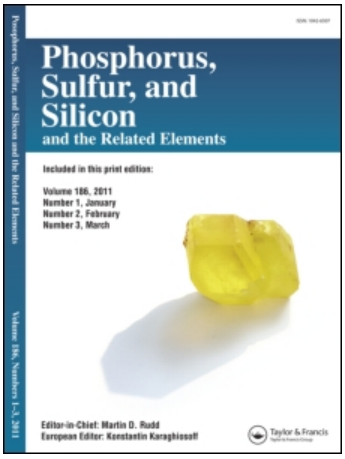

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Recent Applications of Organotin Oxides/Hydroxides and Alkylstannonic Acids in Organic Synthesis

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We describe the application of trimethyltin hydroxide to the solid phase cleavage of the benzyl ester linkage between amino acids/dipeptides and resins. Butylstannonic acid is used as catalyst for transesterification of various carboxylic esters. This method is also applicable to acetylation/deacetylation of alcohols.

Keywords: organotin reagents; deesterification; transesterification; resins

ESTERIFICATIONS, TRANSESTERIFICATIONS, AND DEESTERIFICATIONS MEDIATED BY ORGANOTIN OXIDES/HYDROXIDES AND BUTYLSTANNONIC ACID

Esterifications, transesterifications, and deesterifications are important and well established reactions which are widely used in organic synthesis for various purpose.[1]

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In a polyfunctional substrate, a selective chemical reaction in one site needs in many cases the protection of the other reactive sites. The use of ester group for the protection of carboxylic acids and alcohols in organic synthesis is a common procedure in that the esters are easy to prepare and offer good stability to a variety of reactions conditions.[2]

DEESTERIFICATIONS OF CARBOXYLIC ESTERS BY ORGANOTIN OXIDES/ HYDROXIDES

As part of an ongoing effort, the development of non-acidic, mild and efficient reagents for deprotection of carboxylic esters has been the focus of our interest.[3] In a recent series of papers, we have documented the utility of bis(tributyltin) oxide and trimethyltin hydroxide (henceforth abbreviated BBTO and TMTOH, respectively) as useful, non-acidolytic reagents for the selective cleavage of primary alkyl carboxylic esters, double esters such as (pivaloyloxy)methyl carboxylates as well as phenacyl, benzyl and methyl esters.

Due to our interest in transferring solution phase onto solid phase chemistry, we decided to explore the selective cleavage by TMTOH of Boc-protected amino acids and peptides benzyl ester linked to Merrifield, PAM and Wang resins.[3a]

Model cleavage studies for the Merrifield resin are shown in Table 1 demonstrating the efficiency of this method with yields ranging from 85 to 100%. We also tested the usefulness of the cleavage by TMTOH of the benzyl ester linkage in PAM and Wang resins (see Table 2).

We found that TMTOH selectively cleaves Boc-aspartic acid β-cyclohexyl ester and Boc-glutamic acid γ-cyclohexyl ester attached to Merrifield and PAM resins affording Boc-Asp(OcHex)-OH and Boc-Glu(OcHex)-OH in yields ranging from 90 to 100%. These results demonstrate the potential of this new orthogonal deprotection protocol for

TABLE 1. Release of protected amino acids and peptides from Merrifield resin by TMTOH.

Entry	Substrate	Product[a]	Reaction time (h)	% Isolated yield
1	Boc-Tyr(OBn)-Gly-resin[b] (**1**)	Boc-Tyr(OBn)-Gly-OH (**2**)	10	84
2	Boc-Cys(*Sp*MeOBn)-resin (**3**)	Boc-Cys(*Sp*MeOBn)-OH (**4**)	10	85
3	Boc-Ser(OBn)-resin (**5**)	Boc-Ser(OBn)-OH (**6**)	13	100
4	Boc-Ile-resin (**7**)	Boc-Ile-OH (**8**)	9	100
5	Boc-His(Tos)-resin (**9**)	Boc-His(Tos)-OH (**10**)	9	93

[a]heated at reflux of 1,2-dichloroethane. [b]abbreviations: Bn = benzyl, Tos = tosyl (4-toluene sulfonyl);*Sp*MeOBn = S-*p*-methoxybenzyl.

TABLE 2. Release of protected amino acids and peptides from PAM and Wang resins by TMTOH.

