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Synthesis of 2-Amino-3-cyano-4*H*-chromene-4-carboxamide Derivatives by an Isocyanide-Based Domino Conjugate Addition/O-Trapping Rearrangement Sequence

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An efficient, one-pot domino synthesis of new 2-amino-3-cyano-4*H*-chromene-4-carboxamide derivatives has been developed by the acid-induced conjugate addition of isocyanides to 2-imino-2*H*-chromene-3-carboxamides, followed by an intramolecular O-trapping rearrangement, with yields up to 92 %. This newly established protocol was also used in multicomponent (3CR) mode.

Introduction

Isocyanide-based chemistry, and particularly that involving multicomponent reactions (IMCRs), is of potential for the generation of an enormous number of diverse structures, including heterocycles, natural products, peptidomimetics, and pharmaceutically relevant frameworks.[1a–1e] In the conventional Ugi–Mumm and Ugi–Smiles approaches, a nitrilium carbon center is attacked by the nucleophilic O atom of a carboxylate or phenolate, forming an acylated or arylated isoamide, which can rearrange through intramolecular 1–4(O,N) acyl (Mumm) or aryl (Smiles) transfer.[1,2] Unusual stabilization behavior of the isocyanide carbon center in the α-adduct has also been discussed; in these cases, some other nucleophile source is required to stabilize the nitrilium species through O, S, N, or C trapping.[3–10] However, intramolecular O-trapping rearrangements in which the O atom of the carboxamide moiety is involved in stabilization have received relatively little attention.[3–7] Moreover, isocyanide addition to activated alkenes has been examined.[11–14] To the best of our knowledge, isocyanide conjugate addition followed by intramolecular stabilization has been rarely investigated.[3]

2-Imino-2*H*-chromene-3-carboxamides possess conjugated structural elements, such as α,β-unsaturated carboxamido, 1,3-azadiene, and iminolactone moieties, which lead to high structural complexity and biological relevance (Figure 1).[15] Regioselective transformations of 2-iminochromenes have been investigated.[16–21] Reactions with N-containing nucleophiles gave access to 2-*N*-substituted products,[16] whereas with other nucleophiles, for example, C-, S-, or P-containing compounds, attack at C-4 by conjugate addition was preferred.[17–21]

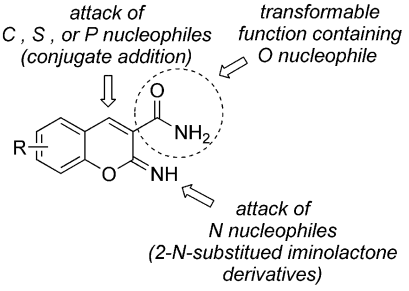

Figure 1. Three-centered imino-chromene-carboxamide framework.

We report here a domino conjugate addition/intramolecular O-trapping rearrangement sequence of isocyanides and 2-imino-2*H*-chromene-3-carboxamides, providing 2-amino-3-cyano-4*H*-chromene-4-carboxamide derivatives as a new type of trifunctionalized chromenes.

Results and Discussion

Starting materials **3a**–**c** were prepared by a Knoevenagel condensation/intramolecular cyclization sequence. Piperidine-catalyzed transformations of salicylaldehydes **1a**–**c** with cyanoacetamide (**2**) in EtOH afforded 2-imino-2*H*-

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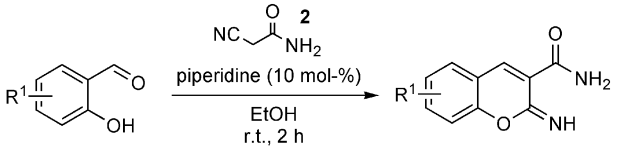
chromene-3-carboxamides **3a**–**c** in yields up to 85% (Scheme 1).[22] The mild reaction conditions proved highly suitable for the design and performance of further efficient one-pot multicomponent reactions.

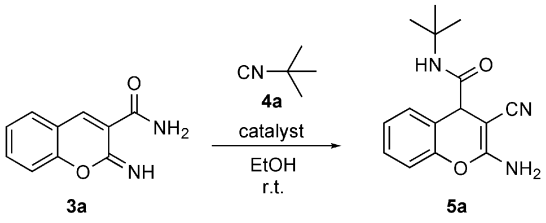


1a,3a: R^1 = H; **1b, 3b**: R^1 = Cl; **1c, 3c**: R^1 = OMe

Scheme 1. Synthesis of 2-iminochromenes.

