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5(4*H*)-Oxazolones. Part X.[1] Acid and Base Effects on the Translactonization Reaction of 4-(2-Oxa-alkylidene)-5(4*H*)-oxazolones: New Synthesis of 5-Alkylidene-3-benzoylamino-2(5*H*)-furanones

Maria Luisa Gelmi,* Francesca Clerici, and Alessandra Melis

Istituto di Chimica Organica, Facoltà di Farmacia, Università di Milano, Via Venezian 21, I-20133 Milano, Italy.

Abstract: 4-(2-Oxa-alkylidene)-5(4*H*)-oxazolones (azlactones) **1** can be transformed in acidic conditions (anhydrous HBr/$CHCl_3$) into 5-alkylidene-3-benzoylamino-2(5*H*)-furanones **2** which have *Z* configuration at the exocyclic double bond. The same reaction conducted in acetic acid as solvent gives, besides the alkylidene-furanones **2**, the furanyl acetates **5**. The result of azlactone transformation in the presence of base (DBU) depends on the steric hindrances in the starting material. The less hindered oxazolones **1a,b** give condensation products **8**, whereas the more hindered azlactone **1c** gives furanone **2c** or, in presence of an alkylating agent, furanone **2d**.

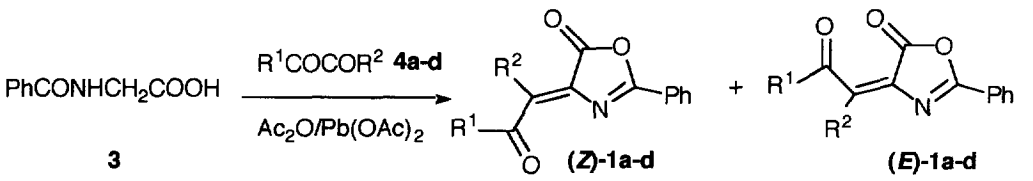
The 5-alkylidene-2(5*H*)-furanones (*i.e* 5-alkylidene-buten-2-olides) are widespread in nature and some of them are reported to have carcinogenic or antitumor activity as well as other important biological properties.[2] The simplest structure known of this class of compounds is protoanemonine which has an antibiotic activity.[3] Many different approaches[4-6] have been used for the synthesis of 5-alkylidene-2(5*H*)-furanones. However, synthetic methods to obtain compounds having a free or protected amino group at C-3 position have been described only occasionally.[7,8] 4-Acetyl-3-amino-5-methylene-2(5*H*)-furanone has been obtained through a rearrangement reaction of a keto-enaminonitrile[8] and few 5-acyloxypropylidene-3-acylamino-2(5*H*)-furanone derivatives have been prepared from aminogluconic acid.[7] The formation of 3-amino-5-methylene-2(5*H*)-furanone was suggested by some authors[9,10] as the metabolite of the *D*-propargylglycine, an inhibitor of the flavoenzyme *D*-aminoacid oxidase. In fact, general synthetic procedures are lacking.

Oxazolones are known to be ideal synthons to obtain heterocycles containing an α-aminosubstituted lactone moiety.[11] In a recent paper[1] we described the synthesis of 3-acylamino enol lactones from oxazolones. We now report on a new and general synthesis of 3-benzoylamino-5-alkylidene-2(5*H*)-furanones **2** through a translactonization reaction of the readily available 4-(2-oxa-alkylidene)-5(4*H*)-oxazolones **1**. This reaction is catalyzed both by acid and base and yields different results depending on the substitution pattern of the starting oxazolone and on reaction conditions.

RESULTS AND DISCUSSION

Oxazolones **1a-d** were prepared, by the known procedure described for compound **1a**,[12] starting from hippuric acid **3** and α-diketones **4a-d** with acetic anhydride and lead acetate. The reaction resulted in a mixture of

two geometric isomers *Z* and *E* in which the thermodynamically more stable isomer *Z* was present as the major product. (Scheme 1) 1,2-Cyclohexanedione was also used as starting material, but the reaction was unsuccessful. As shown in Scheme 1, in the case of the unsymmetrical diketones **1b,d** only one regioisomer, as an *E* and *Z* mixture, was isolated following condensation of the intermediate 2-phenyl-5(4*H*)-oxazolone with the less hindered oxo group of diketone **4**.



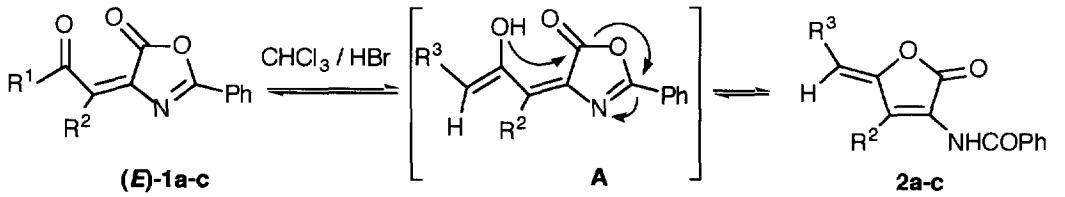
1a, 4a: $R^1 = R^2 = Me$
1b, 4b: $R^1 = Et$, $R^2 = Me$
1c, 4c: $R^1 = R^2 = Et$
1d, 4d: $R^1 = Ph$, $R^2 = Me$

Scheme 1

The IR spectrum of compounds **1** confirmed the presence of the lactone (1790 cm^{-1}) and ketone groups (1760 cm^{-1}).

The transformation of azlactones **1** into furanones **2** could be achieved both with acid or base catalysis.

