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Gold Catalysis

Practical, Modular, and General Synthesis of 3-Coumaranones through Gold-Catalyzed Intermolecular Alkyne Oxidation Strategy

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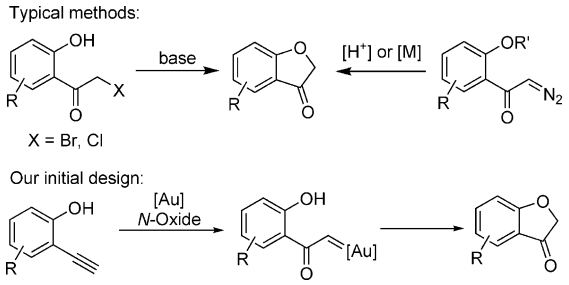
Abstract: A gold-catalyzed intermolecular alkyne oxidation for the preparation of 3-coumaranones has been developed. Using 8-isopropylquinoline *N*-oxides as oxidants, the reactions of *o*-ethynylanisoles afford versatile 3-coumaranones in moderate to good isolated yields. The synthetic utility of this chemistry is also indicated by the synthesis of the natural product sulfuretin.

3-Coumaranone is a type of important heterocyclic compounds that can be found in a range of natural products[1] and patented compounds of medical interest.[2] Functionalized 3-coumaranones have also proven to be valuable intermediates for the synthesis of some complex molecules such as aurones[3] and benzofurans.[4] The synthesis of 3-coumaranones has been mainly realized by base-mediated cyclization of halogenated acetophenones,[5] or by acid-promoted or metal-catalyzed decomposition of diazo ketones (Scheme 1).[6] However, these methods generally suffer from drawbacks such as mutistep synthesis, limited substrate scope, and inaccessible and toxic starting materials. Therefore, a highly efficient, straightforward and modular method is still of great interest.



Scheme 1. Formation of 3-coumaranones through gold-catalyzed intermolecular alkyne oxidation.

Recently, much attention has been paid to the gold α-oxo carbenoid intermediates generated from gold-catalyzed[7] intermolecular alkyne oxidations by using pyridine *N*-oxides or quinoline *N*-oxides, which offers easy access to an incredible variety of useful complex structures.[8–9] Most importantly, this protocol circumvents the use of hazardous and potentially explosive diazo carbonyl compounds, and makes alkynes as equivalents of α-diazo ketones. In our recent study toward such a gold-catalyzed oxidative cyclization,[10] we reported a gold-catalyzed intermolecular oxidation of *o*-ethynylanilines for the synthesis of synthetically useful 3-oxyindoles, which outcompetes the typical indole formation.[10c] Inspired by these results, we envisioned that the synthesis of 3-coumaranones might be accessed directly from the corresponding *o*-ethynylphenol substrates by using a similar strategy (Scheme 1).[11] Herein, we describe the successful implementation of such a gold-catalyzed alkyne oxidation, which leads to a practical and modular synthesis of various functionalized 3-coumaranones. The utility of this strategy is showcased by the concise synthesis of the natural product sulfuretin; a density functional theory (DFT) study on the plausible reaction mechanism for this oxidative cyclization is also investigated.

Our initial investigation focused on the reaction of *o*-ethynylphenol **1a** under our previously established optimal conditions for the *o*-ethynylaniline substrates. However, as illustrated in Eq. (1), the desired 3-coumaranone **4a** was only obtained in 30% NMR yield, and significant formation of the benzofuran **2a** was observed.[12] In addition, unlike the related *o*-ethynylaniline, *o*-ethynylphenol **1a** was not stable and thus its preparation took place with low efficiency.[13] To address these problems, we then turned to synthesize protected *o*-ethynylphenol

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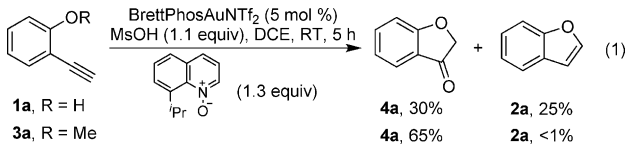
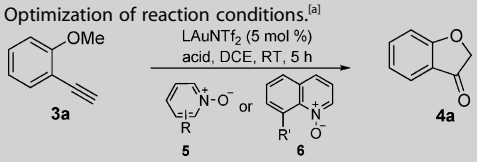
derivatives to investigate the reaction. Pleasingly, it was found that the use of *o*-ethynylanisole substrate **3a** completely suppressed the formation of side product **2a** and furnished the desired 3-coumaranone **4a** in 65% NMR yield. Interestingly, no oxonium ylide [1,2]-shift product was observed in this case.[6b,g]



