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Preparation of α-aza-amino acid precursors and related compounds by novel methods of reductive one-pot alkylation and direct alkylation

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Press

Institute of Chemistry, Faculty of Science and Technology, University of Tartu, Estonia.

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I Mastitski, A., Kisseljova, K., Järv, J. Synthesis of the Fmoc-aza-Arg(Boc)$_2$ precursor via hydrazine alkylation. *Proc. Est. Acad. Sci.*, **2014**, 63, 4, 438−443.

II Mastitski, A., Järv, J. One-Pot Synthesis of Fmoc- and Boc-Protected Aza-Methionine Precursors from 2-Methylthioacetaldehyde Dimethyl Acetal. *Org. Prep. Proc. Int*., **2014**, 46, 6, 559−564.

III Mastitski, A., Haljasorg, T., Kipper, K., Järv, J. Synthesis of aza-phenylalanine, aza-tyrosine, and aza-tryptophan precursors via hydrazine alkylation. *Proc. Est. Acad. Sci*., **2015**, 64,2, 168−178.

IV Mastitski, A., Niinepuu, S., Haljasorg, T., Järv, J. One-pot synthesis of protected alkylhydrazines from acetals and ketals. Method scope and limitations. *Org. Prep. Proc. Int.*, **2015**, 47, 6, 490−498.

V Mastitski, A., Abramov, A., Kruve, A., Järv, J. Potassium iodide catalysis in the alkylation of protected hydrazines. *Proc. Est. Acad. Sci*., **2017**, 66, 1, 10−17.

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V Design of the experiments, synthesis of the major part of the described compounds, manuscript preparation.

VI Design of the experiments, synthesis of the described compounds, optimisation of the reaction conditions, manuscript preparation.

ABBREVIATIONS

1,4-DO	1,4-dioxane
Ac	acetyl
ACN	acetonitrile
AcOH	acetic acid
AIBN	azobisisobutyronitrile
Ala	alanine
Alloc	allyloxycarbonyl
Aq.	aqueous
Ar	aryl
Arg	arginine
Asp	aspartic acid
Bn	benzyl
Boc	tert-Butyloxycarbonyl
Bz	benzoyl
BTC	bis(trichloromethyl)carbonate
Bu	butyl
Cbz	benzyloxycarbonyl
Cys	cysteine
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCM	dichloromethane
Ddz	α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl
DIBAL	diisobutylaluminium hydride
DIC	N,N'-diisopropylcarbodiimide
DiPEA	N,N-diisopropylethylamine
DMAP	N,N-dimethylaminopyridine
DMF	N,N-dimethylformamide
EDA	ethylenediamine
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
Fmoc	fluorenylmethyloxycarbonyl
Glu	glutamic acid
Ile	isoleucine
iPrOH	propan-2-ol
Leu	leucine
Liq.	liquid
Lys	lysine
Met	methionine
NBS	N-bromosuccinimide
NMP	N-methylpyrrolidone
Orn	ornithine

OSu	succinimidyl ester
PG	protecting group
Ph	phenyl
Phe	phenylalanine
PTC	phase transfer catalysis
Py	pyridine
PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
R, R', R'', R'''	alkyl group
Ser	serine
Z	benzyloxycarbonyl
TBAHS	tetrabutylammonium hydrogensulfate
t-Bu	tert-Butyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Thr	threonine
TMG	1,1,2,2-tetramethylguanidine
Troc	2,2,2-trichloroethyloxycarbonyl
Trp	tryptophan
Trt	trityl (triphenylmethyl)
Ts	para-toluenesulfonyl
TsOH	para-toluenesulfonic acid
Tyr	tyrosine
Val	valine
X	halogene

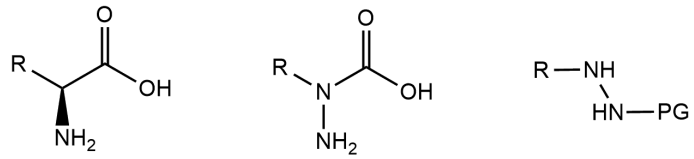
1. INTRODUCTION

Hydrazine derivatives play significant role in nature, being intermediates of nitrogen fixation by nitrification bacteria. [1] Moreover, simple organic derivatives of hydrazine are present in different mushrooms. For example, mushroom *Gyromitra esculenta* contains a toxin and carcinogen acetaldehyde N-formylhydrazone, which, in turn, can form highly toxic methyl hydrazine. The widely spread mushroom *Agaricus bisporus* contains 4-(hydroxymethyl)phenylhydrazine. [2] Systematic studies in hydrazine chemistry started in the 19-th century, after E. Fischer prepared phenyl hydrazine in 1875, [3] and T. Curtius synthesized hydrazine in 1887. [4] Only 7 years later, in 1895, Lorby de Bruyn prepared the anhydrous hydrazine. [5]

The aforementioned discoveries initiated a systematic research of hydrazine derivatives and resulted in discovery of different pharmaceutical compounds. Indeed, the first medicines based on phenylhydrazine (Phenazone, Metamizole etc.) were launched in the last decade of the 19-th century and in the beginning of the 20-th century, [6–7] after L. Knorr reported synthesis of substituted pyrazolones. [8] Further, hydrazine derivatives were studied as potential inhibitors of enzyme monoamine oxidase and anti-tuberculosis medicines. As a result of this work, several potent hydrazine based antidepressants (ex. Iproniazid), [9] and anti-tuberculosis medicines (ex. Isoniazid), [10] were discovered. Today several hydrazine derivatives serve as agricultural chemicals, [11–14] anti-cancer medicines, [15] inhibitors of HIV, [16–17] and hepatitis C virus proteases. [18] Additionally, hydrazine and its simplest organic derivatives are widely applied as reagents in organic synthesis, [19–20] and used for synthesis of various heterocyclic compounds. [21–24]

Due to unique thermodynamic and kinetic parameters of combustion of hydrazine and its simplest alkyl derivatives, these compounds are widely used as an effective rocket fuels, [25] or as a fuel for fuel cells. [26]

More recently, replacement of native amino acid residues with alkylcarbazic acids, also known as α-aza amino acids, has been proposed to increase proteolytic stability of peptides. [27–29] This idea is based on structural similarity of natural amino acids and alkylcarbazic acids. However, the α-aza-amino acids are unstable and spontaneously decompose via decarboxylation. Therefore, alkylcarbazic acids should be synthesized in the form of orthogonally protected monoalkylhydrazines, which are known as aza-amino acid precursors. The structures of natural chiral amino acid (**1**), unstable a-aza-amino acid (**2**) and corresponding α-aza-amino acid precursor (**3**) are depicted in **Figure 1**.



(**1**) (**2**) (**3**)

R= Amino acid side chain. PG= protecting group (Fmoc, Boc, etc.)

Figure 1. Amino acid (**1**), unstable aza-amino acid (**2**) and aza-amino acid precursor (**3**).

If synthesis of simplest alkylhydrazines has been optimized and is carried out on the industrial scale, synthesis of the orthogonally protected hydrazines with simultaneously labile protecting groups and carrying functional groups identical to the natural amino acids, is a challenging task.

Preparation of the required compounds is sometimes complicated by instability or unavailability of the required reagents, contains several synthetic steps, produces target compounds with relatively low yield or requires special equipment or precious metal-based hydrogenation catalysts. Thus, new and more convenient approaches to the synthesis of orthogonally protected alkylhydrazines as aza-amino acid precursors are required.

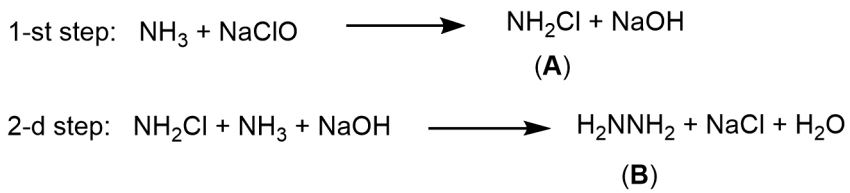
The present work is dedicated to solving the above-mentioned problems and opening access to as complete as possible set of aza-amino acid precursors for replacement of natural amino acids in peptides and proteins.

2. LITERATURE OVERVIEW

2.1. Hydrazine synthesis via formation of N-N bond

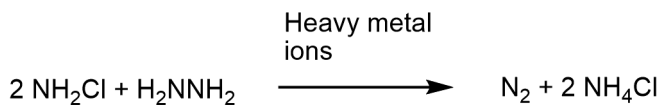
2.1.1. Synthesis of hydrazine from amines and chloramines

Industrial large-scale synthesis of hydrazine and its simple organic derivatives is often performed by reacting ammonia and primary or secondary amines with chloramines. The simplest example of this reaction is the Rashig synthesis of hydrazine starting from ammonia and sodium hypochlorite. This 2-step reaction proceeds according to **Scheme 1**.



Scheme 1. Rashig synthesis of hydrazine from ammonia.

The first step generates unstable chloramine ((**A**), **Scheme 1**), which reacts *in situ* with ammonia and forms the desired hydrazine ((**B**), **Scheme 1**). This reaction proceeds in relatively smooth conditions at temperatures from 0–100 ^{o}C. At the same time, heavy metal (ex. Cu) ions catalyze oxidation of hydrazine by chloramine (**Scheme 2**).



Scheme 2. Heavy metal ions catalyzed oxidation of hydrazine by chloramine.

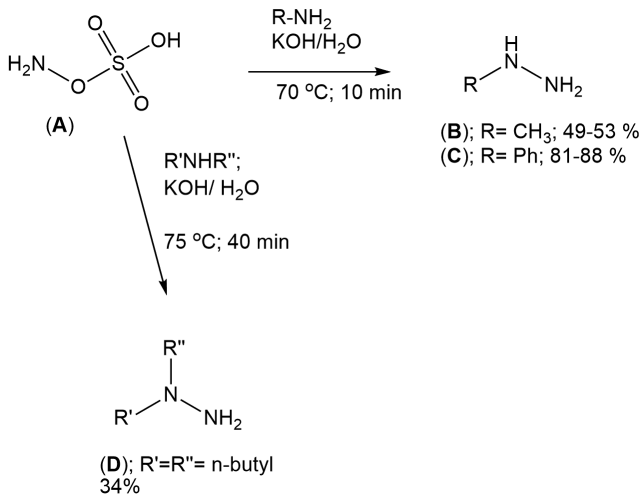
Due to the aforementioned obstacle, several additives with complex formation properties are added to the reaction mixture. The most typical additives include gelatin and amino acids. Both form complexes with heavy metal ions and prevent hydrazine oxidation. Moreover, careful temperature control and holding optimal pH range are required for successful performing of the Rashig synthesis. [30]

Yields of the Rashig synthesis lay in the range between 50–75 %. The Rashig synthesis can also be applied for the synthesis of quaternary hydrazinium salts. [31–32] This reaction could also be carried out by adding mixture of ammonia

and chlorine into liquid primary and secondary amines. [33–34] The main disadvantage of this reaction is instability and difficult dosing of chloramines that makes the Rashig synthesis not a very desirable reaction on laboratory scale.

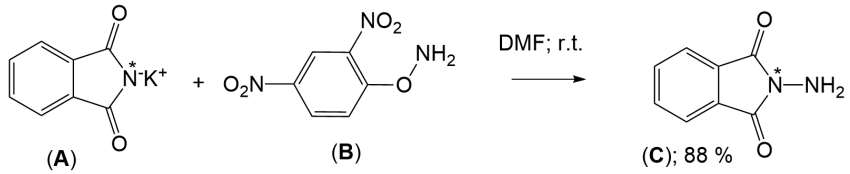
2.1.1.1. Synthesis of hydrazines using other electrophilic amination reagents

Due to difficulties with handling chloramines, described in **2.1.1,** different more stable and easy to handle electrophilic aminating reagents were proposed. The first among these reagents was hydroxylamine-O-sulfonic acid ((**A**), **Scheme 3**) [35–37], which can be synthesized from hydroxylamine sulfate and oleum, [38] or by sulfonation of hydroxylamine with chlorosulfonic acid. [39] This reagent reacts with amines in the same manner like chloramines and forms N-N bonds. Yields are strongly dependent on the structure of amine and vary from satisfactory ((**D**), 34 %) to moderate ((**B**), 49–53 %) and good ((**C**), 81–88 %) as demonstrated on **Scheme 3**.



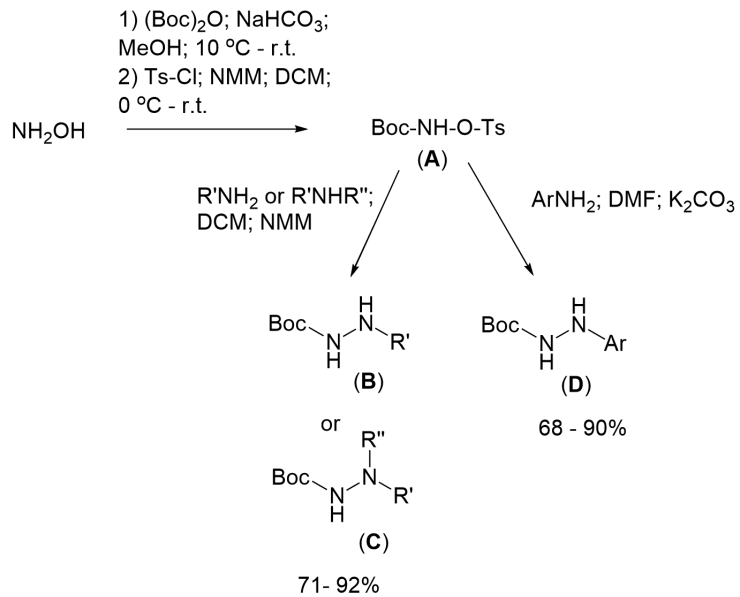
Scheme 3. Reaction of amines with hydroxylamine-O-sulfonic acid.

Another example of electrophilic amination proceeds via reaction of N-labeled phtalimide potassium salt ((**A**), **Scheme 4**) with O-2,4-dinitrophenylhydroxylamine ((**B**), **Scheme 4**). The desired labeled N-aminophtalimide (**C**) was obtained in very good yield (**Scheme 4**). [40]



Scheme 4. Synthesis of N-protected aminophtalimides.

Not a long time ago synthesis of Boc-NH-O-Ts ((**A**), **Scheme 5**) was reported and applied for introduction of Boc-NH group to variety of primary-, and secondary amines as well as to aryl amines (**Scheme 5**). The yields of hydrazines were in the range 71–92 % for alkyl-, and dialkylhydrazines ((**B**) and (**C**), **Scheme 5**). In the case of electrophilic amination of aromatic amines, yields of N-Boc-N'-arylhydrazines ((**D**), **Scheme 5**) were 68–90 %. [41]

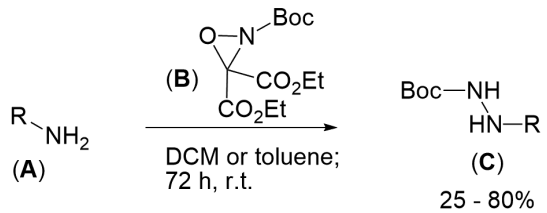


Scheme 5. Reaction of amines with Boc-NHO-Ts.

Despite the effectiveness and easy handling of the Boc-NH-O-Ts, 4 years later the same authors reported that actual products of this reaction are not hydrazines, but isomeric urea derivatives, formed via Lossen rearrangement of Boc-NHOTs to tBu-ONCO. The latter intermediate undergoes a nucleophilic attack by amine and forms corresponding urea derivative. [42]

Another approach to electrophilic amination utilizes N-alkyloxycarbonyl protected oxaziridines. For example, N-Boc protected hydrazines could be

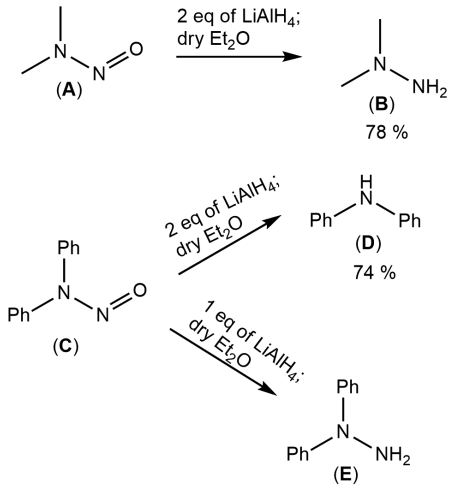
successfully synthesized from diethylketomalonate derived N-Boc protected oxaziridine ((**B**), **Scheme 6**). Different solvents were tested as the reaction media and the best yield of N-Boc –N'-(2-phenylethyl) hydrazine was obtained in DCM and toluene. Different primary amines ((**A**), **Scheme 6**) carrying various alkyl- or aryl substituents (R= Bn; Ph; cyclopropyl; cyclohexyl; n-heptyl, etc.) were tested and corresponding hydrazines ((**C**), **Scheme 6**) were obtained in moderate to good yields (25–80%). The reaction scheme is depicted on **Scheme 6**. [43]



Scheme 6. Synthesis of N-Boc–N'-alkylhydrazine via N-Boc protected oxaziridine.

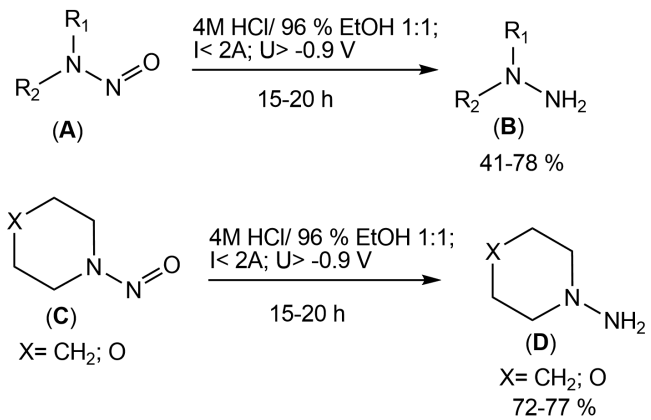
2.1.2. Synthesis of hydrazines via N-nitrosamines

Geuther discovered N-nitrosation reaction in 1863, when he reacted diethyl-amine hydrochloride with sodium nitrite in aqueous solution. [44] Since these times a lot of new properties and reactions of N-nitrosamines were discovered. One on the most important properties of N-nitrosamines for the chemistry of hydrazines is the ability of –N-N=O group to be reduced to hydrazine. [45] Initially, reduction of nitroso group was accomplished by Zn dust in acetic acid. [46] Besides of the Zn/AcOH combination, Na/Hg and Sn/HCl were applied for the reduction of nitrosamines. [47] The classical method worked well in the case of reduction of N-nitrosodialkylamines, carrying methyl-, ethyl-, and propyl groups. In the case of longer alkyl groups, starting from C_4 substituent, reduction of N-N bond begins to concur with reduction of the nitroso group and formation of secondary amines takes place. [48] To overcome this problem, general procedure for reduction of N-nitrosamines by $LiAlH_4$ was developed. [49] It was also mentioned, that the best results can be obtained, if reduction of N-nitrosodimethylamine ((**A**), **Scheme 7**), is accomplished by 2 eq of $LiAlH_4$ in dry diethyl ether. Yield of 1,1-dimethylhydrazine ((**B**), **Scheme 7**) was 78 %. At the same time, reduction of N-nitrosodiphenylamine ((**C**), **Scheme 7**) by 2 eq of $LiAlH_4$ in dry diethyl ether gave only diphenylamine ((**D**), **Scheme 7**). [49] However, if reduction of N-nitrosodiphenylamine was performed by 1 eq of $LiAlH_4$ in dry diethyl ether, 1,1-diphenylhydrazine ((**E**), **Scheme 7**) was obtained with good yield. [50]



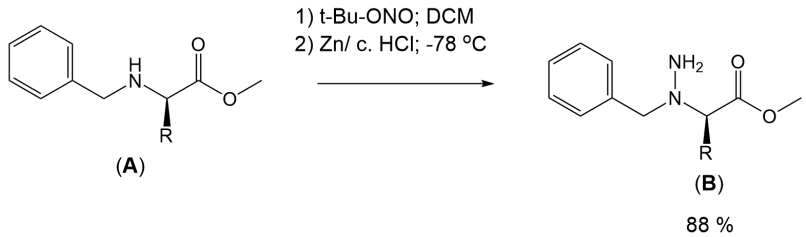
Scheme 7. Reduction of N-nitrosodimethylamine and N-nitrosodiphenylamine by $LiAlH_4$.

Also, an effective and convenient electrochemical reduction of various symmetric, asymmetric and cyclic ((**A**), 1) R_1=R_2= CH_3; n-C_4H_9; isopropyl, allyl etc.; 2) R_1= Ph; R_2= CH_3; C_2H_5 etc.; (**C**), **Scheme 8**) N-nitrosamines in 1:1 mixture of 4 M HCl and 96 % EtOH was performed at potentials above – 0.9 V. The corresponding hydrazines ((**B**) and (**D**), **Scheme 8**) were obtained in moderate to good yields. [51]



Scheme 8. Electrochemical reduction of N-nitrosamines.

Not a long time ago a convenient route to α-hydrazino esters was reported. This method utilized nitrosation of N-benzyl amino acid methyl ester ((**A**), **Scheme 9**) with t-Butyl nitrite in DCM and reduction of the obtained N-nitrosamine with Zn/c. HCl in methanol at – 78 °C (**Scheme 9**). The α-hydrazino ester ((**B**), **Scheme 9**) was obtained with good yield. [52] The authors also reported that their attempts to reduce N-nitrosamines using Zn/AcOH/65°C, Zn/AcOH/rt, Zn/aq. HCl/rt, $TiCl_3$/rt, $TiCl_3$/NH_4OAc/rt, Sn/aq. HCl, Zn/c.HCl/MeOH/rt were not successful. In experiments with $TiCl_3$ and Sn no hydrazine was formed and reduction with Zn in different conditions resulted in cleavage of N-N bond. [52]



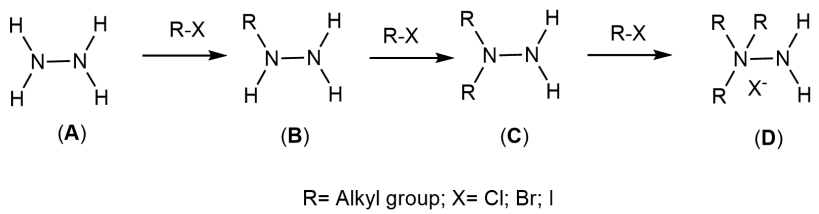
Scheme 9. Synthesis of α-hydrazino esters via reduction of N-nitrosamine.

Despite the effectiveness of reduction of nitrosamines, work with these compounds is complicated and limited by their carcinogenic properties.

2.2. Alkylation of hydrazine and its derivatives

2.2.1. Direct alkylation of hydrazine and its simple alkyl and aryl derivatives

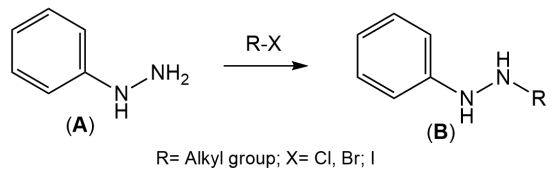
Being a bifunctional and powerful nucleophile, hydrazine ((**A**), **Scheme 10**) can react with variety of electrophiles. For example, hydrazine easily undergoes alkylation with alkylhalogenides forming a mixture of alkylated products (**Scheme 10**). [53–54]



Scheme 10. Alkylation of hydrazine.

The monalkylhydrazine, formed in the first reaction step ((**B**), **Scheme 10**) has increased nucleophilicity and basicity in comparison with non-substituted hydrazine due to electron-donating effect of the alkyl-group. Due to these effects monalkylhydrazine ((**B**) easily reacts further, forming usually non-symmetrical dialkylhydrazine ((**C**), **Scheme 10**) and finally 1,1-dialkylhydrazine may form quarternary hydrazinium salt ((**D**), **Scheme 10**). [53] After quarternisation, alkylation of hydrazinium salt does not proceed further. [53]

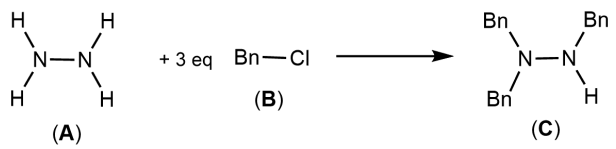
At the same time, alkylation of phenylhydrazine ((**A**), **Scheme 11**) usually takes place on the non-substituted N-atom, forming 1-phenyl-2-alkylhydrazines ((**B**), **Scheme 11**). [53]



Scheme 11. Alkylation of phenyl hydrazine.

This fact can be explained by conjugation of electron pair of the NH-group attached to the phenyl moiety with aromatic system. As a result, non-substituted NH_2 group is much more nucleophilic.

If hydrazine reacts with powerful alkylating reagents (ex. alkyl iodides), only quarternary hydrazinium salts are formed in most cases. [53, 55] Sterical parameters of alkyl groups have a tremendous effect on hydrazine alkylation reaction. For example, if hydrazine ((**A**), **Scheme 12**) reacts with benzyl chloride ((**B**), **Scheme 12**), 1,1,2-tribenzylhydrazine ((**C**), **Scheme 12**) is formed. [53, 56–57]



Scheme 12.Reaction of hydrazine with benzyl chloride.

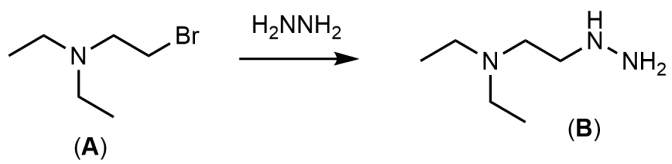
Formation of this product can be explained by sterical hindrance caused by 2 benzyl groups attached to the same nitrogen atom. As a result, third molecule of benzyl chloride reacts with neighboring non-alkylated NH_2 group. If hydrazine reacts with even more sterically hindered halogenides (such as triphenylchloromethane (Trityl chloride)), Trt-$NHNH_2$ is obtained with 87 % yield. [53, 58]

Length of the alkyl chain of halogenide also plays an important role in formation of different alkylated products of alkylation. For example, if hydrazine is alkylated by 1-chloroalkanes (C_8 and longer), almost no quarternisation occurs.

