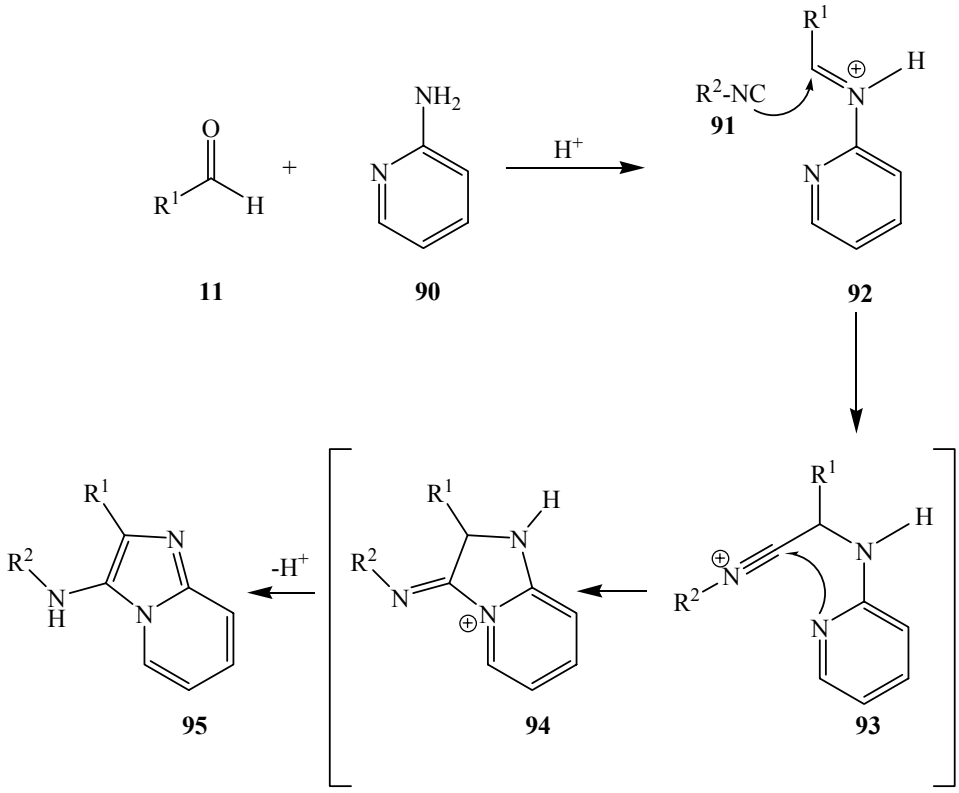
5 Ugi-type reactions with 2-aminopyridine and siloxycyclopropanes – syntheses of masked δ-amino acids

This three component condensation (3CC) may be regarded as a special type of the Ugi-four component reaction.[90] Combination of carbonyl compound **11**, isocyanide **91** and 2-aminopyridine (**90**) afforded 3-aminoimidazo[1,2-*a*]pyridines **95**. The imidazo[1,2-*a*]pyridine structural moiety can be found in pharmacologically active compounds such as benzodiazepine receptor agonists,[91-93] anti-inflammatory agents,[94] inhibitors of gastric acid secretion,[95] calcium channel blockers[96] and antibacterials.[97]

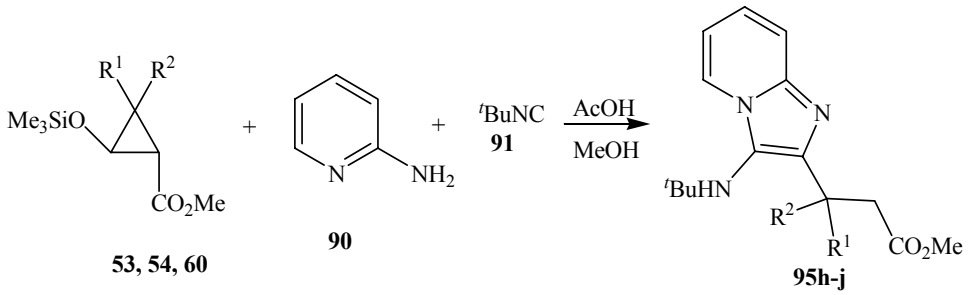
A likely mechanism proceeds *via* an iminium species **92** which is attacked by the isocyanide to give nitrilium ion **93**. The pyridine nitrogen of **93** is in a favourable position for a 5-*exo*-dig cyclization giving the assumed intermediate **94**. Rearomatization of **94** *via* deprotonation and 1,3-H shift results in the formation of bicyclic product **95**. The reaction can be regarded as a [1+4] cyclization or insertion reaction of an isocyanide with a C=N-C=N bond system (Scheme 44).[90]



Scheme 44. Possible mechanism of Ugi-type reaction with 2-aminopyridine (**90**)

5.1 Ugi-type reaction with 2-aminopyridine employing siloxycyclopropanes

In previous work of Zimmer et al.[98] it was found that methyl 2-siloxycyclopropanecarboxylates can be directly introduced as precursor compounds under the protic conditions employed for this reaction. Three siloxycyclopropanes **53**, **54** and **60** were reacted with *tert*-butylisocyanide and 2-aminopyridine (**90**) to obtain bicyclic products **95h-j** in moderate to good yields (Scheme 45).



R^1 = H; R^2 = H 56 %
R^1 = Me; R^2 = H 57 %
R^1 = Me; R^2 = Me 46 %

Scheme 45. Ugi-type reaction with 2-aminopyridine (**90**)

