1,3-Dipolar cycloaddition reaction of heteroaromatic *N*-ylides with 3-[(*E*)-2-aryl(hetaryl)-2-oxoethylidene]indolin-2-ones

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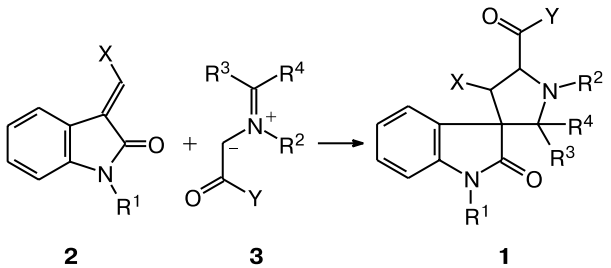
A series of 6a′,7′,8′,9′-tetrahydrospiro[indoline-3,7′-pyrrolo[1,2-*a*]quinoline]-2-one derivatives were synthesized by the 1,3-dipolar cycloaddition reaction. The regio- and stereoselectivity of the reaction were established by X-ray diffraction study.

Key words: 1,3-dipolar cycloaddition, 3-arylideneindolin-2-ones, azomethine ylides, spiro[indoline-3,3′-pyrrolidine], regioselectivity, X-ray diffraction study.

The structural fragment of spiro[indoline-3,3′-pyrrolidine] **1** lies at the basis of six alkaloids from the woody vine *Uncaria tomentosa* (cat's claw). An extract from the bark of this plant is used as a drug for the treatment of a number of immune diseases.[1]

Several procedures have been developed for the synthesis of compounds containing this spiro skeleton. The simplest and most convenient procedure is based on 1,3-dipolar cycloaddition. A large number of studies on the synthesis of such spiroheterocycles[2—4] dealt with the addition of 3-arylideneindolin-2-ones **2** to azomethine ylides **3** generated from α-amino acids and their derivatives (Scheme 1).

Scheme 1



2 **3** **1**

X = Ar; Y = OAlk, OH; R^1, R^2 = H, Alk; R^3, R^4 = H, Alk, Ar

The use of heteroaromatic *N*-ylides **3** in 1,3-dipolar cycloaddition reactions with 3-arylideneindolin-2-ones **2** also provides an approach to the synthesis of compounds containing fragment **1**. An attempt to add phenacylpyridinium ylide to 3-[(*E*)-2-oxo-2-phenylethylidene]indolin-2-one led to the formation a thermally unstable compound, which eliminates pyridine to give a product containing the spiro[cyclopropane-1,3′-indoline] fragment.[5] The reactions of azomethine ylides **4**, which were generated from dihydroisoquinolinium salts, with dipolarophiles **2a,b** afforded[4,6] structures **5** and **6** (Scheme 2). Based on the results of ^{1}H and ^{13}C NMR spectroscopic studies,[4,6,7] it was concluded that the regioselectivity of cycloaddition varies depending on the nature of the substituent X in dipolarophile **2**.

Results and Discussion

We synthesized a series of products containing spiro fragment **1** by cycloaddition of quinolinium ylides **7a—d** to 3-[(*E*)-2-aryl(hetaryl)-2-oxoethylidene]indolin-2-ones **2c—e** (Scheme 3). To determine which regioisomer (**8** or **9**) is produced in the reaction, we performed a complex study. For compound **2c**, the electron density of the C=C bond involved in cycloaddition was calculated by the AM1 method using the HyperChem 6.0 program package. The calculations demonstrated that the difference in the electron density is 0.051 electron charge units and it is shifted to the benzoyl fragment. If only the electronic factors of 1,3-dipolar cycloaddition are considered, the reaction should produce structure **9**. However,

