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One-Pot Construction of 1-Phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one: Application to Total Synthesis of Ningalin B and a Pyrrolocoumarin-Based Electrochromic Switch

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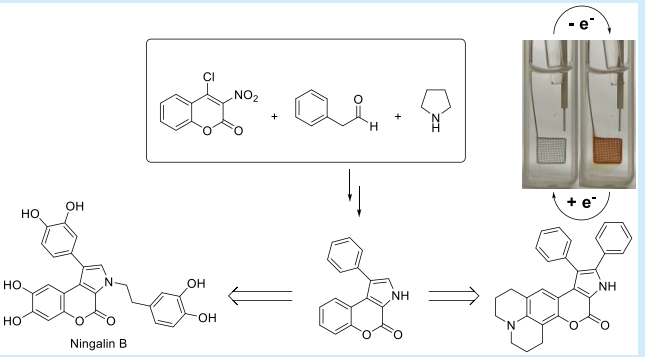
Supporting Information

ABSTRACT: An efficient construction of 1-phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one via coupling of 1-styrylpyrrolidine and 4-chloro-3-nitrocoumarin as a key step is reported. This reaction is further applied to the total synthesis of the natural product ningalin B in five linear steps with an overall yield of 41.5% and a pyrrolocoumarin-based electrochromic switch.



The phenyl-substituted pyrrolocoumarin represents a molecular scaffold that is mainly present in the marine alkaloids lamellarin D[1] and ningalin B[2] (Figure 1).

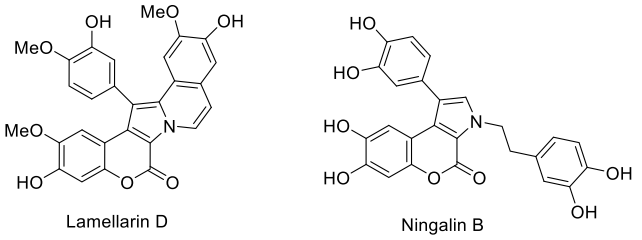
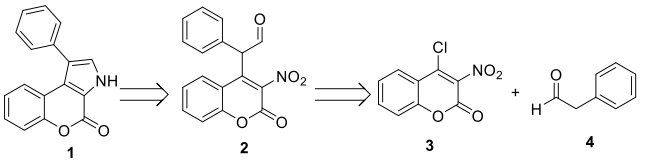


Figure 1. Two phenyl-substituted pyrrolocoumarin-containing natural products.

Compounds containing phenyl-substituted pyrrolocoumarins generally exhibit diverse biological activities including immunomodulatory activity,[3] HIV-1 integrase inhibition,[4] and cytotoxicity.[5] Additionally, some pyrrole-/coumarin-fused heterocycles have been documented to be susceptible to oxidation upon UV irradiation and thus may potentially function as organic redox switches.[6] In light of their pharmacological potential along with the associated intriguing functional properties, the development of efficient synthesis of phenyl-substituted pyrrolocoumarins is highly desired. A simple and efficient route for its preparation would be the base-mediated coupling of 2-phenylacetaldehyde and 4-chloro-3-nitrocoumarin, followed by acid-promoted reductive cyclization as shown in Scheme 1. Unfortunately, all previous attempts[7] for this coupling reaction failed to give the desired

Scheme 1. Proposed Retrosynthesis of Phenyl-Substituted Pyrrolocoumarin 1



product in good yields, presumably due to the fact that 4-chloro-3-nitrocoumarin is unstable under basic conditions and is prone to undergo lactone ring opening.[8] Here, we describe the synthesis of 1-phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one via first coupling of 1-styrylpyrrolidine and 4-chloro-3-nitrocoumarin under neutral conditions, followed by acid-mediated reductive cyclization. This methodology is further extended to the total synthesis of nature product ningalin B and a pyrrolocoumarin derivative. The latter's electrochemical properties are also explored.

Scheme 2 outlines the synthesis of 1-phenylchromeno[3,4-*b*]pyrrol-4(3*H*)-one (**1**), ningalin B skeleton **5**, and diphenyl-substituted pyrrolocoumarin **12**. We initiated our studies by investigating the coupling of 4-chloro-3-nitrocoumarin (**3**)

