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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1439–1442

Synthesis of functionalized THF and THP through Au-catalyzed cyclization of acetylenic alcohols

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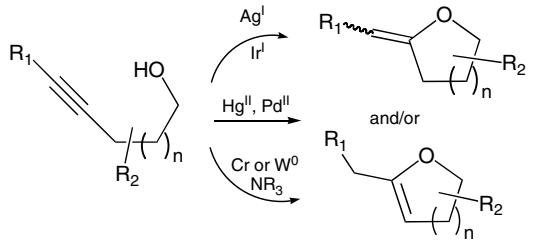
Received 9 November 2006; revised 14 December 2006; accepted 15 December 2006
Available online 20 December 2006

Abstract—ω-Acetylenic alcohols are regio- and stereo-selectively converted to the corresponding α-alkylidene oxygenated heterocycles in the presence of catalytic amounts of AuCl and K_2CO_3.

1. Introduction

Tetrahydrofurans and pyrans (oxolanes and oxanes) are common motifs in a wide variety of natural products.[1] Since such compounds often exhibit interesting biological activities, numerous routes have been developed for their synthesis.[2] Among these methods, the cyclization of acetylenic alcohols is one of the most rapid and convenient. Such cyclizations are usually performed through metal catalysis and can yield to products resulting either from an *exo*-dig or an *endo*-dig process or from both (Scheme 1). Earlier versions were based on intramolecular oxymercuration starting from acetylenic alcohols, usually leading to the corresponding exocyclic enol ether.[3] Later, palladium(II) catalyzed version was pioneered by Utimoto et al., but mixture or *exo*- and *endo*-dig products could be obtained.[4] Silver carbonate catalyzed the exclusive and very effective formation of exocyclic enol ethers.[5] More recently, other transition metals also proved to be useful catalysts for such heterocyclizations. Chromium, tungsten, and molybdenum catalysts led in the presence of base to endocyclic enol ethers,[6] while iridium(I) in methanol led to adducts derived from exocyclic products.[7]



Scheme 1. Formation of di- or tetrahydrofuranes and pyranes through metal-catalyzed cyclization of acetylenic alcohols.

In the last few years, gold salts or complexes also proved to be efficient catalysts in some heterocyclization reactions.[8–11] However, only a few cyclizations of acetylenic alcohols were reported. Hashmi, in one of his seminal papers, mentioned the $AuCl_3$-catalyzed cyclization of 2-methylpent-2-en-4-yn-1-ol to 2,4-dimethylfuran, via probable intermediate 4-methyl-2-methyleneoxolene.[10] The same reaction was reported by Liu et al. with the corresponding aryl substituted penten-yn-ols.[11] Krause et al.[9d] and De Brabander et al.[9i] independently reported the cyclisation–alkoxylation of respectively homopropargylic alcohols to 1-alkoxyoxolanes and some acetylenic diols to spiroketals.

Our investigations in related silver-catalyzed cyclizations showed us that electronic effects play a significant role in such cyclizations.[5b] We thus wondered if gold-catalyzed cyclization of acetylenic alcohols could be a general process or if it is restricted to activated substrates. We reported here the preliminary results in this area, showing that gold chloride and potassium carbonate catalyzed a highly regio- and stereoselective cyclization of acetylenic alcohols (Scheme 2).

2. Results and discussion

Simple terminal acetylenic alcohols of different chain lengths **1a**, **3** were submitted to various gold catalysts

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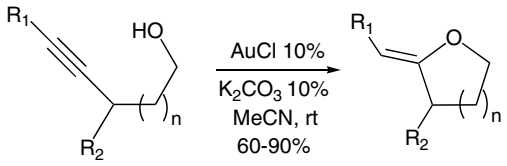
doi:10.1016/j.tetlet.2006.12.100

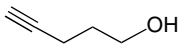
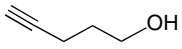
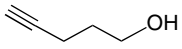
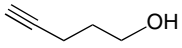
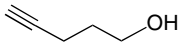
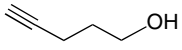
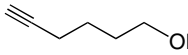
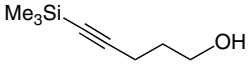
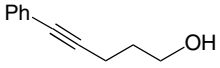
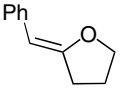
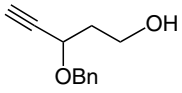
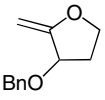
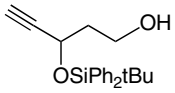
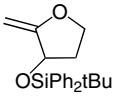
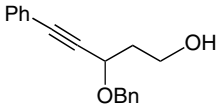
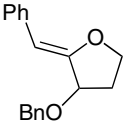
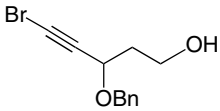
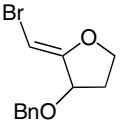
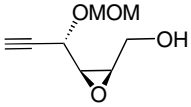
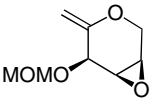


