N-Acylhydrazines: Future Perspectives Offered by New Syntheses and Chemistry

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This is a review of the most recent and useful synthetic methodologies for providing access to di- and trisubstituted hydrazides. New chemistry and new organometallic derivatives of the title compounds offer a new arsenal for the production of new functionalised derivatives, which are also useful as new biologically relevant molecules.

Introduction

Hydrazides (*N*-acyl derivatives of hydrazines) are a very old class of molecules: the first examples of *N*-acylhydrazines were mentioned in 1850,[1] and a number of *N*-unsubstituted, mono- and disubstituted acylhydrazines are now commercially available.

Hydrazides are a versatile class of nitrogen-substituted molecules with a high degree of chemical reactivity, used as precursors and intermediates of many important organic molecules such as heterocycles, pharmaceuticals, polymers, dyestuffs and photographic products.[2] Their use for analytical purposes is well known, and allows the detection of aldehydes, ketones and carboxylic acids. The chemiluminescence of both cyclic and acyclic acyl hydrazines when they undergo oxidation is another interesting and useful property.[3]

All of this chemistry mainly involves unsubstituted or monosubstituted hydrazides, which are very well represented and easily synthesised by general and efficient methods. However, there are far fewer examples of, and synthetic methodologies for, di- and trisubstituted hydrazides.

They also have few applications, possibly because of the lack of a general synthetic strategy (see the section on methods of preparation below) and the difficulties, poor yields and low selectivity often found in their synthesis. These considerations are supported by the large number and variety of specific and not generally applicable synthetic methods published in the literature.

The interest in this class of organic molecules is due not only to the number of derivatives that have well established biological and pharmacological activities, but also to the

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Emanuela Licandro obtained her degree in Chemistry in 1977 at the University of Milan. She next worked for the SIR, a big Italian company, and then completed her training working within a national project called "Piano Finalizzato. Chimica Fine e secondaria", in Prof. Stefano Maiorana's research group, developing new synthesis of aza-steroids and steroid mimetics. In 1982 she became a Researcher at the University of Milan, in 1992 Associate Professor in Organic Chemistry and in 2000 Full Professor at the same university. At the beginning of her career she was interested in the synthesis of heterocycles, and then moved towards organometallic chemistry, in particular developing the chemistry, also under solid-phase conditions, of Fischer-type carbene complexes and arene tricarbonylchromium complexes. More recently her scientific interests have been directed towards the synthesis of oligonucleotide mimetics such as aza- and hydrazino-Peptide Nucleic Acids (PNAs), bioconjugates of PNAs with Fischer-type carbene complexes and arene tricarbonylchromium complexes, and the synthesis of new heterohelicenes as molecules with potential NLO properties.

Dario Perdicchia was born in Lecce, Italy, in 1968. He received his degree in Chemistry in 1995 at the University of Milan, and his PhD in Chemical Sciences in 1999, working with Professor Stefano Maiorana on the synthesis of hydrazinocarbene complexes, a new class of Fischer-type carbene complexes. In 2001 he became a Research Associate at the University of Milan.
His research interest concerns the chemistry of hydrazines in the fields of organometallic chemistry, organic synthesis and medicinal chemistry.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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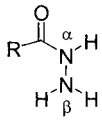
fact that the particular structure has some interesting stereochemical features thanks to the presence of the CO−N−N moiety. Because of the bioisosterism between a methylene and NH group, hydrazides can also be regarded as aza-amino acids, and much interesting research concerning this fascinating and useful modification in amino acid structures to give aza-peptides has been published (see below).[4]

The α-nitrogen atom in hydrazide structures, exactly like the amide nitrogen atom, is engaged in resonance structures, whereas the β-nitrogen atom has a free lone pair that gives the group a Lewis base nature, and allows the formation of additional hydrogen bonds or confers different solubility characteristics.

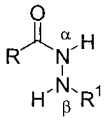
The aim of this review, considering mainly monoacylhydrazine derivatives, is to describe recent synthetic strategies for the formation of di-and trisubstituted hydrazides and recent applications of their use in organic and organometallic chemistry.

Structural Characteristics

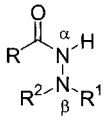
Given the partial double bond character of the N−CO bond, hydrazides can in principle exist as two configurational isomers, *E* and *Z*, which arise from hindered rotation about the N^{α}-carbon bond in the same way as for amides. However, the presence of the second N^{β} atom and its substituents, and the group attached to the carbonyl group, can favour one rotamer over the other. Although no systematic studies of the configurations of substituted hydrazides have yet been published, there are some interesting reports indicating that the configurations of $N^{\alpha},N^{\beta},N^{\beta}$-trisubstituted hydrazides depend on the size of the substituents on the nitrogen atoms and carbonyl group. As a general rule, hydrazides preferentially adopt the *E* configuration about the amide N^{α}−carbon bond when the nitrogen atoms are fully substituted. When more sterically demanding groups are present on the R substituent of the carbonyl, however, there is a mixture of the *E* and *Z* isomers.[5−7]



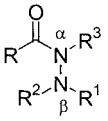
Unsubstituted hydrazide



N^{β}-substituted hydrazide



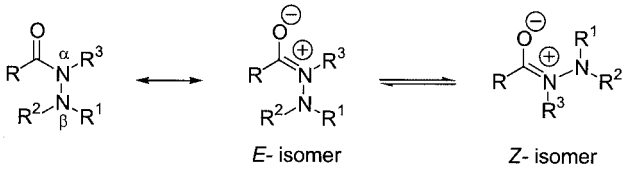
N^{β},N^{β}-disubstituted hydrazide



$N^{\alpha},N^{\beta},N^{\beta}$,trisubstituted hydrazide

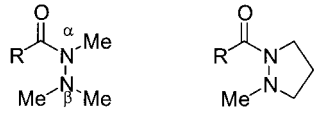
In particular, hydrazides **1a**, **1b**, **2a** and **2b** were the first examples shown to have the *E* configuration about the N^{α}-carbonyl bond both in the crystalline state and in solution.

