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Au(I)-Catalyzed Hydrative Rearrangement of 1,1-Diethynylcarbinol Acetates to Functionalized Cyclopentenones and Allenones

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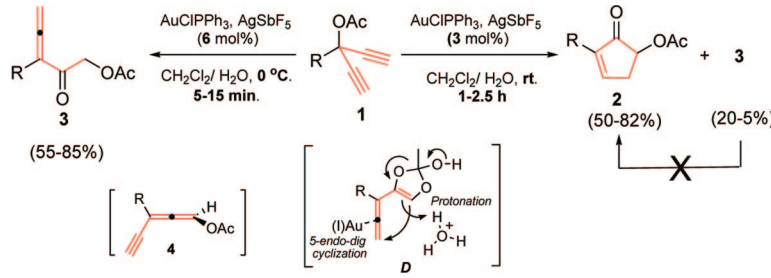

Atom-economical syntheses of isomeric 5-acetoxy-2-alkyl-2-cyclopentenones (**2**) and acetoxymethyl α-alkylallenones (**3**) have been described via Au-catalyzed hydrative rearrangement of 1,1-diethynylcarbinol acetates (**1**). In anhydrous condition, Au(I)-catalyzed [3,3]-rearrangement of **1** afforded the 3-alkynylallenyl acetate **4** in low yield. Treatment of **1** with Au(I) catalyst in wet CH_2Cl_2 produced either **2** or **3** as a major product depending on the temperature, reaction time, and catalyst loading. **D** has been proposed as an intermediate, which might be formed via Au(I)-induced internal oxacyclization of the intermediate **4** followed by chemoselective nucleophilic attack by the water molecule. Formation of **2** or **3** might be explained via sequential 1,3-dioxole ring opening and gold-promoted 5-*endo-dig* carbocyclization or simple protonation of the intermediate **D**, respectively.

Introduction

Substituted cyclopentenones are the important building blocks for the synthesis of a wide array of pharmaceuticals[1] and interesting natural products.[2] Therefore, popular strategies have been developed for the construction of this five-membered ring system, which include the intramolecular aldol reaction,[3] the electrocyclizations such as Nazarov cyclization[4] and Rautenstrauch rearrangement,[5] and the cycloadditions such as Pauson−Khand reaction[6] and [2 + 3]- or [4 + 1]-cycloadditions.[7,8] Judicious placement of double bonds and the scope of appropriate functionalization are of utmost interest of cyclopentenone construction strategy. Specially, introduction of an alkyl group at the α-position of α,β-unsaturated carbonyl compounds is still challenging in organic synthesis,[2d] as many pharmaceuticals (e.g., Prostaglandins, Limaprost, Misoprostol, etc.)[1f] and floral odorants (e.g., Hedione, (+)-(1*R*,2*S*)-methyl *epi*-jasmonate, etc.)[2a] contain an alkyl substituent at the α-position of their cyclopentenone skeleton. Now, we intend to introduce a new methodology for the construction of α-alkyl α′-acetoxy cyclopentenone (**2**), which could be a valuable intermediate in organic synthesis. Additionally, another product, acetoxymethyl α-alkylallenone (**3**), could be an effective building block for the

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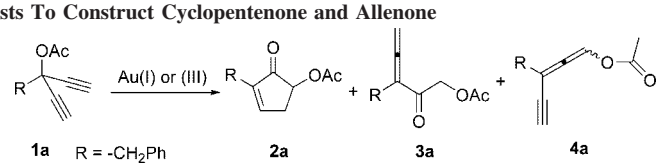
TABLE 1. Optimization of Catalysts To Construct Cyclopentenone and Allenone



