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Tetrahedron Letters

Tetrahedron Letters 46 (2005) 7431–7433

Gold-catalyzed cyclization of *tert*-butyl allenoate: general synthesis of 2,4-functionalized butenolides

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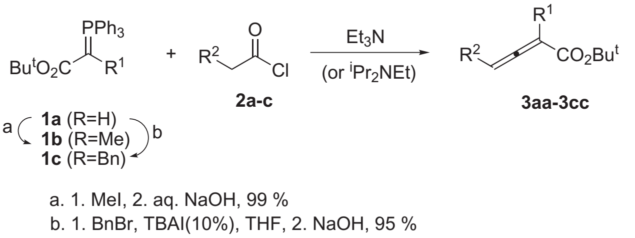
Received 9 July 2005; revised 16 August 2005; accepted 18 August 2005
Available online 9 September 2005

Abstract—$AuCl_3$ efficiently catalyzes cyclization of *tert*-butyl allenoates into γ-butenolides. Advantage of directly using allenic ester precursor instead of corresponding acid is demonstrated in the synthesis of a variety of 2,4-disubstituted butenolides. A low catalyst loading and mild reaction condition makes this process an attractive alternative over conventional methods using strong Lewis acids.

γ-Butenolide is one of the most widely occurring structural motif in a variety of biologically active natural products and also serves as a valuable platform for various diastereoselective transformations.[1,2] Not surprisingly, a great degree of synthetic efforts have been devoted for developing versatile and efficient route to butenolides.[3]

Of particular interest is cyclization of allenic acid precursors catalyzed by transition metal, such as Pd(II), Ag(I), and Au(III).[3] Most of the reported procedure starts from allenic acid, which, in turn, is obtained from hydrolysis of the corresponding ester. Direct use of allenic ester has several advantages over allenic acid: it obviates not only the need for extra deprotection step, but also problems in the deprotection step, such as isomerization into alkynyl acetic acid and/or racemization of axial chirality of allene axis in hydrolytic conditions (LiOH, BCl_3, or TBAF) can be prevented.[3b] Therefore, *direct* use of allenoate ester, whose asymmetric preparation is amply precedented, seems to be a more attractive strategy,[4] although examples using allenoate precursor is quite limited.[3b,g] Herein, we report gold(III)-catalyzed cyclization of *tert*-butyl allenoate, providing a general entry into 2,4-disubstituted γ-butenolide under exceptionally mild conditions.

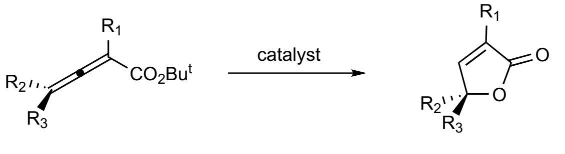
In the course of ongoing projects in our laboratory on the reactivity of electron-deficient allenyl compounds, we were interested in Au(III)-catalyzed cyclization of allenic ester (Scheme 1). Prototypical examples of this process require stoichiometric amount of electrophilic reagents, such as Br_2, PhSeCl,[3b,6] or CuX_2.[3c–f] In light of exceptional 'carbophilic' Lewis acidity of Au(III) complexes in cycloisomerization of α-hydroxyallene and α-amino-allene,[5,6] we envisioned that a similar reaction with *tert*-butyl allenoate would afford γ-butenolides.



a. 1. MeI, 2. aq. NaOH, 99 %
b. 1. BnBr, TBAI(10%), THF, 2. NaOH, 95 %

(1)

Preparation of *tert*-butyl allenoate is shown in Eq. 1. Procedures based on Wittig olefination of ketene were widely applicable to the preparation of various 2,4-disubstituted allenic esters in 42–89% yield.[7] We tested



Scheme 1. Cyclization of *tert*-butyl allenoate.

Keywords: Gold catalysis; Butenolide; Allenoate; Silver catalysis; Phosphine ligand.

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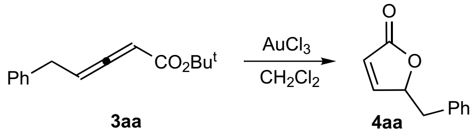
doi:10.1016/j.tetlet.2005.08.084

Table 1. Cyclization of allenoate **3aa** under various conditions



Entry	Catalyst (mol %)	Condition[a]	Yield (%)[b]
1	CuOTf (10)	80 °C/ 1.5 h	37
2	AgOTf (10)	80 °C/ 1.5 h	65
3	$PtCl_2$ (10)	80 °C/ 24 h	NR[c]
4	$AuCl_3$ (5)	80 °C/ 2 h	88
5	$AuCl_3$ (5)	rt/ 8 h	70
6	PPh_3 (10)	80 °C/ 24 h	NR
7	PPh_3 (10) HOAc (10)	80 °C/ 24 h	NR
8	$AuCl_3$ (10) Et_3N (10)	80 °C/ 24 h	NR
9	$AuCl_3$ (10) K_2CO_3 (10)	80 °C/ 24 h	NR
10	$AuCl_3$ (5) PPh_3 (5)	80 °C/ 24 h	NR
11	$AuCl_3$ (5) $P(C_6F_5)_3$ (5)	80 °C/ 2 h	85 (99[d])
12	$AuCl_3$ (5) $P(OEt)_3$ (5)	80 °C/ 1 h	55 (73[d])
13	$AuCl_3$ (5)	80 °C/ 36 h THF	70
14	$AuCl_3$ (5)	80 °C/ 24 h CH_3CN	20

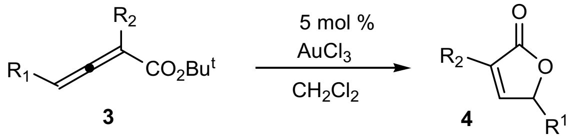
[a] Dry CH_2Cl_2 in a sealed tube.
[b] Isolated yield.
[c] No reaction.
[d] Based on recovered starting material.

