

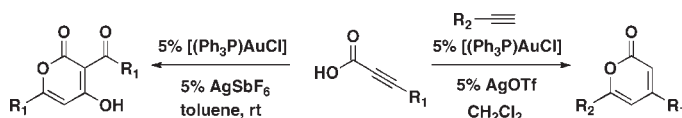
Syntheses of α -Pyrone Using Gold-Catalyzed Coupling ReactionsTuoping Luo,^{†,‡} Mingji Dai,^{†,‡} Shao-Liang Zheng,[‡] and Stuart L. Schreiber^{*,†,‡}

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Received March 25, 2011

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 cyclization³ 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

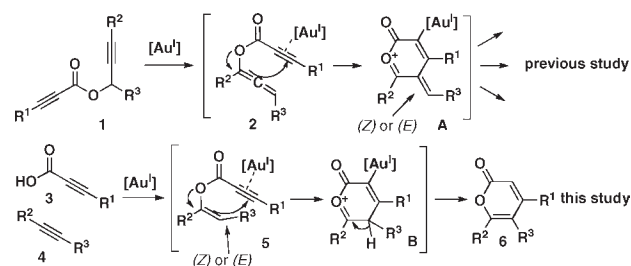
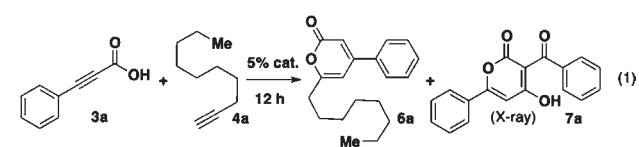
[†] Broad Institute of Harvard and MIT.[‡] Harvard University.(1) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48–56.(2) (a) Luo, T.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8250–8253. (b) Luo, T.; Schreiber, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 5667–5674.(3) For the application of gold-catalyzed 6-*endo*-dig cyclization, see: (a) Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132–8133. (b) Minnihan, E. C.; Colletti, S. L.; Toste, F. D.; Shen, H. C. *J. Org. Chem.* **2007**, *72*, 6287–6289. (c) Imase, H.; Noguchi, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2008**, *10*, 3563–3566. (d) Barabé, F.; Bétournay, G.; Bellavance, G.; Barriault, L. *Org. Lett.* **2009**, *11*, 4236–4238. (e) Menon, R. S.; Findlay, A. D.; Bissemer, A. C.; Banwell, M. G. *J. Org. Chem.* **2009**, *74*, 8901–8903. (f) Jiang, C.; Xu, M.; Wang, S.; Wang, H.; Yao, Z. *J. Org. Chem.* **2010**, *75*, 4323–4325. (g) Liu, Y.; Xu, W.; Wang, X. *Org. Lett.* **2010**, *12*, 1448–1451.(4) (a) Dickinson, J. M. *Nat. Prod. Rep.* **1993**, *10*, 71–98. (b) van Raaij, M. J.; Abrahams, J. P.; Leslie, A. G.; Walker, J. E. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 6913–6917. (c) Steyn, P. S.; van Heerden, F. R. *Nat. Prod. Rep.* **1998**, *15*, 397–413. (d) Salomon, C. E.; Magarvey, N. A.; Sherman, D. H. *Nat. Prod. Rep.* **2004**, *21*, 105–121. (e) McGlacken, G. P.; Fairlamb, I. J. *Nat. Prod. Rep.* **2005**, *22*, 369–385. (f) Sunazuka, T.; Omura, S. *Chem. Rev.* **2005**, *105*, 4559–4580.

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

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



entry	catalyst	conditions ^a	yield% ^b	
			6a	7a
1	[(Ph ₃ P)AuCl]/AgOTf	toluene, rt	43	<5
2	[(Ph ₃ P)AuCl]/AgPF ₆	toluene, rt	52	<5
3	[(Ph ₃ P)AuCl]/AgSbF ₆	toluene, rt	<5	84
4	[(Ph ₃ P)AuCl]/AgNTf ₂	toluene, rt	20	60
5	[(Ph ₃ P)AuCl]/AgPF ₆	CH ₂ Cl ₂ , rt	12	<5 ^c
6	[(Ph ₃ P)AuCl]/AgOTf	CH ₂ Cl ₂ , rt	74	<5
7	[(Cy ₃ P)AuCl]/AgOTf	CH ₂ Cl ₂ , rt	75	<5
8	[(<i>p</i> -CF ₃ C ₆ H ₄) ₃ P]AuCl/AgOTf	CH ₂ Cl ₂ , rt	68	<5
9	AuCl	CH ₂ Cl ₂ , rt		N.R.
10	AgOTf	CH ₂ Cl ₂ , rt		N.R.
11	[(Ph ₃ P)AuCl]/AgOTf	CH ₂ Cl ₂ , rt	83 ^d	<5
12	[(Ph ₃ P)AuCl]/AgPF ₆	toluene, rt	35 ^d	<5 ^e

^a[**3a**] = 0.2 M, 1.5 equiv of **4a**. ^bIsolated yields after column chromatography. ^c39% of **3a** was recovered. ^d5 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 AgPF₆ 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, AgSbF₆ led to α -pyrone **7a** as the predominant product (entry 3; structure determined by X-ray crystallography),⁷ whereas AgNTf₂ gave both α -pyrones (entry 4). The reaction was also sensitive to the identity of the solvent. With [(Ph₃P)AuCl]/AgPF₆ 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 [(Ph₃P)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

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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.

