Synthetic Methods

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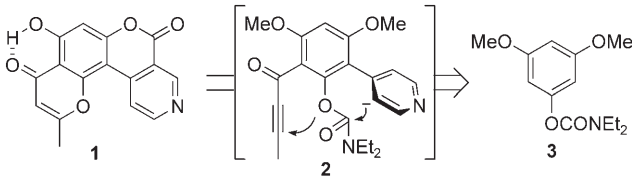
Carbamoyl Translocations by an Anionic *ortho*-Fries and Cumulenolate α-Acylation Pathway: Regioselective Synthesis of Polysubstituted Chromone 3- and 8-Carboxamides**

Todd K. Macklin, Jane Panteleev, and Victor Snieckus**

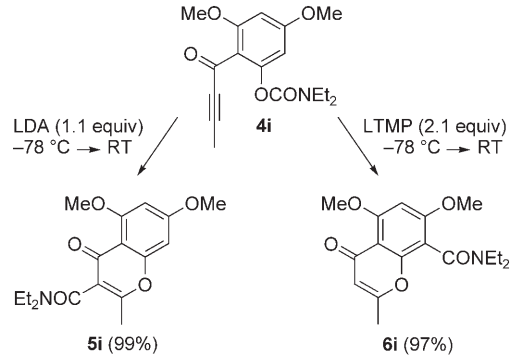
In memory of Albert I. Meyers

In an initial planned foray towards the total synthesis of schumanniophytine **1**,[1] we envisaged (Scheme 1) a concise route incorporating a double intramolecular reaction



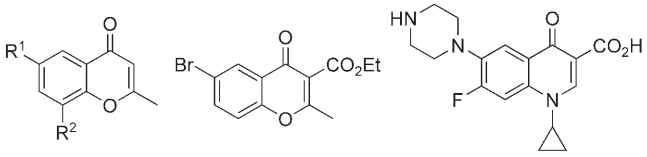
Scheme 1. Proposed retrosynthetic analysis of schumanniophytine (**1**).

sequence of a remote anionic-Fries rearrangement[2] and a Michael addition (see intermediate **2**). While this concept was not placed to the test because of our failure to prepare the requisite precursor **2**,[3] model studies on the conveniently synthesized 2-but-2-ynoyl aryl *O*-carbamate **4i** (Scheme 2) led to the discovery of two new anionic aryl *O*-carbamoyl rearrangements that give isomeric chromones **5i** and **6i** which proceed in essentially quantitative yield under standard conditions mediated by lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidide (LTMP), respectively. The original concept aside (Scheme 1), which represents a successful *ortho*-Fries/Michael addition reaction (**4i**→**6i**, Scheme 2), it was recognized that the chromone heterocycle represents major classes of natural products[4] and is a key component for a plethora of bioactive molecules, commercial drugs, and agrochemicals.[5] This realization



Scheme 2. Synthesis of chromone 3-carboxamide **5i** and 8-carboxamide **6i**.

gave us impetus to extend these initial studies.[6] Herein we report the preliminary results of our synthetic and mechanistic findings which demonstrate: a) the preparation of 3- and 8-substituted chromones, systems represented by bioactive substances **7**[7] and **8**[8] which are difficult to access and are related to the important class of antibacterial 4-quinolone drugs ciprofloxacin (**9**),[9] for which there is a



R^1 = H, Me, Cl, Br
R^2 = CO_2H, CH_2CO_2H

classical heterocyclic interconversion;[10] b) repetitive metalation reactions which allow the construction of polysubstituted chromones (Table 1); and c) the intriguing and unprecedented involvement of a cumulenolate intermediate of **4i**[11] in the anionic carbamoyl translocation reaction. Taken together, this work contributes to the increasing impact of carbanionic-mediated strategies in synthetic aromatic chemistry. By adaption of the approach used for the schumanniophytine alkaloid model compound study (**4i**, Scheme 2), a series of 2-but-2-ynoyl aryl *O*-carbamates **4a**–**k** were prepared[12] and subjected to the strong base-mediated conditions. The results, which are summarized in Table 1, merit selected comment. Complications with the 1,2-addition of LDA to unhindered

[*] T. K. Macklin, Prof. V. Snieckus
Department of Chemistry, Queen's University
Kingston, Ontario K7L 3N6 (Canada)
Fax: (+1) 613-533-6089
E-mail: snieckus@chem.queensu.ca
Homepage: http://www.chem.queensu.ca/people/faculty/snieckus/
J. Panteleev
Department of Chemistry, University of Toronto
Toronto, Ontario, M5S 3H6 (Canada)

