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Cationic Gold(I)-Catalyzed Intramolecular Cyclization of γ-Hydroxyalkynones into 3(2*H*)-Furanones

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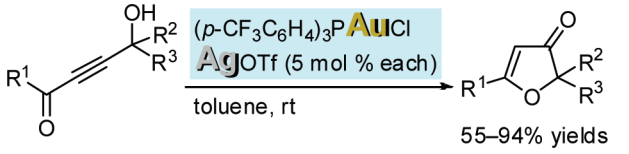

The combination of $(p\text{-}CF_3C_6H_4)_3PAuCl$ and AgOTf generates a powerful catalyst for the intramolecular cyclizations of readily available γ-hydroxyalkynones under mild conditions. The substituted 3(2*H*)-furanones are obtained in 55−94% yields. This method is also applicable to the preparation of 2,3-dihydro-4*H*-pyran-4-ones.

The 3(2*H*)-furanone moiety is well established as one of the most fundamental components observed in abundant naturally occurring products. Representative examples are shown in Figure 1,[1] and this class of natural furanones[2] display a variety of biological activities. In addition, the 3(2*H*)-furanone derivatives are considered to be promising pharmaceutical candidates which exhibit antitumor,[3] antiproliferative,[4] antiulcer,[5] antiallergic,[6] selective COX-2 inhibition,[7] and selective MAO-B inhibition activities.[8] These features have spurred continued interest in exploring more efficient synthetic routes of the 3(2*H*)-furanone framework.

Traditional methods for the preparation of substituted 3(2*H*)-furanones have been based on the acid-catalyzed cyclization/dehydration reaction of 1-hydroxy-2,4-diketones.[3,9] Various alternative methods have also been developed, including the hydrogenolysis and subsequent acidic hydrolysis of isoxazoles,[4,10] the aldol reaction of 3-silyloxyfuranes,[11] the cyclizations of 1-halo-2,4-diketones using bases,[12] and the Knoevenagel-type condensation of α-acyloxycarbonyl compounds.[13] Recently, the transition metal-catalyzed cyclizations for constructing substituted 3(2*H*)-furanones have attracted renewed attention, such as the Pt- or Au-catalyzed cyclization/migration of propargylic alcohols,[14] the gold-catalyzed intramolecular cyclization of 2-oxo-3-butynoates,[15] and the Pd- or Hg-catalyzed cyclization of α′-hydroxyalkynones.[16]

The 3-acyloxyfurans, equivalents of the 3(2*H*)-furanones, were synthesized from the alkynyl ketones via the Cu- or Ag-catalyzed 1,2-migration of the acyloxy group.[17] However, these known synthetic methods have some drawbacks, for example, insufficient yields of the desired compounds, harsh conditions, and/or the absence of an efficient and general procedure for the preparation of the starting materials. In

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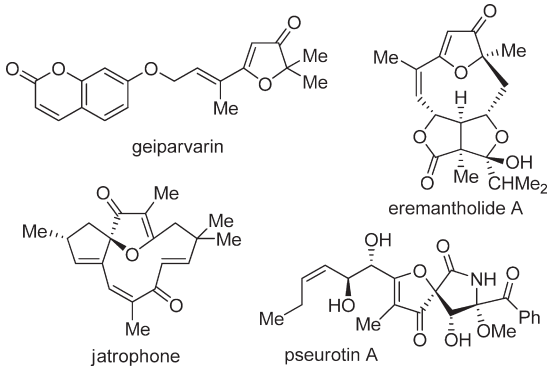
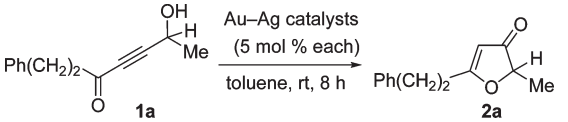


FIGURE 1. Naturally occurring products containing the 3(2*H*)-furanone moieties.

this paper, we report that the combination of $(p\text{-}CF_3C_6H_4)_3$-PAuCl and AgOTf generates a powerful catalyst for the intramolecular cyclizations of the γ-hydroxyalkynones **1** under mild conditions. This method offers advantages over the known methods in terms of the production of a wider range of substituted 3(2*H*)-furanones **2** in good-to-excellent yields and the ready availability of the substrates **1**.

