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Facile synthesis of methylthiomethyl esters through Pummerer-type rearrangement of carboxylic acids and DMSO under metal-free conditions

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ABSTRACT

A green and cost-effective Pummerer-type rearrangement between readily accessible carboxylic acids and DMSO has been achieved under metal-free conditions in satisfactory to excellent yields. The transformation for the synthesis of valuable methylthiomethyl esters is shown to be a convenient strategy for various (hetero)aromatic acids, α,β-unsaturated carboxylic acids and saturated alkyl carboxylic acids with good functional group tolerance.

GRAPHIC ABSTRACT

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KEYWORDS
Carboxylic acids; DMSO; metal-free conditions; MTM esters; Pummerer-type rearrangement

Introduction

Dimethyl sulfoxide (DMSO) is usually utilized as a high-boiling polar aprotic solvent in organic transformation, furthermore, the "C–S–C", "C" and "C–S" fragments of DMSO are able to used as potential synthons in modern synthetic chemistry to construct new C–C and C–Hetero bonds.[1] It is worth to note that introducing sulfurized moiety of DMSO into molecular architectures has a dramatic impact on their chemical, physical and biological properties.[2] Carboxylic acids are widespread and nontoxic compounds, which can undergo decarboxylative coupling with various nucleophiles or electrophiles under transition-metal catalysis along with the extrusion of CO_2,[3] in this regard, our group has recently gained extensive knowledge in the realm of copper-mediated decarboxylative functionalization of aryl carboxylic acids,[4] including decarboxylative methylthiolation,[4a] arylation,[4b] protonation,[4c] halogenation and cyanation.[4d–f] In addition, the carboxylic acids can also be easily converted into esters through different methods.[5]

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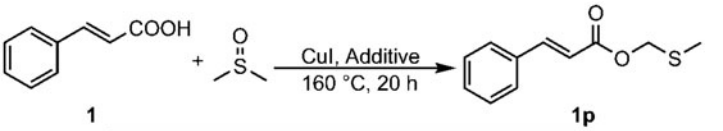
Supplemental data for this article is available online at on the publisher's website

Methylthiomethyl (MTM) esters are of great interest for their featured chemical properties under photochemical conditions involving electron-transfer courses,[6] moreover, they can be served as both rapidly absorbable pro-drugs of nonsteroidal anti-inflammatory agents[7] and flavor additives in dairy products and essential oils.[8] According to the cleavage under neutral non-hydrolytic conditions, MTM group can also be employed as a useful carboxyl protecting group in peptide synthesis.[9] Traditional methods to access MTM ester include the reaction of carboxylate anions with methylthiomethyl chloride (MTM-Cl),[10] treatment of carboxylate salts with DMSO by using *tert*-butyl bromide,[11] *N*-chlorosuccinimide,[12] dicyclohexylcarbodiimide,[13] chlorine or sulfuryl chloride[14] as activator respectively. DMSO is much more accessible than MTM-Cl, furthermore, it can be activated to form thionium ion intermediate as electrophilic reagent via Pummerer-type rearrangement,[15] thus, DMSO is a favorite to undergo Pummerer reaction with nucleophile to construct C–O bond under certain conditions. In this context, Ghosh and coworkers have reported a route to synthesize MTM esters between carboxylic acids and DMSO under Swern oxidation conditions at low temperature (−60 °C),[16] whereas the group of Zimmerman have developed the preparation of MTM esters from carboxylic acids and DMSO by a microwave-assisted technique.[17] Yang and Jiang have enabled a Fe-catalyzed Pummerer-type rearrangement of acyl chlorides with sulfoxides to construct alkylthiomethyl ester.[18] In continuation of our interest in diverse functionalization of cheap and abundant carboxylic acids,[4] herein we reveal an efficient, simple and metal-free approach for the conversion of a large pool of carboxylic acids including (hetero)aromatic acids, α,β-unsaturated carboxylic acids and saturated alkyl carboxylic acids to the corresponding MTM esters through Pummerer-type rearrangement using Et_3N as the sole additive. During the preparation of this manuscript, Lee and Nam have reported the reaction of carboxylic acid with DMSO in the presence of Et_3N to result in the corresponding MTM esters,[15d] however, only cinnamic acids and limited benzoic acids were employed as the coupling partners in their work.

