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Regioselective synthesis of 2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-ones by the cyclization of 3-acyl-4-methoxy-1-methylquinolinones with hydrazines

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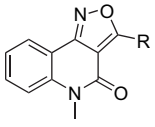
ABSTRACT

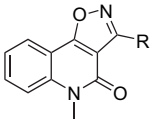
Reaction of 3-acyl-4-methoxy-1-methylquinolinones **2** and **5** with hydrazines has been investigated under different experimental conditions. Compound **2** always gave rise selectively and exclusively to the regioisomeric 1,3-disubstituted- or 2,3-disubstituted-pyrazolo[4,3-*c*]quinolin-4(5*H*)one (compounds **3a**,**b** or **4a**,**b**, respectively), while reaction of **5** with *N*-methylhydrazine led to a mixture of pyrazoles **7a** and **8a**. With *N*-phenylhydrazine, compounds **7b** or **8b** were regioselectively obtained. Compound **8a** could be selectively synthesized working in solventless conditions. Structural elucidation of all products was independently achieved by NMR spectroscopy.

1. Introduction

Following our research in the chemistry of heterocycles, we recently reported the regioselective preparation of isoxazoles **A** and **B** starting from 3-acyl-4-methoxy-1-methylquinolinone (**2**).[1]



A



B

Since the pyrazole nucleus is an important heterocyclic system with a wide variety of biological activities such as anticancer,[2a,b] antiviral,[3] antidepressant[4] and anti-inflammatory,[5a,b] we became interested in the preparation of 1,3-disubstituted- and 2,3-disubstituted-pyrazolo[4,3-*c*]quinolin-4(5*H*)ones. We report here the synthesis of the title compounds together with a discussion on the reaction mechanism under different experimental conditions. Unambiguous structure elucidation of the isomeric products, achieved by ^{13}C NMR spectroscopy, is also reported.

2. Results and discussion

Although the cyclocondensation reaction of *N*-phenylhydrazines with 3-acyl-4-hydroxyquinolinones proceeds efficiently under the well-established conditions reported in the literature,[6a–d] the reaction gives rise regioselectively only to the 1,3-disubstituted derivatives. On the basis of the results obtained for the reaction of the 4-methoxy derivative **2** with hydroxylamine, we decided to carry out the reaction with *N*-substituted hydrazines starting from this derivative, easily obtainable as a single product by treatment of compound **1** with dimethylsulfate in acetone.[1] The reaction with *N*-substituted hydrazines could give rise, in theory, to two different regioisomeric compounds, namely *N*-1 or *N*-2 substituted pyrazoles **3** and **4**, respectively (see Scheme 1). Thus, working in ethanol employing hydrazine hydrochlorides or hydrazine free bases, two different products are obtained (see Table 1), showing that the regiochemistry of the reaction depends on the nature of the reagent.

Unambiguous structure determination of the obtained products is therefore crucial to rationalize the observed regioselectivity. To this end, we started investigating the nature of the unique solid isolated in quantitative yield by reaction of compound **2** with methylhydrazine free base. Structure elucidation was conveniently achieved on the basis of the long-range C–H connectivities (gHMBC spectra) showed by C-3 or C-9b with the protons of the methyl groups. The proposed structure was then confirmed by NOESY-1D

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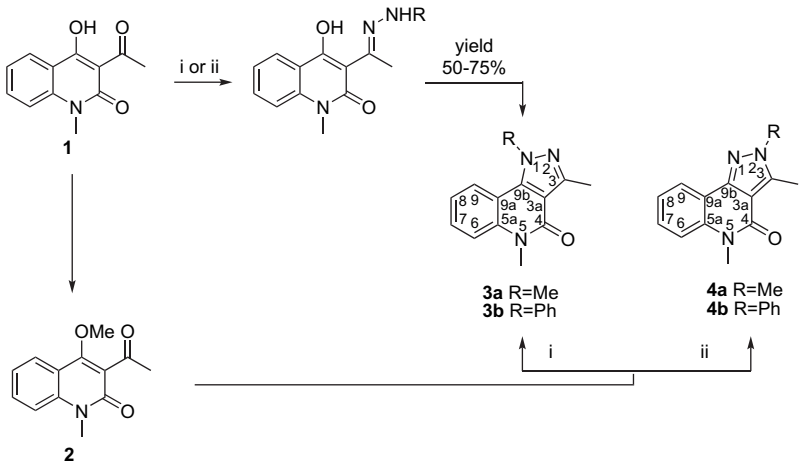


