DISSERTATIONES CHIMICAE UNIVERSITATIS TARTUENSIS
82

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ALEKSEI BREDIHHIN

Use of mono- and polyanions in the synthesis of multisubstituted hydrazine derivatives

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LIST OF ORIGINAL PUBLICATIONS

I. Acidity of di- and triprotected hydrazine derivatives in dimethyl sulfoxide and aspects of their alkylation. Ragnarsson, U.; Grehn, L.; Koppel, J.; Loog, O.; Tšubrik, O.; Bredikhin, A.; Mäeorg, U.; Koppel, I. *J. Org. Chem.* **2005**, 15, 5916–5921.

II. Increasing the N-H acidity: introduction of highly electronegative groups into the hydrazine molecule. Bredikhin, A.; Tšubrik, O.; Sillard, R.; Mäeorg, U. *Synlett* **2005**, 12, 1939–1941.

III. Efficient methodology for selective alkylation of hydrazine derivatives. Bredihhin, A.; Groth, U.; Mäeorg, U. *Org. Lett.* **2007**, 9, 1097–1099.

IV. Use of polyanions for alkylation of hydrazine derivatives. Bredihhin, A.; Mäeorg, U. *Org. Lett.* **2007**, 9, 4975–4977.

V. Effective strategy for the systematic synthesis of hydrazine derivatives. Bredihhin, A.; Mäeorg, U. *Tetrahedron* **2008**, 64, 6788–6793.

Author's contribution

Paper I: Synthesized several substrates for pK_a measurement. Helped to prepare the manuscript.

Paper II: Performed all the experimental work. Prepared the manuscript.

Paper III: Responsible for project planning. Performed all the experimental work. Prepared the manuscript.

Paper IV: Responsible for project planning. Performed all the experimental work. Prepared the manuscript.

Paper V: Responsible for project planning. Performed all the experimental work. Prepared the manuscript.

ABBREVIATIONS

Ac	acetyl
ACN	acetonitrile
aq.	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
n-Bu	butyl
i-Bu	*iso*-butyl (2-methylpropyl)
t-Bu	*tert*-butyl
BuLi	butyllithium
cat.	catalyst
$COIm_2$	1,1' -carbonyldiimidazole
dba	dibenzylideneacetone
DCM	dichloromethane
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)-pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNP	2,4-dinitrophenyl
DO	dioxane
dppf	1,1'-bis(diphenylphosphino)ferrocene
Et	ethyl
equiv	equivalent
Hex	hexane
LAH	lithium aluminum hydride
LiHDMS	lithium hexamethyldisilazide
Me	methyl
NMR	nuclear magnetic resonance
Ph	phenyl
Pr	1-propyl
i-Pr	2-propyl
PTC	phase transfer catalysis
Py	pyridine
TBAHS	tetrabuthylammonium hydrogensulfate

Tf	trifyl (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	*para*-toluenesulfonyl
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
X-phos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
Z	benzyloxycarbonyl

1. INTRODUCTION

Hydrazine derivatives are widely used compounds in the pharmaceutical, agrochemical, polymer and dye industries and are also valuable precursors in organic synthesis [1]. They often show incredible biological activity. Due to this particular property hydrazine derivatives are widely known in pharmacy and attracting an attention of drug developers. Currently known drugs containing hydrazine moiety are used for the treatment of tuberculosis, Parkinson's disease and hypertension [2]. Some hydrazines also exhibit neuroprotecting properties and used as antidepressant drugs [3]. Hydrazine based peptidomimetics were found to be potent agents against hepatitis [4, 34], AIDS [5] and SARS [6]. Several derivatives are shown to have significant activity against leukemia and solid tumors like melanoma, reticulum cell sarcoma, and lung carcinoma [7].

A good example of biologically active hydrazine derivatives is Atazanavir (Reyataz) which is the first once-daily HIV-1 protease inhibitor and used for the treatment of AIDS (approved by US FDA on June 20, 2003). Newer investigations have shown that Atazanavir can also inhibit the growth of brain tumor cells [8].

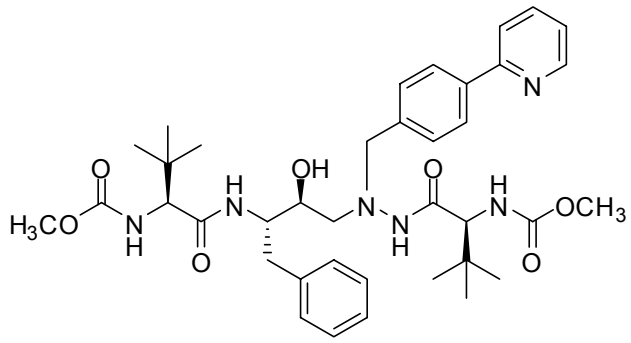
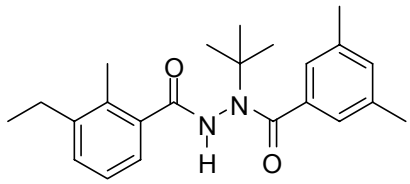
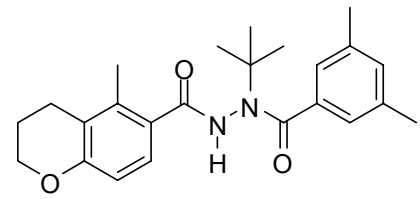


Figure 1. Atazanavir

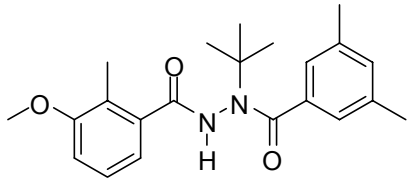
In the agrochemical industry N-*tert*-butyl diacyl hydrazines are an important class of environmentally safe, selective insecticidal compounds [9–12]. For example, N`-*tert*-butyl-N`-3,5-dimethylbenzoyl-N-4-ethylbenzoylhydrazide (tebufenozide; RH-5992) was the first among N-*tert*-butyl diacyl hydrazines to be commercialized as a leptidopteran-specific insecticide. It was used under the trade names "Mimic", "Confirm", and "Romdan" in several countries to selectively control *Lepidopterous larvae* on cotton, vegetables, apples, and pome fruit.



Tebufenozide



Chromafenozide



Methoxyfenozide

Figure 2. Hydrazine-based pesticides

Substituted diphenylhydrazides are found to be effective pharmacophores for the selective cyclooxygenase-2 (COX-2) inhibition, which is necessary in the design of new drugs [13].

Hydrazine derivatives are also being used for the derivatization of nano-structures [14–18]. And of course, hydrazine derivatives are widely used in organic chemistry as building blocks for the synthesis of heterocycles [19–21], dyes etc.

As it can easily be seen, the synthesis of hydrazine derivatives is of great interest. Unfortunately only a limited number of simple hydrazine derivatives can be obtained directly. However biological and pharmaceutical studies generally demand complex and multisubstituted structures to ensure the selectivity and minimize side-effects. Their synthesis however is not a simple task and provides a challenge to the chemist all over the world.

The widespread use of hydrazine derivatives as precursors for heterocycles and peptidomimetics has led to the appearance of numerous specific methods for the synthesis of the target compound. Nevertheless, the development of a strategy that would provide a possibility for the selective synthesis of any desired product systematically and using the same methodology has always been a tempting task for the chemists.

Meeting the increasing demands, the new derivatization methods have been invented and about 12 years ago the first systematic strategy has been presented. Since then a number of tri- and diprotected precursors have been developed and their use for the systematic synthesis of hydrazine derivatives was investigated. Almost all of them were utilizing the same orthogonal protecting group strategy. The invention of these methods provided an access to the different

multisubstituted hydrazines on the systematic base, affording them with the high yields.

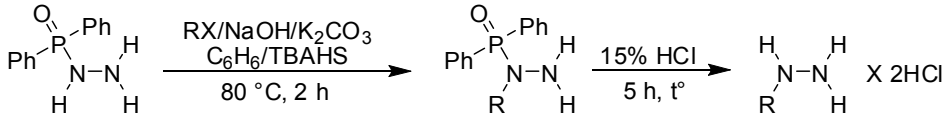
However even this strategy was not ideal requiring a lot of protection/ deprotection steps and time. This thesis presents a new strategy for the systematic synthesis of hydrazine derivatives, which requires significantly less reaction steps and time for obtaining of the desired product. The described strategy uses the polyanion chemistry and significantly differs from all the methods applied before.

2. LITERATURE OVERVIEW

2.1. Alkylation of hydrazine derivatives

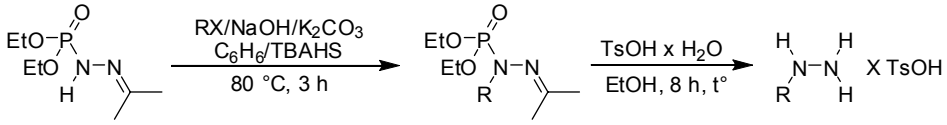
Direct alkylation of hydrazines is a quite complicated task because it generally proceeds unselectively and produces a complex mixture of products including polyalkylated and quaternated side products. This happens because hydrazines have many similar NH groups to react with, and furthermore the resulting monoalkyl derivative is more reactive than starting compound itself.

The first attempts to use protecting groups and develop methods for the selective alkylation of hydrazine were made by Zwierzak *et al.* Applying his method developed for the alkylation of amines he has prepared a series of monoalkylhydrazines. He started from diphenylphosphino-protected hydrazine and used alkylation under solid-liquid PTC conditions. Alkylation proceeded with good to excellent yields (R = Me, Et, Pr, *i*-Pr, *n*-Bu, *i*-Bu, allyl, propargyl, Bn) and after the cleavage of protecting group the monoalkylhydrazines were isolated as salts (Scheme 1) [22].



Scheme 1. Synthesis of monoalkylhydrazines

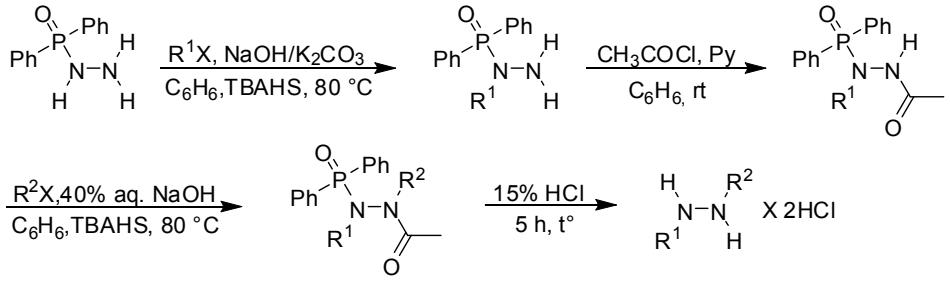
Another method, developed by the same research group, utilized the combination of diethoxyphosphoryl $(EtO)_2PO$ and 2-propylidene $(CH_3)_2C=$ protecting groups [23]. After the alkylation of the starting material under solid-liquid PTC conditions, both protecting groups were removed simultaneously and the corresponding hydrazines were isolated as *p*-toluenesulfonates (Scheme 2).



Scheme 2. Synthesis of monoalkyl hydrazines

Zwierzak *et al.* also presented a method for the preparation of N,N`– dialkylhydrazines. Firstly, diphenylphosphonic hydrazide was alkylated under PTC conditions. Then an additional protecting group was introduced by acetylation, followed by the second alkylation. After that both protecting groups were

removed simultaneously under acidic conditions as shown in Scheme 3. All reaction steps proceeded with good yields [24].

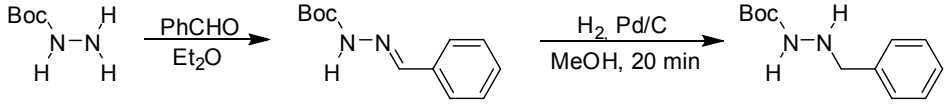


Scheme 3. Synthesis of 1,2-dialkyl hydrazines

The other widely used method for obtaining of alkylated hydrazine derivatives is based on the reduction of hydrazones. This method is especially good if introduction of secondary alkyl fragment or monoalkylation of NH_2 group is required. Hydrazones usually have some substituent or protecting group on the second nitrogen atom, otherwise the formation of dihydrazone can take place. Even if a hydrazone $R^1R^2C{=}NNH_2$ obtained, it can easily disproportionate and form the corresponding dihydrazone.

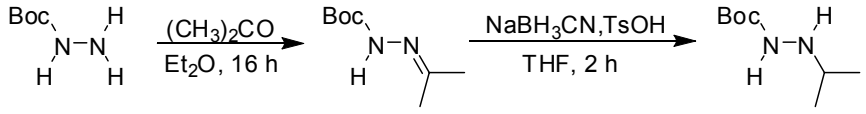
The most common ways for the reduction of hydrazones are catalytic hydrogenation and reduction with complex hydrides, such as $NaBH_3CN$, $NaBH_4$ and $LiAlH_4$. Some more exotic methods employ silicon or tin hydrides.

Mendelez and Lubell used the hydrogenation on Pd/C catalyst for obtaining of *tert*-butyl 2-benzylhydrazinecarboxylate (Scheme 4). The reaction proceeded smoothly and desired compound was obtained with 92% yield [25].



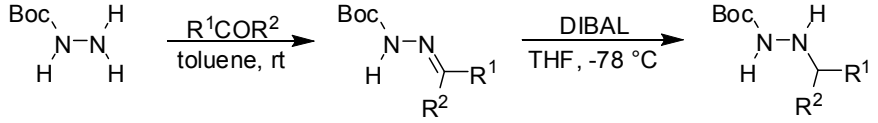
Scheme 4. Catalytic reduction of hydrazone

The same researchers also performed the reduction of hydrazone with $NaBH_3CN$ as illustrated in Scheme 5. Yield was 77%.



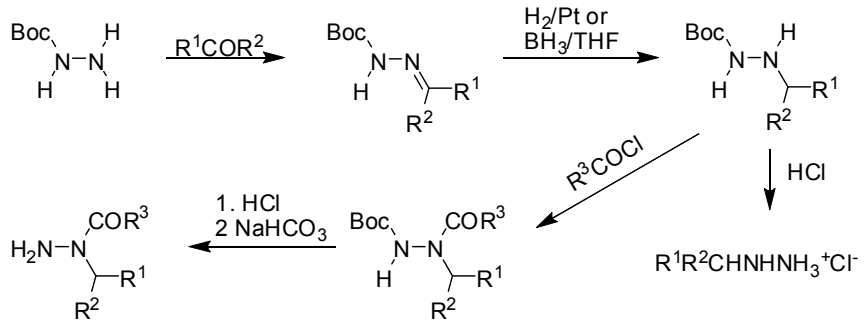
Scheme 5. Hydrazone reduction with complex hydride

Bailey *et al.* successfully used DIBAL for the reduction of hydrazones as shown in Scheme 6 affording 1-Boc-2-alkyl hydrazines (R^1 = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu; R^2 = H, Et) in high yields [26]. DIBAL allows to accomplish the reduction quickly and only one equivalent of reagent is required for performing the reaction. However the use of DIBAL requires low temperatures and an inert atmosphere.



