Reactions of 1-aryl(alkyl)-3-ethoxalyl-5,6,7,8-tetrafluoro-1,4-dihydrocinnolin(quinolin)-4-ones with aromatic dinucleophiles

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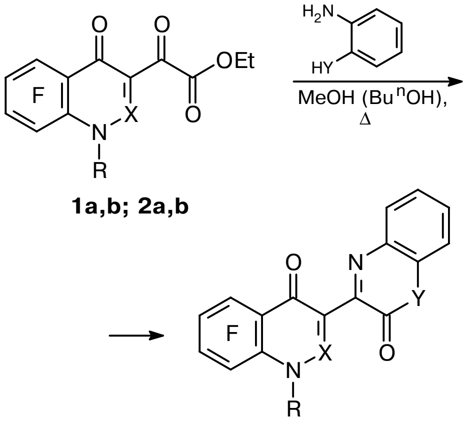
The title compounds react with *o*-phenylenediamine and *o*-aminophenol at the ethoxalyl fragment to form heteryl-substituted quinoxalones and benzooxazinones, respectively. *o*-Aminobenzenethiol acts as both an S-nucleophile replacing the F atom and an N-nucleophile replacing the carbonyl group in the ethoxalyl fragment. Under more drastic conditions, cyclization proceeds to form benzothiazinones.

Key words: 5,6,7,8-tetrafluorocinnolones, 5,6,7,8-tetrafluoroquinolones, *o*-phenylenediamine, *o*-aminophenol, *o*-aminobenzenethiol, quinoxalones, benzooxazinones, benzothiazinones.

Owing to the presence of the α-dicarbonyl fragment, 1-aryl-3-ethoxalyl-5,6,7,8-tetrafluoro-1,4-dihydrocinnolin-4-ones (**1**)[1] and 1-aryl(alkyl)-3-ethoxalyl-5,6,7,8-tetrafluoro-1,4-dihydroquinolin-4-ones (**2**)[2] prepared recently have considerable prospects for their subsequent modifications and can be used for the construction of new heterocyclic systems based on them. Reactions with nucleophilic reagents can involve either one carbonyl group or simultaneously two groups. In addition, aromatic nucleophilic substitution of the F atoms can occur in these heterocycles.

In the present work, we studied the reactivities of cinnolones **1a,b** and quinolones **2a,b** with respect to aromatic dinucleophiles, *viz.*, to *o*-phenylenediamine, *o*-aminophenol, and *o*-aminobenzenethiol.

Scheme 1



1a,b; 2a,b

3; 4a,b; 5a,b; 6a,b

X = N, R = C_6H_4OMe-*p* (**1a**), Y = NH (**3**), O (**4a**);
R = Ph (**1b**), Y = O (**4b**);
X = CH, R = C_6H_4Me-*o* (**2a**), Y = NH (**5a**), O (**6a**);
R = *cyclo*-Pr (**2b**), Y = NH (**5b**), O (**6b**)

Results and Discussion

Refluxing of cinnolones **1a,b** and quinolones **2a,b** in alcohols with a twofold excess of *o*-phenylenediamine or

Table 1. Principal characteristics of compounds **3, 4a,b, 5a,b, 6a,b,** and **7—10**

Compound	M.p. /°C	Yield (%)	Found/Calculated (%) C	H	F	N	Molecular formula
3	>300	80	59.10 58.98	2.57 2.58	16.06 16.23	12.11 11.96	$C_{23}H_{13}F_4N_4O_3$
4a	210	82	58.83 58.87	2.44 2.36	16.14 16.19	8.86 8.95	$C_{23}H_{11}F_4N_3O_4$
4b	224	70	60.13 60.15	1.94 2.07	16.95 17.30	9.73 9.57	$C_{22}H_9F_4N_3O_3$
5a	255	64	63.74 63.86	2.86 2.90	16.87 16.84	9.27 9.31	$C_{24}H_{13}F_4N_3O_2$
5b	>300	73	59.85 59.86	2.78 2.76	18.62 18.94	10.32 10.47	$C_{20}H_{11}F_4N_3O_2$
6a	240	82	63.75 63.72	2.69 2.69	16.75 16.80	6.21 6.19	$C_{24}H_{12}F_4N_2O_3$
6b	195	83	59.47 59.71	2.60 2.51	18.44 18.98	6.87 6.96	$C_{20}H_{10}F_4N_2O_3$
7	194	97	58.25 58.48	3.58 3.64	9.31 8.95	8.79 8.80	$C_{31}H_{23}F_3N_4O_4S_2$
8*	125—127	82	61.75 62.02	3.80 3.90	9.05 9.20	6.76 6.78	$C_{32}H_{24}F_3N_3O_3S_2$
9	>300	98	58.76 58.98	2.68 2.90	10.02 9.65	9.37 9.49	$C_{29}H_{17}F_3N_4O_3S_2$
10	164—166	89	58.72 58.37	3.58 3.53	14.66 14.77	10.83 10.89	$C_{25}H_{18}N_4O_4F_4$

* The compound was present as two isomeric forms.