For investigation of the treatment of 2-iminochromenes with isocyanides, a model reaction was first chosen to optimize the reaction parameters (Table 1). Preliminary experiments indicated that no products were formed without catalytic activation (Table 1, Entry 1). Lewis acids are known to be effective catalysts for activation of the azadiene moiety through 1,4-π-electron shift.[18] Accordingly, we examined the reactions in the presence of different Lewis acid catalysts (Table 1, Entries 2–7).

Table 1. Optimization of the model reaction.[a]



3a **5a**

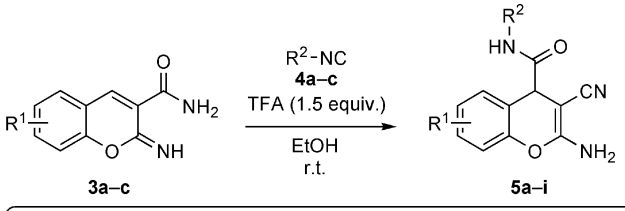
Entry	Catalyst	Equiv.	Solvent	Time [h]	Yield of **5a** [%][b]
1	–	–	EtOH	48	–
2	$InCl_3$	0.2	EtOH	24	23
3	$Dy(OTf)_3$	0.2	EtOH	24	11
4	AgOTf	0.2	EtOH	48	trace
5	$In(OTf)_3$	0.2	EtOH	12	37
6	$In(OTf)_3$	0.2	THF	12	33
7	$In(OTf)_3$	0.2	toluene	24	trace
8	TFA	0.2	EtOH	12	38
9	TFA	1	EtOH	4	61
10	TFA	1.5	EtOH	1.5	75[c]

[a] Reaction conditions: 2-imino-2*H*-chromene-3-carboxamide (0.8 mmol), *tert*-butyl isocyanide (0.8 mmol, 1 equiv.), solvent (6 mL), room temperature. [b] Isolated yield after flash chromatography. [c] Reaction conditions: 2-imino-2*H*-chromene-3-carboxamide (0.8 mmol), *tert*-butyl isocyanide (1.2 mmol, 1.5 equiv.), solvent (6 mL), room temperature.

To induce conjugate addition, 20 mol-% of $InCl_3$ in EtOH was employed as a promoter. Unfortunately, low isolated yields and considerable amounts of unidentified byproducts were obtained. Further Lewis acids and solvents were therefore tested in the model system, but the yields were still unsatisfactory (Table 1, Entries 3–7). Replacement of the Lewis acid catalyst by trifluoroacetic acid (TFA) in EtOH resulted in dramatic improvements in yield and reaction rate (Table 1, Entries 8–10). When 1.5 equiv. of TFA was used, compound **5a** was formed rapidly in good yield (75%). The best reaction performance was obtained with 1.5 equiv. of isocyanide. It was necessary to avoid overlong reaction times at room temperature, or with conventional or microwave heating, which would have increased the likelihood of side effects and led to significant amounts of byproducts (data not shown).

The methodology was extended to the formation of new 2-amino-3-cyano-4*H*-chromene-4-carboxamide derivatives (Table 2, Figure 2). We investigated the reactions between chromenes containing electron-donating and electron-withdrawing groups (i.e., **3a**–**c**) and aliphatic isocyanides (i.e., **4a**–**c**) in the presence of TFA. Under the optimized reaction conditions, derivatives **5a**–**i** were obtained in isolated yields of 48–92%. For starting compound **3c** substituted with a methoxy group, lower isolated yields were observed (Table 2, Entries 7–9). Unfortunately, the application of benzylic and aromatic isocyanides resulted in complex reaction mixtures; desired products could not be isolated.

