

Gold(I)-Catalyzed Cycloisomerization of β -Alkynylpropiolactones to Substituted α -Pyrones

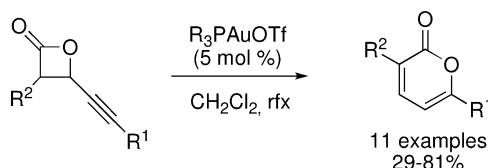
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Received July 3, 2010

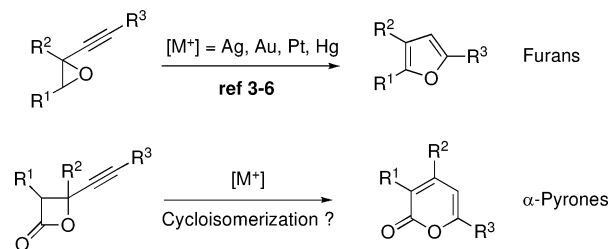
ABSTRACT



Substituted α -pyrones were straightforwardly synthesized in good to excellent yields by a new gold(I)-catalyzed rearrangement of β -alkynylpropiolactones.

Late transition metals, especially silver and gold, proved very efficient catalysts for various organic transformations over the past decade.^{1,2} Among the latter, cycloisomerizations hold a special position, often offering a rapid entry to functionalized heterocycles. The cycloisomerization of alkynylloxiranes is a typical example, providing a powerful method to generate substituted furans. Silver³ and gold,⁴ but also platinum⁵ and mercury,⁶ have been successfully employed

as catalysts for this transformation, although different mechanisms have been proposed (Scheme 1, top).

Scheme 1. Hypothesis for Transition-Metal-Catalyzed Conversion of β -Alkynylpropiolactones to α -Pyrones

On the basis of our precedents in such reactions,^{3,7} we reasoned that incrementation of the epoxide ring in alkynylloxiranes, i.e., alkynylloxetanes, would lead to the corresponding homologated heterocycle, i.e., pyrans. With less strain, alkynylloxetanes would be less prone to ring opening before

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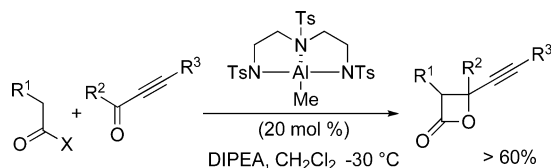
cyclization as shown for alkynyloxiranes,⁷ and thus, other or new mechanisms would occur, improving our mechanistic knowledge of Au-catalyzed reactions.⁸ For further synthetic purpose, we chose β -alkynylpropionolactones (4-alkynyloxetan-2-ones) as starting materials. Such compounds should give α -pyrones upon Ag- or Au-catalyzed cycloisomerization (Scheme 1, bottom).

α -Pyrones (2-pyrones or pyran-2-ones) indeed are an interesting class of compounds in organic chemistry as such structures are found in many natural products and in various pharmacologically active compounds.⁹ They exhibit a wide range of biological activities. Therefore, any new synthetic method affording highly substituted α -pyrones under mild conditions would be valuable in this context, especially since the reported procedures usually required several steps with a relatively modest efficiency (overall yields often lower than 40%).⁹

We report here that gold(I) catalyzes the rearrangement of β -alkynylpropionolactones to substituted α -pyrones, providing an unprecedented route to such heterocycles¹⁰ in a two-step and high overall yield procedure.

β -Lactones¹¹ can be conveniently prepared through the cyclocondensation of acyl halides and propargyl aldehydes using an achiral procedure derived from the reaction described by Nelson and co-workers.¹² Despite the inherent fragility of these substrates, isolated yields were routinely higher than 60% (Scheme 2).

