Hydration of 2-Isoxazoline Leading to a Stable 3,5,5-Trisubstituted 3-Isoxazolidinol − *N*-Acylated Derivatives and Ring-Chain Tautomerism Study

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A new 2-isoxazoline ring-opening pathway leading to β-(acylaminooxy) ketones **9** is described. It occurred through covalent hydration of the C–N double bond giving stable 3-isoxazolidinol **5**, followed by acylation with anhydrides. The ring-chain tautomerism of 3-isoxazolidinol **5** in comparison with its *N*-acyl(aroyl) derivatives **9**, **10** was studied by NMR and chiral liquid chromatography.

Introduction

Hydroxylamine and its *N*-monosubstituted (by alkyl, aryl, acyl, or aroyl groups) derivatives may add to activated C−C double bond in α,β-unsaturated carbonyl compounds as bidentate O,N nucleophile, giving 3- and/or 5-isoxazolidinols, respectively. The factors affecting the regioselectivity of the reaction and novel synthetic applications of these compounds have been reviewed.[1]

By means of IR and NMR spectroscopy, both 3- and 5-isoxazolidinols were found to exhibit ring-chain tautomerism, the tendency towards cyclic form being greater in the latter. Polar solvents favour the acyclic form in the tautomeric equilibria.[2,3a]

The present paper describes the unprecedented formation of a 3,5,5-trisubstituted 3-isoxazolidinol starting with a *preformed* α,β-unsaturated ketoxime, through covalent hydration of the C−N double bond. From this 3-isoxazolinidol, both cyclic and acyclic *N*-acyl(aroyl) derivatives were prepared. The ring-chain tautomerism of the parent 3-isoxazolidinol and of its *N*-substituted congeners was studied by NMR and by chiral liquid chromatography.

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Results

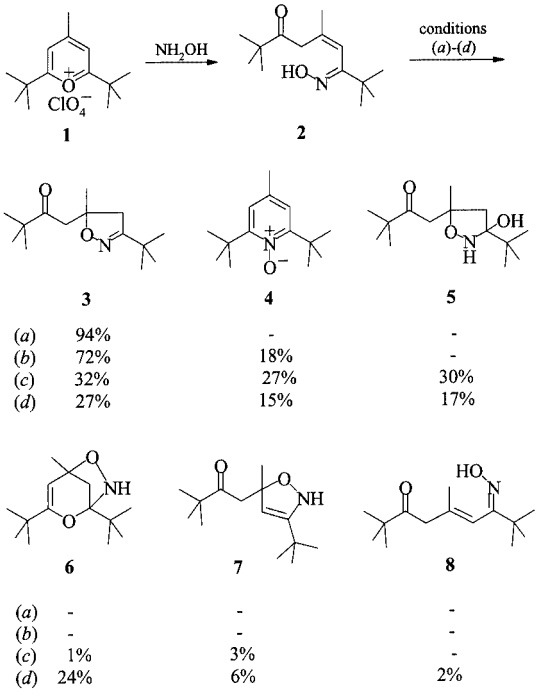
Formation of the 3-Isoxazolidinol 5

On brief treatment with hydroxylamine, 2,6-di-*tert*-butyl-4-methylpyrylium perchlorate (**1**) afforded quantitatively the 2-pentene-1,5-dione 1-oxime **2** as a single stereoisomer with (*Z*,*E*)geometry at the C−C and C−N double bonds (Scheme 1). Heated in methanol with sodium methoxide (Scheme 1, cond. *a*), the ketoxime **2** gave 2-isoxazoline **3** in 94% yield, while heating in glacial acetic acid (cond. *b*) afforded **3** in 72% yield along with pyridine 1-oxide **4** in 18% yield. A reasonable explanation was that 2-isoxazoline **3** originated from (*E*)-oxime **2** as Michael addition product, whereas formation of pyridine 1-oxide **4** required prior isomerization to the (*Z*)-oxime, then cyclization and dehydration, promoted under acidic conditions.[4]

It seemed interesting to find out whether increasing the protonation power of the medium would accelerate the oxime isomerization rate and raise accordingly the yield of **4** for preparative purpose. The cyclization of **2** was therefore performed either in glacial acetic acid or in anhydrous diethyl ether, previously saturated with dry gaseous hydrochloric acid.

The reaction course under these conditions appeared as more complicated and quite sensitive. Indeed, when using an equimolar amount of hydrochloric acid and performing the reaction at room temperature (cond. *c*), three major products were isolated: 2-isoxazoline **3** (32% yield), pyridine 1-oxide **4** (27% yield), and in 30% yield a compound with formula $C_{14}H_{27}NO_3$ assigned as 3-isoxazolidinol **5**.

Basic structure proof for **5** stemmed from the IR spectrum recorded in CCl_4, presenting a broadened weak band at 3230 cm^{-1} assigned to NH vibration and two bands at 3500 (broad) and 3590 (sharp) cm^{-1}, assigned to associated



Scheme 1. (*a*) MeONa/MeOH, reflux; (*b*) AcOH (glacial), reflux; (*c*) HCl/Et_2O (anhydrous) or HCl/AcOH (glacial), 1:1 molar ratio **2**/HCl, room temp.; (*d*) HCl/Et_2O (anhydrous), 1:3 molar ratio **2**/HCl, 0 °C

and free OH vibration, respectively. In KBr pellet, the NH absorbtion appeared as weak sharp band at 3200 cm^{-1} while the OH absorbtion gave a broad band of medium intensity centered at 3420 cm^{-1}.

