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Synthesis of Functionalized Chromeno[2,3-*b*]pyrrol-4(1*H*)-ones by Silver-Catalyzed Cascade Reactions of Chromones/Thiochromones and Isocyanoacetates

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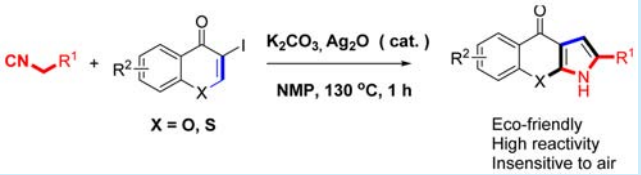
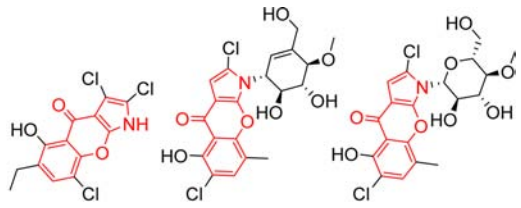
Supporting Information

ABSTRACT: A novel and convenient approach to the synthesis of chromeno[2,3-*b*]pyrrol-4(1*H*)-ones has been developed. Furthermore, the method involves a facile silver-catalyzed cascade cyclization reaction including an intramolecular C−O bond formation. The silver salt acts as a key promoter.



In the past decades, structurally complex and functionally diverse heterocycles have made a great contribution to discovering lead compounds which play important roles in developing new pharmaceutical agents. The benzopyranopyrrole structure was first reported as a core structure of TAN-876A isolated from a *Streptomyces* sp. by a group from the Takeda Company.[1] Subsequently this unique structure was found in pyralomicins which were a set of antibiotics isolated from the soil bacterium *Nonomuraea spiralis* by Takeuchi and co-workers in 1996 (Scheme 1).[2] Surprisingly, few synthetic approaches to obtain the benzopyranopyrrole scaffold or its analogues have been reported.[3] Therefore, it is desirable to continue to devote efforts to developing new synthetic methodologies, which is considered a challenging task in organic synthesis.

Scheme 1. Chemical Structures of the Pyralomicins and Other Related Compound

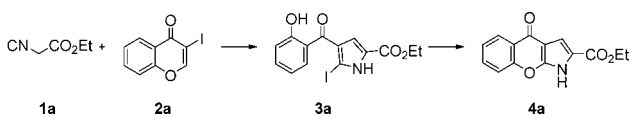


Cascade reactions involving multiple-bond forming events in a single pot are a means to achieve green chemistry and a way to develop economical processes for the manufacture of pharmaceuticals and other organic structures.[4] Moreover, cascade reactions, being artistically appealing, are often associated with cost savings in terms of reagents, catalysts, and solvents, as well as time and effort. In recent years, isocyanoacetate derivatives occupy an important place in the field of synthetic application and reaction diversity, which makes them highly attractive objects for investigation.[5] However, the cycloaddition of isocyanides always met with challenges, including the easy dimerization of isocyanides to produce imidazoles in the presence of a base or transition-metal catalyst.[6] Moreover, only a few methods that could make a transition metal coordinate to the isocyano group and activate isocyanides in some cycloaddition reactions are known so far, while transition-metal-catalyzed cascade cyclization reactions gained little attention.[7] Thus, we focused our attention on the metal-catalyzed cascade reaction of isocyanoacetate.

In an earlier study, our group was devoted to the development of new synthetic pathways for constructing heterocyclic scaffolds.[8] In addition, chromones are a class of greatly useful and versatile starting materials for constructing various heterocycles.[9] On the basis of these efforts, we envisioned that 3-iodochromone **2a**, containing the superior iodine leaving group, would react with ethyl isocyanoacetate **1a** in the presence of silver salts and bases to form the ethyl 4-(2-hydroxybenzoyl)-5-iodo-2*H*-pyrrole-2-carboxylate **3a** which would be easily converted to ethyl 4-oxo-1,4-dihydrochromeno-[2,3-*b*]pyrrole-2-carboxylate **4a** via a cascade silver-catalyed C−O bond-forming cyclization process (Scheme 2).