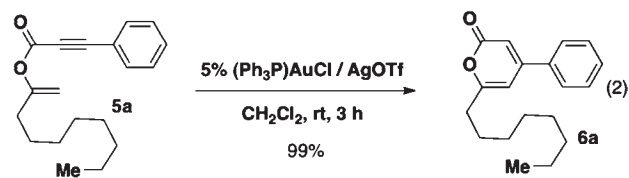


Figure 2. Cyclization of vinyl propiolate **5a** into α -pyrone **6a**.

(entries 9 and 10). The best result was obtained by increasing the amount of alkyne **4a** to 5 equiv and using the catalyst [(Ph₃P)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 [(Ph₃P)AuCl]/AgPF₆ 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).

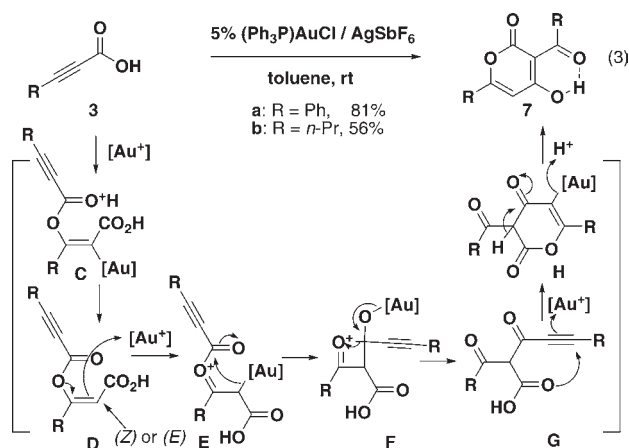
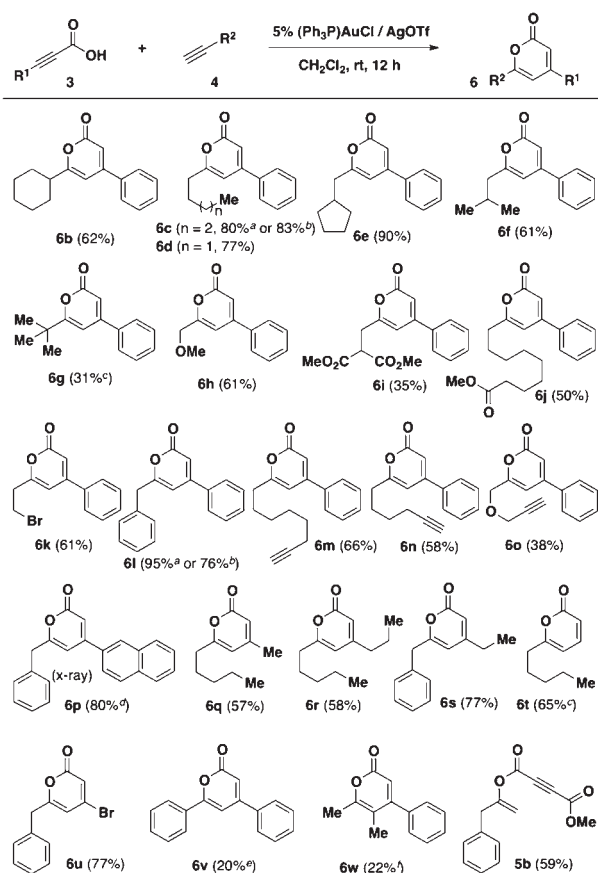


Figure 3. Dimerization of propiolic acid leading to 4-hydroxy α -pyrone.

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.

(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 -Pyrone from Propiolic Acids and Alkynes^a



^a Reaction conditions: propiolic acid (0.2–0.7 mmol, 0.2 M), alkyne (5–6 equiv), $[(\text{Ph}_3\text{P})\text{AuCl}]/\text{AgOTf}$ (5 mol %), CH_2Cl_2 , rt, 12 h; ^b phenylpropionic acid (3.4 mmol), alkyne (5 equiv), $[(\text{Ph}_3\text{P})\text{AuCl}]/\text{AgOTf}$ (5 mol %), CH_2Cl_2 , rt, 24 h; ^c CH_2Cl_2 , 50 °C, 12 h; ^d 3-(naphthalene-2-yl)propionic 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

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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 phenylpropionic 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.

Acknowledgment. The NIGMS-sponsored Center of Excellence in Chemical Methodology and Library Development (P50-GM069721) sponsored this research. S.L.S. is an investigator with the Howard Hughes Medical Institute.

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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