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Autocatalytic methylthiomethylation of carboxylic acid/phenol involving the formation of DMSO enolate: convenient synthesis of methylthiomethyl ester/ether†

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This work reported a simple and practical protocol for the preparation of methylthiomethyl (MTM) esters/ethers directly from carboxylic acid/phenol and dimethylsulfoxide (DMSO) as solvent and methylthiomethyl source. With different types of carboxylic acids/phenols the reactions underwent smooth transformation to afford the corresponding MTM esters/ethers in moderate to excellent yields. This method features catalyst-free, easy to operate, broad substrate scope, good functional group tolerance and involvement of the formation of DMSO enolate.

Introduction

Methylthiomethyl (MTM) groups exist in some functional molecules and have been used as important protecting groups for carboxylic acids.[1] The MTM group could serve as activating group for the amidation of acids.[2] MTM esters also used as flavor additives in some dairy and oil products.[3] In addition, the compounds that contain MTM esters groups displayed varied bioactivities such as anti-viral,[4] anti-inflammatory,[5] and dopaminergic[6] properties (Fig. 1). Consequently, the preparation of MTM esters have gained widespread attention.

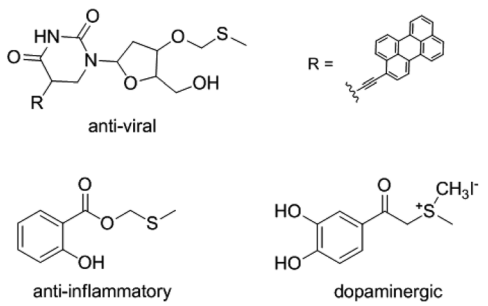

Fig. 1 Selected bioactive MTM ester/ether.

Traditionally, the MTM esters were synthesized from methylthiomethyl chloride (MTM-Cl) and carboxylic acid catalyzed by base and 18-crown-6.[7] However, the application of this method was limited by the use of toxic reagents, MTM-Cl and 18-crown-6. Another typical strategy for the synthesis of MTM esters from activated DMSO and carboxylic acid *via* a Pummerer rearrangement have been explored. However, this methodology need using activating reagents, such as *tert*-butyl bromide,[5] dicyclohexylcarbodiimide,[8] sulfuryl chloride,[9] and *N*-chlorosuccinimide.[10]

Recently, several procedures for the preparation of MTM esters using unactivated DMSO and carboxylic acids/acyl chlorides as the starting materials have been reported.[11] Despite significant advances, these methods suffer some disadvantages such as need of microwave-assisted[11a] and the use of catalysts.[11b–f] Therefore, it is still desirable to develop new convenient, efficient and environment-friendly methods.

We found that MTM esters could be efficiently prepared from carboxylic acid and DMSO under traditional heating conditions. This methylthiomethylation involving the formation of DMSO enolate. Phenols were also compatible with this transformation to give corresponding MTM phenyl ethers which were commonly synthesized in the presence of base catalyst from phenols and DMSO/chloromethyl methyl sulfide.[12] The method has several additional advantages such as easy to operate, broad substrate scope and good functional group tolerance.

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Herein, we wish to report an autocatalytic methylthiomethylation of carboxylic acids/phenols involving the formation of DMSO enolate for the synthesis of MTM esters/ethers.

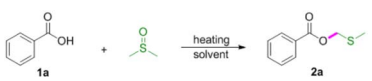
Results and discussion

Initially, our studies were carried out with readily available benzoic acid **1a** as the model substrate to optimize the reaction conditions. A mixture of **1a** (1 equiv.) in DMSO refluxed for 2 h under an air atmosphere to give the desired product **2a** in 23% yield (Table 1, entry 1). To further improve the reaction yield, we then investigated the impact of the reaction time. To our delight, the yield could be extremely improved when the reaction time was decreased and found that 15 min was the best choice (Table 1, entries 2–5). However, further decreasing the reaction time (10 min) had a reduction in yield (Table 1, entry 6). Thus it can be seen that this reaction depends mainly upon the reaction time. Decreasing the reaction temperature led to decreased isolated yields (Table 1, entries 7–8). Subsequently, various solvents such as DMF, 1,4-dioxane, THF and EtOH were screened, and no improvement in transformation was observed (Table 1, entries 9–12). Therefore, the optimized reaction conditions were determined as **1a** (0.3 mmol) in DMSO (1 mL) refluxed for 15 min under an air atmosphere (Table 1, entry 5).

