ORGANIC LETTERS

2006
Vol. 8, No. 9
1839−1841

Copper-Catalyzed Cycloisomerizations of 5-En-1-yn-3-ols

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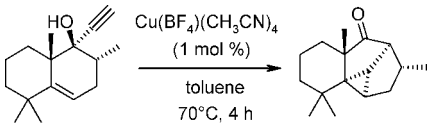
Received February 14, 2006

ABSTRACT



The Cu(I)-catalyzed cycloisomerization of tertiary 5-en-1-yn-3-ols with an 1,2-alkyl shift affords stereoselectively tri- and tetracyclic compounds of high molecular complexity. These results are in agreement with a mechanism in which the cyclopropanation precedes the rearrangement.

During the course of a synthetic approach directed toward the synthesis of Ambrox-type odorants, we wished to apply a known copper-catalyzed rearrangement of the propargylic alcohols into enals[1] to the synthesis of **2** from **1ab**. The acetylenic diol **1ab** (1:1 diastereomeric mixture) was prepared in two steps (highly diastereoselective hydroxylation, then Li acetylide addition) from the readily accessible ketone **3** (Scheme 1).[2]

To our surprise, treatment of **1ab** with 2 mol % of CuCl, 1.5 mol % of $Ti(OBu)_4$, and 17 mol % of *p*-toluic acid in *o*-dichlorobenzene (DCB) at 120 °C for 30 min[1] afforded, after quenching with aq NaOH/Et_2O, exclusively the diastereomerically pure tricyclic diketone **5** in 64% isolated yield (Scheme 1)!

Repeating this reaction at 50 °C, no skeletal rearrangement took place; however, the starting diol mixture **1ab** (1:1) underwent complete epimerization to **1a** in 30 min (Scheme 2).[3] After heating for 4 h at 90 °C, a new tetracyclic product **6a** was generated in 65% yield (containing minor amounts of **6b** and the retro-aldol product **5**).[4] Using CuCl (5 mol %) in the absence of additives, the reaction was slower (100 °C, 16 h; 61% of **6ab**). Treatment of **6ab** with KO-*t*-Bu (0.1 equiv) in *t*-BuOH for 15 min at rt afforded the diketone **5** (86% yield).

This cycloisomerization with skeletal rearrangement is closely related to the Pt-[5a,b] or Au-catalyzed[5b,c] cycloisomerizations with 1,2-H-migration[5d] of *sec*-propargylic enynols (Scheme 3) and allows the use of inexpensive Cu reagents.[6]

It has been proposed that the Pt- or Au-catalyzed cycloisomerizations of *sec*-enynols (e.g., **7** to **8**) proceed either by a cyclopropanation of the electron-rich olefin with the metal-complexed acetylene **A**, followed by 1,2-H-migration of **B** (pathway a),[5b,c] or by an initial 1,2-H-shift and the subsequent cyclopropanation of the transient vinyl carbene **C** (pathway b).[5a]

To ascertain whether the observed cycloisomerization of **1a** could also be effected with Pt catalysis, enynol **1ab** was

(1) Chabardes, P. *Tetrahedron Lett.* **1988**, *29*, 6253.

(2) Fehr, C.; Farris I. Patent submitted (Firmenich SA; prior, 19 Jul 2005.

(3) This isomerization also took place with CuCl alone or under acidic conditions (5% H_2SO_4, THF, H_2O, 20 °C, 2 h).

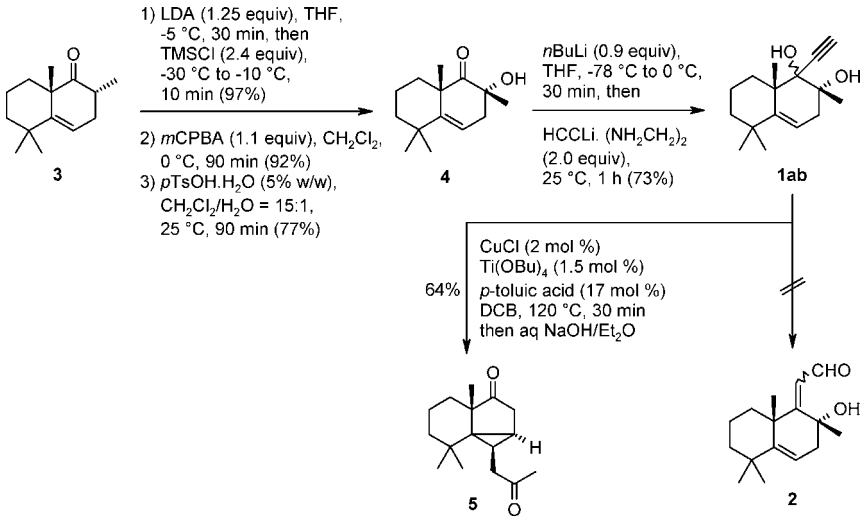
(4) Samples of **6a** in Et_2O/5% aq NaOH gave rise to mixtures of **6a**, **6b**, and **5**. Prolonged stirring led to **5**. Extensive NMR experiments and IR measurement allowed us to assign structures **6a** and **6b**. Moreover, the fact that both of the epimeric aldol products afford the same retro-aldol product **5** proves that **6a** and **6b** differ only in the configuration of the OH-bearing center.