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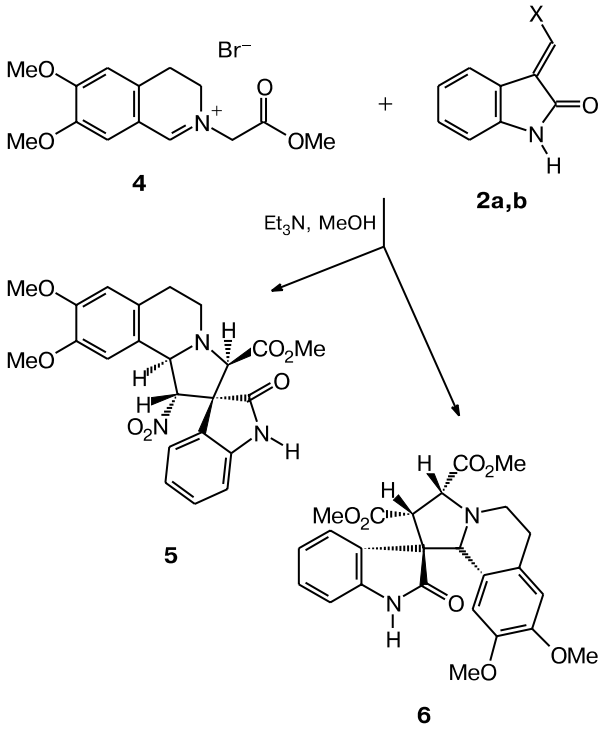
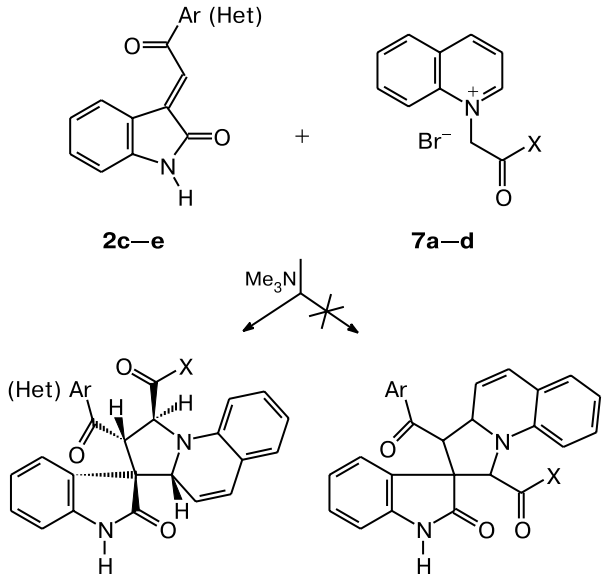
Scheme 2



X = NO_2 (**a**), CO_2Et (**b**)

Scheme 3



2	Ar (Het)	7	X	8	Ar (Het)	X
c	Ph	**a**	4-ClC_6H_4	**a**	Ph	4-ClC_6H_4
d	3-py	**b**	Me	**b**	3-py	Me
e	4-py	**c**	OEt	**c**	4-py	OEt
		d	NH_2	**d**	Ph	NH_2

such a small energy difference does not play a decisive role, and steric factors appear to be of primary importance in cycloaddition giving rise to adducts **8**. This conclusion is confirmed by the results of X-ray diffraction study of compound **8a** (Fig. 1, Tables 1 and 2).

The central five-membered ring C(3)C(7′)C(8′)N(9A′)C(6A′) adopts an envelope conformation with the C(6A′) atom deviating from the plane through the other four atoms of the ring by 0.62 Å (the folding angle along the C(3)...N(9A′) line is 40.7°). The benzoyl substituents at the C(7′) and C(8′) atoms are in transoid positions with respect to the planar fragment of the ring (the C(10)—C(7′)—C(8′)—C(17) torsion angle is 121.5°). The configuration of the N(9A′) atom is slightly nonplanar (the deviation of the substituents from the plane is 0.09 Å). The six-membered ring N(9A′)C(10A)C(4A′)C(5′)C(6′)C(6A′) adopts a flattened *twist* conformation with the N(9A′) and C(6A′) atoms deviating from the plane through the other four atoms of the ring in the opposite directions by 0.17 and 0.09 Å, respectively. The crystal structure contains a diethyl ether molecule of solvation involved in an intermolecular N—H...O hydrogen bond (N(1)...O(1S), 2.838(3) Å; N(1)—H(1), 0.92(2) Å; H(1)...O(1S), 1.94(2) Å; N(1)—H(1)...O(1S), 165°).

