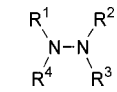
Synthetic methodology for alkyl substituted hydrazines



Ulf Ragnarsson

Department of Biochemistry, University of Uppsala, Biomedical Center, P.O. Box 576, SE-751 23, Uppsala, Sweden. urbki@bmc.uu.se; Fax: +46(18)55 21 39; Tel: +46(18)471 45 55

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Substituted hydrazines have found many technical and commercial applications and this is reflected in the immense number of such compounds synthesized to date. In this review an attempt has been made to supplement the existing comprehensive literature by presenting only a selection of synthetic methods, judged to be of particular principal or practical interest, together with some additional, recent approaches. The important steps in the development from simple substituted hydrazines to rational synthesis of multisubstituted derivatives are recapitulated.

1 Introduction

Hydrazine derivatives are nowadays of considerable technical and commercial importance.[1] With respect to the application of such compounds it should be pointed out that several mono- and also a few disubstituted hydrazines are employed as reagents in organic chemistry and a compilation of such substances is shown in Fig. 1. This includes phenylhydrazine (**1a**), the oldest hydrazine reagent, which played an important role in the making of crystalline derivatives of carbohydrates. It also became the prototype for many other robust reagents like **1b** and **2**, used in simple qualitative tests for carbonyl functions and for identification of carbonyl compounds. Other reagents include the hydrazide **3b**,[2] which after conversion to azide could be applied for protection of amino functions by acid-labile *tert*-butoxycarbonyl (Boc) groups, the use of which is nowadays routine in some areas of synthetic organic chemistry. Reagents **4** and **5** are resolution agents for enantiomers and compound **7** as well as its enantiomer are used in asymmetric synthesis. Various arenesulfonyl derivatives **6** are important sources of diazene and tosylhydrazine especially has found applications in reductive transformations. For more details about the properties and applications of these and other hydrazine reagents in modern organic synthesis, reference is made to a recent encyclopedia.[3]

Another classical application of hydrazines and hydrazides is in the synthesis of heterocycles. More specifically, hydrazines undergo reaction with a large variety of 1,3-difunctional substances to give pyrazoles and in its simplest case a monosubstituted hydrazine can be used to introduce a substituent on a pyrazole nitrogen. Similarly, 1,2-disubstituted hydrazines can be used to make pyrazole derivatives such as

Ulf Ragnarsson was born in Ljungby, Sweden, in 1934. He studied chemistry and received his academic degrees in Lund, Stockholm and Uppsala. After postdoctoral work at the Technical University Munich, Exeter University and Rockefeller University, he has for over 30 years been employed as research assistant and more recently assistant professor at the University of Uppsala. He holds honorary degrees from the Universities of Gdansk, Poland and Tartu, Estonia. His research centers on synthesis of various nitrogen compounds (amino acids, polyamines, hydrazines and, especially, peptides).

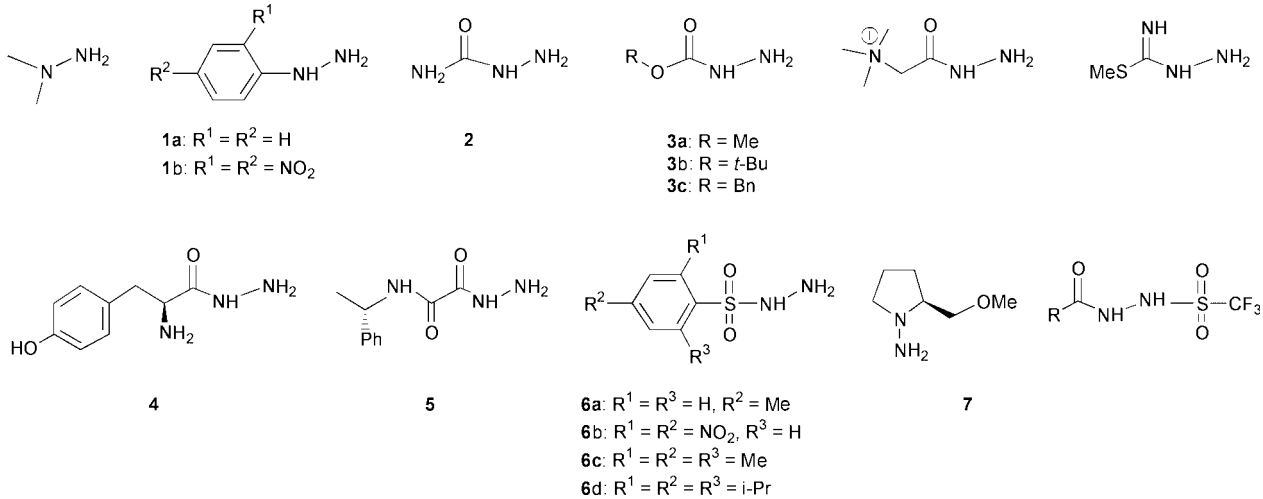
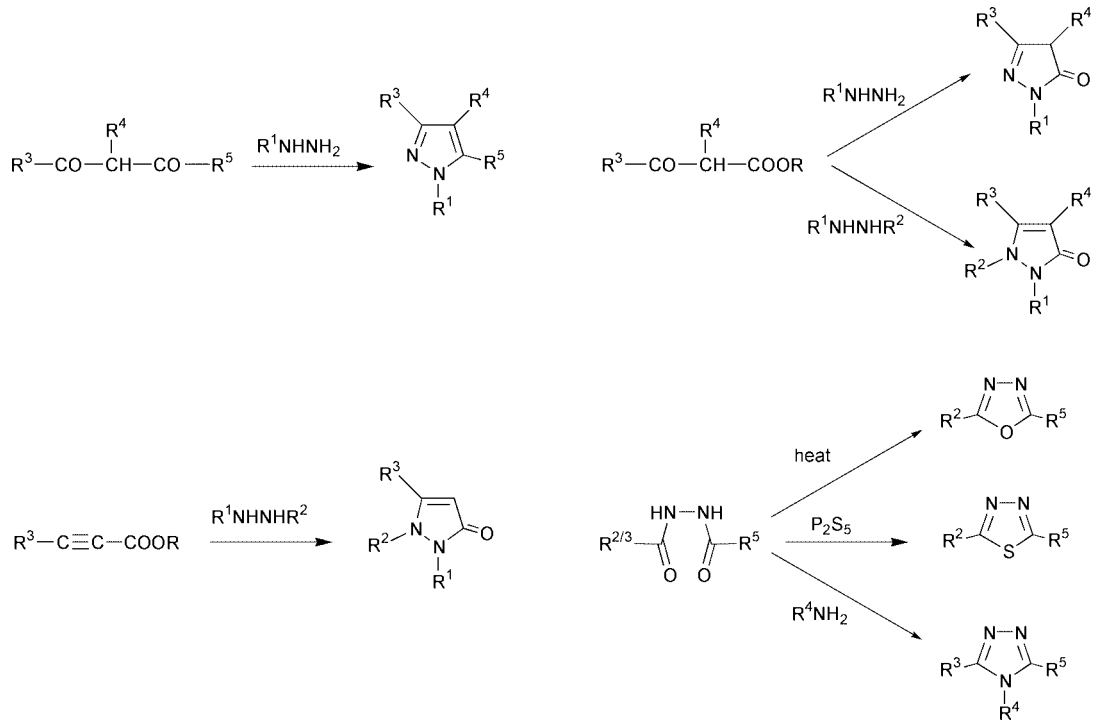


Fig. 1 Selected mono- and disubstituted hydrazines with application as organic reagents.



