Fe_2O_3-catalyzed Pummerer Rearrangement of Acyl Chlorides and Sulfoxides: Facile Synthesis of Alkylthiomethyl Ester

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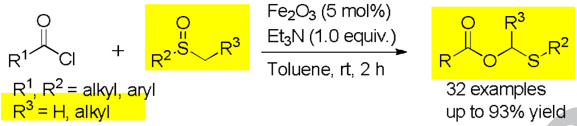

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Fe_2O_3-catalyzed Pummerer Rearrangement of Acyl Chlorides and Sulfoxides: Facile Synthesis of Alkylthiomethyl Ester

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ABSTRACT

A simple, effective approach for the Pummerer rearrangement of acyl chlorides with sulfoxides by using a low-cost and more abundant Fe catalyst has been described. The alkylthiomethyl ester products were prepared in good to excellent yields for a range of different substrates including asymmetrical sulfoxides and acyl chlorides with a variety of functional groups under mild reaction conditions. The reaction features short reaction time, simple manipulation, cheap reagents and a broad substrate scope. Single crystal X-ray analysis of a representative methylthiomethyl (MTM) group containing product was also reported.

Introduction

The incorporation of sulfurized residues into complex molecular architectures has become almost ubiquitous in pharmaceuticals, materials, agricultural chemicals and organic synthesis.[1] In particular, methylthiomethyl (MTM) esters have special chemical property under photochemical conditions involving electron transfer processes.[2] The MTM group could also serve as an important carboxyl protecting group according to its property.[3] The pro-drugs of nonsteroidal anti-inflammatory agents that contain MTM esters groups are more easily absorbable,[4] and some dairy and oil products use MTM esters as the flavor additives.[5] Furthermore, the MTM group could be used in some reductive amination reactions, which would then undergo intramolecular cyclization.[6] Consequently, the development of methods for the construction of MTM group is of great interest for both academic and industrial chemists.

Since the first report in 1909, there are many practical methods to prepare methylthiomethyl esters.[7] Wade reported an approach for the introduction of a valuable methylthiomethyl group that utilized the carboxylic acid react with chloromethyl methyl sulfide in 1978.[8] To get MTM esters, many reagents were used to activate dimethyl sulfoxide such as *tert*-butyl bromide[9] and *N*-chlorosuccinimide.[10] The activated dimethyl sulfoxide could then react with carboxylic acid under different conditions to provide the MTM esters.[11]

During the Pummerer rearrangement, the sulfoxides can be activated by harsh acidic initiators, such as acid anhydride and acyl chloride to generate the thionium ion intermediates. The thionium ions usually act as electrophilic reagents to react with some nucleophiles,[12] which can expand the synthetic utility of the reaction. Therefore, the Pummerer process has been extensively studied and established itself as a very useful method that involves addition of a nucleophile to the thionium ion for C-O bond construction.[13a-d]

Different nucleophiles, such as arenes, alkenes, amides and phenols were used to attack the thionium ions in numerous Pummerer reactions.[14] Moreover, it is an available synthetic strategy to prepare natural and complex heterocyclic compounds[15]. However, most of traditional Pummerer rearrangement require harsh reaction conditions, such as low or high reaction temperature, photolysis and application of microwave. These conditions lead to some limitations on the large scale preparation of MTM ester derivatives. Therefore, the development of low cost and more efficient as well as facile large scale preparation protocols for alkylthiomethyl ester is still desirable and challenging.[13-16] We disclose here a simple and effective method for the iron catalyzed[17] Pummerer rearrangement of acyl chlorides and sulfoxides, providing a facile route for the synthesis of alkylthiomethyl ester.

Results and discussion

The Pummerer rearrangement of benzoyl chloride **1a** with dimethyl sulfoxide (DMSO) **2a** was chosen at the beginning of our investigation as a model reaction. Firstly, the reaction was carried out in the absence of base and metal catalyst in toluene at room temperature under an argon atmosphere for 2 h. But no product was observed (Table 1, entry 1). When 1.0 equiv. triethylamine was added as a base, the desired product was obtained in 20% yield (Table 1, entry 2). Subsequently, optimization of the reaction conditions was aimed at exploring the effectiveness of metal catalyst. A similar yield of **3a** was also obtained when copper powder was used as a catalyst (Table 1,