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Table 2. Data from IR and ^{1}H and ^{19}F NMR spectroscopy of compounds **3, 4a,b, 5a,b, 6a,b,** and **7—10**

Compound	IR, ν/cm^{-1}	NMR spectrum, (DMSO-d$_6$, δ, *J*/Hz)	
		^{1}H	^{19}F
3	2700, 1605 (NH); 1670 (C=O amide); 1630 (C=O); 1500, 1480 (C=C, C=N)	3.84 (s, 3 H, OCH$_3$); 7.88—7.03 (m, 8 H, 2 C$_6$H$_4$); 12.76 (br.s, 1 H, NH)	19.08 (m, 2 F); 15.58 (m, 1 F); 1.70 (m, 1 F)
4a	1740 (C=O lactone); 1635 (C=O); 1595, 1550, 1500, 1480 (C=N, C=C)	3.84 (s, 3 H, OCH$_3$); 7.82—7.05 (m, 8 H, 2 C$_6$H$_4$)	19.33 (m, 2 F); 16.05 (m, 1 F); 2.55 (m, 1 F)
4b	1740 (C=O lactone); 1650, 1640 (C=O, C=N)	7.40—7.93 (m, 9 H, C$_6$H$_4$, C$_6$H$_5$)	2.72 (m, 1 F); 16.26 (m, 1 F); 19.20 (m, 1 F); 20.16 (m, 1 F)
5a	3320, 2780, 2720 (NH); 3040 (CH); 1670 (C=O amide); 1635 (C=O); 1610 (C=N)	2.29 (s, 1 H, CH$_3$); 7.20—7.83 (m, 8 H, 2 C$_6$H$_4$,); 8.09 (s, 1 H, CH); 12.43 (s, NH)	−0.41 (m, 1 F); 11.73—12.96 (m, 2 F); 18.48—19.03 (m, 1 F)
5b	3290, 3060, 2760, 2700 (NH); 3045 (CH); 1675 (C=O amide); 1640 (C=O); 1595 (C=N)	1.12—1.19 (m, 4 H, 2 CH$_2$); 3.83—4.16 (m, 1 H, CH); 7.11—7.83 (m, 4 H, C$_6$H$_4$); 8.26 (s, 1 H, CH); 12.41 (br.s, 1 H, NH)	−0.66 (m, 1 F); 11.33 (m, 1 F); 16.47 (m, 1 F); 18.38 (m, 1 F)
6a	3055 (CH); 1765 (C=O lactone); 1645 (C=O); 1610 (C=N); 1590, 1580, 1520, 1510, 1500, 1490 (C=C)	2,19 (s, 3 H,CH$_3$); 7.40—7.84 (m, 8 H, 4 C$_6$H$_4$); 8.08 (s, 1 H, CH)	−0.41 (m, 1 F); 11.73—12.96 (m, 2 F); 18.48—19.03 (m, 1 F)
6b	3040 (CH); 1765 (C=O lactone); 1640 (C=O); 1600 (C=C)	1.13—1.30 (m, 4 H, 2 CH$_2$); 3.74—4.20 (m, 1 H, CH); 7.41—7.89 (m, 4 H, C$_6$H$_4$); 8.30 (s, 1 H, CH)	0.18 (m, 1 F); 12.01 (m, 1 F); 17.07 (m, 1 F); 18.57 (m, 1 F)
7	3450, 3350 (NH); 1730 (COOEt); 1620 (C=O); 1570, 1500, 1480 (C=N, C=C)	1.12 (t, 3 H, $\mathrm{OCH_2\underline{CH}_3}$, *J* = 7.0); 3.83 (s, 3 H, OCH$_3$); 5.38 (br.s, 2 H, NH$_2$); 4.14 (q, 2 H, $\mathrm{O\underline{CH}_2CH_3}$, *J* = 7.0); 6.43—7.53 (m, 13 H, 3 C$_6$H$_4$, SH)	16.33 (dd, 1 F, F(5)); 25.67 (d, 1 F, F(6)); 53.78 (d, 1 F, F(8)); $J_{5,8} = J_{8,5}$ = 17.2; $J_{5,6} = J_{6,5}$ = 21.5; $J_{6,8} = J_{8,6}$ = 0
8*	3450, 3340 (NH); 3050 (CH); 1740 (C(=O)OEt); 1630 (C=O); 1610, 1580 (C=N, C=C)	1.11, 1.13 (both t, 3 H, $\mathrm{OCH_2\underline{CH}_3}$, *J* = 7.1); 1.88, 1.96 (both s, 3 H, CH$_3$); 4.10, 4.12 (both q, 2 H, $\mathrm{O\underline{CH}_2CH_3}$, *J* = 7.1); 5.28 (br.s, 2 H, NH$_2$); 6.40—7.41 (m, 12 H, 3 C$_6$H$_4$,); 7.34 (br.s, 1 H, SH); 7.72, 7.74 (both s, 1 H, CH)	16.73, 17.02 (both dd, 1 F, F(5)); 24.63, 24.66 (both d, 1 F, F(6)); 46.18, 46.47 (both d, 1 F, F(8)); $J_{5,8} = J_{8,5}$ = 17.1; $J_{5,6} = J_{6,5}$ = 22.0; $J_{6,8} = J_{8,6}$ = 0
9	3450 (NH); 1640 (C(=O)S); 1610 (C=O); 1500, 1490, 1470 (C=N, C=C)	3.84 (s, 3 H, CH$_3$); 5.37 (m, 2 H, NH$_2$); 6.50—8.17 (m, 5 H, C$_6$H$_5$)	17.97 (dd, 1 F, F(5)); 28.36 (d, 1 F, F(6)); 54.58 (d, 1 F, F(8)); $J_{5,8} = J_{8,5}$ =17.2; $J_{5,6} = J_{6,5}$ = 20.1; $J_{6,8} = J_{8,6}$ = 0
10	3240, 1600 (NH); 1680 (CO$_2$Et); 1640, 1630, 1620 (C=O, C=N); 1520—1490 (C=C arom.)	1.23 (t, 3 H, $\mathrm{OCH_2\underline{CH}_3}$, *J* = 7.1); 3.89 (s, 3 H, OCH$_3$); 4.32 (q, 2 H, $\mathrm{O\underline{CH}_2CH_3}$, *J* = 7.1); 7.04—7.69 (m, 9 H, C$_6$H$_4$, C$_6$H$_5$); 12.32 (br.s, 1 H, NH)	20.24 (m, 2 F); 15.11 (m, 1 F); 0.76 (m, 1 F)