entry	catalyst	solvent[a]	temp (°C)/ time (h)	product (% isolated yield)
1	AuCl (5 mol %)	DCE	0/0.5	**4a** (5)
2	$AuCl(PPh_3)$ (5 mol %)	DCE	0/0.5	**4a** (5)
3	$AuCl(PPh_3)/AgSbF_6$ (5 mol %)	DCE	0/0.25	**4a** (20)
4	$AuCl(Me_2S)/AgSbF_6$ (5 mol %)	DCE	rt/3	no reaction
5	$AuBr_3$ (3 mol %)	DCE	0/0.5	**4a** (10)
6	$NaAuCl_4 \cdot 2H_2O$ (3 mol %)	DCE	0/0.5	**4a** (8)
7	$AgSbF_6$ (3 mol %)	DCE	rt/3	complex mixture
8	$AuBr_3$ (3 mol %)	DCM/water	rt/1.0	**3a** (30)
9	$NaAuCl_4 \cdot 2H_2O$ (3 mol %)	DCM/water	rt/1.0	**3a** (25)
10	$AuCl(PPh_3)/AgSbF_6$ (3 mol %)	DCM/water	rt/1	**2a** (82), **3a** (5)
11	$AuCl(PPh_3)/AgSbF_6$ (6 mol %)	DCM/water	0/0.25	**3a** (70)
12	CF_3CO_2H (10 mol %)	DCM/water	rt/4	no reaction
13	*p*-toluenesulfonic acid (10 mol %)	DCM/water	rt/4	no reaction
14	CF_3SO_3H (10 mol %)	DCM/water	rt/4	no reaction

[a] DCE and DCM are abbreviations of 1,2-dichloroethane and dichloromethane, respectively.

numerous elegant transformations as well as for the synthesis of some important natural products and medicinally valuable compounds.[9]

During the course of our studies,[10] we became interested in exploring an efficient transformation involving rearrangement of 1,1-diethynylcarbinol acetate[11] by gold catalysis. Since the electrocyclization of pentadienyl cation must proceed with the conservation of orbital symmetry, the ability to create new carbon−carbon bonds requires the proximity between two reacting triple bonds.[12] Herein, we wish to report a new and facile approach toward the gold-catalyzed water-assisted chemoselective syntheses of structurally isomeric α-alkyl α′-acetoxy cyclopentenones (**2**) and allenones (**3**) utilizing 1,1-diethynylcarbinol acetates as starting material. The excellent alkynophilicity of gold has been well-documented, and propargylic acetates upon treatment with gold catalyst can be activated for the 1,2- and/or 1,3-acetate shift depending on the substrates and reaction conditions.[13] To date, numerous novel endeavors have been made for establishing the central factors which govern such type of regioselective activation of the propargylic acetates.[12a,14]

Results and Discussion

All 1,1-diethynylcarbinol acetates **1a**−**h** were prepared from the corresponding esters via Grignard reaction with ethynylmagnesium bromide followed by acetylation. We initiated our investigation by treating **1a** with various gold catalysts, and those results are summarized in Table 1.

Initially, **1a** was treated with different Au(I) catalysts (AuCl, $AuCl(PPh_3)$, $AuCl(PPh_3)$ with $AgSbF_6$, $AuCl(SMe_2)$ with $AgSbF_6$) and Au(III) catalysts ($AuBr_3$ and $NaAuCl_4 \cdot 2H_2O$) in dry 1,2-dichloroethane (DCE) at low temperature (0 °C to room temperature). Allenyne acetate **4a** was the only isolated product in low yields (5−20%). Among Au(I) and Au(III) catalysts, $AuCl(PPh_3)$ with $AgSbF_6$ (entry 3) catalyzed this conversion significantly. Formation of **4a** can be understood by Au-catalyzed [3,3]-sigmatropic shift of the acetate group (Scheme 1).[4h] Catalysts $AuCl(Me_2S)$ with $AgSbF_6$ (entry 4) and $AgSbF_6$

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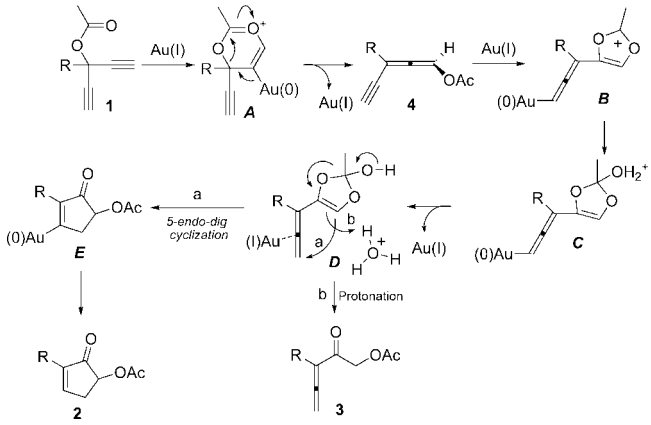
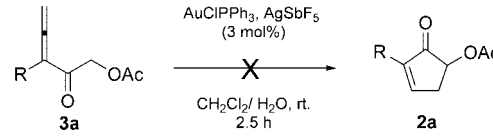
SCHEME 1. Plausible Mechanism for Au(I)-Catalyzed Syntheses of Isomeric Cyclopentenone and α-Allenone



itself (entry 7) were incompetent to result in either no reaction or decomposition due to overreaction.

