

A Novel Coupling 1,3-Dipolar Cycloaddition Sequence as a Three-Component Approach to Highly Fluorescent Indolizines

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Dedicated to Professor Rolf Huisgen on the occasion of his 85th birthday

Indolizines **4** and biindolizines **6** can be synthesized in moderate yields in a consecutive one-pot three-component process by a coupling/1,3-dipolar cycloaddition sequence of a (hetero)arene carbonyl chloride **1**, a terminal alkyne **2**, and a suitable 1-(2-oxoethyl) pyridinium bromide **3** or **5**, respectively (*Schemes 1* and *2*). After the *Sonogashira* coupling, a [2 + 3] cycloaddition of the *in situ* formed pyridinium ylide, an allyl-type 1,3-dipole, furnishes a cycloadduct that is instantaneously oxidatively aromatized to give the highly fluorescent indolizine derivatives that were unambiguously characterized by an X-ray-structure analysis of compound **4d** (*Fig. 1*). Additionally, fluorescence studies with pyridinyl-substituted representatives reveal not only that indolizines and biindolizines are highly interesting fluorescence dyes but that their fluorescence color can also be reversibly switched upon altering the pH of the medium.

Introduction. – Sequential transformations and multicomponent processes have become increasingly interesting in academic research as well as for economical and ecological reasons since they address the very fundamental principles of synthetic efficiency and reaction design [1]. Besides, the prospect of extending one-pot reactions into combinatorial and solid-phase application [1c] [2] promises manifold opportunities for developing novel lead structures of pharmaceuticals, catalysts, and even novel molecule-based materials. Therefore, transition metal catalyzed reactions significantly enhance synthetic efficiency if they can be directed in a domino or sequential fashion generating a suitable reactive functionality *en route*²⁾. In recent years, Pd-catalyzed cross-coupling methodology has considerably revolutionized synthetic methodology and the syntheses of complex natural and nonnatural target molecules. In particular, the bimetallic, catalytic *Sonogashira* coupling has turned out to be a versatile and mild alkyne-to-alkyne transformation, *i.e.*, a powerful tool for transforming a terminal alkyne into an internal one as a consequence of a sp-sp² C–C bond forming reaction³⁾. Besides mild reaction conditions, an excellent compatibility with fragile functional groups dispenses with tedious protection–deprotection operations, and since hydrogen halide (scavenged by weak bases such as amines) is formed as the sole by-product, the *Sonogashira* coupling displays a high degree of atom economy. Most interestingly,

1) X-Ray structure analysis of **4d**.

2) For recent excellent reviews on transition-metal-assisted sequential transformations and domino processes, see, *e.g.*, [3].

3) For lead reviews on *Sonogashira* couplings, see, *e.g.*, [4].

highly reactive and versatile alkynones, that act as 1,3-dicarbonyl synthetic equivalents in heterocyclic syntheses⁴⁾, can readily be formed in catalytic fashion by a *Sonogashira* coupling of an acyl chloride with a terminal alkyne [6][7]. As part of our program directed to design novel multicomponent reactions based on *in situ* activation of alkynes by *Sonogashira* coupling [7][8], we became interested in sequentially combining cycloadditions with cross-coupling reactions. Here, we report the first three-component one-pot synthesis of highly fluorescent indolizines and biindolizines based upon a consecutive coupling/1,3-dipolar cycloaddition⁵⁾ sequence. Furthermore, the peculiar emission properties of this interesting class of compounds are discussed.

Results and Discussion. – Indolizine is an aromatic 10π -electron system and a constitutional isomer of 1*H*-indol and, consequently, has received a considerable theoretical and practical interest [10]. Considering the well-established fluorescence properties of indolizines [11] and biindolizines [11b], and the steadily increasing importance of fluorophores in biolabeling and environmental trace analysis, we were seeking a new, efficient synthesis of fluorescent indolizines. Two general ways of indolizine syntheses have been known so far [10]. The first route is based on the intramolecular formation of the indolizine by cyclizing condensation of suitable pyridinium precursors. However, the second approach takes advantage of a [3 + 2] cycloaddition of pyridinium ylides with various C=C or C $\equiv$ C bond *Michael* systems [9b]⁶⁾. Based upon our methodological background using Pd/Cu-catalyzed cross-coupling of acyl chlorides and alkynes to furnish alkynones [7][8b], the latter access to indolizines seemed to be well suited for probing a three-component synthesis initiated by a *Sonogashira* coupling.

Thus, we submitted a (hetero)arenecarbonyl chloride **1** and a terminal alkyne **2** to the reaction conditions of the *Sonogashira* coupling in a mixture of THF and Et₃N at room temperature and after 2 h, a 1-(2-oxoethyl)pyridinium bromide **3** [13]⁷⁾ was added to furnish after 14 h of stirring at room temperature an indolizine **4** in 41–59% yield as pale yellow to yellow green crystalline solid (*Scheme 1*, *Table 1*).

Likewise the 4,4'-bipyridinediium salt **5**⁸⁾ readily participates in this novel sequence to furnish the 7,7'-biindolizines **6** in modest yields as intensively yellow solids (*Scheme 2*).

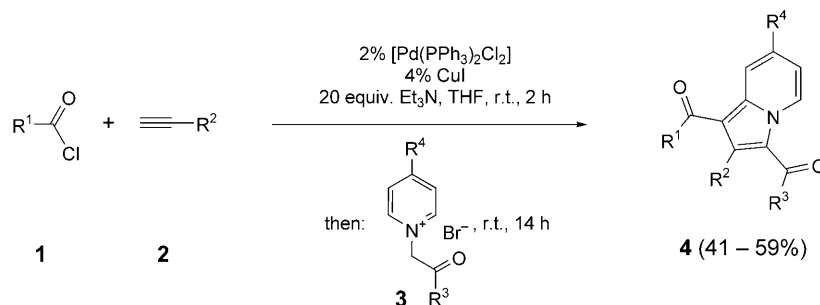
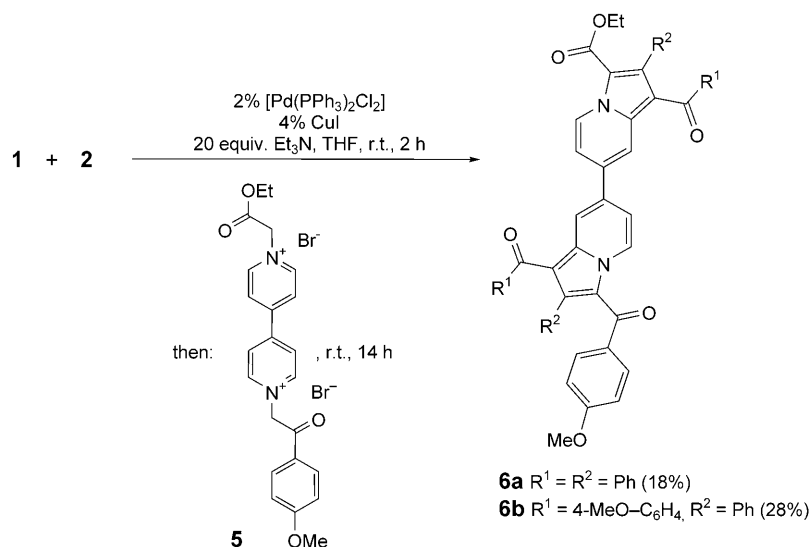
⁴⁾ For recent heterocycle syntheses from ynones, see, *e.g.*, [5].

⁵⁾ For important reviews on 1,3-dipolar cycloadditions, see, *e.g.*, [9].

⁶⁾ For a recent review on indolizine syntheses by 1,3-dipolar cycloaddition, see, *e.g.*, [12a]; for a review on azomethine ylides (=iminium ylides), see, *e.g.*, [12b]; for cycloadditions of pyridinium ylides, see, *e.g.*, [12c].

⁷⁾ Typical procedure for the synthesis of **3**: To a solution of a pyridine derivative (1 mmol) in anhydrous acetone (5 ml) 1.1 mmol of an α -bromo carbonyl compound (1.1 mmol) was added, and the mixture was stirred at room temperature for 3 h. After the complete conversion, the obtained white precipitate was filtered, washed with dry acetone (20 ml), and dried *in vacuo* to furnish a spectroscopically and anal. pure pyridinium salt **3** as white to bluish-white powder in 82–92% yield.

⁸⁾ The 4,4'-bipyridinediium derivative **5** was obtained by heating a mixture of pyridinium salt **3d** (1 mmol) in MeCN (20 ml) and DMF (5 ml) and ethyl bromoacetate (1.1 mmol) in MeCN (2.5 ml) to reflux temperature for 1 h, and after washing of the precipitate with MeCN (10–15 ml), as a yellow green powder in 72% yield.

Scheme 1. *One-Pot Three-Component Coupling-1,3-Dipolar Cycloaddition Synthesis of Indolizines 4*Scheme 2. *One-Pot Three-Component Coupling-1,3-Dipolar Cycloaddition Synthesis of Biindolizines 6*

The structures of the indolizines **4** and biindolizines **6** were unambiguously assigned by ^1H , ^{13}C -COSY, and NOESY-NMR experiments. Furthermore, the structure of **4** was unambiguously supported by an X-ray crystal-structure analysis of compound **4d** (Fig. 1, Table 3)⁹⁾.

