Tetrahedron Letters,Vol.25,No.10,pp 1027-1030,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

CLEAVAGE OF THE N-PChd GROUP FROM PROTECTED AMINO ACIDS AND PEPTIDES BY CATHODIC REDUCTION

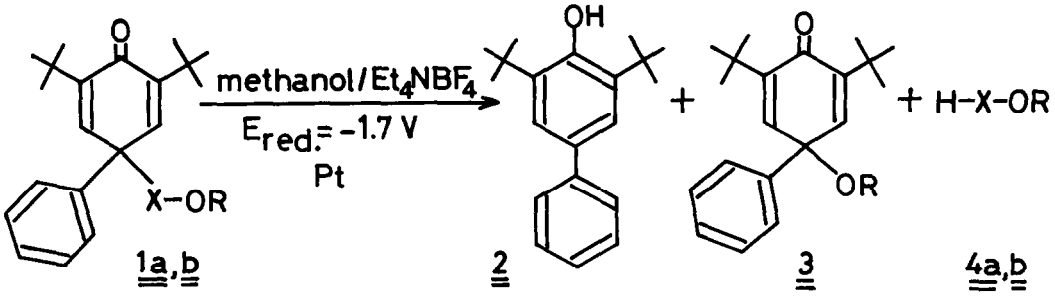
M.Hassen Khalifa and Anton Rieker *
Institut für Organische Chemie der Universität
Auf der Morgenstelle 18
D-7400 Tübingen

Summary: Amino acid and peptide esters protected by the PChd group can be deprotected cathodically under mild conditions.

We have recently introduced the di-tert-butylated 1-phenyl-4-oxo-2,5-cyclohexadienyl(PChd) group for the protection of amino acids [1-3]. The N-PChd group can be chemically removed either by acidic cleavage (e.g. 50% trifluoroacetic acid in dichloromethane) or by hydrogenolysis (e.g. molecular hydrogen/Pd-C in methanol/1N hydrochloric acid). In the following we describe the electrochemical cleavage of the PChd group from N-PChd amino acid and peptide esters.

Since the PChd group is a quinol system, it should be electroactive. Indeed, N-PChd amino acid and peptide esters 1 show half-wave potentials of about -1.6 to -1.7 V (vs. Ag/0.01 M Ag^+) at the dropping mercury electrode in methanol/0.1 M Et_4NBF_4.

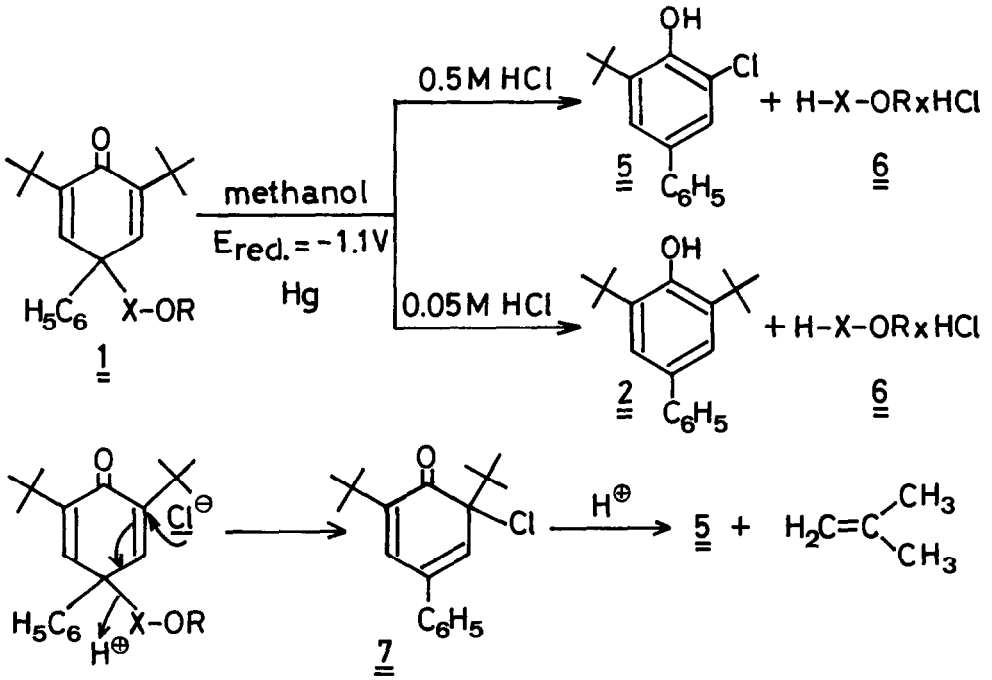
The preparative cathodic reduction of N-PChd amino acid esters 1a at these potentials in undivided cells at Pt electrodes (in methanol/0.1 M Et_4NBF_4) consequently leads to the free amino acid esters 4a. The PChd group is transformed into phenol 2 and quinol methyl ether 3 [4]:



a: X = amino acid residue b: X = peptide residue

The yields of free amino acid esters 4a are moderate (max. 60%), presumably due to their anodic decomposition, and phenol 2 cannot be regenerated quantitatively. Therefore, we preferred to employ a divided electrolysis cell for the subsequent experiments using a clay cylinder (Tonzelle ABS, Haldenwanger, Berlin) as a diaphragm. In this type of cell, the potential controlled electrolysis of N-PChd amino acid esters 1a at -1.7 V at Pt in neutral medium (methanol/0.1 M Et_4NBF_4) also leads to the cleavage of the PChd group. This group is now reduced to phenol 2 as the sole product, and it can be re-used for the electrochemical protection of amino acid esters [1-3]. However, the free amino acid esters 4a cannot be recovered quantitatively from the supporting electrolyte.

On the other hand, the isolation procedure for the free amino acid and peptide esters 4 proved to be convenient using the system methanol/0.5 M HCl as supporting electrolyte, which allows a cleavage of 1 at a mercury pool electrode at potentials as low as -1.1 V vs. Ag/0.01 M Ag^+. Amino acid and peptide ester hydrochlorides 6 are isolated in good yields, whereas the PChd group is found as ortho-chlorophenol 5 [5].



The formation of 5 may be caused by molecular chlorine being formed at the anode and diffusing into the cathodic compartment. Alternatively, a S_N2' reaction might occur (attack of Cl^- at the carbon atom bearing the tert-butyl group; simultaneous leaving of the ester hydrochlorides 6), leading to the ortho-quinol chloride 7 which would be susceptible to acid catalyzed de-tert-butylation to give 5. This reaction would be analogous to the cleavage of the N-PChd group by trifluoroacetic acid [3]. However,

0.5 M HCl in methanol did not react with 1 in a blind test without electrolysis. Thus, the first alternative seems to be the most reasonable, although it could not be proven and other mechanisms may operate.

If the regeneration of 2 is not desirable, the reduction in methanol/0.5 M HCl described above is useful. An optimal procedure, however, should restore phenol 2 instead of 5. Since 5 is a chlorination product, reduction of the overall concentration of chlorine sources might be helpful, regardless of the inherent mechanism. Methanol/0.05 M HCl as electrolyte system did indeed minimize the formation of chlorine in the anodic compartment, and the phenol 2 is recovered in high yield from the PChd group (see Table). This method among others was applied to the intermediates PChd-Ile-Leu-OMe, PChd-Leu-Ala-OMe and PChd-Ile-Leu-Leu-Ala-OMe prepared for the synthesis of the segment 14-20 of human lymphoblastoid interferon, Ala-Leu-Ile-Leu-Leu-Ala-Gln [3]. As shown by gas chromatography on glass capillaries coated with a chiral phase [6], racemization of 6b due to cathodic cleavage was not detectable. The purity of the obtained peptide ester hydrochlorides was checked by tlc, amino acid analysis and elemental analysis.

Under the conditions of this electrochemical cleavage method the benzyloxycarbonyl (Z) group seems to be stable and could be used in combination with the PChd group. Thus, Z-Ala-Gly-OEt is not electroactive in our conditions, and in preliminary experiments with PChd-Lys(Z)-Gly-OH noticeable cleavage of the Z group could not be detected [7]. A detailed mechanistic investigation of the electrochemical cleavage of the PChd group in the absence or presence of other protective groups is in progress.