Scheme 2. Formation of α-alkylidene oxolanes and oxanes catalyzed by gold chloride and base.

in various conditions, but although the starting materials were mostly consumed, several unidentified degradation products were produced (Table 1, entries 2–5, 7). Interestingly, no evolution was observed without gold species (entry 1). Moreover, a reaction performed in deuterated acetonitrile with **1a** and AuCl in the presence of potassium carbonate revealed through ^{1}H NMR monitoring the formation, after 1.5 h, of a cyclization product among side-products, while the major compound in the mixture remained the starting alcohol (entry 6). The detected compound **2a** exhibited the typical NMR pattern of 2-methylene oxolanes.[5,12]

Knowing the high sensitivity of such α-methylene heterocycles,[5c,12] we next turned to non-terminal acetylenic

Table 1. Synthesis of α-alkylidene oxolanes and oxanes from the corresponding acetylenic alcohols

Entry	Acetylenic alcohol		Catalyst[a]	Solvent	Time	Temperature (°C)	Yields[b]	Heterocycle	
1		**1a**	None	CH_2Cl_2 THF MeCN	20 h	−30 to 50	0	SM recovered	**1a**
2		**1a**	AuCl	CH_2Cl_2 THF MeCN	20 h	−30 to 50	dec	—	
3		**1a**	$AuCl_3$	MeCN	20 h	−30 to 50	dec	—	
4		**1a**	$AuCl(PPh_3)$	MeCN	20 h	−30 to 50	dec	—	
5		**1a**	AuCl, K_2CO_3	MeCN	20 h	25	dec	—	
6		**1a**	AuCl, K_2CO_3	CD_3CN	2 h	25	10–20		**2a**[c]
7		**3**	AuCl, K_2CO_3	MeCN	20 h	25	dec	—	
8		**1b**	AuCl, K_2CO_3	MeCN	20 h	25	0	SM recovered	**1b**
9		**1c**	AuCl, K_2CO_3	MeCN	4 h	25	82		**2c**[c]
10		**4a**	AuCl, K_2CO_3	MeCN	1 h	25	90		**5a**
11		**4b**	AuCl, K_2CO_3	MeCN	2 h	25	80		**5b**
12		**4c**	AuCl, K_2CO_3	MeCN	24 h	25	30		**5c**
13					3 h	50	70		
14		**4d**	AuCl, K_2CO_3	MeCN	1 h	25	84		**5d**
15		**6**	AuCl, K_2CO_3	MeCN	15 min	25	76		**7**

[a] 0.1 equiv.
[b] Yield of isolated pure product.
[c] The product is extremely sensitive.

alcohols which could give relatively stable cyclized products. The trimethylsilylated pent-4-yn-1-ol **1b** remained mostly untouched in the same conditions (e.g., entry 8). However, 5-phenylpent-4-yn-1-ol **1c** was readily converted to the corresponding 2-(phenylmethylene) oxolane **2c** in the presence of catalytic amounts of gold chloride and potassium carbonate in acetonitrile (entry 9). Other conditions did not give rise to any characterizable product. Therefore, gold chloride in acetonitrile seems to exclusively promote the *exo*-dig cyclization in the presence of potassium carbonate. Moreover, a *single stereoisomer* was detected, the *Z* stereochemistry of which was assigned from NMR data and by comparison with related compounds.[5,9a]

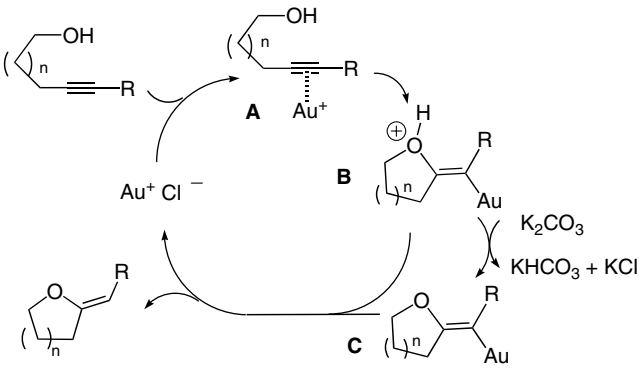
We then investigated the cyclization of acetylenic alcohols bearing an activating group at the propargylic position. 3-Benzyloxypent-4-yn-1-ol **4a** was thus prepared and submitted to these conditions. In contrast to the unsubstituted analog **1a**, **4a** gave the *exo*-dig product **5a** in as high yield at room temperature (entry 10 vs 5, 6). No other product could be isolated. The corresponding O-silylated derivative **4b** behave in the same way, giving **5b** with a slightly lower yield, probably due to the longer reaction time (entry 11 vs 10).