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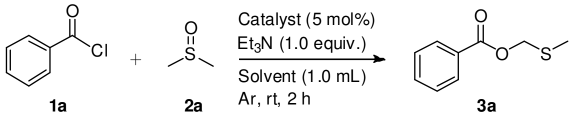
entry 3). To our delight, the yield was improved to 70% when iron powder was utilized instead of copper powder (Table 1, entry 4). Encouraged by these initial results, we further optimized the reaction conditions by using different iron catalysts in different solvents at room temperature. As an alternative iron catalyst, $FeCl_2$ was ineffective for the Pummerer rearrangement, and the yield decreased dramatically (Table 1, entry 5). For comparison, other ferrous catalysts such as $Fe(OAc)_2$, $Fe(acac)_2$ and $Fe(OTf)_2$ afforded product **3a** in 47-61% yields, respectively (Table 1, entries 6-8). It was further found that the valence of the iron salts is an important factor for the yield of the reaction. $FeCl_3$ gave the product in 60% yield (Table 1, entry 9). Notably, when Fe_2O_3 was employed as the catalyst, the reactivity was improved significantly (81% yield, Table 1, entry 10), and Fe_3O_4 provided a similar result. Other bases, such as DMAP, DIPEA, pyridine and inorganic base, were investigated. But no superior result was obtained (see the Supporting Information). A short survey on solvents indicated that the property of solvents was crucial for this transformation. Reactions in polar, aprotic solvents such as dioxane, EtOAc, $CHCl_3$, DMSO and THF afforded low yields (Table 1, entries 12-16). No desired product was observed when protonic solvent methanol was used and an unexpected byproduct methyl benzoate was detected in quantitative yield (Table 1, entry 17). It was noteworthy that the reaction was very sensitive to the reaction temperature. High temperature could decrease the reactivity.

Table 1. Optimization of the reaction conditions.[a]

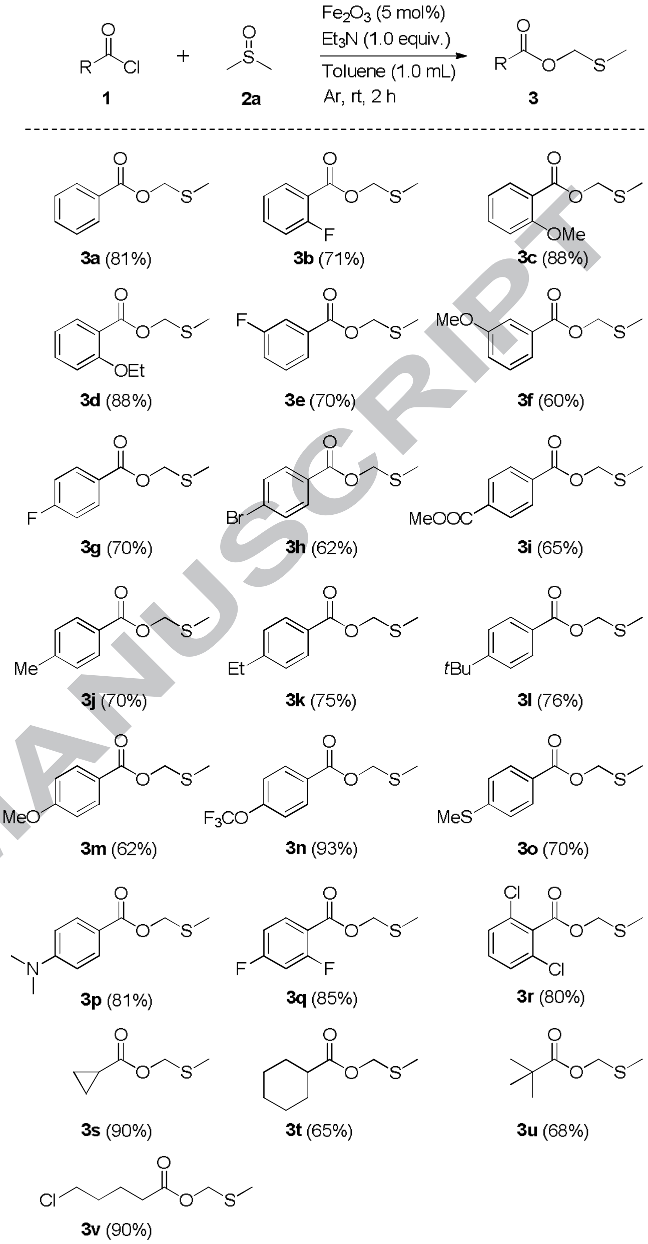


Entry	Catalyst	Solvent	Yield (%)[b]
1[c]	—	Toluene	N.R.[d]
2	—	Toluene	20
3	Cu	Toluene	19
4	Fe	Toluene	70
5	$FeCl_2$	Toluene	10
6	$Fe(OAc)_2$	Toluene	61
7	$Fe(acac)_2$	Toluene	50
8	$Fe(OTf)_2$	Toluene	47
9	$FeCl_3$	Toluene	60
10	Fe_2O_3	Toluene	81
11	Fe_3O_4	Toluene	75
12	Fe_2O_3	Dioxane	60
13	Fe_2O_3	EtOAc	65
14	Fe_2O_3	$CHCl_3$	41
15	Fe_2O_3	DMSO	42
16	Fe_2O_3	THF	57
17	Fe_2O_3	MeOH	0