Scheme 2. Direct Synthesis of β -Alkynylpropionolactones



To establish appropriate reaction conditions, we subjected the 3-(1-heptynyl)propionolactone **1a** to various gold catalysts expecting the formation of the 6-pentyl-2-pyrone **2a** (Table 1). It is noteworthy that pyrone **2a** is a natural product, first identified from *Trichoderma viride*,^{9,13} exhibiting a characteristic coconut-like aroma as well as antibiotic and antifungal properties.¹⁴

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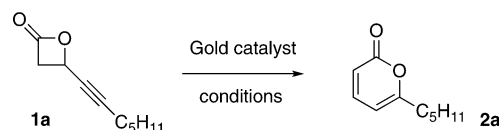
(10) A synthesis of α -pyrones has recently been reported, based on gold-catalyzed [3 + 3]-sigmatropic rearrangement and cyclization. See: (a) Luo, T.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8250–8253. (b) Luo, T.; Schreiber, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 5667–5674.

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Table 1. Screening of Catalysts for the Transformation of β -Alkynylpropionolactones **1a**



entry	catalyst (5 mol %)	conditions ^a	time (h)	yield (%) ^b
1	AgOTf	CH ₂ Cl ₂ , rfx	48	8
2	AgOTf/ <i>p</i> TsOH	CH ₂ Cl ₂ , rfx	24/48	traces ^c
3	PPh ₃ AuX ^d	CH ₂ Cl ₂ /MeOH, rt	48	— ^e
4	AuCl	CH ₂ Cl ₂ , rfx	48	1 ^{c,f}
5	AuCl ₃	CH ₂ Cl ₂ , rfx	48	4 ^{c,f}
6	PPh ₃ AuCl	CH ₂ Cl ₂ , rfx	48	traces ^e
7	PPh ₃ AuBF ₄	CH ₂ Cl ₂ , rfx	3	53
8	PPh ₃ AuSbF ₆	CH ₂ Cl ₂ , rfx	1	75
9	PPh ₃ AuOTf	CH ₂ Cl ₂ , rfx	3	81
10	PPh ₃ AuSbF ₆	CH ₂ Cl ₂ , rt	5	60
11	PPh ₃ AuOTf	CH ₂ Cl ₂ , rt	5	54
12	PPh ₃ AuOTf	CH ₃ CN, rfx	16	— ^g
13	PPh ₃ AuOTf	Toluene, rfx	1	74
14	(<i>p</i> CF ₃ Ph) ₃ PAuOTf	CH ₂ Cl ₂ , rt	5	65
15	(<i>p</i> CF ₃ Ph) ₃ PAuOTf	CH ₂ Cl ₂ , rfx	3	81
16	(F ₅ Ph) ₃ PAuOTf	CH ₂ Cl ₂ , rt	2.5	71
17	(F ₅ Ph) ₃ PAuOTf	CH ₂ Cl ₂ , rfx	1	74

^a Reactions run under argon, C = 0.1 mol/L. ^b Yields of pure isolated products, unless otherwise stated. ^c The starting material was recovered.

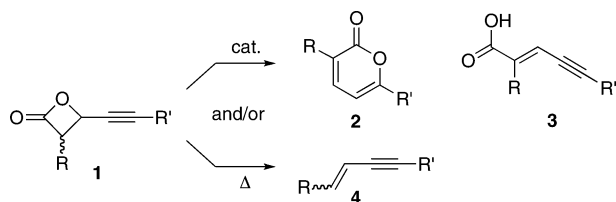
^d Various anions have been checked (X = Cl, SbF₆, OTf, NTf₂). ^e Degradation occurred. ^f Yields of **2a** were estimated from crude ¹H NMR spectra.

^g Decarboxylation occurred (see text).

