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ScienceDirect
Tetrahedron 63 (2007) 11656–11660
Tetrahedron

Unambiguous structure elucidation of the reaction products of 3-acyl-4-methoxy-1-methylquinolinones with hydroxylamine via NMR spectroscopy

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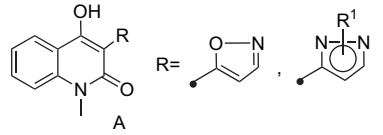
Received 21 June 2007; revised 8 August 2007; accepted 30 August 2007
Available online 5 September 2007

Abstract—Reaction of 3-acyl-4-methoxy-1-methylquinolinones **2a**,**b** with hydroxylamine has been investigated under different experimental conditions. Whereas compound **2a** gives rise selectively and exclusively to the regioisomeric isoxazolo[4,5-*c*]- or isoxazolo[4,3-*c*]quinolin-4(5*H*)one (compound **3a** or **4a**, respectively), reaction of **2b** always led to a mixture of the required isoxazole together with the oxazole derivative. Structural elucidation of all products has been independently achieved by multinuclear (^{13}C and ^{15}N) magnetic resonance spectroscopy.

1. Introduction

Recently, we devoted our attention to the reaction of 1,2-bisnucleophiles with quinolinylenaminones with the aim of synthesizing new 3-isoxazolyl- or pyrazolyl-substituted 4-hydroxy-2(1*H*)-quinolinones of type **A**.[1] Following our research in the chemistry of heterocycles, we became interested in the synthesis of new fused isoxazolo[4,5-*c*]- (**B**) or isoxazolo[4,3-*c*]quinolin-4(5*H*)ones (**C**)[2–5] as biologically attractive tricyclic systems that could act as P-38 mitogen-activated protein (MAP) kinase inhibitors,[6,7] benzodiazepine ligand receptors[8] or selective multidrug resistance protein inhibitors.[9]



Keywords: Isoxazolo[4,5-*c*]quinolin-4(5*H*)ones; 3-Acyl-4-methoxy-1-methylquinolinones; Structure determination; ^{13}C NMR; HMBC; ^{15}N NMR.
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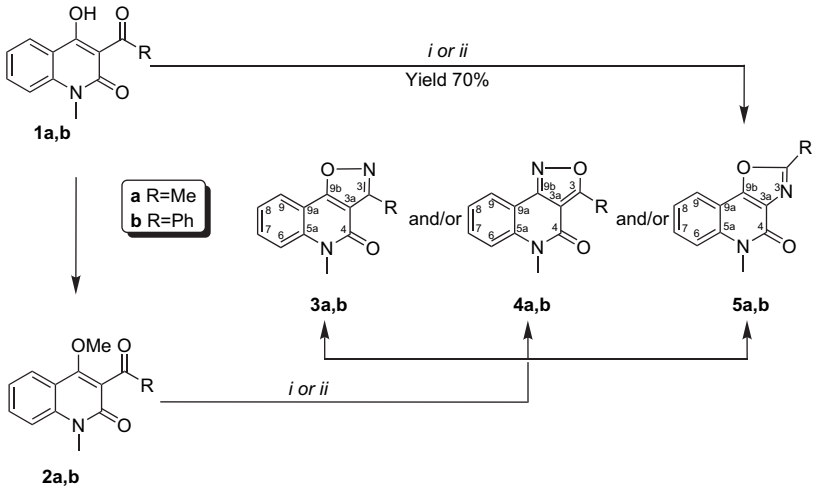
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.08.108

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 being achieved by ^{13}C and ^{15}N NMR spectroscopies.

2. Results and discussion

Reaction of 3-acetyl-4-methoxy-1-methylquinolin-2(1*H*)-one (**2a**), easily obtained as a single product by treatment of compound **1a**[1] with dimethyl sulfate in acetone, with hydroxylamine could, in theory, give rise to three different products, namely compounds **3a**–**5a** (Scheme 1) depending on the experimental conditions. Thus, if the reaction is carried out with hydroxylamine hydrochloride or hydroxylamine free base, two different products are obtained (see Table 1). Structural assignment of the product $C_{12}H_{10}N_2O_2$ deriving from the reaction of **2a** with hydroxylamine hydrochloride can be achieved as follows: (a) the oxazole structure **5a** was excluded on the basis of the presence of a three-bond connectivity between C-3a and the methyl group at position 3 in the ^{13}C NMR spectra (HMBC experiments) of compounds **3a** and **4a**; (b) distinction between the two regioisomeric isoxazole structures was then tentatively based on the chemical shift of the C-3 atom that in the compound under examination is more similar to that of a 3-substituted isoxazole with respect to a 5-substituted one ($\Delta\delta$ ca. 10 ppm). The [4,5-*c*] structural attribution to this product (compound **3a**) was then confirmed by long-range ^{1}H–^{15}N