The *E* configuration in solution was established by means of an ASIS experiment,[8] while an X-ray structure confirmed the same configuration in the solid state.



E- isomer *Z*- isomer

During the course of our studies we have prepared a number of trisubstituted hydrazides[7,9] (see the section dedicated to synthesis below) and determined their preferred configurations in solution by ASIS experiments. As anticipated by S. Knapp,[5] 1,2,2-trisubstituted hydrazides are more stable in the *E* configuration. We found that all of the synthesised hydrazides **3** existed in solution either as single *E* isomers, or as mixtures in which the *E* isomers were highly predominant. As shown, both the *Z* and *E* isomers are present when the carbonyl group bears bulky substituents, such as an *ortho*-substituted phenyl ring.



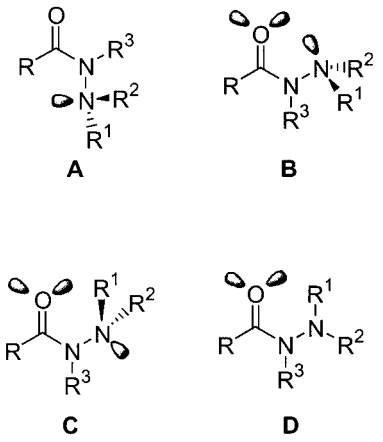
1a, R = Ph **2a,** R = Ph
b, R = n-C_7H_{15} **b,** R = n-C_7H_{15}

The preference for *E* isomers in trisubstituted hydrazides can be attributed to electronic and steric reasons: If the three different conformers of the *Z* isomer, **B**, **C** and **D** are considered, it is clear that both steric and electronic factors contribute to its instability.

E-isomer **3** *Z*-isomer

R = Me, Ph, Et ⟹ *E* isomer
R = 2-Cl-Ph, 2,6-diCl-Ph, 2-MePh, 2-CF_3Ph ⟹ mixture of *E*/*Z* isomers

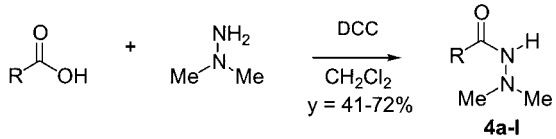
In structure **B**, a lone pair-lone pair repulsion between oxygen and β nitrogen might be expected; structure **C** is disfavoured because of steric crowding between the R^1 and R^2 substituents and the carbonyl group, while structure **D**, with its planar hydrazide skeleton, is unstable because the fully conjugated 6-π electron structure has partially occupied anti-bonding orbitals. This is also true in the case of the *E* isomer **A**, and it has been calculated that the planar structure of a simple model hydrazide lies about 15 kcal/mol above the pyramidal structure.[5]



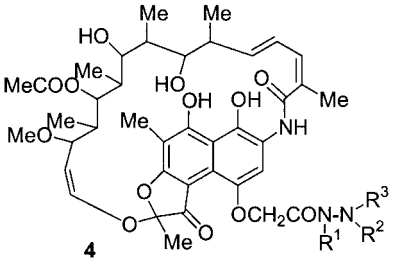
Synthesis of Di- and Trisubstituted Hydrazides

Many synthetic methods for accessing unsubstituted and monosubstituted hydrazides are available, the most important being reactions between hydrazine or its aryl and alkyl derivatives and acyl chloride or carboxylic esters.[10] However, there are not many general synthetic routes to di- and trisubstituted hydrazides: the acylation of 1,1-disubstituted hydrazines with carboxylic acid esters gives very poor hydrazide yields[11] due to the weakly nucleophilic nature of the hydrazine, while 1,2-disubstituted derivatives react with great difficulty and the starting compounds are generally recovered unchanged.[12] On the other hand, the use of acyl chloride or anhydrides gives diacylated α,β-dimethylhydrazide derivatives, and mixtures of mono- and diacylated derivatives can be obtained from 1,1-disubstituted hydrazines.[13] In the case of 1,1-dimethylhydrazine, it has also been reported that the monoacyl derivatives are the sole products when an appropriate solvent is used, in which the monoacyl hydrazines precipitate as soon as they are formed.[13]

A quite interesting and useful method for preparing trisubstituted hydrazides makes use of *N*,*N*′-dicyclohexylcarbodiimide as the condensing agent in reactions between hydrazines and carboxylic acids (Scheme 1). The first example of this method was used to prepare a series of hydrazides of rifamycin B[14] (**4**), which were exceptionally active against Gram-positive bacteria and showed a certain activity against Gram-negative bacteria.

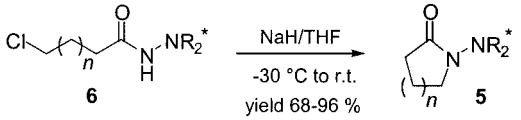


Scheme 1



Four years later, a more systematic study based on this method was published[15] in which variously substituted hydrazides of aromatic and aliphatic carboxylic acids were synthesised (Scheme 1). One of the advantages of this method is the easy recovery of β,β-disubstituted hydrazides in a pure form by acid extraction of the filtrate obtained after filtration of the insoluble *N*,*N*′-dicyclohexylurea. Moreover, the reaction takes place under essentially neutral conditions.