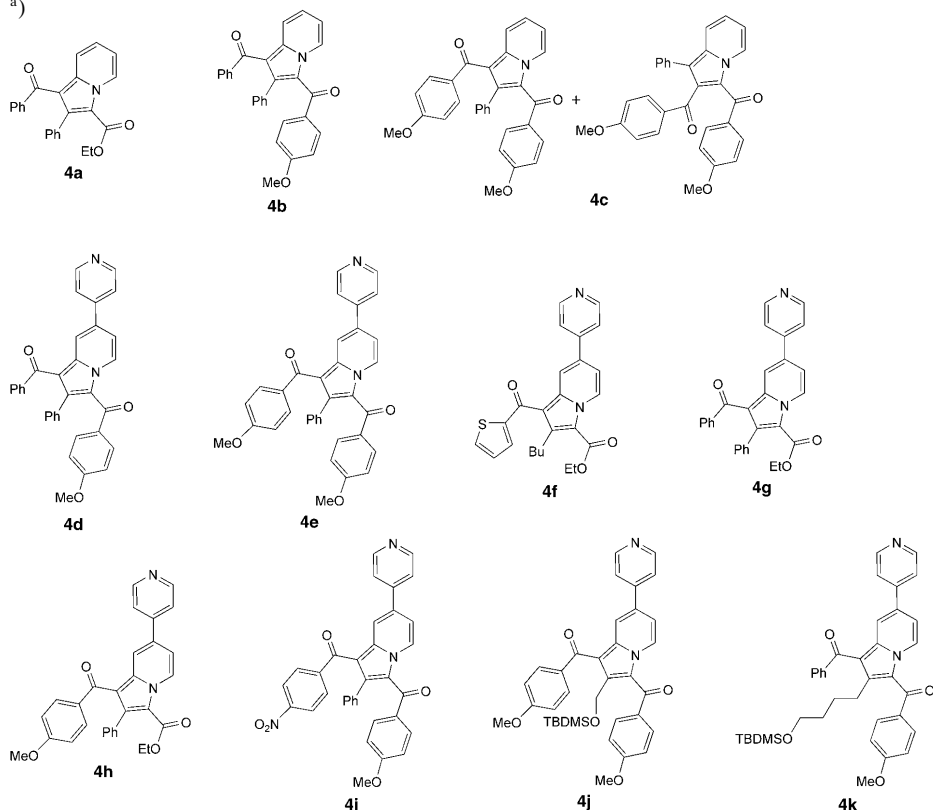
In particular, the ^1H -NMR data of **4** and **6** support the formation of the indolizine core by the indicative appearance and splitting pattern of the two downfield shifted $\text{H}-\text{C}(8)$ and $\text{H}-\text{C}(5)$ resonances at δ 8.07–8.46 and 9.44–9.72, respectively. These protons are in close spatial proximity to the carbonyl groups that are attached to the 1 and 3 positions of the indolizine core. Only in the case of **4c**, a 3 : 1 mixture of regioisomers was formed and could be detected by the characteristic appearance of four discrete s for the MeO protons at δ 3.67, 3.69, 3.70, and 3.74. For all other examples, only a single set of signals in the ^1H - and ^{13}C -NMR spectra clearly

⁹⁾ CCDC-268063 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request.cif.

Table 1. *One-Pot Synthesis of Indolizines 4*

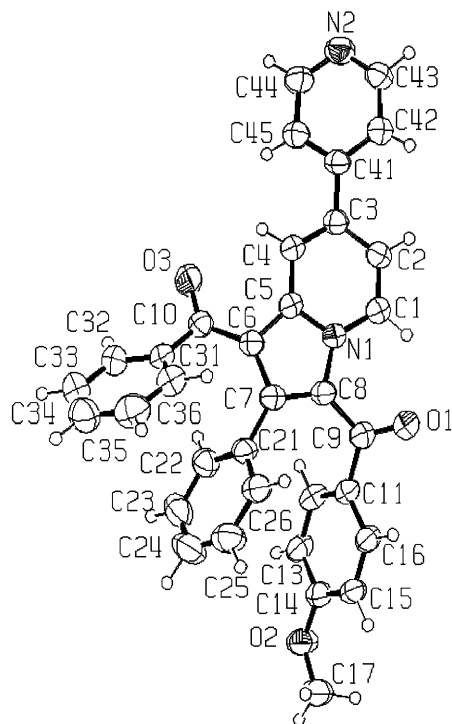
Acyl chloride	Alkyne	Pyridinium salt	Indolizine [yield]
1a R ¹ = Ph	2a R ² = Ph	3a R ³ = EtO, R ⁴ = H	4a (55%)
1a R ¹ = Ph	2a R ² = Ph	3b R ³ = 4-MeO-C ₆ H ₄ , R ⁴ = H	4b (51%)
1b R ¹ = 4-MeO-C ₆ H ₄	2a R ² = Ph	3b R ³ = 4-MeO-C ₆ H ₄ , R ⁴ = H	4c (58%) ^{b)}
1a R ¹ = Ph	2a R ² = Ph	3c R ³ = 4-MeO-C ₆ H ₄ , R ⁴ = pyridin-4-yl	4d (58%) ^{b)}
1b R ¹ = 4-MeO-C ₆ H ₄	2a R ² = Ph	3c R ³ = 4-MeO-C ₆ H ₄ , R ⁴ = pyridin-4-yl	4e (46%)
1c R ¹ = 2-thienyl	2b R ² = Bu	3d R ³ = EtO, R ⁴ = pyridin-4-yl	4f (42%)
1a R ¹ = Ph	2a R ² = Ph	3d R ³ = EtO, R ⁴ = pyridin-4-yl	4g (59%)
1b R ¹ = 4-MeO-C ₆ H ₄	2a R ² = Ph	3d R ³ = EtO, R ⁴ = pyridin-4-yl	4h (42%)
1d R ¹ = 4-NO ₂ -C ₆ H ₄	2a R ² = Ph	3c R ³ = 4-MeOC ₆ H ₄ , R ⁴ = pyridin-4-yl	4i (41%)
1b R ¹ = 4-MeO-C ₆ H ₄	2c R ² = ^t BuMe ₂ SiOCH ₂	3c R ³ = 4-MeO-C ₆ H ₄ , R ⁴ = pyridin-4-yl	4j (53%)
1a R ¹ = Ph	2d R ² = ^t BuMe ₂ SiO(CH ₂) ₄	3c R ³ = 4-MeO-C ₆ H ₄ , R ⁴ = pyridin-4-yl	4k (51%)

a)



b) Obtained as an inseparable 3 : 1 mixture of regioisomers.

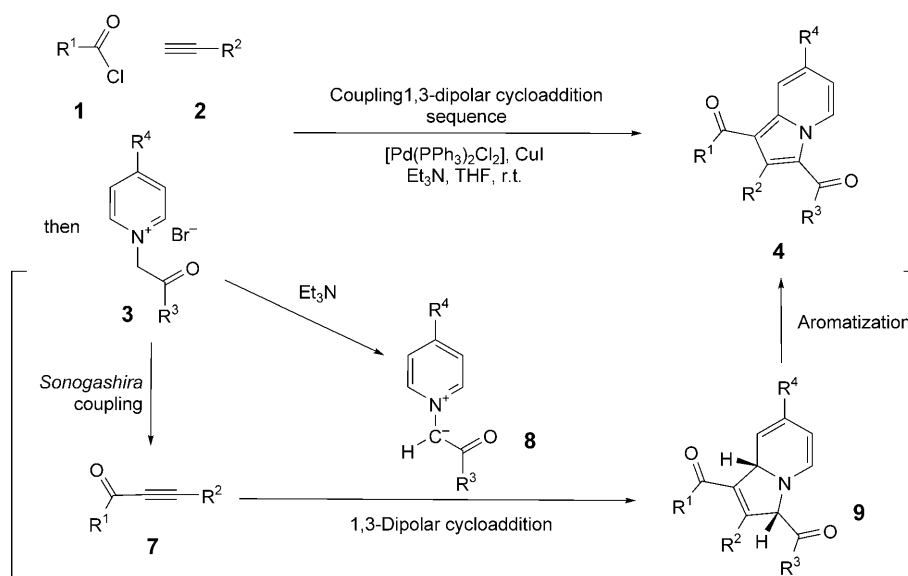
indicated the high regioselectivity of the concluding cycloaddition step. In the ¹³C-NMR spectra of **4** and **6**, the two significant C=O resonances at δ 162.1–187.4 for the ester and the (hetero)aryl ketone moieties and at δ 183.9–192.7 for the aryl ketone carbonyl groups unambiguously support the structural assignment. Likewise, in the IR spectra, the C=O stretching vibrations for the esters can be found at 1674–1681 cm⁻¹ and at 1572–1600 cm⁻¹ for the (hetero)aryl ketones.

Fig. 1. Crystal structure of indolizine **4d**

The tentative mechanism of this one-pot sequence can be described as follows (*Scheme 3*). After the *Sonogashira* coupling of acyl chloride **1** and alkyne **2** furnishing an alkynone **7**, the added 1-(2-oxoethyl)pyridinium bromide **3** is deprotonated by Et_3N to give the resonance-stabilized pyridinium ylide **8**, an allyl-type 1,3-dipole [9], that readily undergoes a 1,3-dipolar cycloaddition with **7** to give the dihydroindolizine **9** as the expected cycloadduct. In agreement with literature precedence [11b][14], only the indolizines **4** were isolated as a consequence of oxidative aromatization. However, a synergistic influence of the Pd and/or Cu species on the aromatization process, still present in the reaction mixture can not be fully excluded.

Fluorescence Properties of Indolizines 4 and Biindolizines 6. As shown in previous studies [11], quite a number of representatives of the class of indolizines and biindolizines with related structure are highly fluorescent, some of the biindolizines even with remarkably high quantum yield. A survey of the emission properties of the 7-(pyridin-4-yl)-substituted indolizines **4d–h, j, k** and biindolizines **6** strongly reveals that the one-pot coupling/1,3-dipolar cycloaddition sequence discloses a new access to this class of yellow-green (**6**) and yellow (**4**) fluorophores (*Table 2*). The *Stokes* shifts for the biindolizines are considerably smaller than for the 7-(pyridin-4-yl)-substituted indolizines. In agreement with [15], the nitrophenyl-substituted compound **4i** shows no fluorescence activity at all.