Scheme 1. *Reagents and conditions*: (i) $NH_2OH \cdot HCl$, Et_3N, ethylene glycol, reflux; (ii) $NH_2OH \cdot HCl$, ethylene glycol, reflux.

heteronuclear shift correlation studies. Thus, not only the isoxazole nature of the compound can be confirmed through the chemical shift value of the nitrogen atom but we may also unambiguously solve the ambiguity between the [4,3-*c*] or [4,5-*c*] ring fusion (compounds **4a** and **3a**, respectively) on the basis of the three-bond correlation between the nitrogen atom (δ −4.0 ppm) and the methyl group resonating at δ 2.68 ppm (Tables 2 and 4). From a mechanistic point of view this product may be considered the 'normal' one arising from the attack of the nitrogen atom of the nucleophile on the acetyl group; this hypothesis was confirmed by the isolation of the corresponding oxime when the reaction was carried out in ethanol at reflux (quantitative yield, see Section 4). Subsequently heating this oxime in xylene or ethylene glycol at reflux gave compound **3a**. The reaction of **2a** with hydroxylamine free base gave a different but very similar (mp, IR, and ^{1}H NMR spectra) compound $C_{12}H_{10}N_2O_2$; once again this product has an isoxazole nature (presence of the three-bond connectivity between the 3-CH_3 and C-3a), but now differently from compound **3a** the nitrogen atom did not show any long-range correlation in the proton-detected ^{1}H–^{15}N HMBC experiments. Moreover, the ^{13}C NMR chemical shifts of **4a** are in perfect agreement with a 5-substituted isoxazole (Table 3). Although the mechanism of the reaction was not ascertained, no intermediates having been isolated, it is reasonable to hypothesize as the first step of the reaction a nucleophilic attack of the reagent on the methoxy group at position 4 of the quinoline ring with a subsequent elimination of methanol. Following this hypothesis, we reacted **2a** with a primary amine in ethanol, thus obtaining the expected substitution product **6** (see Scheme 2).

Table 1. Cyclization reaction of **2a**,**b** with hydroxylamine

Compd	R	Ratio **3**:**4**:**5** (Yield %)	
		NH_2OH	$NH_2OH \cdot HCl$
		i	ii
3a, **4a**, **5a**	Me	0:100:0 (100)	100:0:0 (80)
3b, **4b**, **5b**	Ph	0:50:50 (50)	92:0:8 (50)

On the other hand, the behavior of **1a** in the reactions with hydroxylamine or hydroxylamine hydrochloride is the same in both cases: the reactions gave a $C_{12}H_{10}N_2O_2$ compound different from **3a** and **4a**. The oxazole nature of this product was easily confirmed by ^{13}C NMR, the product showing in the gHMBC experiments only one correlation between the quaternary carbon resonating at δ 162.7 ppm (C-2) with the C-methyl group and the absence of correlations for C-3a (δ 128.8 ppm); once again ^{15}N NMR data are in perfect agreement with the assigned structure **5a** (Table 4). The structure of this compound, previously chemically proved by Stadlbauer by a different synthetic procedure,[5,10] can be rationalized on the basis of a Beckmann rearrangement of the intermediate oxime.