Scheme 6. Hydrazone reduction with DIBAL

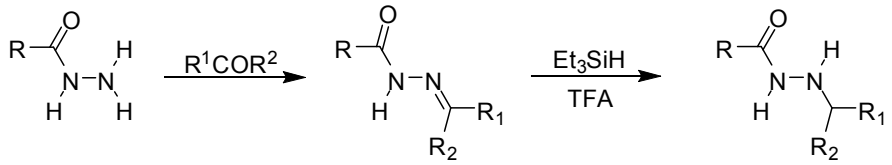
Baumgarten *et al.* studied the preparation of hydrazines with secondary alkyl substituents as shown in Scheme 7. *tert*-Butyl carbazate was used as a starting material and after the reduction of corresponding hydrazones 1-alkyl-2-*tert*-butoxycarbonyl hydrazines were obtained in good yields. Then they were selectively acylated. After the Boc-group was removed, 1-acyl-2-alkyl-hydrazines were isolated in good yields. In case of removing Boc-group before acylation secondary alkyl hydrazines can be obtained [27].



Scheme 7. Synthesis of hydrazines with secondary alkyl substituents

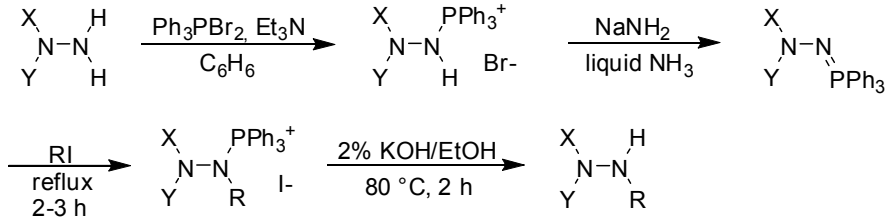
Using the Baumgarten method, Boc group can be also removed from other mono-alkylated derivatives (Schemes 4–6) furnishing corresponding alkyl hydrazines as a salt. That provides a good alternative to the methods for obtaining of alkyl hydrazines reported by Zwierzak.

Wu *et al.* used triethylsilane as a reducing agent to accomplish the reduction of various hydrazones as illustrated in Scheme 8 (R = Me, Ph; R^1 = H, Me; R^2 = Ph, Bn, m-$CH_3OC_6H_4$, C_5H_{11}, *i*-Pr, cyclohexyl, Me) [28].



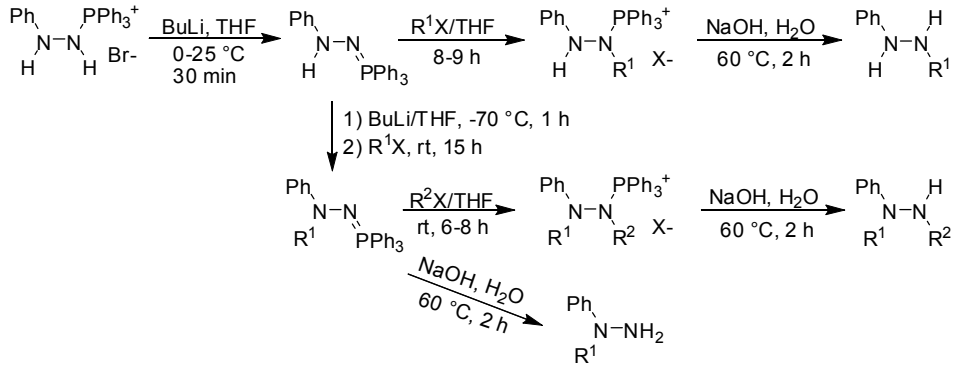
Scheme 8. Hydrazone reduction

Zimmer and Singh synthesized various trisubstituted hydrazines using triphenylphosphonium protecting group [29]. The iminophosphorane was generated by the reaction with sodium amide and alkylated with alkyl halide as illustrated in Scheme 9. Triphenylphosphonium group was thereafter removed by heating the alkylation product with KOH in ethanol. The yields of all steps were high (X and Y = H, Me, Ph; R = Me, Et).



Scheme 9. Synthesis of trisubstituted hydrazines

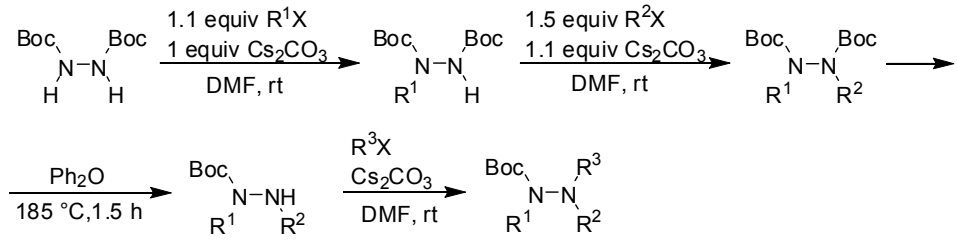
Barluenga *et al.* described an interesting method for the alkylation of phenylsubstituted hydrazines [30]. $PhNHNHP^{+}Ph_3Br^{-}$ was obtained in the reaction between phenyl hydrazine and dibromotriphenylphosphoran. Then it was used as a starting material for further syntheses (R^1= Me, Et, Bn, allyl). Besides the common alkylation of iminophosphorane, Barluenga reported that the iminophosphorane itself could also be deprotonated by butyllithium. Then a second alkyl group was introduced by alkylation of the resulting anion. The cleavage of the triphenylphosphonium group was performed by heating in the 2M NaOH for 2 h (Scheme 10).



Scheme 10. Efficient alkylation of phenyl substituted phosphoranes

The analogous method was used by Song and Yee to prepare a number of disubstituted hydrazines [31]. Starting monoarylhydrazines were transformed into corresponding triphenylphosphonium salts $ArNHNHPPh_3^+Br^-$. Then, after the treatment with LiHMDS, a corresponding phosporane was formed and alkylated with substituted benzyl bromides 2-Br-4-X-$C_6H_3CH_2Br$ (X= H, F, OMe). Triphenylphosphonium group was cleaved by heating in aqueous NaOH, producing the desired product.

Very recently Rasmussen proposed another method for the obtaining of multisubstituted hydrazines starting from 1,2-bis-Boc-hydrazine [32]. He used various alkyl halides (R^1, R^2 = allyl, Bn, propargyl, Bu; R^3 = Me) as alkylating agents, and Cs_2CO_3 as a base. Use of K_2CO_3 as a base afforded only monoalkylated products regardless of the amount of alkyl halide, however use of 2 equivalents of Cs_2CO_3 with excess of alkyl halide furnished dialkylated products. In order to perform monoalkylation selectively 1 equivalent of Cs_2CO_3 was used as shown on the Scheme 11. One of two Boc groups has been selectively removed, and the product was alkylated again furnishing trialkylated derivative. The yields were good to excellent.



Scheme 11. Synthesis of tetrasubstituted hydrazine derivatives

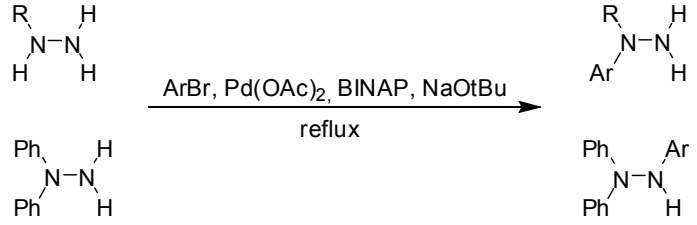
2.2. Arylation of hydrazine derivatives

Arylation of amines and hydrazines is also a quite complicated task and generally possible only through transition metal catalyzed reactions. Currently palladium and copper catalyzed reactions are mostly used. In addition, bismuth and boron organic reagents are often employed. Very important role in the development of palladium and copper catalyzed arylations belongs to Buchwald's group.

2.2.1. Palladium catalyzed reactions

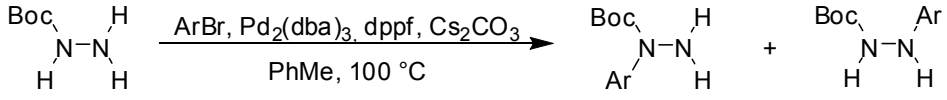
Buchwald *et al.* employed the catalytic system $Pd(OAc)_2$/BINAP for the coupling of benzophenone hydrazone $Ph_2C{=}NNH_2$ with *p*- and *m*-substituted aryl bromides [33, 34]. The process was conducted under heating at 80–100°C in toluene in the presence of Me_3CONa or Cs_2CO_3.

The same research group also studied the reaction of other hydrazines [34] with aryl bromides as illustrated in Scheme 12 (R = Ph, 4-F-C_6H_4, Boc and Ar = Ph, 4-Cl-C_6H_4, 4-CF_3-C_6H_4). Toluene or diisopropylamine was used as a solvent. The reaction time (1–18 h) considerably varies with substrate as well as yields (24–95%).



Scheme 12. Palladium catalyzed arylation of hydrazines

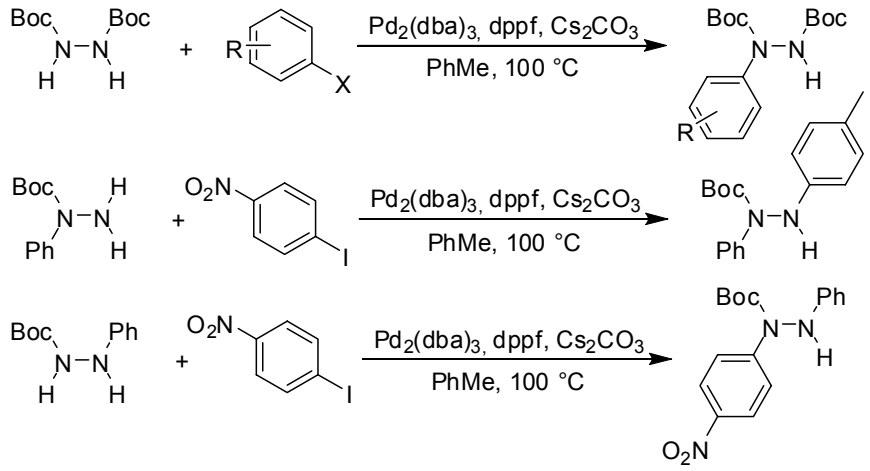
Wang *et al.* reported an efficient arylation method for the synthesis of aryl hydrazides [35]. Substituted aryl bromides were coupled with *tert*-butyl carbazate in the presence of palladium catalyst and a base, as shown in Scheme 13. While the most of aryl bromides reacted with amide NH group, a reversal of regioselectivity was observed for *o*-substituted aryl bromides.



Scheme13. Palladium catalyzed arylation of *tert*-butyl carbazate

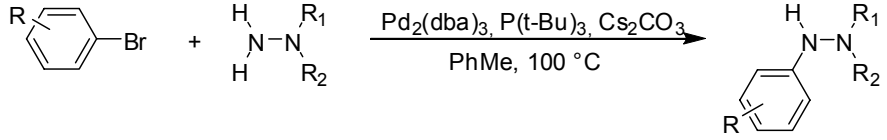
Alterburn *et al.* synthesized protected pyridylhydrazine derivatives in one-step palladium catalyzed heteroarylation reaction using phosphine ligands [36]. 2-pyridyl chlorides, bromides, and triflates were effective electrophiles in these couplings. The compounds $Ph_2C{=}NNH_2$, $BocNHNH_2$ and BocNHNHBoc were used as substrates. The catalytic system $Pd(OAc)_2$/BINAP/*t*-BuONa was the most efficient for the benzophenone hydrazone. On the other hand, $Pd_2(dba)_3$/dppf/Cs_2CO_3 was the best for the BocNHNHBoc.

Using the reaction procedure developed by Alterburn, Cho *et al.* prepared various N,N´-bis-Boc-aryl hydrazines and N,N´-Boc-diarylhydrazines as shown in Scheme 14 [37].



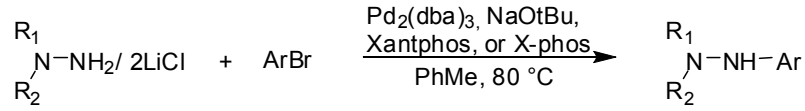
Scheme 14. Synthesis of Boc-protected aryl hydrazines

Palladium-catalyzed arylations of different N,N-dialkylhydrazines with aryl bromides were performed using a similar method (Scheme 15) [38]. The reaction proceeded in moderate to excellent yield (up to 90%) with good functional groups compatibilities (R^1, R^2 = Me, $–(CH_2)_5–$). Functional groups such as cyano, ester, ketone and Boc-amine groups were all well tolerated.



Scheme 15. Arylation of N,N-dialkyl hydrazines

The reaction of N,N-dialkylhydrazine/2LiCl adducts (R^1,R^2 = Me, $-(CH_2)_5-$, $-(CH_2)_2O(CH_2)_2-$) with aryl bromides in the presence of $Pd_2(dba)_3$ as the palladium source, Xantphos or X-phos as the ligands, toluene as a solvent, and *t*-BuONa as a base provided an efficient route to N,N-dialkyl-N-arylhydrazines (Scheme 16). The best results were obtained by using N,N-dialkylhydrazine/2LiCl adducts prepared *in situ*, omitting their isolation [39].

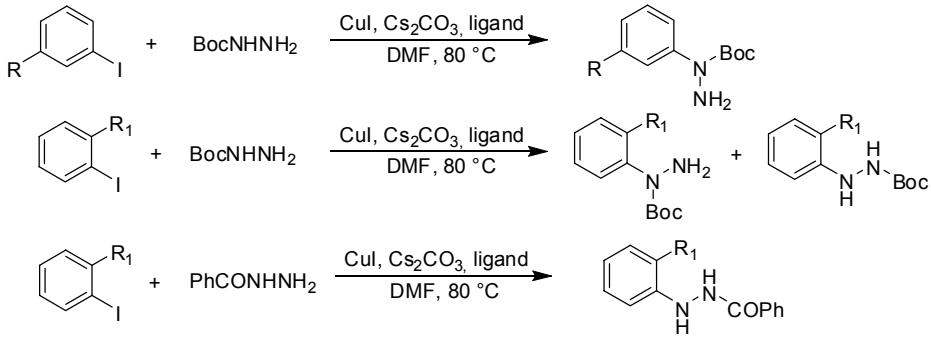


Scheme 16. Arylation of N,N-dialkylhydrazines

2.2.2. Copper catalyzed reactions

Further investigations of N-arylation of nitrogen heterocycles resulted in the development of an extremely general, and inexpensive catalyst system based on CuI and K_3PO_4 [40]. Racemic trans-1,2-cyclohexanediamine was employed as a ligand. N-arylation of *tert*-butyl carbazate, benzoic hydrazide and benzophenone hydrazone proceeded smoothly, affording the corresponding products in good yields.

