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SELECTIVE TRANSFORMATION OF N-t-BUTOXYCARBONYL GROUP INTO N-ALKOXY-CARBONYL GROUP via N-CARBOXYLATE ION EQUIVALENT

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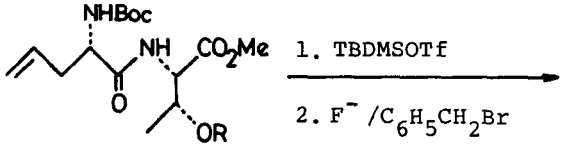
SUMMARY: Reaction of a variety of N-t-butoxycarbonyl compounds with t-butyldimethylsilyl trifluoromethanesulfonate afforded the N-t-butyldimethylsilyloxycarbonyl compounds, chemoselectively, which upon treatment with an alkyl or aryl halide provided the corresponding N-alkoxy- or N-aryloxycarbonyl compounds, efficiently.

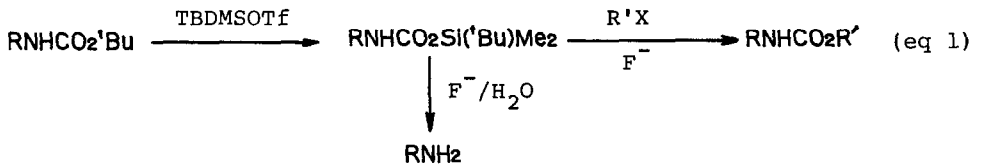
One of the most common amino protecting functionalities used for amino acids, amino sugars, and peptides is the t-butoxycarbonyl (t-Boc) moiety.[1] This group is inactive to a variety of reagents and easy to remove. However, the coexistence with acid-sensitive groups cannot be employed since removal requires relatively strong acidic conditions.[1,2] The interconversion of the t-butoxycarbonyl group into the benzyloxycarbonyl (Z) group, an acid-stable N-protecting group which can be removed under neutral conditions, would be an important method in organic synthesis. To date, no report has appeared dealing with the conversion of the t-Boc group into the Z group via an N-carboxylate ion intermediate.



1a R = H
1b R = THP

2 $R^1 = R^2 = Si(t\text{-}Bu)Me_2$
3a $R^1 = H$, $R^2 = CH_2Ph$
3b $R^1 = THP$, $R^2 = CH_2Ph$

We have discovered that t-butyldimethylsilyl trifluoromethanesulfonate[3] (TBDMSOTf), a powerful silylating reagent of hydroxyl groups, can be used to effect the transformation of the t-Boc group into the t-butyldimethylsilyloxycarbonyl group (1a[4] → 2). The subsequent treatment with benzyl bromide followed by tetra-n-butylammonium fluoride (n-Bu_4NF) provided the N-benzyloxycarbonyl compound 3a[5] in 54% yield; mp 106.0-106.5 °C; $[\alpha]_D^{27}$ -8.5° (c 1.0, CH_3OH). The selective conversion of 1b[4] with a tetrahydropyranyl ether was also successful to give the N-Z dipeptide 3b[5] in 78% yield as an oil. The present method is generally applicable for the conversion of t-Boc group into various alkoxy- or aryloxy-carbonyl groups (eq 1).



(eq 1)

Usually, N-t-butyldimethylsilyloxycarbonyl compounds are stable under the work-up conditions (see experimental procedure). As expected, exposure to a fluoride ion in the presence of water and the following work-up yielded the corresponding free amine in excellent yield (Table II, entry 5). An efficient conversion into several alkoxycarbonyl groups is summarized in Table I. The synthetically useful transformations of N-t-Boc amino acid esters to N-Z amino acid esters were also successful as shown in Table II.

The representative experimental procedure is as follows: Commercially available t-butyldimethylsilyl trifluoromethanesulfonate (0.172 ml, 0.75 mmol) was added dropwise at room temperature to a solution of N-t-butoxycarbonyl-L-valine methyl ester (115.5 mg, 0.5 mmol) and 2,6-lutidine (0.116 ml, 1.0 mmol) in dry dichloromethane (1.0 ml) under nitrogen. The resulting solution was stirred for 15 min and quenched with saturated ammonium chloride solution. The product was extracted several times with ether. The combined ether layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo (153 mg); oil; MS (EI method) 290 $(M+1)^+$. The residue was subjected to the next step without purification. To the resultant N-t-butyldimethylsilyloxycarbonyl-L-valine methyl ester (130 mg, 0.42 mmol) in dry tetrahydrofuran (1.0 ml) at 0 °C was added benzyl bromide (0.101 ml, 0.84 mmol) followed by a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (0.42 ml, 0.42 mmol) under nitrogen. After being stirred for 1 h at the same temperature, the reaction mixture was poured into water, extracted with ether, dried over magnesium sulfate, and concentrated in vacuo. The residue was subjected to column chromatography on silica gel using ether-hexane (1 : 5) as eluent to give N-

Table I. Conversion of N-t-butyldimethylsilyloxycarbonyl-DL-allylglycine methy ester (4)[a] into the N-alkoxycarbonyl derivatives.