* The compound was present as two isomeric forms.

o-aminophenol afforded the corresponding heterocyclic ensembles, *viz*., quinoxalonylcinnolone (**3**), cinnolonylbenzooxazinones (**4a,b**), quinolonylquinoxalones (**5a,b**), and quinolonylbenzooxazinones (**6a,b**) (Scheme 1, Tables 1 and 2).

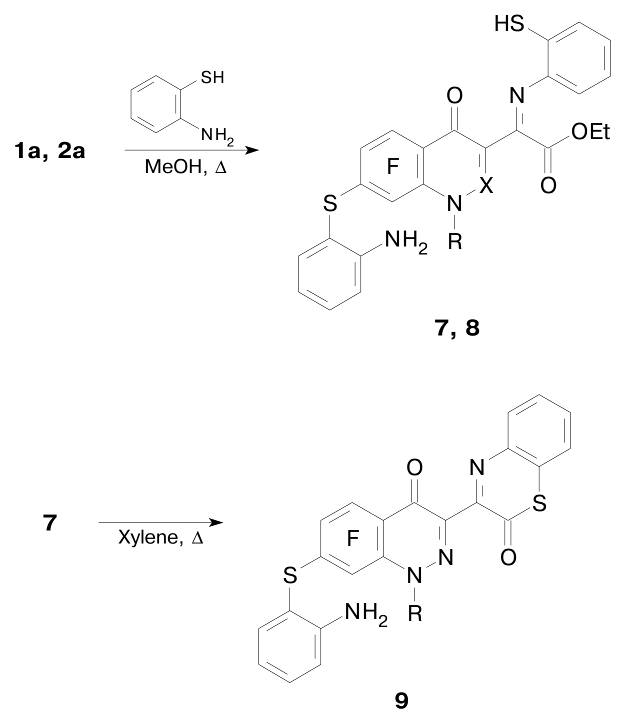
It is of note that the reactions of cinnolones **1** with aromatic dinucleophiles proceed more readily than those of quinolones **2**. Apparently, this is due to the fact that the former are more electron-deficient compounds. Thus, the reactions with quinolones **2** require a substantial increase in the reaction time or the use of higher-boiling *n*-butanol instead of methanol. The course of the reactions was monitored by TLC.

