Recent advances in the synthesis of polysubstituted 3-pyrazolidinones

Uroš Grošelj and Jurij Svete*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Večna pot 113, SI – 1000 Ljubljana, Slovenia
E-mail: jurij.svete@fkkt.uni-lj.si

DOI: http://dx.doi.org/10.3998/ark.5550190.p009.129

Abstract
An account of recent developments in the field of 3-pyrazolidinone chemistry is given with special focus on the synthesis and transformations of 5-substituted 4-benzyloxycarbonylamino-3-pyrazolidinones, pyrazolo[1,2-a]pyrazole-based peptide analogues, and tetrahydropyrazolo[1,5-c]pyrimidine-2,7-diones. In terms of practical application, polyfunctionalized 3-pyrazolidinones as 'aza-deoxa' analogues of cycloserine, peptide mimetics based on 3-amino-2-oxo-1,5-diazabicyclo[3.3.0]octane-7-carboxylic acid, and 1,6-disubstituted tetrahydropyrazolo[1,5-c]pyrimidine-2,7-diones as the first representatives of a novel saturated heterocyclic system were prepared by these newly developed synthetic methods.

Keywords: pyrazolidinones, cycloadditions, cyclizations, fused pyrimidines, peptide mimetics

Table of Contents

1. Introduction
2. Synthesis of 3-Pyrazolidinone Derivatives
   2.1. Synthesis from α,β-unsaturated esters
   2.2. Synthesis from β-hydroxy esters
3. Transformations of 3-Pyrazolidinone Derivatives
   3.1. Transformations on the ring
   3.2. Ring transformations
4. Synthesis of bicyclic 3-Pyrazolidinone Derivatives
   4.1. Pyrazolo[1,2-a]pyrazoles
   4.2. Pyrazolo[1,5-c]pyrimidines
5. Structural Features of 3-Pyrazolidinones
6. References
1. Introduction

3-Pyrazolidinone (Figure 1) and its derivatives are cyclic (internal) hydrazides of 3-hydrazinopropanoic acid, which are commonly available by treatment of α,β-unsaturated carboxylic acid derivatives with hydrazine hydrate. In spite of their structural simplicity and ease of preparation, there were almost no reports on 3-pyrazolidinones in the early times of organic chemistry until the second half of the 20th century. The first reports on 3-pyrazolidinones date to the 1940s.1–6 Since that time, the importance of 3-pyrazolidinones has risen significantly, due to their applicability in industrial processes and biological activity. So far, progress on 3-pyrazolidinone chemistry has been reviewed by Dorn in 1981,7 Claramunt and Elguero in 1991,8 and in part by Svete in 2008.9 Pyrazolidinone derivatives have been employed as dyes in food and other industries.7,10,11 Their bioactivities range from analgesic and antipyretic (phenazone),12–14 anti-inflammatory (phenylbutazone),12–14 and anorectic (BW357U),15 to inhibitory activities of cyclooxygenase and lipoxygenase in BW755C and phenidone, respectively.16,17 Bicyclic pyrazolidinones are used, among others, as drugs to relieve Alzheimer’s disease18 and as antibacterial agents.19–23 Some important 3-pyrazolidinones are presented in (Figure 1).

![Figure 1. Some important 3-pyrazolidinone derivatives.](image)

Due to their applicability and biological activity, pyrazolidin-3-one derivatives, both mono- and bi-cyclic, remain attractive synthetic targets. Particular challenge is associated with their enantio- and/or diastereoselective synthesis. Most of the early studies were performed on achiral and on lightly substituted chiral pyrazolidinones.7,8 Recent studies, however, established the applicability of chiral polysubstituted 3-pyrazolidinones and their derivatives in the stereoselective synthesis of highly functionalized compounds.24–26 Camphor derived pyrazolidin-3-one has been successfully employed as chiral auxiliary27 while pyrazolidinone templates have been used in enantioselective Diels-Alder cycloadditions.28 Several studies demonstrated the potential of pyrazolidin-3-ones as a new scaffold in organocatalysis.29–35
In the last two decades, a substantial part of our research interest has also been devoted to the chemistry of 3-pyrazolidinones.\textsuperscript{9,36–38} Most of our work in this field was based on chiral racemic (4\textsuperscript{R*},5\textsuperscript{R*})-4-benzoylamino-5-phenylpyrazolidin-3-one as the model compound, which is easily available from 4-benzylidene-2-phenyl-5(4\textit{H})-oxazolone by heating with excess hydrazine hydrate.\textsuperscript{3,24} This model compound was successfully employed in the synthesis of β-pyrazolylalanine- and β-amino-β-phenylalanine derivatives and pyrazolo[1,2-\textit{a}]pyrazole-based peptide mimetics.\textsuperscript{9} In extension, we became interested in the preparation of saturated 6-amino-perhydropyrazolo[1,2-\textit{a}]pyrazole-1(or 2)-carboxylates that could serve as building blocks for incorporation into oligopeptides. Another important issue was the preparation of non-racemic peptide analogues, available either by resolution or by asymmetric synthesis. Finally, literature search revealed that saturated bicyclic pyrazolidinone-based heterocyclic systems are pretty much unknown. In this account, our recent developments in the synthesis of 3-pyrazolidinones and their fused analogs are presented.