Heating **5** above its melting point (at 100−110 °C, under inert gas) or in toluene with azeotropic distillation of water, 2-isoxazoline **3** was obtained. Thermal dehydration occurred highly selectively, the GC-MS analysis of the thermolysis product indicating the presence of **3** only. This result was also structure proof for **5**.

Summing up, when using hydrochloric acid the expected raise in yield of **4** was only slight and more surprisingly, the formal hydration product **5** formed although the reaction had been performed under anhydrous conditions. Still, the water liberated during the formation of **4** may account for it and the fact that **4** and **5** were obtained in comparable amounts supports this explanation.

Hydration of the C−N double bond might have occurred in oxime **2** but just as well in 2-isoxazoline **3**. By treating **3** in acetic acid saturated by hydrochloric acid with 1 equiv. of water, a small amount of **5** was obtained, meaning that both pathways are equally conceivable.

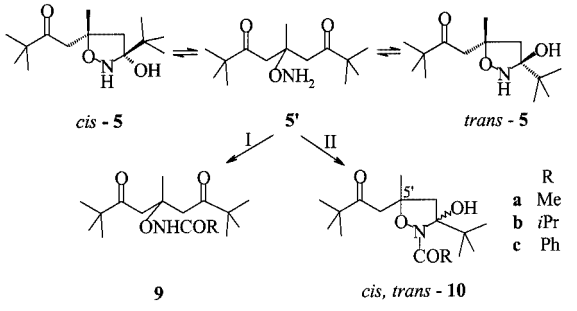
Two minor products were also isolated under conditions *c*, namely the bicyclic compound **6** (1% yield) and the 3-isoxazoline **7** (3% yield). The structure assignment for compounds **6** and **7** was based on NMR (^1H, ^{13}C) and MS data (Exp. Sec.). An interesting observation was made in connection with these side-products. When performing the cyclization of **2** with a threefold molar excess of hydrochloric acid at 0 °C (cond. *d*), the conversion of **2** attained ca. 85−90% in 2.5 h with significant changes in the distribution of the products. The yield of the bicyclic compound **6** heavily increased, mainly at the expense of pyridine 1-oxide **4** and 3-isoxazolidinol **5** (still obtained in comparable amounts). A definite increase in the yield of 3-isoxazoline **7** occurred as well. The open-chain compound **8** was also detected in the mixture. Based on IR and ^1H, ^{13}C NMR spectroscopic data, it was assigned as 2-pentene-1,5-dione 1-oxime with (*E*,*E*) geometry at the C−C and C−N double bonds. With longer reaction times, compound **8** vanished.

These results were rationalized as follows: compound **6** may originate from (2*Z*)-oxime **2**, probably through double cyclization of the enolic form activated by protonation at the nitrogen atom, which seems to be favoured when excess hydrochloric acid is used. On the other hand, (*Z*/*E*) isomerization of the C−C double bond leading to (2*E*)-oxime **8** occurs as well, becoming more competing at lower temperatures when cyclization slows down. The 3-isoxazoline **7** might actually originate from oxime **8**. Indeed, subjected for 2.5 h to conditions *c* in Scheme 1, the oxime **8** partly reverted to oxime **2** and only the cyclization products **3**, **4**, and **7** were found in the mixture. However, the proportion of 3-isoxazoline **7** was much higher (up to 30%) then when starting from oxime **2**. This point will not be further pursued, being not part of the main purpose of the paper. It seemed, however, worth mentioning, particularly since 3-isoxazolines are scarcely reported on.[5]

Ring-Chain Tautomerism of 3-Isoxazolidinol 5

The ^1H and ^{13}C NMR spectra of **5** in $CDCl_3$ presented two sets of signals of almost equal intensities, indicating a *cis*,*trans* diastereomeric pair. The chemical shifts within each stereoisomer were unambiguously assigned using 2D NMR (HETCOR and COLOC) techniques (Exp. Sect.). The stereochemical assignment will be discussed further.

The NMR spectra of **5** recorded in [D_8]toluene or in [D_6]DMSO exhibited also only the signals of equally populated *cis*/*trans* diastereomers, meaning that even the more polar solvent did not bring any change in the tautomeric equilibrium. However, on adding a trace of trifluoroacetic acid (TFA) to the $CDCl_3$ solution of **5** and recording the NMR spectrum immediately thereafter, signals belonging to three species were identified, corresponding to the acyclic tautomer **5′** in a 0.32 molar fraction, in equilibrium with *trans*-**5** and *cis*-**5** in 0.50 and 0.18 molar fractions, respectively (Scheme 2). On standing at room temperature, the sig-



Scheme 2. I: $(RCO)_2O$, reflux; II: RCOCl/Py, room temp.

nals of 2-isoxazoline **3** appeared and steadily increased in the spectrum, while the remaining tautomeric species *cis*-/*trans*-**5** and **5′** kept the relative proportion as above. The dehydration was complete in a few days.

