Organic LETTERS

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# One-Pot Synthesis of Keto Thioethers by Palladium/Gold-Catalyzed Click and Pinacol Reactions

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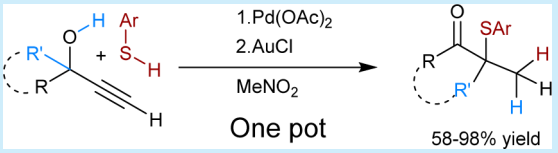
Supporting Information

**ABSTRACT:** An atom-efficient synthesis of keto thioethers was devised via tandem gold/palladium catalysis. The reaction proceeds through a regioselective thiol attack at the $\beta$-position of the alcohol, followed by an alkyl, aryl, or benzyl 1,2-shift. Both acyclic and cyclic systems were studied, in the latter case leading to the ring expansion of cyclic substrates.




The carbon−sulfur bond, which is vital to life, is found in two of the proteinogenic amino acids (Cys and Met). A number of biologically active compounds and their precursors contain the $\alpha$-carbonyl tertiary thioether motif (Figure 1).[1] Therefore, the formation of such bonds are of great value to pharmaceutical and agrochemical industries.

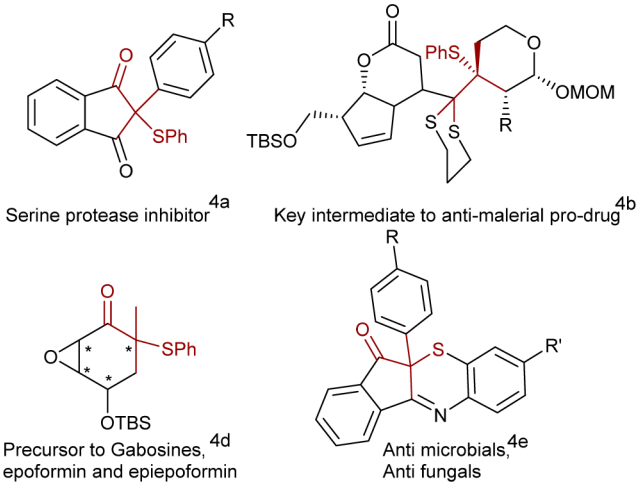
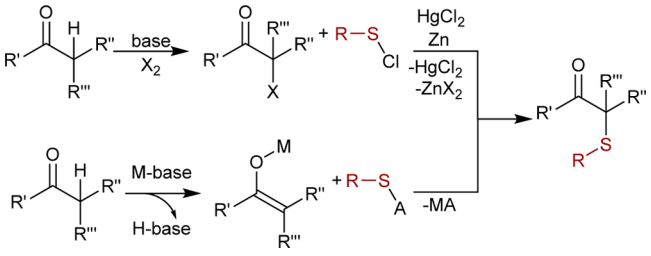



**Figure 1.** Biologically active compounds or precursors containing tertiary thioether groups.

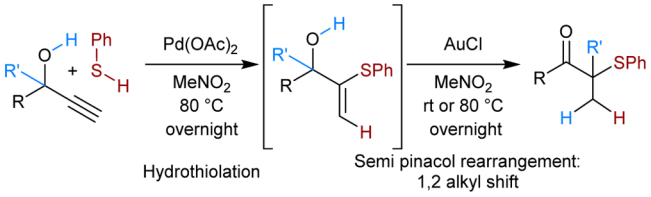
In this paper, we focus on the synthesis of tertiary sulfenylated carbonyl compounds. Traditionally, thioethers are synthesized in several steps from toxic and highly reactive halogenated compounds with mercury salts, leading to stoichiometric amounts of toxic waste.[2] Alternatively, a sulfenylating agent can be used, but they require additional synthetic steps and also generate stoichiometric waste (Scheme 1).[3] These wasteful methods remain prevalent in traditional synthesis, especially for medicinal applications.[4c,e]

