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Syntheses of α-Pyrones Using Gold-Catalyzed Coupling Reactions

Tuoping Luo,[†,‡] Mingji Dai,[†,‡] Shao-Liang Zheng,[‡] and Stuart L. Schreiber*[,†,‡]

Howard Hughes Medical Institute, Broad Institute of Harvard and MIT, 7 Cambridge Center, Cambridge, Massachusetts 02142, United States, and Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States

stuart_schreiber@harvard.edu

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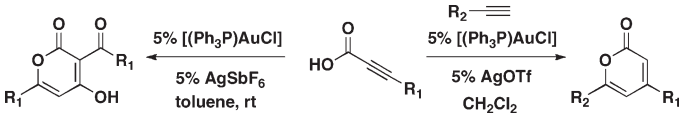
ABSTRACT



Sequential alkyne activation of terminal alkynes and propiolic acids by gold(I) catalysts yields compounds having α-pyrone skeletons. Novel cascade reactions involving propiolic acids are reported that give rise to α-pyrones with different substitution patterns.

In efforts to synthesize compounds having properties that facilitate small-molecule probe and drug discovery,[1] we have developed multicomponent coupling reactions that use gold(I) catalysts and yield, among others, complex α-pyrones.[2] Activation of the electron-deficient alkyne in propargyl propiolate **1** by a cationic gold(I) catalyst results in allenyl propiolate **2**, which undergoes a 6-*endo*-dig cyclization[3] to oxocarbenium intermediate **A** (Figure 1). In order to generate diverse and previously inaccessible α-pyrones,[4] we investigated the possibility of generating the vinyl propiolate **5**. We imagined this intermediate undergoing a similar 6-*endo* cyclization to afford oxocarbenium intermediate **B** and then α-pyrone **6** after deprotonation and proto-demetalation. Intermediate **5** would result from an intermolecular coupling of propiolic acid **3** and alkyne **4** catalyzed by the same gold(I) catalyst.[5] Herein, we describe a new gold(I)-catalyzed cascade reaction based on the concept of sequential alkyne activation,[2,6] synthesizing substituted α-pyrones in one step from readily available propiolic acids.

We initiated our investigation using commercially available propiolic acid **3a** and terminal alkyne **4a**. The counterion of the cationic gold(I) catalyst was determined to have

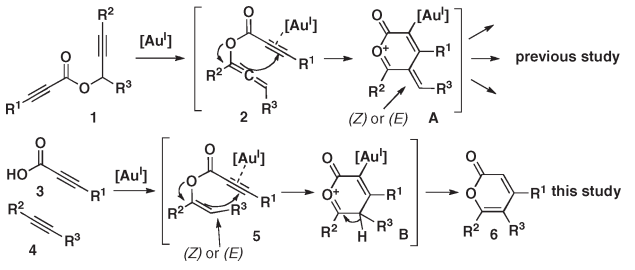


Figure 1. Syntheses of α-pyrones via gold(I)-catalyzed cascade reactions.

[†] Broad Institute of Harvard and MIT.
[‡] Harvard University.

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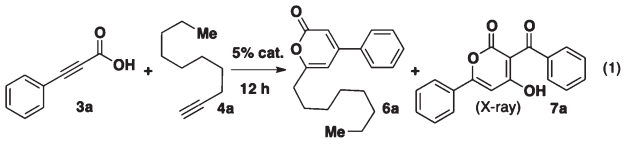
Table 1. Optimization of Reaction Conditions for the Synthesis of **6a**



entry	catalyst	conditions[a]	yield%[b] 6a	7a
1	[(Ph_3P)AuCl]/AgOTf	toluene, rt	43	<5
2	[(Ph_3P)AuCl]/$AgPF_6$	toluene, rt	52	<5
3	[(Ph_3P)AuCl]/$AgSbF_6$	toluene, rt	<5	84
4	[(Ph_3P)AuCl]/$AgNTf_2$	toluene, rt	20	60
5	[(Ph_3P)AuCl]/$AgPF_6$	CH_2Cl_2, rt	12	<5[c]
6	[(Ph_3P)AuCl]/AgOTf	CH_2Cl_2, rt	74	<5
7	[(Cy_3P)AuCl]/AgOTf	CH_2Cl_2, rt	75	<5
8	[(*p*-$CF_3C_6H_4)_3P$]AuCl/AgOTf	CH_2Cl_2, rt	68	<5
9	AuCl	CH_2Cl_2, rt	N.R.	
10	AgOTf	CH_2Cl_2, rt	N.R.	
11	[(Ph_3P)AuCl]/AgOTf	CH_2Cl_2, rt	83[d]	<5
12	[(Ph_3P)AuCl]/$AgPF_6$	toluene, rt	35[d]	<5[e]