On heating the sample in [D_8]toluene in the NMR vial, no line-broadening was observed up to 100 °C. The stereoisomer interconversion being slow at the NMR timescale, *cis*-/*trans*-**5** was submitted to chiral HPLC analysis screening, using mixtures of hexane/2-propanol. On CHIRALCEL OD-H, CHIRALCEL OJ, CHIRALCEL OB-H, and CHIRALPAK AD, single broad and distorted peaks were obtained at 25 °C. On CHIRALPAK AS, a single very broad peak was obtained at 25 °C, but splitting occurred on cooling. Two broad peaks (each presenting a shoulder) centered at 5.8 and 7.6 min were obtained at 6 °C (hexane/2-propanol, 96:4; UV 200 nm, flow rate 1 mL·min^{-1}). The first massif gave a positive response upon polarimetric detection, the second a negative one.

These results are in agreement with the exchange process in Scheme 2, the open-chain achiral tautomer **5′** being the common intermediate for both *cis*/*trans* interconversion and racemization. On the other hand, the chiral chromatography indicated that neither separation between *cis*-/*trans*-**5** nor enantiomeric resolution of each cyclic diastereomer can be accomplished, the exchange being relatively fast at room temperature.

Ring-Chain Tautomers (Isomers) of the *N*-Acyl(aroyl) Derivatives of 3-Isoxazolidinol 5

Brief heating of **5** with excess acetic anhydride (method I, Scheme 2) gave the 3-acetamidooxy-1,5-pentanedione **9a** in very high yield (90−95%). Working similarly with isobutyric anhydride, **9b** was obtained also in good yield. For analytical purposes, compounds **9a**, **9b** were purified by column chromatography on silica gel.

By treating **5** in diethyl ether at room temperature with acetyl (or benzoyl) chloride/pyridine in an equimolar ratio (method II, Scheme 2), the cyclic derivative **10a** (**10c**) along with minor amounts of **9a** (**9c**) was obtained in 90−95% overall yield.

The cyclic compounds **10a**, **10c** presented in the ^{1}H and ^{13}C NMR spectra, recorded in $CDCl_3$ at room temperature, two sets of signals unequally populated, indicating *cis*,*trans* diastereomers. The signal assignments in each stereoisomer were unambiguously achieved using 2D NMR (HETCOR and COLOC) techniques (Exp. Sect.).

The major stereoisomer of **10a** (**10c**) was isolated in almost pure state (≥ 95%) by column chromatography on silica gel, eluting with mixtures of petroleum ether/ethyl ether. The major stereoisomer of **10c** was found to be *trans* by an NOEDIF experiment (see Exp. Sect.). This stereochemical assignment is in agreement with the 5′-Me signal appearing in the ^{1}H NMR spectrum at higher field in *trans*-**10c** (δ = 1.50 ppm) than in *cis*-**10c** (δ = 1.87 ppm), due to the through-space shielding by the OH group. The same observation holds true for **10a**, the 5′-Me signal being upfield shifted by 0.4 ppm in the major stereoisomer compared to the minor one. Based on it, the major stereoisomer **10a** was also assigned as *trans*. Since in the *cis*/*trans* diastereomeric pair **5** there is an upfield shift by 0.15 ppm of the 5′-Me signal in one stereoisomer, provisional *trans* geometry was assigned to it as well.

Some interesting features were observed for compounds **10** in the solid state. Heating of *trans*-**10a** above its melting point (at 125±5 °C) for 2 h under an inert gas, a *trans*/*cis* mixture in a 3:1 ratio was obtained (this is also the ratio found in the crude acetylation product of method II). Additional heating did not change the isomeric ratio. Treated similarly, *trans*-**10c** was converted into a *trans*/*cis* mixture in a 6:1 ratio. However, after standing for two weeks at room temperature, crystallization of the melt occurred and pure *trans*-**10c** was obtained.

Submitted to chiral HPLC analysis on CHIRALCEL OD-H at 25 °C, the pure stereoisomer *trans*-**10c** was baseline-separated into the corresponding enantiomeric pair, with retention time 6.7 min for the (−) form and 9.0 min for the (+) form (hexane/2-propanol, 99:1; UV 254 nm; flow 1 mL·min^{-1}). On raising the temperature to 40 °C, a rather complex plateau indicating exchange between several very unequally populated forms was observed. Under the same analytical conditions, *cis*-/*trans*-**10a** was only poorly separated at 25 °C, exhibiting a cluster of partially resolved rather sharp peaks at 13.8 and 14.2 min. However, the polarimetric detection clearly showed four peaks (two negative and then two positive), accounting for the expected two pairs of enantiomers as well as for their stability at room temperature.

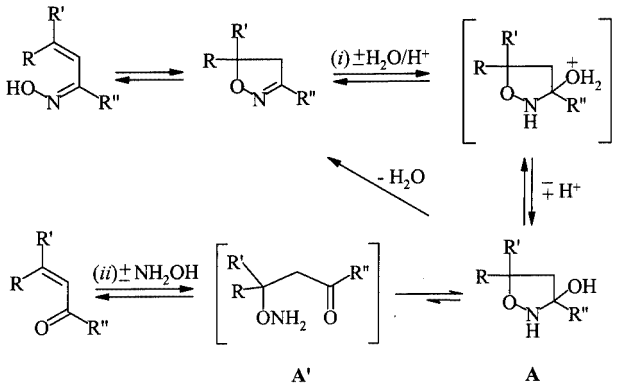
Finally, the acid catalytic effect on the tautomeric compounds **9**, **10** was studied. On adding a trace of TFA to the $CDCl_3$ solution of *trans*-**10a**, a completely new ^{1}H NMR pattern was obtained after 24 h at room temperature. It agreed with the protonated acyclic form **9a**, being identical with that found when TFA was added to the $CDCl_3$ solution of **9a**. The benzoylated derivative *trans*-**10c** behaved similarly.

