A Convenient, Catalyst-free Cross-coupling Reaction of α-Sulfur-substituted Alkylstannanes with Acid Chlorides Leading to α-Sulfur-substituted Ketones

Hirotaka Kagoshima* and Naoshi Takahashi
Center for Instrumental Analysis, Ibaraki University, 2-1-1 Bunkyo, Mito 310-8512

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A thermal cross-coupling reaction of α-sulfur-substituted alkylstannanes with acid chlorides is described. A range of substrates can be used for the present reaction and the reaction proceeds by just mixing two components under reflux in mesitylene to give the corresponding α-sulfur-substituted ketones in good yields.

Transition-metal-catalyzed cross-coupling reactions of organometallic compounds with organic electrophiles are very powerful methods for the construction of carbon–carbon bonds.[1] Significant synthetic and mechanistic progress in this area has been made during the past few decades.

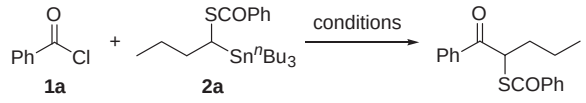
The Stille cross-coupling reaction is one of the most useful and well-documented cross-coupling reactions.[2] The ease of accessibility of various organostannanes, the mildness of the reaction conditions, and the tolerance of functional groups make it possible to build up complex molecules. As a consequence of extensive studies on the Stille cross-coupling reaction, it has been shown that various kinds of stannane/electrophile combinations can be applied to the coupling reaction, and these advances enhance synthetic utility of the reaction.

α-Heteroatom-substituted alkylstannanes are one of the most attractive nucleophiles in the Stille cross-coupling reaction because an alkyl chain with an α-heteroatom functionality can be introduced into the products. In this regard, it has been demonstrated that α-oxygen- and nitrogen-substituted alkylstannanes undergo the coupling reaction with various organic halides to afford the corresponding coupling products.[3–6]

Recently, we have devoted considerable effort to expanding the scope of the reactions using α-heteroatom-substituted alkylstannenes and alkylsilanes as nucleophiles,[7] and reported that α-sulfur-substituted alkylstannenes react with imines to give 1,2-amino sulfide derivatives.[7b] Here, we have anticipated that α-sulfur-substituted alkylstannanes would react with acid chlorides as electrophiles under the proper conditions to produce α-sulfur-substituted ketones, which are useful intermediates in organic synthesis.[8] In this paper, we will present a convenient, catalyst-free cross-coupling reaction of α-sulfur-substituted alkylstannanes with acid chlorides.

At first, we examined the reaction of α-sulfur-substituted alkylstannanes **2a** with benzoyl chloride (**1a**) under the conditions reported by Falck et al.,[5b] and it was found that the desired cross-coupling reaction occurred and the corresponding α-sulfur-substituted ketone **3a** was obtained in 33% yield (Table 1, Entry 1). It is interesting that CuCN alone could catalyze the reaction and improve the yield (Entry 2). On the other hand, the use of $Cu(OTf)_2$, which is the most effective mediator in our previous reports,[7] did not give a good result in the present case (Entry 3). During subsequent examination of reaction conditions, however, we noticed that the catalyst was not necessarily required for the reaction. Accordingly, heating the reaction mixture of **1a** and **2a** in toluene at 75 °C for 24 h in the absence of the catalyst furnished **3a** in 16% yield although a considerable amount of **2a** remained unchanged (Entry 4). This result prompted us to further investigate the cross-coupling reaction under catalyst-free conditions because the reaction can be conveniently carried out. To overcome the low reactivity of **2a**, the reaction was performed under reflux in different solvents (Entries 5–8). Refluxing a mixture of **1a** and **2a** in toluene afforded **3a** in 77% yield although the reaction was still sluggish (Entry 5). Gratifyingly, it was found that the use of mesitylene as a solvent could further improve both the yield and the reaction rate (Entry 6). Polar solvents such as dioxane and *N*,*N*-dimethylformamide proved to be less effective for this reaction (Entries 7 and 8).

Table 1. Optimization of reaction conditions[a]

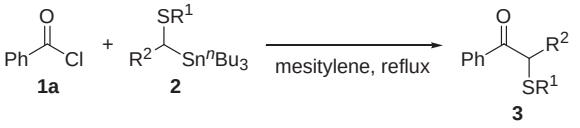


Entry	Conditions	Yield/%
1	$PdCl_2(PPh_3)_2$ (4 mol %), CuCN (8 mol %), toluene, 75 °C, 24 h	33
2	CuCN (8 mol %), toluene, 75 °C, 24 h	60
3	$Cu(OTf)_2$ (8 mol %), toluene, 75 °C, 6 h	22
4	toluene, 75 °C, 24 h	16
5	toluene, reflux, 24 h	77
6	mesitylene, reflux, 1 h	87
7	dioxane, reflux, 24 h	64
8	*N*,*N*-dimethylformamide, reflux, 6 h	0

[a]Molar ratio; **1a**:**2a** = 1.2:1.0.

