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Synthesis of novel tetracyclic chromenes through carbanion chemistry of 4-methyl coumarins

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Dedicated to Professor K. C. Nicolaou on the occasion of his 60th birthday

Abstract—Various substituents were introduced onto the methyl group in 4-methyl coumarins through lithiation, followed by reactions with a wide range of electrophiles. The presence of an alkoxy group on 6′-phenyl ring was found to be pivotal for the success of this reaction. This procedure provided a convenient synthetic pathway to elaborate the methyl group of 4-methylcoumarins. Application of this methodology was showcased with the synthesis of biologically important novel tetracyclic chromene ring systems ($n = 1$–3).

Coumarin derivatives are widespread in nature.[1] Many of them exhibit a broad spectrum of biological activity such as antiinfective, anticancer, antimyotoxic, phytoestrogenic and phytotoxic activities. Among the numerous naturally occurring coumarins, the 4-substituted coumarins are especially interesting, exhibiting anticancer and HIV-1-reverse transcriptase inhibitory properties.[2] In addition, several coumarin derivatives have been identified as nuclear hormone receptor modulators including SERMs, PRMs and SARMs.[3] Although the biological benefits of the 4-substituted coumarins are widespread, there are very few general methods known to prepare these compounds. Besides the classic synthesis by the Perkin and Pechmann condensations,[4,5] several groups[6,7] have recently reported a palladium-catalyzed carbonylative annulation of internal alkynes for the synthesis of coumarin derivatives.

In conjunction with our work on SERMs (Selective estrogen receptor modulators),[8] we needed to develop a general method to prepare substituted tetracyclic ring system **1** such as benzopyranobenzopyran **1a** ($n = 1$), benzopyranobenzoxapane **1b** ($n = 2$) and benzopyranobenzoxocane **1c** ($n = 3$). These tetracyclic ring systems are excellent at mimicking natural ligands as estrogen receptor modulators. Our approach to such a complex tetracyclic system is described in Scheme 1. We envisioned that this complex tetracyclic ring system could be constructed by intramolecular displacement reaction of 4-substituted coumarins **2** bearing a leaving group. Since coumarins **3** are easily synthesized from Perkin and Pechmann condensations between **4** and **5**,[9] the key step for our synthesis is to establish a general method to synthesize 4-substituted coumarins **2** from **3**. To the best of our knowledge, only two general methods are known to functionalize 4-methyl coumarins. The first one is bromination of 4-methyl group using radical chemistry and the second is allylic oxidation of 4-methyl group to alcohols or aldehydes by selenium oxide.[10] Unfortunately, both methods failed when applied to our electron rich coumarin **3**. In this letter, we wish to report a general method to synthesize 4-substituted coumarins **3** using a carbanion approach. Use of these highly functionalized coumarins in construction of biologically important, novel chromene-derived tetracyclic ring systems **1**(**a**–**c**) is also described.

We envisioned that the 4-methyl group of **3** is acidic enough to be deprotonated by a strong base, such as LDA and LiHMDS, to provide the corresponding lithium homoenolate **6**. We were pleased to observe that the deprotonation of the 4-methyl group of **3** went smoothly upon treatment with LiHMDS (1.5 equiv) at −30 °C in THF. This was evidenced by quenching the

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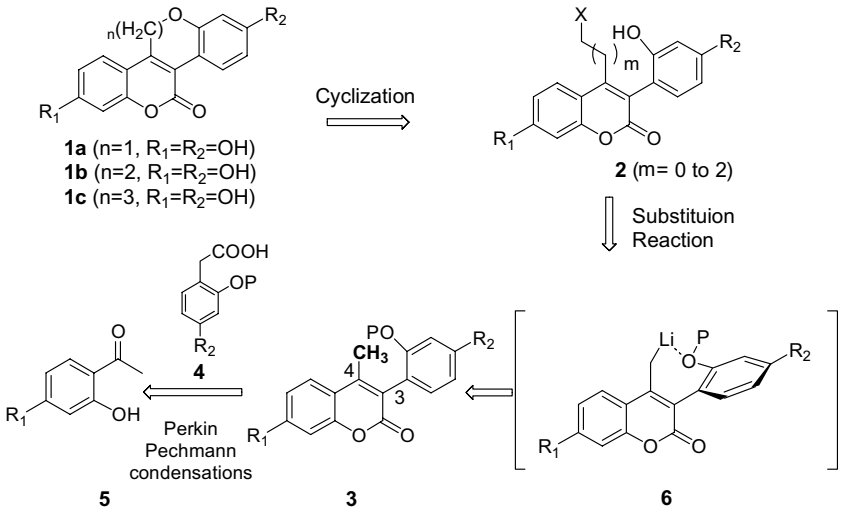


Scheme 1. Synthesis of tetracyclic chromene: retro synthesis.

