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-2H-chromen-2-ones via 1,2-carbon migration was developed. Various 1-arylchromeno[3,4-b]pyrrol-4(3H)-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(3H)-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 activities2 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(3H)-one skeleton include palladium-catalyzed cycloisomerization,6 one-pot multistep synthesis from 4-chloro-3-nitrocoumarin,7 the functionalization of 2,3-dianilypyrrrole,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-2H-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(3H)-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-phenylchro

Results and discussion

We investigated the scope and limitation of the reaction using various 3-amino-4-alkynyl-2H-chromen-2-one derivatives (1, Table 1). As previously reported, when a mixture of
aminocoumarin 1a, [CpRuCl(dppe)] (Cp = \( \eta^5\)-C\(_5\)H\(_5\); dppe = Ph\(_2\)PCH\(_2\)CH\(_2\)PPh\(_2\)) (5 mol%), and NaBAr\(_4\)\(_4\)·3H\(_2\)O (Ar\(_4\) = 3,5-(CF\(_3\))\(_2\)C\(_6\)H\(_3\)) (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%).

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 aminocoumarin 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-indoly derivative 2g (96% yield) and thiophen-3-yl derivative 2h (90% yield) were synthesized cleanly.

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 methoxypyrrrolocoumarin (2k, R\(_2\) = OMe, R\(_3\) = H) as well as a fluoro pyrrrolocoumarin (2l, R\(_2\) = H, R\(_3\) = F) were synthesized in high yields.

We further extended our study to the synthesis of a benzo-fused pyrrrolocoumarin derivative.\(^{19}\) The synthesis and ruthenium-catalyzed cycloisomerization of a benzochromone derivative 1m was summarized in Scheme 2. When we
tried to synthesize 5 by the bromination of 3 \(^{20}\) with NBS in the presence of a catalytic amount of \(\text{NH}_4\text{OAc}\) 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 \(\alpha\)-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 Lamellariins, 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 \(\gamma\)-butyrolactone-fused pyrroles to exemplify the application of this reaction (Table 2). In spite of the simplicity of the structure, only a couple of \(\gamma\)-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 synthesized a series of \(\gamma\)-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 \(\gamma\)-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-arylchroomeno[3,4-b]pyrrol-4(3H)-ones by ruthenium-catalyzed cycloisomerization of 3-amino-4-ethynyl-2H-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.

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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 alkyl or an aliphatic alkyl. See, ref. 13d and f.
17 The importance of dpbbz ligand is unclear at this stage.
Compared to phenylacetylene, 4-alkynylchromen-2-one would be an electron-deficient alkyne.

The synthesis of a closely related compound was reported. See ref. 9.

For details, see the ESI.†

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