Synthesis of Methylthiomethyl Esters by the Reaction of Carboxylic Acid with Dimethylsulfoxide

Subeen Yu, Kye Chun Nam,* and Sunwoo Lee*

Department of Chemistry, Chonnam National University, Gwangju 61186, Republic of Korea.
**E-mail: kcnam@chonnam.ac.kr; sunwoo@chonnam.ac.kr*
Received May 9, 2018, Accepted May 25, 2018

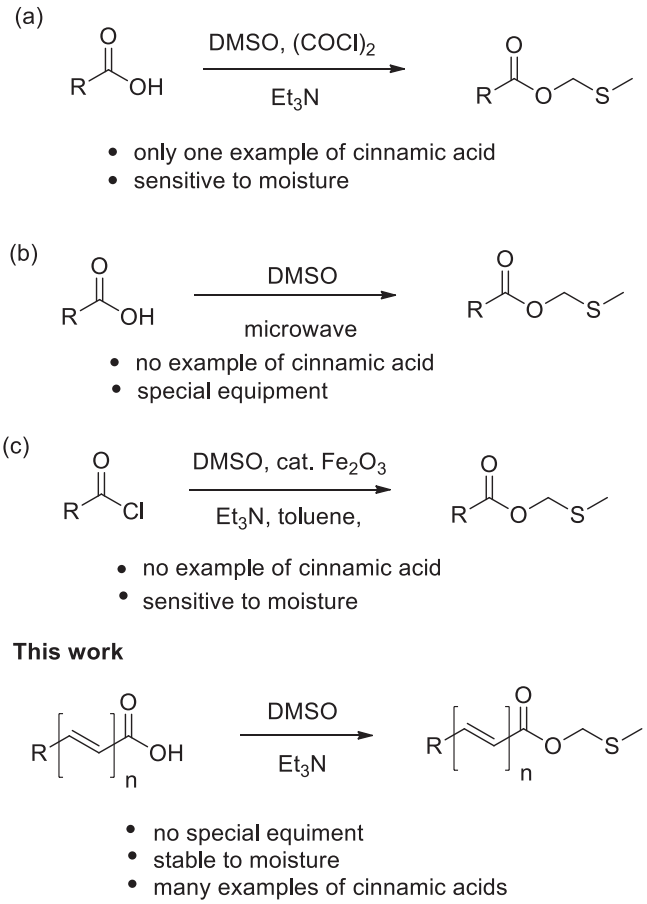
Keywords: Methylthiomethyl esters, Dimethylsulfoxide, Cinnamic acid, Benzoic acid

Methylthiomethyl (MTM) esters are frequently used as protecting groups for carboxylic acids and as activating groups for the amidation of acids.[1] In addition, they exhibit a unique chemical property of electron transfer under photochemical conditions.[2] Furthermore, they are often used in bio-active reagents due to their good absorbability and as flavor additives in some dairy and oil products.[3] Therefore, the synthesis of MTM esters has received much attention in the organic synthesis, materials, and pharmaceutical domains. Many preparation methodologies have been reported for MTM esters. One typical method to synthesize MTM esters is the reaction of methylthiomethyl chloride with carboxylic acid in the presence of a base and 18-crown-6.[4] Although this method is frequently employed in organic synthesis, methylthiomethyl chloride is known to be toxic. To address this issue, dimethylsulfoxide (DMSO) was used and allowed to react with carboxylate salt in the presence of activating reagents, such as *tert*-butyl bromide,[5] *N*-chlorosuccinimide,[6] dicyclohexylcarbodiimide,[7] and sulfuryl chloride,[8] to synthesize MTM esters according to the Pummerer rearrangement.[9]

MTM esters were prepared by Swern oxidation using DMSO, oxalyl chloride, and triethylamine by Ghosh *et al.* (Scheme 1(a)).[10] Using oxalyl chloride has some drawbacks owing to its moisture sensitivity. Zimmerman reported the synthesis of MTM esters using the Pummerer rearrangement with microwave radiation (Scheme 1(b)).[11] Very recently, Yang *et al.* reported iron-catalyzed Pummerer rearrangement of acyl chlorides and DMSO for the synthesis of alkylthiomethyl esters (Scheme 1(c)).[12] However, these processes also have their own sets of limitations. The former method requires special equipment, such as a microwave instrument. On the other hand, the handling of moisture-sensitive acyl chloride is a major drawback in the latter method. Therefore, more convenient methods are desired. To meet this requirement, we attempted to develop a simple method for the synthesis of MTM esters.