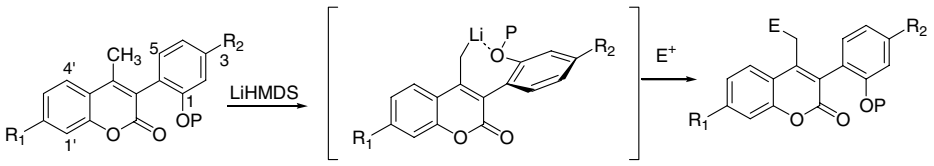
reaction mixture with D_2O. Mono deuterated product **3a**-d_1 was obtained almost exclusively (Table 1, entry 1). Having established a deprotonation condition for 4-methyl coumarins **3**, we then focused our attention to the bromination of **3a**. Again, the deprotonation was carried out using LiHMDS to yield the corresponding homoenolate **6a** (structure not shown). The resulting homoenolate was reacted with several brominating reagents. The reaction with CBr_4 at −78 °C then warmed up to −10 °C over 5 h afforded 33% of brominated product **7a** and about 55% of starting material **3a** was recovered. Several reaction conditions such as increasing the reaction time and adjusting temperature did not improve the yield of these reactions. Reaction of homoenolate **6a** with molecular bromine at −78 °C afforded 88% of **7a** along with 7% of unidentified aromatic bromination products. The best results were obtained when freshly purified NBS was used to react with homoenolate **6a** at −78 °C for 6 h. With the use of NBS, no aromatic bromination was observed. This bromination reaction was used in a large scale preparation of benzopyranobenzopyran **1a** (Scheme 2). Demethylation of **7a** was conveniently accomplished with BBr_3 in dichloromethane at room temperature. In situ treatment of the corresponding tris-phenol with aqueous NaOH solution directly resulted in the formation of benzopyranobenzopyran which was isolated from the alkaline aqueous solution by acid precipitation in more than 89% overall yield for two steps.

For the synthesis of benzopyranobenzoxapane **1b** ($n = 2$), we needed one carbon homologation of **3**. When the solution of the homoenolate of **3a** or **3b** was treated with benzaldehyde at −78 °C, it resulted in an aldol like product **7b** in 78% and **7c** in 83%, respectively. Encouraged by these results, we carried out similar reactions with freshly prepared formaldehyde. All attempts to react with formaldehyde and *para*-formaldehyde failed to give any product **7d** or **7e**. Reactions of homoenolate with freshly prepared formaldehyde (as gas or solution in THF) at various conditions resulted in no reaction (Table 1, entries 7 and 8). At this point, our attention was drawn to SEMCl as an electrophile to carry out one carbon homologation of **3**. To our satisfaction, when the Li-homoenolate of **3a–c** was reacted with SEMCl, it provided SEM homologated product **7f–i** in high yields ranging from 67–81%. As expected, the reaction with MOMCl, MOMBr and CH_3I also produced substituted coumarins **7j–n** in high yields. Compounds **7f** and **7j** were successfully used in the synthesis of benzopyranobenzoxapane **1b** ($n = 2$). The global deprotection of protecting groups was carried out using BBr_3 in CH_2Cl_2, followed by cyclization under Mitsunobu protocol to give **1b** in 73% overall yield for two steps (Scheme 3).

It is interesting to note that, the homoenolate formed from **3e** (OP is absent, Table 1, entry 12), it produced no desired product **7i** with SEMCl under all attempted conditions. Instead, we isolated an undesired product **10** (ca. 12%). We believe that the majority of intermediate **9** may have formed preferentially upon reaction with SEMCl but decomposed during work-up to give back starting material **3e** (Scheme 4). The possibility that the homoenolates failed to form was ruled out with D_2O experiment (Table 1, entry 13). The results suggest that the *ortho* alkoxy group might be playing a key role in directing the electrophilic addition reaction with homoenolate **6**.

