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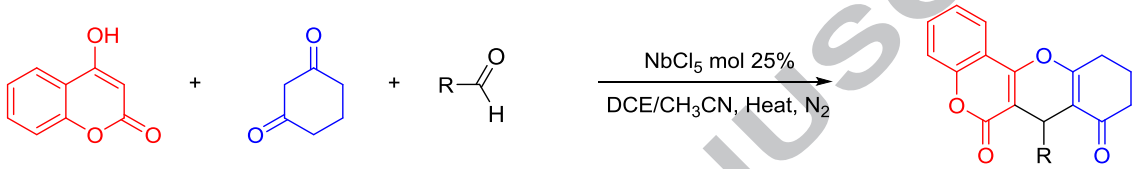

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New Method for the Synthesis of Chromeno[4,3-b]chromene Derivatives via Multicomponent Reaction Promoted by Niobium Pentachloride

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ABSTRACT

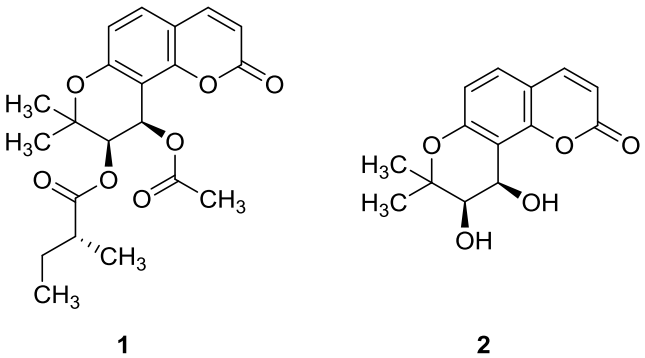
Chromeno[4,3-b]chromene derivatives were synthesized from multicomponent reaction between 4-hydroxycoumarin, aryl aldehyde derivatives and 1,3-cyclohexanedione promoted by niobium pentachloride. This new method is simple, cost-effective, provides good yields with good substrate generality and can be conducted in short reaction times.

Introduction

Heterocyclic compounds of natural and synthetic occurrence containing coumarin nuclei has aroused the interest of several research groups around the world since, for this class of compounds has a wide range of biological activities,[1,2] such as: antibacterial, anticoagulant, antiviral, antifungal, anticancer and anti-inflammatory.[3] The coumarins were isolated from clover flowers (Melilotus officinalis) and Cumaru seeds for the first time by Vogel in 1820, and the first synthesis was conducted in 1868 by Sir William Henry Perkin.[4]

Currently, more than 1400 species of coumarin were described in the literature. They are found in many different families of the plant kingdom, such as Papilonaceae (Fabaceae), Lamiaceae, Asteraceae, Solanaceae, Poaceae, Umbelliferae, and especially Apiaceaee Rutaceae, which are more abundant.[5,6] The coumarins strongly absorb in the visible light region, which makes this class of compounds promising molecules which can potentially be used in Dye Sensitized Solar Cells (DSSCs).[7-14]

On the other hand, bicyclic heterocyclic compounds, with oxygen as heteroatom, that present in its structure the fusion of the benzene ring with the 2*H*-pyran or 4*H*-pyran rings are designated 2*H*-chromene (2*H*-1-benzopyran) and 4*H*-chromene (4*H*-1-benzopyran).[15] Chromene derivatives often appear as important structural components on biologically active natural compounds. Chromene fragments can occur in alkaloids, flavonoids, tocopherols, and anthocyanins. In addition, functionally substituted chromenes have played an increasingly important role in synthetic approaches in compounds with potential application in the field of medicinal chemistry.[16-18] Chromenes can occur in various natural extracts, such as visnadine (**1**) used as coronary and peripheral vasodilator extracted from the fruit of *Ammi visnaga*[19] and Khellactone (**2**) extracted from *Phlojodicarpus sibiricus*, which has vasodilatory properties[20] (Figure 1).



1 **2**

Fig. 1. Visnadine **1** and Khellactone **2** structures

Due to the large application of chromene derivatives, several methods of preparation were described in the literature, of which we can mention: copper-catalyzed intramolecular coupling of aryl bromides with 1,3-dicarbonyls,[21] cycloaddition reaction between propargylic alcohols with 2-naphthols or phenols

