Efficient, non-acidolytic method for the selective cleavage of *N*-Boc amino acid and peptide phenacyl esters linked to a polystyrene resin

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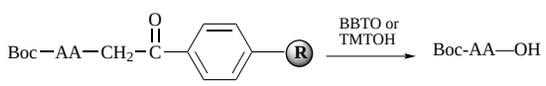
An efficient, non-acidolytic method for the selective cleavage of phenacyl esters of *N*-Boc-amino acids and -peptides linked to a polystyrene resin by $(CH_3)_3SnOH$ (TMTOH) or $[(n\text{-}C_4H_9)_3Sn]_2O$ (BBTO) is described. We highly recommend the use of trimethyltin hydroxide for the selective cleavage of carboxylic esters based on its favourable properties. The method is compatible with an *N*-Boc/*O*-Bn (benzyl ether) strategy and yields enantiomerically pure *N*-Boc-peptides useful for further manipulation, for segment condensations or for cyclization strategies. A mechanism for the cleavage of methyl phenylacetate in solution by TMTOH is postulated.

Selective deprotection of a particular functional group in the presence of others is still one of the most important transformations in organic synthesis.[1] A typical example is the selective cleavage of phenacyl (Pac) esters.[2,3] The development of new non-acidolytic reagents for the selective cleavage of benzyl esters of a variety of heterocyclic structures such as β-lactams, benzodiazepines, hydantoins, pyrrolidines, thiazolidinones, diketopiperazines and other small organic molecules, as well as of biological oligomers such as peptides, oligosaccharides, oligonucleotides and peptidomimetics, from polystyrene resins to increase synthetic efficiency of final products or intermediate protected segments continues to attract the attention of synthetic chemists and is one of the most important steps of solid-phase organic synthesis (SPOS), particularly solid-phase peptide synthesis (SPPS)[4] and its application in the growing field of combinatorial synthesis.[5–8]

While the benzyl ester linkage is the most frequent mode of attachment of the first amino acid or non-peptide carboxylic acid functional molecule to polystyrene chains cross-linked with divinylbenzene (DVB) as in Merrifield,[9] Wang,[10] Pam,[11] Sasrin[12] and Riniker[13] resins, the phenacyl ester–polystyrene resins[14] have not been extensively used in SPOS and SPPS, although this function can be readily introduced into the polystyrene resin, is stable to acidic conditions, and therefore is suitable for orthogonal deprotection of the *N*-*tert*-butoxycarbonyl (Boc) group and other acid-labile protecting groups.

In the Merrifield protocol involving Boc-peptides, the method of cleavage of the benzyl ester linkage from the resin involves anhydrous hydrogen fluoride (HF).[15,16] The cleavage step in the more acid-labile resins, such as Wang,[17] Sasrin[17,18] and Riniker,[19] is effected by trifluoroacetic acid (TFA). In these acidolytic methods all protective groups sensitive to acid are cleaved in the process to yield the free (or unprotected) peptide. Cleavage of Boc peptide Pac ester–polystyrene resins by tetrabutylammonium fluoride (TBAF) was reported by Kiso *et al.*[20]

In a recent series of papers, we have documented the utility of bis(tributyltin) oxide[21] (henceforth abbreviated BBTO) as a useful, non-acidolytic reagent for the selective cleavage of primary alkyl carboxylic esters, double esters such as (pivaloyloxy)methyl carboxylates[22a–c] as well as phenacyl, benzyl and methyl esters of simple N-protected amino acid and dipeptides and N-protected amino acid benzyl esters linked to Wang and Pam resins.[22d] We also investigated the cleavage, in solution, of methyl and isopropyl phenylacetates by trialkyltin, triaryltin and dialkyltin oxides as well as triaryltin and trialkyltin hydroxides under classical heating and microwave irradiation.[23] In this note we report that trimethyltin hydroxide (TMTOH) and BBTO cleave, cleanly and efficiently, *N*-Boc amino acids and peptides linked through a Pac ester to a polystyrene resin, giving the corresponding *N*-Boc amino acids or peptides in high yield (Scheme 1).