[a] [**3a**] = 0.2 M, 1.5 equiv of **4a**. [b] Isolated yields after column chromatography. [c] 39% of **3a** was recovered. [d] 5 equiv of **4a** were employed. [e] **5a** was isolated in 29% yield.

a significant effect on the product distribution (Table 1, entries 1–4). When AgOTf or $AgPF_6$ was used, we isolated α-pyrone **6a** in modest yields (entries 1 and 2), presumably via the vinyl propiolate **5a** resulting from the gold-catalyzed Markovnikov addition of the carboxylic acid to the terminal alkyne.[5] However, $AgSbF_6$ led to α-pyrone **7a** as the predominant product (entry 3; structure determined by X-ray crystallography),[7] whereas $AgNTf_2$ gave both α-pyrones (entry 4). The reaction was also sensitive to the identity of the solvent. With [(Ph_3P)AuCl]/$AgPF_6$ as the catalyst, switching the solvent from toluene to dichloromethane significantly lowered the yield of **6a** with substantial starting material recovery (Table 1, entry 5). In contrast, with [(Ph_3P)AuCl]/AgOTf as the catalyst, dichloromethane afforded **6a** in higher yield than that afforded by toluene (entry 6). The more electron-donating ligand tricyclohexylphosphine and less electron-donating ligand tris(*para*-trifluoromethylphenyl)phosphine had minimal effects on the reaction (entries 7 and 8). AuCl or AgOTf alone failed to catalyze the cascade reaction

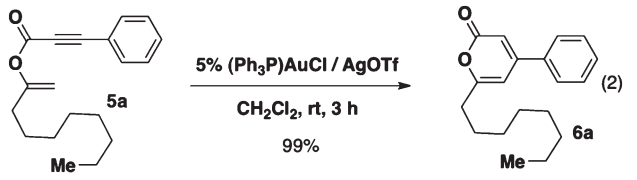


Figure 2. Cyclization of vinyl propiolate **5a** into α-pyrone **6a**.

(entries 9 and 10). The best result was obtained by increasing the amount of alkyne **4a** to 5 equiv and using the catalyst [(Ph_3P)AuCl]/AgOTf in dichloromethane, which gave rise to **6a** in 83% yield (entry 11). Unexpectedly, increasing the amount of alkyne **4a** and using the catalyst [(Ph_3P)AuCl]/$AgPF_6$ in toluene (entry 12) resulted in the isolation of the vinyl propiolate **5a**, which was further subjected to the optimized reaction conditions to give **6a** in excellent yield (Figure 2).

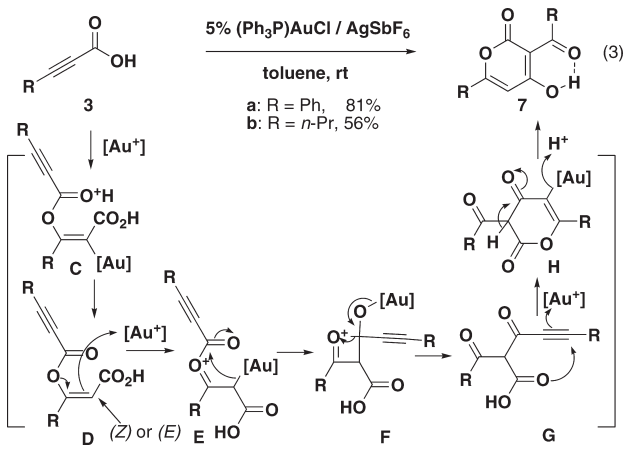


Figure 3. Dimerization of propiolic acid leading to 4-hydroxy α-pyrone.

While we do not understand why different counterions provide different product distributions (**6a** vs **7a**), a proposed mechanism of the serendipitously discovered propiolic acid dimerization is offered in Figure 3. The addition of the carboxylic acid to the *β*-position of the propiolic acid yields vinyl ester **D**. Further activation of **D** by cationic gold(I) generates oxocarbenium **E**, where the acyl group is transferred to the C–Au bond with concomitant regeneration of the gold(I) catalyst.[8] The 6-*endo*-dig cyclization of carboxylic acid **G** onto the activated alkyne followed by enolization affords 4-hydroxy α-pyrone **7** as the final product.

