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

Heslinga, Lammert

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
1959

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Heslinga, L. (1959). De synthese van zuurstofchlorides en peptiden met behulp van alpha-chloorethers Groningen: s.n.

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Chapter I

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

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

\[ HC\equiv C-OC_2H_5 + 2HCl \rightarrow H_2C=CCl-OC_2H_5 + HCl \]

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_20^0 1.4261. The structure of this compound appeared from the following conversions.

a) Reaction with sodium ethoxide in ethanol afforded ethyl-orthoacetate (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:

\[ 2NaOC_2H_5 + CH_3-C-C=O \rightarrow (OC_2H_5)_2C + 2NaCl \]  

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.

We subjected several dichloro ethers to acylation, and the acyl chlorides were obtained times were short (about 15-20 minutes). The products was simple and pure, ethylacetate rather than the expected acyl chlorides.

The results are listed in this thesis).

The use of the dichloro ethers for acylation of pure acyl chlorides is possible. The results are listed in this thesis. The dichloro ethers must be concentrated as SOCl_2, POCl_3 etc.

Chapters II and III.

Synthesis of peptide esters.

Two new methods for the synthesis of peptide esters (dry ethyl acetate and esterification of amino acid ester hydrolyzed ethers, α,α-dichlorodiethyl vinyl ether (III):

Reaction C: One-step synthesis.

AcN(H)-CHR-COOH + HI → AcN(H)-CHR-CO-NH-CH_3 (XXIV)

XII + XIII + H_2C=CCl-OC_2H_5 → \( \text{(b) } \)

Ac = benzyloxycarbonyl

The synthesis of peptide esters was performed by heating the mixture with ethyl acetate. In all experiments, the products were isolated. Excellent results were obtained.
and its use for

We subjected several carboxylic acids to treatment with $\alpha,\alpha$-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 byproduct, ethylacetate.

The results are listed in table I, chapter I, 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 SOCl₂, PCl₃ etc., and their reaction products.

Chapters II and III.

Syntheses of peptides by means of $\alpha$-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, $\alpha$, $\alpha$-dichlorodiethyl ether (IV), or ethyl $\alpha$-chlorovinyl ether (III):

Reaction C: One step procedure.

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 $\alpha$, $\alpha$-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 analog-
ous 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).

\[
\text{AcN(H)-CHR-COOH + CH}_3\text{C-COCI} + \text{HCl} \rightarrow \text{AcN(H)-CHR-COCl} + \text{CH}_3\text{COOC}_2\text{H}_5 + \text{HCl}
\]

**Reaction B:** formation of peptide bond.

\[
\text{AcN(H)-CHR-COCl + HCl. H}_2\text{N-CHR'-COOC}_2\text{H}_5 \rightarrow \text{AcN(H)-CHR-CO-NH-CHR'-COOC}_2\text{H}_5 + 2\text{HCl}
\]

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

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 a, a-
dichloro ether (IV) (reactions A, B and C) was obtained, by per-
forming 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 a-chloro-
vinyl ether (III) these acyl chlorides (XXb) are intermediates.

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

Of the two reagents for the synthesis of protected peptides, pro-
posed here a, a-dichlorodimethyl ether (IV) is to be preferred.

The new method has the following attractive features:

1) simple, "one step" procedures: isolation of intermediates is not necessary.
2) short reaction times (0.5 - 1.5 h).
3) good yields of optically pure N-acyl peptide esters.
4) easy isolation of the crystalline reaction products.