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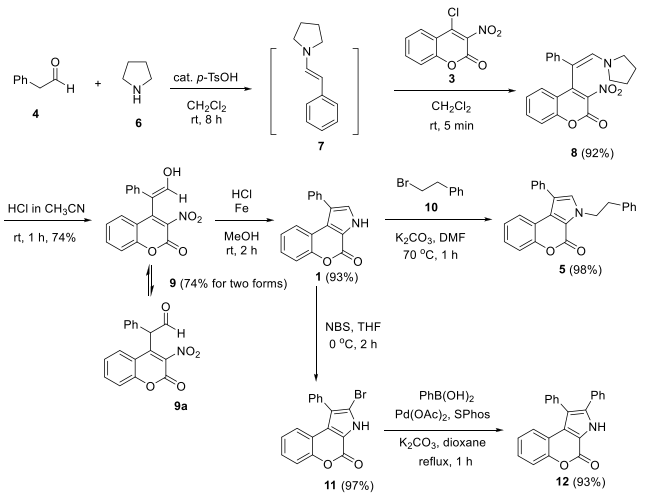
Scheme 2. Synthesis of Compounds 1, 5, and 12



with enamine **7** (prepared *in situ* by *p*-TsOH-catalyzed condensation of 2-phenylacetaldehyde (**4**) with pyrrolidine (**6**)).[9] To our delight, simple mixing of **3** and **7** in methylene chloride at room temperature for 5 min led to the formation of the desired 3-nitrocoumarin **8** in 92% yield. The subsequent hydrolysis of **8** in the presence of HCl in acetonitrile gave a mixture of the keto **9a** and enol **9**. The latter's molecular structure was unambiguously confirmed by X-ray crystal analysis as depicted in Figure 2. Further reduction of the

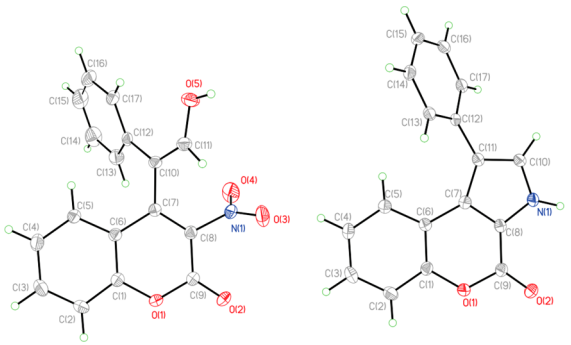
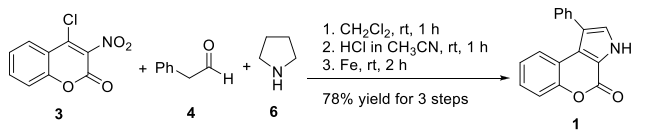


Figure 2. X-ray crystal structures of **9** (left) and **1** (right).

nitro group of the enol **9** to the corresponding amine with iron power, followed by cyclization and aromatization, afforded the target compound **1** (Figure 2). Final alkylation of **1** with (2-bromoethyl)benzene (**10**) in the presence of K_2CO_3 as a base in DMF at 70 °C for 1 h furnished the ningalin B skeleton **5**. To shorten the synthesis, compound **1** can also be prepared in a one-pot multistep manner via mixing of **3**, **4**, and **6** in methylene chloride for 1 h, followed by sequential addition of acid and iron power without isolation of the enamine **8** and enol **9** as shown in Scheme 3. Thus, the ningalin B skeleton **5**

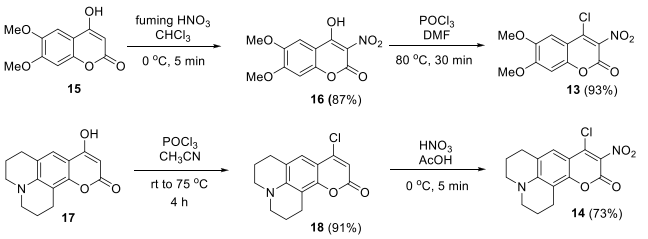
Scheme 3. One-Pot Multistep Synthesis of Pyrrolocoumarin 1



can actually be prepared in just two synthetic steps from 2-phenylacetaldehyde (**4**). Moreover, compound **1** could be brominated with NBS in THF at 0 °C to yield compound **11**.[10] The Suzuki coupling of **11** with phenylboronic acid in the presence of $Pd(OAc)_2$, SPhos, and K_2CO_3 in dioxane afforded the diphenyl-substituted pyrrolocoumarin (**12**) in good yield.[11]

After realizing the preparation of ningalin B skeleton **5**, we then pursue the total synthesis of ningalin B and its derivative. Scheme 4 shows the two-step synthesis of the appropriately

