The Cycloacylation - 1,3-Acylrearrangement Sequence as Tool for Highly Substituted Pyrrolones

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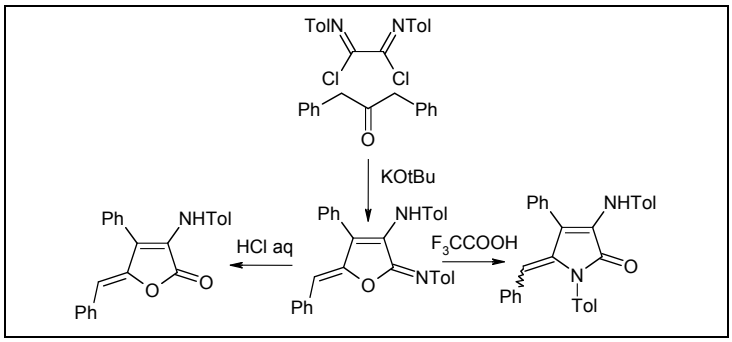

The cyclization reactions between *bis*-imidoylchlorides **1** and ketones, which possess different CH-acidity, were investigated. Diphenylacetone **2** reacts under mild conditions *via* C,O-cyclization of the preformed enolate to yield the iminofurane derivative **3**. Upon treatment with trifluoroacetic acid, the latter can be rearranged quantitatively into the pyrrolone **5**. In contrast, 1,3-acetonedicarboxylate **9** and cyclohexanone **12** immediately lead to highly substituted pyrrolones **11** and **14**. Obviously, the primarily formed cyclization products undergo a very fast 1,3-acyl rearrangement (Dimroth-/Mumm-Rearrangement). The structures of the maleiimide **11** and the indolone **14** were determined by single crystal X-ray structure analysis. Due to its amino/imino substructure, compound **3** is an efficient ligand for metal complexation reactions, exemplified by the synthesis of two different Zn-complexes **7** and **8**.

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INTRODUCTION

During recent years derivatives of γ-butyrolactone have increased in interest and significance, due to the fact that this cyclic template is present in many highly bioactive molecules and especially in sesquiterpene lactones of type **a** (Figure 1) [1]. The α-hydroxy- γ-lactones and their α-amino analogs represent structural units of many biologically active materials and natural products [1b] and in addition, several of their unsaturated derivatives are versatile building blocks for the synthesis of natural products [1c]. For example, sotolone **b** is used as a food additive as well as in tobacco industries as an important aroma. Compound **c** is believed to be its biological precursor [2]. Substituted pyrrolidones, especially 5-alkylidene-2,5-dihydropyrrol-2-ones which occur in a variety of natural products such as pukeleimides A-G (type **d** Figure 1) [3], are of considerable pharmacological relevance [3a]. The simple replacement of oxo- and hydroxyl groups in derivatives **e** by imino- and amino groups should lead to α amino-γ imino-lactones **f** (Figure 1) for which a high biological activity can also be expected. Comparable to type **e** they should easily be transformed to yield novel products with interesting properties. Furthermore, they might undergo a 1,3 (O→N) migration reaction (Dimroth-Rearrangement) [4] to finally give α-amino-pyrrolidones of type **g**. Only few syntheses for derivatives of type **f** are described [5], for example the gallium(III) chloride catalyzed insertion of isocyanides into epoxides [2a].

During the course of our past work, we demonstrated that *bis*-arylimidoyl chlorides **1** [6] are excellent (and selective) bis-electrophiles that can be employed in a wide range as C_2-building blocks for heterocyclic as well as for carbocyclic compounds [7]. Due to their 1,4-diazabutadiene substructures, the cyclization products offer good requirements for the formation of metal complexes [8]. Our aim was therefore to develop a short and new synthetic route to derivatives of type **f** by cycloacylation reactions of ketones with *bis*-imidoyl-chlorides derived from oxalic acid **1** [6].

