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The evaluation of b,b,b-trichloro-*tert.*-butyl (Tcb) group for the protection of carboxyl functionality

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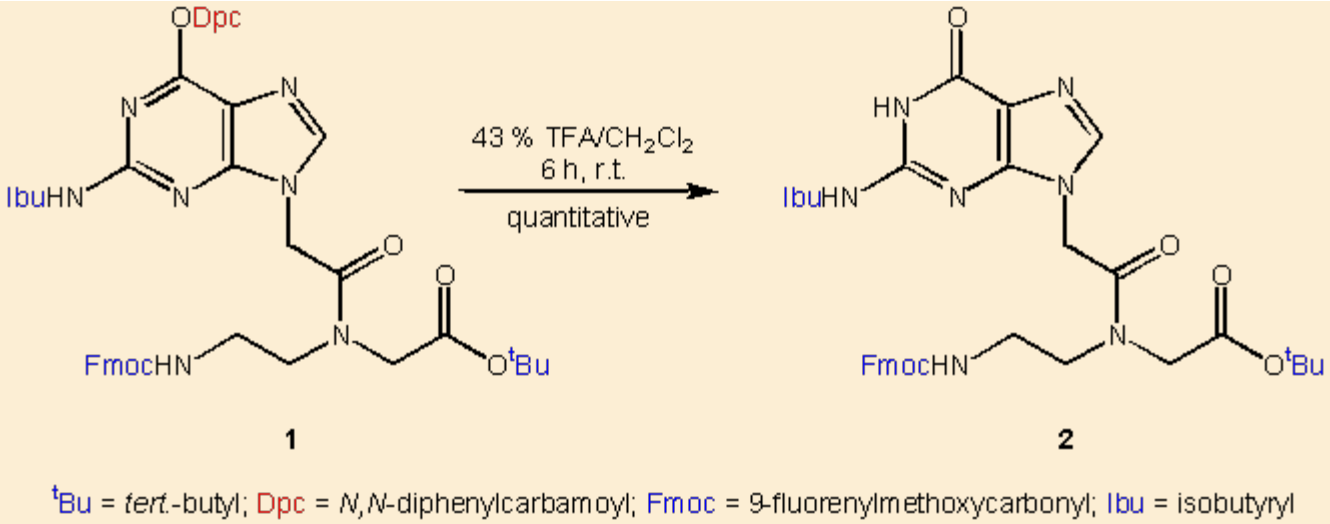
Abstract

The preparation, stability and behaviour of b,b,b-trichloro-*tert.*-butyl (Tcb) esters towards various conditions of deprotection were evaluated. Tcb esters can be prepared from the halide of the corresponding carboxylic acid and b,b,b-trichloro-*tert.*-butanol in the presence of anhydrous zinc chloride. They are stable in acidic and basic medium and can be cleaved under mild conditions (*e.g.* with zinc, cadmium or indium under slightly acidic or neutral pH, with the supernucleophile cobalt(I) phthalocyanine, Table 1). Provided that the requested acyl halides are easily available, the Tcb group can be efficiently used for the protection of carboxyl functionality.

Introduction

En route to peptide nucleic acid monomers [1] we experienced that during the attempted acidic deprotection of compound **1** the carboxyl *tert.*-butyl protecting group survived the acidic conditions while the *N,N*-diphenylcarbamoyl group was removed (® **2**, Scheme 1).



^{t}Bu = *tert.*-butyl; Dpc = *N,N*-diphenylcarbamoyl; Fmoc = 9-fluorenylmethoxycarbonyl; Ibu = isobutyryl

Scheme 1.

This prompted us to undertake the application of a carboxyl protecting group that is *(a)* easily synthesized, *(b)* sterically congested, *(c)* sensitive neither to basic, *(d)* nor to acidic conditions, and *(e)* can selectively be removed under conditions that are compatible with a range of other protecting groups.

