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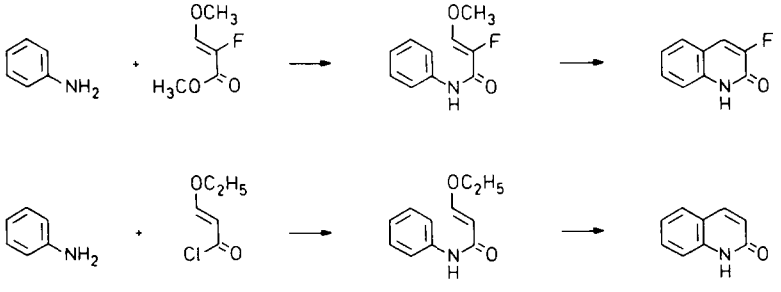
3-Fluoro-2-quinolones from Anilines

Ursula Mävers, France Berruex and Manfred Schlosser *

Institut de Chimie organique de l'Université
Bâtiment de Chimie (BCh), CH-1015 Lausanne-Dorigny, Switzerland

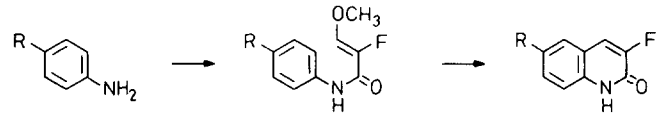
Abstract : *N*-(Fluoro-3-methoxyacryloyl)anilines [2-fluoro-3-methoxyprop-2-enanilides] can be prepared by condensation between lithium anilides and methyl 2-fluoro-3-methoxyprop-2-enoate. Under strongly acidic conditions, these intermediate undergo a cyclization reaction accompanied by elimination of methanol to afford 3-fluoro-2-quinolones. Substituents occupying the *para* or *ortho* position of the aniline appear at the heterocyclic 6- and 8-positions, respectively. In general, substituents attached to the *meta* position of the aniline lead to 1 : 1 mixtures of regioisomers. Only *m*-anisidine [3-methoxy-aniline] and *m*-fluoroaniline make an exception : they produce mainly the 7- and only trace amounts of the 5-substituted quinolone.

A while ago, we have published an efficacious method for the preparation of 3-fluoro-2-quinolone : methyl 2-fluoro-3-methoxyacrylate, readily accessible by chlorofluorocarbene addition to 1,2-dimethoxy-1-(trimethylsilyloxy)ethylene and subsequent hydrolytic ring-opening, was condensed with aniline and the resulting amide submitted to acid catalyzed cyclization during 2 h at 60 °C [1]. Only later we became aware of a very close analogy in the literature. Effenberger *et al.* [2] have been able to extend the scope of the Knorr "carbostyril" synthesis [3 - 5] when replacing the usual β-oxocarboxylic acid component by 3-ethoxyacryloyl chloride. In this way, for example, the two-step conversion of aniline into 2-quinolone was accomplished.



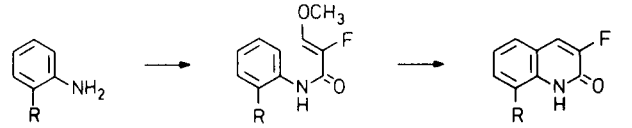
In the meantime, we had already embarked on a systematic study of substituted anilines as starting materials in order to test the generality of the method. As it turned out, a wide variety of *ortho* and *para* substituents is tolerated. On the other hand, *meta* substituted precursors tend to produce regioisomeric mixtures of the heterocyclic products.

The reactions with *p*-trifluoromethylaniline, *p*-anisidine and *p*-fluoroaniline took a normal course. The anilides **1**, **3** and **5** were formed with good yields and the cyclization occurred smoothly to produce the expected quinolones **2**, **4** and **6** almost quantitatively.



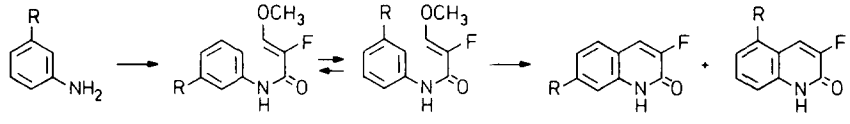
R = F_3C	**1**	**2**
R = F	**3**	**4**
R = H_3CO	**5**	**6**

Again no complications were encountered with *o*-toluidine, *o*-aminobiphenyl and *o*-fluoroaniline. The anilides **7**, **9** and **11** formed and cyclized readily affording the quinolones **8**, **10** and **12**.