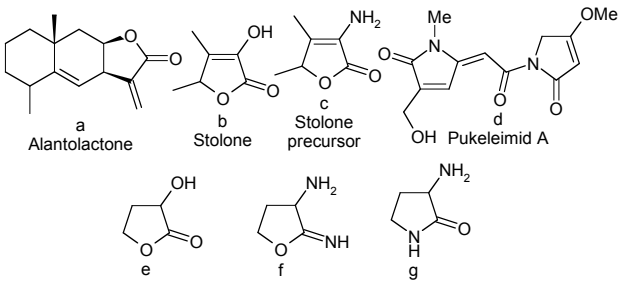


Figure 1

RESULTS AND DISCUSSION

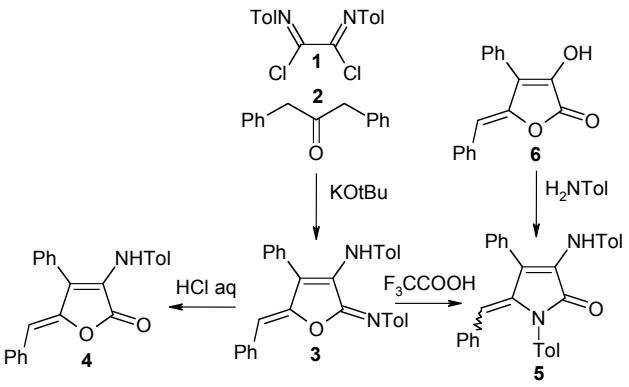
Diphenylacetone **2** reacts with the *bis*-electrophile **1** under quite mild conditions (THF in the presence of KO-*t*Bu at -78°C) forming a yellow crystalline product in a satisfactory yield. Elemental analysis and MS data confirmed the presence of a 1:1 cyclisation product. ^{1}H and ^{13}C NMR spectra with the presence of double sets of signals suggest an unsymmetrical structure. NMR correlation spectroscopy proved that the cyclisation product displays the structure of the 3-amino-2-imino-γ-lactone **3** (Scheme 1). A single crystal X-ray analysis of **3** confirmed this molecular structure (Figure 2). Compound **3** is a monomer in the solid state with the bond lengths and angles being in the expected range (Table 1). According to our expectations, **3** was formed *via* an O,C-cycloacylation reaction of the preformed enolate of **2**. The cyclisation reaction proceeds in a highly stereoselective manner, whereby only the (Z)-isomer is formed. The furan derivative **3** is soluble even in nonpolar solvents forming dark yellow solutions. In addition, **3** show an amphoteric character upon treatment with acids (HCl) and bases (KO-*t*Bu, *n*-BuLi). In each case, the color changes reversibly to deep red under the formation of cations/anions. Derivative **3** is electrochemically active and can be oxidized reversibly. Employing square wave measurements, two peaks at 1.162 V and at 1.538 V can be ascribed to two different electron transfer steps. The quasi-reversibility of the oxidation was confirmed by cyclovoltammetric measurements $\Delta E^{1}_{RED,OX}$ = 0.081 V and $\Delta E^{2}_{RED,OX}$ = 0.097 V and the semiquinone formation constant is K_{SEM} = 1.2*10^{6}.

Thereafter, we studied various synthetic transformations of the γ-imino lactone **3**. Imino groups can often easily be hydrolysed yielding the parent carbonyl compounds. In a mixture of THF/aqueous hydrochloric acid, the lactone **3** easily undergoes hydrolysis. In a straight forward reaction only the imino group is converted to an oxo group giving 3-amino-γ-lactone **4** in high yield. In compound **4** the (Z)-configuration is maintained showing almost the same properties (solubility, amphotheric behaviour) as derivative **3**.

In the past we often employed the Dimroth rearrangement of cyclic isothiourea substructures in order to synthesize new thioxo derivatives [10]. This valuable 1,3 (S→N)-migration reaction can be induced by acids as well as by bases, and in addition, is not only restricted to S,N-compounds. Accordingly, the furan derivative **3** was converted by treatment with anhydrous trifluoroacetic acid *via* 1,3 (O→N)-rearrangement into alkylidene-2,5-dihydropyrrol-2-one **5**. Compound **5** was isolated in the (*E*)-configuration in high yield as pale yellow crystals. In cold DMSO-d$_6$ it was possible to measure the NMR-spectra of the (*E*)-isomer. Upon irradiation by sunlight or by heating the pure solution of the (*E*)-isomer, an isomerisation process takes place and a (*E*/*Z*)-isomer mixture is formed (^{1}H NMR, E:Z = 2:1). In chloroform immediately the isomerisation take place. The yellow solution of compound **5** ($CHCl_3$: λ_{max}: 380 nm, lg ε: 4.2) display a yellow fluorescence with a large stokes shift ($CHCl_3$: λ_{Em}: 577nm).

We also tested an independent synthetic entry to compounds **3**, **4** and **5** *via* the aminolysis reaction of 3-hydroxy-4-phenyl-5-phenylmethylene-2(5*H*)-furanone **6** [9] with *p*-toluidine. Despite a broad variation of the reaction conditions, only the decomposition of the heterocycle to ketone **2** and the corresponding oxanilide was observed, this is most likely due to the retro-aldol reaction. Only when acetic acid was used as solvent the formation of pyrrolone **5** was observed. The two samples of **5** show identical properties.

Scheme 1



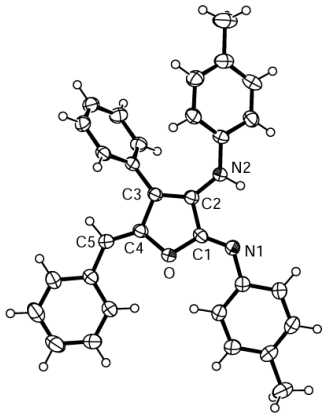


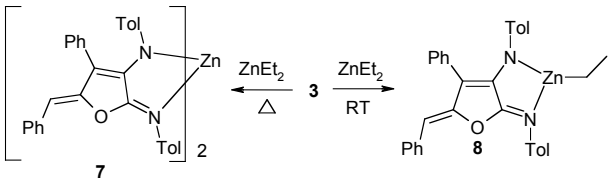
Figure 2. ORTEP-plot (50% probability ellipsoids) of the solid state molecular structure of **3**.

Another interesting feature of heterocycles **3** is their vicinal amino/imino substructure, which has been used recently in our group for the preparation of redox-active group VIII metal complexes [8a]. Upon addition of $ZnEt_2$ to a solution of **3** (two parts of **3**: one part of $ZnEt_2$) and heating of the resulting mixture, the complex **7** was

isolated. Using a 1:1 stoichiometry at ambient temperature, the coordinative unsaturated zinc complex **8** was isolated in the shape of red crystals. The temperature depending exchange of alkyl-groups in similar zinc complexes was reported in the aminotropone series. These complexes proved to be efficient and selective pre-catalysts for hydroamination reactions [11].