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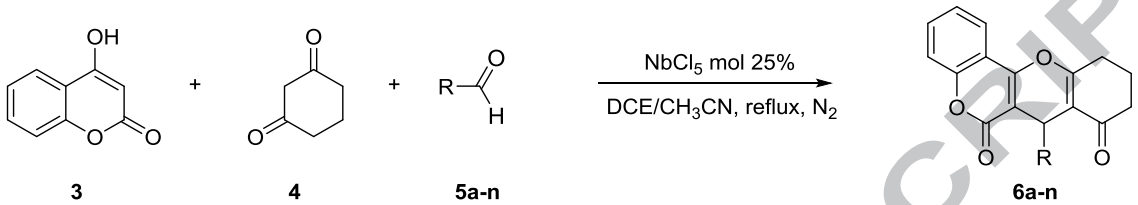
bearing electron-donating groups, via allenylidene intermediates, leading to the formation of the respective 1H-naphtho[2,1-b]pyrans and 4H-1-benzopyrans,[22] cyclization reaction between different substituted α,α-dicyanoolefins with β-naphthol in the presence of efficient bifunctional thiourea catalyst,[23] among others.[24-33]

As part of our research interest on synthetic methodologies by using niobium pentachloride,[34-49] we wish to present in this work a new method for the synthesis of chromeno[4,3-b]chromene derivatives (**6a-n**) via multicomponent reaction between 4-hydroxycoumarin (**3**), 1,3-cyclohexanedione (**4**) and different aryl aldehydes (**5a-n**) promoted by niobium pentachloride (scheme 1). $NbCl_5$ is highly electrophilic, making possible act as a Lewis acid, have a low-cost commercial, and has been used by our group and other researchers as an effective catalyst in synthetic methodologies in a variety of reactions, obtaining excellent results.[50-57]



3 **4** **5a-n** **6a-n**

Scheme 1. MCR of 4-hydroxycoumarin (**3**), 1,3-cyclohexanedione (**4**) and aryl aldehydes (**5a-n**) promoted by $NbCl_5$

Results and discussion

Firstly, the multicomponent reaction between 4-hydroxycoumarin (**3**) (1.0 equiv.), 1,3-cyclohexanedione (**4**) (1.0 equiv.) and benzaldehyde (**5a**) (1.0 equiv.) in the presence of different concentrations (0.0, 10, 25 and 50 mol%) of niobium pentachloride and different solvents (acetonitrile, dichloromethane and 1,2-dichloroethane), was used as a model in order to develop a protocol for the optimization of the reaction conditions. The reaction was performed under N_2 atmosphere. The results are summarized in Table 1.

As shown in Table 1, we were unable to obtain the expected product by using 0.0 mol% of $NbCl_5$, independent of the solvent. The use of 25 mol% of $NbCl_5$ produced the best results for the tested solvents, in which the mixture of DCE/CH_3CN (70:30) presented the best yield (74% in 2 hours) (entry 15, Table 1). With 50 mol % of $NbCl_5$, degradation of the product and formation of by-products were observed, resulting in a reduction in yielding. Based on these results, it was established that Entry 15 (Table 1) presents the best reaction conditions to be applied in the reactions with the other studied aldehydes (**5b-n**). We hypothesize that the low solubility of the same aldehydes and reactive intermediates may explain the differences in the product yields when the solvent mixtures varied (entries 13-20, Table 1).

We investigated the reaction profile of this reaction by using other aldehydes (**5b-n**) containing electron-donating and electron-withdrawing groups obtaining the chromeno[4,3-b]chromene derivatives (**6b-n**) in analogous yields. The results are summarized in Table 2. The products were purified by recrystallization in two steps; the first recrystallization was done from ethanol and the second recrystallization from ethyl acetate. The products were characterized by spectroscopic and spectrometric methods.[58]

Table 1. Optimization of multicomponent reaction between 4-hydroxycoumarin (**3**), 1,3-cyclohexanedione (**4**) and benzaldehyde (**5a**) promoted by $NbCl_5$.[a]

Entry	$NbCl_5$ (mol %)	Solvent	Time (h)	Yield[b] (%)
1	0	DCM	24	-
2	10	DCM	2	15
3	25	DCM	2	21
4	50	DCM	2	18
5	0	DCE	24	-
6	10	DCE	2	18
7	25	DCE	2	29
8	50	DCE	2	20
9	0	CH_3CN	24	-
10	10	CH_3CN	2	10
11	25	CH_3CN	2	15
12	50	CH_3CN	2	Trace
13	25	DCE/CH_3CN 50:50	2	53
14	25	DCE/CH_3CN 60:40	2	59
15	25	DCE/CH_3CN 70:30	2	74
16	25	DCE/CH_3CN 80:20	2	58
17	25	DCM/CH_3CN 50:50	2	18
18	25	DCM/CH_3CN 60:40	2	35
19	25	DCM/CH_3CN 70:30	2	41
20	25	DCM/CH_3CN 80:20	2	38

a) Reaction conditions: 4-hydroxycoumarin (**3**) (1.0 mmol), 1,3-cyclohexanedione (**4**) (1.0 mmol), benzaldehyde (**5a**) (1.0 mmol) and $NbCl_5$ (0–50 mol %) in DCM (4.0 ml), DCE (4.0 ml), CH_3CN (4.0 ml), mixture DCE/CH_3CN (4.0 ml) (50:50, 60:40, 70:30, 80:20) in $NbCl_5$ 25 mol % and mixture DCM/CH_3CN (4.0 ml) (50:50, 60:40, 70:30, 80:20) in $NbCl_5$ 25 mol % at reflux, under N_2 atmosphere. b) isolated yields.