Scheme 3. Mechanistic Rationale of the Coupling-1,3-Dipolar Cycloaddition Sequence

Table 2. Selected UV/VIS and Fluorescence Properties of Indolizines **4** and Biindolizines **6** in CH₂Cl₂

	$\lambda_{\text{max,abs}}$ [nm] (ϵ)	$\lambda_{\text{max,em}}$ [nm]	Stokes shift $\Delta\bar{\nu}^a$ [cm ⁻¹]
4d	382 (28800)	508	6500
e	380 (25500)	509	6700
f	364 (15900)	502	7500
g	374 (16200)	497	6600
h	356 (18600)	495	7900
j	384 (27200)	512	6500
k	382 (22600)	510	6600
6a	432 (36400)	460	1400
b	434 (37500)	460	1300

^a) $\Delta\bar{\nu} = 1/\lambda_{\text{max,abs}} - 1/\lambda_{\text{max,em}}$.

From the perspective of perturbation theory, the inspection of the frontier orbitals of a model, 7-(pyridin-4-yl)indolizine (**10**; see Fig. 2) calculated on the DFT level of theory (B3LYP G-31** density functional)¹⁰ reveals that acceptor substituents at positions 1 and 3 of the indolizine core have a higher impact on the HOMO than on the LUMO (see Fig. 2). Furthermore, the longest-wavelength π - π^* transition, also reflecting the S₀-S₁ excitation, displays a dominant charge-transfer character with a significant mutual HOMO-LUMO overlap in a relatively rigid 7-(pyridin-4-yl)indolizine framework. Therefore, the absorption maxima vary in a wider span than the corresponding emission maxima (see Table 2). Altering the substituent at the 2-position from aryl (see **4d** or **4e**) to alkyl (see **4j** or **4k**) only has a minor influence on

¹⁰) As implemented in PC Spartan Pro, Wavefunction Inc., Irvine, CA, 2002.

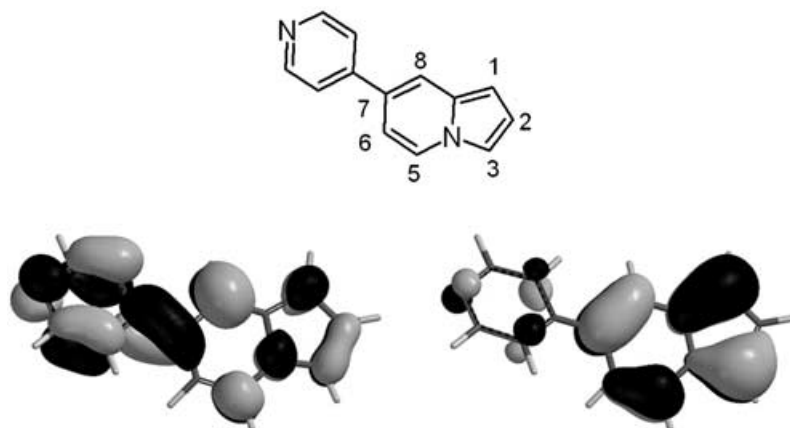


Fig. 2. Numbering (top), LUMO (left), and HOMO (right) of the model 7-(pyridin-4-yl)indolizine (**10**)

absorption and emission properties, consistent with the minor (LUMO) or zero (HOMO) coefficients in the frontier orbitals. The increased extension of the π -electron system in the biindolizines **6** expectedly shifts the absorption maxima bathochromically (see Table 2). Yet, due to the twisted biindolizine framework and the less-pronounced charge-transfer character of the π - π^* transition (see Fig. 3), the emission maxima are considerably shifted to shorter wavelengths, now resulting in smaller Stokes shifts.

The presence of a basic pyridine N-atom in the pyridinyl-substituted indolizines **4d–k** invites to scrutinize the pH dependence of the emission properties. According to DFT calculations (B3LYP G-31** density functional)¹⁰, not only the HOMO–LUMO gap reduces upon protonation (**10**: HOMO – 5.19 eV, LUMO – 1.35 eV; **10**·H⁺: HOMO – 8.60 eV, LUMO – 6.03 eV), but also the ground-state dipole moment increases considerably (**10**: μ = 3.14 D; **10**·H⁺: μ = 7.31 D). Additionally, the charge-transfer character of the S₀–S₁ excitation for **10**·H⁺, as reflected by the geometry of the

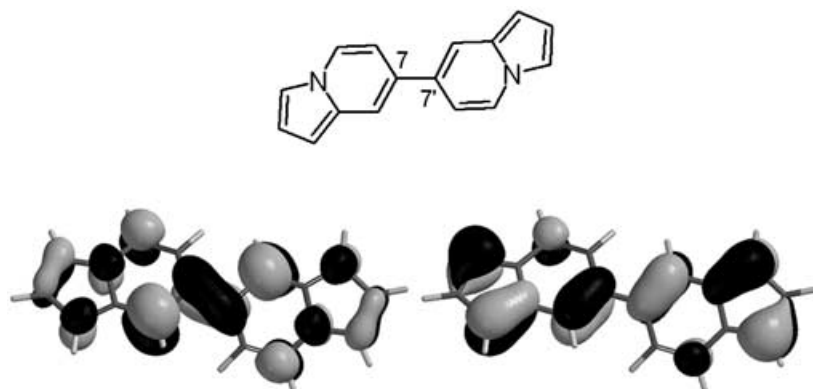


Fig. 3. LUMO (left) and HOMO (right) of the model 7,7'-biindolizine (**11**)

frontier orbitals, should be significantly increased in comparison to that of the conjugated base **10** (Fig. 4).

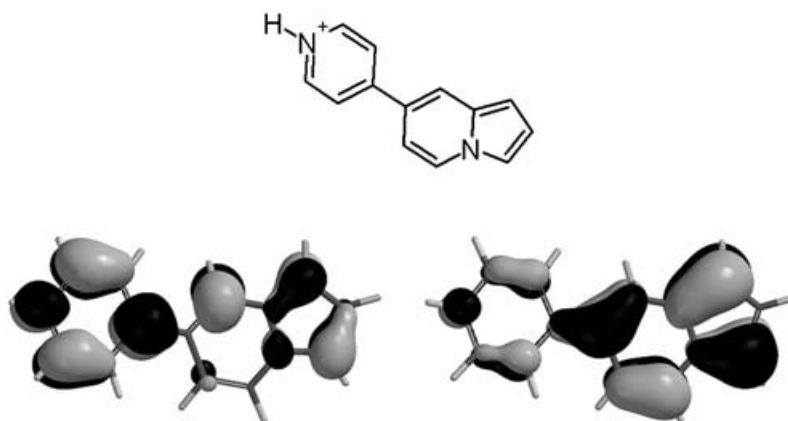


Fig. 4. LUMO (left) and HOMO (right) of the protonated 7-(pyridin-4-yl)-substituted indolizine **10**·H⁺

Therefore, upon varying the pH of a DMSO solution of **4d** from pH 4.50 (0.1M AcOH/AcONa 1:1 at pH 4.50) over pH 5.00, 6.00, 7.00, and 8.00 to pH 9.00 (with a 0.1M AcOH/AcO(Et₃NH) buffer system), the emission maxima are shifted from $\lambda_{\text{max,em}}$ 510 nm (pH 4.50) to 471 nm (pH 9.00) (Fig. 5). Most interestingly, at pH 6.00, both

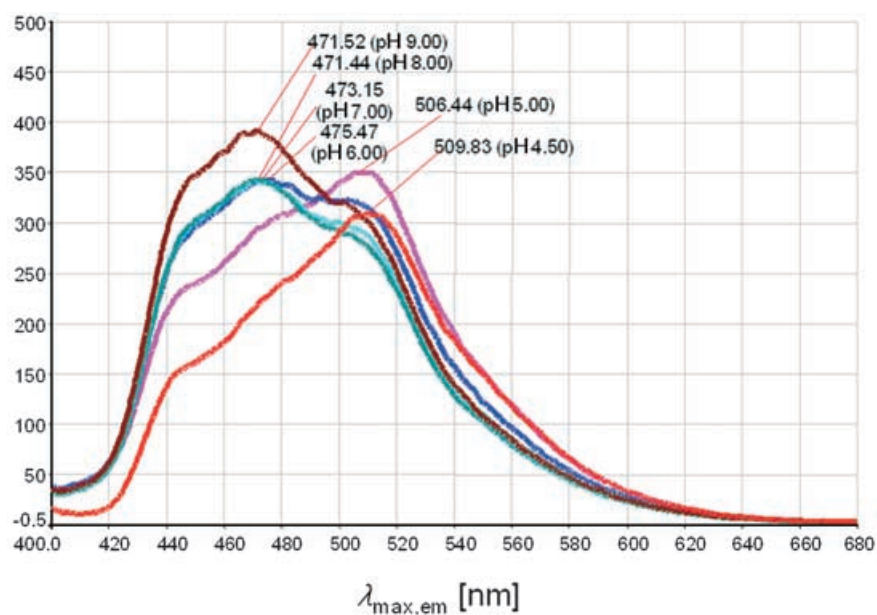
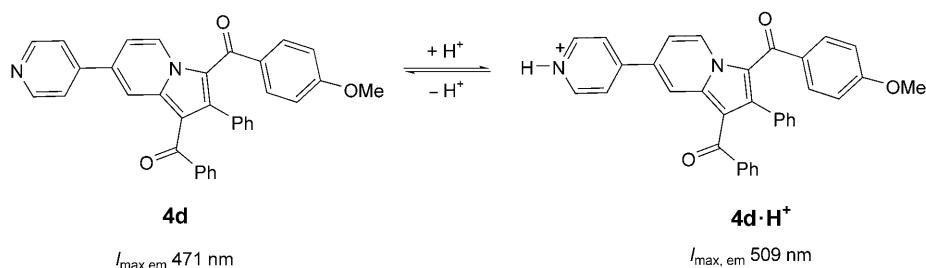


Fig. 5. Emission maxima $\lambda_{\text{max,em}}$ [nm] (arbitrary units) of **4d** at various pH. Recorded in 0.1M acetate-buffered DMSO solution. $T = 298$ K, $\lambda_{\text{max,excit}}$ 382 nm.

