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Synthesis of lactone-fused pyrroles by ruthenium-catalyzed 1,2-carbon migration-cycloisomerization†

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A ruthenium-catalyzed cycloisomerization of 3-amino-4-alkynyl-2*H*-chromen-2-ones *via* 1,2-carbon migration was developed. Various 1-arylchromeno[3,4-*b*]pyrrol-4(3*H*)-ones were synthesized in good to excellent yields. The reaction was applied to the formal total synthesis of marine natural products Ningalin B and Lamellarin H. The efficient synthesis of γ-butyrolactone-fused pyrrole derivatives was also achieved.

Introduction

1-Arylchromeno[3,4-*b*]pyrrol-4(3*H*)-one skeleton is found in natural products such as Ningalin B, Lamellarin H, and related compounds (Fig. 1).[1] These alkaloids are isolated from marine organisms and known to exhibit biological activities[1] such as cytotoxicity,[2] MDR reversal activity,[2] HIV-1 integrase inhibition,[3] and antitumor activity.[4] Due to their promising pharmacological potentials, these pyrrole-containing natural products have been synthesized by various strategies over the years.[1,5]

Recent examples for the synthesis of the chromeno[3,4-*b*]pyrrol-4(3*H*)-one skeleton include palladium-catalyzed cycloisomerization,[6] one-pot multistep synthesis from 4-chloro-3-nitrocoumarin,[7] the functionalization of 2,3-diarylpyrrole,[8] the cyclization of 3-nitrocoumarin and papaverine,[9] and so on. Among these synthetic methods, the palladium-catalyzed cycloisomerization of 3-amino-4-alkynyl-2*H*-chromen-2-ones is a straightforward and powerful method (Scheme 1a).[6] The reaction proceeds *via* intramolecular nucleophilic amination of the π-activated alkyne, and 2-substituted chromeno[3,4-*b*]pyrrol-4(3*H*)-ones were isolated.

We have recently developed ruthenium-catalyzed cycloisomerization reactions that involve the vinylidene rearrangement of internal alkynes by 1,2-carbon migration and cyclization.[10–13] For example, in the presence of a cationic ruthenium catalyst, various 2-alkynylanilides were converted into the 3-substituted indoles in high yields (Scheme 1b).[11] The mode of the reaction is different from other metal-catalyzed cycloisomerization of 2-alkynylanilines, where no 1,2-carbon migration was involved, and 2-substituted indoles were isolated.[14] In that study, we reported one example that 1-phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one can be synthesized by applying the reaction. Considering the importance of the chromeno[3,4-*b*]pyrrol-4(3*H*)-one skeleton in medicinal chemistry and recent active studies related to the synthesis of Ningalin and Lamellarin derivatives, the development of a new and general method for the synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-one derivatives would be highly desirable. In this paper, we report a ruthenium-catalyzed cycloisomerization of 3-amino-4-alkynyl-2*H*-chromen-2-ones that leads to various 1-arylchromeno[3,4-*b*]pyrrol-4(3*H*)-ones *via* 1,2-carbon migration (Scheme 1c). This new methodology enabled the formal total synthesis of Ningalin B and Lamellarin H. Moreover, we describe the synthesis of rare γ-lactone-fused pyrrole derivatives by a similar ruthenium-catalyzed 1,2-carbon migration/cyclization strategy.

Results and discussion

We investigated the scope and limitation of the reaction using various 3-amino-4-alkynyl-2*H*-chromen-2-one derivatives (**1**, Table 1). As previously reported, when a mixture of

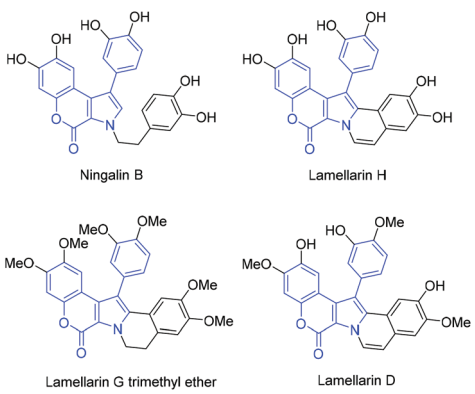

Fig. 1 Representative natural products and analogue containing 1-arylchromeno[3,4-*b*]pyrrol-4(3*H*)-one skeleton.

