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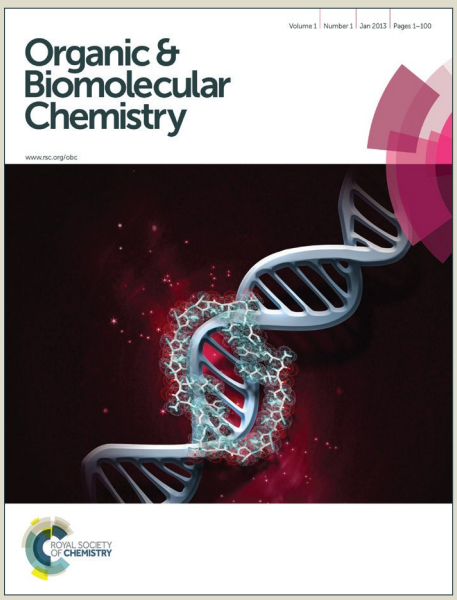

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ARTICLE

Bi(OTf)$_3$-Catalyzed Addition of Isocyanides to 2*H*-Chromene Acetals: An Efficient Pathway for Accessing 2-Carboxamide-2*H*-Chromenes

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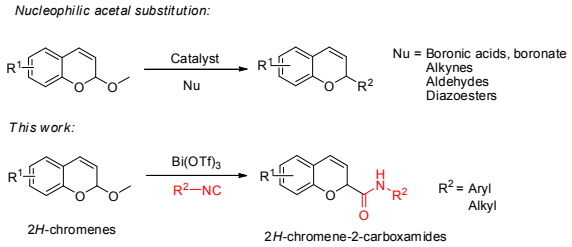
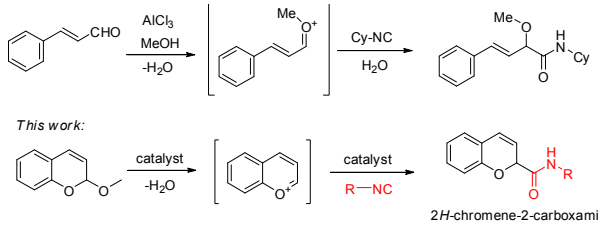
Bismuth triflate (Bi(OTf)3) is identified as an efficient catalyst for the direct addition of isocyanides to 2*H*-chromene acetals. A large scope of isocyanides and chromene acetals are suitable substrates in this catalyst system. By this synthetic strategy, a polyfunctional molecular scaffold, 2-carboxamide-2*H*-chromenes could be prepared efficiently in one step up to 95% yield. In addition, this efficient and practical protocol proceeded smoothly in gram scale even the catalytic loading was reduced to 2 mol%.

2-Substituted 2*H*-Chromenes and their analogs are important flavonoid skeletal structures, which are found in a wide variety of natural products and pharmaceutically active molecules.[1] These compounds have been identified as having antifungal, antibacterial, antiviral, antitumor, anti-inflammatory, anticancer, antidepressive, antihypertensive, antidiabetic, and antioxidant activities.[2] They are also valuable intermediates in synthetic and material chemistry.[3] Due to the vital phytological and pharmaceutical activities of these compounds, as well as the importance in synthetic chemistry, the exploring of new synthetic routes to construct 2-substituted 2*H*-chromenes attracts continuous interests in this area.



Scheme 1 Synthetic strategies for 2-substituted-2*H*-chromenes.

Nucleophilic acetal substitution of 2*H*-chromene acetals offers a versatile solution to the synthesis of 2-substituted 2*H*-chromenes directly. Several nucleophilic acetal substitution reactions have been developed to access this scaffold (Scheme 1). Boronic acids and boronates as suitable nucleophiles were described as a modular and highly efficient protocol for the synthesis of 2-vinyl- and 2-aryl-2*H*-chromenes. Schaus reported a tartaric acid derived Brønsted acid and Yb(OTf)$_3$ catalyzed addition of boronates to 2*H*-chromene acetals in good yields with high enantioselectivities.[4] They aslo use a nickel-catalyzed cross-coupling of chromene acetals and boronic acids was developed by Doyle's group.[5] Watson developed the enantioselective Cu(I)-catalyzed addition of terminal alkynes to isochromane acetal and chromenes acetals.[6] A synergistic catalytic system for the addition of aldehydes to oxocarbenium ions has been developed by Rueping's group.[7] The reaction of diazoacetate with 2*H*-chromene acetals was also realized by using BINOL–phosphoric acid and Yb(OTf)$_3$ catalyst.[8] Lewis- and Brønsted-acid catalyzed insertion of isocyanides into the carbon-oxygen bond of cyclic ketals and acetals was also reported.[9] Nevertheless, concise, efficient, and diversified methods for the synthesis of 2-carboxamide-2*H*-chromenes under mild conditions are still in demand.