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Entry	Fluoride[b]	Electrophile[b]	Product (R)[5]	Yield (%)[c]
1.	n-Bu_4NF	CH_3I	CO_2CH_3	84
2.	n-Bu_4NF	CH_2=$CHCH_2Br$	CO_2CH_2CH=CH_2	82
3.	n-Bu_4NF	$C_6H_5CH_2Br$	$CO_2CH_2C_6H_5$ (Z)	88

[a] Prepared from N-t-Boc allylglycine methyl ester by treatment with 1.5 eq TBDMSOTf and 2.0 eq 2,6-lutidine at room temperature for 15 min. [b] All reactions were conducted at 0 °C under nitrogen using 2.0 eq electrophile in dry tetrahydrofuran. [c] Overall yield from the t-Boc allylglycine methyl ester.

Table II. N-Z amino acid methyl esters from N-t-Boc amino acid methyl esters.[a]

Entry	N-t-Boc amino acid ester	N-Z amino acid ester	Yield (%)	$[\alpha]_D^{27}$ [b]
1.	t-Boc-L-Val-OMe	Z-L-Val-OMe	85	-19.4°
2.	t-Boc-L-Met-OMe	Z-L-Met-OMe[c]	61	-32.7°
3.	t-Boc-L-Phe-OMe	Z-L-Phe-OMe	78	-14.9°
4.	t-Boc-L-Pro-OMe	Z-L-Pro-OMe	75	-62.0°
5.	t-Boc-L-Phe-OMe	H-Phe-OMe[d]	92	———

[a] All reactions were carried out according to the experimental procedure. [b] $[\alpha]_D$ values were measured using methanol as the solvent (c 1.0). The observed values were identical with those of reported.[6] [c] 1.0 eq of benzyl bromide was added. [d] Quenched with water.

benzyloxycarbonyl-L-valine methyl ester as an oil in 85% yield (95 mg in two steps); $[\alpha]_D^{27}$ -19.4° (c 1.0, CH_3OH); lit. $[\alpha]_D^{20}$ -21.9° (c 1.0, CH_3OH).[6]

A further example of the present transformation was examined by using 5[7] which has an acetonide and t-butyl ester groups. The reaction proceeded smoothly and provided the N-Z compound 6[5] in 73% yield, mp 39.0-41.0 °C, as well as compound 7[5] (10% yield; oil), in which t-butyl group had been cleaved.[8]

Generation of N-carboxylate ion through an N-t-butyldimethylsilyl blocking group seems to be applicable to a variety of chemical transformations. Further

studies related to the N-carboxylate ion equivalent are under investigation.

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6 R = t-Bu

7 R = CH_2Ph

REFERENCES AND FOOTNOTES

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2. (a) R.S.Lott, V.S.Chauhan, and C.H.Stammer, J.Chem.Soc., Chem Commun. 495 (1979). (b) Recently, Shioiri et al. have reported the use of trimethylsilyl trifluoromethanesulfonate (TMSOTf) for the removal of t-Boc group; Y.Hamada, S.Kato, and T.Shioiri, Tetrahedron Lett. 3223 (1985). We thank Professor T.Shioiri for informing us of their results prior to publish.
3. E.J.Corey, H.Cho, C.Rücker, and D.H.Hua, Tetrahedron Lett. 3455 (1981).
4. Prepared by the condensation of N-t-Boc-L-allylglycine pyridine thiol ester with L-threonine. Details of the preparation will be described elsewhere.
5. Satisfactory spectroscopic data were obtained for all compounds in the text.
6. T.Yamada, N.Isono, A.Inui, T.Miyazawa, S.Kuwata, and H.Watanabe, Bull.Chem. Soc.Jpn. 51, 1897 (1978).
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8. N-Alkoxycarbonyl group such as N-Z group was found to be stable under the present reaction conditions.

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