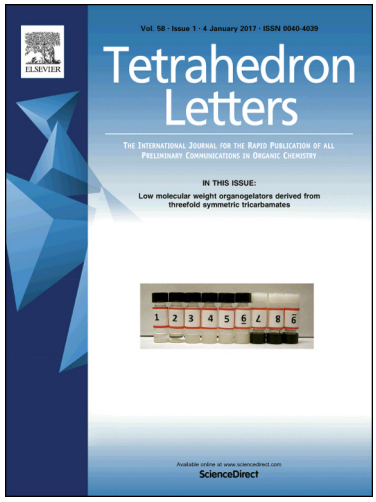

Copper-Catalyzed Pummerer Type Reaction of α-Thio Aryl/Heteroarylacetates: Synthesis of Aryl/Heteroaryl α-Keto Esters

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Graphical Abstract

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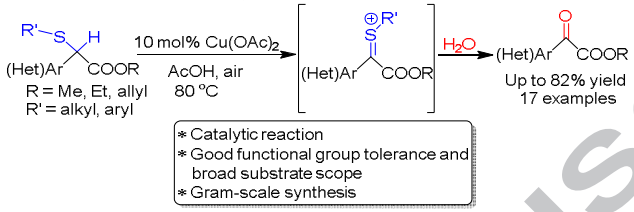

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Copper-Catalyzed Pummerer Type Reaction of α-Thio Aryl/Heteroarylacetates: Synthesis of Aryl/Heteroaryl α-Keto Esters

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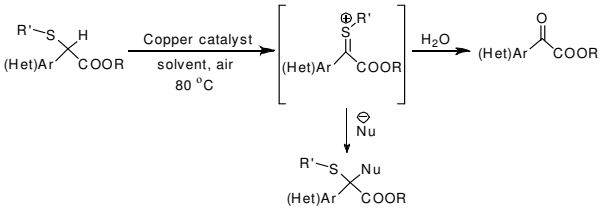
ABSTRACT

A copper catalyzed Pummerer type reaction of α-thio aryl/heteroarylacetates is described for the first time. This transformation represents a new route to synthesize α-keto esters, which are important intermediates for pharmaceuticals and organic synthesis. The reaction proceeds via *in situ* generation of a thionium ion that undergoes hydrolysis to furnish α-keto esters in synthetically viable yields (up to 82%).

Introduction

The Pummerer reaction is a process where an alkyl sulfoxide is activated using acetic anhydride, trifluoroacetic anhydride (TFAA), trifluoromethanesulfonic anhydride (Tf_2O), or silyl chloride, which then undergoes elimination to give a thionium ion.[1] A wide range of nucleophiles such as acetates, arenes, alkenes, amides, and phenols then undergo nucleophilic addition to the *in situ* generated thionium ion.[1,2] The trapping of this ionic intermediate by different nucleophiles has greatly expanded the synthetic utility of the reaction.[3] For example, the Pummerer reaction has been used extensively for the synthesis of thionucleosides,[4] heterocycles,[5] spirocyclic compounds[6] and natural products.[7] In contrast, metal catalyzed Pummerer type reactions of sulfides and sulfoxides are less explored.[8] Moreover, in some cases, stoichiometric amounts of metal catalysts have been used for the reaction.[8a,b]

In continuation of our research interest for the synthesis of organosulfur compounds,[9] it was envisioned that upon treatment with metal catalysts, α-thio aryl/heteroarylacetates would generate a thionium ion *in situ* which could be trapped by a nucleophile (Scheme 1). However, upon treatment with copper catalysts, α-thio aryl/heteroarylacetates were converted into α-keto esters (Scheme 1) which are important intermediates for pharmaceuticals and organic synthesis.[10] Prominent literature reports reveal that α-keto esters are usually prepared by the reaction of Grignard reagents with oxalyl chloride,[11] ethyl α-oxo-1H-imidazole-1-acetate[12] or diethyl oxalate.[13] They are also prepared by the oxidation of α-diazoesters[14] and aryl ketones.[15] In contrast, numerous literature reports are known for the conversion of α-thio carbonyl compounds into α-keto carbonyls.[16] However, to the best of our knowledge, there are no reports regarding the synthesis of α-keto esters *via* C–S bond cleavage of α-thio aryl/heteroarylacetates. Herein, we report a copper-catalyzed Pummerer type reaction of α-thio aryl/heteroarylacetates for the synthesis of aryl/heteroaryl α-keto esters in synthetically viable yields.



