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NEW METHODS IN PEPTIDE SYNTHESIS, BASED ON SUPERNUCLEOPHILES

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Summary:

The fragmentation of β-halogenated alkyl groups and δ-halogenated butenyl groups from the N- and C-termini of α-amino acids and peptide derivatives by the supernucleophilic Co^{I}-phthalocyanine anion as well as related reactions are presented as the basis of some new protecting group techniques and synthetic methods for peptides.

1. Introduction

In the past decades a prolific development of new protecting group techniques for peptide synthesis has taken place, and yet there is not enough variety in conditions and reagents for the removal of protecting groups[1]. In fact, only a few basic types of reagents and conditions are used for the deprotection of blocked functional groups in peptide derivatives; and one type of deblocking techniques seems to be preferred, namely acidolysis. An increase in the number of options in deprotection conditions and more selectivity in the removal of the blocking groups are still desirable. New protecting groups are particularly needed for the synthesis of branched peptides, multi-chain peptides with interchain linkages, and many peptides containing trifunctional amino acids, as well as for the synthesis of peptides by a segment strategy. In order to be a real supplement to the collection of known protecting groups, any new group ought to survive some, or all, of the conditions which are used in the removal of the customary protecting groups, and the new groups ought to be cleaved from a blocked functional group under conditions which do not affect other types of protecting groups.

We wish to report on the development of a new class of protecting groups which have only little in common with the standard set of protecting groups with respect to deprotecting conditions. The new groups are generally stable towards quite strongly acidic, or basic conditions, as well as many reagents that are used during peptide syntheses. Their removal is accomplished in essentially neutral solution at 0 - 20°, often within a few seconds, by treatment with supernucleophiles.

2. Supernucleophiles

The term "supernucleophile" was introduced by Schrauzer and Deutsch[2] for nucleophiles with a relative nucleophilicity[3] $n_{MeI}=\log(k_Y/k_{MeOH}) \geq 10$. The phenomenon of supernucleophilicity was discovered, when the above-mentioned authors observed, that alkylating agents react extremely fast with certain anionoid Co^I complexes (see Table 1), e.g. reduced derivatives of vitamin B_{12} and its model compound cobaloxime (CoOx),[2] as well as Co phthalocyanine (CoPc).[4]

Table 1. The relative nucleophilicity n_{CH_3I} of some nucleophiles

Nucleophile Y	n_{MeI}	Reference
MeOH	0.00	3
Cl^-	4.37	3
Br^-	5.79	3
CN^-	6.70	3
I^-	7.42	3
$S_2O_3^{--}$	8.95	3
$Ph\text{-}S^-$	9.92	3
$[Co^IPc]^-$	10.8	4, 14
$[Co^IOx(\leftarrow PBu_3)]^-$	13.3	2
$[Co^IOx(\leftarrow Py)]^-$	13.8	2
$[Co^IB_{12}]^-$	14.4	2

The supernucleophilic properties of the aforementioned Co^I complexes are due to the spin paired weakly antibonding $3d_{z2}$ orbital of the central atom, combined with the planarity of the tetradentate chelating ligand system.[2,5]

The alkylation of Co^I supernucleophiles produces the corresponding alkyl-Co^{III}-complexes.[2,4,6,7,8]
When treated with acids, the β-hydroxyethyl-σ-Co^{III} derivatives of B_{12} and CoOx undergo fragmentation (see Scheme 1)[9]

Scheme 1

$$HO\text{-}CH_2\text{-}CH_2\text{-}Hal + [Co^I]^- \xrightarrow[-Hal^-]{} HO\text{-}CH_2\text{-}CH_2\text{-}Co^{III} \xrightarrow{H^+}$$

$$H_2O + CH_2{=}CH_2 + [Co^{III}]^+$$

Eckert, Schrauzer and Ugi[10] performed a series of model experiments in order to find out whether or not a protecting group technique can be based on the fragmentation of β-halogenated alkoxy compounds by (2) according to Scheme 2.