Discussion

The key reaction in this paper is the reversible covalent hydration, under acidic catalysis, of the C−N double bond in 2-isoxazoline giving 3-isoxazolidinol **A** (path *i*, Scheme 3). So far, only the opposite irreversible dehydration has been reported. Formation of 3,5,5-trimethyl-2-isoxazoline from mesityl oxide and hydroxylamine under anhydrous basic conditions (MeONa/MeOH) was found to occur through 3-isoxazolidinol **A**, in equilibrium with open-chain tautomer **A′** (path *ii*, R = R′ = R′′ = Me).[6]

Path (*i*) in Scheme 3 is an alternative way of accessing 3-isoxazolidinols. These derivatives had only been previously obtained from α,β-unsaturated carbonyl compounds.[1]

The tautomeric equilibrium between **A** and **A′** was also found to be an opening path of the 2-isoxazoline ring, operating at the C-3−N bond. Indeed, acylation of **5** with anhydrides gave the open-chain *N*-acyl derivatives **9** in almost quantitative yield. It should be recalled that such open-



Scheme 3

chain tautomers had only been observed by NMR in equilibrium with their cyclic counterparts,[7] but never before isolated as stable compounds.

3-Isoxazolidinol **5** as well as its *N*-acyl(aroyl) derivatives **9**, **10** herein described are exceptional in a few ways. Dehydration of **5** occurred at 100 °C, in marked contrast with its trimethyl analog mentioned above, which could only be observed by ^{1}H NMR at −40 °C (its dehydration started at −20 °C).[6] Actually, there is only one previous report in the literature on isolable *N*-unsubstituted 3-isoxazolidinols **A** [R = H, R′ = Ph; R" = $HOC(CH_2)_5$ or $HOCMe_2$, mixture of diastereomers according to ^{1}H NMR].[8] A common possible explanation for this unusual stability might be the steric hindrance of the bulky substituent at C-3 along with stabilizing intermolecular hydrogen bonds between 3-OH or NH and the carbonyl (hydroxy) groups present in the side-chain.

The *cis*/*trans* interconversion of **5** was found to be slow on the NMR time-scale but still too fast to enable separation of stereoisomers by chiral HPLC at normal temperature. Conversely, for the *N*-acyl(aroyl) derivatives not only separation between acyclic **9** and cyclic **10** forms by preparative column chromatography was achieved, but also enantiomeric resolution of each *cis* (or *trans*) cyclic diastereomer **10** by analytical chiral HPLC. In other words, under normal temperature conditions only the interconversion between *cis*-/*trans*-**5** via **5′** falls into the range of kinetic scale characteristic for tautomeric processes ($\Delta G^{\ddagger} \leq 100$ kJ·mol^{-1}),[3b] whereas compounds **9**, *cis*-**10** and *trans*-**10** behave sooner as *true isomers* being separable by physical methods.

The interconversion between cyclic diastereomers *cis*-/*trans*-**10** was found to occur with a reasonable rate in the solid state, the equilibrium being reached at 125 °C within 2 h at most. Interestingly, the solid-state isomerization of compound **10c** was reversible.

While the solvent polarity had no effect on the *cis*/*trans* tautomeric equilibrium of 3-isoxazolidinol **5**, an acid catalyst (TFA) shifted the equilibrium towards a mixture of cyclic *cis*-/*trans*-**5** and acyclic **5′** tautomers. The same acid completely opened the cyclic *N*-acetyl derivative **10a**. It explains the fact that the unbuffered acetylation of **5** (method I) gave exclusively the acyclic isomer **9a** whereas under buffered conditions (method II) the cyclic isomers *cis*-/*trans*-**10a** prevailed.

Conclusion

The paper describes a new 2-isoxazoline ring-opening reaction operating at the C−N double bond and consisting in covalent hydration of this bond under protic acid catalysis, followed by acylation with anhydrides. In the resulting β-(acylaminooxy) ketones, both heteroatoms are preserved at the C-3 atom of the original heterocycle. It adds to the previously known ring-opening paths of 2-isoxazolines, occurring through O−N or C-5−O bond scission and giving access to a large variety of functional derivatives.[9] Being, however, a singular observation, any generalization or attaching preparative value to it would be obviously premature. It should rather be regarded as ringing bell in procedures performed under conditions which might promote hydration of the C−N double bond in 2-isoxazolines and thereby leading to unexpected chemical (or stereochemical) consequences due to ring-chain tautomerism.

Experimental Section

Instrumentation: Melting points were determined with a Boetius hot plate and are uncorrected. The IR spectra were recorded with a Carl Zeiss UR 20 instrument. The NMR spectra were recorded in $CDCl_3$ with a Varian Gemini 300BB instrument (300 MHz for ^{1}H, 75 MHz for ^{13}C) or a Bruker Avance instrument (400 MHz for ^{1}H, 100 MHz for ^{13}C). The δ values are given in ppm from internal TMS, the coupling constants *J* in Hz. The ^{1}H and ^{13}C NMR chemical shifts were determined from 1D (^{1}H, ^{13}C, DEPT) and 2D (COSY, HMQC, HMBC) experiments. The chiral HPLC experiments were performed with a screening unit composed of a Merck D-7000 system manager, a Merck-Lachrom L-7100 pump, a Merck-Lachrom L-7360 oven which may accomodate 12 columns alimented by a Valco 12 positions valve, a Merck-Lachrom L-7400 UV detector, and a Jasco OR-1590 polarimeter detector. Mass spectra were recorded with a Carlo Erba QMD 1000 instrument.