At the same time, if 1-chloroalkanes with even longer chains (C_{12} and longer) are used for alkylation, mostly monoalkyl- and non-symmetrical dialkylhydrazines are formed. [53, 59–60]

As it was mentioned previously, hydrazine polyalkylation remains the most significant problem of hydrazine alkylation reaction. To overcome this problem, alkylhalogenide should be slowly added to vigorously stirred 10 fold excess of hydrazine hydrate. [53, 61] Moreover, extraction of hydrazine from the reaction mixture is usually relatively complicated due to equilibriums between hydrazine hydrate and solvent, and between hydrazine and hydrazinium salt. [53] In some cases, alkylation in alcohol allows to avoid excessive formation of dialkylhydrazines. [53, 62]

It is important to mention that monoalkylhydrazines ((**B**), **Scheme 13**) can be successfully prepared from hydrazine and aliphatic halogenides containing hydroxyl or substituted amino group such as diethylamino group ((**A**), **Scheme 13**). [53, 63–64]



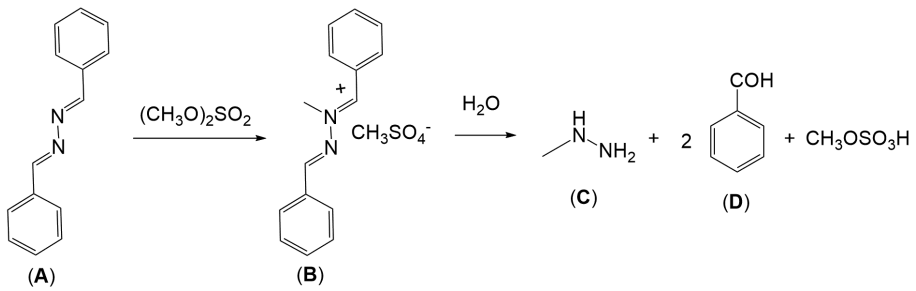
Scheme 13. Reaction of hydrazine with halogenide containing substituted amino group.

Some information is available about hydrazine alkylation by esters of mineral acids. For example, ethylhydrazine was obtained in 32 % yield during alkylation of hydrazine hydrate solution by diethyl sulfate. [53, 65] Reaction of hydrazine with simple alkyl nitrates, such as ethyl nitrate, results is redox process, where various inorganic nitrogen compounds (N_2, NH_3, NO_2^- etc.) In the case of reaction of hydrazine and higher alkyl nitrates such as benzyl nitrate, mixtures of mono-, di-, tri-, and tetra-alkylated hydrazines were obtained. [53, 66–67]

2.2.2. Alkylation of hydrazine derivatives

Due to the previously described difficulties with selective hydrazine alkylation and inevitable overalkylation of monalkylhydrazine, several synthetic approaches starting from hydrazine derivatives were proposed. [53] One of the first methods utilized alkylation of benzalazine ((**A**), **Scheme 14**) by dimethyl sulfate. Methylation results in formation of quarternary hydrazinium salt ((**B**),

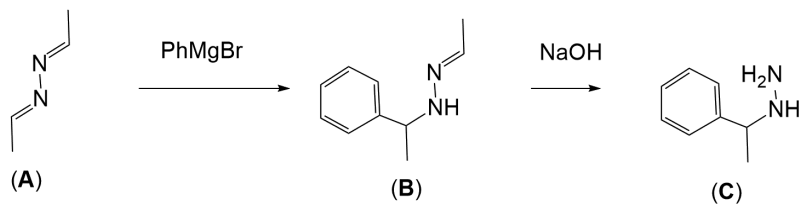
Scheme 14), which is hydrolysed to methylhydrazine ((**C**), **Scheme 14**) and aldehyde ((**D**), **Scheme 14**). [68]



Scheme 14. Synthesis of methylhydrazine via methylation of benzalazine.

Application of this method is limited by reactivity of the alkylating reagent. Thus, dimethyl sulfate easily methylates benzalazine while higher alkyl sulfates do not react with the azine. [53]

An alternative approach to alkylhydrazines starts from azines and Grignard reagents. Organomagnesium compound reacts with -C=N- bond forming hydrazone, which yields hydrazine after hydrolysis. For example, acetaldehyde 1-phenylethylhydrazone ((**B**), **Scheme 15**) was obtained from acetaldazine ((**A**), **Scheme 15**) and phenylmagnesium bromide in 30 % yield and finally hydrolysed to 1-phenylethylhydrazine ((**C**), **Scheme 15**). [53, 69]



Scheme 15. Synthesis of 1-phenylethylhydrazine from acetaldazine and Grignard reagent.

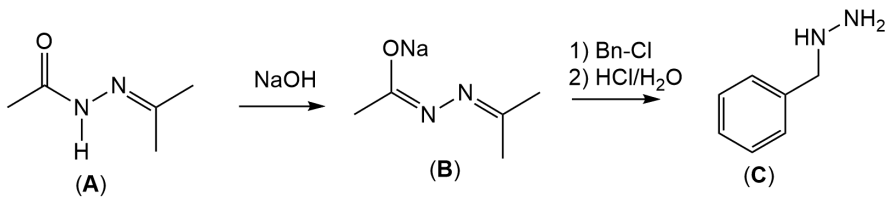
Success of this reaction depends on structure and extent of conjugation in the azine and the hydrazone. Usually organomagnesium compounds react well with aliphatic azines, but in the case of conjugated azines such as benzalazine, shift of hydrazone –N=CH- bond to isomeric -N=N- bond was observed. [53, 70] This results in formation of hydrocarbons. [53, 70]

To improve selectivity of alkylation of hydrazine derivatives, synthesis over sodium hydrazides, generated in liquid ammonia was proposed. This approach

was used for selective alkylation of phenylhydrazine ((**A**), **Scheme 16**) at N-atom, attached to the phenyl moiety, and allowed to synthesize different 1-Alkyl-1-phenylhydrazines ((**B**), **Scheme 16**). [71]

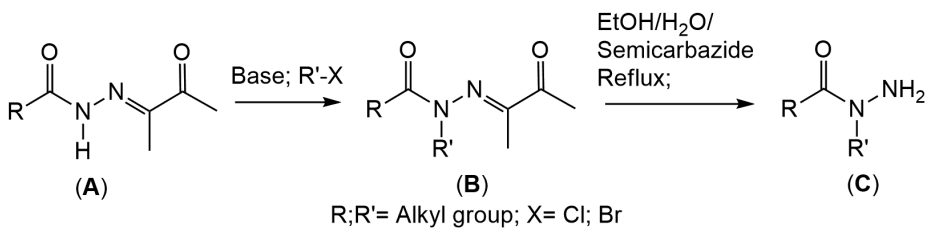
Scheme 16. Synthesis of 1-alkyl-1-phenylhydrazine via sodium phenylhydrazide.

Further, alkylation of enolates of acylhydrazones was proposed. [53] For example, benzylhydrazine ((**C**), **Scheme 17**) was prepared from acetylhydrazone ((**A**), **Scheme 17**) via its sodium enolate ((**B**), **Scheme 17**) in 76 % yield. [72]



Scheme 17. Synthesis of benzylhydrazine via acetone acetylhydrazone enolate.

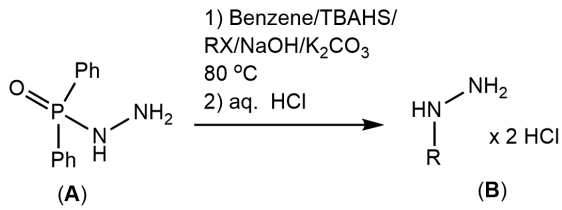
Also, sodium enolates of diacetyl acylhydrazones ((**A**), **Scheme 18**) were used for an effecient synthesis of 1-acylalkylhydrazines ((**C**), **Scheme 18**). [73–75] The main advantage of diacetyl hydrazone is its simple hydrolysis in very mild conditions by refluxing in aqueous ethanol in the presence of semicarbazide.



Scheme 18. Synthesis of 1-acylalkyl hydrazines via diacetyl hydrazone.

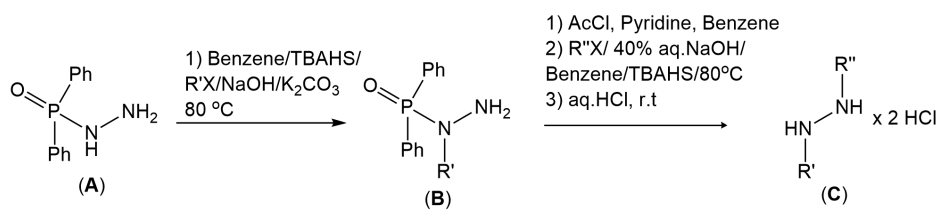
These approaches utilize the acidity of the conjugated NH group in acylhydrazone, its deprotonation results in formation of an enolate, which is selectively alkylated. The same idea was developed further and the increased NH-acidity of protected hydrazine was used for alkylation under PTC conditions. The main advantage of the PTC method is the abscence of necessity for isolation of ionic metal derivatives, as the reaction proceeds in heterogenous aqueous-organic system in the presence of tertiary alkylammonium salts.

For example, diphenylphosphino-protected hydrazine ((**A**), **Scheme 19**) was successfully alkylated by different halogenides. After deprotection of diphenylphosphino protecting group in acidic conditions, monoalkylhydrazine dihydrochlorides ((**B**), **Scheme 19**) were obtained in good yield (**Scheme 19**). [76]



Scheme 19. Synthesis of monoalkylhydrazines from diphenylphosphino-protected hydrazine.

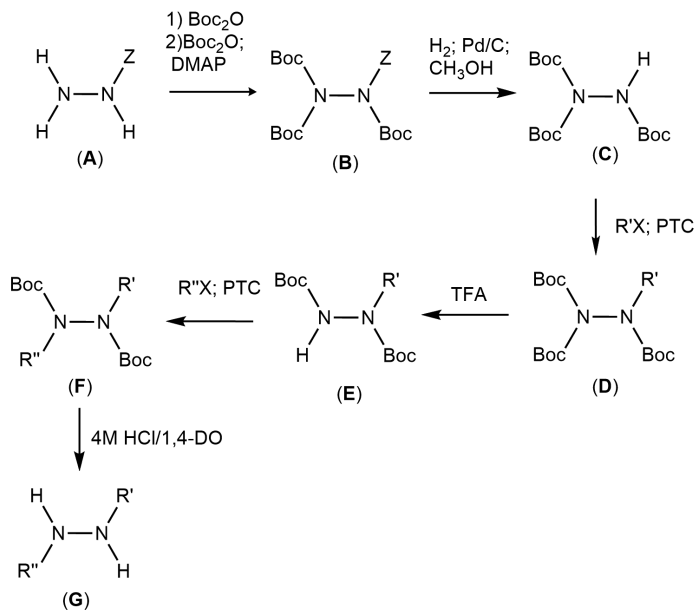
Later, this method was developed further and adjusted for synthesis of symmetrical dialkylhydrazines. In the first step diphenylphosphino-protected hydrazine ((**A**), **Scheme 20**) was alkylated using the PTC conditions. Further, the obtained diphenylphosphino-protected monoalkylhydrazine ((**B**), **Scheme 20**) was acetylated with acetyl chloride and again alkylated using the PTC conditions. Finally, both protecting groups were removed in acidic media and dihydrochlorides of the symmetrical dialkylhydrazines ((**C**), **Scheme 20**) were obtained in good yields (**Scheme 20**). [77]



Scheme 20. Synthesis of symmetrical dialkylhydrazines from diphenylphosphino-protected hydrazine.

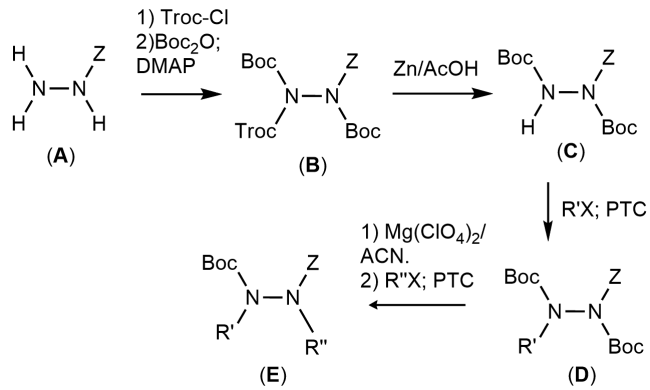
2.2.2.1. Syntheses over di-and triprotected hydrazines

The new era in chemistry of hydrazine began after introduction of the first triprotected hydrazine precursor- 1,1,2-tris(Boc)hydrazine. [78] The protecting groups in triprotected hydrazine precursor should be orthogonal to provide the option of their selective removal. Orthogonal protection does not mandatory require use of different protecting groups and could be achieved even in the case of the same group, as it was demonstrated during the synthesis of 1,1,2-tris(Boc)hydrazine. Indeed, geminal Boc-groups are much more labile in comparison with NHBoc moiety and can be easily removed by treatment with TFA. [78] Synthesis of the aforementioned precursor started from Z-$NHNH_2$ ((**A**), **Scheme 21**), which was treated 2 times with Boc_2O and finally hydrogenated over Pd/C catalyst in CH_3OH. Subsequently, the resulted 1,1,2-tris-(Boc)hydrazine ((**C**), **Scheme 21**) was selectively alkylated using PTC conditions affording 1,1,2-tris-(Boc)-2-alkylhydrazine ((**D**), **Scheme 21**). In the following step one geminal Boc-group was removed by treatment with TFA and the resulted 1,2-bis(Boc)-1-alkylhydrazine ((**E**), **Scheme 21**) was once again alkylated using PTC conditions and 1,2-bis-(Boc)-1,2-dialkylhydrazine ((**F**), **Scheme 21**) was formed. Finally, both Boc-groups were removed by treatment with HCl and the desired 1,2-dialkylhydrazines were obtained ((**G**), **Scheme 21**). [78]



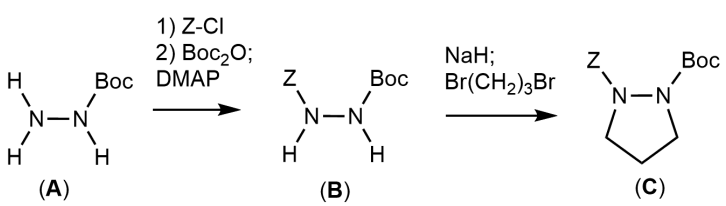
Scheme 21. Synthesis and applications of 1,1,2-tris-Boc hydrazine precursor.

This pioneering work about triprotected precursors was developed further and resulted in construction of tri-protected hydrazine bearing all orthogonal groups- 1,2-bis-Boc-2-Z-hydrazine. [79, 80] Synthesis of this precursor started again from Z-$NHNH_2$ ((**A**), **Scheme 22**). Free NH_2- group was protected with Troc-group followed by incorporation of 2 Boc groups. As a result, fully protected hydrazine ((**B**), **Scheme 22**) was obtained. Finally, Troc-group was reductively cleaved and afforded the desired 1,2-bis-Boc-2-Z-hydrazine ((**C**), **Scheme 22**). The latter compound was alkylated using PTC conditions and the obtained 1,2-bis-Boc-2-Z-2-alkylhydrazine ((**D**), **Scheme 22**) underwent selective $Mg(ClO_4)_2$ mediated removal of Boc-group from N(Boc)(Z) moiety. The obtained 1-Boc-1-alkyl-2-Z-hydrazine was again alkylated using PTC conditions and orthogonally protected 1-Boc-2-Z-1,2-dialkylhydrazine was obtained ((**E**), **Scheme 22**). [79, 80]



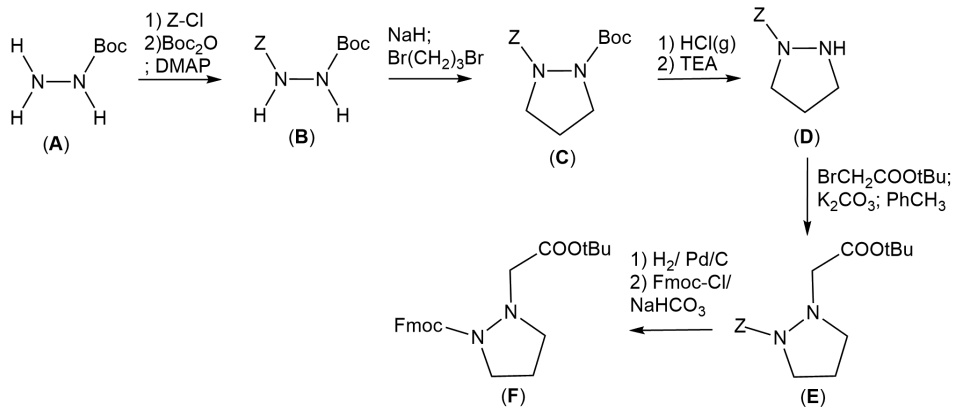
Scheme 22. Synthesis and reactions of 1,2-bis-Boc-2-Z-hydrazine.

Diprotected hydrazine precursors carrying orthogonal protecting groups were also used for preparation of protected hydrazines. For example, 1-Boc-2-Z protected ((**B**), **Scheme 23**) precursor was prepared from Boc-$NHNH_2$ ((**A**), **Scheme 23**) by treatment with Z-Cl and further alkylated by 1,3-dibromopropane in the presence of NaH affording 1-Boc-2-Z-protected pyrazolidine ((**C**), **Scheme 23**). [81]



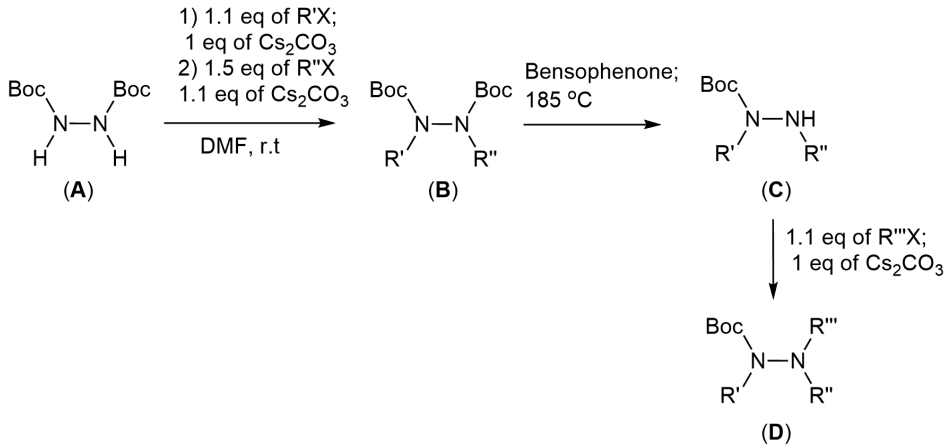
Scheme 23. Alkylation of 1-Boc-2-Z-hydrazine.

The same approach over alkylation of 1-Boc-2-Z-hydrazine ((**B**), **Scheme 24**) with 1,3-dibromopropane was used for preparation of N^b-Fmoc-aza-b^3-Proline precursor. This synthesis utilized the direct alkylation of cyclic Z-protected hydrazine ((**D**), **Scheme 24**) derivative with tert-Butyl bromoacetate and exchanges of protecting groups. Yields were from good to excellent (**Scheme 24**). [82]



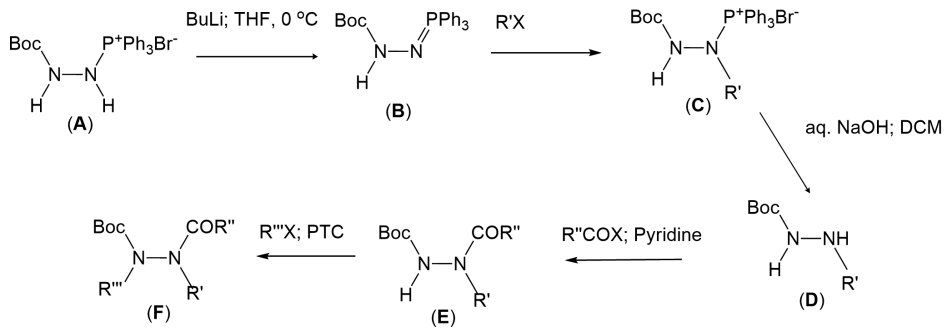
Scheme 24. Synthesis of N^b-Fmoc-aza-b^3-Proline precursor from $BocNHNH_2$.

Additionally, 1,2-bis-Boc-protected hydrazine ((**A**), **Scheme 25**) was successfully alkylated by various halogenides in DMF in the presence of 1 eq of Cs_2CO_3. Use of excess of Cs_2CO_3 and alkylhalogenides resulted in formation of dialkylated products. In order to perform alkylation of 1,2-bis-Boc-protected hydrazine selectively, 1 eq of Cs_2CO_3 and nearly equimolar amount (1.1 eq) of halogenide should be applied. For introduction of the second alkyl group 1.1 eq of Cs_2CO_3 and 1.5 eq of alkylhalogenide were used. The resulting 1,2-bis-Boc-1,2-dialkylhydrazine ((**B**), **Scheme 25**) is selectively deprotected in benzophenone at high temperature affording 1-Boc-1,2-dialkylhydrazine ((**C**), **Scheme 25**). The latter compound was alkylated third time in the presence of Cs_2CO_3 resulting in formation of 1-Boc-1,2,2-trialkylhydrazine ((**D**), **Scheme 25**). [83]



Scheme 25. Alkylation of 1,2-bis-Boc protected hydrazine.

Another example of diprotected hydrazine precursor carrying Boc and triphenylphosphonium protecting group ((**A**), **Scheme 26**) allowed direct deprotonation with BuLi and alkylation with alkylhalogenide. As a result, Boc-, and triphenylphosphonium protected alkylhydrazine ((**C**), **Scheme 26**) was obtained. The triphenylphosphonium protecting group was removed by treatment with NaOH and the obtained N-Boc-N'-alkylhydrazine ((**D**), **Scheme 26**) was acylated. Corresponding Boc-protected alkylated acylhydrazine ((**E**), **Scheme 26**) was alkylated using PTC conditions and resulted in formation of 1-Boc-2-acyl-1,2-dialkylhydrazine ((**F**), **Scheme 26**). [84]

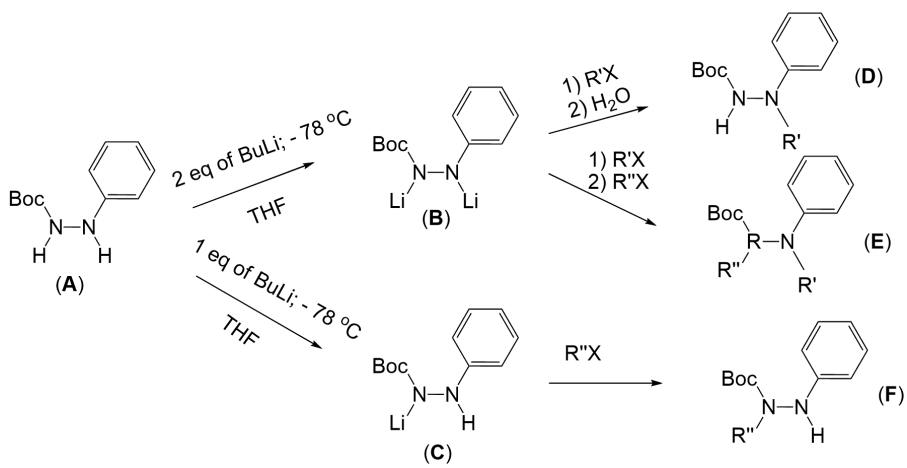


Scheme 26. Modification of 1-Boc-2-triphenylphosphino protected hydrazine.