Scheme 2

$$\underset{(1)}{Y\text{-}CO\text{-}O\text{-}CH_2\text{-}CH_2\text{-}X} + \underset{(2)}{[Co^{I}Ox(\leftarrow py)]^-} \xrightarrow[-X^-]{} \underset{(3)}{Y\text{-}CO\text{-}O\text{-}CH_2\text{-}CH_2\text{-}Co^{III}Ox(\leftarrow py)}$$

$$\longrightarrow Y\text{-}CO_2H \text{ (or } YH + CO_2) + CH_2{=}CH_2 + [Co^{III}Ox(\leftarrow py)]^+ \quad (4)$$

X = Cl, Br; Y = Ph, NHPh, $N(CH_3)Ph$, Val-Ot-Bu

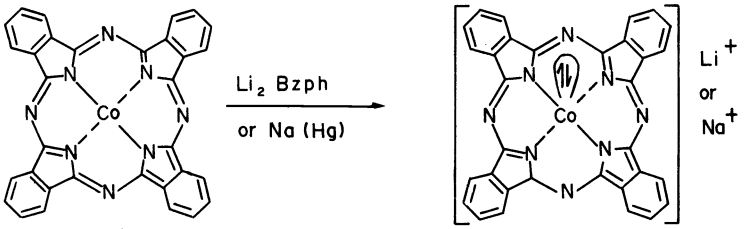
The isolatable β-acyloxyethyl-σ-Co^{III} compounds (3) were formed in 8 - 21% yield, and reacted to form the indicated products in 81 - 98% yield on treatment with acids or nucleophiles (OH^-, CN^-, BH_4^-) under suitable conditions.

The model experiments with (1) and (2) demonstrated not only the general feasibility of a protecting group technique which is based on the fragmentation of β-halogenated alkyl compounds and their analogs by supernucleophiles, but also disadvantages of (2) as a preparative reagent.[10,11] Its preparation requires much skill and care, due to its sensitivity towards protons and oxidizing reagents (e.g. (2) reacts with compounds of the type (1) not only according to Scheme 2, but it showed also a marked tendency to participate in side reactions, some with disintegration of the complex.[12])

3. Co^{I}-Phthalocyanine anion and its Chemistry

In 1963 Taube et al.[13] reported the formation of (6) by reduction of (5), a dark blue commercial pigment (Scheme 3)

Scheme 3



(5) (6)

A dark green 0,1 M solution of $[Co^{I}Pc]Na$ is obtained by shaking a suspension of (5) in dry acetonitrile with Na/Hg under N_2. This solution can be stored under N_2 at 0 - 25° indefinitely.[14] The crystalline lithium salt of (6) is conveniently obtained by reducing (5) in THF by di-lithium benzophenone in 91% yield. The crystalline material forms stable solutions in water, alcohols, acetonitrile, DMSO, acetone, pyridine and monoglyme. The acidity of such solutions may be changed by adding phenol, or 2.6-di-t-butyl phenol.[14]

In its chemistry $[Co^{I}Pc]^-$ differs significantly from $[Co^{I}Ox(\leftarrow py)]^-$, and the reduced B_{12} derivatives.

The redox potential of $[Co^{I}Pc]^{-}$ is with -0.37 V[15] rather far on the positive side, relative to the -0.77 to -1.12 V of rather similar metal^{I}-phthalocyanines,[15,16] as well as the -1.0 to -1.2 V of $[Co^{I}B_{12}]^{-}$ and $[Co^{I}Ox]^{-}$ derivatives.[5,17] The weak reducing properties of $[Co^{I}Pc]^{-}$ are advantageous in its use as a deblocking reagent for peptide derivatives.

