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Synthesis of substituted pyrroles using a silver-catalysed reaction between isocyanoacetates/benzyl isocyanides and chromones†

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A novel synthetic strategy to construct substituted-pyrroles has been developed using silver-catalysed reactions between isocyanides/benzyl isocyanides and chromones. These reactions proceed under mild conditions and yield polysubstituted pyrroles with efficient yields. The silver catalyst plays a key role in sequestering and activating the isocyano group and in sequential Michael addition and cyclization reactions.

Substituted pyrroles represent an important class of nitrogen-containing heterocycles that are often observed in natural products,[1] pharmaceutical substances,[2] and bioactive materials.[3] A large numbers of pyrrole derivatives have been found to act as biological agents, including, a tubulin polymerization inhibitor,[4] a Cdc7 kinase inhibitor,[5] a potassium-competitive acid blocker (P-CAB),[6] and a pesticide, pyoluteorin[7] (Fig. 1). As a result of these findings, considerable attention has been paid to developing efficient methods for the synthesis of pyrrole derivatives. The most frequently used methods to synthesize pyrroles employ the classical Hantzsch and Paal–Knorr procedures, but these synthetic approaches require multistep operations, harsh conditions, and do not confer regioselectivity.[8] More efficient and environmentally friendly reactions, such as the Paal–Knorr reaction, have been reported.[9] Although a variety of methods for the synthesis of functionalized pyrrole derivatives have recently been developed,[10] direct access to polyfunctionalized pyrroles from common, commercially available starting materials, is still a challenge.

Chromones are an additional class of starting materials that are used for constructing various biological heterocycles.[14] The use of 3-formylchromone in the synthesis of pyrroles has previously been reported (Scheme 1 eqn (3)).[15] Based on these previous studies, we believe that chromones may be coupled with the reaction of isocyanoacetates for the synthesis of pyrrole derivatives (Scheme 1 eqn (4)).

Our initial efforts focused on the reaction between 4*H*-chromen-4-one **1a** and ethyl 2-isocyanoacetate **2a** in the presence of silver salts and bases. Following the reaction, the corresponding pyrrole derivative **3a** was produced with

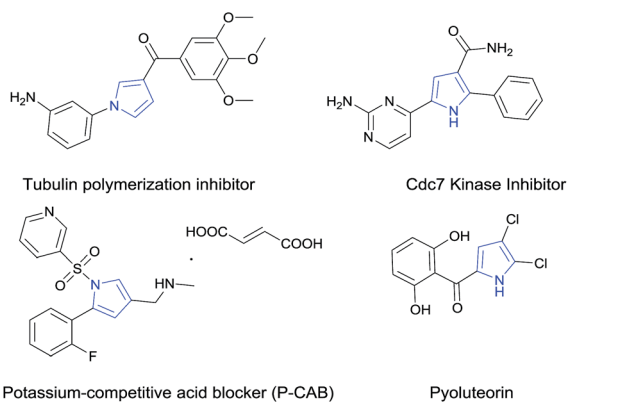

Fig. 1 Representative examples of pyrrole derivatives. Isocyanoacetates have been widely used in organic synthesis and are useful building blocks for the generation of N-heterocycles[11] because of their multi-reaction centres, such as an isocyanide group, which includes an acidic CH fragment and a carboxylic acid with a protecting group. The cycloaddition reaction of isocyanoacetates provides an ideal route to substituted pyrroles due to the efficiency of the reaction. Historically, the Barton–Zard synthesis, which represents the reaction between an activated alkene and an activated methylene isocyanide under basic conditions, has been the most efficient method for the synthesis of substituted pyrroles (Scheme 1 eqn (1)).[12] However, poor yields and unwanted by-products limit this synthesis approach. Recently, the cycloaddition of isocyanide has been extended to incorporate alkynes with the help of a transition metal-catalyst (Scheme 1 eqn (2)).[13] The copper or silver salts employed increase the selective chemical transformations involving terminal alkynes. Based on these results, isocyanoacetates represent a very attractive starting material for investigations of synthetic applications.

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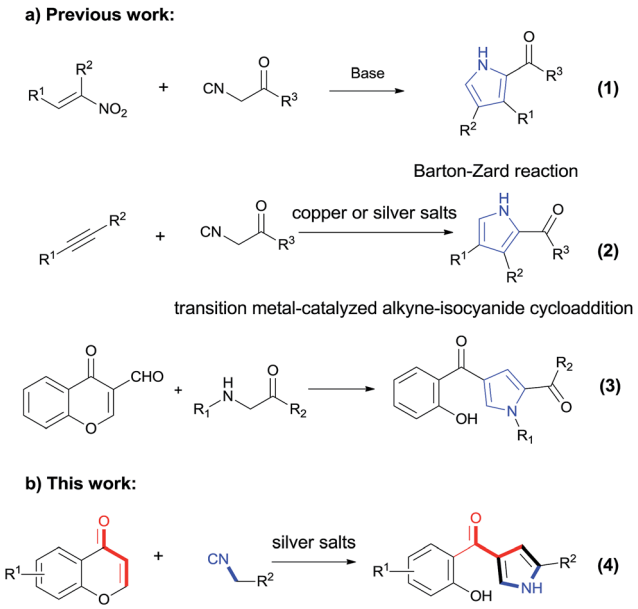
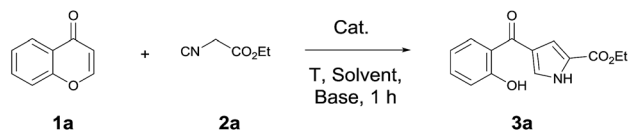


Scheme 1 Methods for the synthesis of pyrroles from isocyanoacetates, including the method described in this manuscript.

moderate yields (Table 1, entry 1). Notably, no by-product from the dimerization of isocyanides was observed in this reaction.

