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# Direct α-Acyloxylation of Organic Sulfides with the Hypervalent (Diacyloxyiodo)benzene/Tetra-*n*-Butylammonium Bromide (TBAB) Reagent Combination

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**A novel metal-free approach to directly synthesize α-acyloxy sulfides from readily available alkyl sulfides utilizing hypervalent (diacyloxyiodo)benzene and TBAB reagent combination is reported. This transformation is characterized by its broad substrate scope in moderate to excellent yields, convenient operating condition and outstanding functional group tolerance.**

Sulfur-containing organic compounds have been attracting more and more interest due to their essential role in the fields of modern organic synthesis,[1] drug design and discovery,[2] food chemistry[3] and material science.[4] Among common organosulfur compounds, α-acyloxy sulfides[5] and their further oxidative derivatives (α-acyloxy sulfones)[6] have been widely employed as aldehyde or ketone synthons in organic synthesis. Moreover, the ester parts of bifunctional α-acyloxy sulfides can subsequently react with a large variety of external or internal nucleophiles, which provide a convenient method for regiospecific carbon-carbon bond formation.[7c, 7f] Therefore, α-acyloxy sulfides are widely used as valuable synthetic precursors and intermediates, especially in the construction of biologically and industrially useful carbocycles and heterocylces (naturally occurring or unnatural), such as Lamivudine,[8a] Strychnine[8b] and Asteltoxin.[8c]

Over the past decades, there were five general methods for the preparation of α-acyloxy sulfides (Scheme 1): (1) Pummerer-type rearrangement of alkyl sulfoxides;[7] (2) the nucleophilic reaction of α-substituted alkyl sulfides;[9] (3) the *anti*-Markovnikov addition of vinyl esters with arylthiols;[10] (4) addition of aryl disulfides with (acyloxymethyl)magnesium chlorides;[11] (5) the anodic oxidation of sulfides.[12]

Stoichiometric hypervalent (diacyloxyiodo)benzene has been frequently used in the direct acyloxylation of C($sp^3$)–H

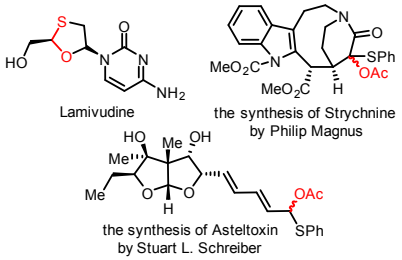
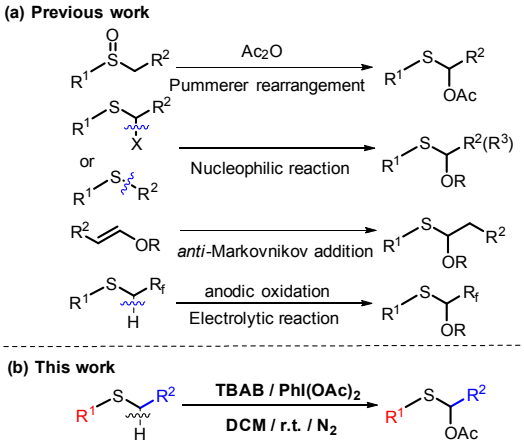



**Figure 1** Examples of α-acyloxy sulfides as valuable intermediates in natural products.




**Scheme 1** Exiting methods for synthesize the α-acyloxy sulfides.

bonds recently. In this regard, various directing groups, such as picolinamide,[13] pyridine,[14] oxime,[14,15] 8-aminoquinoline,[16] *S*-methyl-*S*-2-pyridyl-sulfoximine,[17] Boc-protected *N*-methylamine,[18] *N*2-pyridine-1,2,3-triazole-4-carboxylic acid[19] and 1-aminoanthraquinone,[20] have been successfully utilized for transition-metal-catalyzed chelate-directed oxidative functionalization of C($sp^3$)–H bonds in conjunction with $PhI(OAc)_2$, giving rise to acetoxylated products in excellent yields and extremely high selectivities. In addition, the

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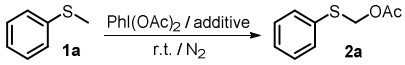
acyloxylation reactions of substrates with activated $C_{sp3}$–H bonds (benzylic position[21] or α-position relative to an electron-withdrawing group[22]) in presence of $PhI(OAc)_2$ have also been emphasized in literatures. Despite the advances in this field, the ability of hypervalent (diacyloxyiodo)benzene to introduce an acyloxy group into organic sulfides has been virtually unexplored, which is probably because organic sulfides are easily oxidized to the corresponding sulfoxides.[23] As a continuation of our research interest in the application of hypervalent iodine reagents in the rapid and efficient preparation of useful sulfur-containing compounds,[24] this work herein report a direct and selective acyloxylation of a variety of sulfides with the combination of hypervalent (diacyloxyiodo)benzene and tetra-*n*-butyl ammonium bromide (TBAB). It is noteworthy that sulfoxides as the traditional precursors of Pummerer reaction[8] need not be synthesized, whilst most of organic sulfides are commercially available or easily prepared. To the best of our knowledge, only relatively rare electrochemical approaches[12] have been reported thus far to construct the high-value α-acyloxy sulfides from readily available sulfides.