The derivatives of $[CoPc]^{-}$ have a pronounced tendency to form $Co^{II}Pc$, while Co^{III} is rather strongly favored by the derivatives of B_{12} and CoOx.[11,18] This has immediate consequences for the reactions of $[Co^{I}Pc]^{-}$ with β-halogenated alkoxy compounds. These reactions do not lead to (9), in analogy to the chemistry of $[CoB_{12}]^{-}$ and $[Co^{I}Ox]^{-}$, but to the formal oxidation of two mole equivalents of $[Co^{I}Pc]^{-}$ according to Scheme 4.[18]

Scheme 4

$$Z\text{-}CH_2CH_2\text{-}X \;+\; [Co^{I}Pc]^{-} \xrightarrow[-X^{-}]{} Z\text{-}CH_2CH_2\text{-}Co^{III}Pc \;\overset{H^{+}}{\not\rightarrow}\; ZH + CH_2{=}CH_2 + [Co^{III}Pc]^{+} \quad (9)$$

(7) (6) (8)

$$(6) \rightarrow Z^{-} + CH_2{=}CH_2 + 2\,Co^{II}Pc \quad (5)$$

X = Halogen, Z = leaving group with O, N, S, a: X = Br, Z = OH
b: X = Br, Z = $Ph\text{-}CO_2$

Table 2. The reaction of β-halogenalkyl compounds (7) with cobalt(I) phthalocyanine anion (6) according to Scheme 4.

Z	X	Reaction time	Yield (%) of isolated Z-H
$C_6H_5\text{-}CO_2$	Br	40 min	66
$C_6H_5\text{-}CO_2$	Cl	50 h	77
$C_6H_5\text{-}NH\text{-}CO_2$	Br	45 min	86[a]
$C_6H_5\text{-}NH\text{-}CO_2$	Cl	60 h	83[a]
$C_6H_5\text{-}O$	Br	80 min	62
$C_6H_5\text{-}S$	Br	95 min	60
$C_6H_5\text{-}N\text{-}CH_3$	Br	- [b]	53

a) $C_6H_5\text{-}NH_2$ was isolated.

b) No evolution of ethylene was observed.

Table 3. The second order overall rate constants of some reactions according to Scheme 4 in methanol at 25°

Z	X	Conductometrically determined rate const. (l/mol·sec)	Gas-volumetrically determined rate const. (l/mol·sec)
C_6H_5-CO_2	Br	$2.5 \cdot 10^{-2}$	$1.7 \cdot 10^{-2}$
BOC-Phe-Ala-O	Br	-	$1.6 \cdot 10^{-2}$
C_6H_5-CO_2	Cl	$5 \cdot 10^{-5}$	-
MeO-Val-CO_2	Br	-	$6.4 \cdot 10^{-3}$
tBuO-Ala-Val-Ala-CO_2	Br	-	$9.7 \cdot 10^{-3}$
C_6H_5-O	Br	$1.5 \cdot 10^{-2}$	$8.7 \cdot 10^{-3}$
C_6H_5-S	Br	-	$7.3 \cdot 10^{-3}$
Br	Br	$2.7 \cdot 10^{-1}$ a)	$2 \cdot 10^{-1}$ a)

a) Corrected for a statistical factor 2.

Table 4. Gas-volumetrically determined time for 50, 90 and 100% completion of the reactions according to Scheme 4 of the listed benzoic acid esters with (6)

Reactant	$\tau_{50\%}$ (min)	$\tau_{90\%}$ (min)	$\tau_{100\%}$ (min)
$\emptyset COOCH_2CH_2Cl$	270	2000	3000
$\emptyset COOCH_2CH_2Br$	2	10	40
$\emptyset COOCH_2CH_2Co(III)Pc$	1	10	40

Side reactions which could affect the coordinative sphere are suppressed by the extreme stability of the metal ligand system in (5)[19]. The high lattice energy of it is responsible for its insolubility in all customary solvents.

Primary alkylating agents R-X react with $[Co^{I}Pc]^-$ fast and well to form $R\text{-}Co^{III}Pc$[20]. With secondary alkylhalides the formation of olefins is observed.[14]

The second order reactions between $[Co^{I}Pc]^-$ and a variety of organic halides in methanol at 25° were followed by conductivity measurements[20]. The dependence of the reaction rate on the structure of the organic halide (see Table 5) is a useful guideline in the design of protective groups which are removable by treatment with $[Co^{I}Pc]^-$.