Table 1 Optimization of the reaction conditions[a]



1a 2a 3a

Entry	Catalyst	Temp (°C)	Solvent	Base	Yield[b] (%)
1	Ag_2O	rt	NMP	K_2CO_3	64
2	Ag_2O	50	NMP	K_2CO_3	66
3	Ag_2O	100	NMP	K_2CO_3	76
4	Ag_2O	130	NMP	K_2CO_3	75
5	Ag_2O	100	DMSO	K_2CO_3	70
6	Ag_2O	100	DMF	K_2CO_3	80
7	Ag_2O	100	Dioxane	K_2CO_3	63
8	Ag_2O	100	DMF	KOAc	73
9	Ag_2O	100	DMF	Cs_2CO_3	70
10	Ag_2O	100	DMF	DBU	50
11	**Ag_2CO_3**	**100**	**DMF**	**K_2CO_3**	**98**
12	$AgNO_3$	100	DMF	K_2CO_3	93
13	AgOTf	100	DMF	K_2CO_3	79
14	$AgNTf_2$	100	DMF	K_2CO_3	80
15[c]	—	100	DMF	K_2CO_3	NR[d]
16[e]	Ag_2CO_3	100	DMF	K_2CO_3	77
17[f]	Ag_2CO_3	100	DMF	—	20

[a] Reaction condition: **1a** (0.5 mmol, 1.0 equiv.), **2a** (0.75 mmol, 1.5 equiv.), base (2.0 equiv.), and silver salts (20 mol%) in solvent (3.0 mL) under air. [b] Isolated yields. [c] The reaction was carried out without silver salt. [d] NR = no reaction. [e] Silver salts (10 mol%) was used. [f] The reaction was carried out without base.

Based on these results, we attempted optimize the reaction conditions (Table 1). The investigation of different reaction temperatures indicated that the optimal temperature was 100 °C (Table 1, entries 1–4). Once the optimum temperature was defined, several solvents were screened (Table 1, entry 3, entries 5–7). DMF, instead of NMP, produced **3a** in an 80% yield, which was the best result (Table 1, entry 6). Moreover the effect of bases was also studied. The results found that K_2CO_3 was the optimal base (Table 1, entry 6, entries 8–10); the presence of base was critical for improving the yield of the reaction (Table 1, entry 17). The effects of silver salts on the reaction were studied, and Ag_2CO_3 was found to be the optimal silver salt (Table 1, entry 6, entries 11–14); it is worth noting that a decrease in the concentration of Ag_2CO_3 resulted in a reduced yield (Table 1, entry 16). It is also worth noting that the reaction would not occur in the absence of silver salts (Table 1, entry 15). As a result of these studies, the optimal reaction conditions were found to include Ag_2CO_3 (20 mol%) and K_2CO_3 (2.0 equiv.) in DMF (3.0 mL) at 100 °C for 1 h.

The structure of **3a** was established by X-ray crystal structure analysis (Fig. 2).

To study the capacity of this reaction method, a variety of chromones **1** were reacted with isocyanides **2** under the optimal reaction conditions to produce substituted-pyrroles **3**. The results are shown in Table 2. When both electron-donating and -withdrawing groups were located on the benzene rings, the chromones yielded substituted-pyrroles with efficient yields (Table 2, **3a–3t**). Electronic effects had little influence on the sequential reactions with isocyanoacetates. Different alkyl, halo, and methoxy groups located in the aryl ring of chromones **1** produced pyrrole derivatives **3a–3o** with excellent yields. Moreover, multigroup chromones **1** were also compatible with the reaction process and produced substituted-pyrroles with excellent yields (Table 2, **3p–3r**). In addition, both an aryl-substituted compound (**1s**) and methyl 2-isocyanoacetate (**2t**) were found to be suitable substrates (Table 2, **3s** and **3t**). Other activated methylene isocyanides, such as tosylmethyl isocyanide and benzyl isocyanide, may be used to incorporate structural diversity into the pyrrole ring. However, when a benzyl isocyanide (**2u**) was used, the pyrrole derivative was produced with a moderate yield and the reaction required more time (Table 2, **3u**). When a tosylmethyl isocyanide was used under the optimal conditions, it failed to yield the expected pyrrole. However, on the whole, the silver-catalysed reaction of