2. Synthesis of 3-Pyrazolidinone Derivatives

2.1. From α,β-unsaturated esters
Heating of α,β-unsaturated esters (acrylates) with excess hydrazine hydrate is the most general and straightforward route to 3-pyrazolidinones.\textsuperscript{7–9} In the case of functionalized acrylates, however, the use of excess hydrazine hydrate represents a limitation, since nucleophile-sensitive functional groups may also react. This limitation cannot be avoided by the use of nucleophile-resistant protecting groups, since they are usually difficult to remove. Consequently, deprotection and further derivatisations are hardly feasible. For example, the amino function in the products derived from (4\textsuperscript{R*},5\textsuperscript{R*})-4-benzoylamino-5-phenylpyrazolidin-3-one (1) could not be deprotected without destroying the heterocyclic system as well. For this reason, we decided to perform the synthesis of N-benzylloxycarbonyl protected compounds to allow N-deprotection and further transformations of the products. First, 3-substituted methyl 2-(benzylloxycarbonylamino)-acrylates 3\textsubscript{a–i} were prepared by Wittig-Horner condensation of methyl 2-(benzylloxycarbonylamino)-2-(dimethoxyphosphoryl)acetate (2) with aldehydes and ketones following a slightly modified procedure by Schmidt and co-workers.\textsuperscript{39} Acrylates 3\textsubscript{a–i} were then treated with excess of N\textsubscript{2}H\textsubscript{4}·H\textsubscript{2}O in an alcohol (MeOH, EtOH, or \textsuperscript{3}PrOH) at 20–100 °C to afford the corresponding 3-pyrazolidinones 4\textsubscript{a–i} in 23–100% yields (Scheme 1).\textsuperscript{40–42}
Scheme 1. Synthesis of 3-pyrazolidinones 4a–i.

Another recent example of utilization of $\alpha,\beta$-unsaturated esters in the synthesis of 3-pyrazolidinones is a ‘ring switching’ transformation of commercially available 5,6-dihydro-$2H$-pyran-2-one (5) with hydrazine hydrate in ethanol at r.t. This reaction gave 5-(2-hydroxyethyl)pyrazolidin-3-one (7a) in quantitative yield. It is also noteworthy, that 2-substituted analogues of 7a could not be prepared in this way. For example, treatment of 5 with phenylhydrazine afforded the 1,4-addition intermediate 6, which could not be converted into the corresponding pyrazolidinone 7b, even under forcing conditions (Scheme 2).

Scheme 2. Synthesis of 5-(2-hydroxyethyl)pyrazolidin-3-one (7a).

2.2 From $\beta$-hydroxy esters
Beside acrylates, $\beta$-sulfonyloxy esters are also suitable substrates for the preparation of 3-pyrazolidinones. Preparation of racemic 4-benzyloxycarbonylamino-3-pyrazolidinone 4j from methyl $N$-benzyloxycarbonyl-$O$-tosylserinate (8) and hydrazine hydrate was reported by Jungheim and co-workers in 1987 (Scheme 3).

Scheme 3. Synthesis of 4-benzyloxycarbonylamino-3-pyrazolidinone (4j).
Recently, non-racemic 3-pyrazolidinones have been prepared from L-phenylalanine. N-Cbz-(S)-3-phenylalanine (9) was converted into the corresponding β-keto ester 10 in 43% yield via the addition of Li-enolate of methyl acetate to the reactive imidazolide of 9. Subsequent reduction of 10 with NaBH₄, followed by chromatographic separation and re-crystallization gave isomerically pure (3R,4S)-β-hydroxy ester 11. Mesylation of 11 in pyridine gave 12, which was further treated with excess hydrazine hydrate in CH₂Cl₂ to yield the desired pyrazolidin-3-one in full conversion as an inseparable mixture of epimers 13 and 13′ in a ratio of 62:38 and in 57% yield. Following the same reaction conditions, cyclization of 12 with methylhydrazine yielded two regioisomeric pyrazolidinones each as a mixture of epimers in 100% conversion. The products 14, 14′, 15, and 15′ were formed in a ratio of 35:26:26:13. Chromatographic separation yielded pure isomers 14, 14′, and 15 in 25%, 18%, and 10% yield, respectively. Performing the reaction under identical conditions in DMF did not significantly change the product ratio. The formation of two regioisomers in the reaction of 12 with methylhydrazine was not unexpected. The poor diastereoselectivity of the formation of 13/13′–15/15′ implies that substitution of the mesylate group with hydrazine proceeds, either via a mixed S_N1/S_N2 mechanism, or alternatively, via initial elimination of mesylate group, followed by 1,4-addition of hydrazine to the so formed α,β-unsaturated ester intermediate (Scheme 4).47

\[ \text{Scheme 4. Synthesis of non-racemic pyrazolidin-3-ones 13/13′–15/15′.} \]
Finally, 5-(2-aminoethyl) substituted 3-pyrazolidinones have also been synthesized in six steps from methyl acrylate (16). Following literature examples, solvent-free DBU-catalysed Michael addition of benzylamine, 1-butylamine, and 1-propylamine to 16 gave methyl β-alaninates 17a–c, which were Cbz-protected and the so formed N-alkyl-N-Cbz-β-alanine esters 18a–c were hydrolyzed to afford N-alkyl-N-Cbz-β-alanines 19a–c in 34–51% yields over three steps. Masamune-Claisen condensation of 19a–c with monomethyl magnesium malonate was carried out according to the literature procedure for homologation of closely related amino acid derivatives to give the corresponding β-keto esters 20a–c in 87–92% yields. Reduction of 20a–c with NaBH₄, mesylation of the alcohols 21a–c, and cyclisation of the mesylates 22a–c with hydrazine hydrate furnished 5-{2-[(alkyl)(benzyloxy carbonyl)amino]ethyl}pyrazolidin-3-ones 23a–c in 43–61% yields over three steps (Scheme 5).

Scheme 5. Synthesis of pyrazolidin-3-ones 23a–c.