These requirements are seemingly simple but there is no general solution to the problem. It is obvious to think of some substituted *tert.*-butyl or trityl groups as possible candidates. The trityl group was modified by Sekine and Hata [2] who introduced the 4,4',4''-tris(benzoyloxy)trityl group (TBTr) which is more resistant to acidic cleavage than native trityl groups and can be removed under alkaline conditions. Among the substituted *tert.*-butyl groups the b,b,b-trichloro-*tert.*-butyl (Tcb) was applied as a phosphate protecting group [3-9]. This sterically hindered group is stable to acids, bases and can selectively be removed with various reagents (*e.g.* with the supernucleophile cobalt(I) phthalocyanine) and can be synthesized from phosphorous halides and b,b,b-trichloro-*tert.*-butanol. In urethane form (b,b,b-trichloro-*tert.*-butoxycarbonyl, Tcboc) this group is well suited for the protection of hydroxyl and amino groups [8][10-12]. The Tcb group was not used for the protection of carboxyl group and later development resulted in the elaboration of the 1,1-dianisyl-2,2,2-trichloroethyl (Date) group for the protection of nucleoside hydroxyl groups [13,14]. The chemistry of this compound family has been reviewed by Ugi *et al.* [15].

Results and discussion

We have investigated of the preparation and applicability of the b,b,b-trichloro-*tert.*-butyl group (Tcb) for the protection of carboxylic acids. The Tcb esters of carboxylic acids have been known since the past century [16], however, their preparation requires harsh conditions [17]. We have investigated a range of substrates (**3-9**, Scheme 2) and conditions for the preparation of Tcb esters and the following conclusions can be drawn:

1. Direct esterification of carboxylic acids **3-5a** and b,b,b-trichloro-*tert.*-butanol (**10**) in the presence of DCC, without or with DMAP [18] failed to give the desired ester. The only isolable by-products, in low yield, were *N*-acyl-*N,N'*-dicyclohexylureas.

2. Mitsunobu condensation [19] (DIAD, Bu_3P, THF) of **5a** and **10** gave several unidentified by-products.

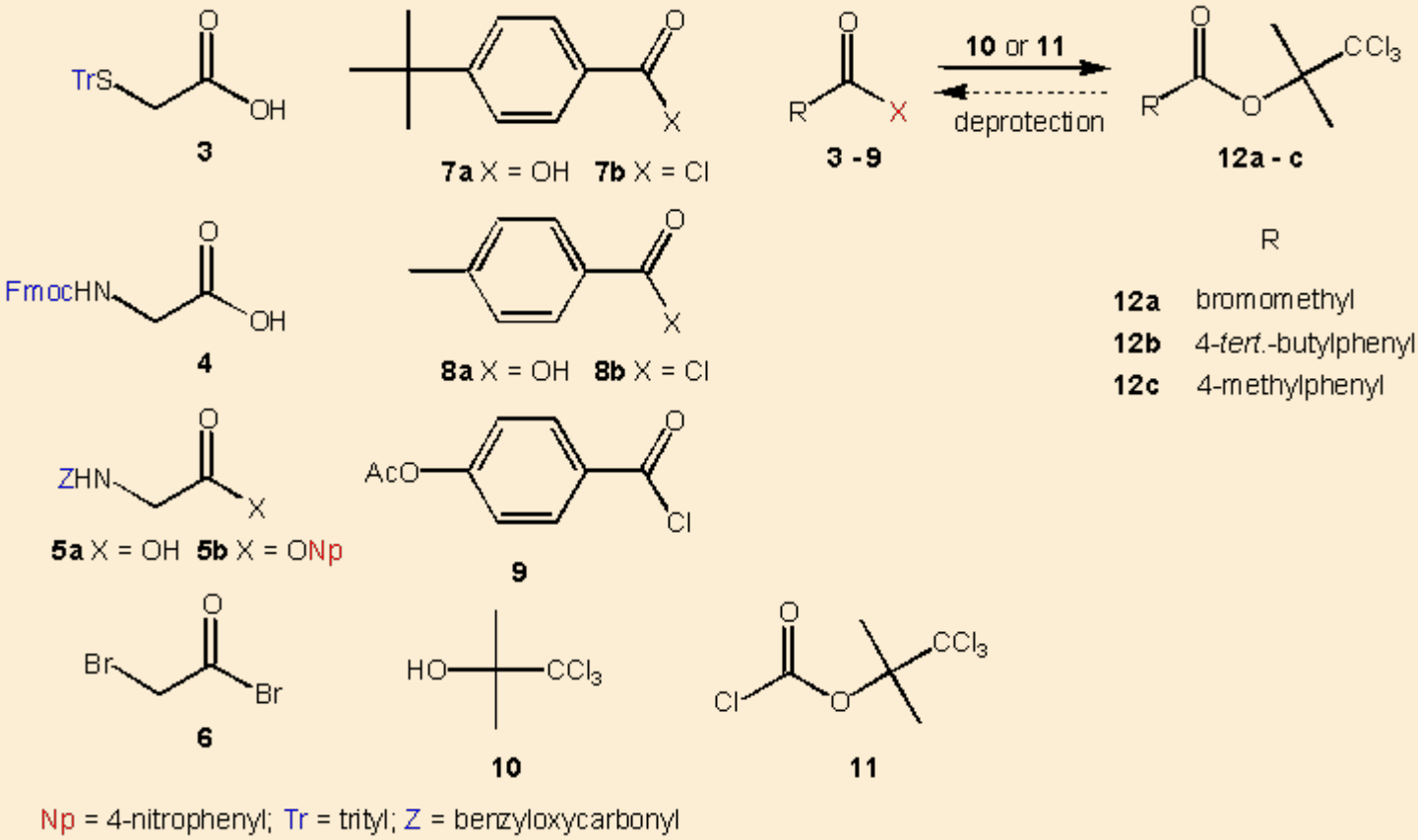
3. The acid **8a** was recovered unchanged from a reaction with alcohol **10** in the presence of HBTU/HOBt.