Mechanistic consideration revealed that any nucleophilic additive might be necessary to bring two reacting partners in close proximity in order to achieve a new C−C bond formation intramolecularly. In this context, Zhang and Wang[4h] showed that Au(I)-catalyzed [3,3]-rearrangement of propargylic acetates could be accomplished effectively in wet dichloromethane (DCM). Notably, water did not participate as a nucleophile in their transformation, rather it acted as a proton shuttle in the proton-transport catalysis strategy.[12a] We, however, considered the possibility of the chemoselective nucleophilic attack by the water molecule on the allenyne acetate **4a** followed by new C−C bond formation leading to any probable cyclization. Again, substrate **1a** was treated with gold(III) catalysts ($AuBr_3$ and $NaAuCl_4 \cdot 2H_2O$) in wet CH_2Cl_2[4h] at room temperature for 1 h (entries 8 and 9). In both experiments, any cyclization was not observed; instead **3a** was isolated in 30 and 25% yields (entries 8 and 9). Gratifyingly, when only 3 mol % of $AuCl(PPh_3)$ with $AgSbF_6$ was used as a catalyst system in wet CH_2Cl_2 (entry 10) at room temperature, cyclopentenone **2a** was isolated in 82% yield within 1 h along with **3a** in 5% yield. Since the substituted allenones have been remarkably utilized as building blocks for various transformations,[9] we were in quest of an optimum condition for the synthesis of **3a**. Surprisingly, when the reaction was carried out with high catalyst loading (6 mol %) using $AuCl(PPh_3)$ with $AgSbF_6$ as catalyst in wet CH_2Cl_2 at low temperature (0 °C) for 15 min, **3a** was isolated in 70% yield (entry 11). By TLC monitoring of the reaction, formation of **2a** was not observed within that reaction time. The observed results (entries 10 and 11) might lead to a conclusion that generation of **2a** required low catalyst loading (3 mol %), relatively high activation energy (rt), and long reaction time (1 h), while formation of **3a** demanded relatively high catalyst loading (6 mol %), low activation energy (0 °C), and short reaction time (10−20 min). Additionally, as there are several examples that gold- and platinum-catalyzed transformations sometimes can be carried out by simple Brønsted acid catalysis,[14d,15] the substrate **1a** was treated with the catalytic amount (10 mol %) of Brønsted acids (entries 12−14) in wet CH_2Cl_2 at room temperature to make an investigation of any probable rearrangement. Notably, **1a** was recovered unchanged under these conditions (entries 12−14). Thus, this rearrangement cannot be catalyzed by simple Brønsted acids. Control experiments were made to get more insight into the mechanism. First of all, when we started the reaction by treating **1a** with $AuCl(PPh_3)/AgSbF_6$ at 0 °C with low catalyst loading (3 mol %) and allowed it to stay at room temperature for 2.5 h, we obtained only **2a** in moderate yield (55%). Second, when the product **3a** was treated under the same conditions, cyclization to **2a** did not occur (eq 1). From those two controlled experimentations, we could get a mechanistic insight, where **3a** might not be the intermediate to **2a**.



(1)

From the synthetic point of view, the condition 10 (Table 1) was applied to diverse 1,1-diethynylcarbinol acetates in order to investigate the generality of this reaction condition (Table 2). Interestingly, 1,1-diethynylcarbinol acetates, having an arylmethylene chain, worked well under the reaction condition (entries 1−4). *p*-Tolylmethylene and naphthylmethylene-substituted 1,1-diethynylcarbinol acetates **1b** and **1d** (entries 2 and 4) on treatment with $AuCl(PPh_3)/AgSbF_6$ (3 mol %) in wet CH_2Cl_2 underwent smooth conversion to the corresponding cyclopentenones **2b** and **2d** in 80 and 75% yields, respectively. Rearrangement of 3,4-dimethoxybenzylmethyl 1,1-diethynylcarbinol acetate (**1c**) required relatively longer reaction time (2 h) to afford **2c** in 73% yield (entry 3). Notably, α-allenone acetates **3a**−**d** were isolated as minor products (5−20%). α-Alkyl-substituted cyclopentenones **2e** and **2f** were also obtained by this method in 60 and 65% yields, respectively (entries 5 and 6). The substrates **1g** and **1h**, having a hydroxyl-protected long alkyl chain, underwent a similar type of cyclization to provide **2g** and **2h** in moderate yields (58 and 50%, respectively; entries 7 and 8). Especially, **1g** required higher catalyst loading (5 mol %) for this conversion.

