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A direct conversion of carboxylic acids to methylthiomethyl esters using a microwave-assisted pummerer rearrangement with dimethylsulfoxide

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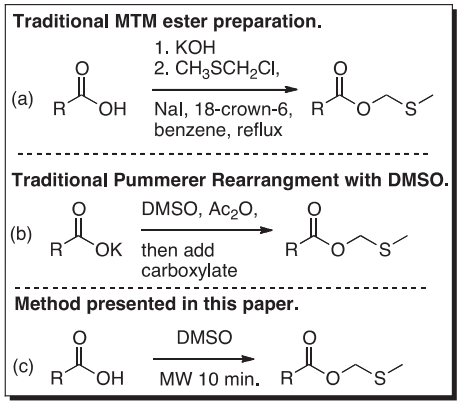
ABSTRACT

A simple microwave-assisted method for the conversion of carboxylic acids to MTM esters is presented. This new process allows for rapid introduction of an MTM ester protecting group to a variety of carboxylic acids including alkyl, electron-rich aromatic, and long chain unsaturated carboxylic acids. The products isolated from this reaction are very pure after a simple extraction, which eliminates the need for further purification. The reaction has also been carried out on 1.50 g without deterioration of product yields or purity.

Methylthiomethyl (MTM) esters have been utilized as protecting groups for carboxylic acids for nearly four decades.[1] Although this protection strategy has been realized in the literature for a long period of time, the synthetic preparation for the MTM ester has seen very little change over the past thirty years.[2] Two traditional routes for converting carboxylic acids to MTM esters involve reacting a carboxylate anion with methylthiomethyl chloride (MTM-Cl)[1c] or treating carboxylic acids with *t*-butyl bromide in dimethyl sulfoxide (DMSO).[1d,e] The former method uses known toxic reagents, MTM-Cl and 18-crown-6.[3] For example, upon exposure, it is known that crown ethers are readily absorbed through the skin, which can ultimately lead to CNS effects.[4] The latter procedure requires a large excess (10 equiv) of a halogenated hydrocarbon, *t*-butyl bromide, which has been found to be a carcinogen.[3] While MTM esters have mostly been employed as protecting groups, they have also been used in the synthesis of chloromethyl esters,[2c] and for *ortho*-thiomethylation of arylacetic acid derivatives.[5] In this report, we present a simple direct transformation of carboxylic acids to MTM esters via a microwave-assisted Pummerer rearrangement with DMSO (Scheme 1). While the Pummerer rearrangement has been known in the literature for over one hundred years,[6] to our knowledge, there are no reports of a Pummerer reaction on DMSO to functionalize carboxylic acids using a microwave-assisted protocol.[7–9]

Our experiments began by evaluating the reaction of benzoic acid with DMSO in a conventional microwave.[10] Initially we found that after 3 min. of microwave irradiation in an open reaction vial, 63% of MTM ester **2a** was obtained (Table 1, entry 1). Although, the yield was modest, the product was very pure (>95%) after a simple extraction, and therefore, no further purification was needed. We then evaluated the same reaction using more traditional heating conditions (entry 2). After a 4 h reflux in DMSO, 27% of **2a** was isolated. Since the microwave-assisted method was found to be superior to traditional heating in both reaction time and product yield, we expanded our studies on this microwave process and focused



Scheme 1. Preparation of MTM esters.

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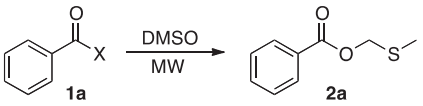
Table 1
MTM ester synthesis of carboxylic acid derivatives via a microwave Pummerer rearrangement with DMSO



Entry	–X	Time (min)	Concn. (M)	Yield[a] (%)
1	–OH	3	2	63
2	–OH	N/A	3.3	27[b]
3	$-O_2CPh$	3	2	83
4	–Cl	<1	2	Decomp.[c]
5	$-OCH_3$	3	2	N.R.[d]
6	$-NH_2$	3	2	N.R.[d]
7	–OH	10	2	71
8	–OH	10	1	71
9	–OH	10	4	62
10	–OH	15	2	65
11	–OH	7	2	49[e]

[a] Isolated yields.
[b] Reaction was refluxed for 4 h.
[c] Reaction mixture decomposed.
[d] No reaction was observed.
[e] Carried out in a microwave reactor at 150 °C (150 W, max. of 140 psi) for 7 min.