**Table 1** Optimization of the reaction conditions[a,b]

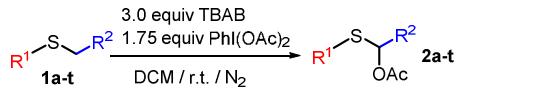


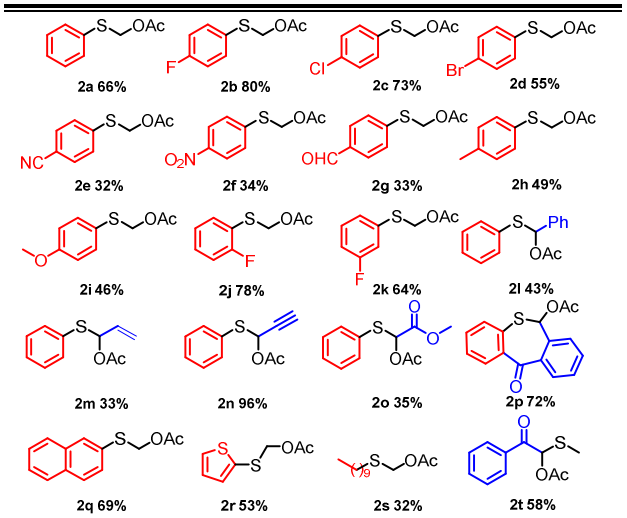

| entry | $PhI(OAc)_2$ (equiv) | additive (equiv) | solvent | yield (%)[b] |
|---|---|---|---|---|
| 1 | 2.0 | *n*-$Bu_4NBr$ (1.0) | $CH_2Cl_2$ | 22 |
| 2 | 2.0 | -- | $CH_2Cl_2$ | <5 |
| 3 | 2.0 | *n*-$Bu_4NBr$ (0.5) | $CH_2Cl_2$ | <10 |
| 4 | 2.0 | *n*-$Bu_4NBr$ (3.0) | $CH_2Cl_2$ | 60 |
| 5 | 2.0 | *n*-$Bu_4NF$ (3.0) | $CH_2Cl_2$ | 0 |
| 6 | 2.0 | *n*-$Bu_4NCl$ (3.0) | $CH_2Cl_2$ | 0 |
| 7 | 2.0 | *n*-$Bu_4NI$ (3.0) | $CH_2Cl_2$ | <5 |
| 8 | 2.0 | *n*-$Bu_4NOAc$ (3.0) | $CH_2Cl_2$ | <5 |
| 9 | 2.0 | NaBr (3.0) | $CH_2Cl_2$ | 0 |
| 10 | 2.0 | *n*-$Bu_4NBr$ (3.0) | toluene | 36 |
| 11 | 2.0 | *n*-$Bu_4NBr$ (3.0) | THF | 0 |
| 12 | 1.75 | *n*-$Bu_4NBr$ (3.0) | $CH_2Cl_2$ | 66 |
| 13 | 4.0 | *n*-$Bu_4NBr$ (3.0) | $CH_2Cl_2$ | <10 |
| 14 | 3.0 | *n*-$Bu_4NBr$ (3.0) | $CH_2Cl_2$ | 19 |
| 15 | 2.5 | *n*-$Bu_4NBr$ (3.0) | $CH_2Cl_2$ | 35 |
| 16 | 1.5 | *n*-$Bu_4NBr$ (3.0) | $CH_2Cl_2$ | 57 |
| 17 | 1.0 | *n*-$Bu_4NBr$ (3.0) | $CH_2Cl_2$ | 35 |

[a]Reaction conditions: thioanisole (0.5 mmol), $PhI(OAc)_2$, additive, solvent (2.0 mL), room temperature. [b] Isolated yield.