Scheme 1. *Reagents and conditions*: (i) $RNHNH_2 \cdot HCl$, EtOH, reflux; (ii) $RNHNH_2$, EtOH, reflux.

Table 1
Reaction of compound **2** with hydrazines

Compd	R	Ratio **3**/**4** (yield %)	
		$RNHNH_2 \cdot HCl$ (i)	$RNHNH_2$ (ii)
3a, **4a**	Me	100:0 (60)	0:100 (100)
3b, **4b**	Ph	100:0 (83)	0:100 (90[a])

[a] In xylene.

experiments (see Fig. 1). On this basis, analysis of the gHMBC spectra of the product led us to attribute the signal at δ 141.1 ppm to the quaternary carbon at position-3 owing to its correlation peaks with the protons of both the methyl groups resonating at δ 2.75 ppm (3-CH_3) and 4.00 ppm (2-*N*–CH_3); on the other hand, the signal at δ 144.7 ppm is attributed to the quaternary carbon at position-9b owing to its correlation peak with the signal at δ 8.20 ppm easily assigned to the proton at position-9 of the quinolinone ring (H-6 was excluded, showing NOE effect by irradiation of the 5-*N*–CH_3). The regiochemistry of the reaction was then confirmed by NOE experiments; a strong NOE effect is observed between 3-CH_3 and 2-*N*-CH_3 groups. Thus, we may conclude assigning structure **4a** to the compound obtained by reaction of **2** with methylhydrazine free base.

As previously stated, a different solid is obtained when the same reaction is carried out on **2** with methylhydrazine hydrochloride. This compound was carefully analyzed by NMR spectroscopy; we notice that the quaternary C-9b now shows a connectivity (besides that one with H-9) with the methyl group resonating at higher frequency (δ 4.30 ppm) and that must be attributed to a *N*–CH_3. More interesting is the significant NOE enhancement observed on H-9 (δ 8.04 ppm) by irradiation of the same *N*-methyl group (see Fig. 1). Thus, all this data allowed us to attribute the 1,3 substituted structure to compound **3a**. Since the synthesis of compound **3a** is not reported in the literature starting from compound **1**, we prepared it by treatment of the hydroxy derivative with *N*-methylhydrazine (both free base and hydrochloride) in EtOH. The reaction

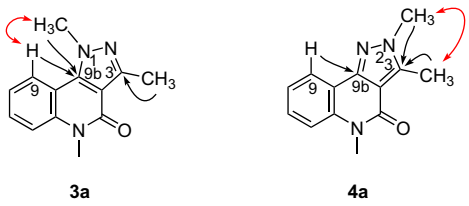
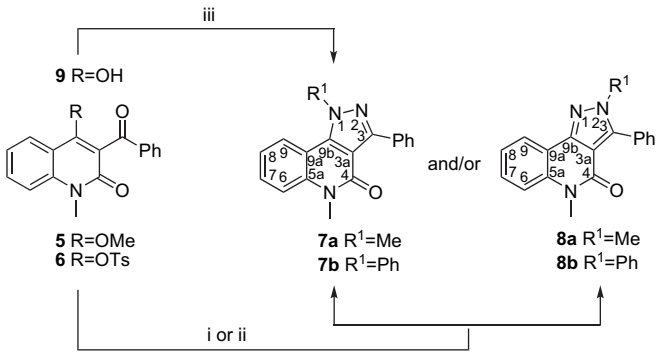


Figure 1. Diagnostic correlations in the gHMBC spectra (black arrows) and NOE effects (red arrows) in compounds **3a** and **4a**.

afforded the corresponding hydrazone that can be subsequently cyclized in xylene to give the desired compound **3a**.

