2-Isoxazolinium Salts and 3-Isoxazolines: Exploratory Chemistry and Uses for the Synthesis of Branched Amino Polyols and Amino Acids*

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Dedicated to Professor Alessandro Dondoni on the occasion of his 75th birthday

2-Isoxazolines represent a well known class of heterocycles, readily accessible in particular by 1,3-dipolar cycloaddition of nitrile oxides to alkenes. 2-Isoxazolines are easily transformed into 2-isoxazolinium salts by N-methylation, and further into 3-isoxazolines by deprotonation. In contrast to the parent system, less is known concerning the chemistry of the derived classes, and potential applications in synthesis. – 2-Isoxazolinium salts, due to their iminium part, are prone to the attack of nucleophiles, and examples for this, addition of hydride (reduction) and C-nucleophiles like methylmagnesium bromide, cyanide, methane nitronate, and malonate are given. With these adducts, syntheses of \( \beta \)- and \( \alpha \)-amino acids with OH-containing side chains have been effected. The cyanide products also are useful as precursors of branched, unsymmetrical 1,2-diamo polyols. – On the other hand, 3-isoxazolines due to their oxy-enamine part, represent species with nucleophilic sites and therefore react with electrophilic reagents. Examples given are \([3+2]\) cycloadditions with nitrile oxides, \([2+2]\) cycloadditions with dimethyl acetylenedicarboxylate, and \([2+1]\) cycloaddition in the form of epoxidation which, however, led to a dihydro-1,3-oxazine nitrone by initial attack at the nitrogen atom, in an unprecedented oxidation/\(N\)-dealkylation/rearrangement sequence.

Key words: 2-Isoxazolines, 2-Isoxazolinium Salts, 3-Isoxazolines, Nucleophilic Additions, Electrophilic Additions

Introduction

2-Isoxazolines A are easily obtained in great variety by 1,3-dipolar cycloaddition of nitrile oxides to olefins, and their utility as intermediates in synthesis has amply been demonstrated [4]. Likewise, isoxazolinium salts B and 3-isoxazolines C are readily accessible by N-methylation of 2-isoxazolines and ensuing deprotonation, respectively. In contrast to the former, however, the latter classes have received scarce attention, and their inherent synthetic potential has remained largely unexploited [5].

In this overview we present exploratory studies on the chemistry of isoxazolinium salts B, in particular on nucleophilic additions to the oxy-iminium moiety. With C-nucleophiles, various structures of branched amino alcohols and amino acids can be elaborated.

3-Isoxazolines C present two nucleophilic sites for attack of electrophiles, and respective examples of \([2+2]\) and \([3+2]\) cycloadditions are given below, as well as results of peracid oxidations involving a clean, multi-step transformation.

2-Isoxazolinium Salts

Over the years, a number of routes have been elaborated in our group, aiming at stereoselective syntheses of amino and imino polyols or acids (Scheme 1).

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A related, albeit often more challenging problem is constituted by branched amino acids and the like, where fragments with a tert-alkylamino moiety have to be constructed. Again, stereoselective access is needed, and often the assignment of configuration at the tetrasubstituted stereocenter presents an additional challenge. The interest in branched amino polyols, sugars, and acids relates to some natural and synthetic products, for example \( \alpha, \alpha \)-disubstituted amino acids such as \( \alpha \)-methylalanine or \( \alpha \)-methyldopa, active as enzyme inhibitors, and – most recently – lactacystin, a dipeptide with a particularly complex amino diacid. Consequently, many different routes to such branched amino compounds (mostly amino acids) have been devised, many of them employing alkylation of deprotonated chiral \( N \)-heterocycles as equivalents of \( \alpha \)-amino acid enolates [10]. Of course, the Ugi reaction, the Strecker amino acid syntheses and related imine additions have been drawn upon to this purpose likewise. Yet another approach uses asymmetric addition of heterofunctions to enoates, for the example the Sharpless asymmetric aminohydroxylation [11] as shown in a synthesis of lactacystin [12].

