Tetrahedron Letters 51 (2010) 378–381

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Gold-catalyzed C–S bond formation from thiols

Mickaël Jean[a], Jacques Renault[a], Pierre van de Weghe[a,*], Naoki Asao[b]

[a] EA Substances Lichéniques et Photoprotection, Faculté des Sciences Biologiques et Pharmaceutiques, Université de Rennes 1, 2 Avenue du Prof. Léon Bernard, F-35043 Rennes, France
[b] Department of Chemistry and Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

ARTICLE INFO

Article history:
Received 1 October 2009
Revised 2 November 2009
Accepted 9 November 2009
Available online 12 November 2009

Keywords:
Gold catalysis
Substitution
Sulfide

ABSTRACT

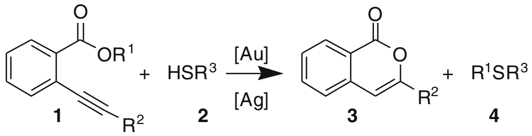
ortho-Alkynylbenzoic acid alkyl esters act as alkylating agents of thiol derivatives with PPh_3AuCl in combination with AgOTf in 1,2-dichloroethane at 80 °C. The corresponding sulfide compounds are obtained in good to excellent yields.

During the last decade, the use of homogenous gold catalysts for organic transformations has enjoyed tremendous popularity among chemists working in the field of catalysis and organic synthesis.[1] To date, gold complexes have been employed for efficient C–C, C–N, C–S, and C–O bond-forming reactions. Since aryl or alkyl thioethers were known to be important for many biologically active and pharmaceutical compounds,[2] the formation of C–S bonds received much attention.[3] Many catalytic systems using transition metals have been studied for the preparation of aryl thioethers such as palladium,[4] nickel,[5] copper,[6] indium,[7] and iron[8] in combination with ligands and bases. Other methods without the use of transition metals were also described to obtain alkyl sulfides.[9] Although gold salts and thiols were shown to have a good affinity, to our knowledge only one work was reported describing the addition of thiols to allenes corresponding to a gold-catalyzed cycloisomerization of α-thioallenes to 2,5-dihydrothiophenes.[10] In this Letter, we report our efforts to prepare various aryl or alkyl sulfide derivatives from thiols by the use of a combination of triphenylphosphine gold chloride and silver triflate as catalytic system.

Recently, one of us described an efficient gold-catalyzed etherification of alcohol using *o*-alkynylbenzoic acid alkyl ester as an electrophile, and the reaction proceeding through a gold-induced construction of leaving group and subsequent nucleophilic attack.[11] Relying on these previous results, we felt that this concept could be used to prepare sulfide derivatives from thiols as nucleophiles (Scheme 1).

The preliminary studies have revealed that the reaction of *o*-pent-1-ynylbenzoic acid benzyl ester[12] **1a** with 1.1 equiv of thiophenol **2a** could be carried out in the presence of 5 mol % PPh_3AuCl and 5 mol % AgOTf in 1,2-dichloroethane at 80 °C to afford the isocoumarin **3a** and the thioether **4a** in 95% and 85% yields, respectively (Table 1, entry 1). In the absence of either PPh_3AuCl or AgOTf, no reaction occurred. Having found a satisfactory system, we turned our attention to the scope of this reaction. The results are reported in Table 1. The benzylation of various thiophenol derivatives worked well, the thioethers **4** being isolated in good yields along with a nearly quantitative yield of isocoumarin **3a**. On the other hand the benzylation of the phenethyl thiol afforded the thioether **4e** in low yield and no reaction took place with the *n*-decanethiol probably due to its low reactivity.[10b]

To overcome this drawback, we decided to study the influence of the electronic density of the alkynyl group of **1** (Table 2). Having a plausible mechanism in mind (Scheme 2),[11] we thought that increasing the affinity of the gold cationic species for the triple bond could promote the formation of the zwitterionic intermediate **A** allowing a better electrophilic transfer of the group R^1 to the thiol. Various *o*-alkynylbenzoic acid benzyl ester have been prepared and treated with 1.1 equiv of phenethyl thiol **2e** in the presence of 10 mol % PPh_3AuCl and 10 mol % AgOTf in dichloroethane at 80 °C. Best yields of thioether **4e** were obtained when the *o*-alkynylbenzoic acid alkyl ester possessed an electron-rich alkynyl part



Scheme 1. Gold-catalyzed sulfides synthesis.

