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COMMUNICATIONS

Published on Web 02/17/2006

Room Temperature Au(I)-Catalyzed *exo*-Selective Cycloisomerization of Acetylenic Acids: An Entry to Functionalized γ-Lactones

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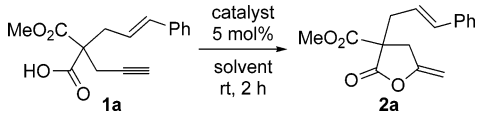
Even though gold has been considered as an expensive and inert metal for a long time, its implication in several highly selective chemical transformations reported recently has been a source of inspiration for organic chemists.[1] Gold catalysts allow indeed the creation of carbon−carbon and carbon−heteroatom bonds under extremely mild conditions.[1] Their ability to activate alkynes and promote the addition of nucleophiles has spurred on growing investigations for selective reactions. Various internal nucleophiles, such as alkenyl,[2] oxygen-,[3] and nitrogen-containing[4] functions, have been used in this regard. Our ongoing research program on metal-catalyzed cycloisomerization reactions[5] prompted us to examine the unprecedented possibility that simple and commercially available gold catalysts might function as promoters for the reaction of other functionalized alkynes, such as acids, despite the weaker nucleophilicity of the carboxylic function. To the best of our knowledge, gold-catalyzed reactions involving carboxylic acids are so far limited to the recent report by He's group on additions to alkenes in the presence of silver salts in toluene at 85 °C.[6a] The intramolecular metal-catalyzed addition of acids to alkynes generally needs to be performed in refluxing solvents, in the presence of additives or ligands, or requires the use of toxic Hg salts.[7] We wish therefore to report the first gold-catalyzed cyclization of acetylenic acids at room temperature leading to functionalized lactones.

A major issue for the success of this reaction was the reactivity of the acid moiety. Our initial attempts were motivated by the easy preparation of functionalized acid **1a**, based on a monosaponification step of the known diester.[5c,d]

Thus we treated **1a** with gold catalysts and other activating agents (Table 1). We were pleased to find that the use of 5 mol % of AuCl in acetonitrile cleanly afforded the corresponding *exo*-lactone **2a** in 90% yield at room temperature in a short reaction time (entry 1).[8] The superior efficiency of gold(I) was demonstrated through a comparison with gold(III), silver triflate, scandium triflate, and HCl in acetonitrile within 2 h (entries 2−5). The use of dichloromethane, dichloroethane, or toluene led to the formation of the desired lactone in lower isolated yields (entries 6−8). The versatility of AuCl was then evaluated for other functionalized acids (Table 2).[9] Acids **1b**−**m** bearing ester, alkenyl, chloro, alkynyl, free and protected alcohols moieties were prepared conveniently according to simple alkylation and monosaponification steps. The reaction was amenable to a wide range of other alkenyl-substituted acids, such as **1b**−**e**, as they were converted in the presence of 5 mol % of AuCl in a short time to the corresponding five-membered lactones **2b**−**e** (entries 1−4) in high isolated yields (72−89%).

The cyclizations proceeded smoothly under a 5-*exo* mode, and no reaction on the alkenyl moieties was observed. Bispropargylic substrate **1f** was also cleanly cyclized to the corresponding acetylenic lactone **2f** in excellent isolated yield (entry 5). The presence of an alkenyl side chain was not critical since chloro-, *n*-butyl, and benzyl containing acetylenic acid **1g**−**i** was similarly converted into its lactone derivative **2g**−**i** in 83−97% yield (entries 6−8). The conditions were also compatible with free, benzyl-, and silyl-protected alcohols (entries 9−11). The presence of a phenyl group instead of an ester or ether function was also possible as the acid **1m** was cleanly cyclized in 98% yield (entry 12). The catalyst loading was successfully reduced to 1 mol % in the case of acids **1a** and **1i**, which prolonged the reaction time to 7 h, but still gave the desired lactones in excellent yields (entries 13 and 14). These lactones are of paramount importance for the synthesis of natural products or biologically active compounds.[7,10]

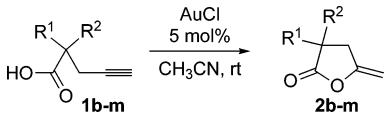
Table 1. Cycloisomerization of Acetylenic Acid **1a**



entry	catalyst[a]	solvent	yield (%)[b]
1	AuCl	CH_3CN	90
2	$AuCl_3$	CH_3CN	84
3	AgOTf	CH_3CN	10[c]
4	$Sc(OTf)_3$	CH_3CN	0
5	HCl	CH_3CN	0
6	AuCl	toluene	60
7	AuCl	CH_2Cl_2	63
8	AuCl	$C_2H_4Cl_2$	57

[a] 5 mol %. [b] Isolated yield. [c] Conversion.