As regards the reaction of **2** with phenylhydrazine or phenylhydrazine hydrochloride, NOESY-1D seems to be the best experiment to distinguish between 2,5-dihydro- or 1,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one structure of the isolated product because in this case the gHMBC spectrum cannot show the diagnostic correlation between C-3 or C-9b and the *ortho*-protons of the phenyl group. Thus, in the NOESY-1D experiment, irradiation of the methyl group resonating at δ 2.78 ppm (3-CH_3), in compound obtained from route (ii), produced a significant enhancement in the signal of the *ortho*-protons of the phenyl group, thus allowing us to assign structure **4b** to this compound. On the other hand, irradiation of the proton resonating at δ 7.26 ppm (H-9), in compound obtained from route (i), leads to a significant enhancement of the signal of the protons of the phenyl substituent (grouped), thus confirming structure **3b** to this compound. In summary, reactivity of compound **2** with hydrazines can be described as follows: when *N*-substituted hydrazine free bases are employed, substitution on C-4 occurred as the first step of the reaction, leading to 2,3-disubstituted compounds. 'Normal' attack on the carbonyl group giving rise to 1,3-disubstitute derivatives is favoured when *N*-substituted hydrazine hydrochlorides are used.

With the aim to verify a possible extension of this reactivity to the corresponding 4-phenylcarbonyl derivatives, we investigated the reaction of compound **5** with *N*-methyl- and *N*-phenylhydrazine in both the reaction conditions (i and ii) employing ethylene glycol and xylene as solvents, respectively, since no reactivity was observed in ethanol (see Scheme 2 and Table 2).



Scheme 2. *Reagents and conditions*: (i) $R^1NHNH_2 \cdot HCl$; (ii) R^1NHNH_2; (iii) R^1NHNH_2, AcOH, H_2SO_4, reflux.

The reaction with *N*-methylhydrazine always gave a mixture of both the regioisomers **7a** and **8a** in different amounts; while with

Table 2
Reaction of compounds **5** and **6** with hydrazines

Starting material	Product(s)	R^1	Ratio **7**/**8** (yield %)	
			$R^1NHNH_2 \cdot HCl$ (i)	R^1NHNH_2 (ii)
5	**7a**, **8a**	Me	75:25 (62)	20:80 (78)
5	**8a**	Me	—	0:100 (70[a])
5	**7b**, **8b**	Ph	100:0 (97)	0:100 (80)
6	**7a**	Me	—	100:0 (90)
6	**8b**	Ph	—	0:100 (90)

[a] Solventless conditions.

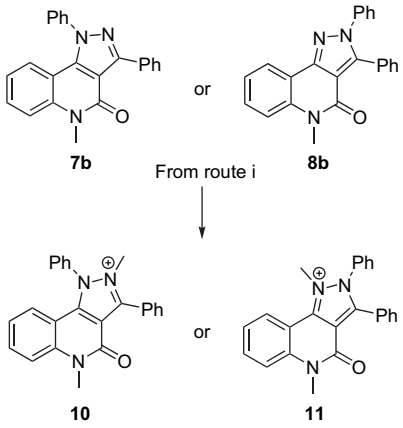
the free base the ratio of the products is 20:80 (^{1}H NMR), the reaction carried out with the hydrochloride gave an inverted ratio (75:25, Table 2).