Results and discussion

Initially, we commenced the optimization studies by performing Pummerer-type rearrangement of cinnamic acid (**1a**) with DMSO as the model reaction under an inert atmosphere. Table 1 presented some selected results from the optimization studies, which showcased the effects of the additive and other parameters on the reaction outcome. Although we have established protodecarboxylation of *o*-nitrobenzoic acids with CuI as catalyst and Et_3N as additive in DMSO under an inert atmosphere in recent exploration,[4c] however, the cinnamic acid (**1**) in the presence of CuI/Et_3N in DMSO smoothly furnished methylthiomethyl cinnamate (**1p**) instead of protodecarboxylation product in good yield (71%) under nitrogen atmosphere (entry 1, Table 1). Much to our delight, the omission of CuI resulted into an improved yield (77%) under otherwise identical conditions (entry 2). A brief survey of the *N*-containing additives revealed that both monodentate amine (n-Pr_3N and morpholine) and bidentate amine (en and DMEDA) were inferior to Et_3N (entries 3–6). Nevertheless, increasing the loadings of Et_3N to two equivalents had no beneficial effect on the reaction (entry 7), while low

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



1 **1p**

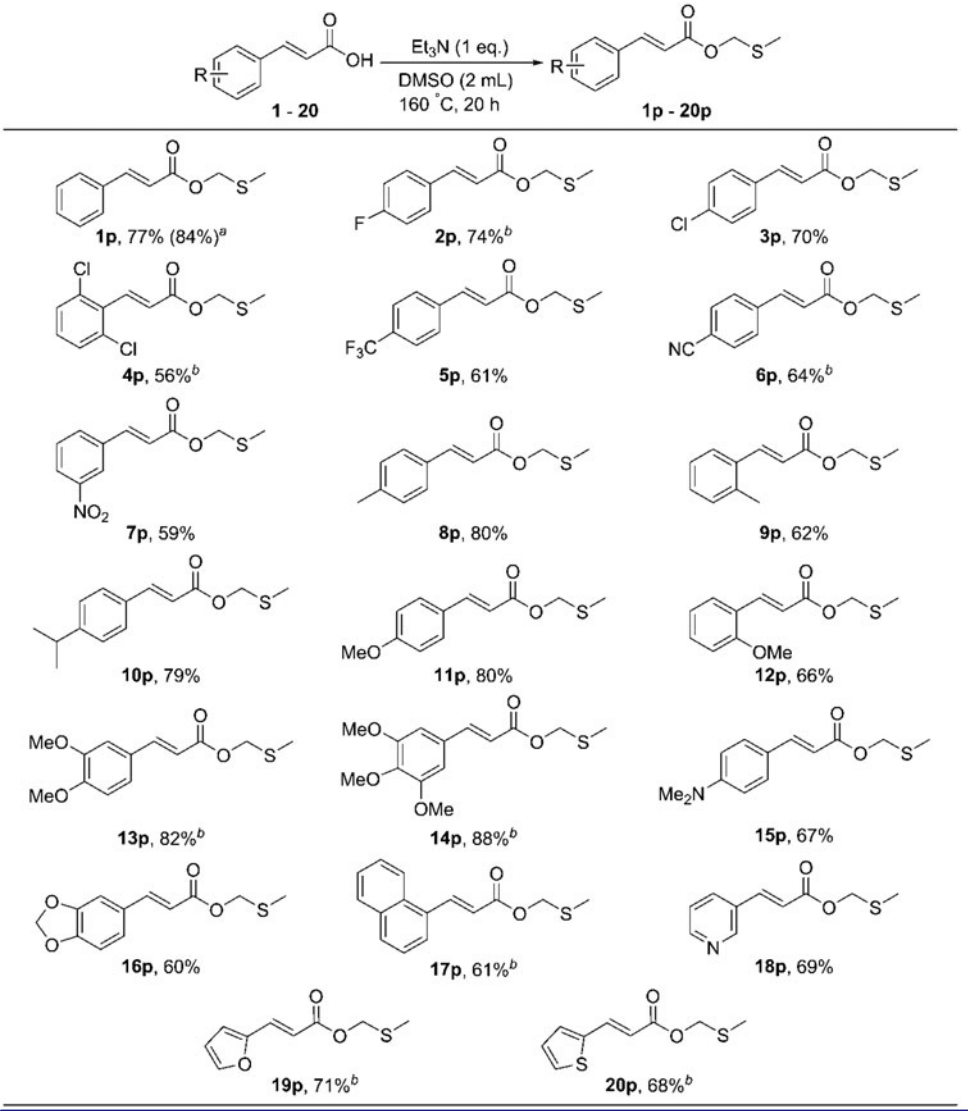
Entry	[Cu] (equiv)	Additive (equiv)	Yield (%)[b]
1	CuI (0.3)	Et_3N (1)	71
2	**---**	**Et_3N (1)**	**77**
3	---	*n*-Pr_3N (1)	62
4	---	morpholine (1)	7
5[c]	---	en (0.5)	5
6[d]	---	DMEDA (0.5)	69
7	---	Et_3N (2)	75
8[e]	---	Et_3N (1)	37
9[f]	---	Et_3N (1)	14
10[g]	---	Et_3N (1)	17
11	---	Et_3N (0)	< 5

