



Gold-catalyzed cyclization of enyne-1,6-diols to substituted furans

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ARTICLE INFO

Article history:

Received 31 December 2009

Revised 2 February 2010

Accepted 5 February 2010

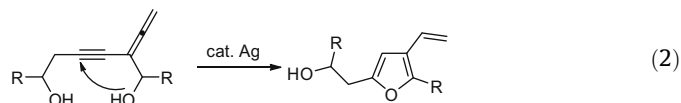
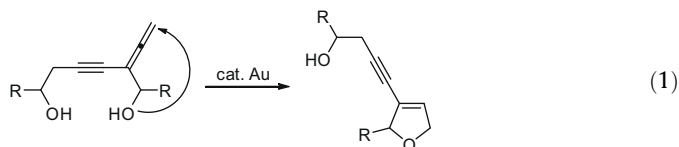
Available online 10 February 2010

ABSTRACT

Treatment of enyne-1,6-diols with 5 mol % Ph₃PAuCl in the presence of 5 mol % AgOTf as a cocatalyst selectively produced trisubstituted furans in good to excellent yields in dichloromethane at room temperature for 5–10 min through cyclization followed by isomerization.

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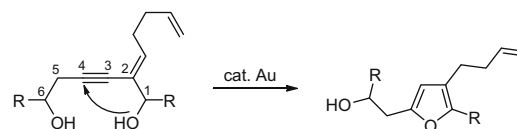
Furan derivatives widely occur as essential structural units in a variety of natural products which can be applied to pharmaceuticals and flavor and fragrance compounds.¹ Because they also represent versatile building blocks for the synthesis of more elaborate heterocyclic compounds, development of new synthetic method of furan compounds is an important and continuing goal of organic synthesis.² To date various transition metal-, acid-, and base-catalyzed synthetic methods of furans have been reported.³ Recently, it has been demonstrated that gold shows efficient catalytic activity for furan and dihydrofuran synthesis.⁴ These include the cyclization of allenyl ketones,⁵ 2-(1-alkynyl)-2-alken-1-ones,⁶ (Z)-2-en-4-yn-1-ols,⁷ 1-(1-alkynyl)cyclopropyl ketones,⁸ alkynyl epoxide⁹, or heteroatom-substituted propargyl alcohol¹⁰ through nucleophilic attack of oxygen atom to a gold-coordinated C–C double or triple bond.¹¹ Also, Belting and Krause described Au-catalyzed tandem cycloisomerization-hydroalkoxylation of homopropargyl alcohols.¹² Recently, we reported that the treatment of allenyne-1,6-diols with 15 mol % AuCl₃ selectively produced 2,5-di-hydrofurans through the selective activation of terminal double bond in alkene (Eq. (1)).¹³ However, subjecting allenyne-1,6-diols to 15 mol % AgOTf selectively afforded furans through the selective activation of triple bond (Eq. (2)).¹³



In pursuit of continuous investigations in this field, we found that the treatment of enyne-1,6-diols with Au catalyst selectively gave furans in contrast with the above-mentioned results.¹³ Herein, we report efficient synthetic routes to trisubstituted-furans through selective cyclization of enyne-1,6-diols catalyzed by gold followed by isomerization (Scheme 1).

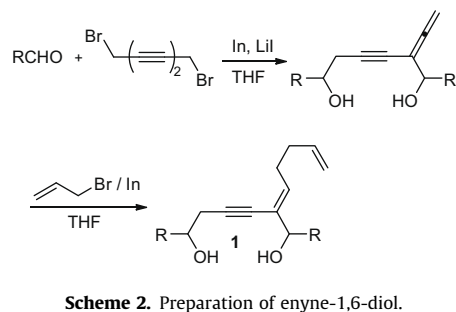
First, a variety of enyne-1,6-diols **1** were prepared from the reaction of aldehydes with organoindium reagent generated in situ from indium and 1,6-dibromo-2,4-hexadiyne in the presence of lithium iodide in THF¹⁴ and subsequent allylation (Scheme 2).¹⁵ Initially, we examined the cyclization of enyne-1,6-diol **1a** by using Ag and Au catalysts. The results are summarized in Table 1. Although the treatment of allenyne-1,6-diol with 15 mol % AgOTf gave selectively furans,¹³ the reaction of **1a** with 5 mol % AgOTf did not produce the cyclized product (entry 1). Exposure of **1a** on 5 mol % TfOH afforded unknown compound (entry 2).

