The 2,2,2-Trichloro-tert-butyloxycarbonyl Group(TCBOC)—An Acid- and Base-Resistant Protecting Group Removable under Mild Conditions

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The driving force of decomposition according to

$$Xe(OTeF_5)_4 \xrightarrow{72\,^\circ C} Xe(OTeF_5)_2 + F_5TeO{-}OTeF_5$$

$$XeF_4 \xrightarrow{ca.\ 450\,^\circ C} XeF_2 + F_2$$

is the strong peroxide bond in $F_5TeOOTeF_5$[5]; in contrast, the analogous decomposition of XeF_4 occurs at much higher temperatures owing to the weak bond present in molecular fluorine[6].

The analogous selenium compound $Xe(OSeF_5)_4$ has not yet been prepared because the required ligand transfer agent $B(OSeF_5)_3$ is not yet available.

Procedure

XeF_4 (1.5 g, 7.2 mmol) is transferred into a quartz trap under argon. To this compound is condensed perfluoro-*n*-hexane (10 ml) and $B(OTeF_5)_3$ (8.8 g, 12.1 mmol) in a dynamic vacuum. The mixture is warmed to −78 °C; evolution of gaseous BF_3 increases as the mixture is warmed to room temperature. All volatile components are subsequently removed at room temperature in an oil-pump vacuum. The residue is $Xe(OTeF_5)_4$, yield 7.2 g (92%).

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CAS Registry numbers:
$Xe(OTeF_5)_4$, 66255-64-9; XeF_4, 13709-61-0; $B(OTeF_5)_3$, 40934-88-1

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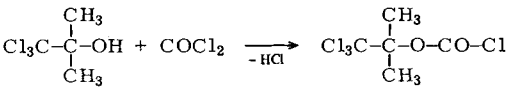
The 2,2,2-Trichloro-*tert*-butyloxycarbonyl Group (TCBOC)—An Acid- and Base-Resistant Protecting Group Removable under Mild Conditions[**]

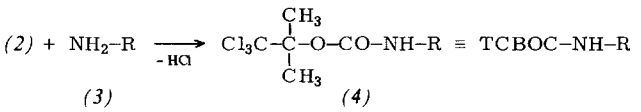
By *Heiner Eckert, Monika Listl*, and *Ivar Ugi*[*]

β-Haloalkoxycarbonyl protecting groups[1-6] are important because they can be removed selectively. The protecting groups 2-chloro-[2], 2-bromo-[3,4], 2-iodo-[4], and 2,2,2-trichloroethoxycarbonyl[5], and also 2-bromo-*tert*-butyloxycarbonyl[6] all show some degree of base lability which limits their preparative scope. However, we have discovered that the 2,2,2-trichloro-*tert*-butyloxycarbonyl group (TCBOC) is so stable towards acids and bases that conditions are fulfilled for its wide application.

The TCBOC group can be introduced by means of the stable and distillable chloroformate *(2)*, which is readily accessible from 2,2,2-trichloro-*tert*-butanol (chloretone) *(1)* and phosgene in dichloromethane or pyridine. Chloretone itself is an inexpensive commercially available reagent.



(1) *(2)*



(3) *(4)*

NH_2–R = amino acid or peptide ester

Table 1. Yields of TCBOC-protected components in the synthesis of tetrapeptide *(4f)*.

Reaction		Yield [%]
(3a) → *(4a)*	TCBOC-Val-OH	82
(4a) → *(4b)*	TCBOC-Val-Ala-OMe	90
(4b) → *(4c)*	TCBOC-Val-Ala-OH	82
(4c) → *(4d)*	TCBOC-Val-Ala-Phe-O*t*Bu	67
(4d) → *(4e)*	TCBOC-Val-Ala-Phe-OH	82
(4e) → *(4f)*	TCBOC-Val-Ala-Phe-Phe-O*t*Bu	94

Reaction of *(2)* with the amino acids or peptide esters *(3)* can be accomplished under the usual Schotten-Baumann conditions. Thus, on treatment with *(2)*, valine *(3a)* affords the TCBOC-protected amino acid *(4a)* in good yield (see Table 1). Subsequent synthesis of the tetrapeptide *(4f)* by the DCCD/HO-Su method[1] proceeds without difficulty (apart from the problems of separation encountered in product work-up after linkage by this method); the excellent crystallization properties of the TCBOC-protected products warrant particular mention. The pronounced hydrophobic behavior of the TCBOC group endows the compounds *(4)* with good solubility in organic solvents such as dichloromethane. The group is easily recognized in the ^{1}H-NMR spectrum by virtue of a characteristic singlet at $\delta = 2.0$.