1 AA = L-Ala-O
2 AA = L-Ala-OH
3 AA = L-Ser(O-Bn)-O
4 AA = L-Ser(O-Bn)-OH
5 AA = L-Phe-L-Pro-O
6 AA = L-Phe-L-Pro-OH
7 AA = L-Leu-L-Pro-O
8 AA = L-Leu-L-Pro-OH

R = polystyrene resin

Scheme 1

Results and discussion

The 2-bromoacetyl resin ($BrCH_2COC_6H_4$-resin) was obtained from reaction of the polystyrene resin (copolystyrene, 3% DVB) beads (200–400 mesh)[24] with 2-bromoacetyl bromide in the presence of $AlCl_3$. The incorporation of *N*-Boc amino acids and dipeptides into the resin was achieved by stirring the 2-bromoacetyl resin with a slight excess of their respective triethylammonium salts in ethyl acetate.[14] The loading of 2-bromoacetyl resin and the degree of incorporation of Boc amino acid or peptide in *N*-Boc-AA-CO_2-$CH_2COC_6H_4$-resin were verified by the modified Volhard method.[25]

Table 1 summarizes the experimental results and illustrates the efficiency of the present cleavage method. Treatment of Boc-L-Ala-Pac-polystyrene resin **1** with BBTO in refluxing 1,2-dichloroethane [$(CH_2Cl)_2$] afforded Boc-L-Ala-OH[26] **2** in quantitative yield (entry 1). When a mixture of substrates **1**, BBTO and dimethylformamide (DMF) was subjected to microwave irradiation at 650 W for 50 min, compound **2** was isolated in 83% yield (entry 2). Treatment of compound **1** with TMTOH in refluxing $(CH_2Cl)_2$ for 15 h furnished compound **2** in 96% yield (entry 3). The Pac ester of Boc-L-serine(*O*-benzyl)-Pac-polystyrene resin **3** was also cleaved with TMTOH, yielding Boc-L-ser(*O*-benzyl)-OH in 96% yield (entry 5). This result demonstrated that the cleavage of the Pac ester by TMTOH proceeded with complete retention of both the *N*-Boc and the side-chain *O*-Bn[26] protecting groups of serine. Cleavage of compound **3** with the sterically hindered BBTO (entry 4), required a longer reaction time and the yield was lower.

We have also studied the cleavage of the *N*-Boc dipeptide

Table 1 Cleavage of Boc-amino acid and -dipeptide Pac ester linked to polystyrene resin by BBTO and TMTOH

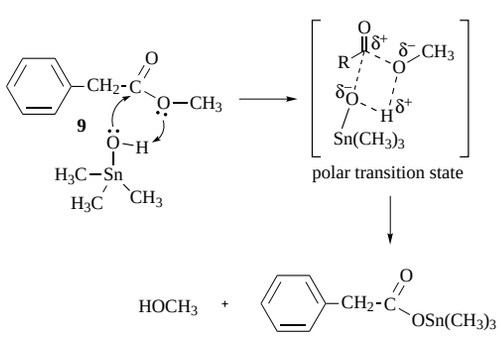
Entry	Starting material	Product[a]	Conditions[b]	Yield (%)[d]
1	**1**	**2**	BBTO, 25 h	100
2	**1**	**2**	BBTO, 50 m[c]	83
3	**1**	**2**	TMTOH, 15 h	96
4	**3**	**4**	BBTO, 22 h	45
5	**3**	**4**	TMTOH, 15 h	96
6	**5**	**6**	BBTO, 15 h	58
7	**5**	**6**	TMTOH, 13 h	80
8	**7**	**8**	BBTO, 15 h	67
9	**7**	**8**	TMTOH, 15 h	78

[a] Comparison of TLC, ^{1}H NMR, ^{13}C NMR and $[\alpha]_D$ with authentic samples confirmed the identity of the products. [b] All reactions were performed with 2.2 mol equiv. of reagent in 1,2-dichloroethane at 83 °C, unless otherwise indicated. [c] Reaction performed under microwave irradiation at 650 W in DMF. [d] Yields reported correspond to isolated compounds that were pure by NMR spectroscopy.