Reagents, Solvents: For preparative column chromatography, silica gel Fluka 60 was used. The elution solvents were petroleum ether (b.p. 35−45 °C) (PE) and diethyl ether (EE) freshly distilled from lithium aluminum hydride. For analytical TLC, aluminum strips (10 cm length) coated with silica gel F_{254} (Merck) were used. The R_f values were measured with PE/EE (1:1, v/v) as eluent. The solvents used in chiral HPLC (hexane and 2-propanol) were HPLC grade (from SDS, Peypine, France), degassed and filtered through a Millipore membrane (0.45 μm) before use. Cellulose-based chiral stationary phases CHIRALCEL OD-H, CHIRALCEL OJ, CHIRALCEL OB-H or amylose-based CSPs CHIRALPAK AD and CHIRALPAK AS DAICEL columns were available from Merck-Eurolab, all of them being (250×4.6 mm) in size. The oxo ketoxime **2** was prepared as previously described.[4] *Compound* **2** *should not be conserved, as it spontaneously cyclizes on standing at room temperature.* It may be purified by chromatography on silica gel eluting with PE/EE (4:1, v/v).

Cyclization of 2; Formation and Isolation of 5: Gaseous hydrochloric acid (generated from 35% aqueous hydrochloric acid and

concd. sulfuric acid and dried by bubbling through concd. sulfuric acid) was absorbed in anhydrous diethyl ether (or alternatively in glacial acetic acid) chilled in an ice/water bath. The hydrochloric acid content was determined by titration with sodium hydroxide using phenolphthalein as indicator.

Cyclization of 2: Reactions under conditions *a* and *b* in Scheme 1 were performed as previously described.[4] The reported yields are of pure compounds, isolated by column chromatography. Reactions under conditions *c* and *d*: Freshly prepared **2** (0.72 g, 3 mmol) in 15 mL of anhydrous diethyl ether was treated dropwise over 20 min with an ethereal solution (10 mL) containing ca. 3 mmol of hydrochloric acid, under magnetic stirring and chilling in an ice-/water bath. Clouding of the solution occurred and eventually a white solid precipitated. After standing overnight at room temperature, aqueous sodium bicarbonate was added until neutrality, when the solid had dissolved. The phases were separated and the aqueous layer was extracted with diethyl ether. The organic extract was washed with brine, dried with Na_2SO_4, and the solvents were evaporated under vacuum. The residue was chromatographed on 12 g of SiO_2, eluting with PE/EE in a ratio (v/v) from 20:1 to 1:1, then with EE. In the elution order, the following fractions were collected: 0.18 g of **4** (27% yield), 0.23 g of **3** (32% yield), 0.02 g of **7** (3% yield), 0.01 g of **6** (1% yield), and 0.23 g of **5** (30% yield). Compounds **3** and **4** were identified by comparing their NMR spectra with those of authentic samples.[10] Working as above but using a threefold molar excess of hydrochloric acid and stopping the reaction after 2.5 h at 0 °C, the following chromatographic fractions were collected: 0.10 g of **4** (15% yield), 0.19 g of **3** (27% yield), 0.09 g of **2** cross-contaminated with **7**, 0.015 g of **8** (2% yield), 0.17 g of **6** (24% yield), and 0.13 g of **5** (17% yield). Further chromatography of the mixed fraction gave 0.04 g of **7** (6% yield).

1-(3′-*tert*-Butyl-3′-hydroxy-5′-methylisoxazolidin-5′-yl)-3,3-dimethylbutan-2-one (5): Colourless crystals, m.p. 77−78 °C, single TLC spot, R_f = 0.10. $C_{14}H_{27}NO_3$ (257.4): calcd. C 65.33, H 10.58, N 5.44; found C 65.59, H 10.48, N 5.52. IR (CCl_4): 1708 (1696 sh), 3230 (brd), 3500 (brd), 3590 (sharp) cm^{-1}. The NMR spectra displayed two equally populated sets of signals, assigned to *cis*/*trans* diastereomeric pair as follows: ***trans*-5:** ^{1}H NMR: δ = 1.09 (s, 9 H, *tBu*C-3′), 1.18 (s, 9 H, *tBu*C-2), 1.24 (s, 3 H, *Me*C-5′), 1.96 (d, J_{AB} = 13.9, 1 H, H_AC-4′), 2.26 (d, J_{BA} = 13.9, 1 H, H_BC-4′), 2.73 (d, J_{AB} = 18.6, 1 H, H_AC-1), 3.03 (d, J_{BA} = 18.6, 1 H, H_BC-1), 4.3 (brd s, 1 H, D_2O exch.), 5.8 (brd s, 1 H, D_2O exch.) (NH, OH) ppm. ^{13}C NMR: δ = 25.3 (Me_3CC-3′), 26.2 (Me_3C-3), 27.9 (*Me*C-5′), 36.5 (*C*C-3′), 42.3 (H_2C-1), 44.7 (C-3), 47.2 (H_2C-4′), 61.2 (C-5′), 113.8 (C-3′), 216.3 (C-2) ppm. ***cis*-5:** ^{1}H NMR: δ = 1.04 (s, 9 H, *tBu*C-3′), 1.15 (s, 9 H, *tBu*C-2), 1.39 (s, 3 H, *Me*C-5′), 1.96 (d, J_{AB} = 13.6, 1 H, H_AC-4′), 2.41 (d, J_{BA} = 13.6, 1 H, H_BC-4′), 2.81(d, J_{AB} = 18.4, 1 H, H_AC-1), 2.97 (d, J_{BA} = 18.4, 1 H, H_BC-1), 4.3 (br s, 1 H, D_2O exch.), 5.8 (br s, 1 H, D_2O exch.) (NH, OH) ppm. ^{13}C NMR: δ = 25.1 (Me_3CC-3′), 26.4 (Me_3C-3), 22.7 (*Me*C-5′), 36.6 (*C*C-3′), 46.2 (H_2C-1), 44.4 (C-3), 47.2 (H_2C-4′), 62.5 (C-5′), 113.7 (C-3′), 215.5 (C-2) ppm.