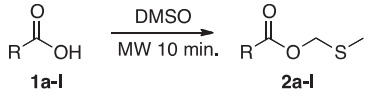
our attention on evaluating other carboxylic acid derivatives. Benzoic anhydride gave an excellent yield of **2a**, again with good purity after extraction. Methyl benzoate and benzamide resulted in no product formation (entries 5 and 6), and benzoyl chloride decomposed under the microwave reaction conditions (entry 4). Next, we evaluated both reaction time and concentration. It was discovered that 10 min. of microwave irradiation was optimal at either 1 or 2 M concentrations (see entries 7 and 8). Longer reaction times and higher concentrations did not improve product yields (see entries 9 and 10). Finally, we explored this method in a microwave synthesizer using a sealed reaction vessel (entry 11). A variety of parameters on the synthesizer were adjusted including reaction time, microwave power, and pressure (not all data shown), yet product yields were consistently lower than irradiating for 10 min. with an open reaction vial in a conventional microwave (1380 W).

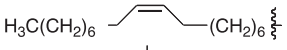
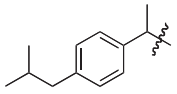
With the optimized conditions in hand, we explored a series of carboxylic acids in order to determine the scope of this reaction (Table 2). It was observed that aliphatic acids such as hydrocinnamic and octanoic acid give superior yields to simple aromatic acids such as benzoic (see entries 1, 4 and 5). Electron rich aromatic carboxylic acids gave excellent yields of the MTM-ester product (see entries 6 and 7), while electron deficient acids resulted in low yields of the desired product (entries 8 and 9). This procedure was also found to be very efficient for converting long chain unsaturated fatty acids, such as oleic acid, to the corresponding MTM ester (entry 11). Branched carboxylic acids including 2-phenylbutyric acid and ibuprofen also proved to give excellent yields of the desired product (entries 10 and 12). In general, lower yields of the reactions were due to incomplete reaction conversion as indicated by TLC of the reaction mixture. In the case of the electron deficient aromatic acids we suspected that decarboxylation[11,8b] may have occurred since we observed some over pressurization in the microwave synthesizer using a sealed reaction vessel. Albeit, when completing the reaction on *m*-chlorobenzoic acid (entry 9) using our method, 38% of the MTM ester (**2i**) and 58% of *m*-chlorobenzoic acid was obtained for a total of 96% recovery of material. Thus, it is likely that only a small amount of decarboxylation may be occurring under the reaction conditions employed here.

Finally, we wanted to test whether this methodology was amenable for larger scale reactions. Therefore, we carried out reactions on 1.50 g scale with 2-phenylbutanoic acid (**1j**), oleic acid (**1k**), and ibuprofen (**1l**) (Scheme 2). The results from the scale-up reactions were very similar to the previously reported reactions.[15] Again, all products were obtained pure after a simple extraction, which eliminated the need for further purification.

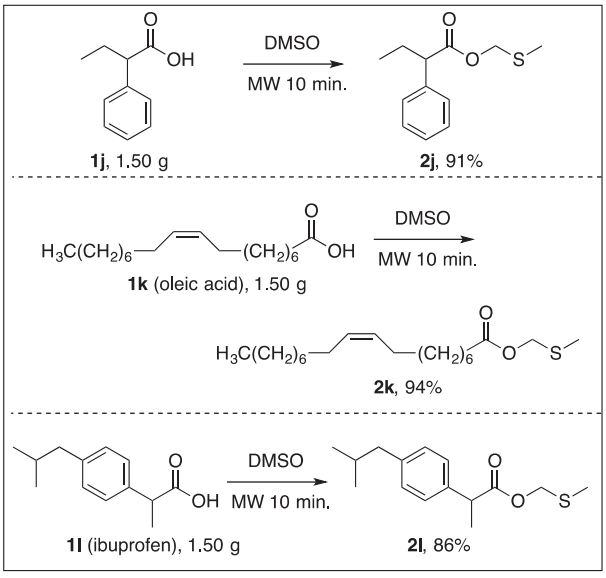
A possible mechanism for this microwave-assisted MTM ester synthesis of carboxylic acids is shown in Figure 1.[16] Initially DSMO reacts with the acid to give the acylated DMSO adduct **4**. Elimination yields the thionium intermediate **5**, which undergoes addition with the carboxylate anion to yield the MTM ester product **6**. An alternate mechanistic route would involve anhydride formation from the dimerization of two carboxylic acids. Once formed, the

