

Gold(I)-catalyzed Cycloisomerization of the Mixed *N,S*-acetals Generated from Homopropargylic Amines; Mechanistic Implication for the Formal Alkyne Prins Reaction

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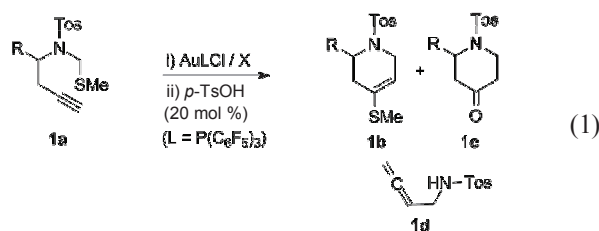
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Developing new methodologies for the synthesis of piperidines have been attracting the interest of synthetic chemists.¹ Recently, we reported gold(I)-catalyzed cycloisomerization of *N,O*-mixed acetals generated from homopropargylic amines, which led to a unique approach to highly substituted piperidin-4-ones.^{2,3} A key aspect of this reaction is the chemoselective activation of alkynes (path A) over the activation of ether groups (path B), as shown in Scheme 1. In an effort to extend the scope of this reaction, we envisioned gold(I)-catalyzed cycloisomerization of the corresponding *N,S*-mixed acetals. Because the thioether groups are known to attack alkynes in the presence of gold catalysts,⁴ the main goal of this study was to compare the reactivity between *N,O*-acetals and *N,S*-acetals for the cycloisomerization reaction. Moreover, the cycloisomerization of mixed *N,S*-acetal would be highly efficient for the preparation of 2-alkylpiperidine alkaloids including coniine and coniceine,⁵ because the thioether moiety can be easily removed with the concomitant hydrogenation of the olefin in single step.⁶

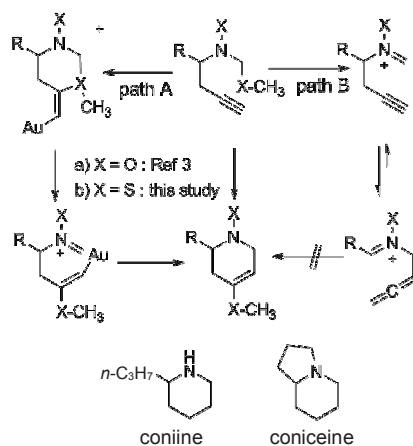
At the outset of the study, we expected that the cycloisomerization reaction of the *N,S*-acetals should be faster than *N,O*-acetal, based on the relative nucleophilicity. However, a preliminary study using 5 mol % of Au[P(C₆F₅)₃]SbF₆ showed only poor conversion. Increasing the catalyst loading to 10 mol % provided a mixture of the cycloisomerization product **1b** and the piperidin-4-one **1c** in ~45% combined yield, although the starting material was completely consumed.⁷ Our extensive

efforts to isolate the cycloisomerization product in good yields were fruitless, due to the extensive hydration of **1b** to form ketone **1c**. Thus, we sought to obtain the ketone **1c** by treating the crude mixture generated from the cycloisomerization reaction with catalytic *p*-TsOH (20 mol %). Under this two-step protocol, the ketone **1c** was obtained in 40% yield (entry 1, Table 1). Then, we explored the effect of various counteranions. Although using AgBF₄ had no effect (entry 2), changing to AgOTf increased the yield to 55% (entry 3).



Surprisingly, considerable amount of the aminoallene **1d** (15%) was obtained in this case.^{8,9} Formation of this product strongly suggests the involvement of the pathway initiated by the thioether-activation (pathway B, Scheme 1). Lowering the temperature to 0 °C efficiently suppresses this undesired process, providing the ketone **1c** in 81% yield with minimal formation (~7%) of the aminoallene **1d** (entry 4).