We then used *o*-ethynylanisole **3a** as the model substrate to further optimize the reaction conditions. The influence of different oxidants was first examined (Table 1, entries 1–6). It was found that quinoline *N*-oxides **6a**–**6c** worked equally well (Table 1, entries 1, 5–6) and **6c** worked best (Table 1, entry 1). However, attempts to improve the yield of this reaction by screening of other gold catalysts and the use of other acids were unsuccessful (Table 1, entries 7–15). During further optimization of this reaction, we were delighted to find that the ratio of oxidant **6c** and MsOH substantially affected the reaction (Table 1, entries 16–17), and 77% yield was achieved in the presence of 1.5 equivalents of MsOH (Table 1, entry 16). Further studies revealed that elevating the equivalent of oxidant **6c** and maintaining it slightly excess to MsOH could lead to a further improved yield, and 3-coumaranone **4a** was isolated in 86% yield using 2.7 equivalents of **6c** and 2.4 equivalents of MsOH (Table 1, entry 19). Notably, in the absence of the gold catalyst, the desired product was not formed under the acidic reaction conditions,[14] and $PtCl_2$ and $AgNTf_2$ could not catalyze this reaction.

With the optimal reaction conditions secured, the reaction scope was then studied. As summarized in Table 2, a variety of *o*-ethynylanisole derivatives **3** were employed to generate the corresponding 3-coumaranones **4** with yields ranging from 53% to 93%. In general, the substrates with electron-withdrawing groups on the aromatic ring gave moderate to good yields (Table 2, entries 1–8), except the one with the nitro group, which only gave 56% yield (Table 2, entry 6). In the case of substrates with electron-donating groups, the reaction proceeded equally well and the methoxy group was also allowed, albeit it

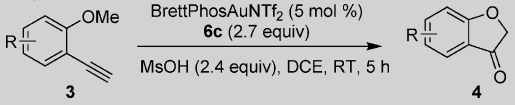
Table 1. Optimization of reaction conditions.[a]

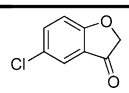
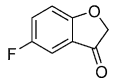
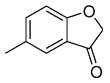
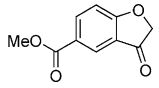
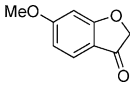
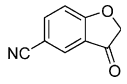
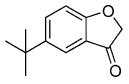
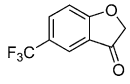
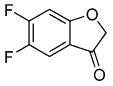
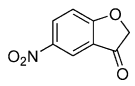
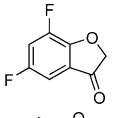
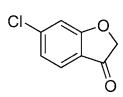
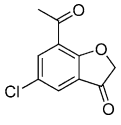


Entry	L	Oxidant (R)	Acid	Yield [%][b]
1	BrettPhos	**6c** (R′ = *i*Pr)	1.1 equiv MsOH	65
2	BrettPhos	**5a** (2-Br)	1.1 equiv MsOH	55
3	BrettPhos	**5b** (3,5-Cl_2)	1.1 equiv MsOH	41
4	BrettPhos	**5c** (2,6-Br_2)	1.1 equiv MsOH	<5[d]
5	BrettPhos	**6a** (R′ = Me)	1.1 equiv MsOH	60
6	BrettPhos	**6b** (R′ = Et)	1.1 equiv MsOH	62
7	PPh_3	**6c** (R′ = *i*Pr)	1.1 equiv MsOH	57
8	(4-$CF_3C_6H_4$)$_3$P	**6c** (R′ = *i*Pr)	1.1 equiv MsOH	53
9	Cy-JohnPhos	**6c** (R′ = *i*Pr)	1.1 equiv MsOH	58
10	XPhos	**6c** (R′ = *i*Pr)	1.1 equiv MsOH	61
11	Et_3P	**6c** (R′ = *i*Pr)	1.1 equiv MsOH	51
12	IPr	**6c** (R′ = *i*Pr)	1.1 equiv MsOH	42
13	Au^{III}[c]	**6c** (R′ = *i*Pr)	1.1 equiv MsOH	<5[d]
14	BrettPhos	**6c** (R′ = *i*Pr)	1.1 equiv CF_3CO_2H	25
15	BrettPhos	**6c** (R′ = *i*Pr)	1.1 equiv $HNTf_2$	13
16	BrettPhos	**6c** (R′ = *i*Pr)	1.5 equiv MsOH	77
17	BrettPhos	**6c** (R′ = *i*Pr)	2.0 equiv MsOH	70
18[e]	BrettPhos	**6c** (R′ = *i*Pr)	2.7 equiv MsOH	91
19[f]	BrettPhos	**6c** (R′ = *i*Pr)	2.4 equiv MsOH	90[g]

