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A mild access to γ- or δ-alkylidene lactones through gold catalysis

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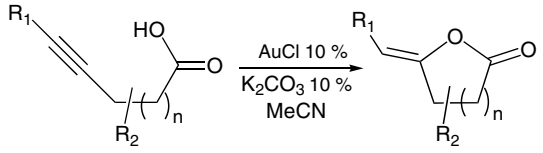
Abstract—ω-Acetylenic acids are efficiently and stereoselectively converted to the corresponding enol lactones in the presence of catalytic amounts of AuCl and K_2CO_3.

Although still its in infancy, gold catalysis is increasingly gaining interest in organic chemistry due to the efficiency, the mildness and the peculiar properties associated with such Lewis acids.[1]

Most of the reactions promoted by gold catalysts are intramolecular or intermolecular additions to triple[1e] or double bonds.[1] Although the intramolecular versions offer an interesting way to get heterocycles,[1–8] only a few possibilities have so far been explored. For example, no cyclization of acetylenic acids is described,[1e,9] despite of the wide interest of the expected enol lactones,[10] which could be either *exo*- or *endo*-cyclic depending on the *exo*-dig or *endo*-dig mode of cyclization.

In this context and due to our interest in such compounds,[11] we looked for a novel and mild access to enol lactones based on the cyclization of acetylenic acids mediated by gold species. Here we report our preliminary results in this area (Scheme 1).

In order to find the appropriate conditions for this cyclization, we submitted the commercially available 4-pentynoic acid **1a** to different gold salts in various conditions (Table 1).



Scheme 1. Formation of enol lactones by Au^I-catalyzed cyclization of acetylenic acids.

Without any catalyst, no cyclization was observed whatever the solvent (see entry 1 for an example). Gold chloride, alone or as its triphenylphosphine complex, did not promote the expected cyclization, whatever the solvent and the amount of catalyst (entries 4–6, 7 and 8). The more electrophilic gold trichloride was not effective in dichloromethane and acetonitrile (entries 2–3).[12] The solvent however seemed to play a critical role, since various products were formed in low yields in acetonitrile while no conversion was observed in dichloromethane (entries 2, 5, 7 vs 3, 6, 8). It is worth noting that both gold chloride and trichloride were not readily soluble in benzene and dichloromethane, although the latter is the most often used solvent in Au-catalyzed reactions.[1]

We reasoned out that gold chloride could not be electrophilic enough in this case to allow for an intramolecular addition of the carboxylic function and that a gold carboxylate would better organize and/or place closer the reacting functional groups (see Scheme 2). We thus added bases into the reaction mixture to produce the more nucleophilic carboxylate in situ. This addition did not change much with gold trichloride (entries 9–10 vs 2–3). Increasing the amount of either gold trichloride or of the base did not improved the reaction, and only traces of the expected product were at best obtained. However, potassium carbonate proved to be a perfect choice with gold chloride (entries 13–16) and with triphenylphosphinogold chloride (entries 11 and 12). Interestingly enough, in these cases, only a catalytic amount of this base was required (entries 11–16). With triphenylphosphinogold chloride as catalyst, the reaction proved to be slower in acetonitrile (entry 12 vs

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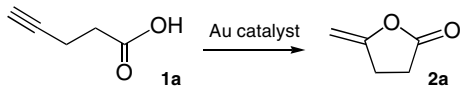
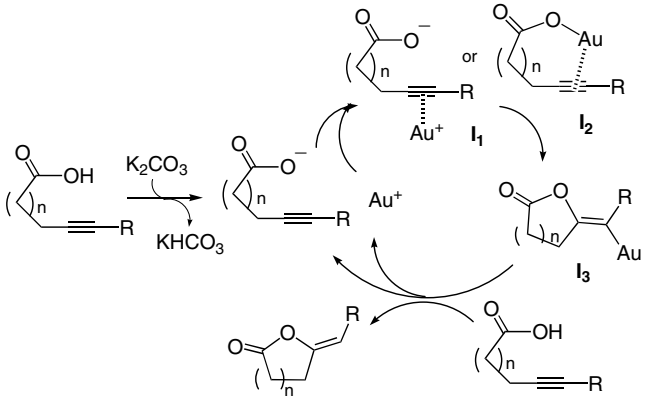
Table 1. Formation of methylene butenolide **2a** from 4-pentynoic acid **1a** in the presence of gold salts in various conditions