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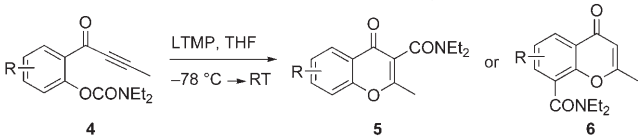
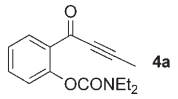
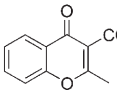
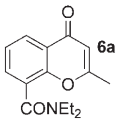
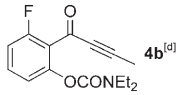
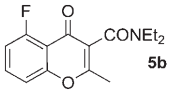
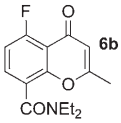
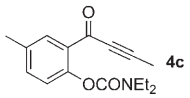
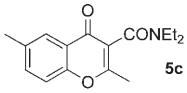
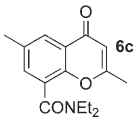
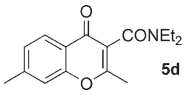
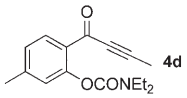
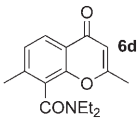
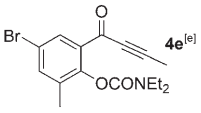
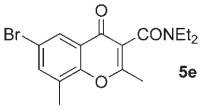
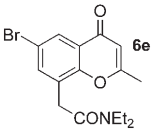
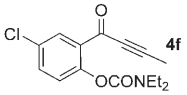
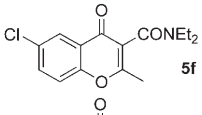
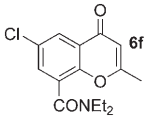
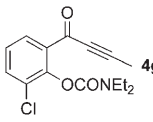
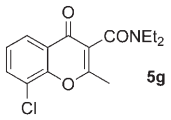
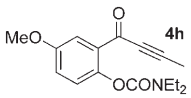
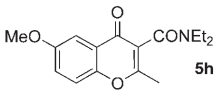
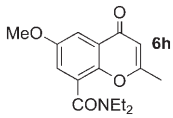
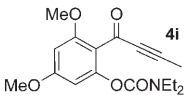
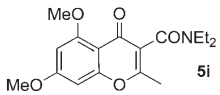
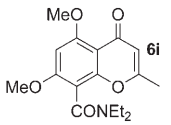
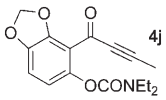
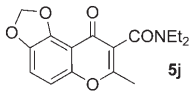
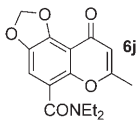
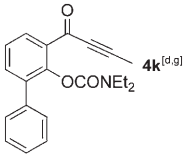
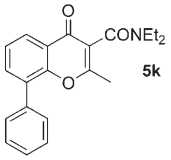
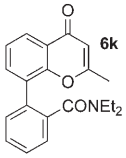
Table 1: Synthesis of chromone 3-carboxamides **5a,c–k** and 8-carboxamides **6a,c–f,h–j**.



Entry	Substrate[a]	Base (equiv)	Product	Yield [%][b]
1	 **4a**	LTMP (1.5)	 **5a**	81
2		LTMP (1.2) *s*BuLi (2.3)	 **6a**	54[c]
3	 **4b**[d]	LTMP (1.1)	 **5b**	0
4		LTMP (2.1)	 **6b**	0
5	 **4c**	LTMP (2.2)	 **5c**	93
6		LTMP (1.1) *s*BuLi (2.5)	 **6c**	44[c]
7		LTMP (2.2)	 **5d**	85
8	 **4d**	LTMP (1.1) *s*BuLi (2.5)	 **6d**	46[c]
9	 **4e**[e]	LTMP (1.5)	 **5e**	92
10		LTMP (3.0)	 **6e**	84
11	 **4f**	LTMP (1.1)	 **5f**	86
12		LTMP (2.1)	 **6f**	93

Entry	Substrate[a]	Base (equiv)	Product	Yield [%][b]
13	 **4g**	LTMP (1.5)	 **5g**	79[f]
14	 **4h**	LTMP (1.5)	 **5h**	90
15		LTMP (5.0)	 **6h**	86
16	 **4i**	LDA (1.1)	 **5i**	99
17		LTMP (2.2)	 **6i**	97
18	 **4j**	LTMP (1.5)	 **5j**	90
19		LTMP (1.3) *s*BuLi (2.6)	 **6j**	36[c]
20	 **4k**[d,g]	LTMP (3.0)	 **5k**	65
21		LTMP (20)	 **6k**	0

