Synthesis of Some New Indolizine and Pyrrolo[1,2-*a*]quinoline Derivatives *via* Nitrogen Ylides

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Z. Naturforsch. **2009**, *64b,* 434 – 438; received November 18, 2008

Pyridine and quinoline react with 3-bromoacetyl-1,5-diphenyl-1*H*-pyrazole-4-carbonitrile (**2**) in dry benzene to give the corresponding pyridinium and quinolinium salts **3** and **9**. The latter salts undergo [3+2] 1,3-dipolar cycloaddition with some acetylene and ethylene derivatives to give the corresponding indolizine and pyrrolo[1,2-*a*]quinoline derivatives.

Key words: Indolizine, Pyrrolo[1,2-*a*]quinolines, Pyrazoles, *N*-Ylides, Cycloaddition

Introduction

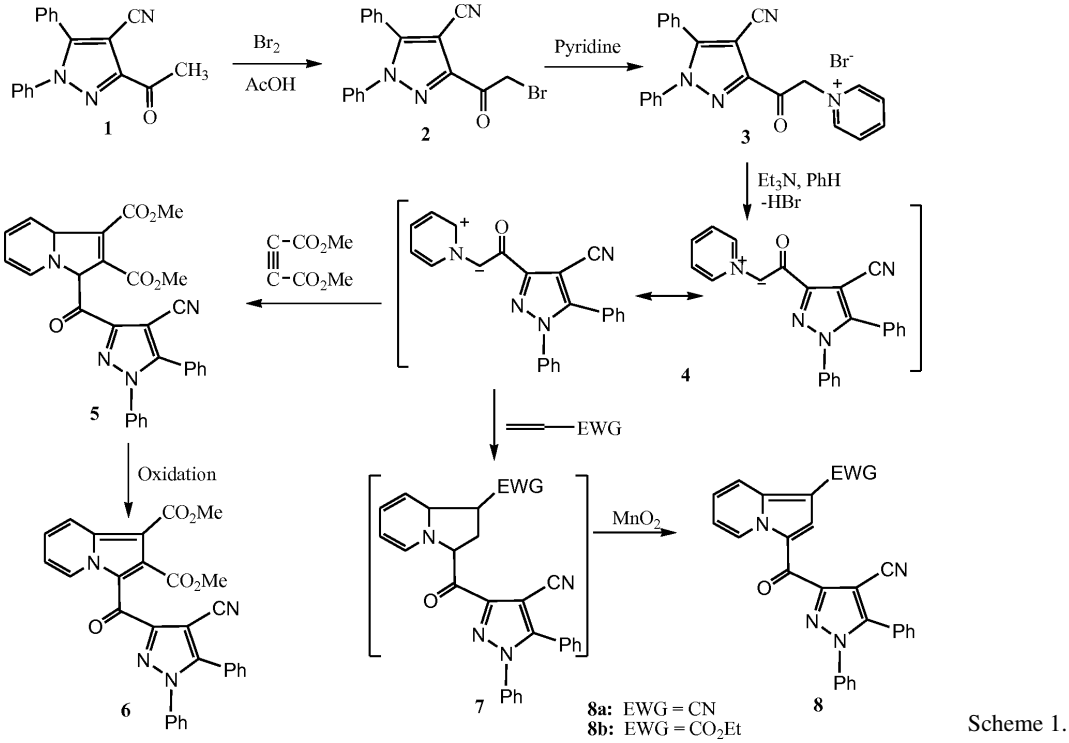
The indolizine moiety was found in several naturally occurring alkaloids with significant biological impotance [1 – 4]. Indolizine derivatives have also been found to possess anti-inflammatory [5], antiviral [6], analgesic [7], and antitumor [8 – 10] activities. Furthermore, quinolinium salts were found to be potent inhibitors of lymphocyte apoptosis [11] and protein kinase C [12]. On the other hand, pyrrolo[1,2-*a*]quinolines are reported as tumor inhibitors [13, 14]. The use of heteroaromatic *N*-ylides as 1,3-dipoles has received increasing interest in the synthesis of new condensed heterocyclic structures *via* [3+2] cycloaddition [15 – 19]. As part of our research work on developing new routes for biologically highly active fused heterocycles [20 – 26], we describe here a facile access to some indolizine and pyrrolo[1,2-*a*]quinoline derivatives utilizing some new versatile *N*-ylides derived from their pyridinium and quinolinium salts.