In principle, the isoxazoline route [4, 13, 14] might offer an advantage here, since the cycloaddition step joins two widely variable components (alkene and nitrile oxide, with precursors nitroalkane and aldehyde, respectively). However, final introduction of a \( C \)-nucleophile is hampered by insufficient electrophilicity of the \( C=\text{N} \) bond in isoxazolines [15–17]. A general solution to this might be offered when “activated” derivatives, such as \( N \)-methylisoxazolinium salts, are employed. The strategy to use these cyclic oxy-iminium salts for syntheses of branched amino polyols, thence branched \( \alpha \) - and \( \beta \)-amino acids, respectively, is outlined in Scheme 2 [2, 5]. After
addition of the nucleophile and reductive ring opening to a \( \gamma \)-amino alcohol, either the R or the \( \text{R}^\prime \) terminus has to be elaborated to provide the required carboxyl function. A more general aspect of this project is evident also: The scope and the (dia)stereoselectivity of nucleophilic additions to such isoxazolinium salts were thought worthwhile to be studied systematically [5].

As mentioned above, isoxazolinium salts had been described in the literature as early as 1955, with dimethyl sulfate serving as the methylating agent (no yield given), and isolated as tetrachloroferrates [18] or later as perchlorates after anion exchange [19]. This resulted from the need to obtain crystalline substances that could be purified. A more efficient solution to this was advanced in 1974, when the Meerwein salt, trimethyloxonium tetrafluoroborate, was shown to give both clean conversion and readily isolable salt products [20] (Scheme 3). Later on, \( \text{N} \)-ethylation was effected alike [21].

Some reactions of \( \text{N} \)-alkylisoxazolinium salts were reported also in this context. Shatzmiller and co-workers showed that \( \alpha \)-deprotonation is facile, occurring already with trimethylamine and leading to a 3-isoxazoline, which was readily transformed into a quaternary ammonium salt on treatment with methyl iodide [21] (Scheme 4).

With the neutral parents, i.e. isoxazolines, a highly active base such as lithium disopropylamide had to be employed for such 4-deprotonations [13, 15]. Interestingly, 3-isoxazolines which contain an enamine moiety with a nucleophilic center at C-4, as far as we know, have never been used in further transformations with electrophiles, unlike the isoxazoline-4-anion derivatives [13, 15, 22].

Iminium salts are well-known electrophiles, with amply documented reactivity towards nucleophilic additions [23]. Surprisingly, this potential has largely been neglected concerning isoxazolinium salts, since there have been few relevant reports (altogether, until 2008, we have found less than 30 papers in the literature dealing with isoxazolinium salts!). There are scattered examples where sodium borohydride [20, 24–26], lithium aluminium hydride [27], methyl and phenyl Grignard reagents [26], methoxide [28], and diphenyl phosphite [21] have been employed for such additions (Scheme 5).

With the tetracyclic isoxazolinium salt (4,5-cis-disubstituted), highly stereoselective \( \text{exo} \)-additions were

\[
\begin{align*}
\text{O} & \quad \text{N} & \quad \text{Et} & \quad \text{Bn} & \quad \text{BF}_4^- \\
\text{Me}_3\text{N}, \text{HCCl}_3 & \quad \text{NMe}_3, \text{HCl} & \quad \text{Me}_3\text{Li} & \quad \text{Me}, \text{r.t.} & \quad \text{Me}, \text{Et} \quad \text{I}^- \\
\text{Bn} & \quad \text{Bn} & \quad \text{Bn} & \quad \text{Bn} & \quad \text{Bn} \\
-65^\circ\text{C}; 80\% & \quad 77\% & \quad \text{LDA} & \quad -80^\circ\text{C} & \quad \text{Et}^\prime \\
\text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} \\
\text{Ph} & \quad \text{Ph} & \quad \text{Ph} & \quad \text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N} & \quad \text{Li} & \quad \text{Li} & \quad \text{Li} \\
\text{Compare:} & \quad \text{Compare:} & \quad \text{Compare:} & \quad \text{Compare:} & \quad \text{Compare:} \\
\end{align*}
\]
found, as expected [Scheme 5 (i)], with the methyl and phenyl Grignard reagents affording rather low yields of isolated products [20]. A less favorable case is presented by the bicyclic substrate (4-substituted) shown in Scheme 5 (ii), where a ca. 2 : 1 mixture of diastereomers is formed (on the way to aminocyclohexane polyols as glycosidase inhibitors) [25].

