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

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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.

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 $^{\circ}$ C (corrected) and n 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:

$$\begin{array}{c} & \begin{array}{c} & \begin{array}{c} 2 \text{ NaOC}_2H_5 \\ & \end{array} \end{array} \\ & \begin{array}{c} \text{CH}_3\text{-CC}(\text{OC}_2H_5)_3 + 2 \text{ NaCl}} \\ & \begin{array}{c} \text{V} \end{array} \end{array} \\ \\ & \begin{array}{c} \text{H}_2\text{O} \\ & \\ \text{IV} \end{array} \end{array} \\ \begin{array}{c} \text{H}_2\text{O} \\ & \begin{array}{c} \text{CH}_3\text{-COOC}_2H_5 + 2 \text{ HCl}} \\ & \begin{array}{c} \text{XXIII} \end{array} \end{array} \\ \\ \begin{array}{c} 2 \text{ CH}_3\text{COONa} \\ & \begin{array}{c} \text{CH}_3\text{-CO-CO-CH}_3 \\ \text{O-CO-CH}_3 \\ \text{hypothetical} \\ & \text{intermediate} \end{array} \\ \\ & \begin{array}{c} \text{(CH}_3\text{CO)}_2\text{O} + \text{CH}_3\text{COOC}_2H_5 \\ & \begin{array}{c} \text{XXIV} \end{array} \end{array} \\ \end{array} \\ \begin{array}{c} \text{XXIV} \end{array} \\ \begin{array}{c} \text{XXIII} \end{array}$$

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.

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

We subjected seved dichlorodiethyl ethechlorides were obtatimes were short (abproducts was simple product, ethylaceta

The results are l of this thesis).

The use of the dich pure acyl chlorides chlorides must be con as SOCl₂, PCl₃ etc.

Chapters II and III.

Synthesis of peptide

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

Reaction C: One step

AcN (H)-CHR-COOH + F

XII

AcN(H)-CHR-CO-NH-CH XIV

XII + XIII + H₂C=CCl-O(

Ac = benzyloxycarbonyl

cbzo = C₆H₅-CH₂-O-C-

The method has been of cbzo-and phth-di-

In all experiments were isolated. Espec good results were obt

The syntheses of a performed by heating

and its use for

cloride to ethoxyer (IV). This di-

$$13$$
-CCl₂-OC₂H₅

r (III) is a known

with b.p. 104.5cture of this comions. nol afforded ethyl-

rolysis. anhydride (XXIV) d yields:

 $_5)_3 + 2 NaCl$

5 + 2 HCl

IIL

$$\begin{bmatrix} CO-CH_3 \\ CO-CH_3 \end{bmatrix}$$
 + 2 NaCl
CH₃ cal
iate
 COC_2H_5

reacted with carand ethyl acetate

y started at room

$$\begin{array}{c} \text{CH}_3\text{-CCl}_2\text{-OC}_2\text{H}_5 + \text{R-COOH} \longrightarrow \text{HCl}^{-1} \begin{bmatrix} \text{OC}_2\text{H}_5 \\ \text{I} \\ \text{CH}_3\text{-C-Cl} \\ \text{O-CO-R} \end{bmatrix} \longrightarrow \text{R-COCl} + \text{CH}_3\text{-COOC}_2\text{H}_5 \\ \text{hypothetical} \\ \text{intermediate} \\ \end{array}$$

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 byproduct, ethylacetate.

The results are listed in table I, chapter I, (page I-9^a, 9^l

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.

Synthesis of peptides by means of α -chlorinated ethers.

Two new methods of peptide-synthesis were developed. Nacyl 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.

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-benzyloxycarbonylamino 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).

(or $H_2C=CC1-OC_2H_5$)

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

Reaction B: formation of peptide bond.

AcN(H)-CHR-COC1 + HCl. H₂N-CHR'-COCC₂H₅——XXb XIII

AcN(H)-CHR-CO-NH-CHR'-COOC₂H₅ + 2HC1 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 -dichloroether (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 acylchlorides (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.

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