2.2.2.2. Syntheses over hydrazine anions

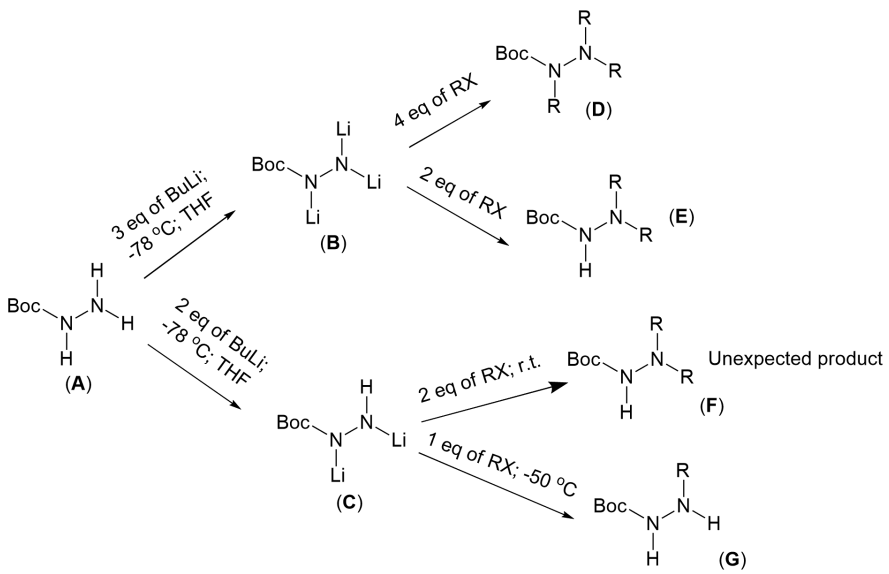
The idea of increased N-acidity of substituted hydrazines was developed further and resulted in design of a new synthetic method for modification of hydrazines processing over hydrazine polyanions. It is important to mention, that generation of dianion from 1,2-bis-trimethylsilylhydrazine and its subsequent alkylation with CH_3J was attempted in the beginning of 1960-s. The reaction proceeded rather unselectively and gave mixture of the 1,2-bis-trimethylsilyl-1,2-dimethylhydrazine and 1,1-bistrimethylsilyl-2,2-dimethylhydrazine. [85]

Later, hydrazine dianions became a topic of a detailed research. The first experiments used PhNHNHBoc ((**A**), **Scheme 27**) as a substrate and deprotonation was done at –78 °C by treatment with BuLi. Boc protected NH group is much more acidic than phenylic NH and treatment of PhNHNHBoc with 1 eq of BuLi results in selective deprotonation of carbamate NH group and formation of anion ((**C**), **Scheme 27**). Alkylation of this anion allows selective alkylation of the carbamate N-atom and formation of hydrazine ((**F**), **Scheme 27**). At the same time, if selective alkylation of phenylic nitrogen is required, the dianion ((**B**), **Scheme 27**), generated by treatment of PhNHNHBoc by 2 eq of BuLi at –78 °C is alkylated by 1 eq of halogenide. Deprotonated phenylic NH group is significantly more nucleophilic than neighbouring deprotonated BocNH- group and undergoes selective alkylation. As a result, hydrazine ((**D**), **Scheme 27**) was obtained. This difference in reactivity could be used for unsymmetric one-pot alkylation of PhNHNHBoc. For this purpose the dianion (**B**) is alkylated by 2 different halogenides. The first halogenide alkylates the anion of phenylic NH, and the second reacts with Boc protected NH producing hydrazine ((**E**), **Scheme 27**). Finally, in order to obtain symmetrically alkylated product, the dianion should be treated by 2 eq of halogenide. The yield of these syntheses vary from good to excellent. The reactions proceed as depicted on **Scheme 27**. [86]



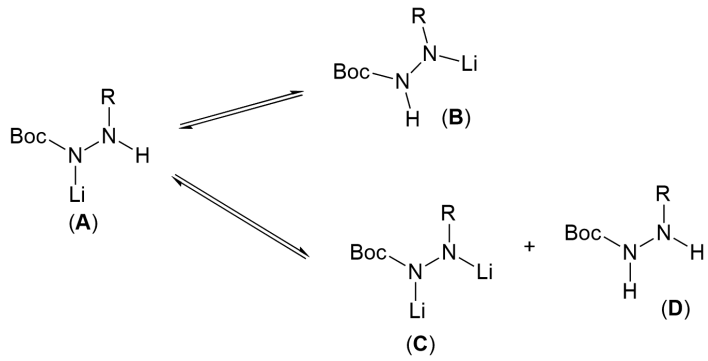
Scheme 27. Alkylation of hydrazine dianions.

Later, alkylation of trianion ((**B**), **Scheme 28**) generated in THF at –78 °C from $BocNHNH_2$ ((**A**), **Scheme 28**) by treatment by BuLi was studied. As a result, Boc-protected trialkylhydrazines ((**D**), **Scheme 28**) were obtained if corresponding trianion was reacted with 4 eq of allyl bromide or methyl iodide. Treatment of trianion (**B**) with 2 eq of allyl bromide, benzyl bromide or CH_3J resulted in selective formation of 1-Boc-2,2-dialkylhydrazines ((**E**), **Scheme 28**). During the subsequent research some exceptions in alkylation of dianion ((**C**), **Scheme 28**), generated from $Boc\text{-}NHNH_2$ by treatment with 2 eq of BuLi were turned out. For example, alkylation of the aforementioned dianion (**C**) by allyl bromide at room temperature gave 1-Boc-2,2-diallylhydrazine ((**F**), **Scheme 28**), but not the expected 1-Boc-1-allyl-2-allylhydrazine. Formation of the desired hydrazine (**G**) became possible if dianion (**C**) was alkylated at –50 °C (**Scheme 28**). [87]



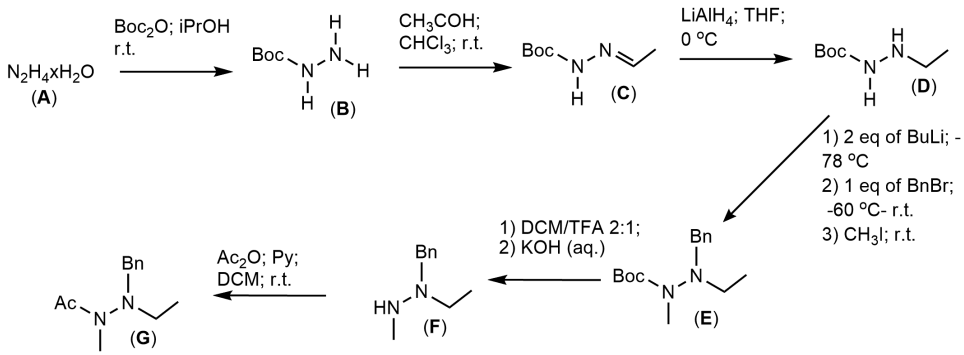
Scheme 28. Alkylation of Boc-protected hydrazine di- and trianions.

The above mentioned formation of the unexpected product - N-Boc-N',N'-dialkylhydrazine ((**F**), **Scheme 28**) can be explained by establishment of eqilibrium between anions ((**A**), (**B**) and (**C**)), as depicted on **Scheme 29**. The first possibility for the formation of N-Boc-N',N'-dialkylhydrazine ((**F**), **Scheme 28**) is the presence of equlibrial amouns of more nucleophilic anion lithiated at R-NH moiety ((**B**), **Scheme 29**). The second proposed pathway for generation of more nucleophilic anion includes formation of dianion by metallation of the initial anion with the same or some other anion present in the reaction mixture. As a result, more nucleophilic anion ((**C**), **Scheme 29**) formed from R-NH moiety reacts with alkylhalogenide more rapidly and forms the unexpected N-Boc-N',N'-dialkylhydrazine. [87]



Scheme 29. Equlibia between hydrazine anions.

This method was extended to the synthesis of tetrasubstituted hydrazines using minimal amount of protecting groups. The syntheses were started from cheap and available strarting materials such as hydrazine hydrate and allowed full derivatisation of the starting compound with minimal amount of synthetic steps. For example, 1-acetyl-1-methyl-2-ethyl-2-benzylhydrazine ((**G**), **Scheme 30**) was synthesized from hydrazine hydrate ((**A**), **Scheme 30**) in 6 steps (**Scheme 30**). [88]

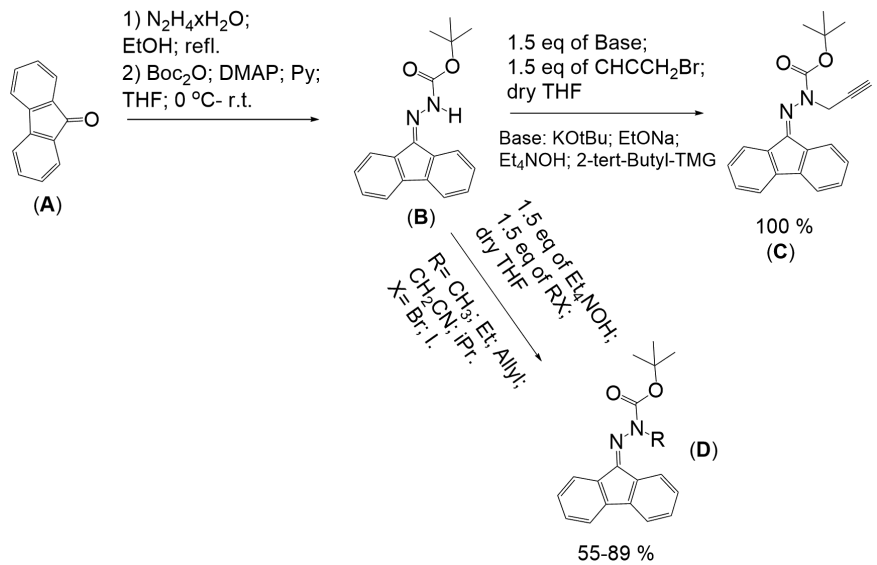


Scheme 30. Synthesis of tetrasubstituted hydrazine derivative from hydrazine hydrate.

Additionally, alkylation of hydrazine anions was successfully applied for the synthesis of heterocyclic compounds. [89]

2.2.2.3. Alkylation of hydrazone anions

Not a long time ago, N-acidity of hydrazones of aromatic ketones (ex. Benzaldehyde, Benzophenone, Fluorenone), caused by conjugation of the -CH=N- bond with aromatic system, was successfully applied for a synthesis of different substituted alkylhydrazines. For example, fluorenylidene *tert*-Butyl carbazate was successfully alkylated by 1.5 eq of propargyl bromide in dry THF in the presence of 1.5 eq of a base (KOtBu; EtONa; Et_4NOH; 2-tert-Butyl-1,1,2,2-tetramethylguanidine (2-tert-Butyl-TMG); Et_3N etc.). Structure and strength of the applied base had great effect on the alkylation reaction and yield of the alkylated carbazate. For example, if alkylation of fluorenylidene *tert*-Butyl carbazate ((**B**), **Scheme 31**) with propargyl bromide was preformed using strong bases (KOtBu; EtONa; Et_4NOH; 2-tert-Butyl-TMG), alkylated product ((**C**), **Scheme 31**) was obtained in quantitative yield (100 %). At the same time, alkylation in the presence of CH_3ONa gave product in 57 % yield and only 30 % of the product (**C**) were obtained if DBU was used as a base. Further, alkylation of fluorenylidene *tert*-Butyl carbazate (**B**) in dry THF by different halogenides (R= CH_3; Et; Bu; Bn; Allyl; CH_2CN; CH_2COOt-Bu; iPr etc; X= Br; I) in the presence of 1.5 eq of Et_4NOH was studied. Yields of the products ((**D**), **Scheme 31**) varied from 55–89 %. [90]

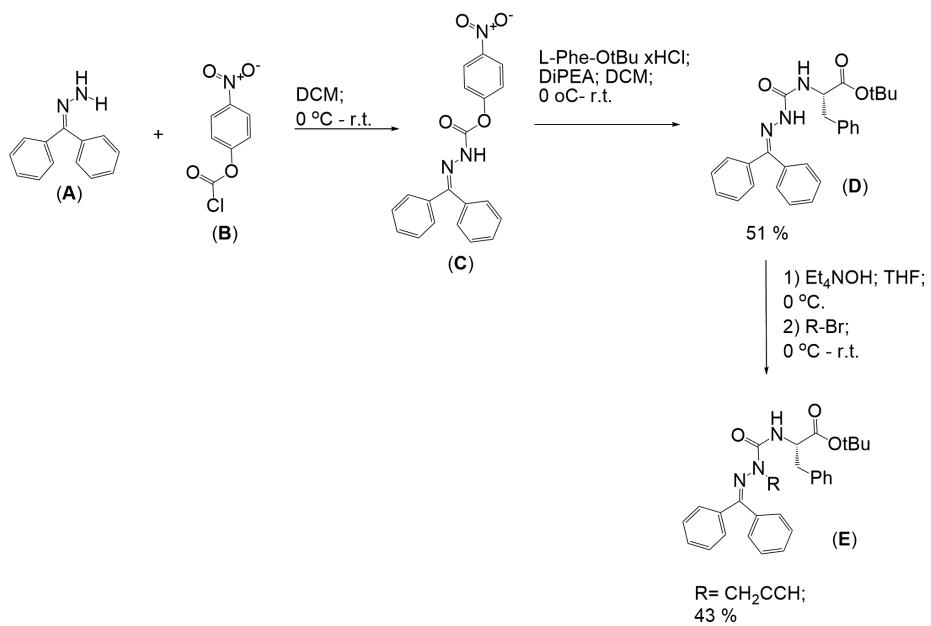


Scheme 31. Synthesis and reactions of fluorenylidene *tert*-Butyl carbazate.

Alkylation of tert-butyl benzylidene carbazate and *tert*-butyl diphenylmethylidene carbazate by 1.5 eq of propargyl bromide in dry THF in the presence of 1.5 eq of a base gave a bit different results. The best yields were obtained if

alkylation was performed in the presence of metal alcoxides and Et_4NOH. Alkylation of tert-Butyl benzylidene carbazate in the presence of 2-tert-Butyl-TMG gave 33 % of the alkylated product and only traces of the desired alkylated product in the case of *tert*-butyl diphenylmethylene carbazate. Attempts to alkylate both carbazates in the presence of DBU were unsuccessful. And finally, attempts to alkylate all the 3 aforementioned carbazates in the presence of Et_3N were completely unsuccessful. [90] These effects can be explained by different sterical hindrence of the reaction centre caused by different structure of the hydrazone part, strength of the applied base and different N-acidity of the substrates caused by different conjugation extent in the hydrazone moiety.

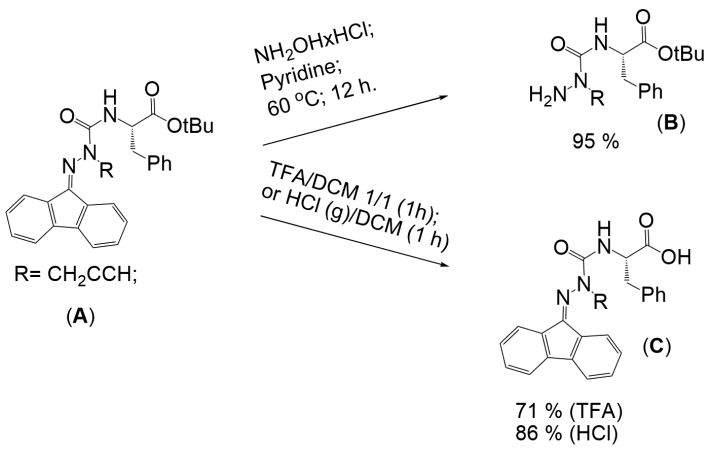
Additionally, benzhydrylidene protected hydrazines were used for a synthesis of aza-dipeptides. For this purpose benzhydrylidene protected hydrazine ((**A**), **Scheme 32**) was activated via reacting it with 4-nitrophenyl chloroformate ((**B**), **Scheme 32**). Subsequently, the activated intermediate ((**C**), **Scheme 32**) was reacted with L-Phe-COOtBu and the obtained dipeptide ((**D**), **Scheme 32**) was alkylated on hydrazone moiety according to the previously described procedure. As a result, benzhyrdylidene protected N-alkylated aza-dipeptide ((**E**), **Scheme 32**) was obtained with moderate yield. It is very important to mention that if alkylation was performed in the presence of a strong base such as KOtBu, aza-dipeptide was obtained as a racemic mixture. At the same time, if weaker base Et_4NOH was used in the alkylation step, the reaction proceeded without racemisation (**Scheme 32**). [90]



Scheme 32. Synthesis of benzhydrylidene protected aza-dipeptides.

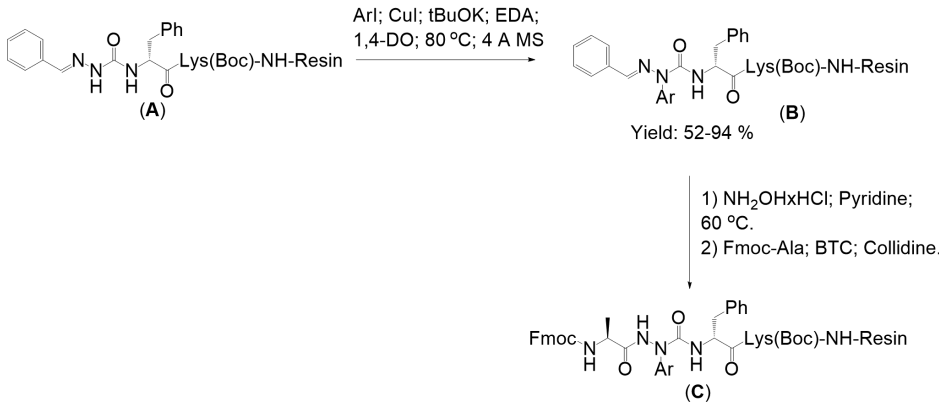
An alternative approach to the synthesis of the fluorenylidene protected aza-dipeptide was also proposed. This procedure used conversion of the L-Phe-COOtBu to the corresponding isocyanate by reacting amino acid with phosgene and subsequent reaction of isocyanate with fluorenone hydrazone. [90]

The same authors reported a convenient orthogonal deprotection strategy for the selective removal of protecting groups from the fluorenylidene aza-propargylglycinyl-D,L-phenylalanine *tert*-butyl ester ((**A**), **Scheme 33**). Thus, fluorenylidene moiety was deprotected by treatment with $NH_2OHxHCl$ in pyridine overnight at 60 ^oC. The product with deprotected hydrazine terminus ((**B**), **Scheme 33**) was obtained in 95 % yield. At the same time, tert-Butyl ester can be removed in the presence of hydrazone group by treatment with DCM/TFA 1/1 mixture (yield 71 %) or gaseous HCl in DCM affording the product with deprotected C-terminus ((**C**), **Scheme 33**), yield 86 %). Reactions are described in **Scheme 33**. [90]



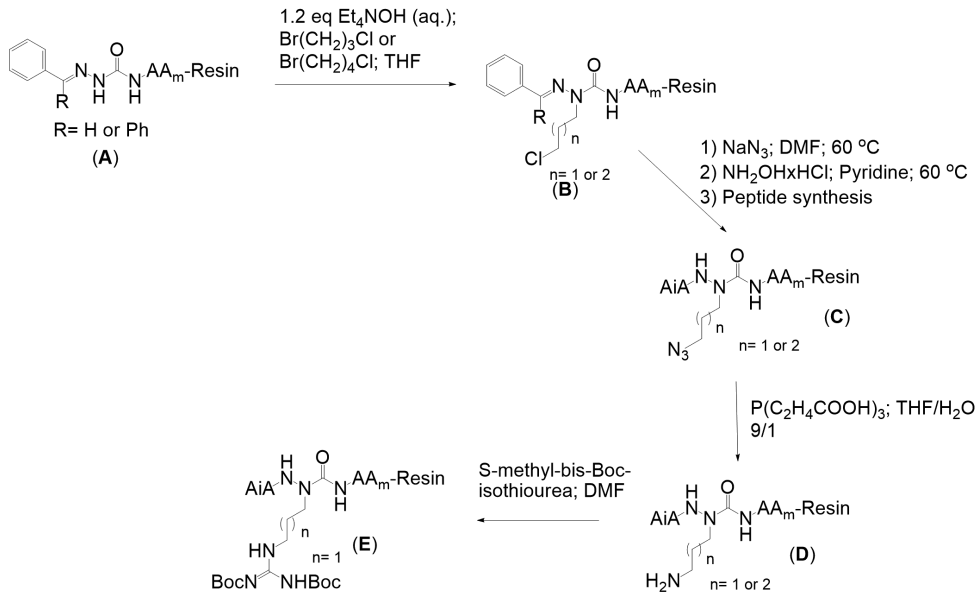
Scheme 33. Selective deprotection of fluorenylidene aza-propargylglycinyl-D,L-phenyl-alanine *tert*-butyl ester.

The above mentioned hydrazone alkylation strategy was successfully applied for synthesis of different aza-peptides. [91–92] Additionally, terminal benzylidene protected aza-Glycine containing peptides ((**A**), **Scheme 34**) were arylated on solid support by different aryl iodides (Ar= Ph; 4-OCH_3-Ph; 3-OCH_3-Ph; 4-CH_3-Ph; N-Boc-indolyl etc.) in the presence of CuI as catalyst and KOtBu as a base. As a result, peptides with terminal N-arylated aza-Gly ((**B**), **Scheme 34**) were obtained. Terminal benzylidene group was deprotected by treatment with $NH_2OHxHCl$ in pyridine and hydrazino terminus of the peptide was coupled with Fmoc-Ala affording the aza-peptide ((**C**), **Scheme 34**). [93]



Scheme 34. Arylation of benzylidene protected aza-Gly residues on solid support and subsequent elongation of peptide chain.

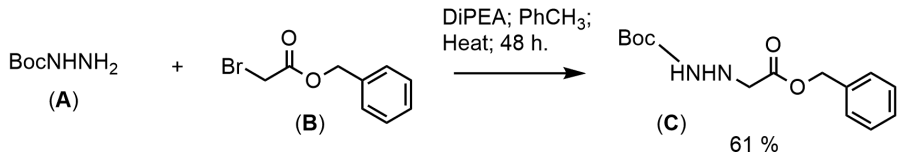
Recently, synthesis of aza-peptides with heteroatomic basic side chains was accomplished via alkylation of the terminal hydrazones. For this purpose, terminal hydrazone protected aza-Gly residue ((**A**), **Scheme 35**) was treated on solid support with 1-bromo-3-chloropropane or 1-bromo-4-chloropropane in dry THF in the presence of 1.2 eq of Et_4NOH as a base. During the alkylation reaction only bromine atom in dihalogenide was substituted and 3-chloropropyl or 4-chlorobutyl group was introduced. Further, in order to convert the obtained itermediates ((**B**), **Scheme 35**) into aza-ornithine, aza-arginine and aza-lysine containing aza-peptides, peptides containing ώ-chloroalkyl chain (**B**) were reacted with NaN_3 in DMF and the peptide chain was elongated. The azido-group of the peptides ((**C**), **Scheme 35**) was reduced to primary amine using $P(C_2H_4COOH)_3$ in THF/water 9/1 mixture, affording corresponding aza-Orn and aza-Lys residues ((**D**), **Scheme 35**). Subsequent formation of aza-Arg moiety containing guanidyl group was achieved by reacting the primary amine with S-methyl-bis-Boc-isothiourea. As a result, aza-Arg containing aza-peptides were prepared ((**E**), **Scheme 35)**. [94]



Scheme 35. Alkylation of hydrazone protected aza-Gly residues with dihalogenides and subsequent modification of the side chain.

2.2.2.4. Alkylation of monoprotected hydrazines

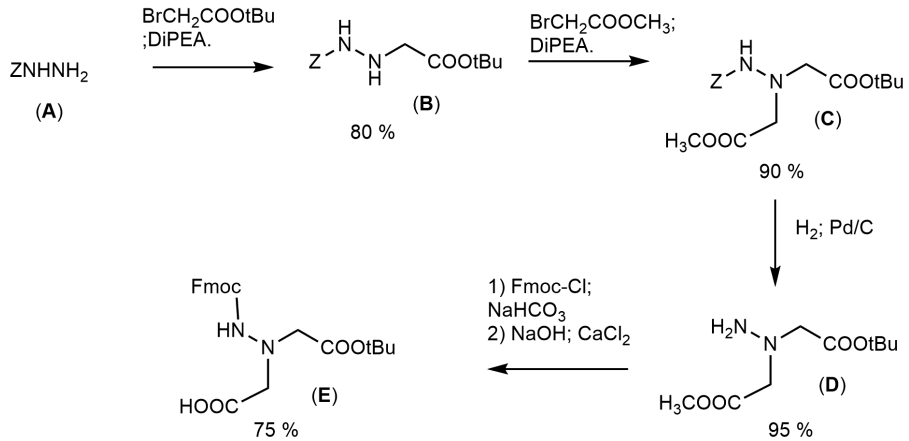
Despite the previously mentioned problems with selectivity of hydrazine alkylation reaction, direct alkylation still remains an easy and rapid method for modification of monoprotected hydrazines with alkyl groups. This approach was successfully applied for a synthesis of protected alkylhydrazines. For example, Boc-$NHNH_2$ ((**A**), **Scheme 36**) was alkylated by benzyl bromoacetate ((**B**), **Scheme 36**) in toluene in the presence of DiPEA and gave the product ((**C**), **Scheme 36**) in 61 % yield. [95]



Scheme 36. Direct alkylation of $BocNHNH_2$ with benzyl bromoacetate.

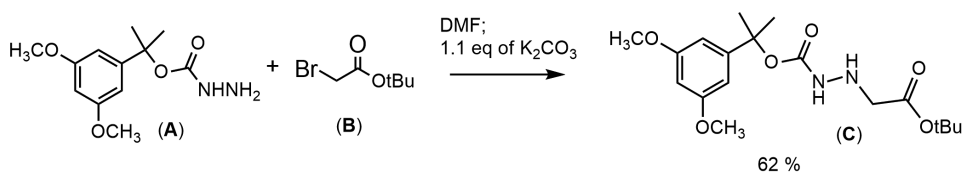
Additionally, preparation of Fmoc-aza-β^3-Asp-OH precursor started from Z-$NHNH_2$ ((**A**), **Scheme 37**) and included 2 alkylations with different 2-bromo-carboxylic acid esters. In the first synthetic step $ZNHNH_2$ (**A**) was alkylated with tert-Butyl 2-bromoacetate using DiPEA as a base. Subsequently, the monoalkylated product ((**B**), **Scheme 37**) was alkylated with 2 eq of methyl bromoacetate and Z-protecting group of the dialkylated hydrazine ((**C**), **Scheme**

37) was removed by hydrogenation over Pd/C. The obtained N,N-dialkyl-hydrazine ((**D**), **Scheme 37**) was treated with Fmoc-Cl in the presence of $NaHCO_3$ as a mild base and in the final step methyl ester was hydrolyzed by NaOH in the presence of $CaCl_2$ affording the Fmoc-aza-β^3-Asp-OH precursor ((**E**), **Scheme 37**). [82] $CaCl_2$ acts as a catalyst and helps to prevent Fmoc cleavage under basic conditions. [96]



Scheme 37. Synthesis of Fmoc-aza-β^3-Asp-OH.