	Catalyst[a]	Solvent	T (°C)	Time (h)	Yield[b]
1	—	CH_2Cl_2	40	5	0[c]
2	$AuCl_3$	CH_2Cl_2	20	6	0[c]
3		MeCN	20	5	Trace[d]
4	AuCl	PhH	80	6	Trace[d]
5		CH_2Cl_2	40	5	0[c]
6		MeCN	20	5	Trace[d]
7	$AuCl(PPh_3)$	CH_2Cl_2	40	6	0[c]
8		MeCN	20	5	Trace[d]
9	$AuCl_3$, K_2CO_3	CH_2Cl_2	40	6	0[c]
10		MeCN	20	5	Trace[d]
11	$AuCl(PPh_3)$, K_2CO_3	CH_2Cl_2	20	3	95
12		MeCN	20	3	96
13	AuCl, K_2CO_3	PhH	80	3	<10[d]
14		CH_2Cl_2	20	3	Trace[d]
15		MeCN	20	1	96
16		THF	20	1	95

[a] 0.1 equiv.
[b] Yield of isolated pure product.
[c] The starting material was recovered.
[d] Several products were formed in low yields (<5%).



Scheme 2. Proposed mechanism for the gold catalyzed cyclization of ω-acetylenic acids.

15) but faster in dichloromethane (entry 11 vs 14). With gold chloride, acetonitrile and tetrahydrofuran were the solvents in which the best yields and rapid reactions were achieved (entries 12, 15–16 vs 13–14). It is worth noting that although acetonitrile has been applied in a few Au-catalyzed reactions,[5,13] no report of the use of THF was so far mentioned.

Interestingly, a *single* compound was formed in these conditions, the spectroscopic data of which corresponded to the known γ-methylene butenolide **2a**.[14] Therefore, these conditions promoted the exclusive formation of the *exo*-dig product.

In order to study the scope of this new formation of enol lactones, various representative acetylenic acids were then submitted to the above conditions (Table 2).

The chain length between the acetylenic and the carboxylic parts was first varied in order to check the *exo*/*endo*-selectivity of this cyclization. As for 4-pentynoic acid **1a**, 5-hexynoic acid **3a** exclusively gave the *exo*-dig product (entry 6 vs 1). Both acetylenic acids exhibited the same reactivity and gave the corresponding methylene lactones **2a**, **4a** with the same yield. However, the longer 6-heptynoic acid **5a** reacted in a much slower way but still gave the *exo*-products **6a**, although in a much lower yield and in a less cleaner reaction (entry 10 vs 6 vs 1).

Using conventional methods, we then prepared substituted acetylenic acids to look at the stereoselectivity of this cyclization. The brominated 4-pentynoic and 5-hexynoic acids **1b**, **3b** were easily obtained from the corresponding acetylenic acids **1a**, **3a** by NBS treatment in the presence of catalytic amounts of silver nitrate.[15] Placed in the presence of gold chloride and potassium carbonate, these bromoacetylenic acids were exclusively again converted to the *exo*-products **2b**, **4b** as *single stereoisomers* (entries 2 and 7). The *Z* stereochemistry of these compounds was assigned from the chemical shift of their vinylic protons (5.34 and 5.37 ppm, respectively) and by comparison with known products.[16,17]

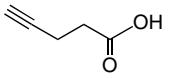
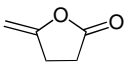
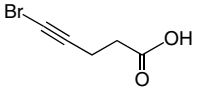
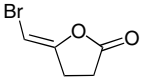
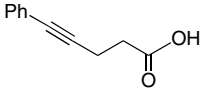
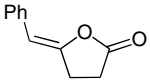
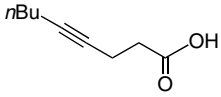
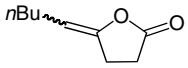
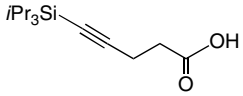
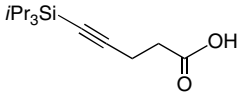
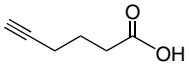
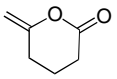
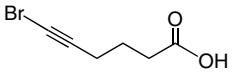
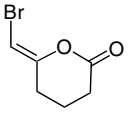
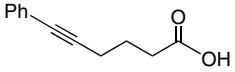
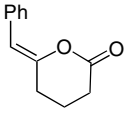
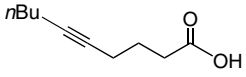
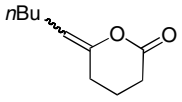
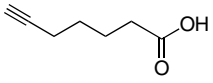
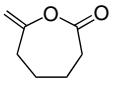
The phenyl substituted 4-pentynoic and 5-hexynoic acids **1c**, **3c** were easily obtained by coupling the butyl 4-pentynoate and 5-hexynoate with phenyl iodide,[18] followed by saponification. Again, gold chloride in the presence of potassium carbonate promoted the exclusive formation of the *exo*-products **2c**, **4c** as *single stereoisomers* (entries 3 and 8). The *Z* stereochemistry was again proved by spectroscopic comparison with known compounds.[19]

The corresponding alkyl substituted acetylenic acids **1d**, **3d**, exclusively led to the *exo*-products **2d**, **4d**. Surprisingly, a 1:1 mixture of *Z* and *E* stereoisomers[20] was obtained from **1d** (entry 4), but only the *Z* stereoisomer was isolated from **3d** although in a modest yield (entry 9). In the latter case, it seems that one of the stereoisomers formed decomposed.