Table 1. Selected bond lengths (*d*) in compound **8a**

Bond	*d*/Å	Bond	*d*/Å
O(1)—C(2)	1.223(2)	C(1′)—C(10A)	1.396(3)
O(2)—C(10)	1.223(2)	C(2′)—C(3′)	1.396(3)
O(3)—C(17)	1.219(2)	C(3′)—C(4′)	1.379(3)
N(1)—C(2)	1.363(3)	C(4′)—C(4A′)	1.391(3)
N(1)—C(9)	1.401(3)	C(4A′)—C(10A)	1.421(3)
C(2)—C(3)	1.535(3)	C(4A′)—C(5′)	1.456(3)
C(3)—C(4)	1.512(3)	C(5′)—C(6′)	1.327(3)
C(3)—C(6A′)	1.554(3)	C(6′)—C(6A′)	1.498(3)
C(3)—C(7′)	1.573(3)	C(6A′)—N(9A′)	1.455(2)
C(4)—C(5)	1.381(3)	C(7′)—C(10)	1.525(3)
C(4)—C(9)	1.390(3)	C(7′)—C(8′)	1.550(3)
C(5)—C(6)	1.393(3)	C(8′)—N(9A′)	1.443(2)
C(6)—C(7)	1.382(3)	C(8′)—C(17)	1.525(3)
C(7)—C(8)	1.392(3)	N(9A′)—C(10A)	1.378(2)
C(8)—C(9)	1.383(3)	C(10)—C(11)	1.490(3)
C(1′)—C(2′)	1.383(3)	C(17)—C(18)	1.503(3)

The chosen method for the synthesis of 3-arylideneindolin-2-ones **2c—e** allows one to prepare only *E* isomers, which is confirmed by the presence of a signal for the ylidene proton in the ^{1}H NMR spectrum at δ 7.7.[8]

anti-Phenacylquinolinium ylide and 3-[(*E*)-2-oxo-2-phenylethylidene]indolin-2-one involved in the reaction form an intermediate *anti—endo* complex, which determines the spatial arrangement of the substituents in the

