JOC Article

Efficient Synthesis of γ-Keto Esters through Neighboring Carbonyl Group-Assisted Regioselective Hydration of 3-Alkynoates

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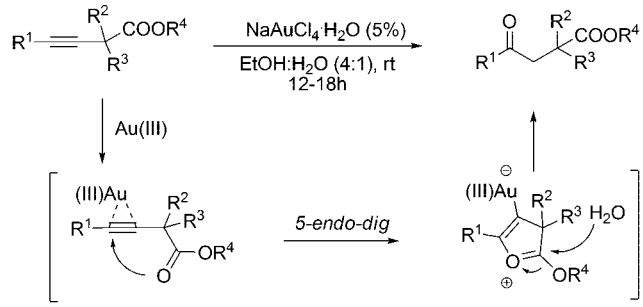

R^1: Me, *n*-C_6H_{13}, Ph; R^2 and R^4: Me or Et; R^3: alkenyl, alkyl, alkyl ether, halide, alkyl ester; R^4: alkyl

The Au(III)-catalyzed hydration of 3-alkynoates led to a practical one-step synthesis of γ-keto esters in high yields, through a carbonyl group participation enabled by a favored 5-*endodig* cyclization. This mild-aqueous ethanol, room temperature, and atom-economical method has been used effectively with a wide range of substrates. Using the same conditions, a 2-alkynoate produced the corresponding β-keto ester in high yield.

1,4-Dicarbonyl compounds are starting materials and intermediates in many important natural products and synthetic drug syntheses.[1] Unlike their 1,3 or 1,5 counterparts, the disconnection of 1,4-dicarbonyl compounds, especially of highly substituted 1,4-dicarbonyl compounds like γ-keto-α,α-substituted esters, is not trivial. Radical or carbene[2] methods or some other relatively complex methods[3] have been used to synthesize them. A tactical approach that enables a one-step synthesis of highly substituted γ-keto esters could be the directed hydration of 3-alkynoates, provided this transformation can be carried out regioselectively, under mild conditions, and with good functional group tolerance. The attractiveness of this approach lies in the fact that the hydration of alkynes is one of the most straightforward methods to obtain carbonyl compounds. Unlike other syntheses of carbonyl compounds, the hydration of alkynes is an atom-economical addition of water without energy-intensive redox chemistry.[4a] In addition, the alkyne functionality is chemically inert toward many reaction conditions, and so it can be considered a masked ketone. Herein we report a neighboring carbonyl group-assisted hydration of internal alkynes in the presence of a gold(III) catalyst that yields a highly regioselective synthesis of γ-keto esters.

The mercury(II)-catalyzed hydration of alkynes has been known for more than a century.[4b] To avoid the use of toxic mercury(II) salts, various catalysts such as Brønsted acids[5] and metal catalysts such as Ru(II),[6] Ru(III),[7] Rh(III),[8] Ir,[9] Pt(II),[10] and Au[11] as well as other systems[12] have been examined. There are excellent catalysts for terminal alkynes but internal alkynes remain a challenge, in part because of regioselectivity issues. Gold catalysis is especially promising for the hydration of alkynes because of the higher affinity of gold toward alkynes compared to other common oxygen- or nitrogen-containing

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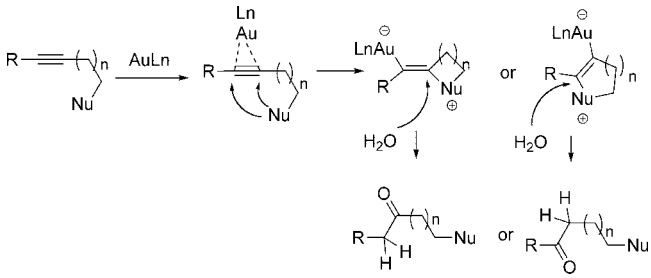
SCHEME 1. Directed Gold-Catalyzed Hydration of Alkynes through Neighboring Group Assistance

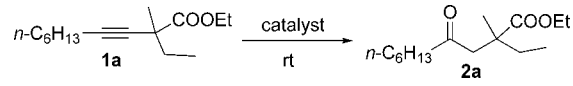


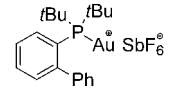
functional groups. In 1991, Fukuda and co-workers reported the use of a Au(III) salt in refluxing aqueous methanol for the hydration of terminal alkynes to methyl ketones (Markovnikov addition).[11c] But their hydration of internal alkynes was sluggish and nonregioselective. Many other gold catalysts also have been examined, but only terminal alkynes showed good regioselectivity (Markovnikov products), and most reactions needed elevated temperatures or strong acid cocatalysts.[11]