To our delight, we observed that the silver-catalyzed cascade cyclization reaction between ethyl isocyanoacetate **1a** and 3-iodochromones **2a** produced chromeno[2,3-*b*]pyrrol-4(1*H*)-one **4a** in good yields. Notably, in this reaction, only a few

Scheme 2. Outline of the Synthesis of Benzopyranopyrrole



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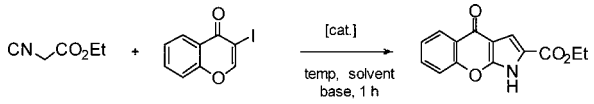
byproducts resulting from dimerization of isocyanides were observed. Inspired by this finding, we continued optimizing the reaction conditions (Table 1). A variety of silver salts were

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 4a

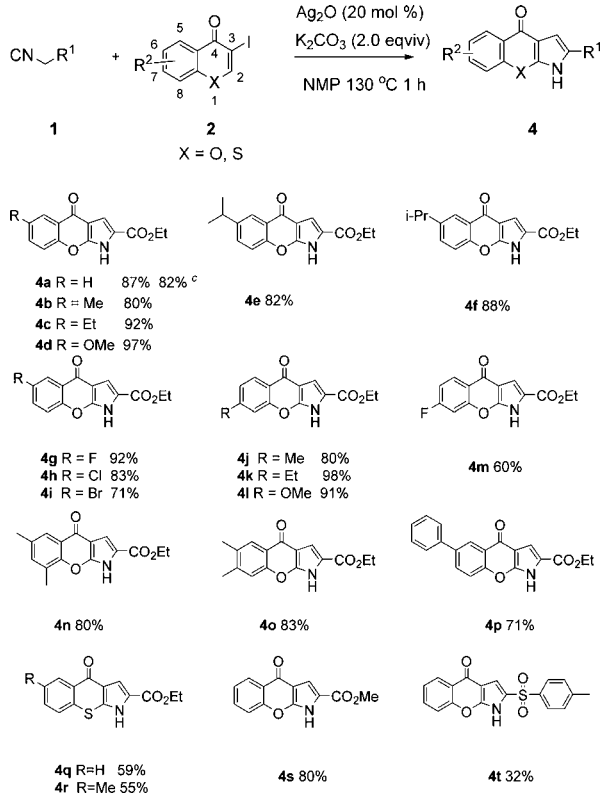
entry	cat. (equiv)	temp (°C)	solvent	base	yield[b] (%)
1	Ag_2CO_3 (0.2)	130	DMSO	K_2CO_3	62
2	$AgNO_3$ (0.2)	130	DMSO	K_2CO_3	63
3	Ag_2O (0.2)	130	DMSO	K_2CO_3	70
4	AgOAc (0.2)	130	DMSO	K_2CO_3	66
5[c]	–	130	NMP	K_2CO_3	0
6	Ag_2O (0.2)	130	DMF	K_2CO_3	66
7	Ag_2O (0.2)	130	NMP	K_2CO_3	79
8	Ag_2O (0.1)	130	NMP	K_2CO_3	55
9	Ag_2O (1.0)	130	NMP	K_2CO_3	52
10	Ag_2O (0.2)	130	NMP	KOtBu	trace
11	Ag_2O (0.2)	130	NMP	Cs_2CO_3	54
12	Ag_2O (0.2)	130	NMP	KOAc	35
13	Ag_2O (0.2)	130	NMP	DBU	trace
14[d]	Ag_2O (0.2)	130	NMP	K_2CO_3	74
15[e]	Ag_2O (0.2)	130	NMP	K_2CO_3	87
16[e]	Ag_2O (0.2)	140	NMP	K_2CO_3	60
17[e]	Ag_2O (0.2)	60	NMP	K_2CO_3	trace
18[e]	Ag_2O (0.2)	100	NMP	K_2CO_3	63

[a]Reaction condition: **1a** (0.6 mmol, 1.5 equiv), **2a** (0.4 mmol, 1.0 equiv), base (1.5 equiv), and silver salts (20 mol %) in solvent (2.0 mL) under air. [b]Isolated yields. [c]The reaction was carried out without silver salt. [d]1.0 equiv of base was used. [e]2.0 equiv of base were used.