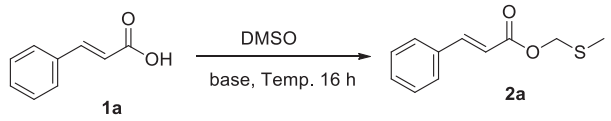
A variety of carboxylic acid derivatives have been evaluated in the past for the formation of the corresponding MTM esters. However, there is not much information available on cinnamic acid derivatives for MTM ester synthesis. Herein, we report the synthesis of MTM esters by the reaction between carboxylic acid derivatives (cinnamic acid and benzoic acid) and DMSO in the presence of a base.

To find the optimal reaction conditions, cinnamic acid (**1a**) was allowed to react with DMSO in the presence of a variety of bases. The results are summarized in Table 1. When Et_3N and *i*-Pr_2EtN were employed as bases, the desired product, methylthiomethyl cinnamate (**2a**), was formed at yields of 87% and 86%, respectively (Table 1, entries 1 and 2). Reactions with pyridine, 1,4-diazabicyclo [2.2.2]octane (DABCO), and 1,5-diazabicyclo(4.3.0)non-5-ene (DBN) led to the desired product with slightly lesser



Scheme 1. Synthesis of methylthiomethyl groups.

Table 1. Optimized conditions for the synthesis of the MTM ester, **2a**, from cinnamic acid.[a]

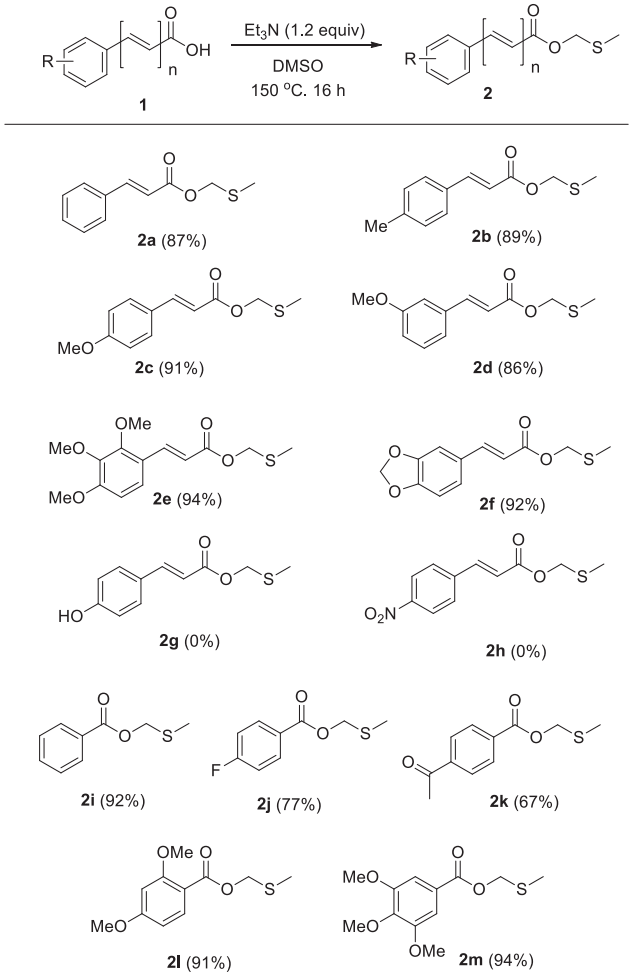


Entry	Base	Temperature (°C)	Yield (%)[b]
1	Et_3N	150	87
2	*i*-Pr_2EtN	150	86
3	Pyridine	150	32
4	DABCO	150	40
5	DBN	150	22
6	DBU	150	0
7	KOAc	150	0
8	NaOAc	150	0
9	K_2CO_3	150	0
10	Na_2CO_3	150	15
11	Cs_2CO_3	150	0
12	K_3PO_4	150	0
13	Na_3PO_4	150	0
14	KOMe	150	0
15	NaOMe	150	0
16	Et_3N	140	73
17	Et_3N	120	44
18	Et_3N[c]	150	77
19	Et_3N[d]	150	62

