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ACTIVATION AND SYNTHETIC APPLICATIONS OF THIOSTANNANES. PROTECTION OF CARBOXYL GROUPS WITH α-METHYLCINNAMYL ALCOHOL AS A MEANS OF CHEMODIFFERENTIATION AND SELECTIVE ACTIVATION

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Abstract. α-Methylcinnamyl (MEC) esters are converted into parent carboxylic acids under mild conditions, various functions being tolerated including acetoxy, siloxy, MEM, and so on. Furthermore, MEC esters are transformed into other esters through CsF-promoted alkylation of intermediary organotin carboxylates.

Protection of carboxyl groups is frequently encountered in organic synthesis. Esterification, in general, serves best for this purpose,[1] but deprotection of the esters employed so far requires basic or acidic conditions. Therefore, we still need novel esters which are hydrolyzed as mildly as possible and differentiated from other ester groups as well as other functionalities.[2] Here, we wish to report conceptually new protection which satisfies such requirement: α-methylcinnamyl (MEC) esters **1** (RCOOMEC), on treatment with thiostannanes together with BF_3·OEt_2, are converted into the parent carboxylic acids exclusively even in the presence of various other functions. In addition, we disclose that the MEC group can activate carboxyl groups, thus allowing the unprecedented one-pot ester exchange of **1** into other esters.

Preparation of **1** is straightforward according to either of the following methods: exposure of MEC alcohol[3] (i) to acyl halides together with 4-dimethylaminopyridine (DMAP) in pyridine (75-88%) or (ii) to carboxylic acids together with 1,3-dicyclohexylcarbodiimide (DCC)-DMAP in THF (~98%).[4] The esters **1** thus obtained were treated with $Me_2Sn(SMe)_2$ (**2a**) (0.6 equiv) in the presence of BF_3·OEt_2 (1.0 equiv) in toluene at 0 °C for 3-24 h (Scheme 1). Then, acetic acid (6 equiv) was added to the reaction mixture. Usual aqueous workup afforded the crude

Scheme 1

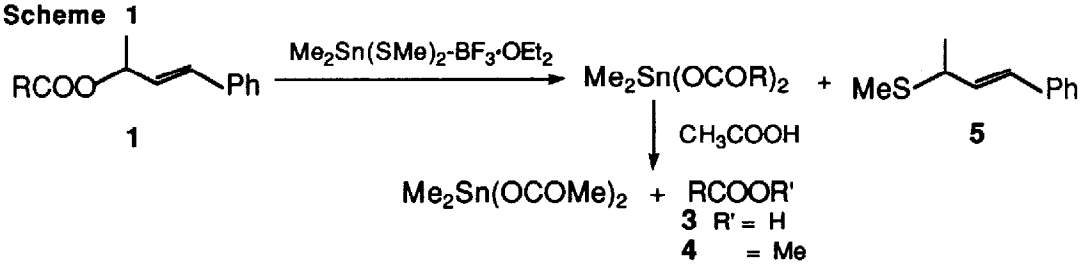
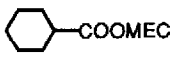
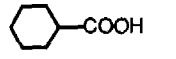
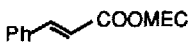
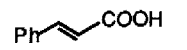
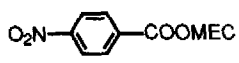
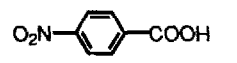
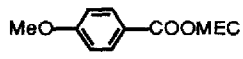
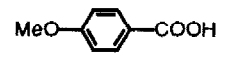
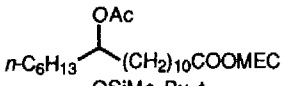
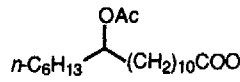
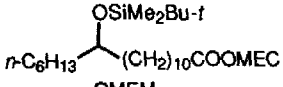
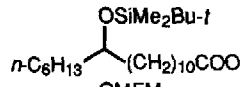
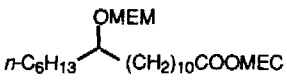
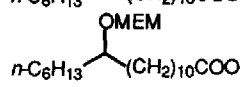
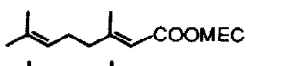
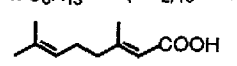
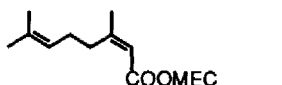
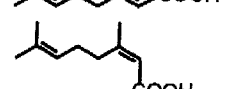
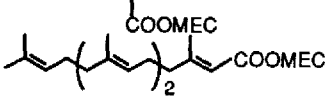
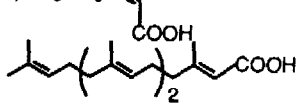