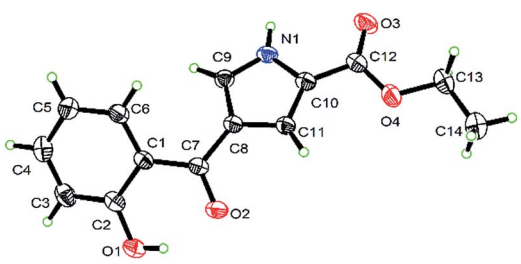
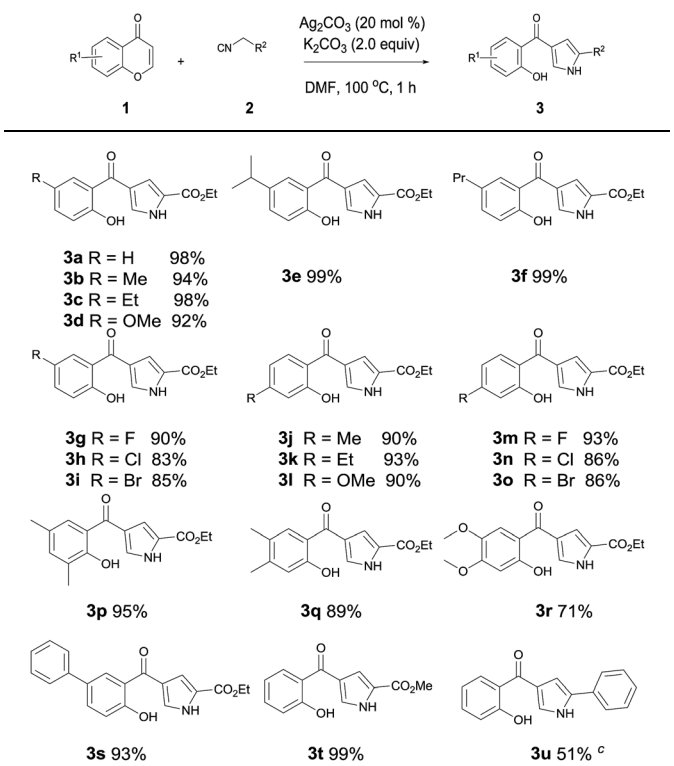


Fig. 2 X-ray crystal structure of ethyl 4-(2-hydroxybenzoyl)-1*H*-pyrrole-2-carboxylate **3a** (probability 30%).

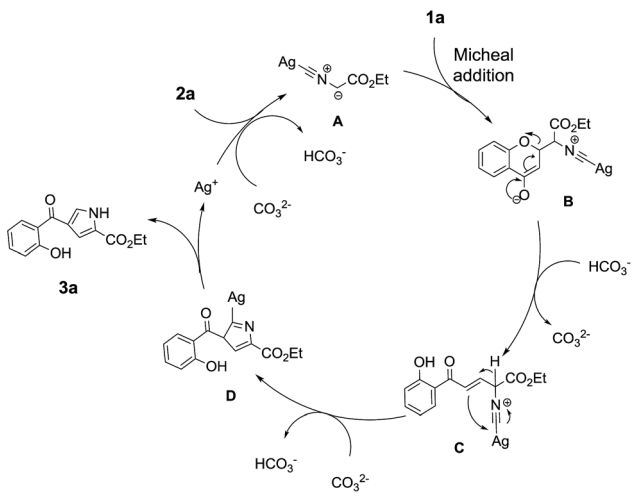
Table 2 Scope of the reaction of chromones with isocyanoacetates/benzyl isocyanide[a,b]



[a] Reaction condition: **1a** (0.5 mmol, 1.0 equiv.), **2a** (0.75 mmol, 1.5 equiv.), K_2CO_3 (1.0 mmol 2.0 equiv.), and Ag_2CO_3 (20 mol%) DMF (2.0 mL) at 100 °C for 1 h under air. [b] Isolated yields. [c] The reaction time is 12 h.

activated methylene isocyanides with a broad range of chromones provides a powerful method for the synthesis of 2,4-disubstituted pyrroles.

The proposed reaction mechanism (Scheme 2) based on previously published works. The initial step involves the formation of a silver-isocyanide complex **A** generated from **2a** in the presence of silver catalyst. As described in previous studies, the silver salts coordinate the isocyano group and activate the isocyanides (**1**) for the cycloaddition reaction.[13c] An intermolecular Michael addition of compound **1a** and complex **A** produces intermediate **C**. An intramolecular cyclization reaction occurs under alkaline conditions to produce complex **D**. Complex **D** undergoes a 1,3-hydrogen shift followed by protonation mediated by $KHCO_3$ to yield **3a**, thus completing the catalytic cycle for Ag_2CO_3.



Scheme 2 Proposed reaction mechanism.

Conclusions

This manuscript described the silver-catalysed synthesis of 2,4-disubstituted pyrroles from isocyanoacetates/benzyl isocyanides and a variety of chromones. This synthetic approach represents an extremely simple, efficient, and economical method of producing biologically active pyrrole derivatives with excellent yields. Further studies of the reaction mechanism and the application of these products are under investigation in our laboratory.

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