R = H_3C	**7**	**8**
R = H_5C_6	**9**	**10**
R = F	**11**	**12**

The cyclization of *meta* substituted anilides should inevitably lead to mixtures of regioisomers. This was found to be correct indeed when the anilides **13**, **15**, **17**, **19**, **21** and **23** derived from *m*-toluidine, *m*-trifluoroaniline, *m*-nitroaniline, *m*-chloroaniline, *m*-fluoroaniline and *m*-anisidine were treated with acid and thus converted into the quinolones **14**, **16**, **18**, **20**, **22** and **24**. However, the ratios of 7- *vs.* 5-substituted products (labelled **a** *vs.* **b**) varied considerably with the nature of the group R. Fluorine and methoxy emerge almost exclusively in the remote 7-position whereas in the four other cases roughly equal amounts of both isomers are obtained.



R = H_3C	**13**	**14a**	55 : 45	**14b**
R = F_3C	**15**	**16a**	60 : 40	**16b**
R = O_2N	**17**	**18a**	45 : 55	**18b**
R = Cl	**19**	**20a**	55 : 45	**20b**
R = F	**21**	**22a**	95 : 5	**22b**
R = H_3CO	**23**	**24a**	95 : 5	**24b**

The high preference of the methoxy substituent for the 7-position had already previously be observed in the context of other acid promoted cyclization reactions, in particular in the conversion of 3-ethoxy-3'-methoxyprop-2-enanilide to 7-methoxyquinol-2(1*H*)-one [2] and the Skraup synthesis of 7-methoxyquinoline from *m*-anisidine and glycerol [6]. As we realize now, fluorine exhibits a similar selectivity pattern as alkoxy groups do.

Although a rational explanation for this strange behavior cannot yet be given, attention is drawn to a similarity that exists between both types of substituents : they withdraw σ-electrons inductively and simultaneously donate π-electrons mesomerically.

The anilide intermediates are graphically represented as (*Z*) isomers merely for convenience. In reality they are invariably composed of both geometrical isomers. The configuration of the side chain could be retained during the ring closure if protonation occurred at the amide oxygen rather than at the fluorine bearing carbon atom. Therefore, one may suspect the regioselectivity in favor of the 7-position to be a consequence of steric hindrance from which essentially the (*E*) anilide would suffer. An obvious objection is that neither a methoxy group nor a fluorine atom are particularly bulky substituents. Nevertheless we have chromatographically separated two pairs of isomers (*Z*-**13**/*E*-**13** and *Z*-**23**/*E*-**23**) and have submitted all components individually to the cyclization procedure. The **a**/**b** ratios of the resulting quinolones **14** and **24** proved to be independent of the configuration of the precursor.

EXPERIMENTAL

1. Generalities

For standard laboratory practice, techniques and abbreviations, see related articles, *e.g.*, ref. [7, 8]. - ^{1}H- and ^{19}F-nmr spectra were recorded of deuteriochloroform solutions and at 250 and 188 MHz, respectively. - All anilides described, except the *p*-trifluoromethyl substituted one (**1**), melt without decomposition whereas all quinolones described except the 7-methoxylated one (**28a**) decompose upon melting. - The cyclization of anilides derived from *meta* substituted anilines invariably produced 5- and 7-substituted quinolones concomitantly. In general, these mixtures were directly submitted to analysis and spectra assignment. The regioisomers can, however, be separated by column chromatography on silica gel (using ethyl acetate diluted with hexane as the eluent) as demonstrated with the trifluoromethyl bearing quinolones **20a** and **20b**.

2. *N*-(2-Fluoro-3-methoxyacryloyl)anilines

Butyllithium (100 mmol) in hexane (65 mL) and methyl 2-fluoro-3-methoxyprop-2-enoate (**1a**; *Z*/*E* ~ 1 : 1; 6.7 g, 50 mmol) were consecutively added to the aniline (100 mmol) in tetrahydrofuran (135 mL) at 0 °C. After 1 h of vigorous stirring at 25 °C, the mixture was poured into 2 M hydrochloric acid (0.10 L) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate (50 mL) and brine (50 mL) and concentrated. The remaining solid was initially slightly ocherous (sometimes even red), but became white upon trituration with diethyl ether. In all cases it was possible to separate the (*Z*) and the (*E*) isomer by chromatography on silica gel using a mixture of ethyl acetate and hexane in the approximate ratio of 1 : 2 (v/v) as the eluent.