Reaction of **2b** with hydroxylamine or hydroxylamine hydrochloride under the same conditions gave a mixture of two products in different amounts: whereas with the free base the ratio of the products is 1:1, when the reaction is carried out with the hydrochloride there is a predominant compound (92:8, see Table 1). In both cases, the obtained compounds have been separated by flash chromatography and then carefully examined by NMR spectroscopy. Once again ^{15}N NMR experiments allowed us to ascertain the oxazole nature of one of the two reaction products in both the reactions. In particular for the reaction with hydroxylamine hydrochloride the minor compound was proved to be the oxazolo[4,5-*c*] derivative **5b**, whereas the predominant one was an isoxazole derivative whose structure was determined on the basis of the chemical shifts of C-3 and C-9b and of their long-range C–H connectivities. On this basis analysis of the gHMBC spectra led us to attribute the signal at δ 160.9 ppm to the quaternary carbon at position 3 owing to its correlation peak with the *ortho* protons of the phenyl group and therefore structure **3b** was assigned to this compound. On the other hand, carbon atom at position 9b resonates now at δ 168.3 ppm, according to the properties of a [4,5-*c*] fused isoxazole ring (see compounds **3a** and **4a**, Table 3). As for the different isoxazole originating from the reaction of **2b** with the free base, the gHMBC spectra show a correlation peak between the *ortho* protons of the phenyl group with the quaternary carbon resonating

Table 2. ^{1}H NMR ($CDCl_3$, 400 MHz) chemical shifts (δ, ppm) of oxazoloquinolinone derivatives **3–5**

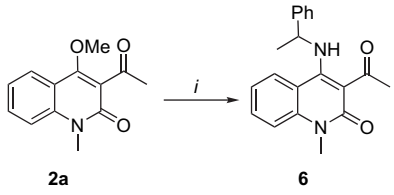
Compd	H-6	H-7	H-8	H-9	H-2′/6′	H-3′/4′/5′	CH_3	N–CH_3
3a	7.44, dd, *J*=8.6, 1.0 Hz	7.68, ddd, *J*=8.6, 7.2, 1.6 Hz	7.35, ddd, *J*=7.8, 7.2, 1.0 Hz	8.08, dd, *J*=7.8, 1.6 Hz			2.68	3.72
4a	7.33, dd, *J*=8.6, 1.0 Hz	7.61, ddd, *J*=8.6, 7.2, 1.6 Hz	7.28, ddd, *J*=7.6, 7.2, 1.0 Hz	8.21, dd, *J*=7.6, 1.6 Hz			2.89	3.60
5a	7.46, dd, *J*=8.6, 1.0 Hz	7.58, ddd, *J*=8.6, 7.2, 1.6 Hz	7.33, ddd, *J*=7.8, 7.2, 1.0 Hz	7.89, dd, *J*=7.8, 1.6 Hz			2.68	3.80
3b	7.49, dd, *J*=8.8, 0.9 Hz	7.72, ddd, *J*=8.8, 7.9, 1.5 Hz	7.40, ddd, *J*=8.8, 7.9, 0.9 Hz	8.19, dd, *J*=7.9, 1.5 Hz	8.24–8.28	7.50–7.55		3.78
4b	7.33, dd, *J*=8.6, 1.0 Hz	7.60, ddd, *J*=8.6, 7.2, 1.6 Hz	7.30, ddd, *J*=7.6, 7.2, 1.0 Hz	8.27, dd, *J*=7.6, 1.6 Hz	8.56–8.62	7.52–7.58		3.67
5b	7.56–7.50	7.64, ddd, *J*=8.6, 7.2, 1.5 Hz	7.40, ddd, *J*=7.8, 7.2, 1.0 Hz	8.06, dd, *J*=7.8, 1.5 Hz	8.35–8.30	7.56–7.50		3.87

Table 3. ^{13}C NMR ($CDCl_3$, 100 MHz) chemical shifts (δ, ppm) of oxazoloquinolinone derivatives **3–5**

Carbon	**3a**	**4a**	**5a**	**3b**	**4b**	**5b**
2	—	—	162.7	—	—	162.6
3	158.6	174.3	—	160.9	172.4	—
3a	108.75	107.1	128.8	107.5	105.9	130.0
4	158.6	158.7	157.3	158.0	158.1	157.75
5a	140.3	140.4	138.2	140.2	140.1	138.6
6	115.4	115.5	115.2	115.3	115.5	115.4
7	132.4	131.95	130.1	132.7	132.05	130.5
8	122.8	123.0	122.45	122.8	123.0	122.7
9	123.3	124.8	121.4	123.4	124.7	121.75
9a	110.65	112.2	111.3	110.4	112.1	111.5
9b	167.2	156.3	152.3	168.3	157.4	152.2
1′	—	—	—	127.2	126.5	126.5
2′/6′	—	—	—	129.6	129.1	127.45
3′/5′	—	—	—	128.4	128.7	129.0
4′	—	—	—	130.6	131.9	131.6
CH_3	10.8	12.85	14.2	—	—	—
N–CH_3	29.1	28.7	29.6	29.5	29.35	29.8

at δ 172.4 ppm, in agreement with a carbon linked to the oxygen atom of the isoxazole moiety, thus allowing us to attribute the structure **4b** to this product.