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (2.5 mmol, 5.0 equiv.), catalyst (5 mol%) and Et_3N (0.5 mmol, 1.0 equiv.) in solvent (1.0 mL) at rt for 2 h. [b] Determined by ^1H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. [c] Without Et_3N. [d] No reaction.

Under the optimized conditions (Table 1, entry 10), a study on the substrate scope of the Fe-catalyzed Pummerer rearrangement was carried out. The results were summarized in Table 2. First, with DMSO as the sulfoxide, various aromatic and alkyl acyl chlorides were then examined. In general, the reactions took place efficiently with good yields (60–93%). This catalyst system was efficient when introducing various substituents such as fluoro and alkoxyl into the *ortho*-positions of the phenyl ring, the corresponding products **3b-3d** were obtained with high yields (71-88%). It is interesting that the substituents on *meta*-position of the aromatic ring had a limited influence on the reactivity (Table 2, **3e-f**). Remarkably, the *para*-position of the phenyl ring bearing different functional group such as halogen, ester, alkane, ether, amide and sulfide were also suitable substrates for the reaction, and afforded the desired products **3g-3p** in high yields. When the substitutes were halogen atoms such as fluorine and bromine, the products **3g-3h** can be achieved in 62-70% yields. The methyl ester as an electron-withdrawing group which was substituted on the phenyl ring could also lead the corresponding product **3i** in good yield (65%). The structure of compound **3i** was further confirmed by X-ray diffraction of its single crystal.[18] The X-ray structure indicates that two molecules **3i** were stacked together by a weak face-to-face (F-tape) π-π stacking interaction

Table 2. Scope of acyl chlorides.[a,b]



[a] Reaction conditions: Acyl chlorides **1** (0.5 mmol), dimethyl sulfoxide **2a** (2.5 mmol, 5.0 equiv.), Fe_2O_3 (5 mol%) and Et_3N (0.5 mmol, 1.0 equiv.) in toluene (1.0 mL) at rt for 2 h. [b] Isolated yield.

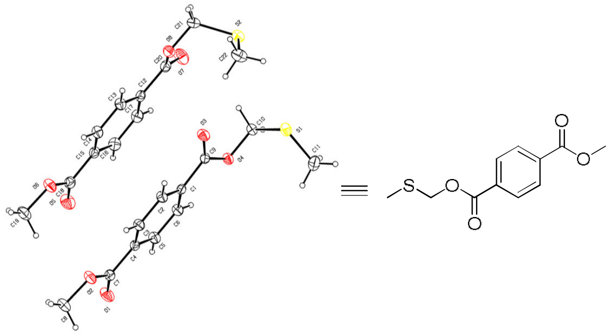
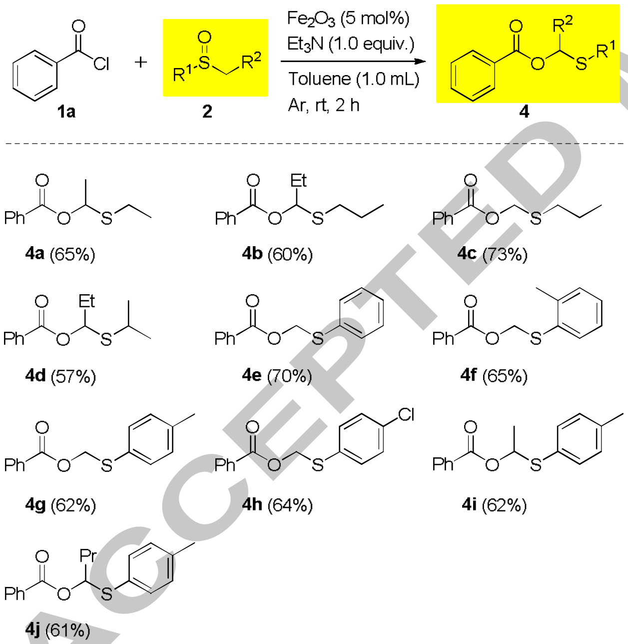


Fig. 1. Single crystal X-ray structure of **3i**.