Table 5. The conductometrically determined second order rate constants of the reaction between cobalt(I)phthalocyanine anion and various organic halides in methanol at 25°

Substrate	Rate const. (l/mol·sec)
$CH_3CH_2CH_2CH_2Cl$	$5 \cdot 10^{-5}$
$C_6H_5CH_2Cl$	2.6
$CH_3CH_2OOCCH_2Cl$	3.1
CH_3CHCl_2	$7.0 \cdot 10^{-4}$
CH_3CCl_3	1.4
$C_6H_5COOCH_2CCl_3$	> 4.5
$C_6H_5COOC(CH_3)_2CCl_3$	> 6
CH_3CH_2Br	$1.1 \cdot 10^{-2}$
$CH_3CH_2CH_2Br$	$1.2 \cdot 10^{-2}$
$CH_3CH_2CH_2CH_2Br$	$1.6 \cdot 10^{-2}$ a)
$(CH_3)_2CHCH_2Br$	$1.0 \cdot 10^{-3}$
$HOCH_2CH_2Br$	$1.7 \cdot 10^{-3}$
$BrCH_2CH_2Br$	$2.7 \cdot 10^{-1}$ b)
$BrCH_2CH_2CH_2Br$	$1.7 \cdot 10^{-2}$ b)
$BrCH_2CH_2CH_2CH_2Br$	$2.0 \cdot 10^{-2}$ b)
CH_3I	7.4 c)
$CH_3CH_2CH_2CH_2I$	$3.1 \cdot 10^{-1}$
CH_3OTs	$1.5 \cdot 10^{-2}$
$CH_3CH_2CH_2CH_2OTs$	$1.3 \cdot 10^{-3}$

a) Erroneously given as $2.9 \cdot 10^{-3}$ l/mol.sec in Ref. 4.
b) Corrected for a statistical factor 2.
c) from Ref. 4.

The influence of the leaving group Z is particularly well illustrated by the following model experiments:[18]

The alkylation of $[Co^{I}Pc]^-$ by β-bromo ethanol (7a) with X = Br, Z = OH yields isolatable (8a) which can be O-benzoylated to form (8b) with Z = O_2C-Ph. The latter cannot be directly prepared from (7b) with X = Br and Z = O_2C-Ph, because (8b) reacts too fast with $[Co^{I}Pc]^-$ according to Scheme 4 (see also Table 4). When isolated (8b) is treated with $[Co^{I}Pc]^-$ the formation of 93% $Co^{II}Pc$, 100% of ethylene and 60% of benzoic acid is observed. Here $[CoPc]^-$ acts as a reducing agent towards (8b). The reductive change of (8b) can also be achieved with $NaBH_4$.

4. Protection of Amino Groups

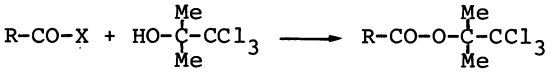
We know from preliminary studies (see also Table 5), that the β-chloroethyl group [1,10,21,27] is cleaved by (6) too slowly to be useful as a protective group. The β-bromoethyl group [1,21,22,27] would react fast enough with (6), but it tends to give side reactions, since it is quite reactive as an alkylating agent. The derivatives of trichloroethanol [1,23,27] and 2,2-dibromopropanol [14,27] are reactive enough towards (6), and they are not reactive as alkylating agents, but they are labile towards bases [1,27].

Nevertheless, the trichloroethyl (TE) group has already been successfully used in Woodward's cephalosporine synthesis [23], where no particular stability of the protecting group was needed. It was then removed by treatment with Zn/AcOH by which the protected compound was not damaged.

To our knowledge, the trichloro-t-butyl group (TCB)[24] is the only one among the simple β-halogenated alkyl groups which is highly reactive towards (6), and is otherwise chemically inert (see Table 7), because it is neither CH-acidic nor an alkylating agent.

Model experiments have shown that the TCB group cannot be used to protect the carboxyl group of amino acids. The formation of the esters (12) from carboxylic acids (10) and chloretone (11) turned out to be difficult, in some cases impossible.