Scheme 1. Working hypothesis

Results and discussion

At the outset, we started our investigation with the reaction of methyl 2-((4-bromophenyl)thio)-2-phenylacetate **1a** (1 equiv) with $Cu(OAc)_2$ (10 mol%) in DMF at 80 °C under air. To our delight, methyl 2-oxo-2-phenylacetate **2a** was isolated in 46% yield along with 28% of 1,2-bis(4-bromophenyl)disulfane **3a** as a by-product (Table 1, entry 1). Afterwards, a systematic optimization was carried out using various solvents such as glacial AcOH, DMSO, toluene and H_2O, where glacial AcOH was found to be superior in terms of yield (Entries 2-5). It was observed that 5 mol% catalyst loading afforded the product **2a** in 40% yield (Entry 7).

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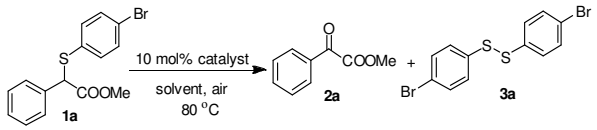
Surprisingly, there was no reaction at room temperature and starting material **1a** was fully recovered (Entry 8). Next, we turned our attention towards the screening of various copper salts for this transformation. Notably, $Cu(OAc)_2$ was the most efficient catalyst, affording product **2a** in 73% yield (Entry 2). It is worth noting that CuOAc could also catalyze the reaction, but furnished **2a** in lower yield (Entry 9) and with unreacted starting material recovered. A trace amount of **2a** was obtained when methyl 2-((4-bromophenyl)thio)-2-phenylacetate **1a** (1 equiv.) was treated with $Cu(OAc)_2$ (10 mol%) in dry toluene under an Ar atmosphere (Entry 15). However, the presence of 4 Å molecular sieves precluded the formation of **2a** (Entry 16). Therefore, based on extensive optimization studies, it was decided to carry out further studies in the presence of $Cu(OAc)_2$ (10 mol%) in glacial AcOH solvent at 80 °C under air.

Table 1. Optimization of Reaction Conditions.[a]



Entry	Catalyst	Solvent	Time (h)	Yield **2a** (%)[b]	Yield **3a** (%)[b]
1	$Cu(OAc)_2$	DMF	50	46	28
2	$Cu(OAc)_2$	AcOH	50	73	27
3	$Cu(OAc)_2$	DMSO	50	48	25
4	$Cu(OAc)_2$	Toluene	55	34	15
5	$Cu(OAc)_2$	H_2O	48	0	0
6	$Cu(OAc)_2$,H_2O	AcOH	50	60	25
7[c]	$Cu(OAc)_2$	AcOH	50	40	16
8[d]	$Cu(OAc)_2$	AcOH	48	0	0
9	CuOAc	AcOH	55	42	20
10	$CuCl_2$	AcOH	55	28	17
11	$CuCl_2$	DMF	48	0	0
12	$Cu(OTf)_2$	AcOH	55	52	29
13	$Cu(OTf)_2$	DMF	55	35	22
14	$Pd(OAc)_2$	AcOH	48	0	0
15[e]	$Cu(OAc)_2$	Toluene	48	trace	trace
16[f]	$Cu(OAc)_2$	Toluene	48	0	0

[a]Reaction conditions: **1a** (0.3 mmol), catalyst (0.03 mmol), solvent (3 mL), 80 °C, under air.

[b]Isolated yield. Products (**2a** and **3a**) were characterized by ^1H, ^{13}C NMR and Mass spectroscopy.

[c]Reaction performed with $Cu(OAc)_2$ (5 mol%).

[d]Reaction performed at rt.

[e]Reaction performed in dry toluene under an Ar atmosphere.

[f]Reaction performed in dry toluene under an Ar atmosphere in the presence of 4 Å molecular sieves.