Scheme 1 Examples of five-membered heterocycles made from hydrazines and hydrazides.

various pyrazolones with substituents on both nitrogens. By simultaneous variation of the hydrazine and the 1,3-difunctional reaction partner a wide spectrum of heterocycles become easily accessible and a few examples, based on a trisubstituted β-diketone, disubstituted acetoacetate and an acetylenic ester, are illustrated in Scheme 1.[4] Diacylhydrazides can be cyclized to give 1,3,4-oxa- and thiadiazoles and 1,2,4-triazoles.[5] Many heterocycles are precursors of drugs, agrochemicals and dyestuffs and are therefore of commercial importance.

Substituted hydrazines are key components of azapeptides, a kind of peptidomimetic in which one or more of the amino acid residues have been replaced by monomers with nitrogens in the positions of the chiral carbons, carrying substituents identical with those of proteinogenic amino acids (Fig. 2). As a result of this modification the azapeptide backbone generally undergoes only a minor change in comparison with that of its prototype. On the other hand, this modification has a dramatic effect on the stability of carbon–nitrogen bonds in the vicinity of the substituted sites to proteolytic enzymes which otherwise alone or together degrade peptides and proteins *via* smaller fragments ultimately to free amino acids. A number of azapeptide analogues of biologically active peptides have been prepared and shown to have a prolonged or otherwise useful effect as a consequence of which they have been exploited commercially as drugs.[6] More recently a compound containing only azapeptide bonds, called an azatide, was also prepared and studied as a potential drug.[7]

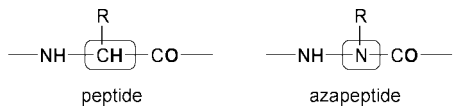


Fig. 2 Structural element of azapeptides.

Isoniacid, 4-pyridinecarboxylic acid hydrazide, (**8**) is the active principle in many compositions used in combating tuberculosis. During clinical trials of an alkylated derivative **9** for treatment of this disease, it was found to have a mood-elevating effect and subsequent studies showed this to be due to an inhibiting effect on the enzyme monoamine oxidase, which oxidatively deaminates neurotransmitters such as noradrenaline and serotonin. Other inhibitors of a similar type such as **10** have been used to treat depression. The hydrazino acid carbidopa (**11**) inhibits the decarboxylation of dopa, (*S*)-3,4-dihydroxyphenylalanine, which is an important antiparkinsonian drug and precursor of dopamine. The combined administration of **11** and dopa results in a slower release of dopamine and a prolonged effect of the drug (Fig. 3).

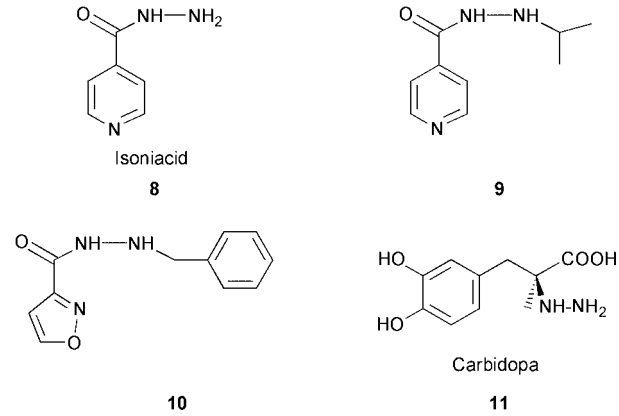


Fig. 3 Examples of simple hydrazine derivatives used as drugs.

After compound **12** had been found to mimic the action of 20-hydroxyecdysone in insects, a new class of diacylhydrazine insecticide with high specificity could be developed by the Rohm and Haas Company.[8] The simpler analogue **13**, known as RH-5849, was found to have commercial-level activity against a range of insect pest species, whereas most importantly it was judged to have a benign ecotoxicological profile and be safe to beneficial insects species. It has also been shown to interact with ecdysteroid receptor proteins. As a result of further development work two more potent analogues **14** (RH-5992, tebufenozide) and **15** (RH-0345, halofenozide) have been produced, of which **14** is marketed worldwide. It exhibits high, specific toxicity against lepidopteran larvae, but is devoid of toxicity to

non-lepidopteran species. By comparison, compound **15** has a broader insect control spectrum (Fig. 4).

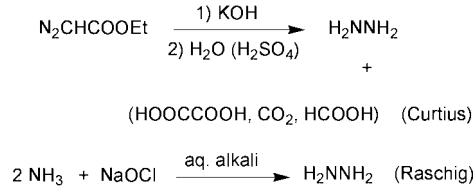
2 Pioneering work on substituted hydrazines

The first substance of this kind to be synthesized and named a hydrazine was phenylhydrazine (**1a**).[9] This was accomplished at a time when hydrazine itself was not yet known. Shortly after the key discovery that aromatic amines on treatment with HNO_2 give rise to diazonium salts, the synthesis of **1a** was based on aniline and direct reduction of the corresponding salt (Scheme 2). Originally reduction was accomplished by sulfite salts but subsequently various other convenient reducing agents have also been applied. Since aromatic amines generally are easily available, this simple method has in the past been applied for the synthesis of a large number of monosubstituted aromatic hydrazines and it still remains the method of choice for such substances.

Shortly afterwards a handful of 1,1-disubstituted hydrazines with both aliphatic and aromatic substituents were prepared by nitrosation of secondary amines and the primarily formed nitrosamines reduced to furnish the desired products (Scheme 2). This procedure is also of wide scope, but as many nitrosamines are established carcinogens their manipulation should be avoided unless special precautions are taken. For the first synthesis of a monoalkylhydrazine a similar nitrosation approach was taken starting from a substituted urea, the subsequent hydrolysis of which furnished the desired product.

A few examples of a fourth type of derivative, *i.e* 1,2-disubstituted hydrazines, were made from **1a** including PhNHNHMe, the synthesis of which anticipated more recent work by first protecting both nitrogens by benzoylation before alkylation was performed (Scheme 2). Subsequent saponification provided the desired product.

