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Tetraethylammonium Bromide-Catalyzed Oxidative Thioesterification of Aldehydes and Alcohols

Xuebin Zhu,[a] Yan Shi,[a] Haibin Mao,[a] Yixiang Cheng,[a] and Chengjian Zhu[a,b,*]

[a] School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093,People's Republic of China
E-mail: cjzhu@nju.edu.cn
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Shanghai 200032, People's Republic of China

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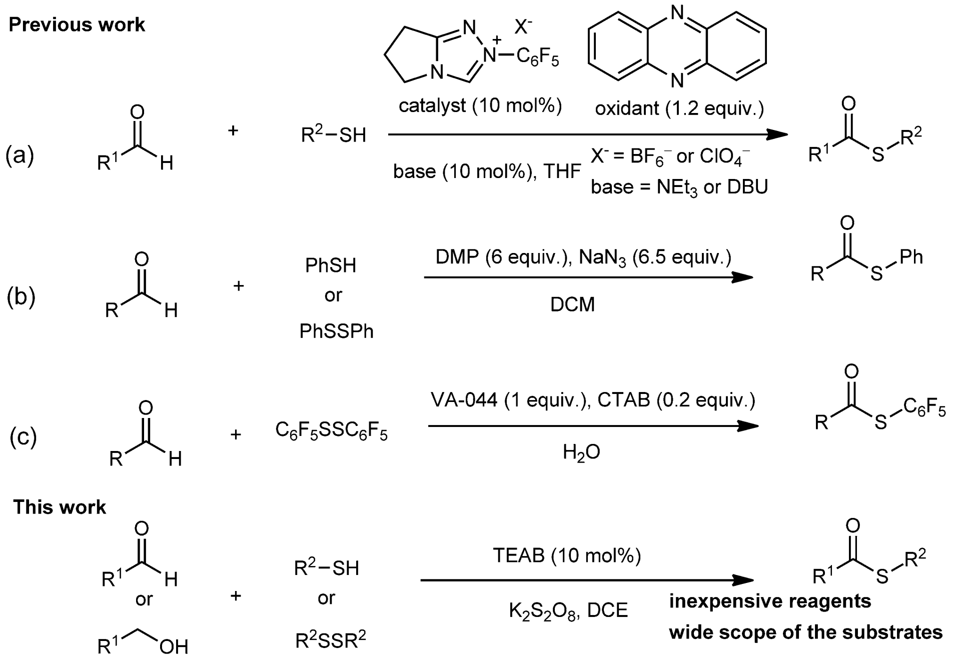
Abstract: A metal-free, tetraethylammonium bromide-catalyzed oxidative coupling of aldehydes or alcohols with thiophenols or disulfides has been developed. This protocol affords an efficient and inexpensive approach to the synthesis of a wide range of thioesters in high yields.

Keywords: metal-free conditions; oxidative coupling; tetraalkylammonium bromides; thioesterification

As a category of activated carboxylic acid derivatives, thioesters are very useful in organic synthesis and synthetic biology. Not only do they play important roles in various biological processes,[1] but they are also versatile building blocks for the construction of various natural products.[2] Inspired by these important scaffolds, in the past few years, some significant methods for producing thioesters have been subsequently developed. Among these approaches, the thioesterifications of carboxylic acid derivatives with sulfocompounds are the most common.[3] However, the direct oxidative thioesterification of aldehydes or alcohols is still largely elusive. To the best of our knowledge,[4] the available thioesterifications with aldehydes usually require the use of azide intermediates,[5] azo-type radical initiators[6] and carbene catalysts[7] (Scheme 1). These methods often suffer from limitations, such as low scope of the substrates, complex systems, expen-

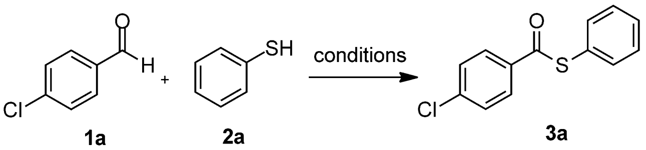


Scheme 1. Thioesterifications of aldehydes or alcohols.

sive or hazardous reagents. The search for direct oxidative thioesterifications of aldehydes or alcohols with regard to a simple, practical and general methodology is of great importance. As part of our continuing interest in metal-free, organocatalyzed oxidative coupling reactions,[8] we wished to develop a simple and practical protocol to accomplish the thioesterification with aldehydes or alcohols. The developed method has a broad substrate scope, simple reaction conditions and gives high yields.