The solid-state structure of **8** was established by single-crystal X-ray diffraction. Compound **8** is a monomer in the solid state, and therefore the zinc atom has a trigonal-planar coordination sphere (Figure 3). The bond lengths and angles at the zinc centre are in the expected range. The changes of the bond lengths and angles between ligand **3** and complex **8** are rather small (Table 1). In contrast to the pyrophoric starting material, complex **8** is relatively stable towards moisture and air. The reasons for this stability of compounds of the general formula [LZnEt] (L = ligand) was described earlier [12].

Scheme 2



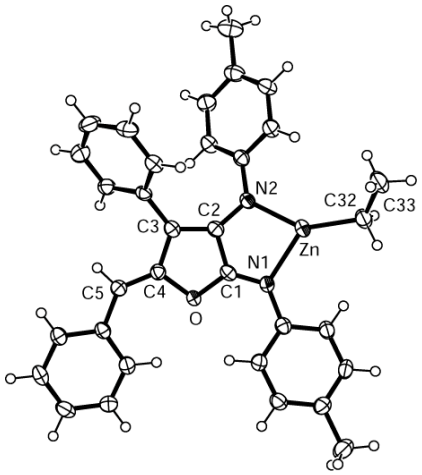


Figure 3. ORTEP-plot (50% probability ellipsoids) of the solid state molecular structure of **8**.

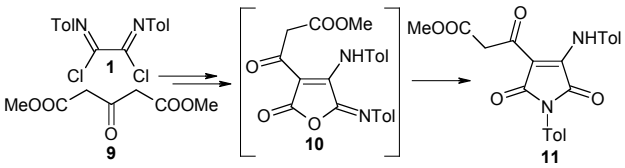
The ^{1}H and ^{13}C NMR spectra of complexes **7** and **8** show the expected sets of signals for the ligands. Compared to the starting material $ZnEt_2$, the signals of the Zn-Et group of **8** (^{1}H: δ = 0.40, 1.28; ^{13}C: δ = 6.1, 13.6 ppm) are shifted towards higher field. The signals of the benzyl-C*H* and the two methyl groups in **7** and **8** were detected as singlets and their chemical shifts are in the range of those for ligand **3**. This fact is somewhat surprising with respect to the different coordination spheres of the central zinc atoms. The comparison of the bond lengths and NMR signals in the furan **3** with those in complex **8** suggests that part of the negative charge is stabilized in the furane ring.

Table 1. selected bond length for **3** and **8**

	Ligand **3** d in Å	Complex **8** d in Å
N2-C2	1.362(4)	1.354(4)
N1-C1	1.270(4)	1.282(4)
O-C1	1.386(3)	1.365(3)
O-C4	1.400(3)	1.415(4)
C1-C2	1.471(4)	1.456(4)
C2-C3	1.368(4)	1.382(4)
C3-C4	1.465(4)	1.445(4)
C4-C5	1.339(4)	1.347(4)
Zn-C32		1.952(3)
Zn-N1		2.115(2)
Zn-N2		1.953(3)

Analogously, dimethyl 1,3-acetonedicarboxylate **9** reacts with the *bis*-electrophile **1** under the similar mild conditions giving a yellow crystalline product in good yield. Elemental analysis, MS data and NMR spectra confirmed the presence of a formal 1:1 cyclisation product. However, also the elimination of a methyl group occurred. The X-ray structure analysis revealed that in the course of a cascade reaction, the maleinimide **11** was formed (Scheme 3). The bond lengths and angles in compound **11**, which exist as a monomer in the solid state are in the expected range (Figure 4). Obviously, only one CH-acidic methylene group of **9** was integrated into the heterocyclic system of **11** and we propose the following mechanism. In the first step, the ester-enolate of **9** is acylated by **1** to form an open-chained intermediate which then attacks the ester group with its second acyl unit. This O-acylation leads to the lactone **10** which finally was converted *via* 1,3 (O→N)-migration (Mumm-Rearrangement) [13] into the maleinimide **11** (Scheme 3).

Scheme 3



Encouraged by these results, less CH acidic carbonyl systems were integrated in these cyclization investigations. Cyclohexanone **12** reacted smoothly with **1** in the presence of KO*t*Bu forming a crystalline product in good yield. Elemental analysis and MS data were in agreement with the structure of the 1:1 cyclization product. The ^{1}H and ^{13}C NMR spectra indicated the presence of a double bond in the cyclohexane ring system. The result of the X-ray analysis of pale yellow single crystals of **14** is shown in Figure 5. Hence, the cycloacylation product has the structure of a 4,5,6-

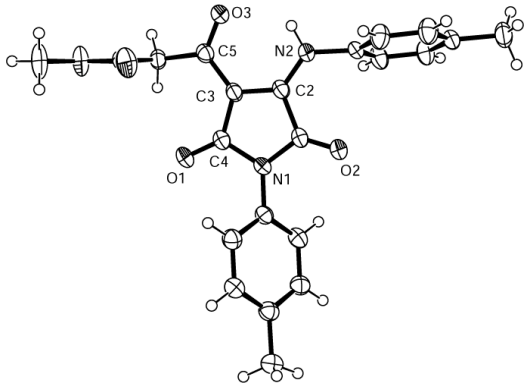
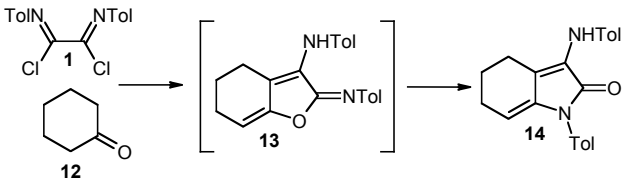


