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QUINOLINE FUSED HETEROCYCLES FROM INTRAMOLECULAR CYCLOADDITION REACTIONS[§]

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Abstract – Ring fused quinoline heterocycles such as isoxazolo-, pyrrolo- and pyrazoloquinolines (**7,9,11,14**) have been prepared by intramolecular 1,3-dipolar cycloaddition reactions starting from the suitable intermediates. The structures of the products were assigned by means of analytical and spectroscopic data.

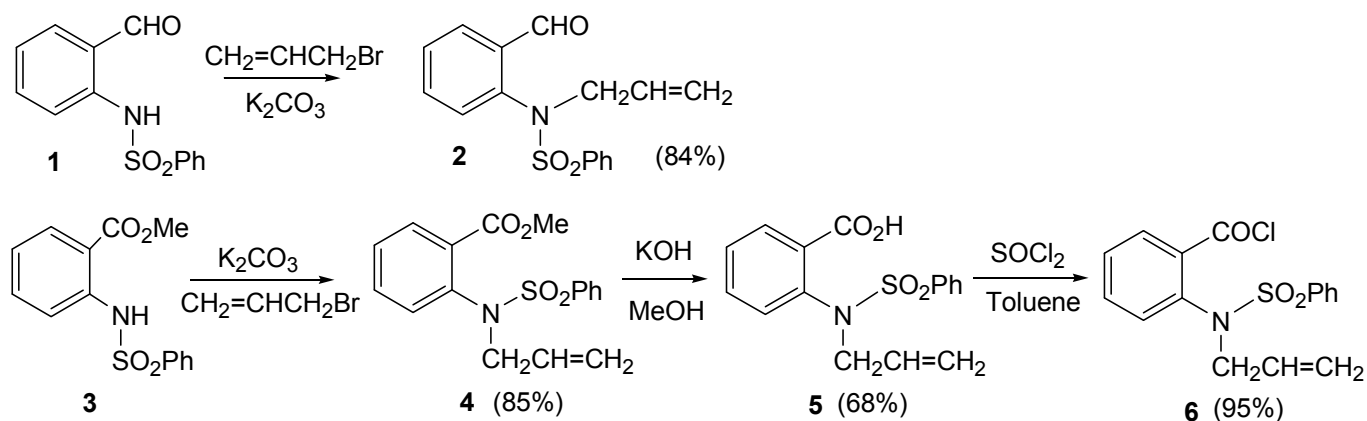
Some our previous papers concerned the use of *o*-substituted derivatives of benzenesulfonamide to obtain different classes of heterocyclic systems.¹⁻³ In continuation of our interest in this field and considering the significant applications of quinoline ring system in bioorganic⁴ and medicinal chemistry,^{5,6} we focused our attention on the synthesis of fused quinoline heterocycles by intramolecular cycloaddition reactions.

Generally, dipolar cycloaddition are an important route to a wide variety of heterocyclic compounds, some of which are intermediates in multistage synthesis or precursors of different functional groups. In particular, intramolecular 1,3-dipolar cycloadditions have proven to be very useful in preparation of ring fused heterocycles.⁷

For our synthetic protocol it was necessary to have compounds such as **2** and **6** bearing a double bond and a 1,3-dipole or its one precursor. The preparation of these substrates has been achieved following standard reactions starting from **1**⁸ and **3**⁹ respectively as reported in Scheme 1.