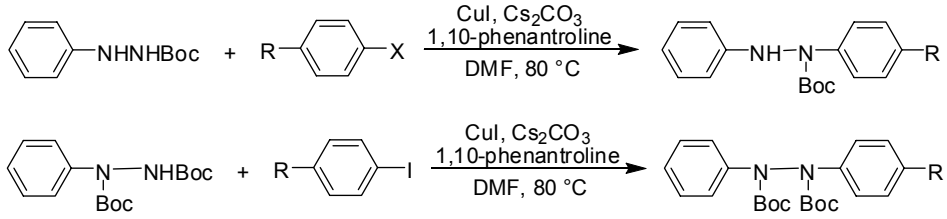
In order to improve the catalytic system for N-arylation of hydrazides Buchwald *et al.* developed a new method for N-arylation of hydrazides using substituted aryl iodides in the presence of copper catalyst CuI and Cs_2CO_3 as a base [41]. 1,10-Phenantroline and picolinic acid were employed as the ligands. Under copper-catalysis (CuI/Cs_2CO_3/DMF/80°C) both electron-withdrawing and electron-donating *p*-substituents were tolerated and the corresponding aryl iodides were successfully coupled with *tert*-butyl carbazate (Scheme 18). The reaction was also carried out with a series of *m*-substituted aryl iodides.



Scheme 18. Copper catalyzed arylation of hydrazides

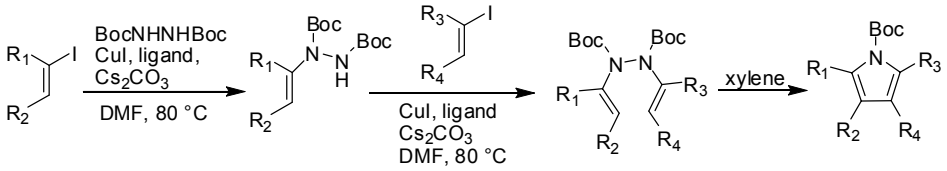
Use of picolinic acid as a ligand under similar conditions was very recently studied [42]. The *tert*-butyl carbazate was coupled with substituted (Me, F, Cl, CF_3, NH_2, CN) aryl halides. The reaction was performed regioselectively and only amide NH group was arylated.

Cho *et al.* carried out copper catalyzed N-arylation of PhNHNHBoc with substituted aryl bromides and iodides as illustrated in Scheme 19 [37]. The yields varied from moderate to high. Arylation of bis-Boc-phenylhydrazine was conducted under the same conditions. Although, the yields were substantially higher if stoichiometric amounts of CuI were used instead of catalytic.



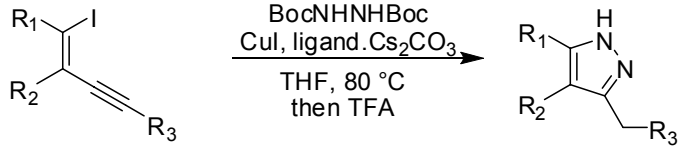
Scheme 19. Synthesis of Boc-protected aryl hydrazines

Very recently Buchwald *et al.* developed a modular route to highly substituted pyrroles [19]. This transformation consists of two sequential copper-catalyzed vinylations of 1,2-bis-Boc-hydrazine followed by thermal rearrangement/ cyclization as shown in Scheme 20. A wide variety of functionalized pyrroles can be prepared in a selective manner from simple and easily accessible precursors.



Scheme 20. Vinylation of 1,2-bis-Boc-hydrazine

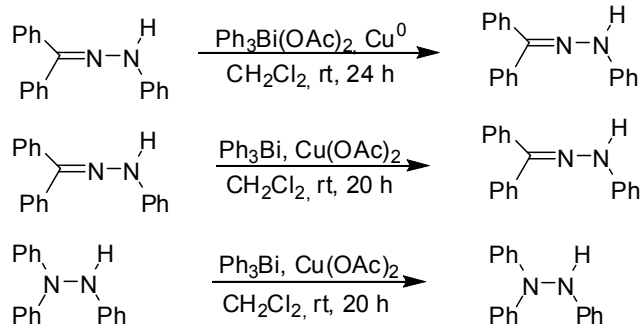
The other example of heterocycle synthesis was developed by the same research group and was performed as illustrated in Scheme 21 [20].



Scheme 21. Vinylation of 1,2-bis-Boc-hydrazine

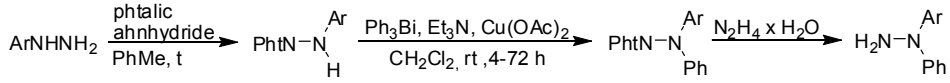
2.2.3. Bismuth reagents

Triphenylbismuthane acted as a phenylating agent towards a variety of amines in the presence of stoichiometric amount of copper diacetate to afford N-phenylated amines in high yields [43]. The results for some hydrazine derivatives, which were also used as substrates in the reaction with organo-bismuth reagents, are demonstrated in Scheme 22 [43, 44]. In contrast to efficient $Ph_3Bi(OAc)_2$ (90% yield) triphenyl bismuthane yielded only 16% of product in the reaction with benzophenone hydrazone.



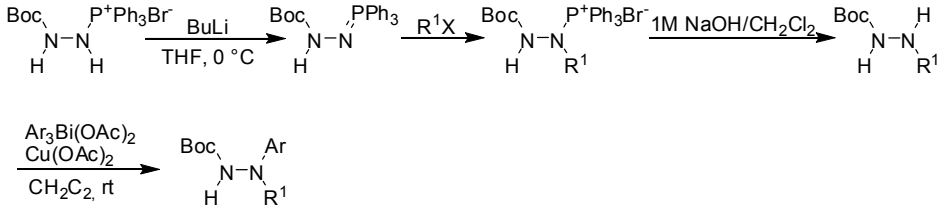
Scheme 22. Arylation of hydrazine derivatives with triaryl bismuthanes

Kikugawa *et al.* developed a method for the synthesis of 1-aryl-1-phenyl-hydrazines, based on the use of phtaloyl protection [45] as shown in Scheme 23. Aryl hydrazines were used as starting materials. Yields of copper-mediated arylation were high to excellent (82–99%).



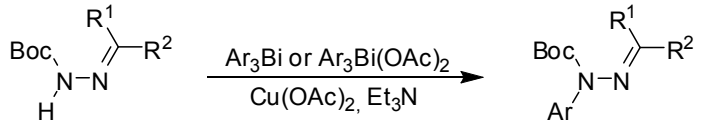
Scheme 23. Synthesis of 1-aryl-1-phenyl hydrazines

Recently Mäeorg *et al.* reported a method for the arylation of disubstituted hydrazines [46]. Compounds of type $R^1NHNHCOR^2$ (R^1 = Me, Bn, Allyl, Boc; R^2CO = Boc, Z, CH_3CO) were selectively arylated under very mild conditions using triarylbismuth diacetates. Most of them were obtained through the sequence shown in Scheme 24.



Scheme 24. Arylation of substituted hydrazines.

Very recently Mäeorg *et al.* studied arylation of substituted hydrazones (R^1 = Ph; R^2 = Me, H;) as shown in Scheme 25. Previously, to allow the synthesis of such compounds, only palladium catalysis was employed. The carbamate-protected hydrazones, which were used as model substrates, generally gave good to excellent yields under mild reaction conditions [47].

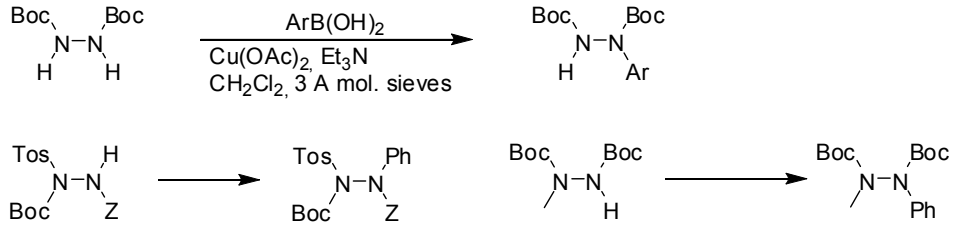


Scheme 25. Arylation of substituted hydrazones

2.2.4. Aryl boronic acids

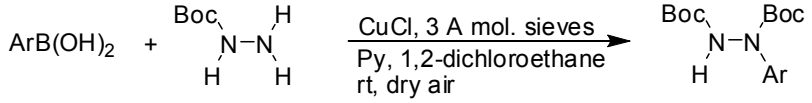
Boronic acids are now widely used as reagents for plenty of useful reactions [48]. The advantages of these compounds over other organometallic reagents are their high tolerance to a wide variety of functional groups, air stability and low toxicity. Boronic acids are readily handled without special precautions. Many of such compounds are commercially available or they can be easily prepared from corresponding organometallic derivative and boronic esters. [48, 49].

The copper catalyzed N-arylation using aryl boronic acids as aryl group donors were firstly reported by Chan [50]. Later Mäeorg *et al.* studied the copper-mediated N-arylation of di- and trisubstituted hydrazines with arylboronic acids as outlined in Scheme 26 [51]. Under Chan conditions with addition of 3 Å molecular sieves the reaction was slow (up to 4 days) and the best yields were obtained in the arylation of 1,2-bis-Boc-hydrazine. Trisubstituted hydrazines afforded low yields probably due to the significant steric hindrance.



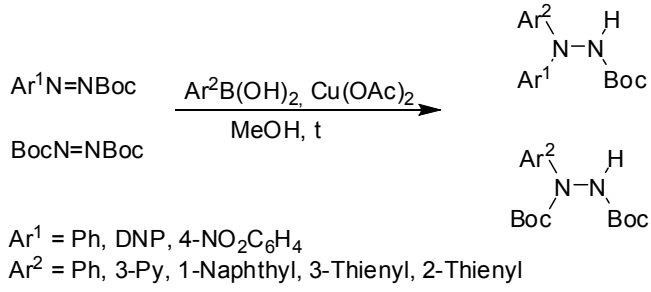
Scheme 26. Arylation of hydrazines with aryl boronic acids

Kabalka and Guchhait studied the reaction of *tert*-butyl carbazate with aryl boronic acids under conditions of copper catalysis [52]. However no expected direct N-arylation took place and diprotected monoarylated hydrazines were isolated in good yields after 6–96 h (Scheme 27). The process was catalyzed by 10 mol % of cuprous chloride. A wide range of substrates including aryl, heteroaryl, and vinylboronic acids were applied. Sterically hindered boronic acids also readily participated in this process. It was suggested that the reaction proceeds via self-coupling of *tert*-butyl carbazate to form 1,2-bis-Boc-hydrazine, which is then arylated by boronic acid.



Scheme 27. Synthesis of BocArNNHBoc

Recently Mäeorg *et al.* reported the addition of aryl- and heteroarylboronic acids to azo compounds [53] and this method was investigated in further studies [54]. The copper salt catalysis was required to perform the reaction under mild conditions and with high yields (Scheme 28). The excellent regioselectivity was observed during addition of aryl boronic acids to unsymmetrical azo compounds.

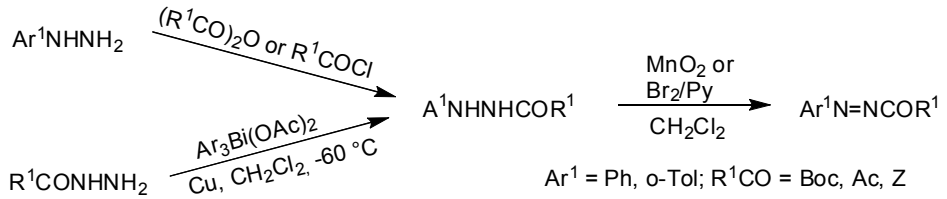


Scheme 28. Addition of arylboronic acids to azo compounds.

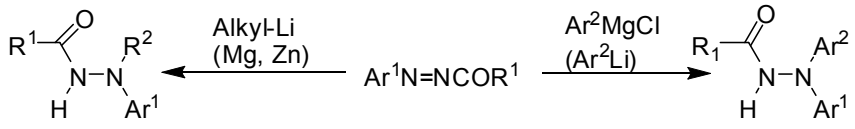
The parallel work was very recently reported by Uemura and Chatani and included azodicarboxylates as an electrophile [55].

Contrary to NH substitution as a way to derivatize a hydrazine precursor, another approach would use direct addition reaction to the N=N bond. Because of the exceptional electrophilicity of N=N bond, azo compounds have found wide use in organic synthesis. Actually, azo compounds with two alkoxycarbonyl groups are known as versatile electrophiles (DEAD, DBAD). The corresponding electrophilic aminations are widely used in the preparation of hydrazines, however, there are only few reports regarding nucleophilic addition to the unsymmetrically substituted azo compounds [56, 57].

Recently a very versatile and efficient method for the alkylation/arylation/heteroarylation was developed by Mäeorg *et al.* [58]. Firstly unsymmetrical azo compounds were synthesized as shown in Scheme 29, and then they were coupled with organometallic reagents (Scheme 30). The excellent regioselectivity was observed during the addition of diverse organometallic nucleophiles to unsymmetrical azo compounds. Primary, secondary and tertiary alkyl, as well as aryl and heteroaryl substituents were introduced this way in high yields.



Scheme 29. Synthesis of unsymmetrical aryl azo compounds



Scheme 30. Regioselective alkylation/arylation

2.3. Orthogonal protecting group strategy

The age of orthogonal protecting group strategy in the synthesis of hydrazine derivatives started in 1996 when Mäeorg and Ragnarsson published their first work on triprotected hydrazine precursors [59]. Hydrazine precursor is a hydrazine derivative containing a combination of orthogonal protecting groups (Figure 3). The conception of orthogonality means that different protecting

groups can be removed under non-overlapping conditions [60]. Normally such precursor contains three protecting groups and one NH group.

