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Access to Coumarins by Rhodium-Catalyzed Oxidative Annulation of Aryl Thiocarbamates with Internal Alkynes

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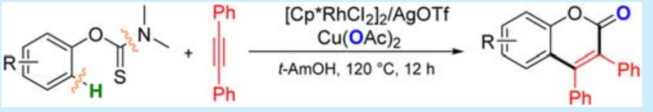
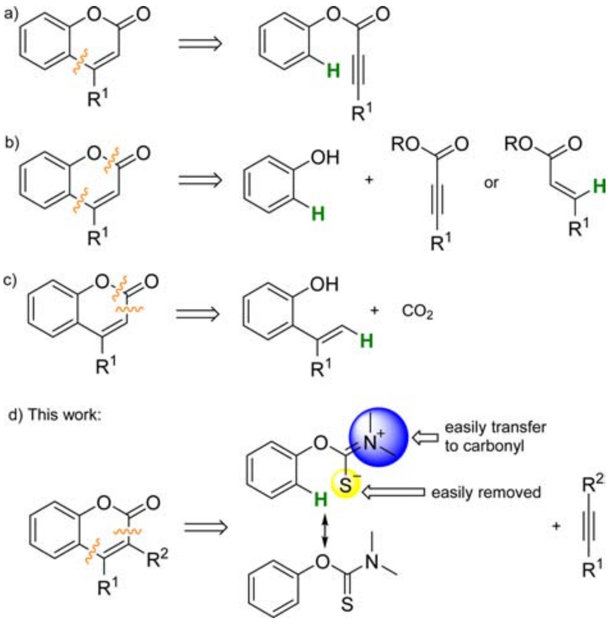
Supporting Information

ABSTRACT: A Rh-catalyzed annulation of aryl thiocarbamates with internal alkynes via C−H bond activation has been developed. This protocol provides a new route to 3,4-disubstituted coumarins.



Coumarin is a well-known structural motif found in numerous natural products and pharmaceuticals with interesting biological activities.[1] It is also frequently employed in highly efficient organoelectroluminescent materials.[2] The most common approach for the synthesis of coumarins is the Pechmann reaction.[3] Other classic methods involve strong acid- or base-catalyzed condensations.[4] In recent years, much research emphasis has been focused on transition-metal-catalyzed coupling[5] and carbonylation reactions.[6] Direct C−H bond activation has also provided a powerful route to replace typical couplings in a lot of cases.[7] The application of this strategy to coumarin synthesis is attractive, and some successful examples have been developed, including Pd-catalyzed intra- (Scheme 1, a)[8] and intermolecular[9] (Scheme 1, b) arylation of aryl propiolates or acrylate esters and direct carboxylation of alkenyl C−H bonds of 2-hydroxystyrenes (Scheme 1, c).[10] However, most of these methods are limited to 4-substituted products. Retrosynthetic analysis suggested that the coupling of a phenyl ester and an internal alkyne might offer a promising route to 3,4-disubstituted coumarins, though only one successful example was subsequently achieved via cleavage of two carbon−carbon σ bonds of an *o*-arylcarboxybenzonitrile.[11] We aimed to construct such molecules by transition-metal-catalyzed oxidative coupling of alkyne with an aryl C−H bond.[12] In our recent study on the *ortho* C−H bond activation of aryl thiocarbamates,[13] we found that the iminium group in one polarization form of a thiocarbamate could transform to a carbonyl easily in the presence of acetic acid. Along with the fact that a C−S bond tends to cleave in the presence of some transition metals,[14] we expected that the coupling of an aryl thiocarbamate and internal alkyne would form 3,4-disubstituted coumarins (Scheme 1, d).

Scheme 1. Preparation of Coumarins through C−H Activation: Retrosynthetic Disconnections



To test our hypothesis, we initially examined palladium, ruthenium, and rhodium catalysts, respectively, using *O*-phenyl-*N*,*N*-dimethylthiocarbamate (**1a**) and diphenylacetylene (**2a**) as our standard substrates and $Cu(OAc)_2$ as the oxidant. The reactions were carried out in *tert*-amyl alcohol at 120 °C for 12 h. It was shown that $Pd(OAc)_2$ and Ru complex are not effective for this reaction (entries 1 and 2, Table 1). To our delight, in the presence of a catalytic amount of AgOTf (10 mol %), $[Cp^*RhCl_2]_2$ could readily promote the reaction, affording 3,4-diphenylcoumarin (**3aa**) in high yield (entry 4). The requirement for a Ag salt (entry 3) implied that the in situ formation of cationic Rh^{III} species was essential for the success of this reaction. $AgSbF_6$ is slightly less efficient than AgOTf but also led to a satisfactory result (entry 5).