In a first experiment compound (*E*)-**1a** was reacted at room temperature in chloroform saturated with anhydrous hydrobromic acid and 3-benzoylamino-5-methylene-2(5*H*)-furanone **2a** was isolated in satisfactory yield. Azlactones (*E*)-**1b,c** reacted in the same way giving furanones **2b,c**. Compounds **1a,b** reacted at room temperature, but oxazolone **1c** needed heating. (Scheme 2)



2a: $R^2 = Me$, $R^3 = H$
2b: $R^2 = R^3 = Me$
2c: $R^2 = Et$, $R^3 = Me$

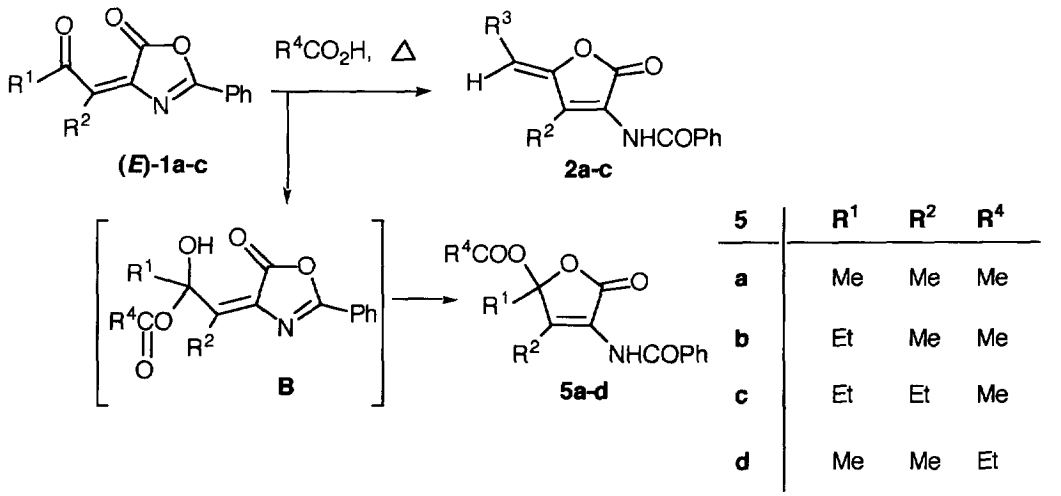
Scheme 2

The formation of compounds **2** is explained considering an initial acid-catalyzed enolisation of the ketone group of the azlactone **1** to give the intermediates **A**, which through a translactonization reaction, are transformed into furanones **2**. As expected, compound **1d** did not provide any reaction product because of the absence of α-protons to the ketone group.

Compounds **2** were obtained in 54-77 % yield. They are very sensitive to moisture and during the elaboration reaction they can undergo hydrolysis (most of all **2a**) to the corresponding acid decreasing the reaction yield. The reaction was carried out also starting from (*Z*)-**1a**. Although in the literature is reported that *Z*-alkylidene-azlactones[11-13] can be isomerized to compounds *E* under these reaction conditions, this transformation was not observed in our case and compound **2a** was not formed. Accordingly only the *E*-isomers could be used as starting materials. However, also *Z*-oxazolones are useful because they could be transformed into the corresponding *E* forms by photochemical isomerization in acetone at $\lambda = 254$ μm.[14]

The structure of compounds **2** was confirmed by IR ($\nu_{max} = 1770$ cm^{-1}, lactone group), ^{1}H NMR and ^{13}C NMR spectra. As typical for alkylidenefuranones,[9,15] the chemical shift of vinylic protons is in the range $\delta = 5.0$-5.5. In the ^{13}C NMR spectrum, the absence of the signal at 200 ppm (CO, ketone), characteristic in compounds **1**, confirmed the formation of enol lactone (δ = 165, 167 associated to C-5 and C-2, respectively). The translactonization reaction is highly stereoselective and only the *Z* isomer was found for compounds **2b,c**, as demonstrated by NOESY experiments in which the spatial proximity of the vinyl proton with those of the chain linked to C-4 was pointed out by a positive Overhauser effect.

The translactonization reaction of azlactones (*E*)-**1** was tried under a variety of acidic conditions (*p*-TSA, $TBAHSO_4$, BF_3) without advantage. Instead, the use of acetic acid as reaction solvent, at the boiling point, gave partially different results, *i.e.* a mixture of products identified as the furanones **2a-c** and the 4-benzoylamino-5-oxo-2,5-dihydro-furan-2-yl acetates **5a-c**, starting from the corresponding oxazolones (*E*)-**1a-c**, respectively. (Scheme 3)



5	R^1	R^2	R^4
a	Me	Me	Me
b	Et	Me	Me
c	Et	Et	Me
d	Me	Me	Et

Scheme 3

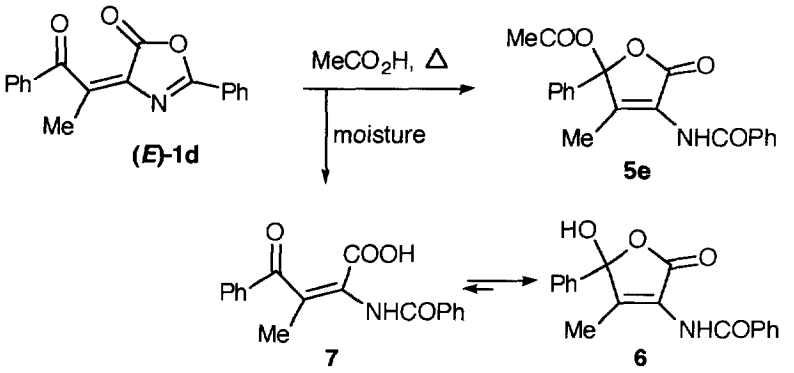
The same reaction was conducted starting from isomer (*Z*)-**1a**. Also in this case compounds **2a** and **5a** were produced but in a lower yield. The poorer yield starting from the *Z* isomer must be ascribed to the unfavourable stereochemistry of the double bond in the starting material; all the same, this result points out the possibility to isomerize compound *Z* to *E* under these reaction conditions.

Refluxing oxazolone (*E*)-**1a** in propionic acid gave, as well as compound **2a**, propionate **5d**, thus

confirming that the acyl group originates from the acid used as reaction solvent.