Our initial attempt started with the reaction of 4-chlorobenzaldehyde **1a** and thiophenol **2a** in the presence of T-HYDRO at 90 °C under an argon atmosphere (Table 1). To our delight, the reaction could take place under the catalysis of several commonly used metal catalysts, in spite of the low yields (Table 1, entries 1–4). Then, it was found that the reaction could be improved by using a tetraalkylammonium salt, TBAB, as the catalyst (Table 1, entry 5). A 28% yield was also obtained in the absence of the catalyst (Table 1, entry 6). Subsequently, we examined the efficiency of a number of oxidants under the catalysis of TBAB as shown in Table 1. It was found that $K_2S_2O_8$ was optimal to give the product **3a** in 72% yield (Table 1, entry 9). The reaction afforded the highest yield when performed at 90 °C. Temperatures lower or higher than that were deleterious to the reaction (Table 1, entries 12 and 13).

Table 1. The oxdative thioesterification of 4-chlorobenzaldehyde with thiophenol.[a]



Entry	Catalyst	Oxidant	Time [h]	Yield[b] [%]
1	CuI	T-HYDRO	12	21
2	$CuCl_2$	T-HYDRO	12	18
3	$FeCl_3{\cdot}6H_2O$	T-HYDRO	12	23
4	$ZnBr_2$	T-HYDRO	12	21
5	TBAB	T-HYDRO	12	36
6	none	T-HYDRO	20	28
7	TBAB	TBHP	12	58
8	TBAB	H_2O_2	12	0
9	TBAB	$K_2S_2O_8$	40	72
10	TBAB	Oxzone	40	0
11	TBAB	$PhI(OAc)_2$	40	0
12[c]	TBAB	$K_2S_2O_8$	80	48
13[d]	TBAB	$K_2S_2O_8$	30	70
14	TBAI	$K_2S_2O_8$	40	60
15	TBAC	$K_2S_2O_8$	40	56
16	I_2	$K_2S_2O_8$	40	44
17	**TEAB**	**$K_2S_2O_8$**	**40**	**92**
18	none	$K_2S_2O_8$	40	0
19[e]	TEAB	$K_2S_2O_8$	40	91

[a] *Reaction conditions:* **1a** (0.2 mmol), **2a** (1.1 equiv.), catalyst (10 mol%), oxidant (2.2 equiv.), DCE (1 mL), under argon, 90 °C. TBAB = $(n\text{-}Bu)_4NBr$; TBAI = $(n\text{-}Bu)_4NI$; TBAC = $(n\text{-}Bu)_4NCl$; TEAB = Et_4NBr; T-HYDRO: *tert*-butyl hydroperoxide solution 70 wt% in H_2O; TBHP = *tert*-butyl hydroperoxide solution 5.5 M in decane.

[b] Isolated yields.

[c] At 70 °C.

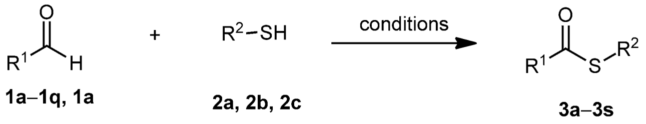
[d] At 110 °C.

[e] The scale of the reaction was increased to 10 mmol (**1a**).