[a] Prepared by DoM of the corresponding aryl *O*-carbamate. Conditions: *s*BuLi (1.2 equiv), −78 °C, 30 min; then $MgBr_2{\cdot}OEt_2$ (2.5 equiv), −78 °C→0 °C; then *N*-methoxy-*N*-methylbut-2-ynamide (1.2 equiv), 0 °C→RT, 2 h; 61–77%. [b] Prepared by DoM of the corresponding aryl *O*-carbamate. Conditions: LTMP, −78 °C→RT, 2–12 h. [c] Conditions: LTMP, −78 °C, 10 min; then *s*BuLi, −78 °C→RT. [d] Conditions: *s*BuLi (1.2 equiv) −78 °C, 30 min; then CuCN·2 LiCl (2 equiv), −78 °C, 30 min; then 2-butynoyl chloride (2 equiv), −78 °C→RT, 1 h; 34–48%. [e] Prepared by metal-halogen exchange from the corresponding aryl bis-bromide. Conditions: *t*BuLi (2.1 equiv), −78 °C, 10 min; then $MgBr_2{\cdot}OEt_2$ (2.5 equiv), −78 °C→0 °C; then *N*-methoxy-*N*-methylbut-2-ynamide (1.2 equiv), 0 °C→RT, 12 h. [f] LTMP, −78 °C→50 °C, 1 h. [g] Reaction performed at −100 °C.

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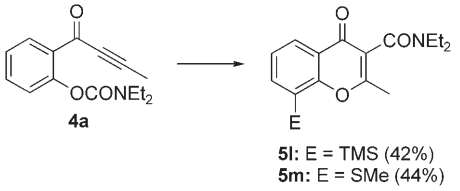
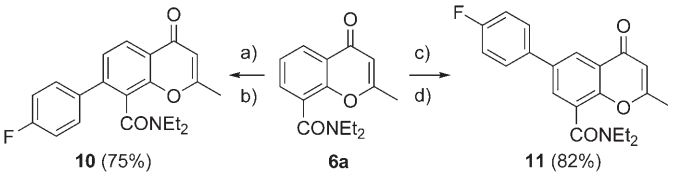
ynones led the use of LTMP, a more hindered base, for the remaining reactions of derivatives **4a**–**h**, **4j**, and **4k**. Conversions of unsubstituted and methyl-substituted *O*-carbamates **4a**, **4c**, and **4d** (entries 1, 5, and 7) as well as the methylenedioxy derivative **4j** (entry 18) proceed smoothly to give chromones **5a**, **5c**, **5d**, and **5j**, respectively, under LTMP conditions. However, their corresponding transformations into chromones **6a**, **6c**, **6d**, and **6j** (entries 2, 6, 8, and 19) require a sequential LTMP/*s*BuLi procedure: the second step with a stronger base was essential to achieve kinetic *ortho*-carbamoyl deprotonation to enable an *ortho*-Fries migration.[13] The 3-fluoro compound **4b** (entries 3 and 4) failed to afford chromone **5b** or **6b**, presumably as a result of complications arising from benzyne formation.[14] On the other hand, the lack of such presumed difficulties in the case of the bromosubstituted **4e** is noteworthy:[15] not only is 3-carbamoylchromone **5e** (entry 9) obtained efficiently, but a known lateral metalation/carbamoyl migration[16] gives the acetamide chromone **6e** (entry 10) in high yield. The chloro *O*-carbamates **4f** and **4g**, which were expected to cause less concern with respect to benzyne formation, smoothly underwent the isomeric carbamoyl transfer/Michael cyclization reactions to afford the expected products **5f**, **6f**, and **5g** (entries 11–13), respectively. Methoxy aryl *O*-carbamate **4h** (entry 15) required increased concentrations of LTMP (5 equiv) to favor formation of **6h**, presumably as a result of coordination and competitive directed *ortho*-metalation (DoM) arising from the presence of the OMe group.[17] The original test substrate **4i** (entries 16 and 17) benefits from synergistic DoM[18] to give **5i** and **6i** in the best overall yields for this general route. The biaryl *O*-carbamate **4k** (entry 20) furnishes the 8-aryl chromone **5k**, which is structurally related to several naturally occurring[19] and synthetic[20] antitumor agents. Structural differences notwithstanding, the unsuccessful conversion of **4k** (entry 21) into **6k** is indicative of the difficulties in proving that the (original untested concept) formation of **2** is a key step in the synthesis of schumanniophytine (**1**).[1]