To improve the yields, we wanted to test a different starting material (tosyloxy derivative **6**) employing again ethanol as solvent; reaction with methylhydrazine free base gives rise now, regioselectively, to one product in 90% yield. Once again, distinction between the two regioisomeric pyrazoles **7a** and **8a** was ascertained on the basis of long-range ^{1}H–^{13}C correlations; the three-bond connectivity between the carbon atom resonating at δ 140.6 ppm, easily attributed to C-9b, and the methyl group at δ 4.45 ppm (attributed to a *N*-CH_3 group) solves the ambiguity between the 2,5-dihydro- or 1,5-dihydro-4*H*-pyrazolo[4,3-*c*]-quinolin-4-ones systems, thus allowing us to attribute structure **7a** to the compound arising from reaction of **6** with methylhydrazine free base and not **8a**, as expected. The NOE effect between the 1-*N*-methyl group and the proton resonating at δ 8.16 ppm (H-9) fully confirms the 1,3-disubstituted nature of **7a**. This quite surprising result confirms that the structure of the reaction product depends on both the nature of the substituent at position-4 of the starting material and that of the reagent. It is noteworthy that the same compound **7a** can be obtained in low yield (21%) starting from the hydroxy derivative **9** (in this case, the corresponding hydrazone cannot be isolated). Thus, having determined the structure of the compound arising from reaction of **6** with methylhydrazine, it is now possible to establish the nature of the predominant compound obtained starting from the methoxy derivative **5**; the major regioisomer is the one derived from the attack of the nucleophile on C-4 when the free base is used (compound **8a**); on the other hand, by employing the hydrochloride, compound **7a** was obtained by attack on the carbonyl group. Trying to find the best experimental conditions for the selective production of **8a** by increasing the amount of reagent, we ascertained that reaction of **5** with methylhydrazine in solventless conditions at rt gives only **8a** in 70% yield.

On the other hand, a regioselective behaviour is observed in the reaction of **5** with phenylhydrazine; whereas the hydrochloride gives the expected compound **7b** in quantitative yield, the reaction with the free base allowed us to isolate the regioisomer **8b** in 80% yield but with low conversion. For this reason we carried out the latter reaction starting from the tosyloxy derivative **6** thus obtaining the 2,3-diphenyl derivative **8b** in near quantitative yields.

The structural distinction between compounds **7b** and **8b** was a little more complex because we cannot rely on the NOE effect between H-9 and the *ortho*-protons of the *N*-1 phenyl group owing to the overlap of the resonances. To establish the correct structure we used the same methodology previously employed in the structure distinction between 4-hydroxy-3-(5-isoxazolyl)- and 4-hydroxy-3-(3-isoxazolyl)-1-methyl-2(1*H*)-quinolinone.[7]

Thus, both the solids were treated with dimethylsulfate at 80 °C and the compound obtained from route (i) gave the corresponding pyrazolium salt in quantitative yield (compound **10** or **11**, Scheme 3). Now, saturation of the N^+–CH_3 group in a NOESY experiment (DMSO-d_6) clearly evidenced a dipolar interaction with the *ortho*-methine protons of both the phenyl groups (Fig. 2).



Scheme 3. *Reagents and conditions*: dimethylsulfate, 80 °C.

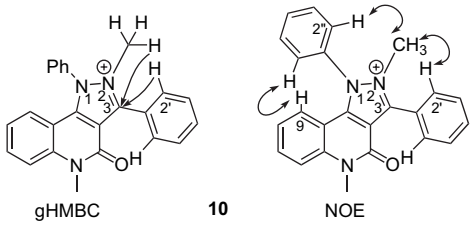


Figure 2. Significant correlations in the gHMBC spectrum and NOE effects in compound **10**.

On this basis, structure **10** was attributed to the compound originating from reaction of **5** with phenylhydrazine hydrochloride (**7b**). Moreover, the gHMBC spectrum confirmed the assigned structure owing to the presence of the diagnostic three-bond connectivity between C-3 and the protons of the N^+–CH_3 group.

3. Conclusions

In summary, we have investigated the reaction of *N*-substituted hydrazines with 3-acyl-4-methoxy(tosyloxy)-1-methylquinolinones **2**, **5** and **6** and unambiguously determined the structures of the obtained products under different reaction conditions. Whereas the reaction of 3-acyl-4-hydroxy-1-methylquinolinones **1** and **9** always afforded only the 1,3-disubstituted derivatives, reaction of 3-acetyl-4-methoxyquinolinone **2** with the free bases gave rise selectively to the new 2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-ones **4a**,**b**.