With the goals set above, additional functional groups were required. Thus, the compatibility of these with the conditions of \( \text{N}-\text{methylation} \) had to be ascertained, and a variety of isoxazolines was submitted to reaction with trimethyloxonium tetrafluoroborate. As seen with the structures and yields given in Scheme 6, this proved very satisfactory for most cases. Notably, ester groups, free hydroxy groups, and acetals remain unchanged, and isolation of the crystalline salts proved simple [2, 5].

The (known) deprotonation was effected with several 2-isoxazolinium salts, to furnish the crystalline \( \text{N,}\text{N}-\text{dimethyl-3-isoxazolinium salts} \) after treatment with triethylamine and, again, Meerwein salt. The case of the ester [Scheme 7 (ii)] is of particular interest since this shows a promising route to unusual derivatives of \( \alpha,\beta\)-dehydroamino acids [2a, 2d, 37].

The addition of nucleophiles to these isoxazolium salts leads to \( \text{N-}\text{methylisoxazolidines} \). Reduction was studied first, a transformation well established in the isoxazoline series [4, 13b, 15b, 22, 29]. While the latter had required lithium aluminium hydride, now milder reagents are applicable. Borohydrides, catecholborane,
and diisobutylaluminium hydride led to clean conversion and high yields of products (cf. Scheme 8). For a study of the diastereoselectivity of these reductions, an isoxazolinium salt with an α-stereocenter in the side-chain (dioxyethyl, serving as a latent carboxy group) was chosen. Here (and in related cases) sodium triacetoxy-borohydride proved superior, affording a 95:5 mixture of stereoisomers (Scheme 8). The major product was found to be the erythro isomer, as seen from the crystal structure analysis of the derived N,N-dimethyl isoxazolinium salt [30] (Scheme 9). In the crystal, there is an anti arrangement of 3-H and the 1'-oxygen atom, and it is tempting to assume a related steric course of hydride delivery as drawn below. The major isomer would then result from a transition state conformation which exactly corresponds to the respective model advanced by Felkin-Anh-Houk for such additions [31].

The highly asymmetric 1,2-induction leading to N-methylisoxazolidines signifies that 1,3-aminoalcohol are accessible along this way by further reduction of the N-O moiety, a standard transformation. Thus,
Reagent — Conditions — Diastereomeric ratio Yield (%)
(i) $\text{H}_2$, Rh/$\text{C}$ MeOH r.t. 1 d [87 : 13] 68
(ii) $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}/\text{NaBH}_4$ MeOH $-30^\circ\text{C}$ 10 min [83 : 17] 87
(iii) 1. $\text{NaBH}(\text{OAc})_3$ THF $-78^\circ\text{C}$ 10 min [95 : 5] 86
2. $\text{H}_2$, Pd/$\text{C}$ MeOH r.t. 3 d [> 95 : 5] 95

Scheme 10. Reduction of $N$-methylisoxazolinium salts. $\gamma$-Amino alcohols [5].

the erythro-isoxazolidine produced with sodium triacetoxyborohydride on hydrogenation with palladium on carbon as catalyst furnished the erythro-$N$-methylaminopentanetriol derivative as a pure isomer in 95 % yield [5] [Scheme 10(iii)].

Direct conversion of isoxazolinium salts to give amino alcohols is feasible likewise, as is well-known in the isoxazoline series [22, 29, 32], albeit with somewhat lower stereoselectivity [Scheme 10, entries (i) and (ii)]. The two-step reduction [entry (iii)] here proved superior. The same products may be obtained, of course, in a shorter way by cyclo-addition of the respective $N$-methylnitrone followed by hydrogenation. Nitrone cycloadditions, however, usually proceed with low diastereoselectivity [33, 34], and introduction of further fragments by nucleophilic addition is precluded.

With the above findings a solid basis is laid for additions of other, notably $C$-nucleophiles, and for the assembly of structures from the four constituents – olefin, aldehyde, methyl, and aldehyde/oxime or nitroalkane (Scheme 11). Again, scope, stereoselectivity, and assignment of configurations to the $N$-$C^*$ stereocenter have to be examined. Some results of these studies with application to the synthesis of branched amino acids are detailed in the following.