In general, the regioselective hydration of internal alkynes may only proceed in the presence of a directing functionality (like heteroatoms, or aromatic rings) nearby.[13] We proposed that with internal alkynes possessing a nucleophilic site, Nu, nearby (Scheme 1), this nucleophile could attack a gold activated triple bond to form two regioisomeric cyclic intermediates. Although both carbons in the triple bond are prone to nucleophilic attack, one cyclic intermediate may be favored over the other according to Baldwin's rules. If Nu is a carboxylic ester, this neighboring group assistance may then lead to a highly regioselective synthesis of γ-keto esters through an alkyne hydration process.

To test this hypothesis, we first examined the effect of transition metal catalysts on the hydration of 3-alkynoate **1a** (Table 1). 3-Alkynoate **1** can be synthesized easily by using our published procedure.[14] Our selection of metal catalysts was based on the known alkynophilicity of gold(I), gold(III), platinum(II), and silver(I).[15] A strong acid alone[5] had no effect on **1a** (Table 1, entry 1). Treatment of **1a** with Au(I) or $PtCl_2$ catalysts gave traces of hydration product **2a** at room temperature (Table 1, entries 2−5). Conversely, the addition of a strong acid to AuCl or $Au(PPh_3)Cl$ produced the desired ketone but in less than desirable yields, due to side reactions induced by the prevailing acidic conditions (Table 1, entries 6 and 7). On the other hand, the use of Au(III) catalysts such as $AuBr_3$, $AuCl_3$, or $NaAuCl_4 \cdot 2H_2O$ offered hope (Table 1, entries 8−10). We decided to investigate the effects of solvents and additives/ligands on the hydration of **1a** employing Au(III) catalysts.

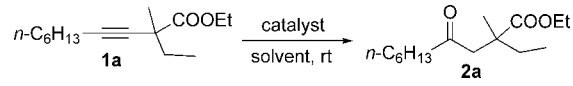
TABLE 1. Screening of Metal Catalysts for the Hydration of 1a



entry	catalyst (5%)	solvent	time	yield[a]
1	10%TsOH	CH_2Cl_2 (S)[b]	24 h	no rxn
2	$PtCl_2$	CH_2Cl_2 (S)	12 h	trace
3	$Au(PPh_3)Cl$	CH_2Cl_2 (S)	12 h	trace
4	AuCl	CH_2Cl_2 (S)	12 h	trace
5		CH_2Cl_2 (S)	12 h	trace
6	AuCl, 10%TsOH	CH_2Cl_2 (S)	24 h	50%
7	$Au(PPh_3)Cl$, 10% H_2SO_4	CH_2Cl_2 (S)	12 h	60%
8	$AuBr_3$	CH_2Cl_2 (S)	12 h	70%
9	$AuCl_3$	CH_2Cl_2 (S)	12 h	41%
10	$NaAuCl_4 \cdot 2H_2O$	CH_2Cl_2 (S)	12 h	71%

[a] Yields are based on ^{1}H NMR. [b] CH_2Cl_2 saturated with water.