With the optimised conditions in hand, the scope of the substrates was explored by varying carboxylic acids **1** (Table 2). As shown in Table 2, this protocol was suitable for various carboxylic acids, including aromatic, aliphatic, unsaturated and heteroaromatic carboxylic acids. Specifically, electron-donating groups (OMe, Me, ethyl and NH_2) on the aromatic acids provided excellent yields (Table 2, **2b–2e** and **2g**). However, the hydroxyl group had limited influence on the yield (Table 2, **2f**). It was observed that the stronger electron-donating effect provided better yields (Table 2, **2b** *vs.* **2c** and **2d** *vs.* **2e**). Electron-withdrawing groups, such as F, Cl, Br, NO_2 and CF_3, led to lower yields (Table 2, **2h–2m**). Cyano-substituted benzoic acid gave the desired product in 95% yield (Table 2, **2n**). It was also found that this procedure was efficient for converting 2-naphthalenecarboxylic acid, niacin, 2-thiophenecarboxylic acid, 3-furoic acid, 5-phenyl-2,4-pentadienoic acid and succinic acid to the corresponding MTM esters in good yields (Table 2, **2o–2u**), and that hydroxyl and amino groups could be tolerated (Table 2, **2f** and **2g**). Interestingly, the dimethylthiomethyl ester **2u** was detected as the main product when prolonging the reaction time to 60 min.

Next, reactions between phenols 3 and DMSO were carried out (Table 3). Phenols were also amenable to this autocatalytic methylthiomethylation to give MTM phenyl ethers in moderate yields (**4a–4g**, reaction condition optimization see Table S1†). We envisioned that the enol form of DMSO was generated in this transformation. In order to gain a clear insight into this reaction, the preliminary mechanistic studies were carried out (Scheme 1). The DMSO enolate **5** was detected from DMSO-d_6 (Scheme 1, eqn (1)), and the desired product **2a** was not detected when methyl benzoate **1ab** was used (Scheme 1, eqn (2)). These

Table 1 Optimization of reaction conditions[a]