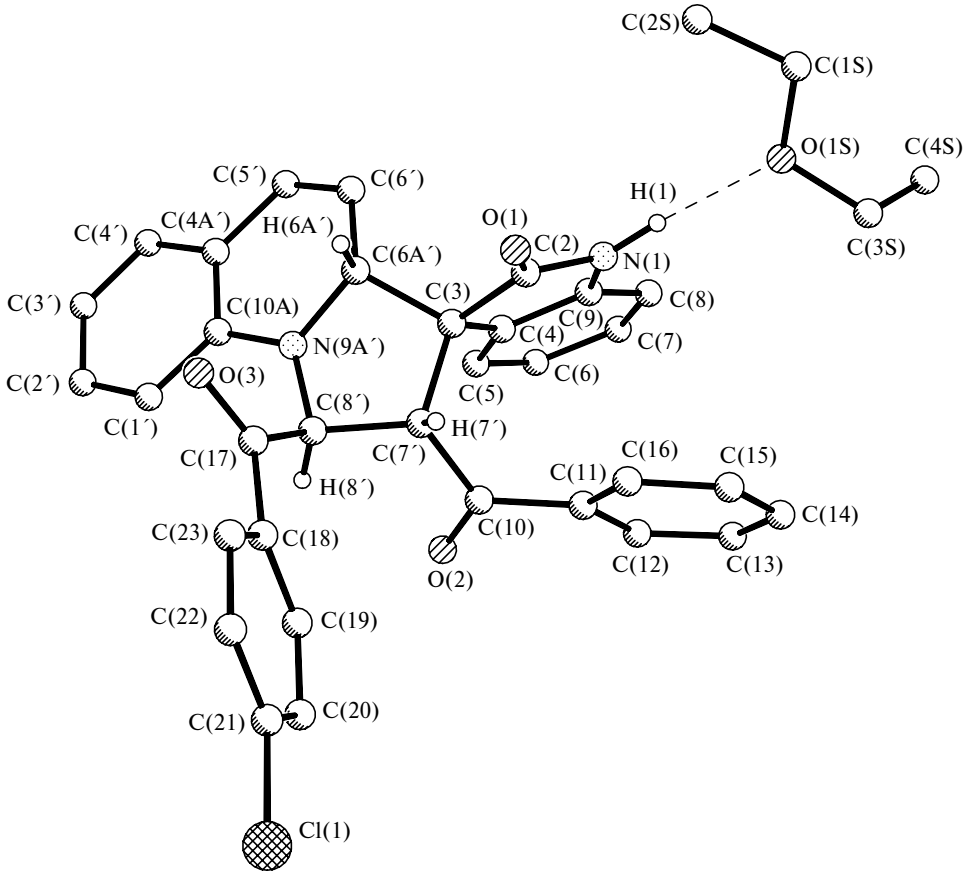


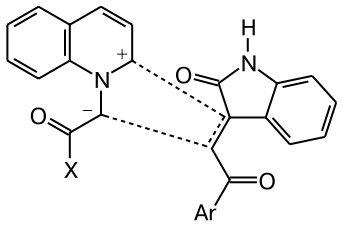
Fig. 1. Structure of the crystal solvate **8a** · OEt_2.

final product.[9,10] We obtained only one of 16 possible stereoisomers of **8**.

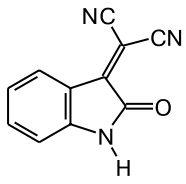
With the aim of extending the scope of this reaction, we used the starting reagents containing different substituents (see Scheme 3). The reactions with 2-arylcarbamoylmethylquinolinium ylides as 1,3-dipoles afforded a set of stereoisomers. Completely substituted activated olefin, *viz.*, 2-(2-oxo-2,3-dihydro-1*H*-3-indolyl-

Table 2. Selected bond angles (ω) in compound **8a**

Angle	ω/deg	Angle	ω/deg	Angle	ω/deg
C(2)—N(1)—C(9)	111.8(2)	C(8)—C(9)—C(4)	122.4(2)	C(8´)—C(7´)—C(3)	105.8(2)
O(1)—C(2)—N(1)	127.1(2)	C(8)—C(9)—N(1)	128.0(2)	N(9A´)—C(8´)—C(17)	113.1(2)
O(1)—C(2)—C(3)	125.2(2)	C(4)—C(9)—N(1)	109.6(2)	N(9A´)—C(8´)—C(7´)	103.9(2)
N(1)—C(2)—C(3)	107.7(2)	C(2´)—C(1´)—C(10A)	120.6(2)	C(17)—C(8´)—C(7´)	109.4(2)
C(4)—C(3)—C(2)	102.4(2)	C(1´)—C(2´)—C(3´)	120.7(2)	C(10A)—N(9A´)—C(8´)	125.5(2)
C(4)—C(3)—C(6A´)	115.8(2)	C(4´)—C(3´)—C(2´)	118.8(2)	C(10A)—N(9A´)—C(6A´)	124.1(2)
C(2)—C(3)—C(6A´)	111.6(2)	C(3´)—C(4´)—C(4A´)	122.1(2)	C(8´)—N(9A´)—C(6A´)	109.2(2)
C(4)—C(3)—C(7´)	114.7(2)	C(4´)—C(4A´)—C(10A)	118.6(2)	N(9A´)—C(10A)—C(1´)	122.5(2)
C(2)—C(3)—C(7´)	111.5(2)	C(4´)—C(4A´)—C(5´)	123.2(2)	N(9A´)—C(10A)—C(4A´)	118.3(2)
C(6A´)—C(3)—C(7´)	101.2(2)	C(10A)—C(4A´)—C(5´)	118.1(2)	C(1´)—C(10A)—C(4A´)	119.2(2)
C(5)—C(4)—C(9)	119.7(2)	C(6´)—C(5´)—C(4A´)	122.3(2)	O(2)—C(10)—C(11)	121.1(2)
C(5)—C(4)—C(3)	131.8(2)	C(5´)—C(6´)—C(6A´)	121.9(2)	O(2)—C(10)—C(7´)	120.2(2)
C(9)—C(4)—C(3)	108.4(2)	N(9A´)—C(6A´)—C(6´)	111.8(2)	C(11)—C(10)—C(7´)	118.5(2)
C(4)—C(5)—C(6)	118.7(2)	N(9A´)—C(6A´)—C(3)	101.5(2)	O(3)—C(17)—C(18)	120.3(2)
C(7)—C(6)—C(5)	120.9(2)	C(6´)—C(6A´)—C(3)	116.6(2)	O(3)—C(17)—C(8´)	120.2(2)
C(6)—C(7)—C(8)	121.0(2)	C(10)—C(7´)—C(8´)	114.0(2)	C(18)—C(17)—C(8´)	119.5(2)
C(9)—C(8)—C(7)	117.3(2)	C(10)—C(7´)—C(3)	109.9(2)		



