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One-pot synthesis of a natural product inspired pyrrolocoumarine compound collection by means of an intramolecular 1,3-dipolar cycloaddition as key step

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ABSTRACT

A general, sequential and efficient one-pot synthesis of natural product inspired chromeno[3,4-*b*]pyrrol-4(3*H*)-ones is described. The one-pot reaction sequence consists of N-Boc deprotection of a *N*-substituted Boc-glycine *O*-aryl ester embodying an *ortho*-alkyne substituent, azomethine ylide generation with an aldehyde, subsequent intramolecular 1,3-dipolar cycloaddition with the alkyne followed by oxidative aromatization. This synthesis method gives efficient access to a collection of highly substituted diverse pyrrolocoumarines.

Natural products enriched in bioactivity are valuable sources and tools for chemical biology and medicinal chemistry research.[1] Molecular scaffolds derived from or inspired by natural products can be considered as biologically prevalidated starting points for the design and synthesis of novel bioactive compounds.[2] Biological relevance and prevalidation are key criteria for the selection of such novel scaffolds and key to the concept of biology-oriented synthesis (BIOS).[3] The synthesis of natural product inspired compound collections demands robust and efficient reaction sequences which ideally can be carried out in one pot. Therefore, the development of such sequential transformations is at the heart of BIOS.[4]

Cycloaddition reactions are among the most powerful methods for the synthesis of complex molecular architectures. For instance, intermolecular 1,3-dipolar cycloaddition reactions with azomethine ylides have been explored extensively for the construction of various five membered heterocycles,[5] and, intramolecular versions of this reaction may yield efficient access to annulated polycyclic ring systems.[6] In the development of intramolecular 1,3-dipolar cycloaddition reaction of azomethine ylides, efforts were mainly directed towards the generation of dipolarophiles tethered to aldehydes.[7] In contrast, dipolarophile tethering to the amine, which will allow the use of numerous readily accessible aldehydes has rarely been explored.[6]

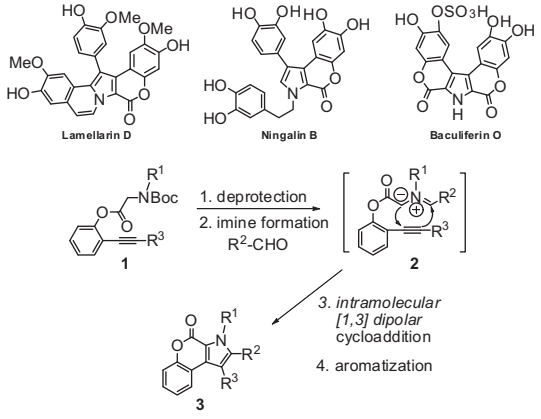

Figure 1. Structures of representative natural products incorporating the chromeno[3,4-*b*]pyrrol-4(3*H*)-one scaffold and strategy for the sequential one-pot synthesis.

The chromeno[3,4-*b*]pyrrol-4(3*H*)-one scaffold defines the structural core of various natural products endowed with diverse bioactivities. For instance, lamellarin D, ningalin B and baculiferin O are characteristic for three classes of marine natural products which exhibit important bioactivities including antitumour activity, HIV-1 integrase inhibition and multidrug resistance (MDR) reversal activity (Fig. 1).[8] Despite this biological significance, only

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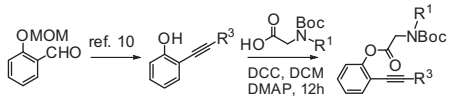
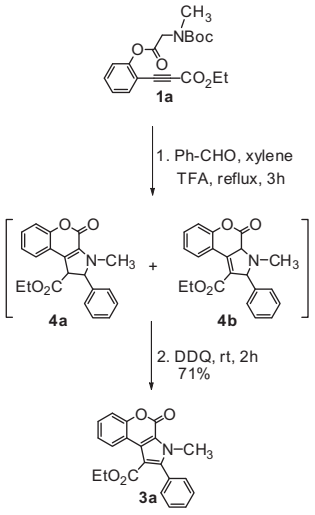


1a; R^1= Me, R^3= CO_2Et, 88%
1b; R^1= Me, R^3= CO_2Me, 80%
1c; R^1= Et, R^3= CO_2Et, 81%
1d; R^1= Bn, R^3= CO_2Et, 77%
1e; R^1= Bn, R^3= CO_2Me, 78%

Scheme 1. Synthesis of substrates.