The pioneering work described so far in this section was all performed by Emil Fischer and initiated in 1875. Within a period of around 10 years before free hydrazine became available about 20 mono- and disubstituted hydrazine derivatives with aliphatic and aromatic substituents were prepared, based mainly on the methods indicated in Scheme 2.[10] Free hydrazine was first prepared by Curtius in 1887 from ethyl diazoacetate according to the overall reaction given below but it would still take about 20 years until a first industrial process was developed by Raschig based on hypochlorite and ammonia (Scheme 3).



Scheme 3 Two classical syntheses of free hydrazine.

Nowadays urea is also used as a starting material in the industrial production of hydrazine.[11] Hydrazine forms an azeotrope with water in the approximate ratio 1:1, usually called hydrazine hydrate. The annual production capacity of hydrazine hydrate worldwide in 1992 was estimated to be over 50 000 t.

Thanks to the work of several prominent chemists, within one generation after Fischer's classical synthetic experiments the author of the first hydrazine monograph, himself an authority in hydrazine chemistry, in the preface stated that with respect to the reactive hydrazine framework 'with much experimental skill and acumen nearly all possibilities had been exhausted'.[10] Nevertheless, when hydrazine compounds proved useful in various fields as exemplified in the introduction, an intensive development started which resulted in many innovations: a brief presentation of these is given below in Section 4.

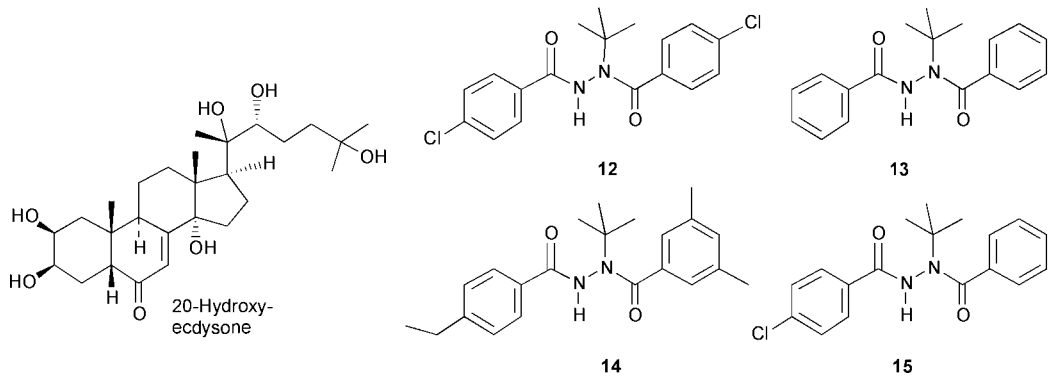
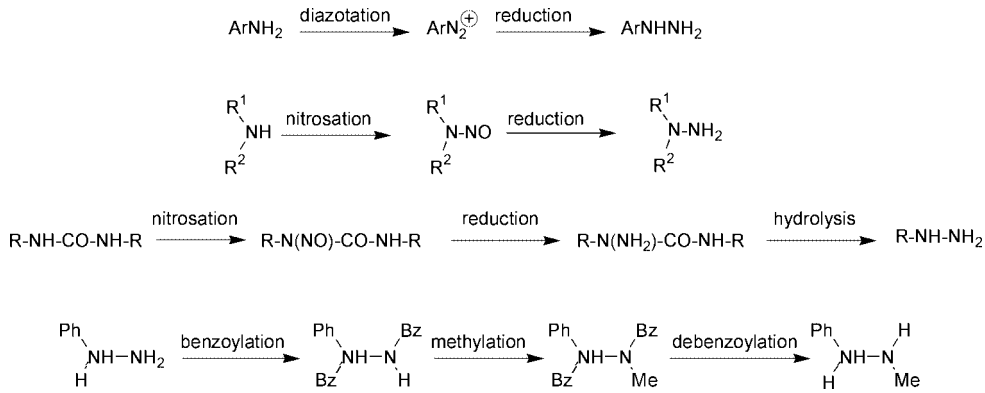


Fig. 4 20-Hydroxyecdysone and some diacylhydrazine ecdysteroid agonists.



Scheme 2 Four early synthetic procedures for substituted hydrazines (E. Fischer).

3 Substituted hydrazines today as reflected in production figures

The previous section gave a short account of the earliest work in the hydrazine field. To illustrate the growth of this research area after the first steps towards synthesis of simple substituted hydrazines and free hydrazine had been taken and to give an idea of its present status, a few figures will be presented. When not otherwise stated, they were all collected from the Beilstein database and reflect the situation in February 2001.[12]

The total number of hydrazine compounds (defined as those with a N–N single bond and four substituents with arbitrary structure or hydrogen) described in the literature is very high and is now over 83 000. Over 25 000 are classified as monosubstituted, about 3800 as 1,1-disubstituted, over 37 000 as 1,2-disubstituted, over 14 500 as trisubstituted and 3000 as tetrasubstituted. To put these figures in a wider perspective, the total number of organic and inorganic compounds in the database of Chemical Abstracts at the same time was about 17 600 000.

Only for the first category in the last paragraph, monosubstituted hydrazines, will a more detailed presentation of the substituent distribution from general structural point of view be given. Among these compounds, cyclic substituents appear with more than double the frequency of their acyclic counterparts. Furthermore, the ratio between heterocyclic and carbocyclic residues is also greater than two. Of the former compounds, in total over 4800, about 40% can be classified as heteroarylhydrazines. Nearly 1800 arylhydrazines, *i.e.* more or less close analogues of **1a**, have also been prepared, whereas the number of cycloalkylhydrazines, which constitute the remaining substances with carbocyclic residues, is only about 100.

To date a very large number (over 3000) of monosubstituted hydrazines with acyclic substituents have also been described. The great majority (nearly 2850) of these compounds carry substituents that contain elements in addition to carbon and are therefore identified as heteroacyclic. Among them nearly 1700 carry a CO group on their nitrogens, of which all except about 100 contain further heteroelement(s) in residues attached to the CO group. The remaining monosubstituted hydrazines, about 180, are carbacyclic, 150 of which are monoalkyl hydrazines or various salts of them.

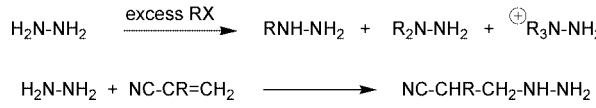
In the next section an outline of synthetic methods related to substituted hydrazines will be presented. Due to the very large number of such compounds available, further restrictions with respect to the substituents are required and therefore primarily only methods for alkylated derivatives will be reviewed. The major emphasis will be on the principles behind such work and only simple examples will be given.