initially examined for the reaction of ethyl isocyanoacetate **1a** and 3-iodochromone **2a** in the presence of K_2CO_3 (1.5 equiv) in DMSO at 130 °C for 1 h, and Ag_2O provided the best result (entries 1–4, Table 1). It was noteworthy that the reaction would not occur in the absence of silver salts (entry 5, Table 1). Afterward some solvents were screened such as dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and *N*-methyl-2-pyrrolidone (NMP), while NMP gave the product in a higher yield (entry 7 vs 3/6, Table 1). Increasing or decreasing the amount of Ag_2O resulted in a reduced yield (entry 3 vs 8/9, Table 1). Moreover the effect of the base was also investigated. When strong bases were employed for this conversion, **4a** could not be generated (entries 10 and 13, Table 1). The screened results led to the identification of K_2CO_3 as the optimal base (entries 7, 10–13, Table 1). Further studies showed that increasing the amount of K_2CO_3 (2.0 equiv) obtained a comparably higher yield (entries 7, 14, 15, Table 1). Finally the investigation of reaction temperature indicated that the optimal temperature was 130 °C (entries 15–18, Table 1). Thus, the optimal reaction conditions were determined, including Ag_2O (0.2 equiv), K_2CO_3 (2.0 equiv) in NMP (2.0 mL) at 130 °C for 1 h.

With the optimal reaction conditions in hand, the scope of substrates for this new reaction was then examined (Scheme 3). The results showed that 3-iodochromones bearing electron-donating substituents on the aromatic rings gave the corresponding products in good to excellent yields (**4b**–**4f**, **4j**–**4l**, Scheme 3). However, the electron-withdrawing groups

Scheme 3. Scope of the Cascade Reaction of 1 with 2[a,b]



[a]Reaction condition: **1a** (0.6 mmol, 1.5 equiv), **2a** (0.4 mmol, 1.0 equiv), K_2CO_3 (0.8 mmol 2.0 equiv), and Ag_2O (20 mol %) NMP (2.0 mL) at 130 °C for 1 h under air. [b]Isolated yields. [c]The procedure was scaled up to 4 mmol.

on the chromone ring had a profound effect on the efficiency of the silver-catalyzed annulation reaction. For example, as we changed the substituents at C-6 of 3-iodochromone from fluoro to bromo groups, the yields of corresponding products were gradually reduced (**4g**–**4i**, Scheme 3). Meanwhile, the presence of an electron-withdrawing fluoro group at the C-7 position of the chromone ring system delivered the corresponding product in diminished yield (**4m**, Scheme 3). In addition, chromone with multisubstituents were compatible with the reaction process as well, providing the corresponding products in good yields (**4n**, **4o**, Scheme 3). The aryl-substituted compound **1p** was found to be a suitable substrate. On the basis of these results, we extended the reaction scope to thiochromones. However, the thiochromones had an obvious impact on the efficiency of this reaction for uncertain reasons (**4q**, **4r**, Scheme 3). Perhaps it weakened the stability of the intermediate during the cyclization process. However, both 3-iodoquinolin-4(1*H*)-one and 3-iodo-1-methylquinolin-4(1*H*)-one failed to give promising results under the present conditions. Besides, we also tried other isocyanides with an electron-withdrawing group such as methyl 2-isocyanoacetate, tosylmethyl isocyanide, and diethyl isocyanomethylphosphonate. The methyl 2-isocyanoacetate **1s** could react satisfactorily and gave the product in a good yield (**4s**, Scheme 3). Tosylmethyl isocyanide **2t** could be tolerated to access the benzopyranopyrrole derivative (**4t**, Scheme 3). However, when diethyl isocyanomethylphosphonate was used under the optimal conditions, it failed to give the desired compound. To highlight the efficiency and practicability of the strategy, we

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successfully scaled up the procedure to 4 mmol and obtained 840 mg of **4a** after 1 h in 82% isolated yield (Scheme 3). Additionally, the structure of **4a** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1).

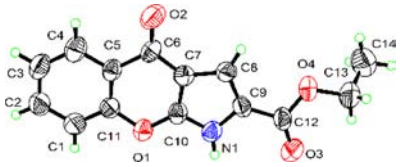
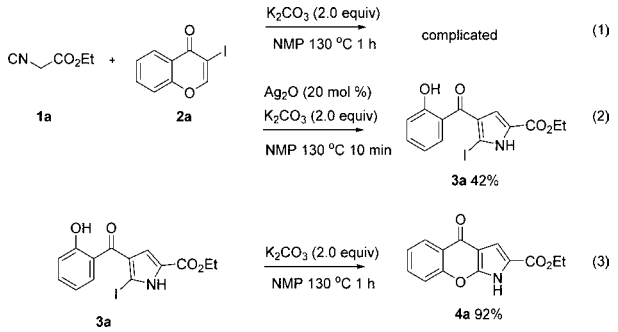


Figure 1. X-ray crystal structure of **4a**.[10]

