De synthese van zuurstofchlorides en peptiden met behulp van alpha-chloorethers

Heslinga, Lammert

SUMMARY

Chapter I

Formation of α,α-dichlorodiethyl ether (IV) and its use for the preparation of acyl clorides.

Addition of two equivalents of hydrogen chloride to ethoxyacetylene (II) yields α,α-dichlorodiethyl ether (IV). This dichloro ether had not yet been described.

$$\underset{\text{II}}{HC{\equiv}C\text{-}OC_2H_5} \xrightarrow{HCl} \underset{\text{III}}{H_2C{=}CCl\text{-}OC_2H_5} \xrightarrow{HCl} \underset{\text{IV}}{CH_3\text{-}CCl_2\text{-}OC_2H_5}$$

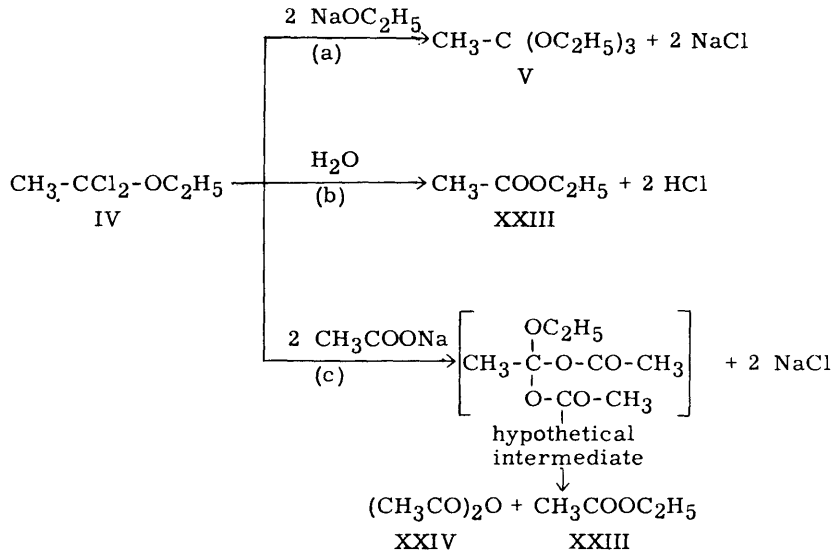
The intermediate ethyl α-chlorovinyl ether (III) is a known substance.

The dichloro ether (IV) is a colourless liquid with b.p. 104.5-105.5°C (corrected) and n_D^{20} 1.4261. The structure of this compound appeared from the following conversions.

a) Reaction with sodium ethoxide in ethanol afforded ethylorthoacetate (V).

b) Ethyl acetate (XXIII) was formed by hydrolysis.

c) By reaction with sodium acetate, acetic anhydride (XXIV) and ethyl acetate (XXIII) were formed in good yields:



At about 40°C the dichloro ether (IV) easily reacted with carboxylic acids, yielding acyl chlorides(XXV)and ethyl acetate (XXIII). In some cases the reaction already started at room temperature.

$CH_3\text{-}CCl_2\text{-}OC_2H_5$ + R-CO
IV

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dichlorodiethyl ethe
chlorides were obta
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The results are l
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The use of the dich
pure acyl chlorides
chlorides must be co
as $SOCl_2$, PCl_3 etc.

Chapters II and III.

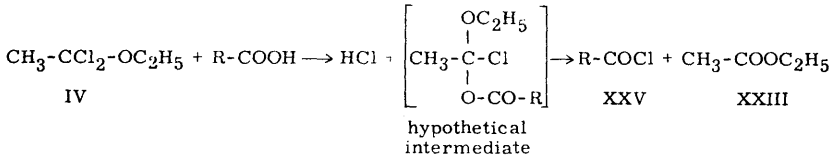
Synthesis of peptide

Two new methods
acyl peptide esters (
dry ethyl acetate a
amino acid ester hyc
ted ethers, α, α-dichl
nyl ether (III):

Reaction C: One step

AcN (H)-CHR-COOH + H
XII
AcN(H)-CHR-CO-NH-CH
XIV
XII + XIII + $H_2C{=}CCl\text{-}OC$
III
Ac = benzyloxycarbonyl
cbzo = $C_6H_5\text{-}CH_2\text{-}O\text{-}C\text{-}$
O

The method has beer
of cbzo-and phth-di-
In all experiments
were isolated. Espec
good results were obt
The syntheses of a
performed by heating



IV — hypothetical intermediate — XXV — XXIII

We subjected several carboxylic acids to treatment with α,α-dichlorodiethyl ether (IV), without a solvent. The pure acyl chlorides were obtained in good yields (70-100%); the reaction times were short (about 30 min). The isolation of the reaction-products was simple, because of the formation of volatile by-product, ethylacetate.

The results are listed in table I, chapter I, (page I-9[a], 9[b] of this thesis).

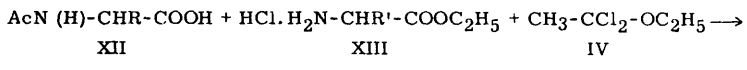
The use of the dichloro ether (IV) for the preparation of very pure acyl chlorides may be advantageous in cases where these chlorides must be completely free from the usual reagents such as $SOCl_2$, PCl_3 etc., and their reaction products.

Chapters II and III.

