Silver-catalyzed cyclization of acetylenic alcohols and acids: a remarkable accelerating effect of a propargylic C–O bond

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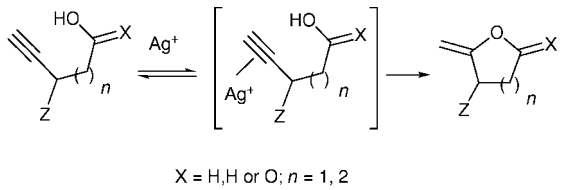
The heteroannulation catalyzed by silver salts of alkynols 1, 2 or alkynoic acids 3 is considerably enhanced by the presence of a propargylic C–O bond. This method allows for a rapid access to highly functionalized heterocycles, such as α-methylene oxolanes 4 or oxanes 5 and as γ-methylene pentanolactones 6.

Tetrahydrofurans and pentanolactones are frequently encountered structures in natural products.[1,2] This has motivated numerous efforts to develop strategies for the synthesis of these compounds.[1,2] Particularly, methods that utilize transition metal-catalyzed ring closure between a hydroxyl or an acid and an unsaturated compound, either olefinic, acetylenic or allenic, have gained considerable preeminence in recent times.[1–5] [Pd[3], Hg[4], and Ag[5] have been the most currently used metals for this purpose].

We recently reported that acetylenic alcohols and acids could be efficiently cyclized by a catalytic amount of silver carbonate in refluxing benzene.[5] The cyclization proved to be regiospecific and the exocyclic α-methylene heterocycles resulting from an exo-dig ring closure were always exclusively isolated. This cyclization is now becoming a useful tool for the synthesis of tetronic acid[6] and tetrahydrofuran[7] derivatives. In this paper, we report on further studies that demonstrate the strongly accelerating effect of the propargylic oxygenated substituent on the ring closure of both acetylenic alcohols and acids and thus expand the scope of this novel route towards oxygenated heterocycles.

Our previous work has shown a marked difference between the cyclization of 4-pentynoic or 5-hexynoic acids and the cyclization of the corresponding alcohols. Acetylenic alcohols cyclized faster but the process was less general. The results suggested that the cyclization seemed to be dependent on the structure of the substrate, requiring a predisposed orientation of the hydroxyl and the acetylenic unit as in *cis* 2,3-epoxy pent-4-yn-1-ols.[5] Considering the mechanism of such transition metal-assisted electrophilic cyclizations[8] (Scheme 1), we

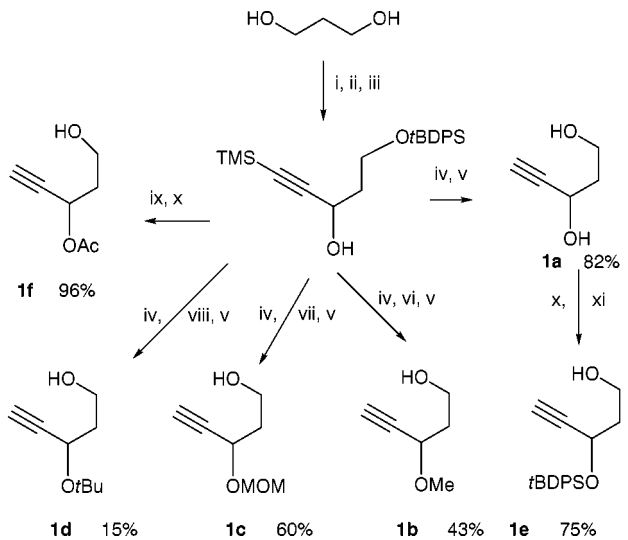


X = H,H or O; *n* = 1, 2

Scheme 1

reasoned that any factor altering the π system would also affect its coordination to the electrophilic metal and eventually the cyclization. We thus studied the cyclization of several acetylenic alcohols and acids bearing various substituents at the propargylic position with different electronic properties. With respect to a coordination-cyclization mechanism, the size of the propargylic substituent would also be expected to play a role in the reaction by preventing access to the triple bond.