Scheme 3 depicts the formation of compounds **5** which derive from the (*E*)-**1** isomer by addition of acetic acid to ketone group (intermediate **B**) followed by the translactonization reaction. Compounds **5** are not the precursors of **2** and *vice versa*. Indeed, pure compound **5a** was refluxed in acetic acid for several hours but it was recovered unchanged confirming its stability. This was not completely unexpected because similar structures are reported to be stable in the above conditions.[3] Likewise, compounds **2** did not give acetates **5** when treated with acetic acid at room or elevated temperature.

Oxazolone(*E*)-**1d** was refluxed in acetic acid giving a mixture of the expected acetate **5e** and the hemiacetal **6**. (Scheme 4)



Scheme 4

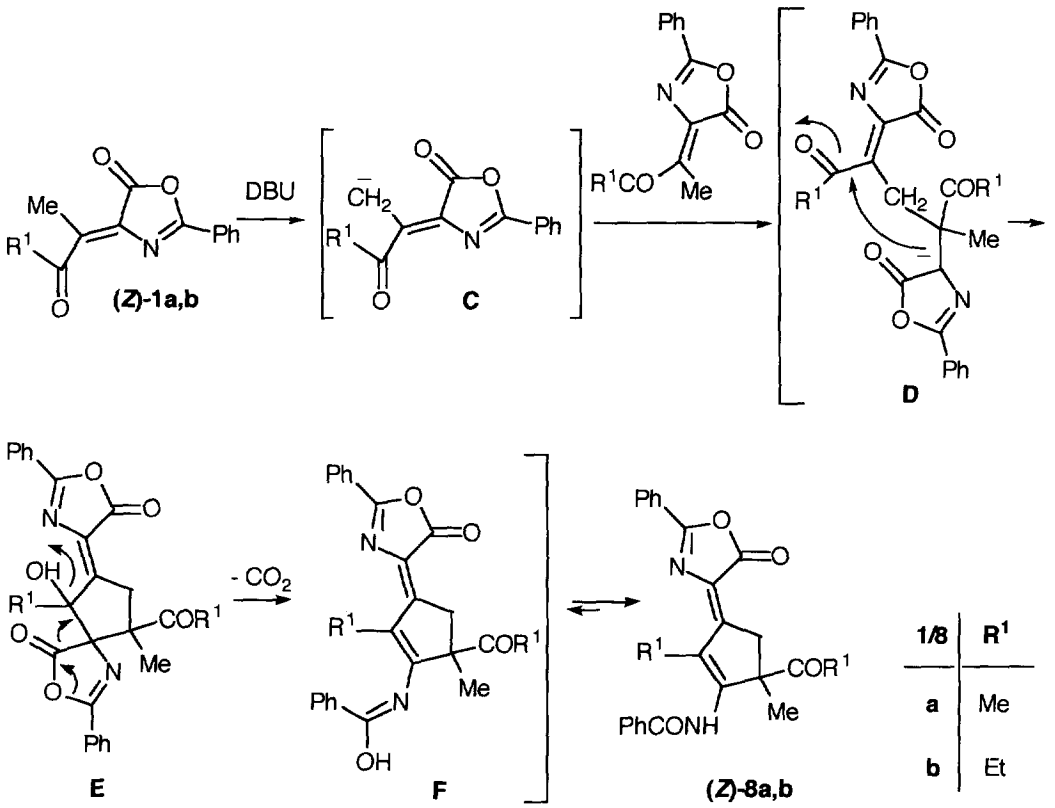
The formation of compound **6** can be explained taking into account that it is not the precursor of **5e** under the adopted conditions nor **5e** can be hydrolysed to **6**, as confirmed in independent experiments. Owing to the lower reactivity of the aromatic ketone group in (*E*)-**1d**, the reaction leading to **5e** was slower and a partial hydrolysis (the reaction was not performed under strictly anhydrous conditions) of the azlactone ring occurred affording the acid **7** which exists in the pseudoacid form **6**. The equilibrium of γ-oxo-α,β-unsaturated acids with the cyclic form is precedented in the literature.[3]

As mentioned above, the translactonization reaction was also studied in basic conditions and the reaction results were different and partially unexpected.

Oxazolones (*Z*)-**1a,b** were treated with a molar equivalent of DBU in dichloromethane at room temperature giving compounds **8a,b** quantitatively. (Scheme 5) Also starting from isomer (*E*)-**1a** the same product **8a** was isolated.

Compounds **8** are the products of a condensation reaction of two molecules of the starting material with loss of CO_2 as confirmed by elemental analysis and mass spectrum of compound **8a** (M^+ = 414). The structure of compounds **8a,b** was inferred from the following data: the absorption at 1775 and 1740 cm^{-1} in the IR spectrum showed the presence of both the azlactone and carbonyl ketone groups. This was confirmed also by ^{13}C NMR spectrum in which two carbonyl signals were found at δ =176 and 207, respectively. The presence in the ^1H NMR spectrum of an AB system at δ = 3.2 (J =19.7 Hz) corresponding to two protons (^{13}C NMR: δ = 42) confirmed that the vinylic methyl groups of the oxazolones **1a,b** were implicated in the condensation reaction.

The ^{1}H NMR spectrum of the compound **8b** presented two multiplets in the δ = 2.4-2.7 region associated to CH_2 α to the keto group, indicating that this group was linked to a diastereocenter (C-5). An exchangeable singlet at δ= 8.3 confirmed the presence of the amide function.