[a]Reaction conditions: **1** (0.2 mmol), DMSO (2 mL), 160 °C, N_2 (1 atm), 20 h.
[b]Isolated yield.
[c]en = ethylenediamine.
[d]DMEDA = *N,N'*-dimethylethylenediamine.
[e]Air conditions instead of N_2.
[f]10 h instead of 20 h.
[g]140 °C instead of 160 °C.

yield (37%) was detected when the reaction atmosphere was switched to air (entry 8). Unfortunately, both shortening reaction time and lowering reaction temperature of the transformation led to unwelcome reaction conversion under otherwise equal conditions (entries 9–10). Control experiment exhibited that Et_3N was essential to the transformation (entry 11). Weighing the pros and cons, we decided to perform metal-free Pummerer-type rearrangement of cinnamic acid (**1a**) with DMSO in the presence of 1 equivalent of Et_3N as additive at 160 °C for 20 h under nitrogen atmosphere (entry 2) and use these data as our standard conditions.

Subsequently, the obtained optimality conditions (entry 2, Table 1) inspired us to explore the scope of this metal-free Pummerer-type rearrangement reaction with respect to cinnamic acids. As outlined in Table 2, the transformation was shown to be an effective strategy for a wide range of cinnamic acids containing electron-withdrawing (fluoro, chloro, trifluoromethyl, cyano and nitro) **2–7** and -donating (methyl, isopropyl, methoxy, dimethylamino and ketal) substituents **8–16**, benzo-fused cinnamic acid **17** and α,β-unsaturated heteroaromatic carboxylic acids **18–20**. Moreover, cinnamic acid substrates bearing electron-donating or -withdrawing substituent directly provided the corresponding MTM esters in satisfactory to excellent yields, thus, the electronic property of substituent on the aromatic ring of cinnamic acid did not significantly affect the efficiency of transformation. The substituent of chloro-moiety in substrates **3** and **4** were well tolerated in the reaction, which offered the possibility for late-stage functionalization via the activation of C-Cl bond. Compared to its isomer **8** or **11** respectively, 2-methylcinnamic acid **9** and 2-methoxycinnamic acid **12** were exceptions that showed moderate Pummerer-type rearrangement yields, indicative of the sensitivity of conversion to steric hindrance. It's found benzo-fused *trans*-3-(1-naphthyl)-2-propenoic acid

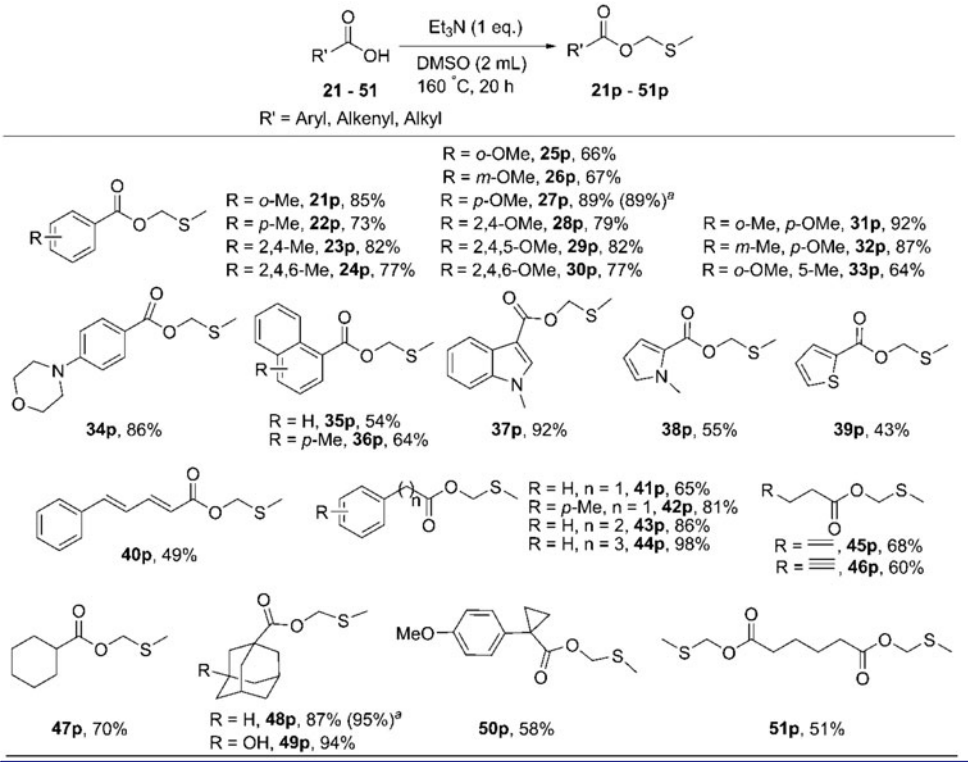
Table 2. Substrate scope of cinnamic acids.