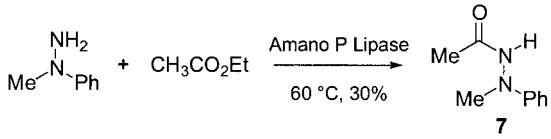
Enders has described a general and convenient two-step synthesis of cyclic trisubstituted hydrazides (*N*-aminolactams) **5**, which were obtained in good overall yield by means of an intramolecular alkylation of ω-chloroalkanohydrazide **6** prepared by treatment of chloroalkanoyl chloride with *N*,*N*-dialkylhydrazines[16] (Scheme 2). Chiral hydrazides **5** are particularly interesting because they can be used as chiral equivalents of lactams and applied to the stereoselective formation of new carbon-carbon bonds (see below).



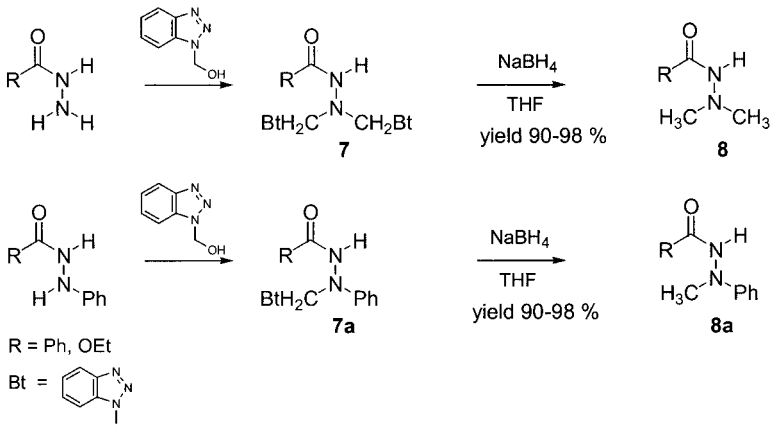
Scheme 2

The Katritzky benzotriazole method is also useful for the preparation of β,β-disubstituted hydrazides.[17] It provides for the alkylation of the β-nitrogen atoms of unsubstituted and β-monosubstituted hydrazides with hydroxymethylbenzotriazole, and the obtained mono- or bis adducts **7** and **7a** were smoothly reduced to the corresponding β-methyl hydrazides **8** and **8a** in high yields (Scheme 3).

One example of a lipase-catalysed hydrazinolysis with a disubstituted hydrazine in ethyl acetate to give the β,β-disubstituted hydrazide **7** has also been reported.[18] The method is in principle very interesting and original, although it mainly seems to work well with monosubstituted hydrazines and hydrazines with electron-withdrawing substituents.

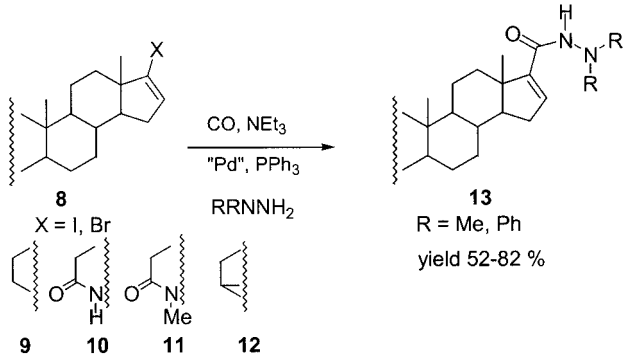


Various homogeneous catalytic carbonylation reactions (aminocarbonylation, alkoxycarbonylation) of iodide and triflate derivatives with palladium catalysts have been re-



Scheme 3

ported and widely used for the synthesis of amides or esters but, surprisingly, no homogeneous catalytic methods for the synthesis even of simple hydrazides were known until a highly efficient, novel synthesis of pharmacologically important steroidal disubstituted hydrazides **13** was published in 1997.[19] The same authors subsequently extended the scope of this interesting method, and demonstrated that palladium-catalysed hydrazinocarbonylation is a powerful tool for obtaining biologically important hydrazides[20] (Scheme 4).

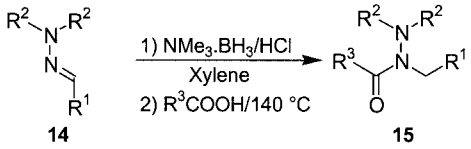


Scheme 4

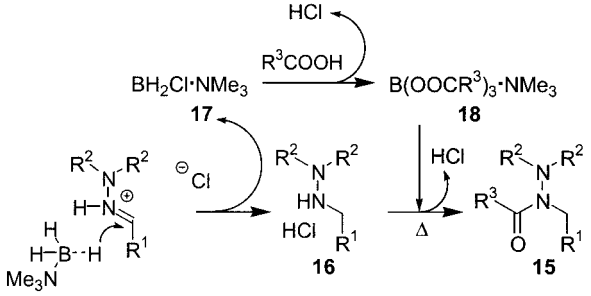
A new "one-pot" synthesis of di- and trisubstituted hydrazides by reduction of the corresponding hydrazones and in situ acylation of the obtained hydrazine has recently been published.[9] The reducing agent for the reaction is the borane·trimethylamine complex, which is commercially available and stable in acidic medium. The overall transformation from aldehyde to hydrazide can be carried out in a "one-pot" manner: hydrazones are generated in a xylene solution, and the borane.trimethylamine complex and hydrochloric acid are then added to the reaction mixture to perform the reduction step. The appropriate aromatic or aliphatic carboxylic acid is finally added to the same reaction mixture to give the hydrazides **15**. In this way, trisubstituted hydrazides can be prepared even on multigram scales (Table 1).