The formation of compound **5b** could be rationalized by postulating a partial conversion of compound **2b** into **1b** thus allowing the formation of the corresponding oxime and its subsequent Beckmann rearrangement. This hypothesis is confirmed by the obtainment of **5b** from **1b** with hydroxylamine in ethylene glycol (see Scheme 1).



2a **6**

Scheme 2. *Reagents and conditions*: (i) 1-phenylethanamine, ethanol, reflux.

Table 4. Chemical shifts ($CDCl_3$, δ, ppm, 40.54 MHz) of five-membered ring nitrogen atom in compounds **3–5**

Compd	δ (^{15}N)
3a	−4.0
4a	−16.0
5a	−135.0
3b	−7.3
4b	−21.4
5b	−140.4

3. Conclusions

We have investigated the reaction of hydroxylamine with 3-acyl-4-methoxy-1-methylquinolinones **2a**,**b** and unambiguously determined the structure of the obtained products under different reaction conditions. Whereas from the reaction of **2a** with hydroxylamine both the regioisomeric isoxazolo[4,5-*c*] and -[4,3-*c*] (compounds **3a** and **4a**) can be selectively and exclusively obtained, reaction of **2b** always gave rise to a mixture of the required isoxazole together with the oxazole derivative. The same reaction carried out on the 4-hydroxy substituted quinolinones **1a**,**b** gave rise uniquely to the oxazoles **5a**,**b**. All the structures of the obtained products have been elucidated by the combined use of ^{13}C and ^{15}N 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 for dispersion in KBr. Elemental analyses were obtained by Elemental Analyzer Perkin–Elmer 240C Apparatus. Mass spectra were registered with a Carlo Erba QMD 1000 instrument at 70 eV. Compounds **1a**,**b** were obtained as reported in the literature.[1,11] 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-400 spectrometer (399.95 MHz for ^{1}H, 100.57 MHz for ^{13}C, and 40.54 for ^{15}N), with a 5 mm indirect detection probe equipped with a gradient coil, at 298 K. Chemical shifts (δ in parts per million) were referenced to the solvent $CDCl_3$, 7.26 for ^{1}H and 77.00 for ^{13}C, and external nitromethane (0.00) for ^{15}N NMR. 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. ^{1}H NMR spectra were acquired using 4.6 kHz spectral width with 32K data points (4.5 μs 90° pulse width, 0.28 Hz/point digital resolution).

4.2. Synthesis of 3-acyl-4-methoxy-1-methylquinolin-2(1*H*)-ones (2a,b)

To a solution of 3-acetyl(benzoyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one **1a**,**b** (2.17 g or 2.79 g, 10 mmol) and dimethyl sulfate (11.1 mmol) in acetone (100 mL) potassium carbonate (11.1 mmol) was added and the mixture was heated at reflux for 5 h. Removal of the solvent left a yellow solid which was suspended in water (100 mL), collected by filtration, and dried. The obtained material was purified by flash chromatography (ethyl acetate/petroleum ether 40/70=1:1 as eluant for **2a** and ethyl acetate/petroleum ether 40/70=2:3 as eluant for **2b**). ^{1}H and ^{13}C NMR data for compounds **3a**,**b**–**5a**,**b** are reported in Tables 2 and 3, respectively.