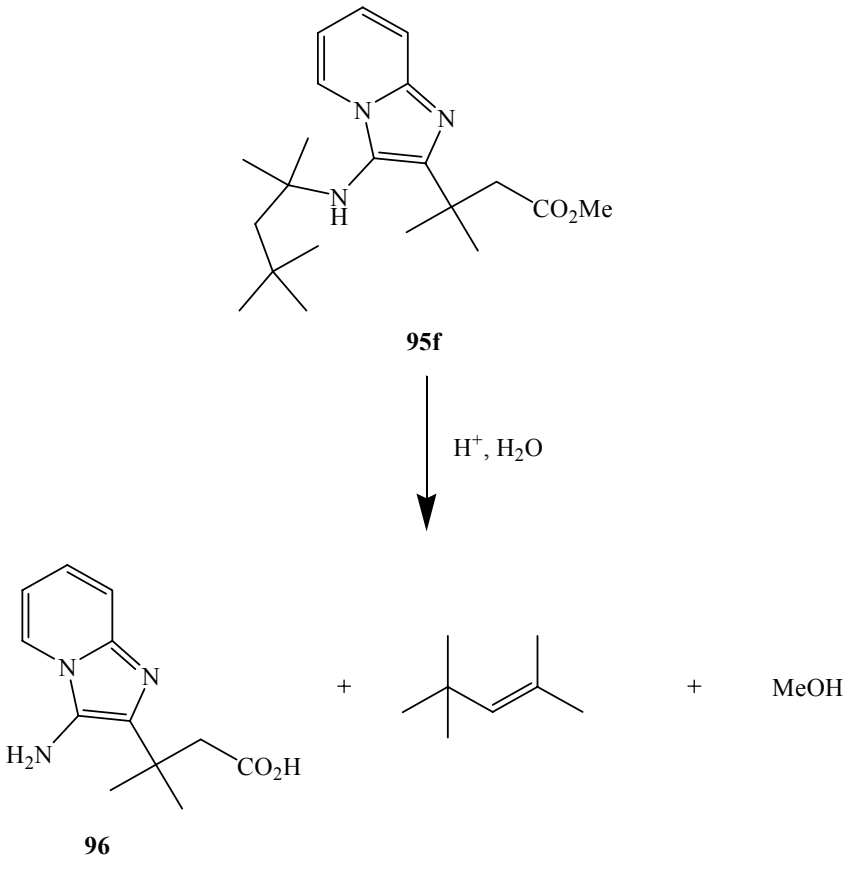
Following these initial experiments the 3CC was attempted with siloxycyclopropanes **53**, **54** and **60**, four isocyanides and 2-aminopyridine. In a typical procedure 2-siloxycyclopropanecarboxylate, 2-aminopyridine and isocyanide were mixed together in MeOH in the presence of acetic acid and reacted at room temperature (Table 4). The second step – condensation of aldehyde and amine – was investigated and it was concluded that acidic conditions are necessary for imine formation. In literature it is also known that reactions between aromatic imines and *tert*-butylisocyanide do not proceed without acid catalysis[99] so the presence of acid might be necessary also for the second step of this multistep reaction. In Table 4 are listed compounds synthesized from three siloxycyclopropanecarboxylates, four isocyanides and 2-aminopyridine (**90**).

Table 4. Results of the Ugi-type reaction with 2-aminopyridine (**60**) (experiments: E18-E22, E24-E26)

Entry	Start. mat.	R^1	R^2	R^3 (**31**)	Product	R. time (h)	Yield (%)
1	**53**	H	H	$PhCH_2$	**95a**	24	33
2	**53**	H	H	1,1,3,3-Tetramethylbutyl	**95b**	48	79
3	**60**	Me	H	$PhCH_2$	**95c**	24	32
4	**60**	Me	H	*n*-Bu	**95d**	19	43
5	**54**	Me	Me	$PhCH_2$	**95e**	19	57
6	**54**	Me	Me	1,1,3,3-Tetramethylbutyl	**95f**	48	56[a]
7	**54**	Me	Me	*p*-Methoxyphenyl	**95g**	20	43

[a]In this experiment was also obtained the free amino acid **96** in 30% yield.

The reaction involving 1,1,3,3-tetramethylbutylisocyanide (entry 6) yielded compound **96** in 30% yield besides the main product **95f**. This is due to the relative instability of **95f** under acidic conditions (Scheme 46).

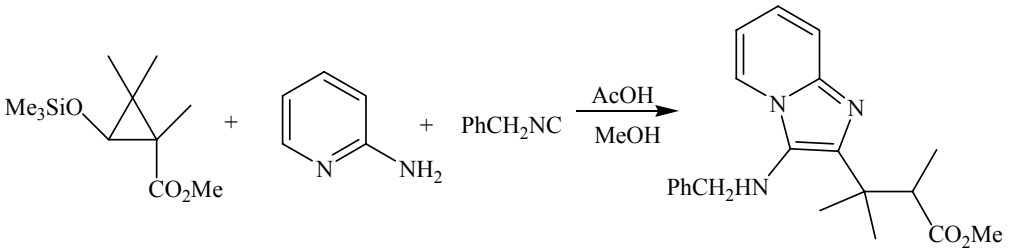


Scheme 46. Conversion of **95f** into **96** under acidic conditions

The reaction comprised both aliphatic and aromatic isocyanides. Yields ranged between 32 and 79%. The initial experiments were typically performed overnight; in latter experiments

better yields were obtained with increased reaction time. Table 4 shows that the best yields were obtained by use of 1,1,3,3-tetramethylbutylisocyanide; however this should be taken with caution since those experiments were performed with longer reaction times, as mentioned above.

The next 3CC was performed with 1-alkylated 2-siloxycyclopropanecarboxylate. 1-Methyl-2-siloxycyclopropanecarboxylate **56** was reacted with 2-aminopyridine (**90**) and benzylisocyanide and product **95h** was obtained in 40% yield (Scheme 47).



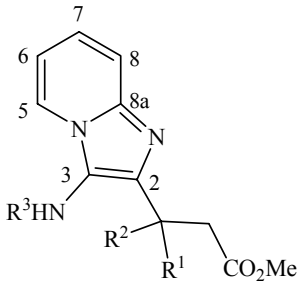
56 **90** **95h**

40%

Scheme 47. Ugi-type reaction with 2-aminopyridine and 1-methyl 2-siloxycyclopropane (**90**) (experiment: E28)

5.1.1 NMR, IR and X-ray data of compounds 95

The most significant signals in the ^{1}H NMR spectra of 3-aminoimidazo[1,2-*a*]pyridines **95** are the protons at positions 5, 6, 7 and 8 in the pyridine ring (Scheme 48). The proton at position 5 appears at δ ≈ 8.0 ppm as a doublet of triplet with J ≈ 6.8 and ≈ 1.2 Hz; the proton at position 6 displays a triplet of doublet with coupling constants of J ≈ 6.8 and 1.2 Hz at δ ≈ 6.7 ppm; a doublet of doublet of doublet at δ ≈ 7.0 ppm with J ≈ 9.0, J ≈ 6.8 and J ≈ 1.2 Hz is displayed by the proton at position 7, while proton at position 8 appears at δ ≈ 7.4 ppm as a doublet of triplet which couple with J ≈ 9.0 and J ≈ 1.2 Hz (Table 5).