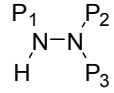
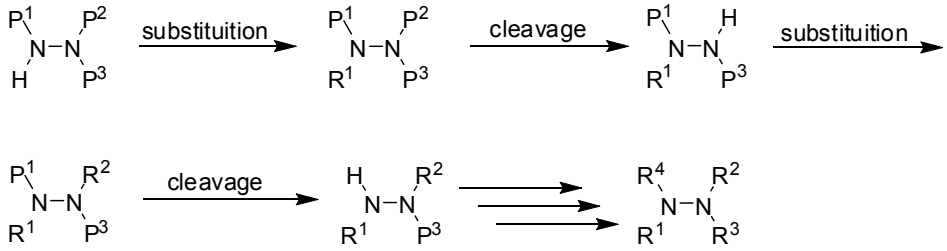


Figure 3. Hydrazine precursor

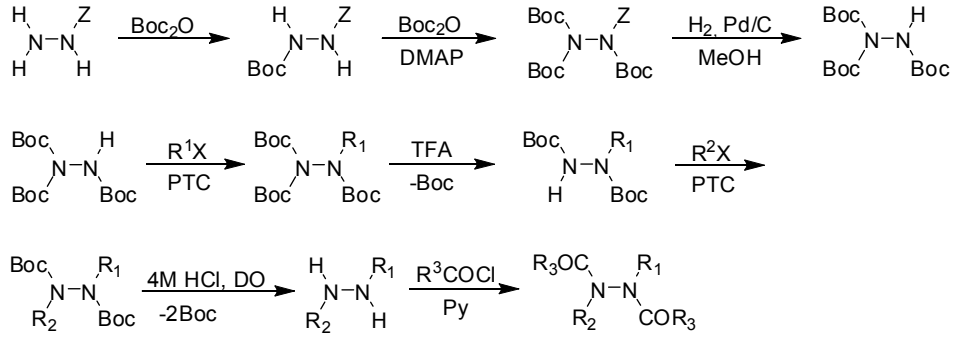
After the derivatization of free position in such precursor, a desired protecting group is selectively removed and the deprotected position can be derivatized again. This procedure is repeated until the desired compound is formed. Using this strategy up to tetrasubstituted hydrazine derivatives (all four substituents are different) can be obtained (Scheme 31).



Scheme 31. Stepwise synthesis of substituted hydrazines

As was already mentioned, in 1996 Mäeorg and Ragnarsson reported a new method for the systematic synthesis of tetrasubstituted hydrazines [59]. The synthetic pathway started with the preparation of 1,1,2-tris-(*tert*-butoxycarbonyl)hydrazine as shown in Scheme 32. This was the first triprotected hydrazine precursor invented and it allowed introducing only three different substituents into the molecule.

Despite this precursor contained three protecting groups they were all of the same type. The key point was that the protecting Boc-groups were not identical. Two Boc groups attached to one nitrogen atom were much more labile under cleavage conditions in comparison to a single Boc group having no geminal acyl neighbours. Thus, it was possible to selectively remove one Boc from $N(Boc)_2$ moiety using trifluoroacetic acid. Two remaining Boc groups, one on each nitrogen, were fully equivalent and could be removed only simultaneously.

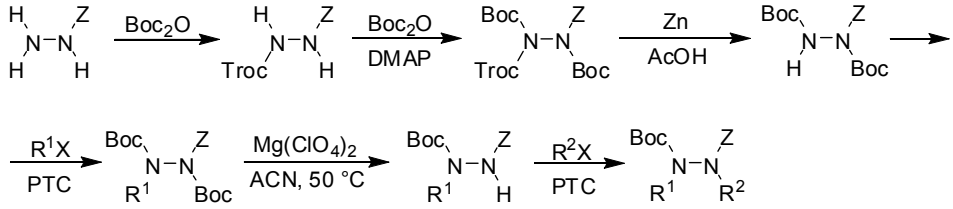


Scheme 32. Synthesis of 1,1,2-tris-Boc-hydrazine and its application

Phase transfer catalysis ($NaOH/K_2CO_3/TBAHS/C_6H_6$) was used to promote efficient N-alkylation of the precursor with primary alkyl halides (R^1 = Me, *n*-C_6H_{13}, Bn, *p*-$NO_2C_6H_4CH_2$). The desired alkylation products were obtained in excellent yields.

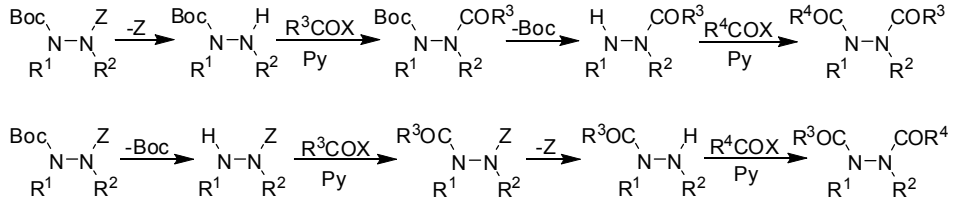
In a short while Mäeorg and Ragnarsson designed the more advanced triprotected precursor 1,2-Boc-2-Z-hydrazine [61,62]. In this precursor all protecting groups were orthogonal. In order to derivatize the precursor it was alkylated under liquid-liquid PTC conditions (10–20% aq. $NaOH/TBAHS/C_6H_6$). The N-alkylation products were afforded in high yields (R^1 = Me, Bn, $EtOCOCH_2$, allyl, 2,4-$(NO_2)_2C_6H_3$, 2,4-$(NO_2)_2$-F-C_6H_2, 4-NO_2-$C_6H_4CH_2$, *n*-C_6H_{13}).

It was also shown that catalytic amounts of $Mg(ClO_4)_2$ in ACN were sufficient to promote a smooth selective removal of one Boc-group from $BocNR^1NBocZ$. This method was recently applied for a cleavage of *tert*-butyl imidodicarbonates and *tert*-butyl acylcarbamates [74] and also worked perfectly on the corresponding hydrazine derivatives. After selective Boc-removal, N-alkylation was performed under PTC conditions (R^2 = Bn, Me, $EtOCOCH_2$, 2,4-$(NO_2)_2C_6H_3$, 4-NO_2-$C_6H_4CH_2$) as shown in Scheme 33.



Scheme 33. 1,2-bis-Boc-2-*Z*-hydrazine and its use for the synthesis of multisubstituted hydrazine derivatives.

The obtained BocR^1NNR^2Z contain two orthogonal groups, which can be cleaved in optional order as demonstrated in Scheme 34.

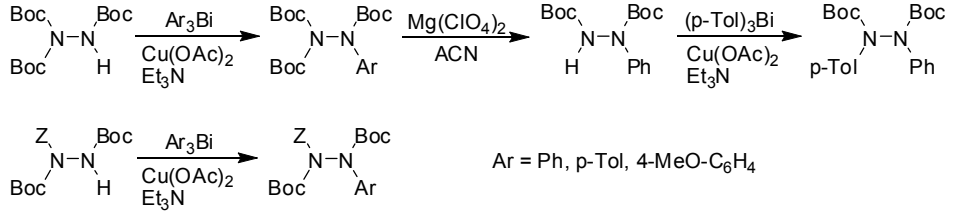


Scheme 34. Synthesis of tetrasubstituted hydrazines.

As a result, tetrasubstituted hydrazines with four different substituents were prepared in high yields (R^3CO, R^4CO = Ac, PhCO) [62].

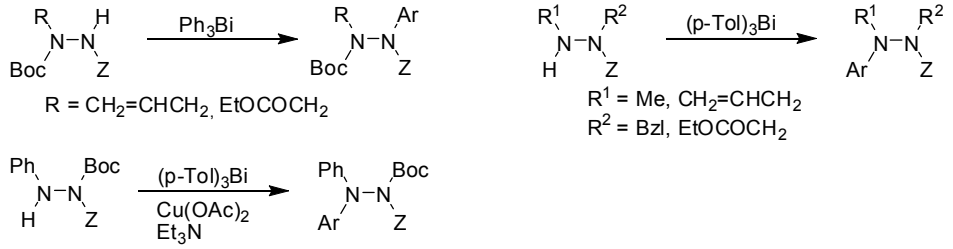
The above described methodology was tested on both 1,1,2-tri-Boc-hydrazine and 1,2-di-Boc-1-Z hydrazine for stepwise introduction of aromatic substituents into hydrazines [63]. In order to perform copper mediated N-arylation with triarylbismutanes, a versatile protocol developed by Chan was chosen [64]. The reaction of 1,1,2-tri-Boc-hydrazine with triphenylbismuthane was optimized in respect to the temperature and the stoichiometry of reagents and catalyst. As a result, the mole ratio 1.5/1.5/1.5 for the system $Ph_3Bi/Cu(OAc)_2/Et_3N$ was established. Refluxing the reagents in dichloromethane decreased the reaction time to 6 h in comparison to 23 h at room temperature.

Using these optimized conditions, a variety of hydrazine derivatives were arylated to give the corresponding monoarylated products as demonstrated in Scheme 35. No side products were detected and full conversion resulted in excellent yields.



Scheme 35. N-arylation of triprotected precursors.

In addition to the carbamate BocNH and ZNH arylation, the reactions were also performed on both amine and amide functions as demonstrated in Scheme 36.

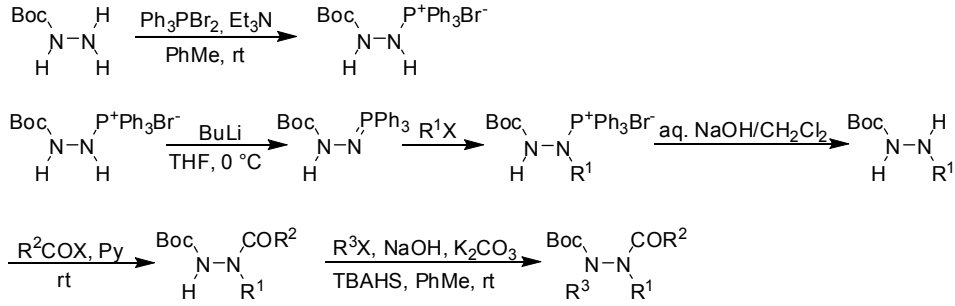


Scheme 36. N-arylation of trisubstituted hydrazine derivatives.

In continuation of efforts aiming at the systematic synthesis of multisubstituted hydrazines, Ragnarsson *et al.* developed two additional precursors, containing three different protecting groups [65, 66]. The first orthogonal combination included Z, Boc and Cbs [65]. The obtained triprotected precursor was subject to alkylation under Mitsunobu and PTC conditions. Several tetrasubstituted hydrazines with four different substituents were synthesized using this precursor.

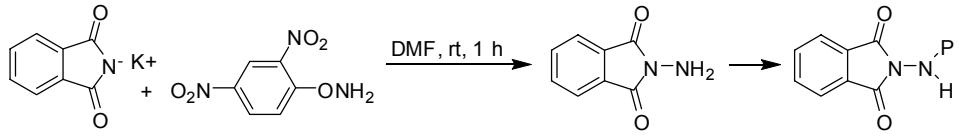
The other triprotected precursor was Ts-Z-Boc-hydrazine. The development of new method for cleavage of tosyl group with magnesium in methanol under sonification gave a possibility of using tosyl instead of Cbs group. The obtained precursor was also applied in the systematic synthesis of multisubstituted hydrazine derivatives [66–69].

After some time another precursor for the systematic synthesis of substituted hydrazines was reported [70]. Unlike previously developed precursors, this one contained only two protecting groups, thus providing a faster approach to multisubstituted derivatives. The selective introduction of alkyl and acyl groups was accomplished as illustrated in Scheme 37. Also a new convenient method for the deprotection of the triphenylphosphonium group was presented.



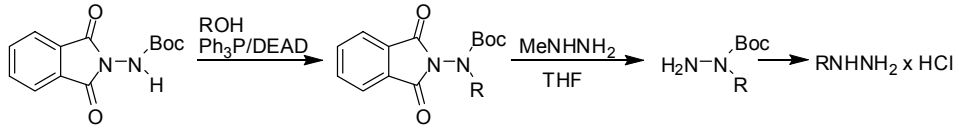
Scheme 37. Preparation of diprotected precursor and its use for obtaining of multisubstituted hydrazine derivatives

Application of phtalimide group in the systematic synthesis of hydrazine derivatives started in 1998, when Jamart-Gregoire *et al.* synthesized a series of labeled N-(protected)aminophtalimides as illustrated in Scheme 38 [71].



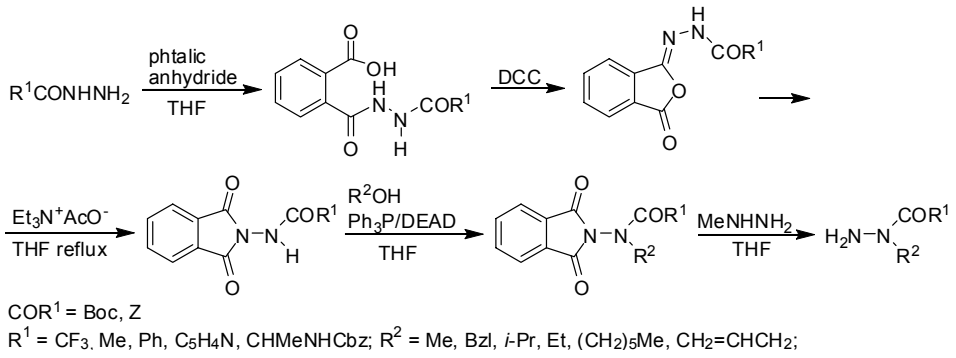
Scheme 38. Synthesis of N-protected aminophtalimides

Jamart-Gregoire *et al.* demonstrated that N-*tert*-butoxycarbonylaminophtalimide can be considered as triprotected precursor and used it as a versatile reagent for the synthesis of multisubstituted hydrazines [72]. The presence of three electron-withdrawing acyl groups increases the acidity of hydrazinyl proton. At the same time, the incorporation of two acyl groups into the phtaloyl moiety reduces steric hindrance. The alkylation of N-*tert*-butoxycarbonylaminophtalimide was performed under Mitsunobu conditions, using both primary and secondary alcohols (R = Me, Bn, Allyl, *i*-Pr, cyclopentyl) as shown in Scheme 39. The dephtaloylation was accomplished by methyl hydrazine. As a result, 1-alkyl-1-Boc-hydrazines and monoalkylhydrazines were obtained in high yields.