3. Transformations of 3-Pyrazolidinone Derivatives

3.1 Transformations on the ring

It is within this context that functionalization at the ring nitrogen atoms is usually performed. On account of the cyclic hydrazide structure of 3-pyrazolidinones, the reactivities of the two nitrogen atoms differ significantly. The more basic and more nucleophilic N(1) is also more reactive. It preferably reacts with sp² electrophiles, such as carbonyls, electron-deficient alkenes
and alkynes, and carbocations (S_N 1 substrates), whereas reactions with sp^3 type of electrophiles (S_N 2 substrates, such as primary alkyl halides) are usually difficult. A better way to obtain the corresponding 1-(primary alkyl)-3-pyrazolidinones is reduction of easily available azomethine imines with complex hydrides, e.g. with NaBH_4 or NaBH_3CN. Once the N(1) is occupied, the amidic nitrogen N(2) can react with primary alkyl halides in the presence of a base in polar aprotic solvents to give the 1,2-disubstituted derivatives (Figure 2).

![Figure 2](image.png)

**Figure 2.** Functionalizations of ring nitrogen atoms with electrophiles.

A recent example of sequential derivatization of 5-substituted (4R*,5R*)-4-benzyloxy carbonylamino-3-pyrazolidinones is a simple five-step synthesis of fully substituted (4R*,5R*)-4-aminopyrazolidin-3-ones as analogues of D-cycloserine. It comprises a two-step preparation of 5-substituted (4R*,5R*)-4-benzyloxy carbonylamino-3-pyrazolidinones 4 (cf. Scheme 1), reductive alkylation at N(1), alkylation of the amidic N(2) with alkyl halides, and simultaneous hydrogenolytic deprotection/reductive alkylation of the primary amino group. The major advantage of the synthesis is that it enables an easy stepwise functionalization of the 3-pyrazolidinone core with only two types of common reagents, aldehydes (or ketones) and alkyl halides (Figure 3).
Acid-catalyzed treatment of 4a–c,e with acetone and aromatic aldehydes in MeOH gave the corresponding azomethine imines 24a–j in 31–99% yields. Reduction of 24a (R₁ = iPr, R₂ = H, R₃ = benzylidene) with NaBH₄ in MeOH at r.t. afforded the 1-benzyl derivative 25a in 93% yield (Path A). The other N(1)-alkylated derivatives 25 were prepared by an one-pot procedure via in situ formation of azomethine imines 24, followed by subsequent reduction with NaBH₄. In this manner, a series of ten N(1)-alkylated 4-(benzyloxycarbonylamino)-3-pyrazolidinones 25a–j were obtained in 21–95% yields (Path B). S_N2-type alkylation of the amidic N(2) was performed with primary alkyl halides in DMF in the presence of K₂CO₃ at r.t. to furnish the fully substituted 4-amino-3-pyrazolidinones 26a–h in 45–97% yields (Scheme 6).42

\[
\begin{align*}
\text{Compounds 24:} & \\
R₁ &= H, \text{Me, } i^\text{Pr}, \text{Pr, Ph} \\
R₂ &= H, \text{Me} \\
R₃ &= \text{benzylidene, isopropylidene, 2,6-dichlorobenzylidene, 3,4,5-trimethoxybenzylidene} \\
\end{align*}
\]

\[
\begin{align*}
\text{Compounds 25 and 26:} & \\
R₁ &= H, \text{Me, } i^\text{Pr}, \text{Pr, Ph} \\
R₂ &= H, \text{Me} \\
R₃ &= \text{benzylidene, isopropylidene, 2,6-dichlorobenzylidene, 3,4,5-trimethoxybenzylidene} \\
R₄ &= \text{Me, Bn, CH₂COOEt, CH₂COO}^{t\text{Bu}} \\
\end{align*}
\]
To bring other functionalities to the amino function, transformations of the benzyloxy carbonylamino group at position 4 were studied as well. Hydrogenolytic deprotection of the 4-amino function in the Cbz-protected 4-aminopyrazolidinones 4, 25, and 26 gave the free amines 27, 28, and 29, respectively, in almost quantitative yields. When hydrogenolytic deprotection of the 1,5-disubstituted 4-benzyloxy carbonylamino-3-pyrazolidinones 25 was carried out in the presence of an aldehyde or a ketone, the 4-alkylamino-3-pyrazolidinones 30 were obtained in 75–100% yields. Somewhat surprisingly, acylations of the 1,2-unsubstituted (4R*,5R*)-4-amino-5-isopropyl-3-pyrazolidinone 27 with acid chlorides or with carboxylic acids in the presence of activating reagents, such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) and 1,1'-carbonyldiimidazole (CDI), did not give the desired carboxamides. The only successful N-acylation of 27 was the reaction with [1,1'-biphenyl]-4-carboxylic acid in the presence of bis(pentafluorophenyl) carbonate (BPC) in DMF, which afforded the corresponding N-acyl derivative 31 in 10% yield. Though surprising, the difficult acylation of the NH2 group could be the result of the highly polar character of 27 as cyclic α-amino hydrazide comprising three different amino groups. On the other hand, acylation of the less polar 1-substituted or 1,2-disubstituted pyrazolidinones 28 and 29 with phenylacetic acid and EEDQ in CH2Cl2 proceeded smoothly to produce the corresponding carboxamides 32 and 33 in 83% and 82% yield, respectively (Scheme 7).42

![Scheme 7. Synthesis of polysubstituted pyrazolidinones 27-33.](image-url)
3.2 Ring transformations

5-Aryl-3-pyrazolidinones undergo thermally- or hydrogenolytically-induced 'ring switching' transformation into N-aminohydantoins. This reaction was observed for the first time in the course of our studies on cycloadditions of \((1Z,4R^*,5R^*)\)-1-arylmethylidene-4-benzoyloxy-carbonylamino-3-oxo-5-phenylpyrazolidin-1-ium-2-ides \(24a,b\) to tert-butyl acrylate in refluxing anisole. Aside from the expected cycloadducts, significant amounts (~25%) of benzylidene-iminohydantoins \(35\) were obtained as side products.\(^{41}\) Heating \(24a,b\) alone in anisole under reflux furnished the corresponding \(N\)-imino-hydantoins \(35a,b\) as the sole products in good yields. This ring transformation can be rationalized by thermal cleavage of benzylidene-type C–N bond in the enol form of azomethine imine \(24'\). The so formed \(\alpha,\beta\)-unsaturated hydrazide \(34\) cyclizes into \(35\) by nucleophilic attack of the amidic nitrogen to the Cbz group (Scheme 8).\(^{40}\)

![Scheme 8](image)

**Scheme 8.** Ring switching’ transformation of pyrazolidinone derivatives \(24a,b\) into the \(N\)-iminohydantoins \(35a,b\).

