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Novel synthesis of 3-oxazolines

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Abstract

A series of new aliphatic 3-oxazolines was obtained in moderate to good yields via oxidation of the corresponding 1,3-oxazolidines by *N*-chlorination with sodium hypochlorite followed by elimination in basic medium. Some of the 3-oxazolines obtained present interesting properties in the field of fragrance chemistry. © 2000 Elsevier Science Ltd. All rights reserved.

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The synthesis and use of 2-oxazolines has been widely developed,[1] particularly as chiral ligands in the field of asymmetric catalysis.[2] In contrast, the practical utilization of 3-oxazolines has been relatively neglected. Certain 3-oxazoline derivatives (or 2,5-dihydro oxazoles) have been isolated and characterized as volatile flavor compounds in food and present important organoleptic properties.[3] Thus, 2,4,5-trimethyl-3-oxazoline was found in various foods such as cooked beef, roasted peanuts or fried chicken, and it has also been used as flavoring agent.[4a–e]

We have been interested in the synthesis of aliphatic and volatile 3-oxazolines of potential applications in food and fragrance chemistry. Reported preparations of 3-oxazolines include photochemically-induced ring opening of substituted 2*H*-azirines,[5a–c] reaction of α-iminoperfluoronitriles,[6] or diazo derivatives.[7] The condensation of an α-hydroxyketone with a carbonyl compound in liquid ammonia has also been described.[8a–d] However, these methods were mainly applied to the preparation of aromatic oxazolines, and no general and efficient procedure is available for the selective access to aliphatic 3-oxazolines. Only one example reports the treatment of oxazolidines with *t*-butylhypochlorite and potassium superoxide.[9] However, only three alkyl substituted oxazolines were synthesized from ketones and the use of *t*-BuOCl and KO_2 as reagents, presented some drawbacks and a limited industrial use due to their low stability.

We report here a selective synthesis of aliphatic and volatile 2-mono- and 2,2-disubstituted-3-oxazolines, based on the oxidation of 1,3-oxazolidines with usual reagents. This strategy tends

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to mimic the biosynthetic pathway for these naturally occurring heterocycles, through a Maillard reaction as it is generally admitted.[10]

A series of 1,3-oxazolidines, **1a–k** was prepared in good yields (65–90%) from the corresponding (DL)-1,2-aminoalcohols and aliphatic aldehydes or ketones.[11] It is noteworthy that, whereas 1,3-oxazolidines derived from aromatic aldehydes are mainly found in solution in their open imine-alcohol form, with imine to oxazolidine ratios ranging from 70/30 to 95/5% (according to ^{1}H NMR, $CDCl_3$, 20°C),[12] we found that the corresponding aliphatic derivatives **1a–k** were mainly present in their cyclic 1,3-oxazolidine structures in ratios ranging from 77/23 to 95/5%.

The oxidation of **1a** to **3a** (Eq. (1)) was tested under different conditions ($NaWO_4/H_2O_2$, $KMnO_4$, MnO_2), but the reaction mainly resulted in product degradation with absence of the desired 3-oxazoline, **3a**. The synthesis of compounds **3** could be carried out through a chlorination–dehydrochlorination procedure, as shown in Eq. (1). Treatment of **1a** with *N*-chlorosuccinimide afforded a mixture of *N*-chloro and dichlorinated compounds. The *N*-chlorooxazolidine **2a** could be more selectively obtained upon treatment with an aqueous solution of NaOCl at room temperature (with the use of a commercial bleach solution). Further dehydrochlorination in EtOH/KOH medium led to **3a** in a 66% yield.

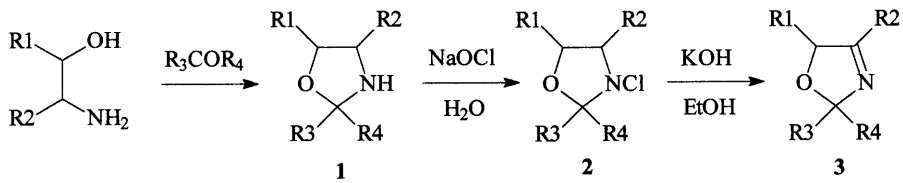
This methodology was applied to the selective synthesis of a series of 3-oxazolines, **3a–f** derived from aliphatic ketones, and the results are presented in Table 1. The intermediate *N*-chlorooxazolidines, as well as some of the derived 3-oxazolines were isolated as a *cis*/*trans* mixture of diastereomers, which ratios were determined by GC and ^{1}H NMR.