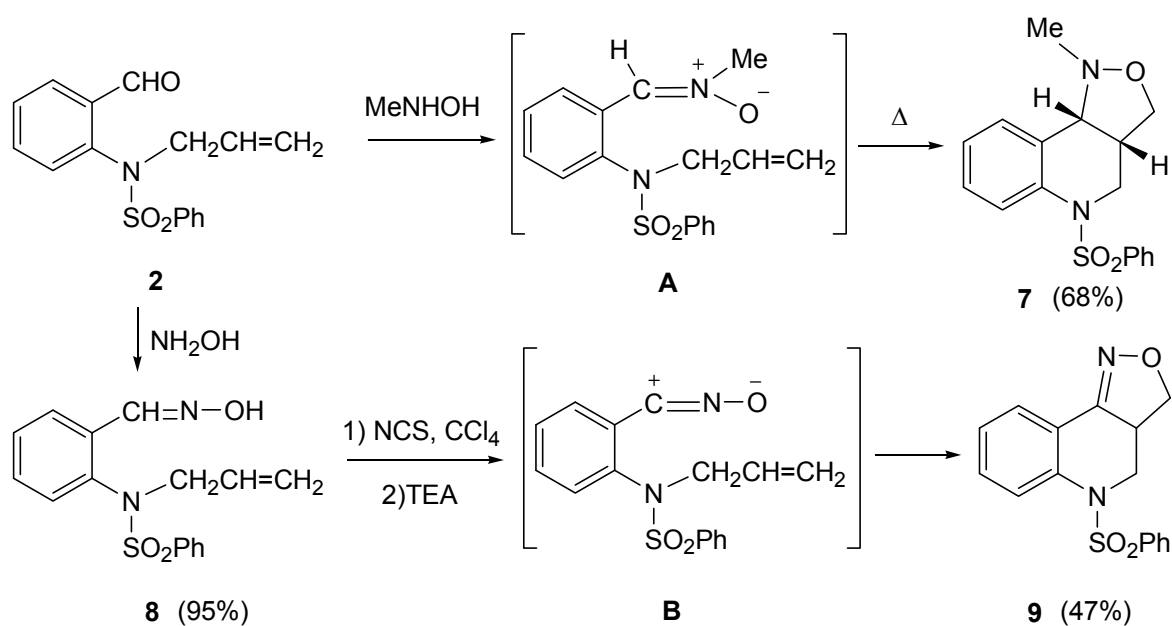
[§] This paper is dedicated to Prof. Albert Padwa in the occasion of his 75th birthday.

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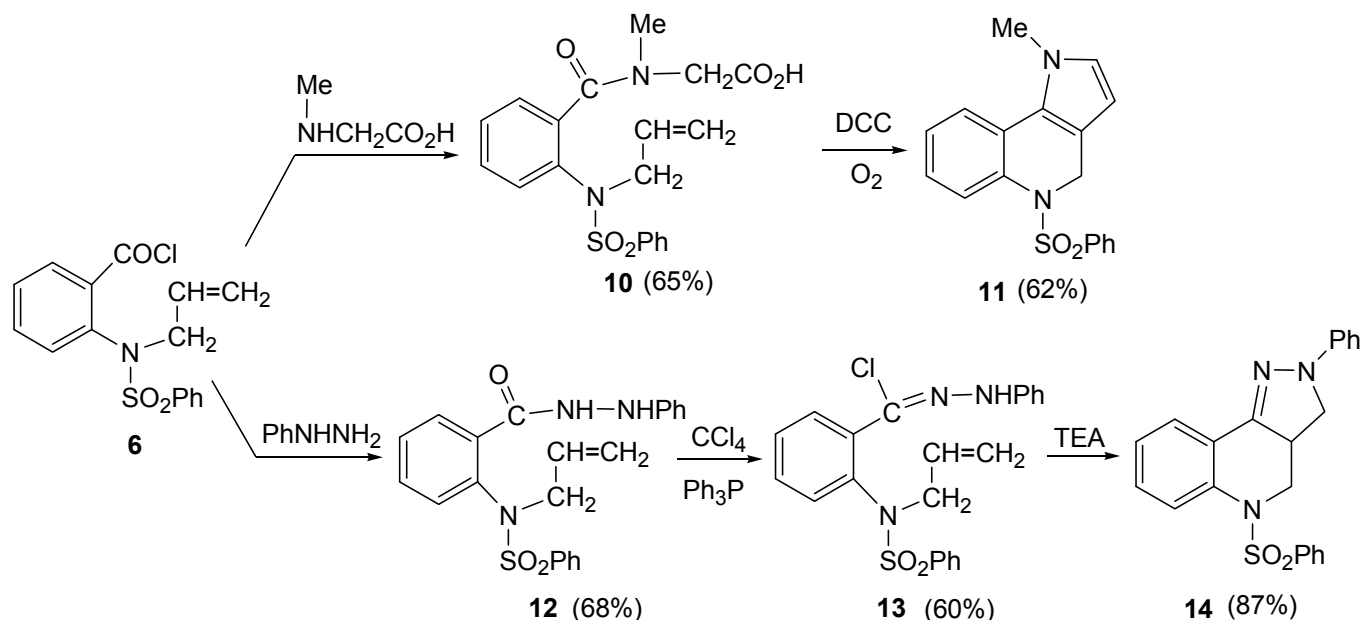
Scheme 1