Another, somewhat surprising, transformation was observed in the attempted preparation of \((1Z,4R^*,5R^*)\)-2-amino-5-phenyl-3-pyrazolidinone (36) by catalytic hydrogenation of the Cbz-protected compound 4e. Instead of the desired product 36, the \(N\)-aminohydantoin 39 was obtained in 69% yield. Also here, the reaction pathway is explainable by sequential hydrogenolitic cleavage of the benzyl C–O and C–N bonds in 4e to give the \(\alpha\)-amino hydrazide 37. Under slightly elevated pressure (3 bar), the amine 37 and \(\text{CO}_2\) are in equilibrium with the carbamic acid 38, which cyclizes to \(N\)-amino hydantoin 39.\(^{40}\) The proposed mechanism is supported by known, closely related examples of cyclizations of \(N\)-benzyloxy carbonyl-\(\alpha\)-amino acid hydrazides\(^{55-57}\) and \(\alpha\)-semicarbazidoacetates\(^{58-60}\) into 3-aminoimidazolidine-2,4-diones. Besides, the above transformation is also related to Bucherer’s synthesis of hydantoin, which proceeds in a closed vessel under slightly elevated pressure utilizing \(\text{CO}_2\) (or carbonate) as a \(\text{C}_1\)-synthon (Scheme 9).\(^{61,62}\)
Scheme 9. Transformation of the pyrazolidinone 4e into N-aminohydantoin 39.

4 Synthesis of Bicyclic 3-Pyrazolidinone Derivatives

4.1 Pyrazolo[1,2-\(a\)]pyrazoles

The synthesis of molecules that can mimic the structure and properties of peptides certainly represents an interesting and important research topic in the fields of organic synthesis and medicinal chemistry.\(^{63-67}\) An important group of conformationally constrained dipeptide analogues are azabicycloalkane amino acids, comprising various saturated fused heterocycles with a bridgehead nitrogen atom.\(^{68-70}\) 6-Amino-7-oxotetrahydropyrazolo[1,2-\(a\)]pyrazole-1-carboxylic acid (40) based scaffolds are a subgroup of 5,5-fused azabicycloalkane amino acids. The applicability of 40 for the preparation of biologically active peptide mimetics was successfully demonstrated by researchers at Eli Lilly almost three decades ago.\(^{19-22}\) Strangely enough, very few other examples of 40-derived compounds have been reported since 1990, meaning that 40 is a practically unexplored scaffold with reasonable applicative potential. The most general and straightforward synthetic approach towards derivatives of 40 includes stereoselective 1,3-dipolar cycloaddition as the key-step and starting from 4-acylamino-3-pyrazolidinones, which in turn are easily available by simple treatment of \(\alpha,\beta\)-dehydro-\(\alpha\)-amino acid derivatives with excess hydrazine hydrate.\(^{7-9,71}\) Retrosynthetic analysis reveals that derivatives of 40 with up to five stereogenic centers are available in four steps and from four building blocks: a) \(N\)-acylglycines, b) aldehydes (or ketones) c) hydrazine hydrate, and d) \(\alpha,\beta\)-unsaturated esters. Thus, combination of just four types of widely available building blocks enables an easy access to structurally diverse heterocyclic dipeptides (Figure 4).
Figure 4. Retrosynthetic analysis of derivatives of 40.

In the last decade, our studies on [3+2] cycloadditions of (1Z,4R*,5R*)-1-arylmethyldene-4-benzoylamino-3-oxo-5-phenyltetrahydropyrazol-1-ium-2-ides 41 to various dipolarophiles has revealed the general reactivity and selectivity of these cycloadditions,9 as well as their applicability in high-throughput synthesis.72,73 Stereocontrol can be illustrated by cycloadditions of 41 to methyl methacrylate (Scheme 10).74

Scheme 10. Cycloadditions of 41a–e to methyl methacrylate.

The stereoselectivity of the cycloadditions of dipoles 41a–e to methyl methacrylate was in agreement with the stereochemistry observed by related cycloadditions9,72,73,75 and could be explained in the following way: an ortho-unsubstituted 1'-aryl group in dipoles 41a–c can rotate around the C(1')–Ar bond, thus shielding equally both faces of the dipole 41a–c. Consequently, the phenyl ring at position 5 is the stereodirecting group, which hinders the (1'Si)-face of the (Z)-
dipole 41'. Formation of the major \((1^R,3^R,5^R,6^R)\)-isomers 42a–c is explainable by preferential endo-attack of methyl methacrylate from the less hindered (1'Re)-face of dipole 41'a–c via the proposed transition state TS1. On the other hand, rotation around the C(1')–Ar bond is not possible in ortho-disubstituted dipoles 41d,e, which presumably adopt a twisted conformation 41''d,e, where steric hindrance of the (1'Re)-face by the ortho-substituent pointing towards the N(2) becomes stronger than hindrance of the (1'Si)-face by the 5-Ph group. Thus, the predominant exo-approach of the dipolarophile from the less hindered (1'Si)-face of the (Z)-dipoles 41''d,e gives the major \((1^R,3^S,5^R,6^R)\)-isomers 42'd,e via the proposed transition state TS1' (Scheme 11).74

Scheme 11. Proposed stereocontrol in cycloadditions of 41 to methyl methacrylate.