Recently, synthesis of Ddz-protected aza-Asp-(OtBu) precursor was reported via direct alkylation of Ddz-$NHNH_2$ ((**A**), **Scheme 38**) with tert-Butyl bromo-acetate ((**B**), **Scheme 38**) in DMF using 1.1 eq of K_2CO_3 as a base. Yield of the target monoalkylated product ((**C**), **Scheme 38**) was 62 %. [97]

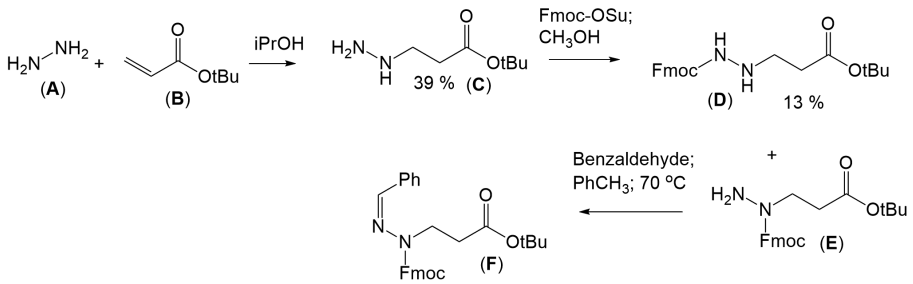


Scheme 38. Synthesis of Ddz-Asp-(OtBu) precursor via alkylation.

In general, synthesis of aza-Asp precursors via alkylation of monoprotected hydrazines with 2-bromoacetic acid esters is much more convenient than 3 step synthesis including reductive alkylation of Fmoc-$NHNH_2$ with glioxylic acid and subsequent esterification with tert-Butyl 2,2,2-trichloroacetimidate. [28] Alkylation of monoprotected hydrazine could be performed using an equimolar amount of halogenoacetic acid ester as secondary NH moiety in monoalkylated

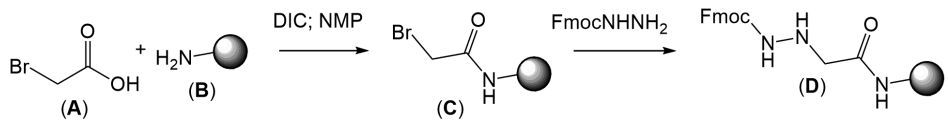
product is more sterically hindered and owns lower nucleophilicity due to electron withdrawing effect of the neigbouring group. For example, alkylation of $BocNHNH_2$ with tert-Butyl bromoacetate at room temperature in DMF and in the presence of 1.1 eq of K_2CO_3 as a base, gave the desired monoalkylated product in 23 % yield. The yield of dialkylated product was only 2 %. [98]

Another interesting approach to synthesis of Fmoc-aza-Glu-OtBu precursor ((**D**), **Scheme 39**) included alkylation of the hydrazine hydrate ((**A**), **Scheme 39**), taken in 10 fold excess, with tert-Butyl acrylate ((**B**), **Scheme 39**) in 2-propanol and subsequent protection of the alkylhydrazine ((**C**), **Scheme 39**) with Fmoc-group. The alkylation reaction gave product (in the form of hydrochloride) in 39 % yield. Protection step also generated product with Fmoc-group on already alkylated nitrogen ((**E**), **Scheme 39**). For separation, the side product was condensated with benzaldehyde and removed in the form of hydrazone ((**F**), **Scheme 39**) as shown on **Scheme 39**. Yield of the protection step was poor and only 13 % of the aza-Glu precursor (**D**) were obtained. [99] Such a low yield can be explained by greater nucleophilicity of the alkylated nitrogen making it significantly more reactive towards Fmoc-OSu.



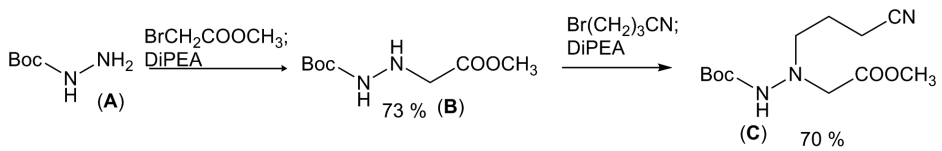
Scheme 39. Synthesis of Fmoc-aza-Glu-OtBu precursor from tert-Butyl acrylate.

Additionally, synthesis of aza-peptides containing C-terminal aza-Asparagine was reported. The synthesis started from immobilisation of 2-bromoacetic acid ((**A**), **Scheme 40**) on Rink resin ((**B**), **Scheme 40**) using DIC in NMP, followed by the on-resin nucleophilic substitution of bromine with $Fmoc\text{-}NHNH_2$ resulting in formation of aza-Asp residue ((**D**), **Scheme 40**) immobilized on solid support (**Scheme 40)**. [100]



Scheme 40. Alkylation of $FmocNHNH_2$ with 2-bromoacetic acid immobilized on solid support.

Not a long time ago an effecient alkylation of Boc-$NHNH_2$ ((**A**), **Scheme 41**) with methyl bromoacetate was reported. The monoalkylhydrazine ((**B**), **Scheme 41**) was again alkylated with 4-bromobutyronitrile. Both alkylations were performed in the presence of DiPEA as a base and gave product ((**C**), **Scheme 41**) in good yields- 70 % and above (**Scheme 41**). [101]



Scheme 41. Alkylation of $BocNHNH_2$ with methyl bromoacetate and 4-bromobutyronitrile.

As it can be seen from the brief overview of the examples of alkylation of the monoprotected hydrazines, direct alkylation approach is mostly used for preparation of N-protected derivatives of hydrazinoacetic acid and thus became especially useful for the synthesis of aza-β^3 amino acids. However, the direct functionalisation of monoprotected hydrazines with alkyl groups is a very effective 1 step approach. Additionally, monoprotected hydrazines are a weak nucleophiles in comparison with nonsubstituted hydrazine and usually corresponding bromides are used for alkylation.

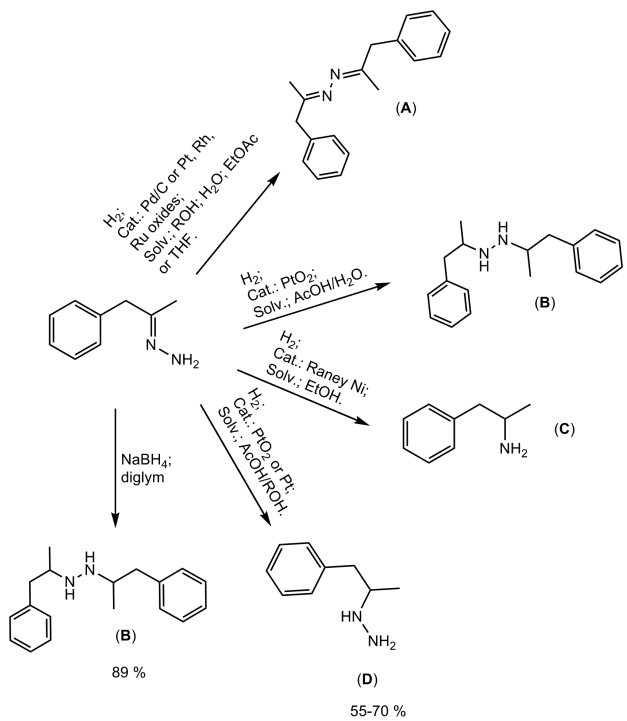
2.3. Reductive alkylation of hydrazines

As it was previously mentioned, direct alkylation of hydrazines is not a very selective process and formation of polyalkylated hydrazines is almost inevitable. At the same time, hydrazine derivatives (hydrazones, aldazines, ketazines, etc.) can be reduced to substituted hydrazines.

Reduction of hydrazones allows selective synthesis of monoalkylhydrazines and will be discussed in details. Selectivity of formation of monoalkylhydrazines can be explained by the selective formation of -CH=N- bond in the reaction of hydrazine -NH_2 group with carbonyl compound in very mild conditions. At the same time, imine 2-bond could be formed during reaction of secondary amino group with carbonyl compounds. However, the resulting imine bears positively charged N-atom and its formation requires more harsh conditions. This method starts from condensation of hydrazine with aldehydes or ketones. If the reaction utilizes reactive aldehydes, it is difficult to stop condensation on the hydrazone step as -NH_2 group of the formed hydrazone reacts further. [102] Hydrazones can be reduced to hydrazines by different reductants, of which catalytic hydrogenation is one of the most general methods and is discussed in subchapter **2.3.1.**

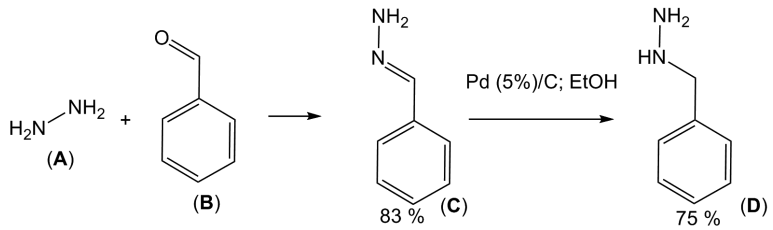
2.3.1. Hydrogenation of hydrazones

N-N bond is sensitive to reductive cleavage and depending on the reaction conditions and the type of applied catalyst formation of various products is possible. [103] For example, during hydrogenation of 1-phenyl-2-propyl hydrazone formation of 4 different compounds was observed. If reduction of hydrazone was performed slowly and incompletely in alcohol, water, ethyl acetate or THF and in the presence of Pd/C or platinum, rhodium or ruthenium oxides as hydrogenation catalysts, large amounts of the corresponding ketazine ((**A**), **Scheme 42**) were obtained. Symmetrical dialkylhydrazine ((**B**), **Scheme 42**) was obtained as a result of slow and complete reduction of hydrazone in aqueous AcOH using platinum oxide as catalyst. Use of Raney Ni as hydrogenation catalyst and performing the reduction in ethanol almost exclusively afforded ketazine (**A**) and 1-phenyl-2-aminopropane ((**C**), **Scheme 42**). The desired 1-phenyl-2-propylhydrazine ((**D**), **Scheme 42**) was obtained if hydrogenation was performed in alcoholic AcOH using platinum oxide as catalyst and at pressure of 2000 pounds. The yields were in the range 55–70 %. At the same time, reduction of the same hydrazone with $NaBH_4$ in diglyme produced the symmetric dialkylhydrazine ((**B**), **Scheme 42**) in 89 % yield. [103] The results described above prove the fact, that Raney Ni cleaved N-N bond and is not suitable for reduction of hydrazine derivatives. [104,105]



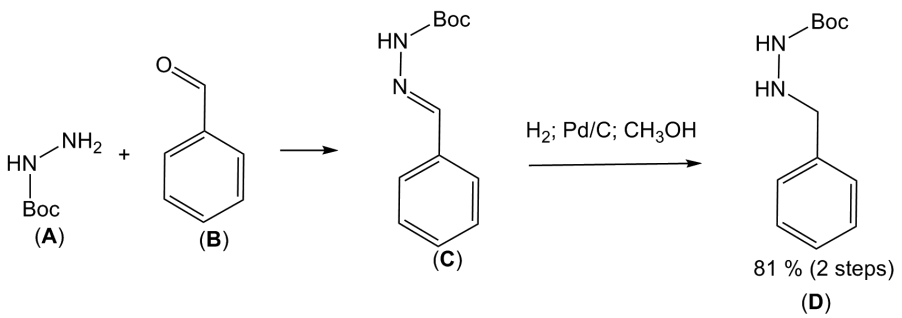
Scheme 42. Formation of different products during hydrogenation of 1-phenyl-2-propyl hydrazone.

To improve stability of the N-N bond, hydrazones are usually protected (ex. acetylated) and subsequently hydrogenated over platinum oxide or platinum on solid support. [53, 106–107] At the same time, benzylhydrazine ((**D**), **Scheme 43**) was successfully synthesized via low pressure hydrogenation of benzylidenehydrazine ((**C**), **Scheme 43**) in ethanol over Pd(5%)/C catalyst. The product (**D**) was obtained in 75 % yield (**Scheme 43**). [108]



Scheme 43. Synthesis of benzylhydrazine via hydrogenation of benzylidenehydrazine.

Hydrogenation of the benzaldehyde N-Boc hydrazone ((**C**), **Scheme 44**) over Pd/C in methanol allowed to obtain corresponding hydrazine ((**D**), **Scheme 44**) in 81 % yield over 2 reaction steps (**Scheme 44**). [109]

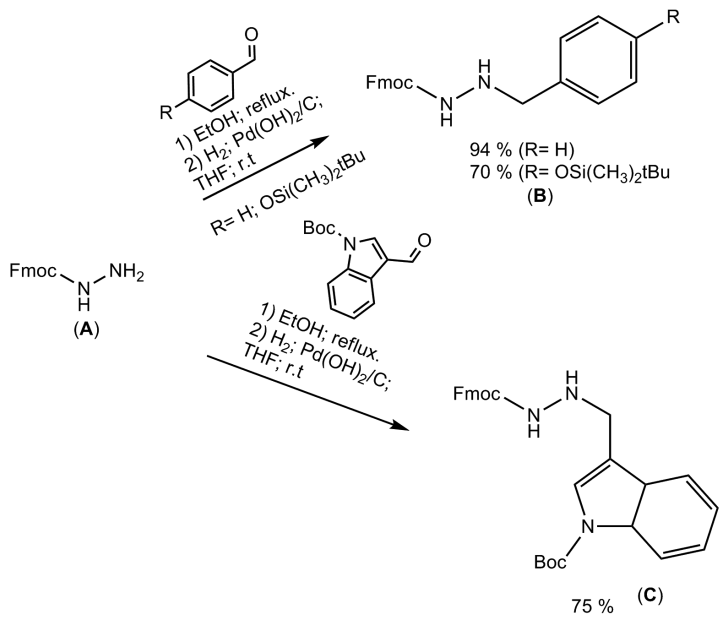


Scheme 44. Synthesis of N-Boc-N'-benzylhydrazine via reduction of corresponding hydrazone.

Additonally, a set of Boc-protected alkylhydrazines corresponding to aza-Val, aza-Ile, aza-Leu, aza-Phe, aza-Tyr and aza-Trp were obtained via hydrogenation of the hydrazones over Pd(5%)/C catalyst in THF at 25 ^{o}C. During this study a tremendous effects of hydrazone structure on the hydrogenation kinetics was observed. For example, hydrogenaton of benzaldehyde N-Boc protected hydrazone proceeded most rapidly and theoretical amount of a hydrogen was uptaken during 20 min. Hydrazones of O-tBu protected and non-protected 4-hydroxybenzaldehyde were also reduced quite rapidly: uptake of a theoretical amount of a hydrogen took 2.5 hours (hydrazone carrying O-tBu group) and 3.5 hours

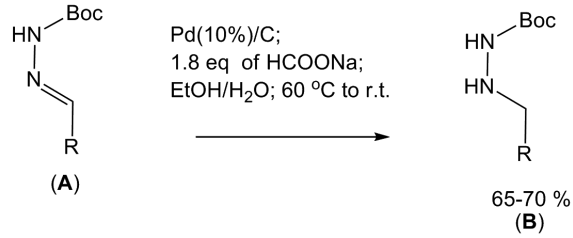
in the case of hydrazone with non-protected phenolic OH group. Reduction of the indole-3-aldehyde N-Boc-protected hydrazone reguired 40–60 hours and hydrogenation of acetone N-Boc protected hydrazone required 60–68 hour long hydrogenation. Attempts to hydrogenate acetone N-Boc protected hydrazone over Pd (30%)/C at higher pressure resulted in formation of a mixture containing only a little amount of the desired product. [81]

Not a long time ago hydrogenation mediated synthesis of Fmoc-protected precursors of aza-Tyr, aza-Phe and aza-Trp was reported. The syntheses started from Fmoc-$NHNH_2$ ((**A**), **Scheme 45**) which was condensated with a corresponding aldehyde in refluxing EtOH. For a reduction step, hydrazone was dissolved in THF and hydrogenated over $Pd(OH)_2/C$ at room temperature and pressure of 100 psi (**Scheme 45**). The yields of hydrazines ((**B**) and (**C**), **Scheme 45**) were good to excellent. [28]



Scheme 45. Synthesis of Fmoc protected aza-Phe, aza-Tyr($OSi(CH_3)_2tBu$) and aza-Trp(Boc) precursors.

An another example of hydrogenation of N-Boc benzylidene hydrazines ((**A**), **Scheme 46**) utilized 1.8 eq of HCOONa as hydrogen source, 0.2 eq of Pd(10%)/C catalyst and $EtOH/H_2O$ 5/1 mixture as a solvent (**Scheme 46**). Different hydrazones (**A**) with variety of substituents on phenyl group (R=Ph; (3-OCH_3)Ph; (2,4-$(OCH_3)_2$)Ph; (4-(2-pyridinyl)Ph; (4-(4-NO_2-Bn))Ph etc.) were used as a reaction substrates. The reaction proceeded for 1.5 h at 60 ^oC, followed by overnight stirring at temperature below 40 ^oC and afforded corresponding hydrazines ((**B**), **Scheme 46**) in good yields. [110]



R= Ph; (3-OCH_3)Ph; (2,4-(OCH_3))$_2$Ph; (4-(2-pyridinyl))Ph; (4-(4-NO_2-Bn))Ph etc.

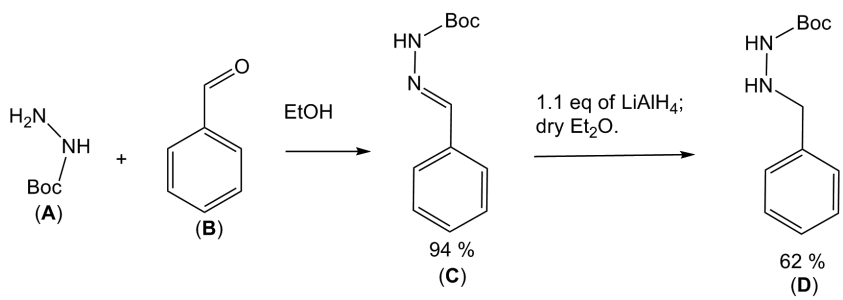
Scheme 46. Synthesis of N-Boc benzylhydrazines using HCOONa and Pd/C.

As it can be seen from the aforementioned brief overview, catalytic hydrogenation is a useful and general method for a reduction of different hydrazones affording hydrazines with yields varying from good to excellent. However, success of this procedure strongly depends on the solvent, type of a catalyst, reaction conditions and hydrazone structure. Due to several obstacles with hydrogenation of hydrazones, alternative selective and convenient methods for reduction are still required. Rapid reseach in the field of chemistry of complex hydrides allowed to overcome many synthetic difficulties and will be discussed in **2.3.2**.

2.3.2. Reduction of hydrazones with complex hydrides

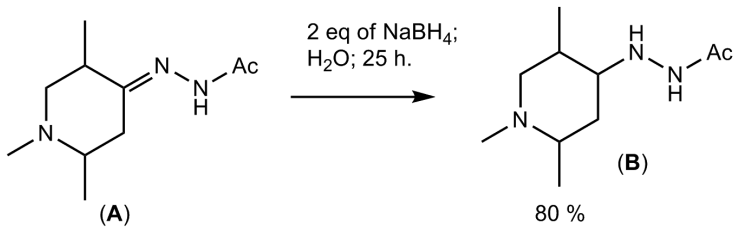
Exploring properties of complex hydrides revealed a lot of new possible synthetic transformations. Among them was a convenient reduction of -CH=N- bond of hydrazones to corresponding hydrazines.

For example, reduction of tert-butyl benzalcarbazate ((**C**), **Scheme 47**) with of $LiAlH_4$ in dry diethyl ether was reported. The hydrazone (**C**) was obtained by reacting $BocNHNH_2$ ((**A**), **Scheme 47**) with benzaldehyde ((**B**), **Scheme 47**) in ethanol. Subsequently, hydrazone (**C**) was reduced by 1.1 eq of $LiAlH_4$ in dry diethyl ether. N-Boc-N'-benzylhydrazine ((**D**), **Scheme 47**) was purified by vacuum destillation and the pure product was obtained in 62 % yield (**Scheme 47**). [111]



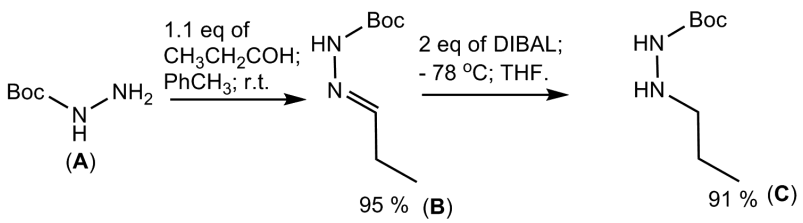
Scheme 47. Synthesis and reduction of tert-Butyl Benzalcarbazate with $LiAlH_4$.

Also, reduction of 1,2,5-trimethyl-4-piperidinone acetylhydrazone ((**A**), **Scheme 48**) with 2 eq of $NaBH_4$ in water over the periood of 25 hours was reported. Vacuum destillation of the obtained crude product afforded the desired 1-acetyl-2-(1,2,5-trimethyl-4-piperidinyl)hydrazine ((**B**), **Scheme 48**) in 80 % yield. [112]



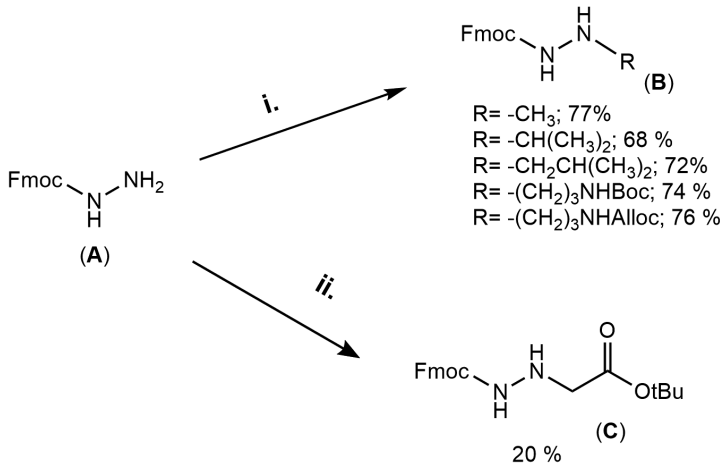
Scheme 48. Reduction of 1,2,5-trimethyl-4-piperidine acetylhydrazone with $NaBH_4$.

An another example of reductive alkylation used DIBAL in reduction step. Tert-Butylcarbazate (Boc-$NHNH_2$) ((**A**), **Scheme 49**) was condensated with 1.1 eq of propanal at room temperature using toluene as solvent. Yield of hydrazone ((**B**), **Scheme 49**) was almost quantitative. For the reduction step, hydrazone (**B**) was dissolved in THF, cooled to -78 ^oC and treated with 2 eq of DIBAL. The desired N-Boc-N'-propylhydrazine ((**C**), **Scheme 49**) was obtained in 91 % yield (**Scheme 49**). [113]



Scheme 49. Reduction of hydrazone with DIBAL.

Recently, an effective reduction of aliphatic N-protected hydrazones with $NaBH_3CN$ in the presence of equimolar amount of AcOH was reported. The desired hydrazones were obtained via condensation of $FmocNHNH_2$ ((**A**), **Scheme 50**) with formaldehyde, acetone, 2-methylpropanal, 3-(N-alkyloxy-carbonylamino)propanal and glyoxalic acid in refluxing etnahol. Subsequent reduction was performed by $NaBH_3CN$ in the presence of AcOH. Complexes with boron were decomposed by refluxing the crude mixture in ethanol. [28] The general reaction scheme, reaction conditions and yields of the protected alkylhydrazines ((**B**) and (**C**), **Scheme 50**) are depicted on **Scheme 50**.

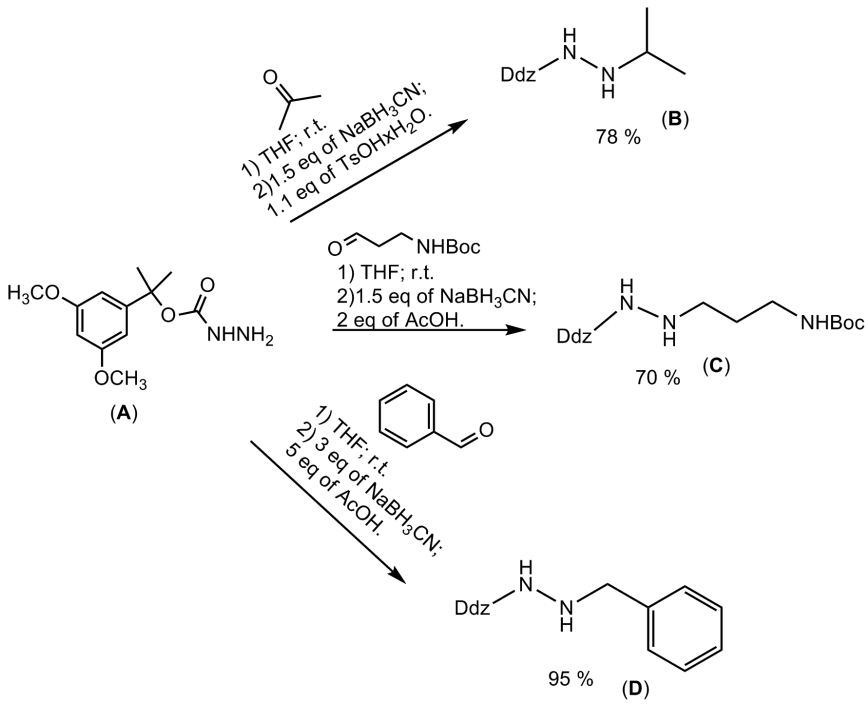


i.1) Aldehyde or ketone;EtOH; reflux. 2) $NaBH_3CN$; AcOH; THF. 3) EtOH; reflux.

ii.1) HOCCOOH; EtOH; reflux. 2) $NaBH_3CN$; AcOH; THF. 3) EtOH; reflux.
4) $CCl_3C(OtBu)NH$; DCM; r.t.

Scheme 50. Synthesis of Fmoc-protected monoalkylhydrazines via reduction with $NaBH_3CN$.