2-Fluoro-3-methoxyprop-2-enanilide : 8.2 g (91%). - Analysis : calc. for $C_{10}H_{10}FNO$ (195.19) C 61.54, H 5.16; found C 61.82, H 5.33%. - (*Z*) Isomer : mp 114 - 115 °C. - ^{1}H-NMR : δ 7.71 (1 H, s, broad), 7.59 (1 H, dq, *J* 8.5, 0.8), 7.34 (1 H, tt, *J* 8.0, 1.9), 7.14 (1 H, tt, *J* 7.5, 1.0), 6.96 (1 H, d, *J* 21.3), 3.90 (3 H, s). - ^{19}F-NMR : δ -96.5 (dd, *J* -21, 2). - MS : 196 (M^+ + 1, 100%), 103 (71%). - (*E*) Isomer : mp 31 - 32 °C. - ^{1}H-NMR : δ 8.47 (1 H, s, broad), 7.58 (1 H, dq, *J* 7.8, 1.2), 7.34 (1 H, ddt, *J* 8.6, 7.8, 1.7), 7.13 (1 H, ddt, *J* 7.5, 6.9, 1.2), 6.96 (1 H, d, *J* 8.8), 3.93 (3 H, s). - ^{19}F-NMR : δ -108.2 (d, *J* 8). - MS : 196 (M^+ + 1, 95%), 103 (100%).

2-Fluoro-3-methoxy-4'-(trifluoromethyl)prop-2-enanilide (1) : 9.1 g (69%). - (*Z*) Isomer : mp 198 - 200 °C. - ^{1}H-NMR : δ 10.27 (1 H, s, broad, 7.9 (2 H, m), 7.7 (2 H, m), 7.21 (1 H, d, *J* 21.2), 3.88 (3 H, s). - ^{19}F-NMR: δ 0.8 (3 F, s), -96.3 (1 F, d, *J* 21). - MS : 264 (M^+ + 1, 53%), 263 (M^+, 74%), 103 (100%). - Analysis : calc. for $C_{11}H_9F_4NO_2$ (263.19) C 50.20, H 3.45; found C 49.90, H 3.18%. - (*E*) Isomer : mp 108 - 109 °C. -

^{1}H-NMR : δ 9.83 (1 H, board, 7.9 (2 H, m), 7.7 (2 H, m), 7.43 (1 H, d, *J* 10.9), 3.85 (3 H, s). - ^{19}F-NMR : δ 0.8 (3 F, s), -111.8 (1 F, d, *J* 11). - MS : 264 (M^+ + 1, 4%), 263 (M^+, 35%), 103 (100%). - Analysis : calc. for $C_{11}H_9F_4NO_2$ (263.19) C 50.20, H 3.45; found C 49.90, H 3.18%.

2,4'-Difluoro-3-methoxyprop-2-enanilide (3) : 8.8 g (83%). - (*Z*) Isomer : mp 151 - 152 °C. - ^{1}H-NMR : δ 7.68 (1 H, s, broad), 7.5 (2 H, m), 7.05 (2 H, tm, *J* 8.7), 6.97 (1 H, d, *J* 21.4), 3.92 (3 H, s). - ^{19}F-NMR : δ -54.8 (1 F, tt, *J* 8, 5), -96.7 (1 F, dd, *J* 21, 4). - MS : 213 (M^+, 15%), 103 (100%). - Analysis : calc. for $C_{10}H_9F_2NO_2$ (213.18) C 56.34, H 4.26; found C 56.36, H 4.02%. - (*E*) Isomer : mp 57 - 58 °C (after sublimation). - ^{1}H-NMR : δ 8.43 (1 H, s, broad), 7.5 (2 H, m), 7.5 (2 H, m), 7.04 (2 H, tm, *J* 8.7), 6.98 (1 H, d, *J* 8.9), 3.95 (3 H, s). - ^{19}F-NMR : δ -55.2 (1 F, tt, *J* 9, 5), -108.1 (1 F, dd, *J* 9, 1). - MS : 213 (M^+, 36%), 103 (100%). - Analysis : calc. for $C_{10}H_9F_2NO_2$ (213.18) C 56.34, H 4.26; found C 56.36, H 4.02%.