Results and Discussion

3-Bromoacetyl-1,5-diphenyl-1*H*-pyrazole-4-carbonitrile (**2**) was found to be an excellent building block for the synthesis of numerous pyrazolyl-indolizines and pyrazolyl-pyrrolo[1,2-*a*]quinolines. Compound **2** was prepared by reaction of 3-acetyl-1,5-diphenyl-1*H*-pyrazole-4-carbonitrile (**1**) with bromine in glacial acetic acid as reported by us earlier [27].

Treatment of the 3-(bromoacetyl)pyrazole **2** with pyridine in refluxing dry benzene afforded the corresponding pyridinium bromide salt **3** in quantitative yield (Scheme 1). The structure of the isolated bromide salt **3** was confirmed by elemental and spectral data as well as chemical transformations that are outlined in Scheme 1. When the pyridinium bromide salt **3** was treated with dimethyl acetylenedicarboxylate (DMAD) as dipolarophile in dry benzene at reflux temperature, in the presence of triethylamine, it furnished only one isolable product based on TLC analysis. The structure of the reaction product was ascertained on the basis of elemental analysis and spectral data, as indolizine-1,2-dicarboxylate **6** (Scheme 1). The ^{1}H NMR spectrum of compound **6** revealed two singlet signals at δ = 3.4 and 3.83 due to two methyl ester groups. The IR spectrum showed three carbonyl absorptions at 1748, 1710 and 1632 cm^{-1}. The indolizine derivative **6** is assumed to be formed *via* the 1,3-dipolar cycloaddition of DMAD to the nitrogen ylide **4** [which was formed *in situ* through the reaction of the pyridinium salt **3** with triethylamine in refluxing benzene] to give the non-isolable intermediate **5** which was oxidized under the reaction conditions to give **6**.

The pyridinium salt **3** reacted also with acrylonitrile and with ethyl acrylate in refluxing benzene, in the presence of triethylamine and manganese dioxide, and afforded in each case only one product. The structures of the isolated products were established as indolizine-1-carbonitrile **8a** and indolizine-1-carboxylate **8b** (Scheme 1) on the basis of elemental analyses and spectral data. For compound **8b** as an example, there were no further aliphatic carbons besides those of the ethyl group in both the ^{1}H and ^{13}C NMR spectra which excludes the presence of the



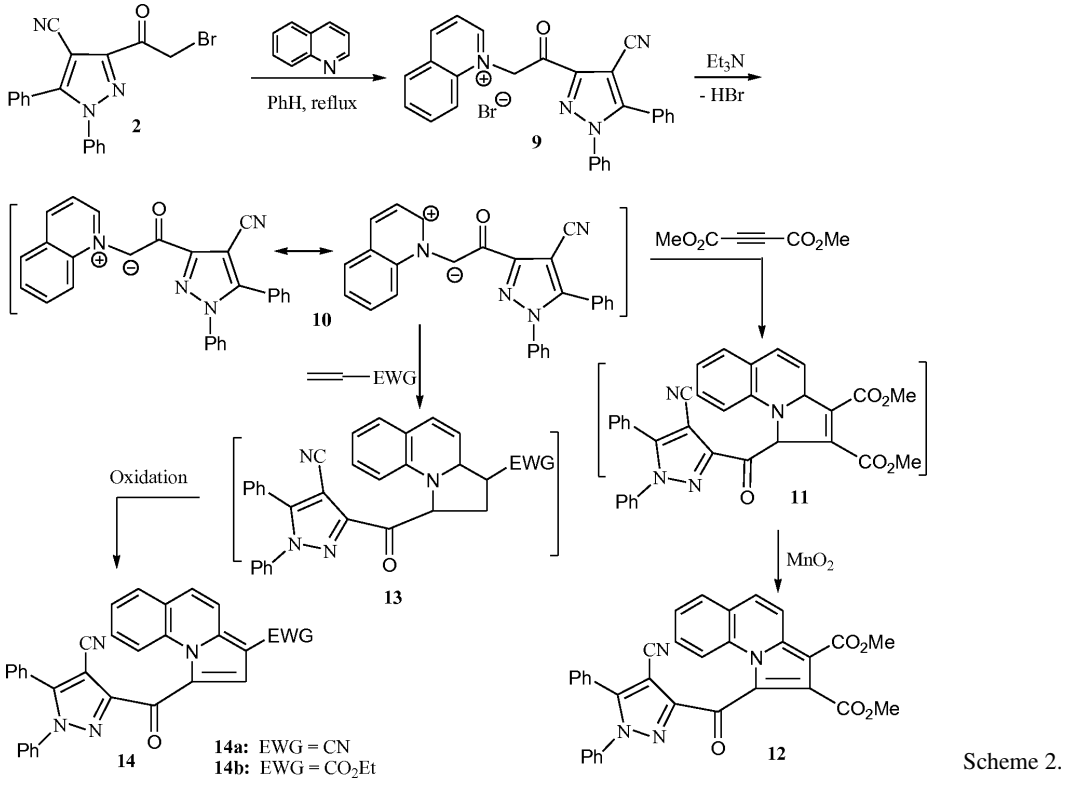
Scheme 1.