4.2.1. 3-Acetyl-4-methoxy-1-methylquinolin-2(1*H*)-one (2a). Colorless needles; 1.62 g (70%); mp 84–85 °C; R_f (ethyl acetate/petroleum ether 40/70=1:1) 0.42; IR (KBr) 2971, 1682, 1610, 1502, 1358 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (1H, dd, ^3J=8.0 Hz, ^4J=1.6 Hz, H-5), 7.59 (1H, ddd, ^3J=8.6, 7.2 Hz, ^4J=1.6 Hz, H-7), 7.32 (1H, dd, ^3J=8.6 Hz, ^4J=1.0 Hz, H-8), 7.24 (1H, ddd, ^3J=8.0, 7.2 Hz, ^4J=1.0 Hz, H-6), 3.95 (3H, s, O–Me), 3.65 (3H, s, N–Me), 2.65 (3H, s, 3-Me); ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 201.6 (s, C=O), 161.7 (s, C-2), 159.9 (s, C-4), 139.5 (s, C-8a), 131.9 (d, C-7), 124.7 (d, C-5), 122.2 (d, C-6), 117.6 (s, C-3), 117.1 (s, C-4a), 114.0 (d, C-8), 61.6 (q, O–Me), 32.35 (q, COMe), 29.1 (q, N–Me); EIMS *m*/*z* (%): 231 (M$^+$, 51), 216 (100), 201 (39), 105 (24), 77 (23). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.78; H, 5.45; N, 6.30.

4.2.2. 3-Benzoyl-4-methoxy-1-methylquinolin-2(1*H*)-one (2b). Yellow needles; 2.08 g (71%); mp 172–173 °C; R_f (ethyl acetate/petroleum ether 40/70=2:3) 0.38; IR (KBr) 3009, 1670, 1619, 1441, 1361 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (1H, dd, ^3J=8.1 Hz, ^4J=1.2 Hz, H-5), 8.00 (2H, m, H-2′), 7.64 (1H, ddd, ^3J=8.5, 7.2 Hz, ^4J=1.7 Hz, H-7), 7.57 (1H, m, H-4′), 7.47 (2H, m, H-3′), 7.38 (1H, dd, ^3J=8.5 Hz, ^4J=1.0 Hz, H-8), 7.64 (1H, ddd, ^3J=8.1, 7.2 Hz, ^4J=1.0 Hz, H-6), 3.89 (3H, s, O–Me), 3.66 (3H, s, N–Me); ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 194.38 (s, C=O), 162.2 (s, C-2), 159.8 (s, C-4), 139.55 (s, C-8a), 138.0 (s, C-1′), 133.5 (d, C-4′), 131.9 (d, C-7), 129.4 (d, C-2′), 128.8 (d, C-3′), 124.7 (d, C-5), 122.2 (d, C-6), 117.0 (s, C-4a), 114.1 (d, C-8), 113.1 (s, C-3), 60.5 (q, O–Me), 29.2 (q, N–Me); EIMS *m*/*z* (%): 293 (M$^+$, 53), 264 (100), 216 (25), 105 (37), 77 (80). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.98; H, 4.95; N, 5.06.

4.3. Synthesis of 4-methoxy-3-(*N*-hydroxyethanimidoyl)-4-methoxy-1-methylquinolin-2(1*H*)-one

To a stirred solution of 3-acetyl-4-methoxy-1-methylquinolin-2(1*H*)-one (**2a**) (0.208 g, 0.9 mmol) in ethanol (10 mL) hydroxylamine hydrochloride (0.076 g, 1.1 mmol) was added in one portion and the reaction mixture heated at reflux for 3 h. Removal of the solvent left a yellow solid (mp 149–150 °C, quantitative yield); IR (KBr) 3300, 1650, 1620, 1604, 1587 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (1H, br s, OH), 7.98 (1H, dd, ^3J=8.1 Hz, ^4J=1.5 Hz, H-5), 7.56 (1H, ddd, ^3J=8.6, 7.2 Hz, ^4J=1.5 Hz, H-7), 7.31 (1H, dd, ^3J=8.6 Hz, ^4J=1.0 Hz, H-8), 7.22 (1H, ddd, ^3J=8.1, 7.2 Hz, ^4J=1.0 Hz, H-6), 3.96 (3H, s, O–Me), 3.66 (3H, s, N–Me), 2.26 (3H, s, 3-Me); ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 163.1 (s, C-2), 160.9 (s, C-4), 153.2 (s, C=N), 139.2 (s, C-8a), 131.4 (d, C-7), 124.6 (d, C-5), 122.0 (d, C-6), 117.6 (s, C-4a), 113.9 (d, C-8), 112.8 (s, C-3), 61.3 (q, O–Me), 29.5 (q, N–Me), 16.5 (q, CNMe); EIMS *m*/*z* (%): 246 (M$^+$, 33), 229 (100), 215 (67), 200 (37), 117 (11), 77 (26), 51 (17). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.18; H, 6.00; N, 11.59.