Then, we explored a number of substrates for the gold(I)-catalyzed transformation of the mixed *N,S*-acetals to the piperidine-4-ones. As summarized in Table 2, introducing the Cbz protective group significantly dropped the yield of the ketone (entry 2). Subjecting the mixed *N,O* acetal **3a** to the reaction condition for the direct comparison gave the ketone in 95% yield (entry 3). As implied by the high yield, **1d** was not detected in



Scheme 1. Gold(I)-catalyzed cycloisomerization of mixed acetals

Table 1. Optimization of the reaction condition

entry	catalyst (mol %)	X (mol %)	temp	rxn time	yield (1c) ^a
1	10	AgSbF ₆ (10)	rt	20 h	40%
2	10	AgBF ₄ (10)	rt	22 h	40%
3	10	AgOTf (10)	rt	4 h	55% ^b
4	10	AgOTf (10)	0 °C	10 h	81% ^c

^aisolated yield after two-step conversion. ^b**1d** was isolated in 15% yield. ^c**1d** was isolated in 7% yield.

Table 2. The scope of the formation of piperidin-4-one from mixed *N,S*-acetals

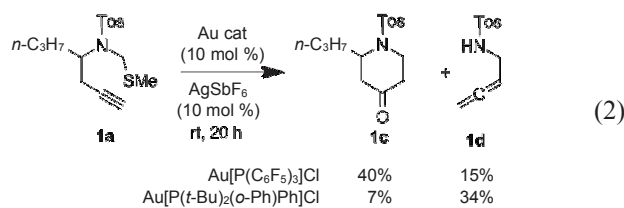
entry	S.M	method ^a	product	yield ^b
1		A		81
2		A		35 (47) ^c
3		B		95
4		A		81
5		A		49 (61) ^c
6		A		60
7		A		55
8		B		99
9		A		44 ^d

^aMethod A: 10 mol % Au[P(C₆F₅)₃]Cl and 10 mol % AgOTf was used at 0 °C; Method B: 5 mol % Au[P(C₆F₅)₃]Cl and 5 mol % AgSbF₆ was used at 0 °C. ^bIsolated yield obtained after the crude mixture was treated with 20 mol % p-TsOH at rt. ^cYield based on recovered starting material. ^dAllene product was obtained in 25% yield.

this case. As can be seen in entries 4 and 5, introducing a longer primary alkyl group little improved the formation of the ketone. Thus, comparable 81% yield of the ketone **4c** was obtained for Ts-protected mixed acetal **4a** (entry 4). Again, Cbz-protected mixed acetal **5a** lowered the yield of the ketone (entry 5). We then investigated the substrates possessing cyclohexyl group at the homopropargylic position. However, a similar pattern was observed (entries 6-7).

Even the substrate having an additional alkyl group at the propargylic position (**9a**) did not improve the result. In this case, cycloisomerization product **9b** was obtained in 44% yield, along with the allene product analogous to **1d** in 25% yield. Thus, it appears that the substituent at the propargylic position promotes the thioether-activation pathway.

As discussed earlier, formation of the allene products in the case of *N,S*-mixed acetals strongly indicates the involvement of thioether-activation pathway. Interestingly, it was found out that the competition between two pathways also depends upon the nature of the phosphine ligands (Eq 2). While electron-poorer gold complex prefers the formation of the ketone **1c**, electron-richer ligand changed the course of the reaction, favoring the formation of the allene product **1d**.



In summary, we studied the gold(I)-catalyzed cycloisomerization of mixed *N,S*-acetals generated from homopropargylic amines. Unlike the reaction of *N,O*-mixed acetals, the reaction pathway mediated by the activation of the thioether participates significantly in the reaction, presumably due to the well-known

thiophilicity of the gold catalysts.⁸ In this regard, this study well supports the viability of the gold (I)-catalyzed formal alkyne Prins reaction of mixed *N,O*-acetals, previously reported by us.³ The present work also represents a formal synthesis of racemic coniine, because the transformation of **1c** to coniine has already been established.^{5a}

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