4 Some major methods for the synthesis of alkyl substituted hydrazines[13,14]

As a result of considerable interest in substituted hydrazines, a large number of synthetic procedures have been developed for such compounds. In this section a selection of the most important ones will be given. A more comprehensive review of this field with hundreds of references to the original literature up to the late eighties has been given elsewhere[13] and even newer references in another review.[14] To keep the number of reference citations to a reasonable level, in the text that follows, references with three instead of two digits refer directly to the corresponding page in ref. 13, where further details are given. In order to make the presentation more transparent a division based on structural considerations has been chosen. The major emphasis is on alkyl substitution, but in a few cases arylation is also discussed. Compounds with N–N bonds forming parts of a ring are not included. For compounds with two or more substituents, these are generally all assumed to be different.

4.1 Monosubstituted hydrazines

4.1.1 Direct substitution of free hydrazine.[425] It should be recalled that alkylation of ammonia with halides is difficult to control and generally produces mixtures, containing overalkylated products in addition to primary amine. This can be avoided by the application of phthalimide or a bisprotected ammonia derivative.[15] Free hydrazine in this respect behaves like ammonia and initially many attempts at the direct synthesis of monoalkylated derivatives by such reagents gave poor results. Systematic work has established that with small substituents alkylation as a rule takes place only on one nitrogen and that products of the following structures are primarily formed (Scheme 4). Only if RX (X typically a halide such as Br)



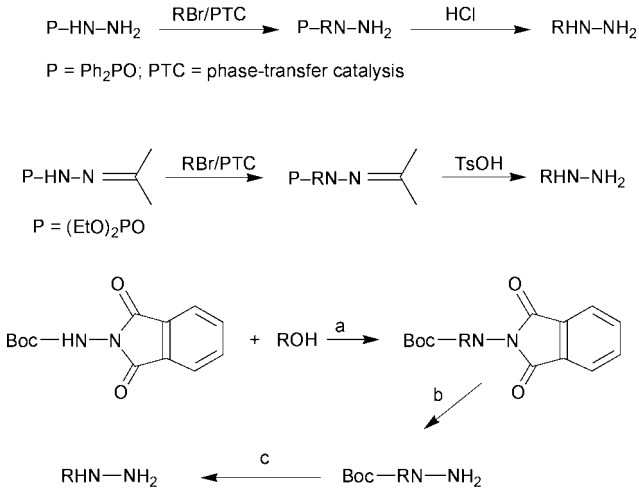
Scheme 4 Direct alkylation of hydrazine.

is bulky or R contains an additional electron-withdrawing function, is a symmetrical product of the type RNH–NHR also formed.

In synthetic practice aiming at monoalkylated products, an excess of hydrazine instead of RX is generally applied to reduce the amounts of oversubstituted derivatives. Since excess hydrazine can be reprocessed, the method is important industrially but in most cases it is less attractive on a laboratory scale with yields in simple cases seldom exceeding 40%. Steric hindrance also favours monosubstitution, as shown for triphenylmethylhydrazine which has been prepared in 87% yield. For aromatic halides to react analogously, additional, strongly electron-withdrawing groups are required. On the other hand, the method has been used successfully to make a few heterocyclic hydrazines.

The reaction between free hydrazine and electron-deficient alkenes is easier to control.[441] Acrylamide, various acrylonitriles and styrene have been applied as alkylating agents and furnished products in satisfactory yields (Scheme 4). In addition to halides and alkenes, many other reagents, *e.g.* dialkyl sulfates, sulfonates, alcohols in the presence of phosphoric acid/hydrogen halides, oxiranes, aziridines *etc.* have been used to make aliphatic hydrazines, but in most cases yields are only modest and careful purification of the products is required.

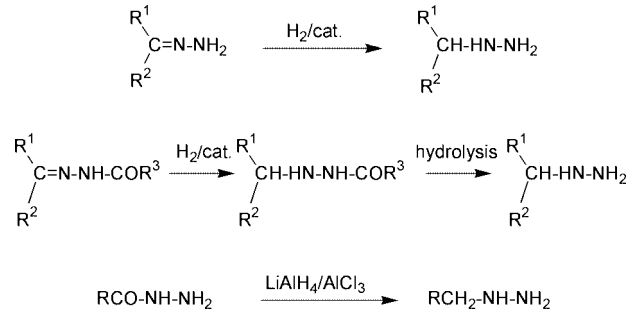
4.1.2 Substitution of protected hydrazines.[14,442] To avoid the multiple alkylation of free hydrazine discussed in the preceding paragraph, various authors have instead used protected derivatives as starting material. One such case, although applied to make a 1,2-disubstituted rather than a monosubstituted hydrazine, has already been mentioned above in Scheme 2. This strategy generally involves at least two extra synthetic steps but as nowadays a large number of convenient protecting groups for amino functions are available,[16] the purity and total yield of the products are often higher and purification steps simpler. Work with mono-, di- and triprotected reagents is illustrated in Scheme 5. Thus, in the presence of a phase-transfer catalyst and solid NaOH, regioselective alkylation at the nonbasic nitrogen can be accomplished. A diprotected reagent, based on hydrazone formation with acetone and claimed to be easily prepared in high yield, can be introduced and used under similar conditions. Both its protecting groups are labile to acid and are cleaved simultaneously with toluene-4-sulfonic acid. Alkylations with alcohols in the presence of triphenylphosphine



Scheme 5 Alkylation of protected hydrazines. *Reagents and conditions*: a: Ph_3P, EtOOCN=NCOOEt; b: $MeNH–NH_2$ in THF, 0 °C; c: TFA.

and dialkyl azodicarboxylate under Mitsunobu conditions are rather mild but efficient and are therefore rapidly gaining in importance. This methodology has recently been used in conjunction with a novel triprotected hydrazine reagent with excellent results.[17] The primary products can easily be cleaved to give monosubstituted hydrazines, but selective cleavage should also give useful intermediates for further nitrogen modification. It should be pointed out that dephthaloylation was accomplished with methylhydrazine as reagent at 0 °C.

4.1.3 Reduction of hydrazones and hydrazides.[14,445] Hydrazones formed with aldehydes and ketones are not only important for identification purposes and occasionally as protecting groups (see previous scheme, second line) but their C=N bonds can also be reduced to give hydrazines (Scheme 6).

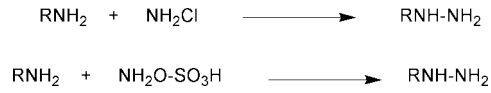


Scheme 6 Reduction of hydrazones and acylhydrazides.