Applying our best conditions for the Ag- or Au-catalyzed alkynyloxirane cycloisomerization in the presence or not of a proton source³ or nucleophile⁷ mostly returned the starting materials or led to decomposition (entries 1–3). Nevertheless, the expected pyrone **2a** could be isolated from Ag-catalyzed reactions, although in very low yield, even in refluxing dichloromethane (entry 1). Switching to simple gold chloride catalysts in pure dichloromethane did not help and led to almost no transformation despite the detection of the expected pyrone (entries 4 and 5). Although more soluble, the corresponding triphenylphosphinogold chloride was not reactive, leaving mostly untouched the starting lactone **1a**, even after prolonged heating (entry 6). In contrast, cationic gold complexes in situ prepared from the chloride complex gave the expected α -pyrones in variable yields depending on the counteranion (entries 7–9). As expected, higher temperatures sped up the reaction and often increased yields (e.g., entries 8 vs 10 and 9 vs 11). Heat could also favor the formation of side products, β -lactones usually leading to enynes resulting from retro-[2 + 2]-cycloaddition (**4** in Scheme 3).¹¹ However, the main side product formed in the presence of gold was the conjugated acid **3a** and surprisingly not the retro-[2 + 2]-cycloaddition enyne product **4a** (Scheme 3). The best compromise between rearrangement

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Scheme 3. Competitive Reactions Sometimes Observed during the β -Alkynylpropiolactone to Pyrone Rearrangement



efficiency and byproduct formation was achieved with triphenylphosphinogold triflate in refluxing dichloromethane (entry 9). With this catalyst, more coordinating solvents proved deleterious, inhibiting the reaction (entry 12), while in apolar noncoordinating solvent, the reaction went faster but some decarboxylation also occurred probably due to the higher temperature (entry 13). It is worth noting that decarboxylation was the only process in refluxing acetonitrile (entry 12).

More electrophilic complexes gave the same trends. With the tris(4-trifluoromethylphenyl)phosphine as the gold ligand, results almost identical to those achieved with triphenylphosphinogold triflate were obtained (entries 15 vs 9) but only in refluxing dichloromethane (entries 14 vs 15). The more electron-withdrawing tris(pentafluorophenyl)phosphine rendered the catalyst more reactive and thus induced a faster reaction (entries 16 and 17). As before, heat slightly improved the reaction efficiency, but again side reactions became competitive (entries 17 vs 16).

Control experiments showed the stability of the 2-pyrone **2a** under the conditions used, confirming that the side products, formed under certain conditions, originated from the starting β -lactone **1a**.

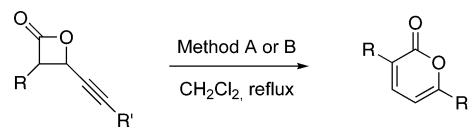
Since two sets of conditions emerged from this screening (entries 9 and 14), we submitted various alkynyl- β -lactone derivatives to both conditions, to examine the scope of this new Au-catalyzed rearrangement (Table 2).

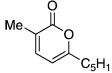
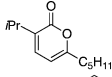
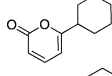
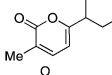
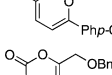
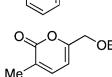
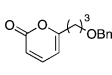
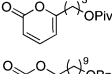
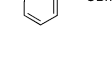
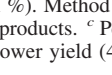
Simple alkyl chains and cycloalkyl derivatives **1a–e** gave the expected 6-substituted 2-pyrones in good to high yields (entries 1–10). With a substituent adjacent to the β -lactone carbonyl group, the pyrone formation was surprisingly slow (entries 3, 4 vs 1, 2 and 9, 10 vs 7, 8), and the larger the group, the larger this slowing effect (entries 5, 6 vs 3, 4).

Aryl groups tended to destabilize the starting β -lactones as well as the corresponding 2-pyrones, and thus these reactions led to more side products, lowering yields (entries 11–18 vs 1–10), even at room temperature or at 0 °C (entries 11–14). Both the corresponding enynes and the conjugated acids (**4** and **3** in Scheme 3) could be isolated or detected (respectively, 1–8% and 2–10%) depending on the conditions and the substrate.