The same reaction carried out on compound **5** employing phenylhydrazine afforded regioselectively the required product **8b**. Finally, 2,5-dimethyl-3-phenyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]-quinolin-4-one (**8a**) was obtained in solventless conditions. All the structures of the isolated compounds have been unambiguously determined by NMR experiments.

4. Experimental

4.1. General

Melting points were taken on a Büchi 510 apparatus and are uncorrected. IR spectra were obtained with a Perkin–Elmer 881 spectrophotometer as dispersions in KBr. Elemental analyses were obtained on an Elemental Analyzer Perkin–Elmer 240C apparatus. Mass spectra were registered on a Carlo Erba QMD 1000 instrument at 70 eV. Compounds **1**,[8] **2**,[1] **5**[1] and **9**[9] were obtained as reported in the literature. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck 230–400 mesh) were used for analytical TLC and for column

chromatography, respectively. Solvents were removed under reduced pressure. All 1D and 2D NMR experiments were performed on a Varian Mercuryplus spectrometer (399.95 MHz for ^{1}H, 100.57 MHz for ^{13}C), with a 5 mm indirect detection probe equipped with a gradient coil, at 298 K. Chemical shifts (δ in ppm) were referenced to the solvent $CDCl_3$, 7.26 for ^{1}H and 77.00 for ^{13}C. All coupling constants are in hertz. Assignments are made using ^{1}H, ^{13}C, DEPT and NOESY-1D experiments and gHSQC, gHMBC, gHMQC and gCOSY 2D experiments. All pulse sequences were used as provided by Varian and processing was done using standard Varian methods.

4.2. General procedure for the preparation of compounds 3 and 4

To a stirred solution of 3-acetyl-4-methoxy-1-methylquinolin-2(1*H*)-one (**2**) (162 mg, 0.70 mmol) in EtOH (8 mL) hydrazine or hydrazine hydrochloride (0.80 mmol) was added and the reaction mixture heated at reflux for 3 h. After cooling, removal of the solvent left a solid, which was crystallized or separated by column chromatography with the appropriate eluant.

*4.2.1. 1,3,5-Trimethyl-1,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one (**3a**)*

White solid; mp 250 °C, dec (from EtOH); IR (KBr) 2936, 1651, 1577, 1497, 1433, 1328 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (3H, s, CH_3), 3.69 (3H, s, 5N–CH_3), 4.30 (3H, s, 1N–CH_3), 7.30 (1H, ddd, ^3J=8.0, 7.8 Hz, ^4J=1.0 Hz, H-8), 7.43 (1H, dd, ^3J=8.4 Hz, ^4J=1.0 Hz, H-6), 7.56 (1H, ddd, ^3J=8.6, 7.8 Hz, ^4J=1.4 Hz, H-7), 8.04 (1H, dd, ^3J=8.0 Hz, ^4J=1.4 Hz, H-9); ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 159.3 (s, C-4), 147.4 (s, C-3), 139.8 (s, C-5a), 139.7 (s, C-9b), 127.9 (d, C-7), 122.8 (d, C-9), 122.0 (d, C-8), 115.8 (d, C-6), 112.5 (s, C-9a), 110.9 (s, 3a), 39.9 (q, 1N–CH_3), 28.9 (q, 5N–CH_3), 12.8 (q, 3-CH_3); EIMS *m*/*z* (%): 227 (M^+, 100), 212 (14), 184 (12), 113 (18), 77 (10). Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.86; H, 5.66; 18.73.

*4.2.2. 3,5-Dimethyl-1-phenyl-1,5-dihydro-4H-pyrazolo[4,3-c]-quinolin-4-one (**3b**)*