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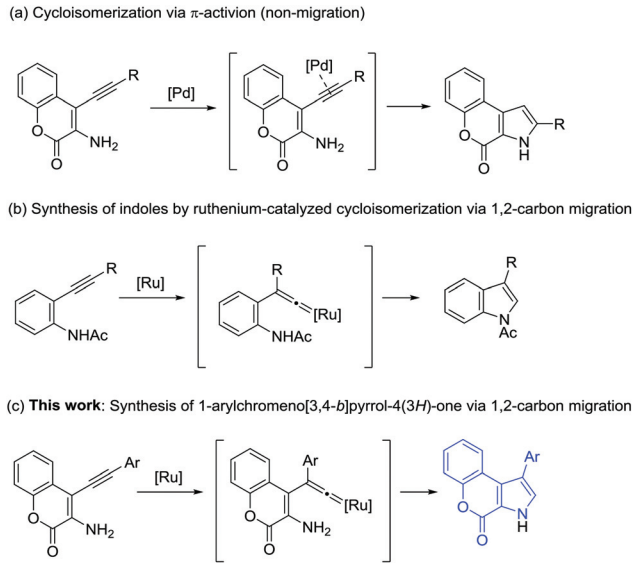
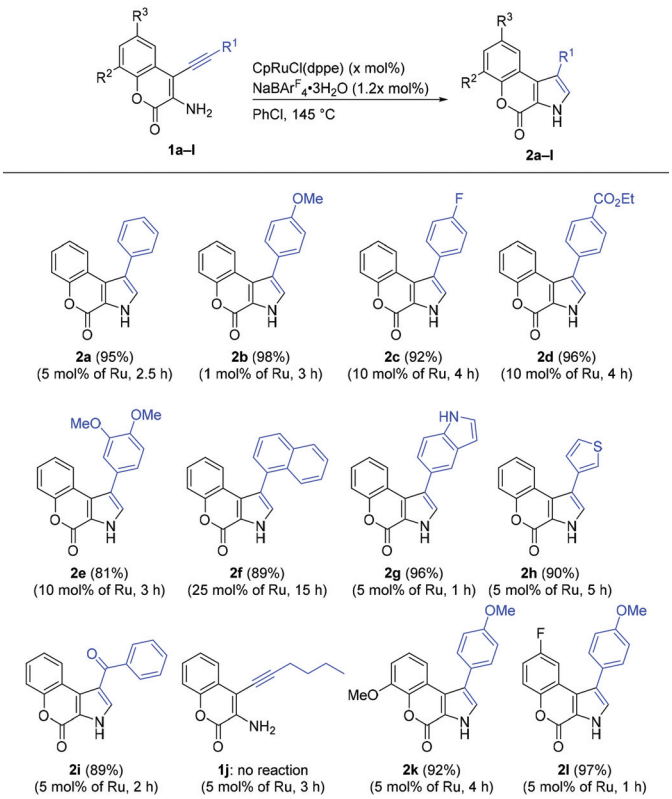


Scheme 1 Cycloisomerization of 3-amino-4-alkynyl-2*H*-chromen-2-ones.

aminocoumarin **1a**, [CpRuCl(dppe)] (Cp = η^5-$C_5H_5^-$; dppe = $Ph_2PCH_2CH_2PPh_2$) (5 mol%), and $NaBAr^F_4{\cdot}3H_2O$ (Ar^F = 3,5-$(CF_3)_2C_6H_3$) (6 mol%) was stirred at 145 °C for 2.5 h in chlorobenzene, the desired 1,2-aryl migration product 3-phenylpyrrolocoumarin (**2a**) was formed in 95% yield.[10,15] Isomeric 2-substituted pyrrole was not observed in the reaction mixture. Although the reaction of **1a** at 130 °C completed in 16 h at the same catalyst loading, the yield of **2a** was lower (82%). [IndRuCl(dppe)] (Ind = η^5-$C_9H_7^-$) and [CpFeCl(dppe)] were inactive catalysts for this reaction, and **2a** was not formed.