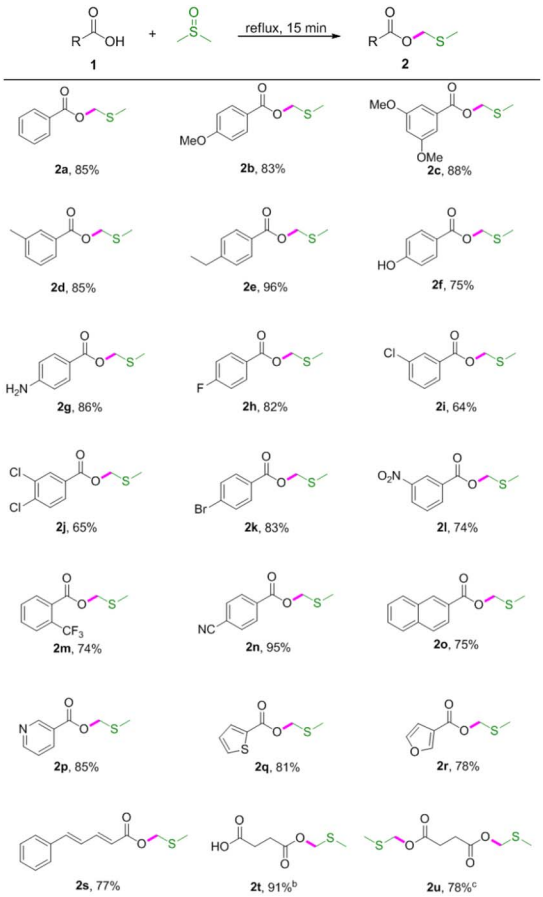


1a 2a

Entry	T (°C)	Time (min)	Solvent	2a[b] (%)
1	Reflux	120	—	23
2	Reflux	60	—	37
3	Reflux	30	—	70
4	Reflux	20	—	79
5	Reflux	15	—	85
6	Reflux	10	—	68
7[c]	180	15	—	11
8	190	15	—	66
9	Reflux	15	DMF	12
10	Reflux	15	1,4-Dioxane	—
11	Reflux	15	THF	—
12	Reflux	15	EtOH	—

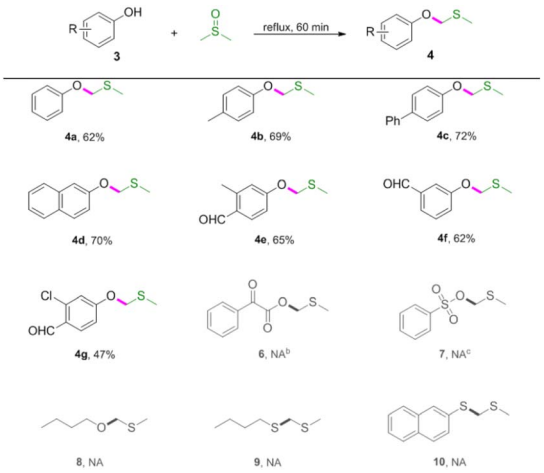
[a] Reaction conditions: **1a** (0.3 mmol), DMSO (1 mL), solvent (1 mL). [b] Isolated yield. [c] Reaction carried out in a pressure-resistant reaction bottle.

Table 2 Substrate scope of carboxylic acids[a]

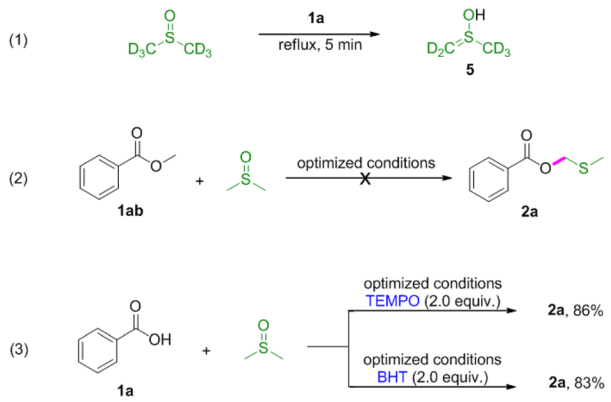


[a] Reaction conditions: **1a** (0.3 mmol), DMSO (1 mL). [b] Reaction time (5 min). [c] Reaction time (60 min).

Table 3 Synthesis of MTM phenyl ethers[a]



[a] Reaction conditions: **3** (0.3 mmol), DMSO (1 mL). [b] Reaction conditions: phenylglyoxylic acid (0.3 mmol), DMSO (1 mL), 200 °C, 3 h. [c] Reaction conditions: benzenesulfonic acid (0.3 mmol), DMSO (1 mL), 200 °C, 3 h. NA referred to "not available".

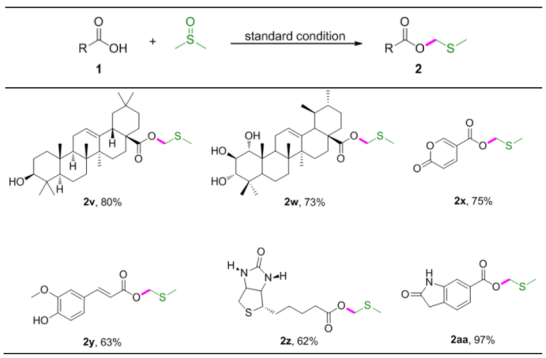


Scheme 1 Control experiments.

observations collectively suggested that the enolization of DMSO was occurred in the presence of benzoic acid. Then, the radical scavenger TEMPO and BHT were employed for this reaction. The reactions were not inhibited which demonstrated that this procedure might rule out the radical pathway (Scheme 1, eqn (3)). The scope and limitation of the reaction was further explored regarding phenylglyoxylic acid, benzenesulfonic acid, *n*-butanol, *n*-butyl mercaptan and 2-naphthalenethiol. Unfortunately, corresponding MTM products were not detected (Table 3, **6–10**).