TABLE 2. Screening of Solvents and Additives



entry	catalyst (5%)/ additive	solvent	time, h	yield,[a] %
1	$AuBr_3$	CH_2Cl_2 (S)[b]	12	70
2	$AuBr_3$	$MeOH/H_2O$ (10:1)	12	17
3	$AuBr_3$	CH_2Cl_2/H_2O (100:1)	72	trace
4	AuBr3	*t*-$BuOH/H_2O$ (10:1)	12	25
5	$AuBr_3$	CH_3CN/H_2O (10:1)	12	35
6	$AuBr_3/Bu_4NBr$ (5%)	CH_2Cl_2 (S)	12	6
7	$AuBr_3/Bu_4NBr$ (5%)	$MeOH/H_2O$ (10:1)	12	trace
8	$AuBr_3$/pyridine (5%)	$MeOH/H_2O$ (10:1)	12	NR[d]
9	$AuBr_3/P(OEt)_3$ (5%)	$MeOH/H_2O$ (10:1)	12	NR[d]
10	$AuCl_3$	$MeOH/H_2O$ (10:1)	24	33
11	$AuCl_3$/AgOTf (15%)	$MeOH/H_2O$ (10:1)	24	complex
12	$NaAuCl_4 \cdot 2H_2O$	CH_2Cl_2 (S)	12	71
13	$NaAuCl_4 \cdot 2H_2O$	*t*-$BuOH/H_2O$	12	56
14	$NaAuCl_4 \cdot 2H_2O$	$EtOH/H_2O$ (50:1)	12	33
15	$NaAuCl_4 \cdot 2H_2O$	$EtOH/H_2O$ (4:1)	12	78
16	$NaAuCl_4 \cdot 2H_2O$	$EtOH/H_2O$ (1:1)	12	33
17	$NaAuCl_4 \cdot 2H_2O$	$MeOH/H_2O$ (10:1)	12	mixture[c]

[a] Yields are based on ^{1}H NMR. [b] CH_2Cl_2 saturated by water. [c] Mixture of **2a** and corresponding methyl ester. [d] NR = no reaction.

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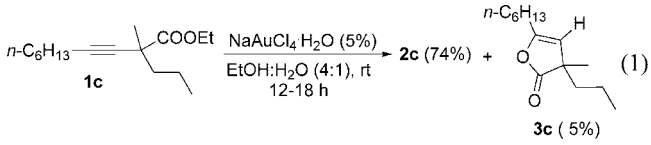
Using $AuBr_3$ in various solvent combinations did not improve the yield of **2a** significantly (Table 2, entries 1−5). We then tested a combination of $AuBr_3$ with various additives or ligands, such as nBu$_4$NBr, P(OEt)$_3$, or pyridine, with disappointing results (Table 2, entries 6−9). A complex mixture was observed when a combination of $AuCl_3$ and AgOTf in MeOH/H_2O was used, whereas $AuCl_3$ alone produced **2a** in only 33% yield (Table 2, entries 10 and 11).

After screening $NaAuCl_4 \cdot 2H_2O$ with different solvent combinations (Table 2, entries 12−17), we concluded that $NaAuCl_4 \cdot 2H_2O$ in EtOH/H_2O (4:1) offered the best conditions for the hydration of alkyne **1a**. When methanol was used as solvent, the reaction gave a mixture of **2a** and corresponding methyl ester because of transesterification (Table 2, entry 17). When a smaller catalyst loading ($NaAuCl_4 \cdot 2H_2O$, 2%) was used the reaction was slower, but hydration of compound **2a** still could be completed after 24 h. With optimal conditions in hand, we explored the scope of this reaction (Table 3). The hydration proceeded smoothly in high yields and regioselectivity, and was tolerant of ether, double bond, and other ester functionalities (Table 3, entries 4, 5, and 8, respectively). Indeed, only one regioisomer was detected in all the crude products examined. The steric hindrance of the quaternary α-carbon could be ruled out as the reason for the high selectivity of the hydration because a 3-alkynoate possessing no substituents in its α-carbon also showed excellent regioselectivity after hydration (Table 3, entry 10). The stereoelectronic effects of a phenyl group could account for the lower yield observed in entry 7 (Table 3). The hydration of 2-fluoro-3-alkynoate **1k** gives α,β-unsaturated ester **2k** (Table 3 entry 11) through concomitant elimination of HF during the hydration process.

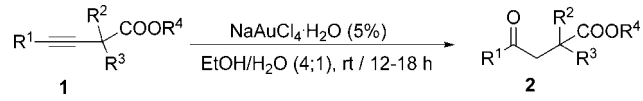
The adjacent carbonyl group in alkyne **1** plays an important role in both reaction rate and regioselectivity. For example, the hydration of dec-2-yne ***1l*** under similar conditions was much slower (Scheme 2, top), and although the chemical yield was high, the regioselectivity was poor. The hydration of the sterically demanding 4,4-dimethylpent-2-yne **1m** was even slower; indeed, after 72 h, almost no reaction had taken place (Scheme 2, bottom). These results were in sharp contrast with the hydration of β-alkynyl esters, for even the hydration of sterically encumbered β-alkynyl esters **1h** and **1i** proceeded smoothly at room temperature (Table 3, entries 8 and 9).

