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Palladium-Catalyzed Thiocarbonylation of Benzyl Chlorides with Sulfonyl Chlorides for the Synthesis of Arylacetyl Thioesters

Wei Wang,[a] Xinxin Qi,[a,*] and Xiao-Feng Wu[b,*]

[a] Department of Chemistry, Zhejiang Sci-Tech University, Hangzhou, Zhejiang 310018, People's Republic of China
E-mail: xinxinqi@zstu.edu.cn
[b] Dalian National Laboratory for Clean Energy, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 116023, Dalian, Liaoning, People's Republic of China
and
Leibniz-Institut für Katalyse e.V. an der, Institution Universität Rostock, Albert-Einstein-Straße 29a, Rostock 18059, Germany
E-mail: xiao-feng.wu@catalysis.de

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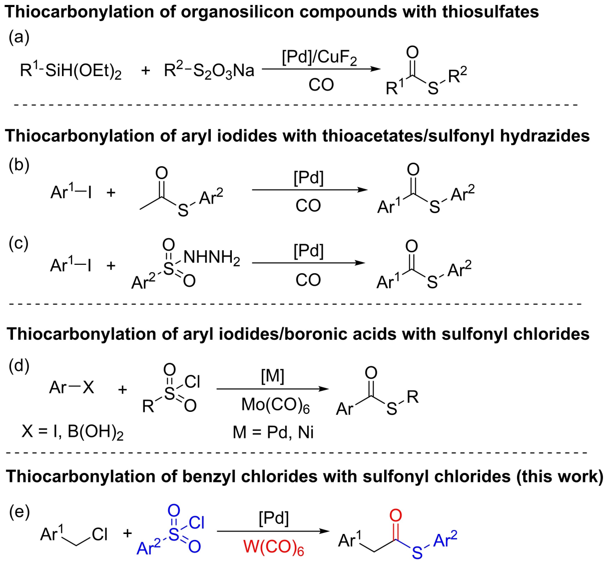
Abstract: A convenient procedure for the synthesis of thioesters has been developed *via* a palladium-catalyzed thiocarbonylation of benzyl chlorides with sulfonyl chlorides. Various arylacetyl thioesters were produced in good yields by using sulfonyl chlorides as an odorless sulfur source. Furthermore, $W(CO)_6$ exhibited dual roles as both a solid CO surrogate and reductant here.

Keywords: palladium catalyst; Carbonylation; Benzyl chloride; Sulfonyl Chloride; Thioester

Thioesters represent a type of useful building scaffolds, which are widely investigated in organic synthesis as air-stable and easy-handling acyl donors for constructing diverse aldehydes,[1] ketones,[2] esters,[3] and so on.[4] They play an important role in biological process, for example, acetyl CoA involved citric acid cycle,[5] or in the case of native chemical ligation, an valuable protein preparation from a *C*-terminal peptide thioester.[6] Therefore, the synthesis of thioesters has drawn much attentions from chemists and much efforts has been put on it. Traditionally, methods for the synthesis of thioesters are mainly based on the acyl substitution, which used thiol as the sulfur source.[7] Alternatively, many other protocols, including oxidative coupling reactions of aldehydes,[8] and substitution of haloalkanes have been explored as well.[9] Although much efforts have been put on this area, the development of novel alternative catalytic system remains an interesting field to study.

In recent decades, transition-metal-catalyzed carbonylation reactions has been intensively investigated since its discovery.[10,11] This catalytic system has been regarded as one of the most atom-economic approach for its broad applications in the synthesis of carbonyl-containing compounds. Hence, various carbonylation reactions has been achieved for the preparation of thioesters from aryl halides[12] and unsaturated compounds.[13] However, these reactions usually employed thiols as sulfur source, which suffered from some disadvantages such as bad odor and poisonous catalyst properties.[14] As a result, several carbonylation reactions with alternative sulfur sources have been reported. For examples, in 2016, thiosulfates were used as sulfurating reagent in a palladium-catalyzed thiocarbonylation in Jiang's group (Scheme 1, eq a).[15]



Scheme 1. Thiocarbonylation Reactions with Sulfur Sources.

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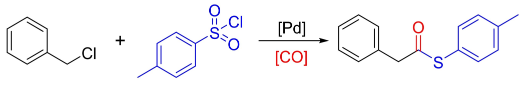
Very recently, Lee and co-workers disclosed the palladium-catalyzed carbonylative synthesis of thioesters in the presence of thioacetates, and sulfonyl hydrazides, respectively (Scheme 1, eq b–c).[16] Additionally, our group also explored the thiocarbonylation reactions with sulfonyl chlorides as an inexpensive and attractive sulfur precursor (Scheme 1, eq d).[17]

On the other hand, compare to aryl halides, the utilization of benzyl halides (a class of special Csp^3–X electrophile) has not been reported in thiocarbonylation reactions. In our continuous study on sulfonyl chlorides involved thiocarbonylation reactions, we wish to disclose here a palladium-catalyzed thiocarbonylation reaction of benzyl chlorides with sulfonyl chlorides (Scheme 1, eq e). With sulfonyl chlorides as an odorless sulfur source, various desired arylacetyl thioesters were produced in good yields by using $W(CO)_6$ as both a solid CO surrogate and reductant.