With the optimized reaction conditions in hand, the substrate scope of the reaction was explored using various α-thio aryl/heteroarylacetates (Fig. 1). It was noted that α-thio aryl/heteroarylacetates **1** underwent the reaction, leading to aryl/heteroaryl α-keto esters **2** in reasonable yields along with disulfides as by-products (Table 2). Interestingly, the different aryl substituents at the C-2 position of α-thio arylacetates **1** have a promising effect on this reaction. It was observed that α-thio arylacetates **1a-b** (Fig. 1) with a phenyl ring at the C-2 position afforded products **2a-b** in 73% and 66% yields, respectively (Table 2). On the other hand, α-thio arylacetates **1c-g** (Fig. 1) with electron donating functional groups (4-Me, 4-OMe) furnished **2c-g** in higher yields than α-thio arylacetate **1l** with an electron withdrawing group (4-NO_2) on the phenyl ring. This could be due to stabilization of the *in situ* generated thionium ion by electron donating groups on the phenyl ring. Additionally, α-thio arylacetates **1h-j** with halogen functional groups (-F, -Cl, -Br), afforded α-keto esters **2h-j** in synthetically viable yields (up to 74%).

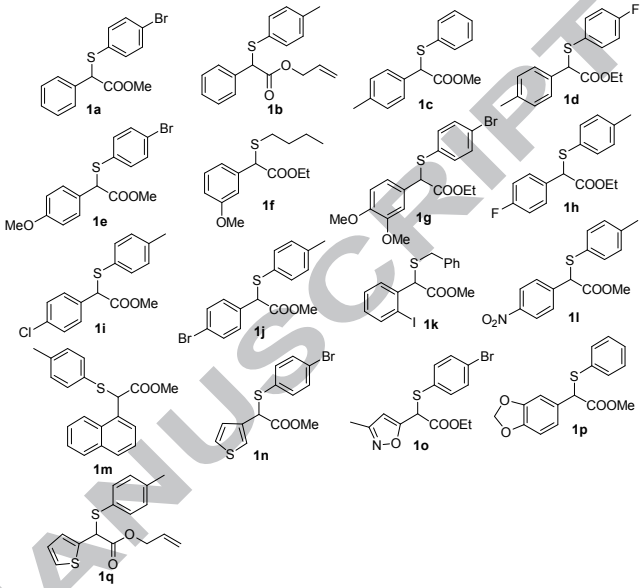
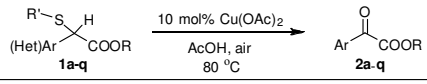
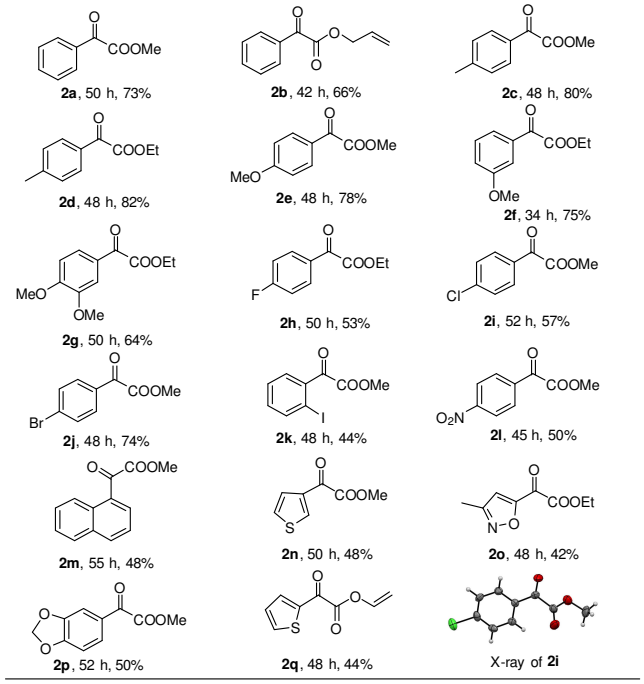


Figure 1. Different α-thio aryl/heteroarylacetates used for the synthesis of aryl/heteroaryl α-keto esters.

The α-thio arylacetate **1f** (Fig. 1) with an alkyl group attached to sulfur afforded α-keto ester **2f** in 75% yield (Table 2). No significant effect was observed when different aryl/alkyl substituents attached to the sulfur in α-thio arylacetates were used.