Scheme 2. Establishment of the one-pot intramolecular 1,3-dipolar cycloaddition.

few synthetic methods to access this scaffold have been reported.[9] Notably, a general and efficient synthesis method for the synthesis construction of this natural product scaffold with broad structural diversity is lacking.

Here we report on the development of such a sequential one-pot synthesis which involves N-Boc deprotection of a *N*-substituted Boc-glycine *O*-aryl ester embodying an *ortho*-alkyne substituent, azomethine ylide formation with an aldehyde, intramolecular [3+2] cycloaddition and subsequent aromatization. The method gives straightforward and efficient access to the pyrrolocoumarine scaffold **3** with fully substituted pyrrole moiety. It was successfully applied for the synthesis of a compound library with broad structural scope.

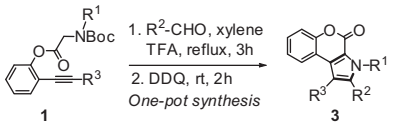
We envisioned to synthesize the pyrrolocoumarine scaffold **3** by means of intramolecular 1,3-dipolar cycloaddition reaction between azomethine ylides **2**, generated in situ from N-Boc-*N*-alkylated glycine esters **1** and aromatic aldehydes (Fig. 1). This strategy would enable the introduction of diverse substituents (R^1, R^2 and R^3) on the pyrrole moiety.

Our study commenced with the preparation of N-Boc glycinyl propiolates **1a**–**1e** (Scheme 1). Phenol derived propiolates were synthesized using a procedure reported by Yamamoto et al.[10] Coupling of different phenol derived propiolates and *N*-substituted Boc glycines gave the corresponding substrates **1a**–**1e** in good yields (Scheme 1).

To establish the reaction sequence, initially we attempted in situ deprotection of Boc-protected glycine *O*-aryl ester **1a** and subsequent azomethine ylide formation with benzaldehyde (Scheme 2). Gratifyingly, TFA mediated NBoc deprotection of **1a**, followed by iminium formation and subsequent intramolecular 1,3-dipolar cycloaddition in refluxing toluene gave a mixture of dihydropyrrolocoumarines **4a** and **4b**. Treatment of the reaction mixture with excess MnO_2 at room temperature yielded the desired pyrrolocoumarine **3a**[11] in moderate yield. To improve the efficiency of this one-pot reaction sequence, optimization of reaction conditions with respect to solvent (e.g., *o*-xylene, toluene, DCE) and oxidizing agents (e.g., MnO_2, DDQ, sulfur) was investigated. The use of DDQ in *o*-xylene as solvent emerged as most favourable and furnished the desired product in viable yields (Scheme 2).

With optimized reaction conditions identified, the scope of the methodology was investigated with various substitutions R^1, R^2 and R^3 (Table 1). Initial experiments indicated that for R^1 several substituents like, Me, Et and Bn are tolerated to yield the cycloadducts in appreciable yields (Table 1, entries 1–11). The one-pot intramolecular cycloaddition strategy was fairly general with respect to substituents R^2 (Table 1, entries 12–21). Irrespective of electronic factors various aromatic and heteroaromatic aldehydes could be successfully employed in the transformation. Thus, in

Table 1
Scope of the one-pot intramolecular 1,3-dipolar cycloaddition reaction[a]