White solid; mp 184–185 °C (from EtOH) (lit.[6d] 190–193 °C from ligroin); IR (KBr) 1655, 1570, 1345, 1255 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77 (3H, s, CH_3), 3.76 (3H, s, N–CH_3), 6.98 (1H, ddd, ^3J=8.2, 7.1 Hz, ^4J=1.2 Hz, H-8), 7.26 (1H, dd, ^3J=8.2 Hz, ^4J=1.4 Hz, H-9), 7.42 (1H, dd, ^3J=8.6 Hz, ^3J=1.2 Hz, H-6), 7.49 (1H, ddd, ^3J=8.6, 7.1 Hz, ^4J=1.4 Hz, H-7), 7.53–7.60 (5H, m, Ar–H); ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 159.5 (s, C-4), 149.3 (s, C-3), 139.8 (s, C-5a), 140.4 (s, C-9b/C-1′), 140.3 (s, C-1′/C-9b), 130.0 (d, C-7), 129.8 (d, Ar), 129.7 (d, Ar), 127.1 (d, Ar), 123.1 (d, C-9), 121.6 (d, C-8), 115.6 (d, C-6), 112.1 (s, C-9a), 111.3 (s, 3a), 29.0 (q, 5N–CH_3), 13.2 (q, 3-CH_3). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.53; H, 5.29; N, 14.66.

*4.2.3. 2,3,5-Trimethyl-2,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one (**4a**)*

White solid; mp 152–154 °C (from EtOH); IR (KBr) 2927, 1656, 1592, 1426, 1342, 1254 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (3H, s, CH_3), 3.66 (3H, s, 5N–CH_3), 4.00 (3H, s, 2N–CH_3), 7.25 (1H, ddd, ^3J=7.8, 7.2 Hz, ^4J=1.0 Hz, H-8), 7.33 (1H, dd, ^3J=8.6 Hz, ^4J=1.0 Hz, H-6), 7.49 (1H, ddd, ^3J=8.6, 7.2 Hz, ^4J=1.6 Hz, H-7), 8.20 (1H, dd, ^3J=7.8 Hz, ^4J=1.6 Hz, H-9); ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 160.0 (s, C-4), 141.1 (s, C-3), 139.0 (s, C-5a), 144.7 (s, C-9b), 129.0 (d, C-7), 122.5 (d, C-9), 122.0 (d, C-8), 115.7 (s, C-9a), 114.9 (d, C-6), 109.4 (s, C-3a), 36.4 (q, 2N–CH_3), 28.4 (q, 5N–CH_3), 10.5 (q, 3-CH_3); EIMS *m*/*z* (%): 227 (M^+, 100), 212 (15), 196 (11), 113 (14), 77 (9), 56 (35), 51 (10). Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.84; H, 5.97; N, 18.32.

*4.2.4. 3,5-Dimethyl-2-phenyl-2,5-dihydro-4H-pyrazolo[4,3-c]-quinolin-4-one (**4b**)*

Yellowish solid; mp 181–183 °C; R_f (ethyl acetate/petroleum ether 40/70=1:2) 0.31; IR (KBr) 1651, 1595, 1493, 1345, 1258 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (3H, s, CH_3), 3.72 (3H, s, N–CH_3), 7.25–7.29 (1H, m, H-8), 7.37–7.39 (1H, m, H-6), 7.50–7.57 (6H, m, H-7 and Ar–H), 8.32 (1H, dd, ^3J=8.2 Hz, ^4J=1.8 Hz, H-9); ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 160.4 (s, C-4), 147.8 (s, C-9b), 142.2 (s, C-3), 139.5 (s, C-5a), 138.7 (s, C-1′), 129.7 (d, C-7), 129.4 (d, Ar), 129.0 (d, Ar), 125.8 (d, Ar), 123.3 (d, C-9), 122.4 (d, C-8), 115.7 (s, C-9a), 113.1 (d, C-6), 110.6 (s, C-3a), 28.7 (q, 5N–CH_3), 12.0 (q, 3-CH_3); EIMS *m*/*z* (%): 289 (M^+, 100), 273 (11), 145 (18), 77 (35), 51 (25). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.46; H, 5.37; N, 14.75.