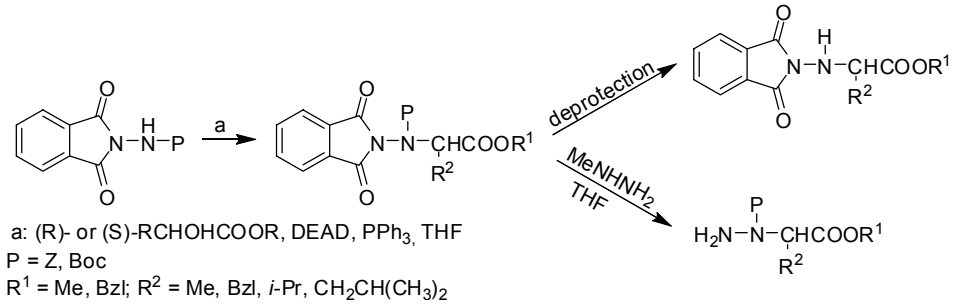
Scheme 39. Synthesis of substituted hydrazines via phtaloyl protection

Some time later, Jamart-Gregoire *et al.* suggested an alternative method for the preparation of a variety of N-acyl- and N-alkoxycarbonylaminophtalimides [73]. Commercially available hydrazides or carbamates were used as starting materials. The subsequent treatment with phthalic anhydride/DCC and triethylammonium acetate resulted in the formation of PhtNNHCOR in high yields as shown in Scheme 40. The obtained compounds were alkylated using the Mitsunobu protocol. After dephtaloylation the corresponding 1-alkylhydrazides and 1-alkylcarbazates such as $BocR^2NNH_2$ and ZR^2NNH_2 were readily obtained.



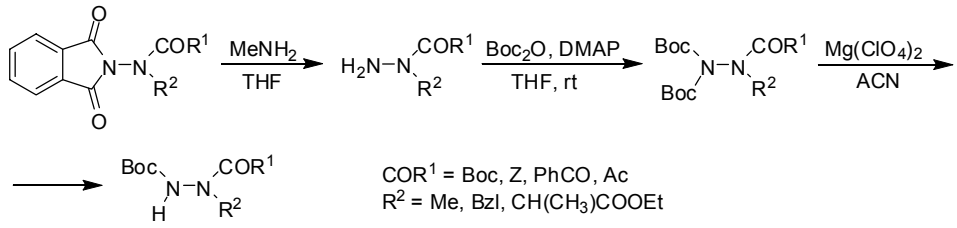
Scheme 40. Synthesis of substituted hydrazines via phtaloyl protection

The current method was extended in order to prepare chiral α-hydrazino acid derivatives with high optical purity [74]. Under Mitsunobu conditions, (R) and (S) –α-hydroxy esters reacted with N-alkoxycarbonylaminophtalimides, producing the corresponding products in high yields (Scheme 41). Subsequent dephtaloylation with methyl hydrazine afforded the protected α-hydrazino esters.



Scheme 41. Synthesis of chiral a-hydrazinoacid derivatives via phtaloyl protection.

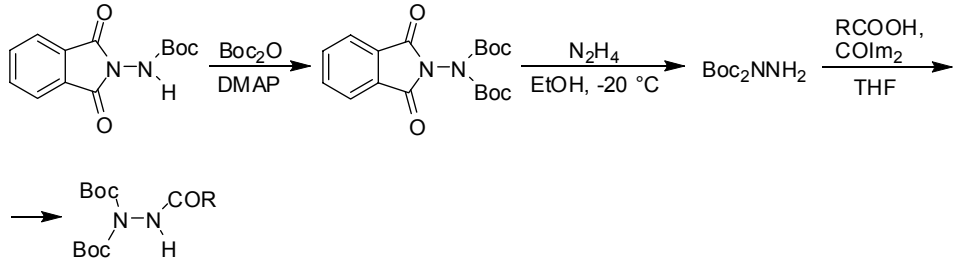
Jamart-Gregoire and Brosse also reported an efficient protocol for the conversion of the phtaloyl group into bis-*tert*-butoxycarbonyl group under very mild conditions [75]. At first, phtaloyl protected hydrazine derivatives were deprotected with methylamine as outlined in Scheme 42. After this, Boc groups were introduced by treatment with Boc_2O. In order to remove one Boc group selectively, catalytic amounts of magnesium perchlorate were used [76]. As a result, the protected hydrazines $BocNHNR^2COR^1$ were obtained in high to excellent yields (Scheme 43). Also these compounds can be considered as precursors to multisubstituted hydrazines.



Scheme 42. Conversion of phtaloyl group into bis-*tert*-butoxycarbonyl group

N-protected phtaloylhydrazide amino acids [74] were used in further studies [77].

Alkylation reactions of trisubstituted hydrazines by Mitsunobu and PTC approaches were thoroughly investigated [78]. It was demonstrated that aminophtalimide derivatives are better acidic partners than their amino-imidodicarbonate ($NBoc_2$) analogues in both Mitsunobu and PTC protocols. Also, PTC alkylation was found to be more sensitive to the steric hindrance than the Mitsunobu reaction.



Scheme 43. Synthesis of trisubstituted hydrazines

The above described phtaloyl protection was successfully applied in the solid phase synthesis of orthogonally protected chiral α-hydrazino acids [79]. Also, several of N-protected phtaloyhydrazides aminoacids exhibited organogelation phenomenon [80].

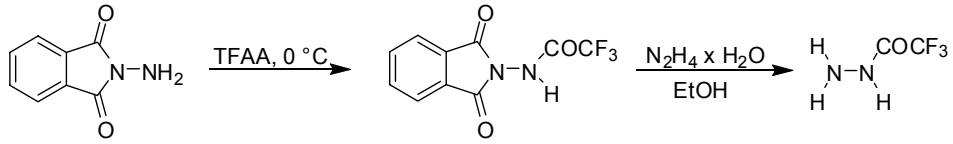
2.4. Synthesis of trifloroacetyl hydrazines

Trifluoroacetyl group is used in organic synthesis for multiple purposes. Due to the strong electronegativity of this group, it increases the acidity of neighboring NH and CH groups, thus providing a possibility to generate corresponding nucleophiles and use them in further synthesis. The trifluoroacetyl group is also used as a protecting group. Strong electronwithdrawing groups can give some

specific properties to the molecule, such as increased water solubility, which can be useful in preparation of the pesticides and drugs. There are not many works that deal with the synthesis of trifluoroacetyl hydrazides. The overview of existing methods is given below.

2.4.1. Synthesis of trifluoroacetylhydrazine

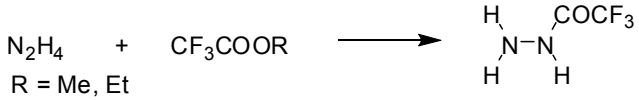
Acylation of hydrazines is a simple reaction and generally do not produce difficulties. However the direct acylation of hydrazine affords 1,2-diacylated product. In order to obtain monoacylatated product milder reagents or protecting groups must be used. For example, Brosse *et al.* obtained corresponding derivatives using phtaloyl group protection as shown in Scheme 44. See also section 2.3.



Scheme 44. Synthesis of trifluoroacetyl hydrazine

According to this method N-aminophtalimide was dissolved in TFAA on ice bath and stirred for 2 h. Yield was 90%. After the hydrazinolysis trifluoroacetyl hydrazine was obtained with 70% yield [70]. Later the same researchers tried to obtain 1-trifluoroacetyl-1-alkyl-hydrazines, but these attempts were not successful despite the corresponding phtaloyl-protected derivatives were obtained in high yields [72].

Multiple researchers [81–85] used the following general scheme (Scheme 45) in their syntheses:



Scheme 45. Synthesis of trifluoroacetyl hydrazine

Ried and Franz mixed methyl trifluoroacetate and hydrazine hydrate at 0°C in methanol. The reaction time was 2 h and the product was separated by vacuum distillation. Yield was 84% [81].

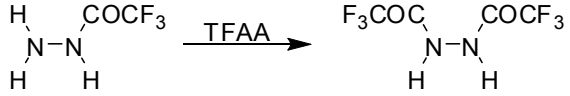
Brown *et al.* used a similar method, but 95% hydrazine was used instead of hydrazine hydrate and the reaction was performed at room temperature (4 h) [82].

Groth obtained trifluoroacetyl hydrazine hydrate starting from ethyl trifluoroacetate and 85% hydrazine hydrate in 95% ethanol. The reaction mixture was refluxed for 3 h and then evaporated, the crude yield was 88%. The product was purified by recrystallization [83].

Recently made investigation [84] showed that trifluoroacetyl hydrazine (mp 39–40°C) is not stable even in solid state, and dismutates to 1,2-bis-trifluoroacetylhydrazinate (mp 132–134°C). The reverse transformation is possible through heating above melting point or distillation.

2.4.2. Synthesis of 1,2-bis-trifluoroacetylhydrazine

Brown *et al.* synthesized 1,2-bis-trifluoroacetylhydrazine directly from TFAA and trifluoroacetyl hydrazine as outlined in Scheme 46. Yield was 86% [82].



Scheme 46. Synthesis of 1,2-bis-trifluoroacetylhydrazine

Groth synthesized 1,2-bis-trifluoroacetylhydrazine starting from trifluoroacetyl hydrazine hydrate and trifluoroacetyl chloride in the presence of Na_3PO_4 as a base. The product was separated by extraction and purified with sublimation. Yield was 83%. An attempt to acylate trifluoroacetyl hydrazine hydrate with trifluoroacetyl chloride in pyridine followed by separation with aq. HCl and crystallization from aq. acid afforded adduct of target compound with pyridine (1:2). The synthesis of 1,2-bis-trifluoroacetylhydrazine from anhydrous hydrazine, trifluoroacetyl chloride and sodium carbonate in Et_2O afforded the desired product with 70 % yield [83].

Young *et al.* added the anhydrous hydrazine to a solution of ethyl trifluoroacetate in absolute ethanol and after overnight stirring TFAA was added. On the other day volatiles were evaporated and the product was recrystallized from toluene [85].

Young *et al.* also attempted to synthesize $CF_3CO\text{-}N{=}N\text{-}COCF_3$ starting with 1,2-bis-trifluoroacetylhydrazine but unsuccessfully. The best method developed was an oxidation of $(CF_3CON)_2Hg$ with ICl in CCl_4. However the reaction yield was about 30–50% and the product contained ~ 20% CCl_4.

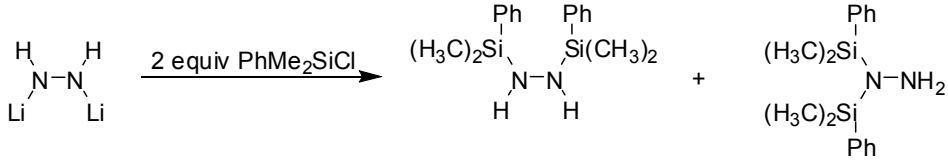
Tetrakis-trifluoroacetylhydrazine was obtained starting with 1,2-bis-trifluoroacetylhydrazine mercury salt $(CF_3CON)_2Hg$ and TFAA, through heating reaction mixture in hermetically sealed bomb [85].

2.5. Polyanions of hydrazine derivatives

The metallation of compounds is nowadays commonly used method in organic synthesis. Use of dianions is much more specific area, but there are many methods utilizing them [86, 87]. The main issues are selectivity of reactions and stability of neighboring groups. The selectivity in dianion reactions is based generally on huge differences in pK_a values of corresponding reaction centers. Also neighboring groups must be stable towards strong bases and organometallic reagents.

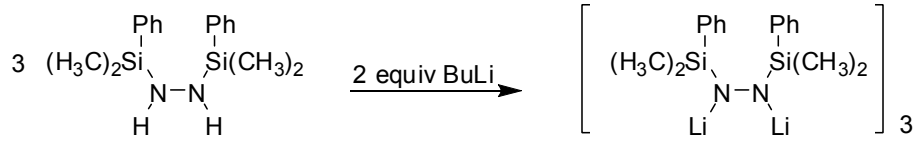
There are very few reports on di- and polyanions of hydrazine or its derivatives. Some of them concern hydrazone dianions which is used for the synthesis of alkenes (Shapiro reaction [88, 89]) or synthesis of heterocycles [90, 91]. Most of other methods deal with simple trimethylsilyl derivatives [92] or lithiated hydrazines like $Li_2N_2H_2$.

The first silyl hydrazines were synthesized in the end of fifties by Aylett [93] and Wannagat [94]. There are two possibilities for synthesis of silyl hydrazines: the first is the reaction of halogenosilanes with hydrazine, and the second is the reaction of halogenosilanes with lithium hydrazides. Lithium derivatives have a big synthetic potential, however there is plenty of reports stating that they have strong tendency for rearrangements [95–97]. For example, when phenyldimetylchlorosilane reacts with dilithiated hydrazine two products are formed (Scheme 47).



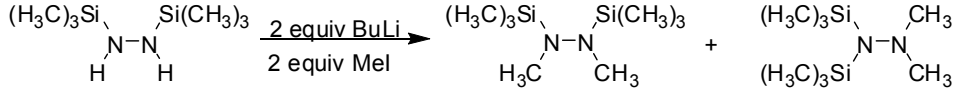
Scheme 47. Silylation of dilithiated hydrazine

Also lithiated derivatives aggregate and produce complexes (Scheme 48), many of them were obtained in crystalline state and their structures were confirmed by X-ray crystallographic analysis [92, 96].



Scheme 48. Aggregation of dianions

The first attempt to alkylate the 1,2-bis-silyl dianion was done by Bailey as illustrated in Scheme 49. However the reaction was not selective and two products were formed in 1:1 ratio [96]. 1,2-bis(trimethylsilyl)-hydrazine was treated with 2 equivalents of *n*-BuLi in tetrahydrofuran followed by 2 equivalents of methyl iodide. The reaction mixture was found to contain both the expected product, 1,2-bis(trimethylsilyl)-1,2-dimethylhydrazine, and the rearranged product, l,l-bis(trimethylsilyl)-2,2-dimethylhydrazine.

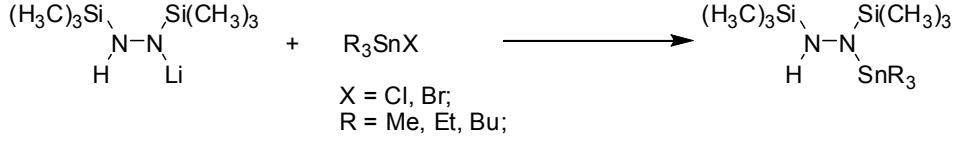


Scheme 49. Alkylation of dianion

However there are remaining concerns that the starting 1,2-bis-trimethylsilyl-hydrazine was already a mixture of two compounds [96].

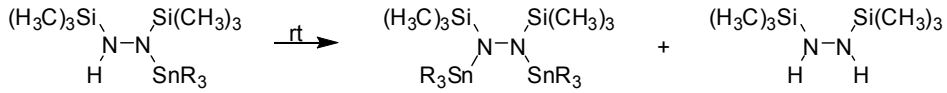
Generally use of mono anions provided more acceptable derivatization results and large variety of silyl hydrazines were obtained in this way [92]. However examples were limited only by silyl derivatives.