95

Scheme 48 Numbering in compounds **95**

Table 5. Characteristic ^{1}H chemical shifts of compounds **95a-g**; δ (ppm) and J (Hz) ($CDCl_3$)

	5-H	$J_{5\text{-H, }6\text{-H}}$	$J_{5\text{-H, }7\text{-H}}$	6-H	$J_{6\text{-H, }7\text{-H}}$	$J_{6\text{-H, }8\text{-H}}$	7-H	$J_{7\text{-H, }8\text{-H}}$	8-H
95a	7.96	6.7	1.2	6.69	6.7	1.2	7.04	9.0	7.40
95b	8.11	6.8	1.2	6.63	6.8	1.2	6.86	9.0	7.34
95c	7.95	6.8	1.2	6.68	6.8	1.2	7.04	9.1	7.45
95d	8.01	6.8	1.2	6.73	6.8	1.2	7.07	9.1	7.47
95e	7.94	6.8	1.2	6.69	6.8	1.2	7.06	9.0	7.25-7.49
95f	8.16	6.8	1.2	6.63	6.8	1.2	6.99	9.0	7.38
95g	7.58	6.8	1.2	6.50	6.8	1.2	6.94	9.1	7.34
95h	7.91	6.8	1.1	6.66	6.8	1.1	7.04	9.0	7.24-7.55

In the ^{13}C NMR spectra characteristic are the chemical shifts of carbons at positions 2, 3, 5, 6, 7, 8 and 8a in the imidazo[1,2-*a*]pyridine ring system (Table 6).

Table 6. Characteristic ^{13}C chemical shifts of compounds **95a-g**; δ (ppm) ($CDCl_3$)

	C-2	C-3	C-5	C-6	C-7	C-8	C-8a
95a	139.4	125.9	122.1	111.0	123.0	116.7	146.0
95b	139.2	123.8	123.5	110.6	123.2	116.6	142.0
95c	140.1	125.1	122.3	111.1	123.0	117.0	141.4
95d	141.3	123.2	122.4	111.2	122.8	116.9	146.0
95e	140.4	124.8	122.2	111.6	123.2	117.1	143.1
95f	140.8	123.8	122.5	110.3	123.1	116.8	144.9
95g	141.4	118.6	115.5	111.4	117.2	114.0	146.3
95h	140.2	125.3	122.1	111.2	123.3	117.0	142.3

IR spectra (KBr) of the compounds **95a-g** show characteristic bands at 1730-1735 [ν(C=O)] and 1630-1675 cm^{-1} [ν(C=N)].

The structure of compound **95g** was also determined by X-ray analysis (Figure 3).

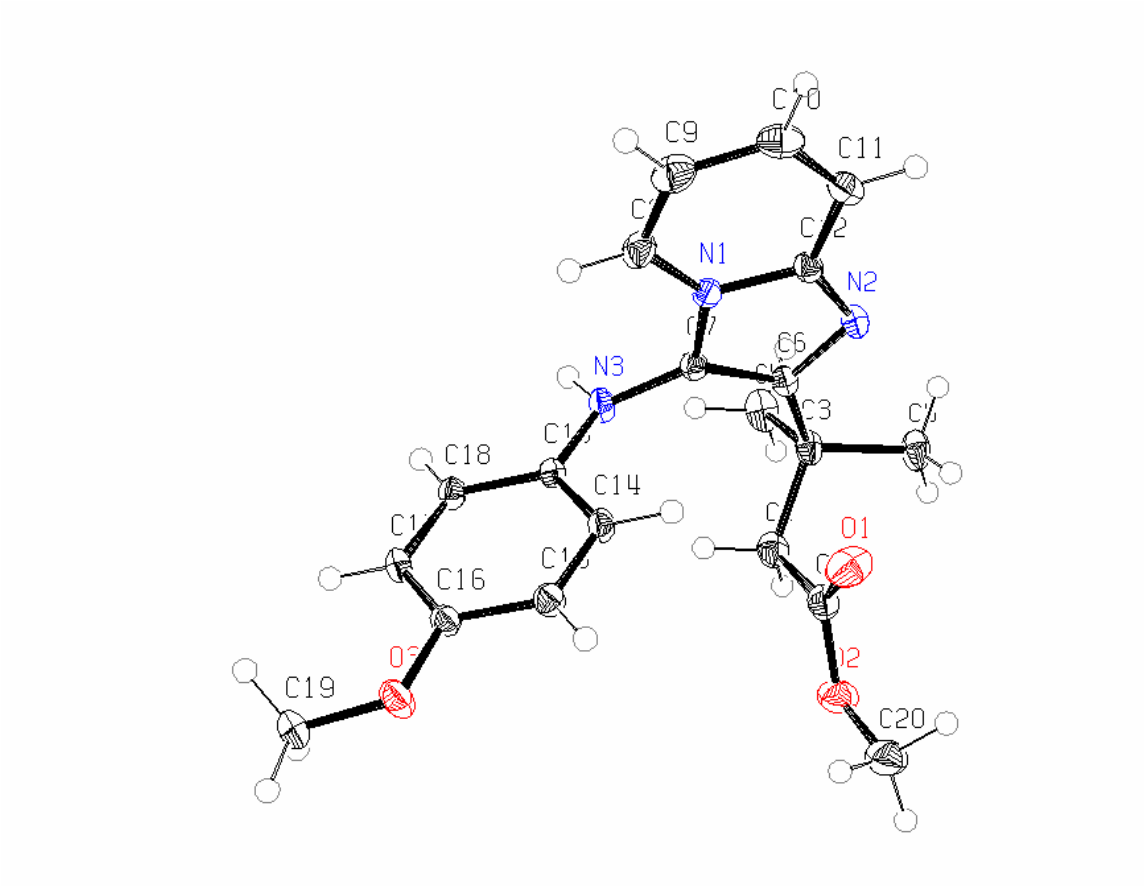


Figure 3. Structure of compound **95g** determined by X-ray crystallography

Figure **4** depicts the intermolecular hydrogen bonding network, linking the straight molecules. The hydrogen bonding links the middle section of the straight molecules. The hydrogen bonding parameters are: N3 – H3N ··· N2: 0.867 and 2.273 Å with an N ··· O separation of 3.109 Å. This is an example of weak hydrogen bonding since the suggested value for weak hydrogen bonds is 3.2 Å.[100]