Table 2. Results for the synthesis of chromeno[4,3-b]chromene derivatives (**6a-n**)

Aryl aldehyde	R	Yield (%)*
5a	C_6H_5	74 (**6a**)[29,30]
5b	4-$CH_3C_6H_4$	67 (**6b**)[29,31]
5c	4-$COOHC_6H_4$	70 (**6c**)
5d	4-$OCH_3C_6H_4$	68 (**6d**)[29,31,32]
5e	2-$OCH_3C_6H_4$	60 (**6e**)[31,32]
5f	4-OH-3-$OCH_3C_6H_3$	75 (**6f**)[29,30]
5g	4-$NO_2C_6H_4$	58 (**6g**)[29,31,32]
5h	4-BrC_6H_4	56 (**6h**)[31,32]
5i	2-BrC_6H_4	53 (**6i**)[31,32]
5j	4-$C_6H_5C_6H_4$	55 (**6j**)[33]
5k	C_4H_3S	71 (**6k**)[30]
5l	4-$(CH_3)_2NC_6H_4$	62 (**6l**)
5m	CH_3	63 (**6m**)
5n	$CH{=}CHC_6H_5$	55 (**6n**)

* Isolated yields.

The results in Table 2 show that by using 1.0 equivalent of $NbCl_5$ and a reaction time of 2 hours, it was possible to obtain chromeno[4,3-b]chromene derivatives (**6a-n**) with good yields (53-75%), under N_2 atmosphere and reflux. Large yield differences were not observed by changing the benzaldehyde derivative. Besides, these methodology was applied successfully on aliphatic aldehyde and corresponding chromeno[4,3-b]chromene derivatives were obtained in good yields.

For comparison, our results for the multicomponent reaction between 4-hydroxycoumarin (**3**) (1.0 mmol), 1,3-cyclohexanedione (**4**) (1.0 mmol) and 4-nitrobenzaldehyde (**5g**) (1.0 mmol) were compared with other studies described in the literature (Table 3).[29]

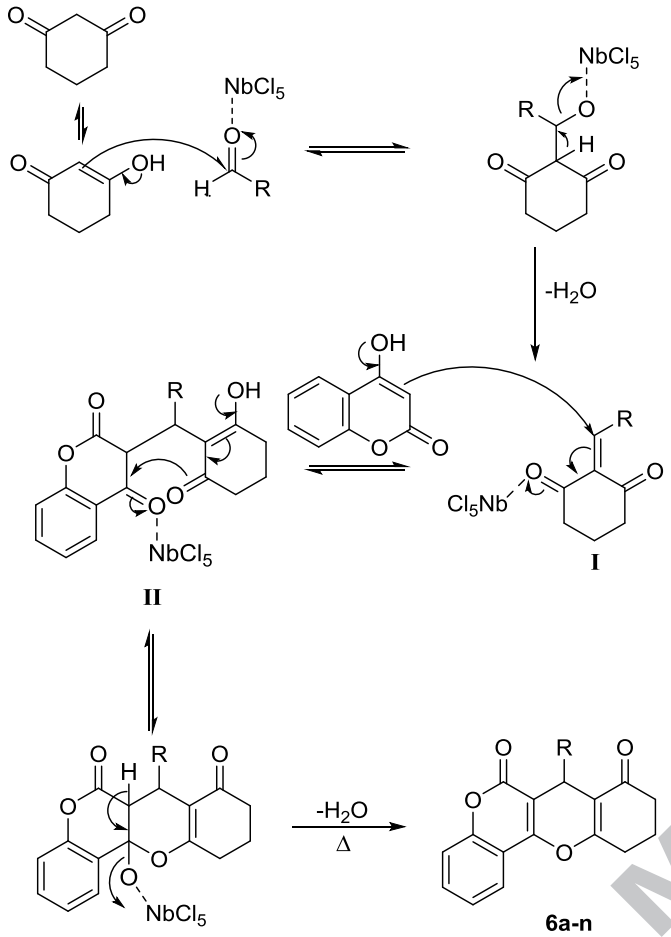
Table 3. Comparison between different Lewis acids in the synthesis of chromeno[4,3-b]chromene derivatives.