Though very useful for the determination of reactivity and selectivity of the above \([3+2]\) cycloadditions,9,38 the obtained cycloadducts were not suitable for incorporation into peptides, since carboxy and amino functions (CO\(_2\)Me and NHCOPh, respectively) could not be selectively deprotected without cleaving the pyrazolo[1,2-a]pyrazolone system as well. Thus, selective deprotection of a heterocyclic dipeptide was mandatory for a viable method for the synthesis of peptide mimetics. To do this, we decided to try out a classical peptide chemistry approach utilizing a combination of Boc and Cbz protecting groups. Cycloadditions of 1-arylmethylidene-4-benzoxycarbonyl-amino-3-oxopyrazolidin-1-azomethine imines to tert-butyl 2-alkenoate would give selectively deprotectable dipeptides enabling derivatization of the carboxy and the amino function. Furthermore, coupling of the racemic dipeptide with an enantiomerically pure
reagent (e.g. with α-amino acid derivative), followed by separation of the so formed diastereomers would give non-racemic tripeptides.41

The starting 3-pyrazolidinones 4 and azomethine imines 24 were prepared as described previously (cf. Schemes 1 and 6).40–42 First, cycloadditions of 5-phenyl substituted dipoles 24a,b to tert-butyl acrylate were carried out under standard conditions, i.e. in refluxing anisole.9 Somewhat expectedly,40 reactions of 5-phenyl substituted dipoles 24a,b furnished, along with cycloadducts 43–46, the hydantoin derivatives 35a,b in ~25% yields. Evaporation of the filtrates followed by separation by column chromatography (CC) and medium pressure liquid chromatography (MPLC) then furnished the corresponding cycloadducts 43a–45a, 44b, and 46b in 5–36% yields (Scheme 12).41

Scheme 12. Cycloaddition of azomethine imines 24a,b to t-butyl acrylate.

On the other hand, the C(5)–N(1) bond in 5-isopropyl substituted dipoles 24c,d is thermally stable and the formation of hydantoins 35 was not observed in cycloadditions of azomethine imines 24c,d to tert-butyl acrylate, which produced only the corresponding cycloadducts 43–47. Subsequent chromatographic separation of isomeric cycloadducts furnished isomerically pure compounds 43c, 45c, and 44d–47d in 7–33% yields (Scheme 13).41
Scheme 13. Cycloaddition of azomethine imines 24c,d to t-butyl acrylate.

In contrast, cycloadditions of 24c,d to tert-butyl methacrylate were regio- and stereo-selective. Cycloaddition to dipole 24c followed by chromatographic separation furnished diastereomeric cycloadducts 43c and 45c in 35% and 9% yield, respectively, while cycloaddition to the ortho-disubstituted dipole 24d gave compound 49d as the only product in 66% yield (Scheme 14).41

Scheme 14. Cycloaddition of azomethine imines 24c,d to t-butyl methacrylate.

The regioselectivity and stereoselectivity of the cycloadditions and configurations of the major isomers 43, 46, 48, and 49 were in agreement with previous results obtained by cycloadditions of closely analogous dipoles to methyl acrylate75 and methyl methacrylate.74 Selectivity of these cycloadditions was somewhat lower than expected on the basis of results with analogous reactions.9,38,72–75 Nevertheless, isolation of multiple isomers may also be advantageous,
providing more stereochemical diversity of the 6-amino-7-oxotetrahydropyrazolo[1,2-α]-pyrazole-1(or 2)-carboxylic acid scaffold (c.f. Schemes 12–14). 41

Having this small, stereochemically diverse library of dipeptides 43–49 in our hands, we continued with selective deprotection of the amino and the carboxy function. Acidolytic deprotection of the carboxy group afforded the corresponding carboxylic acids 50a–e in 67–100% yields, while hydrogenolytic deprotection of the amino group afforded the corresponding free amines 51a–d in 20–94% yields (Scheme 15). 41

Scheme 15. Preparation of the carboxy- (50) and the amino-building blocks 51.

To show that compounds 50 and 51 can serve as useful building blocks for the synthesis of U-shaped peptides, tetrapeptide 54 and hexapeptide 57 with 3-amino-2-oxo-1,4-diaza-bicyclo[3.3.0]octane-7-carboxylic acid (40) as the central part of the sequence were prepared. Amidation of dipeptide 50a with glycine methyl ester gave the tripeptide 52 in 50% yield. Catalytic hydrogenation of 52 followed by acylation of 53 with Boc-glycine in the presence of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) furnished tetrapeptide 54 in 87% yield. Similarly, acylation of 51a with N-(N-benzyloxycarbonylglycyl)glycine gave the tetrapeptide 55 in 74% yield. Treatment of 55 with trifluoroacetic acid in dichloromethane afforded the carboxylic acid 56 in 23% yield. Amidation of the acid 56 with N-(glycyl)glycine methyl ester furnished the hexapeptide 57 in 62% yield (Scheme 16). 41
Finally, sixteen non-racemic tripeptides 58–65 and 58’–65’ were prepared. Amidation of the racemic N-protected dipeptides 50 with methyl (S)-alaninate gave diastereomeric tripeptides 58/58’–62/62’, which were separated by MPLC to furnish the non-racemic, diastereomerically pure N-protected tripeptide esters 58–62, and 58’–62’. Similarly, acylation of the racemic C-protected dipeptides 51 with (S)-Boc-alanine in the presence of EEDQ followed by separation of diastereomers by MPLC afforded the non-racemic tripeptide esters 63–65 and 63’–65’ (Scheme 17).
Scheme 17. Non-racemic tripeptides 58/58′–65/65′ obtained by coupling of the racemic building blocks with (S)-alanine derivatives followed by chromatographic separation.

