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SIDE REACTIONS AND CADMIUM CATALYSED REMOVAL OF THE TRICHLORO-ETHOXYCARBONYL (TROC) PROTECTING GROUP.

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Abstract. The Troc protecting group has been found to be unstable to the hydrogenolytic conditions used for removal of the benzyloxycarbonyl group; an improved method of removal employing cadmium dust in 50% AcOH/DMF is described.

The trichloroethoxycarbonyl (Troc) protecting group was introduced some years ago for the masking of amino-groups during synthesis.[1,2] It was claimed to be stable to hydrogenolysis over palladium on charcoal, trifluoroacetic and sodium hydroxide and that it could be selectively removed under very mild conditions by treatment with zinc in acetic acid.[2] An alternative removal employing the supernucleophilic cobalt(I) phthalocyanine anion has also recently been described.[3]

In a recent piece of research directed at studies on the active site of Insulin[4] it was essential that we were able to selectively protect the α and ε amino functions of lysine and that the side-chain protecting group be stable to catalytic hydrogenolysis and acidic conditions. With these constraints we chose the Troc group for side-chain protection although there were reservations based on an observation by Yajima[5] which indicated that the group was not as stable towards hydrogenolysis as had originally been indicated.

A trial hydrogenolysis of the protected tripeptide (1) over 10% palladium on charcoal in the

$$Z.Lys(Troc).Glu(OBu^t).Gln.NH_2$$

(1)

presence of one equivalent of p-toluene sulphonic acid monohydrate using dimethylformamide as solvent immediately indicated the formation of undesirable side-products. Following this initial observation a variety of hydrogenolytic conditions were investigated as indicated in Table 1.

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Table 1. Hydrogenolysis of (1) in the presence of one equivalent of p-toluene sulphonic acid with DMF as solvent.

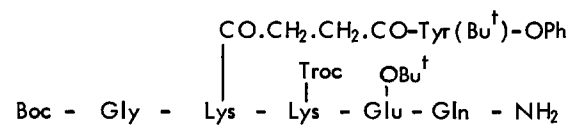
Catalyst	Time	Ratio of required product to side products as estimated by t.l.c.
5% Ru/C	16	No reaction
5% Pt/C	16	No reaction
5% Pd/C	3	3:1 + starti ng material
5% Pd/C	6	3:1
10% Pd/C	16	2:3
5% Pd/C + quinoline (1%)	6	3:1 + starting material
5% Pd/C + trichloro ethanol (25 equiv.)	6	3:1 + starting material
10% Pd/C + $BaSO_4$	6	2:1

From the trial experiments shown in the table the hydrogenolysis conditions were optimised at 6h. over 5% Pd/C. Related experiments using Z.Lys(Troc).OH clearly showed the presence of free lysine on hydrogenolysis. In the case of the tripeptide (1) impurities were produced which ran close to the required compound in all the t.l.c. systems examined. Also ^1H n.m.r. at 220 MHz indicated the replacement of one, two or possibly even all three chlorine atoms by hydrogen.

From these findings we conclude that the Troc group is unstable to hydrogenolysis and that one or more of the chlorine atoms can exchange with hydrogen under standard hydrogenolysis conditions. Such an exchange would obviously alter the lability of any such effected group to zinc in acetic acid. Thus at the end of an extended synthesis it could well be that the temporary side-chain protection used for lysine would have become permanent. In our current work it was impractical to change the Troc groups at the stage the problem was encountered and thus we continued to use the group although only a 44% yield could be obtained for the removal of the Z group from the tripeptide (1).

At a later stage in the synthesis of the insulin active site model[4] the hydrogenation of a fumarate double bond had to be carried out in the presence of the Troc group. Once again the catalytic reduction had to be studied in detail and on this occasion t.l.c. revealed three close running spots, the major one (the required product) corresponding to about 60-65% of the total.

In the subsequent cleavage of the Troc group from (2) using the published method[2]



(2)

employing zinc in acetic acid problems were again encountered and t.l.c. indicated that a side product had been produced in addition to the required material. Trial experiments with other protected peptides indicated that the Boc, Adoc, Acm, phenyl ester, t-butyl ester, and t-butyl ether protecting groups were all stable under these conditions. Attempts to improve the situation were made by modifying the reaction conditions (see Table 2). However, under no conditions could the Troc group be cleanly removed.

Table 2. Conditions for attempted removal of Troc protecting group.

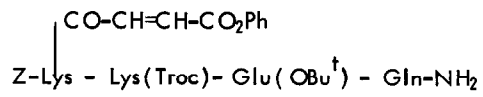
Conditions	Reaction time (h)	Result
Zn/AcOH(glacial)	5	2 products
Zn/50% AcOH/$CF_3.CH_2OH$	5	"
Zn/25% AcOH/CF_3CH_2OH	7	"
Zn/10% AcOH/CF_3CH_2OH	16	"
Zn/50% AcOH/H_2O	16	"
Zn/50% AcOH/DMF	16	"
Zn/p-toluene sulphonic acid/CF_3CH_2OH	24	No reaction
Zn/p-toluene sulphonic acid/DMF	24	" "
Zn/Cu couple/AcOH glacial	5	2 products

The close similarity between zinc and cadmium then prompted us to replace zinc by cadmium dust in the cleavage trials. It was immediately apparent that a considerable improvement had been achieved and optimisation led to the use of cadmium dust in a 1:1 mixture of AcOH(glacial) and DMF. The cleavage was complete in 12 hrs. and filtration and washing followed by gel filtration on Sephadex LH20/DMF generally gave the pure product in yields between 50 and 85%.

The generality of this procedure using cadmium to remove the Troc group was demonstrated by trial cleavages on the compounds shown in Table 3.

Table 3. Compounds subjected to treatment with cadmium dust in AcOH(glacial)/DMF.

Compound	Result
Z-Lys(Troc)-OH	Single product (12h)
Z-Lys(Troc)-Gly-OPh	" " (8h)
(1)	" " (12h)
(2)	" " (12h)
(3)	" " (12h)



(3)

In addition other trial experiments with a variety of fully protected peptides showed that the Z, Boc, Adoc, Acm , phenyl and t-butyl ester and t-butyl ether protecting groups were stable under these conditions.

In conclusions we therefore caution the use of the Troc group for N-protection in syntheses where it is required to survive one or more catalytic hydrogenolyses. Also we propose the use of cadmium dust in glacial acetic acid or glacial acetic acid/DMF in place of zinc in glacial acetic acid as an improved method for the selective removal of the Troc group.

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