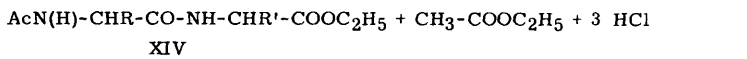
Synthesis of peptides by means of α-chlorinated ethers.

Two new methods of peptide-synthesis were developed. N-acyl peptide esters (XIV) were easily prepared by refluxing in dry ethyl acetate a mixture of a N-acylamino acid (XII), an amino acid ester hydrochloride (XIII) and one of the chlorinated ethers, α,α-dichlorodiethylether (IV), or ethyl α-chlorovinyl ether (III):

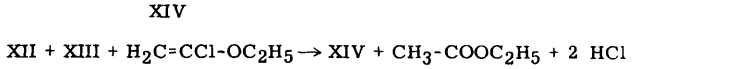
Reaction C: One step procedure.



XII — XIII — IV

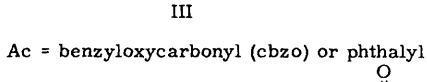


XIV



III

Ac = benzyloxycarbonyl (cbzo) or phthalyl (phth) group;



The method has been applied for the preparation of a number of cbzo-and phth-di- , and a few tripeptide esters.

In all experiments optically pure acyl peptide esters (XIV) were isolated. Especially with α,α-dichlorodiethyl ether (IV) good results were obtained.

The syntheses of a number of *phth* peptide esters were also performed by heating the reactants without a solvent. In these

cases the reactions were very fast: reaction time 10-15 min.

Because of the known sensitivity of N-benzyloxycarbonyl-amino acyl chlorides (which most probably are intermediates) towards heat, this variation could not be applied for the analogous synthesis of N- *cbzo* peptide esters.

The various results are listed in tables IV, V, VIII, IX and X, (chapters II and III of this thesis, pages II-4, 5, 11, 12 and III-2.)

These new peptide syntheses most probably proceed as follows:

Reaction A: formation of N-acyl aminoacyl chloride (XXb).

$$\underset{\text{XII}}{AcN(H)\text{-}CHR\text{-}COOH} + \underset{\text{IV}}{CH_3\text{-}CCl_2\text{-}OC_2H_5} \longrightarrow \underset{\text{XXb}}{AcN(H)\text{-}CHR\text{-}COCl} + CH_3\text{-}COOC_2H_5 + HCl$$

(or $H_2C{=}CCl\text{-}OC_2H_5$)
III

Ac = N-protecting group (phth or cbzo).

Reaction B: formation of peptide bond.

$$AcN(H)\text{-}CHR\text{-}COCl + HCl.H_2N\text{-}CHR'\text{-}COOC_2H_5 \longrightarrow$$

XXb XIII

$$AcN(H)\text{-}CHR\text{-}CO\text{-}NH\text{-}CHR'\text{-}COOC_2H_5 + 2HCl$$

XIV

These two steps (A and B) could also be performed separately.

Evidence for the occurrence of the acyl chloride (XXb) as an intermediate, during the synthesis of phth-gly-gly-Et with α,α-dichloro ether (IV) (reactions A, B and C) was obtained, by performing the reactions at 40°C and 77°C, and interrupting the processes before completion (see tables XI and XII, chapter III, pages III-7 and III-8 of this thesis.

Most probably, also in the peptide syntheses with ethyl α-chlorovinyl ether (III) these acyl chlorides (XXb) are intermediates.

Some *free* phth-peptides were obtained by refluxing a mixture of phth-aminoacyl chloride (XX) and free amino acid in ethyl acetate.

Of the two reagents for the synthesis of protected peptides, proposed here *α,α-dichlorodiethyl ether* (IV) is to be preferred.

The new method has the following attractive features:

a) simple, "one step" procedures: isolation of intermediates is not necessary.
b) short reaction times (0.5 - 1.5 h).
c) good yields of optically pure N-acyl peptide esters.
d) easy isolation of the cristalline reaction products.

1) E. Fischer, Be
2) E. Fischer, en
3) W. Grassmann stoffe 13, 444
4) Th. Curtius en
5) E. Brand, B. F 1849, (1952).
6) W. L. Le Quesn
7) J. C. Sheehan e
8) J. F. Arens, R Festschrift Ar
9) H. J. Pannemar binnenkort in
10) A. E. Favorsk 15, 394, (1945
11) Th. R. Rix en Wetenschap.
12) J. F. Arens en
13) T. L. Jacobs e
14) Y. A. Sinnema
15) R. Broekema, chim. 77, 258
16) Th. R. Rix en Wetenschap.
17) H. Crompton e (1920).
18) I. B. Douglas e (1956).
19) L. Heslinga, C 76, 969, (195
20) G. Imbert, Ko 222194, (1910 Fortschr. d.
21) H. Crompton e
22) P. V. Mc Kie,
23) D. Ben Ishai e
24) M. Bergmann
25) M. Bergmann
26) E. Drechsel,
27) J. C. Sheehan (1950).
28) J. C. Sheehan
29) H. Leuchs, Be
30) S. Gabriel, Be
31) F. E. King, J. J. Chem. Soc.
32) K. Yamashita Soc. Japan 27
33) J. C. Sheehan
34) T. Curtius en
35) J. C. Sheehan, Soc. 74, 382
36) D. A. van Dor chim. 70, 289