Table 2. Stability of the N-terminal TCBOC group towards acidic and basic reagents.

		Conditions	Stability of the C-terminal group	Stability of the TCBOC group
(4g)	TCBOC-Val-OMe	0.1 N NaOH/20 °C/2 h	+	+
(4g)	TCBOC-Val-OMe	1 N NaOH/40 °C/2 h	−	(+) [a]
(4b)	TCBOC-Val-Ala-OMe	0.1 N NaOH/20 °C/2 h	−	+
(4g)	TCBOC-Val-OMe	TFA [b]/20 °C/2 h	+	+
(4d)	TCBOC-Val-Ala-Phe-O*t*Bu	TFA [b]/20 °C/1 h	−	+

[a] 40% of TCBOC-Val-OH are formed.
[b] TFA = trifluoroacetic acid.

The TCBOC group proves to be inert on alkaline hydrolysis of the methyl ester *(4b)* to give *(4c)*, and on acidic cleavage of the *tert*-butyl ester *(4d)* to give *(4e)* (see Table 2).

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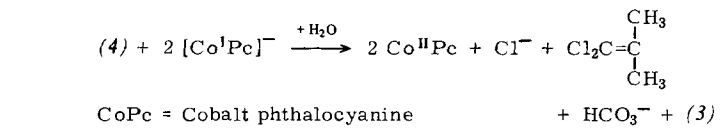
[**] Fragmentations with Supernucleophiles, Part 7. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 6: [8].



CoPc = Cobalt phthalocyanine

Removal of the TCBOC group can be accomplished with the supernucleophilic cobalt(I)-phthalocyanine anion in methanol or acetonitrile[3, 7, 8] and with zinc in glacial acetic acid (see Table 3); the yields of amine component are 66—94%. N-Terminal deprotection by lithium cobalt(I)-phthalocyanine also proceeds smoothly in the case of benzyl esters.

Table 3. Removal of the TCBOC group from compounds *(4)* by lithium cobalt(I)-phthalocyanine in methanol (method A) or acetonitrile (method B) or with zinc in glacial acetic acid (method C) at 20°C.

	(4)	Method	Reaction time	Yield of *(3)* [%]
(4g)	TCBOC-Val-OMe	A	1 min	87
(4h)	TCBOC-Val-OCH_2Ph	A	1 min	93
(4d)	TCBOC-Val-Ala-Phe-O*t*Bu	B	1 h [a]	94
(4g)	TCBOC-Val-OMe	C	3 h	66
(4d)	TCBOC-Val-Ala-Phe-O*t*Bu	C	3 h	73

[a] The actual deprotection reaction only takes 5 min.

Experimental

Synthesis of *(2)*: Anhydrous chloretone *(1)* (178 g, 1.0 mol) dissolved in anhydrous dichloromethane (400 ml) is treated at −20°C with phosgene (140 ml, 2.0 mol). Pyridine (105 ml, 1.5 mol) in dichloromethane (70 ml) is added dropwise at −20°C and the mixture is then stirred for 12 h at 20°C. Subsequent washing of the ether solution at 0°C with water (caution: vigorous evolution of gas owing to liberation of excess phosgene), 2 N sulfuric acid, and water followed by distillation affords 214 g (89%) of *(2)*, b. p. 77—81°C/12 torr.