1 3

Entry	Product No.	R^1	R^2	R^3	Yield[b] (%)
1	**3b**	Me	1-Naphtyl	CO_2Et	72
2	**3c**	Bn	1-Naphtyl	CO_2Et	82
3	**3d**	Me	*p*-$MeOC_6H_4$	CO_2Et	80
4	**3e**	Et	*p*-$MeOC_6H_4$	CO_2Et	88
5	**3f**	Bn	*p*-$MeOC_6H_4$	CO_2Et	74
6	**3g**	Me	*p*-FC_6H_4	CO_2Et	60
7	**3h**	Et	*p*-FC_6H_4	CO_2Et	76
8	**3i**	Bn	*p*-FC_6H_4	CO_2Et	74
9	**3j**	Me	3-Furanyl	CO_2Et	65
10	**3k**	Et	3-Furanyl	CO_2Et	62
11	**3l**	Bn	3-Furanyl	CO_2Et	53
12	**3m**	Et	Ph	CO_2Et	78
13	**3n**	Et	*p*-$NO_2C_6H_4$	CO_2Et	85
14	**3o**	Et	*p*-BrC_6H_4	CO_2Et	73
15	**3p**	Et	*p*-IC_6H_4	CO_2Et	78
16	**3q**	Me	*m*-FC_6H_4	CO_2Et	82
17	**3r**	Me	2-Furanyl	CO_2Et	75
18	**3s**	Bn	Ph	CO_2Et	78
19	**3t**	Bn	*o*-FC_6H_4	CO_2Et	74
20	**3u**	Bn	*p*-$CF_3C_6H_4$	CO_2Et	73
21	**3v**	Bn	3-Thiophenyl	CO_2Et	59
22	**3w**	Me	1-Naphtyl	CO_2Me	82
23	**3x**	Me	*p*-$MeOC_6H_4$	CO_2Me	58
24	**3y**	Me	2-Furanyl	CO_2Me	75
25	**3z**	Bn	Ph	CO_2Me	86
26	**3aa**	Bn	1-Naphtyl	CO_2Me	69
27	**3ab**	Bn	*p*-$MeOC_6H_4$	CO_2Me	56
28	**3ac**	Bn	*p*-$NO_2C_6H_4$	CO_2Me	75
29	**3ad**	Bn	*p*-FC_6H_4	CO_2Me	61
30	**3ae**	Bn	*p*-BrC_6H_4	CO_2Me	71
31	**3af**	Bn	*p*-$CF_3C_6H_4$	CO_2Me	72
32	**3ag**	Bn	3-Furanyl	CO_2Me	51
33	**3ah**	Bn	3-Thiophenyl	CO_2Me	48
34	**3ai**	Bn	*m*-FC_6H_4	CO_2Me	71
35	**3aj**	Bn	*o*-FC_6H_4	CO_2Me	78
36	**3ak**	Me	Ph	CO_2Me	78
37	**3al**	Me	Ph	CONHMe	55
38	**3am**	Me	*p*-$NO_2C_6H_4$	CO_2Me	74
39	**3an**	Me	*p*-$NO_2C_6H_4$	CONHMe	70
40	**3ao**	Me	*p*-$CF_3C_6H_4$	CO_2Me	74
41	**3ap**	Me	*p*-$CF_3C_6H_4$	CONHMe	56
42	**3aq**	Me	*m*-MeC_6H_4	CONHMe	65
43	**3ar**	Me	*o*-BrC_6H_4	CONHMe	63

[a] Reaction conditions: **1** (0.16 mmol), TFA (0.8 mmol) and aldehyde (0.32 mmol) were used for the reaction.
[b] Isolated yields after column chromatography.

the presence of an unsubstituted aryl group (Table 1, entries 12 and 18), an electron-donating (Table 1, entries 3–5) or -withdrawing substituent (Table 1, entries 13–16, 19 and 20) on the aromatic ring the reaction proceeds well to yield the desired pyrrolocoumarines in good yields. In addition, heteroaromatic aldehydes are well tolerated to yield the corresponding cycloadducts in moderate to good yields (Table 1, entries 9–11, 17 and 21). Reactions with aliphatic aldehydes did not proceed well to yield the corresponding cycloadducts. Instead, hydrolysis of the phenolic ester was observed.