We studied the impact of the aryl groups bound to the ethynyl group (R^1) on the reaction. Under the similar reaction conditions described above, 4-methoxyphenyl pyrrole **2b** was obtained in 98% yield with lower catalyst loading. Electron-withdrawing groups were tolerated for this reaction, and pyrrolocoumarins **2c** (92% yield) and **2d** (96% yield) were synthesized in the presence of 10 mol% [CpRuCl(dppe)]. The low reactivity of the alkynes with electron-withdrawing groups (**1c** and **1d**) compared to the substrate with electron-donating group (**1b**) was consistent with our previous studies on the ruthenium-catalyzed cycloisomerizations *via* 1,2-carbon migration[10,11] and probably attributed to the rates of the formation of the disubstituted ruthenium vinylidene complex.[16] Pyrrolocoumarin **2e** with 3,4-dimethoxyphenyl group was also formed from **1e** in 81% yield. When the reaction of sterically congested amionocoumarin **1f** bearing 1-naphthyl group at the alkyne terminus was examined in the presence of 5 mol% of the ruthenium catalyst, the progress of the reaction was sluggish. In the presence of an increased amount (25 mol%) of [CpRuCl(dppe)], however, the corresponding product **2f** was isolated in 89% yield. The compatibility of the substrates with heteroaryl groups was also evaluated, and 5-indolyl derivative **2g** (96% yield) and thiophen-3-yl derivative **2h** (90% yield) were synthesized cleanly.

Table 1 Scope of the ruthenium-catalyzed 1,2-carbon migration/cyclization of 3-amino-4-ethynyl-2*H*-chromen-2-one derivatives (**1**)[a,b]

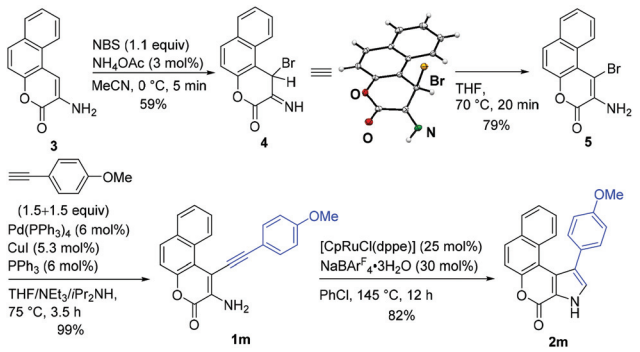


[a] Reaction conditions: **1** (0.25–0.5 mmol, $[\mathbf{1}]^0$ = 0.025–0.2 M in chlorobenzene), [CpRuCl(dppe)] (1–10 mol%), $NaBAr^F_4{\cdot}3H_2O$ (1.2–12 mol%). [b] Isolated yields are shown in parentheses except for **1j**.

The scope of the reaction was further studied by introducing non-aromatic substituents as R^1. The reactivity of benzoyl aminocoumarin **1i** was similar to that of aryl-substituted aminocoumarins, and the corresponding pyrrole **2i** was prepared in 89% yield. The reaction of **1j** (R^1 = Bu) did not proceed, and the starting material was recovered. The low reactivity of **1j** is in contrast to our previous result: the cycloisomerization of a 2-hexynylaniline derivative generated the corresponding 3-butylindole derivative.[10] The reaction of **1j** in the presence of [CpRuCl(dppbz)] (dppbz = 1,2-bis(diphenylphosphino) benzene), which is a more effective catalyst for the synthesis of alkylated indoles,[10,17] also afforded no desired product. We assume that the decreased rate for the alkyne-to-vinylidene rearrangement of electron-deficient and alkyl-substituted acetylene[16,18] could be the reason for this unsuccessful result.

