Reactions of 3-substituted 1-aryl-5,6,7,8-tetrafluoroquinolones(cinnolones) with morpholine

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1-Aryl-3-ethoxalyl(heteryl)-5,6,7,8-tetrafluoroquinoxalinones(cinnolinones) react with morpholine to give 7-morpholino- and 5,7-dimorpholino derivatives, depending on the reaction conditions.

Key words: 5,6,7,8-tetrafluoroquinolones, 5,6,7,8-tetrafluorocinnolones, aromatic nucleophilic substitution, morpholine.

Recently, a series of 1-aryl-3-ethoxalyl(heteryl)-5,6,7,8-tetrafluoro-1,4-dihydroquinolin(cinnolin)-4-ones (**1**—**5**) have been synthesized.[1—3] Like all organofluorine substances, these compounds enter into nucleophilic substitution reactions. Investigations of the behavior of structurally similar compounds, namely, derivatives of fluoroquinolone-3-carboxylic acids[4] and 5,6,7,8-tetrafluorochromen-4-one[5] showed that the monosubstitution reactions with alkylamines mainly give 7-substituted, less often 5-substituted, and, in specific cases, 8-substituted products. The formation of 5,7-disubstituted products was noted only once.[4]

In the present work, we studied the possibility of aromatic nucleophilic substitution in quinolones **1** and **3** and cinnolones **2**, **4**, and **5** exemplified in their reactions with morpholine.

Results and Discussion

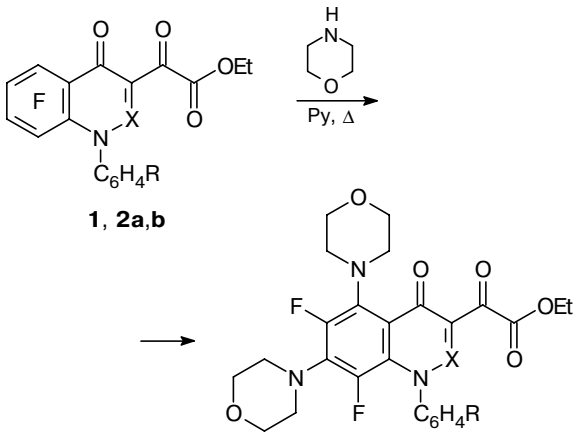
It was found that the reactions of 3-ethoxalylquinolone **1** and -cinnolones **2a**,**b** with an excess of morpholine in boiling pyridine yield 5,7-disubstitution products **6** and **7a**,**b**, respectively (Scheme 1, Table 1). The positions of the morpholine residues were determined from the coupling constants of the F atoms in ^{19}F NMR spectra (see Table 1) with consideration of the literature data.[4,5]

Note that cinnolones react more readily, since their conversion is completed within 1 h, whereas the conversion of quinolones takes 3 h (TLC).

The reaction of quinolone **1** in DMSO at ~20 °C affords 7-morpholino derivative **8** (see Scheme 1, Table 1).

Attempts at preparing an individual monosubstitution product from cinnolone **2** by varying reaction conditions (solvent, temperature, and reagent ratio) were unsuccessful.

Scheme 1



X = CH, R = 2-Me (**1**, **6**)
X = N, R = 4-Br (**2a**, **7a**), 2-Me (**2b**, **7b**)

When studying substitution in quinolone **3** and cinnolones **4a**,**b** under analogous conditions, we found that 5,7-disubstitution products **9** and **10** are formed in boiling pyridine, while 7-monosubstitution derivatives **11** and **12**, in DMSO at ~20 °C (Scheme 2, see Table 1). As in the aforementioned case, compound **3** proved to be less reactive than the corresponding cinnolones. More-

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Table 1. Main physicochemical parameters of compounds **6—13**