α-Allenones can usually be synthesized by Dess−Martin periodinane oxidation of the homopropargylic alcohol or Swern oxidation of the allenic alcohol, and in the past decade, some new methodologies have been developed for their constructions.[16] Considering their wide applicability, we decided to explore the generality of the reaction condition 11 (entry 11 in Table 1). We treated all 1,1-diethynylcarbinol acetates (**1a**−**h**) under that condition. Surprisingly, all the substrates except **1g**, on treatment with $AuCl(PPh_3)$ with $AgSbF_6$ (6 mol %) in wet CH_2Cl_2 at 0 °C, smoothly converted into the corresponding α-allenone acetates (**3a**−**f** and **3h**) within 10 to 15 min in good to excellent yields (55−85%) (Table 3). However, relatively

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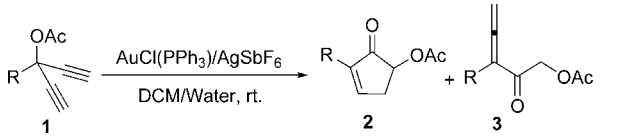
TABLE 2. Au(I)-Catalyzed Hydrative Isomerization of Various 1,1-Diethynylcarbinol Acetates 1a−h



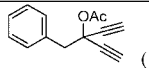
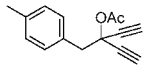
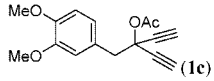
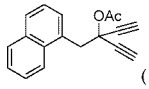
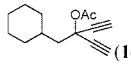
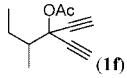
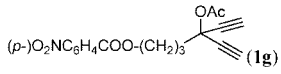
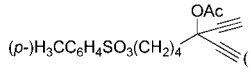
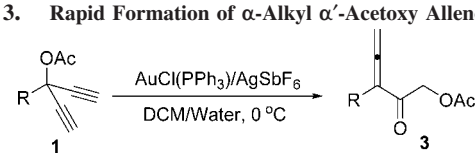
entry	Substrates	mol (%)	Time (h)	Products (% yield)
1	 (**1a**)	3	1	**2a** (82), **3a** (5)
2	 (**1b**)	3	1	**2b** (80), **3b** (5)
3	 (**1c**)	3	2	**2c** (73), **3c** (8)
4	 (**1d**)	3	1	**2d** (75), **3d** (6)
5	 (**1e**)	3	2	**2e** (60), **3e** (18)
6	 (**1f**)	3	3	**2f** (65), **3f** (15)
7	 (**1g**)	5	3	**2g** (58), **3g** (20)
8	 (**1h**)	3	2	**2h** (50), **3h** (10)

TABLE 3. Rapid Formation of α-Alkyl α′-Acetoxy Allenones 3



entry	substrates	mol (%)	time (min)	products **3** (% yield)
1	**1a**	6	15	**3a** (70)
2	**1b**	6	15	**3b** (70)
3	**1c**	6	15	**3c** (65)
4	**1d**	6	15	**3d** (70)
5	**1e**	6	15	**3e** (80)
6	**1f**	6	15	**3f** (85)
7	**1g**	8	5	**3g** (70)
8	**1h**	6	10	**3h** (55)

high catalyst loading (8 mol %) was essential to obtain **3g** in 70% yield within 5 min in wet CH_2Cl_2 at 0 °C.

To rationalize our observations, a plausible mechanistic manifold for the formations of isomeric α,α′-substituted cyclopentenones and α-allenones acetates was hypothesized in Scheme 1. Due to extraordinary alkynophilicity of gold, Au(I) activates the triple bond, which promotes 3,3-sigmatropic shift of the acetate functionality via cationic vinyl gold intermediate **A** to furnish the alkyne allene acetate **4**. Now, Au(I) plays a central role in activating alkyne functionality. Initially, Au(I) coordinates with the triple bond, which induces oxacyclization/1,3-dioxolium ion generation via internal nucleophilic attack by the carbonyl oxygen of the acetoxy group at the C-2 of allene to furnish **B**. A water molecule is expected to be involved at this stage to form an intermediate **C**, which is then converted into **D** by simple protodemetalation. Interestingly, Au(I) further activates the allene functionality,[17] which induces the sequential 1,3-dioxole ring opening and 5-*endo-dig* carbocyclization to furnish the gold-coordinated cyclopentenone **E** via route a (Scheme 1).[18] The latter on prodemetalation can be converted into the cyclopentenone **2**. On the other hand, depending on the reaction condition, the intermediate **D** can rearrange into α-allenone acetates **3** via hydrative 1,3-dioxole ring opening followed by protonation (route b).