Table 2. Synthesis of Aryl/Heteroaryl α-Keto Esters.[a,b]



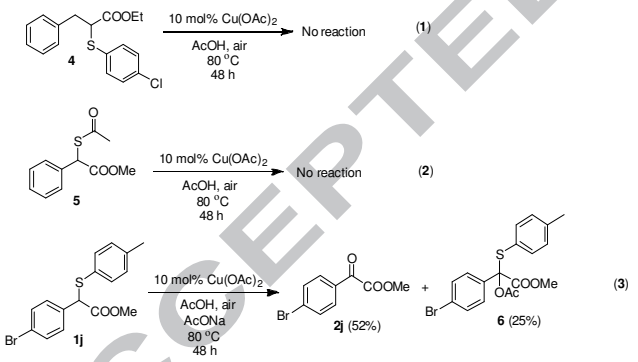


[a]Reaction conditions: **1** (0.3 mmol), $Cu(OAc)_2$ (0.03 mmol), AcOH (3 mL), 80 °C, under air.

[b]Isolated yield. Compounds were characterized by ^{1}H, ^{13}C NMR and Mass spectroscopy.

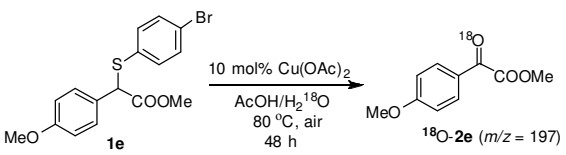
However, lower yields were observed for compound **2k** (44%) and **2m** (48%), clearly suggesting that steric hindrance at the *ortho* position to the phenyl ring has a crucial role in this transformation. Rewardingly, *α*-thio heteroarylacetates **1n-q** with a heteroaromatic moiety at the C-2 position afforded the corresponding *α*-keto esters **2n-q** in moderate yields (up to 50% yields). Recrystallization of **2i** from chloroform produced a single crystal whose structure was confirmed by X-ray analysis (Fig. S1, ESI).[17]

In order to increase the versatility of this methodology, we then directed our efforts to synthesize alkyl *α*-keto esters using the optimized reaction conditions. Towards this, ethyl 2-((4-chlorophenyl)thio)-3-phenylpropanoate **4** was treated with $Cu(OAc)_2$ (10 mol%) in glacial AcOH at 80 °C (Scheme 2, eq 1). Unfortunately, the reaction did not proceed which clearly indicates that only *α*-thio aryl/heteroarylacetates are favorable for this copper catalyzed reaction to afford aryl/heteroaryl *α*-keto esters. Next, to understand the role of the thiol moiety in this reaction, methyl 2-(acetylthio)-2-phenylacetate **5** with an electron withdrawing acetyl group directly attached to the sulfur was subjected to the optimized reaction conditions (Scheme 2, eq 2). However, no reaction was observed, which might be due to the unavailability of the lone pair of electrons on sulfur to participate in the reaction with $Cu(OAc)_2$. To confirm that the copper catalyzed Pummerer type reaction of *α*-thio aryl/heteroarylacetates proceed through *in situ* formation of a thionium ion, methyl 2-(4-bromophenyl)-2-(*p*-tolylthio)acetate **1j** was treated with $Cu(OAc)_2$ (0.1 equiv) in glacial AcOH with the addition of AcONa (1.2 equiv) as an external nucleophile at 80 °C (Scheme 2, eq 3). To our delight, methyl 2-acetoxy-2-(4-bromophenyl)-2-(*p*-tolylthio)acetate **6** was isolated in 25% yield along with methyl 2-(4-bromophenyl)-2-oxoacetate **2j** in 52% yield. The formation of product **6** in this reaction confirms that the reaction proceeds through the *in situ* generated thionium ion.



Scheme 2. Control Experiments.

To gain insight into the reaction mechanism, an isotopic-labelling experiment was performed using $H_2{}^{18}O$. Methyl 2-((4-bromophenyl)thio)-2-(4-methoxyphenyl)acetate **1e** was treated with $Cu(OAc)_2$ (10 mol%) in glacial AcOH at 80 °C in the presence of $H_2{}^{18}O$ (5.0 equiv). Upon reaction completion, the ^{18}O incorporated product was detected by HRMS analysis (see ESI for more details).



Scheme 3. Isotope Labelling Experiment.

The ESI-MS study of the crude reaction mixture of **1a** after 7 h revealed the presence of thionium ion **7** *in situ* (Fig. 2) (see ESI for more details).[18] However, we were unable to isolate species **7** as a single crystal.