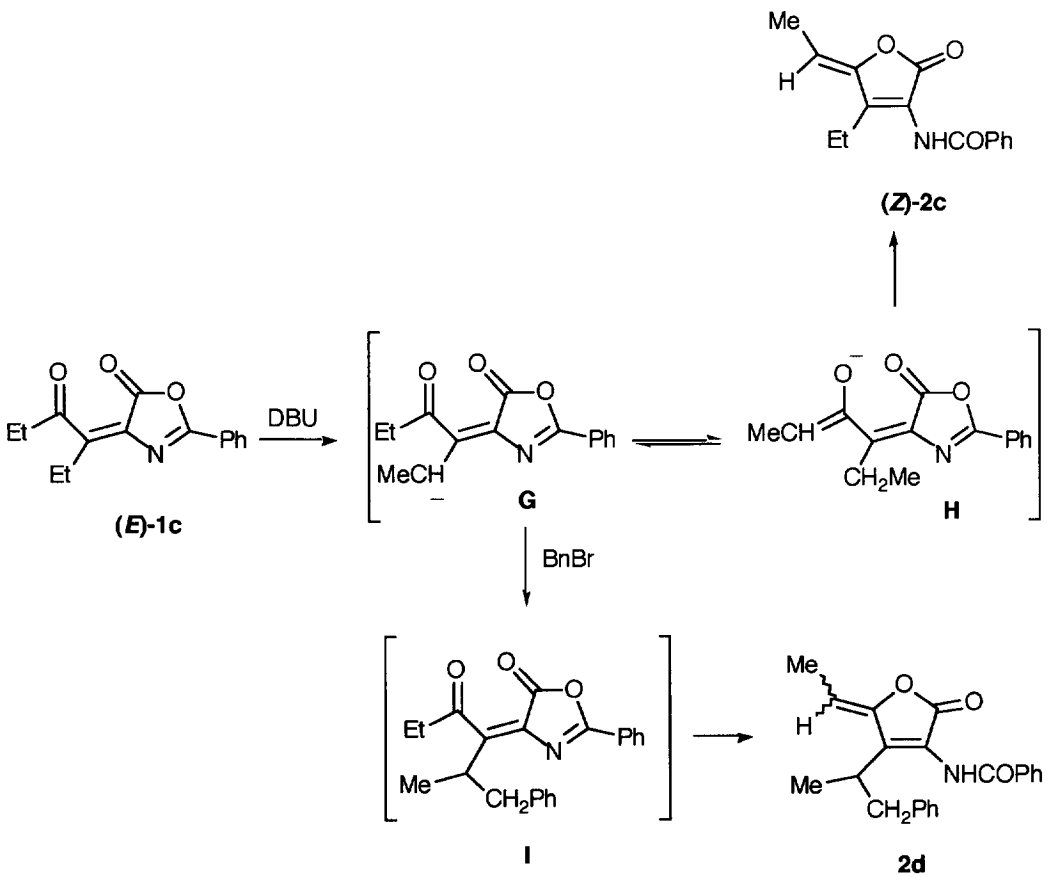
Scheme 5

Taking into account that **8** must derive exclusively from **1**, because compounds **2** were demonstrated to be stable under these conditions, the formation of compounds **8** is rationalized in Scheme 5. Azlactone (*Z*)-**1** is deprotonated at the allylic carbon by the base producing a red solution which is characteristic of a delocalized carbanion like **C**. The Michael addition of intermediate **C** to the double bond of compound **1** gives a new carbanion **D** which undergos intramolecular ring closure by addition to the keto group producing the aldol-like compound **E**. The cleavage of the spiranic oxazolone ring, assisted by loss of hydroxide ion, gives the intermediate **F** which is tautomerized into the more stable amide **8**. As shown in Scheme 5, the configuration of the double bond of compounds **8** is *Z* and this is in agreement both with the configuration of the double bond in the starting material and with the proposed mechanism.[16] Interestingly, starting from (*E*)-**1a** the same isomer (*Z*)-**8a** was obtained. This result confirms the conformational mobility of intermediate **C**.

Different results were found starting from azlactone (*E*)-**1c** and working in basic condition at 40 °C.[17] In

this case only lactone (*Z*)-**2c** was isolated. Compound **2c** is formed as depicted in Scheme 6 by a translactonization reaction of the enolate **H** which is in equilibrium with the primary deprotonation product of **1c**, *i. e.* anion **G**. The existence of this equilibrium was confirmed both by the red color of the reaction mixture after addition of DBU, and by the addition of benzyl bromide, which acted as alkylating agent, affording directly a 2 : 1 mixture of *E* and *Z* furanones **2d** through translactonization reaction of azlactone intermediate **I** which was alkylated at the allylic carbon. (Scheme 6)

The structure of the *E* and *Z* furanones **2d** was confirmed by ^{1}H NMR spectrum and the configuration of the two isomers was assigned by comparison of NMR spectra of isomers (*Z*)- and (*E*)-**2c** (see experimental and note 17).



Scheme 6

As expected, oxazolone **1d** gave only decomposition products when treated with DBU. Nor a compound **8**, because of steric hindrance, nor a compound **2**, owing to the absence of α-hydrogens, could be produced.

On the basis of these results we can conclude that the distribution of the products under base catalysis depends on the steric features of double bond and/or ketone. On the contrary, all oxazolones **1** showed the same behaviour in acidic conditions allowing to synthesize, in easy way and by a stereoselective process, the (*Z*)-3-

benzoylamino-5-alkylidenefuran-2(5*H*)ones **2** having different substitution patterns.

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EXPERIMENTAL

Melting points were determined using a Büchi 510 (capillary) apparatus. IR spectra were recovered on a JASCO IR Report 100 spectrophotometer. NMR spectra ($CDCl_3$ as solvent) were obtained with Bruker AC 200 and Varian Gemini 200 instruments. TLC: ready-to-use silica gel plates. Column chromatography: silica gel [Kieselgel 60-70 230 ASTM (Merck)] with the eluant indicated.

Material. Oxazolone **1a** is known compound.[12]

*General Procedure for the Preparation of Oxazolones **1a-d**.* Hyppuric acid (**3**) (10 g, 0.056 mol), diketone **3** (0.056 mol) and $Pb(OAc)_2$ (9 g, 0.028 mol) were suspended in anhydrous THF (120 mL). Acetic anhydride (24 mL) was added under nitrogen and the mixture was stirred at 70 °C for 2-4 h. After cooling, inorganic salt was filtered and washed with CH_2Cl_2. The organic solvents were evaporated and the crude reaction mixture was chromatographed on silica gel column (*n*-pentane/CH_2Cl_2, 1:0 to 0:1). Compound **1d** was directly crystallized from CH_2Cl_2/*i*-Pr_2O giving a mixture of *E* and *Z* isomers and then the mother liquor was chromatographed as above. Column chromatography gave three fractions containing the pure *Z* isomer, a mixture of *E* and *Z* isomers and the pure *E* isomer, respectively, in a ratio indicated below.