We initiated our investigation by choosing thioanisole **1a** and 2 equivalents of $PhI(OAc)_2$ as the model substrates for the target α-acyloxylation reaction in the presence of 1 equivalent of TBAB in $CH_2Cl_2$ at room temperature for 6 h (Table 1, entry 1). To our delight, the desired product **2a** was isolated, albeit in only 22% yield. Importantly, the controlled reaction in the absence of tetra-*n*-butyl ammonium bromide (Table 1, entry 2) was carried out and clearly showed that only trace amount of expected product **2a** was formed. By adjusting the amount of TBAB (Table 1, entries 3-4) to 3 equivalents, the α-acyloxylation product **2a** can be formed as the dominant product (60% yield; Table 1, entry 4). The excessive amounts of TBAB is necessary because of the competing oxidation of the sulfur with the $PhI(OAc)_2$. The increase of the amount of TBAB is beneficial to the production of tetra-*n*-butylammonium [di(acyloxy)bromated (I)], which might be the critical intermediate in this reaction. In stark contrast, the replacement of TBAB by other additives was completely unsuccessful and led to the formation of expected product **2a** in less than 5% yield (Table 1, entries 5-9), confirming the unique reactivity of the $PhI(OAc)_2$/TBAB system. Subsequently, other solvents, including toluene and THF, were also surveyed but substantially decreased the reaction efficiency (Table 1, entries 10-11). Finally, the amount of $PhI(OAc)_2$ can be reduced to 1.75 equivalents, which led to improvement in both starting material consumption and product formation providing a slightly higher yield of 66% (Table 1, entry 12). Interestingly, it was found that the improper substrates ratio between thioanisole **1a** and $PhI(OAc)_2$ had negative effects on the reaction (Table 1, entries 13-17). Therefore, the condition described in entry 12 in Table 1 was chosen as the standard condition to verify the general applicability of the present methodology. To our disappointment, methyl phenyl sulfone or methyl phenyl sulfoxide failed to yield the corresponding α-acyloxylated sulfone or sulfoxide under the optimized condition, suggesting the requirement of two lone pairs on the sulfur for the α-acyloxylation transformation.

**Table 2** Scope of thioether derivatives[a,b]




[a]Reaction conditions: thioether (0.5 mmol), TBAB (1.5 mmol), $PhI(OAc)_2$ (0.875 mmol), DCM (2.0 mL), room temperature. [b] Isolated yield.

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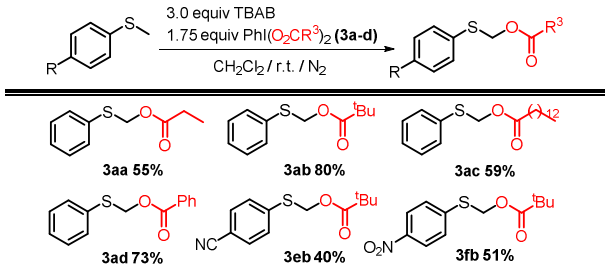
With the optimized reaction condition in hand, we first examined the scope of sulfide substrates (Table 2). Various alkyl phenyl sulfides (**1a**-**1i**) with different substituents on the phenyl ring, including electron-donating and electron-withdrawing groups, can react smoothly with the combination of $PhI(OAc)_2$ and TBAB to afford the corresponding α-acyloxylation products in yields from 32% to 80%. Moreover, the introduction of the substituents in *ortho*, *meta*, and *para* positions of the phenyl group is in fact also tolerated under the standard reaction condition (**1j, 1k** and **1b**). Remarkably, this transformation is compatible with a variety of synthetically valuable functional groups (**1b**-**1o**), including fluoro, chloro, bromo, methoxy, nitro, cyano, carbonyl, alkenyl and alkynyl, thus offering ample opportunities for further derivation. Among these, there are still several sulfide substrates containing cyano (**1e**), nitro (**1f**) and carbonyl (**1g**), can get corresponding α-acyloxylation products with low yields, which is mainly because of the competing oxidation of the sulfur with the $PhI(OAc)_2$. In particular, sulfide **1p**, possessing the important dibenzo[b,e]thiepin framework[25] with a broad-ranging pharmacological potential, can also provide the desired α-acyloxylation product **2p** in 72% yield. Besides the benzene ring, naphthyl-substituted sulfide (**1q**) and heteroaryl-substituted sulfide (**1r**) are also amenable to this transformation. Likewise, unsymmetrical alkyl methyl sulfides also proved to be suitable substrates for this transformation. For *n*-decyl methyl sulfide **1s**, excellent regioselectivity favoring functionalization of the less hindered C–H bond was observed and sole α-acyloxylation product **2s** was achieved in 32% yield. On the contrary, acetoxylation of 2-(methylthio)-1-phenylethan-1-one **1t** took place only at the more sterically accessible position, which is mainly because of the further advantage in the formation of the more stable thionium ion, and a 58% isolated yield of α-acyloxylation product **2t** was obtained. Notably, α-acyloxy β-ketosulfide products **2o** and **2t** might be easily rearranged into α-acyloxy thioesters as versatile building blocks *via* acyl migration in enolate form.[26] Based on the results for the above different regioselectivities between $2^o$ and $3^o$ C–H bonds, we presumed that it perhaps originated from the stability of the thioniumion intermediates.