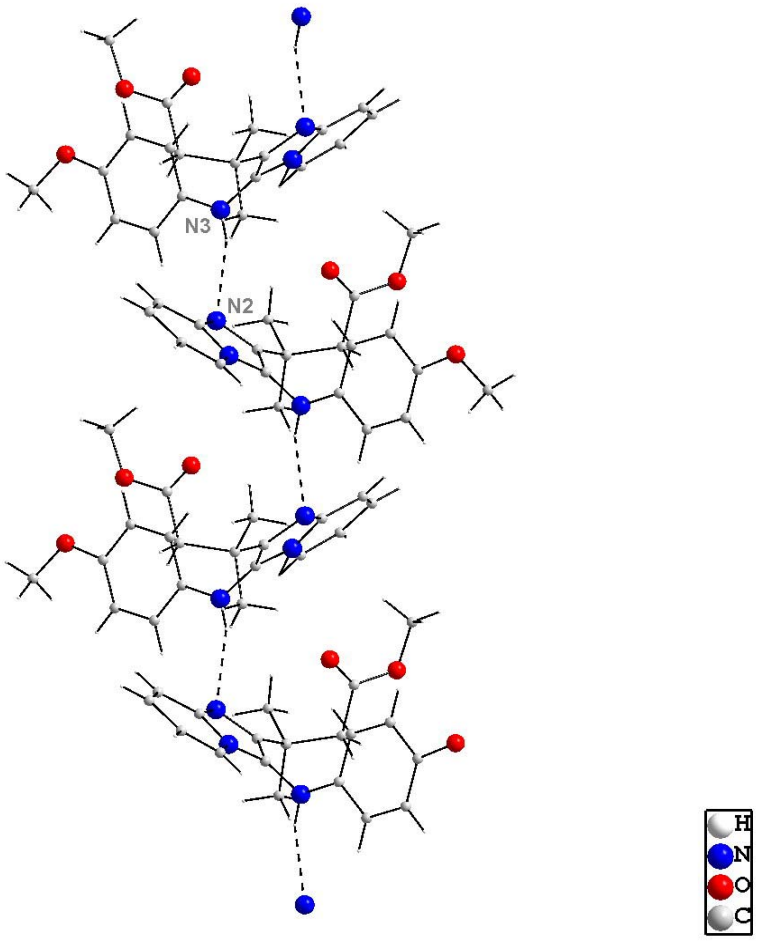
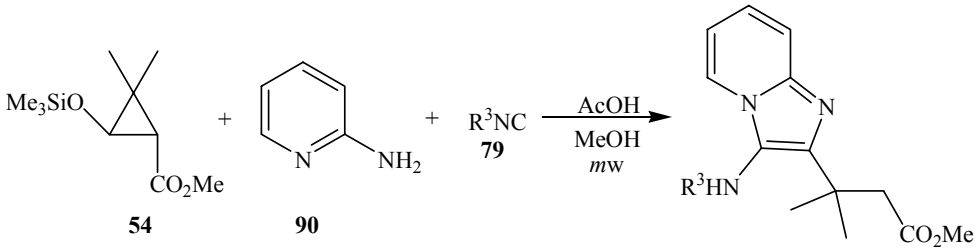


Figure 4. Intermolecular hydrogen bonds of compound **95g**

5.2 Microwave-assisted 3CC with 2-aminopyridine

To shorten the reaction times and improve the yields reactions with microwave irradiation have been attempted. 2-Siloxycyclopropane **54** has been reacted with benzyl- and *p*-methoxyphenylisocyanide and 2-aminopyridine (**90**) in microwave oven, in methanol as a solvent and in the presence of acetic acid (Scheme 49).



R^3=$PhCH_2$ **95e** 14%
R^3=*p*-Methoxyphenyl **95g** 62%

Scheme 49. 3CC with 2-aminopyridine under microwave conditions (experiments: E23, E27)

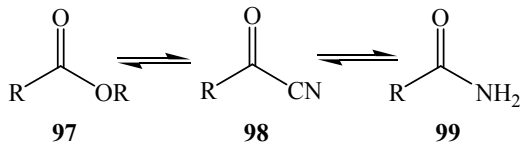
Compound **95e** was obtained in only 14% yield compared to 60% under standard conditions. On the contrary, the yield for compound **95g** was significantly improved: 62% as compared to 43% in the previous experiment.

5.3 Cyclization reactions

Lactam rings can be found in many biologically active molecules. Aside from the well-known antibacterial properties of β-lactams,[101, 102] other therapeutic uses have been found for different lactams such as cholesterol absorption modulators,[103] analgetics[104] and bronchodilatators.[105] Recently, an example of a γ-lactam was found in the fungal product argadin,[106, 107] and a δ-lactam was characterized in the marine natural product dolastatin.[108] Dipeptide lactams can be utilized as conformational constraints for biologically active peptides.[109]

It was attempted to cyclize compound **95e** to the δ-lactam by refluxing in THF, toluene and in the presence of sodium methoxide,[110, 111] but all this attempts failed and only starting material was recovered in those reactions.

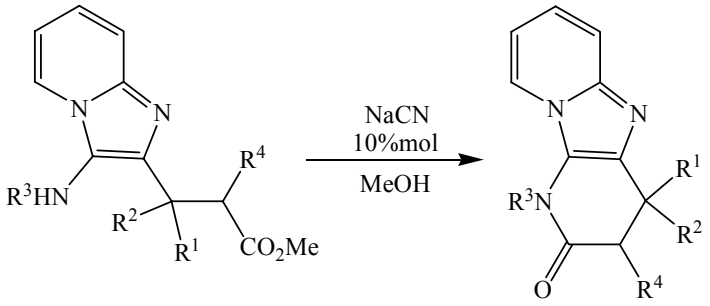
The aminolysis of esters is generally a sluggish reaction unless esters having good leaving groups such as nitrophenyl, thiophenyl, vinyl, hydroxylamines and N-hydroxyimides are used. Numerous acidic and basic catalysts have been investigated in order to enable the use of simple alkyl esters.[112] Acyl cyanides act as mild acylating agents for various heteronucleophiles and carbon nucleophiles.[113] The cyanide ion serves as a strong nucleophile with low basicity to provide the reactive acyl cyanide intermediate **98** in the aminolysis of esters **97** and it proved to be an effective catalyst in the aminolysis of nonactivated aliphatic and aromatic esters with ammonia, primary and secondary amines (Scheme 50).[114]



97 **98** **99**

Scheme 50. Cyanide catalyzed aminolysis of esters

It was demonstrated that compounds **95e**, **g** and **h** cyclize in the presence of sodium cyanide to afford δ-lactams **100e**, **g** and **h** (Scheme 45, Table 7). In a typical experiment the starting material was dissolved in methanol and refluxed for 48 hours in the presence of 10 mol% of NaCN. After extraction with ethyl acetate and solvent evaporation, the residue was purified by column chromatography.