Conclusions

We have developed a new and general method for the synthesis of isomeric 5-acetoxy-2-alkyl-2-cyclopentenones (**2**) and acetoxymethyl α-alkylallenones (**3**). Former was formed via Au(I)-catalyzed 5-*endo-dig* carbocyclization of a plausible intermediate **D** derived from gold-catalyzed hydrative rearrangement of the allene yne acetate **4** (Scheme 1), whereas formation of **3** might be realized by sequential 1,3-dioxole ring opening and protonation of the same intermediate. In a wider sense, reactions described herein may take a modular entry to a metal-mediated rearrangement of the allene yne acetoxy system in the presence of a nucleophile, and this methodology can be useful to construct some important building blocks, such as α,α′-substituted cyclopentenones **2** and α-allenones **3**.

Experimental Section

General Experimental Procedure for Compound 2. In a 5 mL new test tube, 3 mol % (in case of **1g**, 5 mol %) of $AuCl(PPh_3)$ and $AgSbF_6$ was taken in 1.0 mL of wet dichloromethane[19] at 0 °C. It was then allowed to reach room temperature (25 °C) followed by addition of 1,1-diethynylcarbinol acetate (**1a**−**h**) (0.2 mmol) dissolving in a minimum volume of wet dichloromethane. The resulting mixture was stirred for 1−3 h (as stated in Table 2) at room temperature by monitoring TLC of the reaction periodically. Upon completion, the solvent was removed under vacuum and the crude product was subjected to flash column chromatography (10:1 hexane/EtOAc) to afford the pure products **2a**−**h**.

3-Benzyl-2-oxocyclopent-3-enyl acetate (2a). Compound **2a** (45 mg, 0.19 mmol) was synthesized following the general procedure starting from **1a** (50 mg, 0.23 mmol): IR (film, cm^{-1}) 1744, 1718, 1627; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.18 (m, 5H), 7.06 (s, 1H), 5.17 (dd, $J = 6.6$, 3.0 Hz, 1H), 3.52 (s, 2H), 3.04 (d, $J = 18.8$ Hz, 1H), 2.47 (dm, $J = 18.8$, 2.4 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203, 171, 156, 145, 138, 129, 129, 127, 72, 34, 32, 21; HRMS calcd for $C_{14}H_{14}NaO_3$ 253.0841; found, 253.0835.

General Experimental Procedure for Compound 3. In a 5 mL new test tube, 6 mol % (in the case of **1g** 8 mol %) of

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(17) Gandon, V.; Lemière, G.; Hours, A.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7534–7538.

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(19) Prepared by shaking distilled dichloromethane with deionized water in a separatory funnel.

$AuCl(PPh_3)$ and $AgSbF_6$ was taken in 0.5 mL of wet dichloromethane at 0 °C followed by addition of 1,1-diethynylcarbinol acetate (**1a**−**h**) (0.2 mmol) dissolving in a minimum volume of wet dichloromethane. The resulting mixture was stirred for 10−15 min at 0 °C and the reaction monitored by TLC periodically. Upon completion, the solvent was removed under vacuum and the crude product was subjected to flash column chromatography (10:1 hexane/EtOAc) to afford the pure products **3a**−**h**.

α-Benzyl-α′-acetoxy allenone (3a). Compound **3a** (37 mg, 0.161 mmol) was synthesized following the general procedure starting from **1a** (50 mg, 0.23 mmol): IR (film, cm^{-1}) 1950, 1925, 1745, 1690, 1554; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29−7.18 (m, 5H), 5.24 (t, J = 2.6 Hz, 2H), 4.99 (s, 2H), 3.54 (t, J = 2.4 Hz, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216, 192, 171, 139, 129, 128.6, 127, 106, 82, 66, 33, 21; HRMS calcd for $C_{14}H_{14}NaO_3$ 253.0841; found, 253.0835.

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Supporting Information Available: General experimental procedures for the synthesis of compounds **2** and **3** and spectral data for all new compounds This material is available free of charge via the Internet at http://pubs.acs.org.

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