In the past decade, gold catalysis has been an ever growing research area in organic synthesis, and provided a variety of reactions to construct complex chemical architectures.[18] As part of our interest in the gold-catalyzed reactions,[19] we reported that the combination of 1 mol % each of (Ph_3P)-AuCl, AgOTf, and $MoO_2(acac)_2$ showed a high catalytic activity for the rapid 1,3-rearrangement of propargyl alcohols to afford a variety of α,β-unsaturated carbonyl compounds in excellent yields.[19a] During our further study on its application to various substrates, we disclosed that the reaction of the propargyl alcohol **1a** having a carbonyl group gave the 3(2*H*)-furanone **2a** instead of the expected α,β-unsaturated carbonyl compound (entry 1, Table 1). Related intramolecular cyclizations of γ-hydroxyalkynones to substituted 3(2*H*)-furanones have been reported with use of Hg compounds, Pd complexes, H_2SO_4, and Et_2NH as catalysts.[7,20] Although these reactions were efficient and convenient, they were susceptible to some improvement of the yields, reaction conditions, and the scope of the reaction. Therefore, we optimized the conditions for the transformation of **1a** into **2a** by screening the combination of Au, Ag, or Mo catalysts. As a result, this type of intramolecular cyclization did not always require Mo catalysts to obtain **2a** in 68% NMR yield (entry 2). Additionally, in the presence of (Ph_3P)AuCl or AgOTf alone as a catalyst, the intramolecular cyclization did not take place at all. The commercially available cationic gold(I) catalyst, $(Ph_3P)Au^+NTf_2^-$, and trimeric gold complex, $[(Ph_3PAu)_3O]^+BF_4^-$, also showed catalytic activities in toluene albeit the yields of **2a** were moderate (entries 3 and 4). In a further survey, the combination of the more electrophilic

TABLE 1. Preliminary Survey for the Transformation of γ-Hydroxyalkynones 1a into 2a



entry	Au cat.	Ag cat.	NMR yield (%)[a]
1[b]	(Ph_3P)AuCl	AgOTf	68
2	(Ph_3P)AuCl	AgOTf	68
3	$(Ph_3P)Au^+NTf_2^-$	none	44
4	$[(Ph_3PAu)_3O]^+BF_4^-$	none	53
5	$(p\text{-}CF_3C_6H_4)_3PAuCl$	AgOTf	90 (62)[c]
6	$(p\text{-}CF_3C_6H_4)_3PAuCl$	$AgNTf_2$	23
7	$(p\text{-}CF_3C_6H_4)_3PAuCl$	$AgClO_4$	trace
8	$(p\text{-}CF_3C_6H_4)_3PAuCl$	$AgBF_4$	26
9	$(p\text{-}CF_3C_6H_4)_3PAuCl$	$AgSbF_6$	23
10[d]	$(p\text{-}CF_3C_6H_4)_3PAuCl$	AgOTf	− (60)[c]
11[e]	$(p\text{-}CF_3C_6H_4)_3PAuCl$	AgOTf	− (30)[c]

[a]NMR yield with 1,1,2,2-tetrachloroethane as the internal standard. [b]5 mol % of $MoO_2(acac)_2$ was added. [c]Isolated yield is shown in parentheses. [d]Run in CH_2Cl_2. [e]Run in acetone.

$(p\text{-}CF_3C_6H_4)_3PAuCl$ and AgOTf transformed **1a** into **2a** in 90% NMR yield (entry 5). Among a variety of silver catalysts, AgOTf was the most effective for generating **2a** (entries 5−9). Moreover, the screening of solvents revealed that CH_2Cl_2 was similarly effective, although the yield of **2a** was somewhat inferior (entry 10). When acetone was used as the solvent, **2a** was formed in 30% yield accompanied by a 56% yield of an aldol product obtained by the further condensation of **2a** with acetone (entry 11).

With the optimized conditions in hand, the substrate scope for this method was next evaluated, mainly in terms of the synthesis of the 2,2-disubstituted 3(2*H*)-furanones, which are included as central structural elements in naturally occurring products (see Figure 1). As the results depict in Table 2, the intramolecular cyclization provided an excellent generality and delivered good isolated yields of **2**. Having an alkyl or aryl group as R^1, the reactions of **1b**−**i** proceeded at room temperature to give the substituted 3(2*H*)-furanones **2b**−**i**. Even in the presence of the sterically demanding $t\text{-}C_4H_9$ substituent, **2d** was obtained in 75% yield (entry 3). The transformation of **1f** led to a 92% yield of the natural product, bullatenone **2f**,[2a] in 3 h (entry 5). It is noteworthy that the reaction was applicable to the γ-hydroxyalkynone with an ethenyl group **1h** for the direct synthesis of the 5-(1-alkenyl)-3(2*H*)-furanone **2h** (entry 7). Such compounds have been synthesized by the strong base-mediated aldol reaction of 5-alkyl-3(2*H*)-furanones with aldehydes, followed by dehydration.[3−5,21] However, this multistep sequence produced only modest yields of the desired products, and the *E*/*Z*-stereoselectivity of the alkenyl groups was not satisfactory. The employment of the combination of $(p\text{-}CF_3C_6H_4)_3PAuCl$ and AgOTf resulted in the formation of **2h** in 94% in 3 h with retention of the olefinic configuration.