For two-carbon and three-carbon elongation reactions, homoenolates of **3c** and **3b** were reacted with α-chloroacetyl chloride to yield products **7o** and **7p** in good yields. (Table 1, entries 20 and 21). To our delight, when homoenolates of **3b** and **3d** were treated with allyl bromide, homo allyic coumarins **7q** and **7u** were obtained in excellent yields. Compound **7o** was converted to benzopyranone **1c** (X=O) in a one-pot reaction. The global deprotection of SEM groups was achieved by 1 N HCl, followed by treatment with 2 N NaOH to give **1c** (X=O) in 96% yield. The synthesis of benzopyranobenzoxacane **1d** ($X=H_2$) was achieved in four steps starting from homo allylic coumarin **7q**. The first step is the oxidation of double bond using catalytic amount of OsO_4

Table 1. 4-Substituted coumarins

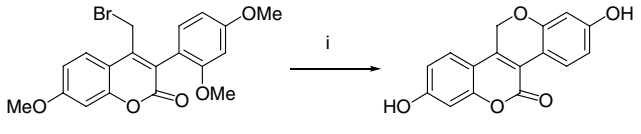


3 **6** **7**

Entry	SM[a]	OP	R_1	R_2	E^+	Product, E	Conditions[b,c,d]	Yield (%)
1	**3a**	OMe	OMe	OMe	D_2O	**3a**-d_1, D–	−30 °C/10 min.[f]	>90
2	**3a**	OMe	OMe	OMe	CBr_4	**7a**, Br–	−10 °C, 5 h[f]	33
3	**3a**	OMe	OMe	OMe	Br_2	**7a**	−78 °C, 15 min[e]	88
4	**3a**	OMe	OMe	OMe	NBS	**7a**	−78 °C, 8 h[e]	82
5	**3a**	OMe	OMe	OMe	PhCHO	**7b**, PhCH(OH)–	−78 °C, 8 h[e]	78
6	**3b**	OMe	OMe	H	PhCHO	**7c**, PhCH(OH)–	−78 °C, 8 h[e]	83
7	**3a**	OMe	OMe	OMe	H_2CO	**7d**, $HOCH_2$–	−78 °C, 8 h[e]	0
8	**3c**	OSEM	OSEM	OSEM	H_2CO	**7e**, $HOCH_2$–	−78 °C, 8 h[e]	0
9	**3a**	OMe	OMe	OMe	SEMCl	**7f**, SEM–	−10 °C, 28 h[f]	81
10	**3b**	OMe	OMe	H	SEMCl	**7g**, SEM–	−10 °C, 28 h[f]	77
11	**3d**	OMe	F	H	SEMCl	**7h**, SEM–	−10 °C, 28 h[f]	67
12	**3e**	Absent	OMe	H	SEMCl	**7i**, SEM–	−10 °C, 28 h[f]	Trace
13	**3e**	Absent	OMe	H	SEMCl	**3e**-d_1, D–	−30 °C/10 min.[f]	>90
14	**3a**	OMe	OMe	OMe	MOMBr	**7j**, MOM–	−20 °C, 28 h[f]	77
15	**3b**	OMe	OMe	H	MOMBr	**7k**, MOM–	−20 °C, 28 h[f]	81
16	**3b**	OMe	OMe	OMe	MOMCl	**7j**, MOM–	−10 °C, 28 h[f]	67
17	**3d**	OMe	F	H	MOMBr	**7l**, MOM–	−20 °C, 28 h[f]	83
18	**3c**	OSEM	OSEM	OSEM	MOMBr	**7m**, MOM–	−20 °C, 28 h[f]	76
19	**3b**	OMe	OMe	OMe	CH_3I	**7n**, CH_3–	−30 °C, 28 h[f]	97
20	**3c**	OSEM	OSEM	OSEM	$ClCH_2COCl$	**7o**, $ClCH_2CO$–	−78 °C, 2 h[e]	66
21	**3b**	OMe	OMe	OMe	$ClCH_2COCl$	**7p**, $ClCH_2CO$–	−78 °C, 2 h[e]	82
22	**3a**	OMe	OMe	OMe	$CH_2{=}CHCH_2Br$	**7q**, $CH_2{=}CHCH_2$–	−30 °C, 16 h[f]	77
23	**3d**	OMe	F	H	$CH_2{=}CHCH_2Br$	**7u**, $CH_2{=}CHCH_2$–	−30 °C, 18 h[f]	86