Figure 4. ORTEP-plot (50% probability ellipsoids) of the solid state molecular structure of **11**, selected bond lengths in Å: O1-C4 1.212(3), O2-C1 1.205(4), O3-C5 1.240(3), N1-C1 1.387(3), N1-C4 1.429(4), N2-C2 1.314(4), C1-C2 1.514(4), C2-C3 1.389(4), C3-C4 1.450(4), C3-C5 1.439(4).

trihydro-indolone. This cyclic hydro-isatine derivative **14** is a dimer in the solid state in which the two units are connected *via* NH-O bridges. The bond lengths and angles are in the expected range (Figure 5).

The reaction between cyclopentanone and **1** under similar conditions resulted in a complex reaction mixture. As in the previously reported cases, the enolate of **12** reacts with **1** to give the 2-imino furan derivative (imino-γ-lactone) **13** which could be neither isolated nor detected. In a fast rearrangement sequence **13** was then transformed into indolone **14** (Scheme 4). The synthesis of **14** and of its phenyl analogue was described earlier by a two-step protocol [14]. Previously, the reaction between **1** and 1,3-dicarbonyl compounds in the presence of LDA has been employed for the preparation of 5-alkylidene-2,5-dihydropyrrol-2-ones [7b]. Accordingly to our observations these enolates reacted with **1** to give 2-imino furan derivatives (imino-γ-lactones) which fast rearrange into the pyrrolones. We could substitute the base LDA by KO-*t*Bu which is easier to handle and needs no special reaction techniques.

Scheme 4



It is noteworthy that not only the *bis*-tolylimidoylchloride **1** but also *bis*-imidoylchlorides, which possess other aryl moieties *e.g.* Ar = 4-BrC_6H_4, 3-$CF_3C_6H_4$ or 4-*tert*BuC_6H_4, can be employed as cyclization partners. Analogously, heterocycles of type **3-5**, **11** and **14** with the appropriate aryl substituents can be isolated as main products.

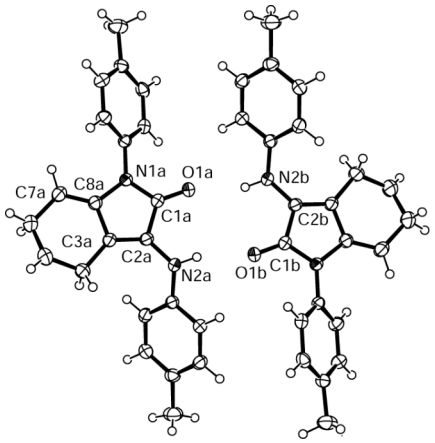


Figure 5. ORTEP-plot (50% probability ellipsoids) of the solid state molecular structure of **14**, selected bond length in □: N1-C1 1.380(2), N1-C8 1.421(3), N2-C2 1.380(3), C1-C2 1.479(3), C2-C3 1.354(3), C3-C8 1.457(3), C7-C8 1.334(3).

CONCLUSION

An short and efficient synthesis for highly substituted iminofuranes and pyrrolones based on the cyclisation reaction of different enolates with *bis*-imidoylchlorides **1** was developed. Whereas diphenylacetone **2** reacted to iminofurane **3** 1,3-acetonedicarboxylate **9** and cyclohexanone **12** immediately formed *via* subsequent 1,3-acyl-rearangment reactions the pyrrolones **11** and **14**. The proton induced Dimroth-Rearrangment of **3** quantitatively yields the pyrrolone **5**. Due to its vicinal amino-imino substructure derivative **3** proved to be an excellent chelating ligand, exemplified by the preparation of two Zn complexes. The solid state structures of the new products were determined by single crystal X-ray diffraction.

EXPERIMENTAL

General. The reagents described in the following section were purchased from commercial sources and were used directly unless otherwise stated in the text. The *bis*-imidoylchloride **1** [6] and lactone **6** [9] were synthesized according to literature procedures. All solvents were of reagent grade and were dried according to common practice and were distilled prior to use.

Reactions were monitored by TLC, carried out on 0.2 mm Merck silica gel plates (60 F_{254}). The ^1H and ^{13}C NMR spectra were recorded on Bruker AVANCE 250 and 400 spectrometers, shifts are relative to the signals of the solvent.

Melting points were measured with a Galen III apparatus (Boëtius system) and are uncorrected.

3-Tolylamino-4-phenyl-5-phenylmethylen-2(5*H*)-furan-tolylimine 3. The solution of 2.00 g (9.5 mmol) diphenylacetone **2** in 100 mL of dry THF was cooled down to -78 °C and 6.00 g (54 mmol) KO-*t*Bu was added. To the solution 4.60 g (15.1 mmol) *bis*-tolylimidoylchloride **1** was added. The deep red

reaction mixture was stirred at -30 °C for 30 minutes. The mixture was acidified by addition of HCl/isopropyl alcohol to pH 7. The mixture was concentrated *in vacuo* to dryness. The remaining solid was dissolved in $CHCl_3$/*n*-heptane and was dried over Na_2SO_4. Upon removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel ($CHCl_3$/*n*-heptane) and the crude product was purified by recrystallization from $CHCl_3$/*n*-heptane to yield **3** as yellow crystals.