Table 2. Transformations of 2-imino-2*H*-chromene-3-carboxamides and isocyanides.[a]



3a–c **5a–i**

4a: R^2 = *t*Bu; **4b**: R^2 = 1,1,3,3-tetramethylbutyl; **4c**: R^2 = cyclohexyl

Entry	Starting compound	Isocyanide	Product	Yield [%][b]
1	**3a**	**4a**	**5a**	75
2	**3a**	**4b**	**5b**	92
3	**3a**	**4c**	**5c**	73
4	**3b**	**4a**	**5d**	80
5	**3b**	**4b**	**5e**	91
6	**3b**	**4c**	**5f**	72
7	**3c**	**4a**	**5g**	71
8	**3c**	**4b**	**5h**	80
9	**3c**	**4c**	**5i**	48

[a] Reaction conditions: 2-imino-2*H*-chromene-3-carboxamide (0.8 mmol), isocyanide (1.2 mmol, 1.5 equiv.), TFA (89 μL, 1.2 mmol, 1.5 equiv.), solvent (EtOH, 6 mL), room temperature, 1.5 h. [b] Isolated yield after flash chromatography.

A mechanism was proposed for this domino transformation (Scheme 2). The imino side of the azadiene moiety forms a H-bond with TFA, resulting in a 1,4-π-electron shift and electron deficiency at C-4. Isocyanide adduct formation leads to nitrilium ion intermediate **B**, which can be stabilized by intramolecular O-trapping and subsequent tandem imine–enamine tautomerism (**D**). Bisiminofuran moiety **E** formed undergoes further rearrangement to gen-

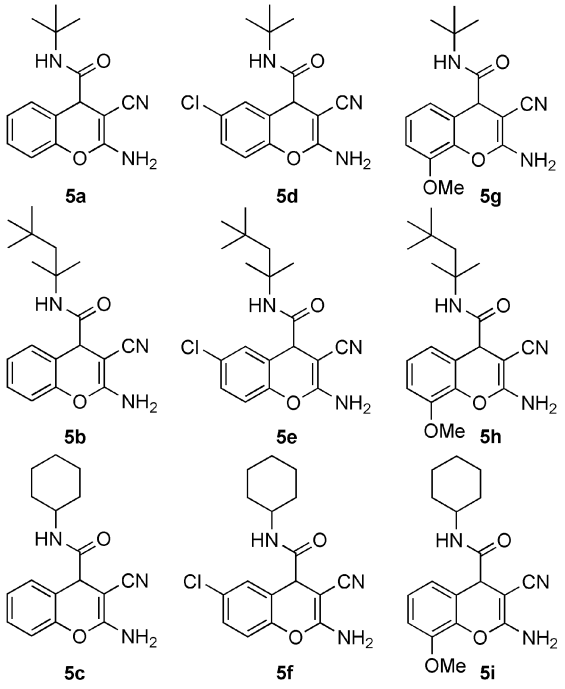
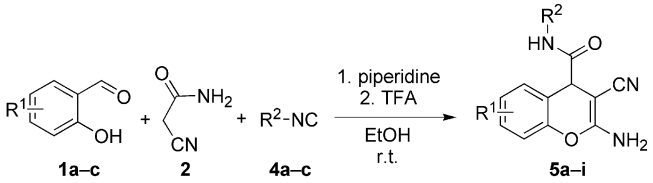


Figure 2. Synthesized 2-amino-3-cyano-4*H*-chromene-4-carboxamide derivatives **5a**–**i**.

Table 3. Novel isocyanide-based three-component reaction.[a]



Entry	Aldehyde	Isocyanide	Product	Yield [%][b]
1	**1a**	**3a**	**5a**	60
2	**1a**	**3b**	**5b**	77
3	**1a**	**3c**	**5c**	56
4	**1b**	**3a**	**5d**	63
5	**1b**	**3b**	**5e**	75
6	**1b**	**3c**	**5f**	54
7	**1c**	**3a**	**5g**	55
8	**1c**	**3b**	**5h**	62
9	**1c**	**3c**	**5i**	30