Surprisingly, the treatment of **1a** with 5 mol % AuCl₃ selectively provided trisubstituted furan **2a** in 40% yield in CH₂Cl₂ at room temperature for 12 h (entry 3). The use of 10 mol % AuCl₃ did not increase the yield of **2a** (entry 4). When dichloroethane was used as a solvent, the cyclic compound **2a** was obtained in 35% yield

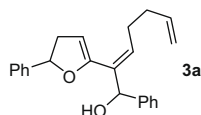


Scheme 1. Selective cyclization of enyne-1,6-diols catalyzed by Au.

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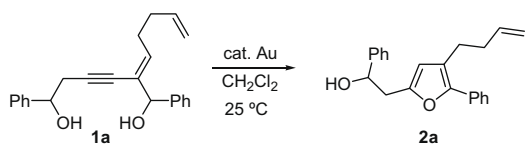


at 80 °C for 12 h (entry 5). Reaction of **1a** with 3 mol % AuCl₃ and 9 mol % AgOTf or 5 mol % AuCl₃ and 15 mol % AgOTf gave **2a** in 15% and 8% yields, respectively (entries 6 and 7). However, the exposure of **1a** to 5 mol % Ph₃PAuCl and 5 mol % AgOTf selectively produced trisubstituted furan **2a** in 89% yield in CH₂Cl₂ at room temperature for 5 min through nucleophilic attack of the hydroxyl oxygen atom on C-1 position to a gold-coordinated C–C triple bond (entry 8). Treatment of **1a** with 5 mol % Ph₃PAuCl did not proceed, indicating that the catalytic system combining with Ph₃PAuCl and AgOTf is essential for cyclization (entry 9). There is no 4,5-dihydrofuran **3a** formed in any entries through nucleophilic attack of the hydroxyl oxygen atom on C-6 position to a gold-coordinated C–C triple bond. The use of Au catalysts having other phosphine ligands such as (C₆F₅)₃PAuCl and (4-MeO–C₆H₄)₃PAuCl gave the desired product **2a** in 64% and 70% yields, respectively (entries 10 and 11).



Next, we examined the cyclization of protected alcohols (**1k** and **1l**) obtained from subjecting diol **1a** to NaH followed by the treatment of methyl iodide. Although allyl alcohol **1k** having methyl-protected homopropargyl ether gave the cyclized product **2k** in 66% yield under the optimum reaction conditions (Eq. (3)), homo-propargyl alcohol **1l** having methyl-protected allyl ether did not produce the corresponding furan (Eq. (4)). This result indicates that the presence of double bond on propargylic position is critical to produce the furan.

Table 1
Reaction optimization of Au-catalyzed cyclization of **1a**

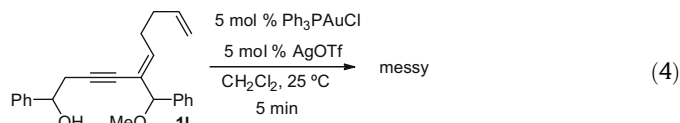
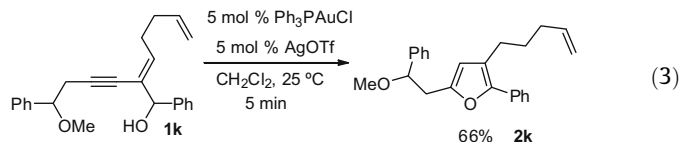