**Scheme 1. Traditional Synthesis of Sulfenylated Carbonyls**




Efficient synthetic chemistry should rely on catalytic cycles and strive toward high atom efficiency.[5] Recently, novel catalytic methodologies using gold catalysis have flourished.[6] In this group, AuCl,[6k,l] CuI,[7] and $Pd(OAc)_2$/AuCl systems[8] have been devised to generate secondary thioethers. For terminal alkynes, palladium was employed in order to promote the addition of the thiol exclusively to the internal position (Scheme 2).[9] A competing terminal attack was catalyzed by gold in the absence of the terminal substituent group. Similar systems involving one-pot gold(I)-catalyzed 1,2-shifts and oxidation of propargylic alcohols have been developed in Hashmi's group, leading, when applicable, to the ring expansion of the substrates.[10] The (semi)

**Scheme 2. This Work: Palladium/Gold-Catalyzed C−S Bond Formation Followed by a Semipinacol Rearrangement**

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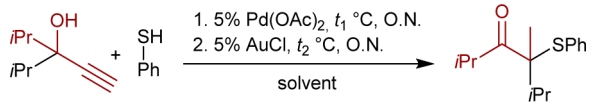
pinacol rearrangement is a well-known reaction, and among its many uses is the ring expansion of cyclopropyl phenyl sulfites to form spiro-ketone.[11] Recently, the use of the semipinacol rearrangement in combination with alkyne/ketone metathesis to synthesize disubstituted furans has been reported.[12] The ring expansions of cyclobutanols and propanols were recently achieved under photochemical conditions using a dual catalyst system: Au/Ru or Au/Ir.[13]

On the basis of the system previously developed to operate a hydride shift in terminal alkynes,[8] a brief optimization of the reaction conditions was performed (Table 1). In all cases, the

**Table 1. Optimization of the System**[a]



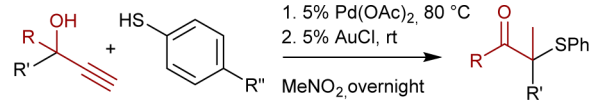

| | $t_1$ (°C) | $t_2$ (°C) | solvent | conversion[b] (%) |
|---|---|---|---|---|
| 1 | 80 | 80 | $MeNO_2$ | >95 |
| 2 | 80 | 23 | $MeNO_2$ | >95 |
| 3 | 80 | *c* | $MeNO_2$ | <5 |
| 4 | 80 | 23 | 1,2-DCE | 74 |
| 5 | 80 | 23 | PhMe | 22 |
| 6 | 60 | 23 | $MeNO_2$ | 92 |
| 7 | 40 | 23 | $MeNO_2$ | 57 |

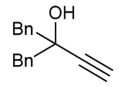
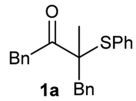
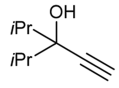
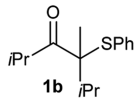
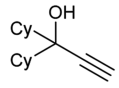
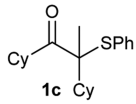
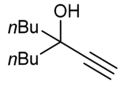
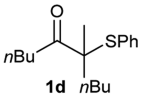
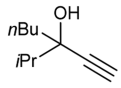
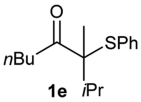
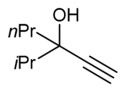
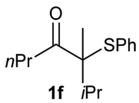
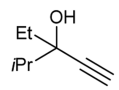
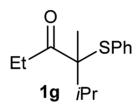
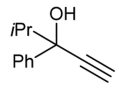
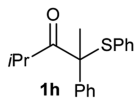
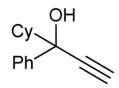
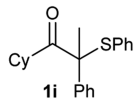
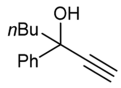
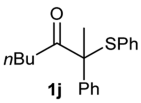
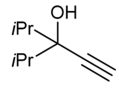
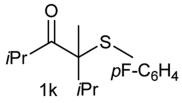
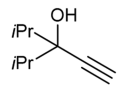
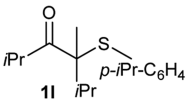
[a]Conditions: alcohol (100 mg, 1 equiv), PhSH (1.5 equiv), $Pd(OAc)_2$ (5 mol %), solvent (1 mL) at $t_1$ °C, overnight, then AuCl (5 mol %), at $t_2$ °C overnight. [b]Determined by NMR spectroscopy [c]AuCl and $Pd(OAc)_2$ added simultaneously.

reactions were run without the need for any additional ligand. Nitromethane proved to be the optimal solvent. While heating to 80 °C was necessary to perform the thiol addition, room temperature proved sufficient to promote the alkyl shift (entry 2). The thiol addition was catalyzed faster via AuCl than $Pd(OAc)_2$, leading to undesirable terminal addition rather than the desired product (entry 3). Therefore, stepwise addition of the catalysts was required.