To stabilize the N–N bond to cleavage during catalytic hydrogenation, the second nitrogen is generally protected. The resulting reduced protected intermediates are themselves also attractive starting materials for the synthesis of azapeptides.[6,7] Other mild reducing agents like $NaBH_4$ and $NaBH_3CN$ have been applied as alternatives to catalytic hydrogenation.

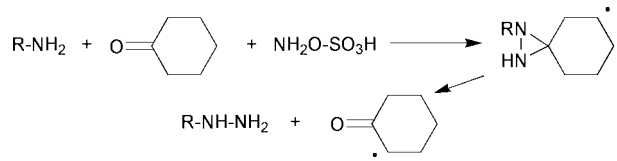
Hydrazides on reduction with $LiAlH_4$ directly provide the corresponding alkyl derivatives. Among other important reductive processes for the synthesis of hydrazines, that for diazonium salts resulting in aromatic derivatives was mentioned previously (Scheme 2).

4.1.4 Direct amination.[14,464] The reaction between chloramine and primary amines gives rise to alkylhydrazines. This is in analogy with the Raschig procedure mentioned above (Scheme 3). *tert*-Butyl hydrazine is made on a technical scale in this way. Hydroxylamine-*O*-sulfonic acid also reacts with amines to give similar products. It is commercially available and more easily handled on a laboratory scale. Chloramine and hydroxylamine-*O*-sulfonic acid both behave as electrophilic reagents (Scheme 7).



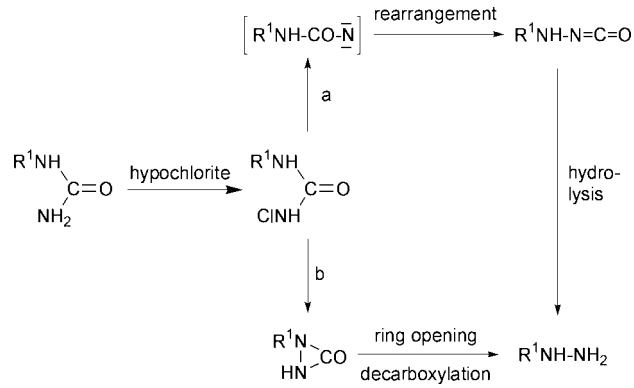
Scheme 7 *N*-Amination of amines.

4.1.5 Amination *via* diaziridines.[14,458] In the presence of aldehydes or ketones, primary amines and hydroxylamine-*O*-sulfonic acid give rise to 1-alkyldiaziridines. Like the structurally related acetals they are easily cleaved under acidic conditions liberating alkylhydrazines (Scheme 8).



Scheme 8 Monosubstituted hydrazine *via* diaziridine.

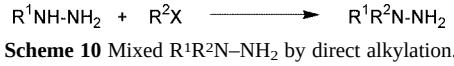
4.1.6 From ureas.[14,466] The reaction between urea and hypochlorite can also be exploited to make monoalkyl derivatives from the corresponding alkyl ureas. The primarily formed *N*-chlorosubstituted product can formally undergo (a) a geminal or (b) a 1,3-elimination of HCl. In the first case an electron-deficient species is formed, capable of rearrangement like intermediates in Hofmann reactions, and subsequent hydrolysis, whereas in the second alternative a transient cyclization *via* a diaziridine would accomplish intramolecular amination. Opening of the ring followed by decarboxylation should lead to hydrazine (Scheme 9).



Scheme 9 Monosubstituted hydrazine from urea.

4.2 Disubstituted hydrazines

4.2.1 1,1-Disubstituted hydrazines. *Direct substitution of free or monosubstituted hydrazine.*[14,469] From what was said under monosubstituted hydrazines it follows that in principle it is possible to make 1,1-dialkyl substituted hydrazines from free hydrazine and alkyl halides, but that such experiments generally would require tedious fractionations of the product mixtures formed. On the other hand, starting from free alkyl- or benzylhydrazine, especially with substituted benzyl halides, such products with different substituents have been obtained in high yield (Scheme 10).



Scheme 10 Mixed $R^1R^2N–NH_2$ by direct alkylation.

Barton *et al.* have shown that various amines including hydrazines react with triphenylbismuthane in the presence of

copper(II) acetate to give the corresponding *N*-phenylated products under mild conditions in high yields.[18] This procedure is of wide scope for work on a laboratory scale and will be further mentioned at the end of section 5.1.

Nitrosation followed by reduction.[14,484] Nitrosation of secondary amines followed by reduction (Scheme 2) with zinc and acetic acid was the first method used in this context. Since nitrosation can in principle be accomplished with all secondary amines[19] and because many other reducing agents such as hydrogen in the presence of a catalyst, $LiAlH_4$, amalgamated zinc, $NaHSO_3$ *etc*. and also electrochemical reduction can be applied, this method is of wide scope. Thus, aliphatic, mixed aliphatic/aromatic and aromatic 1,1-disubstituted hydrazines have all been prepared in this way in high yield and purity. Its major drawback, as already pointed out, resides in the fact that nitrosamines are problematic from the hygienic point of view.

Amination.[14,499] 1,1-Dimethylhydrazine is a rocket fuel and its industrial preparation is based on the reaction of dimethylamine with chloramine, *i.e.* the Raschig method as described already under monosubstituted hydrazines. Many other secondary amines including aromatic ones have been reacted in this way to give mixed 1,1-alkyl/aryl derivatives. For laboratory scale synthesis of 1,1-dialkylhydrazines it is often more convenient to use hydroxylamine-*O*-sulfonic acid instead of chloramine.

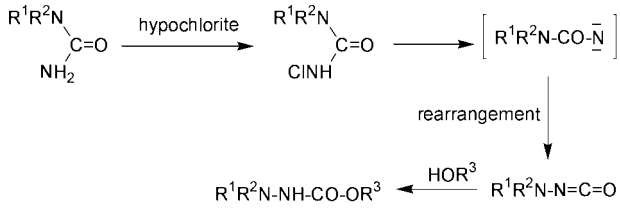
More recently a series of *N*-protected oxaziridines with various substituents on their carbons have been developed for electrophilic amination of amines with simultaneous transfer of the protecting group (Scheme 11).[20] These reagents have been

R = CCl_3, Ph or substituted phenyl; PG = urethane protecting group

Scheme 11 Electrophilic amination of secondary amines by *N*-protected oxaziridines.

reacted with both primary and secondary amines to give N^2-protected mono- and 1,1-disubstituted hydrazines, but whereas the former amines often give rise to a side product with the liberated aldehyde, the latter afford the corresponding products in very high yields. On deprotection they furnish free 1,1-disubstituted hydrazines but prior to that they would also constitute ideal precursors for monosubstitution at N^2. These oxaziridines have also been reacted with a host of substituted amines including amino acids, work that will be further discussed separately in Section 5.2.