Table 2. AuCl-Catalyzed Cyclization of Acetylenic Acids in Acetonitrile at Room Temperature

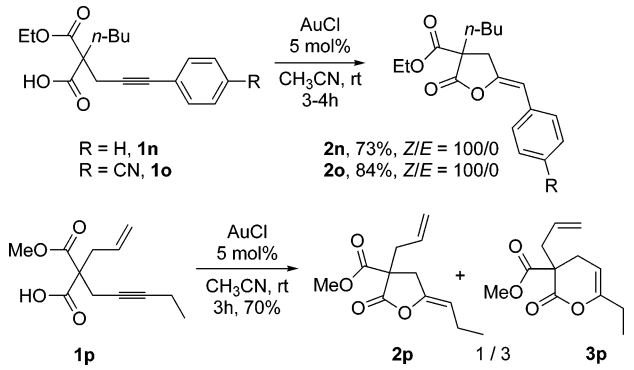


entry	acid	R^1	R^2		time (h)	yield (%)[a]
1	**1b**	CO_2Me	cyclohex-2-enyl	**2b**	2	89
2	**1c**	CO_2Me	but-2-enyl[b]	**2c**	2	78
3	**1d**	CO_2Me	allyl	**2d**	2	72
4	**1e**	CO_2Me	but-3 -enyl	**2e**	2	87
5	**1f**	CO_2Me	propargyl	**2f**	2	97
6	**1g**	CO_2Me	Cl	**2g**	2	95
7	**1h**	CO_2Et	*n*-Bu	**2h**	2	83
8	**1i**	CO_2Et	Bn	**2i**	1	97
9	**1j**	CH_2OBn	propargyl	**2j**	2	97
10	**1k**	CO_2Me	4-hydroxybut-2-enyl[b]	**2k**	2	85
11	**1l**	CO_2Me	C_4H_6OTIPS[b]	**2l**	2	75
12	**1m**	Ph	propargyl	**2m**	2	98
13[c]	**1a**	CO_2Me	cinnamyl	**2a**	7	90
14[c]	**1i**	CO_2Et	Bn	**2i**	7	94

[a] Isolated yield. [b] *E*/*Z* isomers. [c] 1 mol % catalyst.

10.1021/ja056857j CCC: $33.50

Scheme 1



The stereochemical outcome of the addition was then investigated. For this purpose, we reasoned that an internal alkyne would give either the *Z* or *E exo*-methylene lactone during the cyclization process. Acids **1n**,**o**, easily prepared via classic Sonogashira couplings, were cyclized in the presence of 5 mol % of AuCl (Scheme 1). The reaction afforded selectively the (*Z*)-γ-lactones **2n**,**o**, the stereochemistry of which was demonstrated by NOESY experiments. As expected, the alkyl-substituted triple bond induced a different polarity of the alkyne and therefore modified the regioselectivity of the cyclization.[11] The cyclization of the ethyl-substituted acid **1p** afforded the (*Z*)-γ-lactone **2p** accompanied with the 6-*endo*-lactone **3p**.

The stereochemistry of the substituted γ-lactones **2n**−**p** is therefore consistent with a mechanism implying an *anti* intramolecular addition of the carboxylic acid to the Au−alkyne intermediate, resulting from an initial activation of the triple bond. The total stereocontrol and the high selectivity of the reaction may be due either to a Thorpe−Ingold effect or to the presence of ester, ether, or unsaturated functions that could potentially participate in an intramolecular complexation with gold.[5a,12]

In conclusion, we have demonstrated that functionalized acetylenic acids may be cyclized under extremely mild conditions, at room temperature in the presence of AuCl catalyst, and without additives. The corresponding *exo*-methylene lactones were isolated in high yields, and this process constitutes an easy and efficient access to highly valuable building blocks of natural products or biologically active compounds. The high activity of gold catalysts associated with very mild reaction conditions would allow further synthesis of lactones.

Acknowledgment. This work was supported by the Centre National de la Recherche Scientifique and partially by a grant from CPER (action 10040 "Pole Chimie du vivant"). E.G. is grateful to the Ministère de l'Education et de la Recherche for financial support (2003−2006).

Supporting Information Available: Experimental procedure and full analyses of lactones **2a**−**p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Standard procedure: a mixture of acetylenic acid, AuCl (5 mol %) in degassed acetonitrile (1.2 mol·L^{-1}) was stirred under argon atmosphere at room temperature. After completion of the reaction, the mixture was filtered through a short pad of silica (EtOAc), and the solvents were evaporated under reduced pressure to give the corresponding lactone. No traces of methyl ketone were detected, even after reaction of the resulting lactone in the presence of AuCl and 10 equiv of water.

(9) The cyclizations of simpler alkynes, such as pent-4-ynoic acid, 2-phenyl-pent-4-ynoic acid, and 2-prop-2-ynylmalonic acid monomethyl ester, afforded a mixture of the *exo*-methylene lactones and the methyl ketones, presumably resulted from the formal Markovnikov-type hydration of the triple bond. For Au-catalyzed hydration reactions, see: (a) Schneider, S. K.; Herrmann, W. A.; Herdtweck, E. *Z. Anorg. Allg. Chem.* **2003**, *629*, 2363−2370. (b) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4563−4565. (c) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729−3731.

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JA056857J