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Solution Phase

Peptide synthesis steps

1. Protect $-NH_2$ of NTAA (BOC, Phthaloyl)
2. Activate $-COOH$ of NTAA (PCl_5 / $SOCl_2$ / PCl_3)
3. Protect $-COOH$ of CTAA (H_3COH, tOH, etc alcohol)
4. Use coupling agent to couple $-COOH$ of NTAA with $-NH_2$ of $-NTAA$ (DMF / DCC)

Protecting Gp

By using (BOC, Phthaloyl)

Deprotection of group

B: HCl / AcOH or HBr/AcOH, CF_3COOH.

Protecting gp

1. N-T-AA NH_2 gp
   - (a) BOC.
   - (b) Phthaloyl

Deprotection of group

1. (a) HCl or HBr/AcOH, CF_3COOH.
   (b) a) N_2H_4 (or NH_2NH_2) – EtOH · followed by b) HCl

Protection of C-T-AA carboxylic gp

2. C-T-AA – COOH gp.
   (a) Esterification by Alcohol
   (a) O_2N-(O)-OH
   (b) CH_3OH.
   (c) $PhCH_2OH$
   (d) $CH_3-C(CH_3)_2-OH$ — t-Butanol

Deprotection of carboxylic gp

(B) NaOH / hydro

(A) H_2 / Pd (Reduction)
Nitrobenzene.
CH_4 methane
$PhCH_3$. Toluene
$-H$. t-butane
Side-products

3. Activation of $-COOH$ of NT-AA.
   (a) by PCl_5
   (b) Azide
   (c) DCC.

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(2) starting from N-T-AA to C-T-AA

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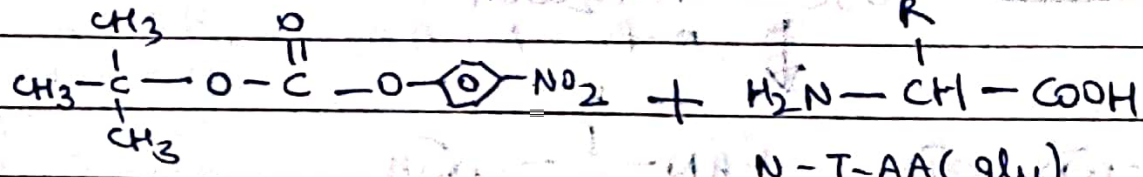
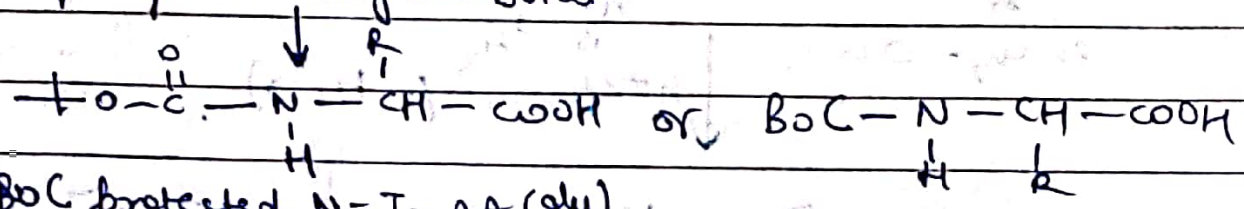
Solution Phase Peptide Synthesis

H·gly·val·OH | gly→val | G-V | gly·val | glycylvaline

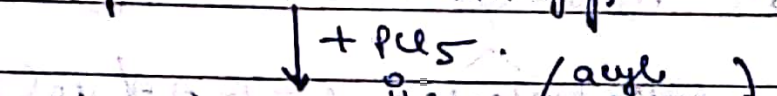
(I) method



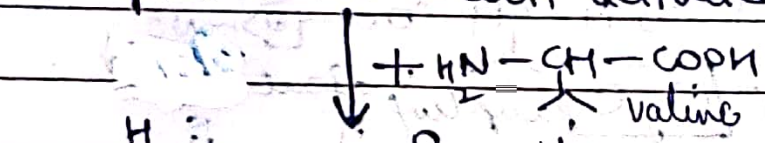
p-Nitrophenyl-t-butylcarbonate + N-T-AA(gly)