| Entry | Cat. Au | Time | Yield ^a (%) |
|----------------|---------------------------------------------------------------------------------|-------|------------------------|
| 1 | 5 mol % AgOTf | 24 h | 0 |
| 2 | 5 mol % TFOH | 2 h | ^b |
| 3 | 5 mol % AuCl ₃ | 12 h | 40 (35) |
| 4 | 10 mol % AuCl ₃ | 12 h | 30 (41) |
| 5 ^c | 5 mol % AuCl ₃ | 12 h | 35 (37) |
| 6 | 3 mol % AuCl ₃ /9 mol % AgOTf | 12 h | 15 (48) |
| 7 | 5 mol % AuCl ₃ /15 mol % AgOTf | 12 h | 8 (60) |
| 8 | 5 mol % Ph ₃ PAuCl/5 mol % AgOTf | 5 min | 89 |
| 9 | 5 mol % Ph ₃ PAuCl | 19 h | 0 |
| 10 | 5 mol % (C ₆ F ₅) ₃ PAuCl/5 mol % AgOTf | 5 min | 64 |
| 11 | 5 mol % (4-MeO–C ₆ H ₄) ₃ PAuCl/5 mol % AgOTf | 5 min | 70 |

^a Isolated yield. Numbers in parentheses indicate the recovery yield of **1a**.

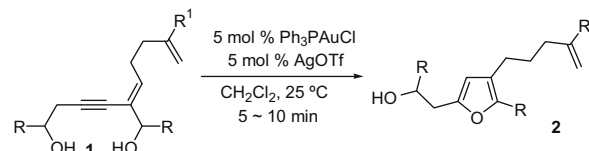
^b Unknown was obtained.

^c Reaction performed in dichloroethane at 80 °C.



To demonstrate the efficiency and scope of the present method, we applied the catalytic system to a variety of enyne-1,6-diols **1** (Table 2). Enyne-1,6-diol **1b** obtained from butanal was treated with 5 mol % Ph₃PAuCl and 5 mol % AgOTf in dichloromethane for 5 min to selectively produce trisubstituted furan **2b** in 83% yield

Table 2
Cyclization of enyne-1,6-diols catalyzed by Au



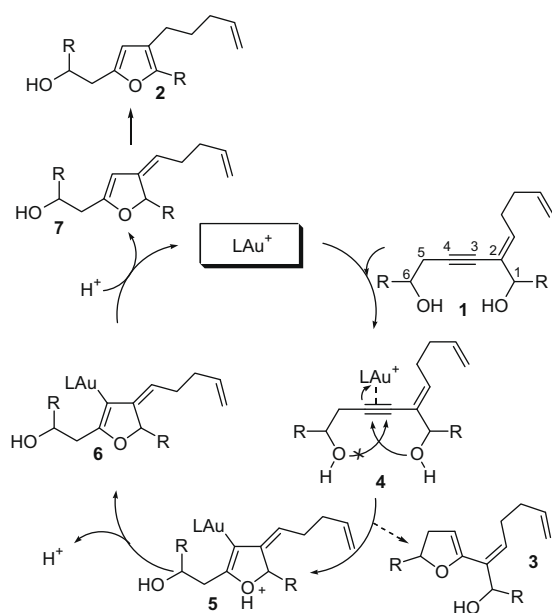
| Entry | R, R ¹ | Product | Yield ^a (%) |
|-------|--------------------------------------------------------------------|-----------|------------------------|
| 1 | <i>n</i> -Propyl, H 1b | 2b | 83 |
| 2 | C ₆ H ₁₁ , H 1c | 2c | 71 |
| 3 | Ph, H 1a | 2a | 89 |
| 4 | Ph, Me 1d | 2d | 81 ^b |
| 5 | 4-Cl–C ₆ H ₄ , H 1e | 2e | 84 |
| 6 | 4-Me–C ₆ H ₄ , H 1f | 2f | 83 |
| 7 | 2,4,6-Me ₃ –C ₆ H ₂ , H 1g | 2g | 68 |
| 8 | 3-MeO–C ₆ H ₄ , H 1h | 2h | 80 |
| 9 | 3-HO–C ₆ H ₄ , H 1i | 2i | 89 |
| 10 | 4-MeO ₂ C–C ₆ H ₄ , H 1j | 2j | 90 |

^a Isolated yield.