Entry	Substrate	Product[a]	Reaction time (h)	% Isolated yield
1	Boc-Phe-Met-PAM resin (**11**)	Boc-Phe-Met-OH (**12**)	10	80
2	Boc-Ser(OBn)-Ala-PAM resin (**13**)	Boc-Ser(OBn)-Ala-OH (**14**)	9	97
3	Boc-Ala-PAM resin (**15**)	Boc-Ala-OH (**16**)	9	94
4	Boc-Met-PAM resin (**17**)	Boc-Met-OH (**18**)	9	90
5	Boc-Pro-PAM resin (**19**)	Boc-Pro-OH (**20**)	9	80
6	Boc-Leu-Wang resin (**21**)	Boc-Leu-OH (**22**)	12	100
7	Boc-Pro-Phe-Wang resin (**23**)	Boc-Pro-Phe-OH (**24**)	12	100
8	Boc-Thr(OBn)-Leu-Wang resin (**25**)	Boc-Thr(OBn)-Leu-OH (**26**)	11	100

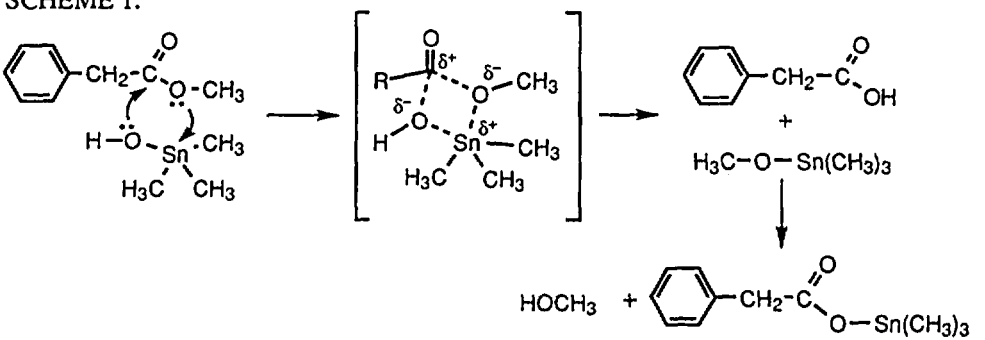
[a]heated at reflux of 1,2-dichloroethane.

TABLE 3. Release of *N*-α-Boc-aspartic acid β-cyclohexyl ester and *N*-α-Boc-glutamic acid γ-cyclohexyl ester from Merrifield and PAM resins by TMTOH.

Entry	Substrate	Product[a]	Reaction time (h)	% Isolated yield
1	Boc-Asp(OcHex)-Merrifield resin[b] (**27**)	Boc-Asp(OcHex)-OH (**28**)	12	97
2	Boc-Glu(OcHex)-Merrifield resin (**29**)	Boc-Glu(OcHex)-OH (**30**)	12	97
3	Boc-Glu(OcHex)-PAM resin (**31**)	Boc-Glu(OcHex)-OH (**30**)	10	100
4	Boc-Asp(OcHex)-PAM resin (**32**)	Boc-Asp(OcHex)-OH(**28**)	11	90

[a]heated at reflux of 1,2-dichloroethane. [b]cHex = cyclohexyl.

SCHEME 1.



solid phase synthesis, when aspartic and glutamic acid side chain carboxylate groups are protected as cyclohexyl esters (see Table 3).

A mechanism for the cleavage of methyl phenylacetate by TMTOH have been proposed by us (see Scheme 1).[3a]

TRANSESTERIFICATIONS OF CARBOXYLIC ESTERS CATALYZED BY BUTYLSTANNONIC ACID.

Transesterification of carboxylic esters constitute a powerful method to synthesize a variety of carboxylic esters.[4] Typically the reaction is catalyzed by strong acids and bases,[4] however these methods fail with molecules containig acid or base-labile functional groups. In contrast, iodo-trimethylsilane,[5] bis[1-(hydroxydi-n-butyl)-3-(isothiocyanatodi-n-butyldis-tannoxane], bis[1-(hydroxydi-n-butyl)-3-chlorodi-n-butyl)di-stannoxane],[6] and a series of mono-organotin (IV) compounds,[7-9] as well as a number of titanium tetraalkoxides developed by Seebach *et al.*,[10] have been recommended as exceptionally mild and efficient catalysts for the transesterification of carboxylic esters in the presence of acid-sensitive groups.

Herein we would like to present that using butylstannonic acid [BuSn(O)OH] as a catalyst, an unprecedented transesterification reaction takes place leading to excellent yields of carboxylic esters in the presence of several functional groups, and we also found this catalyst can be applied for a facile and selective O-acylation/O-deacylation of alcohols.[11]

As reported in Table 4, good yields of transesterified esters were obtained from primary neopentyl alcohol (entry 3), secondary (entries 4 and 5) and benzyl alcohols (entries 1, 2, and 6). The optical purity of chiral alcohols does not decrease during transesterification, for example, (1R,2S,5R)-(-)-menthol and [(1S)-endo-](-)-borneol are recovered

without loss of optical purity by the TMTOH cleavage of the transesterification product, bornyl 4-bromocrotonate (**40**) and menthyl 2-butynoate (**42**) (entries 4 and 5). Boc protected esters of dipeptides (i.e. entry 6) can be transesterified using BuSn(O)OH and this procedure provides a good way of converting methyl esters into their benzyl counterparts; such reactions proceeded in 90% isolated yield. Our attention was then directed towards the reaction of transesterification catalized by BuSn(O)OH using the alcohols as solvent. The results for the three examples shown in Table 5 indicate that the ease with which a target ester is formed is dependent upon the combination of alcohol and ester reactants. i) Ethanol (entry 1) has the strongest replacing power. ii) The replacing power of n-propanol, a longer alkyl chain, is lower (entry 2). iii) Branching of the chain (isopropanol) causes the decrease in the reactivity (entry 3).