Table 2
Carboxylic acid screening for microwave-assisted MTM ester synthesis[12]



Entry	Product	R	Yield[a] (%)
1	**2a**	Ph–	71
2	**2b**	PhCHCH–	65
3	**2c**	$PhCH_2$–	69
4	**2d**	$PhCH_2CH_2$–	88
5	**2e**	$CH_3(CH_2)_6$–	91
6	**2f**	*p*-CH_3-Ph–	82
7	**2g**	3,4-Dimethoxy-Ph–	94
8	**2h**	*p*-CHO-Ph–	20
9	**2i**	*m*-Cl-Ph–	38
10	**2j**		92[13]
11	**2k**		95
12	**2l**		94[14]

[a] Isolated yields.



Scheme 2. Scaled-up reactions to form MTM esters.

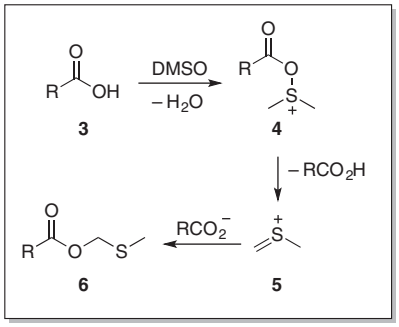


Figure 1. Proposed mechanism for microwave-assisted MTM ester synthesis from carboxylic acids and DMSO.

anhydride would also produce the activated DMSO intermediate **4** and ultimately yield desired product **6**.

In conclusion, we have reported a simple method for the preparation of MTM esters from carboxylic acids using a microwave-assisted protocol. This method is compatible with a variety of carboxylic acids including alkyl, electron-rich aromatic, and long chain unsaturated carboxylic acids. The procedure was also successfully carried out on up to 1.50 g scale without deterioration in yields or product purity. The products obtained from this method are very pure after a simple extraction, and therefore, the need for further purification is not necessary.

Acknowledgments

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of all the compounds and other data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.136.