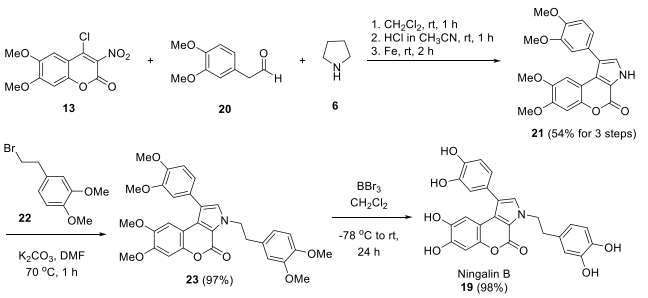
Scheme 4. Preparation of 4-Chloro-3-nitrocoumarins 13 and 14



substituted 4-chloro-3-nitrocoumarin precursors **13** and **14**. Coumarin **13** was prepared by first nitration of 4-hydroxy-6,7-dimethoxycoumarin (**15**) with fuming nitric acid in chloroform to give 3-nitrocoumarin **16**. The subsequent heating of **16** with $POCl_3$ in DMF afforded the 4-chlorocoumarin **13** in good yield. Conversely, the 4-chlorocoumarin **14** was prepared the other way around by first chlorination of 4-hydroxycoumarin **17** with $POCl_3$ in acetonitrile to generate the 4-chlorocoumarin **18**. The following nitration of **18** with nitric acid in acetic acid at low temperature furnished the compound **14**.

Scheme 5 outlines the preparation of ningalin B (**19**) from **13**. Similar to that of **1**, the pyrrolocoumarin **21** was prepared

Scheme 5. Synthesis of Ningalin B



via mixing of coumarin **13**, 2-(3,4-dimethoxyphenyl)-acetaldehyde (**20**), and pyrrolidine (**6**) in methylene chloride for 1 h, followed by sequential addition of acid and iron power to yield the tetramethoxy-substituted pyrrolocoumarin **21** in 54% yield. Alkylation of **21** with 4-(2-bromoethyl)-1,2-dimethoxybenzene (**22**) in the presence of K_2CO_3 as a base in DMF afforded the fully protected ningalin B (**23**). Final exhaustive demethylation of **23** with excess of boron tribromide in methylene chloride at low temperature gave rise to the target ningalin B (**19**) in five linear steps with an overall yield of 41.5% from commercially available coumarin **15**.

Scheme 6 depicts the preparation of diphenyl-substituted pyrrolocoumarin **24** from coumarin **14**. Again, the pyrrolocoumarin **25** was prepared via mixing of coumarin **14**, 2-

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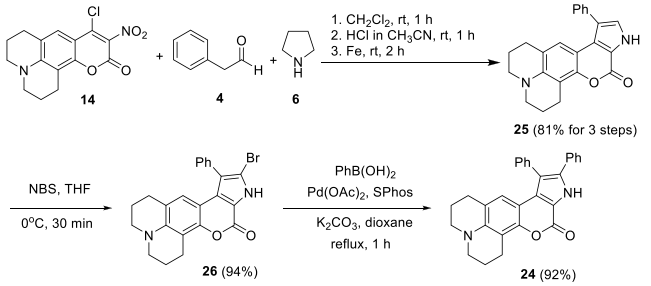
Scheme 6. Synthesis of Diphenyl-Substituted Pyrrolocoumarin 24



phenylacetaldehyde (**4**), and pyrrolidine (**6**) in methylene chloride for 1 h and followed by sequential addition of acid and iron power to yield the pyrrolocoumarin **25** in 81% yield. The subsequent bromination of **25** with NBS in THF gave the brominated **26**. Final Suzuki coupling of **26** with phenylboronic acid in the presence of K_2CO_3 under refluxed conditions in dioxane afforded the compound **24** in five steps with an overall yield of 46.5% starting from coumarin **17**.

With both compounds **12** and **24** in hand, their potential functional properties were then evaluated. Figure 3 shows the

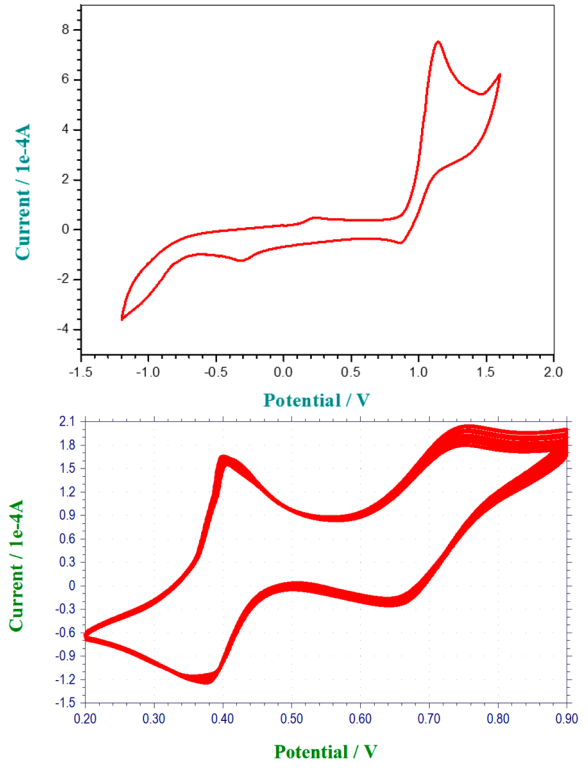


Figure 3. Cyclic voltammogram of **12** (top) and **24** (bottom, 40 cycles) recorded in CH_3CN (1×10^{-3} M) containing $TBAPF_6$ (0.1 M) as supporting electrolyte at a scan rate of 100 mV/s.