5-(Aminooxy)-2,2,5,8,8-pentamethylnonane-3,7-dione (5′): ^{1}H NMR ($CDCl_3$ + TFA trace): 1.15 (s, 18 H, *tBu*C-3, *tBu*C-7), 1.45 (s, 3 H, *Me*C-5), 3.08 (d, J_{AB} = 18.4 Hz, 2 H, H_AC-4, H_AC-6), 3.17 (d, J_{BA} = 18.4 Hz, 2 H, H_BC-4, H_BC-6).

1,3-Di-*tert*-butyl-5-methyl-2,6-dioxa-7-azabicyclo[3.2.1]oct-3-ene (6): Colourless crystals, m.p. 114−115 °C, R_f = 0.15. MS: *m*/*z* (%) = 240 (0.2) [M + 1], 239 (0.6) [M], 224 (12.3), 207 (78.9) [M − NHOH], 140 (77.6) [M − *t*BuCOCH$_2$], 57 (100.0). ^{1}H NMR: δ = 1.07 (s, 9 H, *tBu*C-3), 1.08 (s, 9 H, *tBu*C-1), 1.32 (s, 3 H, *Me*C-5), 1.95 (d, J_{AB} = 10.8, 1 H, H_AC-8), 2.09 (d, J_{AB} = 10.8, 1 H, H_BC-8), 4.70 (s, 1 H, *H*C-4), 5.40 (brd s, 1 H, NH) ppm. ^{13}C NMR: δ = 18.6 (*Me*C-5), 25.3 (Me_3CC-1), 27.8 (Me_3CC-3), 34.4 (*C*C-3), 36.2 (*C*C-1), 42.3 (H_2C-8), 58.1 (C-5), 99.0 (HC-4), 112.7 (C-1), 162.2 (C-3) ppm.

1-(3′-*tert*-Butyl-2′,5′-dihydro-5′-methylisoxazol-5′-yl)-3,3-dimethylbutan-2-one (7): Colourless crystals, m.p. 146−147 °C, R_f = 0.45. IR (KBr): $\tilde{\nu}$ = 3320 cm^{-1} (brd, NH). MS: *m*/*z* (%) = 239 (0.1) [M$^+$], 224 (2.7) [M$^+$ − CH_3], 140 (62.2) [M$^+$ − *t*BuCOCH$_2$], 57 (100.0). ^{1}H NMR: δ = 1.13 (s, 9 H, *tBu*C-3′), 1.15 (s, 9 H, *tBu*C-2), 1.56 (s, 3 H, *Me*C-5′), 3.34 (s, 2 H, H_2C-1), 5.48 (s, 1 H, *H*C-4′), 7.50 (brd, 1 H, NH) ppm. ^{13}C NMR: δ = 19.8 (*Me*C-5′), 26.3 (Me_3C-3), 27.8 (Me_3CC-3′), 37.6 (Me_3*C*C-3′), 44.6 (C-3), 46.4 (H_2C-1), 118.5 (HC-4′), 138.7 (C-5′), 163.0 (C-3′), 213.0 (C-2) ppm.

(3*E*,4*E*)-2,2,5,8,8-Pentamethylnon-4-ene-3,7-dione 3-Oxime (8): Colourless crystals, m.p. 127−129 °C, R_f = 0.30. IR ($CHCl_3$): $\tilde{\nu}$ = 1705, 3275 (brd), 3585 (sharp) cm^{-1}. ^{1}H NMR: δ = 1.17 (s, 9 H, *tBu*C-7), 1.26 (s, 9 H, *tBu*C-3), 1.73 (s, 3 H, *Me*C-5), 3.26 (s, 2 H, H_2C-6), 5.65 (s, 1 H, *H*C-4), 8.40 (1 H, brd s, O*H*) ppm. ^{13}C NMR: δ = 18.2 (*Me*C-5), 26.4 (Me_3C-8), 27.7 (Me_3C-2), 37.0 (C-2), 44.7 (C-8), 46.8 (H_2C-6), 124.5 (HC-4), 136.1 (C-5), 162.4 (C-3), 213.1 (C-7) ppm.