The treatment of **2** with *N*-methylhydroxylamine gave the nitron **A** (not isolated), from which the final product of cycloaddition **7** was directly obtained (Scheme 2). The structure was assigned on the basis of analytical and spectroscopic data. The relative *cis* configuration between H-3a and H-9b was assigned by means of $^1\text{H-NMR}$ spectrum on the basis of their coupling constant value (6.2 Hz) as reported for other similar compounds.^{10,11} This stereochemical result is the consequence of the intramolecular pathway of the reaction and it is due to the more organized transition state, which feels the effect of the strict geometric constrain between dipole and dipolarophile, enforcing a preferred orientation of the reagents. Likewise, the action of hydroxylamine on **2** afforded oxime **8** which, after chlorination and base-mediated dehydrohalogenation, led to the nitrile oxide **B** (Scheme 2). The intramolecular addition to the double bond gave **9** whose structure was confirmed by spectroscopic data (see Experimental).



Scheme 2

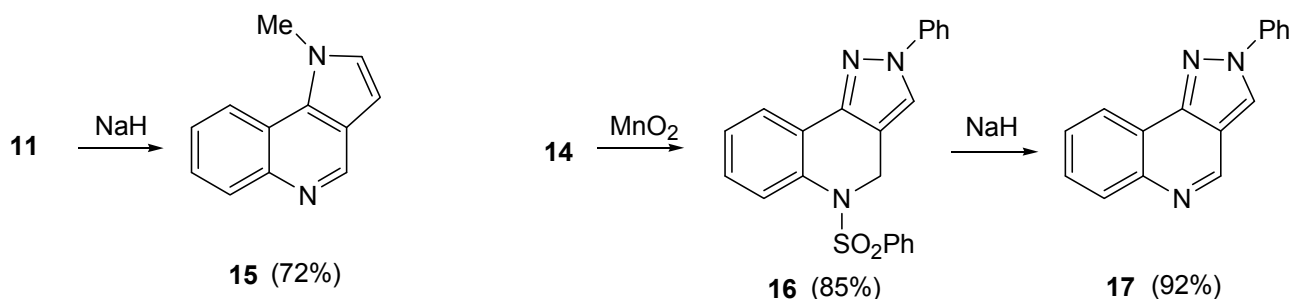
In the same way starting from **6** the reaction with sarcosine or phenylhydrazine produced the precursors of the mesoionic system and the nitrile imine, **10** and **13** respectively. From these intermediates pyrrolo- and pyrazoloquinoline **11** and **14** were obtained and their structures fully established as usually (Scheme 3).



Scheme 3

Regard to the regioselective outcome of the cycloaddition reactions, it was complete being operative only with the approach which binds carbon atom of dipoles to the inner atom of the double bond leading to the contemporary formation of two condensed rings.

Finally, according to the known behaviour of *N*-phenylsulfonyl protected heterocycles, it is possible, under basic conditions, to eliminate this group with sodium hydride in DMSO and gain the complete aromaticity of fused quinolines **15** and **17** in high yields (Scheme 4).



Scheme 4

In conclusion, this work allowed us to obtain new ring fused quinoline heterocycles with good yields and stereoselectivity, by means of the powerful intramolecular 1,3-dipolar cycloaddition methodology.

EXPERIMENTAL

Melting points were determined on a *Büchi* B-540 apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the Department. ^1H NMR spectra were recorded in CDCl_3 solution (unless otherwise indicated) using a *Bruker AMX 300 MHz* spectrometer, and chemical shifts are given in ppm relative to TMS. The MS spectra were determined using a *VG Analytical 7070 EQ* mass spectrometer with an attached *VG Analytical 11/250* data system.

