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OXIDATIVE AND METHYLATIVE DEPROTECTION OF METHYLTHIOMETHYL ESTERS

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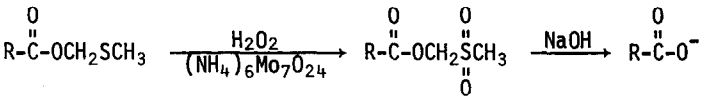
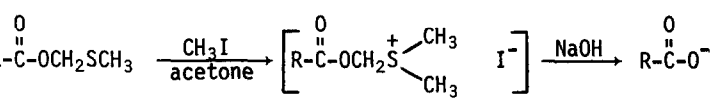
Methylthiomethyl (MTM) esters (1) have been shown to be accessible via S_N2 esterification[1] or DBU esterification[2] using chloromethyl methyl sulfide. They are stable to mild reducing agents such as $NaBH_4$ and Zn-MeOH,[3] and can withstand pH ranges of 0-15 for one hour at room temperature. Deprotection has been effected[1] through $HgCl_2$-assisted hydrolysis followed by treatment with H_2S to remove all mercurial compounds.

Although both protection and deprotection can be accomplished in good yields by the above procedures, deprotection is often accompanied by liberation of H^+ and a resulting pH of 1-2. Highly acid-sensitive functional groups can therefore be retained only through careful pH control.[1,4] In addition, the removal of mercury salts is cumbersome, and the use of H_2S is relatively dangerous and inconvenient. For these reasons, we have developed two additional methods for deprotection of MTM esters. Both of these methods are characterized by high yields and simplicity, and facile control of pH can be exercised in the oxidative deprotection procedure.



1 2

Ammonium molybdate-catalyzed peroxide oxidation[5] of a MTM ester affords the corresponding sulfone (2) in quantitative yield.[6] Basic (pH 11) hydrolysis of the sulfone, followed by reprotonation, affords the parent acid in excellent yield and >95% purity.[7] Although 2 can be isolated and recrystallized, better yields are obtained (with little or no loss in purity) if NaOH solution is added directly to the reaction mixture at the conclusion of the oxidation. An additional advantage of the one-pot deprotection is the presence of molybdenum salts which undergo a color change at the proper pH for hydrolysis of the sulfone.



1 (not isolated)

Treatment of a MTM ester with iodomethane results in the formation of an unstable sulfonium iodide which decomposes to the acid salt on extraction with base.

OXIDATIVE AND METHYLATIVE DEPROTECTION

MTM Ester	Oxidation-hydrolysis yield (%)[8]	Methylation-hydrolysis yield (%)[8]
benzoic	98	97
cinnamic	99	96
mesitoic	92	93
pivalic	90	87
Ph-CH(OTHP)-COOMTM	98(Ph-CH(OTHP)-COOH)	97(mandelic acid)

The following procedures are representative:[9,10]

Oxidation Deprotection of MTM Cinnamate: MTM cinnamate (2.07 g, 10.0 mmole) was dissolved in a mixture of 50 ml of acetone and 10 ml of water. Hydrogen peroxide (20 ml of 30% H_2O_2) was added, followed by 10 ml of aqueous ammonium molybdate (0.3N in Mo). The slightly exothermic reaction was stirred for 2 h, and then enough 1N NaOH was added to bring the pH of the solution to 11, indicated by a color change from yellow to gold-orange. An additional 40 ml of 0.25M NaOH solution was then added at such a rate as to keep the pH at 11; or it may be added all at once in insensitive cases. The mixture was allowed to stir for 30 min after all of the base has been added. The mixture was acidified to pH 6, partially evaporated under reduced pressure, acidified to pH 4, and was extracted three times with ether. The combined ether extracts were washed with brine, dried, and evaporated under reduced pressure to give 1.47 g (9.9 mmole, 99%) of crystalline cinnamic acid, mp 130-131° (lit. 133°).

Methylative Deprotection of MTM Cinnamate: MTM cinnamate (1.04 g, 5.0 mmole) was dissolved in 10 ml acetone, and 3.7 g (25 mmole) of iodomethane was added. The mixture was allowed to reflux for 24 h, evaporated under reduced pressure, and redissolved in chloroform. The product was extracted into 1N NaOH. The aqueous phase was reacidified to pH 3 and extracted three times with CH_2Cl_2. The combined CH_2Cl_2 extracts were combined, washed with brine, dried, and evaporated to give 0.71 g (4.8 mmole, 96%) of crystalline cinnamic acid, mp 131° (lit. 133°).

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6. Structures assigned to the sulfones were confirmed by infrared, proton magnetic resonance (pmr), and mass spectrometric data. The methyl protons in the sulfones are characteristically about 0.7 ppm more deshielded than are those in the parent MTM ester.
7. Structures assigned to the deprotected acids were confirmed by comparison with authentic samples.
8. Crude products, generally crystalline and 95-99% pure by pmr.
9. The authors would like to thank Prof. Stephen J. Weininger for helpful discussions and suggestions and Rosemary Wood and David Near for assistance in yield determination.
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