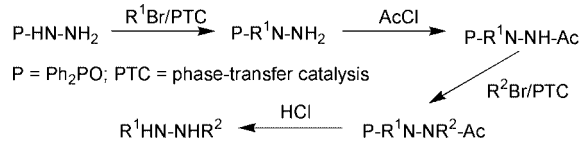
From ureas.[14,501] 1,1-Disubstituted hydrazines, including mixed alkyl/aryl and diaryl types, can also be prepared by analogy with amines from amides with hypochlorite under basic conditions from the corresponding ureas. This method has already been mentioned above. Although NaOCl is the standard chlorinating reagent, organic hypochlorite can also be used. A modern variant of this reaction takes place in alcohol, whereby the corresponding carbamate is formed (Scheme 12). The latter



Scheme 12 Direct synthesis of an 1,1-dialkylhydrazine-2-carbamate.

should be useful for introduction of an additional substituent, as will be discussed later in connection with stepwise synthesis.

4.2.2 1,2-Disubstituted hydrazines. *Alkylation of monosubstituted hydrazines.*[14,504] Since free monosubstituted hydrazines preferentially undergo alkylation on the same nitrogen, this position must be blocked by a protecting group in order to direct a second substituent to the alternative position. To ensure subsequent smooth monoalkylation with a suitable reagent in this position, one of its two NH-sites also has to be protected. This was realized by Fischer and he accordingly used benzoyl as a protecting group in the synthesis of 1-phenyl-2-methylhydrazine, which was the first derivative of this type made (Scheme 2). Benzoyl requires strong acid or base and heating for its cleavage. Nowadays many other amino-protecting groups, especially of amide or carbamate type, are available that cleave under much milder conditions and they are gaining in importance at the cost of groups such as benzoyl and acetyl previously used for this purpose.[16] For alkylation of an amide and carbamate NH, halides or sulfonates are the preferred reagents. In a relatively recent illustration of relevant methodology, the intermediate $Ph_2PO–R^1N–NH_2$ from Scheme 5 was acetylated and alkylated, whereupon both protecting groups were removed simultaneously with hydrochloric acid to give $R^1HN–NHR^2$ (Scheme 13).

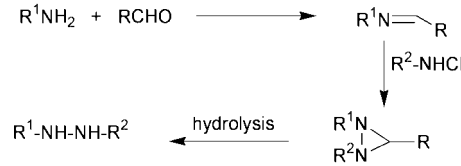


Scheme 13 Synthesis of 1,2-disubstituted hydrazine.

Reduction of hydrazone C=N bonds.[14,514] By analogy with reduction of hydrazones or protected hydrazones as a route to alkylated hydrazines (Scheme 6), monoalkyl- and arylhydrazones give rise to the corresponding symmetrically substituted hydrazines. Catalytic reduction with hydrogen and more recently also diborane or metal hydrides such as $LiAlH_4$ are the preferred reagents. Phenylhydrazine has been reported to undergo very clean reductive alkylation with ketones in the presence of $NaBH(Ac)_3$.[21]

Reduction of hydrazides.[14,522]. Reduction of 1-alkyl-2-acylhydrazines with $LiAlH_4$ should in principle lead to 1,2-dialkylated derivatives, but such precursors are not always simple to make due to formation of isomers. 1,2-Diacylated compounds, including those with different acyl groups, are more easily prepared and have been reduced in this way to give the corresponding products.

From azomethines and N-chloramines.[14,525] *N*-Chloro derivatives of primary amines react with azomethines by analogy with $NH_2O–SO_3H$ (see 4.1) to diaziridines. After acid hydrolysis and neutralization, the latter give rise to 1,2-disubstituted hydrazines.



Scheme 14 1,2-Disubstituted hydrazine *via* diaziridine.

4.3 Tri- and tetrasubstituted hydrazines

These compounds will be treated more briefly than mono- and disubstituted hydrazines to avoid reiteration of methods already mentioned.

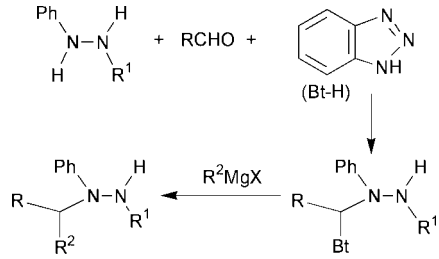
4.3.1 Trisubstituted hydrazines. *By alkylation of disubstituted derivatives with activated alkenes.*[14,531] The disadvantages of alkyl halides and sulfates as *N*-alkylating agents

will not be further discussed here. On the other hand, activated alkenes, especially those derived from acrylic acid, have been applied extensively as alkylating agents by a Michael addition mechanism. Much less side product due to quaternization is encountered and the yields have therefore been more satisfactory.

By reduction of hydrazones and hydrazides.[14,549] If a suitable 1,1-disubstituted hydrazine precursor is available, hydrazones and hydrazides can obviously be easily prepared therefrom. For the reduction of such compounds, as mentioned earlier, various alternative reagents are available, leading to the corresponding trisubstituted derivatives. Several relevant hydrazones have recently been prepared in excellent yield by the treatment of azides with hydrazines in the presence of catalytic amounts of $FeCl_3 \cdot 6H_2O$.[22]

By direct amination.[551] By analogy with hydroxylamine-*O*-sulfonic acid, *N*-methylhydroxylamine-*O*-sulfonic acid has been applied for preparation of trisubstituted hydrazines. It would seem that other alkylated reagents would be applicable in a similar context.

Via N-(1-benzotriazolylalkyl)-intermediates. Recently a few trisubstituted hydrazines have also been prepared from 1,2-disubstituted precursors, aldehydes and benzotriazole *via* stable, crystalline *N*-(1-benzotriazolylalkyl)-1,2-disubstituted intermediates. The latter undergo electrophilic substitution by Grignard or other organometallic reagents at the 1′-position with benzotriazole as leaving group.[23] By variation of the aldehyde and organometallic reagent this method can obviously provide access to products difficult to make by other means (Scheme 15).

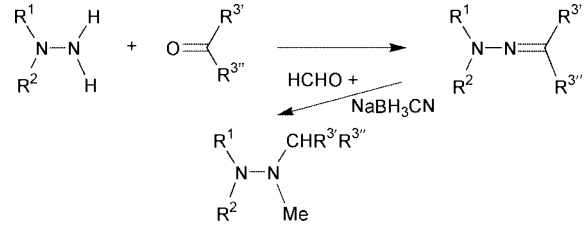


Scheme 15 Synthesis of trisubstituted hydrazines *via* benzotriazolylalkyl intermediates.