Attempts to obtain tin-organic derivatives from lithiated sylil hydrazine were also recently made as illustrated in Scheme 50 [98].



Scheme 50. Stannylation of 1,2-bis-(trimethylsilyl)-hydrazine

However the product was unstable and disproportionated at rt as outlined in Scheme 51.



Scheme 51. Decomposition of stannylated hydrazine

3. AIMS OF THE STUDY

1) To provide faster and more efficient method for the systematic synthesis of hydrazine derivatives

2) To study the generation, stability and reactivity of polyanions

3) To study the influence of neighboring group effects and steric hindrance in polyanions

4) Investigate scope and limitations of polyanion strategy.

5) To contribute to the development of preparative methods for the synthesis of hydrazine derivatives.

6) Synthesize series of hydrazine derivatives with strong electron-withdrawing groups.

10

4. RESULTS AND DISCUSSION

4.1. Synthesis of acidic hydrazines and their importance

Hydrazine is a quite strong base, similarly with ammonia and amines. However it can be considered as very weak acid. Acidity and nucleophilicity are different concepts, and consider different properties of a molecule, but very often they are bound to each other because they both reflect the state of electron density on particular atom.

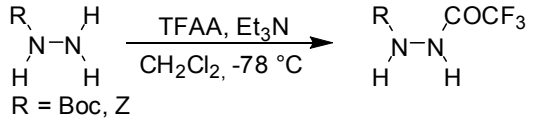
The reactivity of compounds also strongly depends on their acidity. For example, in the alkylation of hydrazides with alcohols under Mitsunobu conditions (in the presence of triphenylphosphine and an azodicarboxylate) an acidic nitrogen component is required [99]. It was demonstrated that for imidodicarbonates and tosylcarbamates there is a clear connection between their pK_a value in DMSO and the yield of product with a selected alcohol in the Mitsunobu reaction [100]. Also our further research showed that reactivity of lithiated hydrazine derivatives clearly depends on the acidity of corresponding NH-groups. Moreover differences in acidities can easily be used for achievement of the selectivity of reactions.

The acidity can be expressed in pK_a values. These values can be measured experimentally or estimated from the quantum mechanical calculations. However calculations provide only the gas phase acidity, which significantly differs from the acidity in a solvent. Finding the correlation between these two values, opens the way for predicting real pK_a values from calculated data, thus predicting properties and reactivity of new compounds. Also the acidity of hydrazines may be correlated with the acidity of amines, thus providing another approach for prediction of pK_a values. Such correlations were studied in Paper I. These investigations have fundamental meaning in the field of structure-property relationship.

There are very few pK_a values of hydrazine derivatives measured experimentally, so we needed to synthesize more hydrazine derivatives to provide experimental data for the correlations. Most of known pK_a values are "in the middle" of the scale. There are two possibilities to improve the precision of correlation: one to measure acidic derivatives, and other to measure basic derivatives. However alkyl hydrazines and hydrazine itself are too weak NH acids for a measurement of their pK_a in DMSO due to the autoprotolysis of the solvent. Thus the only way is to synthesize acidic hydrazine derivatives and measure their pK_a values.

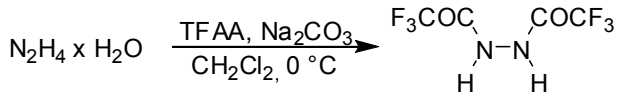
While trifluoroacetyl and trifluoromethanesulfonyl groups are very strong electron-withdrawing groups, we decided to synthesize a series of compounds containing them. Firstly $ZNHNH_2$ and $BocNHNH_2$ were treated with TFAA in the presence of triethylamine furnishing after the purification $ZNHNHCOCF_3$

and $BocNHNHCOCF_3$ with high yields as shown in the Scheme 52. Also BocNHNHTf and ZNHNHTf were obtained by the Hendricson procedure [101].



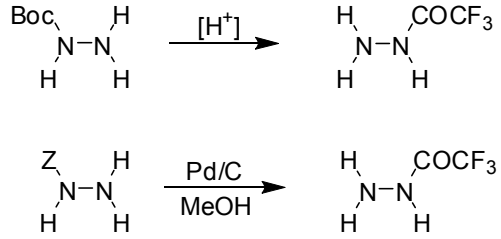
Scheme 52. Trifluoroacylation of Boc- and Z-hydrazines

1,2-bis-trifluoroacetylhydrazine was obtained directly from hydrazine hydrate and TFAA, in the presence of Na_2CO_3 in dichloromethane (Scheme 53).



Scheme 53. Synthesis of 1,2-bis-trifluoracetylhydrazine

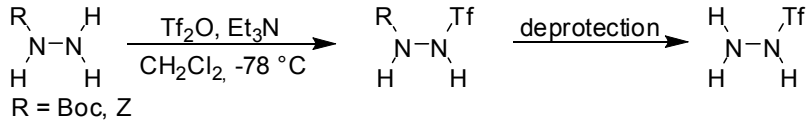
Mono trifluoroacetyl hydrazine was obtained indirectly through removing of protecting groups. Boc group was cleaved by TFA/CH_2Cl_2 or HCl/dioxane. The attempt to recrystallyze trifluoroacetyl hydrazine hydrochloride from boiling acetonitrile surprisingly yielded 1,2-bis-trifluoroacetylhydrazine. On the other hand the instability of mono trifluoroacetyl hydrazine is known [84]. In order to obtain the trifluoroacetyl hydrazine as a free base, Z group was removed by the reduction with H_2 on the Pd/C catalyst as illustrated in Scheme 54.



Scheme 54. Synthesis of mono trifluoroacetyl hydrazine

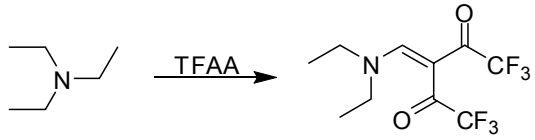
Attempts to obtain mono trifluoromethanesulfonyl hydrazine were made by removing Boc group with an acid and Z group through the hydrogenation (Scheme 55). However there was no convincing evidence that the obtained sub-

stance is actually $TfNHNH_2$. Very recently published studies have confirmed that $TfNHNH_2$ decomposes at the temperatures higher than –30°C [107].



Scheme 55. Trifylation and synthesis of trifyl hydrazine

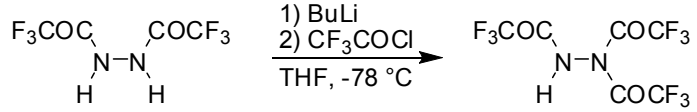
Attempts for di- and triacylation of $BocNHNH_2$ resulted a mixture of products. Under low temperatures only $BocNHNHCOCF_3$ was formed, and at the higher temperatures mixture of products containing mainly $Et_2NCH=C(COCF_3)_2$ was observed. The formation of $Et_2NCH=C(COCF_3)_2$ happens due to the oxidation of Et_3N by TFAA as shown in the Scheme 56 [102–104]. Change of the base as well as the use of $ZNHNH_2$ as starting material gave no effect.



Scheme 56. Oxidation of triethylamine

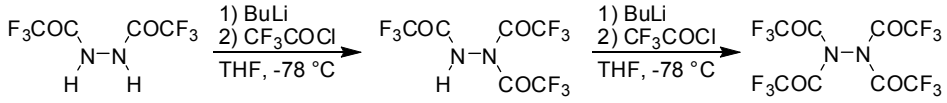
1,2-bis-trifluoroacetylhydrazine was chosen as the next substrate, because trifluoroacetyl groups are quite stable towards acids. Thus use of the base could be omitted as well as purification step. This is important because according to the literature $N(TFA)_2$ group is an acylating agent [85]. It can react with amines, alcohols, water and silicagel, thus making its separation and purification extremely complicated task. Then the direct acylation with TFAA was attempted, however no reaction was observed.

We proposed that this happens due to the lack of nucleophilicity of the corresponding NH groups. Thus a metallation of 1,2-bis-trifluoroacetyl-hydrazine was carried out by the addition of one equivalent of BuLi as shown in Scheme 57. Trifluoroacetyl chloride was used as an acylating agent. The main point was in a formation of LiCl, which do not interfere with the product in spectra. Trifluoroacetyl chloride was generated immediately before the use, according to the known procedure, from pyridine hydrochloride and TFAA [105]. Formation of the product was confirmed by NMR, but also presence of THF has been noticed. We proposed that THF produced a solvate with LiCl. Thus the procedure was changed and Et_2O was used as a solvent in next experiments. After the reaction lithium chloride has precipitated from the reaction mixture and no solvates were observed. The tris-triflouoroacetyl-hydrazine was formed in a good yield.



Scheme 57. Synthesis of tris-trifluroacetyl hydrazine

The metallation of 1,2-bis-trifluoroacetylhydrazine was also accomplished with 2 equivalents of BuLi, and after this excess of CF_3COCl was added. However it was not possible to obtain tetrakis-trifluoacetylhydrazine in Et_2O and only tris-trifluoroacetylhydrazine was obtained. The formation of $(CF_3CO)_2NN(COCF_3)_2$ was observed only in THF, furthermore stepwise addition of reagents was required in order to ensure the formation of the product (Scheme 58).



Scheme 58. Synthesis of tetrakis-trifluoroacetylhydrazine

Synthesis of trifluoroacetyl hydrazides was fully covered in Paper II. The pK_a values of synthesized compounds were measured and partially used for the obtaining of correlations in Paper I. The measurement results are presented in Table 1.

Table 1. pK_a values of acidic hydrazines

Compound	**pK_a value**
$CF_3CONHNH_2$	16.6
$CF_3CONHNH_3^+TFA^-$	6.4
$CF_3CONHNHBoc$	10.0
TfNHNHBoc	8.2
TFANHNHTFA	7.4

Study of the synthesis of acidic hydrazine derivatives gave us the unique experience. We have observed how thermodynamic properties and reactivity of hydrazine derivatives were changing with the growth of acidity. For example, trifluoroacetyl and trifluoromethanesulfonyl derivatives have much better solubility in water comparing with other hydrazine derivatives and also they cannot be acylated in common ways due to the lack of nucleophilicity on nitrogen atoms. Such observations have led us towards a discovery of the polyanion strategy. Also attempts of synthesis of tetrakis-trifluoroacetyl-

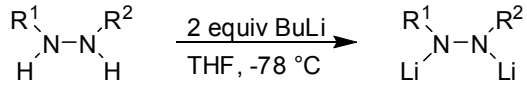
hydrazine were actually the first implementation of dianion, but it wasn't recognized that time.

4.2. Polyanion strategy

In recent years many methods for the derivatization of hydrazine were invented. Most of them are utilizing the orthogonal protecting group strategy, which is very versatile and gave access to a large variety of multisubstituted hydrazines on the systematic base. However this strategy requires many of protection/ deprotection steps for the obtaining of desired product. Further investigations have led to the development of precursors containing only two protecting groups. But still the atom efficacy was not very good. Only few general methods for the synthesis of hydrazine derivatives, which do not utilize orthogonal protecting group strategy, were published [32, 58].

The fast progress in field of structure-properties relationship, measurements of the acidity of organic compounds and wide distribution of strong bases such as organolithium compounds as synthetic reagents, led us to a development of the completely new strategy, which is not based on the use of protecting groups. This is an excellent example of how achievements in physical organic chemistry and good understanding of theoretical bases of the process lead to the development of new synthetic methods.

The key step of our strategy is the formation of dianion, which is subsequently used for the obtaining of target compound.



Scheme 59. Formation of dianion

The selectivity of alkylation or acylation of such dianion is ensured by the differences in acidity of corresponding NH-groups. The more acidic group has lower nucleophilicity and reactivity. In case when $R^1 = R^2$ selectivity can be achieved by careful control of stoichiometry of reagent and the temperature of reaction mixture.

Actually Rasmussen [32] also used strong bases in one or two equivalent quantities for obtaining of desired derivatives. However author said nothing about the formation of mono- or dianions in these reactions. Nevertheless taking into account our results it may be supposed that his methodology was quite near to our methods.

There are few reports utilizing a similar methodology for the preparation of pyrazolidine ring systems [25, 106], but again there were no words about mechanism of reaction or formation of dianions. Also there were no reports

about the selective alkylation. Furthermore, our method provides the possibility to carry out reactions under milder conditions, more safely and with simpler separation of products with an excellent yield.

The existence of dianions is often being debated, but there are numerous things that prove the formation of dianions. Firstly, disubstituted hydrazines are treated with BuLi, which is a very strong base and readily deprotonates any NH groups in disubstituted hydrazines. The reaction proceeds very fast even at –78°C. Secondly, the formation of many dianions brings a colour change of the reaction mixture i.e. the reaction mixture sharply changes its colour after the addition of two equivalents of BuLi. Thirdly, the reaction purity and the yields of alkylation prove that the dianion is present and BuLi has fully reacted. If the reaction would be incomplete, BuLi would be still present in the solution. When an alkyl halide is added, it would firstly react with BuLi, and only after BuLi is consumed the reaction with the nitrogen nucleophile could take place. This means that the yield should be low in such case and the reaction would not be selective. For example, if only one of two equivalents of added BuLi has reacted, the other would be present in the solution. When two equivalents of alkyl halide are added, one equivalent reacts with remaining BuLi, and other one with lithiated hydrazine, thus furnishing only monoalkylated derivative. If only one equivalent of alkyl halide is added, the desired product should not be observed at all. And finally there are many reports on the structure (X-ray analysis) of dilithiated silyl hydrazides confirming that the dilithiation actually takes place [92, 96].

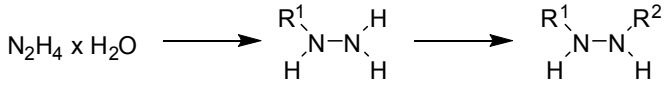
Dianions can be generated from a variety of substrates bearing alkyl, aryl and acyl groups, which can belong to the different classes of compounds (for example: BocNHNHBoc, PhNHNHPh, EtNHNHBoc). The dianions obtained from phenyl containing hydrazine derivatives are colored substances. For example, the dianion obtained from BocNHNHPh is bright yellow, from PhNHNHPh is green, but the dianions obtained from BocNHNHEt and BocNHNHBoc are colorless.

In the early stages the stability of dilithiated derivatives was one of the biggest concerns, but we found that they are very stable under inert atmosphere. BocNHNHPh dianion is completely stable even at room temperature. However PhNHNHPh dianion was very sensitive to the oxygen, and rapidly decomposed if oxygen was present. Z protecting group cannot be used in this strategy due to decomposition. This proceeds through the metallation of benzylic CH_2 in Z group. The corresponding mono- and dimethylated products were identified after the trapping with CH_3I.