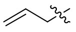
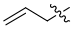
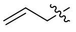
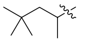
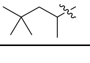
the feasibility of cyclization of allenic ester **3aa** under a variety of conditions (Table 1). Group 11 metals, such as CuOTf, AgOTf, and $AuCl_3$ showed promising activity with varying efficiency (entries 1–4). The conversion efficiency dramatically increased by employing $AuCl_3$ (5%), where and the conversion was essentially complete after 2 h at 80 °C to give 88% yield of **4aa** (entry 4). Even at rt, a significant catalytic activity remained, although a longer reaction time was required (entry 5). We also tried various other conditions, such as phosphine catalysis or $AuCl_3$ in combination with inorganic and organic bases, of no avail (entries 6–9). Use of ligand in combination with $AuCl_3$ is an area of increasing attention because of the possibility of tuning the reactivity as well as the potential applicability to asymmetric catalysis (entries 10–12).[8] When we used $AuCl_3$ along with PPh_3, no reaction was observed after 24 h at 80 °C. In contrast, use of electron-deficient $P(C_6F_5)_3$ with $AuCl_3$ led to 78% yield (99% brsm) of butenolide in 2 h at 80 °C. Finally, among the various solvents, CH_2Cl_2 turned out to be the most beneficial (entries 13 and 14).

With our optimized conditions, we tested the scope of current method. Various allenoates **3aa**–**eb** underwent a smooth reaction to afford corresponding butenolides (Table 2). Alkyl substituent at 2-position generally led to higher yield of obtained butenolide. Alkyl, aryl, and allyl substituents at 4-position were well accommodated in the current reaction without event. For example, for the formation of **4ca**–**cc**, no ring-opened by-product was observed. However, the reaction of 4-phenyl allenoates **3bc** was very sluggish and extensive decomposition was observed. In some cases, a higher temperature was not beneficial, presumably because of the undesired decomposition (entries 3 and 4).

Mechanistically two scenarios are possible: (1) Au(III)-coordinated allene is first attacked by adjacent carbonyl

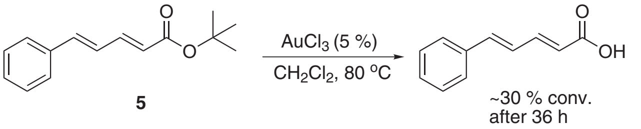
Table 2. $AuCl_3$-catalyzed cyclization of allenoates



Entry	Allenoate	R^1	R^2	Temp (°C)[a]/time (h)	Yield (%)[b]
1	**3aa**	$PhCH_2$	H	80/2	88
2	**3ab**	$PhCH_2$	CH_3	80/5	77
3	**3ac**	$PhCH_2$	$PhCH_2$	80/10 min	72
4	**3ac**	$PhCH_2$	$PhCH_2$	rt/1.5	96
5	**3bc**	Ph	$PhCH_2$	80/20	32
6	**3ca**		H	80/2	57
7	**3cb**		CH_3	80/3	71
8	**3cc**		$PhCH_2$	80/0.5	81
9	**3da**	$CH_3(CH_2)_8$	H	80/1.5	65
10	**3ea**[c]		H	80/0.6	64[d]
11	**3eb**[c]		CH_3	80/1	72[d]

[a] Dry CH_2Cl_2 in sealed tube.
[b] Isolated yield.
[c] Diastereomeric mixture (1:1) of **3eb** was used.
[d] **4eb** was obtained as 1:1 mixture of diastereomers.

followed by removal of butene or (2) Au(III) promotes cleavage of *tert*-butyl group to generate allenic acid, which immediately cyclize into butenolide. We observed no allenic acid by TLC in the course of cyclizations of **3**. However, a control experiment using *tert*-butyl 5-phenyl-penta-2,4-dienoate (**5**) showed that the corresponding acid *indeed* slowly formed under AuCl$_3$ catalysis at 80 °C (Eq. 2). Even at rt, a significant amount of dienoic acid was still observed. Therefore, we believe that Au(III)-catalyst, at least in part, plays a dual role of facilitation of hydrolysis of *tert*-butyl ester as well as cyclization of allenoic acid into **4**.



5

(2)

In conclusion, we have demonstrated that AuCl$_3$ efficiently catalyzes the cyclization of *tert*-butyl allenoates, providing a variety of γ-butenolides. Possibility of chirality transfer of enantiopure substrate is currently being explored in our laboratory.

Acknowledgments

This was supported by the research fund from Korea Sanhak Foundation in 2005. This work was also supported by a research fund from Research Institute for Natural Sciences at Hanyang University in 2004. J.E.K. thanks the BK21 program for the financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.08.084.

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