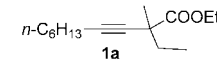
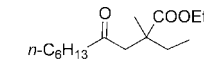
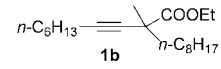
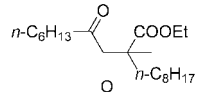
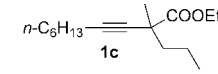
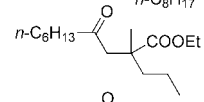
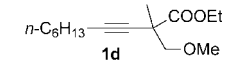
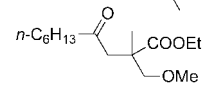
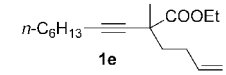
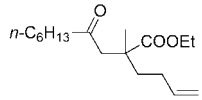
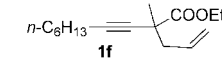
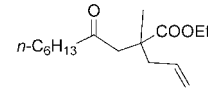
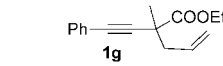
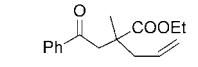
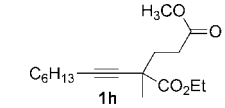
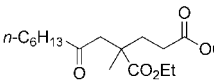
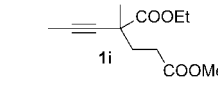
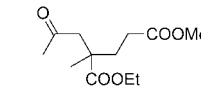
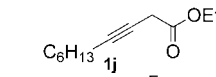
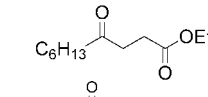
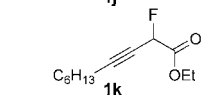
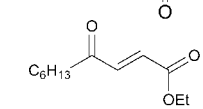
It is noteworthy that in some cases we obtained small or trace amounts of a cyclic byproduct (e.g., **3c** in eq 1).



The proposed mechanism for the reaction based on similar reaction systems[3c,16] is shown in Scheme 3. First, the gold(III) catalyst coordinates with alkyne **1**, activating the triple bond; this triggers the nucleophilic carbonyl group nearby, which then goes after the triple bond to form a cyclized vinyl gold intermediate of type **A** or **B**.[17] According to Baldwin's rules,[18] if the carbonyl oxygen attacks the β-carbon, it is considered a 4-*exo-dig* process, which is disfavored. But if the carbonyl oxygen attacks the γ-carbon, it would then be a 5-*endo-dig* attack, which is favored.[19,20] Hashmi and co-workers have reported the cyclization of an ethynyl ketone to a furan through the 5-*endodig* process.[19] Thus, **B** should be the predominating intermediate. Then, upon interacting with water, **B** forms the

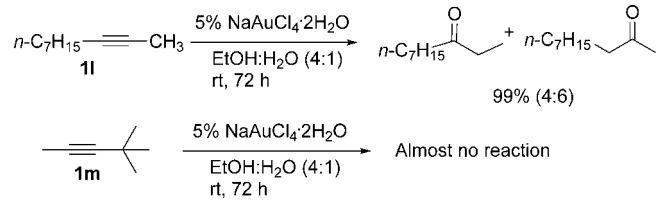
TABLE 3. Au(III)-Catalyzed Hydration of Internal 3-Alkynoates[a]



entry	1	2[a]	isolated yield
1			**2a**, 78%
2			**2b** 93%
3			**2c** 74%
4			**2d** 89%
5			**2e** 91%
6			**2f** 91%
7			**2g** 58%
8			**2h** 92%
9			**2i** 80%
10			**2j** 74%
11			**2k** 74%

[a] Reactions were performed with 5 mol % of $NaAuCl_4 \cdot 2H_2O$, alkyne **1** (0.5 mmol), EtOH/H_2O (4:1, 1.0 mL).

