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Synthesis of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones by cyclocondensation of 1,3-dicarbonyl compounds with 4-chloro-3-nitrocoumarin

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ABSTRACT

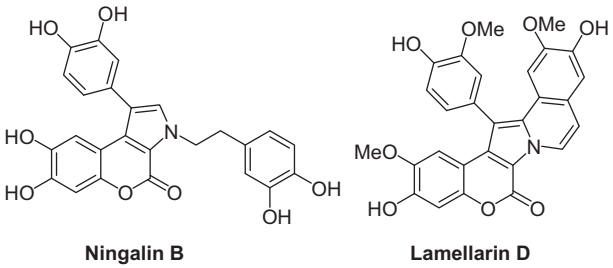
The base-mediated cyclocondensation of 1,3-dicarbonyl compounds with 4-chloro-3-nitrocoumarin provides a convenient approach to various chromeno[3,4-*b*]pyrrol-4(3*H*)-ones.

Pyrrolocoumarins are of considerable pharmacological relevance and occur in a variety of natural products. A chromeno[3,4-*b*]pyrrol-4(3*H*)-one core structure occurs, for example, in the marine alkaloids ningalin B and lamellarin D which exhibit HIV-1 integrase inhibition, immunomodulatory activity and cytotoxicity (Scheme 1).[1]

Previous syntheses of chromeno[3,4-*b*]pyrrol-4(3*H*)-ones rely on the formation of the pyrrole moiety by Claisen reaction[2] or by Fischer indole synthesis[3] using 3-aminocoumarins as starting materials. Recently, the Sonogashira reaction of 4-chloro-3-nitrocoumarin (**3**) to give a 4-alkynyl-3-nitrocoumarin and subsequent reductive cyclization has been reported.[4] Herein, we report what are, to the best of our knowledge, the first cyclocondensation reactions of 1,3-dicarbonyl compounds with 4-chloro-3-nitrocoumarin. These reactions provide a convenient approach to various chromeno[3,4-*b*]-pyrrol-4(3*H*)-ones. These products are not readily available by other methods.

4-Chloro-3-nitrocoumarin (**1**) is readily available in two steps from 4-hydroxycoumarin (by nitration and subsequent exchange of the OH-group to chlorine). The reaction of **1** with methyl acetoacetate (**2a**), in the presence of K_2CO_3 (DMF, 20 °C, 3 h),[5] afforded the condensation product **3a**[6] in 85% yield (Scheme 2, Table 1). The employment of other bases (e.g., NaOMe, MeOH) resulted in a decrease of the yield. The formation of **3a** can be explained by conjugate addition and subsequent cleavage of the chloride group. The hydrogenation of **3a**, in the presence of Pd/C (10 mol %),[7] afforded the chromeno[3,4-*b*]pyrrol-4(3*H*)-one **4a**[8] in 67% yield.

The preparative scope was studied. The reaction of **1** with 3-oxoalkanoates **2b–e** and subsequent hydrogenation afforded the chromeno[3,4-*b*]pyrrol-4(3*H*)-ones **4b–e**. The reaction of **1** with 1,3-diketones **2f–i** and subsequent hydrogenation afforded the chromeno[3,4-*b*]pyrrol-4(3*H*)-ones **4f–i**. The cyclization of **3g,h–4g,h** proceeded with excellent regioselectivity via the more electrophilic keto group (i.e., the keto group attached to the alkyl rather than the phenyl group). The tetracyclic products **4j,k** were



Scheme 1. Structure of ningalin B and lamellarin D.

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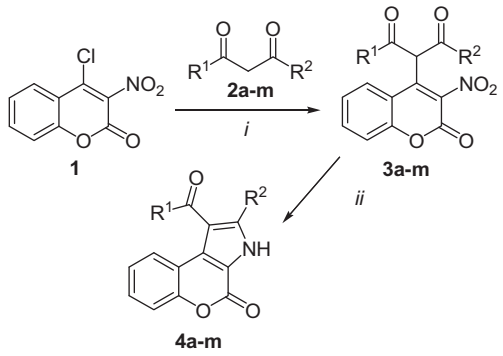

Scheme 2. Synthesis of **3a**–**m** and **4**–**m**. Reagents and conditions: (i) DMF, K_2CO_3, 20 °C, 3 h; (ii) MeOH, H_2, Pd/C (10 mol %), 20 °C, 2 days.