4.4. Synthesis of 3,5-dimethylisoxazolo[4,5-*c*]quinolin-4(5*H*)-one (3a)

To a stirred solution of 3-acetyl-4-methoxy-1-methylquinolin-2(1*H*)-one (**2a**) (0.208 g, 0.9 mmol) in ethylene glycol (10 mL) hydroxylamine hydrochloride (0.076 g, 1.1 mmol) was added in one portion and the reaction mixture heated at reflux for 1 h. After cooling, the yellow precipitate was collected by filtration, dried, and recrystallized from ethanol (mp 190–191 °C, 0.154 g, yield 80%); IR (KBr) 2947, 1670, 1570, 1413, 1315 cm^{-1}; EIMS *m*/*z* (%): 214 (M$^+$, 100), 185 (31), 104 (57), 77 (39), 63 (19), 51 (31). Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.08; H, 4.71; N, 13.08. Found: C, 66.74; H, 4.60; N, 13.17.

4.5. Synthesis of 3,5-dimethylisoxazolo[4,3-*c*]quinolin-4(5*H*)-one (4a)[4]

A solution of hydroxylamine hydrochloride (0.042 g, 0.6 mmol) and Et_3N (0.08 mL, 0.6 mmol) in ethylene glycol (6 mL) was stirred for 10 min at room temperature. 3-Acetyl-4-methoxy-1-methylquinolin-2(1*H*)-one (**2a**) (0.092 g, 0.4 mmol) was subsequently added and the solution was heated at 200 °C for 30 min. After cooling, the white precipitate was collected by filtration, dried, and recrystallized from ethanol [mp 193–194 °C, lit.[4] mp 205–206 °C (from dioxane), 0.086 g, quantitative yield].

4.6. Synthesis of 2,5-dimethyl[1,3]oxazolo[4,5-*c*]quinolin-4(5*H*)-one (5a)[5]

To a stirred solution of 3-acetyl-4-methoxy-1-methylquinolin-2(1*H*)-one (**2a**) (0.304 g, 1.4 mmol) in ethylene glycol (10 mL) hydroxylamine hydrochloride (0.118 g, 1.7 mmol) was added in one portion and the reaction mixture heated at reflux for 2 h. After cooling, water was added and the solid obtained was filtered and purified by column chromatography with ethyl acetate as eluant, R_f 0.50 [mp 190–191 °C, lit.[5] mp 191 °C (from toluene/hexane), 0.210 g, yield 70%].

4.7. Synthesis of 3-acetyl-1-methyl-4-[(1-phenylethyl)-amino]quinolin-2(1*H*)-one (6)

To a stirred solution of 3-acetyl-4-methoxy-1-methylquinolin-2(1*H*)-one (**2a**) (0.231 g, 1.0 mmol) in ethanol (10 mL) 1-phenylethanamine (0.153 mL, 1.2 mmol) was added and the reaction mixture was heated at reflux for 3 h. Removal of the solvent left a yellow solid (mp 140–141 °C, quantitative yield); IR (KBr) 2978, 2246, 1612, 1563, 1440, 1300 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.98 (1H, d, ^3J=6.6 Hz, NH), 7.76 (1H, dd, ^3J=8.4 Hz, ^4J=1.5 Hz,

H-5), 7.52 (1H, ddd, ^3J=8.4, 7.0 Hz, ^4J=1.4 Hz, H-7), 7.40–7.28 (5H, m, Ar–H), 7.24 (1H, dd, ^3J=8.4 Hz, ^4J=1.0 Hz, H-8), 6.96 (1H, ddd, ^3J=8.4, 7.0 Hz, ^4J=1.0 Hz, H-6), 5.18 (1H, dq, ^3J=6.6 Hz, H-1′), 3.58 (3H, s, N–Me), 2.75 (3H, s, COMe), 1.63 (3H, d, ^3J=6.6 Hz); ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 202.6 (s, C=O), 162.6 (s, C-2), 159.8 (s, C-4), 143.7 (s, C-1″), 141.5 (s, C-8a), 132.7 (d, C-7), 129.1 (d, C-3″), 128.4 (d, C-5), 127.5 (d, C-4″), 125.6 (d, C-2″), 120.35 (d, C-6), 114.55 (d, C-8), 114.5 (s, C-4a), 105.65 (s, C-3), 58.1 (d, C-1′), 33.4 (q, COMe), 29.45 (q, N–Me), 26.7 (q, 1′-Me); EIMS *m/z* (%): 320 (M^+, 49), 305 (38), 215 (67), 229 (28), 215 (41), 201 (67), 105 (100), 77 (48). Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.71; H, 6.45; N, 8.50.