SCHEME 2. Hydration of Simple Internal Alkynes



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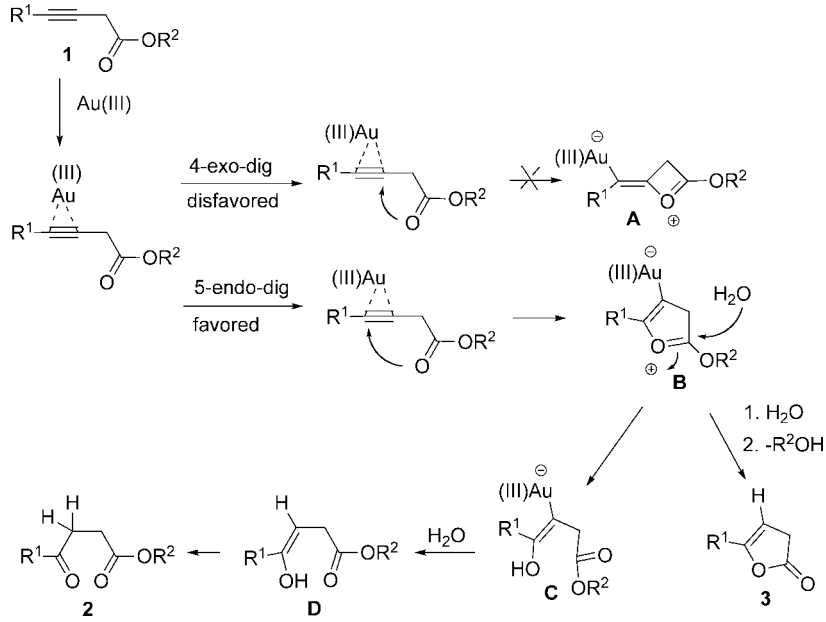
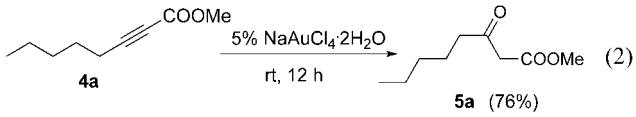
(18) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.

SCHEME 3. Proposed Mechanism for the Hydration of 3-Alkynoates



ring-opened product **C**, which in turn would form intermediate **D** by proto-deauration. Finally, isomerization of **D** produced γ-keto ester **2**. A competing side reaction, namely the elimination of R^2OH from **B**, is also possible. This would account for the trace amounts of cyclic byproduct obtained in some cases (eq 1). Hydration of 2-alkynoate **4a** by using the optimized conditions described above furnished the β-keto ester **5a** in high yield (eq 2); this reaction is also highly regioselective. Its selectivity may be the result of the strong electron withdrawing effect of the conjugated ester; the β-carbon of **4a** is more electronically deficient, promoting an attack by water to this position to give **5a**.



(2)

In summary, we have developed an effective and straightforward hydration of 3-alkynoates in the presence of catalytic amounts of Au(III) salt in aqueous ethanol at room temperature to give γ-keto esters regioselectively and in high yields. This mild and atom-economical method can be used effectively with a wide range of substrates, yielding densely functionalized products. With a propargyl ester this reaction yields β-keto esters in high yield.

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Experimental Section

Synthesis of 2a (General Procedure for Hydration of Alkyne 1). $NaAuCl_4 \cdot 2H_2O$ (3 mg, 5% equiv) was added to a stirring solution of alkyne **1a** (71.4 mg, 0.3 mmol) in EtOH/H_2O (4:1, 1 mL). After stirring for 12−18 h at rt, the reaction mixture was concentrated under reduced pressure and the crude product was purified by flash silica gel chromatography (EtOAc/hexane 1:20 to 1:4) to give the final product **2a** as a colorless oil (60 mg, 78%). IR (neat) 2957, 2930, 2859, 1734, 1457, 1177, 1134 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.83−0.89 (m, 6H), 1.20 (s, 3H), 1.22−1.32 (m, 9H), 1.52−1.67 (m, 4H), 2.34−2.38 (m, 2H), 2.49 (d, J = 17.5 Hz, 1H), 2.89 (d, J = 17.5 Hz, 1H), 4.13 (q, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.7, 14.2, 14.4, 21.3, 22.7, 24.0, 29.1, 31.8, 32.7, 43.6, 44.0, 50.8, 60.6, 176.8, 209.1; GC/MS (EI) *m*/*z* 257, 211, 171, 143, 113, 85, 69, 42; HRMS (ESI) calcd for $(C_{15}H_{28}O_3 + Na)^+$ 279.1936, found 279.1930.

Acknowledgment. We are grateful to the National Science Foundation for financial support (CHE-0809683). The authors also thank Dr. Leping Liu for supplying compounds **1h** and **1i**.

Supporting Information Available: Experimental procedures and spectral data for **1**, **2**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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