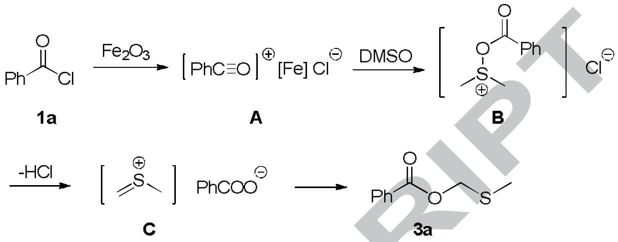
(Fig. 1). When the phenyl ring bearing electron-donating groups, such as alkyl, alkoxyl, methylthio and dimethylamino, were compatible with the reaction conditions affording the corresponding products with excellent yields (Table 2, **3j-p**, 62-93%). It is interesting that difluoro and dichloro substituted benzoyl chlorides were suitable for the reaction and the desired products **3q-3r** were observed with satisfactory yields (80-85%). Finally, alkyl acyl chlorides were examined for the Pummerer rearrangement. Cyclic substrates such as cyclopropylformyl chloride and cyclohexaylformyl chloride could be smoothly converted to MTM ester derivatives **3s-t** with 90% and 65% yield, respectively. Aliphatic branched and linear acyl chlorides also proceeded smoothly in the reaction leading to the corresponding adducts **3u-v** in 68-90% yields.

Table 3. Scope of sulfoxides.[a,b]



[a]Reaction conditions: Benzoyl chloride **1a** (0.5 mmol), sulfoxides **2** (2.5 mmol, 5.0 equiv.), Fe$_2$O$_3$ (5 mol%) and Et$_3$N (0.5 mmol, 1.0 equiv.) in toluene (1.0 mL) at rt for 2 h. [b]Isolated yield.

To further expand the scope of sulfoxides, various alkyl and aromatic sulfoxides were tested under the optimized conditions to afford the corresponding products, including alkylthioalkyl and arylthioalkyl esters, in good yields from 57% to 73%. The reactions of benzoyl chloride with symmetric alkyl sulfoxides such as diethyl and dipropyl sulfoxides occurred smoothly after 2 h at room temperature to give the products **4a-b** in 65% and 60% yield, respectively. Remarkably, when asymmetric alkyl sulfoxides were used as substrates, the reaction occurred in the less hindered moiety of sulfoxides. The corresponding alkylthioalkyl esters **4c-d** were observed with excellent regioselectivity favoring the ^{1}H NMR spectroscopy. Finally, under the similar reaction conditions, aryl sulfoxides were tested. Likewise, either the electronic nature or the position of the substituents on the aromatic ring of aryl sulfoxides had a limited influence on the reactivity. The desired adducts **4e-j** were obtained in satisfactory yields.



Scheme 1. Proposed reaction mechanism for the formation of compound **3a**.

On the basis of the above results and related publications, a plausible mechanism of this transformation is proposed (Scheme 1).[15-16, 19-20] Initially, benzoyl chloride **1a** was activated by an iron catalyst to produce iron acylium ion **A**, which attacks DMSO **2a** to generate the acylated dimethylsulfoxide adduct **B**. Further decomposition of intermediate **B** affords the thionium salt **C** and hydrochloric acid that was scavenged by the base Et$_3$N. Finally, the thionium intermediate **C** recombines with the carboxylate anion to provide the final methylthiomethyl ester **3a**.

In conclusion, we have established a simple and practical protocol to construct alkylthiomethyl ester via an iron promoted Pummerer rearrangement of acyl chlorides with sulfoxides under mild reaction conditions. The alkylthiomethyl ester products were prepared with a variety of functional groups in good to high yields (up to 93%). The advantage of the current method compared to the previous method is that it uses the inexpensive and widely utilized Fe$_2$O$_3$ as the catalyst. Thus, potentially, it will afford a general method for the construction of any desired alkylthiomethyl ester building blocks. Application of this property of iron catalyst on other type of reactions and further investigation of the reaction mechanism are underway in our laboratory.

Acknowledgments

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18. Crystal data of **3i**: Crystallographic data (excluding structure data factors) for the structures in this letter have been deposited with the Cambrige Crystallographic Data Centre as supplementary publication number CCDC 1534089. Copies of the data can be obtained free of charge on an application to CCDC, 12 Union Road, Cambrige CB21 EZ, UK [fax: +44 1223336033 or e-mail: deposit@ccdc.cam.ac.uk].
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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

(1) A Fe_2O_3-catalyzed Pummerer rearrangement was explored.

(2) Applications of the method led to a series of important alkylthiomethyl molecules.

(3) The product structure was further confirmed by X-ray analysis of its single crystal.