4d·H⁺ and its conjugated base **4d** are present in the equilibrium (*Scheme 4*) in approximately equal concentrations, hence determining the p*K*_a of **4d** to be around 6.0 in DMSO.

Scheme 4. Protonation Equilibrium of **4d** at pH 6.0



The reversibility of the pH-dependent fluorescence behavior could be nicely demonstrated by an acid-base titration of a 0.1M HCl solution of **4d** (pH 1.00) with 0.1M NaOH until pH 12.00 and back to pH 1.00 by subsequent addition of 0.1M HCl. There was no depression of the initial emission intensity indicating that the fluorescence dye **4d** is acid- and base-stable over a wide pH range and, in particular, in physiologically interesting regions. In 0.1M aqueous solutions of HCl, H₂SO₄, and AcOH, the emission maximum essentially is not shifted and appears constantly at $\lambda_{\text{max,em}}$ 520 nm indicating the absence of a counter-ion effect on the fluorescence behavior of **4d**·H⁺ (*Fig. 6*).

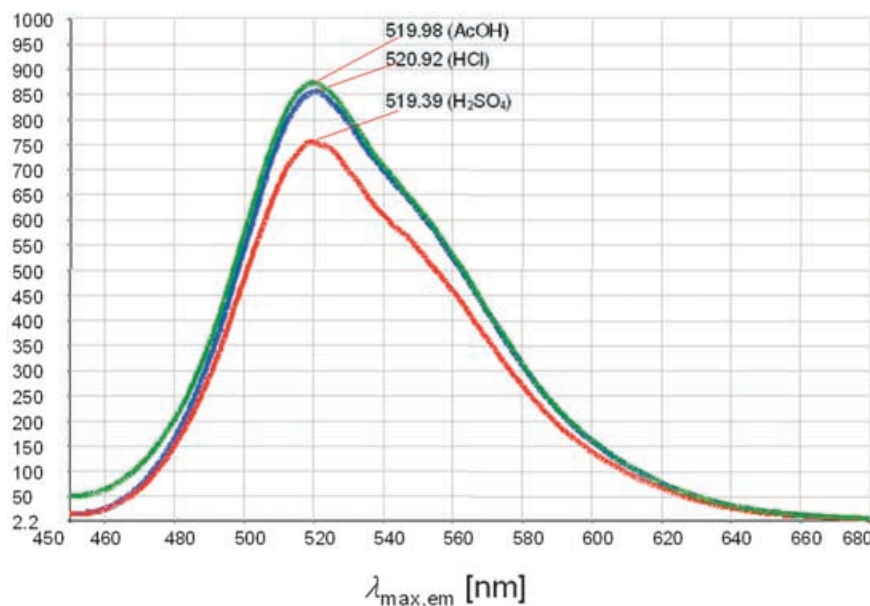


Fig. 6. Emission spectra $\lambda_{\text{max,em}}$ [nm] (arbitrary units) of **4d** in 0.1M aqueous solutions of HCl, H₂SO₄, and AcOH
T 298 K. $\lambda_{\text{max,excit}}$ 382 nm.

In conclusion, the consecutive one-pot three-component coupling-1,3-dipolar cycloaddition sequence of a (hetero)arenecarbonyl chloride, a terminal alkyne, and a suitable 1-(2-oxoethyl)pyridinium bromide is a novel methodological showcase for the combination of a cross-coupling and a sequential cycloaddition, giving rise to a broad variety of indolizines and biindolizines. In particular, this class of 7-(pyridin-4-yl)-substituted representatives display pronounced fluorescence and even strong day-light fluorescence in their protonated form. The reversibility of the protonation as well as its fluorescence sensitivity in weakly acidic media make 7-(pyridin-4-yl)indolizines ideal candidates for fluorescence labels for studying pH-dependent and pH-alternating cellular processes. Further studies are directed to the methodological development of this novel three-component reaction, and the implementation of the fluorophores in biolabeling is currently under progress.

The financial support of the DAAD (scholarship for A. V. R.), the *Fonds der Chemischen Industrie* and the *Dr.-Otto-Röhm Gedächtnisstiftung* is gratefully acknowledged.

Experimental Part

General. All reactions involving Pd/Cu catalysis were performed in degassed O₂-free solvents under N₂ by using *Schlenk* and syringe techniques. The solvents were dried according to standard procedures [16] and were distilled prior to use. For fluorescence measurements, only solvents of the corresponding purity purchased from *Fluka*, *Merck*, or *Acros*. Acyl chlorides **1**, alkynes **2**, alkynyl alcohols, α -bromo carbonyl compounds, pyridine, and 4,4'-dipyridine were purchased from *Acros* or *Merck* and used without further purification. The ^tBuMe₂Si-protected hex-5-ynol **2d** was prepared in 92% yield according to [17]. The 1-(2-oxoethyl)pyridinium bromides **3** [13⁷] and the bipyridinediium salt **5**⁸) were synthesized in analogy to literature procedures. Column chromatography (CC): silica gel 60 (mesh 70–230) or 60M (mesh 230–400) from *Merck*, Darmstadt. TLC: silica gel plates (60 F₂₅₄) or silica gel 60 F₂₅₄ on aluminium foil from *Merck*, Darmstadt. M.p.: *Büchi B-540* melting-point apparatus; uncorrected. UV/VIS Spectra: *Perkin-Elmer Lambda 16*; λ_{max} (ϵ) in nm. Fluorescence: *Perkin-Elmer LS-55*. IR Spectra: *Perkin-Elmer Lambda 3*; $\tilde{\nu}$ in cm⁻¹. ¹H- and ¹³C-NMR Spectra: *Bruker ARX-300*, *Varian VXR 400S*; CDCl₃ and (D₆)DMSO solns.; δ in ppm, J in Hz; ¹³C multiplicities from DEPT spectra. MS: *Finnigan MAT 90* and *MAT 95 Q*; 70 eV, FAB in the pos. mode; m/z (rel. int. in %). Elemental analyses were carried out in the Microanalytical Laboratories of the Organisch-Chemisches Institut, Ruprecht-Karls-Universität Heidelberg.

X-Ray Structure Determination of 4d. Suitable crystals were mounted on a capillary or on a *Hampton Research Cryo* loop and transferred to a *Bruker Smart-APEX* diffractometer. The structures were solved by direct methods and refined anisotropically on F^2 (program SHELXS-86, SHELXL-93, SHELXTL V6.12, and SADABS V2.03 for absorption correction; *G. M. Sheldrick*, University of Göttingen, and *Bruker Analytical X-ray-Division*, Madison, Wisconsin 2000 and 2001). H-Atoms were found from differential *Fourier* synthesis and refined isotropically. The data of the X-ray structure analysis of **4d** are summarized in Table 3.

One-Pot Three-Component Synthesis of Indolizines 4: General Procedure 1 (G.P. I). In a screw-cap pressure vessel, Pd(PPh₃)₂Cl₂ (14 mg, 0.02 mmol) and CuI (7 mg, 0.04 mmol) were dissolved in degassed THF (5 ml). Then acyl chloride **1** (1 mmol), alkyne **2** (1 mmol), as well as Et₃N (2 ml) were successively added to the soln. The mixture was stirred for 2 h at r.t. until the conversion was complete (monitored by TLC). Then the quaternary salt **3** (1.1 mmol) was added, and the mixture was stirred overnight at r.t. After complete conversion of the alkynone to indolizines (TLC), the mixture was evaporated and the residue purified by CC (silica gel, hexane/AcOEt 3:1): pure indolizine **4** (for exper. details, see Table 4). Further purification was achieved by crystallization.

Ethyl 1-Benzoyl-2-phenylindolizine-3-carboxylate (4a). According to G.P. I: 203 mg (55%) of **4a**. Pale-yellow crystals. M.p. 115–116° ([18] 115–116°). UV/VIS (CH₂Cl₂): 250 (36900), 358 (11400). ¹H-NMR (CDCl₃, 300 MHz): 0.93 (*t*, J = 7.1, 3 H); 4.11 (*q*, J = 7.1, 2 H); 7.01 (*dd*, J = 1.5, 6.9, 1 H); 7.03–7.34 (*m*, 10 H); 7.46 (*m*, 1 H); 8.07 (*dd*, J = 1.2, 9.1, 1 H); 9.65 (*dd*, J = 1.2, 7.1, 1 H). MS: 369 (100, M^+), 340 (11, [M – C₂H₅]⁺), 324 (2, [M – C₂H₅O]⁺), 297 (19, [M^+ – C₃H₅O₂]⁺), 292 (13, [M – C₆H₅]⁺), 264 (21, [M – C₇H₅O]⁺), 105 (18, C₇H₅O⁺), 77 (44, C₆H₅).