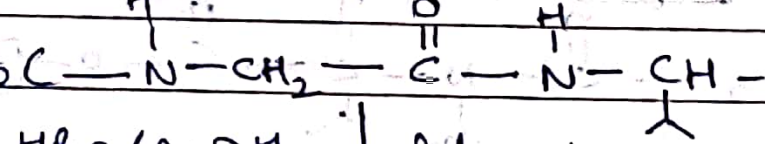


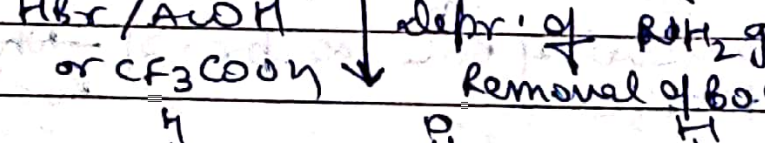
BoC protected N-T-AA(gly) or BoC-N-CH-COOH



BoC protected ⊗ = COOH activated N-T-AA.







glycylvaline

(I) Steps are

a) N-T-AA (gly) is BoC protected

b) N-T-AA is activated at -COOH end using PCl_5.

c) coupling with C-T-AA (valine)

d) deprotection of N-T-AA by removal of BoC.

OR

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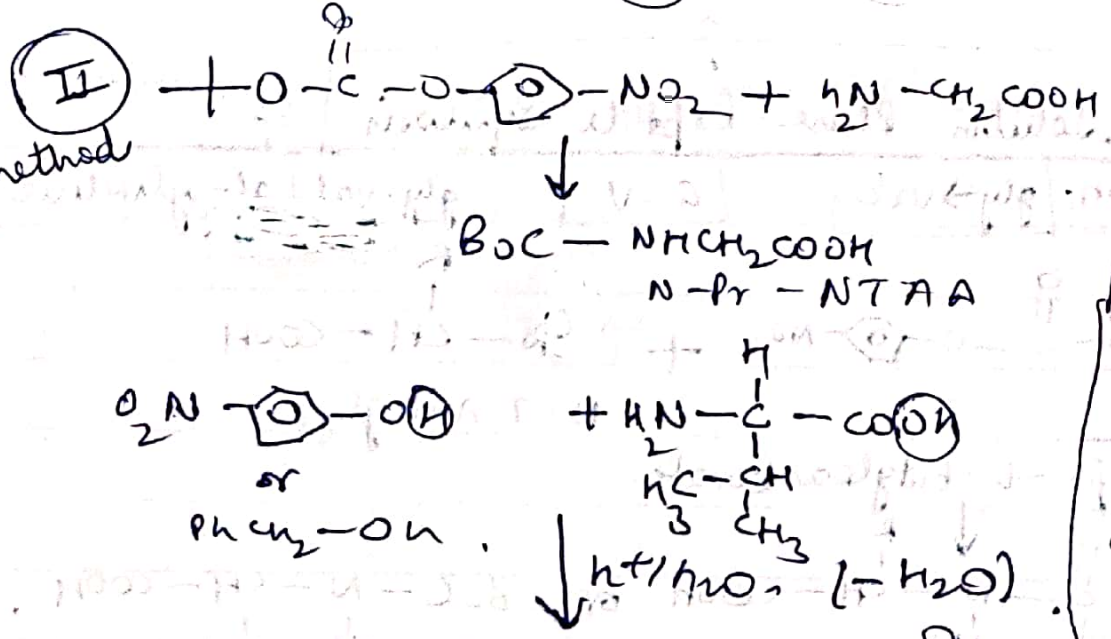
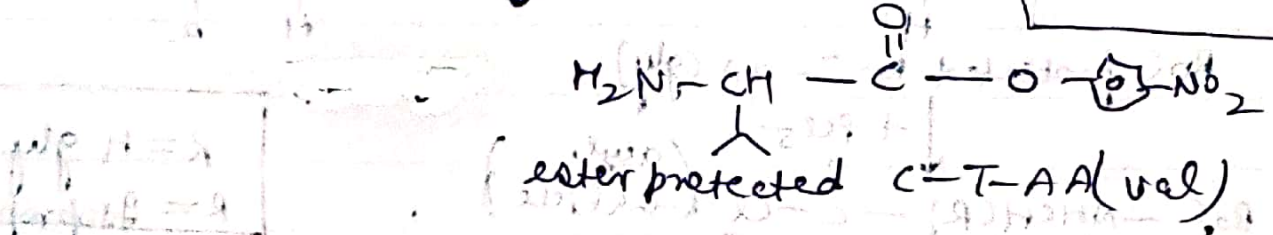
II method