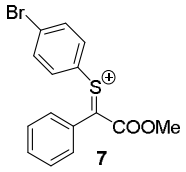
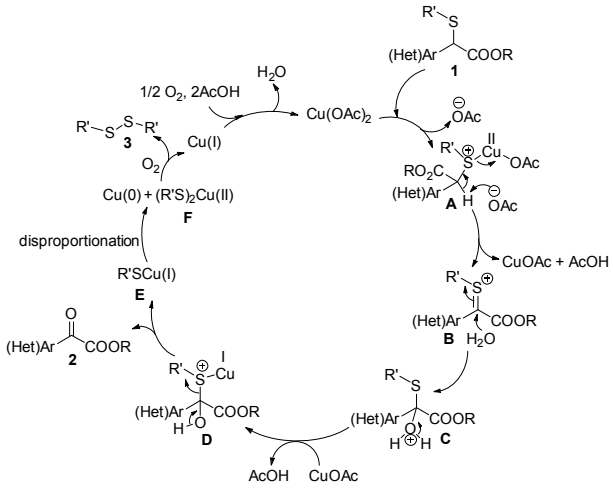


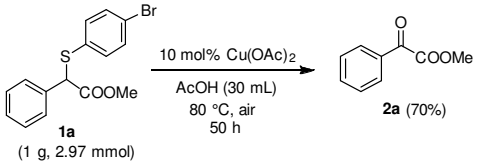
Figure 2. Major species identified using ESI-MS analysis of the reaction mixture of **1a**.

Based on the results shown in Schemes 2 and 3, ESI-MS analysis of the crude reaction mixture of **1a** and previous reports on copper(II)-catalyzed oxidative reactions,[19] we postulate the following catalytic cycle for the copper(II)-catalyzed Pummerer type reaction of *α*-thio aryl/heteroarylacetates (Scheme 4). Initially, the *α*-thio aryl/heteroarylacetate reacts with $Cu(OAc)_2$ to furnish *α*-sulfonium aryl/heteroarylacetate copper(II) species **A**, from which the acetate anion abstracts a proton to generate thionium ion **B** followed by the reduction of Cu(II) to Cu(I) species. Subsequently, nucleophilic addition of H_2O to thionium ion **B** generates species **C**. Next, *in situ* generated CuOAc promotes the removal of sulfur from species **D** to afford *α*-keto ester along with species **E**. Species **E** then undergoes a disproportionation reaction followed by an aerobic oxygen-mediated reductive elimination to generate Cu(I) species along with disulfide as a by-product.[19h] Eventually, the Cu(I) species in the presence of aerobic oxygen and AcOH is converted to $Cu(OAc)_2$,[19g] thereby completing the catalytic cycle (Scheme 4).



Scheme 4. Proposed Catalytic Cycle.

Finally, in order to rationalize the practical applicability of this copper catalyzed Pummerer type reaction of *α*-thio aryl/heteroarylacetates, a gram scale reaction of methyl 2-((4-bromophenyl)thio)-2-pheylacetate **1a** was performed under the optimized reaction conditions (Scheme 5). To our delight, product **2a** was furnished in 70% yield.



Scheme 5. Gram-Scale Reaction.

Conclusions

In summary, we have developed a copper catalyzed Pummerer type reaction of α-thio aryl/heteroarylacetates for the synthesis of aryl/heteroaryl α-keto esters in moderate to good yields. This process tolerates a broad range of functionalized substrates to afford aryl/heteroaryl α-keto esters using catalytic $Cu(OAc)_2$. A gram scale reaction was also performed. The scope and synthetic application of this reaction are currently under study in our laboratory.

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Supplementary Material

Experimental procedures and full spectroscopic data for all compounds, isotope labelling experiment, single crystal X-ray data of **2i**, NMR spectra (^{1}H and ^{13}C) of the starting materials **1a-q**, **4**, **5** and products **2a-q**, **6**, ESI-MS spectra of **7** have been provided in a separate electronic file as a supplementary data.

Highlights

- Pummerer type reaction for the synthesis of the α-keto ester is described.
- The reaction proceeds through the generation of a thionium ion *in situ*.
- The source of oxygen in α-keto ester is confirmed by isotopic-labeling experiment.