The important synthetic value of this method was further examined by its application in several biologically relevant molecules to prepare corresponding MTM esters (Table 4). Oleanolic acid and 1α,2β-dihydroxyursolic acid were compatible with the reaction, giving rise to the target MTM products **2v**, **2w** in good yields. Coumalic acid is a lactone compound that could be converted to MTM ester in good yield (Table 4, **2x**). Ferulic

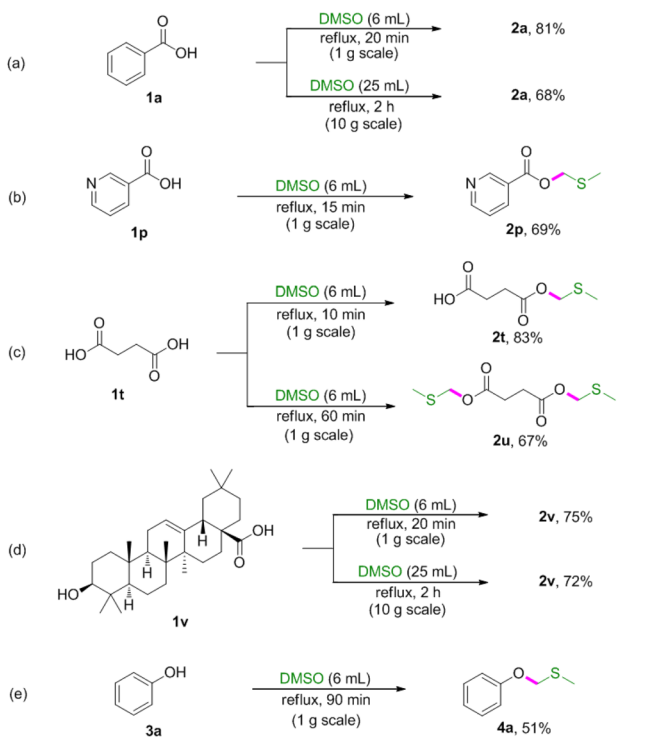
Table 4 Applications in biologically relevant natural products



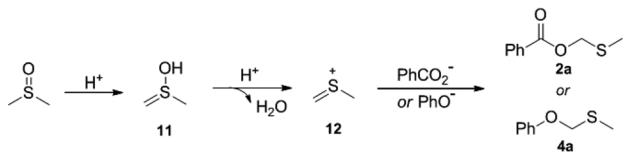
acid also proved to give modulate yield of the desired product (Table 4, **2y**). Furthermore, biotin and 6-carboxyoxindole were also applicable to the reaction system, and the desired products **2z** and **2aa** were assembled in 62% and 97% yields, respectively.

To demonstrated the synthetic potential of this methodology, reactions were conducted on gram scale (Scheme 2). The gram-scale reactions also proceeded well to afford corresponding products in moderate to good yields.

A plausible mechanism was proposed as described in Scheme 3. Intermediate **11** is formed from the enolization of DMSO, which after subsequent dehydration gives the thionium species **12**. Then, intermediate **12** undergoes addition with carboxylate or phenoxy anion to produce **2a** or **4a**.



Scheme 2 Gram-scale reactions.



Scheme 3 Plausible mechanism.

Conclusions

In summary, herein we developed a convenient and practical procedure for the preparation of MTM esters/ethers directly from carboxylic acids/phenols and DMSO under traditional heating conditions. This autocatalytic methylthiomethylation showed a broad substrate scope and good tolerance for functional groups such as hydroxyl, amino and amide group. This protocol also features easy to operate, catalyst-free and involvement of the formation of DMSO enolate.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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