The addition of methyl derivatives is shown in Scheme 12. With the Grignard compound high stereoselectivity was achieved (d. r. 90 : 10). The steric course of this addition could not be established by any of the NMR spectroscopic methods applied, but – fortunately – after deprotection the isoxazolidine-triol was amenable to crystal structure determination [35] (Scheme 13). Again, the nucleophilic addition had occurred according to the Felkin-Anh-Houk model, to furnish the erythro $N, O$-product.

With other $C$-nucleophiles, derived from $C$-$H$ acidic compounds such as hydrocyanic acid, nitromethane, malonate, or the lithium enolate of ethyl acetate, smooth additions were observed likewise [2, 36, 37] (Scheme 14). These additions bear some potential for synthesis, since the first ones provide precursors of optically active, unsymmetrical 1,2-diamines, and the

<table>
<thead>
<tr>
<th>$\text{H}_2\text{C}=\text{M}$</th>
<th>Solvent</th>
<th>Yield (%)</th>
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</thead>
<tbody>
<tr>
<td>$\text{Me}_2\text{CuLi}$</td>
<td>THF</td>
<td>–</td>
</tr>
<tr>
<td>MeLi</td>
<td>THF</td>
<td>23</td>
</tr>
<tr>
<td>MeMgBr</td>
<td>Et$_2$O/THF</td>
<td>[90 : 10] ca. 70 %</td>
</tr>
</tbody>
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Scheme 12. Addition of $C$-nucleophiles to $N$-methylisoxazolinium salts, I [2a – c].
latter two furnish intermediates for access to β-amino acids.

Applications of these isoxazolidines with various 3-substituents are manifold. One example is given in Scheme 15, with the conversion of the ethylene-derived isoxazolidine to the respective β-amino acid, by hydrogenation of the isoxazolidine and ensuing oxidation of the primary alcohol to a carboxy group. Structure and configuration of the β-amino acid hydrochloride again were confirmed by crystal structure analysis [2b, 2c, 5, 38]. Another example is the production of a branched aminotriol from the 3-methyl-
isoxazolidine cited earlier (Scheme 13). Now, nearly quantitative catalytic hydrogenation completes the sequence [2b, 2c, 36, 39].

Cyanide adducts of isoxazolium salts contain a latent \( \alpha \)-amino acid moiety; this is illustrated in Scheme 16.

First, hydrolysis of the cyano-isoxazolidine furnishes a spiro-lactone [2a, 2b, 36, 40] which then is catalytically hydrogenated. The primary product, an \( \alpha \)-methylamino-\( \beta \)-hydroxy-butyrolactone with an \( \alpha \)-hydroxyethyl side-chain, equilibrates in deuteromethanol according to NMR observations to form preferentially the structural isomer with an \( \alpha \)-dihydroxyethyl side-chain (ratio 81 : 19), as proven again by crystal structure analysis [2a, 2b, 36, 40].

The addition products of 2-isoxazolium salts with nitronate or cyanide (equivalents of aminomethyl \( d^1 \)-synthons) can be considered as precursors of unsymmetrical 1,2-diamines, with some promise as to the use as ligands in various asymmetric catalytic processes. Thus, the glyceraldehyde-derived isoxazolium salts added cyanide to produce the 3-cyanoisoxazolidines with good diastereoselectivity (d.r. 88 : 12) [2a, 2b, 2e, 36]. On treatment with lithium aluminium hydride (in excess!) the cyano group was reduced first to afford 3-aminomethyl-isoxazolidines (Scheme 17). Reduction of the isoxazolidine moiety to the 1,3-aminoalcohol, however, proved to proceed very slowly both with excess LiAlH\(_4\) and under hydrogenation conditions [Pd(OH)\(_2\), H\(_2\) (4 bar), 7 d].
3-Isoxazolines

The \( N \)-methylisoxazolinium salts are readily deprotonated by triethylamine to form the respective conjugated base, \( i.e. \) 3-isoxazolines, in analogy to what is known from the parent family of iminium salts/enamines. On the other hand, significant differences were found as to the stability and the reactivity of these 3-isoxazolines which constitute cyclic \( N \)-oxy-enamines. The 3-isoxazolines studied here proved rather unstable with regard to isolation and storage; all of them were prepared \textit{in situ}, and then subjected to the respective reagents. The lower stability of the 3-isoxazolines as compared to enamines in general was also accompanied by lower reactivity \([2a, 2b, 2d]\).