Scheme 51. Lactam formation in the presence of cyanide ion

Table 7. Results of the lactam formation reaction (experiments: E29-E31)

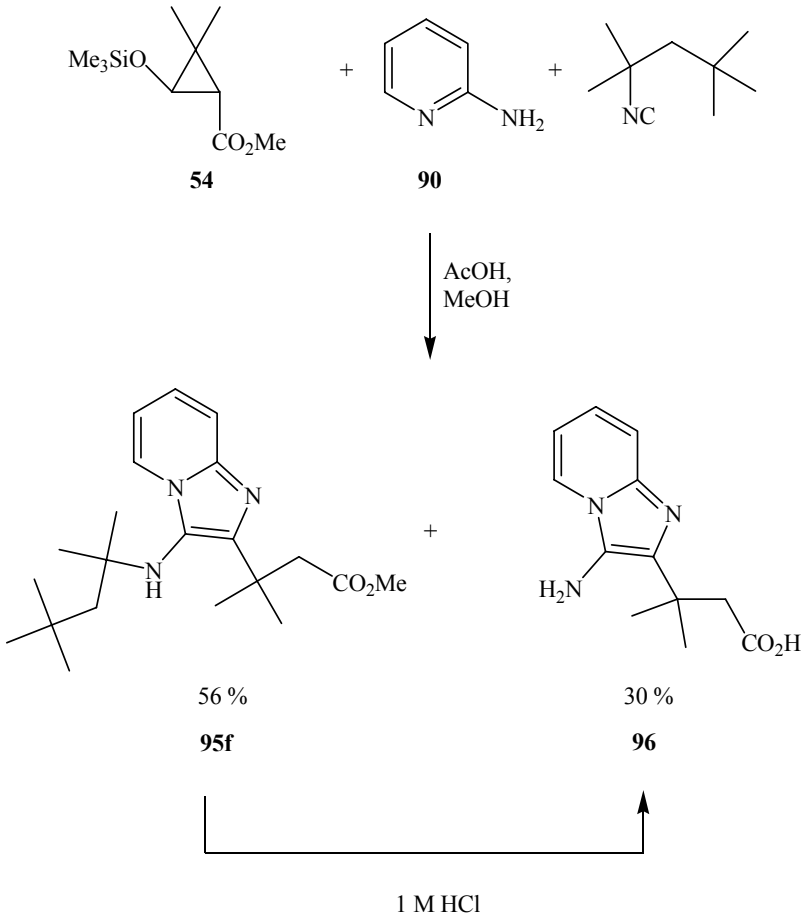
Entry	Start. mat.	R^1	R^2	R^3	R^4	Product	R. time (h)	Yield (%)
1	**95e**	Me	Me	$PhCH_2$	H	**100e**	43	88
2	**95g**	Me	Me	*p*-Methoxyphenyl	H	**100g**	48	29[a]
3	**95h**	Me	Me	$PhCH_2$	Me	**100h**	48	98

[a]39 % of starting material **95g** was recovered.

The cyclization of compounds with benzyl-substituted nitrogen **95e** and **h** was considerably more efficient (88 and 98%) than of compound **95g** with *p*-methoxyphenyl substituted nitrogen (29%); in this experiment 39% of starting material was recovered. This may occur due to the sterical hindrance caused by the benzene ring in compound **95g** and lower nucleophilicity of the aromatic amine.

5.4 Dealkylation and hydrolysis reactions

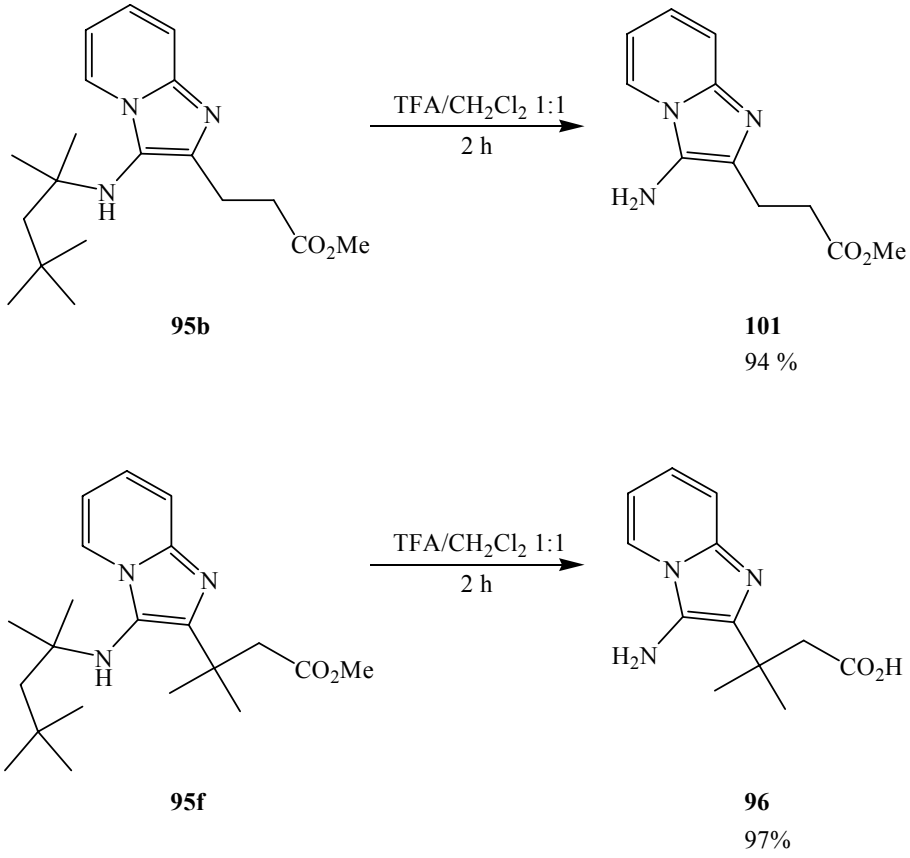
It was observed that 3CC product **95f** derived from 1,1,3,3-tetramethylbutylisocyanide and 2-siloxycyclopropane **54** was unstable towards acid treatment during the workup. Besides the main product, free δ-amino acid **96** was also obtained under the conditions employed (Scheme 52).



Scheme 52. Preparation of compounds **95f** and **96**

When stirring with 1 M HCl during the workup procedure was elongated (1 h), compound **96** was isolated exclusively in 60% yield (exp. E30). On the contrary, 3CC product **95b** obtained from the same isocyanide and less substituted methyl 2-siloxycyclopropane **53** proved to be stable during acidic workup and no dealkylation or hydrolysis products have been observed in this case (Table 4, entry 2).