4.3. 1,2-Dihydro-3-(phenylcarbonyl)-1-methyl-2-oxoquinolin-4-yl-4-methylbenzensulfonate (6)

A solution of **9** (250 mg, 0.895 mmol), tosyl chloride (190 mg, 1.00 mmol) and triethylamine (140 μL, 1.00 mmol) in dry toluene (6 mL) was heated under reflux for 5 h. After cooling to rt dichloromethane was added and the organic phase was washed several times with diluted hydrochloric acid (3×10 mL) in a separatory funnel. The organic phase was dried with sodium sulfate and the solvent removed under reduced pressure to give a yellow solid (0.309 g, 79%) that was crystallized from EtOH. Yellowish needles; mp 201 °C, dec (lit.[10] 199 °C, dec from toluene).

4.4. 1,5-Dimethyl-3-phenyl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]-quinolin-4-one (7a)

This compound was obtained from compound **6** (51 mg, 0.12 mmol) with methylhydrazine (14.8 μL, 0.28 mmol) in EtOH (5 mL) for 4 h at rt as described below for **8b** (method B). Yellowish solid; mp 146–147 °C (from EtOH); IR ($CDCl_3$) 3010, 1653, 1578, 1104 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (3H, s, 5N–CH_3), 4.45 (3H, s, 1N–CH_3), 7.35 (1H, ddd, ^3J=8.3, 7.2 Hz, ^4J=1.2 Hz, H-8), 7.38–7.50 (4H, m, H-6, H-3′, H-4′), 7.62 (1H, ddd, ^3J=8.6, 7.2 Hz, ^4J=1.4 Hz, H-7), 8.09–8.12 (2H, m, H-2′), 8.16 (1H, dd, ^3J=8.3 Hz, ^4J=1.4 Hz, H-9); ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 158.7 (s, C-4), 149.9 (s, C-3), 140.6 (s, C-9b), 139.5 (s, C-5a), 131.9 (s, C-1′), 129.8 (d, C-7), 129.4 (d, Ar), 128.5 (d, Ar), 128.0 (d, Ar), 122.8 (d, C-9), 121.9 (d, C-8), 115.8 (d, C-6), 112.5 (s, C-9a), 109.9 (s, C-3a), 40.7 (q, 1N–CH_3), 29.4 (q, 5N–CH_3); EIMS *m*/*z* (%): 289 (M^+, 100), 274 (29), 144 (27), 137 (22), 77 (18), 63 (6), 51 (15). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.88; H, 5.04; N, 14.61.

4.5. 5-Methyl-1,3-diphenyl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]-quinolin-4-one (7b)

This compound was obtained from compound **5** (52 mg, 0.18 mmol) with phenylhydrazine hydrochloride (30 mg, 0.21 mmol) in ethylene glycol for 1 h as described below for **8b** (method A). White solid; mp 195–196 °C (from EtOH) (lit.[6a] 200–202 °C from ligroin); IR (KBr) 1651, 1615, 1596 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (3H, s, N–CH_3), 6.99 (1H, ddd, ^3J=8.1, 7.0 Hz, ^4J=1.2 Hz, H-8), 7.26 (1H, dd, ^3J=8.1 Hz, ^4J=1.4 Hz, H-9), 7.41–7.53 (5H, m, H-6, H-7, H-3′, H-4′), 7.61–7.62 (5H, m, Ar–H), 8.15–8.19 (2H, m, H-2′); ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 158.8 (s, C-4), 151.5 (s, C-3), 141.3 (s, C-9b), 140.5 (s, C-1″), 139.6 (s, C-5a), 131.7 (s, C-1′), 130.1 (d, C-7), 129.9 (d, Ar), 129.7 (d, C-2′), 128.7 (d, C-4′), 128.0 (d, C-3′), 127.3 (d, Ar), 123.2 (d, C-9), 121.5 (d, C-8), 115.5 (d, C-6), 111.9 (s, C-9a), 110.1 (s, C-3a), 29.4 (q, 5N–CH_3). Anal. Calcd for $C_{23}H_{17}N_3O$: C, 78.61; H, 4.88; N, 11.96. Found: C, 78.52; H, 4.98; N, 12.04.