Pac-polystyrene resins **5** and **7**. Treatment of Boc-L-Phe-L-Pro-Pac-resin **5** with TMTOH in refluxing $(CH_2Cl)_2$ for 15 h led to detachment of Boc-L-Phe-L-Pro-OH **6** from the solid matrix in 80% yield (entry 7), while the cleavage with BBTO provided acid **6** in 58% yield after treatment for 15 h (entry 6). In the cleavage of peptide-resin **5** with TMTOH or BBTO there was no evidence of free Pro-OH, demonstrating that the peptide bond is unaffected. A similar result was obtained in the cleavage of Boc-L-Leu-L-Pro-Pac resin **7** by TMTOH and BBTO, which yielded the corresponding *N*-Boc-dipeptide Boc-L-Leu-L-Pro-OH **8** in 78 and 67%, respectively (entries 8 and 9). Based on a comparison of the yield of products **4**, **6** and **8** it may be concluded that the cleavage reaction of resins **3**, **5** and **7** with BBTO is hampered by steric hindrance around the carboxyl and carbinol carbons as previously evidenced.[22a] These results indicate that the versatile TMTOH reagent is much more efficient than BBTO for the cleavage of the Pac ester of these resins.

Anchoring of *N*-Boc-amino acids and dipeptides through Pac esters to the 2-bromoacetyl resin and subsequent cleavage with TMTOH occurs without noticeable racemization. For example, the optically active *N*-Boc-amino acids **2**, **4** (entries 3 and 5) and *N*-Boc-dipeptides **6** and **8** (entries 7 and 9) were obtained without loss of enantiomeric purity.

Our efforts were directed at determining some mechanistic aspects of the reaction with TMTOH. A 0.05 M aq. solution of TMTOH was shown to have pH 7.6. The regiochemistry of the acyl-oxygen bond cleavage was documented when methyl phenylacetate **9** was treated with TMTOH and the product of reaction was analyzed using IR spectroscopy, and ^{1}H, ^{13}C and ^{119}Sn NMR spectroscopy to reveal $C_6H_5CH_2CO_2Sn(CH_3)_3$ **10** as the only organotin product isolated[27] (Scheme 2). On the basis



Scheme 2

of the above information it is likely that the mechanism of cleavage of carboxylic esters with the weakly basic TMTOH is similar to the proposed mechanism with BBTO, a weak Lewis acid,[22a,23] which implies that the 'hard' oxygen atom of TMTOH coordinates with the 'hard' electrophilic carbonyl carbon, through a polar transition state.

Most of the organotin oxides and hydroxides and their by-products are highly soluble in nonpolar solvents and very insoluble in water. TMTOH is the only organotin compound soluble in water and very insoluble in most organic solvents. We have used these properties extensively to purify carboxylic acids and alcohols.[22a,23]

In conclusion we have described an application of TMTOH and BBTO for the selective cleavage of Pac esters of *N*-Boc-amino acids or -dipeptides linked to a polystyrene resin, rendering *N*-Boc-amino acids and -peptides. The TMTOH reagent overcame the limitations of the BBTO reagent, including the steric congestion, which is reflected in the rate of cleavage of hindered carboxylic esters and *N*-Boc-amino acid benzyl esters bound to the Merrifield resin.[22d] We highly recommend the use of TMTOH based (i) on the simplicity in the separation of TMTOH and its organotin by-products; (ii) on the high yield of products and (iii) because the cleavage of Pac ester *N*-Boc-amino acids and *N*-Boc-dipeptides linked to polystyrene resins with TMTOH afforded *N*-Boc-amino acids and *N*-Boc-dipeptides with complete retention of enantiomeric purity. The method is compatible with an *N*-Boc/*O*-Bn ether strategy (*i.e.*, for protection on the side-chain) yielding protected peptides useful for further manipulation, for segment condensations or for cyclization strategies.[28]