*4-(1-Methyl-2-oxo-propylidene)-2-phenyl-4H-oxazol-5-one (**1a**):* Total yield: 36 % (*Z*/*E*: 3:1). (*Z*)-**1a**: M.p.: 142-143 °C, (143-145 °C).[12] IR (nujol): 1795 (CO lactone), 1760 (CO ketone), 1660 (C=N) cm^{-1}. ^1H NMR: 2.44 (s, 3 H, MeC=), 2.78 (s, 3 H, MeCO), 7.51-8.10 (m, 5 H, Aryl-H) ppm. ^{13}C NMR: 13.6 (*Me*C=), 31.7 (*Me*CO), 125.0-133.8 (C arom), 135.6 (C=), 143.6 (C-4), 162.3 (C-2), 166.1 (C-5), 201.4 (CO) ppm. (*E*)-**1a**: M.p.: 86-87 °C, (87-88 °C).[12] IR (nujol): 1795 (CO lactone), 1760 (CO ketone), 1660 (C=N) cm^{-1}. ^1H NMR: 2.47 (s, 3 H, MeC=), 2.50 (s, 3 H, MeCO), 7.51-8.10 (m, 5 H, Aryl-H) ppm. ^{13}C NMR: 17.6 (*Me*C=), 29.5 (*Me*CO), 125.7,-134.0 (C arom), 133.0 (C=), 148.5 (C-4), 164.1, 164.4 (C-2 and C-5), 203.7 (CO) ppm. *m/z*: 229 (M^+).

*4-(1-Methyl-2-oxo-butylidene)-2-phenyl-4H-oxazol-5-one (**1b**):* Total yield: 25 % (*Z*/*E*: 4:1). (*Z*)-**1b**: M.p.: 101-102 °C, (CH_2Cl_2/*n*-pentane). IR (nujol): 1795 (CO lactone), 1760 (CO ketone), 1660 (C=N) cm^{-1}. ^1H NMR: 1.21 (t, J = 7.3 Hz, 3 H, *Me*CH_2), 2.45 (s, 3 H, Me), 3.14 (q, J = 7.3 Hz, 2 H, CH_2), 7.52-8.10 (m, 5 H, Aryl-H) ppm. ^{13}C NMR: 8.4 (*Me*CH_2), 14.6 (*Me*C=), 37.3 (CH_2), 125.0-134.1 (C arom), 134.9 (C=), 145.1 (C-4), 162.5 (C-2), 166.5 (C-5), 205.4 (CO) ppm. (*E*)-**1b**: M.p.: 67-68 °C, (CH_2Cl_2/*n*-pentane). IR (nujol): 1795 (CO lactone), 1760 (CO ketone), 1655 (C=N) cm^{-1}. ^1H NMR: 1.22 (t, J = 7.1 Hz, 3 H, *Me*CH_2), 2.38 (s, 3 H, Me), 2.79 (q, J = 7.1 Hz, 2 H, CH_2), 7.40-8.10 (m, 5 H, Aryl-H) ppm.

4-(1-Ethyl-2-oxo-butylidene)-2-phenyl-4H-oxazol-5-one (1c): Total yield: 40 % (*Z*/*E*: 2:1). (*Z*)-**1c**: M.p.: 61-62 °C, (CH_2Cl_2/*i*-Pr_2O). IR (nujol): 1795 (CO lactone), 1750 (CO ketone), 1650 (C=N) cm^{-1}. ^1H NMR: 1.14 (t, *J* = 7.6 Hz, 3 H, *Me*CH_2), 1.21 (t, *J* = 7.2 Hz, 3 H, *Me*CH_2CO), 2.99 (q, *J* = 7.6 Hz, 2 H, Me*CH_2*), 3.07 (q, *J* = 7.2 Hz, 2 H, CH_2CO), 7.51-8.10 (m, 5 H, Aryl-H) ppm. (*E*)-**1c**: M.p.: 76-77 °C, (CH_2Cl_2/*n*-pentane). IR (nujol): 1790 (CO lactone), 1750 (CO ketone), 1650 (C=N) cm^{-1}. ^1H NMR: 1.21 (t, *J* = 7.7 Hz, 3 H, *Me*CH_2), 1.22 (t, *J* = 7.0 Hz, 3 H, *Me*CH_2CO), 2.76 (q, *J* = 7.0 Hz, 2 H, CH_2CO), 2.85 (q, *J* = 7.7 Hz, 2 H, Me*CH_2*), 7.51-8.10 (m, 5 H, Aryl-H) ppm.

4-(1-Methyl-2-oxo-2-phenyl-ethylidene)-2-phenyl-4H-oxazol-5-one (1d): Total yield: 86 % (*Z*/*E*: 8:1). (*Z*)-**1d**: M.p.: 135-136 °C, (CH_2Cl_2/*i*-Pr_2O). IR (nujol): 1795 (CO lattone), 1750 (CO ketone), 1650 (C=N) cm^{-1}. ^1H NMR: 2.60 (s, 3 H, Me), 7.30-7.90 (m, 10 H, Aryl-H) ppm. (*E*)-**1d**: M.p.: 165-167 °C, (CH_2Cl_2/*i*-Pr_2O). IR (nujol): 1795 (CO lactone), 1745 (CO ketone), 1650 (C=N) cm^{-1}. ^1H NMR: 2.54 (s, 3 H, Me), 7.46-8.14 (m, 10 H, Aryl-H) ppm.