[a]8 mmol substrate was used.
[b]170 °C instead of 160 °C.

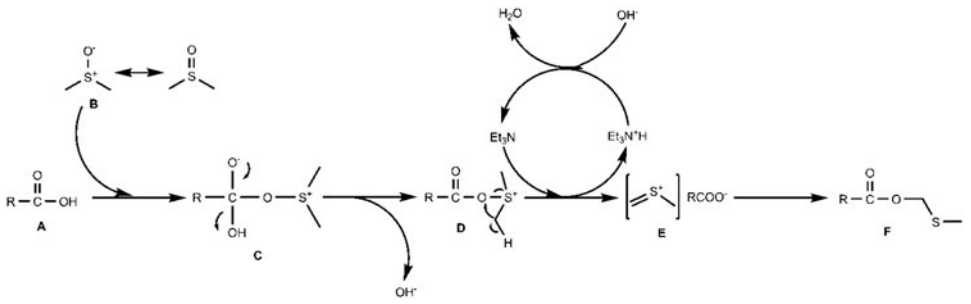
17 was a suitable substrate to furnish hoped-for product in synthetically useful levels. Although the substrates of α, β-unsaturated heteroaromatic carboxylic acids including 3-(3-pyridyl)acrylic acid **18**, 3-(2-furyl)acrylic acid **19** and 3-(2-thienyl)acrylic acid **20** had not been displayed in previous Pummerer-type rearrangement protocols under Swern oxidation[16] or microwave-assisted conditions,[17] it's observed for the first time to undergo the transformation with DMSO to afford desired products in satisfactory yields. The yields of the corresponding products in conversion were determined via the average of two runs, and the products were unambiguously characterized by ^{1}H and ^{13}C NMR spectral analyses to be an exclusive *E* stereochemistry.

Table 3. Substrate scope of other carboxylic acids.



[a]8 mmol substrate was used.

The feasibility of Pummerer-type rearrangement of cinnamic acids **1–20** with DMSO promoted us to further evaluate the generality of other carboxylic acids substrates with diverse structure, and the results were compiled in Table 3. A wealth of benzoic acids bearing methyl and methoxy substituents at different positions **21–33** as well as morpholino group at the *para* position **34**, α-naphthoic acids **35–36**, *N*- and *S*-containing heteroaromatic carboxylic acid **37–39**, unsaturated carboxylic acid containing a conjugated diene unit **40**, alkyl carboxylic acids **41–50** and alkyl dicarboxylic acid **51** were favorably carried out with DMSO under the standard conditions to afford the desired MTM esters products in satisfactory to excellent yields. Although the Pummerer-type rearrangement of *ortho*-toluic acid **21** was implemented in previous method,[16] it's also identified to be an effective substrate to afford the target product with high yield in this protocol. Similar to 2-methylbenzoic acid **21**, an array of benzoic acids bearing methyl or methoxy group **22–33** successfully participated in the process to give the hoped-for MTM esters. It's noteworthy benzoic acid tolerated methyl group at the *ortho*-position **21** gave superior yield to that of benzoic acid with methoxy substituent at the *ortho*-position **25**, likewise, 4-methoxy-2-methylbenzoic acid **31** was more efficient to deliver anticipated product than its isomeric compound **33** with methoxy substituent at the *ortho*-position, presumably due to the subtle electronic effect on the reactivity for benzoic acids toward this transformation. For the substrates of *N*- and *S*-containing heteroaromatic carboxylic acids **37–39**, they were detected for the first time to undergo this



Scheme 1. Proposed mechanism for this transformation.

conversion to give the desired products.[16–17] Cinnamic acids effectively took place in the transformation as illustrated in Table 2, furthermore, cinnamalacetic acid **40** comprised a conjugated diene unit to generate the end product under the standard conditions. Delightfully, the protocol was also efficiently applied to primary, secondary, and tertiary alkyl monocarboxylic acids **41–50** that tolerated different types of functional groups including aryl, C=C double bond, C≡C triple bond, cyclohexyl and adamantyl. Moreover, for the case of hexanedioic acid **51**, it worked well in the optimized system to supply the desired product in 51% yield.