The postulated mechanism by which hydrazones are transformed into hydrazides is shown in Scheme 5.

Table 1. Synthesis of trisubstituted hydrazides **15** by the reduction of hydrazones **14**



Hydrazide	R^1	NR^2_2	R^3	Yield [%]
15a	Ph	NMe_2	Me	95
15b	Ph	NMe_2	Ph	81
15c	Ph	NMe_2	Et	88
15d	4-$O_2NC_6H_4$	NMe_2	Me	91
15e	3-thienyl	NMe_2	2-Cl-C_6H_4	62
15f	3-pyridyl	NMe_2	Me	60
15g	1-naphthyl	NMe_2	Me	80
15h	Et	NMe_2	2,6-Cl_2-C_6H_3	25
15i	Ph	morpholinyl	Me	90

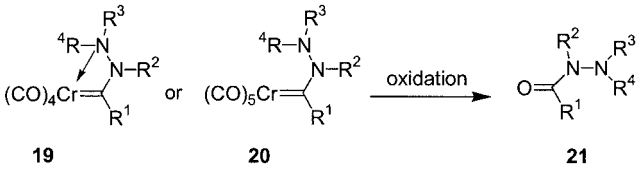


Scheme 5. Mechanism of the reduction and acylation of hydrazones

In acidic medium, the hydrazone is protonated and can easily accept a hydride ion from the amine·borane complex to give hydrazine **16**. In addition, the chloroborane **17** is

formed, and this is transformed into acyloxyborane **18** by treatment with the carboxylic acid R^3COOH, added to the reaction mixture after the reduction step. The acyloxyborane **18** is known to be an acylating species[21,22] and therefore acylates the hydrazine to give the corresponding hydrazides **15**. This "one-pot, multi-step" synthesis of hydrazides has a number of advantages: i) high hydrazide yields, ii) few by-products, iii) easy purification, iv) the use of solvent and reagents that are available in bulk and in principle compatible with an industrial process, and v) short reaction times.

A new approach to trisubstituted hydrazides has been published very recently. During the course of a study of Fischer-type hydrazinocarbene complexes, it was necessary to find efficient and useful means of recovering the organic ligand as a stable molecule from the new functionalised tetra- and pentacarbonyl hydrazinocarbene complexes **19** and **20**. The easiest and most efficient of the reported procedures for the recovery of the organic ligand from Fischer-type carbene complexes is oxidation of the metal-carbon double bond into the isolobal carbonyl bond, which transforms the carbene complex into the corresponding carbonyl compound. In the case of hydrazinocarbene complexes **19** and **20**, the oxidation produces the organic isolobal analogue hydrazides **21** (Scheme 6).



Scheme 6

The problem of finding appropriate oxidation conditions for complexes **19** and **20** is not trivial because the hydrazides are very sensitive to many oxidants, poor yields of compounds **21** being obtained if, for example, ceric ammonium nitrate (CAN) is used. Furthermore, hydrazides are bidentate Lewis base ligands that can chelate transition metal cations such as the Cr^{III} arising from the complexes upon oxidation, or the Ce^{III} formed when oxidation is performed with CAN.

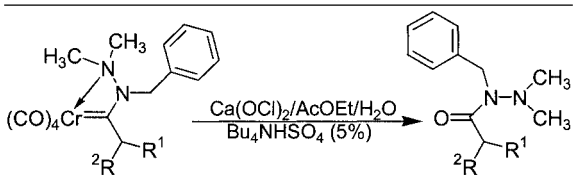
Three new and complementary oxidation methods using two different oxidants have been established.[23]

The first approach uses NaOCl or KOCl, generated slowly in situ from $Ca(OCl)_2$ (which is not very soluble in the reaction medium), and $NaHCO_3$ or a phosphate buffer (Table 2).

The second, which is also suitable for complexes **19**, uses a catalytic amount of iodine generated in situ by the oxidation of KI with sodium perborate at pH 7 by addition of KH_2PO_4 to the biphasic water/EtOAc system (Table 3).

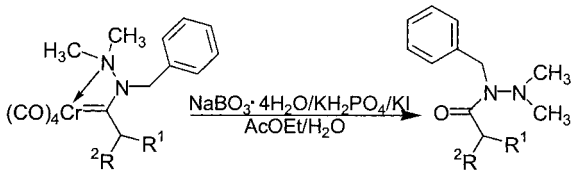
This method is very mild because of the neutral conditions and the small amount of free iodine, and can therefore be applied to substrates sensitive to further oxidation, such the aldol adduct **21b**.