(5) (a) Harrak, Y.; Blaszykowski, C.; Bernard M.; Cariou, K.; Mainetti, E.; Mouriès, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656. (b) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2005**, *70*, 9345. (c) Gagosz, F. *Org. Lett.* **2005**, *7*, 4129. (d) Reviews: Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. Echavarren, A. M.; Nevado, C.; *Chem. Soc. Rev.* **2004**, *33*, 431. Méndez, M.; Mamane, V.; Fürstner, A. *Chemtracts: Org. Chem.* **2003**, *16*, 397. Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813.

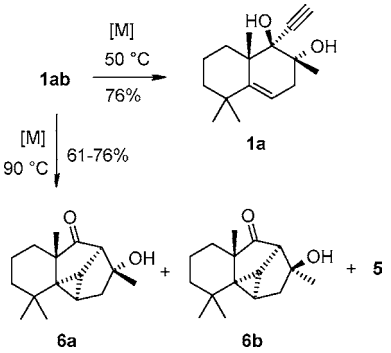
(6) For nucleophilic additions to copper-coordinated alkynes, see: Bouyssi, D.; Monteiro, N.; Balme, G. *Tetrahedron Lett.* **1999**, *40*, 1297. Monteiro, N.; Balme, G.; Gore, J. *Synlett* **1992**, 227. Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531 and references therein.

10.1021/ol0603864 CCC: $33.50
Published on Web 04/05/2006

Scheme 1. Synthesis and Cycloisomerization of **1ab**



Scheme 2. Copper-Catalyzed Cycloisomerization of **1ab**



heated with $PtCl_2$ (5 mol %) in toluene (70 °C, 1 h). Indeed, the tetracyclic compound **6a** was formed in 76% yield. This is the first known example of a Pt-catalyzed cyclopropanation with subsequent skeletal rearrangement starting from a *tert*-5-en-1-yn-3-ol.[7]

We next asked ourselves whether the Cu-catalyzed cycloisomerization could be extended to enynols devoid of the vicinal OH group. For this purpose, we prepared the enynol **9ab** (**9a**/**9b** = 4:1) by addition of $HCCLi(NH_2CH_2)_2$ (1.2 equiv) in THF to **3** (−20 °C to rt, 15 h, 84%) (Table 1).

We screened several Cu(I) and Cu(II) catalysts as well as $PtCl_2$ (see Table 1). Under all of the tested reaction conditions, **9a** was readily converted into tetracyclic ketone **10** in good yield and with perfect stereocontrol, whereas **9b**,

Scheme 3. Possible Reaction Pathways for the Pt-Catalyzed Cycloisomerization of Enynols

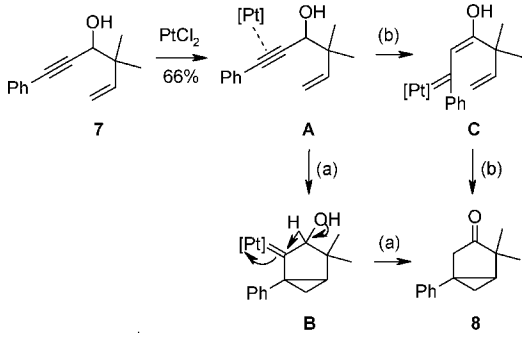
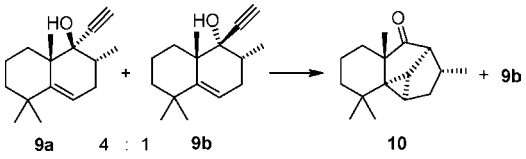


Table 1. Cycloisomerization of **9ab** to **10**



entry	cat. (mol %), solvent	*T* (°C)/ time (h)	**9a**[a]	**9b**[a]	**10**[a,b]
1	CuCl (2), $Ti(OBu)_4$ (1.5), *p*-tolCO_2H (17), DCB[c]	70/6	1	14	54[d]
2	CuCl (5), *p*-tolCO_2H (17), DCB[b]	75/4	30	18	50
3	CuCl (5), $Ti(OBu)_4$ (5), DCB[b]	75/4	32	21	35
4	CuCl (5), DCE[c]	75/6	3	19	75 (68)
5	CuI (5), DCE[c]	75/5	19	22	48
6	CuBr·Me_2S (5), DCE[c]	75/5	30	22	30
7	$CuCl_2·2H_2O$ (5), DCB[c]	75/4	27	18	43
8	$CuCl_2·2H_2O$ (5), *p*-tolCO_2H (0.17), DCB[c]	75/4	40	18	26
9	$(CuOTf)_2(C_6H_6)$ (5), DCE[c]	50/3	3	18	72
10	$(CuOTf)_2(C_6H_6)$ (2), toluene	70/6		13[e]	82
11	$Cu(BF_4)(CH_3CN)_4$ (2), DCE[c]	50/4	1	16	69
12	$Cu(BF_4)(CH_3CN)_4$ (1), toluene	70/4		17	83 (85)
13	$PtCl_2$ (2), DCE[c]	70/6	0.6	17	81 (87)