Table 3. *Crystal Data and Structure Refinements for 4d*

Empirical formula	C ₃₄ H ₂₄ N ₂ O ₃
M_r	508.55
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	triclinic
Space group	$P\bar{1}$
Z	2
Unit-cell dimensions	$a = 7.4689(6)$ Å, $\alpha = 98.532(2)^\circ$ $b = 11.941(1)$ Å, $\beta = 91.475(2)^\circ$ $c = 15.019(1)$ Å, $\gamma = 106.543(2)^\circ$
Volume	1266.6(2) Å ³
Density (calc.)	1.33 g/cm ³
Absorption coefficient	0.09 mm ⁻¹
Crystal size	0.39 × 0.25 × 0.08 mm ³
θ range for data collection	2.4 to 23.3°
Index ranges	$-8 \leq h \leq 8$; $-13 \leq k \leq 13$; $-16 \leq l \leq 16$
Reflections collected	8820
Independent reflections	3620 ($R(\text{int}) = 0.022$)
Observed reflections	2729 ($I > 2\sigma(I)$)
Absorption correction	
semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.97
Refinement method	full-matrix least-squares on F^2
Data/restraints/parameters	3620/0/448
Goodness-of-fit on F^2	0.99
Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.035$, $wR_2 = 0.090$
Largest diff. peak and hole [eÅ ⁻³]	0.10 and -0.17

Table 4. *Experimental Details of the One-Pot Synthesis of Indolizines 4*

Acid chloride	Alkyne	Pyridinium salt	Indolizines [yield]
1a (140 mg, 1.00 mmol)	2a (108 mg, 1.00 mmol)	3a (270 mg, 1.10 mmol)	4a (203 mg, 55%)
1a (140 mg, 1.00 mmol)	2a (108 mg, 1.00 mmol)	3b (339 mg, 1.10 mmol)	4b (295 mg, 51%)
1b (170 mg, 1.00 mmol)	2a (108 mg, 1.00 mmol)	3b (339 mg, 1.10 mmol)	4c (295 mg, 58%; 3 : 1 mixture of regioisomers)
1a (140 mg, 1.00 mmol)	2a (108 mg, 1.00 mmol)	3c (423 mg, 1.10 mmol)	4d (295 mg, 58%)
1b (170 mg, 1.00 mmol)	2a (108 mg, 1.00 mmol)	3c (423 mg, 1.10 mmol)	4e (247 mg, 46%)
1c (147 mg, 1.00 mmol)	2b (86 mg, 1.00 mmol)	3d (355 mg, 1.10 mmol)	4f (181 mg, 42%)
1a (140 mg, 1.00 mmol)	2a (108 mg, 1.00 mmol)	3d (355 mg, 1.10 mmol)	4g (263 mg, 59%)
1b (170 mg, 1.00 mmol)	2a (108 mg, 1.00 mmol)	3d (355 mg, 1.10 mmol)	4h (201 mg, 42%)
1d (186 mg, 1.00 mmol)	2a (108 mg, 1.00 mmol)	3c (423 mg, 1.10 mmol)	4i (226 mg, 41%)
1b (170 mg, 1.00 mmol)	2c (170 mg, 1.00 mmol)	3c (423 mg, 1.10 mmol)	4j (320 mg, 53%)
1a (140 mg, 1.00 mmol)	2d (212 mg, 1.00 mmol)	3c (423 mg, 1.10 mmol)	4k (315 mg, 51%)

(1-Benzoyl-2-phenylindolizin-3-yl)(4-methoxyphenyl)methanone (**4b**). According to *G.P.* 1: 295 mg (58%) of **4b**. Pale-yellow crystals. M.p. 172–173°. UV/VIS (CH₂Cl₂): 246 (38600), 366 (19300). IR (KBr): 3063, 2836, 1597, 1573, 1495, 1466, 1450, 1419, 1384, 1311, 1256, 1230, 1168, 1053, 1026, 890, 849, 758, 698, 658, 611. ¹H-NMR (CD₂Cl₂, 300 MHz): 3.66 (s, 3 H); 6.48 (m, 2 H); 6.77 (m, 3 H); 6.90 (m, 2 H); 7.04 (m, 3 H); 7.21 (dd, $J = 1.5, 7.3$, 1 H); 7.32–7.39 (m, 3 H); 7.42–7.45 (m, 2 H); 8.09 (dd, $J = 1.1, 9.2$, 1 H); 9.44 (dd, $J = 1.1, 6.9$, 1 H). ¹³C-NMR (CD₂Cl₂, 75 MHz): 55.6 (q); 113.1 (d); 113.9 (d); 115.1 (s); 119.4 (d); 121.7 (s); 126.7 (d); 127.0 (d); 127.5 (d);

127.7 (d); 127.8 (d); 129.7 (s); 131.6 (d); 132.1 (d); 134.1 (s); 138.1 (d); 139.0 (s); 139.6 (s); 139.9 (d); 162.6 (s); 187.4 (s); 192.7 (s). MS: 432 (100, $[M + H]^+$), 431 (54, M^+), 416 (5, $[M - CH_3]^+$), 354 (5, $[M - C_6H_5]^+$), 324 (3, $[M - C_7H_7O]^+$). Anal. calc. for $C_{29}H_{21}NO_3$ (431): C 80.72, H 4.91, N 3.25; found: C 80.47, H 4.88, N 3.32.

(2-Phenylindolizine-1,3-diyl)bis[(4-methoxyphenyl)methanone]/(1-Phenylindolizine-2,3-diyl)bis[(4-methoxyphenyl)methanone] (**4c**). According to G.P. I: 295 mg (58%) of **4c** (3:1 regioisomer mixture). Pale-yellow crystals. M.p. 53–54°. UV/VIS (CH_2Cl_2): 274 (28200), 362 (15400). IR (KBr): 3063, 2935, 2838, 1599, 1572, 1509, 1495, 1463, 1422, 1383, 1311, 1255, 1232, 1168, 1053, 1028, 894, 849, 785, 755, 732, 607. 1H -NMR (CD_2Cl_2 , 300 MHz): 3.67 (s, 3 H); 3.70 (s, 3 H); 6.49 (dd, $J = 2.2, 6.9, 2$ H); 6.51–6.55 (m, 2 H); 6.58 (dd, $J = 2.2, 6.9, 2$ H); 6.80–6.85 (m, 2 H); 6.91–6.94 (m, 2 H); 6.99 (td, $J = 1.5, 6.9, 1$ H); 7.26–7.33 (m, 2 H); 7.38 (dd, $J = 2.2, 6.9, 1$ H); 7.47 (dd, $J = 2.2, 6.9, 1$ H); 7.97 (dt, $J = 1.1, 8.8, 1$ H); 8.45 (dt, $J = 1.1, 6.9, 1$ H); additional signals for the minor regioisomer: 3.68 (s); 3.73 (s); 7.49–7.52 (m); 6.67 (m); 7.56–7.61 (m). ^{13}C -NMR (CD_2Cl_2 , 75 MHz): 55.64 (q); 55.66 (q); 113.1 (d); 113.4 (d); 114.3 (s); 119.3 (d); 121.5 (s); 125.1 (d); 126.2 (d); 127.0 (d); 127.6 (d); 128.5 (d); 131.1 (d); 132.0 (d); 132.1 (d); 132.4 (s); 134.3 (s); 137.9 (C_{quat}); 138.6 (s); 162.6 (s); 162.8 (s); 163.2 (s); 187.3 (s); 191.4 (s); additional signals for the minor regioisomer: 55.72 (q); 113.2 (d); 113.5 (d); 114.8 (d); 126.6 (d); 127.5 (d); 127.7 (d); 132.1 (d); 132.2 (d); 132.5 (d). FAB-MS: 462 (100, $[M + H]^+$), 461 (74, M^+). Anal. calc. for $C_{30}H_{23}NO_4$ (461.5): C 78.08, H 5.02, N 3.03; found: C 77.76, H 5.09, N 3.09.

[1-Benzoyl-2-phenyl-7-(pyridin-4-yl)indolizin-3-yl](4-methoxyphenyl)methanone (**4d**). According to G.P. I: 295 mg (58%) of **4d**. Yellow crystals. M.p. 196–197°. UV/VIS (CH_2Cl_2): 260 (44000), 382 (28800). IR (KBr): 3059, 3028, 2838, 1598, 1575, 1510, 1479, 1449, 1416, 1378, 1256, 1229, 1169, 1052, 1025, 903, 750, 659. 1H -NMR (CD_2Cl_2 , 300 MHz): 3.67 (s, 3 H); 6.49 (d, $J = 8.8, 2$ H); 6.76–6.81 (m, 3 H); 6.92 (dd, $J = 6.9, 1.5, 2$ H); 7.07 (t, $J = 7.7, 2$ H); 7.22 (t, $J = 7.3, 1$ H); 7.33 (dd, $J = 7.3, 2.2, 1$ H); 7.40 (d, $J = 8.8, 2$ H); 7.46 (d, $J = 7.7, 2$ H); 7.63 (d, $J = 6.2, 2$ H); 8.46 (s, 1 H); 8.69 (d, $J = 5.8, 2$ H); 9.49 (d, $J = 7.3, 1$ H). ^{13}C -NMR (CD_2Cl_2 , 75 MHz): 55.6 (q); 113.1 (d); 113.3 (d); 115.2 (s); 117.1 (d); 121.3 (d); 122.1 (s); 127.2 (d); 127.6 (d); 127.9 (s); 128.1 (d); 129.7 (d); 131.6 (s); 131.7 (d); 131.8 (s); 132.1 (d); 133.7 (s); 135.7 (s); 138.5 (d); 138.6 (s); 139.6 (s); 145.5 (d); 150.8 (d); 162.7 (s); 187.2 (s); 192.7 (s). MS: 509 (100, $[M + H]^+$), 508 (52, M^+), 431 (5, $[M - C_6H_5]^+$), 401 (3, $[M - C_7H_7O]^+$), 375 (3, $[M + 1 - C_8H_8O_2]^+$). Anal. calc. for $C_{34}H_{24}N_2O_3$ (508.5): C 80.30, H 4.76, N 5.51; found: C 80.21, H 4.72, N 5.59.