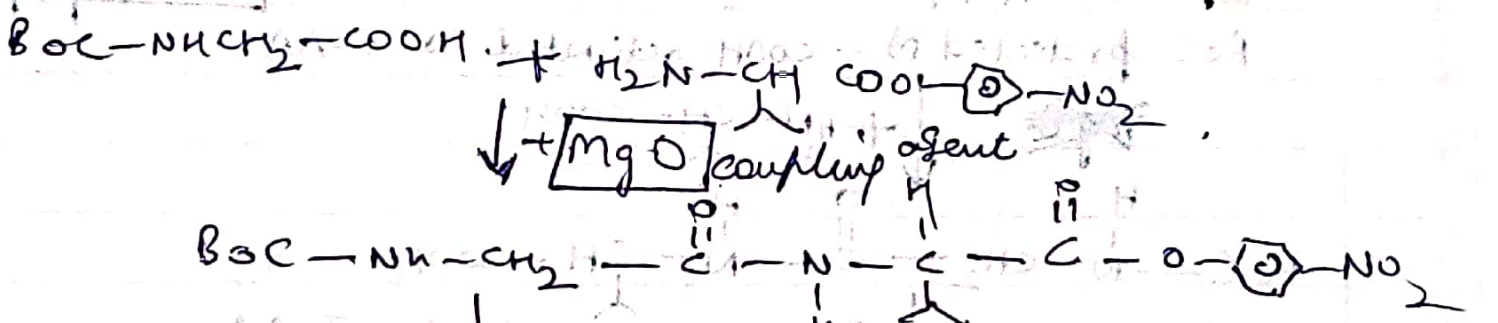


Steps of II are (gly)

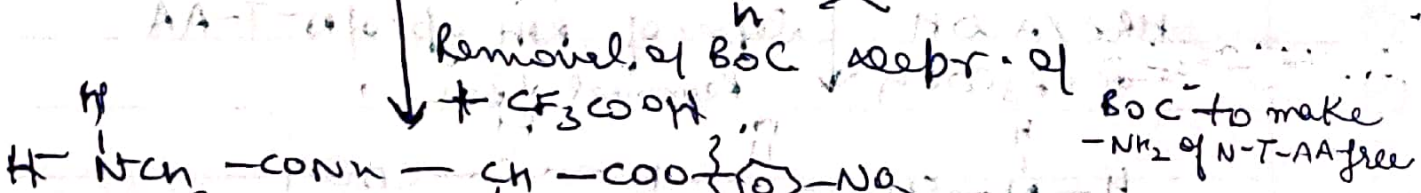
a) N-T-AA is protected with BOC
b) C-T-AA is protected by ester formation (Val)
c) coupling of gly & val using MgO
d) Removal of ester Removal of BOC



ester protected C-T-AA (val)