Table 1
Synthesis of **3a**–**m** and **4a**–**m**

3, **4**	R^1	R^2	%[a] (**3**)	%[a] (**4**)
a	OMe	Me	85	67
b	OMe	*n*Pr	63	50
c	OMe	*i*Pr	62	44
d	OEt	*n*Bu	72	52
e	OEt	4-(MeO)C_6H_4	73	53
f	Me	Me	80	66
g	Ph	Me	78	60
h	Ph	Et	56	41
i	Ph	Ph	67	47
j	–$(CH_2)_3$–		65	42
k	–$CH_2CMe_2CH_2$–		61	46
l	OMe	CH_2CO_2Me	70	51
m	4-MeC_6H_4	CO_2Me	60	45

[a] Yields of isolated products.

prepared from cyclohexane-1,3-dione (**2j**) and dimedone (**2k**), respectively. The reaction of **1** with dimethyl acetone-1,3-dicarboxylate (**2l**) gave **3l** which was transformed into **4l**. The reaction of **1** with pyruvate derivative **2m** afforded **3m**. The hydrogenation of the latter resulted in regioselective formation of product **4m**. The moderate yields can be explained by practical problems during the chromatographic purification (especially for second step).

In conclusion, we have reported the first cyclocondensation reactions of 1,3-dicarbonyl compounds with 4-chloro-3-nitrocoumarin. These reactions provide a convenient approach to various chromeno[3,4-*b*]-pyrrol-4(3*H*)-ones.

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5. *General procedure for synthesis of* **3a**–**m**: To a solution of **1** (0.451 g, 2.0 mmol) and **2a**–**m** (4.0 mmol) in DMF (8 mL) was added anhydrous K_2CO_3 (0.453 g, 4.0 mmol) at 20 °C. The mixture was stirred at room temperature for 3 h and then poured into ice/water (100 mL). The solution was acidified by addition of concd hydrochloric acid to pH 1. The solution was allowed to stand for 12 h at room temperature. The precipitate formed was filtered, washed with water until the washing solution was neutral and subsequently dried.
6. *2(3-Nitro-2-oxo-2H-chromen-4-yl)-3-oxo-butyric acid methyl ester* (**3a**): starting with **1** (0.451 g, 2.0 mmol) and **2a** (0.465 g, 4.0 mmol), **3a** (0.519 g, 85%) isolated by filtration as a colourless solid, mp 183–185 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.64 (s, 3H), 3.78 (s, 3H, OCH_3), 4.23 (s, 1H), 7.37–7.42 (m, 2H), 7.65–7.71 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 20.4, 48.4 (CH_2), 52.8 (OCH_3), 117.1 (C), 117.6, 120.3, 125.9, 127.0, 134.6 (CH), 141.9, 152.6, 167.4, 168.1, 194.7 (C). GC–MS (EI, 70 eV): *m*/*z* (%) = 305 ([M]$^+$, 100), 260 (15), 160 (9), 144 (8), 116 (14), 115 (17), 101 (46). HRMS (EI): calcd for $C_{14}H_{11}NO_7$ ([M]$^+$): 305.0536; found: 305.0537
7. *General procedure for the synthesis of* **4a**–**m**: In a 50 mL one-necked round Schlenk flask under a flow of dry argon were placed 1.0 mmol of compound **3** and Pd/C (50 mg, 10 mol %). Subsequently, 25 mL of dry degassed methanol was added. The system was washed three times with hydrogen. The hydrogenation was conducted with the help of a glass burette under atmospheric pressure. After 3 equiv of hydrogen were consumed, the mixture was stirred for 2 days at 20 °C (TLC control). The reaction mixture was filtered through a Celite pad (2–3 cm). The Celite was washed three times with methanol. The solvent of the filtrate was removed under reduced pressure. The residue was purified by preparative chromatography (silica gel, heptanes/EtOAc).
8. *2-Methyl-4-oxo-1,4-dihydro-chromeno(3,4-b)pyrrol-1-carboxylic acid methyl ester* (**4a**): starting with **3a** (0.305 g, 1.0 mmol), Pd/C (50 mg, 10 mol %) and 25 mL of dry degassed methanol, **4a** (0.172 g, 67%) was isolated by chromatography (silica gel, heptanes/EtOAc) as a colourless solid, mp 300–302 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.56 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 7.31–7.50 (m, 3H), 8.92 (d, *J* = 8.0 Hz, 1H), 13.12 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.3 (CH_3), 51.3 (OCH_3), 108.61, 115.9 (C), 116.8 (CH), 123.9 (C), 124.0, 126.3 (CH), 127.8 (C), 128.4 (CH), 145.9, 151.0, 153.6, 164.6 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3304 (w), 3216 (m), 3096 (w), 2950 (w), 2831 (w), 2568 (w), 1722 (m), 1682 (s), 1609 (w), 1548 (m), 1499 (m), 1442 (m), 1379 (m), 1318 (m), 1267 (s), 1177 (s), 1139 (m), 1081 (s), 1042 (m), 986 (m), 906 (w), 751 (s), 710 (m), 710 (m), 636 (m), 564 (w). GC–MS (EI, 70 eV): *m*/*z* (%) = 257 ([M]$^+$, 100), 227 (11), 226 (81), 225 (34), 224 (10), 197 (12), 115 (8). HRMS (EI): calcd for $C_{14}H_{11}NO_4$([M]$^+$): 257.0428; found: 257.0427.