intermediate **7b**. The two carbonyl functions appeared at 1701 and 1643 cm^{-1} in the IR spectrum and at δ = 162.9, 172.6 in the ^{13}C NMR spectrum. Formation of the indolizine derivatives **8a**,**b** is assumed to proceed *via* a reaction sequence of [3+2] cycloaddition of the *N*-ylide **4** with the alkene derivative to form the non-isolable tetrahydroindolizine **7** followed by oxidation with manganese dioxide to give the target indolizine products **8a**,**b** as depicted in Scheme 1.

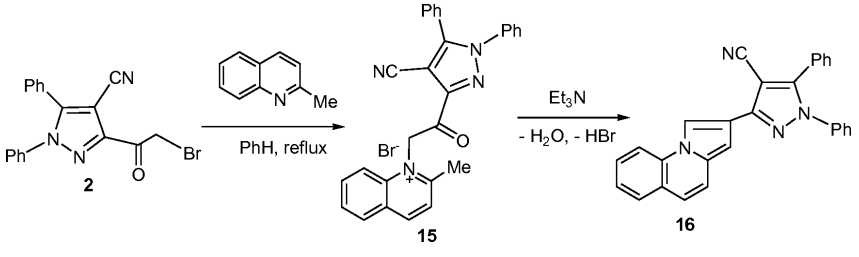
Treatment of the 3-(bromoacetyl)pyrazole **2** with quinoline in refluxing dry benzene afforded the quinolinium bromide salt **9** in quantitative yield (Scheme 2). The structure of **9** was established on the basis of elemental analyses and spectroscopic data. When salt **9** was treated with DMAD in dry benzene at refluxing temperature, in the presence of triethylamine, it gave only one isolable product based on the TLC analysis. The structure of the reaction product was confirmed, based on elemental analysis and spectral data, as the pyrrolo[1,2-a]quinoline-2,3-dicarboxylate **12** (Scheme 2). The ^1H NMR spectrum of compound **12** revealed two characteristic singlet signals at δ = 3.59 and 3.85 due to two methyl ester groups. The IR spectrum showed three carbonyl absorption peaks at 1740, 1708 and 1661 cm^{-1}. **12** is assumed to be formed *via* the 1,3-dipolar cycloaddition of DMAD to the nitrogen ylide **11** [which was formed *in situ* through the reaction of the quinolinium salt **9** with triethylamine in benzene] to give the non-isolable intermediate **11** which was then oxidized under the reaction conditions to give the product **12**, as depicted in Scheme 2.

Reaction of the quinolinium salt **9** with acrylonitrile or with ethyl acrylate in refluxing benzene in the presence of triethylamine and manganese dioxide resulted in the formation of the corresponding pyrrolo[1,2-*a*]quinoline-3-carbonitrile **14a** and ethyl pyrrolo[1,2-*a*]quinoline-3-carboxylate **14b**, respectively (Scheme 2). The assignment of structures **14a**,**b** was based on the elemental analyses and spectral data of the reaction products.