[2-Phenyl-7-(pyridin-4-yl)indolizin-1,3-diyl]bis[(4-methoxyphenyl)methanone] (**4e**). According to G.P. I: 247 mg (46%) of **4e**. Yellow-green crystals. M.p. 215–216°. UV/VIS (CH_2Cl_2): 274 (42500), 380 (25500). IR (KBr): 3058, 3027, 2935, 2886, 1599, 1572, 1509, 1482, 1463, 1420, 1377, 1343, 1309, 1289, 1256, 1168, 1052, 1027, 925, 906, 848, 792, 757, 611. 1H -NMR (CD_2Cl_2 , 300 MHz): 3.67 (s, 3 H); 3.7 (s, 3 H); 6.50 (d, $J = 8.8, 2$ H); 6.58 (d, $J = 8.8, 2$ H); 6.84 (m, 3 H); 6.95 (m, 2 H); 6.30 (dd, $J = 1.8, 7.3, 1$ H); 7.41 (d, $J = 8.8, 2$ H); 7.49 (d, $J = 8.8, 2$ H); 7.62 (dd, $J = 1.8, 4.4, 2$ H); 8.35 (m, 1 H); 8.68 (dd, $J = 1.5, 4.8, 2$ H); 9.50 (dd, $J = 1.1, 7.7, 1$ H). ^{13}C -NMR (CD_2Cl_2 , 75 MHz): 55.7 (q); 113.2 (d); 113.3 (d); 115.7 (s); 116.9 (d); 119.6 (d); 121.3 (s); 121.8 (d); 127.1 (d); 127.6 (d); 128.1 (d); 131.1 (d); 131.9 (s); 132.0 (d); 134.0 (s); 135.3 (s); 138.3 (d); 138.3 (s); 145.7 (d); 150.6 (d); 162.8 (s); 187.3 (s); 191.4 (s). MS: 539 (100, $[M + H]^+$), 509 (3, $[M - CH_2O]^+$), 431 (5, $[M - C_7H_7O]^+$), 403 (3, $[M - C_8H_8O_2]^+$). Anal. calc. for $C_{35}H_{26}N_2O_4$ (538.6): C 78.05, H 4.87, N 5.20; found: C 77.78, H 4.87, N 5.31.

Ethyl 2-Butyl-7-(pyridin-4-yl)-1-(2-thienylcarbonyl)indolizine-3-carboxylate (**4f**). According to G.P. I: 181 mg (42%) of **4f**. Yellow crystals. M.p. 145–146°. UV/VIS (CH_2Cl_2): 278 (44300), 364 (15900). IR (KBr): 2958, 2930, 1679, 1616, 1597, 1512, 1434, 1413, 1395, 1380, 1360, 1344, 1229, 1149, 1121, 1043, 1028, 795, 727. 1H -NMR (CD_2Cl_2 , 300 MHz): 0.91 (t, $J = 7.3, 3$ H); 1.37 (m, 2 H); 1.48 (t, $J = 7.1, 3$ H); 1.63 (m, 2 H); 3.15 (t, $J = 7.1, 2$ H); 4.48 (q, $J = 7.1, 2$ H); 7.20 (m, 2 H); 7.49 (d, $J = 5.4, 2$ H); 7.56 (d, $J = 3.2, 1$ H); 7.78 (d, $J = 4.6, 1$ H); 7.87 (s, 1 H); 8.66 (d, $J = 4.2, 2$ H); 9.71 (d, $J = 7.1, 1$ H). ^{13}C -NMR (CD_2Cl_2 , 75 MHz): 14.0 (q); 14.6 (q); 23.4 (t); 26.8 (t); 34.4 (t); 60.8 (t); 112.2 (s); 114.3 (d); 116.2 (s); 116.3 (d); 121.2 (s); 128.2 (s); 128.7 (d); 133.9 (d); 134.0 (s); 134.1 (s); 137.7 (d); 141.6 (d); 145.6 (d); 150.9 (s); 154.3 (d); 162.4 (s); 183.9 (s). MS: 433 (100, $[M + H]^+$), 405 (13, $[M - C_2H_5]^+$), 317 (5, $[M - C_4H_5S]^+$). Anal. calc. for $C_{25}H_{24}N_2O_3S$ (432.5): C 69.42, H 5.59, N 6.48; found: C 69.13, H 5.47, N 6.56.

Ethyl 1-Benzoyl-2-phenyl-7-(pyridin-4-yl)indolizine-3-carboxylate (**4g**). According to G.P. I: 263 mg (59%) of **4g**. Yellow crystals. M.p. 180–181°. UV/VIS (CH_2Cl_2): 248 (31500), 374 (16200). IR (KBr): 3132, 3059, 3028, 2982, 1681, 1637, 1620, 1597, 1511, 1479, 1480, 1447, 1415, 1398, 1380, 1343, 1243, 1187, 1149, 1036, 798, 750, 697, 661. 1H -NMR (CD_2Cl_2 , 300 MHz): 0.96 (t, $J = 7.4, 3$ H); 4.12 (q, $J = 7.3, 2$ H); 7.08–7.12 (m, 3 H); 7.14 (s, 1 H); 7.16–7.21 (m, 3 H); 7.28 (t, $J = 1.3, 7.3, 1$ H); 7.34 (dd, $J = 2.2, 7.3, 1$ H); 7.48 (m, 2 H); 7.59 (dd, $J = 1.8, 4.8, 2$ H); 8.34 (dd, $J = 0.7, 1.8, 1$ H); 8.67 (dd, $J = 1.8, 4.8, 2$ H); 9.72 (dd, $J = 1.1, 7.3, 1$ H). ^{13}C -NMR (CD_2Cl_2 , 75 MHz): 13.8 (q); 60.6 (t); 113.4 (d); 113.7 (s); 116.2 (s); 117.2 (d); 121.4 (d); 121.7 (s); 127.2 (d); 127.5 (d); 128.0 (d); 128.7 (d); 129.0 (s); 129.6 (d); 131.3 (d); 131.7 (d); 134.7 (s); 135.3 (s); 138.8 (s); 139.5 (s); 139.9 (s); 145.6 (s); 150.9

(*d*); 151.1 (*s*); 162.1 (*s*); 192.7 (*s*). MS: 447 (100, $[M+H]^+$), 446 (47, M^+), 341 (7, $[M-C_7H_5O]^+$), 105 (15, $C_7H_5O^+$). Anal. calc. for $C_{29}H_{22}N_2O_3$ (446.5): C 78.01, H 4.97, N 6.27; found: C 77.67, H 4.87, N 6.46.

Ethyl 1-(4-Methoxybenzoyl)-2-phenyl-7-(pyridin-4-yl)indolizine-3-carboxylate (4h). According to *G.P. 1*: 201 mg (42%) of **4h**. Pale-yellow crystals, M.p. 272–273°. UV/VIS (CH_2Cl_2): 248 (30000), 356 (18600). IR (KBr): 3059, 2979, 2886, 1680, 1636, 1599, 1573, 1510, 1482, 1466, 1415, 1396, 1380, 1257, 1228, 1186, 1168, 1150, 1078, 1031, 794, 613. 1H -NMR (CD_2Cl_2 , 300 MHz): 0.98 (*t*, $J=7.3$, 3 H); 3.75 (*s*, 3 H); 4.14 (*q*, $J=7.3$, 2 H); 6.66 (*dd*, $J=1.8$, 6.6, 2 H); 7.13–7.16 (*m*, 3 H); 7.21–7.25 (*m*, 2 H); 7.30 (*dd*, $J=1.8$, 7.3, 1 H); 7.53 (*dd*, $J=2.2$, 6.9, 2 H); 7.58 (*dd*, $J=1.5$, 4.4, 2 H); 8.23 (*m*, 1 H); 8.67 (*dd*, $J=1.5$, 4.4, 2 H); 9.70 (*dd*, $J=1.1$, 7.7, 1 H). ^{13}C -NMR (CD_2Cl_2 , 75 MHz): 13.9 (*q*); 55.8 (*q*); 60.6 (*t*); 113.4 (*d*); 116.7 (*s*); 117.2 (*d*); 121.4 (*d*); 127.3 (*d*); 127.5 (*d*); 128.0 (*d*); 128.6 (*d*); 129.6 (*d*); 131.3 (*d*); 131.8 (*d*); 132.4 (*s*); 134.7 (*s*); 134.8 (*s*); 138.3 (*s*); 139.0 (*s*); 145.6 (*s*); 150.9 (*d*); 154.2 (*s*); 162.1 (*s*); 163.0 (*s*); 191.2 (*s*). MS: 477 (100, $[M+H]^+$), 476 (49, M^+), 431 (5, $[M-C_7H_5O]^+$), 369 (6, $[M-C_7H_7O]^+$), 341 (4, $[M-C_8H_7O_2]^+$). Anal. calc. for $C_{30}H_{24}N_2O_4$ (476.5): C 75.62, H 5.08, N 5.88; found: C 75.62, H 5.12, N 5.92.