It should be noted that quinoxalonylcinnolones of the type **3** can be prepared from 3-[(1-arylhydrazo-2-oxo-2-(pentafluorophenyl)ethyl]-1,2-dihydroquinoxalin-2-ones by thermal intramolecular cyclization.[2]

Unlike *o*-phenylenediamine and *o*-aminophenol, *o*-aminobenzenethiol reacted with heterocycles **1a** and **2a** to form products **7** and **8**, respectively (Scheme 2, see Tables 1 and 2), due to the replacement of the carbonyl group in the ethoxalyl fragment by the amino group of *o*-aminobenzenethiol and the nucleophilic replacement of the F(7) atom in the aromatic ring by the 2-aminophenylthio group. The direction of the replacement was established taking into account the published data[3] and based on the spin-spin coupling constants for the F atoms (see Table 2). Apparently, the nucleophilic substitution in the fluoroaromatic ring occurs due to the high nucleophilicity of the S atom of this reagent.

Upon refluxing in xylene for 10 h, compound **7** underwent intramolecular cyclization to form substituted cinnolonylbenzothiazinone (**9**) (see Scheme 2, Tables 1 and 2). Under analogous conditions, quinolone **8** gave a mixture of products, which was difficult to separate, instead of the expected quinolonylthiazinone. It should be noted that attempts to perform cyclization of compounds **7** and **8** in boiling *n*-butanol failed.

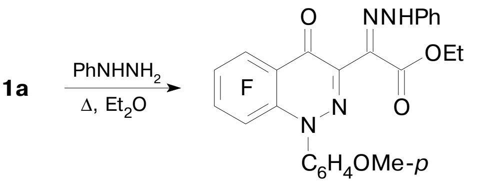
Scheme 2



X = N, R = C_6H_4OMe-*p* (**7**, **9**)
X = CH, R = C_6H_4Me-*o* (**8**)

The reactions with phenylhydrazine provided additional evidence for the higher reactivities of cinnolones **1** compared to quinolones **2**. It appeared that the reaction of cinnolone **1a** with phenylhydrazine afforded readily phenylhydrazone (**10**) upon refluxing in diethyl ether (Scheme 3, see Tables 1 and 2). Under these conditions, quinolone **2b** did not enter into the reaction, while in boiling alcohols it gave a mixture of nonidentified products.

Scheme 3



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Thus, 1-aryl(alkyl)-3-ethoxalyl-5,6,7,8-tetrafluoro-1,4-dihydrocinnolones(quinolones) are convenient substrates in the synthesis of a wide range of novel heterocyclic compounds.

Experimental

The IR spectra were recorded on a Specord IR-75 spectrometer in the range of 400—4000 cm^{-1} in Nujol mulls. The ^{1}H NMR spectra were measured on Tesla BS-587 A (80 MHz) and Bruker DRX-400 (400 MHz) spectrometers relative to Me_4Si. The ^{19}F NMR spectra were recorded on a Tesla BS-587 A spectrometer (75 MHz) relative to C_6F_6. Elemental analyses were carried out on a Carlo Erba CHNS-O EA 1108 instrument.

The starting compounds **1a,b** and **2a,b** were prepared according to known procedures.[1,2]

5,6,7,8-Tetrafluoro-1-(4-methoxyphenyl)-3-(2-oxo-1,2-dihydroquinoxalin-3-yl)-1,4-dihydrocinnolin-4-one (3). A solution of *o*-phenylenediamine (0.216 g, 2 mmol) in MeOH (5 mL) was added to a solution of cinnolone **1a** (0.424 g, 1 mmol) in MeOH (5 mL). The reaction mixture was refluxed for 1 min. The precipitate that formed was filtered off and washed with MeOH. Compound **3** was obtained in a yield of 0.375 g (see Tables 1 and 2).

3-(5,6,7,8-Tetrafluoro-1-(4-methoxyphenyl)-4-oxo-1,4-dihydrocinnolin-3-yl)-1,2-dihydrobenzooxazin-2-one (4a). A solution of *o*-aminophenol (0.218 g, 2 mmol) in MeOH (7 mL) was added to a solution of cinnolone **1a** (0.422 g, 1 mmol) in MeOH (7 mL). The reaction mixture was refluxed for 3 h and then cooled to ~20 °C. The precipitate that formed was filtered off and recrystallized from MeOH. Compound **4a** was obtained in a yield of 0.238 g (see Tables 1 and 2).