Our screening of different oxidants revealed that only copper acetate was suitable. Although Ag salts prove to be good oxidants in many Rh- or Pd-catalyzed reactions, they were not efficient in this case (entries 6 and 7). Compared to anhydrous $Cu(OAc)_2$, its crystalline hydrate led to a relatively lower yield of the product (entry 8). Examination of copper salts with

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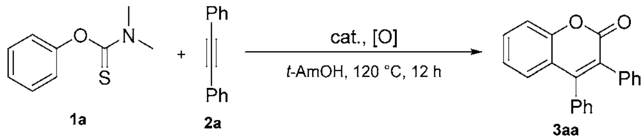
Table 1. Effect of Reaction Parameters[a]



entry	catalyst	oxidant	yield[b] (%)
1[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	0
2	$[(p\text{-cymene})RuCl_2]_2$/AgOTf	$Cu(OAc)_2$	0
3	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	trace
4	$[Cp^*RhCl_2]_2$/AgOTf	$Cu(OAc)_2$	81
5	$[Cp^*RhCl_2]_2$/$AgSbF_6$	$Cu(OAc)_2$	71
6	$[Cp^*RhCl_2]_2$	AgOAc	trace
7	$[Cp^*RhCl_2]_2$	AgOTf	0
8	$[Cp^*RhCl_2]_2$/AgOTf	$Cu(OAc)_2 \cdot H_2O$	67
9	$[Cp^*RhCl_2]_2$/AgOTf	$CuSO_4$	12
10	$[Cp^*RhCl_2]_2$/AgOTf	$Cu(OTf)_2$	0
11[d]	$[Cp^*RhCl_2]_2$/AgOTf	$Cu(OTf)_2$/KOAc	42
12	$[Cp^*RhCl_2]_2$/AgOTf	$Cu(CF_3CO_2)_2$	25
13[e]	$[Cp^*RhCl_2]_2$/AgOTf	O_2/AcOH	trace

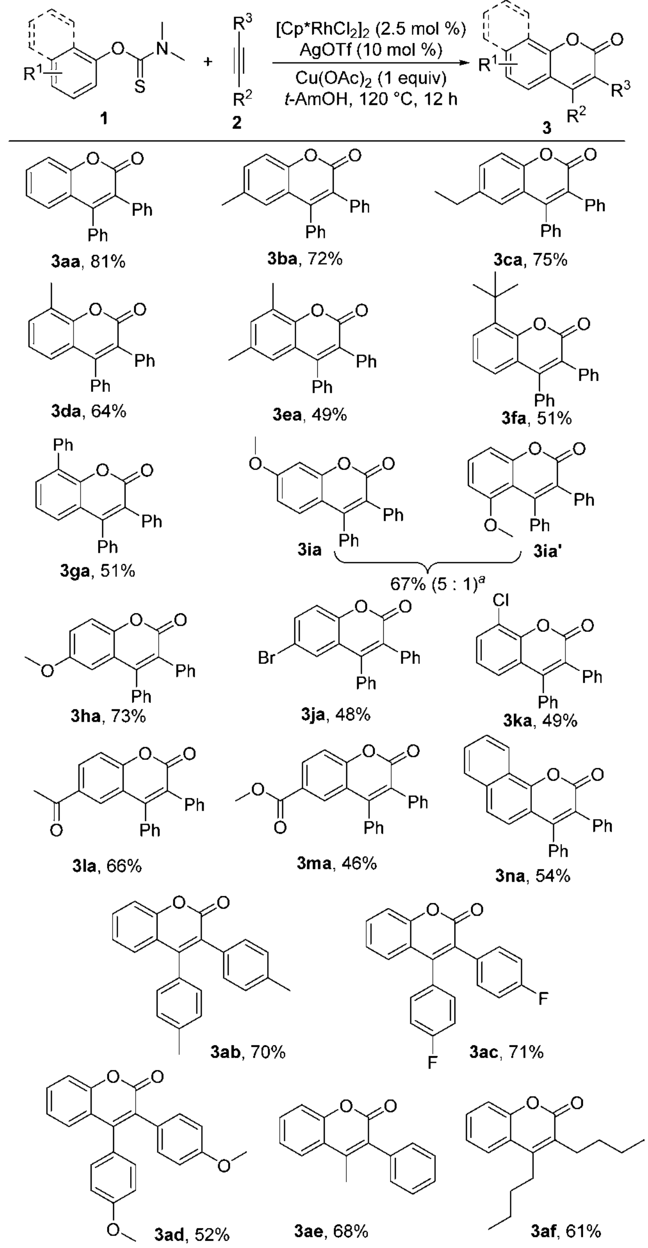
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), catalyst (0.0125 mmol), Ag salt (0.05 mmol), oxidant (0.5 mmol), *t*-AmOH (1.5 mL). All the reactions were performed in sealed tubes under Ar. [b]Isolated yield. [c]0.025 mmol of $Pd(OAc)_2$. [d]1 mmol of KOAc. [e]1 atm of O_2 and 1 mmol of AcOH.