Next, 2-methylquinolinium salt **15** was prepared in quantitative yield by the reaction of 3-(bromoacetyl)pyrazole **2** with 2-methylquinoline in dry benzene at reflux (Scheme 3). The structure of the salt **15** was confirmed by elemental analyses and spectral data. When salt **15** was subjected to heating in dry benzene at reflux and in the presence of triethylamine, it furnished a single product as evidenced by TLC. The elemental analyses and mass spectrum of the obtained product were in accordance



Scheme 2.



Scheme 3.

with the molecular formula $C_{28}H_{18}N_4$. The ^{1}H NMR spectrum was free of any signals due to methylene protons, and the IR spectrum was also free of any carbonyl absorption. These results suggest the formation of 1,5-diphenyl-3-(pyrrolo[1,2-α]quinolin-2-yl)-1*H*-pyrazole-4-carbonitrile (**16**) through the intramolecular cyclization of compound **15** *via* loss of water and hydrogen bromide molecules, as illustrated in Scheme 3.

Experimental Section

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide disks on Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC spectrophotometers. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H NMR spectra were run at 300 MHz, and ^{13}C NMR spectra were run at 75.46 MHz in [D_6]DMSO. Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. 3-Acetylpyrazole-4-carbonitrile (**1**) [27] and 3-bromoacetylpyrazole-4-carbonitrile (**2**) [27] were prepared following procedures reported in the literature.

*Synthesis of pyridinium, quinolinium and 2-methylquinolinium bromides **3**, **9** and **15***

To a solution of **2** (3.77 g, l0 mmol) in dry benzene (50 mL), pyridine, quinoline or 2-methylquinoline

(10 mmol) was added. The mixture was refluxed for 30 min, then left to cool. The solid product was filtered off, washed with benzene/diethyl ether and dried to afford the pyridinium, quinolinium and 2-methylquinolinium bromide salts **3**, **9**, and **15**, respectively.

*1-(2-(4-Cyano-1,5-diphenyl-1H-pyrazol-3-yl)-2-oxoethyl) pyridinium bromide (**3**)*

Yield 74 %; m. p. 224 – 226 °C. – IR (KBr); ν = 2232 (C≡N), 1710 (C=O) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 6.3 (s, 2H, CH_2), 7.4 – 7.56 (m, 10H, ArH), 8.28 – 8.33 (m, 2H, ArH), 8.76 (m, 1H, ArH), 9.05 (d, 2H, J = 6.0 Hz, ArH). – $C_{23}H_{17}N_4OBr$ (445.32): calcd. C 62.03, H 3.85, N 12.58; found C 62.11, H 3.89, N 12.46.

*1-(2-(4-Cyano-1,5-diphenyl-1H-pyrazol-3-yl)-2-oxoethyl) quinolinium bromide (**9**)*

Yield 89 %; m. p. 243 – 245 °C. – IR (KBr); ν = 2236 (C≡N), 1706 (C=O), 1613 (C=N) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 6.9 (s, 2H, CH_2), 7.36 – 7.58 (m, 10H, ArH), 8.1 – 9.58 (m, 7H, ArH). – $C_{27}H_{19}BrN_4O$ (495.38): calcd. C 65.46, H 3.87, N 11.31; found C 65.32, H 3.91, N 11.22.

*1-(2-(4-Cyano-1,5-diphenyl-1H-pyrazol-3-yl)-2-oxoethyl)-2-methylquinolinium bromide (**15**)*

Yield 89 %; m. p. 212 – 214 °C. – IR (KBr); ν = 2233 (C≡N), 1643 (C=O), 1604 (C=N) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 2.9 (s, 3H, CH_3), 4.87 (s, 2H, CH_2), 7.36 – 7.49 (m, 10H, ArH), 7.86 – 8.91 (m, 6H, ArH). – $C_{28}H_{21}N_4OBr$ (509.41): calcd. C 66.02, H 4.16, N 11.00; found C 65.89, H 4.12, N 11.04.

*Indolizine-1,2-dicarboxylate (**6**) and pyrrolo[1,2-a]quinoline-2,3-dicarboxylate (**12**)*

To a mixture of the pyridinium bromide **3** or quinolinium bromide **9** (1 mmol) and dimethyl acetylenedicarboxylate (0.29 g, 2 mmol) in dry benzene (20 mL), triethylamine (0.2 mL) was added. The reaction mixture was refluxed for 3 h, then cooled to r. t. The triethylamine hydrobromide was filtered off, and the filtrate was evaporated under reduced pressure. The residue was treated with methanol to give a orange-yellow solid product which was filtered off, washed with methanol and recrystallized from EtOH/DMF to afford the corresponding indolizine **6** or pyrrolo[1,2-*a*]quinoline **12** derivatives, respectively.