***N*-Allyl-*N*-(2-formylphenyl)benzenesulfonamide (2).** To a suspension of potassium carbonate (20 mmol) in DMF (20 mL) were added **1**⁸ (19 mmol) and allyl bromide (20 mmol). The mixture was stirred overnight at rt and then treated with water (20 mL) and acetic acid to pH 6.5 to precipitate the product. The solid was filtered and purified by crystallization. Mp 75 °C (cyclohexane). Yield 84%. ^1H NMR δ : 5.1 (m, 2H, N-CH₂); 5.8 (m, 1H, CH=); 6.76 (dd, 1H, $J = 1.3$, 10.0 Hz, CH=); 7.48-7.68 (m, 9H, Ar); 8.0 (dd, 1H, $J = 1.3$, 10.0 Hz, CH=); 10.4 (s, 1H, CHO). ^{13}C NMR δ : 54.0 (N-CH₂); 120.0 (CH₂=); 127.0-145.0 (Ar); 190.0 (CHO). I.R. (cm⁻¹): 1696 ($\nu\text{C=O}$). *Anal.* Calcd for C₁₆H₁₅NO₃S: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.59; H, 4.98; N, 4.32.

2-(Allylbenzenesulfonylamino)benzoic acid methyl ester (4). This compound was prepared starting from **3**⁹ following the procedure described for **2**. Oil. Yield 84.5%. ^1H NMR δ : 3.77 (s, 3H, OCH₃); 5.03 (m, 2H, N-CH₂); 5.9 (m, 1H, CH=); 6.96 (m, 1H, CH=); 7.26-7.66 (m, 9H, Ar); 7.85 (m, 1H, CH=). ^{13}C NMR δ : 52.2 (CH₃); 54.7 (N-CH₂); 119.0 (CH₂=); 123.0-139.0 (Ar); 166.5 (CO). I.R. (cm⁻¹): 1717 ($\nu\text{C=O}$). *Anal.* Calcd for C₁₇H₁₇NO₄S: C, 61.61; H, 5.17; N, 4.23. Found: C, 61.55; H, 5.03; N, 4.08.

2-(Allylbenzenesulfonylamino)benzoic acid (5). To a solution of KOH (90 mmol) in MeOH (100 mL), **4** (30 mmol) was added and the mixture was heated to reflux for 40 h. After evaporation of the solvent and treatment with water (50 mL) the mixture was extracted with AcOEt. The aqueous layer was separated and acidified with aq. HCl 10% solution (20 mL). The product was extracted with AcOEt, the solvent evaporated to give **5** as a solid, mp 152-154 °C (toluene). Yield 68%. ^1H NMR δ : 5.06 (m, 2H, N-CH₂); 5.86 (m, 1H, CH=); 6.87 (dd, 1H, $J = 3.6$, 9.3 Hz, CH₂=); 7.42-7.86 (m, 9H, Ar); 8.63 (dd, 1H, $J = 3.6$, 9.3 Hz, CH₂=). *Anal.* Calcd for C₁₆H₁₅NO₄S: C, 60.55; H, 4.76; N, 4.41. Found: C, 60.51; H, 4.53; N, 4.28.

2-(Allylbenzenesulfonylamino)benzoyl chloride (6). A suspension of **5** (20 mmol) in toluene (40 mL) was treated with thionyl chloride (30 mmol) and stirred at 80 °C for 20 h. The solvent was evaporated and

the residue was washed with *i*-Pr₂O and filtered. Solid. Mp 98-100 °C. Yield 95%. The product was used without further purification.