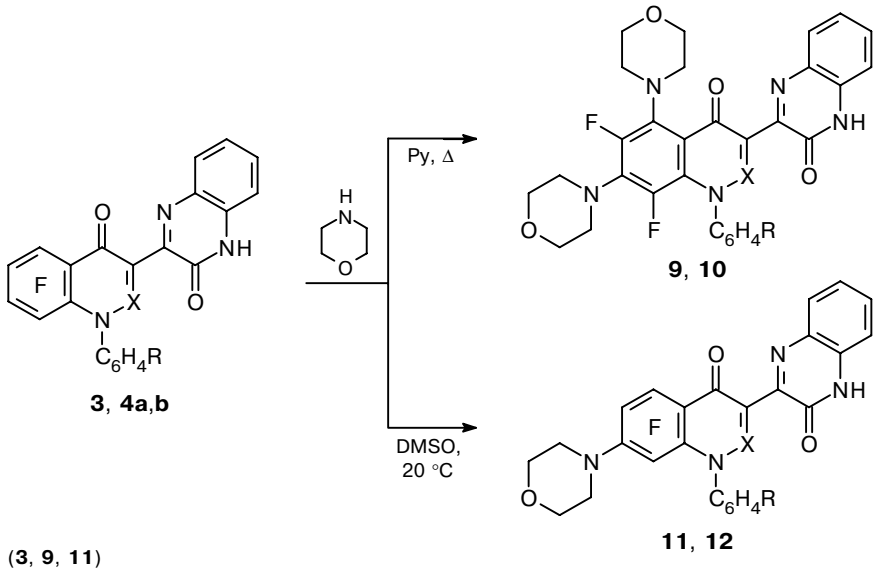
Compound	M.p. /°C	Yield (%)	Found / Calculated (%) C	H	F	N	Molecular formula	IR, ν/cm^{-1}	NMR (DMSO-d_6), δ, *J*/Hz ^{1}H	^{19}F
6	197—200	75	62.18 62.10	5.36 5.40	6.98 7.02	7.79 7.76	$C_{28}H_{29}F_2N_3O_6$	3050 (CH); 1735 (COOEt); 1665 (C=O); 1630 (C=O ring); 1595 (C=N, C=C)	1.33 (t, 3 H, Me, *J* = 7.1); 2.11 (s, 3 H, Me); 2.96—3.81 (m, 16 H, CH_2); 4.33 (q, 2 H, CH_2, *J* = 7.1); 7.24—7.57 (m, 4 H, C_6H_4); 8.15 (s, 1 H, CH)	29.57 (br.s, 1 F); 29.83 (br.s, 1 F)
7a	209—210	92	51.70 51.41	4.19 4.15	6.24 6.26	9.03 9.22	$C_{26}H_{25}BrF_2N_4O_6$	1725 (COOEt); 1700 (C=O); 1620 (C=O ring); 1595 (C=N, C=C)	1.26 (t, 3 H, Me, *J* = 7.3); 3.10—3.86 (m, 16 H, CH_2); 4.32 (q, 2 H, CH_2, *J* = 7.3); 7.65 (m, 4 H, C_6H_4)	31.64 (d, 1 F); 32.53 (d, 1 F); *J* = 6.5
7b	169—171	85	59.70 59.77	5.11 5.20	6.76 7.00	10.30 10.33	$C_{27}H_{28}F_2N_4O_6$	1730 (COOEt); 1710 (C=O); 1625 (C=O ring); 1595 (C=N, C=C)	1.27 (t, 3 H, Me, *J* = 7.3); 3.10—3.86 (m, 16 H, CH_2); 4.31 (q, 2 H, CH_2, *J* = 7.3); 7.66 (m, 4 H, C_6H_4)	31.64 (d, 1 F); 32.53 (d, 1 F); *J* = 6.4
8	226—228	69	60.79 60.76	4.51 4.46	12.12 12.01	5.93 5.91	$C_{24}H_{21}F_3N_2O_5$	3045 (CH); 1735 (COOEt); 1665 (C=O); 1640, 1620 (C=O ring, C=N); 1585 (C=C)	1.31 (t, 3 H, Me, *J* = 7.1); 2.14 (s, 3 H, Me); 3.03—3.85 (m, 8 H, CH_2); 4.33 (q, 2 H, CH_2, *J* = 7.1); 7.26—7.58 (m, 4 H, C_6H_4); 8.17 (s, 1 H, CH)	14.74 (dd, 1 F, F(6)); 18.24 (dd, 1 F, F(5)); 26.92 (dd, 1 F, F(8)); $J_{5,6}$ = $J_{6,5}$ = 19.5; $J_{5,8}$ = $J_{8,5}$ = 12.2; $J_{6,8}$ = $J_{8,6}$ = 5.4
9	318—310	89	65.33 65.63	5.07 4.99	6.42 6.49	11.72 11.96	$C_{32}H_{29}F_2N_5O_4$	1660 (C=O lactam); 1625 (C=O); 1610, 1595 (C=N, C=C)	2.22 (s, 3 H, Me); 3.05—3.71 (m, 16 H, CH_2); 7.44—7.71 (m, 8 H, 2 C_6H_4); 7.89 (s, 1 H, CH); 12.28 (br.s, 1 H, NH)	29.76 (s, 1 F); 29.86 (s, 1 F)
10	>300	96	61.69 61.79	4.73 4.68	6.10 6.31	13.77 13.95	$C_{31}H_{28}F_2N_6O_5$	1770 (C=O lactam); 1620 (C=O); 1595 (C=N, C=C)	3.09—3.84 (m, 16 H, CH_2); 3.79 (s, 3 H, OMe); 6.96—7.85 (m, 8 H, C_6H_4); 12.60 (s, 1 H, NH)	29.81 (br.s, 1 F); 29.36 (br.s, 1 F)
11	328—330	88	64.89 64.86	4.05 4.08	10.70 10.99	10.89 10.81	$C_{28}H_{21}F_3N_4O_3$	3150 (NH); 1685 (C=O lactam); 1620 (C=O); 1590 (C=C, C=N)	2.21 (s, 3 H, Me) 3.03—3.71 (m, 8 H, CH_2); 7.21—7.64 (m, 8 H, 2 C_6H_4); 7.75 (s, 1 H, CH) 12.28 (br.s, 1 H, NH)	11.42 (d, 1 F, F(6)); 17.11 (dd, 1 F, F(5)); 25.25 (d, 1 F, F(8)); $J_{5,6}$ = $J_{6,5}$ = 18.8; $J_{5,8}$ = $J_{8,5}$ = 13.3