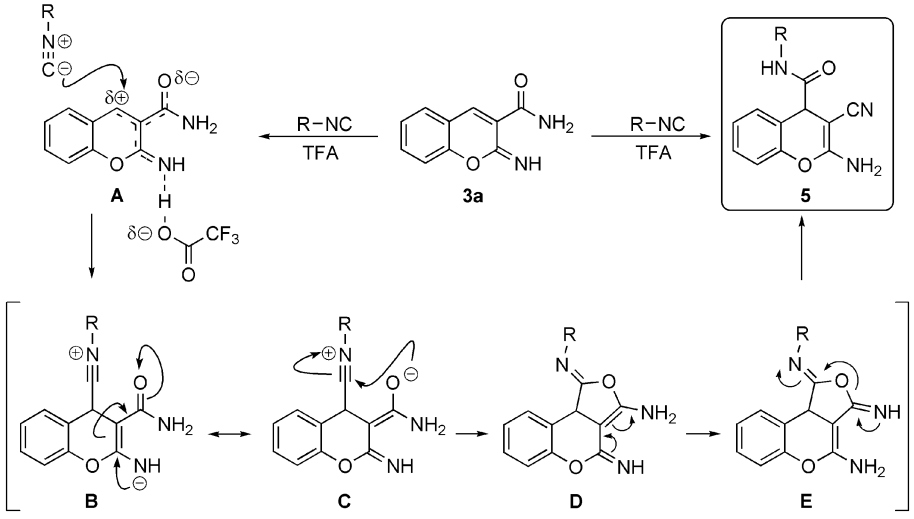
[a] Reaction conditions: salicylaldehydes **1a**–**c** (0.8 mmol), 2-cyanoacetamide (**2**; 0.8 mmol, 1 equiv.), piperidine (10 mol-%), solvent (EtOH, 6 mL) room temperature; then TFA (95 μL, 1.28 mmol, 1.6 equiv.), isocyanides **4a**–**c** (1.2 mmol, 1.5 equiv.), room temperature, reaction time: 3.5 h. [b] Isolated yield after flash chromatography.

erate thermodynamically favored carbamoylated product **5**.[3] Formally, this process can be regarded as an intramolecular cross-amide conversion.

Furthermore, a novel three-component coupling of derivatives **5a**–**i** was accomplished (Table 3, Entries 1–9). Treatment of salicylaldehydes **1a**–**c** with 2-cyanoacetamide (**2**) in the presence of piperidine (10 mol-%) as catalyst furnished chromenes **3a**–**c** quantitatively at room temperature in 2 h. Addition of isocyanides **4a**–**c** and TFA (1.6 equiv.) then afforded **5a**–**i** in 1.5 h in overall yields of 30–77%.

Conclusions

In conclusion, we have reported here a new, acid-induced efficient transformation involving 2-imino-2*H*-chromene-3-carboxamides and isocyanides. The reaction can be regarded as a sequential conjugate addition/O-trapping rearrangement conversion of isocyanides. The protocol was utilized to generate a new class of trifunctionalized chromenes. A novel isocyanide-based 3CR approach has been developed.



Scheme 2. Mechanistic proposal.

Experimental Section

General Procedure for the Preparation of 5a–i: To the solution of 2-imino-2*H*-chromene-3-carboxamides **3a**–**c** (0.8 mmol) and TFA (1.2 mmol) in ethanol (6 mL) was added an excess amount of isocyanides **4a**–**c** (1.2 mmol). The resulting mixture was stirred for 1.5 h at ambient temperature and monitored by TLC (*n*-hexane/ethyl acetate, 1:2). Then, the solution was poured into saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic phases were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Crude products **5a**–**i** were purified by flash chromatography (*n*-hexane/ethyl acetate).

MCR Procedure: To a solution of salicylaldehydes **1a**–**c** (0.8 mmol) and a catalytic amount of piperidine (0.08 mmol) in ethanol (6 mL) was added 2-cyanoacetamide (**2**; 0.8 mmol). The resulting mixture was stirred for 2 h at room temperature. When the Knoevenagel reaction was carried out, TFA (1.28 mmol) and isocyanides **4a**–**c** (1.2 mmol) were added, and stirring was continued for another 1.5 h at room temperature. Next, the solution was poured into a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic phases were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Afterwards, target compounds **5a**–**i** were purified by flash chromatography (*n*-hexane/ethyl acetate).

Supporting Information (see footnote on the first page of this article): Copies of the NMR spectra and characterization data for all compounds.

Acknowledgments

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