2106 Russian Chemical Bulletin, International Edition, Vol. 51, No. 11, pp. 2106—2108, November, 2002

Three-component cyclization of hydroxylamino-substituted quinoline with reactive methylene compounds and formaldehyde: new method for the synthesis of 7-(isoxazolidin-2-yl)-6-fluoroquinolones

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A one-step procedure was developed for the synthesis of new 6-fluoro-7-(isoxazolidin-2-yl)-4-oxo-1,4-dihydroquinolines. The procedure is based on the 1,3-dipolar cycloaddition of the azomethine oxide and 1,1-disubstituted alkenes, which are generated *in situ* from 6-fluoro-7-hydroxylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and CH-active compounds (dialkyl malonates, ethyl acetoacetate), respectively, in the presence of formaldehyde at 100—120 °C.

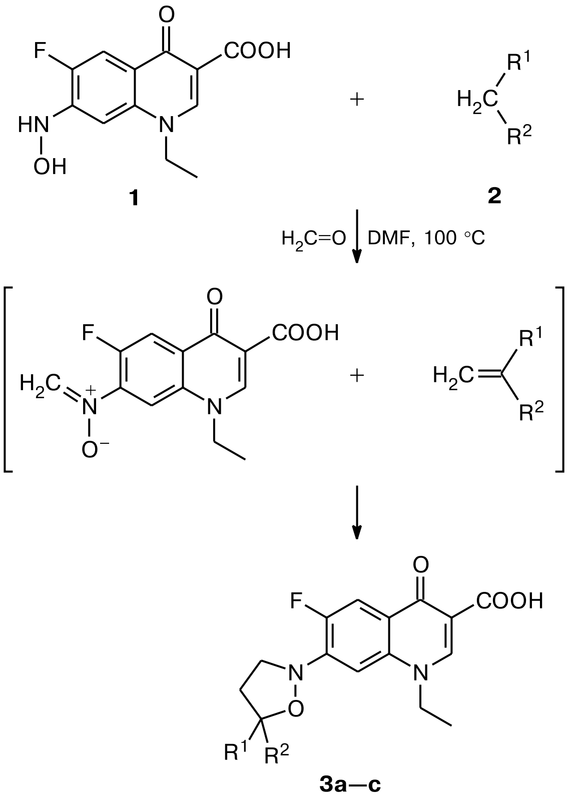
Key words: fluoroquinolones, three-component cyclization, *β*-dicarbonyl compounds, formaldehyde, 1,3-dipolar cycloaddition, 6-fluoro-7-(isoxazolidin-2-yl)-4-oxo-1,4-dihydroquinolones.

Fluorine-containing substances occupy an important place in the modern spectrum of chemotherapeutic drugs.[1] Among fluorinated azaheterocycles, derivatives of 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (the so-called fluoroquinolones) are of particular interest.[2—5] The development of new procedures for structural modifications of fluoroquinolones is still a topical problem.[6,7]

Previously,[8] we have reported the use of the 1,3-dipolar cycloaddition in the synthesis of 7-(isoxazolidin-2-yl)-substituted 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acids by the reactions of 7-azomethine oxide of 1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid with a broad spectrum of unsaturated compounds, *viz.*, with alkenes containing C=C bonds of different polarity as well as with mono-, bi-, and tricyclic alkenes containing strained and unstrained C=C double bonds. In these reactions, azomethine oxide was generated *in situ* by condensation of 6-fluoro-7-hydroxylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid with paraformaldehyde. The reactions of azomethine oxide with alkenes were carried out in the presence of an excess of these reagents in an autoclave at 100—120 °C.[8,9]

Taking into account the high reactivity of formaldehyde to compounds containing the active methylene groups,[10] it was reasonable to expect that a three-component mixture consisting of 6-fluoro-7-hydroxylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**1**), a β-dicarbonyl compound (**2**), and paraformaldehyde could be a source of both the reactive 1,3-dipole and di-