[3-(4-Methoxybenzoyl)-2-phenyl-7-(pyridin-4-yl)indolizin-1-yl](4-nitrophenyl)methanone (4i). According to *G.P. 1*: 226 mg (41%) of **4i**. Yellow solid. M.p. 231–232°. UV/VIS (CH_2Cl_2): 246 (35400), 274 (36500), 384 (25400). IR (KBr): 3068, 1600, 1573, 1520, 1477, 1419, 1379, 1347, 1315, 1257, 1226, 1198, 1169, 1111, 1074, 1053, 1028, 927, 907, 866, 849, 793, 764, 749, 730, 709, 666, 633, 613. 1H -NMR (CD_2Cl_2 , 300 MHz): 3.65 (*s*, 3 H); 6.48 (*dd*, $J=2.1$, 6.9, 2 H); 6.71–6.78 (*m*, 3 H); 6.83–6.86 (*m*, 2 H); 7.37–7.42 (*m*, 3 H); 7.47 (*dd*, $J=2.1$, 6.9, 2 H); 7.69 (*d*, $J=5.2$, 2 H); 7.80 (*dd*, $J=1.7$, 6.9, 2 H); 8.75 (*m*, 3 H); 9.49 (*dd*, $J=0.7$, 7.3, 1 H). ^{13}C -NMR (CD_2Cl_2 , 75 MHz): 55.7 (*q*); 113.2 (*d*); 113.9 (*s*); 114.2 (*d*); 117.3 (*d*); 121.5 (*d*); 122.9 (*d*); 127.7 (*d*); 128.4 (*d*); 130.3 (*d*); 131.5 (*s*); 132.1 (*d*); 132.2 (*d*); 133.4 (*s*); 137.3 (*s*); 138.6 (*s*); 139.5 (*s*); 145.3 (*s*); 145.4 (*s*); 149.1 (*s*); 151.1 (*d*); 154.3 (*s*); 163.1 (*s*); 187.3 (*s*); 190.9 (*s*). MS: 554 (73, $[M+H]^+$), 553 (42, M^+), 538 (5, $[M-CH_3]^+$), 508 (3, $[M+H-NO_2]^+$), 154 (100, $[M-C_7H_4NO_3]^+$). Anal. calc. for $C_{34}H_{23}N_3O_5$ (553.6): C 73.77, H 4.19, N 7.59; found: C 73.34, H 4.23, N 7.52.

[2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-7-(pyridin-4-yl)indolizin-1,3-diyl]bis[(4-methoxyphenyl)methanone] (4j). According to *G.P. 1*: 320 mg (53%) of **4j**. Yellow solid. M.p. 178–179°. UV/VIS (CH_2Cl_2): 246 (32200), 384 (27200). IR (KBr): 2954, 2929, 2855, 1600, 1573, 1509, 1472, 1437, 1370, 1311, 1259, 1259, 1167, 1142, 1072, 1058, 1029, 976, 912, 872, 839, 776, 632, 611. 1H -NMR (CD_2Cl_2 , 300 MHz): –0.38 (*s*, 6 H); 0.61 (*s*, 9 H); 3.85 (*s*, 3 H); 3.87 (*s*, 3 H); 4.50 (*s*, 2 H); 6.96 (*d*, $J=2.1$, 1 H); 6.98 (*d*, $J=2.4$, 2 H); 7.00 (*d*, $J=2.1$, 1 H); 7.15 (*dd*, $J=1.7$, 7.3, 1 H); 7.48 (*dd*, $J=1.4$, 4.5, 2 H); 7.78 (*d*, $J=2.1$, 1 H); 7.80 (*s*, 2 H); 7.83 (*d*, $J=2.1$, 1 H); 7.87 (*m*, 1 H); 8.62 (*d*, $J=5.6$, 2 H); 9.15 (*dd*, $J=1.0$, 7.7, 1 H). ^{13}C -NMR (CD_2Cl_2 , 75 MHz): 6.1 (*q*); 18.2 (*s*); 25.7 (*q*); 55.8 (*q*); 55.9 (*q*); 57.7 (*t*); 112.4 (*d*); 113.9 (*d*); 114.2 (*d*); 115.7 (*s*); 116.7 (*d*); 121.1 (*d*); 122.3 (*s*); 127.8 (*d*); 131.6 (*d*); 131.8 (*d*); 133.2 (*s*); 133.4 (*s*); 134.3 (*s*); 136.9 (*s*); 137.6 (*s*); 145.6 (*s*); 150.8 (*d*); 163.6 (*s*); 163.7 (*s*); 186.7 (*s*); 190.9 (*s*). MS: 607 (100, $[M+H]^+$), 606 (12, M^+), 549 (82, $[M-C_4H_9]^+$), 475 (61, $[M-C_6H_5OSi]^+$), 135 (52, $C_8H_4O_2$). Anal. calc. for $C_{36}H_{38}N_2O_5Si$ (606.8): C 71.26, H 6.31, N 4.62; found: C 71.61, H 6.35, N 4.74.

[1-Benzoyl-2-[4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]butyl]-7-(pyridin-4-yl)indolizin-3-yl](4-methoxyphenyl)methanone (4k). According to *G.P. 1*: 315 mg (51%) of **4k**. Yellow solid. M.p. 128–129°. UV/VIS (CH_2Cl_2): 248 (32200), 292 (25700), 382 (22600). IR (KBr): 3059, 2953, 2930, 2856, 1597, 1512, 1472, 1447, 1427, 1375, 1344, 1305, 1257, 1233, 1171, 1158, 1106, 1051, 1025, 984, 938, 904, 870, 837, 799, 774, 752, 698, 653, 632, 612, 570, 517. 1H -NMR (CD_2Cl_2 , 300 MHz): –0.08 (*s*, 6 H); 0.79 (*s*, 9 H); 1.06–1.17 (*m*, 2 H); 1.30–1.48 (*m*, 2 H); 2.55 (*t*, $J=7.6$, 2 H); 3.24 (*t*, $J=6.6$, 2 H); 3.88 (*s*, 3 H); 7.02 (*dd*, $J=1.9$, 6.9, 2 H); 7.21 (*dd*, $J=2.2$, 7.4, 1 H); 7.48 (*dd*, $J=1.7$, 4.6, 2 H); 7.54–7.61 (*m*, 2 H); 7.69 (*tt*, $J=1.5$, 7.4, 1 H); 7.78 (*dd*, $J=0.9$, 2.2, 1 H); 7.82–7.87 (*m*, 4 H); 8.68 (*d*, $J=5.9$, 2 H); 9.21 (*dd*, $J=0.7$, 7.4, 1 H). ^{13}C -NMR (CD_2Cl_2 , 75 MHz): –5.4 (*q*); 18.4 (*s*); 25.9 (*q*); 26.6 (*t*); 28.8 (*t*); 32.9 (*t*); 55.8 (*q*); 62.9 (*t*); 112.3 (*d*); 114.2 (*d*); 115.3 (*s*); 116.7 (*d*); 121.1 (*d*); 123.4 (*s*); 128.17 (*d*); 128.8 (*d*); 129.3 (*d*); 131.7 (*d*); 132.4 (*d*); 132.9 (*s*); 134.8 (*s*); 138.8 (*s*); 140.1 (*s*); 141.2 (*s*); 145.5 (*s*); 150.8 (*d*); 163.7 (*s*); 187.2 (*s*); 192.6 (*s*). MS: 619 (92, $[M+H]^+$), 603 (6, $[M-CH_3]^+$), 561 (32, $[M-C_4H_9]^+$), 135 (100, $C_8H_4O_2$). Anal. calc. for $C_{38}H_{42}N_2O_4Si$ (618.8): C 73.75, H 6.84, N 4.53; found: C 73.43, H 6.94, N 4.58.

Synthesis of Biindolizine 6: General Procedure 2 (G.P. 2). In a screw-cap pressure vessel, $[Pd(PPh_3)_2Cl_2]$ (14 mg, 0.02 mmol) and CuI (7 mg, 0.04 mmol) were dissolved in degassed THF (5 ml). Then acyl chloride **1** (1 mmol), alkyne **2** (1 mmol), as well as Et_3N (2 ml) were successively added to the soln. The mixture was stirred for 2 h at r.t. until the conversion was complete (monitored by TLC). Then the diquaternary salt **5** (0.5 mmol) was added, and the mixture was stirred at r.t. for 14 h. After complete conversion of the alkyne to the indolizines (TLC), the mixture was evaporated and the residue purified by CC (silica gel, hexane/AcOEt 4:1): pure biindolizine **6** (for exper. details, see Table 5). Further purification was achieved by crystallization.

Ethyl 1,1'-Dibenzoyl-3'-(4-methoxybenzoyl)-2,2'-diphenyl-[7,7'-bisindolizine]-3-carboxylate (6a). According to *G.P. 2*: 144 mg (18%) of **6a**. Yellow solid. M.p. 174–175°. UV/VIS (CH_2Cl_2): 250 (49500), 280 (48500),

Table 5. *Experimental Details of the One-Pot Synthesis of Biindolizidines 6*

Acid chloride	Alkyne	Bipyridinediium salt	Biindolizines (yield)
1a (140 mg, 1.00 mmol)	2a (108 mg, 1.00 mmol)	5 (276 mg, 0.50 mmol)	6a (144 mg, 18%)
1b (170 mg, 1.00 mmol)	2a (108 mg, 1.00 mmol)	5 (276 mg, 0.50 mmol)	6b (240 mg, 28%)

418 (38400), 432 (36400). IR (KBr): 3059, 2979, 1682, 1639, 1599, 1577, 1511, 1469, 1448, 1418, 1415, 1378, 1337, 1311, 1256, 1224, 1184, 1169, 1026, 697, 660, 614. ¹H-NMR (CD₂Cl₂, 300 MHz): 0.97 (*t*, *J* = 7.3, 3 H); 3.67 (*s*, 3 H); 4.14 (*q*, *J* = 7.3, 2 H); 6.50 (*dd*, *J* = 2.2, 6.9, 2 H); 6.74–6.83 (*m*, 3 H); 6.91–6.94 (*m*, 2 H); 7.05–7.13 (*m*, 5 H); 7.15 (*s*, 1 H); 7.18–7.24 (*m*, 4 H); 7.26–7.31 (*m*, 1 H); 7.32–7.44 (*m*, 4 H); 7.46–7.51 (*m*, 5 H); 8.35 (*d*, *J* = 1.4, 1 H); 8.46 (*d*, *J* = 1.1, 1 H); 9.46 (*d*, *J* = 7.3, 1 H); 9.69 (*dd*, *J* = 0.7, 7.3, 1 H). ¹³C-NMR (CD₂Cl₂, 75 MHz): 13.8 (*q*); 55.7 (*q*); 60.6 (*t*); 113.2 (*d*); 113.3 (*d*); 115.1 (*s*); 116.5 (*d*); 116.6 (*d*); 122.1 (*s*); 127.2 (*d*); 127.3 (*d*); 127.4 (*d*); 127.6 (*d*); 127.9 (*d*); 128.1 (*d*); 128.6 (*d*); 129.6 (*d*); 129.8 (*d*); 131.3 (*d*); 131.7 (*d*); 131.8 (*d*); 131.9 (*s*); 132.1 (*d*); 132.2 (*d*); 133.9 (*s*); 134.8 (*s*); 135.3 (*s*); 135.8 (*s*); 138.7 (*s*); 138.9 (*s*); 139.0 (*s*); 139.8 (*s*); 140.1 (*s*); 162.1 (*s*); 162.8 (*d*); 187.3 (*s*); 192.6 (*s*); 192.8 (*s*). MS: 799 (100, [*M* + H]⁺), 798 (79, *M*⁺), 753 (9, [*M* – C₂H₅O]⁺), 135 (68, C₈H₄O₂). Anal. calc. for C₃₃H₃₈N₂O₆ (798.9): C 79.68, H 4.79, N 3.51; found: C 78.82, H 4.78, N 3.56.