Despite of the recent introduction of several useful methods for the protection of hydroxyl groups,[12] still exists a real need for high yield and mild conditions to introduce and remove O-acetyl groups by a highly specific reagent. This is highly desirable for synthetic reactions involving multifunctional compounds.

The use of BuSn(O)OH as catalyst and ethyl acetate as an acetylating agent and, conversely, use of methanol as a deacetylating agent, proved to be exceedingly effective. The specific reactions which are outlined in Scheme 2 provide an illustration of the applicability of butylstannonic acid catalysis for the acetylation/deacetylation of alcohols. The acetyl group was introduced in 1-adamantanemethanol in 83% yield (eq. 1). Complementary, the deprotection of 3-acetyl group in 3-O-acetyl-1,2,5,6-di-isopropyliden-α-D-glucofuranose (**50**) with methanol and BuSn(O)OH as catalyst, was accomplished in quantitative yield (eq. 2).

Further investigation concerning to the scope and mechanism of the present reaction is now in progress.

TABLE 4. Transesterification mediated by BuSn(O)OH in toluene at reflux.

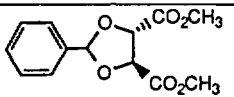
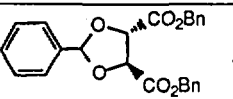
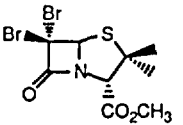
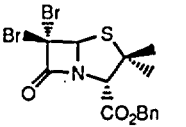
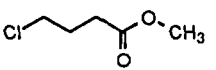
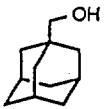
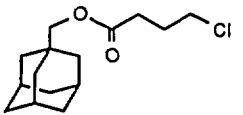
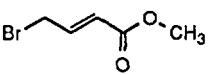
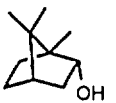
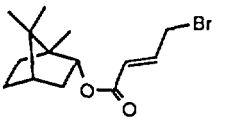
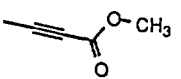
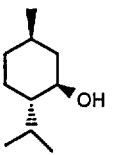
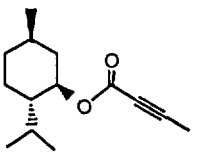
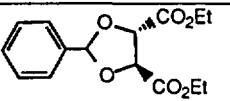
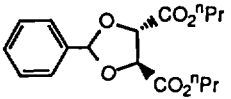
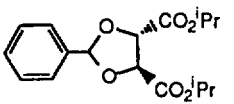
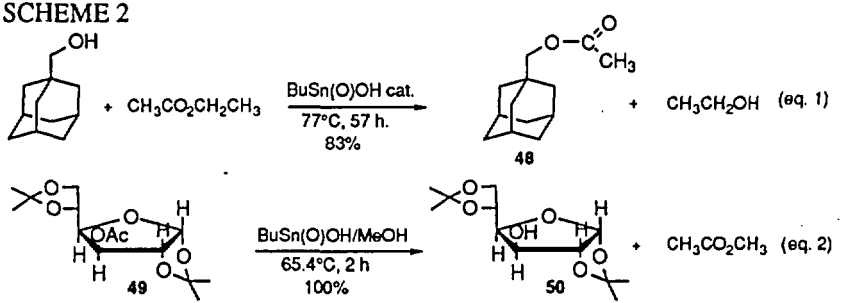
Entry	Substrate		Alcohol	Time (h)	Product		Isolated yield (%)
1		**33**	Benzyl alcohol	19		**34**	90
2		**35**	Benzyl alcohol	41		**36**	84
3		**37**		22		**38**	94
4		**39**		21		**40**	87
5		**41**		23		**142**	89
6	Boc-Phe-Pro-OCH_3	**43**	Benzyl alcohol	25	Boc-Phe-Pro-OBn	**44**	90

TABLE 5. Transesterification mediated by BuSn(O)OH in alcohols at reflux

Entry	Substrate	Alcohol	Time (h)	Product		Isolated yield (%)
1	**33**	CH_3CH_2OH	16		**45**	80
2	**33**	$CH_3(CH_2)_2OH$	16		**46**	65
3	**33**	$(CH_3)_2CHOH$	27		**47**	46

SCHEME 2



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