Yellow crystals, yield: 1.83 g (43%), mp 146°C ($CHCl_3$/*n*-heptane). ^{1}H NMR (400MHz, DMSO-d_6): δ = 8.26 (s, 1H, NH), 7.58 (d, 2H, J = 8 Hz CH-Ph), 7.36 (d, 2H, J = 8 Hz CH-Tol), 7.28-7.18 (m, 10H, CH-Ar), 6.68 (d, 2H, J = 8 Hz CH-Tol), 6.62 (d, 2H, J = 8 Hz CH-Tol), 5.66 (s, 1H, CH-Benzal), 2.36 (s, 3H, CH-Tol), 2.08 (s, 3H, CH-Tol) ppm. (250MHz, THF-d_8): δ = 7.63-7.06 (m, 14H, CH-Ar), 6.68 (d, 2H, J = 8 Hz CH-Tol), 6.59 (d, 2H, J = 8 Hz CH-Tol), 5.69 (s, 1H, CH-Benzal), 2.37 (s, 3H, CH-Tol), 2.11 (s, 3H, CH-Tol) ppm. ^{13}C NMR (100MHz, DMSO-d_6): *δ* = 152.7 (C-1), 152.0 (C-2), 142.4, 137.0, 134.7, 134.0, 131.13, 131.10, 130.05, 129.4, 128.9, 128.5, 128.3, 128.05, 128.01, 127.7, 126.4, 123.4, 119.7, 116.7 (C-3), 101.2 (C-Benzal), 20.6, 20.2 ppm. MS(EI) *m/z*: 442 (60) [M^+], 365 (20), 191 (100), 91 (50) [$C_7H_7^+$]. Elemental analysis calculated for $C_{31}H_{26}N_2O$ (442.57) C 84.13, H 5.92, N 6.33; found C 83.83, H 5.95, N 6.32%. IR(ATR): ν_{max}/cm^{-1} 3331 (NH), 3022, 2916, 1667, 1610, 1590, 1530, 1442, 1105, 813, 750, 690. UV/VIS (CCl_3H): λ_{max} (lg ε) = 405 (4.41) nm.

3-Tolylamino-4-phenyl-5-phenylmethylen-2(5*H*)-furanone 4. The solution of 0.50 g (1.1 mmol) of **3** in 30 mL of THF was treated with 3 mL of hydrochloric acid and heated to 60°C. The reaction was monitored by TLC and when no starting material was detected (after 5 minutes) the reaction mixture was neutralised by addition of diluted sodium hydroxide solution and the mixture was then concentrated *in vacuo* to dryness. The remaining solid was dissolved in $CHCl_3$/*n*-heptane and was dried over Na_2SO_4. Upon removal of the solvent *in vacuo*, the crude product was purified by recrystallization from $CHCl_3$/*n*-heptane to yield **4** as yellow crystals.

Yellow crystals, yield: 0.34 g (87%), mp 202°C ($CHCl_3$/*n*-heptane). ^{1}H NMR (250MHz, DMSO-d_6): δ = 8.56 (s, 1H, NH), 7.67 (d, 2H, J = 8 Hz CH-Ph), 7.40-7.21 (m, 8H, CH-Ar), 6.72 (d, 2H, J = 8 Hz CH-Tol), 6.57 (d, 2H, J = 8 Hz CH-Tol), 5.86 (s, 1H, CH-Benzal), 2.09 (s, 3H, CH-Tol) ppm. ^{13}C NMR (63MHz, DMSO-d_6): *δ* = 165.7 (C-2), 148.0 (C-3), 137.2, 133.9, 130.2, 130.1, 129.4, 129.0, 128.6, 128.3, 128.2, 127.5, 126.3, 123.2, 119.1, 105.9 (C-Benzal), 20.2 ppm. MS(EI) *m/z*: 353 (100) [M^+], 324 (20), 191 (60), 91 (30) [$C_7H_7^+$]. Elemental analysis calculated for $C_{24}H_{19}NO_2$ (353.42) C 81.65, H 5.42, N 3.96; found C 81.51, H 5.39, N 3.89%. IR(ATR): ν_{max}/cm^{-1} 3333 (NH), 3037, 2916, 1745 (conjugated lactone C=O), 1620, 1591, 1528, 1255, 751, 693. UV/VIS (CCl_3H): λ_{max} (lg ε) = 394 (4.42) nm.

1-Tolyl-3-tolylamino-4-phenyl-5-phenylmethylene-2(5*H*)-pyrrolidone 5.

Method A. The solution of 0.50 g (1.1 mmol) **3** in 30 mL of dry THF was treated with a mixture consisting of 10 mL of trifluoroacetic acid and 0.2 mL of trifluoroacetic anhydride and then heated to 70°C. The reaction was monitored by TLC and when no starting material was detected (after 40 minutes) the reaction mixture was neutralised by addition of diluted sodium hydroxide solution and the mixture was concentrated *in vacuo* to dryness. The remaining solid was dissolved in $CHCl_3$/*n*-heptane and was dried over Na_2SO_4. Upon removal of the solvent *in vacuo*, the crude product was purified by recrystallization from $CHCl_3$/ *n*-heptane to yield **5** as pale yellow crystals, yield: 0.41 g (82%).