^b Isomeric ratio = 1 (internal alkene):3.2 (terminal alkene).

(entry 1). In the case of compound **1c** generated from cyclohexanecarbaldehyde, furan **2c** was selectively obtained in 71% yield (entry 2). Enyne-1,6-diol **1d** having 4-methyl-4-pentenylidene group at C-2 position turned out to be compatible with the employed reaction conditions, affording **2d** (1:3.2) in 81% (entry 4). This isomerization may be due to the coordination of gold to the C–C double bond or acidic conditions. Altering the electron demand of the substituents on aromatic rings did not diminish the efficiency or selectivity (entries 5–10). Under the optimum reaction conditions, 3-hexyne-1,6-diol **1e** having 4-chlorophenyl group gave rise to the desired product **2e** in 84% yield (entry 5). Enyne-1,6-diol (**1f** and **1h**) bearing 4-methylphenyl and 3-methoxyphenyl group were cleanly converted to the desired furans (**2f** and **2h**) in 83% and 80% yields, respectively (entries 6 and 8). However, enyne-1,6-diol having 2,4,6-trimethyl-phenyl group afforded furan **2g** in 68% yield due to steric hindrance (entry 7). It is noteworthy that the additional hydroxyl group on substrate did not affect the efficiency of the cyclization reactions, producing furan **2i** in 89% yield (entry 9). Enyne-1,6-diol **1j** bearing electron-withdrawing group such as 4-methoxycarbonyl group was treated with 5 mol % Ph_3PAuCl in the presence of 5 mol % AgOTf as a cocatalyst to result in the selective formation of functionalized furan **2j** in 90% yield (entry 10).

A plausible reaction pathway is described in Scheme 3. Thus, coordination of the gold catalyst to triple bond in 3-hexyne-1,6-diols **1** results in the formation of the intermediate **4** which, upon nucleophilic attack of the hydroxyl oxygen atom on 1-position to a gold-coordinated C–C triple bond, is cyclized to the vinylgold complex **5**. Release of the proton from **5** followed by protodeauration of **6** affords the 4,5-dihydrofuran derivatives **7** and regenerates the gold cationic active species. Finally, compounds **7** easily isomerize to functionalized furans **2**. Surprisingly, no other cyclic compound such as **3** (disubstituted 4,5-dihydrofuran) through nucleophilic attack of the hydroxyl oxygen atom on C-6-position to a gold-coordinated C–C triple bond is formed. Although the reason for selective attack of the hydroxyl oxygen atom on C1-position to gold-coordinated C–C triple bond has not been established at present, it seems that geometry and bond distance between triple bond and hydroxyl group and bond angle on C-2 and C-5-position might be impor-



Scheme 3. Plausible mechanism for furan synthesis catalyzed by Au.

tant factors. The elucidation of the detailed reaction mechanism must wait further study.

In summary, we have developed an efficient synthetic method of trisubstituted furans from the treatment of enyne-1,6-diols with 5 mol % Ph_3PAuCl and 5 mol % AgOTf in CH_2Cl_2 at room temperature through selective cyclization followed by isomerization.

Acknowledgments

This work was supported by the KRF Grant funded by the Korean Government (KRF-2008-314-C00213), by the KOSEF through the NRL Program funded by the MOST (No. M10600000203-06j0000-20310), by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (2009-0087013), and by Korea Sanhak Foundation. This work was supported by the second phase of the Brain Korea 21 Program in 2009. Dr. Sung Hong Kim at the KBSI (Daegu) is thanked for obtaining the MS data. The NMR data were obtained from the central instrumental facility in Kangwon National University.

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