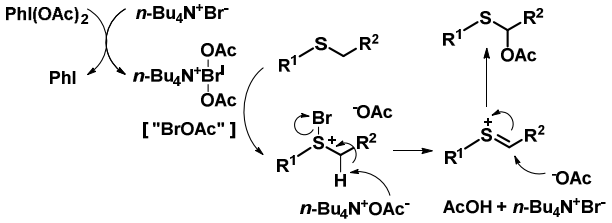
**Table 3** Scope of hypervalent iodine (III) reagents derivatives[a,b]




[a]Following the general procedure. [b] Isolated yield.

Next, we evaluated α-acyloxylation between methyl phenyl sulfide **1a** and other hypervalent (diacyloxyiodo)benzenes with the aid of tetra-*n*-butyl ammonium bromide. As expected, all four hypervalent (diacyloxyiodo)benzenes smoothly participated in this transformation leading to the desired products in good yields (Table 3). Higher yields obtained than $PhI(OAc)_2$ implied that we can select the appropriate hypervalent iodine reagents as the acylate source (e. g., hypervalent (dipivaloxyiodo)benzene) to efficiently afford the analogous α-acyloxy sulfide products, which might give a handgrip for a variety of further transformations in organic synthesis. Actually, the clearly improved yields were indeed observed as illustrated in Table 3 (**3eb** and **3fb**).

Although further studies may be still required to discover and understand the mechanism in more detail, on the basis of our present results and the previously reported literatures,[27] a plausible mechanism for this α-acyloxylation transformation, exemplified by the reaction of organic sulfides with $PhI(OAc)_2$/TBAB system, is proposed in Scheme 2. Initially, a highly active intermediate tetra-*n*-butylammonium [di(acyloxy)bromated (I)], which might be really responsible for the α-acyloxylation reactions, is generated by the interaction of hypervalent (diacyloxyiodo)benzene with tetra-*n*-butyl ammonium bromide. As a matter of fact, subjection of methyl phenyl sulfide **1a** in the presence of other tetra-*n*-butyl ammonium salts and NaBr (Table 1, entries 5-9) resulted in less than 5% of the desired product, which is likely a result of inexistence of tetra-*n*-butylammonium [di(acyloxy)bromated (I)] and competitive undesired oxidation.[28] Then, organic sulfides undergoes Br-activation by the nucleophilic attack at the electrophilic bromine centre to form an bromosulfonium salt. Afterwards, deprotonation next to the positively charged sulfur by the acetate anion would lead to the generation of acetic acid and a new thionium ion. The existence of acetic acid has been confirmed by the *in situ* $^1H$ and $^{13}C$ NMR investigation. Finally, the nucleophilic addition of acetate anion to the double C=S bond completes the formation of the α-acyloxy sulfide products. The excess of TBAB for this α-acyloxylation transformation would be indispensable and helpful to avoid the alternative and competing undesired oxidation.[23]




**Scheme 2** Proposed mechanism for the reaction.

In summary, we have developed an unprecedented metal-free α-acyloxylation process of a broad range of alkyl sulfides with the combination of hypervalent (diacyloxyiodo)benzenes and tetra-*n*-butyl ammonium bromide. The key features of the present protocol are metal-free reaction condition, operational simplicity, a wide ranging substrate scope and tolerance of various synthetically useful functional groups. This methodology could also potentially streamline the synthesis by minimizing the unnecessary oxidation operation to organic sulfoxides as the traditional precursors of Pummerer reaction[8]

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and reducing the number of steps. Preliminary studies have shown that the success of this reaction might be mainly attributed to the generation of the tetra-*n*-butylammonium [di(acyloxy)bromated (I)]. Further investigations on mechanistic details as well as other related transformation events are currently underway in our laboratory.

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A novel metal-free approach to directly synthesize α-acyloxy sulfides from readily available alkyl sulfides utilizing hypervalent (diacyloxyiodo)benzene and TBAB reagent combination was developed.