Table 2. Oxidation of tetracarbonyl hydrazinocarbene complexes **19a−d**



R^1	R^2	conditions[a]	hydrazide	yield (%)
Ph	Ph	A	**21a**	92
CH_3	Ph	A	**21b**	96
H	CH_3	B	**21c**	90
H	HO	B	**21d**	28

Table 3. Oxidation of tetracarbonyl hydrazinocarbene complexes with the in situ generated iodine



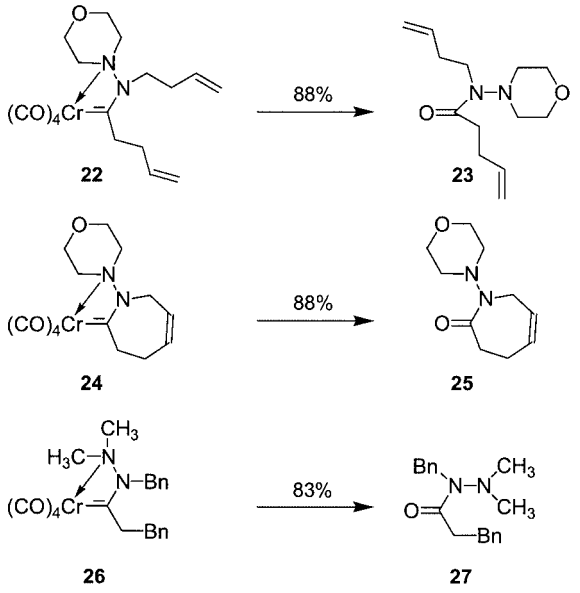
R^1	R^2	conditions[a]	hydrazide	yield (%)
CH_3	Ph	A	**21a**	96
H	HO	B	**21b**	84
H	O	A	**21c**	96

[a] Reaction conditions: water/EtOAc = 1:1, 10 equiv. of KH_2PO_4; A: 6.7 equiv. of $NaBO_3{\cdot}4H_2O$, 10 mol % of KI; B: 5 equiv. of $NaBO_3{\cdot}4H_2O$, 3 mol % of KI. [b] For the synthesis of starting complexes, see ref.[3]

When the starting carbene complex is less prone to oxidation (as in the case of complexes **22** and **24**), a third method can be used. This simply involves equimolar amounts of iodine and the carbene complex in a biphasic system of water/EtOAc and sodium hydrogencarbonate (Scheme 7).

The oxidation of hydrazinocarbene complexes can be considered a good method of obtaining variously trisubstituted hydrazides not easily obtainable by other methods. As described below, it is possible to functionalise hydrazinocarbene complexes in several ways, allowing the synthesis of a

wide range of complexes from which the corresponding new and highly functionalised hydrazides are obtained by means of oxidation.



Scheme 7. Reagents and conditions: 1.1 equiv. of I_2, 10 equiv. $NaHCO_3$, water/EtOAc (1:1)

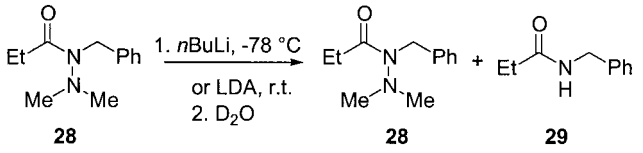
Reactions of Hydrazides

The cyclisation of hydrazides to give heterocyclic compounds (mainly five-membered heterocyclic rings) is an important reactivity, but is not considered here because good reviews have already been published.[24]

α-Functionalisation through Enolate Formation

As mentioned in the introduction, the peculiarity of hydrazides is the simultaneous presence of an amide-like function (which can allow enolate chemistry) and the β-amino group Lewis base residue, which can play an important role in the formation of rigid and stereochemically defined enolates. However, despite this a priori interesting combination of factors, the reactivity of substituted hydrazides with bases depends on their structures. This has considerably limited the use of hydrazides as aza-homologues of amides in the formation of new carbon-carbon bonds by enolate chemistry. In particular, to the best of our knowledge, there are no reports of the enolate formation and use in organic synthesis of acyclic hydrazides. In the course of recent studies of Fischer-type hydrazinocarbene complexes, it became necessary to verify the possibility of forming enolates from acyclic hydrazides, which was done by studying the reactions of hydrazide **28** with a number of different bases.

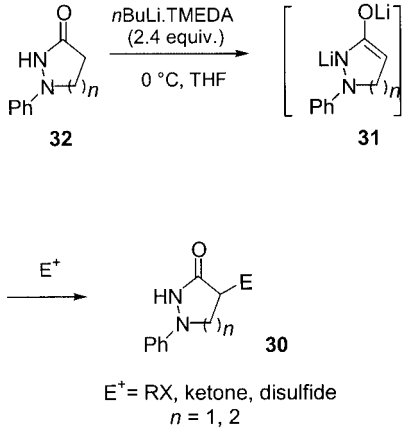
It was quite surprising to find that no deuterium incorporation on the α-carbon atom was ever observed, thus indicating that no deprotonation occurred in that position. The hydrazide does not react with LDA or LiHMDS at −20 °C, but does so at 20 °C with LDA or at −78 °C with *n*BuLi, and after quenching with D_2O, the *N*-benzyl amide **29** is obtained together with the unchanged hydrazide **28** (Scheme 8).[7]



Scheme 8

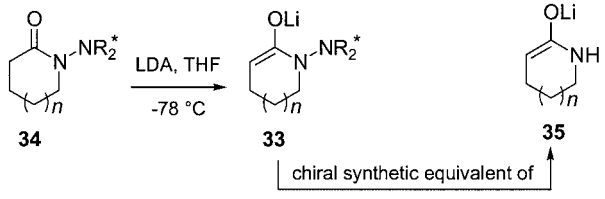
In contrast, it has been reported that cyclic substituted hydrazides are useful synthons in the formation of new carbon-carbon bonds as a result of reactions between the corresponding enolates and electrophilic reagents.

In particular, 4-substituted pyrazolidinones and pyridazinones **30** were obtained on treatment of dianions **31** − generated from phenidone **32** [*n* = 1] or pyridazinone **32** [*n* = 2] with 2.5 equiv. of *n*-butyllithium·*N,N,N′,N′*-tetramethylethylenediamine complex − with various electrophiles[25] (Scheme 9). These compounds inhibit the 5-lipoxygenase enzyme.