Scheme 5



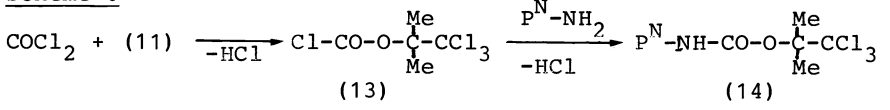
(10) (11) (12)

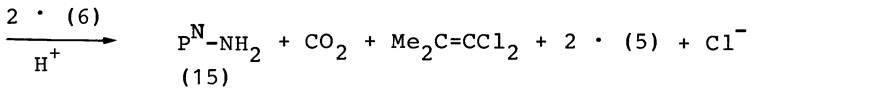
X = OH, Cl, O_2C-CF_3

The direct esterification could not be achieved under any condition. The chloroacetate (12a) with R = CH_2Cl of (11) was obtained in 17% yield by refluxing (11) for four days in $ClCH_2COCl$, and the o-nitrocinnamate (12b), R = o-NO_2-C_6H_4-Ch=CH (mp 90°C) resulted in 60% yield by treating o-nitrocinnamyl chloride with (11) for 48h at 160°C. Analogously, TCB bromo acetate is formed in 68% yield in 3h. To our surprise (12b) was also formed in 75% yield by treating o-nitrocinnamic acid and (11) with trifluoro acetic anhydride for 30 min at 40°C [25,26]. When diketene is refluxed in ether for seven days 71% of the acetoacetate of chloretone (12c), R = Me-CO-CH_2 are produced. We have not yet succeeded in producing TCB esters of amino acid derivatives in a similar manner.

In contrast to the carboxylic group, chloretone (11) has proven its value in the protection of amino groups and other acylatable groups (see Scheme 6)[24].

Scheme 6





Trichloro-t-butoxy carbonyl chloride,TCBOC chloride, (13) is readily available through phosgenation of anhydrous chloretone (11). In order to test the value of the TCBOC group in the protection of amino groups in a peptide synthesis, it was used in the synthesis of a H-Val-Ala-Phe-Phe-OH derivative (14f) by the DCCD/HO-Su method (see Table 6)

Table 6. Yields of TCBOC-protected components in the synthesis of tetrapeptide

		Yield [%]
(14a)	TCBOC-Val-OH	82
(14b)	TCBOC-Val-Ala-OMe	90
(14c)	TCBOC-Val-Ala-OH	82
(14d)	TCBOC-Val-Ala-Phe-OtBu	67
(14e)	TCBOC-Val-Ala-Phe-OH	82
(14f)	TCBOC-Val-Ala-Phe-Phe-OtBu	94

The TCBOC group is not affected by acidic and basic condition, which might occur during some peptide syntheses (see Table 7).

Table 7. Stability of the N-terminal TCBOC group towards acidic and basic reagents

		Conditions	Stability of the C-terminal group	TCBOC group
(14g)	TCBOC-Val-OMe	0.1 N NaOH/20°C/2h	+	+
(14g)	TCBOC-Val-OMe	1 N NaOH/40°C/2h	-	(+) [a]
(14b)	TCBOC-Val-Ala-OMe	0.1 N NaOH/20°C/2h	-	+
(14g)	TCBOC-Val-OMe	TFA[b]/20°C/2h	+	+
(14d)	TCBOC-Val-Ala-Phe-OtBu	TFA[b]/20°C/1h	-	+

[a] 40% of TCBOC-Val-OH are formed.

[b] TFA = trifluoroacetic acid.

The removal of the TCBOC group is shown in Table 8.

Table 8. Removal of the TCBOC group from compounds (14) by lithium cobalt (I)-phthalocyanine in methanol (method A) or acetonitrile (method B) or with zinc in glacial acetic acid (method C) at 20°C.