Initially, benzyl chloride and *p*-toluenesulfonyl chloride were chosen as the model substrates for this thiocarbonylation reaction. Conducting the reaction in CH_3CN at 110 °C for 24 h with $Pd(OAc)_2$ as the catalyst, DPEphos as the ligand, K_3PO_4 as the base, $Mo(CO)_6$ as the CO source in the presence of H_2O, unfortunately, no desired thioester **3ab** was detected (Table 1, entry 1). Then various bases, such as Na_2CO_3, Et_3N, DIPEA, and DBU were studied to promote this reaction (Table 1, entries 2–5), to our delight, 19% yield was observed with Et_3N as the base (Table 1, entry 3). We subsequently examined the ligands effect, and a slightly higher yield was obtained with Xantphos (Table 1, entry 6). When the temperature was decreased to 100 °C, 36% yield of **3ab** was formed (Table 1, entry 10). Solvent screening showed that CH_3CN tended to be the optimal solvent for this transformation (Table 1, entries 11–14). Subsequently, various palladium catalysts were used, including $Pd(TFA)_2$, $Pd(acac)_2$, and $PdCl_2$, the yields were all dropped (Table 1, entries 15–17). In addition, by using $W(CO)_6$ as the CO source, the yield of **3ab** increased to 62% (Table 1, entry 18). This improvement is benefited by the fact that $W(CO)_6$ can release CO at lower temperature. This decreased reaction temperature then favor the target reaction due to the high reactivity of benzyl chloride and low stability of benzylpalladium intermediate. When employing 3 mol% of $Pd(OAc)_2$ along with 3 mol% of Xantphos could also provide comparable yield as with 5 mol% of $Pd(OAc)_2$ (Table 1, entry 19). It was noteworthy that the concentration of the reaction mixture affected the product yield dramatically, 72% yield of the expected thioester was obtained with 0.2 molar-scale in 1 mL CH_3CN (Table 1, entry 20). Decreased concentration improves the reaction selectivity significantly, because less thioether were formed at lower concentration. It is also important to mention that no reaction occurred in the absence of palladium catalyst. Additionally, no target product could be detected by using CO gas (1 bar) instead of $W(CO)_6$.

Table 1. Screening of Reaction Conditions.[a]



1a **2b** **3ab**

Entry	[Pd]	Ligand	Base	Solvent	Yield (%)
1	$Pd(OAc)_2$	DPEphos	K_3PO_4	CH_3CN	0
2	$Pd(OAc)_2$	DPEphos	Na_2CO_3	CH_3CN	trace
3	$Pd(OAc)_2$	DPEphos	Et_3N	CH_3CN	19
4	$Pd(OAc)_2$	DPEphos	DIPEA	CH_3CN	11
5	$Pd(OAc)_2$	DPEphos	DBU	CH_3CN	6
6	$Pd(OAc)_2$	Xantphos	Et_3N	CH_3CN	23
7	$Pd(OAc)_2$	DPPP	Et_3N	CH_3CN	trace
8	$Pd(OAc)_2$	Xphos	Et_3N	CH_3CN	trace
9	$Pd(OAc)_2$	Sphos	Et_3N	CH_3CN	trace
10[b]	$Pd(OAc)_2$	Xantphos	Et_3N	CH_3CN	36
11	$Pd(OAc)_2$	Xantphos	Et_3N	DMF	20
12	$Pd(OAc)_2$	Xantphos	Et_3N	DMSO	trace
13	$Pd(OAc)_2$	Xantphos	Et_3N	1,4-Dioxane	trace
14	$Pd(OAc)_2$	Xantphos	Et_3N	Toluene	trace
15	$Pd(TFA)_2$	Xantphos	Et_3N	CH_3CN	25
16	$Pd(acac)_2$	Xantphos	Et_3N	CH_3CN	18
17	$PdCl_2$	Xantphos	Et_3N	CH_3CN	20
18[c]	$Pd(OAc)_2$	Xantphos	Et_3N	CH_3CN	62
19[c,d]	$Pd(OAc)_2$	Xantphos	Et_3N	CH_3CN	63
20[c,d,e]	$Pd(OAc)_2$	Xantphos	Et_3N	CH_3CN	72

[a] Reaction conditions: benzyl chloride (0.5 mmol), *p*-toluenesulfonyl chloride (0.6 mmol), catalyst (5 mol%), ligand (10 mol% for monodentate ligands, 5 mol% for bidentate ligands), $Mo(CO)_6$ (1.5 equiv.), base (1.5 equiv.), H_2O (1 equiv.), CH_3CN (2 mL), 110 °C, 24 h. GC yield, with dodecane as the internal standard.