Scheme 2 Synthetic strategies for2-Carboxamide-2*H*-Chromenes.

In our previous work on *O*-alkylative Passerini reaction of isocyanides, aldehydes and alcohols, we proposed the mechanism that cinnamaldehyde reacts with alcohol to generate oxocarbenium species which is attacked by isocyanide to give α-alkoxy-β,γ-enamide.[10] Catalyzed by Lewis or Brønsted acid, 2*H*-chromenes was known for the in situ generation of oxocarbenium ions[4-8], then it is highly

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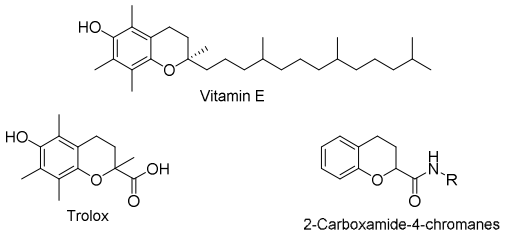
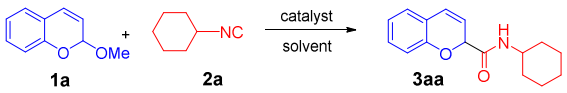
practicable to add isocyanide to 2*H*-chromenes to form 2-carboxamide-2*H*-chromenes. Moreover, 2-carboxamide-chromanes have been shown more potent antioxidants than Vitamin E and Trolox which are also comprised with chroman skeleton.[11] In addition, 2-carboxamide-4-chromanes have been shown to exert a beneficial action through the specific inhibition of transcription factor NF-κB.[12]



Scheme 3 Examples of chromanes with antioxidant activity.

We embarked this investigation using chromene acetal **1a** and cyclohexyl isocyanide (Cy-NC) **2a** as benchmark substrates. To our delight, moderate yields could be obtained catalyzed by several Lewis acids. Selected results are summarized in table 1. Among them, $Bi(OTf)_3$ was the most efficient catalyst which gave the expected N-cyclohexyl-2*H*-chromene-2-carboxamide **3aa** in 73% yield (entry 4, Table 1). The other Lewis acids, such as $AlCl_3$, $In(OTf)_3$ were also effective in the reaction, while lower yields were obtained (entries 1-8). The dioxane was indicated best solvent for this catalyst system among toluene, CH_3CN, CH_2Cl_2 and THF (entires 9-12). The reaction temperature and ratio of chromene acetal **1a** and cyclohexyl isocyanide (Cy-NC) **2a** were also investigated (entries 13-15). The yield was improved to 80% when 1.5 or 2.0 equivalent isocyanide was used instead of 1.2 equivalent isocyanide (entries 15, 16). Moreover, a suitable mount of H_2O was favorable for the formation of 2*H*-chromene-2-carboxamides. Interestingly, the yield was increased from 80% to 85% when 2 equivalent of H_2O (0.009 mL, 0.5 mmol) was added (entry 17). When the reaction was carried in Dioxane/H_2O = 10:1 (volume ratio), the best yield 95% was obtained (entry 18).

Table 1 Optimization of the reaction conditions of additional reaction of chromene acetal **1a** and cyclohexyl isocyanide (Cy-NC) **2a** for accessing *N*-cyclohexyl-2*H*-chromene-2-carboxamide **3aa**.[a]