Lewis acid	Solvent	Time (h)	Yield (%)
None	DCE/CH_3CN 70:30	24	-
$NbCl_5$*	DCE/CH_3CN 70:30	2	58
$NbCl_5$*	CH_3CN	2	10
$FeCl_3$**	CH_3CN	6	40
$MgCl_2$**	CH_3CN	6	20
$ZnCl_2$**	CH_3CN	6	20

* Reaction conditions: 4-hydroxycoumarin (**3**) (1.0 mmol), 1,3-cyclohexanedione (**4**) (1.0 mmol), 4-nitrobenzaldehyde (**5g**) (1.0 mmol) and 25 mol % of $NbCl_5$, at reflux, under N_2 atmosphere.
** Reaction conditions: 4-hydroxycoumarin (**3**) (1.0 mmol), 1,3-cyclohexanedione (**4**) (1.0 mmol), 4-nitrobenzaldehyde (**5g**) (1.0 mmol) and 10 mol % $FeCl_3$ or $MgCl_2$ or $ZnCl_2$, at reflux.

When compared with other Lewis acids,[29] niobium pentachloride is more effective, requiring shorter reaction times and providing better yields. These notable features make this procedure a useful and attractive process for the synthesis of chromeno[4,3-b]chromene derivatives, compounds with high biological interest.

In a recently published study by our research group, we described a new synthetic method for xanthenedione derivatives in the presence of $NbCl_5$ between 1,3-cyclohexanedione (**4**) and aryl-aldehydes.[54] Based on this work and our experimental results we proposed a plausible mechanism that begins with the Knoevenagel condensation reaction between the enol form of 1,3-cyclohexanedione (**4**) and aldehydes activated by $NbCl_5$ followed by the elimination of H_2O, producing, as intermediate, the β-dicarbonyl enone (**I**), which can act as Michael acceptors. The β-dicarbonyl enone (**I**) forms a complex with $NbCl_5$, and can be attacked by 4-hydroxycoumarin (**4**) via Michael addition, giving rise to a novel intermediate **II** that can be readily converted into the product by an intramolecular hemiketalization followed by loss of water in the presence of $NbCl_5$, leading to **6a-n** products.



Scheme 2. Mechanistic proposal for multicomponent reaction promoted by $NbCl_5$.

Finally, we can conclude that the use of niobium pentachloride as a promoter agent in the multicomponent reaction between 4-hydroxycoumarin (**3**), 1,3-cyclohexanedione (**4**) and aryl aldehydes (**5a-n**), produces chromeno[4,3-b]chromene derivatives (**6a-n**) with good-yielding, good substrate generality and in short reaction times.

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(58) General procedure for synthesis of chromeno[4,3-b]chromene derivatives (**6a-n**): To a solution of $NbCl_5$ (67.5 mg, 0.25 mmol) dissolved in 1.0 mL of the mixture of anhydrous solvents DCE/CH_3CN (0.7:0.3 mL), were added a solution of 4-hydroxycoumarin (**3**) (162.0 mg, 1.0 mmol), 1,3-cyclohexanedione (**4**) (112.0 mg, 1.0 mmol) and the respective aldehyde (**5a**–**n**) (1.0 mmol) in 3.0 mL of anhydrous DCE/CH_3CN (2.1:0.9 mL), under N_2 atmosphere. The reaction mixture was stirred at reflux for 2 hours. After this time, the reaction was poured into water and the product was extracted with dichloromethane. The organic layer was concentrated under reduced pressure. The products (**6a-n**) were obtained by recrystallization in two steps, the first recrystallization was done from ethanol and a second recrystallization from ethyl acetate. 7-phenyl-7,9,10,11-tetrahydro-6H,8H-chromeno[4,3-b]chromene-6,8-dione (**6a**): White solid. **NMR ^{1}H** ($CDCl_3$, 400 MHz, 25°C, TMS): δ = 7.89 (dd, J = 8.1; 1.5 Hz, 1H); 7.60-7.54 (m, 1H); 7.40-7.37 (m, 2H); 7.35-7.29 (m, 2H); 7.26-7.25 (m, 1H); 7.23-7.13 (m, 2H); 5.00 (s, 1H); 2.93-2.84 (m, 1H); 2.84-2.72 (m, 1H); 2.70-2.52 (m, 2H); 2.48-2.39 (m, 2H) ppm. **NMR ^{13}C** ($CDCl_3$, 100 MHz, 25°C, TMS): δ = 196.9; 163.5; 160.3; 153.6; 152.3; 144.0; 131.9; 128.3; 127.8; 126.8; 126.1; 123.9; 116.6; 115.4; 113.3; 105.3; 36.6; 33.0; 26.8; 19.9 ppm.

Supplementary Material

Supplementary data associated with this article can be found in the online version.

Highlights

- Chromeno[4,3-b]chromene derivatives are an important class of organic compounds

- Synthesis of Chromeno[4,3-b]chromene derivatives by MCR promoted by $NbCl_5$

- Synthesis of Chromeno[4,3-b]chromene derivatives in mild reaction conditions