(14)		Method	Reaction time	Yield of (3) [%]
(14g)	TCBOC-Val-OMe	A	1 min	87
(14h)	TCBOC-Val-OCH_2Ph	A	1 min	93
(14d)	TCBOC-Val-Ala-Phe-OtBu	B	1 h [a]	94
(14g)	TCBOC-Val-OMe	C	3 h	66
(14d)	TCBOC-Val-Ala-Phe-OtBu	C	3 h	73

The conditions for the removal of the TCBOC group are mild enough for its successful use in a synthesis of ampicillin [28].

5. Protection of Carboxyl Groups

Once a suitable β-halogenated alcohol is found, the protection of amino groups by the corresponding alkoxy carbonyl group is no problem, because the formation of the chlorocarbonates, e.g. (13) is generally easy, and they react well with amino groups to form urethanes [27].

When a protecting group technique for carboxyl groups is developed the introduction of the protecting group presents often a problem which must be solved besides the problems which are also found in the protection of amino groups.

We do not have yet any β-halogenated alcohol whose esters are easy to prepare, sufficiently stable, and rapidly cleaved by (6).

Eckert [29] exploited the high degree of reactivity of chloral (17_b) and 2.2-dibromo-propanal (17e) as components of the Passerini reaction [30] (Scheme 7) which takes place under extremely mild conditions. In spite of the CH-acidity of the H_α, the esters (19) are remarkably stable.

Scheme 7

$$P^C\text{-}CO_2H + R'\text{-}CX_2\text{-}CHO + CN\text{-}t\text{-}Bu \longrightarrow P^C\text{-}CO\text{-}O\text{-}\underset{\displaystyle R'CX_2}{\underset{|}{C}}H_\alpha\text{-}CO\text{-}NH\text{-}t\text{-}Bu$$

(16) (17) (18a) (19)

$$\xrightarrow{2 \cdot (6)} P^C\text{-}CO_2^- + R'XC{=}CH\text{-}CO\text{-}NH\text{-}t\text{-}Bu + X^- + 2 \cdot (5)$$

$(16)^-$

b: R' = X = Cl

e: R' = Me; X = Br

When chiral amino acid derivatives (16) are used, the esters (19) should be formed as a mixture of epimers which differ by the configuration of the newly formed asymmetric C-atom. Nevertheless, most of the esters encountered crystallized well. Probably a mixture of the epimers of (19) is converted into one of them on crystallization, by fast exchange of the acidic proton H_α.

As is seen from Table 9, the required Passerini reaction proceeds well, but the yields in the cleavage step are relatively low.

Table 9. Protecting group technique based on Passerini reaction according to Scheme 7.

N-acyl amino acid ester		Yield [%]	Deblocked N-acyl amino acid	Yield [%]
(19a)	Z-Ala-O-CH(CO-NH-t-Bu)-CH_2Cl	75	Z-Ala-OH	11
(19b)	Z-Ala-O-CH(CO-NH-t-Bu)-CCl_3	73	Z-Ala-OH	59
(19c)	Z-Ala-O-CH(CO-NH-t-Bu)-CBr_3	95	Z-Ala-OH	67
(19d)	Z-Ala-O-CH(CO-NH-t-Bu)-CHBr-CH_3	76	--	--
(19e)	BOC-Phe-O-CH(CO-NH-t-Bu)-CBr_2-CH_3	95	BOC-Phe-OH	66

Recently some γ-halogenated derivatives, (23a) - (23c) of crotonaldehyde have been synthesized by the Wittig reaction [31] of (21a) - (21c) with (22) [32] according to Scheme 7 for the protection of carboxyl groups by the Passerini reaction and for use as potential aldehyde components in peptide coupling (see Schemes 11 and 13) [33]

Scheme 8

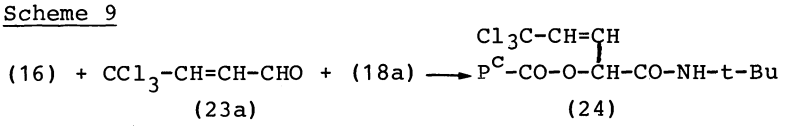
$$R'\text{-}CX_2\text{-}CHO + Ph_3P{=}CH\text{-}CHO \longrightarrow R'\text{-}CX_2\text{-}CH{=}CH\text{-}CHO$$