Treatment of both **95b** and **95f** with trifluoroacetic acid (TFA) over 2 hours in dichloromethane at ambient temperature resulted in clean dealkylation, giving primary amines **101** and **96** in excellent yields. In a typical procedure crude product was loaded on Dowex cation exchange resin, washed with methanol until acid - free and eluted with methanolic ammonia. Under the reaction conditions employed hydrolysis of ester group of compound **95f** also occured and δ-amino acid **96** was obtained (Scheme 53).[115]



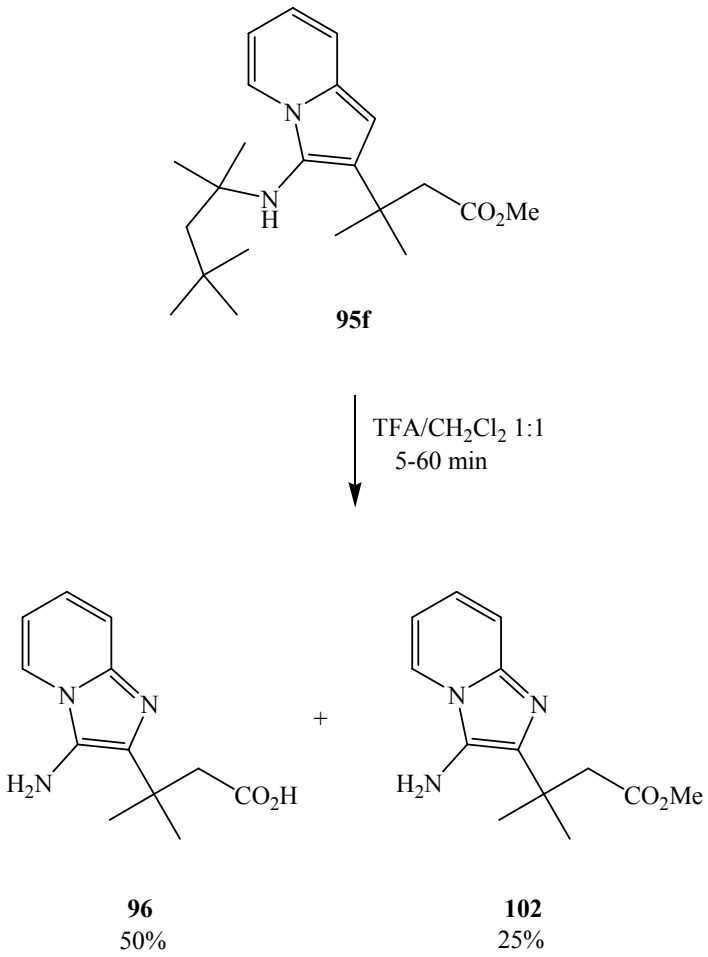
95b **101** 94 %

95f **96** 97%

Scheme 53. Dealkylation with TFA (experiments E32, E33)

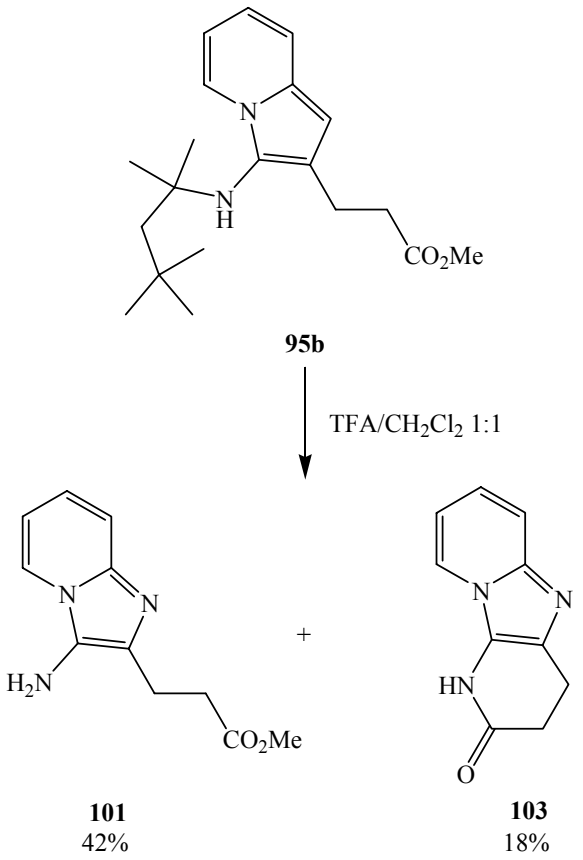
Presumably, this reaction is based on the ability of the 3-aminoimidazopyridine system to function as a leaving group and the stability of a carbocation formed by the cleavage or its elimination product. 1,1,3,3-Tetramethylbutylisocyanide thus serves as a cyanide ion equivalent in the 3CC reaction, affording access to the primary amines.[115]

It was observed that in shorter reaction times (5min – 1h) compound **95f** could be cleaved to afford both δ-amino acid **96** and δ-amino ester **102** in ratio 2:1 (Scheme 54).



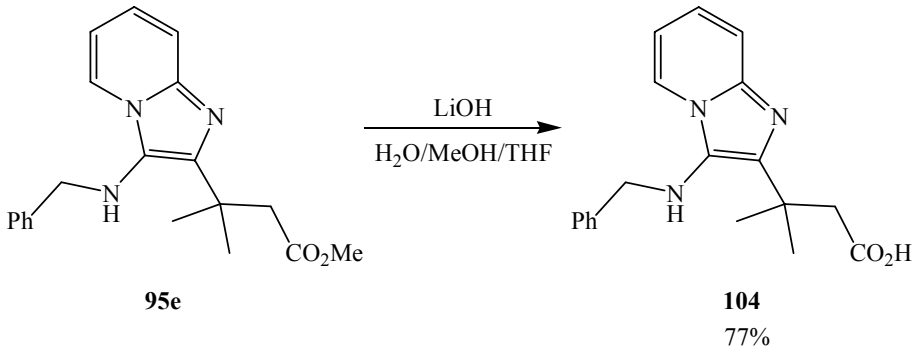
Scheme 54. Dealkylation with TFA (experiment: E34)

Similarly, compound **95b** could be cleaved to afford δ-amino ester **101** which partially cyclized to δ-lactam **103** in a ratio of ca. 2:1 (Scheme 55).



Scheme 55. Dealkylation of **95b** with TFA (experiment: E35)

Ester **95e** was hydrolyzed in a base-mediated reaction. Upon treatment with 3 equivalents of LiOH in a H_2O/MeOH/THF mixture,[89] carboxylic acid **104** was obtained in 77% yield (Scheme 56).

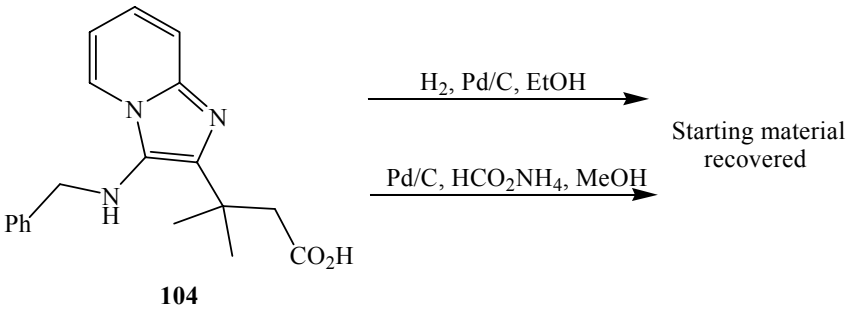


Scheme 56. Base-mediated hydrolysis of **95a** (experiment: E36)

5.5 Attempts of debenzylation reactions

In order to obtain δ-amino acid **96** debenzylation of carboxylic acid **104** and ester **95e** have been attempted. Unfortunately, all attempts to perform debenzylation were not successful. The reasons for these failures are not completely clear.