The 5-tri-*iso*-propylsilyl-4-pentynoic acid **1e** did not cyclize in these conditions, even after prolonged reaction time (entry 5). It seems that a silyl atom adjacent to the π-system withdraws electron density by d–π conjugation, thus lowering the coordination ability of the acetylenic moiety towards Au^I.

In contrast to other Au-catalyzed reactions,[1] the cyclization of ω-acetylenic acids described here can only be catalyzed by Au^I. These results rule out redox processes (disproportionation)[1a] and suggest an electrophilic activation of the acetylenic moiety by Au^I. The fact that a mild base (K_2CO_3) is required also suggests a deproto-

Table 2. Formation of alkylidene lactones from various acetylenic acids[a]

	Acetylenic acid		Lactone		Yield[b]
1		**1a**		**2a**	96
2		**1b**		**2b**	96
3		**1c**		**2c**	96
4		**1d**		**2d**	88[d]
5		**1e**		**2e**	0[c]
6		**3a**		**4a**	97
7		**3b**		**4b**	98
8		**3c**		**4c**	97
9		**3d**		**4d**	50–60[e]
10		**5a**		**6a**	25[f]

[a] 0.1 equiv of AuCl and 0.1 equiv of K_2CO_3 in acetonitrile at 20 °C for 2 h unless otherwise stated.
[b] Yield of the pure product after column chromatography.
[c] The starting material was recovered.
[d] Isolated as a 1:1 *Z*/*E* mixture.
[e] One of the stereoisomers formed seemed unstable.
[f] The reaction required longer time (48 h) and by-products were also formed (<10%).

nation of the acid group. Whatever their order, these events would lead to an intermediate like $\mathbf{I}_1$ or $\mathbf{I}_2$ in Scheme 2. The latter, analog to intermediates calculated for methanol addition to alkynes,[21] does not account for the observed stereochemistry, since it should lead to *syn* auration and thus to *E* isomers. The former however would be perfectly oriented for a nucleophilic addition of the carboxylate moiety to the gold-activated acetylenic group (*anti* auration).[8] The organogold intermediate $\mathbf{I}_3$ would thus be produced through an *exo*-dig process. In contrast to other known Au-catalyzed cyclizations,[1,4,5] the *exo*-dig cyclization seems to be always preferred here, even when both *exo*- or *endo*-dig pathways are possible (Table 2, entries 1–4). It is nevertheless worth noting that a few other Au-catalyzed *exo*-dig cyclizations have been described.[2b,3,8,22] Hydrolysis of the carbon–gold bond would then liberate the enol lactone and regenerate the gold catalyst. The fact that only catalytic amount of potassium carbonate is necessary suggests that the proton source in the later step is the starting acid itself (Scheme 2).

These hypotheses could account for the observed stereochemistry of the cyclized products in the case of the bromo- and phenyl-substituted γ- and δ-acetylenic acids (**2b**, **2c** and **4b**, **4c**, respectively) but not in the case of the butyl analogs (**2d**). The reasons for this discrepancy are still unknown. Equilibration does not occur in the present conditions, since the *E*/*Z* equilibrium ratio is known for the bromomethylene lactones **2b**, **4b** (1/1.2,

1/6.5, respectively)[17] and is far from what is observed here (Table 2, entries 2 and 7).

In conclusion, we have developed a simple and very efficient method for the synthesis of γ- and δ-alkylidene lactones by intramolecular cyclization of ω-acetylenic acids catalyzed by AuCl and K_2CO_3. Moreover, a single *Z* stereoisomer was formed with bromo- and phenyl substituted derivatives.

Further works are now underway to expand and better understand this cyclization of ω-acetylenic acids.

Typical procedure for the formation of enol lactones from ω-acetylenic acids: To a solution of ω-acetylenic acid (1 equiv) in acetonitrile (3 ml/mmol) at room temperature, was added gold chloride (0.1 equiv) and then K_2CO_3 (0.1 equiv). The reaction mixture, initially a white suspension, turned to a dark brown solution within minutes. After the disappearance of the starting material (TLC monitoring, usually 2 h), water was added to the reaction mixture and the resulting two layers were separated. After extraction with dichloromethane, the combined organic layers were dried over $MgSO_4$. After filtration and solvent evaporation, the crude product was purified by column chromatography when necessary.

Acknowledgements

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