Scheme 9

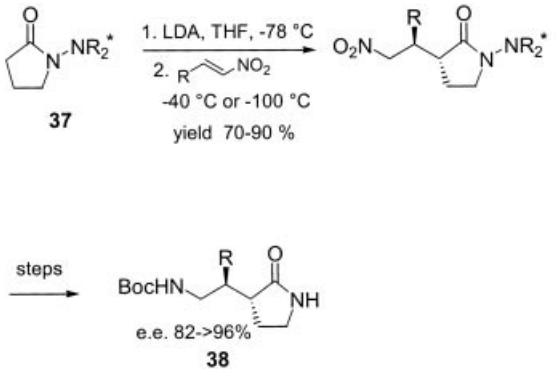
Enders has reported the generation of metallated *N*-dialkylaminolactams **33** from *N*-aminolactams **34**, and their use as chiral synthetic equivalents of the achiral parent enolate **35**[26] (Scheme 10).



Scheme 10

The anions **33** were treated with various alkylating agents at −100 °C to give 2-substituted lactams in reasonable to high diastereomeric excess. More recently, the same authors[27] reported the Michael addition of the enantiomerically pure hydrazide (*N*-amino-γ-lactam) **37** to aliphatic

and aromatic nitroolefins to give the corresponding 1,4-addition products, with higher diastereoselectivity when aliphatic nitroolefins were used. After reducing the nitro group with sodium borohydride, and the N−N bond with lithium in liquid ammonia, the authors recovered the corresponding enantiomerically enriched lactams **38**, which are precursors of double GABA analogues (Scheme 11).



Scheme 11

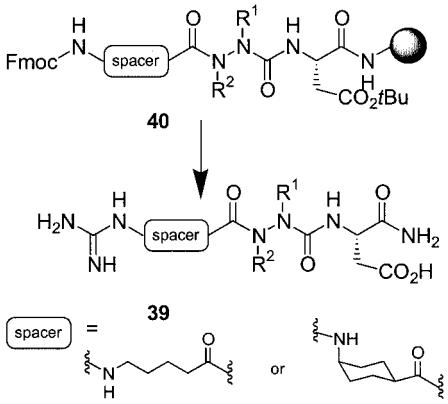
Azapeptides

The final targets in applications of the hydrazide chemistry described above were enantiomerically pure lactams, the hydrazides acting in these cases as useful synthons bearing the chiral auxiliary. However, the hydrazide moiety is itself present in many biologically active compounds[28] in which the hydrazide functionality per se has interesting and important properties. For example, azapeptides are a class of peptidomimetics in which the α-CH group of one or more amino acid residues is replaced by a nitrogen atom.

This structural modification allows the preparation of peptide analogues, which possess greater metabolic stability thanks to the fact that azapeptides are more resistant than natural peptides to enzymatic cleavage. They also show enhanced bioavailability and biological absorption, which has made them a subject of research interest[29] and resulted in their application as inhibitors of serine[30] and cysteine proteases.[31]

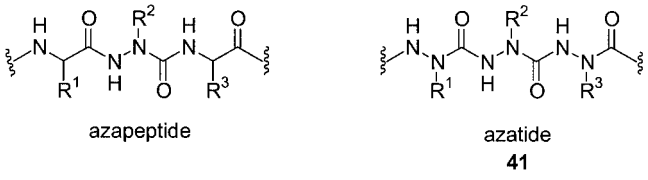
Azapeptides were first introduced and studied a long time ago, but they still arouse the interest of organic chemists. An excellent review was published by Gante in 1989,[4] and so we concentrate here on more recent reports dealing with new structures and new synthetic strategies.

Gante's review considered only solution-phase syntheses of azapeptides, but it is now known that solid-phase synthesis (SPS) is one of the most useful methods in automated synthesis and combinatorial chemistry, and there are now a number of very well established procedures for peptide SPS. Unlike other non-peptidic compounds, azapeptides lend themselves very well to SPS. Kessler et al.[32] described the first study of the design and synthesis of azapeptides on a solid support, using the Fmoc strategy generally used in solid-phase peptide synthesis. They prepared the aza-RGD-mimetics **39** (RGD = Arg-Gly-Asp) shown in Scheme 12 by solid-phase guanylation of the supported precursors **40**.



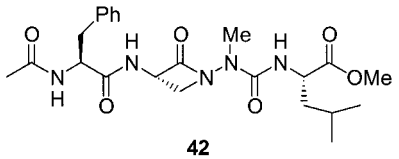
Scheme 12

Janda[33] described an interesting stepwise synthesis of what he calls "*azatides*" (**41**): biopolymers consisting of α-aza-amino acids linked in a repetitive manner.



This was the first example of a "pure azapeptide" in the sense that all of the monomers of the polymer or oligomer are α-aza-amino acids coupled in a linear, stepwise, chain-lengthening fashion by solution- or liquid-phase synthetic methods. The aim of the authors was to set up a general procedure for accessing these new materials with potential biological properties, and to establish a combinatorial library construction to provide a means of producing peptidomimetic libraries.

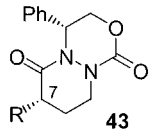
Malachowski[34] has recently reported the synthesis of a conceptually new azapeptidomimetic in which an *N*-amino-β-lactam moiety is incorporated in the peptide backbone. In particular, the authors synthesised the tetrapeptidomimetic **42** as a potential second-generation protease inhibitor.