The solubility of polyanions was the other concern, but we were lucky. The PhNHNHBoc dianion, which was used as the starting compound for our investigations, was well soluble in THF in concentration range we used. Sometimes it has unexpectedly precipitated from the solution, but the reactivity was not remarkably affected, and after the first alkylation the product was soluble again. The PhNHNHPh dianion was also very soluble as well as EtNHNHBoc

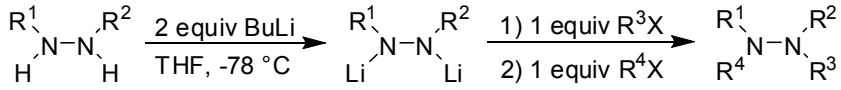
dianion. However BocNHNHBoc anions had a tendency to precipitate from the reaction mixture, and especially its monoanion. In this case the reactivity was also affected. The BocNHNHCOOEt dianion always precipitated from THF solution after a short period of stirring and no reaction with alkyl halides was observed. The $CF_3CONHNHCOCF_3$ dianion precipitated rapidly, the precipitate was stable at the air and was not soluble even in DMSO.

The first step of the synthesis is the obtaining of a monosubstituted hydrazine derivative, and the second step is the creation of a disubstituted derivative (Scheme 60). These transformations can be done by variety of conventional methods. Commercially available mono and disubstituted hydrazine reagents may also be used.



Scheme 60. Synthesis of mono- and disubstituted derivatives

The third step (Scheme 61) was carried out by the addition of two equivalents of *n*-BuLi to the disubstituted hydrazine derivative followed by the addition of one equivalent of alkyl halide. After the first equivalent of alkyl halide has reacted, the second one was added. The first alkylation occurs at the most basic and nucleophilic nitrogen and the second happens on the other one.



R^1=Boc, Ph; R^2=Boc, Ph, Et;
R^3, R^4=alkyl; X=Br, I

Scheme 61. Selective dialkylation of dianion.

Selectivity and steric effects of this reaction were studied in Paper III using PhNHNHBoc as the model compound (Table 2). The study begun with a symmetrical alkylation (R^3 = R^4). Reactions were monitored by TLC. The stepwise character of alkylation could easily be observed; i.e. monoalkylated products were formed quickly (2 h) and dialkylated products were formed very slowly (1–4 days). However this can be explained with huge differences in acidities (and nucleophilicity) of PhNH and BocNH groups. Dialkylation took from 3 h to 4 days for the completion depending on the bulkiness of the employed electrophile and its reactivity. The reaction rate increases in the following order of leaving groups: chloride, bromide and iodide.

It was also noticed that the steric effects may play an important role in this reaction. As it was already mentioned the bulkier alkylating agents reacted slower, and moreover it was not possible to obtain dialkylated product from sterically more hindered aliphatic electrophiles (Pr, *i*-Pr, etc) even using a great excess of alkylating agent. On the other hand allyl bromide and benzyl bromide readily reacted with dianion to form dialkylated product. Also if one substituent is Pr and other is Me the alkylation is still possible (Table 2; entries 8, 9).

The temperature control is very important. The first alkylation of dianion was not very selective if the addition of alkyl halide was made at the room temperature. And actually if the first alkylation proceeds unselectively, the subsequent alkylations are useless. Thus to improve the selectivity the addition of alkyl halide was made at lower temperatures. The best results were achieved with the following procedure. The addition of BuLi was made at –78°C and after that the reaction mixture was allowed to stir and warm up in 15 min to –60°C. Then alkyl halide was added and the reaction mixture was allowed to warm up slowly (~ 1 h) to the room temperature, and thereafter the reaction mixture was stirred for another 1 h. Then another alkyl halide was added and the reaction mixture was stirred for 2–96 hours depending on the alkyl halide. As it was already mentioned the second alkylation is slow due to the low nucleophilicity at Boc nitrogen and steric hindrance. Under such conditions reactions proceeded selectively with good to excellent yields (Table 2).

In our further studies (Paper V) we have found that the formation of dianion and its subsequent dialkylation with diverse alkylating agents in one-pot fashion, can be readily accomplished with a variety of substrates bearing alkyl, phenyl and alkoxycarbonyl groups (PhNHNHBoc, EtNHNHBoc, PhNHNHPh, BocNHNHBoc). The results are presented in Table 3.

As it was already mentioned the metallation of PhNHNHPh must be conducted under carefully controlled inert atmosphere. If there is a significant amount of oxygen present, it will lead to a quick decomposition of the corresponding dianion. The water addition workup of the reaction mixture under inert atmosphere is also required before the purification step. In opposite case the decomposition of the product may occur when it comes into contact with the air. We suppose that decomposition happens by the radical mechanism. For the other substrates (PhNHNHBoc, EtNHNHBoc, BocNHNHBoc) such phenomenon has not been noticed.

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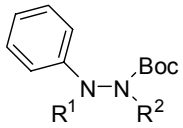
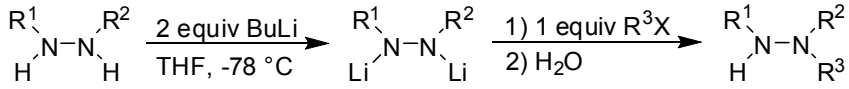
Table 2. Investigation of steric effects and optimization of conditions



Entry	R^1	R^2	Conditions	Yield, %
1	Me	Me	2 equiv MeI, 3 h, rt	89
2	Et	Et	2 equiv EtBr, 4 d, rt	87
3	allyl	allyl	2 equiv allyl bromide, 1 d, rt	85
4	Bn	Bn	2 equiv BnBr, 1 d, rt	92
5	$-(CH_2)_3-$		IPrI, 1 h, rt	72
6	Me	Et	MeI, –60°C to rt, 2 h; EtBr, 1 d, 40°C	84
7	Et	Me	EtBr, –60°C to rt, 2 h; MeI 12 h, rt	91
8	Me	Pr	MeI, –60°C to rt, 2 h; PrBr, 1 d, 40°C	76
9	Pr	Me	PrBr, –60°C to rt, 2 h; MeI, 12 h, rt	89
10	Me	H	MeI, –60°C to rt, 2 h, rt	86
11	Et	H	EtBr, –60°C to rt, 2 h, rt	82
12	Pr	H	PrBr, –60°C to rt, 2 h, rt	80
13	*i*-Pr	H	*i*-PrI, –60°C to rt, 2 h, rt	76
14	allyl	H	allyl bromide, –60°C to rt, 2 h, rt	90
15	Bn	H	BnBr, –60°C to rt, 2 h, rt	76
16	C_7H_{13}[a]	H	$C_7H_{13}Br$, –60°C to rt, 2 h, rt	78
17	H	Me	MeI, 3 h, –20°C[b]	80
18	H	Et	EtBr, 3 d, –20°C[b]	45
19	H	*i*-Pr	*i*-PrI, 3 d, –20°C[b]	41
20	H	allyl	allyl bromide, 1 d, –20°C[b]	60
21	H	Bn	BnBr, 1 d, –20°C[b]	62

[a] C_7H_{13} = cyclohexylmethyl, [b] addition was made at –60°C

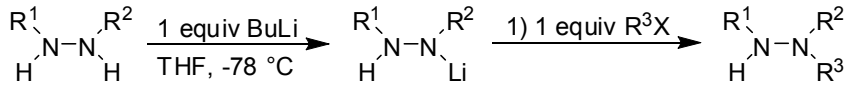


R^1=Boc, Ph; R^2=Boc, Ph, Et;
R^3=alkyl; X=Br

Scheme 62. Monoalkylation of dianions

In case of trisubstituted derivative is required, it can be easily obtained just adding only one equivalent of alkylating agent (Table 2; Entries 10–21 and Table 3; Entries 12–15). The alkylation occurs on the most basic and nucleophilic nitrogen and the other one remains unreacted as lithium salt. After the addition of water the product is obtained. Again, the addition of BuLi was made at –78°C and the addition of alkyl halide at –60°C. Then the reaction mixture

was allowed to warm up slowly (~1 h) to the room temperature. This method was studied in Paper III and in Paper V.



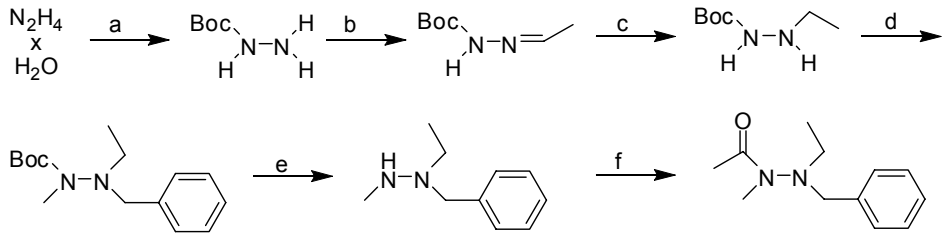
R^1=Boc, Ph; R^2=Boc, Ph, Et;
R^3=alkyl; X=Br

Scheme 63. Monoalkylation of monoanion

The other possibility is to use only one equivalent of *n*-BuLi in order to increase the atom efficacy (Scheme 63) of the reaction. This can be especially good in case of symmetrical substrates. If the substrate is unsymmetrical the use of one equivalent of *n*-BuLi should lead to the metallation and subsequent alkylation of the most acidic and the least nucleophilic nitrogen. However, as was shown in Paper III, the careful temperature control is required for obtaining of the desired product. For example, the monoanion of PhNHNHBoc could be selectively alkylated only if the temperature was maintained at –20°C. If the temperature was below –30°C the reaction was not taking place, and if the temperature was higher than –10°C a mixture of products have formed. The amount of side products was as bigger as higher was the temperature of the reaction mixture. This can be explained by the equilibria between monoanions in the reaction mixture and kinetic control of the reaction. The metallation of EtNHNHBoc with one equivalent of *n*-BuLi followed by alkylation with allyl bromide, should result formation of the *tert*-butyl-1-allyl-2-ethylhydrazinecarboxylate, however as was shown in Paper V, we have obtained *tert*-butyl 2-allyl-2-ethylhydrazinecarboxylate as the main product. Also other authors have faced the tendency of dianions to form mixture of isomers or disproportionate [95–98].

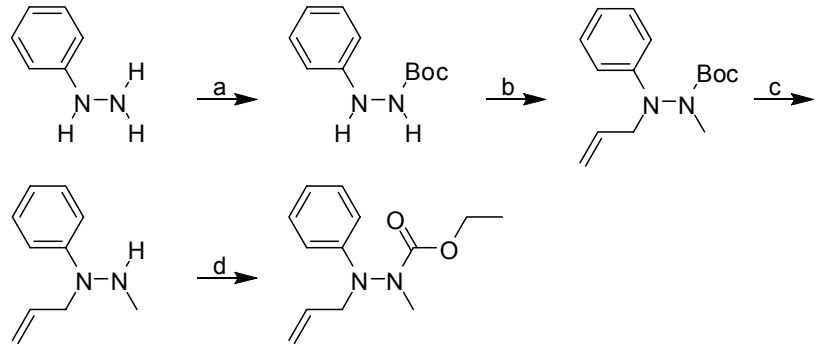
As an illustration of application of our strategy we have accomplished the systematic synthesis of tetrasubstituted hydrazine derivatives as shown on the schemes 64 and 65.

If the obtained derivative contains protecting groups as substituents (Table 1; Table 2, Entries 6–15), they can be removed by the appropriate method and optionally replaced with any desired group (Scheme 64).



Scheme 64. Systematic synthesis of tetrasubstituted hydrazine derivatives. (a) Boc_2O, PrOH, 2h, rt. (b) CH_3CHO, $CHCl_3$, 1h, rt. (c) LAH, THF, 0 ºC. (d) 1) 2 equiv BuLi, THF, –78 ºC; 2) 1 equiv BnBr, 2h, –60 ºC to rt; 3) MeI, 3h, rt. (e) 1) TFA:DCM 1:2, 1h, rt; 2) KOH(aq). (f) Ac_2O, Py, DCM, 2h, rt

Scheme 64 shows full synthetic sequence starting with hydrazine hydrate and ending with the fully substituted hydrazine derivative. In the first step $BocNHNH_2$ was made from hydrazine hydrate. Then *tert*-butyl-2-ethylidene-hydrazine-carboxylate, obtained by condensation of $BocNHNH_2$ with ethanal, has been reduced with lithium aluminum hydride yielding compound BocNHNHEt. The dialkylation was accomplished via standard procedure (Scheme 61). Thereafter Boc group was removed with DCM/TFA mixture and the product was treated with aqueous 1M KOH to obtain the free trialkyl hydrazine 16. Finally, 16 was acylated with Ac_2O in the presence of pyridine.



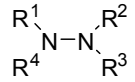
Scheme 65. Systematic synthesis of tetrasubstituted hydrazine derivatives. (a) Boc_2O, ACN, rt. (b) 1) 2 equiv BuLi, THF, –78 ºC; 2) 1 equiv allyl bromide, 2h, –60 ºC to rt; 3) MeI, 3h, rt. (c) 1) TFA:DCM 1:2, 1h, rt; 2) KOH (aq). (d) ClCOOEt, Py, DCM, 2h, rt

Scheme 65 shows the other possible route that starts with phenyl hydrazine. It is much shorter and also very useful when aryl substituted hydrazine derivative is required. Phenyl hydrazine was converted to PhNHNHBoc with Boc_2O in ACN. Later it was dialkylated via dianion according to the standard procedure. Then

Boc group was removed by treating with TFA in dichloromethane and the obtained hydrazine derivative was acylated again with ethyl chloroformate.

Also our strategy can be used for the synthesis of heterocycles via reaction of corresponding dianion with dihalide (Table 2; entry 5).

Table 3. Synthesized compounds



Compound	R^1	R^2	R^3	R^4	Yield, %
1	Boc	H	H	H	75
2	Boc	$=CHCH_3$	–	H	100
3	Boc	Et	H	H	57
4	Boc	Ph	H	H	69
5	Boc	Boc	H	H	85
6	Boc	Et	Bn	Me	60
7	Boc	Ph	allyl	Me	93
8	Boc	Et	allyl	Me	70
9	Ph	Ph	Me	Me	97
10	Ph	Ph	allyl	Me	71
11	Boc	Boc	Bn	Bn	97
12	Boc	Et	allyl	H	65
13	Ph	Ph	allyl	H	96
14	Boc	Boc	Bn	H	71
15	Boc	Boc	allyl	H	80
16	H	Et	Bn	Me	93
17	H	Ph	allyl	Me	97
18	Ac	Et	Bn	Me	67
19	Ac	Ph	allyl	Me	98
20	COOEt	Ph	allyl	Me	97
21	$COCF_3$	Ph	allyl	Me	93

In addition to the alkylation, dianions can also be successfully acylated and sulfonated. Some interesting examples are shown in Figure 4. However there are simpler methods often available for such transformations.