[b] 100 °C.

[c] $W(CO)_6$ (1.5 equiv.).

[d] $Pd(OAc)_2$ (3 mol%), Xantphos (3 mol%).

[e] Benzyl chloride (0.2 mmol), *p*-toluenesulfonyl chloride (0.24 mmol), CH_3CN (1 mL).

With the optimal reaction conditions in hand, the substrate scope of benzyl chlorides was investigated and shown in Scheme 2. Benzyl chlorides with electron-rich group, including methyl, tert-butyl, and methoxy groups, the target products were produced in moderate to good yields (**3ab**–**3fb**). Substrate with disubstituted group could also work well to provide the desired thioester product in good yield (**3gb**). Benzyl chlorides bearing electron-deficient group such as trifluoromethyl and ester groups, the targeted products were obtained in moderate yields (**3hb**–**3ib**). Additionally, halogen groups, involving fluoro and chloro substituents were tested, the corresponding thioesters were formed in 48–75% yields (**3jb**–**3mb**). Substrates with 1-naphthalene moiety also worked well in this thiocarbonylation reaction, resulting the final product

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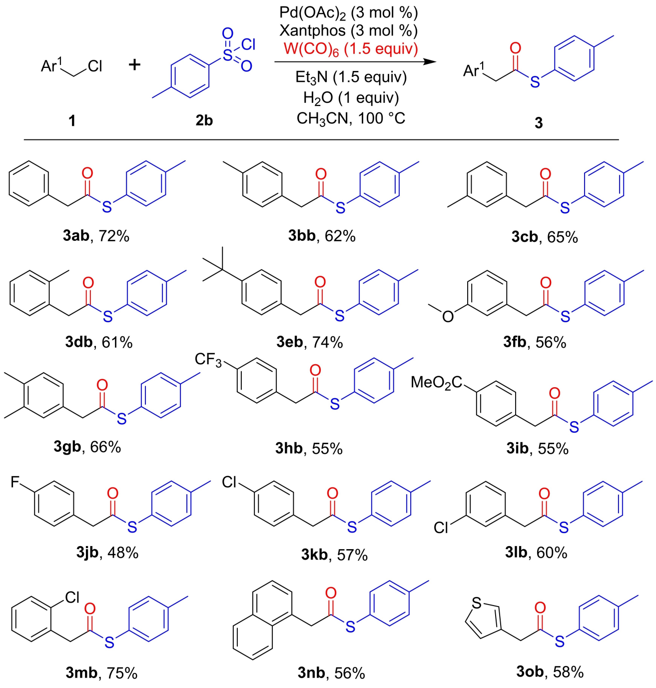
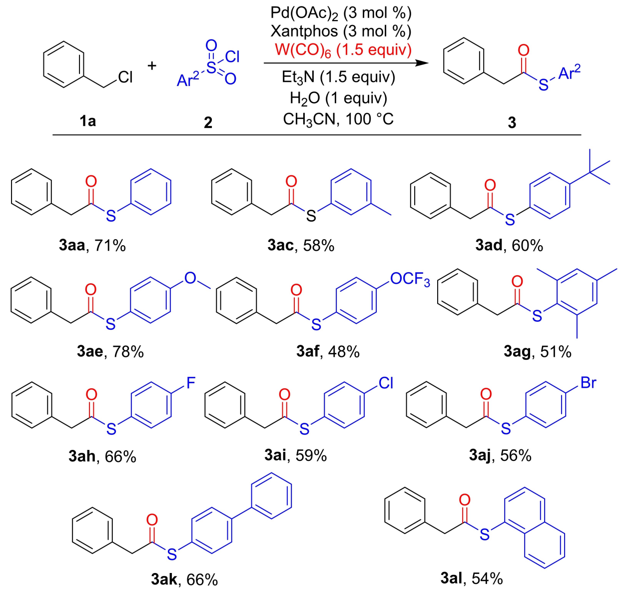


Scheme 2. Substrate Scope of Benzyl Chlorides. Reaction conditions: benzyl chlorides (0.2 mmol), *p*-toluenesulfonyl chloride (0.24 mmol), $Pd(OAc)_2$ (3 mol%), Xantphos (3 mol%), $W(CO)_6$ (1.5 equiv.), Et_3N (1.5 equiv.), H_2O (1 equiv.), CH_3CN (1 mL), 100 °C, 24 h, isolated yield.