*Dimethyl 3-(4-cyano-1,5-diphenyl-1H-pyrazole-3-carbonyl)indolizine-1,2-dicarboxylate (**6**)*

Yield 70 %; m. p. 135 – 137 °C. – IR (KBr); ν = 2235 (C≡N), 1748, 1710, 1632 (3 C=O) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.41 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 7.29 – 7.52 (m, 11H, ArH), 7.69 – 7.74 (m, 1H, ArH), 8.32 (d, 1H, J = 6.9 Hz, ArH), 9.54 (d, 1H, J = 9.3 Hz, ArH). – MS (EI, 70 eV): *m/z* (%) = 504 (57) $[M]^+$. – $C_{29}H_{20}N_4O_5$ (504.50): calcd. C 69.04, H 4.00, N 11.11; found C 69.19, H 4.11, N 11.37.

*Dimethyl 1-(4-cyano-1,5-diphenyl-1H-pyrazol-3-carbonyl)pyrrolo[1,2-a]quinoline-2,3-dicarboxylate (**12**)*

Yield 70 %; m. p. 239 – 240 °C. – IR (KBr); ν = 2237 (C≡N), 1740, 1708, 1661 (3 C=O) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.59 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 7.02 – 7.18 (m, 1H, ArH), 7.25 – 7.52 (m, 14H, ArH), 7.58 – 7.65 (m, 1H, ArH). – MS (EI, 70 eV): *m/z* (%) = 554 (74) $[M]^+$, 272 (100). – $C_{33}H_{22}N_4O_5$ (554.56): calcd. C 71.47, H 4.00, N 10.10; found C 71.37, H 4.11, N 10.08.

*Indolizine derivatives **8a,b** and pyrrolo[1,2-a]quinoline derivatives **14a,b***

A mixture of the pyridinium salt **3** or quinolinium bromide **9** (1 mmol) and the appropriate olefin (acrylonitrile or ethyl acrylate) (6 mmol) in benzene (30 mL) containing triethylamine (0.15 mL, 1.5 mmol), manganese dioxide (0.7 g, 8 mmol) was added. The mixture was refluxed for 4 h, then cooled to r. t. The undesired solid salts were removed by filtration, and the filtrate was evaporated under vacuum. The residue was treated with methanol to give a solid precipitate which was filtered off, washed with methanol and dried. Recrystallization from EtOH/DMF afforded the corresponding indolizine derivatives **8a**,**b** and pyrrolo[1,2-*a*]quinoline derivatives **14a**,**b**, respectively.

*3-(4-Cyano-1,5-diphenyl-1H-pyrazole-3-carbonyl)indolizine-1-carbonitrile (**8a**)*

Yield 70 %; m. p. 230 – 231 °C. – IR (KBr); ν = 2364, 2216 (2 C≡N), 1697 (C=O) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 7.33 – 7.49 (m, 13H, ArH), 8.72 (s, 1H, ArH), 9.98 (d, 1H, J = 6.9 Hz, ArH). – MS (EI, 70 eV): *m/z* (%) = 413 (100) $[M]^+$. – $C_{26}H_{15}N_5O$ (413.44): calcd. C 75.53, H 3.66, N 16.94; found C 75.73, H 3.70, N 16.85.

*Ethyl 3-(4-cyano-1,5-diphenyl-1H-pyrazole-3-carbonyl)-indolizine-1-carboxylate (**8b**)*