Synthesis of Ddz-protected monoalkylhydrazines ((**B**), (**C**) and (**D**), **Scheme 51**) from Ddz-$NHNH_2$ ((**A**), **Scheme 51**) was reported and different methods for a reduction of different types of Ddz-protected hydrazones with $NaBH_3CN$ were proposed. For example, hydrazones of propanal, acetone and 2-methylbutanal were reduced in THF by 1.5 eq of $NaBH_3CN$ in the presence of 1.1 eq of $TsOHxH_2O$. Yield of the products (**B**) varied from 78–86 %. The second method was applied for a reduction of 2-methylpropanal, 2-butanone and Alloc- and Boc-protected 3-aminopropanal hydrazones. The reaction was performed in THF and used 1.5 eq of $NaBH_3CN$ and 2 eq of AcOH. The yields of hydrazines (**C**) were in the range of 70–87 %. Attempts to reduce conjugated hydrazones of benzaldehyde, 4-(tert-butoxy)benzaldehyde or N-Boc-Indole-3-aldehyde using the aforementioned conditions resulted in very long reduction times. Successful reduction was achieved by using 3 eq of $NaBH_3CN$ and 5 eq of AcOH in THF. Corresponding protected benzyl-, or substituted (3-methyl)indolylhydrazines (**D**) were obtained in good to excellent yields (68–95 %). The reaction scheme and aforementioned methods for reduction of hydrazones are shown on **Scheme 51**. [97]



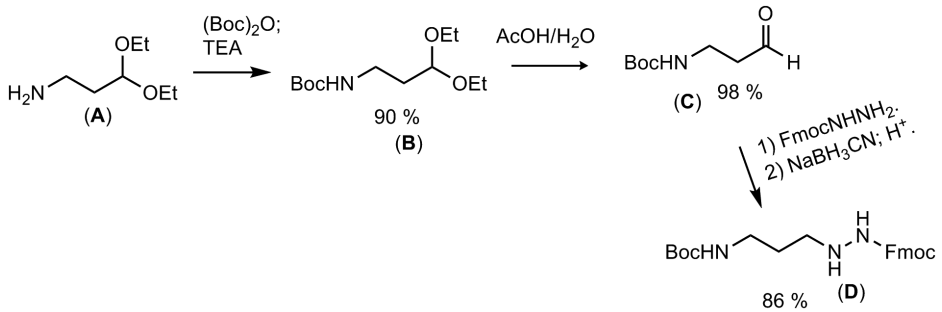
Scheme 51. Synthesis of Ddz-protected monoalkylhydrazines.

Recently, reduction of acetone N-Boc protected hydrazone with $NaBH_3CN$ in acidic media was described. It s very important to mention, that in this case treatment of the crude mixture with 1 M NaOH can be used for decomposing the formed boron adducts. The required N-Boc-N'-isopropylhydrazine was obtained in 75 % yield. The same authors reported that their attemts to synthesize N-Boc-N'-methylhydrazine by reduction of formaldehyde N-Boc hydrazone were unsuccessful. [109]

As it can be seen from the above mentioned information, reduction of hydrazones with $NaBH_3CN$ in acidic media is one of the most preferred methods for preparation of monoprotected monoalkylhydrazines. This can be explained by several special advantages of $NaBH_3CN$. Firstly, this reagent reduces iminium salts and imines much faster than carbonyl compounds and this property makes it very selective reagent for reductive alkylation. [114] Secondly, $NaBH_3CN$ tolerates protic solvents and acidic conditions. [114] Thirdly, this reductant does not reduce amide-, ether-, nitrile- and nitro groups. [115] The main disadvantage of $NaBH_3CN$ is its toxicity and possible formation of highly toxic byproducts such as NaCN and HCN.

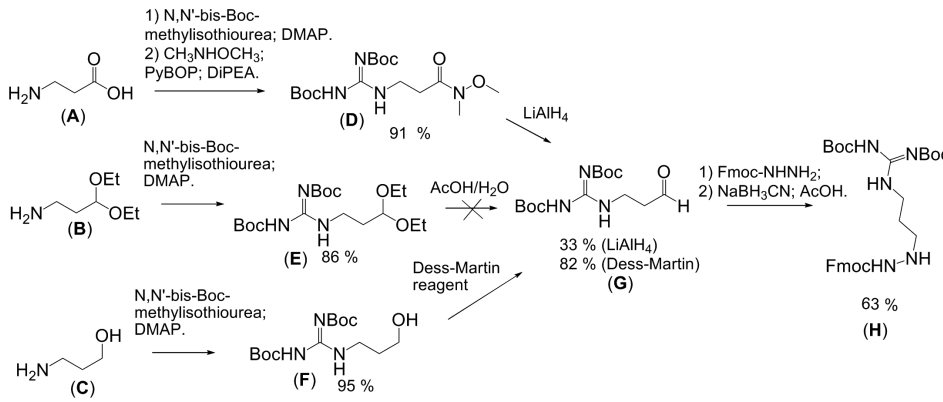
At the same time, reductive alkylation is complicated by some drawbacks. Firstly, this method is limited by availability of carbonyl compounds. For example, difficulties were encountered during preparation of the Fmoc-aza-Asp precursors from glyoxilic acid, [28] and direct alkylation of correspoding

monoporotected hydrazine was much more preferable (see **2.2.2.4**). Secondly, application of the method is limited by stability of the carbonyl compound. For example, if carbonyl compound contains nucleophilic groups such as -NH_2, it is very prone to undergo self-condensation. Due to this problem such carbonyl compounds are usually available in protected form (ex. as acetals). At the same time, use of protecting groups requires additional synthetic steps for de-protection. For example, synthesis of Fmoc-aza-β^3-Arg(Boc)$_2$ precursor started from 3,3-diethoxypropylamine ((**A**), **Scheme 52**). Afterwards the -NH_2 group was protected with Boc group followed by deprotection of the carbonyl group in aqueous AcOH. The obtained aldehyde ((**C**), **Scheme 52**) was condensated with Fmoc-$NHNH_2$ and reduced with $NaBH_3CN$ to orthogonally protected Fmoc-aza-Orn(Boc) precursor ((**D**), **Scheme 52**). [95]



Scheme 52. Preparation of aldehyde from acetal and reductive alkylation of Fmoc-$NHNH_2$.

At the same time, difficulties with hydrolysis of 3-(di-Boc)guanidinopropanal diethyl acetal ((**E**), **Scheme 53**) were faced. Indeed, all the attempts to hydrolyze the acetal in a mixture of AcOH/H_2O were completely unsuccessful. The 3-(di-Boc)guanidinopropanal was obtained via oxidation of 3-(di-Boc)guanidinopropanol ((**F**), **Scheme 53**) with Dess-Martin reagent (yield 82 %) and also via reduction of Weinreb amide ((**D**), **Scheme 53**) with $LiAlH_4$ (yield 33 %). Condensation of the aldehyde with Fmoc-$NHNH_2$ followed by the subsequent reduction with $NaBH_3CN$ proceeded without complications and gave product ((**H**), **Scheme 53**) in 63 % yield. [116]

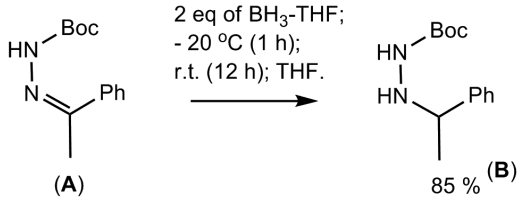


Scheme 53. Synthesis of Fmoc-aza-Arg precursor.

2.3.3. Reduction of hydrazones with BH_3 complexes

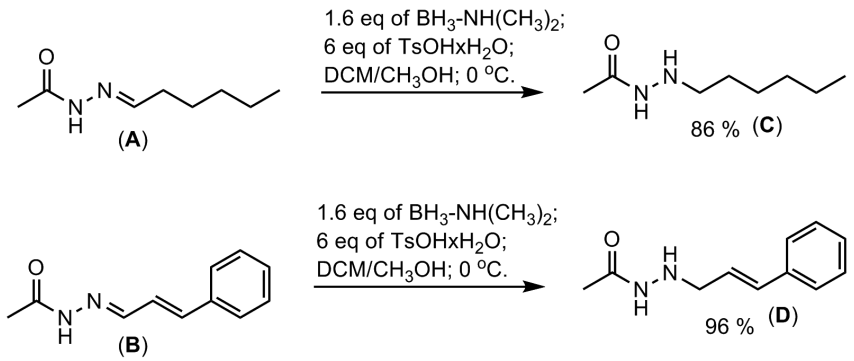
BH_3 can form donor-acceptor complexes with different compounds bearing a heteroatom with electron pair (amines, THF, dimethyl sulfide, pyridine etc.). Many of these complexes have found different synthetic applications being applied as powerful, mild and selective electrophilic reductants. For example, BH_3 complexes are good reagents for reduction of carboxylic acids, aldehydes, ketones, amides, imines and nitriles in the presence different functional groups such as nitro, ester, lactone, carbamate groups and halogen substituents. [117]

BH_3 complexes have also been applied for reduction of different hydrazones. For example, acetophenone N-Boc hydrazone ((**A**), **Scheme 54**) was reduced by 2 eq of BH_3-THF complex in dry THF and afforded corresponding hydrazine ((**B**), **Scheme 54**) in 85 % yield. At the same time, reduction of the same hydrazone by hydrogenation over Pd(10 %)/C catalyst in 95 % EtOH at pressure of 45–50 psi afforded hydrazine in 94 % yield. [118] The described results prove, that reduction of hydrazones with borane-THF complexes can be exploited instead of hydrogenation.



Scheme 54. Reduction of Boc protected hydrazone with BH_3-THF copmlex.

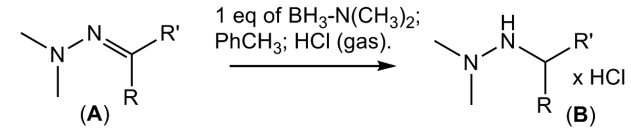
Not a long time ago reduction of unconjugated and α,β-unsaturated acylhydrazones was reported. For example, hexanal acetylhydrazone ((**A**), **Scheme 55**) and cynnamaldehyde acetylhydrazone ((**B**), **Scheme 55**) were reduced at 0 ^{o}C by 1.6 eq of BH_3-$NH(CH_3)_2$ complex in the presence of 6 eq of TsOH and using DCM/CH_3OH mixture as a solvent (**Scheme 55**). During optimization of this reaction authors tested methanolic HCl, acetic acid and aqueous HCl as acidic agents. As a result, several disadvantages of each acid were revealed. For example, reduction with BH_3-$NH(CH_3)_2$ in the presence of methanolic HCl required preparation of titrated HCl solutions and high dilution of the reaction mixture. Experiments with AcOH were not successful. Application of aqueous HCl on the small scale gave the same results as methanolic HCl, however, if performed on larger scale, reduction in the presence of aqueous HCl gave significantly lower yields. TsOH turned out to be the best option because of its good solubility in different solvents, cheapness and strength. The desired acetylhydrazines ((**C**) and (**D**), **Scheme 55**) were obtained in very good yields. [119]



Scheme 55. Reduction of acetylhydrazones with BH_3-$N(CH_3)_2$.

In addition to the above mentioned applications, BH_3-$N(CH_3)_3$ complexes were successfully used for reduction of different hydrazones. Borane-amine complexes are stable towards acids and can be used for reduction in the presence of acid excess. For reduction step 1 eq of aldehyde or ketone dimethylhydrazone ((**A**), **Scheme 56**) and 1 eq of BH_3-$N(CH_3)_3$ were dissolved in toluene and the obtained solution was saturated with gaseuos HCl for 30 min (**Scheme 56**). The obtained precipitate was filtered out and was a pure hydrazine hydrochloride. This method was used for reduction of different hydrazones of different aldehydes and ketones (ex. Acetophenone, benzaldehyde, 4-nitrobenzaldehyde, propanal, 3-formylpyridine etc.). The yields of corresponding hydrazines ((**B**), **Scheme 56**) varied from excellent to almost quantitative. [120] The authors also reported that reduction of benzaldehyde dimethylhydrazone with BH_3-$N(CH_3)_3$ in acetic acid media gave large amount (76 %) of 1-acetyl-2-benzyl-2,2-dimethylhydrazine and 13 % of 1-benzyl-1-ethyl-2,2-dimethylhydrazine.

Application of strong acid allowed to protonate hydrazone completely, to greatly improve selectivity of the reduction step and to obtain hydrazines in the form of stable and safe to handle hydrochlorides. [120]



R= -H; -CH_3.
R'= -Et; -Ph; -NO_2-Ph; 3-Pyridinyl.

1) R= H; R'= Et; 96 %
2) R= H; R'= Ph; 97 %
3) R= CH_3; R'= Ph; 94 %
4) R= H; R'= 4-NO_2-Ph; 96 %
5) R= H; R'= 3-pyridyl; 98 %.

Scheme 56. Reduction of hydrazones with BH_3-$N(CH_3)_3$.

3. AIMS OF THE STUDY

1) To develop alternative and more convenient approach for the synthesis of Fmoc-NHNH$(CH_2)_3$-NHC=N(Boc)NH(Boc) (aza-Arginine precursor).
2) To develop procedure and optimize conditions for direct alkylation of alcoxycarbonyl-protected hydrazines with halogenomethylarenes in order to prepare aza-phenylalanine, aza-tyrosine and aza-tryptophan precursors in one step and to avoid precious metal catalyzed hydrogenation of corresponding hydrazones.
3) To prepare previously unknown Fmoc- and Boc-protected aza-Methionine precursors from commercially available 2-methylthioacetaldehyde dimethylacetal.
4) To study scope and limitations of the one-pot synthesis of alcoxycarbonyl-protected monoalkylhydrazines from acetals and ketals.
5) To develop procedure for effective reacting of protected hydrazines with alkylhalogenides with rather low reactivity (ex. Alkyl chlorides).
6) To broaden applicability of the one-pot synthesis of protected monoalkylhydrazines from acetals to the synthesis of protected benzylhydrazines without catalytic hydrogenation of hydrazones at elevated pressure.

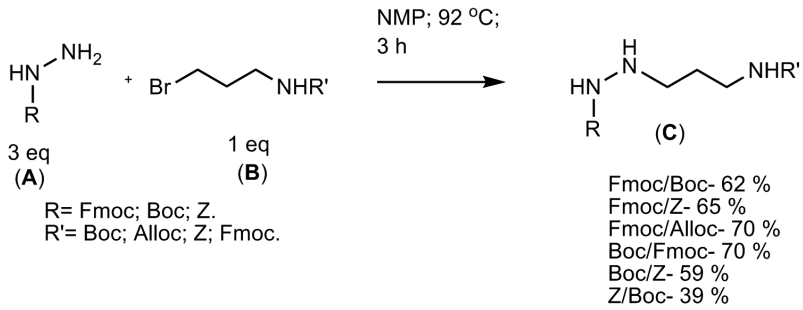
4. RESULTS AND DISCUSSION

4.1. Synthesis of aza-amino acid precursors via alkylation of protected hydrazines

Arginine is structurally and functionally very important amino acid and therefore its replacement with aza-analoge in peptides and proteins is an interesting challenge. However, two approaches reported in literature did not solve the problems with synthesis of corresponding aza-arginine precursor. In the first study attempt was made to introduce aza-arginine via introduction of aza-ornithine into the peptide sequence, deprotection of its side chain and guanidilation of the primary NH_2-group with *N*,*N*'-bis-Boc-1-guanylpyrazole. [28] Secondly, synthesis of Fmoc-aza-Arg(Boc) precursor was accomplished by reductive alkylation of Fmoc-$NHNH_2$ with 3-(di-Boc)guanidylpropanal. The required aldehyde was obtained by oxidation of 3-(di-Boc)guanidylpropanol with Dess-Martin reagent. Another approach included conversion of 3-(di-Boc)guanidylpropanoic acid to Weinreb amide and reduction of the latter compound by $LiAlH_4$. Attempts to hydrolize 3-(di-Boc)guanidylpropanal diethyl acetal in aqueous AcOH were completely unsuccessful (see **Scheme 53**). [116]

Due to these difficulties a simple and convenient synthesis of Fmoc-Arg$(Boc)_2$ precursor via direct alkylation of protected hydrazine was worked out as the first task of the present study. For this synthesis, 3-bromopropylamine was protected with Boc group and the obtained halogenide ((**B**), **Scheme 57**) was used for alkylation of protected hydrazines ((**A**), **Scheme 57**). Alkylation reaction was performed in NMP as in DMF formation of formylated side product RNHNHCOH took place. Also, 3 fold excess of monoprotected hydrazine was used to suppress formation of the dialkylated products. Indeed, if 3-fold excess of monoprotected hydrazine (**A**) was used, yields of monoalkylated hydrazines ((**C**), **Scheme 57**) were around 60–70 % (**Scheme 57**). At the same time, if equimolar amounts of bromide (**B**) and protected hyrazine (**A**) were used, yield of the monoalkylated product (**C**) did not exceed 35 %.

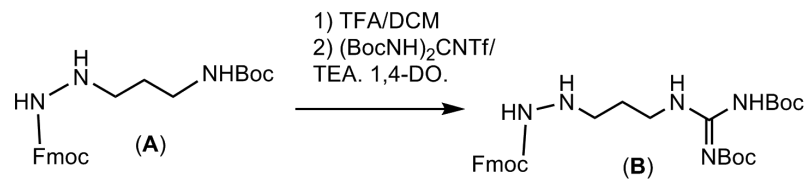
Further, different orthogonal combinations of protecting groups were studied in order to reveal the influence of hydrazine (**A**) and halogenide (**B**) protecting groups. Alkylation was performed in NMP and 3-fold excess of the protected hydrazine was taken. As a result, yields of the obtained monoalkylhydrazines (**C**) revealed no significant effects on the alkylation reaction. The average yields of the products (**C**) layed between 59–70 %. The only exception was observed in the case of alkylation of Z-$NHNH_2$ by N-Boc-3-bromopropylamine. The alkylation of protected hydrazines with different bromides is summarized on **Scheme 57**.



Scheme 57. Alkylation of carbazates with N-protected 3-bromopropylamine.

Most of the obtained orthogonally protected alkylhydrazines can be used for synthesis of aza-peptides. However, due to the selected Fmoc-strategy of peptide synthesis, the Fmoc-aza-Orn(Boc) precursor was modified further in order to prepare Fmoc-aza-Arg(Boc)$_2$ precursor.

This synthesis has 2 steps. At first, side chain of Fmoc-aza-Orn(Boc) precursor ((**A**), **Scheme 58**) was deprotected by treatment with TFA in DCM (2:1 mixture). Further, the obtained Fmoc-aza-Orn precursor was guanidilated by reacting with N',N'-di-Boc-N''-Tf-guanidine in 1,4-DO in the presence 3 eq of TEA as shown on **Scheme 58**. Yield of the Fmoc-aza-Arg(Boc)$_2$ ((**B**), **Scheme 58**) precursor was 66 %. [121]



Scheme 58. Modification of Fmoc-aza-Orn side chain.

The synthetic pathway described above is shorter, allows to avoid condensation and reduction steps, does not require relatively expensive oxidizing reagents or multi step synthesis of 3-(di-Boc)guanidylpropanal via Weinreb amide. A detailed information about the syntheses can be found in **Paper 1**.

As the results of aza-arginine synthesis via alkylation of protected hydrazine were positive, we were encouraged to broaden the applicability of direct alkylation of protected hydrazines to the synthesis of aza-Phe, aza-Tyr and aza-Trp precursors, which were previously obtained by precious metal catalyzed hydrogenation of corresponding hydrazones of benzaldehyde, O-protected 4-hydroxybenzaldehyde and N-protected indole-3-aldehyde. [28; 109; 111; 118; 81; 97]. Therefore it was decided to synthesise the aforementioned precursors

via direct alkylation of protected hydrazines. Due to limited amount of information about direct alkylation of monoprotected hydrazines, this reaction required detailed optimisation. To accomplish the task a systematic study of benzylation of different carbazates (Fmoc-, Boc-, and Z-$NHNH_2$) with different benzylhalogenides (chloride, bromide and iodide) was performed. Effects of different solvents, conditions and types of the applied bases were also studied and described in **Table 1** and **Table 2**.

Table 1. Benzylation of Fmoc-$NHNH_2$.

Experimental conditions:	**Monoalkylated hydrazine yield:**
3 eq of Fmoc$NHNH_2$; 0.6 M DMF solution; 1 eq of Bn-Br; 70 ^oC; 12 h	46 %
2 eq of Fmoc$NHNH_2$; 0.6 M DMF solution; 1.5 eq of DiPEA; 1 eq of Bn-Br; 70 ^oC; 13 h	- (Fmoc removal occurred)
2 eq of Fmoc$NHNH_2$; 0.6 M DMF solution; 1 eq of Bn-Br; rt.; 11 h	26 % *
2 eq of Fmoc$NHNH_2$; 0.1 M DMF solution; 1 eq of benzyl bromide; rt.; 12 h	30 % **
3 eq of Fmoc$NHNH_2$; 0.1 M DMF solution; 1 eq of Bn-Br; 70 ^oC; 12 h	43 %
1.5 eq of Fmoc$NHNH_2$; 0.1 M ACN solution; 1 eq of Bn-Br; reflux 5 h	36 %
3 eq of Fmoc$NHNH_2$; 0.1 M ACN solution; 1 eq of Bn-Br; reflux; 11 h	45 % ***
2 eq of Fmoc$NHNH_2$; 0.1 M CH_3OH solution; 1 eq of Bn-Br; reflux 3 h; 12 h at rt.	21 %
3.5 eq of Fmoc$NHNH_2$; 0.1 M CH_3OH solution; 1 eq of Bn-Cl; reflux 4 h	14 %
4 eq of Fmoc$NHNH_2$; 0.1 M EtOH solution; 1 eq of Bn-Br; reflux 11 h.	61 %
3 eq of Fmoc-$NHNH_2$; 0.1 M ACN solution; 1 eq of 2,4,6-trimethylpyridine; 1 eq Bn-Br; 6 h reflux	68 %
4 eq of Fmoc-$NHNH_2$; 0.1 M ACN solution; 1 eq of 2,4,6-trimethylpyridine; 1 eq of Bn-I; reflux 12 h	74 %

*- dibenzylated product obtained in 64 % yield.
**- dibenzylated product obtained in 36 % yield.
***- dibenzylated product obtained in 40 % yield

Table 2. Benzylation of Boc-$NHNH_2$ and Z-$NHNH_2$.

Experimental conditions:	**Monoalkylated hydrazine yield (%):**
1 eq of $BocNHNH_2$; 1 eq of Bn-Br; 0.75 M ACN solution; reflux 4 h.	13 %
2 eq of $BocNHNH_2$; 1 eq of Bn-Br; 0.75 M NMP solution; overnight at rt.	14 %
3.4 eq of $BocNHNH_2$; 1 eq of Bn-Br; 2.3 M DMF solution; 70 ^oC; 5 h.	63 %
3 eq of $BocNHNH_2$; 1 eq of Bn-Br; 0.1 M DMF solution; 70 ^oC; 11 h.	70 %
3 eq of $BocNHNH_2$; 1 eq of Bn-Br; 0.1 M CH_3OH solution; reflux 5 h.	11 %
4 eq of $BocNHNH_2$; 1 eq of Bn-Br; 0.1 M EtOH solution; reflux 6 h.	57 %
4 eq of $BocNHNH_2$; 1 eq of Bn-I; 0.1 M ACN solution; 1.3 eq of 2,4,6-trimethylpyridine; reflux 13 h.	75 %
4 eq of $BocNHNH_2$; 1 eq of Bn-Br; 0.1 M ACN solution; 1.3 eq of 2,4,6-trimethylpyridine; reflux 11 h.	79 %
3 eq of $ZNHNH_2$; 1 eq of Bn-Br; 0.1 M ACN solution; reflux 6 h.	64 %

As can be seen in **Table 1** and **Table 2**, if equimolar mixture of protected hydrazine and benzyl halogenide or 2 fold excess of protected hydrazine is alkylated with benzyl halogenide, relatively poor yields of monoalkylated hydrazine are obtained and dialkylated hydrazine is obtained as a main product.

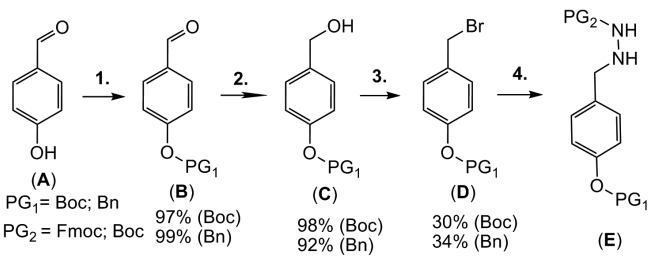
This is explained by the fact that alkyl group increases the nucleophilicity of already alkylated product and second alkylation proceeds at the same N-atom, as was described in **2.2.1**. Due to this obstacle, at least 3-fold excess of hydrazine was used in the following experiments. Additionally, it was noticed that application of the suitable weak base helps to increase the yield of the monoalkylated product. It is important to emphasize that type of the suitable base strongly depends on the properties of the hydrazine protecting group. For example, weakly nucleophilic amines such as TEA or DiPEA can be effectively used in combination with Boc- or Z-protecting group even at elevated temperatures. At the same time, attempts to benzylate Fmoc-$NHNH_2$ at 70 ^oC in the presence of 1.5 eq of DiPEA resulted in complete scission of the Fmoc-group.

In several papers about hydrazine alkylation it was mentioned that performing this reaction in alcohol helps to suppress excessive dialkylation of hydrazine. [53, 62] In the present work 3 fold excess of Fmoc-$NHNH_2$ and 4-fold excess of Boc-$NHNH_2$ was alkylated with Bn-Br in refluxing EtOH. As a result, Fmoc-NHNH-Bn was isolated in 61 % and Boc-NHNH-Bn in 57 % yield. Attempts to alkylate 3 eq of Boc-$NHNH_2$ and 2 eq of Fmoc-$NHNH_2$with Bn-Br in refluxing CH_3OH gave monoalkylated products with relatively poor yields: Boc-NHNH-Bn was isolated in 11 % yield and Fmoc-NHNH-Bn in 21 % yield.