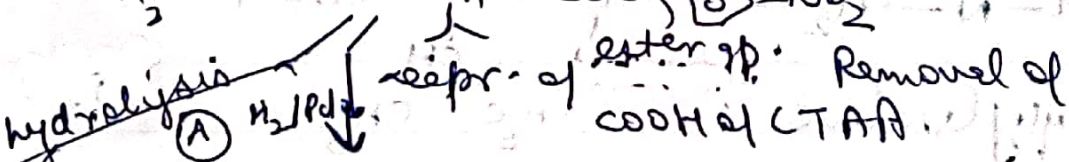


Removal of BOC reqr. of BOC to make $-NH_2$ of N-T-AA free



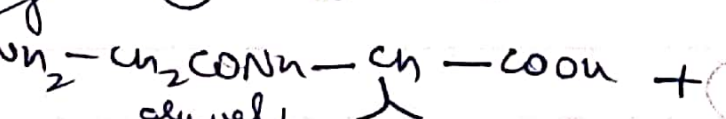
B Alkali hydrolysis

A H_2/Pd reqr. of ester gp. Removal of ester COOH of CTAA



glycyl

side product



side pdt

Removal of ester gp A H_2/Pd OR B Alkaline hydrolysis $^{\ominus}OH/H_2O$

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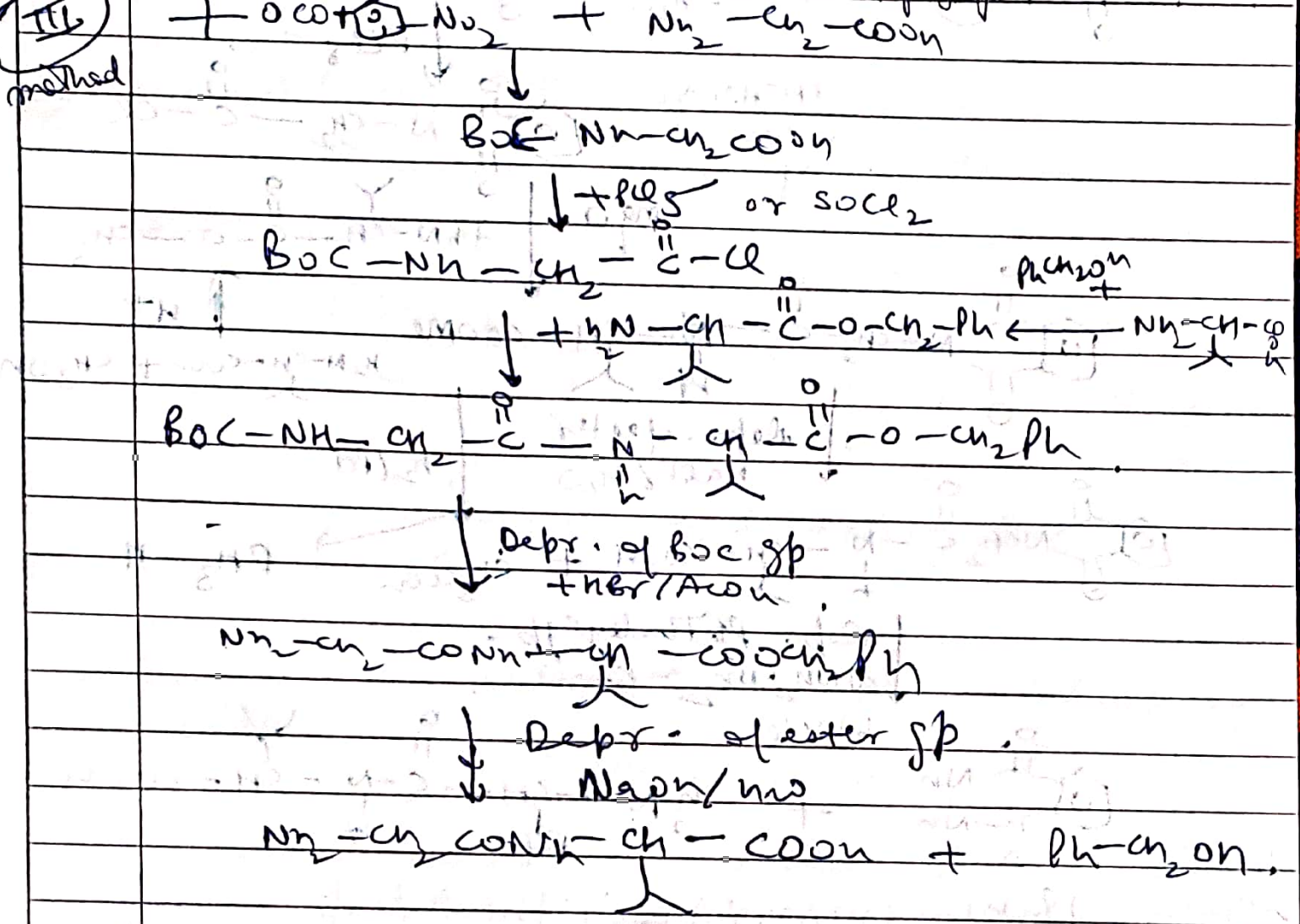
Solution phase Peptide Synthesis of gly-val

III method



Steps of III are a) Protection of $-NH_2$ of N-T-AA(gly) with Boc
b) Activation of $-COOH$ of N-T-AA with PCl_5.
c) Protection of $-COOH$ of C-T-AA(val) with alcohol forming ester.
d) Coupling of gly & val from N-T-AA to C-T-AA direction.
e) Removal of Boc & ester to make $-NH_2$ of N-T-AA(gly) & $-COOH$ of C-T-AA(val) free.