Method B. A mixture of 0.50 g (1.9 mmol) **6** and 0.50 g (4.7 mmol) *p*-toluidine in 5 mL of acetic acid was heated to 80°C for one day. Upon cooling the product crystallised. The crude product was colleted by filtration, was washed with diethyl ether and was purified by recrystallization from $CHCl_3$/*n*-heptane to yield **5** as pale yellow crystals, yield: 0.53 g (70%).

Pale yellow crystals, mp 226°C ($CHCl_3$/*n*-heptane). ^{1}H NMR ((E/Z)-mixer, 250MHz, $CDCl_3$): δ = 7.35-6.50 (m, 18H, CH-Ar), 6.24 + 6.23 (s, 1H, CH-Benzal), 2.45 + 2.22 + 2.18 + 2.14 (s, 6H, CH-Tol) ppm. ^{1}H NMR ((*E*)-isomer, 250MHz, DMSO-d_6): δ = 8.09 (s, 1H, NH), 7.26 (s, 5H, CH-Ph), 6.97-6.83 (m, 9H, CH-Ar), 6.67 (d, 2H, J = 8 Hz CH-Tol), 6.57 (d, 2H, J = 8 Hz CH-Tol), 6.08 (s, 1H, CH-Benzal), 2.15 (s, 3H, CH-Tol), 2.08 (s, 3H, CH-Tol) ppm. ^{13}C NMR ((*E*)-isomer, 63MHz, DMSO-d_6): *δ* = 167.4 (C-2), 138.5, 138.4, 136.0, 134.7, 134.1, 132.7, 130.1, 129.7, 129.6, 129.4, 128.9, 128.6, 128.5, 128.0, 127.4, 127.3, 126.4, 120.0, 119.3, 110.2(C-Benzal), 21.0, 20.7 ppm. MS(EI) *m/z*: 442 (100) [M^+], 191 (50), 91 (30) [$C_7H_7^+$]. Elemental analysis calculated for $C_{31}H_{26}N_2O$ (442.57) C 84.13, H 5.92, N 6.33; found C 83.70, H 5.98, N 6.27%. IR(ATR): ν_{max}/cm^{-1} 3298 (NH), 3058, 2915, 1692, 1620, 1596, 1534, 1411, 816, 695, 656. UV/VIS (CCl_3H): λ_{max} (lg ε) = 380 (4.22) nm.

Preparation of zinc complex 7. The solution of 0.50 g (1.1 mmol) of **3** in 10 mL of dry THF and 20 mL of dry *n*-heptane was treated at ambient temperature with 0.6 mL of a hexane solution of $ZnEt_2$ (1 *M*, 0.6 mmol). The mixture was stirred for 30 minutes at room temperature and then was heated briefly under reflux. The solvent was removed and the remaining orange solid was washed twice with dry *n*-pentane and dried *in vacuo*. Yield 0.46 g (89%).

^{1}H NMR (250MHz, Benzol-d_6): δ = 7.72-6.80 (m, 18H, CH-Ar), 5.94 (s, 1H, CH-Benzal), 2.07 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), ppm. ^{13}C NMR (63MHz, Benzol-d_6): δ = 165.5 (C-1), 155.1 (C-2), 145.2, 139.2, 138.6, 136.1, 135.6, 133.2, 130.0, 129.6, 128.9, 128.7, 128.5, 126.8, 126.3, 123.7, 122.2, 109.4, 102.9 (C-Benzal), 20.6, 20.5 ppm. MS (EI) *m/z*: 951 (4) + 950 (5) + 949 (7) + 948 (5) and 947 (8) [M + H^+], 442 (100) calculated and measured isotope patterns for $C_{62}H_{51}N_4O_2Zn^+$ are conform.

Preparation of zinc complex 8. The solution of 250 mg (0.56 mmol) of **3** in 5 mL of dry THF and 20 mL of dry *n*-heptane was treated at ambient temperature with 0.6 mL of a solution of $ZnEt_2$ in hexane (1 *M*, 0.6 mmol). The mixture was stirred for 30 minutes at room temperature and then was treated with 80 mL of dry *n*-heptane. The solution was cooled at –16°C over one month, yielding the zinc complex **8** as dark red crystals. Yield 201 mg (67%).

^{1}H NMR (250MHz, THF-d_8): δ = 7.30-7.05 (m, 14H, CH-Ar), 6.58-6.45 (m, 4H, CH-Tol), 5.78 (s, 1H, CH-Benzal), 2.39 (s, 3H, CH-Tol), 2.08 (s, 3H, CH-Tol), 1.28 (t, 3H, J = 8 Hz CH_3-Ethyl), 0.40 (q, 2H, J = 8 Hz CH_2-Ethyl) ppm. ^{13}C NMR (63MHz, THF-d_8): δ = 164.5 (C-1), 154.0 (C-2), 143.7, 138.0, 137.3, 135.1, 134.5, 131.9, 128.2, 127.6, 127.4, 127.1, 126.9, 126.4, 125.5, 125.1, 124.6, 123.1, 120.4, 108.9, 102.2 (C-Benzal), 20.2, 19.9, 13.6 (CH_3-Ethyl), 6.1 (CH_2-Ethyl) ppm.