Scheme 1



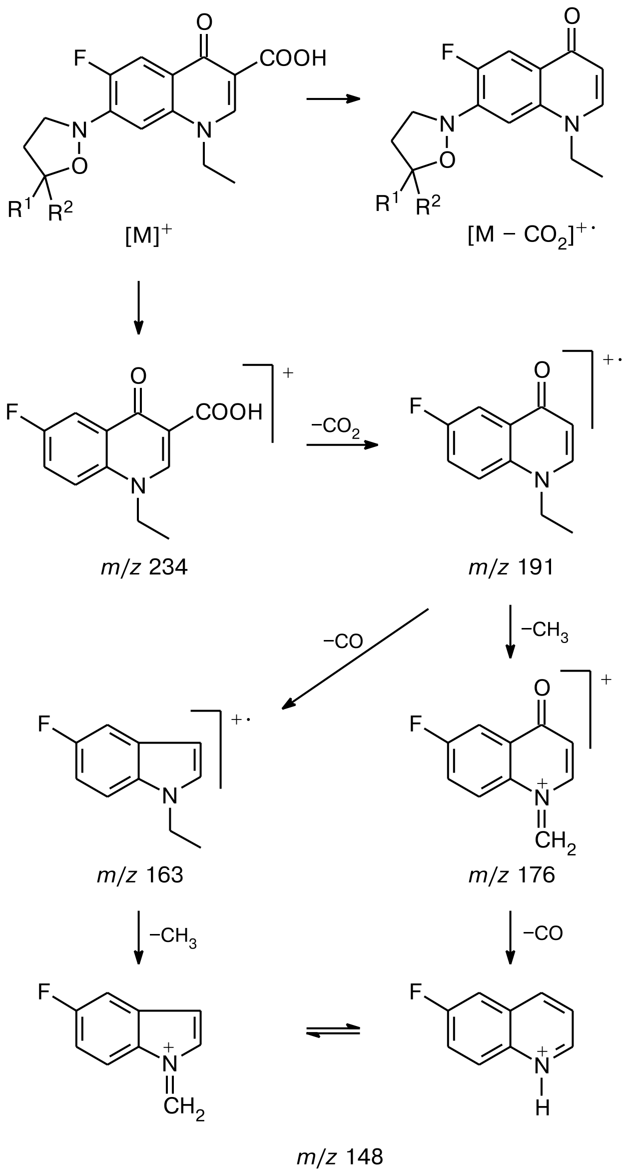
a: $R^1 = R^2 = CO_2Me$; **b:** $R^1 = R^2 = CO_2Et$; **c:** $R^1 = COMe$, $R^2 = CO_2Et$

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 1951—1953, November, 2002.

polarophile. Actually, the reactions of acid **1** with β-dicarbonyl compounds **2** (ethyl acetoacetate, malonic esters) and paraformaldehyde in an autoclave at 100—120 °C afforded 5′,5′-disubstituted 6-fluoro-7-(isoxazolidin-2-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acids **3a—c** in 31—46% yields (Scheme 1).

The structures of the resulting cyclic adducts **3a—c** were established based on the data from ^{1}H NMR spectroscopy and mass spectrometry. The mass spectra of compounds **3a—c** have a molecular ion peak at *m/z* 234 corresponding to the structure of the fluoroquinolone fragment formed through the cleavage of the bond between the C(7) atom and the saturated isoxazolidine residue. The fragmentation of fluoroquinolone accompanied by the loss of the carboxy group proceeded as a competitive reaction. The pathways of further fragmentations are shown in Scheme 2.

Scheme 2



The ^{1}H NMR spectra of compounds **3a—c** have averaged triplets of two adjacent methylene units of the isoxazolidine fragments at δ 2.8—2.9 and 3.8—3.9 with the vicinal constants ^3J = 5.4—6.4 Hz. Such spectral patterns unambiguously confirm the above-mentioned regioselectivity of coupling of the alkene with the 1,3-dipole. Otherwise, the methylene units in the isoxazolidine ring would be separated by the tetrasubstituted C atom resulting in the simplification of the spectral pattern.

Therefore, the three-component cyclization of 7-(hydroxylamino)quinolines with reactive methylene compounds and formaldehyde, which was developed in the present study, simplifies the scheme and extends the possibilities of preparing new 7-isoxazolidine derivatives of 6-fluoroquinolones.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker-250 spectrometer (250.135 MHz) in DMSO-d_6 with Me_4Si as the internal standard. The mass spectra (EI, 70 eV) were measured on a Varian MAT-311A spectrometer with direct inlet of the sample into the ion source. The synthesis of 6-fluoro-7-hydroxylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid has been described previously.[9]

Derivatives of 1,4-dihydroquinoline-3-carboxylic acid 3a—c (general procedure). A suspension containing acid **1** (1.0 g, 3.8 mmol), a 1,3-dicarbonyl compound (75 mmol), and paraformaldehyde (1.0 g, 33 mmol) in DMF (10 mL) was kept in a steel autoclave at 100—120 °C for 11—17 h. The reaction mixture was cooled to ~20 °C and poured into ice water (100 mL). The aqueous layer was decanted and propan-2-ol (10 mL) was added to the oily residue. The precipitate that formed was filtered off and recrystallized from EtOH.