2-Fluoro-3,4'-di(methoxy)prop-2-enanilide (5) : 8.6 g (76%). Analysis : calc. for $C_{11}H_{12}FNO_2$ (225.22) C 58.66, H 5.37; found C 58.74, H 5.16%. - (*Z*) Isomer : mp 142.5 - 143.5 °C. - ^{1}H-NMR : δ 7.62 (1 H, s, broad), 7.5 (2 H, m), 6.96 (1 H, d, *J* 20.7), 6.9 (2 H, m), 3.91 (3 H, s), 3.82 3 H, s). - ^{19}F-NMR : δ -96.4 (1 F, dd, *J* 21,4). - MS : 226 (M^+ + 1, 45%), 225 (M^+, 100%). - (*E*) Isomer : mp 37.5 - 38.5 °C. - ^{1}H-NMR : δ 8.3 (1 H, m), 7.5 (2 H, m), 6.96 (1 H, d, *J* 8.9), 6.9 (2 H, m), 3.94 (3 H, s), 3.81 (3 H, s). - ^{19}F-NMR : δ -107.9 (1 F, dd, *J* 9.1). - MS : 226 (M^+ + 1, 54%), 225 (M^+, 100%).

2-Fluor-3-methoxy-2'-methylprop-2-enanilide (7) : 6.8 g (65%). - Analysis : calc. for $C_{11}H_{12}FNO_2$ (209.22) C 63.15, H 5.78; found C 63.13, H 5.62%. - (*Z*) Isomer : mp 104 - 105 °C. - ^{1}H-NMR : δ 7.90 (1 H, d, *J* 8.1), 7.59 (1 H, s, broad), 7.24 (1 H, d, broad, *J* 7.5), 7.20 (1 H, d, *J* 6.5), 7.10 (1 H, td, *J* 7.5, 1.2), 6.97 (1 H, d, *J* 21,3), 3.91 (3 H, s), 2.29 (3 H, s). - ^{19}F-NMR : δ -96.7 (dd, *J* 22, 4. - MS : 210 (M^+ + 1, 100%), 178 (18%), 103 (49%). - (*E*) Isomer : mp 94 - 95 °C. - ^{1}N-NMR : δ 8.53 (s, broad), 8.17 (1 H, dd, *J* 8.2, 1.0), 7.23 (1 H, d, broad, *J* 7.7), 7.19 (1 H, d, broad, *J* 7.5), 7.06 (1 H, td, *J* 7.5, 1.2), 6.99 (1 H, d, *J* 8.2), 3.94 (3 H, s), 2.26 (3 H, s). - ^{19}F-NMR : δ -107.5 (d, *J* 8). - MS : 210 (M^+ + 1, 100%), 178 (13%), 103 (32%).

2-Fluor-3-methoxy-2'-phenylprop-2-enanilide (9) : 10.6 g, (78%). - Analysis : calc. for $C_{16}H_{14}FNO_2$ C 70.84, H 5.20; found C 70.71, H 5.31%. - (*Z*) Isomer : mp 128 - 129 °C. - ^{1}H-NMR : δ 8.38 (1 H, dd, *J* 8.2, 1.1), 7.9 (1 H, m), 7.5 (2 H, m), 7.4 (4 H, m), 7.30 (1 H, dd, *J* 7.6, 1.6), 7.22 (1 H, td, *J* 7.3, 1.3), 6.92 (1 H, d, *J* 20.9), 3.87 (3 H, s). - ^{19}F-NMR : δ -96.2 (1 F, dd, *J* 21, 4). - MS : 272 (M^+ + 2, 12%), 271 (M^+, 58%), 196 (10%), 168 (14%), 103 (100%). - (*E*) Isomer : mp 66 - 67 °C. - ^{1}H-NMR : δ 8.70 (1 H, s, broad), 8.58 (1 H, dm, *J* 8.3), 7.5 (2 H, m), 7.4 (4 H, m), 7.22 (1 H, dd, *J* 7.4, 1.8), 7.17 (1 H, td, *J* 7.4, 1.2), 6.75 (1 H, d, *J* 7.9), 3.36 (3 H, s). - ^{19}F-NMR : δ -108.2 (1 F, d, *J* 8).