Preparation of maleinimide 11. The solution of 2.00 g (11.5 mmol) ketone **9** in 100 mL of dry THF was cooled down

to -78 °C and 4.00 g (35.7 mmol) of KO-*t*Bu was added. To the solution 3.70 g (12.1 mmol) *bis*-tolylimidoylchloride **1** was added. The deep red reaction mixture was stirred at -30 °C for 30 minutes. The mixture was acidified by addition of hydrochloric acid to pH 7. Then the mixture was concentrated *in vacuo* to dryness. The remaining solid was dissolved in $CHCl_3$/*n*-heptane and was dried over Na_2SO_4. Upon removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel ($CHCl_3$/*n*-heptane) and the crude product was purified by recrystallization from $CHCl_3$/*n*-heptane to yield **11** as yellow crystals.

Yellow crystals, yield: 2.62 g (58%), mp 140°C ($CHCl_3$/*n*-heptane). ^{1}H NMR (250MHz, $CDCl_3$): δ = 9.30 (s, 1H, NH), 7.57-7.18 (m, 8H, CH-Tol), 4.05 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 2.38 (s, 3H, CH-Tol), 2.36 (s, 3H, CH-Tol) ppm. ^{13}C NMR (63MHz, $CDCl_3$): δ = 189.5 (C=O), 157.4, 152.7, 138.5, 138.2, 135.3, 133.7, 132.7, 129.8, 129.6, 126.3, 124.6, 119.8, 99.9, 52.3 (CH_3-ester), 46.6 (CH_2), 21.1, 21.0 ppm. MS(EI) *m/z*: 392 (80) [M^+], 318 (80), 216 (50), 158 (100), 107 (30), 91 (90) [$C_7H_7^+$]. Elemental analysis calculated for $C_{22}H_{20}N_2O_5$ (392.42) C 67.34, H 5.14, N 7.15; found C 67.47, H 5.53, N 7.17%. IR(ATR): ν_{max}/cm^{-1} 3184 (NH), 2956, 1714, 1638, 1593, 1511, 1358, 1155, 797. UV/VIS (CCl_3H): λ_{max} (lg ε) = 415 (3.73) nm.

1-Tolyl-3-tolylamino-4,5,6-trihydro-indolone 14. The solution of 1.00 g (10.2 mmol) cyclohexanone **12** in 100 mL of dry THF was cooled down to -78 °C and 3.80 g (40.0 mmol) of KO-*t*Bu was added. To the solution 3.20 g (10.5 mmol) of *bis*-tolylimidoylchloride **1** was added. The deep red reaction mixture was stirred at -30 °C for 30 minutes. The mixture was acidified by addition of hydrochloric acid to pH 7. The mixture was concentrated *in vacuo* to dryness. The remaining solid was dissolved in $CHCl_3$/*n*-heptane and was dried over Na_2SO_4. Upon removal of the solvent *in vacuo*, the crude product was purified by recrystallization from $CHCl_3$/*n*-heptane to yield **14** as pale yellow crystals.

Pale yellow crystals, yield: 2.42 g (72%), mp 213°C ($CHCl_3$/*n*-heptane), Lit. [14b] 211°C (ethanol). ^{1}H NMR (250MHz, DMSO-d_6): δ = 7.74 (s, 1H, NH), 7.28 (d, J = 8 Hz, 2H, CH-Tol), 7.15 (d, J = 8 Hz, 2H, CH-Tol), 7.02 (d, J = 8 Hz, 2H, CH-Tol), 6.81 (d, J = 8 Hz, 2H, CH-Tol), 5.34 (t, J = 5 Hz, 1H, CH-cycle), 2.34 (s, 3H, CH-Tol), 2.29-2.23 (m, 7H, CH_2-cycle + CH-Tol), 2.20 (quint., J = 6 Hz, 2H, CH_2-cycle) ppm. ^{13}C NMR (63MHz, DMSO-d_6): δ = 165.8, 140.1, 138.9, 136.9, 132.2, 130.0, 129.5, 127.4, 126.9, 120.8, 118.8, 115.6, 106.9, 24.4 (CH-cycle), 23.8 (CH-cycle), 23.5 (CH-cycle), 21.1 (CH-Tol), 20.7 (CH-Tol) ppm. MS(EI) *m/z*: 330 (100) [M^+], 268 (90), 135 (40), 106 (100), 91 (90) [$C_7H_7^+$]. Elemental analysis calculated for $C_{22}H_{22}N_2O$ (330.43) C 79.97, H 6.71, N 8.48; found C 79.87, H 6.55, N 8.39%. IR(ATR): ν_{max}/cm^{-1} 3292 (NH), 2949, 2933, 2863, 1677, 1639, 1609, 1531, 1511, 1404, 1325, 1170, 821. UV/VIS (CCl_3H): λ_{max} (lg ε) = 301 (4.06), 349 (3.89) nm.