Nevertheless, 3-isoxazolines behaved well in \([3+2]\) cycloadditions in the role of dipolarophiles towards nitrile oxides \([42]\), and several respective adducts were obtained, showing high asymmetric induction with the chiral 5-chloromethyl-3-isoxazoline (Scheme 18) \([2d, 36a, 43]\).

Optimum conditions for this transformation remain to be elaborated \([36b, 41]\).
bicyclic cyclobutene derivatives (Scheme 19). In contrast to the case of “normal” enamines [44, 45], electrocyclic ring opening to the respective 7-membered ring products (1,2-oxazepines) here is considerably slowed down, and the bicyclic primary addition products were isolated in good to fair yield [2d, 36a].

Attempted [2+1] cycloaddition, i.e., epoxidation, also led to unexpected results (Scheme 20): with an excess of m-chloroperbenzoic acid a crystalline product was obtained and shown to be a dihydro-1,3-oxazine N-oxide, i.e., a cyclic nitrene. The first part of this unprecedented transformation, upon action of the first equivalent of peracid, must involve initial N-oxidation, then elimination/ring opening to a methylene nitrene, and re-cyclization. As for the second part, it seems likely that another oxidation at nitrogen takes place, forming an ene-nitrosonium cation (or an unsaturated nitrone) intermediate, which then adds an m-chlorobenzoate anion in a Michael fashion to end the sequence. The structure of this unexpected product, isolated in crystalline form in 72% yield, was established by crystal structure analysis [2d, 36a, 46] (Scheme 20). Likewise, starting from the N-ethyl-3-oxazoline, the corresponding 2-methyl-dihydro-1,3-oxazine N-oxide was obtained in 66% yield [2d, 36a].

In summary of these first results with 3-oxazoline reactions, we can state that these heterocyclic systems are rather special enamine species, prone to a variety of surprising reaction modes.

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[3] Results on 2-isoxazolinium salts were presented first at the 6th Conference on Iminium Salts (ImSaT-6), Stimpfach-Rechenberg (Germany), 2003.
[6] See refs. given in refs. [1, 4, 5].
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[37] a) Structure and configuration of (3S,1’S)-3-(1,2-cyclohexyldenedioxyethyl)-2-methyl-isoxazolidine-3-carbonitrile: W. Frey, P.-Y. LeRoy, V. Jäger, unpublished results, Universität Stuttgart, Stuttgart 1996; see also ref. [2a]; CCDC-776602 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif; b) structure and configuration of the respective 5,5-dimethylisoxazolidine-3-carbonitrile: W. Frey, M. Ibrahim, V. Jäger, Z. Kristallogr. NCS 2008, 223, 453–454; c) structure and configuration of (3S,1’S)-3-(1,2-cyclohexyldenedioxyethyl)-2-methyl-3-nitromethylisoxazolidine: W. Frey, M. Henneböhle, V. Jäger, unpublished results, Universität Stuttgart, Stuttgart 2000; see also ref. [2b]; CCDC-776605 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


[39] Aminotriolhydrochloride: W. Frey, V. Bathich, V. Jäger, unpublished results, Universität Stuttgart, Stuttgart 2003; see also ref. [2c]; CCDC-776606 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[40] a) Spiro-lactone: W. Frey, M. Henneböhle, V. Jäger, unpublished results, Universität Stuttgart, Stuttgart 2002; see also ref. [2b]; CCDC-776603 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif; b) α-(1,2-dihydroxyethyl)-α-methylamino-γ-butyrolactone: W. Frey, M. Henneböhle, V. Jäger, unpublished results, Universität Stuttgart, Stuttgart 2000; see also ref. [2b]; CCDC-776604 contains the supple-
mentary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[41] The configuration of a free diaminotriol – (2S,3R)-3-aminomethyl-3-methylamino-pentane-1,2,5-triol bis(hydrochloride) – was established by crystal structure analysis: ref. [2e].


[46] a) W. Frey, S. Shiva, V. Jäger, Z. Kristallogr. NCS, to be submitted; b) earlier, the structure of the final oxidation product had erroneously been interpreted as a dihydro-1,3-oxazinium enolate zwitterion [2d, 36].