Furthermore, a 40-fold scale-up of the synthesis was also carried out to illustrate the practicality of this protocol. As the isolated yields were showed in parentheses in Tables 2 and 3, employing 8 mmol of carboxylic acid (**1**, **27** and **48**) as starting material with Et_3N (1 equiv) in DMSO under the standard reaction conditions, as a result, the transformation of the carboxylic acids reached nearly the same efficiency as the reaction conducted on a 0.2 mmol scale, which declared a great potential of the method on large-scale synthesis.

Although the proposal of a detailed mechanism need to be awaited further investigation, basing on the above results and related reports,[16–18] a plausible mechanism for this transformation was hypothesized in Scheme 1. Initially, the resonance hybrid **B** of DMSO nucleophilic attacked carbonyl carbon of starting substrate carboxylic acid **A** to produce intermediate **C** followed by losing hydroxyl ion OH^- to give acylated DMSO adduct **D**. Once formed, deprotonation of α-H of the resultant intermediate **D** to afford thionium salt **E** in the presence of Et_3N, followed by combination of the thionium intermediate **E** with carboxylate anion to generate the final MTM ester **F**, while the Et_3N was regenerated with the assistance of liberated OH^-, and that's why increasing the amount of Et_3N to two equivalents had no beneficial effect on the transformation.

Conclusion

In summary, we have established a simple and practical method for the Pummerer-type rearrangement of easily available carboxylic acids with DMSO under metal-free conditions. The transformation demonstrated a highly efficient protocol to synthesize the corresponding MTM esters in satisfactory to excellent yields from a wide range of carboxylic acids substrates. There are several distinguishing features in the protocol: extensive substrate scope including readily available (hetero)aromatic acids, α,β-unsaturated carboxylic acids and saturated alkyl carboxylic acids with good

functional group tolerance; a simple reaction system to efficiently afford MTM esters products with cheap Et_3N as the sole additive under metal-free conditions. Thereby, this environment-friendly and robust method will attract much attention in academic and industrial fields, and further investigation to extend the practical application of this method is currently in progress.

Experimental

General information

The reagents used for experiments were commercially available and were used as received unless otherwise noted. DMSO was distilled from CaH_2 under reduced pressure and stored under nitrogen. All reactions were performed under nitrogen with the strict exclusion of moisture using Schlenk techniques. Column chromatography was performed on silica gel 300–400 mesh. The yields reported are the isolated yields and the average of two runs. ^1H, ^{13}C and ^{19}F NMR spectra of compounds were recorded at 400, 100 and 377 MHz with $CDCl_3$ as solvent respectively. All coupling constants (J values) were reported in Hertz (Hz). HRMS was performed by Comprehensive Laboratory Center of the College of Chemistry, Nanchang University.

Typical procedure for the synthesis of MTM ester

An oven-dried Schlenk tube equipped with a stir bar was charged with carboxylic acid (0.2 mmol) and Et_3N (28 μL, 0.2 mmol, 1 equiv). The tube was fitted with a rubber septum, and then it was evacuated and refilled with nitrogen three times. Under nitrogen, DMSO (2 mL) was added via syringe. The rubber septum was replaced with a Teflon screwcap under nitrogen flow, and the Schlenk tube was pressurized to 1 atm. With stirring, the reaction mixtures were heated at 160 °C for the indicated amount of time (unless otherwise specified). After cooling to room temperature, the reaction mixtures were diluted with ether (10 mL) and filtered through a pad of silica gel that was then washed with ether (10 mL × 3). The combined organic phase was washed with brine (20 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography over silica gel to provide the corresponding product with ethyl acetate/hexane as eluent.

(E)-(methylthio)methyl cinnamate (1p)[16]

Colorless oil, 77% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 16.4 Hz, 1H), 7.53–7.51 (m, 2H), 7.38 (t, J = 2.8 Hz, 3H), 6.46 (d, J = 16.0 Hz, 1H), 5.27 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 145.6, 134.2, 130.5, 128.9, 128.2, 117.4, 68.3, 15.5.

Full experimental detail, ^1H, ^{13}C and ^{19}F NMR spectra data, and references for all the products. This material can be found via the "Supplementary Content" section of this article's webpage.

Disclosure statement

No potential conflict of interest was reported by the authors.

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