With the reaction conditions optimized, the scope of the reaction was probed. A number of acyclic substrates were reacted, giving either good or very good yields (Table 1). Symmetrical compounds provided the best results (entries 1−4). The dibenzylic compound yielded **1a** in 92% yield, most likely owing to the benzyl's electronegativity. Secondary alkyl groups also migrated smoothly to give products **1b** and **1c** in very good yields (entries 2 and 3). A good yield was observed for the di-*n*-butyl compound (entry 4), which is gratifying considering the primary carbon's lower migrational aptitude compared to a secondary group. Nonsymmetrical propargylic alcohols were reacted by this procedure. Overall, the migration of the *i*-Pr group proceeded well when competing with linear aliphatic chains (entries 5−7). An increase in yield of the product from *i*-Pr migration accompanying an increase in chain length of the nonmigrating linear aliphatic chain was observed. The combination of a phenyl and an aliphatic group led to good results (entries 8−10). The aryl group displayed a higher migrational aptitude than the alkyl groups. However, a diphenylic substrate yielded a complex product mixture. In order to probe the electronic effects of the thiophenol, three different thiophenols were screened (entries 2, 11, and 12), and the reaction proved to be tolerant of both electron-donating and -withdrawing groups.

**Table 2. Addition and Rearrangement of Acyclic Substrate**[a]




| | compound | R" | Products | yield (%)[b] |
|---|---|---|---|---|
| 1 |  | H |  **1a** | 92 |
| 2 |  | H |  **1b** | 90 |
| 3 |  | H |  **1c** | 88 |
| 4 |  | H |  **1d** | 79 |
| 5 |  | H |  **1e** | 82 |
| 6 |  | H |  **1f** | 80[c] |
| 7 |  | H |  **1g** | 64[c] |
| 8 |  | H |  **1h** | 73 |
| 9 |  | H |  **1i** | 79 |
| 10 |  | H |  **1j** | 84 |
| 11 |  | F |  1k | 94 |
| 12 |  | *i*Pr |  1l | 92 |

[a]Conditions: alcohol (100 mg, 1 equiv), thiol (1.5 equiv), $Pd(OAc)_2$ (5 mol %), $MeNO_2$ (1 mL) at 80 °C, overnight, then AuCl (5 mol %), at room temperature overnight. [b]Isolated yields. [c]Conversion.

The methodology was expanded from acyclic to cyclic substrates. As can be seen in Table 3, the ring expansion was performed with good to excellent yields in all but one case. The large difference in yields between 1-ethynylcyclobutanol and 1-


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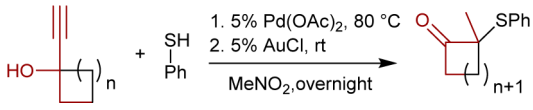
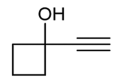
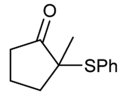
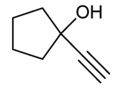
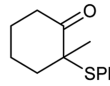
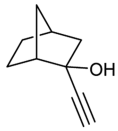
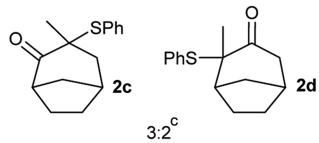
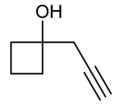
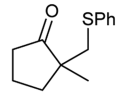
**Table 3. Ring Expansion of Cyclic Propargylic Alcohols**[a]




| | compound | products | | yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  | **2a** | 93 |
| 2 |  |  | **2b** | 58 |
| 3 |  |  | **2c** / **2d** 3:2[c] | 98 |
| 4 |  |  | **2e** | 75 |

[a]Conditions: alcohol (100 mg, 1 equiv), PhSH (1.5 equiv), $Pd(OAc)_2$ (5 mol %), $MeNO_2$ (1 mL) at 80 °C, overnight, then AuCl (5 mol %), at 80 °C, overnight. [b]Isolated yields. [c]Ratio determined by NMR spectroscopy.

ethynylcyclopentanol is likely due to the ring stability of the starting materials (entries 1 and 2). Ring expansion of 1-ethynylcyclohexanol was attempted, though the stability of the six-membered ring made an expansion to seven-membered unfavorable.