The effect of the substituents introduced to R^2 and R^3 on the coumarin moiety was explored. A methoxypyrrolcoumarin (**2k**, R^2 = OMe, R^3 = H) as well as a fluoropyrrolocoumarin (**2l**, R^2 = H, R^3 = F) were synthesized in high yields.

We further extended our study to the synthesis of a benzo-fused pyrrolocoumarin derivative.[19] The synthesis and ruthenium-catalyzed cycloisomerization of a benzochromenone derivative **1m** was summarized in Scheme 2. When we

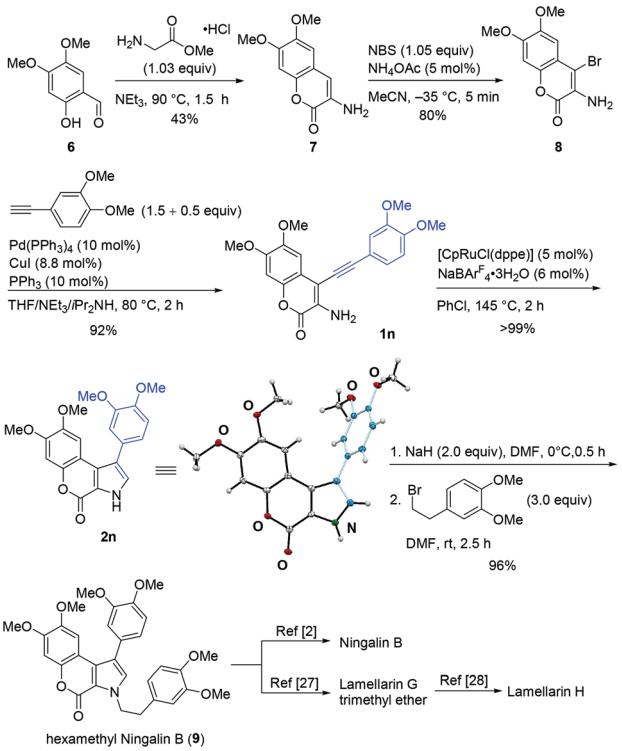


Scheme 2 Preparation of **1m** and the synthesis of **2m**.

tried to synthesize **5** by the bromination of **3** [20] with NBS in the presence of a catalytic amount of NH_4OAc at 0 °C,[21] an unexpected product **4** was isolated in 59% yield. Since the corresponding bromide was not isolated in the reaction of the bicyclic 3-amino-2*H*-chromen-2-one under similar reaction conditions,[21] we assume that the presence of the C–H bond in the proximity of the bromine atom inhibited the isomerization reaction of **4** at 0 °C. Due to the steric hindrance, the rate of the conversion of **4** to **5** should be lower compared to those of other aminocoumarins. The isomerization of **4** smoothly proceeded at elevated temperature (70 °C), and compound **5** was isolated in 79% yield. Subsequently, **1m** was synthesized in 99% yield by Sonogashira reaction of **5** with 4-methoxyphenylacetylene under modified Stoddart's conditions.[22] The reactivity of **1m** was similar to that of sterically congested substrate **1f**: the desired product **2m** was isolated in 82% yield when a larger amount (25 mol%) of the catalyst was employed.

