixture gave the coupling product **14a** in 92% yield (Scheme 4, Fig. 4). Additionally, other SM coupling products **14b**–**d** were also generated by treating the compound **13** with other functionalized arylboronic acids (Scheme 4, Fig. 4).

Spirocycles as well as indole motif containing compounds are useful candidates from a biological point of view.[13] Therefore, the molecular skeleton, which integrates spirocyclic as well as indole moieties might possess properties of both and provide new

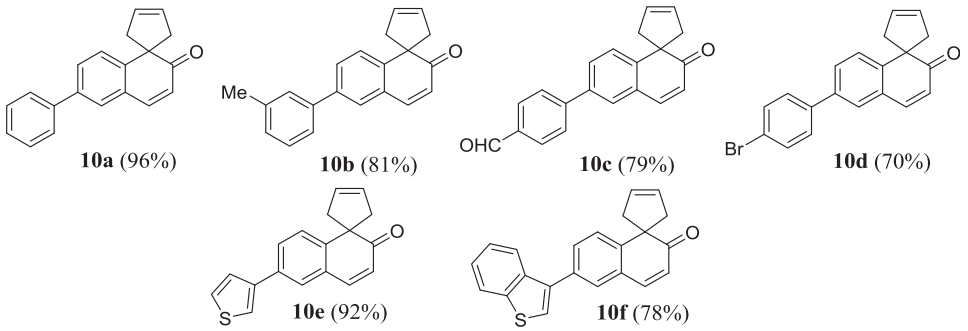


Fig. 3. List of the SM cross-coupling products of **9**.