7-[5,5-Di(methoxycarbonyl)isoxazolidin-2-yl]-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3a). The yield was 31%, m.p. 190—192 °C. Found (%): C, 54.03; H, 4.64; N, 6.52. $C_{19}H_{19}FN_2O_8$. Calculated (%): C, 54.03; H, 4.53; N, 6.63. MS, *m/z* (I_{rel} (%)): 422 $[M]^+$ (21), 379 (12), 348 (15), 234 (15), 232 (50), 219 (11), 218 (31), 217 (19), 206 (11), 203 (14), 191 (7), 190 (12), 176 (4), 163 (4), 148 (5), 113 (100). ^{1}H NMR, δ: 1.51 (t, 3 H, $NCH_2C\underline{H}_3$, J = 7.0 Hz); 2.84 (t, 2 H, C(4′)H_2, ^3J = 6.4 Hz); 3.84 (s, 6 H, 2 OMe); 3.90 (t, 2 H, C(3′)H_2, ^3J = 6.4 Hz); 4.55 (q, 2 H, $NC\underline{H}_2Me$, J = 7.0 Hz); 7.94 (d, 1 H, H(8), ^4J = 7.0 Hz): 7.96 (d, 1 H, H(5), ^3J = 11.9 Hz); 8.98 (s, 1 H, H(2)); 14.86 (br.s, 1 H, COOH).

7-[5,5-Di(ethoxycarbonyl)isoxazolidin-2-yl]-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3b). The yield was 37%, m.p. 200—202 °C. Found (%): C, 56.12; H, 5.20; N, 6.17. $C_{21}H_{23}FN_2O_8$. Calculated (%): C, 56.00; H, 5.15; N, 6.22. MS, *m/z* (I_{rel} (%)): 450 $[M]^+$ (43), 407 (23), 406 (100), 362 (33), 234 (20), 232 (100), 219 (19), 218 (45), 217 (33), 206 (15), 203 (19), 191 (10), 190 (16), 176 (6), 163 (5), 148 (8), 127 (67). ^{1}H NMR, δ: 1.23 (t, 6 H, 2 $OCH_2C\underline{H}_3$, J = 6.9 Hz); 1.45 (t, 3 H, $NCH_2C\underline{H}_3$, J = 7.0 Hz); 2.82 (t, 2 H, C(4′)H_2,

^3J = 5.4 Hz); 3.90 (t, 2 H, C(3´)H$_2$, J = 5.4 Hz); 4.28 (q, 4 H, 2 OC$\underline{H}_2$Me, J = 6.9 Hz); 4.54 (q, 2 H, NC$\underline{H}_2$Me, J = 7.0 Hz); 7.99 (d, 1 H, H(8), ^4J = 6.6 Hz); 8.00 (d, 1 H, H(5), ^3J = 12.1 Hz); 9.02 (s, 1 H, H(2)); 15.12 (br.s, 1 H, COOH).

7-(5-Acetyl-5-ethoxycarbonylisoxazolidin-2-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3c). The yield was 46%, m.p. 175—177 °C. Found (%): C, 57.19; H, 5.07; N, 6.51. $C_{20}H_{21}FN_2O_7$. Calculated (%): C, 57.14; H, 5.04; N, 6.66. MS, m/z (I_{rel} (%)): 420 [M]$^+$ (57), 377 (17), 376 (79), 259 (12), 248 (17), 245 (34), 234 (37), 232 (31), 219 (33), 218 (100), 206 (37), 205 (11), 203 (14), 191 (18), 190 (17), 176 (6), 163 (8), 148 (7), 142 (24). ^{1}H NMR, δ: 1.27 (t, 3 H, OCH$_2$C$\underline{H}_3$, J = 7.0 Hz); 1.51 (t, 3 H, NCH$_2$C$\underline{H}_3$, J = 7.2 Hz); 2.80—2.90 (m, 2 H, C(4´)H$_2$); 3.80 (t, 2 H, C(3´)H$_2$, ^3J = 6.3 Hz); 4.27 (q, 2 H, OC$\underline{H}_2$Me, J = 7.0 Hz); 4.57 (q, 2 H, NCH$_2$C$\underline{H}_3$, J = 7.2 Hz); 7.86 (d, 1 H, H(8), J = 6.5 Hz); 7.98 (d, 1 H, H(5), J = 12.0 Hz); 8.99 (s, 1 H, H(2)); 14.86 (br.s, 1 H, COOH).

This study was financially supported by the Ministry of Education of the Russian Federation (Grants TOO-9.3-1966 and EOO-5.0-316) and the Russian Foundation for Basic Research (Project Nos. 00-03-32785a and 01-03-96427).

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Received March 19, 2002;
in revised form July 10, 2002