other anions indicated the importance of the acetate anion (entries 9−12). These results are consistent with the mechanism we proposed in our previous work related to the intramolecular cyclization of **1a**.[13] The acetate anion is most efficient in attacking the iminium intermediate, leading to its transformation to the carbonyl group. Finally, the Rh/O_2 catalytic system[12q] is not applicable for the reaction, even under acidic conditions (also see the Supporting Information).

Having gained preliminary insight into this novel reaction and identified the optimized reaction conditions, we next explored the scope and generality of this process. First, a variety of substituted aryl thiocarbamates **1**, which could be readily prepared from the condensation of corresponding phenols with dimethylthiocarbamoyl chloride, were allowed to react with diphenylacetylene (**2a**) (Scheme 2). Generally, the aryl thiocarbamates with electron-donating substituents such as alkyl and methoxyl group on the phenyl ring at the *para* position gave good yields (**3aa**−**ca**). However, when the substituent was on the *ortho* position (**3da**−**ga**,**na**), the corresponding coumarin was obtained in relatively lower yield. The *m*-methoxyl-substituted precursor cyclized to give a mixture of 7-substituted **3ia** and 5-substituted **3ia′** in 67% total yield with 5:1 regioselectivity, indicating that the cyclization tends to take place at the side of less steric hindrance.

The electron-deficient thiocarbamates also exhibited medium reactivity (**3ja**−**ma**). It is noteworthy that the potentially labile halogen group was inert in this reaction (**3ja** and **3ka**). In addition, a series of other functional groups, such as a ketone (**3la**) and an ester (**3ma**), were also compatible. Next, the scope of the internal alkynes was also surveyed. Annulation of the model thiocarbamate **1a** with the electron-rich 4-methylphenyl-substituted alkyne (**2b**) or 4-methoxylphenyl-substituted alkyne (**2d**) produced the desired coumarins **3ab** and **3ad** in 70% and 52% yields, respectively. Similarly, the electron-deficient 4-fluorophenyl-substituted alkyne **2c** underwent annulation with **1a** efficiently. Reaction of **1a** with

Scheme 2. Substrate Scope*



*All reactions were performed with **1** (0.5 mmol), **2** (0.75 mmol), $[Cp^*RhCl_2]_2$ (0.0125 mmol), AgOTf (0.05 mmol), $Cu(OAc)_2$ (0.5 mmol), in *t*-AmOH (1.5 mL) at 120 °C under Ar for 12 h. Yields shown are of isolated products. [a]The ratio of these two isomers was determined by GC.

phenylpropyne (**2e**) afforded 4-methyl-3-phenyl-2*H*-chromen-2-one (**3ae**) as the sole product, the structures of which were established on the basis of comparison of NMR spectra with those reported in the literature.[6a] The present reaction was successfully extended to aliphatic alkyne. The expected coumarin **3af** was furnished from **1a** and 5-decyne in 61% yield.