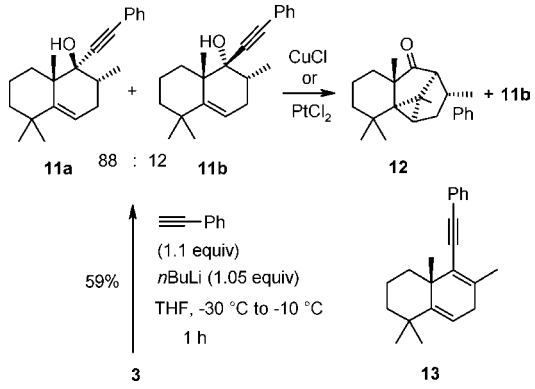
[a] Percent by GC. Starting composition: **9a**, 81; **9b**, 19. [b] In parentheses: isolated yields based on **9a**. [c] DCB = 1,2-dichlorobenzene; DCE = 1,2-dichloroethane. [d] In addition, 26% of aldehydes corresponding to **2** (H instead of OH), *E*/*Z* ca. 1:1). [e] In addition, 5% of an apolar product (possibly dehydrated **9b**).

possessing a pseudoequatorial ethynyl group, was recovered unchanged.[8]

The most effective catalysts of the tested Cu species were $(CuOTf)_2(C_6H_6)$ (entries 9 and 10) and $Cu(BF_4)(CH_3CN)_4$ (entries 11 and 12) (1−2 mol %), followed by CuCl (entry 4) (2−5 mol %). CuBr (entry 6), CuI (entry 5), and Cu(II) reagents (entries 7 and 8) were less reactive.

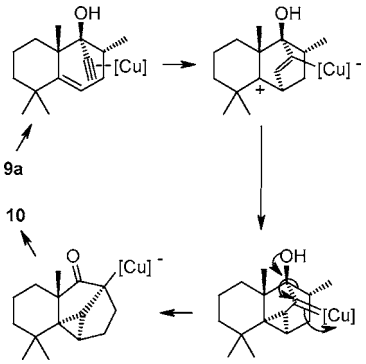
As a further application, this reaction could be applied to the phenyl-substituted acetylene **11a**, but this sterically hindered system required a higher temperature for the reaction to proceed, both with CuCl (DCB, 130 °C, 15 h; 50% conversion) and with $PtCl_2$ (toluene, 110 °C, 7 h, 70% conversion). As expected from the prior example (**9a** to **10**), **11a** afforded **12** selectively, whereas the isomeric **11b** did not undergo the cycloisomerization. $Cu(BF_4)(CH_3CN)_4$ showed the highest reactivity (70 °C, toluene, 3h, 100% conversion), but dehydration giving **13** became the major reaction pathway (**12**:**13** = 12:88) (Scheme 4).

Scheme 4. Preparation of **11ab** and Cycloisomerization of **11a**



These results are in agreement with a mechanism in which the cyclopropanation precedes the skeletal rearrangement (Scheme 5 and pathway a in Scheme 3).[5b,c,7] Otherwise, it would be difficult to understand why **9b** (or **11b**) (which would lead to the same vinyl carbene as **9a** (or **11a**) (pathway b in Scheme 3) does not undergo the cycloisomerization. Moreover, the perfect stereocontrol of the cyclopropanation with respect to the orientation of the acetylene unit gives further support to this mechanism. Therefore, the other postulated mechanism following pathway b (Scheme 3) is very unlikely, at least in our systems.

Scheme 5. Proposed Reaction Course, As Exemplified for the Cycloisomerization of **9a**



In conclusion, we have succeeded in effecting the unprecedented, Cu(I)-catalyzed cycloisomerization of *tert*-5-en-1-yn-3-ols to afford stereoselectively tri- and tetracyclic compounds of high molecular complexity. These results have important mechanistic implications.

We are presently expanding the copper-catalyzed cycloisomerizations to other systems.

Acknowledgment. We thank Professor A. Alexakis (University of Geneva, Switzerland) for suggesting to us the use of $CuBF_4(CH_3CN)_4$ and for giving us a sample.

Supporting Information Available: Experimental procedures, spectral data, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0603864

(7) For a gold-catalyzed cyclopropanation/alkyl shift of a 1-en-5-yne, see: Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc*. **2004**, *126*, 10858. See also: Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc*. **2004**, *126*, 11806.

(8) In the case of **1ab**, the epimerization of the propargylic center via a carbocation may be facilitated by the presence of the neighboring OH group.