The starting materials **1** were easily prepared in 36−100% yields by the nucleophilic substitution of the Weinreb amides

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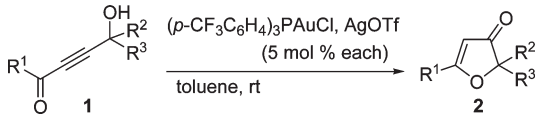
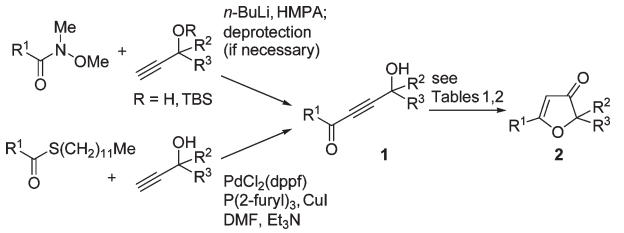
TABLE 2. Transformation of 1 into the 3(2*H*)-Furanones 2 with the Combination of $(p\text{-}CF_3C_6H_4)_3PAuCl$ and AgOTf

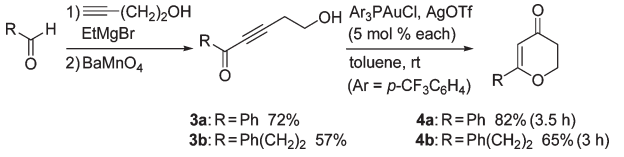


	substrate **1**					product **2**	
entry	compd no.	R^1	R^2	R^3	time (h)	compd no.	isolated yield (%)
1	**1b**	$Ph(CH_2)_2$	Me	Me	2.0	**2b**	91
2	**1c**	Me	Ph	Me	2.0	**2c**	94
3	**1d**	*t*-C_4H_9	Me	Me	5.0	**2d**	75
4	**1e**	*n*-C_5H_{11}	$-(CH_2)_4-$		1.0	**2e**	83
5	**1f**	Ph	Me	Me	3.0	**2f**	92
6	**1g**	*p*-$MeOC_6H_4$	Me	Me	3.5	**2g**	88
7	**1h**	(*E*)-PhCH=CH	Me	Me	3.0	**2h**	94
8	**1i**	$Ph(CH_2)_2$	H	H	3.0	**2i**	55

SCHEME 1. Preparation of the Starting Materials 1



SCHEME 2. The Intramolecular Cyclization of 3 into 6-Substituted 2,3-Dihydro-4*H*-pyran-4-ones 4

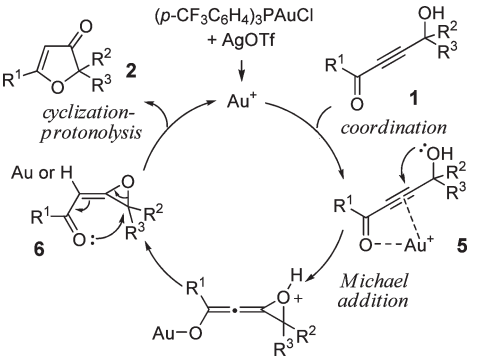


with lithium acetylides. In the case of **1i**, the TBS-protected propargyl alcohol was used. Alternatively, the palladium-catalyzed Sonogashira-type reaction of thioesters with propargyl alcohols[22] was also suitable for the synthesis of the γ-hydroxyalkynones such as **1c** (84% yield). Therefore, the overall transformation provides a short and effective preparation of the 3(2*H*)-furanones **2** from readily available starting materials (Scheme 1).

We have successfully applied this methodology to the synthesis of 2,3-dihydro-4*H*-pyran-4-ones **4**,[23] a class of heterocyclic compounds with extensive synthetic utilization in the synthesis of natural or unnatural products (Scheme 2). The intramolecular cyclizations of **3a**,**b** with $(p\text{-}CF_3C_6H_4)_3$-PAuCl/AgOTf were completed within a few hours to afford the corresponding products **4a** and **4b** in 82% and 65% yields, respectively.