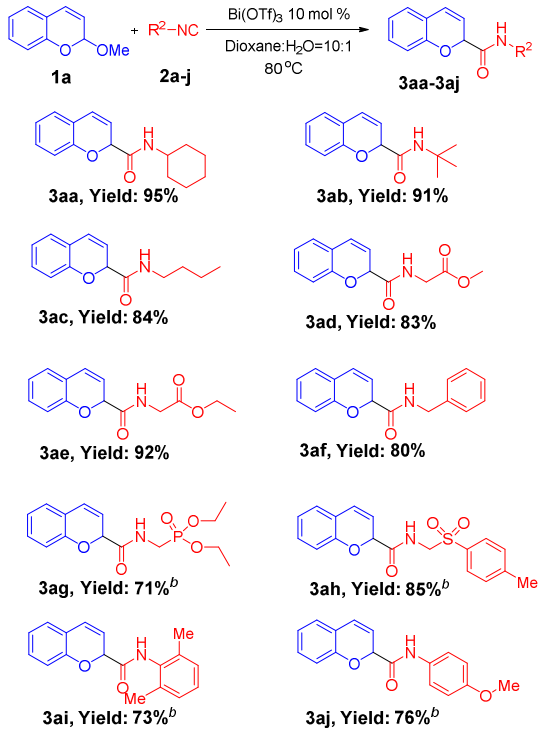


Entry	Catalyst (10 mol%)	Solvents	T. (°C)	Time (h)	Yield (%)[b]
1	$AlCl_3$	Dioxane	80	20	37
2	$BiCl_3$	Dioxane	80	20	31
3	$InCl_3$	Dioxane	80	20	trace
4	$Bi(OTf)_3$	Dioxane	80	20	73
5	$Zn(OTf)_2$	Dioxane	80	20	41
6	$Fe(OTf)_3$	Dioxane	80	20	40
7	$In(OTf)_3$	Dioxane	80	20	61
8	AgOTf	Dioxane	80	20	trace
9	$Bi(OTf)_3$	THF	80	20	32
10	$Bi(OTf)_3$	Toluene	80	20	29
11	$Bi(OTf)_3$	CH_3CN	80	20	trace
12	$Bi(OTf)_3$	DCM	80	20	5
13	$Bi(OTf)_3$	Dioxane	r.t.	48	60
14	$Bi(OTf)_3$	Dioxane	50	24	67
15[c]	$Bi(OTf)_3$	Dioxane	80	20	80
16[d]	$Bi(OTf)_3$	Dioxane	80	18	80
17[c, e]	$Bi(OTf)_3$	Dioxane	80	20	85
18[c, f]	$Bi(OTf)_3$	Dioxane	80	20	95

[a]Reaction conditions: To a solution of 10 mol % catalysts in 1.0 mL solvent added chromene acetal **1a** (0.25 mmol, 1.0 equiv) and Cy-NC **2a** (1.2 equiv) in sequence. The reaction mixtures were stirred at 80 °C for 20 h unless otherwise noted. [b] Isolated yield. [c] 1.5 equiv of **2a** was used in 80 °C for desired time. [d] 2.0 equiv of **2a** was used in 80 °C for desired time. [e] H_2O (2 equiv) was added. [f] dioxane/H_2O = 10:1 (1.0 mL) was used as mixture solvent.

With the optimized reaction conditions in hand, a series of 2-carboxamide-2*H*-chromenes were synthesized successfully. As shown in table 2, the reaction between chromene acetal **1a** and various isocyanides **2a-j** proceeded smoothly to give corresponding 2-carboxamide-2*H*-chromenes in 71-95% yields. Both aliphatic and aromatic isocyanides were suitable substrates in this catalytic system. In some cases, 2 equiv of isocyanide was desired to give better yields (**3ag, 3ah, 3ai** and **3aj**). The steric effect of isocyanides showed no obvious influence on the yields of products. 91% and 84% yields were obtained for **3ab** and **3ac** with *tert*-butyl isocyanide **2b** and *n*-butyl isocyanide **2c** separately.

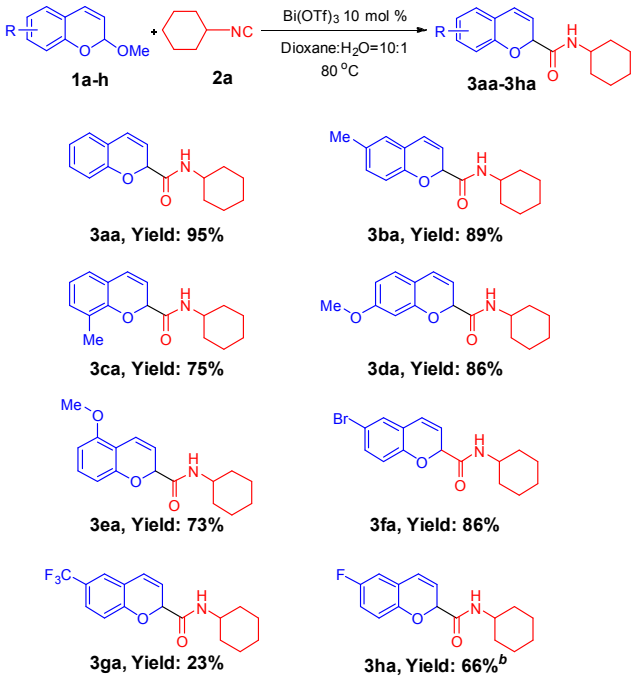
Table 2 The scope of synthesis of 2-carboxamide-2*H*-chromenes with chromene acetal **1a** and various isocyanides **2a-2j**.[a]