cyclic voltammogram (CV) of **12** and **24** recorded in acetonitrile with 0.1 M $TBAPF_6$ supporting electrolyte at a scan rate of 100 mV/s. An oxidation potential of 1.14 V (vs Ag/AgCl) was detected for the pyrrolocoumarin moiety of **12**. On the other hand, two one-electron reversible oxidation waves at +0.40 and +0.76 V corresponding to aminocoumarin and pyrrolocoumarin moieties were clearly observed for **24**. This observation suggests that incorporation of an amino functional group on coumarin of **24** decreases the oxidation potential of the pyrrolocoumarin moiety from 1.14 to 0.76 V. Further, the CV of **24** showed no substantial changes in the redox potentials even after being scanned for 40 cycles, implying that it may potentially possess electrochromic properties.

Figure 4 depicts the spectroelectrochemical spectra of **24** in acetonitrile prior to and after the applied external potential. In

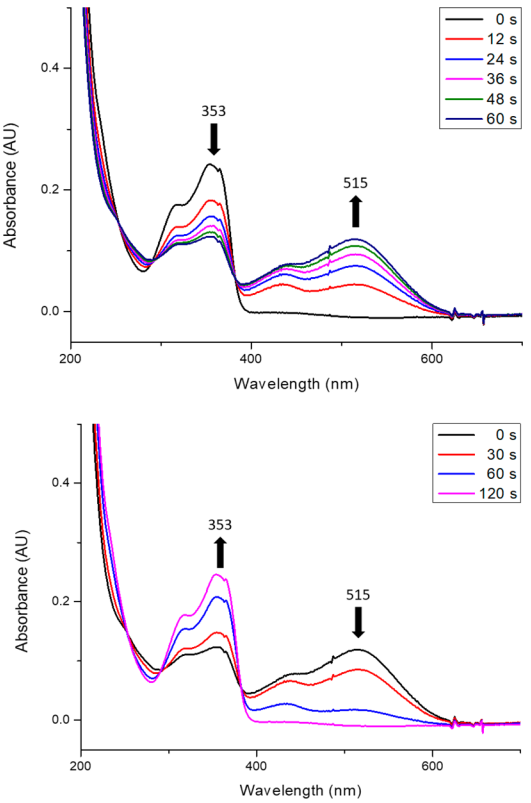


Figure 4. (Top) Spectroelectrochemical spectra of **24** in CH_3CN (5×10^{-5} M) with 0.1 M $TBAPF_6$ at an applied oxidation potential of 0.55 V (vs Ag/AgCl). (Bottom) Spectroelectrochemical spectra of the oxidized **24** at an applied reduction potential of 0.20 V (vs Ag/AgCl).

the absence of the external potential, compound **24** was virtually colorless with absorption maximum wavelength at 353 nm. With the increase of exposure time (0–60 s) to an oxidation potential of 0.55 V, a new broad absorption band with the peak wavelength around 515 nm gradually emerged, along with the appearance of three isosbestic points at 254, 290, and 383 nm. We speculate that the colorless solution changes to red may be attributed to the formation of an amine cation radical on the coumarin moiety.[12] Conversely, applying a reduction potential of 0.20 V (vs Ag/AgCl) to the oxidized **24** resulted in the gradual decrease of the absorbance at 515 nm (Figure 4, bottom). The initial UV–vis spectra of **24** were almost fully recovered, and the solution became colorless again after 2 min. That is, the absorbance intensity at 515 nm of the oxidized pyrrolocoumarin **24** can be reversibly modulated by the external potentials. Thus, a new organic redox switch was established on the basis of an amino-substituted pyrrolocoumarin scaffold.

In summary, we have demonstrated that the phenyl-substituted pyrrolocoumarin **1** can be efficiently constructed via coupling of 1-styrylpyrrolidine and 4-chloro-3-nitro-

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coumarin, followed by sequential hydrolysis, reduction, and cyclization. This methodology was further extended to the total synthesis of natural product ningalin B in five linear steps with an overall yield of 41.5% and diphenyl-substituted pyrrolocoumarin **24** in five linear steps with an overall yield of 46.5%. Finally, the cyclic voltammogram and spectroelectrochemical studies indicated pyrrolocoumarin **24** exhibits electrochromic properties.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01830.

Synthesis of compounds **1**, **5**, **8**, **9**, **11**−**19**, **21**, and **23**−**26** and experimental details (PDF)

Accession Codes

CCDC 1916726, 1917203, 1917205−1917206, and 1917208 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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