The evidence that the formation of the C8 carbanion was possible under *s*BuLi conditions (entries 2, 6, ,8, and 19) prompted us to investigate trapping experiments with other electrophiles at low temperatures. Thus, using sequential LTMP/*s*BuLi metalation of unsubstituted 2-but-2-ynoyl phenyl *O*-carbamate (**4a**; Scheme 3) followed by TMSCl and MeSSMe treatment led to the formation of 8-silyl- and 8-thiomethylchromones **5l** and **5m**, respectively, in modest overall yields.



Scheme 3. One-pot DoM/chromone 3-carboxamide synthesis. Reagents and conditions: LTMP (1.3 equiv), THF, −78 °C, 10 min; then *s*BuLi (2.5 equiv), −78 °C, 30 min; then E = TMSCl or MeSSMe (2.5 equiv), −78 °C → RT, 2 h. TMS = trimethylsilyl.

The availability of the new 8-carbamoylchromones **6** inspired us to perform additional DoM reactions. Thus, treatment of **6a** (Scheme 4) with LHMDS, to necessarily



Scheme 4. Differential borylation and arylation of chromone **6a**. Reagents and conditions: a) LHMDS (1.5 equiv), THF, −78 °C, 10 min; then TMEDA (3 equiv), *s*BuLi (3 equiv), −78 °C, 30 min; then $B(OMe)_3$ (4 equiv), −78 °C, 1 h; b) $[Pd_2(dba)_3]$ (0.01 equiv), S-Phos (0.02 equiv), 1-bromo-4-fluorobenzene (1.1 equiv), K_3PO_4 (2 equiv), PhMe, 100 °C, 2 h; c) $[Ir(OMe)(cod)]_2$ (0.02 equiv), dtbpy (0.04 equiv), B_2pin_2 (0.6 equiv), hexanes, 80 °C, 18 h; d) $[Pd(PPh_3)_4]$ (0.02 equiv), 1-bromo-4-fluorobenzene (1.1 equiv), Na_2CO_3 (10 equiv), DME/H_2O (4:1), 80 °C, 4 h. LHMDS = lithium hexamethyldisilazide, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, dba = dibenzylideneacetone, S-Phos = dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl, cod = 1,5-cyclooctadiene, dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridyl, B_2pin_2 = bis(pinacolato)diboron, DME = 1,2-dimethoxyethane.

effect the formation of a protected dienolate,[21] followed by DoM and treatment with $B(OMe)_3$ afforded the 7-borylated chromone, which was immediately subjected to modern Suzuki cross-coupling conditions[22] to furnish the 7-(4-fluorophenyl)chromone **10** in reasonable yield. To provide regiochemical complementarity, advantage was taken of the substituent effects from the C–H activation/borylation route by using B_2pin_2 in the presence of an iridium catalyst.[23] Thus, subjecting **6a** to one-pot borylation/Suzuki cross-coupling conditions[24] afforded isomeric 6-(4-fluorophenyl)chromone **11** in very good yield.

A mechanistic study of the LDA-mediated reaction was undertaken on the high-yielding conversion of **4i** into [D]-**5i** (Scheme 5). First, treatment of **4i** with LDA (1.1 equiv) at −78 °C for 1 hour and subsequent trapping with AcOH and AcOD at −78 °C gave the 1,2-dienones (α-allenyl ketones) [H]-**13** and [D]-**13**, respectively in reasonable yields (21% monodeuterium incorporation was determined by ^{1}H NMR spectroscopy). This result confirms the generation of the kinetic cumulenolate intermediate **12** and its α-carbonyl protonation, in agreement with previous experimental and semiempirical calculations (MNDO).[25] Treatment of **4i** with LDA (1.1 equiv, −78 °C, 20 min) followed by quenching with MeOH at −78 °C gave (2*E*)-aryl-3-methoxy-but-2-en-1-one **15** (confirmed by NOE experiments), which is the expected thermodynamically stable diastereomer resulting from α-carbonyl protonation and 1,4-addition of the generated methoxide.[26,27] Allowing the cumulenolate **12** to warm to room temperature to promote carbamoyl transfer resulted in the appearance of a deep red solution indicative of the formation of the lithium dienolate **16**; this was confirmed by the rapid disappearance of color upon treatment with AcOD to give a clear solution and a high yield of [D]-**5i** (> 95% deuterium incorporation was determined by ^{1}H NMR spec-