5-Benzenesulfonyl-1-methyl-1,3,3a,4,5,9b-hexahydroisoxazolo[4,3-*c*]quinoline (7). A mixture of **2** (3.3 mmol), sodium acetate trihydrate (6.6 mmol) and *N*-methylhydroxylamine hydrochloride (5.4 mmol) in MeOH (10 mL) was stirred at 50 °C for 6 h. The solvent was evaporated off and the residue taken up with water/dichloromethane. The organic layer was evaporated and the residue crystallized. Solid, mp 97-98 °C (toluene/hexane 1/1). Yield 68%. ¹H NMR δ : 2.7 (s, 3H, N-CH₃); 2.8 (m, 1H, H-3a); 3.2 (d, 1H, *J* = 6.2 Hz, H-9b); 3.51 (dd, 1H, *J* = 10.0, 14.0 Hz, H-4); 3.64 (m, 1H, H-3); 4.09 (dd, 1H, *J* = 6.0, 14.0 Hz, H-4); 4.15 (m, 1H, H-3); 7.15-7.71 (m, 9H, Ar). ¹³C NMR δ : 41.5 (C-3a); 43.8 (N-CH₃); 47.6 (C-4); 65.85 (C-9b); 68.6 (C-3); 132.9-140.2 (Ar). *Anal.* Calcd for C₁₇H₁₈N₂O₃S: C, 61.80; H, 5.49; N, 8.48. Found: C, 61.84; H, 5.33; N, 8.35.

***N*-Allyl-*N*-[2-(hydroxyiminomethyl)phenyl]benzenesulfonamide (8).** A mixture of **2** (3.3 mmol), sodium acetate trihydrate (6.6 mmol) and hydroxylamine hydrochloride (5 mmol) in MeOH (10 mL) was stirred at rt for 6 h. The solvent was evaporated off and the residue treated with water. The solid precipitated was filtered, dried and crystallized from hexane. Mp 92-94 °C. Yield 95%. ¹H NMR δ : 5.0 (m, 2H, N-CH₂); 5.7 (m, 1H, CH=); 6.6 (dd, 1H, *J* = 1.3, 8.0 Hz, CH=); 7.3-7.7 (m, 9H, Ar); 7.9 (dd, 1H, *J* = 1.3, 8.0 Hz, CH=); 8.45 (s, 1H, CH=N). *Anal.* Calcd for C₁₆H₁₆N₂O₃S: C, 60.74; H, 5.10; N, 8.85. Found: C, 60.63; H, 4.97; N, 8.57.

5-Benzenesulfonyl-3,3a,4,5-tetrahydroisoxazolo[4,3-*c*]quinoline (9). To a solution of **8** (4.61 mmol) in CCl₄ (20 mL), cooled to 10 °C, NCS (4.61 mmol) was added and the mixture was stirred for 12 h. Water (20 mL) was added and the organic phase separated. The solvent was evaporated and the residue used crude owing to the low stability of the intermediate **B**. This one was dissolved in toluene (20 mL), treated with triethylamine (4.61 mmol), and the solution heated at 60 °C for 6h. After cooling, the mixture was washed with water, the toluene solution dried and the solvent evaporated. After column chromatography (SiO₂-hexane/AcOEt : 80/20) **9** was obtained as solid, mp 166-168 °C (toluene). Yield 47%. ¹H NMR δ : 3.27 (m, 1H, H-4); 3.48 (t, 1H, *J* = 14.0 Hz, H-5); 3.8 (dd, 1H, *J* = 9.0, 13.4 Hz, H-3); 4.60 (t, 1H, *J* = 9.0 Hz, H-3); 4.75 (dd, 1H, *J* = 5.0, 14.0 Hz, H-5); 7.2-7.9 (m, 9H, Ar). ¹³C NMR δ : 44.2 (C-4); 49.3 (C-5); 72.1 (C-3); 124.8-139.5 (Ar); 153.9 (C=N). *Anal.* Calcd for C₁₆H₁₄N₂O₃S: C, 61.13; H, 4.49; N, 8.91. Found: C, 60.94; H, 4.65; N, 8.85.