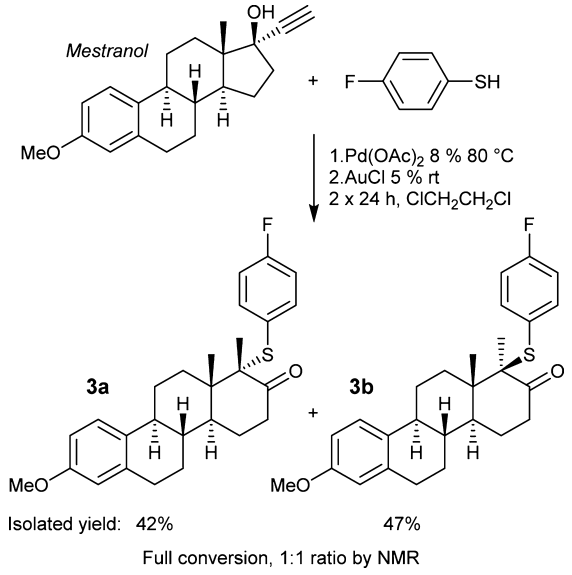
However, another six-membered ring was successfully ring expanded when the bicyclic norcamphor derivative was successfully ring expanded from a six-membered to a seven-membered ring in near quantitative yield (entry 3). The propensity toward the 1,2 shift was probed through entry 4, as a 1,3 shift was plausible. However, the four- to six-membered ring expansion did not occur. Instead, a five-membered ring was obtained. The alkyne was too distant from the oxygen to have its usual directing role, which caused an alternate regioselectivity.

The methodology was applied to the biologically active contraceptive mestranol. The study of D-ring expanded estrogens are garnering increasing interest, particularly for their antitumoral and cytostatic activities.[14] Therefore, a D-ring expansion of mestranol was performed using the process developed above (Scheme 3).

Nitromethane was replaced with 1,2-dichloroethane for solubility reasons. The reaction proceeded with full conversion and complete regioselectivity. The stereochemistry of the cycle was maintained throughout the reaction at the methyl (C20) on the C13 position (Figure 2). However, the chirality was not transferred from C17 to C18 in the 1,2-alkyl shift (both diastereomers were isolated through silica chromatography).

In conclusion, a series of cyclic and acyclic tertiary sulfenylated ketones were synthesized through a tandem palladium/gold system in good to excellent yields. The possibilities of this process were exemplified by the D-ring expansion of an estradiol to obtain novel homo-D steroids.

**Scheme 3. Synthesis of D-Ring-Expanded Steroids**



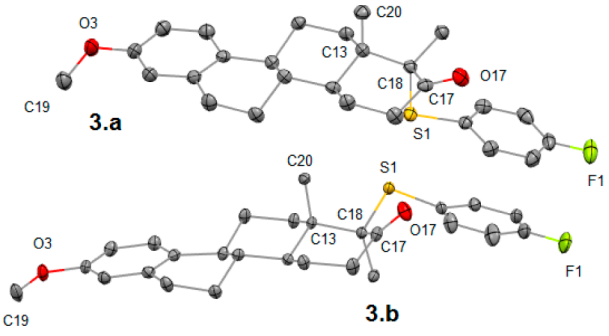




**Figure 2.** X-ray of structure of steroid products **3.a** and **3.b**. Ellipsoids set at 50% probability and hydrogen atoms omitted for clarity.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and spectra and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC-1027282 and CCDC-1027283 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. A summary of the data can be found in the Supporting Information.

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### Notes

The authors declare no competing financial interest.

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