We chose to study acetylenic compounds incorporating an oxygen atom at the propargylic position since both its electronic influence and its size could be easily modulated by the proper selection of substituent. Various pentynols **1a**–**f** with an oxygenated group at the propargylic position were prepared according to conventional sequences from 1-*tert*-butyldiphenylsiloxypent-4-yn-3-ol. This compound was obtained from 1,3-propanediol after monoprotection, oxidation and addition of lithium trimethylsilylacetylide (Scheme 2). Contrary to the parent unsubstituted 4-pentynols, which do not cyclize under our standard conditions (Table 1, run 1), all the substituted 4-pentynols **1a**–**e** readily cyclized in high yields (runs 2–6) except the acetate **1f** (run 7). Diol **1a** underwent complete cyclization in only 1 h (run 2), while propargylic ethers **1b**–**d** required longer but reasonable periods of time to be totally consumed (runs 3–5). However, the silyloxy deriv-



Scheme 2 (*i*) *t*BDPSCl, 68%. (*ii*) PCC, 90%. (*iii*) TMSacetylide, 75%. (*iv*) K_2CO_3, MeOH, 95%. (*v*) TBAF·$3H_2O$, 67–86%. (*vi*) NaH, HMPA and MeI, 78%. (*vii*) MOMCl, 79%. (*viii*) Isoprene, montmorillonite K10, 22%. (*ix*) Ac_2O, 4-DMAP, 100%. (*x*) 2.2 equiv. TBAF·3 H_2O, 96%. (*xi*) *a*: TMSCl, *b*: *t*BDPSCl, *c*: citric acid, MeOH, 75%.

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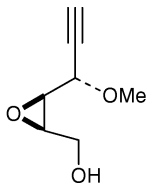
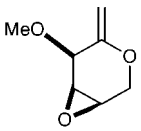
Table 1 Silver-catalyzed cyclization of miscellaneous alkynols bearing a propargylic oxygenated substituent

1–2 4–5

	Acetylenic alcohol				
Run[a]	*n*	Z		Time/h	Product (yield/%)[b]
1	1	H	**1**	6	**4** (0)
2	1	OH	**1a**	1	**4a** (99)
3	1	OMe	**1b**	2.5	**4b** (99)
4	1	OMOM	**1c**	3	**4c** (99)
5	1	O*t*Bu	**1d**	4	**4d** (99)
6	1	O*t*BDPS	**1e**	24	**4e** (99)
7	1	OAc	**1f**	2.5	**1f** recovered
8[c]	1	OAc	**1f**	6	Decomposition
9	2	H	**2**	6	**2** recovered
10				7.5	



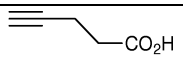
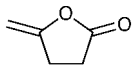
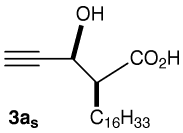
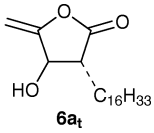
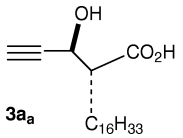
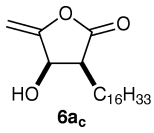
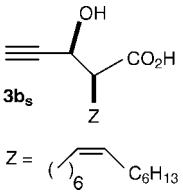
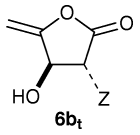
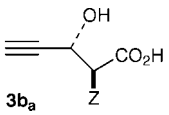
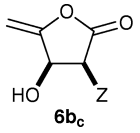
2a



5a (43)

[a] Reactions were carried out in refluxing benzene with 0.1 equiv. Ag_2CO_3 as the catalyst. [b] Yields were evaluated from the ^1H NMR spectra of the crude products. [c] The reaction was performed in refluxing toluene.