{[2-(Allylbenzenesulfonylamino)benzoyl]methylamino}acetic acid (10). Sarcosine (8.5 mmol) was dissolved in a solution of sodium bicarbonate (8.5 mmol) in water (20 mL). This solution was cooled to 10 °C and TEA (8.5 mmol) was added followed by a solution of **6** (8.5 mmol) in THF (15 mL). The mixture was then stirred at rt for 4 h and evaporated. The residue was taken up with aq 10% HCl (15 mL) and AcOEt, the solvent separated and evaporated. The residue was crystallized from trichloroethylene. Solid, mp 128-130 °C. Yield 65%. ¹H NMR (DMSO) (mixture of conformers) δ : 2.82, 2.97 (2s, 3H, N-CH₃); 3.58 (m, 2H, CH₂COO); 4.95 (m, 2H, N-CH₂); 5.73 (m, 1H, CH=); 6.89 (m, 1H, CH₂=); 7.19-7.74 (m, 10H, Ar and CH=); 12.82 (broad s, 1H, COOH). ¹³C NMR (mixture of conformers) δ : 34.0, 38.8 (N-CH₃); 49.2, 55.2 (N-CH₂); 119.3 (CH₂=); 127.3-139.6 (Ar and CH=); 169.7 (COO); 173.3 (CO-N). I.R. (cm⁻¹): 1736 (ν C=O). *Anal.* Calcd for C₁₉H₂₀N₂O₅S: C, 58.75; H, 5.19; N, 7.21. Found: C, 58.56; H, 5.04; N, 7.08.

5-Benzenesulfonyl-1-methyl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline (11). To a suspension of **10** (2.6 mmol) in CH₂Cl₂ (20 mL), DCC (3.0 mmol) was added and the reaction mixture was stirred at rt 24 h, insufflating dry oxygen. The precipitated dicyclohexylurea was filtered and the solvent evaporated. The residue was purified by column chromatography (SiO₂-toluene/AcOEt-9/1). Solid, mp 154-156 °C (toluene). Yield 62%. ¹H NMR δ : 3.35 (s, 3H, N-CH₃); 4.78 (s, 2H, H-4); 5.87 (d, 1H, *J* = 2.5 Hz, H-3); 6.32 (d, 1H, *J* = 2.5 Hz, H-2); 7.0-7.8 (m, 9H, Ar). MS (FAB) *m/z* = 324 [M⁺]. *Anal.* Calcd for C₁₈H₁₆N₂O₂S: C, 66.64; H, 4.97; N, 8.64. Found: C, 66.55; H, 4.88; N, 8.43.

N-Allyl-N-[2-(N'-phenylhydrazinocarbonyl)phenyl]benzenesulfonamide (12). To a solution of phenylhydrazine (11.0 mmol) in toluene (40 mL) containing TEA (11.0 mmol), cooled to 10 °C, a solution of **6** in THF (15 mL) was added. The reaction mixture was stirred at rt overnight and the solvent was evaporated. The residue was taken up with aq 10% Na₂CO₃ and CH₂Cl₂. The organic layer was dried (Na₂SO₄) and the solvent evaporated. Column chromatography (SiO₂-hexane/toluene- 50/50) gave **12** as a solid, mp 118-120 °C (toluene/hexane – 50/50). Yield 68%. ¹H NMR δ : 4.2 (broad s, 1H, NH); 5.01 (m, 2H, N-CH₂); 5.69 (m, 1H, CH=); 6.49 (d, 1H, *J* = 8.0 Hz, CH₂=); 6.91-7.8 (m, 15H, Ar and CH₂=); 9.07 (broad s, 1H, NH). ¹³C NMR δ : 55.6 (N-CH₂); 120.6 (CH₂=); 127.8-148.0 (Ar and C=); 166.9 (CO). I.R. (cm⁻¹): 1688 (ν C=O). *Anal.* Calcd for C₂₂H₂₁N₃O₃S: C, 64.85; H, 5.19; N, 10.31. Found: C, 64.72; H, 5.07; N, 10.14.

N-Allyl-N-[2-(N'-phenylhydrazonochloromethyl)phenyl]benzenesulfonamide (13). A solution of **12** (4.9 mmol) in acetonitrile (20 mL) containing triphenylphosphine (6.5 mmol) and CCl₄ (5.2 mmol) was

stirred at rt for 48 h. The solvent was evaporated and the residue purified by column chromatography (SiO₂-toluene /AcOEt-80/20). Solid, mp 92-94 °C (*i*-Pr₂O). Yield 60%. ¹H NMR δ: 4.33 (broad s, 1H, NH); 5.09 (m, 2H, N-CH₂); 5.98 (m, 1H, CH=); 6.95-7.85 (m, 15H, Ar and CH₂=). *Anal.* Calcd for C₂₂H₂₀ClN₃O₂S: C, 62.04; H, 4.73; N, 9.87. Found: C, 61.87; H, 4.62; N, 9.69.