[a] Reaction conditions: **1a** (0.3 mmol), DMSO (1.0 mL), and base (0.36 mmol).
[b] Determined by gas chromatography with internal standard.
[c] 0.18 mmol was used.
[d] 0.6 mmol was used.

yields (Table 1, entries 3–5). However, no product was formed with all other tested bases, except for Na_2CO_3 (entries 6–15). As the reaction temperature decreased, the product yield decreased (entries 16 and 17). When the amount of base was decreased to 0.6 equiv. or increased to 2.0 equiv., the product yields decreased to 77 and 62%, respectively (Table 1, entries 18 and 19). On the basis of these results, we optimized the reaction conditions to be 2 mmol of carboxylic acid, 2.4 mmol of Et_3N, and 8 mL of DMSO at 150°C for 16 h.

At these optimized conditions, a variety of substituted cinnamic acids were evaluated for the formation of the corresponding MTM esters (see Supporting Information). As expected, **2a** could be isolated at a yield of 87%. 4-Methyl substituted cinnamic acid (**2b**) was formed at a yield of 89%. Alkoxy-substituted cinnamic acids were successfully converted into the corresponding methylthiomethyl esters **2c**, **2d**, **2e**, and **2f** (as shown in Scheme 2) with good yields. However, hydroxyl- and nitro-substituted cinnamic acids did not yield the desired product. The optimized conditions were also employed for the protection of benzoic

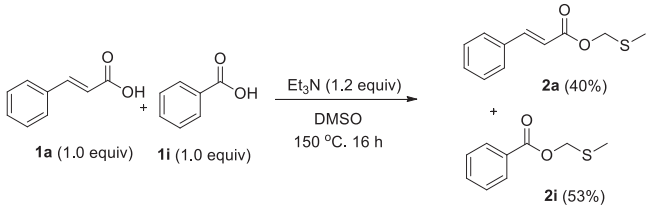


Scheme 2. Synthesis of methylthiomethyl esters from cinnamic acid and benzoic acid derivatives.[aa]Reaction conditions: **1** (2.0 mmol), Et_3N (2.4 mmol), DMSO (8.0 mL), 150°C, and 16 h.

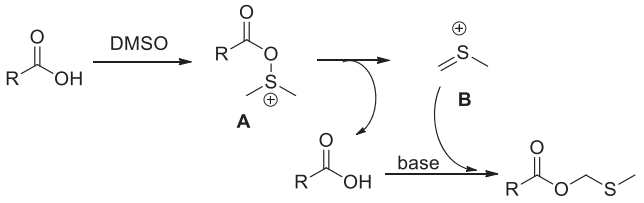
acid derivatives. Benzoic acid led to the synthesis of **2i** with 92% yield. 4-Fluoro and 4-acetyl substituted benzoic acids were transformed into the corresponding methylthiomethyl esters **2j** and **2k** with 77 and 67% yield, respectively. Alkoxy-substituted benzoic acids showed good yields in the formation of **2l** and **2m**.

We studied the reactivity of cinnamic acid and benzoic acid at the optimized conditions. When cinnamic acid (**1a**) and benzoic acid (**1i**) were allowed to react in the same reaction vessel at the optimized conditions, **2a** and **2i** were formed at yields of 40 and 53%, respectively (Scheme 3). This result proves that benzoic acid exhibits a slightly higher reactivity than cinnamic acid at the optimized reaction conditions.

Based on our observations and previous studies, we suggest a possible mechanism for the formation of MTM esters (Scheme 4). When heated, carboxylic acid reacted with DMSO to yield an acylated DMSO adduct, **A**; this was followed by thermal elimination resulting in the thionium



Scheme 3. Competitive reaction of cinnamic acid and benzoic acid.



Scheme 4. Proposed mechanism for the formation of MTM esters.

intermediate, **B**. The carboxylate formed during the reaction between carboxylic acid and the base reacts with the intermediate product, **B**, to yield the final product.

In summary, we developed a simple method for the preparation of MTM esters. Carboxylic acids, such as cinnamic acid derivatives and benzoic acid derivatives, reacted with DMSO in the presence of Et_3N to result in the corresponding MTM esters; further, the yields were found to be good. It was found that benzoic acid was slightly more reactive than cinnamic acid in this reaction.

