Journal of Organometallic Chemistry 694 (2009) 502–509

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

A facile approach to spirocyclic butenolides through cascade cyclization/oxidative cleavage reactions of (*Z*)-enynols catalyzed by gold under dioxygen atmosphere

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ARTICLE INFO

Article history:
Received 22 May 2008
Received in revised form 15 September 2008
Accepted 29 October 2008
Available online 6 November 2008

Keywords:
Gold catalysis
(*Z*)-Enynols
Cyclization
Oxidative cleavage
Spirocyclic butenolides

ABSTRACT

A facile approach for the syntheses of spirocyclic butenolides through cascade cyclization/oxidative cleavage reactions of (*Z*)-enynols bearing cyclic substituents at the C-1 position catalyzed by gold under dioxygen atmosphere has been developed. A variety of substituted butenolides was constructed in a regioselective manner from suitably substituted (*Z*)-2-en-4-yn-1-ols. (*Z*)-Enynols substituted both at C2 and C3-position afforded the spirocyclic butenolides in moderate to good yields, C-2 unsubstituted (*Z*)-enynols afforded the products in moderate yields, and the C-3 unsubstituted (*Z*)-enynols afforded the desired products in low yields.

1. Introduction

Spirolactones such as spirocyclic butenolides constitute an important class of heterocyclic compounds due to the fact that they widely occur as key structural subunits in natural products and synthetic products. In addition, a high number of these compounds has displayed useful biological activities which can find a variety of applications in pharmaceutical use [1]. For example, naturally occurring Lambertellol A [1d] exhibits remarkable growth inhibition of spores, Securinine exhibits antimalarial and antibacterial activity [1d], man-made spirodiclofen are highly active acaricides and insecticides [1h] (Fig. 1). Therefore, the development of synthetic routes that allow the facile assembly of spirocyclic butenolides remains an important objective [2].

Recently we reported a new approach to 2(5*H*)furanone derivatives through gold-catalyzed [3,4] cascade cyclization/oxidative cleavage reactions of (*Z*)-enynols with molecular oxygen [5]. This strategy provided an efficient route to fully substituted lactones under mild conditions from readily available starting materials. Especially, this methodology was applicable to the synthesis of spirocyclic butenolides. In this paper, we present our detailed studies of gold-catalyzed approach to spirocyclic butenolides from (*Z*)-enynols bearing a cyclic substituent at the C-1 position (Scheme 1).

2. Results and discussion

2.1. Preparation of substituted (*Z*)-2-en-4-yn-1-ols bearing a cyclic substituent at C-1

We recently reported an efficient synthetic approach to stereodefined (*Z*)-enynols via zirconium-mediated cross-coupling reactions of three different components involving alkynes, ketones, and alkynyl bromides in a one-pot procedure [6]. Thus, a variety of (*Z*)-enynols **3** bearing the substituents both at C-2 and C-3 and a cyclic group at C-1 were readily synthesized employing cyclic ketones as substrates by this method. According to our previous report, when an alkyl group was used as a terminal group of alkyne moiety, the cyclization/cleavage reaction proceeded much faster than the corresponding phenyl-substituted one [5]. Thus in most cases, enynols bearing a butyl group at the C-5 position were synthesized. The results are shown in Table 1. Cyclic ketones such as cycloheptanone, cyclooctanone or even cyclododecanone with large-membered ring were well suitable for the reaction, furnishing the corresponding enynols **3b**–**e** in 43–71% yield (Table 1, entries 2–5), however, cyclopentanone only afforded a 26% yield of **3a** (Table 1, entry 1). The reaction of zirconacycles bearing an alkenyl substituent with 4-methylcyclohexanone also gave a low yield of **3h** (17%, Table 1, entry 8). As for alkynes, alkyl, aryl, heteroaryl, and TMS (to afford *E*-**3g**) substituted alkynes were all compatible with this coupling reaction.

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doi:10.1016/j.jorganchem.2008.10.046

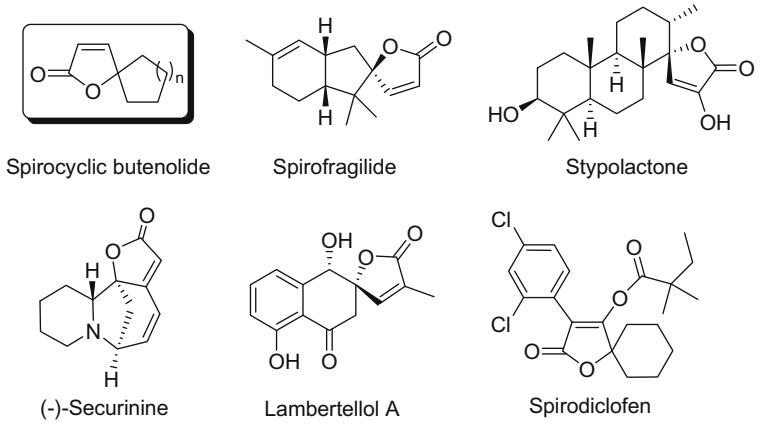
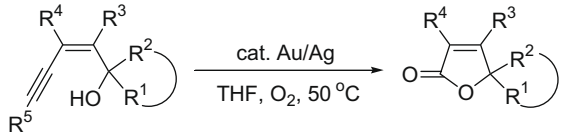


Fig. 1. Some representative compounds bearing the spirocyclic butenolide moiety.



