Gold-catalyzed alkylation of silyl enol ethers with ortho-alkynylbenzoic acid esters

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Abstract
Unprecedented alkylation of silyl enol ethers has been developed by the use of ortho-alkynylbenzoic acid alkyl esters as alkylating agents in the presence of a gold catalyst. The reaction probably proceeds through the gold-induced in situ construction of leaving groups and subsequent nucleophilic attack on the silyl enol ethers. The generated leaving compound abstracts a proton to regenerate the silyl enol ether structure.

Findings
Silyl enol ethers have been widely used in organic synthesis as effective carbon nucleophiles for the construction of carbon frameworks [1-4]. Generally, they react with a variety of electrophiles to give carbonyl compounds as products due to cleavage of the silicon-oxygen bond. For example, the Lewis acid-catalyzed reaction of silyl enol ethers with alkyl halides is well known as one of the most efficient preparative methods for regio-defined α-alkylated ketones (path a in Scheme 1) [5-17]. In contrast, in this paper, we report a gold-catalyzed reaction of silyl enol ethers with ortho-alkynylbenzoic acid esters which leads to the formation of α-alkylated silyl enol ethers (path b).
We examined the reactions of silyl enol ether 1a with ortho-alkynylbenzoic acid benzyl esters 2 in the presence of gold catalysts under several reaction conditions and the results are summarized in Table 1 [18-21]. With a cationic gold catalyst, derived from Ph3PdAuCl and AgClO4, the reaction of 1a with 2a proceeded at 80 °C over 2 h and the benzylated silyl enol ether 3a was obtained in 35% yield, along with the eliminated isocoumarin 4a and recovered 2a in 32% and 65% yields, respectively (entry 1). On the other hand, no products were obtained from the reaction of 1a with benzyl benzoate (having no alkynyl group at the ortho-position) under similar reaction conditions. These results clearly show that the alkynyl moiety of ester 2a is essential for the formation of 3a. It is well known that concerted pericyclic ene-type reaction of silyl enol ethers with electrophiles, such as aldehydes or ketones, gives functionalyzed silyl enol ethers without desilylation [22-36]. To the best of our knowledge, however, this is the first example of the alkylation of silyl enol ethers without desilylation [22-36]. To the best of our knowledge, however, this is the first example of the alkylation of silyl enol ethers without desilylation [22-36].

Table 1: Gold-catalyzed alkylation of silyl enol ethera.

| Entry | 2        | AxG | Solvent | Conditions | Yield (%)b |
|-------|----------|-----|---------|------------|------------|
| 1c    | 2a       | AgClO4 | benzene | 80 °C, 2 h | 35         |
| 2     | 2a       | AgClO4 | benzene | 80 °C, 2 h | 55         |
| 3     | 2a       | AgClO4 | (CH3Cl)2 | 80 °C, 2 h | 44         |
| 4     | 2a       | AgClO4 | dioxane | 100 °C, 2 h | 58         |
| 5d    | 2a       | AgClO4 | dioxane | 100 °C, 1 h | 72         |
| 6d    | 2a       | AgOTf  | dioxane | 100 °C, 10 h | 80         |
| 7d    | 2b       | AgOTf  | dioxane | 80 °C, 5 h | 75         |

aReaction conditions: 0.25 M solution of 2 was treated with 1a (3 equiv) in the presence of the gold catalyst. bNMR yield using CH2Br2 as an internal standard. cPh3PdAuCl was used instead of (o-Tol)3PdAuCl. d5 equiv of 1a was used.
Table 2: Gold-catalyzed alkylation of silyl enol ethera.

| Entry | 1     | 2     | R1    | R2   | 3   | Yield (%)b |
|-------|-------|-------|-------|------|-----|------------|
| 1c    | 1b    | 2b    | Bn    | Bu   | 3b  | 61         |
| 2     | 1c    | 2b    | Bn    | Bu   | 3c  | 70         |
| 3d    | 1c    | 2c    | Ph    | 3d   | 60c |
| 4c,f  | 1d    | 2a    | Bn    | Ph   | 3e  | 61         |
| 5     | 1a    | 2d    | p-Anisyl | Ph | 3f | 70         |

*Reaction conditions: 0.25 M solution of 2 was treated with 1 (5 equiv) in the presence of the gold catalyst. *NMR yield using CH$_2$Br$_2$ as an internal standard. c10 mol % of the catalyst was used. d3 equiv of 1 was used. eYield of isolated product. fAgOTf was used instead of AgClO$_4$. 

Scheme 2: Plausible mechanism for the alkylation of silyl enol ether.
with the silicon atom, and cleave the silicon–oxygen bond of 7. However, in the present reaction system, intermediate 8 would prefer to act as a base and abstract a proton, H₈, from the α-position rather than attack the silyl group as a nucleophile, probably due to steric and electronic reasons. For these reasons, deprotonation of 7 occurs to give the product 3 together with 4 as a final leaving compound.

On the other hand, in the case of reactions with silyl enol ethers having a proton, H₈, at the α’-position, compound 9 might be produced through the deprotonation of H₈ by 8. However, such products were not obtained in any of the examples studied. These results imply that isomerism from 9 to 3 would occur during the reaction. Thus, compound 1e was prepared according to a known procedure and treated with the gold catalyst at 100 °C for 2 h (Scheme 3). As expected, the isomerization of the double bond occurred and 3a was obtained in 80% yield. This result shows that the indirect pathway from 7 to 3 via deprotonation of H₈ is also possible. In addition, it was found that the reaction of 1f, having no hydrogen at the α-position, proceeded smoothly and α,α-dialkyl silyl enol ether 3g was obtained in good yield (Scheme 4). Obviously, this result supports the possibility of the indirect pathway.

In conclusion, we have developed an unprecedented alkylation method for silyl enol ethers, using a gold catalyst and ortho-alkynylbenzoic acid esters as alkylating agents. The reaction probably proceeds through the gold-induced in situ construction of a leaving group and subsequent nucleophilic attack on the silyl enol ether. Unlike ordinary leaving groups, such as halide ions, the generated leaving compound 8 acts as a base and abstracts a proton to regenerate the silyl enol ether structure. The current protocol can also be used with substrates having no hydrogen at the α-position, such as 1f. Further studies to elucidate the mechanism of this reaction and to extend the scope of synthetic utility are underway.

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