4.8. Reaction of 3-benzoyl-4-methoxy-1-methylquinolin-2(1*H*)-one (2b) with hydroxylamine hydrochloride

To a stirred solution of 3-benzoyl-4-methoxy-1-methylquinolin-2(1*H*)-one (**2b**) (0.117 g, 0.4 mmol) in ethylene glycol (5 mL) hydroxylamine hydrochloride (0.035 g, 0.5 mmol) was added in one portion and the reaction mixture heated at reflux for 4 h. After cooling, the reaction mixture was poured into water (15 mL) and the solid obtained was filtered and dried. The crude product consisting of the isomeric 5-methyl-3-phenylisoxazolo[4,5-*c*]quinolin-4(5*H*)-one (**3b**) and 5-methyl-2-phenyl[1,3]oxazolo[4,5-*c*]quinolin-4(5*H*)-one (**5b**)[5] was separated by column chromatography with ethyl acetate/petroleum ether 40/70=1:3 as eluant; the first fraction, R_f 0.41, afforded a white solid (0.051 g, yield 46%) which was identified as **3b** whereas the second eluted fraction, R_f 0.15, gave a small amount of compound **5b** (0.0044 g, yield 4%). An analytical sample of **3b** obtained by recrystallization from ethyl acetate had mp 153–154 °C; IR (KBr) 3017, 1666, 1219, 1207 cm^{-1}; EIMS *m/z* (%): 276 (M^+, 100), 247 (37), 104 (59), 77 (42), 51 (38). Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90, H, 4.38; N, 10.14. Found: C, 74.01; H, 4.18; N, 10.29.

4.9. Reaction of 3-benzoyl-4-methoxy-1-methylquinolin-2(1*H*)-one (2b) with hydroxylamine

3-Benzoyl-4-methoxy-1-methylquinolin-2(1*H*)-one (**2b**) (0.176 g, 0.6 mmol) was added at room temperature under stirring to a solution of hydroxylamine hydrochloride (0.055 g, 0.8 mmol) and Et_3N (0.11 mL, 0.8 mmol) in ethylene glycol (5 mL) and the solution was then heated at reflux for 3 h. After cooling, the reaction mixture was poured into water (15 mL) and exhaustively extracted with dichloromethane. Evaporation to dryness of the organic layer afforded a crude product consisting of the isomeric 5-methyl-3-phenylisoxazolo[4,3-*c*]quinolin-4(5*H*)-one (**4b**) and **5b** in the ratio 1:1. Compounds were separated by column chromatography with ethyl acetate/petroleum ether 40/70=1:3 as eluant; the first band, R_f 0.67, afforded a white solid (0.041 g, yield 25%) which was identified as **4b** whereas the second eluted fraction, R_f 0.15, gave the derivative **5b** (0.041 g, yield 25%). Analytical samples were obtained by recrystallization from ethanol: **4b** mp 173–174 °C (lit.[5] mp 177.5–178 °C from ethanol) and **5b** mp 194–195 °C (lit.[5] mp 246 °C from toluene/hexane and lit.[12] 199 °C from ethanol). Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90, H, 4.38; N, 10.14. Found: C, 73.98; H, 4.22; N, 10.21 and C, 74.11; H, 4.24; N, 10.19, for **4b** and **5b**, respectively.

Acknowledgements

The authors wish to thank MIUR for financial support and Ente Cassa di Risparmio di Firenze, Italy for granting a 400 MHz NMR spectrometer. Mrs. Brunella Innocenti and Mr. Maurizio Passaponti (Dipartimento di Chimica Organica 'Ugo Schiff', Università di Firenze) are acknowledged for technical assistance.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2007.08.108.

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