Cathodic cleavage of the PChd group

N-PChd amino acid or peptide esters 1 (1-5 mmol) in methanol/0.05 M HCl (150 ml) were electrolyzed in a divided cell (working electrode: mercury pool; counter electrode: platinum sheet; anodic compartment: glass tube with D4 glass frit also containing the above electrolyte system) at controlled potential (E_{red} = -1.1 Volt vs. Ag/0.01 M Ag^+). After quantitative cleavage, monitored by tlc (2-4 h), the catholyte was evaporated and the residue treated with ether. The ether solution gave phenol 2 after evaporation. The ether-insoluble residue, consisting of the peptide ester hydrochlorides 6b was recrystallized from methanol/ether.

Acknowledgement. This work was kindly supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We have to thank also Prof.G.Jung for helpful discussions.

Table : Cathodic cleavage of N-PChd amino acid and peptide esters 1

N-PChd derivatives 1	Amino acid and peptide ester hydrochlorides 6 [%]	Recovery of phenol 2 [%]
PChd-Leu-OEt	92	93
PChd-Phe-OMe [8]	90	92
PChd-Aib-Aib-OEt [9]	93	91
PChd-Ile-Leu-OMe	90	90
PChd-Leu-Ala-OMe	91	94
PChd-Ile-Leu-Leu-Ala-OMe	88	92

References and Notes

1) M.H.Khalifa, G.Jung and A.Rieker, Angew.Chem. 92, 739 (1980); Angew.Chem., Int.Ed.Engl. 19, 712 (1980).

2) A.Rieker, M.H.Khalifa and G.Jung, in Peptides 1980, Proc. 16th. Eur. Pept. Symp. (K.Brunfeldt, Ed.) p. 116-120, Scriptor, Copenhagen 1981.

3) M.H.Khalifa, G.Jung and A.Rieker, Liebigs Ann.Chem. 1068 (1982).

4) The reaction resembles the cathodic cleavage of the tritylone (10-phenylanthron-9-yl) group from protected alcohols, see: C.van der Stouwe and H.J.Schäfer, Chem.Ber. 114, 946(1981); Tetrahedron Lett. 2643 (1979).

5) 3-tert-Butyl-5-chloro-biphenyl-4-ol 5: m.p. 64-67°C (from light petroleum, b.p. 30-50°C); ^{1}H-NMR(CCl_4): δ_{ppm} = 1.41 (s, 9H, t-Bu), 5.85 (s, 1H, OH), 7.20-7.55 (m, 7H, ring-H); see D.Koch, Thesis, University of Tübingen, 1979; G.G.I.Moore and A.R.Kirk, J.Org.Chem. 44, 925 (1979).

6) H.Frank, G.J.Nicholson and E.Bayer, J.Chromatogr. 146, 197 (1978).

7) For the selective electrochemical removal of carboxyl protective groups see: M.F.Semmelhack and G.E.Heinsohn, J.Am.Chem.Soc. 94, 5139 (1972).

8) PChd-Phe-OMe was prepared according to lit.[3]. Yield: 89%, m.p. 75-76°C (from methanol). $C_{30}H_{37}NO_3$ (459.6), Calc. C: 78.39, H: 8.11, N: 3.05; Found C: 78.52, H: 8.34, N: 3.10. ^{1}H-NMR ($CDCl_3$): δ_{ppm} = 1.01 (s, 9H, t-Bu), 1.18 (s, 9H, t-Bu), 2.4-3.3 (m, 4H, aliphatic H,N-H), 3.67 (s, 3H, OMe), 5.85 (d, J = 2.9 Hz, 1H, quinolide H), 6.47 (d, J = 2.9 Hz, 1H, quinolide H), 7.1 - 7.4 (m, 1 OH, phenyl-H).

9) For the synthesis and further coupling reactions see: R.Beisswenger, M.H.Khalifa, G.Jung and A.Rieker, to be published.

(Received in Germany 1 December 1983)