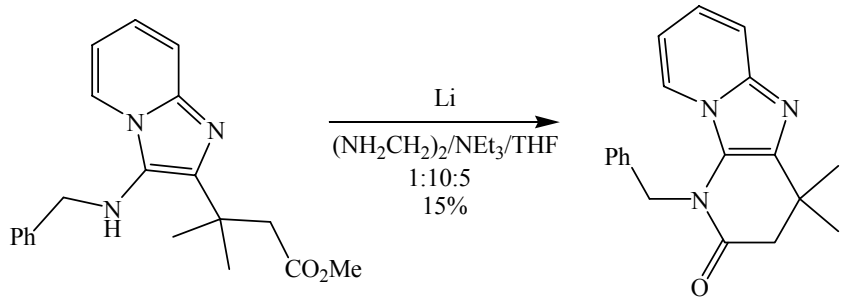
In hydrogenation experiments starting material was recovered (Scheme 57).



104

Scheme 57. Attempts of hydrogenation reaction

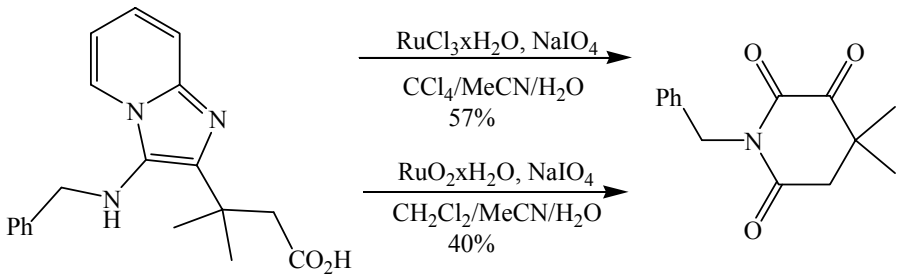
Reaction with lithium in liquid ammonia[116] resulted in disintegration of starting material.
A procedure for debenzylation with lithium using a solvent mixture of ethylenediamine, triethylamine and THF 1:10:5 which was carried out at room temperature and completely avoided the use of liquid ammonia[117] resulted in formation of δ-lactam **100e** in low yield (Scheme 58).



95e **100e**

Scheme 58. Reaction with lithium in THF

Oxidative procedures with ruthenium tetraoxide[118] resulted in lactamization and oxidative degradation of the 3-aminoimidazopyridine aromatic system and only afforded compound **74** (Scheme 59).



Scheme 59. Reaction with ruthenium tetraoxide (experiment: E37)

Tricarbonyl compound **105** was characterized by NMR, MS and IR spectroscopy. The most significant signals in the ^{13}C NMR spectra are the carbonyl carbons at positions 2, 3 and 6 at δ = 158.4, 169.0 and 192.2 ppm, which corresponds well with literature data for some similar compounds.[119, 120]

5.6 Esterification reactions and protection of the amino group

It is already described that δ-amino ester **102** can be obtained as one of the two cleavage products from compound **95f**. Standard procedures with methanol and $SOCl_2$ or TMSCl failed to convert **96** into **102**. Successful esterification, although in very moderate yield (25%), was achieved employing diazomethane[121] and commercially available trimethylsilyldiazomethane reagent (Scheme 60).[122] Under the reaction conditions employed for the latter reactions it is likely that oligomerization of the aminoester occurred which is the reason why yields were so low.

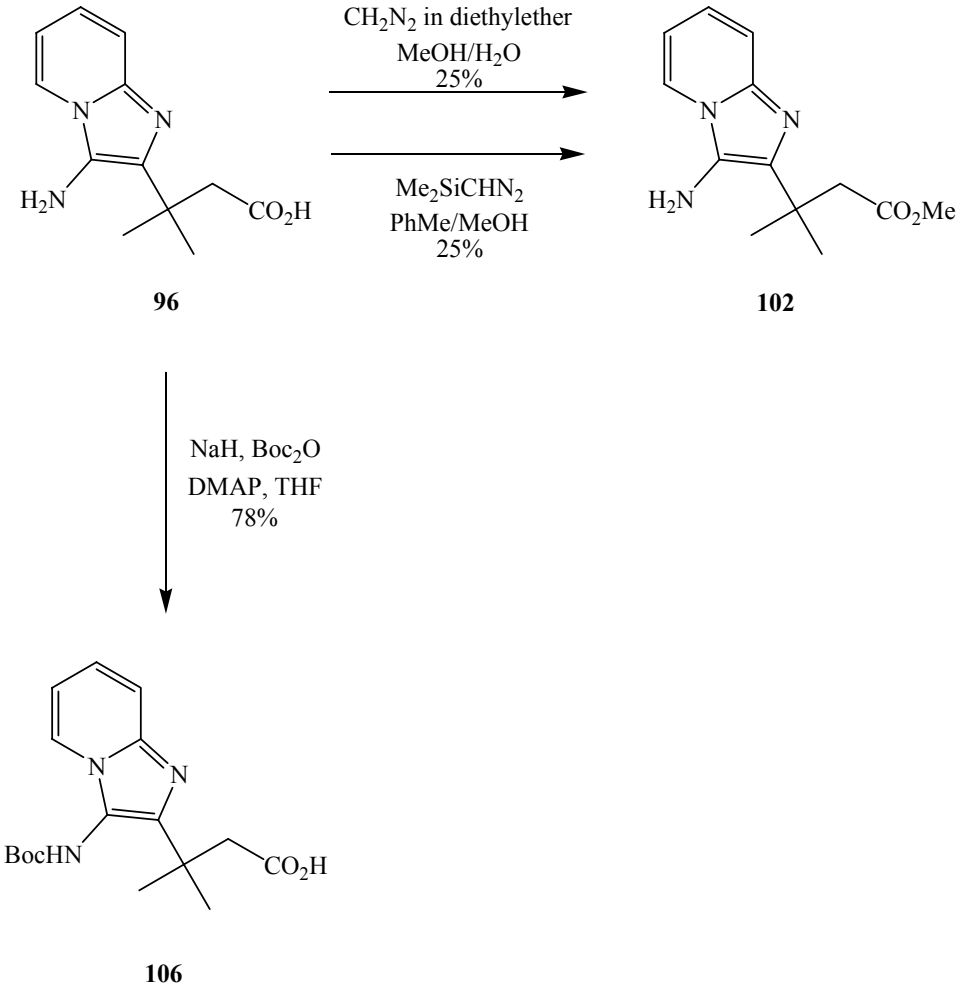
In order to form a dipeptide from its constituent amino acids, all the functional groups except those that will be actually involved in the formation of the peptide bond should be protected. Protecting group orthogonality is a criterion that is especially important for the success of a peptide synthesis. Orthogonality means that subsets of protecting groups present in a molecule

can be cleaved selectively under certain reaction conditions, while all other protecting groups remain intact.