Crystal Structure Determination for 3, 8, 11 and 14. The intensity data for the compounds were collected on a Nonius KappaCCD diffractometer, using graphite-monochromated Mo-K_α radiation. Data were corrected for Lorentz and polarization effects, but not for absorption effects [15, 16]. The structure was solved by direct methods (SHELXS [17]) and refined by full-matrix least squares techniques against Fo^2 (SHELXL-97 [18]). For the amino groups of **3**, **11** and **14** as well as the CH_2-protons at C32 of **8** the hydrogen atoms were located by difference Fourier synthesis and refined isotropically. The other hydrogen atoms were included at calculated positions with fixed thermal parameters. All non hydrogen atoms were refined anisotropically [18]. The program XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations.

CCDC-661235 (**3**), CCDC-661236 (**8**), CCDC-661237 (**11**), and CCDC-661238 (1**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Crystal Data for **3** (CCDC-661235): $C_{31}H_{26}N_2O$, Mr = 442.54 gmol^{-1}, yellow prism, size 0.05 x 0.05 x 0.04 mm^3, monoclinic, space group $P2_1$, a = 13.9374(8), b = 6.3810(3), c = 15.3665(9) Å, β = 107.320(3)°, V = 1304.6(1) Å^3, T= -90 °C, Z = 2, $\rho_{calcd.}$ = 1.127 gcm^{-3}, μ (Mo-K_α) = 0.68 cm^{-1}, F(000) = 468, 8972 reflections in h(-16/18), k(-8/7), l(-19/19), measured in the range 2.96° ≤ Θ ≤ 27.47°, completeness Θ_{max} = 99%, 5227 independent reflections, R_{int} = 0.0430, 4105 reflections with $F_o > 4\sigma(F_o)$, 315 parameters, 1 restraints, $R1_{obs}$ = 0.0642, wR^2_{obs} = 0.1688, $R1_{all}$ = 0.0882, wR^2_{all} = 0.1871, GOOF = 1.083, Flack-parameter -4(2), largest difference peak and hole: 0.754 / -0.257 e Å^{-3}.

Crystal Data for **8** (CCDC-661236): $C_{33}H_{30}N_2OZn$, Mr = 535.96 gmol^{-1}, red prism, size 0.06 x 0.06 x 0.06 mm^3, triclinic, space group Pī, a = 7.3782(6), b = 12.5394(11), c = 15.6793(15) Å, α = 110.074(4), β = 95.163(5), γ = 100.185(5)°, V = 1323.1(2) Å^3 , T= -90 °C, Z = 2, $\rho_{calcd.}$ = 1.345 gcm^{-3}, μ (Mo-K_α) = 9.57 cm^{-1}, F(000) = 560, 9074 reflections in h(-9/9), k(-15/16), l(-20/20), measured in the range 1.81° ≤ Θ ≤ 27.49°, completeness Θ_{max} = 96.6%, 5879 independent reflections, R_{int} = 0.0446, 4032 reflections with $F_o > 4\sigma(F_o)$, 342 parameters, 0 restraints, $R1_{obs}$ = 0.0527, wR^2_{obs} = 0.1081, $R1_{all}$ = 0.0926, wR^2_{all} = 0.1251, GOOF = 1.006, largest difference peak and hole: 0.329 / -0.556 e Å^{-3}.

Crystal Data for **11** (CCDC-661237): $C_{22}H_{20}N_2O_5$, Mr = 392.40 gmol^{-1}, yellow prism, size 0.06 x 0.06 x 0.05 mm^3, monoclinic, space group $P2_1/c$, a = 7.0583(2), b = 12.1473(5), c = 22.5441(9) Å, β = 96.933(3)°, V = 1918.78(12) Å^3 , T= -90 °C, Z = 4, $\rho_{calcd.}$ = 1.358 gcm^{-3}, μ (Mo-K_α) = 0.97 cm^{-1}, F(000) = 824, 11305 reflections in h(-9/8), k(-15/14), l(-29/29), measured in the range 2.91° ≤ Θ ≤ 27.49°, completeness Θ_{max} = 96.8%, 4263 independent reflections, R_{int} = 0.0556, 2950 reflections with $F_o > 4\sigma(F_o)$, 266 parameters, 0 restraints, $R1_{obs}$ = 0.0702, wR^2_{obs} = 0.1714, $R1_{all}$ = 0.1042, wR^2_{all} = 0.1875, GOOF = 1.073, largest difference peak and hole: 0.300 / -0.289 e Å^{-3}.

Crystal Data for **14** (CCDC-661238): $C_{22}H_{22}N_2O$, Mr = 330.42 gmol^{-1}, colourless prism, size 0.06 x 0.06 x 0.06 mm^3, orthorhombic, space group Pbca, a = 12.3420(4), b = 16.5660(6), c = 17.1098(6) Å, V = 3498.2(2) Å^3 , T= -90 °C, Z = 8, $\rho_{calcd.}$ = 1.255 gcm^{-3}, μ (Mo-K_α) = 0.77 cm^{-1}, F(000) = 1408, 22277 reflections in h(-15/16), k(-19/21), l(-22/22), measured in the range 2.38° ≤ Θ ≤ 27.48°, completeness Θ_{max} = 99.9%, 3998 independent reflections, R_{int} = 0.0753, 2622 reflections with $F_o > 4\sigma(F_o)$, 232 parameters, 0 restraints, $R1_{obs}$ = 0.0550, wR^2_{obs} = 0.1386, $R1_{all}$ = 0.0965, wR^2_{all} = 0.1663, GOOF = 0.904, largest difference peak and hole: 0.535 / -0.392 e Å^{-3}.

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