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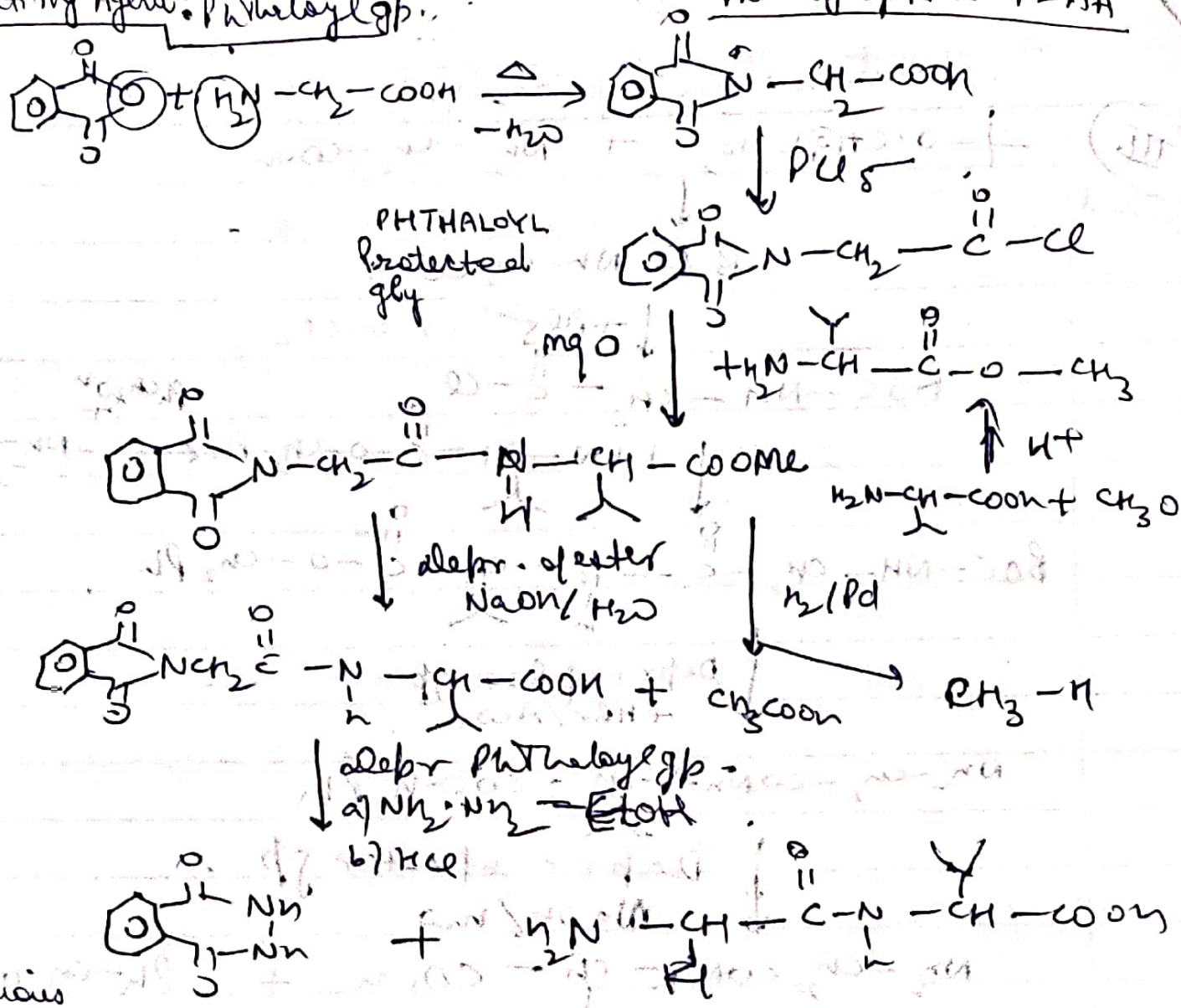
Protecting Agent: Phthaloyl gp.