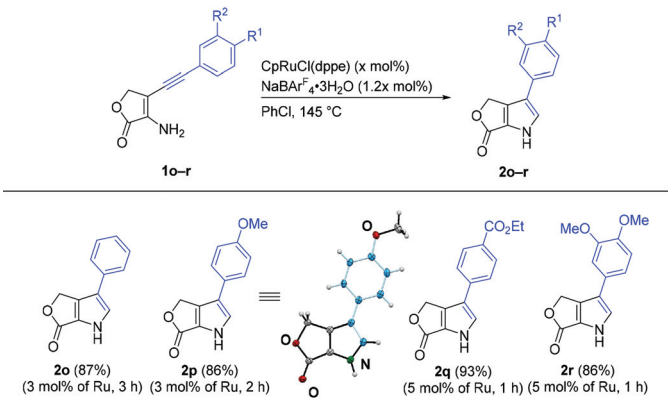
Next, we applied this reaction to the formal total synthesis of Ningalin B and Lamellarin H (Scheme 3). When **6** [23,24] was treated with methyl aminoacetate hydrochloride,[25] aminocoumarin **7** was obtained in 43% yield. The bromination of **7** proceeded at −35 °C to afford **8** in 80% yield. No α-bromoimine, which was similar to **4**, was isolated. Compound **1n** was synthesized in 92% yield by Sonogashira reaction. To our delight, **2n** was obtained in quantitative yield in the presence of 5 mol% of the ruthenium catalyst. The structure of **2n** was confirmed by an X-ray diffraction analysis.[26] With the key intermediate (**2n**) in hand, hexamethyl Ningalin B (**9**) was synthesized in 96% yield by alkylation of **2n**.[7] The demethylation of **9** to Ningalin B was reported by Boger and co-workers.[2] Compound **9** is also the intermediate of Lamellarins, and the conversion of **9** into Lamellarin G trimethyl ether[27] and subsequent transformation to Lamellarin H were reported.[28] Therefore, we achieved the formal total synthesis of natural products, Ningalin B and Lamellarin H.

Furthermore, we examined the synthesis of γ-butyrolactone-fused pyrroles to exemplify the application of this reaction (Table 2). In spite of the simplicity of the structure, only a couple of γ-butyrolactone-fused pyrroles has been reported in the literature,[29,30] and a general method for the synthesis of these compounds has not been established. We successfully



Scheme 3 Synthesis of the key intermediate **2n** for the synthesis of bioactive compounds.

Table 2 Synthesis of γ-butyrolactone-fused pyrrole derivatives[a,b]



[a] Reaction conditions: **1** (0.25–0.4 mmol, $[\mathbf{1}]^0$ = 0.1–0.2 M in chlorobenzene), [CpRuCl(dppe)] (3–5 mol%), $NaBAr^F_4{\cdot}3H_2O$ (3.6–6.0 mol%). [b] Isolated yields are shown in parentheses.

synthesized a series of γ-butyrolactone-fused pyrroles by the ruthenium-catalyzed cycloisomerization of 3-amino-4-arylethynylfuranones. Under the established reaction conditions described for the reaction of 3-amino-4-alkynyl-2*H*-chromen-2-one, the desired γ-butyrolactone-fused pyrroles **2o** and **2p** were isolated in 87% and 86% yields, respectively. The molecular structure of **2p** was confirmed by a single-crystal X-ray diffraction analysis. The reaction of aminobutenolide **1q** with an

ethoxycarbonyl group also afford the corresponding pyrrole **2q** in high yield. The reaction of **1r** with 3,4-dimethoxyphenyl group proceeded cleanly, and **2r** was obtained in 86% yield.

Conclusions

We have developed a synthetic method for various 1-arylchromeno[3,4-*b*]pyrrol-4(3*H*)-ones by ruthenium-catalyzed cycloisomerization of 3-amino-4-ethynyl-2*H*-chromen-2-ones *via* 1,2-carbon migration. The formal total synthesis of Ningalin B and Lamellarin H was achieved by employing this reaction. Moreover, a general method for the synthesis of uncommon γ-butyrolactone-fused pyrroles was established. Our studies will contribute to the development of a new method for the synthesis of heavily substituted pyrrole derivatives.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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16 It has been reported that the rate of the 1,2-carbon migration decreases in the reaction of an electron-deficient aromatic alkyne or an aliphatic alkyne. See, ref. 13*d* and *f*.
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