Synthesis of *(4a)*: Valine (11.7 g, 0.1 mol), dissolved in water (200 ml) and 1 N sodium hydroxide solution (250 ml), is treated with diethyl ether (100 ml) and then emulsified at 0°C with *(2)* (33.8 g, 0.14 mol) in dioxane (140 ml) for 1 h. The aqueous phase is washed with diethyl ether, acidified with 5 N hydrochloric acid, and extracted into ethyl acetate. After washing with water, compound *(4a)* (26 g, 82%) crystallizes from the extract; the product is recrystallized from hexane; m. p. 102°C.

Deprotection of *(4d)* (method B): A solution of lithium cobalt(I)-phthalocyanine[3, 7, 8] (2.5 g, 2.8 mmol) in acetonitrile (15 ml), phenol (600 mg, 6 mmol), and *(4d)* (500 mg, 0.84 mmol) are stirred together at 20°C under N_2 for 1 h. Water (20 ml) and 1 N HCl (2 ml) are added to the dark green mixture; the dark blue precipitate is centrifuged off, and the residue is washed with 1% citric acid and water. The supernatant liquors (pH 4.0) are washed with ether, rendered alkaline with Na_2CO_3 and extracted with ethyl acetate. Evaporation of the extract affords *(3d)* (310 mg, 94%) (identification by ^{1}H-NMR, IR).

Deprotection of *(4d)* (method C): Compound *(4d)* (595 mg, 1.0 mmol) is dissolved in 95% acetic acid (10 ml) and zinc dust (*ca.* 1 g) is added portionwise over 3 h to the stirred solution. Zinc is then filtered off, washed with water, and the filtrate and washings washed with ether. After rendering alkaline with caustic soda solution and extraction with ethyl acetate, *(3d)* (286 mg, 73%) is obtained from the extract by evaporation (identification by ^{1}H-NMR, IR).

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(2), 66270-36-8; *(3a)*, 72-18-4; *(3d)*, 66270-37-9; *(4a)*, 66270-38-0; *(4b)*, 66270-39-1; *(4c)*, 66270-40-4; *(4d)*, 66270-41-5; *(4e)*, 66270-42-6; *(4f)*, 66270-43-7; *(4g)*, 66270-44-8; *(4h)*, 66270-45-9

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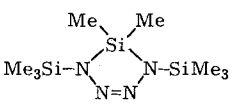
Preparation and Some Reactions of Dimethyl(trimethylsilylimino)silane, $Me_2Si{=}NSiMe_3$[1]

By *Nils Wiberg* and *Gerhard Preiner*[*]

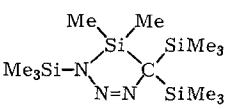
Having synthesized the silaethene *(1)*[2], we have now found a facile entry to iminosilane *(2)*—a representative of the poorly characterized, highly reactive compounds containing a Si=N double bond which have not yet been isolated[3].

(1) *(2)*

Our study was prompted by observation of differing behavior on thermolysis of the "isosteric" heterocycles *(3)* and *(4)*:

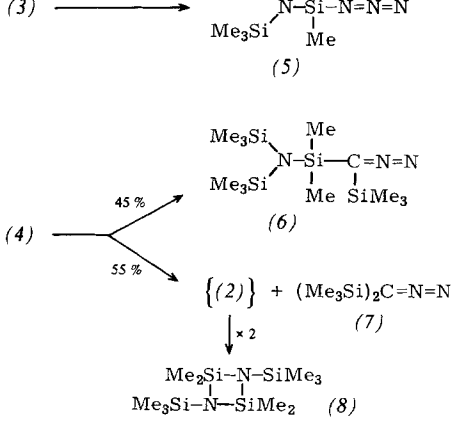


(3)



(4)

While thermolysis of *(3)* at 180°C leads quantitatively *via* isomerization to the aminosilyl azide *(5)*[4], compound *(4)* (readily accessible from *(1)* and Me_3SiN_3; metastable below −5°C)[2, 5] is not converted exclusively into *(6)* (analogous to *(5)*); fragmentation also occurs, affording the iminosilane *(2)*, which dimerizes to *(8)* in the absence of a trapping reagent, and the diazomethane derivative *(7)*[5].



(5) *(6)* *(7)* *(8)*

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