References and notes

1. (a) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd Ed.; Wiley: New York, 1999. p 389; For seminal publications using MTM esters as carboxylic acid protecting groups, see: (b) Ho, T.-L.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1973**, 224–225; (c) Wade, L. G.; Gerdes, J. M.; Wirth, R. P. *Tetrahedron Lett.* **1978**, *8*, 731–732; (d) Dossena, A.; Marchelli, R.; Casnati, G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2737–2739; (e) Dossena, A.; Marchelli, R.; Casnati, G. *J. Chem. Soc., Chem. Commun.* **1979**, 370–371.
2. For recent modifications to MTM ester preparation, see: (a) Ghosh, U.; Jadhav, S. B. *Tetrahedron Lett.* **2007**, *48*, 2485–2487; (b) Liu, J.-S.; Tao, Y. *Tetrahedron* **1992**, *48*, 6793–6798; (c) Ragan, J. A.; Ide, N. D.; Cai, W.; Cawley, J. J.; Colon-Cruz, R.; Kumar, R.; Peng, Z.; Vanderplas, B. C. *Org. Process Res. Dev.* **2010**, *14*, 1402–1406.
3. See the MSDS (Aldrich) for methoxythiomethyl chloride, 18-crown-6, and/or *t*-butyl bromide toxicity information.
4. Hendrixson, R. R.; Mack, M. P.; Palmer, R. A.; Ottolenghia, A.; Ghirardellia, R. G. *Toxicol. Appl. Pharmacol.* **1978**, *44*, 263–268.
5. (a) Bourgaux, M.; Gillet-Berwart, A.-F.; Marchand-Brynaert, J.; Ghosez, L. *Synlett* **1995**, 113–115; (b) Jaroskova, L.; Bourgaux, M.; Wenkin, I.; Ghosez, L. *Tetrahedron Lett.* **1998**, *39*, 3157–3160.
6. 6. For seminal publications see: (a) Pummerer, R. *Berichte* **1909**, *42*, 2282–2291; (b) Pummerer, R. *Berichte* **1910**, *43*, 1401–1412; For reviews of the Pummerer Rearrangement see: (c) Padwa, A.; Gunn, D. E., Jr.; Osterhout, M. H. *Synthesis* **1997**, 1353–1357; (d) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401–2432; (e) de Lucchi, O.; Miotti, U.; Modena, G. *Org. React.* **2004**, 157–405.
7. A recent publication reports a microwave-assisted triple process that includes a Pummerer rearrangement as one step of this multi-component reaction. Islas-Jácome, A.; González-Zamora, E.; Gámez-Montaño, R. *Tetrahedron Lett.* **2011**, *52*, 5245–5248.
8. A thermal (215 °C, 3 h) KOH catalyzed esterification of dehydroabietatic acid with DMSO to give a methylthiomethyl ester was recently reported: (a) Shi, Z.; Wan, Y.; Yao, X. *Adv. Mat. Res.* **2012**, 1694–1996. The synthesis of methylthiomethyl esters under thermal conditions was also reported; (b) Chen, C.-T.; Wang, C.-H. *Bull. Ins. Chem., Acad. Sinica* **1971**, *19*, 79–83.
9. Some relevant aromatic substitution reactions via a Pummerer rearrangement on DMSO under thermal conditions include: (a) Liu, J.; Wang, X.; Guo, H.; Shi, X.; Ren, X.; Huang, G. *Tetrahedron* **2012**, *68*, 1560–1565; (b) Guzei, I. A.; Zimmerman, H. E.; Shorunov, A.; Spencer, L. C. *J. Chem. Crystallogr.* **2009**, *39*, 399–406; (c) Doucet, J.; Gagnaire, D.; Robert, A. *Synthesis* **1971**, 556.
10. This procedure uses a 1380 W conventional microwave. Results using a 725 W microwave did not yield product under the optimized conditions outlined in the procedure.
11. (a) March, J. *J. Chem. Educ.* **1963**, *40*, 212–213; (b) Brown, B. R. *Quart. Revs.* **1951**, *5*, 131–146.
12. *General Procedure for the preparation of MTM esters:* The carboxylic acid (2 mmol) and DMSO (1 mL) were added to a 5 dram 24-400 neck vial and heated in a conventional microwave (1380 W) for 10 min. Once cool, the solution was transferred into a separatory funnel with diethyl ether (50 mL) and washed with water (2 × 10 mL) and 0.5 M NaOH (2 × 20 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the pure MTM ester product. Caution: This procedure should be carried out in a hood as the MTM ester products have a strong odor.
13. *Spectroscopic data for (methylthio)methyl 2-phenylbutanoate (**2j**)*: 92% yield; IR (cm^{-1}) 3063 (m), 2966 (s), 2962 (s), 2875 (m), 1736 (s), 1454 (m), 1146 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33–7.31 (m, 5H), 5.11 (s, 2H), 3.51 (t, J = 8 Hz, 1H), 2.13 (quint, 1H), 2.08 (s, 3H), 1.84 (quint, 1H), 0.92 (t, J = 7.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.8, 140.0, 128.8, 128.2, 127.5, 68.5, 53.7, 26.8, 15.3, 12.3; HRMS exact mass Calcd for $C_{12}H_{16}O_2SNa$ $[M+Na]^+$: 247.0769. Found: 247.0765.
14. *Spectroscopic data for (methylthio)methyl 2-(4-isobutylphenyl) propanoate (**2l**)*: 94% yield;: IR (cm^{-1}) 3455 (m), 2953 (s), 2924 (s), 2868 (m), 1738 (m), 1512 (w), 1462 (m), 1420 (m), 1146 (s); ^{1}H NMR (200 MHz, $CDCl_3$) 1. 7.22 (d, J = 8 Hz, 2H), 7.10 (d, J = 8 Hz, 2H), 5.12 (s, 2H), 3.73 (q, J = 7.0, 14.3 Hz, 1H), 2.45 (d, J = 8 Hz, 3H), 2.06 (s, 3H), 1.85 (sep, J = 6 Hz, 1H), 1.51(d, J = 7.3 Hz, 2H), 0.89 (d, J = 6.6 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.5, 140.9, 137.7, 129.6, 127.4, 68.4, 45.4, 45.3, 30.4, 22.6, 18.5, 15.2; HRMS exact mass Calcd for $C_{15}H_{22}O_2SNa$ $[M+Na]^+$: 289.1238. Found: 289.1224.
15. The reactions in Tables 1 and 2 were all run on 2 mmol scale.
16. Johnson, C. R.; Phillips, W. G. *J. Am. Chem. Soc.* **1969**, *91*, 682–687.