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* Corresponding author. Tel.: +33 (0)2 23 23 38 03; fax: +33 (0)2 23 23 44 25.
E-mail address: pierre.van-de-weghe@univ-rennes1.fr (P. van de Weghe).

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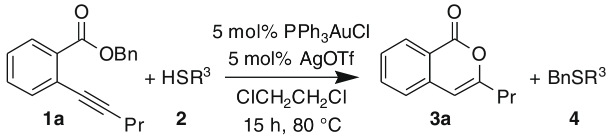
doi:10.1016/j.tetlet.2009.11.025

Table 1
First results of sulfide formation



Entry	2	R^3	Yield (**3a**) (%)	4	Yield (**4**) (%)
1	**2a**	C_6H_5	95	**4a**	85
2	**2b**	4-CH_3–C_6H_4	90	**4b**	79
3	**2c**	4-Cl–C_6H_4	94	**4c**	93
4	**2d**	4-CH_3O–C_6H_4	100	**4d**	96
5	**2e**	$C_6H_4CH_2CH_2$	28	**4e**	28
6	**2e**	$C_6H_4CH_2CH_2$	44	**4e**	45[a]
7	**2f**	$C_{10}H_{21}$	n.d.[c]	**4f**	n.d.[b,c]

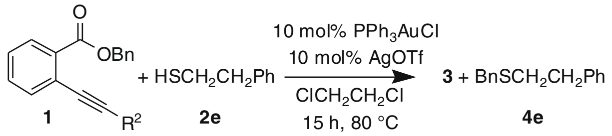
[a] 10 mol % PPh$_3$AuCl, 10 mol % AgOTf.
[b] Conversion <20%.
[c] n.d. = not determined.

(entries 5 and 6). However the reaction seems sensitive to the steric hindrance, the presence of a methoxy group in the *ortho* position decreasing slightly the yield (entry 6). This shows the importance of the substituent R^2 on the efficiency of the reaction.

Using the *o*-[2-(4-methoxyphenyl)ethynyl]benzoic acid benzyl ester **1e** as alkylating agent in the presence of 1.1 equiv *n*-decanethiol **2f** in our catalytic system, the thioether **4f** was isolated in 37% yield. Interestingly, when 3.0 equiv of **2f** was employed the chemical yield was improved significantly and **4f** was obtained in 86% yield along with 89% yield of isocoumarin **3e** (Scheme 3).

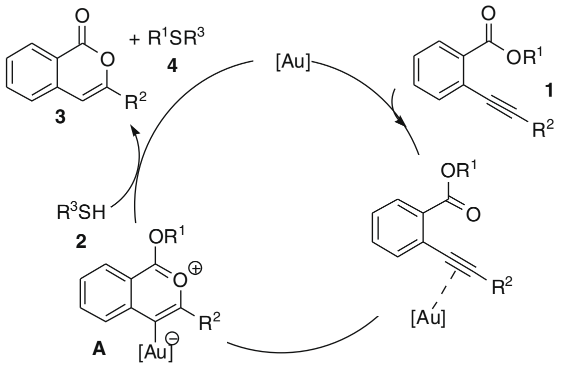
We next investigated the scope of this gold-catalyzed alkylation of thiols. The results are reported in Table 3. As expected the benzylation of various thiophenol derivatives led to the thioethers in high yields (91–99%, entries 1–5). On the other hand the *n*-butyl transfer to thiophenol derivatives afforded the thioethers in satisfactory but in lower yields (54–80%, entries 6–13). In general, the reaction was unaffected by electronic factor of the aryl group. We also examined the formation of dialkyl sulfides. Using 10 mol % PPh$_3$AuCl and 10 mol % AgOTf the reaction also furnished the sulfides **4s** and **4t** but the yields were low (17–42%, entries 14–16). Unsatisfactory results were observed when we tried to transfer an *iso*-propyl group to the thiophenol **2a**. Although the isocoumarin **3e** was quantitatively isolated, the resulting thioether **4u** was obtained in very low yield (24%, entry 17). In the case of a cyclohexyl moiety, only the isocoumarin **3e** was formed and no thioether was observed. The reaction proceeding probably via a S$_N$1 mechanism,[11] the carbocationic species decomposed in these