(*to be continued*)

Table 1 (*continued*)

Compound	M.p. /°C	Yield (%)	Found / Calculated (%) C	H	F	N	Molecular formula	IR, ν/cm^{-1}	NMR (DMSO-d$_6$), δ, *J*/Hz ^{1}H	^{19}F
12	>300	54	61.52 61.73	3.42 3.59	11.46 11.28	13.53 13.86	$C_{26}H_{18}F_3N_5O_3$	3460 (NH); 1665 (C=O lactam); 1630 (C=O); 1585 (C=C, C=N)	3.24, 3.67 (both m, 8 H each, CH_2); 7.33—7.84 (m, 9 H, C_6H_4, C_6H_5); 12.67 (s, 1 H, NH)	13.89 (dd, 1 F, F(6)); 16.58 (dd, 1 F, F(5)); 32.62 (dd, 1 F, F(8)); $J_{5,6}$ = $J_{6,5}$ = 19.4; $J_{5,8}$ = $J_{8,5}$ = 13.6; $J_{6,8}$ = $J_{8,6}$ = 5.7
13	278—280	50	62.87 62.82	4.32 4.39	6.70 6.63	12.22 12.21	$C_{30}H_{25}F_2N_5O_5$	1750 (C=O lactone); 1625 (C=O); 1590 (C=N, C=C)	3.04—3.29 (m, 16 H, CH_2); 6.77—7.91 (m, 9 H, C_6H_4, C_6H_5)	30.28 (br.s, 1 F); 30.77 (br.s, 1 F)

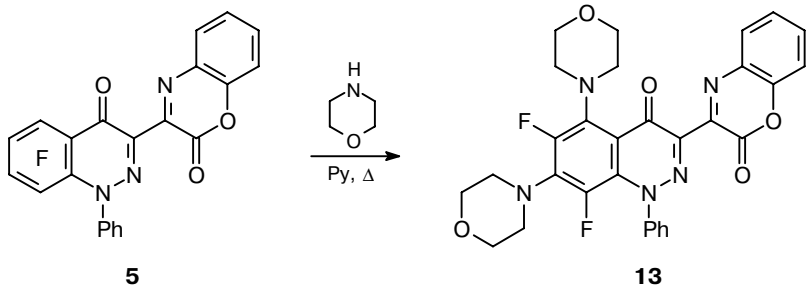
Scheme 2



over, in the case of quinoxalinonylquinolone **3**, the reaction in DMSO is completed only in the presence of Et_3N.

Cinnolinonylbenzooxazinone **5** reacts with an excess of morpholine in pyridine to give 5,7-disubstitution product **13** (Scheme 3, see Table 1). In DMSO, the

Scheme 3



benzooxazinone ring of compound **5** undergoes opening, yielding morpholide and an unseparable mixture of substitution products for F atoms. The same result was obtained in attempting to replace the F atoms in tetrafluoroquinolinonylbenzooxazinone.

Thus, one can conclude that morpholine predominantly attacks position 7 of the cinnolone (quinolone) system. In addition, our results suggest that aromatic nucleophilic substitution in the case of quinolone **1** is slower and more selective than S_NAr reactions of its aza analogs, cinnolones **2**.

Experimental

IR spectra were recorded on a Specord IR-75 spectrometer (400—4000 cm^{-1}, Vaseline oil). ^1H NMR spectra were recorded on Tesla BS-587 A (80 MHz) and Bruker DRX-400 (400 MHz) spectrometers relative to Me_4Si; ^{19}F NMR spectra were recorded on a Tesla BS-587 A spectrometer (75 MHz) relative to C_6F_6. Elemental analysis was carried out on a Carlo Erba CHNS-O EA 1108 instrument.

The starting 3-ethoxalyl-5,6,7,8-tetrafluoro-1-(2-tolyl)-1,4-dihydroquinolin-4-one (**1**),[1] 1-aryl-3-ethoxalyl-5,6,7,8-tetrafluoro-1,4-dihydrocinnolin-4-ones **2a**,**b**,[2] and 1-aryl-5,6,7,8-tetrafluoro-3-heteryl-1,4-dihydroquinolin(cinnolin)-4-ones **3**, **4a**,**b**, and **5** (see Ref. 3) were prepared according to the known procedures.