5-Benzenesulfonyl-2-phenyl-3,3a,4,5-tetrahydro-2H-pyrazolo[4,3-*c*]quinoline (14). To a solution of **13** (1,12 mmol) in toluene (10 mL), TEA (1.7 mmol) was added and the mixture was heated at 50 °C for 12 h. The solvent was evaporated and the residue purified by column chromatography (SiO₂-toluene). Solid, mp 127-129 °C (toluene/hexane). Yield 87%. ¹H NMR δ: 3.14 (m, 2H, H-4 and H-5); 3.47 (m, 1H, H-3); 4.06 (m, 1H, H-5); 4.77 (dd, 1H, *J* = 4.2, 13.6 Hz, H-3); 6.88-7.97 (m, 14H, Ar). ¹³C NMR δ: 40.9 (C-4); 49.6 (C-3); 53.0 (C-5); 113.4-146.7 (Ar). I.R. (cm⁻¹): 1600 (ν C=N). *Anal.* Calcd for C₂₂H₁₉N₃O₂S: C, 67.84; H, 4.92; N, 10.79. Found: C, 67.75; H, 4.86; N, 10.65.

1-Methyl-1H-pyrrolo[3,2-*c*]quinoline (15). To a solution of **11** (0.9 mmol) in DMSO (5 mL), NaH (1.0 mmol) was added and the mixture was stirred at rt for 12 h. After addition of water (10 mL) the mixture was extracted with AcOEt and the solvent evaporated. The crude product was crystallized from cyclohexane. Solid, mp 80-82 °C. Yield 72%. ¹H NMR δ: 4.3 (s, 3H, N-CH₃); 6.73 (d, 1H, *J* = 3.0 Hz, H-3); 7.1 (d, 1H, *J* = 3.0 Hz, H-2); 7.6 (m, 2H, Ar); 8.25 (d, 1H, *J* = 8.3 Hz, Ar); 8.42 (d, 1H, *J* = 7.8 Hz, Ar); 9.14 (s, 1H, H-4). MS (FAB) *m/z* = 183 [M⁺]. *Anal.* Calcd for C₁₂H₁₀N₂: C, 79.10; H, 5.53; N, 15.37. Found: C, 78.95; H, 5.46; N, 15.22.

5-Benzenesulfonyl-2-phenyl-4,5-dihydro-2H-pyrazolo[4,3-*c*]quinoline (16). A mixture of **14** (2.3 mmol) and MnO₂ (10.0 mmol) in CH₂Cl₂ (20 mL) was stirred at rt overnight. The suspension was filtered, washed with the same solvent and evaporated. The residue was purified by column chromatography (SiO₂-ACOEt) and crystallized from *i*-Pr₂O. Solid, mp 165-166 °C. Yield 85%. ¹³C NMR δ: 40.9 (C-4); 49.6 (C-3); 53.0 (C-5); 113.4-146.7 (Ar). MS (EI) *m/z* = 387 [M⁺]. *Anal.* Calcd for C₂₂H₁₇N₃O₂S: C, 68.20; H, 4.42; N, 10.85. Found: C, 68.07; H, 4.35; N, 10.74.

2-Phenyl-2H-pyrazolo[4,3-*c*]quinoline (17). To a solution of **16** (1.0 mmol) in DMSO (10 mL) NaH (1.1 mmol) was added and the mixture was stirred at rt for 12 h. After addition of water (20 mL) the suspension was extracted with AcOEt (20 mL) and the solvent evaporated. The residue was crystallized from *i*-Pr₂O. Solid, mp 144-146 °C. Yield 92%. MS (EI) *m/z* = 246 [M⁺]. Lit.,¹² 140-142 °C. The spectroscopic data (¹H NMR) agree with those reported.

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