A variety of amino-protecting groups, which are cleavable under different reaction conditions, is available. The most useful compounds are *tert*- butyloxycarbonyl (Boc), readily cleaved by acidic hydrolysis, benzyloxycarbonyl (Cbz or Z), cleaved by catalytic hydrogenolysis; fluorenyl-9-methoxy-carbonyl (Fmoc), cleaved by β-elimination with base; allyloxycarbonyl (Aloc), readily cleaved by Pd-catalyzed isomerization.

The Boc group has been chosen for the protection of the amino group, in accordance with the strategy envisaged for the synthesis of particular peptides. It is not hydrolyzed under basic conditions and is inert to many other nucleophilic reagents. It should also be mentioned that amino-protecting groups of the urethane-type like Boc safeguard racemization-free peptide bond formations.

N-Boc protection was achieved using Boc-anhydride (*tert*-butyloxycarbonyl anhydride). Amino acid **96** was first treated with NaH in THF, then Boc-anhydride (2 equivalents) and finally DMAP (N,N-dimethylaminopyridine) in catalytic amounts were added.[123] After workup and purification by column chromatography, compound **106** was isolated in 78% yield (Scheme 60).



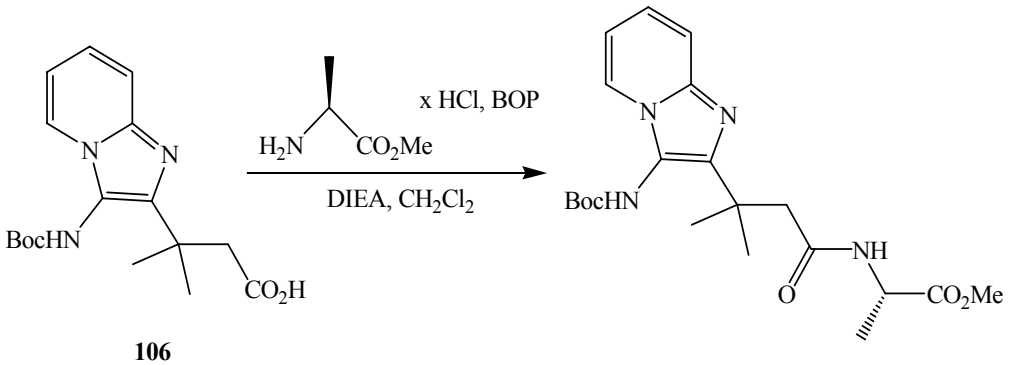
Scheme 60. Esterification reactions and Boc-protection of the amino-group (experiments E38-E40)

Reactions attempted only with Boc-anhydride and DMAP and with reagent BOC-ON[124] failed to afford compound **106** and only starting material was recovered.

5.7 Couplings of newly synthesized unnatural δ-amino acids

δ-Amino acids which incorporate 3-aminoimidazopyridine system proved to be unreactive in coupling reactions involving the coupling reagents DCC, HOBt, TBTU and only partially reactive in reactions mediated with BOP and TFFH.

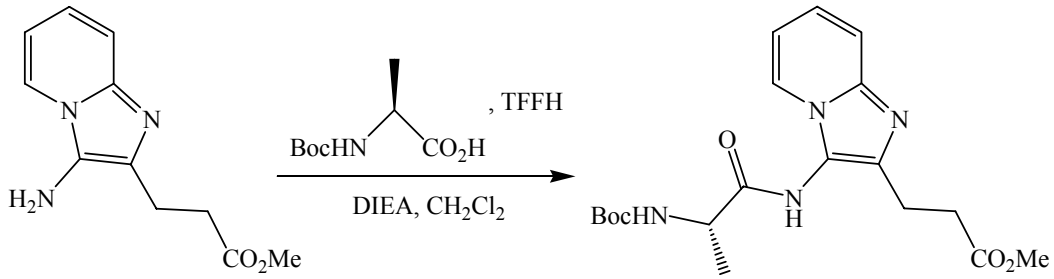
Coupling of amino-protected compound **106** with L-alanine methyl ester in the presence of BOP and DIEA in dichloromethane[125] afforded after workup and purification by column chromatography followed by HPLC peptidomimetic **107** in 97% yield as a yellowish oil (Scheme 61). Although reaction times in BOP-mediated couplings are usually short (in experiment E58 reaction time for BOP-mediated coupling was only 30 minutes), in this case it took 10 days, probably due to the sterical hindrance in the proximity of the carboxylic group in compound **106**.



106 **107**
97%

Scheme 61. BOP-mediated coupling of **106** with L-alanine methyl ester to **107** (experiment: E41)

Attempts to couple compound **102** with N-Boc L-alanine have been unsuccessful. δ-Amino ester **101**, which does not possess two methyl-groups in position 2 comparing to δ-amino ester **102**, has been coupled with N-Boc L-alanine *via* acid-fluoride applying TFFH. After four days stirring at room temperature, followed by workup and column chromatography, peptidomimetic **108** was isolated in 26% yield (Scheme 62).



101 **108**
26%

Scheme 62. TFFH-mediated coupling of **101** with N-Boc alanine to **108** (experiment: E42)

The low yield in this coupling reaction is probably due to the poorly nucleophilic character of the amino-group of compound **101** and its sterically hindered position, which is even worse in compound **102**.

5.8 Conclusion

In conclusion, methyl 2-siloxycyclopropanecarboxylates **53**, **54** and **60** have been applied as precursor compounds in the Ugi-type three component condensation with 2-aminopyridine (**90**) and four isocyanides affording moderate to good yields of pharmaceutically relevant 3-aminoimidazo[1,2-*a*]pyridines **95a-h**. These compounds could be further converted to several products, for example lactams (**100**, **103**), δ-amino esters (**101**, **102**) and carboxylic acids (**96**, **104**). Furthermore, new building blocks (**101**, **106**) have been coupled with L-alanine and peptidomimetics **107** and **108** have been synthesized. This methodology should prove useful for the synthesis of libraries of such derivatives since precursor cyclopropanes are easily available in many structural variations.