To gain insight into the mechanism of this cascade reaction, a series of controlled experiments were performed. First, ethyl isocyanoacetate **1a** and 3-iodochromones **2b** produced a complicated mixture through a highly inefficient process without silver salts (Scheme 4, eq 1). Under standard

Scheme 4. Mechanism Investigations



conditions, the reaction of ethyl isocyanoacetate **1a** with 3-iodochromone **2a** would produce ethyl 4-(2-hydroxybenzoyl)-5-iodo-1*H*-pyrrole-2-carboxylate **3a** in a moderate yield within 10 min (Scheme 4, eq 2). The intermediate **3a** could be smoothly transformed to the target molecule **4a** in high yield under alkaline and high temperature conditions without the presence of silver oxide (Scheme 4, eq 3), which demonstrated that this step reaction depended on the base and temperature instead of the silver catalyst. The structure of **3a** was also confirmed by X-ray crystallographic analysis (Figure 2).

On the basis of the above observations and considerations, a plausible reaction mechanism is proposed in Scheme 5. In this pathway, the silver−isocyanide complex **A** could be generated from **1a**, in the presence of a silver catalyst, according to some papers demonstrating that silver salts could coordinate to the isocyano group and activate isocyanides **1** in the cycloaddition

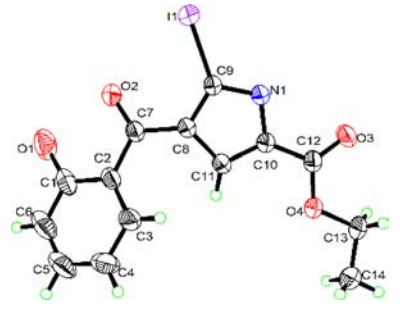
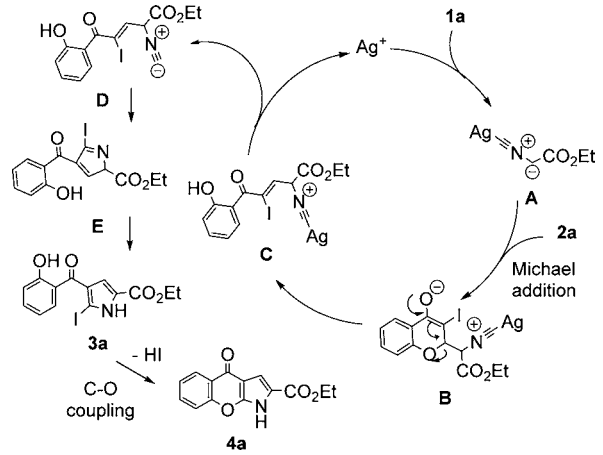


Figure 2. X-ray crystal structure of **3a**.[11]

Scheme 5. Plausible Reaction Mechanism



reaction.[7b] Subsequently, the cycloaddition between complex **A** and **2a** could afford the key intermediate complex **C** through a Michael addition reaction. Then intermediate **D** along with **A** are generated from **C** to end the catalytic cycle. Based on the literature precedent,[12] we know that acyl chlorides reacting with isocyanides can afford the corresponding α-addition products, the acyl imidoyl chlorides. Thus, an insertion reaction of isocyanide to the C−I bond might occur giving the complex **E**. Next the complex **E** experienced a subsequent 1,5-hydrogen shift to generate intermediate **3a**. Finally ethyl 4-(2-hydroxybenzoyl)-5-iodo-2*H*-pyrrole-2-carboxylate **3a** could be easily converted to ethyl 4-oxo-1,4-dihydrochromeno[2,3-*b*]pyrrole-2-carboxylate **4a** via intramolecular C−O bond formation under alkaline and high temperature conditions.

In conclusion, we have developed a novel silver catalyzed cascade reaction of ethyl isocyanoacetate on an activated double bond of 3-iodochromanone, involving nucleophilic conjugate addition of an isocyanoacetate anion on the activated double bond of chromanone followed by ring opening of the chromanone ring, subsequent pyrrole ring formation, and reconstruction of the chromanone ring via intramolecular C−O bond formation leading to diverse chromeno[2,3-*b*]pyrrol-4(1*H*)-ones. The reaction represents an extremely simple, practical, efficient, and atom-economic way to construct benzopyranopyrroles. Further studies of the detailed mechanism and application of this transformation are under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02795.

General experimental information, copies of ^{1}H and ^{13}C NMR of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(10) CCDC-1412630 contains the supplementary crystallographic data for compound **4a**. Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk.
(11) CCDC-1412633 contains the supplementary crystallographic data for compound **3a**. Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk.
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