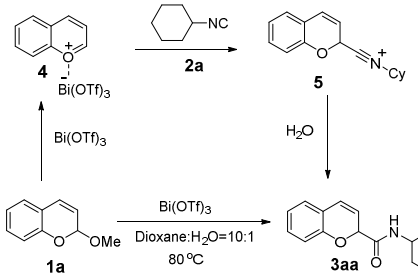
[a] Reaction conditions: To a solution of 10 mol % $Bi(OTf)_3$ in 1.0 mL dioxane/H_2O (10:1) added chromene acetal **1a** (0.25 mmol, 1.0 equiv) and isocyanides **2a-2j** (1.5 equiv) in sequence. The reaction mixtures were stirred at 80 °C for 20 h unless otherwise noted. All were isolated yield. [b] 2 equiv of isocyanides **2g-2j** was used in 80 °C for 20 h.

To further investigate the substrate scope, a series of substituted 2*H*-chromene acetals **1b**-**1i** were investigated as shown in table 3. No significant steric effects were observed as most of the desired 2*H*-chromene-2-carboxamides were obtained in moderate to good yields, indicating good substrate tolerate for this synthetic methodology. However, substrate with electron-donating group always showed high reactivities than those with electron-withdrawing group. Substrate **1g** with strong electron-withdrawing group CF_3 was sluggish in this reaction condition, only affording the desired 2-carboxamide-2*H*-chromenes **3ga** in 23% yield (Table 3). The bromide remained intact under the present reaction conditions (**3fa**, 86% yield), that allows further potential functionalization using traditional cross-coupling methods.[13] To evaluate the efficacy of this addition reaction in gram scale, the reaction was investigated with 1.14 g (7 mmol) of chromene acetal **1a** with only 2% catalyst loading. The product **3aa** was isolated in excellent yield (1.56 g, 87 %) in 20 h.

Table 3 The scope of synthesis of 2-carboxamide-2*H*-chromenes with various chromene acetals **1a-1h** and Cy-NC **2a**.[a]



[a] Reaction conditions: To a solution of 10 mol % $Bi(OTf)_3$ in 1.0 mL dioxane/H_2O (10:1) added chromene acetals **1a-h** (0.25 mmol, 1.0 equiv) and isocyanides **2a** (1.5 equiv) in sequence. The reaction mixtures were stirred at 80 °C for 20 h unless otherwise noted. All were isolated yield. [b] 2 equiv of **2a** was used in 80 °C for 20 h.



Scheme 4 The mechanism of synthesis of 2-carboxamide-2*H*-chromenes.

On the basis of the result, a mechanism for the Lewis acid-catalyzed formation of 2-carboxamide-2*H*-chromene derivatives via addition of isocyanides to oxocarbenium ion was shown in Scheme 4. Acetal **1a** was treated with Lewis acid $Bi(OTf)_3$ to generate oxocarbenium species **4**. Trapping of this intermediates oxocarbenium ion with isocyanide gave nitrilium intermediate **5**. Then, the hydrolysis of the intermediate **5** result the formation **3aa**.

In summary, we developed an efficient Lewis acid $Bi(OTf)_3$ catalyzed addition reaction for accessing 2*H*-chromene-2-carboxamide derivatives. A large scope of isocyanides and chromene acetals are suitable substrates in this catalyst system. By this synthetic strategy, a polyfunctional molecular scaffold, 2*H*-chromene-2-carboxamide could be prepared efficiently in one step (up to 95% yield). Further investigations

on asymmetric synthesis methodology of 2-carboxamide-2*H*-chromene derivatives and their biological activities evaluation are ongoing in our laboratory.

Acknowledgements

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