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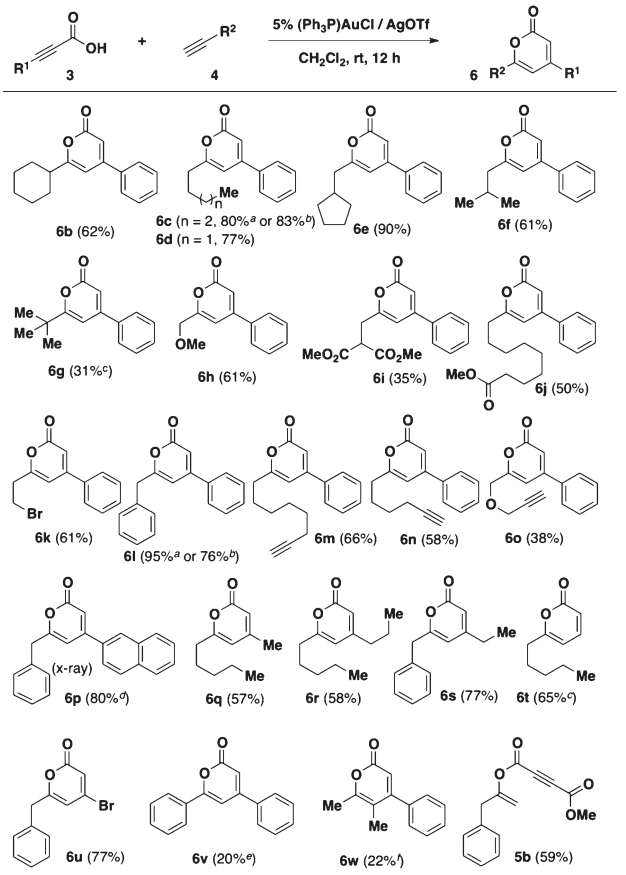
(7) Crystallographic Information Files (CIFs) for **7a** and **6p** are available at the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See Supporting Information for further details.

(8) For an example of a related acyl transfer involving a gold(III) intermediate, see: Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 8414–8415.

Scheme 1. Gold(I)-Catalyzed Syntheses of α-Pyrones from Propiolic Acids and Alkynes[a]



[a] Reaction conditions: propiolic acid (0.2−0.7 mmol, 0.2 M), alkyne (5−6 equiv), [(Ph_3P)AuCl]/AgOTf (5 mol %), CH_2Cl_2, rt, 12 h; [b]phenylpropiolic acid (3.4 mmol), alkyne (5 equiv), [(Ph_3P)AuCl]/AgOTf (5 mol %), CH_2Cl_2, rt, 24 h; [c]CH_2Cl_2, 50 °C, 12 h; [d]3-(naphthalene-2-yl)propiolic acid (0.1 M); [e]phenylacetylene (6 equiv), toluene, 60 °C, slow addition of acid (over 2 h), 12 h; [f]2-butyne (10 equiv), toluene, 60 °C, 12 h.

The scope of the cascade reaction was explored with a variety of propiolic acids and alkynes (Scheme 1). Generally, moderate to excellent yields were obtained with different terminal alkynes and propiolic acids. More sterically hindered alkynes gave lower yields (**6g**). Ether (**6h** and **6o**), ester (**6i** and **6j**), halide (**6k**), and alkyne (**6m**, **6n**, and **6o**) functional groups are compatible with the reaction conditions. The structure of α-pyrone **6p** was verified by X-ray analysis.[7] Notably, α-pyrone **6t** is a natural product with antibiotic and antifungal activity,[9] which recently has been synthesized using a gold(I)-catalyzed cycloisomerization of β-alkynylpropiolactone.[10] Using the new method reported here, **6t** was synthesized in one step from the commercially available propiolic acid and 1-heptyne. Pyrone **6u** was synthesized in 77% yield from 3-bromopropiolic acid. The bromide functionality provides a handle to introduce other groups at the C-4 position via transition-metal-catalyzed cross-coupling reactions. Gratifyingly, in separate reactions using 0.5 g of phenylpropiolic acid, pyrones **6c** and **6l** were obtained in good yields. Unfortunately, neither phenylacetylene nor the internal alkyne 2-butyne reacts at room temperature in CH_2Cl_2. Only a low yield of the corresponding α-pyrone was obtained using elevated reaction conditions (**6v** and **6w**). When 4-methoxy-4-oxobut-2-ynoic acid was used, only a 1,2-addition of the acid to 3-phenyl-1-propyne took place, yielding **5b** in 59% yield. A higher reaction temperature (50 °C) gave a similar result, presumably because the capacity of the triple bond of 4-methoxy-4-oxobut-2-ynoic acid to coordinate gold is diminished by the existing ester group.

The method described herein provides an efficient and simple route to multiply substituted α-pyrones. The generality observed thus far suggests that it will find many future applications.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds and CIFs for **7a** and **6p**. The material is available free of charge via the Internet at http://pubs.acs.org.

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