However, the weakest link in the above synthesis of peptide analogues was the [3+2] cycloaddition step, which had to be performed in refluxing anisole to assure a complete
conversion of the starting dipole (cf. Schemes 10 and 12–14). Since epimerization of an α-amino acid (and their derivatives) is usually fast above 100 °C, the use of enantiopure azomethine imines for the synthesis of the non-racemic cycloadducts would not make sense. This serious drawback could by overcome by catalysis, which should significantly lower the required reaction temperature. This has been previously shown by regio- and stereo-selective copper(I) iodide-catalyzed cycloadditions of ethyl propiolate in refluxing dichloromethane. In contrast, the non-catalyzed cycloadditions required harsh thermal activation (~150 °C) and led to mixtures of isomeric cycloadducts. In extension, an optimized Cu-catalyzed method that allowed the preparation of separable non-racemic products under mild conditions was developed. Cycloaddition of azomethine imine 41a with methyl propiolate was chosen as the model reaction in search for suitable reaction conditions. Since the cycloadduct 66a is highly fluorescent (bright yellow fluorescence at 375 nm), simple and effective monitoring of the reaction progress was feasible by TLC. Optimization process revealed, that a full conversion of reactants at room temperature was performed at best in acetonitrile in the presence of CuI and Hüning base. Under these optimized conditions, the conversion of 41a was complete after 12 hours and the cycloadduct 66a was isolated in 98% yield upon chromatographic workup. Cycloadditions of racemic azomethine imines 41a–c,f,g to tert-butyl (S)-(3-oxopent-4-yn-2-yl)carbamate (67) under the above conditions afforded mixtures of diastereomeric cycloadducts 68a–c,f/68'a–c,f and 69g/69'g in 68–95% yields. Subsequently, diastereomers 68a–c,f/68'a–c,f and 69g/69'g were separated by medium-performance liquid chromatography (MPLC) to furnish diastereomically pure non-racemic compounds 68a–c,f, 68'a–c,f, 69g, and 69'g in 3–45% yields. Also here, the regioselectivity and stereoselectivity of the cycloadditions and relative configurations of cycloadducts were in agreement with previous results obtained by closely related cycloadditions (Scheme 18).
Scheme 18. Formation of non-racemic products 66, 68, and 69.

4.2 Pyrazolo[1,5-c]pyrimidines
Recently, a series of tetrahydropyrazolo[1,5-c]pyrimidine-2,7(1H,3H)-diones 73a-h, the first representatives of a so far unexplored saturated heterocyclic system, has been synthesized in twelve steps from methyl acrylate (16). The first part of the synthesis comprises a seven-step preparation of 5-{2-[(alkyl)(benzyl oxycarbonyl)amino]ethyl}pyrazolidin-3-ones 23a-c (cf. Scheme 5). Unfortunately, attempts to prepare N(2)-substituted pyrazolidinones by cyclizations of the mesylates 22 with cyclohexyl-, tert-butyl-, and phenylhydrazine failed. Consequently, a different, somewhat longer approach was applied. First, the pyrazolidinone 23a was treated with ClCOOBn to afford the Cbz-protected derivative 70a (R = Cbz) in 70% yield. However, subsequent N-methylation with MeI did not proceed to completion and the N-methylated intermediate 71a was obtained in only 18% yield. Subsequent removal of both Cbz groups by catalytic hydrogenation, cyclisation of the intermediate 1,4-diamine with 1,1′-carbonyldiimidazole (CDI), and chromatographic workup furnished the first final product 73a in 30% yield over two steps (Path A, Scheme 19). On the other hand, 1-Boc analogues of 70, prepared by treatment of 23a-c with Boc2O in 73–97% yields, readily underwent alkylation of the amidic nitrogen N(2) to give the fully substituted intermediates 71b-h in 49–73% yields. Acidolytic
removal of the Boc group gave the 1-unsubstituted pyrazolidinones 72b–g in 77–99% yields. Subsequent hydrogenolysis of the Cbz group followed by cyclisation of the so-formed free 1,4-diamine with CDI, and chromatographic workup furnished title compounds 73b–h in 28–65% yields over the last two steps. This somewhat tedious twelve-step synthesis was simplified by performing it, as far as possible, in a one-pot manner (Path B, Scheme 19).53

Soon afterwards a novel simpler five-step synthesis of 1,6-disubstituted tetrahydropyrazolo[1,5-c]pyrimidine-2,7(1H,3H)-diones 73 was developed. This starts with a ‘ring switching’ transformation of the commercially available 5,6-dihydro-2H-pyran-2-one (6) with hydrazine hydrate in ethanol, giving 5-(2-hydroxyethyl)pyrazolidin-3-one (7a) in quantitative yield (cf. Scheme 2). Subsequent reaction of 7a with isocyanates 74a–d in anh. DMF at r.t. afforded the urea derivatives 75a–d in 73–97% yields. Appel-type bromination of the alcohols 75 with PPh3–CBr4 in CH2Cl2 followed by evaporation gave the crude bromoethyl intermediates 76a–d, which were used in the subsequent step without further purification. Cyclisation of 76 with t-BuOK in anh. DMF, followed by chromatographic purification gave the 6-substituted tetrahydropyrazolo[1,5-c]pyrimidine-2,7(1H,3H)-diones 77a–d in 40–65% yields over two steps. Finally, Sn2-type alkylation of 77 with primary alkyl halides, followed by isolation by thorough chromatographic workup (FC then MPLC) furnished the final products 73i–r in 22–93% yields (Scheme 20).44

Scheme 19. Preparation of pyrazolo-pyrimidinediones 73a-h.