2,2'-Difluor-3-methoxyprop-2-enanilide (11) : 9.3 g (87%). - (*Z*) Isomer : mp 80 - 81 °C. - ^{1}H-NMR : δ 8.33 (1 H, td, *J* 7.9, 1.6), 7.95 (1 H, s), 7.1 (3 H, m), 6.98 (1 H, d, *J* 20.5), 3.92 (3 H, s). - ^{19}F-NMR : δ -68 (1 F, m), -96.4 (1 F, dd, *J* 21, 4). - MS : 214 (M^+ + 1, 12%), 213 (M^+, 36%), 103 (100%). - Analysis : calc. for $C_{10}H_9F_2NO_2$ (213.18) C 56.34, H 4.26; found C 56.18, H 4.32%. - (*E*) Isomer : mp 65 - 66 °C. - ^{1}H-NMR : δ 8.94 (1 H, s), 8.47 (1 H, td, *J* 8.0, 1.6), 7.2 (1 H, m), 7.1 (2 H, m), 7.02 (1 H, d, *J* 8.2), 3.97 (3 H, s). - ^{19}F-NMR : δ -69 (1 F, m), -108.2 (1 F, d, *J* 8). - MS : 214 (M^+ + 1, 20%), 213 (M^+, 38%), 103 (100%). - Analysis : calc. for $C_{10}H_9F_2NO_2$ (213.18) C 56.34, H 4.26; found C 56.32, H 4.25%.

2-Fluoro-3-methoxy-3'-methylprop-2-enanilide (13) : 8.5 g (81%). - (*Z*) Isomer : mp 95 - 96 °C. - ^{1}H-NMR: δ 7.66 (1 H, s, 7.4 (2 H, m), 7.24 (1 H, t, *J* 7.7), 6.97 (1 H, dm, *J* 7.5), 6.96 (1 H, d, *J* 21.2 (3.91 (3 H, s), 2.36 (3 H, s). - ^{19}F-NMR : δ -96.1 (1 F, dd, *J* 21, 4). - MS : 210 (M^+ + 1, 18%), 209 (M^+, 63%), 103 (100%). - Analysis : calc. for $C_{11}H_{12}FNO_2$ (209.22) C 63.15, H 5.78; found C 62.74, H 5.76%. - (*E*) Isomer : mp 64 - 65 °C. - ^{1}H-NMR : δ 8.41, (1 H, s), 7.4 (2 H, m), 7.23 (1 H, t, *J* 7.6), 6.96 (1 H, d, *J* 8.7), 6.95 (1 H, dm, *J* 7.4), 3.94 (3 H, s), 2.36 (3 H, s). - ^{19}F-NMR : δ -107.5 (1 F, d, *J* 8). - MS : 210 (M^+ + 1, 25%), 209 (M^+, 65%), 103 (100%). - Analysis : calc. for $C_{11}H_{12}FNO_2$ (209.22) C 63.15, H 5.78; found C 63.00, H 5.68%.

2-Fluoro-3-methoxy-3'-(trifluoromethyl)prop-enanilide (15) : 9.3 g (71%). Analysis : calc. for $C_{11}H_9F_4NO_2$ (263.19) C 50.20, H 3.45; found C 50.14, H 3.15. - (*Z*) Isomer : mp 142 - 143 °C. - ^{1}H-NMR : δ 10.26 (1 H, s, broad), 8.16 (1 H, s), 7.99 (1 H, d, *J* 8.3), 7.57 (1 H, t, *J* 7.9), 7.44 (1 H, d, *J* 7.8), 7.18 (1 H, d, *J* 21.2), 3.88 (3 H, s). - ^{19}F-NMR : δ -0.2 (3 F, s, -96.1 (1 F, d *J* 21). - MS : 263 (M^+, 14%), 103 (100%). - (*E*) Isomer : mp 76 - 77 °C. - ^{1}H-NMR : δ 9.82 (1 H, s, broad), 8.15 (1 H, s). 7.94 1 H, d, *J* 8.2), 7.57 (1 H, t, *J* 7.9), 7.45 (1 H, d, *J* 10.7), 7.44 (1 H, d, *J* 7.5), 3.85 (3 H, s). - ^{19}F-NMR : δ -0.2 (3 F, s), -111.7 (1 F, d, *J* 11). - MS : 263 (M^+, 15%), 103 (100%).