Reaction of 5 with Anhydrides (Method I): 514 mg (2 mmol) of **5** in 2 mL of acetic anhydride was heated at 100−110 °C (oil bath) for 15 min. After cooling, 25 mL of water was added and several extractions with diethyl ether were made. The ethereal phase was carefully neutralized with sodium bicarbonate solution, washed with brine and the solvents were evaporated, giving **9a** (570 mg, 95% yield). An analytical sample was obtained by column chromatography on silica gel, eluting with PE/EE (4:1, v/v). Working similarly with isobutyric anhydride, **9b** was obtained in 87% yield.

5-(Acetamidooxy)-2,2,5,8,8-pentamethylnonane-3,7-dione (9a): Oil. $C_{16}H_{29}NO_4$ (299.4): calcd. N 4.68, found N 4.63; R_f = 0.30. IR ($CHCl_3$): $\tilde{\nu}$ = 1475 (1462 sh), 1703, 1740, 3240 cm^{-1}. ^{1}H NMR: δ = 1.11 (s, 18 H, *tBu*C-3, *tBu*C-7), 1.21 (s, 3 H, *Me*C-5), 2.08 (s, 3 H, *Me*-CO), 2.95 (d, J_{AB} = 18.3, 2 H, H_AC-4, H_AC-6), 3.04 (d, J_{BA} = 18.3, 2 H, H_BC-4, H_BC-6), 8.0 (brd s, 1 H, NH) ppm. ^{13}C NMR: δ = 19.2 (*Me*-CO), 22.4 (*Me*C-5), 26.3 (Me_3C-2, Me_3C-8), 41.0 (H_2C-4, H_2C-6), 44.8 (C-2, C-8), 58.5 (C-5), 169.9 (CONH), 215.5 (C-3, C-7) ppm.

5-(Isobutyramidooxy)-2,2,5,8,8-pentamethylnonane-3,7-dione (9b): R_f = 0.50. ^{1}H NMR: δ = 1.11 (s, 18 H, *tBu*C-3, *tBu*C-7), 1.20 (d, *J* = 7, 6 H, Me_2CH), 1.22 (s, 3 H, *Me*C-5), 2.61 (sept, *J* = 7, 1 H, Me_2C*H*), 2.95 (d, J_{AB} = 18.3, 2 H, H_AC-4, H_AC-6), 3.04 (d, J_{BA} = 18.3, 2 H, H_BC-4, H_BC-6), 8.13 (br s, 1 H, N*H*) ppm. ^{13}C NMR: δ = 19.0 (Me_2CH), 22.4 (*Me*C-5), 26.3 (Me_3C-2, Me_3C-8), 33.0 (*C*HMe_2), 40.9 (H_2C-4, H_2C-6), 44.7 (C-2, C-8), 58.6 (C-5), 175.8 (CONH), 215.4 (C-3, C-7) ppm.

Reaction of 5 with Acetyl or Benzoyl Chloride (Method II): 514 mg (2 mmol) of **5** and 160 mg (2 mmol) of pyridine in 5 mL of diethyl ether was treated dropwise over 15 min at room temperature and under magnetic stirring with 160 mg (2 mmol) of freshly distilled acetyl chloride, dissolved in 5 mL of diethyl ether. After additional 45 min of stirring, the pyridine hydrochloride precipitate was filtered off and washed on the funnel with diethyl ether. The ethereal filtrate was washed with brine, dried with sodium sulfate, and the solvents were evaporated under vacuum leaving 535 mg acetylation product (89% yield). The molar composition of the crude product (determined by ^{1}H NMR) was **10a** (0.97) and **9a** (0.03). The cyclic

derivative **10a** consisted of two diastereomers in a 3:1 ratio. Column chromatography with EE/PE (1:2.3, v/v) gave the major stereoisomer *trans*-**10a** in ≥ 95% purity (295 mg, 50% yield). The reaction of **5** with benzoyl chloride, performed similarly, gave a mixture consisting of **10c** and **9c** in a 0.87:0.13 molar fraction. The diastereomeric ratio in **10c** was 6:1. Column chromatography afforded **9c** in 9% yield and in 54% yield the major stereoisomer *trans*-**10c** in ≥ 95% purity. Crystalline samples (ca. 100 mg) of *trans*-**10a** and *trans*-**10c** above were heated in open vessel (under a slow stream of an inert gas) with an oil bath at 125±5 °C for 2 h. No significant change in the sample weights was found. The NMR analysis indicated the appearance of the *cis* stereoisomer in the heated samples.

5-(Benzamidooxy)-2,2,5,8,8-pentamethylnonane-3,7-dione (9c): R_f = 0.50. ^{1}H NMR: δ = 1.12 (s, 18 H, *tBu*C-3, *tBu*C-7), 1.33 (s, 3 H, *Me*C-5), 3.06 (d, J_{AB} = 18.2, 2 H, H_AC-4, H_AC-6), 3.14 (d, J_{BA} = 18.2, 2 H, H_BC-4, H_BC-6), 7.46 (t, *J* = 7.6, *meta*-2 H), 7.59 (t, *J* = 7.9, *para*-1 H), 7.98 (d, *J* = 7.9, *ortho*-2 H), 8.50 (brd s, 1 H, NH) ppm.