With the optimized conditions (reflux in mesitylene, Entry 6, Table 1), we then examined the effect of substituents of stannanes.[9] As summarized in Table 2, various stannanes could be used for the coupling reaction. When an acetyl-substituted stannane **2b** was allowed to react with **1a**, the corresponding product **3b** was obtained in 80% yield (Entry 2). The ethoxythiocarbonyl-substituted stannanes **2c** produced **3c** in 85% yield (Entry 3) whereas *N*,*N*-diethylthiocarbamoyl-substituted stannanes **2d** afforded **3d** in somewhat lower yield (68%, Entry 4). Stannanes having either a phenyl or methyl group on the sulfur, such as **2e** and **2f**, were found to be inferior to **2a**–**2d** (Entries 5 and 6). From these results, higher reactivity of **2a**–**2d** compared to **2e** and **2f** could be attributed to intramolecular coordination of the carbonyl oxygen or the thiocarbonyl sulfur to the tin atom, which makes the stannanes more nucleophilic. Next, we tested the reactions of stannanes bearing an isopropyl or a phenyl group at the α-carbon with **1a**. As a result, **3g** and **3h** were obtained in 87 and 84% yield, respectively (Entries 7 and 8). In addition, an

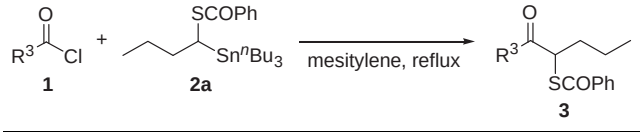
Table 2. Effect of substituents of stannanes **2**[a]



Entry	Stannane **2**			Time/h	Product **3**	
		R^1	R^2			Yield/%
1	**2a**	COPh	*n*-Pr	1	**3a**	87
2	**2b**	COMe	*n*-Pr	6	**3b**	80
3	**2c**	CSOEt	*n*-Pr	1	**3c**	85
4	**2d**	$CSNEt_2$	*n*-Pr	2	**3d**	68
5	**2e**	Ph	*n*-Pr	24	**3e**	37
6	**2f**	Me	*n*-Pr	6	**3f**	34
7	**2g**	COPh	*i*-Pr	1	**3g**	87
8	**2h**	COPh	Ph	1	**3h**	84
9	**2i**	COPh	H	1	**3i**	74

[a]Molar ratio; **1a**:**2** = 1.2:1.0.

Table 3. Cross-coupling reactions of **2a** with various acid chlorides **1**[a]



Entry	Acid Chloride **1**		Time/h	Product **3**	
		R^3			Yield/%
1	**1a**	Ph	1	**3a**	87
2	**1b**	*p*-$MeOC_6H_4$	1	**3j**	61
3	**1c**	*p*-ClC_6H_4	1	**3k**	69
4	**1d**	(*E*)-styryl	1	**3l**	68
5[b]	**1e**	Me	2	**3m**	55
6	**1f**	*n*-C_7H_{15}	1	**3n**	67
7	**1g**	*c*-C_6H_{11}	1	**3o**	72

[a]Molar ratio; **1**:**2a** = 1.2:1.0. [b]Molar ratio; **1e**:**2a** = 5.0:1.0.

unsubstituted stannane **3i** also worked well in the cross-coupling reaction to furnish **3i** in 74% yield (Entry 9).

Finally, we examined the scope of the reactions of **2a** with the representative acid chlorides, and the results are shown in Table 3.[11] In all cases, moderate to good yields were achieved under the optimized conditions. Aromatic acid chlorides with both electron-donating and electron-withdrawing substituents at the para-position, such as **1b** and **1c**, reacted smoothly with **2a** to afford **3j** and **3k** in 61 and 69% yield, respectively (Entries 2 and 3). Not only aromatic acid chlorides but also an α,β-unsaturated acid chloride **1d** could be used for the reaction (68%, Entry 4). Furthermore, alkanoic acid chlorides **1e**–**1g** were found to be good electrophiles in the present coupling reaction (Entries 5–7).

In summary, we have developed a thermal cross-coupling reaction of α-sulfur-substituted alkylstannanes with acid chlorides. Because the reaction proceeds without catalysts, this method provides a new, convenient access to α-sulfur-substituted ketones. Development of a catalytic version of the present cross-coupling reaction under milder conditions is in progress.

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

References and Notes

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9 These stannanes were prepared by nucleophilic substitution of sulfur nucleophiles with methanesulfonates of α-hydroxy alkylstannanes. A representative procedure for **2a**: To a cooled (0 °C) solution of tributyl(1-hydroxybutyl)stannane (5.7 g, 16 mmol), which was prepared from butanal and tributylstannyllithium by the literature procedure,[5b] in CH_2Cl_2 (40 mL) was added Et_3N (2.8 mL, 20 mmol) and methanesulfonyl chloride (1.3 mL, 17 mmol), sequentially. The reaction mixture was stirred for 2 h at this temperature and then the reaction was quenched with an ice–water mixture. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution followed by brine, dried over Na_2SO_4. Concentration under reduced pressure afforded the corresponding methanesulfonate (6.9 g, 97%). To a mixture of thiobenzoic acid (2.4 mL, 20 mmol) and DBU (3.9 mL, 26 mmol) in DMF (10 mL) at room temperature was added a solution of the methanesulfonate (5.6 g, 13 mmol) in DMF (30 mL).[10] The reaction mixture was stirred for 1 h and then the reaction was quenched with water and diluted with ether. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (hexane) followed by Kugelrohr distillation (190 °C/0.3 mmHg) afforded **2a** (4.9 g, 78%).
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11 A typical experimental procedure (Table 3, Entry 1): A mixture of **1a** (17 mg, 0.12 mmol) and **2a** (48 mg, 0.10 mmol) in mesitylene (1.5 mL) was refluxed for 1 h. The resulting mixture was diluted with hexane (1 mL) and passed through a silica gel short column to remove the bulk of mesitylene (hexane to hexane/AcOEt = 5/1). The crude product was purified by preparative thin layer chromatography (hexane/AcOEt = 5/1) to give **3a** (26 mg, 87%).

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