3-Ethoxalyl-6,8-difluoro-5,7-dimorpholino-1-(2-tolyl)-1,4-dihydroquinolin-4-one (6). Morpholine (0.43 g, 5 mmol) was added to a solution of quinolone **1** (0.41 g, 1 mmol) in 30 mL of dry pyridine. The reaction mixture was refluxed for 3 h and concentrated. The residue was dissolved in 50 mL of $CHCl_3$ and washed with 5% HCl (100 mL) and water to pH 7. The chloroform layer was separated and dried with $MgSO_4$. The solvent was removed, and the residue was recrystallized from MeOH to give product **6** (0.38 g) (see Table 1).

1-(4-Bromophenyl)-3-ethoxalyl-6,8-difluoro-5,7-dimorpholino-1,4-dihydrocinnolin-4-one (7a). Analogously, product **7a** (0.9 g) was obtained from cinnolone **2a** (0.85 g, 1.8 mmol) and morpholine (0.8 g, 9 mmol) over 30 min (see Table 1).

3-Ethoxalyl-6,8-difluoro-5,7-dimorpholino-1-(2-tolyl)-1,4-dihydrocinnolin-4-one (7b). Analogously, product **7b** (1.38 g) was obtained from cinnolone **2b** (1.18 g, 3 mmol) and morpholine (1.31 g, 9 mmol) (see Table 1).

3-Ethoxalyl-5,6,8-trifluoro-7-morpholino-1-(2-tolyl)-1,4-dihydroquinolin-4-one (8). Morpholine (0.43 g, 5 mmol) was added to a solution of quinolone **1** (0.407 g, 1 mmol) in 30 mL of dry DMSO. The reaction mixture was kept at 20 °C for 4 days and poured into 50 mL of 5% HCl. The precipitate that formed was filtered off, washed with water, and dried. Recrystallization from Pr^iOH gave product **8** (0.31 g) (see Table 1).

3-[6,8-Difluoro-5,7-dimorpholino-4-oxo-1-(2-tolyl)-1,4-dihydroquinolin-3-yl]-1,2-dihydroquinoxalin-2-one (9). Morpholine (1.37 mL, 10 mmol) was added to a solution of compound **3** (0.7 g, 1.6 mmol) in 20 mL of pyridine. The reaction mixture was refluxed for 10 h and concentrated, and the residue was dissolved in 70 mL of $CHCl_3$. The chloroform solution was washed with 5% HCl (100 mL) and water to pH 7, dried with $MgSO_4$, and concentrated. Recrystallization of the residue from Pr^iOH gave compound **9** (0.83 g) (see Table 1).

6,8-Difluoro-1-(4-methoxyphenyl)-5,7-dimorpholino-3-(2-oxo-1,2-dihydroquinoxalin-3-yl)-1,4-dihydrocinnolin-4-one (10). Analogously, product **10** (0.14 g) was obtained from compound **4a** (0.35 g, 0.8 mmol) and morpholine (0.645 g, 7.4 mmol) over 1 h (see Table 1).

3-[5,6,8-Trifluoro-7-morpholino-4-oxo-1-(2-tolyl)-1,4-dihydroquinolin-3-yl]-1,2-dihydroquinoxalin-2-one (11). Triethylamine (0.28 mL, 2 mmol) and morpholine (0.09 g, 1 mmol) were added to a solution of compound **3** (0.45 g, 1 mmol) in 10 mL of DMSO. The reaction mixture was kept at 20 °C for 190 h and poured into 100 mL of 5% HCl. The precipitate that formed was filtered off, washed with water, and recrystallized from Pr^iOH. The yield of compound **11** was 0.46 g (see Table 1).

5,6,8-Trifluoro-7-morpholino-3-(2-oxo-1,4-dihydroquinoxalin-3-yl)-1-phenyl-1,4-dihydrocinnolin-4-one (12). Morpholine (0.17 g, 1.5 mmol) was added to a solution of compound **4b** (0.18 g, 0.38 mmol) in 30 mL of DMSO. The reaction mixture was kept at 20 °C for 90 h and poured into 100 mL of 5% HCl. The precipitate that formed was filtered off, washed with water, and recrystallized from Pr^iOH. The yield of compound **12** was 0.11 g (see Table 1).

3-[6,8-Difluoro-5,7-dimorpholino-4-oxo-1-phenyl-1,4-dihydrocinnolin-3-yl]-1,2-dihydrobenzooxazin-2-one (13). Analogously, compound **13** (0.143 g) was obtained from compound **5** (0.23 g, 0.5 mmol) and morpholine (0.44 g, 5 mmol) (see Table 1).

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