The postulated reaction mechanism of the acyl-oxygen bond-cleavage regiochemistry, supported by the products **10** and methanol, involves attack of the 'hard' oxygen atom on the carbonyl carbon, followed by attack of the 'hard' nucleophilic oxygen of the carbinol moiety on the 'hard' electrophilic hydrogen atom, in analogy with our previously published mechanism for BBTO.[22a,23]

The present reaction with TMTOH provides a synthetic method for the selective cleavage of Pac esters linked to polystyrene resins, which we hope will be useful for further applications to solid-phase synthesis and to production of combinatorial libraries, in particular of small organic compounds where acid-sensitive functional groups are present.

We are currently exploiting the TMTOH reagent for the cleavage of larger peptides with a variety of side-chain functional groups linked through phenacyl and benzyl esters of polymeric resins.

Experimental

General details

The IR spectrum of compound **10** was run on a Bruker IF525 FTIR spectrophotometer. NMR spectra were measured in $CDCl_3$ or $(CD_3)_2SO$ ([$^2H_6$]DMSO) at 200 MHz for protons and 20.15 MHz for ^{13}C, on a Bruker AC200 spectrometer. *J*-Values are in Hz. Optical rotations were measured with a JASCO DIP-1000 polarimeter at ambient temperature using a 1-ml capacity cell. $[\alpha]_D$-Values are in 10^{-1} deg cm^2 g^{-1}. TLC and spectral analyses (^{1}H and ^{13}C NMR) indicated that all products were identical with commercial authentic material. Boc-L-Ala-OH, *N*-Boc-L-Ser-(OBn)-OH, Boc-L-Phe-L-Pro-OH and Boc-L-Leu-L-Pro-OH were purchased from Bachem Bioscience Inc. The polystyrene/3% divinylbenzene resin (Bio-Beads S-X3) was purchased from Bio-Rad. The $BrCH_2COC_6H_4$-resin was prepared using a literature procedure[14] and was analyzed using the modified Volhard method.[25]

Representative procedure for the attachment of the preformed Boc-amino acid or Boc-peptide derivatives to resin

Bromoacetyl resin (1.0 g) containing 1.94 mmol equiv. Br/g was stirred with 6 ml of AcOEt for 30 min. To this was added a solution of Boc-L-Ala (488 mg, 2.58 mmol) and Et_3N (290 mg, 286 mmol) in 3 ml of AcOEt, and the mixture was stirred for

22 h at room temp. The esterified resin was then collected by filtration and washed successively with AcOEt, $CHCl_3$, 1,4-dioxane–water (3:1, v/v), water, 1,4-dioxane and MeOH, and dried overnight at reduced pressure to give 1.21 g of resin **1**.

Similarly prepared were the resin analogues of *N*-Boc-(OBn)-L-Ser (**3**), Boc-L-Phe-L-Pro (**5**) and Boc-L-Leu-L-Pro (**7**).

Determination of *N*-Boc-L-Ala residue on resin 1

A 0.2 g portion of resin **1** was stirred with 2.5 M dry HCl/AcOEt for 40 min and collected by filtration. The resin was then washed successively with AcOEt, 1,4-dioxane, aq. 1,4-dioxane, water and MeOH. The resulting alanyloxyacetyl-resin hydrochloride was suspended in DMF and treated with 10 ml of DMF containing 1 ml of Et_3N, filtered, and washed with DMF. The combined filtrate and washings were evaporated to dryness under reduced pressure and the residue, triethylamine hydrochloride, was analyzed by the Volhard method and found to have a substitution level of 1.38 mmol Boc-Ala/g.