Phthaloyl pr. N-T-AA



Various Steps are a) Protection of NTAA (gly) using phthaloyl gp.

b) Activation of COOH of NTAA (gly) same as using $PCl_5/PCl_3/SOCl_2$

c) Coupling of NTAA with CTAA using MgO as coupling agent

d) Removal of ester & Nthaloyl gp. to get free $-NH_2$ of NTAA (gly) & free $-COOH$ of CTAA (Val) to get the desired dipeptide gly-Val using Solution Phase Synthesis

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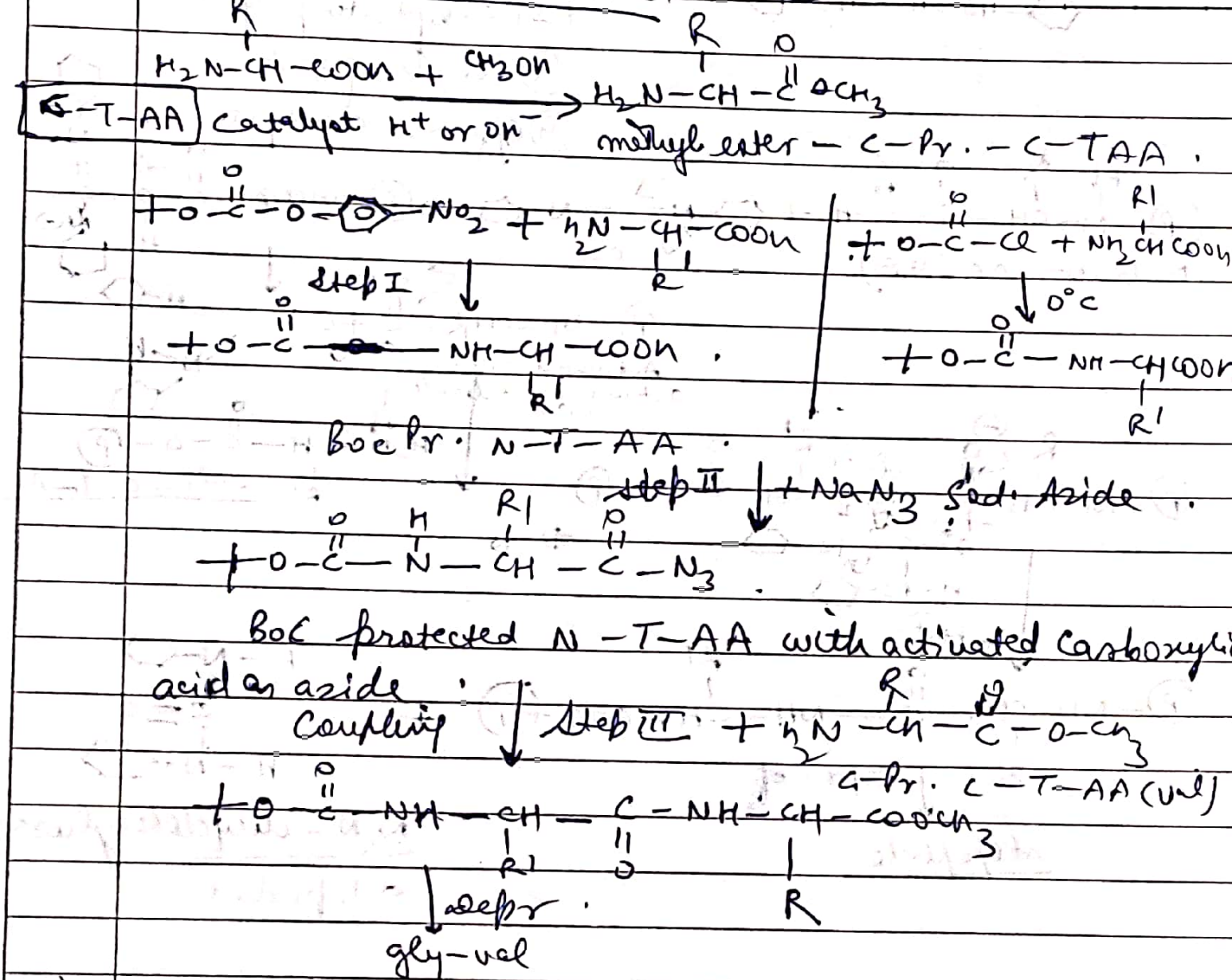
glycylvaline

$R' = H$, $R = CH(CH_3)_2$

Acid Curtius Azide method



a) C-T-AA is protected by using alcohol (MeOH) to make ester (val)

b) Boc Protected N-T-AA (gly)

c) –COOH of N-T-AA (gly) is activated using Sodium Azide, NaN_3

d) Coupling of gly & val.

e) deprotect

Solution phase dipeptide (gly-val) synthesis using Acid Curtius Azide method.