Table 2 Silver-catalyzed cyclization if miscellaneous alkynoic acids bearing a propargylic oxygenated substituent

Run[a]	Acetylenic acid	Product
1[b]	 **3**	 **6**
2	 **3a$_s$**	 **6a$_t$**
3	 **3a$_a$**	 **6a$_c$**
4	 **3b$_s$**	 **6b$_t$**
5	 **3b$_a$**	 **6b$_c$**

[a] Reactions were performed in refluxing benzene with 0.1 equiv. of Ag_2CO_3. The reactions proceeded in 5 min., except as noted. Yields were evaluated by ^1H NMR spectroscopy on the crude product and were 99% in all cases. [b] The reaction proceeded in 10 h.

ative **1e** proved to be only slowly cyclized (run 6). The beneficial influence of a propargylic C–O bond is also clear in the homologous 5-hexynol series. Although 5-hexynol **2** does not cyclize in the presence of a catalytic amount of silver carbonate (run 9), derivative **2a** methoxylated at the propargylic position does cyclize (run 10).

All the α-methylene oxolanes **4** so obtained proved to be very air- and moisture-sensitive and decomposed rapidly under exposure to ambient atmosphere or to slightly acidic conditions, thus preventing purification by silica gel chromatography. Nevertheless, due to the cleanliness of the reaction, they could be kept intact for several months by storing in a matrix of benzene or deuteriated benzene at −20 °C after simple filtration of the heterogeneous reaction medium.[4] NMR in deuteriated benzene clearly showed in each case the sole presence of the exocyclic enol ether function with the two methylene protons (4.01 and 4.48 ppm for **4a**, 3.81 and 4.4 ppm for **4b**, 4.17 and 4.6 ppm for **4c**, 4.11 and 4.54 ppm for **4d**, 4.16 and 4.57 ppm for **4e**, 3.93 and 4.8 ppm for **5a**) and the characteristic exocyclic carbons (81 and 166.2 ppm for **4a**, 83.4 and 161.7 ppm for **4b**, 83.4 and 162 ppm for **4c**, 82.6 and 161.9 ppm for **4d**, 81.5 and 163.4 ppm for **4e**, 93.3 and 127.6 ppm for **5a**).

The failure observed in the case of **1f**, in which an electron-withdrawing acetate is present (entry 7), supports the crucial role of electronic effects. These results are in agreement with one of our hypotheses. Hyperconjugation between the adjacent C–O bond and the triple bond would impoverish the electronic density and preclude complexation with silver ion and thus the cyclization. Since the size of the propargylic substituent would also influence the reaction by preventing access to the triple bond, one may reason that the reaction is slower for the more sterically demanding propargylic oxygenated group. This is what was indeed observed (Table 1, entries 2–6). The hindered *tert*-butyldiphenylsilyl derivative **1e** underwent complete cyclization but required a reaction time 4 times longer than the cyclization of the analogous *tert*-butyl **1d** (entry 5 *vs.* 6).

The remarkable effect of a propargylic C–O bond reached its maximum in the cyclization of 4-pentynoic acids. Thus, *syn* or *anti* 2-hexadecyl-3-hydroxy-4-pentynoic acids **3a$_{s-a}$**, as well as their 2-(*z*-tetradec-7-enyl) analogs **3b$_{s-a}$**, readily cyclized within a few minutes (Table 2, runs 2–5) when reacted under our standard conditions, while the unsubstituted parent **3** required 10 h for complete transformation (run 1). Surprisingly, no difference was detected between the two *syn* and *anti* diastereoisomers in each series, although the cyclization forces the two substituents into a *cis* relationship in the case of the *anti* isomer.

In conclusion, this work shows that the presence of oxygen at the propargylic position of acetylenic alcohols and acids greatly favored their cyclizations catalyzed by silver carbonate. The results reported here improve the scope of our reaction, which thus appears to be a method of choice for the synthesis of highly oxygenated 5- and 6-membered oxacycles.

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8 In such transition metal-assisted electrophilic cyclizations, the accepted mechanism postulates a previous activation of the π system by coordination to the metal cation, rendering the so-formed complex electrophilic enough for further reaction with a nucleophile. See, for example: K. Utimoto, Y. Fukuda and H. Nozaki, *Heterocycles*, 1987, **25**, 297.

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