<table>
<thead>
<tr>
<th>Cpd.</th>
<th>Path</th>
<th>R</th>
<th>R1</th>
<th>R2</th>
</tr>
</thead>
<tbody>
<tr>
<td>73a</td>
<td>A</td>
<td>Cbz</td>
<td>Bn</td>
<td>Me</td>
</tr>
<tr>
<td>73b</td>
<td>B</td>
<td>Boc</td>
<td>Bn</td>
<td>Et</td>
</tr>
<tr>
<td>73c</td>
<td>B</td>
<td>Boc</td>
<td>Bn</td>
<td>Bn</td>
</tr>
<tr>
<td>73d</td>
<td>B</td>
<td>Boc</td>
<td>Bu</td>
<td>Me</td>
</tr>
<tr>
<td>73e</td>
<td>B</td>
<td>Boc</td>
<td>Bu</td>
<td>Et</td>
</tr>
<tr>
<td>73f</td>
<td>B</td>
<td>Boc</td>
<td>Bu</td>
<td>Bu</td>
</tr>
<tr>
<td>73g</td>
<td>B</td>
<td>Boc</td>
<td>Bu</td>
<td>Bn</td>
</tr>
<tr>
<td>73h</td>
<td>B</td>
<td>Boc</td>
<td>Pr</td>
<td>Me</td>
</tr>
</tbody>
</table>

i) ClCOOBn or Boc2O, 1,4-dioxane-H2O, Na2CO3, r.t.; ii) R2-X, DMF, K2CO3, r.t.; iii) H2, Pd-C, MeOH, r.t.; iv) CDI, DMF, r.t.; v) TFA-CH2Cl2, r.t.
### Scheme 20

A five-step synthesis of 1,6-disubstituted tetrahydropyrazolo[1,5-c]pyrimidine-2,7(1H,3H)-diones 73i–r.

### 5. Structural Features of 3-Pyrazolidinones

The structures of several representative 3-pyrazolidinones and their fused analogues in the solid state have been unambiguously determined by X-ray crystallography.40–42,44,47,72–77

The $^1$H-NMR spectroscopic data of the pyrazolidinones 4 and 25–33 and azomethine imines 24 revealed some interesting structural features of these compounds. In solution, these pyrazolidinone derivatives can equilibrate between two envelope conformers A and C via the planar conformer B (Scheme 21). The conformations in solution were established on the basis of the magnitude of the vicinal coupling constant. According to the coupling constants, $^3J_{1H-5H} \sim 11$ Hz, the 4,5-disubstituted compounds 4, 27, and 31 exist as envelope conformers A with pseudo axial H–N(1), H–C(4), and H–C(5) ($\theta \sim 180$ °C). In contrast, small vicinal coupling constants, $^3J_{4H-5H} \sim 3$ Hz, in 1,2,4,5-tetrasubstituted pyrazolidinones 26, 29, 30, and 33 were in agreement with conformer C where H–C(4) and H–C(5) were pseudo equatorial ($\theta \sim 100$ °C). The conformation of 1,4,5-trisubstituted compounds 25, 28, and 32 was dependent on the substituent at position 5: compounds 25 with a Ph substituent adopted conformation A with...
pseudo axial H–C(4) and H–C(5) ($J_{4H-5H} \sim 11$ Hz), while the coupling constant, $J_{4H-5H} \sim 7$ Hz, in 5-isopropylpyrazolidinones 25, 28, and 32 is in agreement, either with the flat conformer B ($\theta \sim 120^\circ$ C), or with a rapid equilibrium between the conformers A and C. In the more rigid dipoles 24 with a sp$^2$-hybridised N(1)-atom, however, the coupling constant, $J_{4H-5H} \sim 5$ Hz, is clearly consistent with the planar conformer B (Scheme 21).

Scheme 21. Substituent-dependent conformational equilibrium in solution.

The anticipated U-shaped structure of the pyrazolo[1,2–a]pyrazole-based peptides 43–65 and 58′–65′ was confirmed by X-ray diffraction and by NMR. The X-ray structures of dipeptides 46b and its free amino derivative, 46d, and tripeptides 60′, 61′, and 63′ exhibit the U-shaped structure of the peptide chain. The U-shape of 60′ is additionally stabilized by intramolecular N-H·O=C hydrogen bond donated by N13 from the alanyl residue and accepted by O9 of the C=O group. In CDCl$_3$ solution, formation of (7′)C=O·H–N–C(2) intramolecular hydrogen bond in tripeptides 58/58′–62/62′ with the C-terminal (S)-alanyl residue was supported by $^1$H NMR spectroscopy. Typically, the signals for the non-hydrogen bonded amidic NH protons appeared at a chemical shift of $\delta = 5$–7 ppm, while the signals for the hydrogen bonded 2-NH protons exhibited higher chemical shift, $\delta = 7.5$–9.3 ppm. For example, in the $^1$H NMR spectrum of
tripeptide 60′ with the C-terminal (S)-alanine residue, a doublet for the H–N-C(2) proton at 8.39 ppm indicates non-covalent interactions of this NH group, explainable by (7′)C=O·H–N-C(2) intramolecular hydrogen bond. In contrast, a broad singlet for 2-NH proton at 4.94 ppm in the 1H NMR spectrum of tripeptide 64′ with the N-terminal (S)-alanine residue does not support hydrogen bonding of this NH group (Figure 5).41

**Figure 5.** Characteristic chemical shifts of the NH protons in tripeptide 60′ (intramolecular hydrogen bond) and 64′ (without intramolecular hydrogen bond).

The absolute configurations of the non-racemic tripeptides 60′, 61′, and 63′ were unambiguously established by X-ray diffraction. Consequently, the configurations of their diastereomers 60, 61, and 63 were determined unambiguously as well.41 Unfortunately, we have so far been unable to prepare single crystals for unambiguous determination of the absolute configuration of the other representative diastereomers. In the absence of a firm proof, tentative configurations were proposed for the other diastereomers on the basis of correlation between specific rotation and absolute configuration.41,81

In addition to X-ray structures of the representative tetrahydropyrazolo[1,5-c]pyrimidine-2,7(1H,3H)-diones 73,44,53 a more detailed 3D structure of title compounds 73a–r was also established on the basis of characteristic vicinal coupling constants, 3JH–H. Large coupling constants, 3J3Ha–3aH = 3J4Ha–5Hb = 12.5 Hz and 3J4Ha–3aH = 10.5 Hz are in agreement with antiperiplanar trans-orientation of these nuclei. Accordingly, the pyrimidine and the pyrazole part of tetrahydropyrazolo[1,5-c]pyrimidine-2,7(1H,3H)-dione system must both adopt a half-chair conformation in which C(3) and C(4) point out of the plane of the system and 3-Ha, 3a-H, 4-Ha, and 5-Hb are axial (Figure 6).44,53
Figure 6. Characteristic NMR data for compounds 73a–r.