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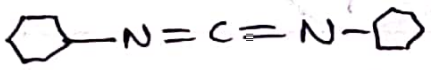
(7)

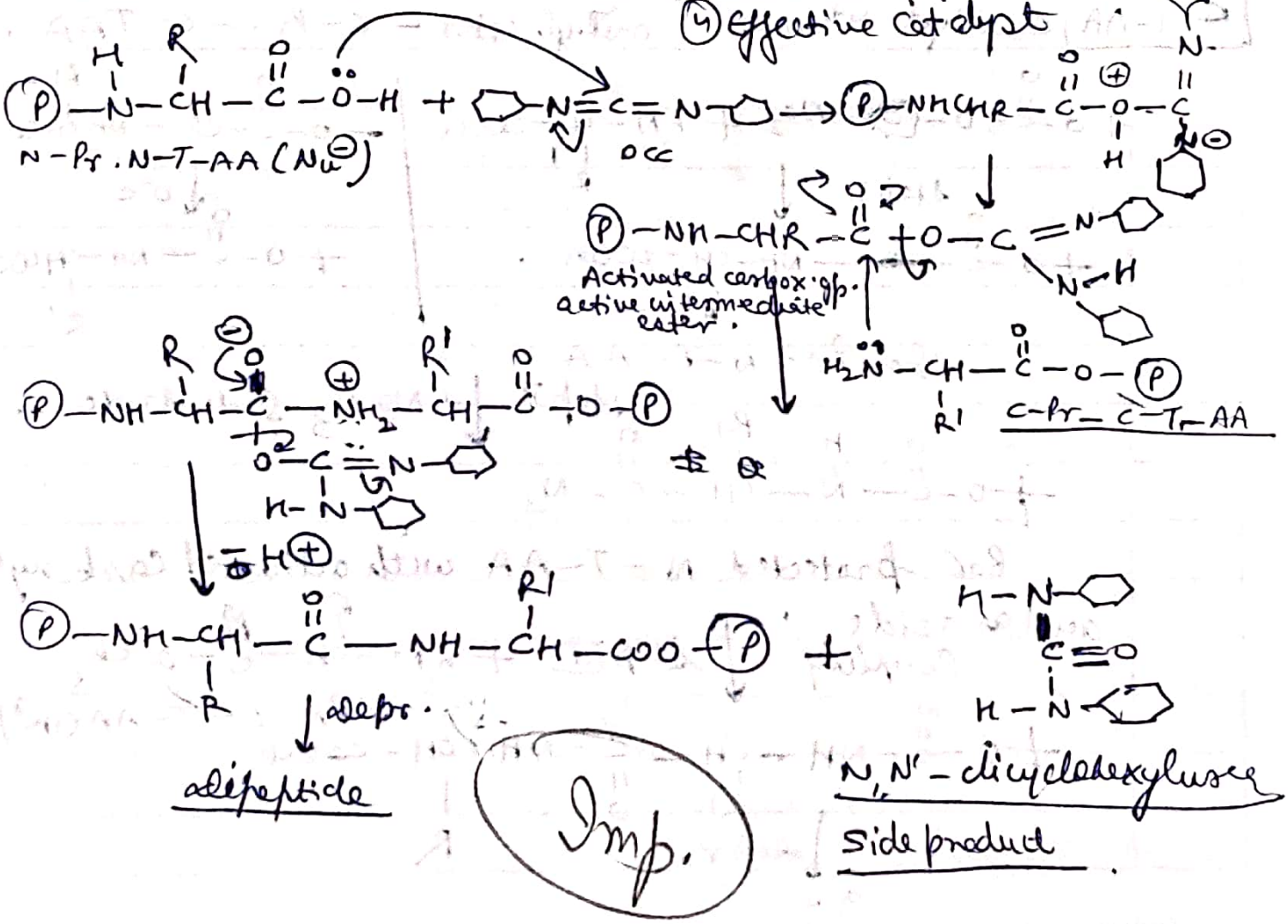
DCC = Dicyclohexylcarbodiimide



Role

Function / Role / Adv. of DCC

1. Cyclising agent
2. dehydrating ag.
3. Coupling agent
4. Effective catalyst



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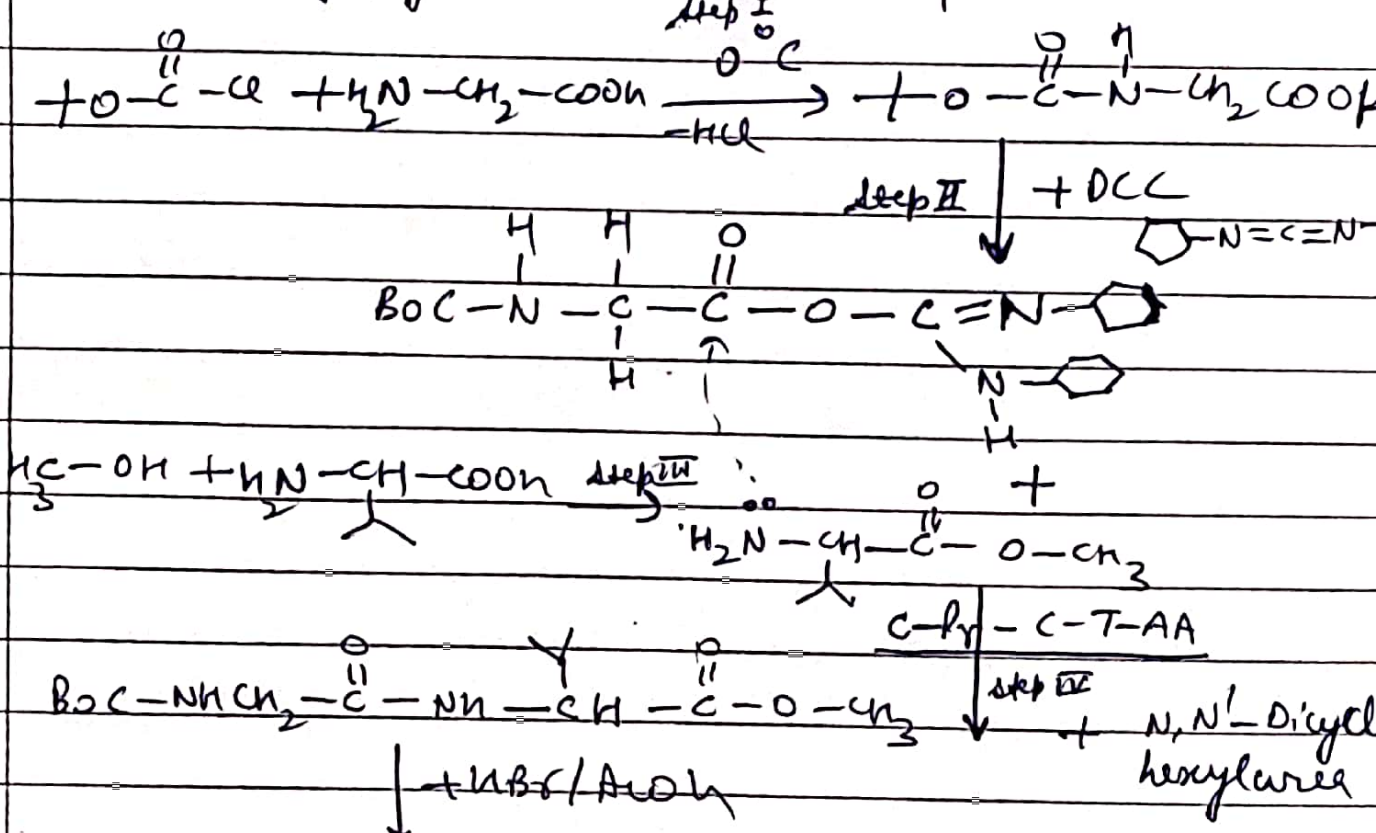
Q → Show various steps for the synthesis of dipeptide glycylvaline using DCC.



Solution Phase DCC using synthesis of gly-val

a) Protect $-NH_2$ of NTAA (gly) using BoC

b) Using DCC as a cyclising agent/ coupling agent which will activate $-COOH$ of NTAA of glycine

c) Protected C-T-AA (val) using Methanol is esterified at $-COOH$ end of val. Then coupled with glycine using DCC

d) Removal of ester & BoC to get dipeptide, gly-val

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