idene)malononitrile (**10**),[11] does not react with phenacylquinolinium ylides **7** as a dipolarophile.



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Therefore, a series of spiro[indoline-3,3′-pyrrolidine] derivatives synthesized in the present study provide evidence that this reaction has wide application and enables one to prepare compounds containing various substituents. These reactions proceed regio- and stereoselectively, except for the reactions with the use of 2-arylcarbamoylmethylquinolinium ylides. The successful reactions of 3-arylideneindolin-2-ones with heteroaromatic *N*-ylides are promoted by the presence of the hydrogen atom at the double bond, which is involved in cycloaddition.

Experimental

The melting points were determined on a Kofler block. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument (300 and 75 MHz for ^{1}H and ^{13}C, respectively) in DMSO-d_6. The course of the reactions was monitored and the purities of the reaction products were checked by TLC on Silufol UV-254 plates in a 2 : 1 benzene—AcOEt system, and spots were visualized with iodine vapor. 3-Arylideneindolin-2-ones **2c—e** were synthesized according to a known procedure.[8] Acylmethylquinolinium bromides **7a—d** were prepared according to a procedure described in the study.[9]

9′-Acyl-8′-aroyl-substituted 6a′,7′,8′,9′-tetrahydrospiro[indoline-3,7′-pyrrolo[1,2-*a*]quinoline]-2-ones 8a—d (general procedure). A 1% Me_3N solution in Pr^iOH (17.5 mL) was added dropwise to a solution of ylide **7** (0.0023 mol) and indolinone **2** (0.0023 mol) in isopropyl alcohol (100 mL) for 45 min. The reaction mixture was stirred for 2 h. The solvent was evaporated under reduced pressure. The product was isolated by column chromatography (Florisil, Aldrich, 60—100 mesh, benzene—AcOEt, 2 : 1, as the eluent).