Scheme 1.

(*Z*)-Enynols bearing a substituent at the C-2 position were prepared by the lithium–bromine exchange reaction of (*Z*)-1-en-3-yn-1-bromide **4** [7] with *n*-BuLi at −78 °C followed by the addition reaction of cyclic ketones with the organolithium intermediate. Using this strategy, C-2 phenyl-substituted (*Z*)-enynols **3i** and **3j** were synthesized in 54% and 36% yields, respectively (Scheme 2).

(*Z*)-Enynols bearing a substituent at the C-3 position were prepared by the Sonogashira coupling reaction of iodinated allylic alcohols with terminal alkynes. The iodide precursors were conveniently synthesized from the corresponding propargylic alcohols **5** by their reaction with lithium aluminum hydride or Red-Al (Red-Al = sodium bis(2-methoxyethoxy)aluminumhydride) followed by iodination of the organoaluminum intermediate (Scheme 3) [8]. A variety of enynols bearing alkyl, aryl and TMS groups (*E*-**3n**–**o**) could be easily synthesized by this reaction. It is noteworthy that the chiral (*Z*)-enynol **3p** could be obtained without any racemization, as determined by chiral-column HPLC analysis.

2.2. Synthesis of spirocyclic butenolides via gold-catalyzed cyclization/cleavage reactions with molecular oxygen

With various (*Z*)-enynols in hand, we were next interested in applying the gold-catalyzed cyclization/oxidative cleavage reaction of enynols with dioxygen for the synthesis of spirolactones. The synthesis of fully substituted spirocyclic butenolides was first investigated under the optimized reaction conditions, and the results are summarized in Table 2. Alkyl, alkenyl, aryl, heteroaryl and TMS groups in enynols were all compatible with this reaction, furnishing the desired products in 44–87% yield. It is noteworthy that the cyclization of (*Z*)-enynols substituted with phenyl or 2-thienyl groups at C-2 and C-3 proceeds smoothly to form **7a**–**e** in good yields (70–87%, Table 2, entries 1–5) regardless of the size of the ring substituted at C-1 (5–8 and 12-membered rings). The reactions of enynols with alkyl or TMS substituent at C-3 position afforded the desired products in much lower yield under the present reaction conditions (32% for **7f**, 17% for **7g**). However, when the reactions were carried out at room temperature, the yields could be improved to 52% and 44%, respectively (Table 2, entries 6 and 7). C-2-alkenyl-substituted (*Z*)-enynol **3h** afforded **7h** in moderate yield of 50% (Table 2, entry 8).

Enynols unsubstituted at C-3 proved to be less favorable with respect to analogous fully substituted substrates **3a**–**h**. As illustrated in Table 3, C-2 phenyl-substituted enynols **3i** and **3j** afforded the desired products **7i** and **7j** in 31% and 34% yields, respectively, along with several undefined byproducts (Table 3, entries 1 and 2). Enynols unsubstituted at C-2 afforded the desired products in moderate yields. For example, C-3-alkyl or phenyl-substituted (*Z*)-enynols **3k** and **3l** generated the desired spirolactone **7k** and **7l** in moderate yields of 53% and 61%, respectively (Table 3, entries 3 and 4). However, C-3 TMS substituted enynol **3n** only resulted in a low yield of **7m** (22% at 50 °C, decreasing the reaction temperature to room temperature could not give better result). We envisioned that this may be due to the less stability of a butyl-substituted dihydrofuran intermediate from a C5-butyl-substituted enynol **3n**. It was pleased to find that a higher yield of **7m** (59%) was achieved when changing the substrate **3n** to a C5-phenyl-substituted **3o** (Table 3, entry 6). It was noteworthy that when chiral (*Z*)-enynol bearing a bulky substituent at C-1 position was employed, the desired product **7n** was obtained in 44% yield without any loss of enantiomeric excess (Table 3, entry 7). The structure of **7n** was further confirmed by X-ray crystallographic analysis (Fig. 2).

2.3. Mechanism aspects

To elucidate the reaction mechanism, we carried out the oxidative cleavage reaction from dihydrofuran **8**. During the further investigation of this reaction [9], we found that the conversion of dihydrofuran **8** to the butenolide **7** could proceed without the use of a gold catalyst (Table 4). In the case of a dihydrofuran **8a** with R^1 = Me, R^2–R^5 = Ph, the oxidation reaction required longer reaction time compared with the use of gold catalyst, and lower yields were obtained (without gold catalyst, the reaction time varied from 28 h to 51 h, and the yields were in a range of 66–80%; in the presence of gold(I) catalyst, the reaction completed in 18–22 h with the yields of 89–94%, Table 4, entries 1–2). A similar result was also obtained in spirocyclic substrate **8b**, especially, the reaction time could be further decreased to 18 h when 10 mol% gold catalyst was employed (without gold catalyst, 38 h, Table 4, entries 3 and 5). In the case of butyl-substituted **8c**, a higher yield of 86% was observed with the use of gold catalyst (Table 4, entry 7). Thus the gold catalyst may play a role in the step of oxidative cleavage reaction. Controlled experiments showed that the cleavage of the C=C double bond of dihydrofuran **8** to the butenolide **7** was completely suppressed in the presence of a radical scavenger [5], such