Attempts to alkylate Fmoc-$NHNH_2$ with benzyl chloride in refluxing methanol gave the monoalkylated product in 14 % yield. At the same time, alkylation

of Fmoc-, and Boc-$NHNH_2$ with 4-fold excess of Bn-I in ACN gave almost the same yields of monobenzylated products in 74 % (Boc-NHNH-Bn) and 75 % (Fmoc-NHNH-Bn) yields.

In general, the best yields were obtained in ACN as a solvent (0.1 M solution of starting hydrazine) using Bn-Br and Bn-I as alkylating reagents in the presence of 1–1.3 eq of 2,4,6-trimethylpyridine. The optimized conditions were applied for synthesis of aza-Tyr and aza-Trp precursors. The required bromides were prepared from corresponding O-, and N-protected 4-hydroxybenzaldehyde ((**B**), **Scheme 59**) and indole-3-aldehyde by reduction of aldehydes to alcohols (ex. (**C**), **Scheme 59**), followed by bromination with PBr_3 in DCM. It is important to mention that 1-(tert-Butyloxycarbonyloxy)-4-(bromomethyl)benzene and 1-(benzyloxy)-4-(bromomethyl)benzene ((**D**), **Scheme 59**) decomposed during storage at low temperatures and should be consumed after their preparation. Yields of the protected monoalkylhydrazines ((**E**), **Scheme 59**) were in the range of 36–61 %. The synthesis can be illustrated by preparation of the protected aza-Tyr precursors as shown on **Scheme 59**.



Reaction conditions: **1.** 1.05 eq of Boc_2O, 0.1 eq of DMAP; Or 1.1 eq of BnBr, 3 eq of DiPEA, ACN reflux; **2.** 1 eq of $NaBH_4$, CH_3OH, 0 °C, 2 h; **3.** 0.77 eq of PBr_3, 1 eq of TEA, dry DCM, 0 °C, 2 h; **4.** 3 eq of PG-$NHNH_2$, 1 eq of 2,4,6-trimethylpyridine, 0.1 M ACN sol-on, reflux.

Scheme 59. Synthesis of N-(Fmoc/Boc) aza-Tyr-O(Boc/Bn) precursors.

Synthesis of Fmoc/Boc-aza-Trp(Z) precursor started from formylation of indole by Vilsmeyer reagent ($POCl_3$/DMF), followed by protection of NH group with Z protecting group. Subsequent reduction was accomplished by $NaBH_4$ in methanol followed by conversion of alcohol to bromide by PBr_3 in DCM in the presence of TEA and $NaHCO_3$. The obtained bromide was used for alkylation of Fmoc-$NHNH_2$ and Boc-$NHNH_2$. Monoalkylated products were obtained in 43 % (alkylation of Fmoc-$NHNH_2$) and in 56 % (alkylation of Boc-$NHNH_2$) yield.

An alternative synthesis of 1-(tert-Butyloxycarbonyloxy)-4-(bromomethyl)benzene and N-Boc-3-(bromomethyl)indole via free radical bromination of 1-(tert-Butyloxycarbonyloxy)-4-methylbenzene and N-Boc-3-methylindole using NBS/AIBN in refluxing CCl_4, [122] was not successful. For example, attempt to brominate methyl group of the N-Boc-3-methylindole resulted in complete degradation of the reaction mixture. A more detailed information as well as spectral and analytical data can be found in **Paper 3**.

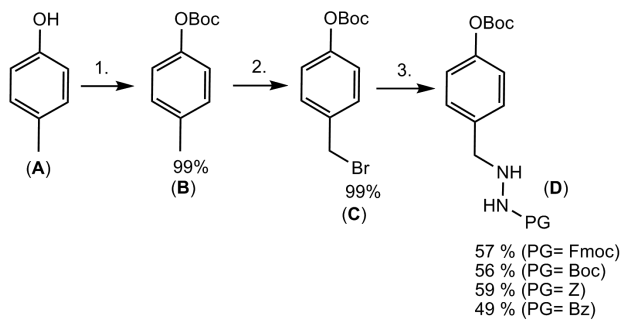
Summing up, the optimal conditions for alkylation of monoprotected hydrazines with benzylic halogenides were found and the developed method was successfully applied for synthesis of different aza-amino acid precursors.

4.2. Potassium iodide catalysis in alkylation of protected hydrazines

It was found in our previous studies that application of benzyl chloride gave one of the poorest yields of monobenzylated hydrazine. At the same time, the best yields of protected monoalkylhydrazines were obtained if benzyl bromide and benzyl iodide were used as alkylating reagents. Application of alkyl iodides is often limited by their instability, these compounds tend to decompose during prolonged storage and, finally, iodides are not readily commercially available.

Due to this obstacles possibility of *in situ* generation of alkyl iodides from less reactive alkyl halogenides was studied, using readily available inorganic iodides such as NaI or KI. Inorganic iodide catalysis was previously applied for the synthesis of different organic compounds, [123–124] but there is no information about applicability of inorganic iodides for alkylation of protected hydrazines.

It was found in the present study that addition of a catalytic amount of KI (0.1 eq) to the reaction mixture containing monoprotected hydrazine, halogenide (chloride or bromide), suitable base and ACN as a solvent, greatly improved the alkylation of protected hydrazines. At first, KI catalysis was applied for alkylation of Fmoc-, Boc-, Z-, and Bz-protected hydrazines with 1-(tert-Butyloxycarbonyloxy)-4-(bromomethyl)benzene ((**C**), **Scheme 60**) prepared via radical BzOOBz initated bromination of 1-(tert-Butyloxycarbonyloxy)-4-(methyl)benzene ((**B**), **Scheme 60**). The obtained bromide was applied for alkylation of the hydrazines and the yields of monoalkylated products ((**D**), **Scheme 60**) were 49–59 %.



Reaction conditions: **1.** 1.05 eq Boc_2O, $CHCl_3$, 0.05 eq DMAP; **2.** CCl_4, 1.05 eq of NBS, 0.016 eq BzOOBz, reflux; **3.** 3 eq of $PGNHNH_2$, 0.1 M solution in ACN, 0.1 eq of KI, 1.5 eq of DiPEA or 2,4,6-trimethylpyridine, reflux.

Scheme 60. Aza-Tyr precursors from p-cresole.

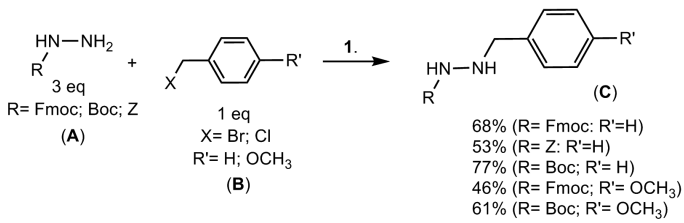
Further, the KI catalysis was applied for preparation of different alkylhydrazines. Namely, alkylation of Fmoc-, Boc-, and Z-$NHNH_2$ ((**A**), **Scheme 61**) was studied using Bn-Cl, Bn-Br, 4-methoxybenzyl chloride, methyl bromoacetate, tert-Butyl bromoacetate and ethyl chloroacetate as alkylating reagents. At first, benzylation of hydrazines was studied using 3 benzyl halogenide ((**B**), **Scheme 61**) and the results of the experiments clearly proved that application of KI allows to react protected hydrazines (**A**) with halogenides of rather low reactivity (such as chlorides) and nearly equal yields are obtained in the experiments with Bn-Br and Bn-Cl (**B**) after 5 hour long refluxing. However, in the case of alkylation of protected hydrazines (**A**) with Bn-Cl (**B**) in the abscence of KI only traces of monoalkylhydrazines ((**C**), **Scheme 61**) were obtained after 6 hour long refluxing and 21–55 % of the monoalkylated product (**C**) after 24 hours of refluxing (**Table 3**; **Scheme 61**).

The same trend was observed in the case of alkylation with 4-methoxybenzyl chloride (**B**) (**Table 3**; **Scheme 61**). The desired 4-methoxybenzyl hydrazines (**C**) were obtained in 46 % yield (alkylation of Fmoc-$NHNH_2$) and 61 % (alkylation of Boc-$NHNH_2$). Attempts to perform the same reactions without KI gave only 13–27 % of monoalkylated hydrazines after 24 hours of refluxing.

Table 3. KI catalyzed benzylation vs. non-catalyzed benzylation of protected hydrazines.

Reaction conditions:	**Yield of monoalkylated hydrazine (%):**
3 eq of Fmoc-$NHNH_2$, 1.5 eq of 2,4,6-trimethylpyridine, 1 eq of Bn-Br, 0.1 eq of KI, 0.1 M solution in ACN, reflux 5 h.	68 %
3 eq of Boc-$NHNH_2$, 1.5 eq of 2,4,6-trimethylpyridine, 1 eq of Bn-Br, 0.1 eq of KI, 0.1 M solution in ACN, reflux 5 h.	71 %
3 eq of Boc-$NHNH_2$, 1.5 eq of 2,4,6-trimethylpyridine, 1 eq of Bn-Cl, 0.1 eq of KI, 0.1 M solution in ACN, reflux 5 h.	77 %
3 eq of Fmoc-$NHNH_2$, 1.5 eq of 2,4,6-trimethylpyridine, 1 eq of Bn-Cl, 0.1 eq of KI, 0.1 M solution in ACN, reflux 6 h.	49 %
3 eq of Z-$NHNH_2$, 1.5 eq of DiPEA, 1 eq of Bn-Cl, 0.1 eq of KI, 0.1 M solution in ACN, reflux 6h.	53 %
3 eq of Boc-$NHNH_2$, 1.5 eq of DiPEA, 1 eq of Bn-Cl, 0.1 eq of KI, 0.1 M solution in ACN, reflux 6h.	65 %
3 eq of Boc-$NHNH_2$, 1.5 eq of DiPEA, 1 eq of Bn-Cl, 0.1 M solution in ACN, reflux 24 h.	55 %
3 eq of Fmoc-$NHNH_2$, 1.5 eq of 2,4,6-trimethylpyridine, 1 eq of Bn-Cl, 0.1 M solution in ACN, reflux 24 h.	22 %
3 eq of Z-$NHNH_2$, 1.5 eq of DiPEA, 1 eq of Bn-Cl, 0.1 M solution in ACN, reflux 24 h.	21 %
3 eq of Boc-$NHNH_2$, 1.5 eq of DiPEA, 1 eq of 4-methoxybenzyl chloride, 0.1 M solution in ACN, 0.1 eq of KI, reflux 6 h.	61 %

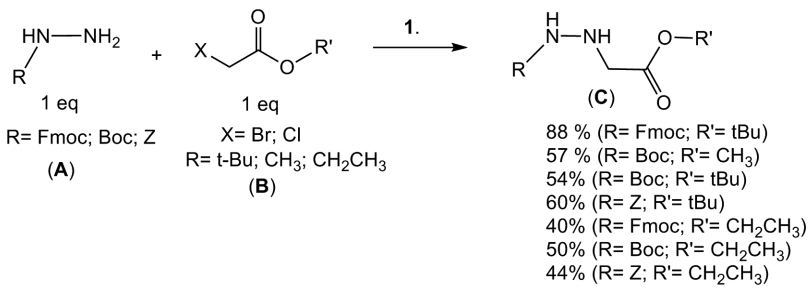
Reaction conditions:	Yield of monoalkylated hydrazine (%):
3 eq of Z-$NHNH_2$, 1.5 eq of DiPEA,1 eq of 4-methoxybenzyl chloride, 0.1 M solution in ACN, 0.1 eq of KI, reflux 6 h.	49 %
3 eq of Fmoc-$NHNH_2$, 1.5 eq of 2,4,6-trimethylpyridine, 1 eq of 4-methoxybenzyl chloride, 0.1 M solution in ACN, 0.1 eq of KI, reflux 6 h.	46 %
3 eq of Boc-$NHNH_2$, 1.5 eq of DiPEA, 1 eq of 4-methoxybenzyl chloride, 0.1 M solution in ACN, reflux 24 h.	27 %
3 eq of Z-$NHNH_2$, 1.5 eq of DiPEA,1 eq of 4-methoxybenzyl chloride, 0.1 M solution in ACN, reflux 24 h.	18 %
3 eq of Fmoc-$NHNH_2$, 1.5 eq of 2,4,6-trimethylpyridine, 1 eq of 4-methoxybenzyl chloride, 0.1 M solution in ACN, reflux 24 h.	13 %



1. 0.1 M ACN sol-n, 1.5 eq of 2,4,6-trimethylpyridine (for Fmoc) or DiPEA (for Boc or Z), 0.1 eq KI, 1 eq of halogenide, reflux.

Scheme 61. KI catalyzed benzylation of protected hydrazines.

In the following experiments the effect of KI catalysis on alkylation of protected hydrazines with halogenoacetic acid esters was studied. In these experiments equimolar mixture of protected hydrazine ((**A**), **Scheme 62**) and halogenoacetic acid ester ((**B**), **Scheme 62**) was refluxed in the presence of 0.1 eq of KI and 1.5 eq of suitable base (DiPEA or 2,4,6-trimethylpyridine). The yields of monoalkylated products ((**C**), **Scheme 62**) were 54–88 % (alkylation by methyl and t-Butyl bromoacetate). At the same time, application of ethyl chloroacetate gave 40–50 % of monoalkylated hydrazines after 24 hour refluxing in the presence of 0.1 eq of KI (**Scheme 62**). Control experiments with ethyl chloroacetate in the same conditions without KI afforded only 15–20 % of monoalkylated product after 24 hour long refluxing.



1. 0.1 M ACN sol-n, 1.5 eq 2,4,6-trimethylpyridine (for Fmoc) or DiPEA (for Boc or Z), 0.1 eq KI, 1 eq of halogenide, reflux.

Scheme 62. KI catalyzed synthesis of aza-Asp precursors.

In summary, the methods listed above allow to alkylate protected alkylhydrazines with reagents of relatively low reactivity (chlorides), to improve the reaction times and yields. Detailed descriptions of these synthetic procedures, as well as spectral and analytical data are given in **Paper 5**.

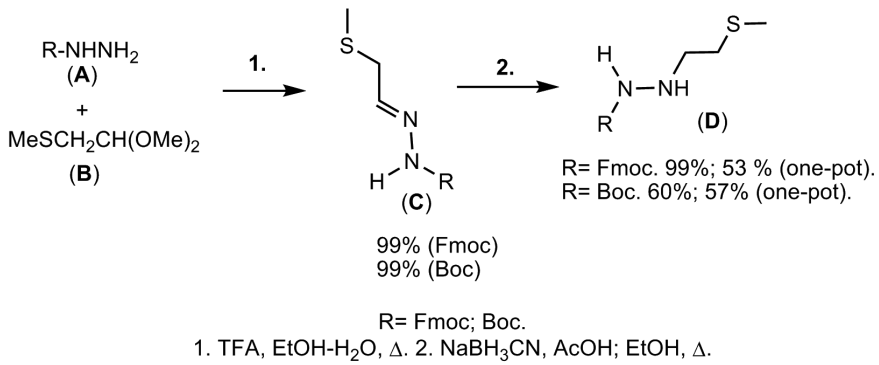
4.3. One-pot synthesis of protected alkylhydrazines from protected carbonyl compounds

The only attempt to obtain aza-methionine containing aza-dipeptide included reaction of Fmoc-Lys(Boc)-$CONHNH_2$ with 2-methylthioacetaldehyde, followed by reduction of the formed hydrazone. The desired 2-methylthioacetaldehyde was synthesized from commercially available 2-methylthioacetaldehyde dimethyl acetal by hydrolysis of the acetal group. [27] In general, presence of a nucleophilic groups or heteroatoms in the molecule of the carbonyl compound destabylize aldehyde or a ketone and makes it prone to undergo self-condensation. This problem can be solved by protection of the carbonyl group, which, in its turn, requires additional deprotection steps. For example, synthesis of Fmoc-aza-β^3-Arg$(Boc)_2$ precursor started from 3,3-diethoxypropylamine. The aminoacetal was Boc-protected and acetal group was hydrolyzed in AcOH/H_2O mixture (**Scheme 52**). [95]

To overcome additional hydrolysis step, a convenient one-pot synthesis of Fmoc-, and Boc-protected aza-methionine precursors was developed. This approach allowed to effeciently condensate protected hydrazines ((**A**), **Scheme 63**) with 2-methylthioacetaldehyde dimethyl acetal ((**B**), **Scheme 63**) without separate preparation of the appropriate aldehyde. Condensation reaction was conducted in refluxing ethahol, containing 10 % of water, equimolar amounts of protected hydrazine and acetal and 0.05–0.13 eq of TFA. The amount of the applied TFA strongly depends on the properties of the protecting group. Thus, 0.05 eq of TFA was used in the experiments with Boc-$NHNH_2$ and in the case of acid stable Fmoc-$NHNH_2$ significantly larger amounts of TFA (0.13 eq) can

be applied. The resulted hydrazones ((**C**), **Scheme 63**) were isolated in nearly quantitive yields by simple evaporation of the reaction mixture and this procedure could be applied for preparation of different hydrazones from protected carbonyl compounds.

The desire to skip separation of the hydrazone and solvent exchange resulted in transformation of the condensation with acetal into a one-pot synthesis. According to the modified procedure, reduction step was carried out by addition of $NaBH_3CN$ and AcOH to the reaction mixture at room temperature. After completion of the reduction reaction, the neutralized reaction mixture was heated to reflux in order to decompose the boron adduct (**Scheme 63**). [125] The yield of Fmoc-, and Boc-protected aza-Methionine precursors ((**D**), **Scheme 63**) was good (Boc-protected precursor) and quantitative (Fmoc-protected precursor).

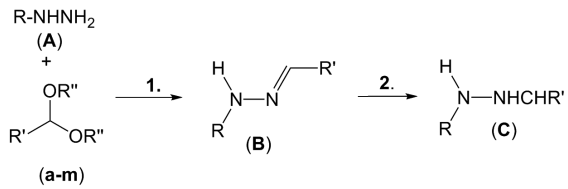


Scheme 63. Synthesis of Fmoc/Boc-aza-methionine precursors from 2-methylthioacetaldehyde dimethyl acetal.

It is important to mention that in the case of 2 step synthesis of Fmoc-aza-Met precursor condensation and subsequent reduction proceeded with almost quantitative yields. At the same time, one-pot syntesis of the same precursor gave corresponding hydrazine with almost 2 times lower yield. This could be caused by low solubility of Fmoc-protected hydrazone (**C**) in ethanolic reaction mixture or by partial Fmoc scission during refluxing of the reaction mixture containing $NaHCO_3$ residues. The detailed procedures for preparation of 2-methylthioacetaldehyde N-protected hydrazones (**C**) and N-protected N'-(2-methylthio)ethylhydrazines (**D**) together with spectral and analytical data can be found in **Paper 2**.

The one-pot synthetic method described above turned out to be very promising and was explored in the following study about the scope and limitations of the one-pot synthesis (**Paper 4**). For this purpose a set of aza-amino acid precursors and related compounds carrying Fmoc and Z protecting groups ((**C**), **Scheme 64**) was prepared. Acetals and ketals carrying sulfide, ether, nitrile, carbamate, amide and branched, cyclic and unbranched alkyl groups were used

as electrophilic compounds ((**a-m**); **Table 4**; **Scheme 64**). Condensation was carried out in ethanol containing 90 % of water and in the presence of 0.05 eq of TFA. The obtained hydrazones ((**B**), **Scheme 64**) were reduced by $NaBH_3CN$ in the presence of equimolar amount of AcOH. During the present study was found that neutralisation of the reaction mixture with $NaHCO_3$ (**Paper 2**) is not necessary. Also, basic conditions, caused by decomposition of the $NaHCO_3$ to more basic Na_2CO_3 could easily cleave the base-sensitive Fmoc groups. Additionally, decomposition of the formed boron adduct, [125] by simple refluxing of the reaction mixture proceeded very slowly in several cases. Decomposition of the boron adducts by treatment of the reaction mixture with 1.5 % HCl was found to be very effective and can be used in combination with all the acid-stable groups. However, previously reported refluxing of the reaction mixture should be exploited in the case of acid-labile groups such as Boc.



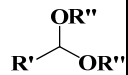
R = Fmoc; Cbz., R' = $-CH_2SCH_3$; $-(CH_2)_2CN$; $-(CH_2)_2Cl$; $-CH_2OBn$; $-CH_2NHCH_3$; $-CH_2NH_2$; $-CH_2NHCbz$; $-CH_3$; $-CH_2NHBz$; $-CH_2NHBoc$; $-CH{=}CH_2$; $-(CH_3)_2$; $-(CH_2)_5-$., R'' = $-CH_3$; $-CH_2CH_3$.

1. TFA, EtOH - H_2O, Δ. **2.** 1. $NaBH_3CN$, AcOH, EtOH-H_2O, Δ.

Scheme 64. One-pot synthesis of protected hydrazines.

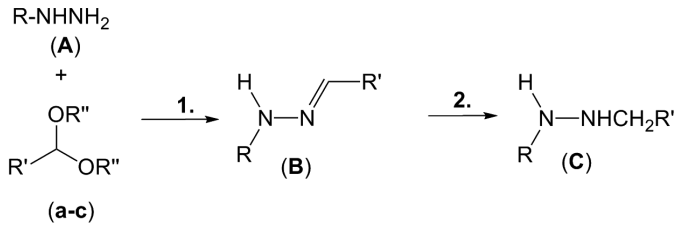
It was found that this method works perfectly in combination with protected carbonyl compounds containing sulfide, ether, nitrile, carbamate, amide as well as branched and cyclic alkyl groups (acetals **a**, **b**, **d**, **g**, **h**, **i**, **l**, **m**) (**Table 4**). Yields of the protected monoalkylhydrazines ((**C**), **Scheme 64**) were 62–98 % (**Table 4**). However, several limitations of the procedure were also revealed. Namely, the procedure was not efficient in combination of primary and secondary amino groups (acetals **e** and **f**) or Boc-protected amino group (acetal **j**) and unsaturated bonds (acetal **k**) were involved (**Table 4**). Additionally, acetaldehyde hydrazones, generated from acetal (**h**) tended to decompose back to starting materials if reduction was carried out in the protic media. Yield of the protected hydrazines did not exceed 20 % and THF was found to be the most preferable solvent for reduction of these hydrazones. At the same time, reduction of hydrazones with branched or cyclic alkyl groups afforded good yields of hydrazines in ethanol (**Table 4**). Some more detailed information about this study can be found in **Paper 4**.

Table 4. One-pot synthesis of protected hydrazines from acetals and ketals.

	R’	R’’	R-NHNH$_2$	
			R = Fmoc	R = Cbz
a	-CH_2SCH_3	-CH_3	Yield: 98%	Yield: 67%
b	-$(CH_2)_2CN$	-CH_3	Yield: 62%	Yield: 76%
c	-$(CH_2)_2Cl$	-CH_2CH_3	a)	a)
d	-CH_2OBn	-CH_2CH_3	Yield 67%	Yield 65%
e	-CH_2NHCH_3	-CH_3	(Fmoc scission)	(No reaction)
f	-CH_2NH_2	-CH_3	(Fmoc scission)	(No reaction)
g	-CH_2NHCbz	-CH_3	Yield 70%	Yield: 63%
h	-CH_3	-CH_2CH_3	Yield 74% in THF.<20%in EtOH	Yield 66 % in THF.<20%in EtOH
i	-CH_2NHBz	-CH_3	Yield: 86%	Yield: 80%
j	-CH_2NHBoc	-CH_3	b)	b)
k	-CH=CH_2	-CH_2CH_3	c)	c)
l	-$(CH_3)_2$	-CH_3	Yield: 77%	Yield: 64%
m	-$(CH_2)_5$-	-CH_3	Yield: 72%	Yield: 87%

a) Formation of alkylated products and subsequent decomposition of the reaction mixture.
b) Only trace amounts of the hydrazone were detected, as *Boc* removal by TFA occurred.
c) Only trace amounts of the hydrazone were formed.

The encouragemet from the excellent results of the one-pot synthesis of protected hydrazines (**Paper 2** and **Paper 4**) and extensive research on the synthesis of protected benzylhydrazines described above and in **Paper 3** and **Paper 5** gave an idea to extend the one-pot synthesis to preparation of protected benzylhydrazines. In this study (**Paper 6**) a set of 5 hydrazines, monosubstituted with Fmoc, Z, Bz, 3-NO_2-Bz-, and 3,4-$(OCH_3)_2$Bz groups ((**A**), **Scheme 65**) was reacted with benzaldehyde dimethyl acetal and 2-bromo- and 3-bromobenzaldehyde diethyl acetals ((**a-c**), **Table 5** and **Scheme 65**). The condensation step was carried out in 90 % EtOH, as was initially reported in **Paper 2**. However, in this study the previosly exploited volatile TFA (one-pot syntheses described in **Paper 2** and **Paper 4**) was replaced with TsOH. Application of a solid and strong TsOH allowed to overcome difficult dosing of the small amounts of a volatile TFA.



R = Fmoc; Cbz; Bz; 3-NO_2Bz; 3,4-$(OCH_3)_2$Bz; R' = Ph; 2-BrPh; 3-BrPh; R" = -CH_3; -CH_2CH_3;
1. TsOH, EtOH - H_2O, Δ. **2.** 1. BH_3-THF, THF, rt., 2. EtOH-THF, Δ.

Scheme 65. One-pot synthesis of protected benzylhydrazines from acetals.

Table 5. One-pot synthesis of protected benzylhydrazines from acetals.

