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PROTECTION OF CARBOXYLIC ACIDS AS METHYLTHIOMETHYL ESTERS

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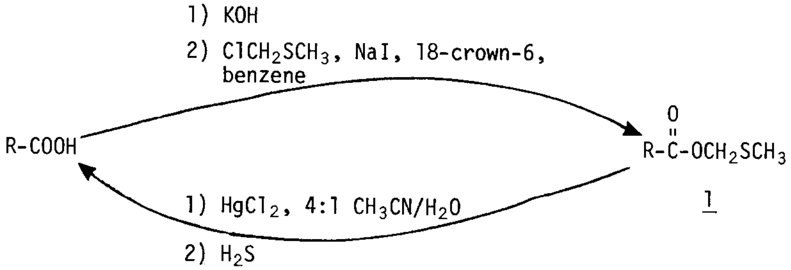
Although a synthesis of methylthiomethyl.(MTM) esters (1) was reported[1] over four years ago, their extensive utilization as a carboxylic acid protecting group has yet to be realized. Routine use of MTM ester protecting groups has been hindered primarily by the lack of sufficiently mild and convenient protection and deprotection methods giving consistently good yields. This letter describes methods for the formation and hydrolysis of MTM esters in good yields under mild conditions, compatible with the presence of sensitive functional groups.

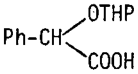
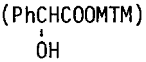
Using an adaptation of the procedure developed by Corey and Bock[2] for the synthesis of MTM ethers, a carboxylic acid can be converted to its MTM ester by treatment of the potassium salt of the acid with chloromethyl methyl sulfide in refluxing benzene, to which catalytic amounts of sodium iodide and 18-crown-6 have been added. Products from this reaction are generally sufficiently pure (>95%) to allow their use in subsequent reactions without further purification.[3]



Deprotection may be effected cleanly and conveniently by treatment of the MTM ester with $HgCl_2$ in refluxing acetonitrile/water, followed by treatment with H_2S to remove all mercurial compounds. Products from this reaction are also generally sufficiently pure to allow their use in subsequent reactions without further purification. The mildness and versatility of these procedures were exemplified by the formation of a MTM ester derivative of mandelic acid in the presence of a tetrahydropyranyl ether protecting group on the hydroxyl function and the subsequent removal of the THP group leaving the MTM ester intact (see table).

The MTM ester function is stable to mild reducing agents such as NaBH and Zn-MeOH.[1] It also survives untouched after one hour at room temperature in contact with aqueous solutions of pH 0-15. We have, however, observed oxidative hydrolysis of MTM esters left exposed to the air for prolonged periods of time (several weeks), and suggest that they be stored under nitrogen. Oxidative hydrolysis of similar compounds has been well established.[4]

FORMATION AND HYDROLYSIS OF METHYLTHIOMETHYL ESTERS

Acid	Ester Yield (%)[5]	Deprotection Yield[7]
benzoic	90	98
cinnamic	97	92
mesitoic	85	98
pivalic	95	82
 $Ph-CH(OTHP)COOH$	88[6]	95 ( $PhCH(OH)COOMTM$)

The following are representative procedures for the formation and cleavage of MTM esters.[8]

Formation of MTM Cinnamate: Potassium cinnamate (0.372 g, 2.0 mmole), sodium iodide (0.075 g, 0.50 mmole), 18-crown-6 (0.106 g, 0.40 mmole), and chloromethyl methyl sulfide (0.233 g, 2.4 mmole) were suspended in 25 ml of benzene and heated under reflux for 6 hr. After cooling to room temperature, the reaction mixture was washed twice with 15 ml portions of saturated aqueous sodium carbonate solution, washed with brine, and then dried ($MgSO_4$) and evaporated to give 0.406 g (1.95 mmole, 97%) of 98% pure (by pmr) methylthiomethyl cinnamate: pmr ($CDCl_3$) δ 2.30 (3H, s, $-SCH_3$), 5.29 (2H, s, $-OCH_2S-$), 6.42 (1H, d, J=15 Hz, vinyl), 7.42 (5H, m, ArH), 7.73 (1H, d, J=15 Hz, vinyl); ir (neat) 3075, 3040, 2935, 1720, 1645, 1583, 1500, 1345, 1155, 985, and 767 cm^{-1}; ms m/e 208 (parent), 190, 188, 162, 161, 148, 147, 132, 131.

Cleavage of MTM Cinnamate: The above material (0.406 g, 1.95 mmole) and mercuric chloride (1.59 g, 5.9 mmole) were suspended in 25 ml of 4:1 acetonitrile/water and heated at reflux for 6 hr. The mixture was cooled to room temperature and treated with H_2S bubbled through the mixture for 30 min. The mixture was filtered under suction (with Celite), added to 30 ml of pH 4 buffer solution (to reprotonate the acid), and extracted twice with 30 ml portions of methylene chloride. The combined methylene chloride extracts were washed with brine, dried ($MgSO_4$), and evaporated to give 0.267 g (1.80 mmole, 92%) of crystalline cinnamic acid, mp 125-129° (lit. 133°), spectroscopically identical with an authentic sample and 97% pure by pmr.

REFERENCES

1. T.-L. Ho and C. M. Wong, *J. Chem. Soc., Chem. Commun.*, 224 (1973).
2. E. J. Corey and M. G. Bock, *Tetrahedron Lett.*, 3269 (1975).
3. The structures assigned to the compounds reported herein were confirmed by infrared, proton magnetic resonance (pmr), and mass spectrometric data. MTM ester derivatives are easily distinguished by the characteristic pmr singlets at 2.2-2.3 δ ($-SCH_3$) and at 5.15-5.4 δ ($-OCH_2S-$). MTM esters are thermally stable and sufficiently resistant to fragmentation during mass spectrometric measurements that molecular ions may be observed.
4. P. M. Hardy, H. N. Rydon, and R. C. Thompson, *Tetrahedron Lett.*, 2525 (1968).
5. Crude product, generally 95-99% pure by pmr.
6. Based on the potassium salt of THP-mandelic acid.
7. Crude products, generally crystalline and 96-99% pure by pmr.
8. This work was supported by a Biological Research Support Grant and by a Faculty Research Grant from Colorado State University.