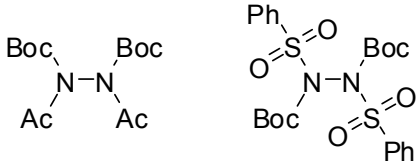


Figure 4. Dianion acylation and sulfonation products

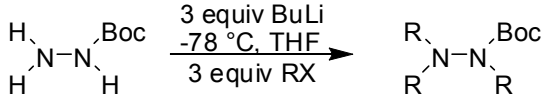
Currently we were unable to introduce the aryl substituents into hydrazine derivatives via dianion. However the aryl group can be already present in the substrate (like phenyl hydrazine) or introduced separately by the methods described in Section 2.2.

4.2.1. Trianion

During the development of our polyanion strategy we have attempted to create the trianion of substituted hydrazine and investigate its possible application in the systematic synthesis of hydrazine derivatives. Relying on our previous experience we have decided to use *tert*-butyl carbazate as the model compound. As can be seen from our previous studies, the Boc group has excellent stability towards strong bases such as BuLi, and furthermore it provides two types of different NH groups, which can be used in subsequent synthesis.

The $BocNHNH_2$ has three reactive NH groups with different acidities. The difference between amine and amide reaction centers can be roughly estimated as 10 pK_a units. The reactivity of corresponding anions is also different. Thus, this difference can be used for the selective alkylation.

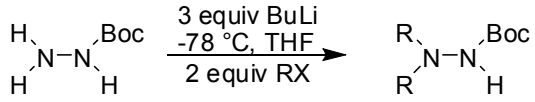
The trianion was generated by the addition of three equivalents of *n*-BuLi to a solution of *tert*-butyl carbazate in THF. Our resent investigations have shown that the trianion was stable in the THF solution at low temperatures, but partial decomposition was detected at room temperature. We have also noticed that the trianion was unstable in the presence of air, so all reactions must be carried out in an inert atmosphere. The trianion can be alkylated using 4 equivalents of alkyl halide (R = Me, Bn, allyl, X = Br, I), to form corresponding trialkyl derivative (Scheme 66). Methyl iodide and allyl bromide reacted as expected. 1,1,2-trimethyl-2-Boc hydrazine was a volatile liquid (bp 40°C, 150 mm Hg) thus providing considerable difficulties in its separation. Surprisingly the benzyl bromide was unable to form the corresponding tribenzyl derivative even with excess of benzyl halide, affording only 2,2-dibenzyl-Boc-hydrazine, probably due to the steric hindrance.



Scheme 66. Alkylation of trianion with 3 equivalents of alkyl halide

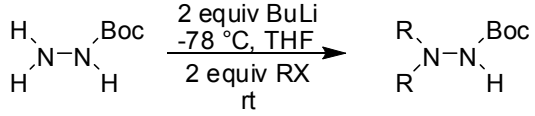
Typically the addition of *n*-BuLi was made at –90°C and after 15 min of stirring alkyl halide was added at –40°C. Then the reaction mixture was allowed to warm up slowly (~1 h) to room temperature and after this stirred until the completion of the reaction.

Use of two equivalents of alkyl halide (R = Me, Bn, allyl, X = Br, I) expectedly gave corresponding 2,2-dialkyl derivatives (Table 4, Entries 3–5) (Scheme 67). Reaction proceeded selectively because of the low reactivity of Boc-connected nitrogen. The reactions were made as it was described for the trialkylation, but the addition of alkyl halide was made at –60°C. Generally reactions have an excellent selectivity even if the addition of alkyl halide is made at room temperature, but the yields in such case are lower. Probably this happens due to decomposition of trianion. An attempt to use 1-bromo-4-clorobuthane as alkylating agent yielded the *tert*-butyl pyrrolidin-1-ylcarbamate. This method provides an easy access to the cyclic hydrazine derivatives.



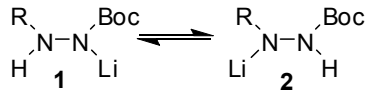
Scheme 67. Alkylation of trianion with two equivalents of alkyl halide

The treatment of $BocNHNH_2$ with two equivalents of *n*-BuLi should produce 1,2-dianion, because the first equivalent of BuLi reacts with the most acidic (BocNH) group and the second reacts with amine NH group. Consequently the reaction of this dianion with two equivalents of alkyl halide should give corresponding 1,2-dialkyl derivative, but alkylation of 1,2-dianion unexpectedly gave 2,2-dialkyl derivative (Table 4, Entries 7,8) as a main product (Scheme 68). The procedure was the same as for the alkylation of trianion with two equivalents of alkyl halide.



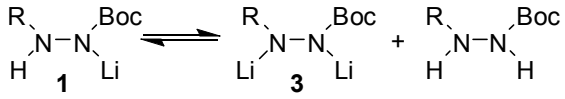
Scheme 68. Alkylation of dianion with two equivalents of alkyl halide

Thermodynamically the formation of 1,2-dialkylated product is much more preferable; however the obtained products show that we have a kinetic control here. The one of possible explanations is the relatively fast intramolecular equilibrium between anions 1 and 2 in the reaction mixture (Scheme 69). The anion 2 is rapidly consumed by the reaction with alkyl halide bringing the reaction towards the formation of dialkylated product.



Scheme 69. Equilibrium of anions

The other possible way is the equilibrious lithiation of anion 1 by itself (Scheme 70) or by any other anion producing dianion 3.



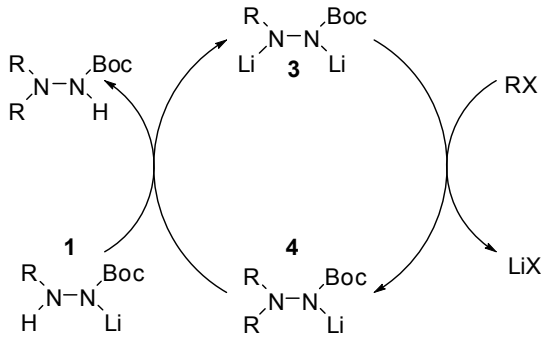
Scheme 70. Self lithiation of anion 1

Taking into account the difference in acidities of amine and amide centers (or basicities of corresponding anions) it can be assumed that the equilibrium is strongly shifted towards anion 1, but the reactivity of the formed dianion 3 is much higher, so it reacts rapidly and is continuously consumed.

Once the dianion 3 is formed, it reacts with alkyl halide producing the anion 4. The anion 4 equilibriously metallates the anion 1 yielding dialkylated product and again the dianion 3 (Scheme 71). Thus anions 1, 3 and 4 are acting like catalytic cycle.

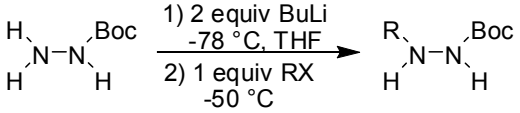
Other equilibria are also possible, but those discussed above are in better accordance with the experimental data. Firstly we suppose that the first alkylation goes fast. Therefore after short time most of the anions in the reaction mixture are represented by anion 1. Secondly if one of the equilibrium components continuously consumed, equilibrium becomes practically irreversible and can be presented as disproportionation. Thus any equilibrium with the retention of lithium at amide nitrogen would give large amount of starting material or monoalkylated product and yield would be lower than 50 %. In our case the reaction proceeded cleanly with yield substantially more than 50%. However if the addition of alkyl halide was made at room temperature some amount of mono- and trialkylated products could be observed.

The formation of the 2-allyl-Boc-hydrazine (Table 4, Entry 9) was achieved only by freezing down the equilibrium at –50°C and using one equivalent of allyl bromide. Nevertheless use of other alkylating agents at the same conditions gave a mixture of products.



Scheme 71. Equilibrium of anions

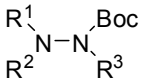
All attempts to use one equivalent of BuLi for the alkylation gave a mixture of products. 2,2-dialkylated products also have been separated from the mixture. Mechanism of its formation should also be related to anion equilibria discussed above. It seems that anion equilibrium is quite general feature of hydrazine anions. Some other reports on formation of unexpected product isomers from hydrazine anions (probably due to the interanion equilibrium) were previously described in literature [95–97].



Scheme 72. Alkylation of dianion with one equivalent of alkyl halide

The Boc protecting group can be removed from all of reported compounds and then they can be further derivatized by common methods.

Table 4. Alkylation products



Entry	R^1	R^2	R^3	Conditions	yield, %
1	Me	Me	Me	4 equiv MeI, 1 d, rt	89
2	allyl	allyl	allyl	4 equiv allyl bromide, 1 d, rt	68
3	Me	Me	H	2 equiv MeI, 3 h, rt	74
4	allyl	allyl	H	2 equiv allyl bromide, 3 h, rt	77
5	Bn	Bn	H	2 equiv BnBr, 3 h, rt	72
6	$-(CH_2)_4-$		H	1 equiv $Br(CH_2)_4Cl$, 2 h, rt	65
7	allyl	allyl	H	2 equiv allyl bromide, 2 h, rt	67
8	Bn	Bn	H	2 equiv BnBr,3 h, rt	62
9	allyl	H	H	1 equiv allyl bromide, 2 h, –50°C	50

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5. CONCLUSIONS

Current thesis describes the discovery and development of a completely new strategy for the systematic synthesis of hydrazine derivatives. Also its connection with physical organic chemistry has been shown.

The key step of the polyanion strategy is a formation of di- and trianions of hydrazine derivatives and their subsequent selective alkylation with the diverse substituents. A possibility of acylation and sulfonation of polyanions has been shown. Also the polyanion strategy can be successfully applied for the synthesis of heterocycles. The use of monoanions is studied during our investigations and found to be effective in certain cases.

The discovered strategy contains many unprecedented results. For example existence of trianion was firstly reported. Furthermore the application of polyanions for the systematic synthesis of hydrazine derivatives is also firstly reported. The polyanion strategy includes several methods, which can be applied according to the structure and complexity of the target compound.

The polyanion strategy provides much faster approach to the substituted hydrazines. Tetrasubstituted products with any desired substituents (all substituents are different) are obtained in five steps starting from hydrazine hydrate. In contrast to that, all the methods reported before demand at least twice as much steps. Furthermore, the desired product can be prepared in one step if starting from a disubstituted hydrazine derivative.

The formation, stability and use of dianions for the systematic synthesis of hydrazine derivatives were investigated. Also the formation and use of trianion for the same purposes was firstly reported. The dianions have formed very efficiently and mainly they were found to be completely stable under inert atmosphere. Numerous substrates bearing Boc, Ph, Et, $COCF_3$, COOEt groups were studied.

Neighboring group effects and steric hindrance of polyanions were investigated. It was found that neighboring groups had a very big influence to the reactivity of corresponding dianions. Steric effects were not a problem, however in some cases they shown to be strong enough to prevent a formation of the desired product.

The scope and limitations of polyanion strategy were also thoroughly investigated and demonstrated. It was found that this new strategy is very general and can be applied in the systematic synthesis of hydrazine derivatives. Despite some limitations due to instability of the substituents with complex functionality, the polyanion strategy is a very fast and selective approach to the substituted hydrazines.

During the preliminary studies a number of acidic hydrazine derivatives were synthesized. Their pK_a values were measured and used for the development of structure-property correlations of hydrazine derivatives.

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SUMMARY IN ESTONIAN

Mono- ja polüanioonide kasutamine hüdrasiini derivaatide sünteesil

Käesolev dissertatsioon kirjeldab täiesti uue strateegia leiutamist ja arendamist hüdrasiini derivaatide süstemaatilise sünteesi jaoks. Samuti näidati selle strateegia seos füüsikalise orgaanilise keemiaga.

Polüanioonide strateegia võtme etapiks on di- ja trianioonide moodustumine ning nende edasine selektiivne alküülimine erinevate asendajatega. Lisaks sellele näidati võimalust polüanioone atsüülida ja sulfoonida. Polüanioonide strateegiat võib rakendada ka heterotsüklite sünteesiks. Uuriti monoanioonide kasutamist ning näidati nende efektiivsust kitsamatel juhtudel.

Leiutatud strateegia sisaldab palju uusi tulemusi. Näiteks trianiooni eksisteerimist publitseeriti esmakordselt. Peale selle polüanioonide kasutamine hüdrasiini derivaatide sünteesi jaoks pole varem kirjeldatud. Polüanioonide strateegia sisaldab mitmed meetodid mis kasutatakse sõltuvalt sihtmolekuli struktuurist ja komplitseeritust.

Polüanioonide strateegia on väga kiire meetod asendatud hüdrasiinide sünteesi jaoks. Tetraasentadatud produktid mistahes asendajatega (kõik võivad olla erinevad) võivad olla saadud viie etappiga lähtudes hüdrasiinhüdraadist. Kõik teised seni tuntud meetodid nõuavad vähemalt kaks korda rohkem etappe. Peale selle juhul kui lähtutakse diasendatud hüdrasiini derivaadist soovitud produkti on võimalik saada ühe etappiga.

Uuriti dianioonide moodustumist, stabiilsust ning kasutamist hüdrasiini derivaatide sünteesiks. Samuti uuriti trianiooni moodustamist ning kasutamist samal eesmärgil. Dianioonid tekkisid väga efektiivselt ja põhiliselt nad olid täiesti stabiilsed inertse atmosfääri all. Mitmed substraadid Boc, Ph, Et, $COCF_3$, COOEt rühmadega olid uuritud.

Uuriti naaberrühmade efekte ja steerilist takistust polüanioonides. Leiti et naaberrühmad mõjutavad dianioonide reaktiivsust väga tugevasti. Steeriline takistus peamiselt ei seganud reaktsioonide kulgemist, kuid teatud juhtudel see oli piisav selleks et vältida soovitud produkti teket.

Põhjalikult uuriti ja demonstreeriti polüanioonide strateegia kasutusala ja piiranguid. Leiti et see strateegia on väga üldine ja saab olla kasutatud hüdrasiini derivaatide süstemaatiliseks sünteesiks. Vaatamata mõnedele piirangutele, mis on seotud funktsionaalsete rühmade ebastabiilsusega, polüanioonide strateegia on väga kiire ja selektiivne meetod asendatud hüdrasiinide saamiseks.

Algsete uuringute käigus sünteesiti mitmeid happelisi hüdrasiini derivaate. Mõõdeti nende pK_a konstante ja kasutati neid hüdrasiini derivaatide struktuur-omadus korrelatisionide tegemiseks.

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Scientific publications

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