(21) (22) (23)

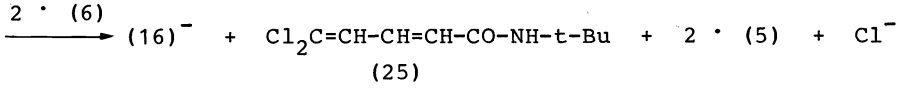
a: R' = X = Cl
b: R' = X = Br
c: R' = Me; X = Br

According to preliminary studies (23a) is the aldehyde of choice among (23a) - (23c) for a protection group technique which is based on the Passerini reaction (see Scheme 9) [34].

Scheme 9



(16) + CCl_3-CH=CH-CHO (23a) + (18a) → P^C-CO-O-Cl_3C-CH=CH-CH-CO-NH-t-Bu (24)

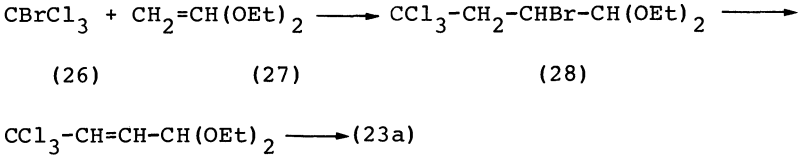


2 · (6) → $(16)^-$ + Cl_2C=CH-CH=CH-CO-NH-t-Bu (25) + 2 · (5) + Cl^-

Our first results indicate that Scheme 9 is superior to Scheme 7 with regard to yields.

The synthesis of (23a) from (26) and (27) is being studied. In this synthesis the removal of by-products seems to be the main problem.

Scheme 10 [35]

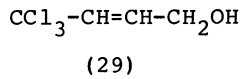


$CBrCl_3$ + CH_2=CH(OEt)$_2$ → CCl_3-CH_2-CHBr-CH(OEt)$_2$ →

(26) (27) (28)

CCl_3-CH=CH-CH(OEt)$_2$ → (23a)

We are investigating the protection of the NH, OH and SH groups in the side chains of Asn, His, Tyr and Cys by alkylating derivatives of the δ,δ,δ-trichlorocrotyl alcohol (29) which can be made from (23a)



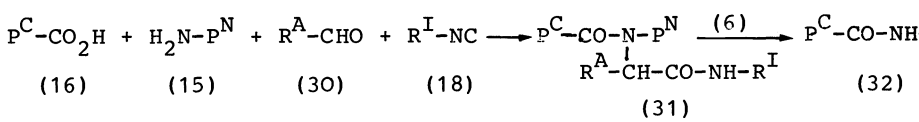
CCl_3-CH=CH-CH_2OH

(29)

5. Coupling of Peptide Segments by Four Component Condensation

Since 1972 a series of aldehyde components (30) has been tried out [36] in attempt to couple suitably protected α-amino acid derivatives (15) and (16) to Scheme 11.

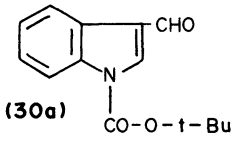
Scheme 11



P^C-CO_2H + H_2N-P^N + R^A-CHO + R^I-NC → P^C-CO-N(-CH(R^A)-CO-NH-R^I)-P^N (31) —(6)→ P^C-CO-NH-P^N (32)

(16) (15) (30) (18)

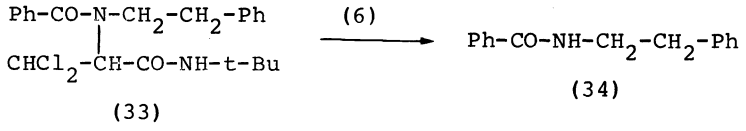
Up to now (30a) [36b] has been one of the favored aldehydes in Scheme 11, but neither (30a), nor any other aldehydes with acidolytically cleavable FCC products were satisfactory.