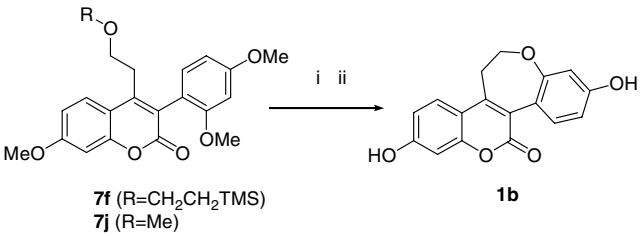
[a] Compounds **3**(**a**–**e**) were prepared by a modified protocol of Perkin and Pechmann condensation (see Ref. 4).
[b] Anhydrous THF was used as solvent.
[c] 1 M LiHMDS in THF (Aldrich) was used in all reactions.
[d] Enolization was carried out at −30 °C.
[e] The enolization was carried out at −30 °C and then cooled down to −78 °C and electrophile was added.
[f] The electrophile was added at −30 °C and then warmed to the respective temperature. General experimental procedure for the formation of homoenolates of 4-methyl coumarins and reactions with electrophiles illustrated with preparation of **7f**: A 200 mL single neck flask was charged with lithium bis(trimethylsilyl)amide ($(TMS)_2NLi$, 16 mL 1 M solution in THF, 16 mmol). 3-(2,4-Dimethoxy-phenyl)-7-methoxy-4-methyl-chromen-2-one (3.45 g, 10.6 mmol, 1.51 equiv) in anhydrous THF (105 mL) was added to the reaction mixture over a 10-min period stirred at −30 °C for 45 min. (2-Chloromethoxy-ethyl)-trimethyl-silane (1.95 g, 11.7 mmol) was added to the reaction mixture over a 10-min period at −30 °C and stirring was 11.7 mmol continued at −10 °C for 12 h. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl (250 mL) and extracted with EtOAc (250 mL). The organic phase was condensed in vacuo at 60 °C to yield a crude product which was purified by flash chromatography to yield the title compound **7f** as a white solid. MS (Cl) *m*/*z* 456 (M^+), 457 (M+H, loop positive). HRMS, *m*/*z* calcd for (M^+) 456.1968; found 456.1979. ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (1H, d, $J = 8.8$ Hz), 7.11 (1H, d, $J = 8.8$ Hz), 6.93–6.89 (2H, m), 6.62–6.59 (2H, m), 3.92 (3H, s), 3.88 (3H, s), 3.79 (3H, s), 3.51 (2H, t, $J = 7.6$ Hz), 3.42–3.35 (m, 2H), 3.03–2.83 (m, 2H), 0.89 (3H, t, $J = 7.8$ Hz), 0.01 (9H, s). ^{13}C NMR (400 MHz, $CDCl_3$): 163.57, 162.70, 162.62, 159.66, 156.31, 151.03, 133.11, 127.82, 123.50, 117.37, 114.93, 113.58, 106.22, 102.25, 100.52, 69.90, 69.48, 57.19, 56.97, 56.82, 31.87, 19.49, 0.01.

and $NaIO_4$ with 2,6-lutidine protocol,[11] followed by $NaBH_4$ reduction[12] to yield primary alcohol **2b**. The primary alcohol was converted to bromide using CBr_4/PPh_3 in 85% yield.[13] The global deprotection of all three methyl groups was effected by BBr_3, followed by spontaneous cyclization in 20% w/v NaOH to afford benzopyranobenzoxacane **1d** in 65% yield (Scheme 5).