4.3.2 Tetrasubstituted hydrazines. *By alkylation of trisubstituted derivatives with activated alkenes.*[14,555] Whereas simple 1,2-dialkylhydrazines easily undergo dialkylation with excess acrylic acid esters, much lower yields have been reported in the corresponding reactions with 1,1-dialkyl substituted compounds and influence of the ester moiety has been noted, pointing to steric hindrance. This is also indicated in experiments with some trialkylhydrazines. 1,1,2-Trimethylhydrazine seems to react smoothly with acrylamide but for other trialkyl analogues only poor yields have been reported with acrylic acid esters. Vinylpyridines have also been reacted with 1,1-dialkylhydrazine to give tetrasubstituted derivatives.

By reduction of hydrazones and hydrazides.[14,561,574] A few simple tetraalkylhydrazines have been prepared starting from 1,1-dialkylhydrazines by first converting them to hydrazones. Reduction of these with $NaBH_3CN$ in the presence of formaldehyde has given the corresponding methyltrialkyl derivatives (Scheme 16).

With powerful reducing agents like diborane or $LiAlH_4$ one or more acyl functions present in hydrazines can generally be transformed into alkyl groups. Reduction of hydrazides would therefore seem to be a straightforward method to make tetrasubstituted hydrazines and a large number of simple as well as more complex derivatives, including cyclic ones, have been prepared in this way.



Scheme 16 Reductive methylation of a hydrazone.

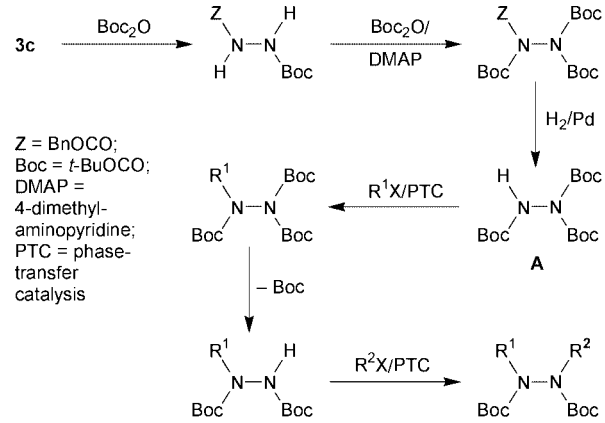
As demonstrated above, *N*-alkylation of hydrazine(s) with application of protecting groups, reduction of hydrazone C=N, hydrazide C=O or nitrosamine N=O bonds and electrophilic *N*-amination of amines with simple reagents has played a major role in the synthesis of various kinds of alkylated hydrazines so far, although additional methods are also available.[13,14] Rather than expanding the list of these synthetic methods, in the next section a brief discussion of a few relevant recent approaches will be presented.

5 Some recent developments

5.1 Stepwise synthesis of substituted hydrazines

With a *triprotected* hydrazine reagent it should in principle be possible to introduce a simple substituent on nitrogen with complete consumption of the reagent without side reactions. If then one protecting group could be cleaved selectively from this intermediate, the stage would be set for a second *N*-substitution step. The feasibility of this approach was first demonstrated with the reagent Boc-NH-$NBoc_2$ (**A**).[24]

A very large number of variously protected hydrazine derivatives have already been prepared including **3** (Fig. 1). One of them, **3c**, was used as starting material in a simple synthesis of reagent **A** over 2–3 steps in high overall yield, as shown in Scheme 17. The reagent stands basic conditions surprisingly

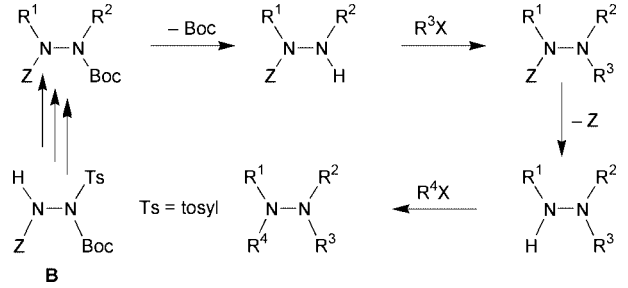


Scheme 17 Synthesis and application of hydrazine reagent **A**.

well and could initially be alkylated with primary alkyl and benzyl halides R^1X under phase-transfer catalysis (PTC) conditions which resulted in products in essentially quantitative yield. Moreover, in these intermediates one Boc group on the diprotected nitrogen could be cleaved regiospecifically under mild conditions, whereupon a second alkylation with R^2X was performed under similar conditions. In the resulting products the two Boc groups, one on each hydrazine nitrogen, no longer differ significantly in structure, as a result of which selective cleavage is no longer possible.

To date a second generation of reagents related to **A** but with orthogonal protecting groups has been prepared, with the common feature that after two alkylation steps products with

one Boc and one Z instead of two Boc groups were obtained. Boc and Z are well-known groups that can be cleaved selectively, as a result of which the shortcoming of reagent **A** is eliminated and the stepwise strategy outlined above now can be fully implemented to make tetrasubstituted hydrazines (Scheme 18). Among these more versatile hydrazine reagents the tosyl



Scheme 18 Synthesis of tetrasubstituted hydrazines.

derivative **B** can easily be made and used on a multigram scale.[24]

More recently the scope of the stepwise approach has been expanded from simple to functionalised 1,2-dialkyl-1,2-diacylsubstituted hydrazines. As mentioned above, such compounds can in principle be transformed to tetraalkylhydrazines with diborane, $LiAlH_4$ or similar reducing agents. Highly substituted products with secondary alkyl residues, urea and sulfonylurea functions and aromatic groups have also been prepared. *N*-Arylation was in this context accomplished by the previously quoted procedure of Barton *et al.*[18] using triarylbismuthanes in the presence of copper acetate and amine which invariably furnished products in essentially quantitative yields.[25] Moreover, stepwise synthesis of substituted hydrazines appears to be compatible with the requirements of combinatorial chemistry,[26] although a convenient solid-phase methodology remains to be developed.

In connection with synthesis of multisubstituted hydrazines it is now in many cases feasible to force reactions to go to completion, circumvent side reactions and avoid lengthy purifications of products, problems sometimes associated with older synthetic methods, by instead properly manipulating protecting groups as exemplified by those present in hydrazine reagent **B**. The price to be paid: extra steps required for the preparation of the starting material and the selective cleavage of the protecting groups. The first seems reasonable and the second, with suitable groups, in many cases can be reduced to routine.

5.2 Synthesis of protected chiral α-hydrazino acids

As mentioned already in the introduction, substituted hydrazines are components of azapeptides. Hydrazino acids are analogues of amino acids with hydrazino instead of amino functions and they are also finding increasing application as substitutes for amino acids in peptide synthesis. Hydrazino acids can be synthesized by various methods but in order to incorporate them in one or more positions into synthetic peptides it is generally necessary to selectively protect one of their nitrogens. This is not a straightforward business and is generally accompanied by severe loss of material. Electrophilic amination of amino acids with simultaneous transfer of a protecting group would obviously solve this synthetic problem and since this can be accomplished with some *N*-protected oxaziridines, as mentioned briefly under 1,1-disubstituted hydrazines, these reagents will be discussed in more detail below.