8′-Benzoyl-9′-(4-chlorobenzoyl)-6a′,7′,8′,9′-tetrahydrospiro[indoline-3,7′-pyrrolo[1,2-*a*]quinoline]-2-one (8a). The yield was 56%. Yellow crystals, m.p. 215—217 °C. Found (%): C, 74.72; H, 4.51; N, 5.43. $C_{33}H_{23}ClN_2O_3$. Calculated (%): C, 74.64; H, 4.37; N, 5.28. ^{1}H NMR, δ: 4.59 (d, 1 H, CHCO, J = 4.2 Hz); 4.82 (d, 1 H, CH=, J = 6.0 Hz); 5.36 (s, 1 H, NCHCH=CH); 6.17 (d, 1 H, CH=, J = 6.3 Hz); 6.26 (d, 1 H, H arom., J = 4.8 Hz); 6.32 (d, 1 H, NCHCO, J = 4.2 Hz); 6.46—6.55 (m, 2 H, H arom.); 6.75—6.83 (m, 3 H, H arom.); 6.96 (t, 1 H, H arom., J = 8.8 Hz); 7.03 (t, 1 H, H arom., J = 12.2 Hz); 7.25 (d, 4 H, H arom., J = 3.3 Hz); 7.42—7.51 (m, 1 H, H arom.); 7.77 (d, 2 H, H arom., J = 5.8 Hz); 7.97 (d, 2 H, H arom., J = 6.1 Hz); 10.46 (s, 1 H, NH). ^{13}C NMR, δ: 56.9 (C(7′); 61.0 (C(3)); 61.6 (C(6a′)); 69.8 (C(8′)); 109.1; 109.3; 117.2; 118.2; 119.5; 121.4; 125.6; 126.7; 127.2; 127.8; 128.2; 128.5; 129.2; 129.7; 130.4; 133.2; 133.4; 135.8; 139.1; 141.6; 141.8; 175.1 (CONH); 195.4 (COAr); 197.4 (COAr).

9′-Acetyl-8′-(3-pyridylcarbonyl)-6a′,7′,8′,9′-tetrahydrospiro[indoline-3,7′-pyrrolo[1,2-*a*]quinoline]-2-one (8b). The yield was 46%. Yellow crystals, m.p. 152—154 °C. Found (%): C, 74.65; H, 4.91; N, 9.67. $C_{27}H_{21}N_3O_3$. Calculated (%): C, 74.47; H, 4.86; N, 9.65. ^{1}H NMR, δ: 2.31 (s, 3 H, Ac); 4.76 (d, 1 H, CHCO, J = 4.2 Hz); 4.89 (d, 1 H, CH=, J = 6.0 Hz); 5.20 (s, 1 H, NCHCH=CH); 5.35 (d, 1 H, H arom., J = 4.3 Hz); 6.17 (d, 1 H, CH=, J = 6.3 Hz); 6.42—6.60 (m, 4 H, H arom. + NCHCO); 6.72—6.80 and 6.99—7.10 (both m, 2 H each, H arom.); 7.33 (t, 1 H, H arom., J = 8.0 Hz); 7.69 (d, 1 H, H arom., J = 5.3 Hz); 8.44 (s, 1 H, H arom.); 8.65 (d, 1 H, H arom., J = 3.2 Hz); 10.46 (s, 1 H, NH). ^{13}C NMR, δ: 28.0 (Me); 49.8 (C(7′)); 65.3 (C(6a′)); 70.1 (C(8′)); 72.3 (C(3)); 109.8; 113.2; 118.3; 119.5; 121.6; 122.0; 122.3; 123.6; 124.0; 127.1; 127.7; 128.1; 129.2; 134.1; 134.6; 142.3; 144.5; 148.9; 153.4; 171.9 (CONH); 196.8 (COAr); 200.5 (COMe).

9′-Ethoxycarbonyl-8′-(4-pyridylcarbonyl)-6a′,7′,8′,9′-tetrahydrospiro[indoline-3,7′-pyrrolo[1,2-*a*]quinoline]-2-one (8c). The yield was 49%. Yellow crystals, m.p. 214—216 °C. Found (%): C, 72.39; H, 4.93; N, 8.93. $C_{28}H_{23}N_3O_4$. Calculated (%): C, 74.25; H, 4.98; N, 9.03. ^{1}H NMR, δ: 1.24 (t, 3 H, Me, J = 9.9 Hz); 4.25 (q, 2 H, OCH_2, J = 12.3 Hz); 4.83 (d, 1 H, CHCO, J = 4.2 Hz); 4.89 (d, 1 H, CH=, J = 6.0 Hz); 5.29 (s, 1 H, NCHCH=CH); 5.32 (d, 1 H, H arom., J = 4.4 Hz); 6.17 (d, 1 H, CH=, J = 6.3 Hz); 6.48 (d, 1 H, NCHCO, J = 4.0 Hz); 6.52—6.63 (m, 3 H, H arom.); 6.73—6.83 and 7.01—7.14 (both m, 2 H each, H arom.); 7.18 and 8.59 (both d, 2 H each, H arom., J = 3.2 Hz); 10.49 (s, 1 H, NH). ^{13}C NMR, δ: 14.2 (Me); 49.6 (C(7′)); 60.9 (CH_2); 66.7 (C(8′)); 67.1 (C(6a′)); 71.8 (C(3)); 109.2; 112.8; 117.9; 118.8; 121.5; 121.7; 123.6; 124.3; 124.8; 127.4; 127.9; 128.2; 128.7; 142.5; 145.0; 145.6; 149.9; 169.8 (COO); 173.3 (CONH); 196.9 (COAr).