Ethyl 1,1',3'-Tris(4-methoxybenzoyl)-2,2'-diphenyl-[7,7'-biindolizine]-3-carboxylate (6b). According to G.P. 2: 240 mg (28%) of **6b**. Yellow solid. M.p. 205–206°. UV/VIS (CH₂Cl₂): 284 (67600), 416 (39700), 434 (37500). IR (KBr): 3059, 2979, 1680, 1638, 1600, 1573, 1510, 1467, 1418, 1377, 1338, 1309, 1256, 1227, 1183, 1168, 1029, 844, 792, 699, 612. ¹H-NMR (CD₂Cl₂, 300 MHz): 0.99 (*t*, *J* = 6.9, 3 H); 3.67 (*s*, 3 H); 3.7 (*s*, 3 H); 3.76 (*s*, 3 H); 4.14 (*q*, *J* = 6.9, 2 H); 6.50 (*dd*, *J* = 2.2, 6.9, 2 H); 6.58 (*dd*, *J* = 2.2, 6.9, 2 H); 6.67 (*dd*, *J* = 2.2, 6.9, 2 H); 6.80–6.86 (*m*, 3 H); 6.93–6.97 (*m*, 2 H); 7.14–7.17 (*m*, 3 H); 7.23–7.26 (*m*, 2 H); 7.31–7.34 (*m*, 1 H); 7.37–7.38 (*m*, 1 H); 7.41 (*dd*, *J* = 1.8, 6.6, 2 H); 7.50 (*dd*, *J* = 1.8, 6.6, 2 H); 7.55 (*dd*, *J* = 1.8, 6.6, 2 H); 8.26 (*d*, *J* = 1.1, 1 H); 8.35 (*d*, *J* = 1.1, 1 H); 9.46 (*dd*, *J* = 0.7, 7.3, 1 H); 9.67 (*dd*, *J* = 0.7, 7.3, 1 H). ¹³C-NMR (CD₂Cl₂, 75 MHz): 13.8 (*q*); 55.6 (*q*); 55.7 (*q*); 60.5 (*t*); 113.1 (*d*); 113.2 (*d*); 113.25 (*d*); 113.3 (*d*); 116.3 (*d*); 116.4 (*d*); 116.5 (*s*); 121.8 (*s*); 127.1 (*d*); 127.3 (*d*); 127.4 (*d*); 127.6 (*d*); 127.9 (*d*); 128.5 (*d*); 131.3 (*d*); 131.9 (*s*); 132.0 (*d*); 132.1 (*d*); 132.2 (*d*); 132.4 (*s*); 134.1 (*s*); 134.8 (*s*); 134.9 (*s*); 135.4 (*s*); 138.3 (*s*); 138.4 (*s*); 139.1 (*s*); 162.1 (*s*); 162.7 (*d*); 162.9 (*s*); 187.2 (*s*); 191.1 (*s*); 191.4 (*s*). MS: 859 (81, [*M* + H]⁺), 858 (73, *M*⁺), 751 (8, [*M* – C₇H₇O]⁺), 135 (100, C₈H₄O₂). Anal. calc. for C₅₅H₄₂N₂O₈ (858.9): C 76.91, H 4.93, N 3.26; found: C 74.35, H 4.96, N 3.16.

REFERENCES

- [1] a) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300; *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; b) G. H. Posner, *Chem. Rev.* **1986**, *86*, 831; c) L. Weber, K. Illgen, M. Almstetter, *Synlett* **1999**, 366; d) H. Bienaymé, C. Hulme, G. Odon, P. Schmitt, *Chem.-Eur. J.* **2000**, *6*, 3321; e) I. Ugi, A. Dömling, B. Werner, *J. Heterocycl. Chem.* **2000**, *37*, 647; f) M. Murakami, *Angew. Chem.* **2003**, *115*, 742; *Angew. Chem., Int. Ed.* **2003**, *42*, 718.
- [2] S. Kobayashi, *Chem. Soc. Rev.* **1999**, *28*, 1.
- [3] G. Balme, E. Bossharth, N. Monteiro, *Eur. J. Org. Chem.* **2003**, 4101; G. Battistuzzi, S. Cacchi, G. Fabrizi, *Eur. J. Org. Chem.* **2002**, 2671; E.-i. Negishi, C. Copéret, S. Ma, S.-Y. Liou, F. Liu, *Chem. Rev.* **1996**, *96*, 365; L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115.
- [4] S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara, *Synthesis* **1980**, 627; K. Sonogashira, in 'Metal-Catalyzed Cross-coupling Reactions', Wiley-VCH, Weinheim, 1998, p. 203–229; K. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46; E.-i. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979.
- [5] M. C. Bagley, D. D. Hughes, P. H. Taylor, *Synlett* **2003**, 259; C. G. Savarin, J. A. Murry, P. G. Dormer, *Org. Lett.* **2002**, *4*, 2071.
- [6] Y. Tohda, K. Sonogashira, N. Hagihara, *Synthesis* **1977**, 777.
- [7] A. S. Karpov, T. J. J. Müller, *Org. Lett.* **2003**, *5*, 3451; A. S. Karpov, T. J. J. Müller, *Synthesis* **2003**, 2815.
- [8] a) D. M. D'Souza, F. Rominger, T. J. J. Müller, *Angew. Chem.* **2005**, *117*, 156; *Angew. Chem., Int. Ed.* **2005**, *44*, 153; b) A. S. Karpov, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2004**, 1502; c) A. S. Karpov, F. Rominger, T. J. J. Müller, *J. Org. Chem.* **2003**, *68*, 1503; d) R. U. Braun, K. Zeitler, T. J. J. Müller, *Org. Lett.* **2001**, *3*, 3297; e) T. J. J. Müller, J. P. Robert, E. Schmälzlin, C. Bräuchle, K. Meerholz, *Org. Lett.* **2000**, *2*, 2419; f) T. J. J. Müller, M. Ansorge, D. Aktah, *Angew. Chem.* **2000**, *112*, 1323; *Angew. Chem., Int. Ed.* **2000**, *39*, 1253.

- [9] a) R. Huisgen, *Angew. Chem.* **1963**, 75, 604; *Angew. Chem., Int. Ed.* **1963**, 2, 565; b) A. Padwa, '1,3-Dipolar Cycloaddition Chemistry', John Wiley & Sons, New York, 1984.
- [10] A. R. Katritzky, A. J. Boulton, *Adv. Heterocycl. Chem.* **1978**, 23, 104.
- [11] a) A. Vlahovici, M. Andrei, I. Druta, *J. Lumin.* **2002**, 96, 279; b) A. Vlahovici, I. Druta, M. Andrei, M. Cotlet, R. Dinica, *J. Lumin.* **1999**, 82, 155; c) H. Sonnenschein, G. Hennrich, U. Resch-Genger, B. Schulz, *Dyes Pigments* **2000**, 46, 23.
- [12] a) G. Broggini, G. Zecchi, *Synthesis* **1999**, 905; b) C. Nájera, J. M. Sansano, *Curr. Org. Chem.* **2003**, 7, 1105; c) A. Padwa, D. J. Austin, L. Precedo, L. Zhi, *J. Org. Chem.* **1993**, 58, 1144.
- [13] F. Kröhnke, *Angew. Chem.* **1953**, 65, 605.
- [14] I. Druta, C. Cuciuc, C. Blanaru, E. Avram, *Ann. St. Univ. 'Al. I. Cuza' Iasi* **2001**, 9, 109; A. V. Rotaru, R. P. Danac, I. D. Druta, *J. Heterocycl. Chem.* **2004**, 41, 893; I. Druta, R. Dinica, E. Bacu, I. Humelnicu, *Tetrahedron* **1998**, 54, 10811.
- [15] B. Valeur, 'Molecular Fluorescence', Wiley-VCH, Weinheim, 2002.
- [16] 'Organikum', 21st edn., Eds. H. G. O. Becker, R. Beckert, G. Domschke, E. Fanghänel, W. D. Habicher, P. Metz, D. Pavel, and K. Schwetlick, Wiley-VCH, Weinheim – New York – Chichester – Brisbane – Singapore – Toronto, 2001.
- [17] M. W. Tongue, K. Teng, *J. Am. Chem. Soc.* **1982**, 47, 2549.
- [18] Y. Miki, Y. Hiroishi, H. Hachiken, S. Takemura, *J. Heterocycl. Chem.* **1991**, 20, 45.

Received March 4, 2005