Table 2
Electronic effect of the alkynyl group

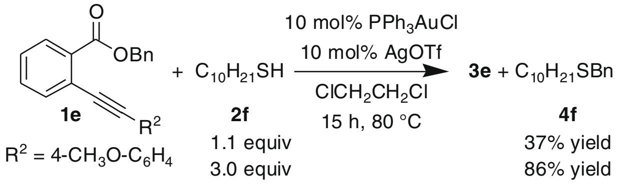


Entry	1	R^2	Yield (**4e**) (%)
1	**1b**	4-NO_2–C_6H_4	28[a,b]
2	**1c**	4-CF_3–C_6H_4	18[a,b]
3	**1d**	C_6H_5	37[b]
4	**1a**	Pr	46[b]
5	**1e**	4-CH_3O–C_6H_4	75[c]
6	**1f**	2,4-$(CH_3O)_2$–C_6H_3	61[c]

[a] Isolation of a mixture of isocoumarin and isobenzofuranone in 20% yield.
[b] Incomplete reaction.
[c] >95% yield of isocoumarin **3**.

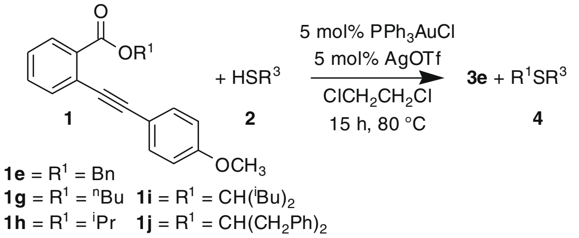


Scheme 2. Plausible mechanism.



Scheme 3. Benzylation of *n*-decanethiol **2f**.

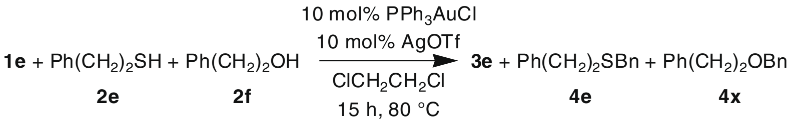
Table 3
Evaluation of the scope of thioether formation



Entry	1	2	R^3	4	Yield (**4**) (%)
1	**1e**	**2d**	4-CH_3O–C_6H_4	**4d**	93
2	**1e**	**2g**	3-CF_3–C_6H_4	**4g**	94
3	**1e**	**2h**	3-Br–C_6H_4	**4h**	99
4	**1e**	**2i**	4-Br–C_6H_4	**4i**	99
5	**1e**	**2j**	2-Naphthyl	**4j**	91
6	**1g**	**2a**	C_6H_5	**4k**	65
7	**1g**	**2b**	4-CH_3–C_6H_4	**4l**	68
8	**1g**	**2c**	4-Cl–C_6H_4	**4m**	80
9	**1g**	**2d**	4-CH_3O–C_6H_4	**4n**	54
10	**1g**	**2g**	3-CF_3–C_6H_4	**4o**	72
11	**1g**	**2h**	3-Br–C_6H_4	**4p**	75
12	**1g**	**2i**	4-Br–C_6H_4	**4q**	70
13	**1g**	**2j**	2-Naphthyl	**4r**	65
14	**1g**	**2e**[a]	$C_6H_4CH_2CH_2$	**4s**	25[b,c]
15	**1g**	**2e**[a]	$C_6H_4CH_2CH_2$	**4s**	42[b,d,e]
16	**1g**	**2f**[a]	$C_{10}H_{21}$	**4t**	17[b,f]
17	**1h**	**2a**	C_6H_5	**4u**	24[g]
18	**1i**	**2a**	C_6H_5	**4v**[h]	55
19	**1j**	**2a**	C_6H_5	**4w**[h]	82

[a] 3.0 equiv of **2**.
[b] 10 mol % PPh$_3$AuCl, 10 mol % AgOTf.
[c] 60% conversion.
[d] PhCl used as a solvent.
[e] 70% conversion.
[f] 50% conversion.
[g] >95% yield of **3e**.
[h] See structure Fig. 1.