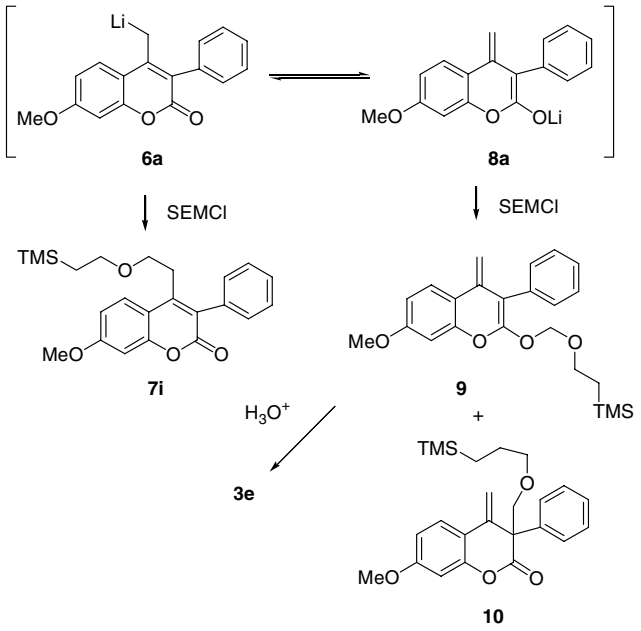
7a **1a**

Scheme 2. Synthesis of benzopyranobenzopyran. Reagents and conditions: BBr_3, CH_2Cl_2, rt, 14 h, followed by workup with 20% NaOH (aq) and 2 N HCl (aq). Yield, 89%.



7f (R=CH_2CH_2TMS)
7j (R=Me) **1b**

Scheme 3. Synthesis of benzopyranobenzoxapane. Reagents and conditions: (i) BBr_3, CH_2Cl_2, rt, 14 h, followed by workup with 20% NaOH (aq) and 2 N HCl (aq). (ii) DIAD, PPh_3, THF, 26 h. Overall yield 73% (for **7f**), 77% (for **7j**).



Scheme 4. Proposed mechanism associated with regioselectivity.

In summary, we have developed a highly efficient and divergent methodology to elaborate the 4-methyl group in 4-methyl coumarins through anion chemistry. The homoenolates are reactive enough to undergo reactions with a wide range of electrophiles, including carbon electrophiles. This procedure offered easy access to the synthesis of coumarins with complex substitutions at 4-position. Application of this methodology was showcased with the synthesis of biologically important tetracyclic ring systems **1**.[8]

Supplementary data

Supplementary data (^{1}H and ^{13}C NMRs) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.047.

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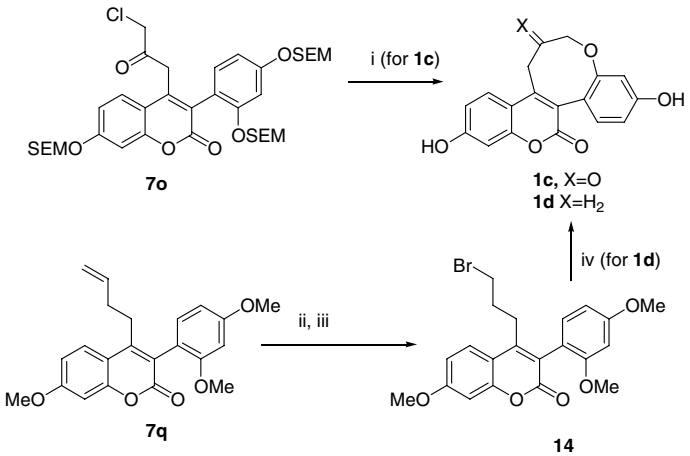

Scheme 5. Synthesis of benzopyranobenzoxacane. Reagents and conditions: (i) 1 N HCl (aq)–THF–CH_3CN (1:1:1), 3 h, followed by 2 N NaOH. Yield, 96%. (ii) OsO_4 (0.02 equiv), $NaIO_4$ (4.0 equiv), 2,6-lutidine (2.0 equiv), dioxane–water (3:1) followed by $NaBH_4$ (0.5 equiv). Yield 88%. (iii) CBr_4 (3.0 equiv), PPh_3 (3.0 equiv), CH_2Cl_2, 12 h, rt. Yield, 85%. (iv) BBr_3, CH_2Cl_2, 0 °C, rt, followed by work-up with 20% NaOH. Yield 65%.

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