3-(5,6,7,8-Tetrafluoro-4-oxo-1-phenyl-1,4-dihydrocinnolin-3-yl)-1,2-dihydrobenzooxazin-2-one (4b). Analogously, compound **4b** was obtained from cinnolone **1b** (0.4 g, 1.2 mmol) and *o*-aminophenol (0.222 g, 2.4 mmol) in a yield of 0.312 g (see Tables 1 and 2).

3-[5,6,7,8-Tetrafluoro-4-oxo-1-(2-tolyl)-1,4-dihydroquinolin-3-yl]-1,2-dihydroquionoxalin-2-one (5a). Analogously, compound **5a** was obtained from quinolone **2a** (0.407 g, 1 mmol) and *o*-phenylenediamine (0.218 g, 2 mmol) in a yield of 0.372 g (the reaction time was 2 h; see Tables 1 and 2).

3-(1-Cyclopropyl-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinolin-3-yl)-1,2-dihydroquionoxalin-2-one (5b). Analogously, compound **5b** was obtained from quinolone **2b** (0.365 g, 1 mmol) and *o*-phenylenediamine (0.216 g, 2 mmol) in a yield of 0.293 g (the reaction time was 3h; see Tables 1 and 2).

3-[5,6,7,8-Tetrafluoro-4-oxa-1-(2-tolyl)-1,4-dihydroquinolin-3-yl]-1,2-dihydrobenzooxazin-2-one (6a). A solution of *o*-aminophenol (0.216 g, 2 mmol) in Bu^{n}OH (20 mL) was added to a solution of quinolone **2a** (0.407 g, 1 mmol) in Bu^{n}OH (20 mL). The reaction mixture was refluxed for 1 h and poured into water. The precipitate that formed was filtered off and recrystallized from Bu^{n}OH. Compound **6a** was obtained in a yield of 0.289 g (see Tables 1 and 2).

3-(1-Cyclopropyl-5,6,7,8-tetrafluoro-4-oxa-1,4-dihydroquinolin-3-yl)-1,2-dihydrobenzooxazin-2-one (6b). Analogously, compound **6b** was obtained from quinolone **2b** (0.356 g, 1 mmol) and *o*-aminophenol (0.220 g, 2 mmol) upon refluxing in MeOH for 10 h in a yield of 0.332 g (see Tables 1 and 2).

Ethyl 2-[7-(2-aminophenylthio)-5,6,8-trifluoro-1-(4-methoxyphenyl)-4-oxo-1,4-dihydrocinnolin-3-yl]-(2-mercaptophenylimino)glyoxylate (7). A solution of cinnolone **1a** (0.270 g, 0.64 mmol) and *o*-aminobenzenethiol (0.137 mL, 1.28 mmol) in MeOH (7 mL) was refluxed for 4 h and then cooled to ~20 °C. After recrystallization from MeOH, compound **7** was obtained in a yield of 0.302 g (see Tables 1 and 2).

Ethyl 2-[7-(2-aminophenylthio)-5,6,8-trifluoro-4-oxo-1-(2-tolyl)-1,4-dihydroquionolin-3-yl]-2-(2-mercaptophenylimino)acetate (8). *o*-Aminobenzenethiol (0.674 mL, 6.3 mmol) was added to a solution of quinolone **2a** (0.845 g, 2.1 mmol) in MeOH (20 mL). The reaction mixture was refluxed for 10 h and poured into water (100 mL). The precipitate that formed was filtered off and recrystallized from Bu^{n}OH. Compound **8** was obtained in a yield of 0.332 g (see Tables 1 and 2).

3-[7-(2-Aminophenylthio)-5,6,8-trifluoro-1-(4-methoxyphenyl)-4-oxo-1,4-dihydrocinnolin-4-on-3-yl]-1,2-dihydrobenzothiazin-2-one (9). A solution of ester **7** (0.250 g, 0.4 mol) was refluxed in *m*-xylene (10 mL) for 10 h. Then the reaction mixture was poured into hexane (100 mL). The precipitate that formed was filtered off and washed with hexane. Compound **9** was obtained in a yield of 0.236 g (see Tables 1 and 2).

Ethyl 2-[5,6,7,8-tetrafluoro-1-(4-methoxyphenyl)-4-oxo-1,4-dihydrocinnolin-3-yl]-2-phenylhydrazonoacetate (10). Phenylhydrazine (0.098 mL, 1 mmol) was added to a solution of cinnolone **1a** (0.423 g, 1 mmol) in Et$_2$O (20 mL). The reaction mixture was refluxed for 10 h and the solvent was evaporated. After recrystallization from MeOH, hydrazone **10** was obtained in a yield of 0.560 g (see Tables 1 and 2).

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