***trans*-1-(2′-Acetyl-3′-*tert*-butyl-3′-hydroxy-5′-methylisoxazolidin-5′-yl)-3,3-dimethylbutan-2-one (10a):** Colourless crystals, m.p. 68−71 °C. $C_{16}H_{29}NO_4$ (299.4): calcd. N 4.68; found N 4.59; R_f = 0.20. IR ($CHCl_3$): $\tilde{\nu}$ = 1633 (1608 sh), 1698, 3365 (brd) cm^{-1}. ^{1}H NMR: δ = 1.02 (s, 9 H, *tBu*C-3′), 1.11 (s, 9 H, *tBu*C-2), 1.32 (s, 3 H, *Me*C-5′), 1.94 (s, 3 H, *Me*CO), 2.20 (d, J_{AB} = 13.3, 1 H, H_AC-4′), 2.33 (d, J_{BA} = 13.3, 1 H, H_BC-4′), 2.77 (d, J_{AB} = 19.1, 1 H, H_AC-1), 4.01 (d, J_{BA} = 19.1, 1 H, H_BC-1), 7.10 (s, 1 H, OH) ppm. ^{13}C NMR: δ = 21.9 (*Me*CO), 25.0 (*Me*$_3$CC-3′), 26.8 (*Me*$_3$C-3), 27.0 (*Me*C-5′), 36.2 (*CC*-3′), 43.2 (H_2C-1), 44.5 (C-3), 48.9 (H_2C-4′), 61.0 (C-5′), 109.0 (C-3′), 167.4 (NCO), 216.5 (C-2) ppm.

***cis*-10a:** ^{1}H NMR: δ = 1.04 (s, 9 H, *tBu*C-3′), 1.12 (s, 9 H, *tBu*C-2), 1.73 (s, 3 H, *Me*C-5′), 2.02 (s, 3 H, *Me*CO), 2.33 (d, J_{AB} = 13.2, 1 H, H_AC-4′), 2.54 (d, J_{BA} = 13.2, 1 H, H_BC-4′), 2.76 (d, J_{AB} = 18.0, 1 H, H_AC-1), 3.66 (d, J_{BA} = 18.0, 1 H, H_BC-1), 7.4 (brd s, 1 H, OH) ppm. ^{13}C NMR: δ = 22.1 (*Me*CO), 23.9 (*Me*C-5′), 25.0 (*Me*$_3$CC-3′), 26.2 (*Me*$_3$C-3), 36.8 (*CC*-3′), 44.5 (C-3), 44.6 (H_2C-1), 47.9 (H_2C-4′), 63.5 (C-5′), 108.2 (C-3′), 166.0 (NCO), 214.1 (C-2) ppm.

***trans*-1-(2′-Benzoyl-3′-*tert*-butyl-3′-hydroxy-5′-methylisoxazolidin-5′-yl)-3,3-dimethylbutan-2-one (10c):** Colourless crystals, m.p. 109−110 °C. $C_{21}H_{31}NO_4$ (361.5): calcd. N 3.87; found N 3.90; R_f = 0.30. IR ($CHCl_3$): $\tilde{\nu}$ = 1578, 1618, 1694, 3370 (brd) cm^{-1}. ^{1}H NMR: δ = 1.06 (s, 9 H, *tBu*C-3′), 1.17 (s, 9 H, *tBu*C-2), 1.50 (s, 3 H, *Me*C-5′), 2.35 (d, J_{AB} = 13.2, 1 H, H_AC-4′), 2.45 (d, J_{BA} = 13.2, 1 H, H_BC-4′), 2.87 (d, J_{AB} = 19.2, 1 H, H_AC-1), 4.29 (d, J_{BA} = 19.2, 1 H, H_BC-1), 7.34 (t, *J* = 7.2, *meta*-2 H), 7.39 (t, *J* = 7.2, *para*-1 H), 7.53 (s, 1 H, OH), 7.87 (d, *J* = 6.8, *ortho*-2 H) ppm. ^{13}C NMR: δ = 25.0 (*Me*$_3$CC-3′), 26.3 (*Me*C-5′), 26.9 (*Me*$_3$C-3), 36.2 (*CC*-3′), 43.3 (H_2C-1), 44.8 (C-3), 48.8 (H_2C-4′), 61.6 (C-5′), 109.3 (C-3′), 127.5 (*meta*-2CH), 129.4 (*ortho*-2CH), 130.6 (*para*-CH), 134.3 (Cq in C_6H_5), 165.0 (NCO), 216.8 (C-2) ppm. The stereochemical assignment of *trans*-**10c** was based on the following NOEDIF experiment: Irradiation of the proton H_B at C-1 (δ = 4.29 ppm) gave a positive signal for the *t*Bu group at C-3′ (δ = 1.06 ppm), meaning that substituents 3′-*t*Bu and CH_AH_B (linked to C-5′) are on the same side of the heterocyclic ring.

***cis*-10c:** ^{1}H NMR: δ = 1.02 (s, 9 H, *tBu*C-3′), 1.16 (s, 9 H, *tBu*C-2), 1.87 (s, 3 H, *Me*C-5′), 2.38 (d, J_{AB} = 13.5, 1 H, H_AC-4′), 2.65 (d, J_{BA} = 13.5, 1 H, H_BC-4′), 2.93 (d, J_{AB} = 18.0, 1 H, H_AC-1), 3.83 (d, J_{BA} = 18.0, 1 H, H_BC-1), 7.3−7.4 (m, 3 H, *para*-1 H, *meta*-2 H), 7.76 (d, *J* = 6.8 Hz, 2 H, *ortho*-2 H) ppm.

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