Representative procedure for the cleavage of Boc-amino acids and Boc-peptide-Pac-polystyrene resin by BBTO

To a stirred suspension of Boc-L-Ala resin **1**, 1.16 mmol equiv. Boc-Ala/g of resin (0.151 g, 0.175 mmol), in 1 ml of $(CH_2Cl)_2$ was added BBTO (178 ml, 0.350 mmol) at room temp. under nitrogen. The reaction mixture was then refluxed (83 °C) for 25 h and the resulting suspension was filtered, and washed successively with CH_2Cl_2 and AcOEt. The combined organic solution was evaporated to dryness *in vacuo* and the resultant residue was dissolved in 20 ml of AcOEt and then extracted with 5% aq. $NaHCO_3$ (3 × 5 ml). The combined aqueous solution was acidified to pH 4.5 with 0.5 M aq. $KHSO_4$ and extracted with AcOEt (3 × 10 ml). The AcOEt solution was dried (Na_2SO_4) and evaporated to dryness to give 0.0331 g (100%) of *N*-Boc-Ala-OH **2** as a solid, $[\alpha]_D^{20}$ −26.3 (*c* 2.0, AcOH) [lit.,[29] −26.2 (*c* 2.0, AcOH)]; $\delta_H([^2H_6]DMSO)$ 0.97 (d, *J* 7.34, 3 H), 1.12 (s, 9 H), 3.66 (m, 1 H) and 6.78 (d, *J* 7.62, 1 H).

Representative procedure for the cleavage of Boc-amino acids and peptide-Pac-polystyrene resin by TMTOH

To a stirred suspension of Boc-L-ser-(OBn)-resin **3**, 0.8 mmol equiv. Boc-Ser-(OBzl)/g of resin (0.141 g, 0.113 mmol) in 1 ml of $(CH_2Cl)_2$, was added TMTOH (0.068 g, 0.249 mmol) at room temp. under nitrogen. The reaction mixture was then refluxed (83 °C) for 15 h and the resulting suspension was filtered, and washed successively with $(CH_2Cl)_2$, CH_2Cl_2 and AcOEt. The combined organic solution was evaporated to dryness under reduced pressure and the resultant residue was dissolved in 10 ml of AcOEt, washed with 0.5 M HCl (3 × 5 ml), and dried with Na_2SO_4. The solvent was removed by rotatory evaporator to yield a solid (0.032 g, 96%). ^1H NMR analysis of the crude reaction product showed only *N*-Boc-Ser-(OBn)-OH **4**. No other product was detected by ^1H NMR analysis. $[\alpha]_D^{20}$ +19.5 (*c* 2.0, 80% EtOH) [lit.,[29] +19.8 (*c* 2.0, 80% EtOH)]; $\delta_H(CDCl_3)$ 1.45 (s, 9 H), 3.70 (dd, *J* = 9.45 and 3.95, 1 H), 3.91 (dd, *J* 9.45 and 3.95, 1 H), 4.47 (m, 1 H), 4.52 (s, 2 H), 5.46 (d, *J* 8.16, 1 H) and 7.29 (m, 5 H).

Procedure for the cleavage of Boc-L-Ala-Pac-polystyrene resin 1 by BBTO, under microwave irradiation

Boc-L-Ala resin **1**, 1.16 mmol equiv. Boc-Ala/g of resin (0.151 g, 0.176 mmol) in 2 ml of DMF, and BBTO (179 ml, 0.351 mmol) were mixed in a 10 ml Erlenmeyer flask, covered with an inverted funnel and placed in a commercial microwave oven and irradiated at 650 W. After 5 min of heating the microwave irradiation was discontinued and the DMF solution was cooled. This protocol was repeated until an overall heating time of 50 min had been attained. The approximate temperature was estimated to be 110 °C, the mp of resorcinol in a closed capillary placed into the reaction flask. After cooling, the resin was collected by filtration and washed successively with DMF, CH_2Cl_2 and AcOEt. The combined organic solution was evaporated to dryness under reduced pressure and the resultant residue was dissolved in 15 ml of AcOEt and the solution was extracted with 5% aq. $NaHCO_3$ (3 × 5 ml). The combined aqueous solution was acidified to pH 4.5 with 0.5 M aq. $KHSO_4$ and extracted with AcOEt (3 × 10 ml). The AcOEt solution was dried (Na_2SO_4) and evaporated to dryness to give pure Boc-Ala-OH **2** as a solid (0.0275 g, 83%).