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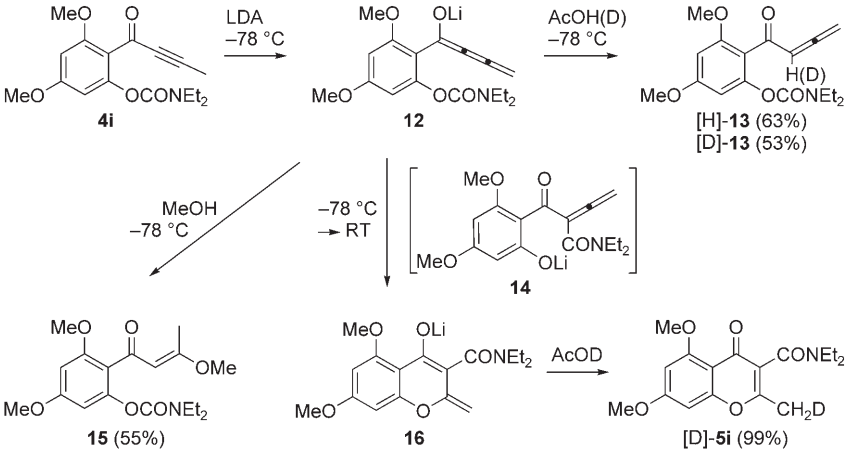

Scheme 5. Reactions of cumulenolate **12**.

troscopy). This result suggested a reaction pathway which proceeds via the buta-2,3-dienamide **14** followed by intramolecular Michael addition of the resulting phenolate and then protonation to give the chromone product **5i**.[28] As suggested by the need for additional amounts of base for effective conversion of **4** into **6** (Table 1), this reaction may also involve the cumulenolate **12**, which undergoes anionic *ortho*-Fries rearrangement followed by protonation and Michael addition, although evidence for this suggestion is currently unavailable.

In conclusion, new general and regioselective syntheses of chromone derivatives **5** and **6** by anionic carbamoyl translocation reactions have been developed. The reactions, which involve sequential intramolecular anionic *ortho*-Fries rearrangement and Michael addition that proceed, as suggested by mechanistic studies (Scheme 5), via an intriguing cumulenolate **12**, provide routes to chromones which show uncommon and difficult to access C8 substitution[7] as well as common and biologically significant[8,9] 3-substitution patterns. The DoM reactions (Scheme 3) as well as the complementary *ortho*- and iridium catalyzed *meta*-borylation and Suzuki cross-coupling chemistry (Scheme 4) provide added conceptual and practical value for heterocyclic synthesis. As a proposed tenet, in juxtaposition with Brönsted or Lewis acid-mediated electrophilic substitution, this study and related aromatic carbanionic reactions[18] offer advantages for allowing the introduction of varied substituents under mild conditions with regiochemical control. Potentially of more general significance, the observation of cumulenolate **12**, which represents a rarely studied species,[25] provides impetus for increased attention in the synthesis of cumulenes and allenes,[11] especially in view of recent developments in transition metal catalyzed reactions.[11]

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[13] The low yields of products **6c**, **6d**, and **6j** are undoubtedly due to competitive thermodynamically driven benzylic and methylenedioxy deprotonation which ultimately disfavors *ortho* to *O*-carbamate deprotonation and subsequent *ortho*-Fries rearrangement, even in the presence of excess LTMP (up to 8 equiv) and thus results, by default, in the formation of chromones **5**. In an attempt to trap a thermodynamically generated anion, treatment of **4j** under Martin conditions (**4j**/LTMP/TMSCl = 1:1.5:1.5–1:1.5:3, see T. D. Krizan, J. C. Martin, *J. Am. Chem. Soc.* **1983**, *105*, 6155 – 6157) led to several TMS products including those with benzylic and methylene bridge incorporation (^{1}H NMR spectroscopic evidence). For a viewpoint of the ability of the methylenedioxy group to prevent desired aromatic anionic chemistry under strong base conditions, see C. A. James, PhD thesis, University of Waterloo (Canada), **1998**.

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[28] The observation that γ-proton abstraction and cumulenolate formation is obligatory in these reactions is further corroborated by the failure to obtain a chromone product upon treatment of 2-(3-phenylpropioloyl)phenyl diethyl *O*-carbamate under LTMP reaction conditions.

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