(30a) N-CO-O-t-Bu, CHO

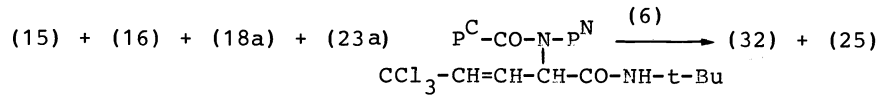
Since the model FCC product (33) is neither formed nor cleaved in good yield [14,20,37], and since the aldehydes (17) fail to undergo the required FCC, (23a) - (23c) were tested as potential aldehyde components in the formation of peptide bonds by FCC (see Schemes 11 and 13) [33,37].

Scheme 12



(33) (34)

Scheme 13

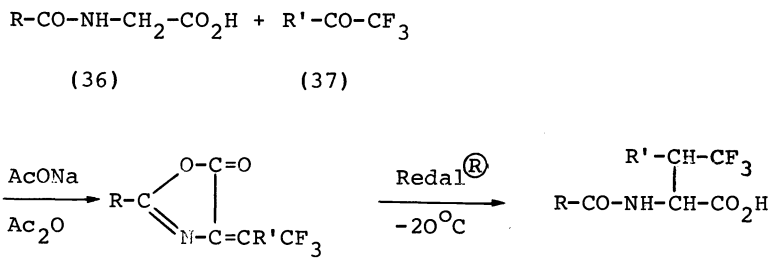


(35)

The feasibility of peptide syntheses by FCC according to Scheme 13 was demonstrated by some model experiments, e.g. the synthesis of BOC-Gly-Ala-Leu-OMe from BOC-Gly-Ala-OH and H-Leu-OMe.

The racemization tendency of the C-terminal amino acid unit of (15) during FCC peptide syntheses with (23a) was studied with the aid of a new type of racemization test which is based on ^{19}F-NMR. The p and n diastereoisomers[38] of the β-trifluoromethyl α-acyl-amino acids as well as their hitherto known derivatives differ substantially in free energy. The labile diastereomers of (39) can be obtained according to Scheme 14.

Scheme 14



(38) (39)

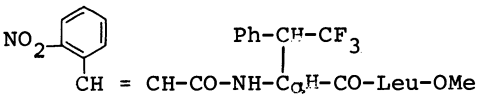
a: R = Ph; R' = Et

b: R = 2-NO_2-Ph-CH=CH, R' = Ph.

The derivatives of the labile diastereomers of (39a) and (39b) with ^{19}F doublets at δ_a = - 11.25 ppm. and δ_b = - 0.25 ppm., are easy to distinguish by ^{19}F-NMR from their stable diastereomers with doublets at δ_a = -7.98 ppm and δ_b = -1.00 ppm.

When (39a) or (39b) is used as (16) in a model experiment for peptide syntheses, the relative amounts of the diastereoisomeric products which differ in ^{19}F-NMR provide information on the relative extent of racemization which can be expected for the tested synthetic methods and conditions.

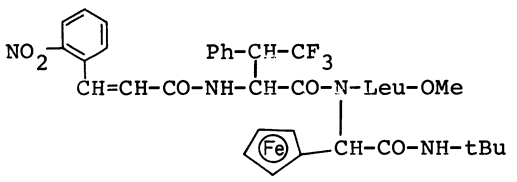
It was found that the synthesis of (40) by the mixed anhydride method (isobutyl chloroformate, N-methyl-morpholine) [39] proceeds with 96 - 100% "racemization".



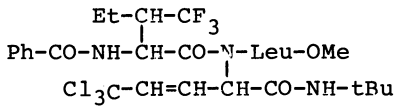
(40)

The synthesis of (40) by the DCCD-HOSu method [40] is accompanied by 10 - 11% "racemization" (inversion at C_α), and the DCCD-HBT method [41] with 13% "racemization".

The formation of (41) by FCC takes place with 12% "racemization", while the FCC synthesis of (42) is with 0.25% practically free of racemization.



(41)



(42)

An extensive investigation of the ^{19}F-NMR racemization test is presently being conducted, including its applications to FCC peptide coupling with (23a).

ACKNOWLEDGEMENTS

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