OR" / R' / OR"	R'	R''	RNHNH$_2$				
			R = Fmoc	R = Cbz	R = Bz	R = 3-NO_2Bz	3,4-$(OCH_3)_2$Bz
a	Ph	-CH_3	92 %	65 %	93 %	61 %	92 %
b	2-BrPh	-CH_2CH_3	78 %	71 %	79 %	79 %	73 %
c	3-BrPh	-CH_2CH_3	56 %	51 %	74 %	91 %	90 %

Due to the conjugated nature of the obtained hydrazones ((**B**), **Scheme 65**), BH_3-THF complex was used in the reduction step. This modification required a solvent exchange to THF as BH_3-THF complex rapidly decomposes in ethanol and other protic medias. The yields of the obtained alcoxycarbonyl- and acyl substituted benzylhydrazines ((**C**), **Scheme 65**) were good to excellent (**Table 5**). The developed method allows to effeciently synthesize hydrazones from benzaldehyde acetals, protected hydrazines and carboxylic acid hydrazides. Also, the reported procedure allowed to effeciently reduce the obtained conjugated hydrazones without the need for precious metal catalyzed hyrogenation. Detailed synthetic procedure and all the spectral data can be found in **Paper 6**.

4.4. Synthesis of aza-amino acid precursors

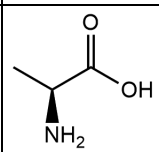
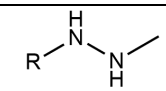
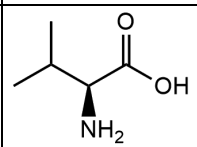
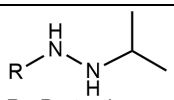
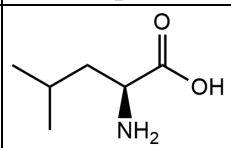
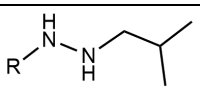
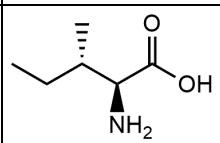
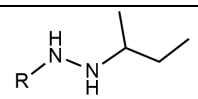
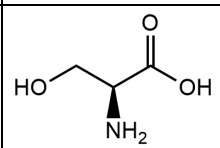
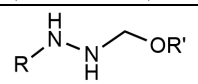
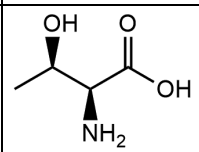
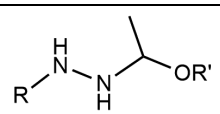
In the overview of synthetic methods for preparation of alkylhydrazines given in **II**, the most common and general synthetic approaches to the protected monoalkylhydrazines (aza-amino acid precursors) were briefly bescribed. In this part a systematic overview of the aza-amino acid precursors including the latest methods and procedures developed during the current research (**Paper 1** – **Paper 6**) will be given. Due to a great amount of the possible protecting groups

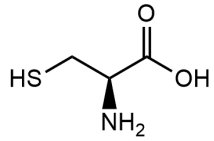
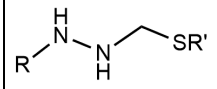
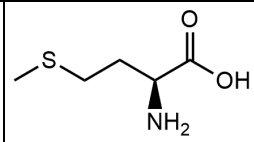
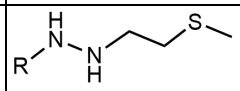
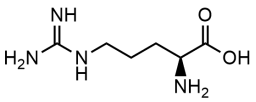
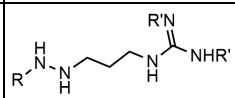
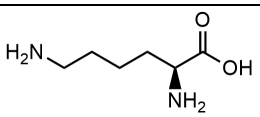
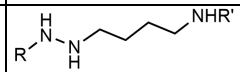
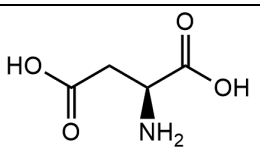
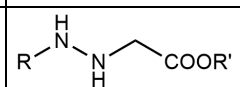
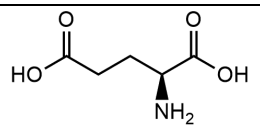
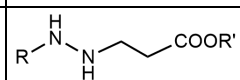
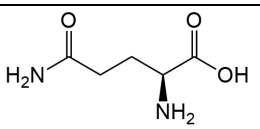
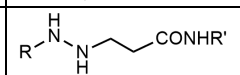
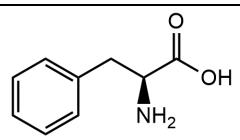
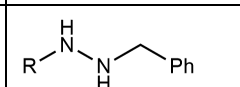
for hydrazine moiety, it is almost impossible to cover synthesis of all the types of monoalkylhydrazines and references to synthesis of the most valuable Fmoc-, Boc-, and in smaller extent Z-, and Ddz-protected monoalkylhydrazines will be given.

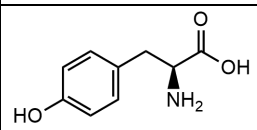
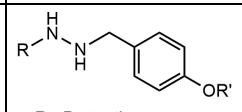
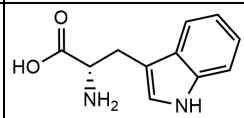
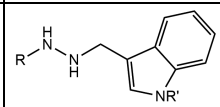
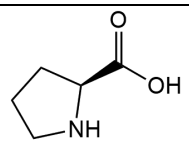
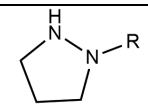
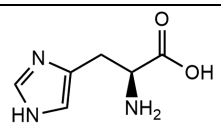
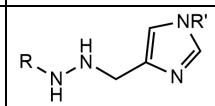
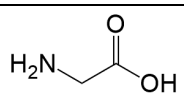
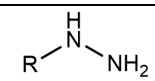
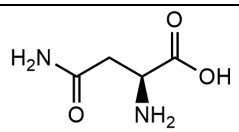
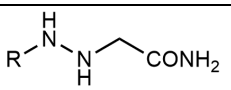
As it was mentioned and described previously, synthesis of these compounds usually utilizes reductive alkylation and in significantly lower extent the direct alkylation of monoprotected hydrazines with alkylhalogenides or related electrophilic compounds (ex. Michael acceptors).

Structures of a native amino acid, corresponding aza-amino acid precursor and references to synthetic procedures are given in the **Table 6**.

Table 6. Structures of DNA encoded amino acids, corresponding α-aza-amino acid precursors and references to synthesis of different precursors.

Amino acid	**α-Amino acid structure**	**α-Aza-amino acid precursor**	**References**
Alanine		 R= Protecting group, (ex. Fmoc; Boc)	1)[28; 95], R= Fmoc; 2)[84; 109; 126], R=Boc.
Valine		 R= Protecting group, (ex. Fmoc; Boc)	1)[28; 127; This work], R= Fmoc. 2)[109; 128; 129], R= Boc.
Leucine		 R= Protecting group, (ex. Fmoc; Boc)	1)[28], R= Fmoc. 2)[16; 113; 130, 131], R= Boc.
Isoleucine		 R= Protecting group, (ex. Fmoc; Boc)	1)[81; 129], R= Boc. 2)[97], R= Ddz.
Serine		 R= Protecting group, (ex. Fmoc; Boc); R'= tBu or Bn.	No precursor
Threonine		 R= Protecting group, (ex. Fmoc; Boc); R'= tBu or Bn.	No precursor

Amino acid	α-Amino acid structure	α-Aza-amino acid precursor	References
Cysteine		 R= Protecting group, (ex. Fmoc; Boc); R'= Trt.	No precursor
Methionine		 R= Protecting group, (ex. Fmoc; Boc).	1) [This work], R= Fmoc. 2) [This work], R= Boc. 2)[27]-introduction of Met side chain to Fmoc-Lys(Boc)-$CONHNH_2$.
Arginine		 R= Protecting group, (ex. Fmoc; Boc). R'= Boc or Z.	1)[116; This work], R= Fmoc; R'= Boc. 2)[28]- guanidilation of aza-Orn side chain on solid support. 3)[94], construction and guanidilation of aza-Orn side chain on solid support.
Lysine		 R= Protecting group, (ex. Fmoc; Boc). R'= Boc or Z.	1)[28], R= Fmoc; R'= Boc. 2)[94], construction and modification of aza-Lys side chain on solid support.
Aspartic acid		 R= protecting group;(ex.Fmoc; Boc). R'= tBu; Bn.	1)[28; 82; 127; This work], R= Fmoc; R'= tBu. 2)[98; This work], R= Boc; R'= tBu.
Glutamic acid		 R= protecting group;(ex.Fmoc; Boc). R'= tBu; Bn.	1)[99], R= Fmoc; R'= tBu. 2)[82], R= Boc; R'= CH_3.
Glutamine		 R= protecting group;(ex.Fmoc; Boc). R'= Trt; H.	1)[82; 132], R= Boc.
Phenyl-alanine		 R= protecting group (ex.Fmoc; Boc).	1)[28; 127; 133; This work], R= Fmoc. 2)[109; 111; 118; This work], R= Boc.

Amino acid	α-Amino acid structure	α-Aza-amino acid precursor	References
Tyrosine		 R= Protecting group, (ex. Fmoc; Boc). R'= $Si(CH_3)_2tBu$; tBu.	1)[28], R= Fmoc. R'= $Si(CH_3)_2tBu$. 2)[97], R= Ddz; R'= tBu. 3)[81], R= Boc; R'= tBu. 4) [This work], R= Fmoc; Boc; R'= tBu; Bn. 5) [This work], R= Fmoc; Boc; Z., R'= Boc.
Trypto-phan		 R= protecting group (ex. Fmoc, Boc). R'= Boc; Z.	1)[81], R= Boc. R'= H. 2)[28], R= Fmoc; R'=Boc. 3)[97], R= Ddz; R'= Boc. 4)[This work], R= Fmoc; Boc. R'=Z.
Proline		 R= protecting group (ex. Fmoc; Boc).	1)[81], R= Boc. 2)[82], R= Z. 3)[116], R= Fmoc.
Histidine		 R= protecting group (ex. Fmoc, Boc). R'= Trt, Boc.	No precursor
Glycine		 R= Protecting group, (ex. Fmoc; Boc or Z)	1)[28; 134], R= Fmoc. 2)[135–137], R= Boc. 3)[138–140], R= Z.
Asparagine		 R= protecting group, (ex.Fmoc; Boc).	1)[82], R= Boc. 2)[141], R= Z.

As it can be seem from the data in **Table 6**, major part (16 amino acids) have corresponding aza-precursors bearing different protecting groups making them suitable for different types of peptide synthesis. Most of them are synthesized via reductive alkylation of protected hydrazines. At the same time, several difficulties were encountered during the reductive alkylation of monoprotected hydrazines. For example, Fmoc-aza-Asp(tBu) precursor was synthesized via reductive alkylation with glyoxylic acid and subsequent esterification with $CCl_3C{=}NH(OtBu)$. Yield of the Fmoc-aza-Asp(otBu) precursor was only 20 %. [28] Additionally, synthesis of the Fmoc-aza-$Arg(Boc)_2$ precursor was complicated with difficult synthesis of aldehyde (**2.3.2**; **Scheme 53**). [116] Also,

direct alkylation with esters of halogenoacetic and propanoic acid were successfully applied for the synthesis of aza-Asp, [28; 82; 98; 127] and aza-Asn precursors. [82] Additionally, Fmoc-aza-Glu(tBu) precursor was prepared via alkylation of hydrazine with tert-Butyl acrylate (**2.2.2.4**; **Scheme 39**). [99]

At the same time, α-aza-Ser, Thr and Cys have aminal-like structure and are unstable. [28; 109] Additionally, there is no literature information about precursor of aza-His. Also, by the beginning of 2014 there was no information about aza-Methionine precursor and, as it was mentioned previously, syntheses of several aza-amino acid precursors required optimization and more convenient approaches.

All the new methods and alternative synthetic routes to previously reported compounds, as well as synthesis of previously unknown aza-Methionine precursors are referred as [**This work**] (**Table 6**).

5. CONCLUSIONS

Current thesis describes a new and convenient synthetic procedures for preparation of aza-amino acid precursors and structurally related alkylhydrazines. These compounds are required for preparation of aza-peptides and different biologically active compounds.

Firstly, an alternative and convenient synthesis of Fmoc-aza-Arg(Boc)$_2$ precursor via direct alkylation of monoprotected hydrazine was developed. Effects of hydrazine and 3-bromopropylamine protecting groups were studied as well as the most suitable ratio of the reagents was found for these reactions.

Secondly, conditions for benzylation of alcoxycarbonyl protected hydrazines were optimized in terms of the applicable solvents, bases, electrophilicity of the alkylating agents, and ratio of reagents in the reaction mixture. These optimal conditions were used for preparation of variously protected aza-Tyr and aza-Trp precursors.

Thirdly, potassium iodide (KI) catalyzed alkylation of the monoprotected hydrazines was developed. This method is based on *in situ* generation of reactive alkyl iodides from less reactive halogenides that improves the yields and shortens the reaction time. The method was successfully validated by synthesis of aza-Phe, aza-Asp and aza-Tyr precursors.

Fourthly, convenient and effective one-pot synthesis protocol for preparation of protected alkylhydrazines from acetals and ketals was developed and applied for preparation of Fmoc- and Boc-protected precursors of aza-methionine. Further it was shown that the one-pot method is compatible with the majority of functional groups such as ether, amide, sulfide, nitrile, carbamate and cyclic or branched alkyl groups, while attempts to condensate hydrazines with acetals and ketals containing halogenes, unsaturated double bonds, amino groups and acid-sensitive protecting groups were not effecient.

Finally, applicability of the one-pot method was extended for preparation of monoprotected benzylhydrazines. Due to conjugation of hydrazone double bond with aromatic ring, BH_3-THF complex was used in the reduction step of this synthesis.

REFERENCES

1. Hoffman, B. M., Lukoyanov, D., Zhi-Yong Yang, Z.-Y., Dean, D. R., Seefeldt, L. C., Mechanism of Nitrogen Fixation by Nitrogenase: The Next Stage*, Chem Rev*., 2014, 114, 8, 4041–4062.
2. Toth, B. Hepatocarcinogenesis by hydrazine mycotoxins of edible mushrooms, *J. Toxicol. Environ. Health.,* **1979**, 5, 2–3, 193–202.
3. Fischer, E. On aromatic hydrazine compounds, *Berichte der Deutschen chemischen Gesellschaft zu Berlin*, **1875**, 8, 589–594.
4. Curtius, T., On diamide (hydrazine), *Berichte der Deutschen chemischen Gesellschaft zu Berlin*, **1887**, 20, 1632–1634.
5. Lobry de Bruyn, C. A., On the hydrate of hydrazine, *Recueil des Travaux Chimiques des Pays-Bas*, **1895**, 14**,** 3, 85–88.
6. Brune, K. The early history of non-opioid analgesics, *Acute Pain*. **1997**, 1, 1, 33–40.
7. Brogden, R. N., Pyrazolone Derivatives, *Drugs*, **1986**, 32, 4, 60–70.
8. Knorr, L., Einwirkung von Acetessigester auf Phenylhydrazin, *Berichte der deutschen chemischen Gesellschaft* (in German), **1883**, 16, 2, 2597–2599.
9. Yáñez , M., Padín, J.F., Arranz-Tagarro, J. A., Camiña, M., Laguna, R. History and therapeutic use of MAO-A inhibitors: a historical perspective of mao-a inhibitors as antidepressant drug, *Curr Top Med Chem.*, **2012**, 12, 20, 2275–2282.
10. Steenken, W. J., Wolinsky, E., Antituberculous Properties of Hydrazines of Isonicotinic Acid (Rimifon, Marsilid), *American Review of Tuberculosis*, **1952**, 65, 4, 365–375.
11. Das, N. B., and Mittra, A. S., Heterocyclic fungicides. Part-III, *Journal of the Indian Chemical Society*, **1978**, 55, 8, 829–831.
12. Misra, P. K., Misra, S. C., Mohapatra, R. M., Mittra, A. S., Heterocyclic fungicides and insecticides, *Journal of the Indian Chemical Society*, **1979**, 56, 404–408.
13. Worthington, P. A., Synthesis and Fungicidal Activity of Triazole Tertiary Alcohols, *Synthesis and Chemistry of Agrochemicals*, **1987**, Ch. 27, 302–317, *ACS Symposium Series*, Vol. 355.
14. Balasubramanyan, S., Diastereoisomers and enantiomers of paclobutrazol: Their preparation and biological activity, *Pest Management Science*, **1984**, 15, 3, 296–302.
15. Kaur, R., Dwivedi, A. R., Kumar, B., Kumar, V., Recent Developments on 1,2,4-Triazole Nucleus in Anticancer Compounds: A Review, *Anti-Cancer Agents in Medicinal Chemistry*, **2016**, 16, 4,465–489.
16. Fässler, A., Bold, G., Capraro, H.-G., Cozens, R., Mestan, J.,Poncioni, B., et al. Aza-peptide analogs as potent human immunodeficiency virus type-1 proteaseinhibitors with oral bioavailability, *J. Med. Chem.*, **1996**, 39, 16, 3203–3216.
17. Bold, G., Fässler, A., Capraro, H. G., Cozens, R., Klimkait, T., Lazdins, J., Mestan, J., Poncioni, B., Rösel, J., Stover, D., et al., New Aza-Dipeptide Analogues as Potent and Orally Absorbed HIV-1 Protease Inhibitors: Candidates for Clinical Development, *J.Med. Chem.*, **1998**, 41, 18, 3387–3401.
18. Venkatraman, S., Wu, W., Shih, N.-Y., Njoroge, F. G., Potent aza-peptide derived inhibitors of HCV NS3 protease, *Bioorg. Med. Chem. Lett.,* **2009**, 19, 16, 4760–4763.

19. Furst, A., Berlo, R. C., Hooton, S., Hydrazine as a Reducing Agent for Organic Compounds (Catalytic Hydrazine Reductions), *Chem. Rev.*, **1965**, 65, 1, 51–68.
20. Evans, R. F., Recent advances in the organic chemistry of hydrazine,*Rev. Pure Appl. Chem*., **1962**, 12,146–164.
21. Coispeau, G., Elguero, J., Reaction of hydrazines with 1,3-difunctional compounds. Synthesis of pyrazole derivatives, *Bull. Soc. Chim.Fr.*, **1970**, 7, 2717–2736.
22. Sakai, K., Anselme, J.-P., 5-Methyl- and 5-Phenyl-1-Aminotetrazoles, *Org. Prep. Proc. Int.*, **1975**, 7, 2, 61–65.
23. Park, I.-K., Suh, S.-E., Lim, B.-Y., Cho, C.-G., Aryl Hydrazide beyond as Surrogate of Aryl Hydrazine in the Fischer Indolization: The Synthesis of *N*-Cbz-indoles, *N*-Cbz-carbazoles, and *N*,*N*′-Bis-Cbz-pyrrolo[2,3-*f*]indoles, *Org. Lett.*, **2009**, 11, 23, 5454–5456.
24. Robinson, B., The Fischer Indole Synthesis, *Chem. Rev.*, **1963**, 63, 4, 373–401.
25. Зрелов, В.Н., Серегин, Е.П.,Жидкие ракетные топлива, М.: Химия, **1975**, 320.
26. Serov, A., Kwak, C., Direct hydrazine fuel cells: A review, *Applied Catalysis B: Environmental*, **2010**, 98, 1–2, 1–9.
27. Quibell, M., Turnell, W. G., Johnson, T., Synthesis of Azapeptides by the Fmoc/tert-Butyl/Polyamide Technique, *J. Chem. Soc., Perkin Trans. 1*, **1993**, 2843–2849.
28. Boeglin, D., Lubell, W. D., Aza-Amino Acid Scanning of Secondary Structure Suited forSolid-Phase Peptide Synthesis with Fmoc Chemistry and Aza-Amino Acids with Heteroatomic Side Chains, *J. Comb. Chem.*, **2005**, 7, 6, 864–878.
29. Zega, A., Azapeptides as pharmacological agents, *Curr. Med. Chem.*, **2005**, 12, 5, 589–597.
30. Cahn, J. W., Powell, R. E., The Raschig Synthesis of Hydrazine, *J. Am. Chem. Soc.*, **1954**, 76, 9, 2565–2567.
31. Rowe, R. A., Audrieth, L. F., Preparation of Some N-Disubstituted Hydrazines by Reaction of Chloramine with Secondary Amines, *J. Am. Chem. Soc,* **1956**, 78, 3, 563–564.
32. Omietanski, G. M.,Sisler, H. H., The Reaction of Chloramine with Tertiary Amines.[1] 1,1,1-Trisubstituted Hydrazinium Salts[2], *J. Am. Chem. Soc.*, **1956**, 78, 6, 1211–1213.
33. Hoegerle, K., Erlenmeyer, H., Über die Reaktion von α-Pyridon mit Chloramin, *Helv.Chima.Acta.*, **1956**, 39, 5, 1203–1207.
34. Omietanski, G. M., Melmers, A. D., Shellman, R. W., Sisler, H. H., Reactions of Chloramine with Anhydrous Primary and Secondary Amines, *J. Am. Chem. Soc.*, **1956**, 78, 16, 3874–3877.
35. Gever, G., Hayes, K., Alkylhydrazines, *J. Org. Chem.*, **1949**, 14, 5, 813–818.
36. Gösl, R., Meuwsen, A., Synthese substituierter Hydrazine aus Aminen mit Hydroxylamin-*O*-sulfonsäure, *Chem. Ber.*, **1959**, 92, 10, 2521–2531.
37. Wallace, R. G., Hydroxylamine-O-sulfonic acid – a versatile synthetic reagent, *Aldrichimica Acta*, **1980,** 13, 1, 3–11.
38. Matsuguma, H. J., Audrieth, L. F., Wehrmeister, H. L., Hydroxylamine-O-Sulfonic Acid, *Inorg. Synth*., **1957**, 5, 122–125.
39. Sommer, F., Schulz, O. F., Nassau, M., Über die Sulfoperamidsäure [About Sulfoperamic Acid], *Z. Anorg. Allg. Chem. (in German)*, **1925**, 147, 1, 142–155.

40. Brosse, N., Pinto, M-F., Jamart-Grégoire, B. Synthesis of *N*-(protected)amino-phthalimides: application to thesynthesis of singly labelled isoniazid, *J. Chem. Soc*., *Perkin Trans. 1*, **1998**, 3685–3688.
41. Baburaj, T., Thambidurai, S.,*N*-Boc-*O*-Tosyl Hydroxylamine as a Safe and Efficient Nitrogen Source for the N-Amination of Aryl and Alkyl Amines: Electrophylic Amination, *Synlett*, **2011**, 22, 14, 1993–1996.
42. Baburaj, T., Thambidurai, S.,*N*-Boc-*O*-Tosyl Hydroxylamine as a Safe and Efficient Nitrogen Source for the N-Amination of Aryl and Alkyl Amines: Electrophylic Amination, *Synlett***, 2015**, 26, 08, 1137–1137.
43. Armstrong, A., Jones, L. H., Knight, J. D., Kelsey, R. D., Oxaziridine-Mediated Amination of Primary Amines: Scope and Application to a One-Pot Pyrazole Synthesis, *Org. Lett.*, **2005**, 7, 4, 713–716.
44. Geuther, A., Ueber die Einwirkung von salpetrigsaurem Kali auf salzsaures Diäthylamin. *Eur. J. Org. Chem.*, **1863,** 128, 2, 151–156.
45. Fridman, A. L., Mukhametshin, F. M., Novikov, S. S., Advances in the chemistry of aliphatic N-nitrosamines, *Russ. Chem. Rev.,* **1971**, 40, 1, 34–50.
46. Fischer, E., Ueber die Hydrazinverbindungen der Fettreihe, *Berichte der deutschen chemischen Gesellschaft*, **1875**, 8, 1587–1590.
47. Rohde, W., Ueber einige Zersetzungen des Tribenzylamins, *Lieb. Ann*., **1869**, 151, 3, 366–372.
48. Leicester, J., Vogel, A., New methods for the preparation of asymmetrical dialkyl hydrazines. Bond refractions and bond parachors of the N—N and N= N links, *Research*, **1950**, 3, 148.
49. Schueler, F., Hanna, C., A Synthesis of Unsymmetrical Dimethyl Hydrazine Using Lithium Aluminium Hydride*, J. Am. Chem. Soc*, **1951**, 73, 10, 4996–4996.
50. Poirier, R. H., Benington, F., Reduction of N-Nitrosodiphenylamine to unsym-Diphenylhydrazine by Lithium Aluminium Hydride*, J. Amer. Chem. So*c, **1952**, 74, 12, 3192–3192.
51. Iversen, P. E., Reduction of N-nitrosamines, *Acta. Chem. Scand*., **1971**, 25, 2337–2340.
52. Oguz, U., Guilbeau, G. G., McLaughlin, M. L., A facile stereospecific synthesis of α-hydrazino esters, *Tetrahedron Letters*, **2002**, 43, 15, 2873–2875.
53. Kost, A. N., Sagitullin, R. S., Monoalkylhydrazines, *Russ. Chem. Rew*., **1964**, 33, 4, 159–176.
54. Harries, C., Haga, T., Ueber die Methylirung des Hydrazinhydrats, *Eur. J. Inorg. Chem*., **1898**, 31, 1, 56–64.
55. Curtius, T., Wirsing, F., Pyrazoline and its derivatives, *J. Pract. Chem*., **1894**, 50, 2, 531–554.
56. Franzen, H., Kraft, F., N-Amino-heterocyclic Compounds. III. Properties of α-Acylhydrazines, 1-Amino-2-5-diphenyl-1-3-4-triazole, and 1-Amino-2-5-dibeazyl-1-3-4-triazole, *J. Pract. Chem*., **1911**, 84, 1, 122–139.
57. Franzen, H., Kraft, F., N-Amino-heterocyclic Compounds. III. Properties of α-Acylhydrazines, 1-Amino-2-5-diphenyl-1-3-4-triazole, and 1-Amino-2-5-dibeazyl-1-3-4-triazole, *J. Chem. Soc. Abstr.*, **1911**, 100, 816–817.
58. Cohen, S., Wang, C. H., The Effects of Structure on the Kinetics of Decomposition of Substituted Phenyl-azo-triphenylmethanes, *J. Am. Chem. Soc*., **1953**, 75, 22, 5504–5507.
59. Westphal, O., Über die Alkylierung des Hydrazins, *Berichte der deutschen chemischen Gesellschaft,* **1941**, 74, 5, 759–776.