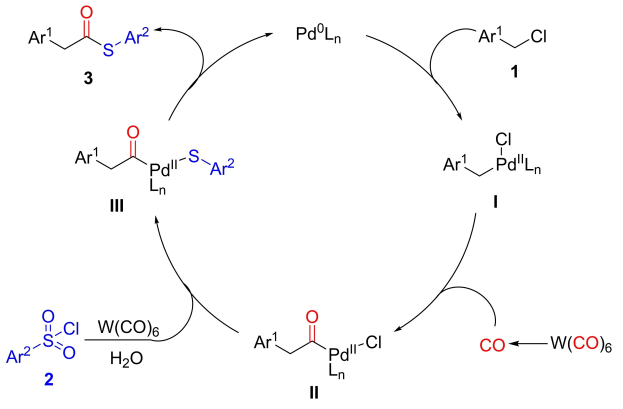
in 56% yield (**3 nb**). Moreover, 3-(chloromethyl) thiophene could smoothly reacted with *p*-toluenesulfonyl chloride to afford the expected product in 58% yield (**3 oa**) as well.

We then continue our studies with the variation of arylsulfonyl chlorides under our standard reaction conditions, and the results are summarized in Scheme 3. Arylsulfonyl chlorides with electron-donating group, including methyl, tert-butyl, methoxy, and trifluoromethoxy groups worked very well to provide the desired products in moderate to good yields (**3 aa**–**3 af**). Substrate with poly-substituents was also tolerated well to afford the corresponding thioester in 51% yield (**3 ag**). Furthermore, Halogen groups, such as fluoro, chloro, and bromo groups were examined, the target thioesters were obtained in 66%, 59%, and 56% yields, respectively (**3 ah**–**3 aj**). 1-Biphenyl and 1-naphthalene substituents were also found to be compatible; the desired products were obtained in 66% and 54% yields (**3 ak**–**3 al**), respectively.

Based on the previous study, a plausible reaction mechanism is proposed (Scheme 4). Firstly, the oxidative addition of benzyl chlorides to Pd^0L_n leads to benzylpalladium complex **I**, which is then transformed into acylpalladium complex **II** via insertion of CO (released from $W(CO)_6$). Meanwhile, a reduced sulfide intermediate was obtained by reduction of sulfonyl chloride promoted by $W(CO)_6$ in the presence of water. Nucleophilic attack of the sulfide to acylpalladium complex **II** affords intermediate **III**,[17b] which undergoes reductive elimination to furnish the desired thioester products and regenerates the active palladium complex for the next catalytic cycle.



Scheme 3. Substrate Scope of Arylsulfonyl Chlorides. Reaction conditions: benzyl chloride (0.2 mmol), arylsulfonyl chlorides (0.24 mmol), $Pd(OAc)_2$ (3 mol%), Xantphos (3 mol%), $W(CO)_6$ (1.5 equiv.), Et_3N (1.5 equiv.), H_2O (1 equiv.), CH_3CN (1 mL), 100 °C, 24 h, isolated yield.



Scheme 4. Proposed Reaction Mechanism.

In summary, we have disclosed a general and straightforward palladium-catalyzed thiocarbonylation reaction of benzyl chlorides with sulfonyl chlorides. A variety of arylacetyl thioesters were obtained in moderate to good yields with good functional group tolerance. Notably, benzyl chlorides were first utilized as carbon electrophiles in thiocarbonylation reaction, and sulfonyl chlorides served as odorless sulfur source.

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Moreover, $W(CO)_6$ played a dual role as both the CO source and reductant.

Experimental Section

$Pd(OAc)_2$ (3 mol%, 1.4 mg), Xantphos (3 mol%, 3.5 mg), $W(CO)_6$ (0.3 mmol, 105.6 mg) were added to an oven-dried tube (15 mL), which was then placed under vacuum and refilled with nitrogen for three times. Benzyl chlorides (0.2 mmol), sulfonyl chlorides (0.24 mmol), H_2O (0.2 mmol, 3.6 mg), Et_3N (0.3 mmol, 30.4 mg), and CH_3CN (1 mL) were added into the tube via syringe. The tube was sealed, and the mixture was stirred at 100 °C for 24 h. After the reaction was completed, the crude mixture was filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 50/1, volume ratio) to afford the desired thioester products.

Acknowledgements

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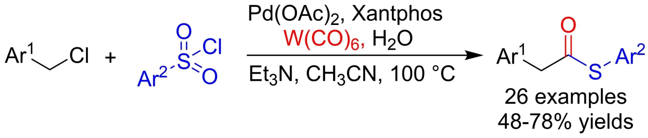

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