8′-Benzoyl-9′-carbamoyl-6a′,7′,8′,9′-tetrahydrospiro[indoline-3,7′-pyrrolo[1,2-*a*]quinoline]-2-one (8d). The yield was 35%. Yellow crystals, m.p. 209—211 °C (with decomp.). Found (%): C, 74.61; H, 4.98; N, 9.69. $C_{27}H_{21}N_3O_3$. Calculated (%): C, 74.47; H, 4.86; N, 9.65. ^{1}H NMR, δ: 4.56 (d, 1 H, CHCO, J = 4.2 Hz); 4.90 (d, 1 H, CH=, J = 6.0 Hz); 5.14 (d, 1 H, H arom., J = 4.0 Hz); 5.37 (s, 1 H, NCHCH=CH); 6.13 (d, 1 H, CH=, J = 6.2 Hz); 6.47 (d, 1 H, NCHCO, J = 4.2 Hz); 6.52—6.62 (m, 3 H, H arom.); 6.68—6.80 (m, 2 H, H arom.); 7.01 and 7.10 (both t, 1 H each, H arom., J = 10.4 Hz); 7.25 (br.s, 1 H, $CONH_2$); 7.34 (t, 2 H, H arom., J = 8.7 Hz); 7.44 (d, 2 H, H arom., J = 4.4 Hz); 7.53 (t, 1 H, H arom., J = 8.8 Hz); 7.70 (br.s, 1 H, $CONH_2$); 10.39 (br.s, 1 H, NH). ^{13}C NMR, δ: 49.8 (C(7′)); 61.9 (C(8′)); 66.0 (C(6a′)); 74.7 (C(3)); 109.4; 112.7; 117.8; 119.1; 121.1; 121.9; 123.6; 124.2; 126.5; 127.4; 127.7; 128.0; 128.2; 132.4; 141.9; 142.5; 146.4; 167.5 ($CONH_2$); 170.4 (CONH); 196.4 (COAr).

X-ray diffraction study of the crystal solvate 8a·OEt_2. Yellow crystals were grown by slow evaporation of a solution in diethyl ether. The crystals ($C_{37}H_{33}C1N_2O_4$) are monoclinic, space group $P2_1/n$, at 110 K a = 14.452(3) Å, b = 8.886(2) Å, c = 24.492(5) Å, β = 97.525(5)°, V = 3118(1) Å^3, Z = 4, M = 605.10, d_{calc} = 1.289 g cm^{-3}. The intensities of 9121 inde-

pendent reflections were measured on an automated Bruker SMART 1000 CCD diffractometer (graphite monochromator, λ(Mo-Kα) = 0.71073 Å, ω scanning technique, $2\theta_{max} = 60°$). The structure was solved by direct methods and refined by the full-matrix least-squares method against F^2_{hkl} with anisotropic displacement parameters for all nonhydrogen atoms. The hydrogen atoms were located from difference electron density maps and refined isotropically. The final R factors were as follows: $R_1 = 0.0562$ (based on F for 4197 observed reflections with $I > 2\sigma(I)$), $wR_2 = 0.1359$ (based on F^2 for all independent reflections), 529 parameters were refined. All calculations were carried out on a PC with the use of the SHELXTL program package.[12]

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