The β -phenylethynyl- β -lactone **1f** gave the expected 6-phenyl-2-pyrone **2f** (entries 11 and 12) together with 1-phenylbut-3-en-1-yne **4f** and the conjugated acid **3f**. With Ph_3PAuOTf as catalysts, the latter could be isolated in, respectively, 8 and 10% yield, while only as traces for **4f**

Table 2. Scope of Gold(I)-Catalyzed α -Pyrone Formation



entry (cat.) ^a	β -lactones	2-pyrones	time (h)	yields (%) ^b
1 (A) 2 (B)	R = H R' = C ₅ H ₁₁	1a 	2a 2.5 3.5	81 81
3 (A) 4 (B)	R = Me R' = C ₅ H ₁₁	1b 	2b 22 7	45 71
5 (A) 6 (B)	R = <i>i</i> Pr R' = C ₅ H ₁₁	1c 	2c 30 32	33 15
7 (A) 8 (B)	R = H R' = cyclohexyl	1d 	2d 2 6	80 69
9 (A) 10 (B)	R = Me R' = cyclohexyl	1e 	2e 5 5	65 65
11 (A) 12 (B)	R = H R' = Ph	1f 	2f 2 ^c 3 ^c	35 65
13 (A) 14 (B)	R = Me R' = Ph	1g 	2g 4.5 ^c 0.5	52 50 ^d
15 (A) 16 (B)	R = H R' = <i>p</i> -ClPh	1h 	2h 2 2.5	50 52
17 (A) 18 (B)	R = Me R' = <i>p</i> -ClPh	1i 	2i 4 3.5	36 29
19 (A) 20 (B)	R = H R' = -CH ₂ OBn	1j 	2j 27 24	65 48
21 (A) 22 (B)	R = Me R' = -CH ₂ OBn	1k 	2k 48 48	- ^e - ^e
23 (A) 24 (B)	R = H R' = -(CH ₂) ₃ OBn	1l 	2l 20 24	37 29
25 (A) 26 (B)	R = H R' = -(CH ₂) ₃ OPiv	1m 	2m 4 3.5	65 68
27 (A) 28 (B)	R = H R' = -(CH ₂) ₉ OBn	1n 	2n 3 3.5	58 65

^a Method A: Ph_3PAuOTf (5 mol %). Method B: $(p\text{CF}_3\text{Ph})_3\text{PAuOTf}$ (5 mol %). ^b Yields of pure isolated products. ^c Performed at 0 °C. ^d The reaction performed at 0 °C gave a lower yield (46%). ^e No conversion.

and 8% for **3f** with $(p\text{CF}_3\text{Ph})_3\text{PAuOTf}$ as the catalyst. With a methyl adjacent to the carbonyl group, the reactions were again slower, and heat improved yield when $(p\text{CF}_3\text{Ph})_3\text{PAuOTf}$ was used as catalyst (entries 14 vs 13). Interestingly, adding an electron-withdrawing group on the phenyl ring stabilized the β -lactone and restored its reactivity toward gold (entries 15–16 vs 11–12). However, if this group was strongly electron-withdrawing, no evolution occurred (e.g., *p*-nitrophenyl; not mentioned in Table 2). Such behavior is reminiscent from the electronic effects observed in decarboxylation of β -lactones.¹⁵

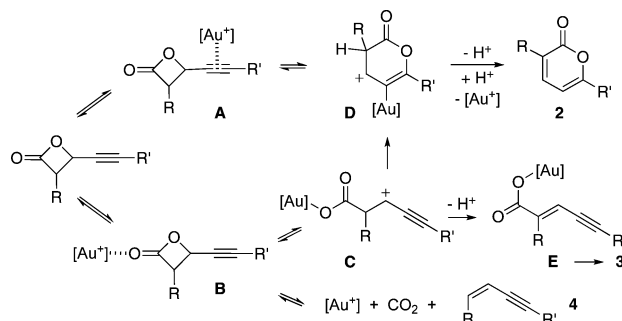
Ether substituents at the propargylic position dramatically slowed the reaction (entries 19–20 vs 1–2) and favored the side formation of the unsaturated acid **3** (28% of **3j**). The concomitant presence of a substituent α to the β -lactone carbonyl group slowed even more the reaction, so that almost no evolution occurred (entries 21–22 vs 19–20). Unexpectedly, a decrease in reaction time was also observed if the same ether substituent was remote from the propargylic position (entries 23–24 vs 19–20 vs 1–4). When this benzyl ether was replaced by a pivaloyl ester, the normal behavior was restored, and the corresponding pyrone was obtained in high yield within a few hours (entries 25–26 vs 23–24). The same normal behavior was also observed when this benzyl ether was far remote from the alkyne moiety (entries 27–28). These results revealed a special role of the benzyl ether unit when placed relatively close from the Au-coordinating sites, reminiscent of Au-catalyzed Friedel–Crafts reactions,¹⁶ or from the benzyloxy fragmentation recently reported.^{17,18}