60. Westphal, O., Über Invertseifen, IX. Mitteil.: Aziniumsalze, *Berichte der deutschen chemischen Gesellschaft*, **1941**, 74, 8, 1365–1382.
61. Kost, A. N., Sagitullin, R. S., Reactions of hydrazine derivatives. XXII. 1-Benzylpyrazolones, *Вестн. МГУ, сер. Хим.*, **1959**, 14, 1, 225–228.
62. Grandberg, I. I., Kost, A. N., Исследование пиразолов. XXIII. Синтез 4-замещенных 1-гептил-3,5-диметилпиразолов, *J. Gen. Chem.*, **1962**, 32, 874–878.
63. Biel, J., Hoya, W., Leiser, H., Aminolysis and hydrazinolysis products of N-methyl-3-chloropiperidine. Non-mercurial diuretic agents, *J. Am. Chem. Soc.*, **1959**, 81, 10, 2527–2532.
64. Biel, J., Nuhfer, P., Drukker, A., Mitchell, T., Conway, A., Horita, A., A new class of potent monoamine oxidase inhibitors. Chemistry and structure-activity relationships of aminoalkylhydrazines, *J. Org. Chem*., **1961**, 26, 9, 3338–3341.
65. Brown, R., Kearley, R., The Preparation of Ethylhydrazine by Direct Ethylation, *J. Am. Chem. Soc.*, **1950**, 72, 6, 2762–2762.
66. Kuhn, L., Catalytic reduction with hydrazine, *J. Am. Chem. Soc*., **1951**, 73, 4, 1510–1512.
67. Merrow, R., Van Dolah, R., Reactions of Nitrate Esters. II. Reactions with Hydrazine, *J. Am. Chem. Soc*., **1954**, 76, 18, 4522–4525.
68. Thile, J., Über Nitrosohydrazine, Isoazotate und Azoverbindungen der Fettreihe, *Eur. J. Org. Chem*., **1910**, 376, 3, 239–268.
69. Overberger, C., Di-Giulio , A., Azo Compounds. XXVII. Synthesis of α-Alkyl and α, α-Dialkylbenzylazoalkanes and Intermediate Hydrazines and Hydrazones, *J. Am. Chem. Soc*., **1958**, 80, 24, 6562–6568.
70. Busch, M., Fleischmann, M., Alkylmagnesiumhaloide und Aldazine, *Berichte der deutschen chemischen Gesellschaft*, **1910**, 43, 1, 740–750.
71. Audrieth, L. F., Weisiger, J. R., Carter, H. E., Alkylation of phenylhydrazine in liquid ammonia, *J. Org. Chem.*, **1941**, 6, 3, 417–420.
72. Grandberg, I. I., Kost, A. N., IV. New synthesis of benzylhydrazine, *Вестн. МГУ, сер. Хим.*, **1955**, 10, 12, 119–120.
73. Ronco, K., Erlenmeyer, H., Aminosäure-Analoge aus der Hydrazinreihe I, *Helv. Chim. Acta*, **1956**, 39, 4, 1045–1051.
74. Ronco, K., Prijs, B., Erlenmeyer, H., Aminosäure-Analoge aus der Hydrazinreihe II, *Helv. Chim, Acta*., **1956**, 39, 5, 1253–1257.
75. Ronco, K., Prijs, B., Erlenmeyer, H., Aminosäure-Analoge aus der Hydrazinreihe III, *Helv. Chim. Acta*., **1956**, 39, 7, 2088–2095.
76. Miotkowska, B., Zwierzak, A., Solid $NaOH/K_2CO_3$-A new highly effective base for phase-transfer catalysed N-alkylation of diphenylphosphinic hydrazide, *Tetrahedron Lett.*, **1978**, 19, 47, 4731–4734.
77. Kluba, M., Zwierzak, A., Synthesis of 1, 2-Dialkylhydrazines by Stepwise Phase-Transfer-Catalysed N-Alkylation of Diphenylphosphinic Hydrazide, *Synthesis*, **1981**, 1981, 07, 537–539.
78. Mäeorg, U., Grehn, L., Ragnarsson, U., Prototypical Reagent for the Synthesis of Substituted Hydrazines, *Angew. Chem. Int. Ed. Engl*., **1996**, 35, 22, 2626–2627.
79. Mäeorg, U., Ragnarsson, U., Synthesis, application and scope of a new protected hydrazine reagent, *Tetrahedron Lett*., **1998**, 39, 7, 681–684.
80. Mäeorg, U., Pehk, T., Ragnarsson, U., Synthesis of substituted hydrazines from triprotected precursors, *Acta. Chem. Scand*., **1999**, 53, 12, 1127–1133.

81. Dutta, A. S., Morley, J. S., Polypeptides. Part XI1I.l Preparation of a-Aza-amino-acid (Carbazic Acid) Derivatives and Intermediates for the Preparation of a-Aza-peptides, *J. Chem. Soc., Perkin Trans. 1,* **1975**, 1712–1720.
82. Busnel, O., Baudy-Floc'h, M., Preparation of new monomers aza-b^3-aminoacids for solid-phase syntheses of aza-β^3-peptides, *Tetrahedron Lett*., **2007**, 48, 33, 5767–5770.
83. Rasmussen, L. K., Facile Synthesis of mono-, di-, and trisubstituted alpha-unbranched hydrazines, *J. Org. Chem*., **2006**, 71, 9, 3627–3629.
84. Tsubrik, O., Maeorg, U., Combination of tert-butoxycarbonyl and triphenylphosphonium protecting groups in the synthesis of substituted hydrazines, *Org. Lett*., **2001**, 3, 15, 2297−2299.
85. Bailley, R. E., West, R*.,* A Novel Rearrangement of 1, 2-Bis(trimethylsilyl)hydrazine, *J. Am. Chem. Soc*., **1964**, 86, 23, 5369–5370.
86. Bredihhin, A., Groth. U. M., Mäeorg, U., Effecient Methodology for Selective Alkylation of Hydrazine Derivatives, *Org. Lett*., **2007**, 9, 6, 1097–1099.
87. Bredihhin, A., Mäeorg, U., Use of polyanions for alkylation of hydrazine derivatives, *Org. Lett*., **2007**, 9, 24, 4975–4977.
88. Bredihhin, A., Mäeorg, U., Effective strategy for the systematic synthesis of hydrazine derivatives, *Tetrahedron*, **2008**, 64, 28, 6788–6793.
89. Lebedev, O., Bredihhin, A., Tsupova, S., Mäeorg, U., The use of polyanions of hydrazines in the synthesis of heterocycles, *Tetrahedron*, **2009**, 65, 27, 5438–5442.
90. Garcia-Ramos, Y., Proulx, C., Lubell, W. D., Synthesis of hydrazine and aza-peptide derivatives by alkylation of carbazates and semicarbazones, *Can. J. Chem*., **2012**, 90, 11, 985–993.
91. Bourguet, C. B., Proulx, C., Klocek, S., David Sabatino, D., Lubell, W. D., Solution-phase submonomer diversification of aza-dipeptide building blocks and their application in aza-peptide and aza-DKP synthesis, *J. Pept. Sci.* **2010**, 16, 6, 284–296.
92. Garcia-Ramos, Y., Lubell, W. D., Synthesis and alkylation of aza-glycinyl dipeptide building blocks, *J. Pept. Sci*., **2013**, 19, 12, 725–729.
93. Proulx, C., Lubell, W. D., Copper-Catalyzed *N*-Arylation of Semicarbazones for the Synthesis of Aza-Arylglycine-Containing Aza-Peptides**,** *Org. Lett.,* **2010**, 12, 13, 2916–2919.
94. Traoré, M., Doan, N.-D., Lubell, W. D., Diversity-Oriented Synthesis of Azapeptides with Basic Amino Acid Residues: Aza-Lysine, Aza-Ornithine, and Aza-Arginine, *Org. Lett.*, **2014**, 16, 13, 3588−3591.
95. Busnel, O., Bi, L., Dali, H., Cheguillaume, A., Chevance, S., Bondon, A., Muller, S., Baudy-Floc'h, M. Solid-Phase Synthesis of "Mixed" Peptidomimetics Using Fmoc-Protected Aza-β^3-amino Acids and α-Amino Acids, *J. Org. Chem.*, **2005**, 70, 26, 10701–10708.
96. Pascal, R., Sola, R., Preservation of the protective group under alkaline conditions by using $CaCl_2$. Applications in peptide synthesis, *Tetrahedron Lett.,* **1998**, 39, 28, 5031–5034.
97. Freeman N. S., Hurevich M., Gilon C., Synthesis of N′-substituted Ddz-protected hydrazines and their application in solid phase synthesis of aza-peptides, *Tetrahedron*, **2009**, 65, 8, 1737–1745.

98. Bouayad-Gervais S. H., Lubell, W. D., Examination of the Potential for Adaptive Chirality of the Nitrogen Chiral Center in Aza-Aspartame, *Molecules,* **2013**, 18, 12, 14739–14746.
99. Hart, M., Beeson C., Utility of azapeptides as major histocompatibility complex class II protein ligands for T-cell activation, *J. Med. Chem*,, **2001**, 44, 22, 3700–3709.
100. Lee, J. Bogyo, M., Development of near-infrared fluorophore (NIRF)-labeled activity-based probes for *in vivo* imaging of legumain, *ACS Chem. Biol.*, **2010**, 5, 2, 233–243.
101. Gwaltney, S. L., O'Connor, S. J., Nelson, L. T. J., Sullivan, G. M., Imade, H., Wang, W. Et al., Aryl Tetrahydropyridine Inhibitors of Farnesyltransferase: Bioavailable Analogues with Improved Cellular Potency, *Bioorg. Med. Chem. Lett*., **2003**, 13, 7, 1363–1366.
102. Clark, C. C., "Hydrazine," first edition, Mathieson ChemicalCorn. Baltimore, Md., **1953**, p. 39.
103. Biel, J. H., Drukker, A. E., Mitchell, T. F., Sprengeler, E. P., Nuhfer, P. A., Conway, A. C., Horita, A., Central Stimulants. Chemistry and Structure-Activity Relationship of Aralkyl Hydrazines, *J. Am. Chem. Soc.*, **1959**, 81, 11, 2805–2813.
104. Ainsworth, C., The Conversion of Carboxylic Acid Hydrazides to Amides with Raney Nickel, *J. Am. Chem. Soc.*, **1954**, 76, 22, 5774–5775.
105. Ainsworth, C., The Reductive Alkylation of Primary Aromatic Amines with Raney Nickel and Alcohols, *J. Am. Chem. Soc.*, **1956**, 78, 8, 1635–1636.
106. Fox, H. H., Gibas, J. T., Synthetic tuberculostats. VII. Monoalkyl derivatives of isonicotinyhydrazine, *J. Org. Chem.*, **1953**, 18, 8, 994–1002.
107. Yale, H. L., Losee, K., Martins, J., Holsing, M., Perry, F. M., Bernstein, J., Chemotherapy of Experimental Tuberculosis. VIII. The Synthesis of Acid Hydrazides, their Derivatives and Related Compounds, *J. Am. Chem. Soc.*, **1953**, 75, 8, 1933–1942.
108. Kline, G. B., Cox, S. H., A New Synthesis of DL-Glutamine, *J. Org. Chem.*, **1961**, 26, 6, 1854–1856.
109. Melendez, R. E., Lubell, W. D., Aza-Amino Acid Scan for Rapid Identification of Secondary Structure Based on the Application of N-Boc-Aza1-Dipeptidesin Peptide Synthesis, *J. Am. Chem. Soc*., **2004**, 126, 21, 6759–6764.
110. Casanova, B. B., Muniz, M. N., Oliveira, T., Oliveira, F. L., Machado, M. M., Fuentefria, A.M., Gosmann, G., Gnoatto, S. C. B., Synthesis and Biological Evaluation of Hydrazone Derivatives as Antifungal Agents, *Molecules,* **2015**, 20, 5, 9229–9241.
111. Carpino, L. A., Santilli, A. A., Murray, R. W., Oxidative Reactions of Hydrazines. V. Synthesis of Monobenzyl 1,1-Disubstituted Hydrazines and 2-Amino-2,3-dihydro-1H-benz[de]isoquinoline, *J. Am. Chem. Soc.*, **1960**, 82, 11, 2728–2731.
112. Vartanyan, S.A., Vartanyan, R. S., Karamyan, S. A., Avetyan, L. O., Apoyan, N. A., Melkonyan, Zh. S., Synthesis and biological activity of 1,3,4-substituted pyrazolin-5-ones, *Pharm. Chem. J.*, **1985**, 19, 7, 470–473.
113. Bailey, M. D., Halmos, T., Goudreau, N., Lescop, E., Llinàs-Brunet, M., Novel Azapeptide Inhibitors of Hepatitis C Virus Serine Protease, *J. Med. Chem.*, **2004**, 47, 15, 3788–3799.
114. Borch, R.F., Bernstein, M. D., Durst, H. D., Cyanohydridoborate anion as a selective reducing agent, *J. Am. Chem. Soc.,* **1971**, 93, 12, 2897–2904.

115. Clinton F. L., Sodium cyanoborohydride—a highly selective reducing agent for organic functional groups, *Synthesis*, **1975**, 3, 135–146.
116. Freeman, N. S., Tal-Gan, Y., Klein, S., Levitzki, A., Gilon, C., Microwave Assisted Solid-Phase Aza-peptide Synthesis: Aza Scan of a PKB/Akt Inhibitor Using Aza-arginine and Aza-proline Precursors, *J. Org. Chem.,* **2011**, 76, 9, 3078–3085.
117. Burkhardt, E. R., Matos, K., Boron Reagents in Process Chemistry: Excellent Tools for Selective Reductions, *Chem. Rev*., **2006**, 106, 7, 2617–2650.
118. Baumgarten, H. E., Chen, P. Y. N., Taylor, H. W., Hwang D.-R., Reactions of amines. 20. Syntheses of racemic and optically active alkylhydrazines and N-acyl-N-alkyl- and N-acyl-N-arylhydrazines, *J. Org. Chem.*, **1976**, 41, 24, 3805–3811.
119. Casarini, M. E., Ghelfi, F., Libertini, E.,Pagnoni, U. M., Parsons, A. F., 1,2-Reduction of a,b-unsaturated hydrazones using dimethylamine–borane/p-toluenesulfonic acid: an easy route to allyl hydrazines, *Tetrahedron*, **2002**, 58, 39, 7925–7932.
120. Perdicchia, D., Licandro, E., Maiorana, S., Clara Baldoli, C., Giannini, C., A new 'one-pot' synthesis of hydrazides by reduction of hydrazones, *Tetrahedron*, **2003**, 59, 39, 7733–7742.
121. Feichtinger, K., Zapf, C., Sings, H. L., Goodman, M., Diprotected triflylguanidines: a new class of guanidinylation reagents. *J. Org. Chem.*, **1998**, 63, 12, 3804–3805.
122. Liu, R., Zhang, P., Gan, T., and James M. Cook, J. M., Regiospecific Bromination of 3-Methylindoles with NBS and Its Application to the Concise Synthesis of Optically Active Unusual Tryptophans Present in Marine Cyclic Peptides., *J. Org. Chem.,* **1997**, 62,21,7447–7456.
123. Romera, J. L., Cid, J. M., Trabanco, A., A. Potassium iodide catalyzed monoalkylation of anilines under microwave irradiation., *Tetrahedron Lett*., **2004**, 45,48, 8797–8800.
124. Kabalka, G. W., Reddy, N. K., and Narayana, C., Lithium iodide-catalyzed alkylation of carboranes, *TetrahedronLett.*, **1992**, 33, 50, 7687–7688.
125. Calabretta, R., Gallina, C., Giordano, C., Sodium cyanoborohydride reduction of (benzyloxycarbonyl)- and (tert-butoxycarbonyl)hydrazones, *Synthesis*, **1991**, 07, 536-539.
126. Dupont, V., Lecoq, A., Mangeot, J. P., Aubry, A., Boussard, G., Marraud, M., Conformational perturbations induced by N-amination and N-hydroxylation of peptides, *J. Am. Chem. Soc.*, **1993**, 115 , 20, 8898–8906.
127. Spiegel, J., Mas-Moruno, C., Horst Kessler, H., Lubell, W. D., Cyclic Aza-peptide Integrin Ligand Synthesis and Biological Activity, *J. Org. Chem*., **2012**, 77, 12, 5271−5278.
128. Hess, H-J., Moreland, W. T., Laubach, G. D., N- [2-Isopropyl-3-(L-aspartyl-L-arginyl)-carbazoyl]-L-tyrosyl-L-valyl-L-histidyl-L-prolyl-L-phenylalanine,[1] an Isostere of Bovine Angiotensin II, *J. Am. Chem. Soc.*, **1963**, 85, 24, 4040–4041.
129. Wieczerzak, E., Kozlowska, J., Lankiewicz, L., Grzonka, Z., The efficient synthesis of aza-amino acids, *Pol. J. Chem*., **2002**, 76, 12, 1693–1697.
130. Frochot, C., Vanderesse, R., Driou, A., Linden, G., Marraud, M., Cung, M. T., A solid-phase synthesis of three aza-, iminoaza- and reduced aza-peptides from the same precursor, *Lett. Pept. Sci*., **1997**, 4, 6, 219–225.
131. Oliveira, R., Guedes, R. C, Meireles, P., Albuquerque, I. S., Goncalves. L. M. Et al., Tetraoxane−Pyrimidine Nitrile Hybrids as Dual Stage Antimalarials, *J. Med. Chem.,* **2014**, 57, 11, 4916−4923.

132. Gray, C. J., Quibell, M., Jiang, K. L., Baggett, N., Synthesis and spectroscopic properties of azaglutamine amino acid and peptide derivatives, *Synthesis,* **1991**, 2, 141–146.
133. Bondebjerg, J., Fuglsang, H., Valeur, K. R., Kaznelson, D. W., Hansen, J. A., Novel semicarbazide-derived inhibitors of human dipeptidyl peptidase I (hDPPI), *Bioorg. Med. Chem*., **2005**, 13, 14, 4408–4424.
134. Carpino, L. A., Han, G. Y. The 9-fluorenylmethoxycarbonyl amino-protecting group, *J. Org. Chem.*, **1972**, 37, 22, 3404–3409.
135. Carpino, L. A., Collins, D., Göwecke, S., Mayo, J., Thatte, S.D., Tibbetts, F., tert-Butyl carbazate, *Org. Synth*., **1964**, 44, 20–23.
136. Ovchinnikov, Y. A., Kiryushkin, A. A., Miroshnikov, A. I., A new convenient method for the synthesis of tert-butyloxycarbonylhydrazine, *Cell.Mol. Life Sci.,* **1965**, 21, 7, 418–419.
137. Jablonski, J. J., Basu, D., Engel, D. A., Geysen, H. M., Design, synthesis, and evaluation of novel small molecule inhibitors of the influenza virus protein NS1, *Bioorg. Med. Chem*., **2012**, 20, 1, 487–497.
138. Rabjohn, N. The synthesis and reactions of disazodicarboxylates. *J. Am. Chem. Soc.*, **1948**, 70, 3, 1181–1183.
139. Mccord, T. J., Ravel, J. M., Skinner, C. G., Shive, W., O-Carbazyl-DL-serine, an Inhibitory Analog of Glutamine, *J. Am. Chem. Soc.*, **1958**, 80, 14, 3762–3764.
140. Gao, Y., Lam, Y., Synthesis of Pyrazolo[5,1-*d*][1,2,3,5]tetrazine-4(3*H*)-ones, *J. Comb. Chem.* **2010**, 12, 1, 169–174.
141. Hartmut, H., Hydrazinoacids as heterocomponents of peptides. VI. Hydrazino-acetic acid derivatives and their use for the synthesis of hydrazino- and N-aminopeptides, *Chemische Berichte*, **1965**, 98, 11, 3451–3461.

SUMMARY IN ESTONIAN

α-asa-aminohapete prekursorite ja nendega sarnaste ühendite valmistamine kasutades uudseid redutseeriva ühe-poti alküülimise ja otsese alküülimise meetodeid

Käesolev dissertatsioon kirjeldab uusi ja mugavaid α-asa-aminohapete prekursorite ja nendega struktuurilt sarnaste alküülhüdrasiinide sünteesimeetodeid. Sellised ühendid on tähtsad modifitseeritud peptiidide ja paljude bioloogiliselt aktiivsete ühendite valmistamisel.

Esiteks, töötati välja alternatiivne otsest monokaitstud hüdrasiini alküülimist kasutav Fmoc-asa-Arg(Boc)$_2$ prekursori sünteesimeetod. Töö käigus uuriti hüdrasiini ja 3-bromopropüülamiini kaitserühmade efekte ning leiti antud reaktsiooni jaoks kõige sobivam reagentide suhe.

Teiseks, optimeeriti alkoksükarbonüül-kaitstud hüdrasiinide bensüülimise tingimusi, uurides kasutatavate solventide, aluste, alküülivate reagentide elektrofiilsuse ja reagentide koguste suhte mõju. Leitud optimaalsed tingimused olid rakendatud erinevaid kaitserühmi kandvatate asa-Tyr ja asa-Trp prekursorite sünteesis.

Kolmandaks, töötati välja kaaliumjodiidi (KI) poolt katalüüsitud kaitstud hüdrasiinide alküülimise meetod. See meetod põhineb reaktsioonivõimeliste alküüljodiidide genereerimisel väiksema reaktsioonivõimega halogeniididest *in situ* ning võimaldab parandada saagiseid ja lühendada reaktsiooniaegu. Meetodi efektiivsust tõestati asa-Phe, asa-Asp ja asa-Tyr prekursorite sünteesi käigus.

Neljandaks, loodi mugav kaitstud alküülhüdrasiinide ühe-poti sünteesimeetod atsetaalidest ja ketaalidest ning rakendati seda Fmoc-, ja Boc-kaitstud asa-metioniini prekursorite sünteesiks. Järgnevalt näidati, et ühe-poti meetod on edukalt kasutatav enamuse põhiliste funktsionaalrühmade korral nagu eeter, amiid, sulfiid, nitriil, karbamaat, tsükliline ja hargnenud alküülrühm. Samal ajal hüdrasinide kondensatsiooni katsed halogeene, küllastamata kaksiksidemeid, aminorühmasid ning happetundlikke kaitserühmi sisaldavate atsetaalidega ja ketaalidega ei olnud edukad.

Lõpetuseks, ühe-poti sünteesi meetodi rakendatavust laiendati monokaitstud bensüülhüdrasiinide sünteesile ja see meetod optimeeriti. Moodustunud hüdrasooni kaksiksideme aromatase tuumaga konjugatsiooni tõttu kasutati redutseerijana BH_3-THF kompleksi.

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4) Arujõe, M., Ploom, A., Mastitski, A., Järv, J. (2017). Comparison of various coupling reagents in solid-phase aza-peptide synthesis. Tetrahedron Letters, 58 (35), 3421−3425.
5) Mastitski, A., Niinepuu, S., Haljasorg, T., Järv, J. (2015). One-pot synthesis of protected alkylhydrazines from acetals and ketals. Method scope and limitations. Organic Preparations and Procedures International, 47 (6), 490−498.
6) Mastitski, A., Haljasorg, T., Kipper, K., Järv, J. (2015). Synthesis of aza-phenylalanine, aza-tyrosine, and aza-tryptophan precursors via hydrazine

alkylation. Proceedings of the Estonian Academy ofSciences, 64 (2), 168−178.
7) Mastitski, A., Kisseljova, K., Järv, J. (2014). Synthesis of the Fmoc-aza-Arg(Boc)2 precursor via hydrazinealkylation. Proceedings of the Estonian Academy of Sciences, 63 (4), 438−443.
8) Mastitski, A., Järv, J. (2014). One-Pot Synthesis of Fmoc- and Boc-Protected Aza-Methionine Precursors from 2-Methylthioacetaldehyde Dimethyl Acetal. Organic Preparations and Procedures International, 46 (6), 559−564.

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1) Arujõe, M., Ploom, A., Mastitski, A., Järv, J. (2018). Influence of steric effects in solid-phase aza-peptide synthesis. Tetrahedron Lett. [forthcoming].
2) Mastitski, A., Niinepuu, S., Haljasorg, T., Järv, J., One-Pot Synthesis of Protected Benzylhydrazines from Acetals, *Org. Prep. Proc. Int*. [forthcoming].
3) Mastitski, A., Abramov, A., Kruve, A., Järv, J. (2017). Potassium iodide catalysis in thealkylation of protected hydrazines. Proceedings of the Estonian Academy of Sciences, 66 (1), 10−17.
4) Arujõe, M., Ploom, A., Mastitski, A., Järv, J. (2017). Comparison of various coupling reagents in solid-phase aza-peptide synthesis. Tetrahedron Letters, 58 (35), 3421−3425.
5) Mastitski, A., Niinepuu, S., Haljasorg, T., Järv, J. (2015). One-pot synthesis of protected alkylhydrazines from acetals and ketals. Method scope and limitations. Organic Preparations and Procedures International, 47 (6), 490−498.
6) Mastitski, A., Haljasorg, T., Kipper, K., Järv, J. (2015). Synthesis of aza-phenylalanine, aza-tyrosine,and aza-tryptophan precursors via hydrazine

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7) Mastitski, A., Kisseljova, K., Järv, J. (2014). Synthesis of the Fmoc-aza-Arg(Boc)2 precursor via hydrazine alkylation. Proceedings of the Estonian Academy of Sciences, 63 (4), 438−443.
8) Mastitski, A., Järv, J. (2014). One-Pot Synthesis of Fmoc- and Boc-Protected Aza-Methionine Precursors from 2-Methylthioacetaldehyde Dimethyl Acetal. Organic Preparations and Procedures International, 46 (6),559−564.

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