Table 4
Competitive reaction



$$\underset{}{\mathbf{1e}} + \underset{\mathbf{2e}}{Ph(CH_2)_2SH} + \underset{\mathbf{2f}}{Ph(CH_2)_2OH} \xrightarrow[\substack{ClCH_2CH_2Cl \\ 15\ h,\ 80\ °C}]{\substack{10\ mol\%\ PPh_3AuCl \\ 10\ mol\%\ AgOTf}} \mathbf{3e} + \underset{\mathbf{4e}}{Ph(CH_2)_2SBn} + \underset{\mathbf{4x}}{Ph(CH_2)_2OBn}$$

Entry	**1e** (equiv)	**2e** (equiv)	**2f** (equiv)	Yield (**4e**) (%)	Yield (**4x**) (%)
1	1.0	1.0	0	75	–
2	1.0	0	1.0	–	70
3	1.0	1.0	1.0	51	26

reaction conditions faster than its reaction with **2a**. The S_N1 mechanism was also consolidated when the thiophenol **2a** was treated with the esters **1i** and **1j**. In each case the carbocationic secondary alkyl group, generated from the species **A**, rearranges in a more stable tertiary carbocation before its reaction with **2a** to afford **4v** and **4w** in good yields (55 and 82%, respectively, entries 18–19) (Fig. 1).

A competitive reaction was also conducted to determine the chemoselectivity between the alkylation of an alcohol and a thiol. The *o*-[2-(4-methoxyphenyl)ethynyl]benzoic acid benzyl ester **1e** was placed with 1.0 equiv phenethyl alcohol **2f** and 1.0 equiv phenethyl thiol **2e** in the presence of the gold/silver catalytic system (Table 4). While the reaction of benzylation of the alcohol **2f** gave similar yield as the reaction with the thiol **2e**, surprisingly we obtained the thioether **4e** as a major product in the competitive reaction, **4e** being isolated with 51% yield and the ether **4x** with 26% yield (entry 3).[13] In a similar manner, a competitive reaction was realized between phenol and thiophenol. Only the benzylation of the thiophenol was observed. However after a control experiment we noticed the absence of reactivity of phenol in these reaction conditions.

We were also curious to see if our methodology could be extended to disulfides as synthetic equivalents of thiols.[14] The *o*-[2-(4-methoxyphenyl)ethynyl] benzoic acid benzyl ester **1e** and diphenyl disulfide **2k** were treated with 5 mol % PPh_3AuCl and 5 mol % AgOTf in 1,2-dichloroethane at 80 °C for 15 h, the expected thioether **4a** was isolated in a satisfactory yield (Scheme 4). Besides **4a**, a mixture of the usual isocoumarin **3e** and a functionalized isocoumarin **3i** was obtained in 2:3 ratio, **3i** being isolated in 48% yield. A heterolytic cleavage of the disulfide **2k** occurred probably, one moiety acting as a nucleophile to afford **4a** and the second moiety playing the role of an electrophile to cleave the gold-carbon bond in the intermediate **A** (Scheme 2). This result appears interesting. On the one hand the use of the disulfide allows the obtaining of the thioether and on the other hand it leads to a functionalized isocoumarin. This last point could be later used to prepare new functionalized isocoumarin derivatives.[15]

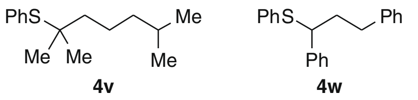
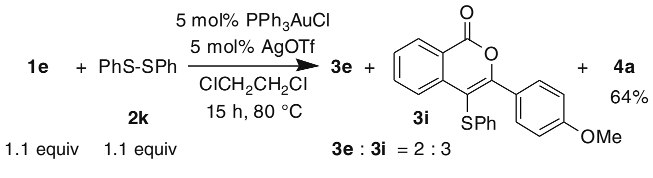


Figure 1. Structures of **4v** and **4w**.



Scheme 4. Thioether formation from diphenyl disulfide **2k**.

In conclusion, we have described a gold-catalyzed C–S bond formation from various thiols. The reaction proceeded with PPh_3AuCl in combination with AgOTf as a catalytic system in 1,2-dichloroethane at 80 °C via an activation of leaving group. This procedure was shown to furnish arylalkyl sulfides in good to high yields but afforded dialkyl sulfides in low yields. Further investigations of the scope as well as synthetic applications are currently in progress and will be reported in due course.

Acknowledgments

This work was supported by the Université de Rennes 1, the Région Bretagne and Rennes Metropole. One of us, Professor Naoki Asao, thanks the Université de Rennes 1 for financial support during his stay as visiting professor at the Université de Rennes 1.2

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.025.

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