The effect of solvents was also investigated, and DCE was proved to be the optimal solvent. Other solvents furnished the product in poor yields (see the Supporting Information). We further examined several different tetraalkylammonium salts. It was found that TEAB showed the best activity (Table 1, entry 17). The use of iodine as catalyst delivered the product with moderate yield (Table 1, entry 16). Finally, the optimal reaction conditions were established: TEAB (10 mol%) and $K_2S_2O_8$ (2.2 equiv.) under argon in DCE at 90 °C for 40 h. The reaction was scalable, and nearly the same yield was obtained on a larger scale (Table 1, entry 19).

With the optimized conditions in hand, the substrate scope of the reaction with aldehydes and thiols was examined as shown in Table 2. It was found that a wide range of aromatic aldehydes bearing both elec-

Table 2. Scope of the reaction with aldehydes and thiols.[a]



Entry	R^1	R^2	Product	Yield[b] [%]
1	$4\text{-}ClC_6H_4$	C_6H_5	**3a**	92
2	$2\text{-}ClC_6H_4$	C_6H_5	**3b**	90
3	$3\text{-}ClC_6H_4$	C_6H_5	**3c**	85
4	$3\text{-}BrC_6H_4$	C_6H_5	**3d**	82
5	C_6H_5	C_6H_5	**3e**	90
6	$4\text{-}MeC_6H_4$	C_6H_5	**3f**	92
7	2-naphthyl	C_6H_5	**3g**	80
8	$4\text{-}FC_6H_4$	C_6H_5	**3h**	78
9	$3\text{-}O_2NC_6H_4$	C_6H_5	**3i**	75
10	$4\text{-}NCC_6H_4$	C_6H_5	**3j**	68
11	$2\text{-}MeOC_6H_4$	C_6H_5	**3k**	86
12	$4\text{-}MeOC_6H_4$	C_6H_5	**3l**	94
13	2-furyl	C_6H_5	**3m**	84
14	2-thienyl	C_6H_5	**3n**	80
15	3-pyridyl	C_6H_5	**3o**	0
16	*n*-Bu	C_6H_5	**3p**	82
17	$C_6H_5CH_2CH_2$	C_6H_5	**3q**	80
18	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	**3r**	88
19	$4\text{-}ClC_6H_4$	Bn	**3s**	78

[a] *Reaction conditions:* **1** (0.2 mmol), **2** (1.1 equiv.), TEAB (10 mol%), $K_2S_2O_8$ (2.2 equiv.), DCE (1 mL), under argon, 90 °C, 40 h.

[b] Isolated yields.

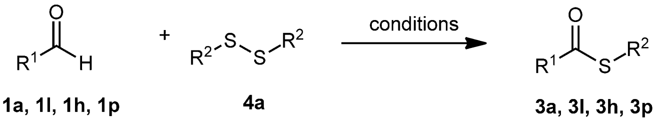
tron-donating and electron-withdrawing groups could be used regardless of their substituent positions to give the corresponding thioesters **3a**–**3l** in moderate to excellent yields (Table 2, entries 1–12), and obviously aromatic aldehydes bearing strong electron-withdrawing substituents on the aromatic ring gave lower yields (Table 2, entries 8–10). Heteroaryl aldehydes such as furfural and 2-thienaldehyde could also be used to afford the thioesters **3m** and **3n** in good yields (Table 2, entries 13 and 14) while 3-pyridinecarboxaldehyde gave no product (Table 2, entry 15). Aliphatic aldehydes were also compatible in the reaction to give products **3p** and **3q** in good yields. With regard to the thiols used, we found that both aryl thiols **2a** and **2b** and the alkyl thiol **2c** were compatible (Table 2, entries 1, 18, and 19).

As disulfides hold the advantages of easy operation, less odour and high stability in comparison to thiols, we conceived to further extend the reaction to disulfides. To our delight, the reaction could also proceed easily to give even better results (Table 3).

Considering the stability and the availability of alcohols, we next studied the thioesterifications of alcohols with sulfur compounds. Several different substituted aryl alcohols were allowed to react with thiophenol **2a** and disulfide **4a**, affording the corresponding products in good yields (Table 4, entries 1–11, and 13). However, when the aliphatic alcohol **5p** was used, only a trace of product was obtained (Table 4, entry 12).