Boc-L-Phe-L-Pro-OH 6. $[\alpha]_D^{20}$ −32.0 (*c* 1.0, EtOH) [lit.,[29] −32.2 (*c* 1.0, EtOH)]; $\delta_H([^2H_6]DMSO)$ 1.30 (br s, 9 H), 1.79–2.25 (m, 4 H), 2.69–3.01 (m, 2 H), 3.45–3.75 (m, 2 H), 4.25–4.49 (m, 2 H), 6.97 (d, *J* 8.3, 1 H) and 7.26 (m, 5 H); $\delta_H(CDCl_3)$ 1.38 (s, 9 H), 1.81–2.38 (m, 5 H), 2.94–3.07 (m, 2 H), 3.56–3.73 (m, 1 H), 4.49–4.72 (m, 2 H), 5.40–5.50 (br s, 1 H) and 7.25 (br s, 5 H); $\delta_C(CDCl_3)$ 174.35, 171.98, 155.18, 136.03, 129.45, 128.27, 126.83, 79.69, 59.15, 53.29, 47.00, 38.80, 28.18, 28.11 and 24.57.

Boc-L-Leu-L-Pro-OH 8. $[\alpha]_D^{20}$ −71.5 (*c* 2.0, MeOH) [lit.,[29] −72.0 (*c* 2.0, MeOH)]; $\delta_H(CDCl_3)$ 0.94 (d, *J* 6.28, 3 H), 0.98 (d, *J* 6.28, 3 H), 1.43 (s, 9 H), 1.20–1.80 (m, 3 H), 2.00–2.25 (m, 4 H), 3.50–3.85 (m, 2 H), 4.40–4.63 (m, 2 H) and 5.20–5.35 (m, 1 H); $\delta_C(CDCl_3)$ 173.69, 173.43, 155.63, 79.67, 59.16, 50.24, 47.03, 41.46, 28.21, 28.01, 24.73, 24.41, 23.21 and 21.59.

$C_6H_5CH_2CO_2Sn(CH_3)_3$ 10. The data for compound **10** are as follows: ν_{max}(KBr)/cm^{-1} 1576, 1428, 1206 and 775; $\delta_H(CDCl_3)$ 0.52 [CH_3Sn, *J*(Sn,H) 58.2, 9 H], 3.62 (s, 2 H) and 7.28 (s, 5 H); $\delta_C(CDCl_3)$ 129.12, 128.27, 126.48, 41.77 and −2.59; ^{119}Sn $\delta_{Sn}(C_6D_6$; Me_4Sn internal standard) 118.66. The IR and ^1H spectra of $CH_3CO_2Sn(CH_3)_3$ are identical with those reported in ref. 27.

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26 Abbreviations used in this paper for amino acids and for the designation of peptides follow the rules of the IUPAC–IUBC Commission of Biochemical Nomenclature in *J. Biol. Chem.*, 1972, **247**, 977. Other abbreviations are as follows: Bn, benzyl; Boc, *tert*-butoxycarbonyl; DVB, divinylbenzene.
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28 For recent reviews on convergent solid-phase peptide synthesis, see: P. L. Williams, F. Albericio and E. Giralt, *Tetrahedron*, 1993, **49**, 11 065; H. Benz, *Synthesis*, 1994, 337.
29 $[a]_D$-Values for compounds **2**, **4**, **6** and **8** were taken from the Analytical Data Sheet from Bachem Feinchemikalien AG (Switzerland).

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