*Photochemical Isomerization of Oxazolones (Z)-**1a-c** to (E)-**1a-c**. General Procedure.* A solution of oxazolone (*Z*)-**1** (1 mmol) in acetone (5 mL) was irradiated with a pyrex filtered light from an high pressure Hg lamp (HPK-125 W Philips). The conversion of isomer *Z* to isomer *E* was complete (**1a**: 9 h, **1b**: 1.30 h, **1c**: 8 h) and the product (*E*)-**1** was used without further purification.

*General Procedure for the Preparation of N-(4-Alkyl-5-alkylidene-2-oxo-2,5-dihydro-furan-3-yl)-benzamides(**2a-c**).* Azlactone (*E*)-**1** (1 mmol) was dissolved in anhydrous $CHCl_3$ (15 mL) saturated with gaseous HBr. The solution was stirred under nitrogen at room temperature for **1a,b**, and at reflux for **1c**, until the starting material disappeared (0.30-4 h). The solvent was eliminated and the crude reaction mixture was recrystallized from CH_2Cl_2/Et_2O.

*N-(4-Methyl-5-methylene-2-oxo-2,5-dihydro-furan-3-yl)-benzamide (**2a**):* Yield: 54 %. M.p.: 104-105 °C. IR (nujol): 3380 (NH), 1770 (CO), 1630 (CONH) cm^{-1}. ^1H NMR: 2.30 (s, 3 H, Me), 5.04, 5.20 (AB system, *J* = 3.0 Hz, 2 H, CH_2), 7.46-7.90 (m, 5 H, Aryl-H), 8.20 (s, 1 H, NH, exchangeable) ppm.

*(Z)-N-(5-Ethylidene-4-methyl-2-oxo-2,5-dihydro-furan-3-yl)-benzamide (**2b**):* Yield: 66 %. M.p.: 185-186 °C. IR (nujol): 3400 (NH), 1770 (CO), 1640 (CONH) cm^{-1}. ^1H NMR: 1.98 (d, *J* = 7.4 Hz, 3 H, *Me*CH), 2.26 (s, 3 H, Me-4), 5.49 (q, *J* = 7.4 Hz, 1 H, CH), 7.45-7.92 (m, 5 H, Aryl-H), 7.74 (s, 1 H, NH, exchangeable) ppm. ^{13}C NMR: 12.1, 12.2 (Me), 108.7 (CH), 122.7 (C-4), 128.0-133.0, 133.4 (C arom), 137.4 (C-3) 150.1 (CONH), 165.5 (C-5), 167.5 (C-2) ppm.

*(Z)-N-(4-Ethyl-5-ethylidene-2-oxo-2,5-dihydro-furan-3-yl)-benzamide (**2c**):* Yield: 77 %. M.p.: 133-134 °C. IR (nujol): 3300 (NH), 1770 (CO), 1630 (CONH) cm^{-1}. ^1H NMR: 1.2 (t, *J* = 7.7 Hz, 3 H, *Me*CH_2), 1.98 (d, *J* = 7.5 Hz, 3 H, *Me*CH), 2.76 (q, *J* = 7.7 Hz, 2 H, CH_2), 5.52 (q, *J* = 7.5 Hz, 1 H, CH), 7.44-7.91 (m, 5 H, Aryl-H), 7.74 (s, 1 H, NH, exchangeable) ppm.

Reaction of Oxazolone (E)-1a in Acetic Acid: Azlactone *E*-**1a** (200 mg, 0.87 mmol) was dissolved in acetic acid (5 mL) and heated at reflux under nitrogen for 40 min. After cooling, the solvent was evaporated and the crude reaction mixture was chromatographed on silica gel column (*n*-pentane/CH_2Cl_2, 1:0 to 0:1) affording two fractions containing **2a** (36 mg, 0.15 mmol, 18 %) and **5a** (160 mg, 0.55 mmol, 64 %), respectively.

4-Benzoylamino-2,3-dimethyl-5-oxo-2,5-dihydro-furan-2-yl acetate (5a): M.p.: 99-100 °C. IR (nujol): 3300 (NH), 1760 (CO), 1670 (CONH) cm^{-1}. ^1H NMR: 1.77 (s, 3 H, Me-2), 2.04, 2.14 (two s, 3 + 3 H, Me-3 and MeCO), 7.48-8.15 (m, 6 H, Aryl-H and NH, exchangeable) ppm. ^{13}C NMR: 13.5 (Me-3), 22.1, 24.2 (Me-2 and *Me*CO), 106.5 (C-3), 123.4, 128.0-133.1 (C arom), 133.4 (C-4), 144.1 (C-2), 165.4 (CONH), 168.0, 168.6 (C-5, Me*C*O) ppm. *m/z* 289 (M^+).

Reaction of Oxazolone E-1b in Acetic Acid: Compound *E*-**1b** (122 mg, 0.5 mmol) was dissolved in acetic acid (3 mL) and heated at reflux under nitrogen for 3.30 h. After cooling, the solvent was evaporated and the crude reaction mixture was crystallized from CH_2Cl_2/Et_2O giving pure **2b** (30 mg, 0.12 mmol, 25 %). The mother liquors were chromatographed on a silica gel column (cyclohexane/AcOEt, 1:0 to 0:1) affording **5b** which was recrystallized from CH_2Cl_2/*i*-Pr_2O (75 mg, 0.24 mmol, 49 %).

4-Benzoylamino-2-ethyl-3-methyl-5-oxo-2,5-dihydro-furan-2-yl acetate (5b): M.p.: 176-177 °C. IR (nujol): 3500 (NH), 1760 (CO), 1660 (CONH) cm^{-1}. ^1H NMR: 0.94 (t, J = 7.4 Hz, 3 H, *Me*CH_2), 1.80-1.98 (m, 2 H, CH_2), 2.07, 2.10 (two s, 3 + 3 H, Me-3 and MeCO), 7.42-7.89 (m, 5 H, Aryl-H), 8.11 (s, 1 H, NH exchangeable) ppm. ^{13}C NMR: 6.5 (*Me*CH_2), 12.8 (Me-3), 21.7 (*Me*CO), 29.2 (CH_2), 108.2 (C-3), 123.8, 127.6-133.7 (C arom), 132.3 (C-4), 144.5 (C-2), 165.1 (CONH), 168.4, 171.1 (C-5, Me*C*O) ppm.