To obtain insight into the reaction mechanism, some control experiments were carried out (Scheme 3). The reaction of phenyl dimethylcarbamate (**3a**) with diphenylacetylene (**2a**) under "standard conditions" as described in Table 1 led to complex unknown products, and no desired coumarin **3aa** was observed (eq 1). In addition, *S*-phenyl dimethylcarbamothioate

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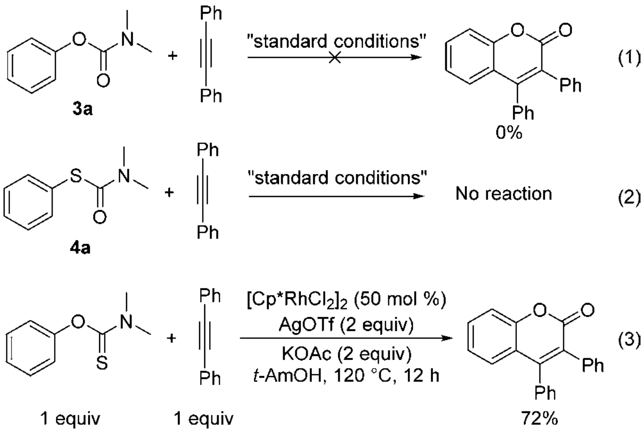
Scheme 3. Control Experiments

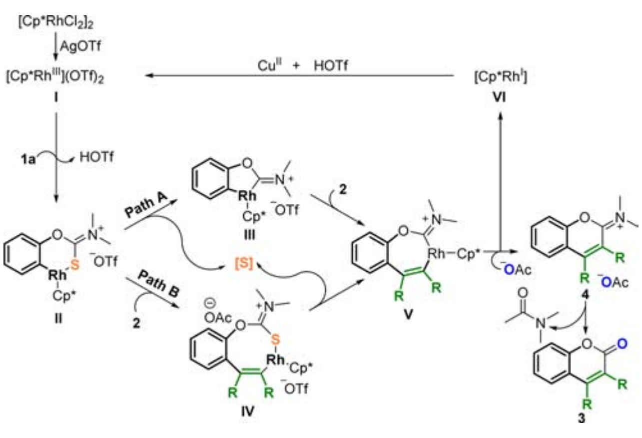


(**4a**) was inert in this catalytic system (eq 2). These results indicate that the soft but easily removable sulfur atom containing thiocarbamate group is essential for the success of the annulation with alkyne to afford coumarins.

In addition, a stoichiometric Rh catalyst (50 mol % of $[Cp^{*}RhCl_2]_2$) was allowed to react with **1a** and **2a** under standard conditions, except for the addition of 2 equiv of KOAc instead of $Cu(OAc)_2$ (eq 3). A 72% yield of **3aa** could be obtained, which indicates that a Rh^{I}–Rh^{III} cycle might be involved in this reaction. This experiment could also prove that in the catalytic reaction it is Cu^{2+} that reoxidizes Rh^{I} to Rh^{III}, and the acetic anion is required to form the carbonyl in the final coumarin product.

Although XPS experiments were carried out to identify the final form of sulfur in the reaction system (see Supporting Information), the detailed desulfurization process in this reaction system is still unclear. Based on previous mechanistic studies on C–S bond cleavage[13,14] and Rh-catalyzed C–H activation involving the insertion of alkyne into Rh–C bond of a Rh–Het intermediate complex,[15] we could propose the following mechanism as illustrated in Scheme 4. In the presence

Scheme 4. Proposed Mechanism



of AgOTf, cationic $[Cp^{*}Rh^{III}]$ (**I**) is first generated in situ as the active catalyst, which coordinates with the soft sulfur atom with high negative charge density in the thiocarbamate **1a**. Owing to the easy resonance to polarized structure of **1a**, its Rh complex tends to exist in Rh-*S*-enolate species, which further undergo *ortho* C–H activation to afford rhodacyclic complex **II**. Subsequently, as it is unclear in which step the desulfurization occurs, two possible pathways can be considered. In path A, desulfurization followed by migratory insertion gives the seven-membered rhodacycle **V**, while in path B, alkyne insertion takes place at first to afford the eight-membered ring **IV** which could then transfer to **V**. Next, reductive elimination releases the iminium salt **4** and Rh^{I} (**VI**) which can be reoxidized by $Cu(OAc)_2$ in the presence of trifluoromethanesulfonic acid to complete the catalytic cycle. The nucleophilic attack of acetic anion onto the iminium carbon followed by C–N bond cleavage affords the desired coumarin **3** and dimethylacetamide, which has been confirmed in our previous work.[13]

In summary, we have developed a new and efficient Rh-catalyzed oxidative annulation protocol to construct coumarins. This process exploits a thiocarbamate group directed C–H bond activation, an annulation with an alkyne, and a desulfurization. Control experiments and mechanism studies revealed that $Cu(OAc)_2$ acts both as the oxidant for Rh^{I} and as the oxygen source of the carbonyl group. Further investigations to gain a detailed mechanistic understanding of this reaction and the extension of this reaction are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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