Table 1. Conversion of RCOOMEC **1** into RCOOH **3**.[a]

entry	**1**	reactn time/h	**3**	yield/%[b]
1	n-$C_{11}H_{23}$COOMEC	7	n-$C_{11}H_{23}$COOH	91(100)
2		7		(85)
3		12		(78)
4		7		83(100)
5	PhCOOMEC	6	PhCOOH	99(100)
6		5		(86)
7		5		88(100)
8		8		100
9		3		94
10		7.5		91
11		9		82(89)
12		14		82(75)
13		24		75

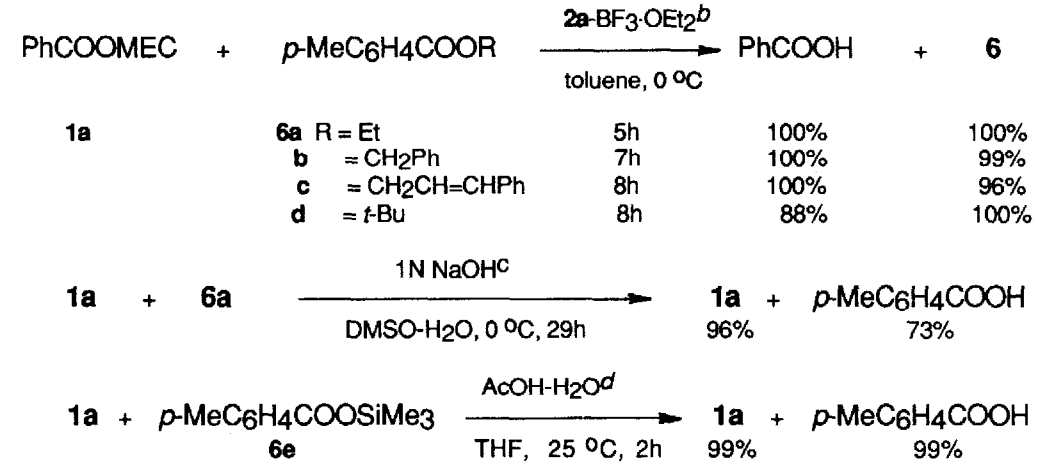
[a] Reaction conditions: **1** (1 mmol), **2a** (0.6 mmol), BF_3·OEt_2 (1 mmol), toluene, 0 °C; AcOH (6 mmol), 0 °C, 30 min. [b] Isolated yields as methyl esters. Yields based on GLC are given in parentheses.

mixture of carboxylic acids **3** and methyl α-methylcinnamyl sulfide (**5**). The mixture was treated with diazomethane and the resulting methyl ester **4** was identified by GLC analysis or isolated by column chromatography.[5] Although Bu_3SnSMe (**2b**) (1.2 equiv) also proved effective, **2a** was preferable because insoluble dimethyltin oxide formed by aqueous workup could be easily separated from the organic layer. Table 1 features the present method to be applicable to a wide scope of carboxylic acids bearing such as primary, secondary, or tertiary alkyl as well as vinyl and aromatic groups (entries 1-7). The mildness of the reaction led to successful deprotection of esters involving various functionalities such as acetoxy, *t*-butyldimethylsiloxy, and 2-methoxyethoxymethoxy (MEM) groups (entries 8-10). Especially noteworthy is that

neither cyclization nor isomerization was detected at all for terpenic trisubstituted α,β-unsaturated esters (entries 11-13), efficient hydrolysis of which was rather difficult by conventional methods.[6]