6. References

http://dx.doi.org/10.1111/j.1471-4159.1982.tb04733.x

http://dx.doi.org/10.1007/BF01966164

http://dx.doi.org/10.1021/bi00101a008


http://dx.doi.org/10.1016/S0040-4039(00)95708-3

http://dx.doi.org/10.1021/jo00227a013


http://dx.doi.org/10.1021/jm00074a002

http://dx.doi.org/10.1016/1072-6671(94)00079-G

http://dx.doi.org/10.1002/jhet.5570340438

http://dx.doi.org/10.1002/hlca.20000809838;<1734::AID-HLCA1734>3.0.CO;2-E

http://dx.doi.org/10.1016/S0040-4020(01)01195-4

http://dx.doi.org/10.1021/jo034807w

http://dx.doi.org/10.1021/ja0664250

http://dx.doi.org/10.1002/adsc.200600268

http://dx.doi.org/10.1021/jo060339p
http://dx.doi.org/10.1016/j.tet.2010.09.021
http://dx.doi.org/10.1016/j.tet.2009.10.009
http://dx.doi.org/10.1039/b602645a
http://dx.doi.org/10.1016/j.tet.2005.08.110
http://dx.doi.org/10.1002/jhet.5570390302
http://dx.doi.org/10.1016/j.tet.2013.05.122
http://dx.doi.org/10.1002/hlca.201300169
http://dx.doi.org/10.1002/jlac.199619961013
http://dx.doi.org/10.1055/s-0033-1339977
http://dx.doi.org/10.1080/00397919008052321
http://dx.doi.org/10.1016/S0040-4039(00)86044-X


   [http://dx.doi.org/10.1021/ar700259k](http://dx.doi.org/10.1021/ar700259k)
   [http://dx.doi.org/10.1021/ar8000052](http://dx.doi.org/10.1021/ar8000052)
   [http://dx.doi.org/10.1038/nature06526](http://dx.doi.org/10.1038/nature06526)
   [http://dx.doi.org/10.1016/S0040-4020(97)00476-6](http://dx.doi.org/10.1016/S0040-4020(97)00476-6)
   [http://dx.doi.org/10.1002/bip.20213](http://dx.doi.org/10.1002/bip.20213)
   [http://dx.doi.org/10.1016/B978-008096518-5.00059-9](http://dx.doi.org/10.1016/B978-008096518-5.00059-9)
   [http://dx.doi.org/10.1016/j.tet.2006.11.012](http://dx.doi.org/10.1016/j.tet.2006.11.012)
   [http://dx.doi.org/10.1021/cc070041s](http://dx.doi.org/10.1021/cc070041s)
   [http://dx.doi.org/10.1021/cc102041s](http://dx.doi.org/10.1021/cc102041s)
   [http://dx.doi.org/10.1071/CH09074](http://dx.doi.org/10.1071/CH09074)
   [http://dx.doi.org/10.1021/jo00221a004](http://dx.doi.org/10.1021/jo00221a004)
   [http://dx.doi.org/10.1002/hlca.200690010](http://dx.doi.org/10.1002/hlca.200690010)
   [http://dx.doi.org/10.1002/ejoc.201402033](http://dx.doi.org/10.1002/ejoc.201402033)
   [http://dx.doi.org/10.5560/ZNB.2014-4011](http://dx.doi.org/10.5560/ZNB.2014-4011)
Authors' Biographies

**Uroš Grošelj** was born in 1975 in Kranj, Slovenia. He studied chemistry at the University of Ljubljana and received his BSc in 2000. He continued his studies under the supervision of Professor Dr. Jurij Svete and received his PhD in 2004. His PhD work focused on the preparation of new camphor derived heterocycles using enaminone methodology. In 2008/2009 he was a post-doctoral fellow in the group of Professor Dr. Dieter Seebach at the ETH Zürich, Switzerland, where he worked on the isolation and X-ray structural characterization of intermediates in organocatalysis with diarylprolinol ethers and imidazolidinones. From 2014 he is employed as Assistant Professor at the Faculty of Chemistry and Chemical Technology, University of Ljubljana. He is author or co-author of 80 scientific papers and recipient of *Futurum Prize* and *Krka Prize* national awards. His research interests encompass synthesis of heterocyclic compounds, stereoselective synthesis, chemistry of terpene enaminones, and organocatalysis.

**Jurij Svete** was born in Ljubljana, Slovenia in 1962. He studied chemistry at the University of Ljubljana where he received his PhD in chemistry in 1990 under supervision of Professor Branko Stanovnik. He continued to work as a researcher with the group of Professor Stanovnik. In 1997 he spent one year as a Humboldt Fellow at the University of Stuttgart, Germany, working with Professor Volker Jäger on the synthesis of iminopolyols from furan-nitrile oxide.
cycloadducts. In 1996, he became an Assistant Professor, an Associate Professor in 2001, and a Full Professor in 2006. His research interest involve fundamental and applied organic synthesis with emphasis on development of novel reagents and synthetic methods, heterocyclic synthesis, combinatorial synthesis, stereoselective synthesis, 1,3-dipolar cycloaddition reactions, and chemistry of enaminoles and 3-pyrazolidinones. He is particularly interested in the synthesis of novel chemical entities based on functionalized heterocycles, such as heterocyclic analogues of peptides.