Reaction of Oxazolone E-1c in Acetic Acid: Compound *E*-**1c** (257 mg, 1 mmol) was dissolved in acetic acid (5 mL) and heated at reflux under nitrogen for 2 h. After cooling, the solvent was evaporated and the reaction mixture was chromatographed on a silica gel column (*n*-pentane/CH_2Cl_2, 1:0 to 0:1) affording three fractions: pure **2c** (61 mg, 0.24 mmol, 24 %), a mixture of **2c** and **5c** (54 mg) and acetate **5c** (70 mg, 0.22 mmol, 22 %) which was recrystallized from Et_2O/*n*-pentane.

4-Benzoylamino-2,3-diethyl-5-oxo-2,5-dihydro-furan-2-yl acetate (5c): M.p.: 106-107 °C. IR (nujol): 3500 (NH), 1760 (CO), 1660 (CONH) cm^{-1}. ^1H NMR: 0.95 (t, J = 7.4 Hz, 3 H, *Me*CH_2-2), 1.09 (t, J = 7.7 Hz, 3 H, *Me*CH_2-3), 1.80-2.48, 2.70-2.91 (m, 4 H, CH_2), 2.07 (s, 3 H, MeCO), 7.42-7.90 (m, 5 H, Aryl-H), 8.11 (s, 1 H, NH, exchangeable) ppm.

Reaction of Oxazolone E-1d in Acetic Acid: Compound *E*-**1d** (140 mg, 0.48 mmol) was dissolved in acetic acid (6 mL) and heated at reflux under nitrogen for 8 h. After cooling, the solvent was evaporated and the reaction mixture was chromatographed on a silica gel column (*n*-pentane/CH_2Cl_2, 1:0 to 0:1) affording **5e** which was recrystallized from CH_2Cl_2/*i*-Pr_2O (33 mg, 0.09 mmol, 19 %) as the first fraction and hemiacetal **6** as the second one (55 mg, 0.18 mmol, 38 %) which was recrystallized from CH_2Cl_2/*i*-Pr_2O.

4-Benzoylamino-3-methyl-5-oxo-2-phenyl-2,5-dihydro-furan-2-yl acetate (5e): M.p.: 126-127 °C. IR

(nujol): 3300 (NH), 1760 (CO), 1670 (CONH) cm^{-1}. ^1H NMR: 2.09, 2.23 (two s, 3 + 3 H, Me-3 and MeCO), 7.40-7.90 (m, 11 H, Aryl-H and NH, exchangeable) ppm.

*N-(5-Hydroxy-3-methyl-5-oxo-2-phenyl-2,5-dihydro-furan-2-yl)-benzamide (**6**):* M.p.: 185-186 °C. IR (nujol): 3400-3100 (NH and OH), 1750 (CO), 1650 (CONH) cm^{-1}. ^1H NMR: 2.40 (s, 3 H, Me-3), 5.10 (s, 1 H, OH, exchangeable), 7.40-7.90 (m, 10 H, Aryl-H), 7.8 (s, 1 H, NH, exchangeable) ppm.

*Reaction of Oxazolone (E)-**1a** in Propionic Acid*: Compound (*E*)-**1a** (229 mg, 1 mmol) was dissolved in propionic acid (5 mL) and heated at reflux under nitrogen for 30 min. After cooling, the reaction mixture was treated with a solution of $NaHCO_3$ until neutral, extracted with CH_2Cl_2 (2 x 10 mL) and dried over Na_2SO_4. The crude reaction mixture was recrystallized from CH_2Cl_2/Et_2O giving pure **2a** (50 mg, 22 %). The mother liquor was chromatographed on a silica gel column (*n*-pentane/CH_2Cl_2, 1:0 to 0:1) giving **5d** (114 mg, 0.38 mmol, 38 %).

*4-Benzoylamino-2,3-dimethyl-5-oxo-2,5-dihydro-furan-2-yl propionate (**5d**):* IR (nujol): 3300 (NH), 1760 (CO), 1670 (CONH) cm^{-1}. ^1H NMR: 1.10 (t, J = 7.6 Hz, 3 H, *Me*CH_2), 1.77 (s, 2 H, Me-2), 2.15 (s, 3 H, Me-3), 2.34 (q, J = 7.6 Hz, 2 H, CH_2), 7.60-8.06 (m, 5 H, Aryl-H), 8.10 (s, 1 H, NH, exchangeable) ppm.

*Reaction of Oxazolones(Z)-**1a,b** with DBU. General Procedure.* DBU (167 mg, 1.1 mmol) in CH_2Cl_2 (3 mL) was dropped during 15 min into a stirred solution of azlactone (*Z*)-**1** (1.1 mmol) in CH_2Cl_2 (10 mL). The yellow solution turned red and the starting material disappeared. The organic layer was washed with HCl (10 mL, 10 %), H_2O (10 mL) and dried over Na_2SO_4. The solvent was concentrated and after addition of *i*-Pr_2O the yellow solid **8** was separated. The mother liquors were chromatographed on a silica gel column (*n*-pentane/CH_2Cl_2, 1:0 to 0:1) affording a further crop of **8**.

*(Z)-N-[5-Acetyl-2,5-dimethyl-3-(5-oxo-2-phenyl-oxazol-4-ylidene)-cyclopent-1-enyl]-benzamide (**8a**):* Total yield: 81 %. M. p.: 239-240 °C. IR (nujol): 3250 (NH), 1750, (CO lactone), 1700 (CO), 1660 (CONH) cm^{-1}. ^1H NMR: 1.59, (s, 3 H, Me-5), 2.27 (s, 3 H, Me-2), 2.45 (s, 3 H, *Me*CO), 3.25 (AB system, J = 19.7 Hz, 2 H, C-4), 7.40-8.10 (m, 10 H, Aryl-H), 8.35 (s, 1 H, NH, exchangeable) ppm. ^{13}C NMR: 12.5 (Me-2), 23.1 (Me-5), 26.2 (*Me*CO), 42.1 (C-4), 59.4 (C-5), 126.5-133.0 (C arom, C-1, C-2 and C-3), 154.3 (C_{ox}-4), 156.6 (CONH), 163.6 (C_{ox}-2), 167.3 (C_{ox}-5), 207.1 (CO ketone) ppm. *m/z* 414 (M^+).