Whereas the amino acid proline [R^1,R^2 = $(CH_2)_3$] reacts with *N*-Boc-protected oxaziridines to give the N^{β}-Boc-hydrazine analogue with liberation of aldehyde without side reactions, other amino acids (with R^2 = H) to a variable extent undergo additional reaction with the aldehyde formed to give rise also to an imine product (Scheme 19) which lowers the yield significantly.[27] This side product could be eliminated by using *N*-benzyl protected amino acids as starting materials.

The authors inserted their protected α-L-hydrazino acids into various synthetic peptides related to a substrate of human leukocyte elastase (HLE). Two of these peptides, structurally modified at the cleavage site of the enzyme or its immediate vicinity, exhibited binding to HLE but were not cleaved and could be characterized as competitive inhibitors.[28] Many similar applications of these protected hydrazino acids can be foreseen in the future.

5.3 Synthesis of ^{15}N-labelled hydrazine

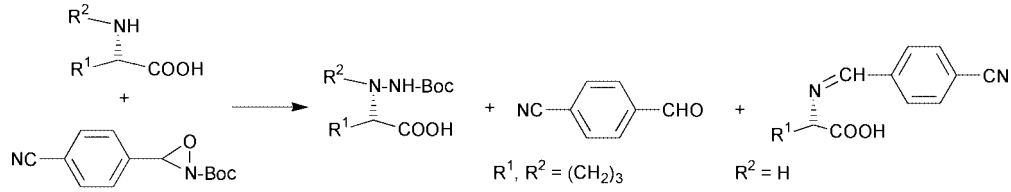
As mentioned in the introduction isoniacid (**8**) is a very important drug against tuberculosis, a disease to which millions of people annually fall victim worldwide. For research aimed at elucidating the mechanism of action of **8**, Jamart-Grégoire *et al.* recently prepared the two ^{15}N-labelled analogues.[29]

The project started from commercial potassium [^{15}N]phthalimide which was efficiently aminated by a powerful electrophile *O*-(2,4-dinitrophenyl)hydroxylamine with properties similar to chloramine and hydroxylamine-*O*-sulfonic acid (section 4.1) to give phthaloylhydrazine. This was acylated by isonicotinic acid in the presence of carbonyldiimidazole and then dephthaloylated with hydrazine hydrate, which is a usual reagent for cleavage of this protecting group, to afford [^{14}N,^{15}N]-**8**, *i.e.* isoniacid with ^{15}N on the remote nitrogen (Scheme 20).

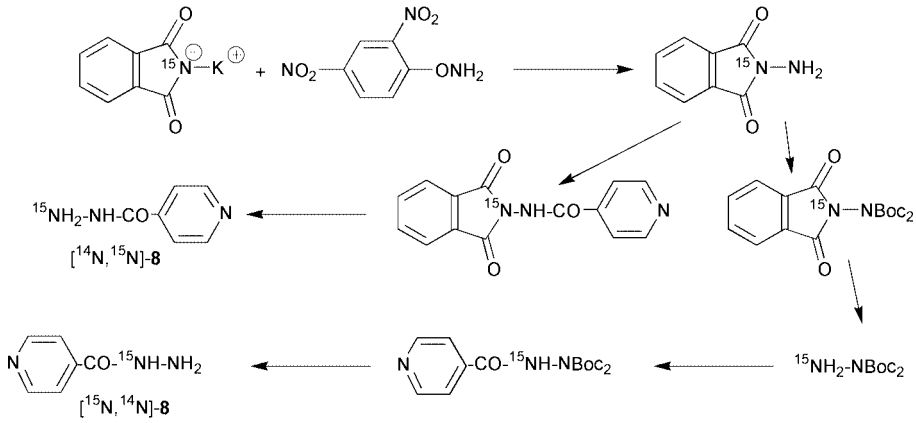
The other isoniacid isotopomer, [^{15}N,^{14}N]-**8**, with ^{15}N instead on the amide nitrogen was prepared directly from the primarily obtained labelled intermediate by protection of its free amino group, dephthaloylation, acylation at the labelled nitrogen and final deprotection of the auxiliary groups (Scheme 20, last line). Very importantly in work with precious material, thanks to the protecting groups, all steps furnished intermediates in high yield and purity which could be purified by crystallization.

6 Summary and conclusions

In this article an attempt has been made to place the most recent synthetic efforts on alkyl substituted hydrazines in a perspective with respect to previous work in the field, the beginning of which can be traced back exactly 125 years. This would hardly have been worthwhile within an article of this length without



Scheme 19 Synthesis of N^{β}-Boc-protected hydrazino acids.



Scheme 20 Synthesis of both ^{15}N-labelled isoniacid isotopomers.

access to an excellent comprehensive review[13] extending nearly up to 1990. The present article essentially supplements that review with work that appeared after 1990.

As exemplified in the introduction, during the last decades hydrazine derivatives became of considerable commercial importance, as a result of which a clearly noticeable interest in better laboratory methods for such substances gradually developed. It took a very long time for the shortcomings of simple alkylating reagents and procedures in this context to be fully realized, and with a few exceptions a wider acceptance of protecting groups to accomplish regioselective substitutions is of relatively recent origin. As a consequence, a lack of more general synthetic methodology for tri- and tetrasubstituted hydrazines especially was long missing.

Starting from the work of Raschig (Scheme 3) electrophilic *N*-amination has repeatedly demonstrated its potential in the synthesis of hydrazine(s). Most recently the power of this technique was demonstrated in conjunction with the ^{15}N-labelling of isoniacid and the synthesis of protected chiral α-hydrazino acids. Within the next few years chiral amines can be expected to play an important role as precursors in such reactions. Also, Mitsunobu chemistry will certainly find increasing application for introduction of chiral substituents on hydrazine nitrogens[17] and perhaps also chiral auxiliaries for induction of stereospecificity.[30]

Considering the various biological effects already discovered and/or exploited for simple, achiral compounds as drugs (Fig. 3) and insecticides (Fig. 4) exciting prospects open up with respect to what responses related chiral compounds, with or without further functionalized substituents, might elicit in similar biological environments. Such are the questions that can now be asked and which are going to require synthesis of further analogues for experimental investigations.

Note added in proof (May 8th, 2001). When this review was in press, a paper with the title *A new synthetic route to protected α-hydrazinoesters in high optical purity using the Mitsunobu protocol* appeared.[31]

7 Acknowledgements

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