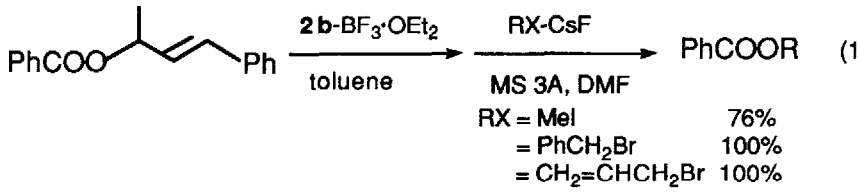
Scheme 2 demonstrates the excellent chemodifferentiation in the deblocking procedure. The MEC esters **1a** were unmasked under these conditions predominantly over the esters **6a** and **6b**. On the other hand, exposure of **1a** and **6a** to 1N NaOH aqueous solution-DMSO (1:1) resulted in selective deprotection of the latter. Of further interest is the clear distinction between **1a** and its primary homologue **6c**,[7] suggestive of a cationic reaction path.[8] Neverthless, acid-sensitive **6d** remained intact under the present reaction conditions. On exposure to acetic acid-water in THF, a mixture of **1a** and the trimethylsilyl ester **6e** resulted in exclusive deprotection of the latter, leaving **1a** unchanged. As a whole, the appropriate choice of reaction conditions enables us to differentiate **1** from most of trivial esters.

Scheme 2[a]



[a] Determined on the basis of GLC analyses after treatment with CH_2N_2. [b] **1a** and methyl *p*-methylbenzoate were not detected. [c] PhCOOH (3%) and **6a** (18%) were detected. [d] Methyl benzoate and **6e** were not detected.

In view of somewhat enhanced reactivity of Sn-O bonds, the intermediacy of organotin carboxylates in the above process implied potentiality of additional chemical transformation other than the simple deprotection. Unfortunately, however, in contrast to organotin alkoxides, the carboxylates had found few available reactions.[9] Now we have revealed that CsF promotes alkylation of organotin carboxylates.[10] Coupled with this new reaction, the thiostannane method effected conversion of **1** into other esters (eq. 1). After completion of the reaction between **1a** and **2b**, the toluene solvent was replaced by DMF. To this solution was added molecular sieves 3A, CsF (1.5 equiv to **1a**) and alkyl halides (1.5 equiv) in this order. The mixture was stirred at room temperature for overnight. Usual workup and column chromatography afforded quantitative yields of the new esters with diverse reactivities, i.e.



methyl, benzyl, and allyl esters. In short, we have succeeded in selective activation of the protected carboxyl groups in a one-pot manner which obviously meets broad synthetic demands. In summary, the MEC esters resist to alkaline and weekly acidic (i.e. acetic acid-water) hydrolysis although they failed to survive on treatment with *p*-toluenesulfonic or trifluoroacetic acids. Despite this bilateral stability, the esters are readily deblocked under mild conditions.[11] The combined use of Lewis acid-promoted thiostannane and the secondary cinnamyl esters is crucial for this purpose, and an alkoxy fission in MEC esters plays a key role for unique reactivities.

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(3) Prepared from cinnamaldehyde and MeMgBr in THF at 0 °C in 95% yield: Bp 80-85 °C/0.5 mm.

(4) Satisfactory IR, NMR, and HRMS data were obtained for **1**.

(5) In addition, **5** was obtained quantitatively.

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(7) Cinnamyl esters were deprotected by the two-step procedure ($Hg(OAc)_2$-KSCN): E. J. Corey and M. A. Tius, Tetrahedron Lett., 2081 (1977).

(8) Racemic **5** was obtained from optically active α-methylcinnamyl benzoate ($[\alpha]_D$ 4.31°, *c* 0.50, EtOH, >95% ee).

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(11) Analogous properties were reported for 9-anthrylmethyl esters, deprotection of which, however, required the use of the sodium salt of methyl mercaptan in DMF or HMPA: N. Kornblum and A. Scott, J. Am. Chem. Soc., **96**, 590 (1974).

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