4.6. 2,5-Dimethyl-3-phenyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]-quinolin-4-one (8a)

A stirred solution of 3-benzoyl-4-methoxy-1-methylquinolin-2(1*H*)-one (**5**) (74 mg, 0.25 mmol) in methylhydrazine (1.5 mL) was kept for 2 h at rt. The mixture was poured into water (20 mL) and the solid collected by filtration, dried and purified by column chromatography with ethyl acetate/petroleum ether 40/70=1:1 as eluant. Colourless waxy solid; R_f (ethyl acetate/petroleum ether 40/70=1:1) 0.48; IR ($CDCl_3$) 1650, 1571, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.67 (3H, s, 5N–CH_3), 4.01 (3H, s, 2N–CH_3), 7.30 (1H, m, H-8), 7.38 (1H, d, ^3J=8.0 Hz, H-6), 7.40–7.59 (6H, m, Ar, H-7), 8.30 (1H, dd, ^3J=7.8 Hz, ^4J=1.7 Hz, H-9); ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 159.3 (s, C-4), 147.5 (s, C-9b), 144.4 (s, C-3), 139.2 (s, C-5a), 130.3 (d, Ar), 129.6 (d, Ar), 129.5 (d, C-7), 128.4 (d, Ar), 128.2 (s, C-1′), 122.9 (d, C-9), 122.3 (d, C-8), 115.8 (s, C-9a), 115.1 (d, C-6), 109.7 (s, C-3a), 37.9 (q, 1N–CH_3), 28.8 (q, 5N–CH_3); EIMS *m*/*z* (%): 289 (M^+, 100), 274 (34), 144 (30), 137 (18), 77 (15), 63 (10), 51 (21). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.48; H, 5.39; N, 14.63.

4.7. 5-Methyl-2,3-diphenyl-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]-quinolin-4-one (8b): typical procedure

Method A. To a stirred solution of 3-benzoyl-4-methoxy-1-methylquinolin-2(1*H*)-one (**5**) (59 mg, 0.20 mmol) in xylene (3 mL), phenylhydrazine (32 mg, 0.30 mmol) was added and the reaction mixture heated at reflux for 30 h. After cooling, removal of the solvent left a solid, which was separated by column chromatography with ethyl acetate/petroleum ether 40/70=1:3 as eluant. White solid; mp 228–230 °C (from EtOAc); R_f (ethyl acetate/petroleum ether 40/70=1:3) 0.63; IR ($CDCl_3$) 1650, 1617, 1597, 1497 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.70 (3H, s, N–CH_3), 7.29–7.33 (1H, m, H-8), 7.39–7.41 (1H, m, H-6), 7.34–7.46 (10H, m, 2×Ar–H), 7.56 (1H, ddd, ^3J=8.8, 7.2 Hz, ^4J=1.6 Hz, H-7), 8.39 (1H, dd, ^3J=7.8 Hz, ^4J=1.6 Hz, H-9); ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 159.4 (s, C-4), 148.4 (s, C-9b), 144.0 (s, C-3), 139.5 (s, C-1″), 139.4 (s, C-5a), 130.8 (d, Ar), 129.7 (d, C-7), 129.2 (d, Ar), 129.0 (d, Ar), 128.3 (d, Ar), 128.2 (s, C-1′), 128.0 (d, Ar), 125.9 (d, Ar), 123.2 (d, C-9), 122.3 (d, C-8), 115.8 (s, C-9a), 115.1 (d, C-6), 110.6 (s, C-3a), 28.9 (q, 5N–CH_3); EIMS *m*/*z* (%): 351 (M^+, 100), 335 (13), 175 (27), 168 (18), 77 (27). Anal. Calcd for $C_{23}H_{17}N_3O$: C, 78.61; H, 4.88; N, 11.96. Found: C, 78.49; H, 5.03; N, 12.16.

Method B. To a stirred solution of 3-benzoyl-4-tosyloxy-1-methylquinolin-2(1*H*)-one (**6**) (80 mg, 0.18 mmol) in EtOH (8 mL) phenylhydrazine (40 mg, 0.37 mmol) was added and the reaction mixture heated at reflux for 6 h. After cooling, removal of the solvent left a solid, which was suspended in water, collected by filtration, dried and crystallized.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.028.

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