[a] Reaction conditions: [**3a**] = 0.05 M, oxidant (2.0 equiv); DCE: 1, 2-dichloroethane; MsOH: methanesulfonic acid. [b] Estimated by ^{1}H NMR using diethyl phthalate as internal reference. [c] Dichloro(2-picolinato)gold(III). [d] Most **3a** remained unreacted. [e] 3.0 equiv of **6c** was used. [f] 2.7 equiv of **6c** was used. [g] 86% isolated yield.

Table 2. Reaction scope study.[a]

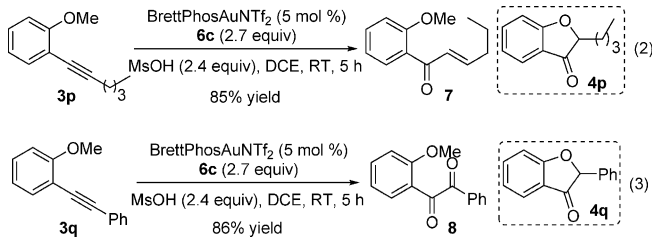


Entry	Product	4	Yield [%]	Entry	Product	4	Yield [%]
1		**4b**	79	8		**4i**	84
2		**4c**	68	9		**4j**	93
3		**4d**	84	10		**4k**	66
4		**4e**	88	11		**4l**	88
5		**4f**	79	12		**4m**	53
6		**4g**	56	13		**4n**	57
7		**4h**	85	14		**4o**	53

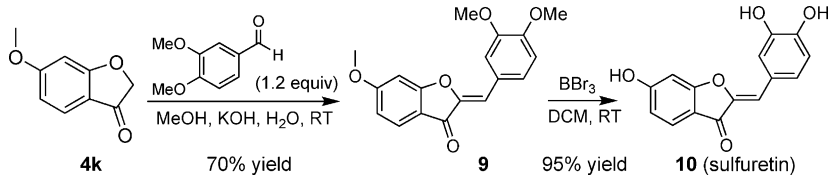
[a] Reactions run in vials; [**3**] = 0.05 M; isolated yields are reported.

led to product with a relatively low yield (Table 2, entry 10). It is notable that this chemistry could also be extended to the synthesis of disubstituted 3-coumaranones **4m**–**4o** with reasonable yields (Table 2, entries 12–14).

We then considered the possibility of extending the reaction to internal alkynes. However, no formation of the desired 3-coumaranone was observed under the above optimized reaction conditions. As shown in Equation (2) and Equation (3), the treatment of substrate **3p** only led to the isolation of α,β-unsaturated ketone **7**[15] in 85% yield while only diketone compound **8** was formed upon treatment of substrate **3q**.[16] In spite of this, these alkylated or arylated 3-coumaranones might be readily achieved from the 3-coumaranone **4a** according to the known procedures.[17]