The phenyl substituted acetylenic alcohol **4c** also gave the expected *exo*-dig product **5c**, but this cyclization surprisingly proceeded more slowly than the corresponding terminal alkyne **1c** at room temperature (entry 12 vs 9). Raising the temperature to 50 °C speeded up the reaction without increasing too much the decomposition of the formed product (entry 13 vs 12). Interestingly, a *single* compound was again formed, the spectroscopic data of which corresponded to the *Z* stereoisomer.

In order to have a flexible entry toward substituted alkylidene heterocycles, we prepared the corresponding brominated derivative **4d**. In the same conditions, this compounds readily cyclized, giving again a single *Z* stereoisomer **5d** in good yields (entry 14). This bromomethylene oxolane could be a useful starting point toward polyenyne derivatives through cross-coupling reactions.

To check if larger cycles can be produced, 2,3-epoxyhex-5-yn-1,4-diol, protected at its secondary alcohol, **6**, was prepared and submitted to the above mentioned conditions. This substrate proved to be very reactive since, after only a few minutes, the corresponding cyclized product **7** was formed (entry 15). Here again, only the compound resulting from an *exo*-dig process was observed.

From a mechanistic point of view, the results summarized here suggest a cyclization based on electrophilic activation of the acetylenic moiety by gold ion. Surprisingly, only Au^I is an effective catalyst, indicating that disproportionation is not involved in this reaction. The observed regio- and stereoselectivity suggest an activation of the acetylenic moiety through Au^I-coordination (**A** in Scheme 3), which would induce a nucleophilic addition of the alcohol group in an *anti* auration process.[9h] This cyclization would lead to a protonated alkoxyorganogold intermediate **B**. Potassium carbonate probably deprotonated this intermediate leading to a neutral organogold species **C**. Hydrolysis of the carbon–gold bond would then liberate the α-alkylidene heterocycle and regenerate the gold catalyst. The fact that only catalytic amount of potassium carbonate is necessary suggests that the deprotonation as well as the carbon–gold bond hydrolysis are linked in the later step (Scheme 3).



Scheme 3. Proposed mechanism for the gold catalyzed cyclization of ω-acetylenic alcohols.

The cyclization was effective without or with an oxygenated propargylic substituent (entry 9 vs 10). Moreover, when the oxygen atom of this substituent carried a bulky and electron-withdrawing group, there is only a slight decrease in yield and an increased reaction time. Therefore, such oxygenated propargylic substituent may not have a role as important as in the corresponding silver catalyzed cyclization.[5b]

It is worth noting that only *exo*-dig cyclization products were observed here, in contrast with the recently described cyclization–alkoxylation of some acetylenic alcohols[9d] and diols.[9i]

3. Conclusion

In conclusion, we have developed a simple and efficient method for the synthesis of α-alkylidene oxolanes and oxanes by intramolecular cyclization of ω-acetylenic alcohols catalyzed by AuCl and K_2CO_3. Moreover, besides being highly regioselective, this cyclization is also highly stereoselective since a single *Z* stereoisomer was formed.

The Au-catalyzed cyclization of acetylenic alcohols is thus a general process, since terminal as well as non-terminal alkynes, functionalized or not, could be cyclized. Nevertheless, the role of a propargylic substituent appeared to be a key factor.

Further works are now underway to expand the scope of this reaction, as well as to develop its applications in organic synthesis.

4. Typical procedure for the formation of α-alkylidene oxolanes or oxanes from ω-acetylenic alcohols

To a solution of ω-acetylenic alcohol (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, rapidly turned to a dark brown solution. After disappearance of the starting material (TLC monitoring, see Table 1), a filtration over a short path silica gel column and solvent evaporation provided the product, which was repurified by flash chromatography when necessary. It is worth noting that these compounds are extremely sensitive.[12]

Acknowledgements

H.H. thanks the Algerian government for a PhD fellowship. P.P. and J.M.W. thank the 'CNRS' and the French Ministry of Research for financial support.

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