The use of azapeptides and reactive monocyclic β-lactams as protease inhibitors has been documented, and so

the fusion of the two functionalities in the same molecule may give rise to enhanced activity against the protease enzyme.

Conformationally constrained peptidomimetics **43** containing the bicyclic hydrazinolactam functionality have been prepared by Husson et al.[35]



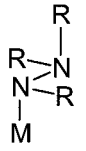
43

R = Me, allyl, benzyl, CH_2CO_2tBu,
yield 50-68 %, d.e. = 0->95 %

The synthetic strategy proposed by Husson et al. consists of the formation of a new carbon-carbon bond at C-7 by means of enolate chemistry and reaction with several electrophilic reagents, the reaction occurring in most cases with remarkable diastereoselectivity. This is another example of cyclic hydrazide reactivity through enolate formation. It is necessary to choose the right base to generate the enolate regioselectively in position 7 because the use of LDA resulted in benzylic deprotonation and subsequent β-elimination with N−N bond-breaking. This confirms the previously mentioned observation (Scheme 8) that enolate generation depends on the base and the structure of the hydrazide.

Metallahydrazides

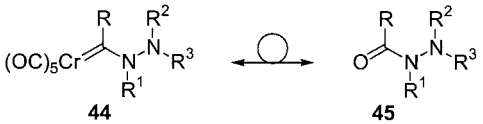
A number of published papers concern transition metal organohydrazide complexes containing a metal-nitrogen-nitrogen linkage.[36,37] Many of these complexes have interesting biological properties and have received considerable attention as potential model systems for intermediates in biological nitrogen fixation.



M = transition metal

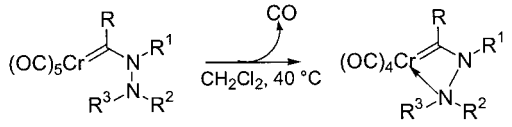
However, we will not consider them here because they are not directly related to the classical hydrazide structure, and no hydrazide can be obtained from them.

In contrast, a new class of heteroatom-stabilised Fischer-type carbene complexes, the alkyl(hydrazino)carbene complexes of general formula **44**, are metallahydrazides strictly related to the hydrazide analogues **45**.



44 **45**

Because of the isolobal analogy between a $(CO)_5Cr$ moiety and an oxygen atom,[38] hydrazides **45** can be regarded as organic isolobal analogue molecules of carbene complexes **44**. However, although it is easy to transform complexes **44** into the organic molecules **45** by oxidation (see the above section dedicated to synthesis, Scheme 6), the reactivities and potential applications of the two classes to organic synthesis are quite different. In particular, as pointed out above, acyclic hydrazides, unlike amides, are unsuitable substrates for enolate chemistry because they are unreactive or unstable towards bases. During some studies of hydrazinocarbene complexes, it has been found that these organometallics are good and efficient synthetic equivalents of their organic isolobal analogues **45**, and can be used with high synthetic potential in carbon-carbon bond-forming reactions. In particular, the presence of the lone pair on the β-nitrogen atom means that the (*Z*)-pentacarbonyl complexes of type **44** can be quantitatively transformed into the stable chelate complexes **46**, in which the β-nitrogen atom replaces one of the four *cis* CO ligands of the metal[39] (Scheme 13).



44 **46**

Scheme 13

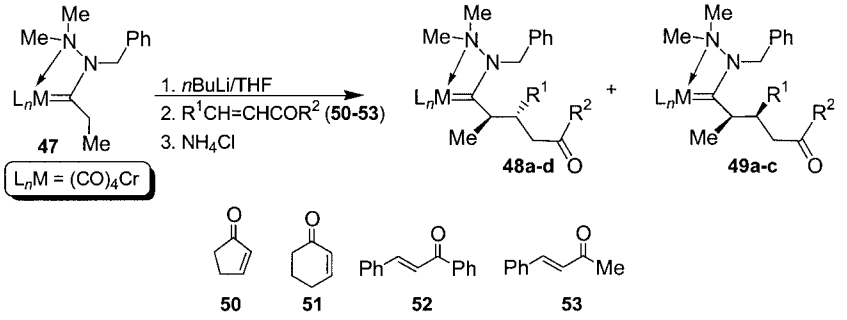
Moreover, hydrogen atoms located in the α-position with respect to the carbene carbon atom are acidic; these complexes can be efficiently deprotonated with strong bases, and the obtained anions react easily with various electrophiles.[40] It has very recently been reported[41] that highly diastereoselective Michael and aldol additions of the Fischer-type alkyl(hydrazine)carbene complex **47** can be used as a synthetic strategy to obtain new substituted hydrazides. The Michael additions are shown in Scheme 14.

At −78 °C, the soft anion of complex **47** smoothly adds to the enones **50**−**53** in a 1,4 regioselective manner to give the diastereoisomeric keto complexes **48a**−**c** and **49a**−**d** with the *de* values shown in Table 4. The major diastereoisomer obtained in all cases was the *anti* diastereoisomer (complexes **48**).

In addition, in aldol-type addition reactions with aromatic and aliphatic aldehydes **54**−**58**, the anion generated from complex **47** reacted at −78 °C to give the diastereoisomeric mixtures **59a**−**e** and **60a**−**e** with very high yields and *de* values (Scheme 15, Table 5).