*(Z)-N-[2-Ethyl-5-methyl-5-propionyl-3-(5-oxo-2-phenyl-oxazol-4-ylidene)-cyclopent-1-enyl]-benzamide (**8b**):* Total yield: 70 %). M. p.:228-229 °C. IR (nujol): 3250 (NH), 1770, (CO lactone), 1700 (CO), 1660 (CONH) cm^{-1}. ^1H NMR: 1.1 (t, J = 7.1 Hz, 3 H, *Me*CH_2CO), 1.30 (t, J = 7.4 Hz, 3 H, *Me*CH_2-2), 2.40-2.52, 2.62-2.77 (two m, 2 H, CH_2CO), 2.96 (q, J = 7.4 Hz, 2 H, CH_2-2), 3.20 (AB system, J = 19.7 Hz, 2 H, C-4), 7.48-8.07 (m, 10 H, Aryl-H), 8.25 (s, 1 H, NH, exchangeable) ppm. ^{13}C NMR: 8.4 (*Me*CH_2CO), 13.2 (*Me*CH_2-2), 19.6 (C-2), 23.5 (Me-5), 31.9 (*C*H_2CO), 43.4 (C-4), 59.7 (C-5), 124.4-133.8 (C arom, C-1, C-2 and C-3), 154.7 (C_{ox}-4), 157.3 (CONH), 164.1 (C_{ox}-2), 167.5 (C_{ox}-5), 209.1 (CO ketone) ppm.

*Reaction of Oxazolone (E)-**1c** with DBU: Synthesis of (Z)-N-(4-Ethyl-5-ethylidene-2-oxo-2,5-dihydro-*

furan-3-yl)-benzamide (2c). DBU (118 mg, 0.78 mmol) in CH_2Cl_2 (3 mL) was dropped in 15 min into a solution of azlactone (*E*)-**1c** (200 mg, 0.78 mmol) in boiling CH_2Cl_2 (8 mL). The yellow solution turned red and after 1.30 h the starting material disappeared. After cooling, the organic layer was washed with HCl (10 mL, 10%), H_2O (10 mL) and dried over Na_2SO_4. After solvent evaporation the crude reaction mixture was chromatographed on a silica gel column (cyclohexane/AcOEt, 7:3) affording pure **2c** (93 mg, 0.36 mmol, 47 %).

Reaction of Oxazolone (E)-1c with DBU and benzyl bromide: DBU (152 mg, 1 mmol) in CH_2Cl_2 (3 mL) was dropped during 15 min into a solution of azlactone (*E*)-**1c** (257 mg, 1 mmol) and benzyl bromide (194 mg, 1.1 mmol) in CH_2Cl_2 (8 mL) at room temperature. The yellow solution turned red and the starting material disappeared. The organic layer was washed with HCl (10 mL, 10 %), H_2O (10 mL) and dried over Na_2SO_4. After solvent evaporation the crude reaction mixture was chromatographed on a silica gel column (*n*-pentane/CH_2Cl_2, 1:0 to 0:1) affording pure **2d** (180 mg, 0.52 mmol, 52 %) as a mixture of *Z* and *E* isomers.

(Z)- and (E)-N-[4-(1-Methyl-2-phenyl-ethyl)-5-ethylidene-2-oxo-2,5-dihydro-furan-3-yl]-benzamide (2d). IR (nujol): 3330 (NH), 1770 (CO), 1640 (CONH) cm^{-1}. (*E*)-**2d**: ^1H NMR: 1.59 (t, J = 7.3 Hz, 3 H, *Me*CH_2), 1.67 (d, J = 7.7 Hz, 3 H, *Me*CH-4), 3.13, 3.28, 4.89-5.17 (AB system, J_{AB} = 12.8 Hz, J_{AX} = 15.6 Hz, J_{BX} = 19.4 Hz, 3 H, Ph*CH*$_2$ and CH-4), 5.42 (q, J = 7.3 Hz, 1 H, CH=), 6.85 (s, 1 H, NH, exchangeable), 7.10-7.75 (m, 5 H, Aryl-H) ppm. (*Z*)-**2d**: ^1H NMR: 1.71 (t, J = 7.3 Hz, 3 H, *Me*CH_2), 1.82 (d, J = 7.7 Hz, 3 H, *Me*CH-4), 3.13, 3.28, 4.89-5.17 (AB system, J_{AB} = 12.8 Hz, J_{AX} = 15.6 Hz, J_{BX} = 19.4 Hz, 3 H, Ph*CH*$_2$ and CH-4), 6.00 (q, J = 7.3 Hz, 1 H, CH=), 6.95 (s, 1 H, NH, exchangeable), 7.10-7.87 (m, 5 H, Aryl-H) ppm.

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16. The structure of compound **8a** was confirmed by X-Ray analysis.

17. The same reaction was also performed at room temperature starting from (*Z*)-**1c**. In this case a mixture of products was obtained from which traces of the isomer (*E*)-**2c** was isolated and characterized by ^{1}H NMR: 1.19 (t, J = 7.2 Hz, 3 H, *Me*CH_2), 1.55 (d, J = 6.6 Hz, 3 H, *Me*CH), 2.63 (q, J = 7.2 Hz, 2 H, CH_2), 5.38 (q, J = 6.6 Hz, 2 H, CH), 7.47-7.91 (m, 5 H; Aryl-H), 8.21 (s, 1 H, NH, exchangeable).

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