Investigation of the intramolecular 1,3-dipolar cycloaddition with variation of R^3 (Table 1, entries 22–43) revealed a clear influence of electronic factors. Thus, electron withdrawing groups such as esters and amides at this position favour the cycloaddition reaction with various aromatic and heteroaromatic aldehydes to yield the desired cycloadducts in good yields (Table 1, entries 22–36). Introduction of a phenyl group at R^3 did not yield any cycloadduct. Instead hydrolysis of the phenolic ester was observed. Also, introduction of various electron withdrawing aryl substituents such as *p*-$NO_2C_6H_4$, *p*-$CO_2EtC_6H_4$, *p*-FC_6H_4 and 3,5-di-FC_6H_3 at this position was not fruitful. Finally, replacement of the ester by an amide was well tolerated to produce the corresponding pyrrolocoumarines in appreciable yields (Table 1, entries 37, 39, 41–43).

In conclusion, we have developed a general and efficient one-pot method for the synthesis of a natural product-inspired pyrrolocoumarine compound collection. The sequential one-pot synthetic strategy includes N-Boc deprotection of a *N*-substituted Boc-glycine *O*-aryl ester embodying an *ortho*-alkyne substituent, azomethine ylide generation with an aldehyde, subsequent intramolecular 1,3-dipolar cycloaddition with the alkyne followed by oxidative aromatization. The developed methodology was used for the synthesis of a diverse compound collection based on the pyrrolocoumarine scaffold.

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Supplementary data

Supplementary data (experimental procedures, characterization data for all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.021.

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11. (a) *General procedure for the synthesis of cycloadducts* **3a**–**3ar**: To a solution of N-Boc alkinylamine (0.16 mmol) in *o*-xylene, aldehyde (0.32 mmol) and TFA (0.8 mmol) were added and the resulting mixture was heated to reflux using a Dean–Stark apparatus. After complete conversion of the substrate (monitored by means of thin layer chromatography (TLC)) approximately in 3 h, the reaction mixture was cooled down to rt, DDQ (0.20 mmol) was added and the mixture was stirred for another 2 h at room temperature. The resulting crude reaction mixture was filtered and purified by means of column chromatography to yield the desired pyrrolocoumarines.
(b) *Characterization data for* **3a**: Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.53–7.47 (m, 3H), 7.42–7.38 (m, 2H), 7.37–7.33 (m, 2H), 7.31–7.26 (m, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.8, 155.3, 151.6, 147.9, 131.0, 130.0, 129.5, 128.8, 128.7, 128.5, 126.6, 124.3, 117.6, 117.2, 117.1, 110.8, 60.5, 34.5, 13.5; FT-IR: $\tilde{\nu}$ = 2977, 1700, 1503, 1433, 1143, 1053, 751, 698 cm^{-1}; HRMS: calcd for $[M+H]^+$ $C_{21}H_{17}NO_4$: 348.1236 found: 348.12338.
(c) *Characterization data for* **3s**: Yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92–8.78 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.52–7.39 (m, 5H), 7.34 (ddd, *J* = 8.4, 6.6, 2.0 Hz, 1H), 7.27–7.18 (m, 5H), 6.86 (t, *J* = 3.5 Hz, 1H), 6.85 (d, *J* = 4.5 Hz, 1H), 5.66 (s, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.9, 154.9, 151.7, 148.2, 137.2, 130.7, 130.2, 129.5, 129.1, 128.9, 128.6, 128.3, 127.6, 126.6, 126.5, 124.4, 117.2, 117.1, 117.1, 111.6, 60.6, 49.6, 13.5; FT-IR: $\tilde{\nu}$ = 1702, 1502, 1454, 1436, 1276, 1248, 1141, 1108, 1053, 752, 732, 697 cm^{-1}; HRMS: calcd For $[M+H]^+$ $C_{27}H_{22}NO_4$: 424.15433 found: 424.15422.