In these cases, the major diastereoisomers were the *syn* diastereoisomers **59a**−**e**. The classical chair-like Zimmermann−Traxler model used to explain diastereoselectivities in aldol additions of organic compounds can also be used to explain the diastereoselectivity in this case.[41]

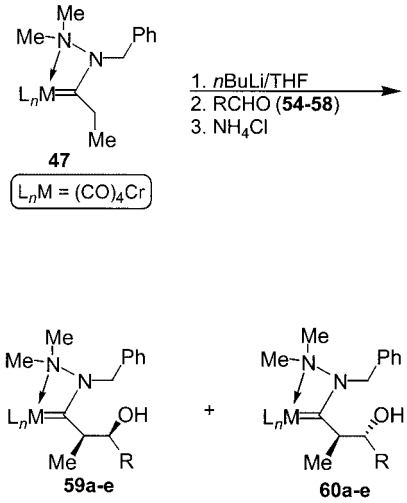
As described above, complexes **48**, **49**, **59** and **60** give the corresponding functionalised hydrazides in high yields and



Scheme 14

Table 4. Michael addition of carbene **47** to enones **50**−**53**

Product	Enone	Yield [%]	*de* (%)
48a + **49a**	**50**	87	47
48b + **49b**	**51**	82	92
48c + **49c**	**52**	60	98
48d + **49d**	**53**	87	>98



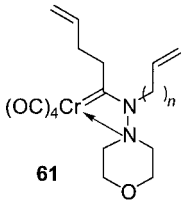
Scheme 15

Table 5. Aldol addition of carbene **47** to aldehydes **54**−**58**

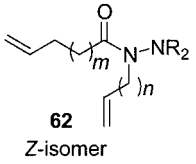
Product	Aldehyde	Yield [%]	*de* (%)
59a + **60a**	**54**	90	95
59b + **60b**	**55**	86	74
59c + **60c**	**56**	93	91
59d + **60d**	**57**	80	98
59e + **60e**	**58**	84	90

without any racemisation through oxidation of the chromium-carbon bond to the carbonyl group.

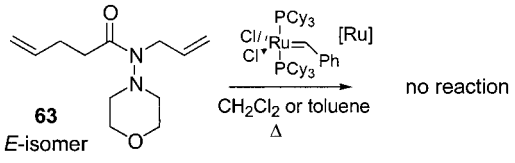
In another application of the chemistry of hydrazinocarbene complexes, the synthesis of complexes **61** substituted with unsaturated chains suitable for performing ring-closing metathesis (RCM) reactions has been designed.[42]



Once again, the results obtained in this study demonstrate that hydrazinocarbene complexes (particularly the chelate derivatives **61**) are useful synthetic equivalents of isolobal hydrazides. There are no published reports concerning RCM reactions on hydrazides, perhaps because of the impossibility of obtaining the stereochemically defined (*Z*)-*N*,*N*′,*N*′-trisubstituted organic hydrazides **62** necessary for efficient RCM processes.



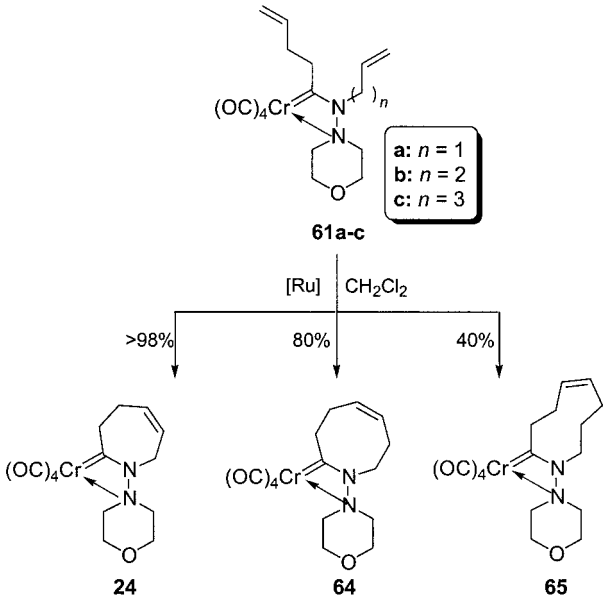
This is supported by the fact that no reaction was observed when hydrazide **63**, which is obtainable exclusively as an *E* isomer, was subjected to RCM conditions in the presence of the Grubbs catalyst [Ru][42] (Scheme 16).



Scheme 16

In contrast, complexes **61a**−**c** (synthesised as reported[42]), in which the two unsaturated chains are forced into the appropriate *syn* position for cyclisation, easily give the RCM reactions to afford the seven-, eight- and nine-membered ring heterocycles **64a**−**c** (Scheme 17).

As shown above in Scheme 7, complex **24** can be oxidised to the corresponding hydrazide **25**. Once again, hydrazinocarbene complexes demonstrate their usefulness as synthetic equivalents of hydrazides in that their particular chemistry



Scheme 17

can serve to provide access to otherwise inaccessible substituted and functionalised hydrazides.

Conclusions and Outlook

This microreview describes a number of methods, some of which are new and general, for providing access to variously di- and trisubstituted hydrazides. A large variety of different and complementary methodologies are now available in the synthetic arsenal of chemists for the preparation of this class of molecules. In addition, the discovery of a number of interesting new reactivities of organometallic precursors, such as Fischer-type hydrazinocarbene complexes, have allowed the exploitation of their potential in organic synthesis. Since a number of hydrazides have interesting properties, and also in view of their application in various fields, it is clearly important to have new routes to more highly functionalised and decorated derivatives. By focusing on potential biological and pharmacological properties, one of the most recent and still very promising uses of hydrazide function relies on the production of aza-mimetics of natural and synthetic active molecules. The advantage of obtaining analogues that are more stable towards the physiological environment and natural enzymes certainly opens up important perspectives for the possible use of peptides in human therapy.

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