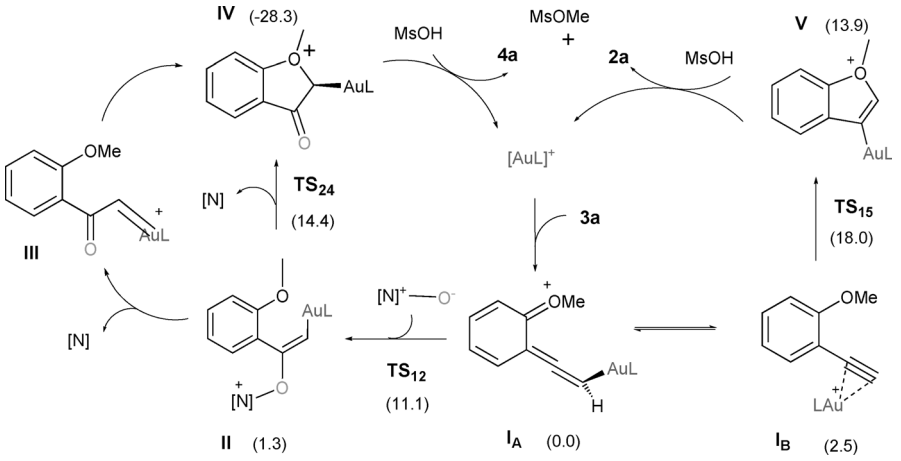


3-Coumaranones have been demonstrated well as key precursors in the synthesis of aurones, which exist in a number of natural products and bioactive molecules. As outlined in Scheme 2, for example, condensation of 3-coumaranone **4k** with 3,4-dimethoxybenzaldehyde in basic conditions, followed by demethylation with BBr_3, provided the natural product sulfuretin **10**, which exerts diverse biological activities, such as anti-nociceptive, anti-oxidant, anti-mutagenic, and anti-diabetic activities.[1a,18]



Scheme 2. Synthetic applications.

The mechanism[19] accounting for the oxidative formation of 3-coumaranones is depicted in Scheme 3, based on experimental observations and DFT computations (Figure 1, see the Supporting Information for details). Initially, coordination of substrate **3a** to the catalytic gold(I) species forms the gold-alkyne complex $\mathbf{I_A}$. This allene-like intermediate is subject to nucleophilic attack of the *N*-oxide, forming the alkenyl gold intermediate **II**. Subsequent N–O bond cleavage was noteworthily found by DFT computations to give directly the oxonium ylide intermediate **IV**,[20,21] thus bypassing the presumed α-oxo gold carbene intermediate **III**.[22] Proto-demetallation and demethylation from intermediate **IV** would furnish the final 3-coumaranone **4a**. The accompanying MsOMe could be detected from the crude ^{1}H NMR in all cases. Competitively, an *N*-oxide-free pathway (Scheme 3) could be initiated by 1,5-cyclization within the gold-alkyne complex $\mathbf{I_B}$, followed by protodemetallation and demethylation of the as-formed benzofuran-3-yl gold intermediate **V** to afford benzofuran **2a** as side product. However, preliminary DFT computations showed that starting from the gold-alkyne intermediates, the formation of oxonium ylide intermediate **IV** is quite exothermic (−28.3 kcal mol^{-1}) and irreversible, while formation of benzofuran-3-yl gold intermediate **V** is endothemic (13.9 kcal mol^{-1}) and highly reversible (Scheme 3). That is, the *N*-oxide-involving pathway affording 3-coumaranone **3a** (with an activation barrier of ~14.4 kcal mol^{-1}) is both thermodynamically and kinetically favored over the *N*-oxide-free pathway that affords byproduct benzofuran **2a** (with an activation barrier of 18.0 kcal mol^{-1}).



Scheme 3. Mechanistic proposal for the gold-catalyzed synthesis of 3-coumaranones (left) and benzofuran (right). Relative free energies (in kcal mol^{-1}, in DCE at 298 K) of key intermediates and transition states given in parentheses were computed at the SMD-M06/6-31+G*&SDD(Au) level of theory with L = PH_3[23] and [N] = pyridine.

In summary, we have developed a practical and general solution for the synthesis of various 3-coumaranones via a gold-catalyzed intermolecular oxidation of alkynes. The utility of this methodology is demonstrated by the synthesis of the natural product sulfuretin. Moreover, theoretical investigations on the reaction pathways for this oxidative cyclization were also performed. The high flexibility, broad substrate scope, and mild nature of this reaction and, in particular, the absence to exclude moisture or air ('open flask') render it a viable alternative for the synthesis of synthetically useful 3-coumaranones.