Table 1
Preparation of 3-oxazolines **3a–f** derived from aliphatic ketones[a]

Starting oxazolidine	R_1	R_2	R_3	R_4	Yield of **2** (%)	Yield of **3** (%)
1a	H	H	Et	Me	80	66
1b	H	H	*i*-Pr	Me	87	65
1c	Me	H	Et	Me	85[b]	66[b]
1d	Me	H	*i*-Pr	Me	76[b]	55[b]
1e	H	Et	Et	Me	91[b]	83
1f	H	Et	*i*-Pr	Me	83[b]	72

[a] Chlorination–dehydrochlorination (Eq. (1)) experimental procedure: see Ref. 13.
[b] Diastereomer mixtures calculated from GC and ^{1}H NMR. *Cis*/*trans* ratios for **2c** and **3c**: 50/50; **2d** and **3d**: 50/50; **2e**: 60/40; **2f**: 60/40.

Starting 1,2-aminoalcohols were racemic compounds. The *cis*/*trans* configuration of the heterocyclic structures was determined by 2D-NOESY NMR experiments and the relative ratios given in Tables 1 and 2.



(1)

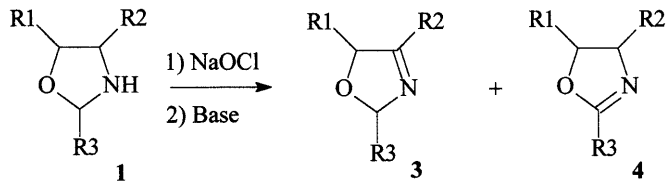
The oxidation of 1,3-oxazolidines, **1g–k** derived from the condensation of (DL)-1,2-aminoalcohols with aldehydes, afforded a mixture of 2- and 3-oxazolines, **4** and **3**, respectively (Eq. (2)). The results obtained with these substrates are presented in Table 2.

Table 2
Preparation of 2-oxazolines, **4** and 3-oxazolines, **3** from aliphatic 2-monosubstituted oxazolidines **1**[a]

Entry	R_1	R_2	R_3	Elimination step	Yield of oxazolines (**3**+**4**, %)	Selectivity **3**:**4**
1g	Me	H	*i*-Pr	KOH/EtOH, 0°C	57[b]	5:95
1h	H	Et	*n*-Pr	KOH/EtOH, 0°C	61	40:60
1i	H	Et	*i*-Pr	KOH/EtOH, 0°C	65	65:35
1j	H	Et	*i*-Bu	KOH/EtOH, 0°C	61	65:35
1k	H	Et	*t*-Bu	KOH/EtOH, 0°C	60	30:70
1g	Me	H	*i*-Pr	*t*-BuOK/pentane, 0°C	45[b]	40:60
1h	H	Et	*n*-Pr	*t*-BuOK/pentane, 0°C	47	45:55
1i	H	Et	*i*-Pr	*t*-BuOK/pentane, 0°C	45	75:25

[a] For experimental part, see Ref. 13. Eliminations from **2g–k** with potassium *t*-butylate (1 equiv., 9 M solution) proceeded in pentane, at 0°C.
[b] Diastereomeric ratios were calculated by GC and ^{1}H NMR. *Cis*/*trans* ratios for **3g**: 50/50.

The selectivity between 2- and 3-oxazolines was found very dependent on the nature of the basic medium used for the elimination step. Thus, whereas **2g** treated with KOH/EtOH gave a mixture of **3g** and **4g** in a 5:95 ratio, the treatment with *t*-BuOK/pentane afforded a **3g**:**4g** ratio of 40:60.



1 **3** **4** (2)

The use of *t*-BuOK enhanced the regioselectivities of **3** in the reactions tested with **1g–i**.

In conclusion, the methodology developed for the preparation of 3-oxazolines uses cheap and easily available starting materials and reagents and may be well-adapted for high-scale applications. Moreover, preliminary olfactive tests carried out with some of the newly prepared 3-oxazolines indicated interesting fragrance properties; thus **3g** presents a typical note of mango and **2f** a woody and pine note, with promising applications of these compounds in the field of flavor and perfume chemistry.

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13. To a commercial solution of bleach (0.2 mol), oxazolidine (0.02 mol) was added at 18°C. After stirring for 3–12 h, and keeping the temperature below 18°C, the mixture was extracted with 100 ml of dichloromethane, washed twice with 50 ml of a 10% aqueous sodium thiosulfate and twice with 50 ml of a 5% potassium iodide solution. Solvent evaporation afforded the *N*-chlorooxazolidine **2**. Reactions were followed by GC analysis of aliquots until complete consumption. To a solution of potassium hydroxide (0.02 mol, 0°C) in ethanol (7 M) was added a solution of **2** in ethanol (7 M). After stirring for 40 min at room temperature, the liquid residue was washed with 30 ml of CH_2Cl_2 and the organic phase washed with water and dried. Evaporation of the solvent gave the crude product, which was purified by column chromatography on alumina with pentane/CH_2Cl_2 mixtures (95:5) as the eluents. Products **3** were characterized by ^1H and ^{13}C NMR, and mass spectra.