Control experiments for the mechanistic studies were carried out as shown in Scheme 2. When a mixture of 4-chlorobenzaldehyde (**1a**) and thiophenol (**2a**) was subjected to the standard reaction conditions in the presence of the radical scavenger TEMPO (Scheme 2, conditions 1), no reaction was observed, indicating that this reaction involves radical intermediates. Performing the reaction with the catalyst KBr in place of TEAB failed to produce any product (Scheme 2, conditions 2). Additionally, the reaction could be carried out smoothly using the bis(tetraethylammonium) peroxydisulfate $(Et_4N)_2S_2O_8$,[9] and this gave the product **3a** in 76% yield (Scheme 2, conditions 3). These results reveal that the quaternary ammonium cationic group is a critical part of the catalyst system.

Table 3. Scope of the reaction with aldehydes and disulfide.[a]

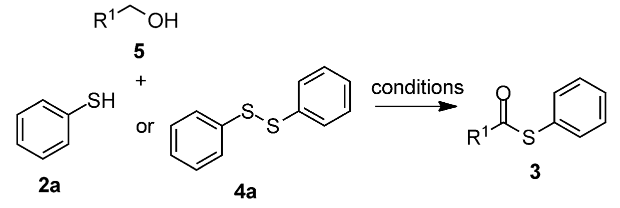


Entry	R^1	R^2	Product	Yield[b] [%]
1	4-ClC_6H_4	C_6H_5	**3a**	92
2	4-$MeOC_6H_4$	C_6H_5	**3l**	96
3	4-FC_6H_4	C_6H_5	**3h**	80
4	*n*-Bu	C_6H_5	**3p**	84

[a] *Reaction conditions:* **1** (0.2 mmol), **4a** (0.55 equiv.), TEAB (10 mol%), $K_2S_2O_8$ (1.2 equiv.), DCE (1 mL), under argon, 90 °C, 40 h.

[b] Isolated yields.

Table 4. Scope of the reaction with alcohols and thiophenol/disulfide.[a]

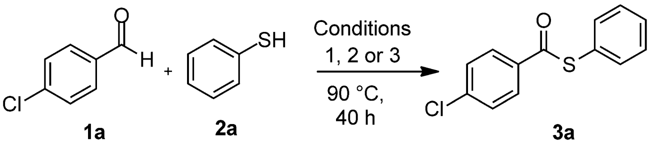


Entry	R^1	**2a/4a**	Product	Yield[b] [%]
1	4-ClC_6H_4	**2a**	**3a**	90
2	2-ClC_6H_4	**2a**	**3b**	89
3	C_6H_5	**2a**	**3e**	87
4	4-MeC_6H_4	**2a**	**3f**	88
5	2-naphthyl	**2a**	**3g**	80
6	4-FC_6H_4	**2a**	**3h**	70
7	3-$O_2NC_6H_4$	**2a**	**3i**	68
8	4-NCC_6H_4	**2a**	**3j**	65
9	4-$MeOC_6H_4$	**2a**	**3l**	90
10	2-furyl	**2a**	**3m**	84
11	2-thienyl	**2a**	**3n**	77
12	*n*-Bu	**2a**	**3p**	trace
13[c]	4-ClC_6H_4	**4a**	**3a**	91

[a] Reaction conditions: **5** (0.2 mmol), **2a** (1.1 equiv.), TEAB (10 mol%), $K_2S_2O_8$ (4.4 equiv.), DCE (1 mL), under argon, 90 °C, 40 h.

[b] Isolated yields.

[c] **4a** (0.55 equiv.) and $K_2S_2O_8$ (3.3 equiv.) were used.