Although the mechanistic studies have not yet been completed in detail, we propose the following mechanism for this

SCHEME 3. Proposed Reaction Mechanism



reaction (Scheme 3). The initial coordination of the π-bond of **1** to a cationic gold species, generated in situ from Au and Ag compounds, enhances its electrophilicity (**5**).[24] The subsequent Michael addition of a hydroxyl group leads to the transient formation of the epoxide intermediate **6**, which cyclizes through the nucleophilic attack of the carbonyl oxygen,[25] along with regeneration of the cationic gold catalyst. Gold catalysts are well-known to accelerate the alkyne hydration reaction,[26] and the previously reported reactions that convert **1** into **2** proceed most likely through hydration of the triple bond followed by nucleophilic attack of the intramolecular hydroxyl group.[7,20] However, we found that the addition of 1.0 equiv of water inhibited the intramolecular cyclization of **1a** to give **2a** in only 19% NMR yield (eq 1). Moreover, similar reactions of the hydroxy-protected derivatives **1j** and **1k** gave only trace amounts of the product **2a** with recovery of most of the substrates (eq 2). Hence, we are considering that this cationic gold-catalyzed reaction proceeds via the epoxide intermediate **6**, which is also consistent

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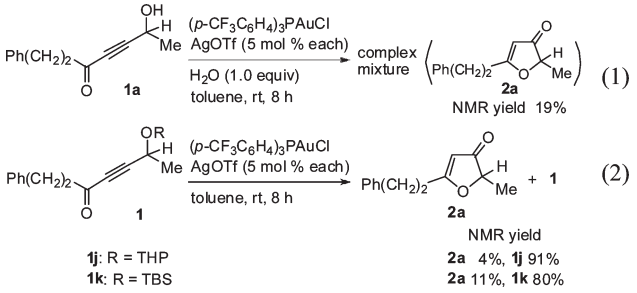
with the fact that our method is more suitable for **1** having a tertiary hydroxyl group (see Tables 1 and 2).



In conclusion, we have found that the combination of $(p\text{-}CF_3C_6H_4)_3PAuCl$ with AgOTf provides a powerful catalyst for the intramolecular cyclization of readily available γ-hydroxyalkynones **1**. The advantages of this method include the rapid and clean reactions at room temperature and the production of a variety of substituted 3(2*H*)-furanones **2** in good-to-excellent yields (55−94% yields). This method is also applicable to the preparation of 2,3-dihydro-4*H*-pyran-4-ones **4**. Further investigation of the practical extension of this method and elucidation of the mechanism are now in progress in our laboratory.

Experimental Section

Representative Procedure for Cationic Gold(I)-Catalyzed Formation of 3(2*H*)-Furanones (Entry 1 in Table 2). To a solution of 6-hydroxy-6-methyl-1-phenyl-4-heptyn-3-one **1b** (111 mg, 0.51 mmol) in toluene (2.6 mL, 0.20 M) were added $(p\text{-}CF_3C_6H_4)_3PAuCl$ (17.9 mg, 0.026 mmol) and AgOTf (6.6 mg, 0.026 mmol) in this order at room temperature. The reaction mixture was stirred at room temperature for 2.0 h and then quenched with saturated aqueous NH_4Cl. The organic materials were extracted with EtOAc, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 4:1) to give 2,2-dimethyl-5-(2-phenylethyl)-3(2*H*)-furanone **2b** (101 mg, 91%) as a pale yellow solid. Mp 66−68 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (6H, s), 2.81 (2H, t, J = 8.0 Hz), 2.97 (2H, t, J = 8.0 Hz), 5.32 (1H, s), 7.17−7.32 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.8, 32.1, 32.4, 88.6, 101.6, 126.6, 128.3, 128.6, 139.6, 190.4, 207.4; IR ($CHCl_3$) ν 3015, 2985, 2930, 1690, 1590 cm^{-1}.

Representative Procedure for the Preparation of γ-Hydroxyalkynones (Scheme 1). To a solution of 2-methyl-3-butyn-2-ol (747 mg, 8.9 mmol) in THF (15 mL) were added HMPA (6.18 mL, 36 mmol) and *n*-butyllithium (1.6 M in hexanes; 11.1 mL, 18 mmol) sequentially at −78 °C under nitrogen atmosphere. After the mixture was stirred for 30 min at −78 °C, a solution of *N*-methoxy-*N*-methyl-3-phenylpropanamide (1.43 g, 7.5 mmol) in THF (5.0 mL) was added. The reaction mixture was allowed to come to room temperature, stirred for 2 h, and quenched with saturated aqueous NH_4Cl. The organic materials were extracted with EtOAc, and the combined organic extracts were washed with H_2O several times and then brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 5:1) to give 6-hydroxy-6-methyl-1-phenyl-4-heptyn-3-one **1b** (1.15 g, 72%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 (6H, s), 2.10 (1H, br s), 2.88−3.01 (4H, m), 7.15−7.34 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.8, 30.6, 46.8, 65.1, 81.0, 95.8, 126.3, 128.3, 128.5, 140.1, 186.8; IR ($CHCl_3$) ν 3595, 3020, 2990, 2210, 1675 cm^{-1}. HRMS (ESI) m/z calcd for $C_{14}H_{16}O_2Na$ $[M + Na]^+$ 239.1048, found 239.1086.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.