It is worth noting that most derivatives with a substituent adjacent to the β -lactone carbonyl group proved far less reactive with a concomitant increase in reaction time (entries 3–4 vs 1–2, 5–6 vs 1–2, 9–10 vs 7–8, 13–14 vs 11–12, 17–18 vs 15–16, and 21–22 vs 19–20). Moreover, large groups reduced the reactivity more strongly than small groups (entries 5–6 vs 3–4 vs 1–2). These series of disubstituted β -lactones were produced as an approximate 3:1 mixture of diastereoisomers, but no significant difference was observed in their evolution, whatever the catalyst used. The results obtained with this series suggested some hindrance at some stage of the rearrangement, most probably at the coordination step (vide infra).

From a mechanistic point of view, it is not possible to naively extend the mechanism we proposed for alkynyl epoxide rearrangement after our detailed investigations.^{7a} In the latter, a nucleophile, either introduced in purpose or adventitiously present, opened the epoxide, and the resulting alkoxide then cyclized in a gold-catalyzed process. In the present case, running the alkynyl- β -lactone to α -pyrone rearrangement in the presence of a nucleophile proved deleterious, while without it, the reaction proceeded well (see Table 1). Nucleophilic opening of alkynyl- β -lactone and Au-catalyzed cyclization is thus not the major pathway.

The general trend observed with an extra group close to the β -lactone carbonyl group on one hand and the role of some alkynyl substituent on the other hand suggested changes in coordination ability and thus supported equilibrium between σ - and π -Au complexes (Scheme 4, **A** and **B**).¹⁹

Scheme 4. Proposed Mechanism for the Au(I)-Catalyzed Rearrangement of β -Alkynylpropiolactones to α -Pyrone



The formation of side products, especially the acid **3** (see Scheme 3), also supported σ -coordination at the β -lactone carbonyl. The resulting σ -Au β -lactone complexes **B** could be more prone to decarboxylation, especially when fully conjugated enynes—e.g., **4f,g** ($R' = \text{Ph}$)—could be obtained (Table 2, entries 11–18). Such σ -Au complexes **B** could also evolve to an open cationic gold carboxylate **C**, a precursor of the enynoic acids **3** (Scheme 4). It is worth mentioning that such cationic intermediates have been postulated to rationalize the stereochemical outcome of β -lactone decarboxylation²⁰ and must be involved in the Lewis acid promoted ring expansion of β -lactones.²¹ Both σ - and π -Au complexes **A** and **B** would lead to cationic pyrone gold intermediate **D**, possibly through either a 1,3-oxygen shift or Hashmi-type cyclization⁴ from **A** and through cyclization of **C** from **B**. The intermediate **D** would then give the corresponding pyrones **2** upon proton elimination and subsequent protodeauration (Scheme 4).²²

In conclusion, we have reported a novel synthesis of α -pyrones through Au-catalyzed cycloisomerization of β -alkynylpropiolactones. Since the latter can be obtained by condensing acyl chlorides to aldehydes, this synthesis is particularly appealing, providing in two steps with good to high yields a wide diversity of α -pyrones starting from very simple compounds.

Acknowledgment. The authors thank the CNRS and the French Ministry of Research for financial support. T.D. thanks the French Ministry of Research for a PhD fellowship.

Supporting Information Available: Selected experimental procedures and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(18) It is worth noting that no benzaldehyde¹⁷ could be detected in the crude mixture by NMR, but modified aromatic compounds were detected ($\leq 10\%$).¹⁶

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