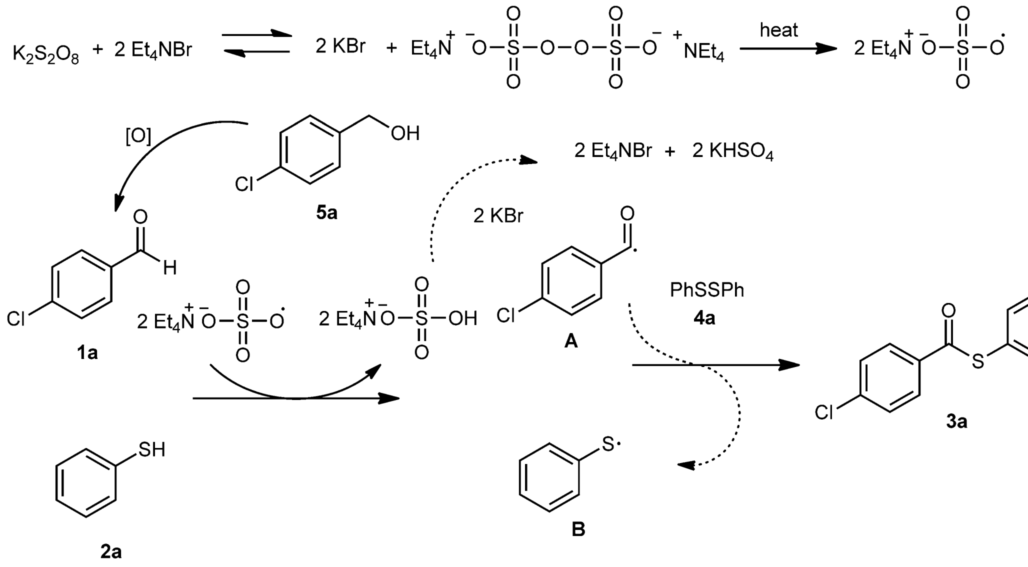
Conditions 1: 10 mol% TEAB, 2.2 equiv. $K_2S_2O_8$, 2.2 equiv. TEMPO — 0%

Conditions 2: 10 mol% KBr, 2.2 equiv. $K_2S_2O_8$ — 0%

Conditions 3: 2.2 equiv. $(Et_4N)_2S_2O_8$ — 76%

Scheme 2. Control experiments.

A plausible mechanistic scenario that is consistent with experimental data and literature precedents[10] is summarized in Scheme 3. The peroxydisulfate was reacted with tetraethylammonium bromide, generating the bis(tetraethylammonium) peroxydisulfate which is readily convertible to the tetraethylammonium sulfate



Scheme 3. Plausible mechanism of reaction.

radical anions. Alcohol **5a** was transformed into aldehyde **1a** in the oxidizing environment, then the tetraethylammonium sulfate radical reacted with the aldehyde **1a** and the thiol **2a** to form an acyl radical **A** and a sulfur radical **B**. Cross-coupling of the radicals **A** with **B** leads to the formation of the corresponding thioester **3a**. Disulfide **4a** could easily trap an acyl radical **A** to generate a target thioester **3a** and a sulfur radical **B**.

In summary, we have developed an efficient method for the synthesis of thioesters by the oxidative coupling of easily available aldehydes or alcohols with thiols or disulfides. Wide scope of the substrates, transition metal-free system, and extreme inexpensiveness of the reagents outline the notable features of the reaction. Exploration of novel oxidative coupling reactions with this catalytic system is under way in our laboratory.

Experimental Section

Typical Procedure for the Thioesterification of Aldehyde 1a with Thiophenol 2a

To a screw-capped test tube equipped with a magnetic stir bar was added aldehyde **1a** (0.2 mmol), thiophenol **2a** (0.22 mmol), TEAB (0.02 mmol) and $K_2S_2O_8$ (0.44 mmol). Then DCE (anhydrous, 1 mL) was added. After being stirred at 90 °C for 40 h under an argon atmosphere, the reaction mixture was filtered and the filtrate was concentrated under vacuum. The resulting residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 20:1 to 15:1) to give **3a** as a white solid; yield: 45.7 mg (92%); mp 59–61 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.96$–7.98 (m, 2H), 7.50–7.52 (m, 2H), 7.45–7.48 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 189.0$, 140.1, 135.1, 135.0, 129.7, 129.1, 128.8, 126.9; MS (ESI): $m/z = 249$ $[M+H]^+$.

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