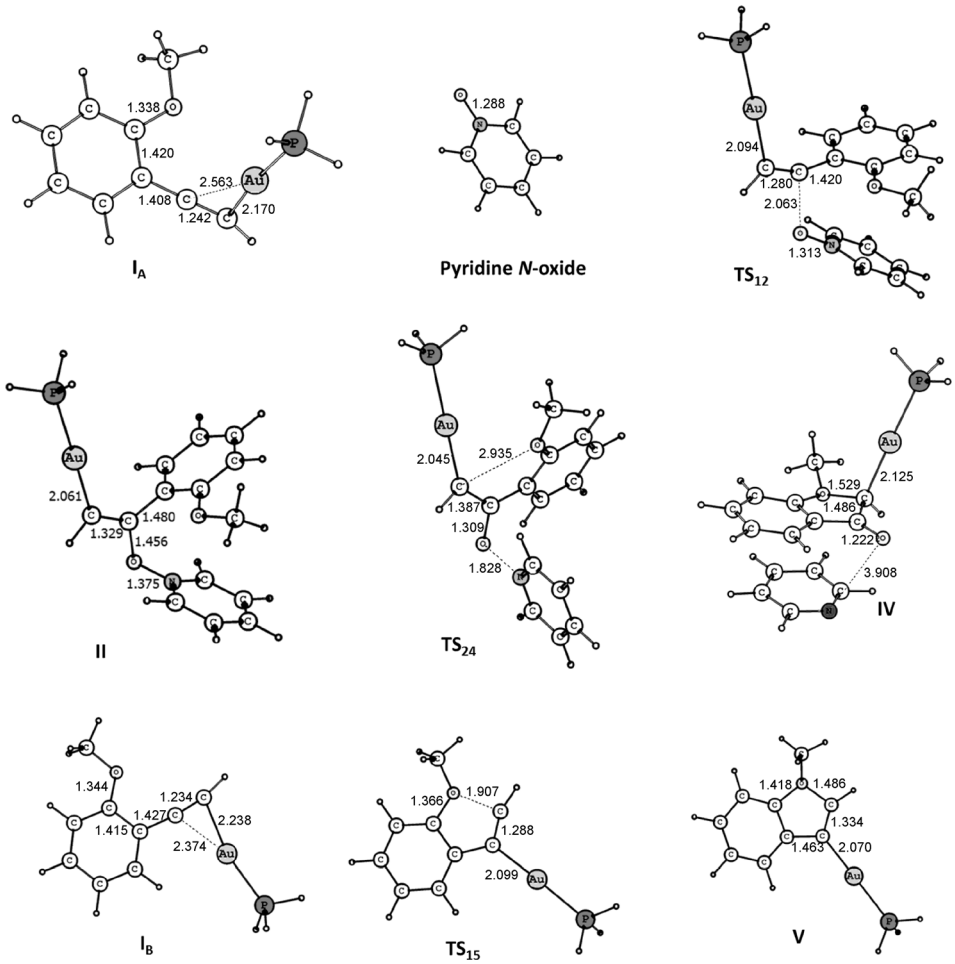


Figure 1. Optimized structures of the intermediates and transition states from SMD-M06/6-31+G(d)&SDD(Au) calculations.

Experimental Section

Typical procedure for gold-catalyzed oxidative cyclization of o-ethynylanisoles

8-Isopropylquinoline *N*-oxide **6c** (151.6 mg, 0.81 mmol), MsOH (3.0 mL, 0.24 M in DCE), and BrettPhosAuNTf$_2$ (15.2 mg, 0.015 mmol) were added in this order to a solution of the 2-ethynylanisole substrate **3** (0.30 mmol) in 1, 2-dichloroethane (DCE, 3.0 mL) at room temperature. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. The reaction typically took 5 h for completion. The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and washed with saturated aqueous $NaHCO_3$ (2×15 mL). The resulting solution was extracted again with CH_2Cl_2 (30 mL) and the combined organic layers were dried with $MgSO_4$. The mixture was then concentrated and the residue was purified by chromatography on silica gel (hexanes/ethyl acetate 10:1) to afford the desired product **4**.

Acknowledgements

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Keywords: alkynes · gold · heterocycles · homogeneous catalysis · oxidation

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Gold Catalysis

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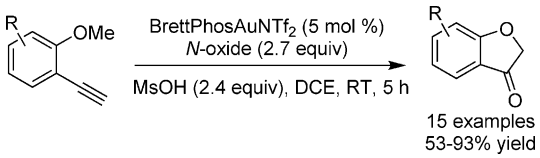
Practical, Modular, and General Synthesis of 3-Coumaranones through Gold-Catalyzed Intermolecular Alkyne Oxidation Strategy



Gold is a treasure: A gold-catalyzed intermolecular alkyne oxidation for the preparation of 3-coumaranones has been developed. Using 8-isopropylquinoline *N*-oxides as oxidants, the reactions of *o*-ethynylanisoles afford versatile 3-coumaranones in moderate to good isolated yields.