4. The pyridine-catalyzed transesterification of active ester **5b** with compound **10** did not afford the expected product.

5. The mixed anhydride method [20] invariably failed to afford the wanted esters from carboxylic acids **3, 7a, 8a, 9** and b b b-trichloro-*tert.*-butyl chloroformate (TcbocCl, **11**). Similar observation were made with 2,2,2-trichloroethyl

, ,
chloroformate [20].

6. The condensation of acyl halides **6, 7b, 8b** with compound **10** in the presence of anhydrous fused zinc chloride [17] afforded the esters **12a-c** in 67-82 % yield.



Scheme 2.

Tcb esters **12a-c** display characteristic carbon resonances in their ^{13}C NMR spectra at 88-90 ppm ($\underline{C}Cl_3$) and at 105-107 ppm [$O\underline{C}(CH_3)_2CCl_3$]. Their mass spectrometric investigation (chemical ionization with isobutane) revealed molecular ions with an isotopic distribution pattern characteristic to the presence of three chlorine atoms. The carbonyl group of these esters resonate at 1720 (chloroform solution) or at 1750 cm^{-1} (neat, **12c**).

After obtaining the requested esters their stability was checked under the following conditions: *(a)* cc. HCl/methanol/dioxane 1:2:2, *(b)* 3 % dichloroacetic acid in dichloromethane, *(c)* cc. ammonia/dioxane 1:1, *(d)* 30 % TFA in dichloromethane. At room temperature there was not any appreciable transformation of esters **12b-c** for 72 h. The ester **12a** was also tested and it displays similar reactivity under acidic conditions *(a, b, d)* (in ammonia its stability was not investigated as it would fast transform into a glycine derivative due to the reactive bromo group).

The deprotection experiments were conducted with ester **12c** (Table 1). Not surprisingly, the Tcb ester group displays analogous behaviour as its phosphate ester or *N*-Tcboc counterparts. It is noteworthy that it can be deprotected under conditions (*e.g.* zinc, cadmium or indium under slightly acidic or neutral pH, the supernucleophile cobalt(I) phthalocyanine) which are compatible with a wide range of other functional groups. Attempts to deprotect ester **12c** with tributylphosphine [6] or with zinc/acetylacetone/triethylamine [9] left the starting material unchanged. Similar results were obtained with manganese/aq. THF or manganese/50 % AcOH/THF (in the latter case the reaction of manganese with acetic acid proceeds).

Table 1. The deprotection of ester 12c to acid 8a under various conditions.

Condition	Yield (%)
Zn/50 % AcOH/THF, r.t.	65-70
Zn/1 M NH_4OAc/THF, 80 °C	73
Cd/50 % AcOH/THF, r.t.	74-79
Cd/1 M NH_4OAc/THF, 80 °C	74
In/50 % AcOH/THF, r.t.	73-75
Co(II) phthalocyanine/$NaBH_4$/EtOH, r.t.	68-70

The experience we obtained with Tcb esters allows us to conclude that this group can be useful for the protection of carboxyl functional group because it is sterically hindered, stable in acidic and basic medium and can be chemoselectively removed under conditions which are compatible with many other protecting groups. The only disadvantage of its application is the difficult preparation of Tcb esters (acyl halides are requested for their efficient synthesis). Further research towards protecting groups with similar advantageous properties is in progress.

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