Yield 65 %; m. p. 233 – 234 °C. – IR (KBr); ν = 2333 (C≡N), 1701, 1643 (2 C=O) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.35 (t, 3H, CH_3, J = 7.05 Hz), 4.32 (q, 2H, CH_2, J = 7.1 Hz), 7.37 – 7.53 (m, 11H, ArH), 7.74 (t, 1H, ArH, J = 7.3 Hz), 8.37 (d, 1H, ArH, J = 8.8 Hz), 8.73 (s, 1H, ArH), 10.04 (d, 1H, ArH, J = 7.0 Hz). – ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 14.3 (CH_3), 59.9 (CH_2), 94.3, 106.4, 113.3, 116.7, 119.1, 120.8, 125.9, 126, 128.3, 128.9, 129.2, 129.4, 129.5, 129.6, 130.5, 138.1, 139.4, 150, 151.3, 162.9 (C=O), 172.6 (C=O). – MS (EI, 70 eV): *m/z* (%) = 460 (100) $[M]^+$. – $C_{28}H_{20}N_4O_3$(460,48): calcd. C 73.03, H 4.38, N 12.17; found C 73.19, H 4.20, N 12.45.

*1-(4-Cyano-1,5-diphenyl-1H-pyrazole-3-carbonyl)pyrrolo-[1,2-a]quinoline-3-carbonitrile (**14a**)*

Yield 77 %; m. p. 192 – 194 °C. – IR (KBr); ν = 2229, 2177 (2 C≡N), 1632 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.27 – 7.62 (m, 12H), 7.73 – 7.88 (m, 4H, ArH), 8.24 (s, 1H, ArH). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 86.8, 94.4, 113, 114.7, 115.1, 120, 124.7, 125.1, 125.4, 125.7, 125.9, 126.3, 127.1, 128.9, 129, 129.2, 129.3, 129.4, 129.5, 129.7, 130.5, 130.6, 132, 132.3, 137.8, 141.9, 150.1, 150.5, 150.7, 173.5. – MS (EI, 70 eV): *m/z* (%) = 463 (100) $[M]^+$. – $C_{30}H_{17}N_5O$ (463.5): calcd. C 77.74, H 3.70, N 15.11; found C 77.53, H 3.58, N 14.99.

*Ethyl 1-(4-cyano-1,5-diphenyl-1H-pyrazole-3-carbonyl) pyrrolo[1,2-a]quinoline-3-carboxylate (**14b**)*

Yield 65 %; m. p. 180 – 182 °C. – IR (KBr); ν = 2334 (C≡N), 1702, 1640 (2 C=O) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.36 (t, 3H, CH_3, J = 6.96 Hz), 4.35 (q, 2H, CH_2, J = 6.98 Hz), 7.35 – 7.51 (m, 12H, ArH), 7.62 – 6.78 (m, 2H, ArH), 8.05 – 8.11 (m, 2H, ArH), 8.28 – 8.32 (m, 1H, ArH). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 14.3 (CH_3), 60.1 (CH_2), 94.5, 107.8, 113.2, 116.9, 120.3, 124.6, 125.6, 125.7, 125.9, 126, 126.6, 128.3, 128.9, 129.2, 129.4, 129.6, 129.8, 130.3, 130.6, 131.1, 131.2, 132.3, 137.9, 140, 150.3, 150.9, 162.9, 173.7. – MS (EI, 70 eV): *m/z* (%) = 510 (100) $[M]^+$. – $C_{32}H_{22}N_4O_3$ (510.55): calcd. C 75.28, H 4.34, N 10.97; found C 75.41, H 4.24, N 10.63.

*1,5-Diphenyl-3-(pyrrolo[1,2-a]quinolin-2-yl)-1H-pyrazole-4-carbonitrile (**16**)*

To a solution of the quinolinium bromide **15** (0.51 g, 1 mmol) in dry benzene (10 mL) was added triethylamine (0.15 mL, 1.5 mmol). The mixture was refluxed for 3 h, then left to cool. The solvent was evaporated under reduced pressure, and the residue was treated with methanol. The solid product was filtered off, dried and recrystallized from DMF to afford the pyrrolo[1,2-*a*]quinoline derivative **16**. Yield: 72 %; m. p. 235 – 237 °C. – IR (KBr); ν = 2233 (C≡N), 1554 (C=N) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 6.74 (s, 1H, Ar H); 7.06 – 7.12 (m, 4H, Ar-H), 7.24 – 7.41 (m, 12H, Ar-H), 7.83 (s, 1H, Ar-H). – MS (EI, 70 eV): *m/z* (%) = 410 (52) $[M]^+$. – $C_{28}H_{18}N_4$ (410.48): calcd. C 81.93, H 4.42, N 13.65; found C 81.79, H 4.46, N 13.52.

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