Experimental

General Method for the Synthesis of (Methylthio) Methyl Cinnamate from Cinnamic Acid. Cinnamic acid (296 mg, 2.0 mmol) and Et_3N (243 mg, 2.4 mmol) were reacted with DMSO (8.0 mL) at 150°C for 16 h. The mixture was charged to a separating funnel containing water and extracted with EtOAc. The organic layer was washed with water and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure yielded the crude product, which was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 8/1).

General Method for the Synthesis of (Methylthio) Methyl Benzoate from Benzoic Acid. Benzoic acid (244 mg, 2.0 mmol) and Et_3N (243 mg, 2.4 mmol) were reacted with DMSO (8.0 mL) at 150°C for 16 h. The mixture was charged to a separating funnel containing water and extracted with EtOAc. The organic layer was washed with water and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure yielded the crude product, which was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 10/1).

Acknowledgment. This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (NRF-2017R1D1A3B03035736, NRF-2015R1A4A1041036). The spectral data were obtained at the Korea Basic Science Institute, Gwangju Branch.

Supporting Information. Additional supporting information is available in the online version of this article.

References

1. (a) S. Kim, Y. H. Park, I. S. Kee, *Tetrahedron Lett.* **1991**, *32*, 3099. (b) T.-L. Ho, C. M. Wong, *J. Chem. Soc. Chem. Commun.* **1973**, 224. (c) U. Ghosh, R. Bhattacharyya, A. Keche, *Tetrahedron* **2010**, *66*, 2148.
2. A. G. Greisbeck, M. Oelgemoller, J. Lex, *J. Org. Chem.* **2000**, *65*, 9028.
3. (a) T. Loftsson, J. J. Kaminski, N. Bodor, *J. Pharm. Sci.* **1981**, *70*, 743. (b) S. Vandenbosch, E. Van't Land, J. Stoffelsma, *Pat. Appl. EP* **1980**, 7673. (c) S. Vandenbosch, E. Van't Land, J. Stoffelsma, *Chem. Abstr.* **1980**, *93*, 113981. (d) S. Vandenbosch, E. Van't Land, J. Stoffelsma, *US Patent 4* **1983**, *332*, 829. (e) S. Vandenbosch, E. Van't Land, J. Stoffelsma, *Chem. Abstr.* **1984**, *100*, 84460. (f) M. Moir, I. M. Gallacher, J. Hobkirk, J. C. Seaton, A. Suggett, *Tetrahedron Lett.* **1980**, *21*, 1085.
4. L. G. Wade, J. M. Gerdes, R. P. Wirth, *Tetrahedron Lett.* **1978**, *8*, 731.
5. A. Dossena, R. Marchelli, G. Casnati, *J. Chem. Soc. Chem. Commun.* **1979**, 370.
6. E. Vilasmaier, K. H. Dittrich, W. Sprügel, *Tetrahedron Lett.* **1974**, *15*, 3601.
7. K. E. Pfitzner, J. G. Moffatt, *J. Am. Chem. Soc.* **1965**, *87*, 5661.
8. T.-L. Ho, *Synth. Commun.* **1979**, *9*, 267.
9. (a)R. Pummerer, *Berichte* **1909**, *42*, 2282. (b) R. Pummerer, *Berichte* **1910**, *43*, 1401. (c) A. Padwa, D. E. Gunn Jr. , M. H. Osterhout, *Synthesis* **1997**, 1353. (d) S. K. Bur, A. Padwa, *Chem. Rev.* **2004**, *104*, 2401. (e) O. de Lucchi, U. Miotti, G. Modena, *Org. React.* **1191**, *40*, 157.
10. S. B. Jadhav, U. Ghosh, *Tetrahedron Lett.* **2007**, *48*, 2485.
11. A. McCarthy, R. Spatney, M. Manpadi, B. J. Myers, J. R. Zimmerman, *Tetrahedron Lett.* **2012**, *53*, 4782.
12. H. Xing, L. Chen, Y. Jia, Z. Jiang, Z. Yang, *Tetrahedron Lett.* **2017**, *58*, 2199.