2-Fluoro-3-methoxy-3'-nitroprop-2-enanilide (17) : 4.3 g, 36%). - (*Z*) Isomer : mp 179 - 180 °C. - ^{1}H-NMR : δ 8.51 (1 H, t, *J*. 2.1), 8.01 (1 H, ddd, *J* 8.2, 2.1, 1.0), 7.95 (1 H, ddd, *J* 8.1, 2.1, 1.0), 7.9 (1 H, m), 7.53 (1 H, t, *J* 8.2), 7.03 (1 H, d, *J* 21.4), 3.95 (3 H, s). - ^{19}F-NMR : δ -96.9 (1 F, dd, *J* 21, 4). - MS : 242 (M^+ + 2, 6%), 241 (M^+ +1, 9%), 240 (M^+, 12%), 103 (100%). - Analysis : calc. for $C_{10}H_9FN_2O_4$ (240.19) C 50.01, H 3.78; found C 50.09, H 3.60%. - (*E*) Isomer : mp 145 - 146 °C. - ^{1}H-NMR : δ 8.69 (1 H, s), 8.36 (1 H, t, *J* 2.2), 8.08 (1 H, ddd, *J* 8.2, 2.2, 0.9), 7.99 (1 H, ddd, *J* 8.2, 2.1, 1.0), 7.52 (1 H, t, *J* 8.1), 7.06 (1 H,

d, *J* 8.4), 4.01 (3 H, s). - ^{19}F-NMR : δ -108.3 (1 F, d, *J* 9). - MS : 241 (M^+ + 1, 6%), 240 (M^+, 2%), 103 (100%). - Analysis : calc. for $C_{10}H_9FN_2O_4$ (240.19) C 50.01, H 3.78; found C 49.58, H 3.68%.

3'-Chloro-2-fluoro-3-methoxyprop-2-enanilide (19) : 8.7 g (76%). - (*Z*) Isomer : mp 116 - 117 °C. - ^{1}H-NMR : δ 7.72 (1 H, t, *J* 1.9), 7.70 (1 H, s), 7.42 (1 H, ddd, *J* 8.1, 2.1, 1.0), 7.27 (1 H, t, *J* 8.1), 7.12 (1 H, ddd, *J* 7.9, 2.0, 0.9), 6.97 (1 H, d, *J* 21.3), 3.92 (3 H, s). - ^{19}F-NMR : δ -96.6 (1 F, dd, *J* 21, 4). - MS : 231 (M^+ + 2, 14%), 230 (M^+ + 1, 11%), 229 (M^+, 37%), 103 (100%). - Analysis : calc. for $C_{10}H_9ClFNO_2$ (229.64) C 52.30, H 3.95; found C 52.48, H 3.81%. - (*E*) Isomer : mp 72.5 - 73.5 °C. - ^{1}H-NMR : δ 8.48 (1 H, s), 7.68 (1 H, t, *J* 2.1), 7.46 (1 H, ddd, *J* 8.2, 2.1, 1.0), 7.26 (1 H, t, *J* 8.2), 7.10 (1 H, ddd, *J* 8.2, 2.1, 1.0), 6.99 (1 H, d, *J* 8.6), 3.96 (3 H, s.) - ^{19}F-NMR : δ -107.9, (1 F, dd, *J* 8, 1). - MS : 230 (M^+ + 1, 5%), 229 (M^+, 14%), 103 (100%). - Analysis : calc. for $C_{10}H_9ClFNO_2$ (229.64) C 52.30, H 3.95; found C 52.34, H 3.99%.

2,3'-Difluoro-3-methoxyprop-2-enanilide (21) : 8.6 g (81%). - (*Z*) Isomer : mp 115 - 117 °C. - ^{1}H-NMR : δ 7.74 (1 H, s, broad), 7.56 (1 H, dt, *J* 10.9, 2.2), 7.2 (2 H, m), 6.99 (1 H, d, *J* 21.3), 6.85 (1 H, tdd, *J* 8.3, 2.5, 1.1), 3.93 (3 H, s). - ^{19}F-NMR : δ -48.5 (1 F, symm. m), -96.8 (1 F, dd, *J* 21, 4). - MS : 214 (M^+ + 1, 43%), 213 (M^+, 92%), 103 (100%). - Analysis : calc. for $C_{10}H_9F_2NO_2$ (213.18) C 56.34, H 4.26; found C 56.63, H 4.24%. - (*E*) Isomer : mp 68.5 - 69.5 °C. - ^{1}H-NMR : δ 8.51 (1 H, s, broad), 7.56 (1 H, dt, *J* 10.9, 2.2), 7.3 (2 H, m), 7.00 (1 H, d, *J* 8.9), 6.84 (1 H, tdd, *J* 8.3, 2.5, 1.2), 3.96 (3 H, s). - ^{19}F-NMR : δ -48.8 (1 F, symm. m), -108.1 (1 F, d, *J* 9). - MS : 214 (M^+ + 1, 89%), 213 (M^+, 47%), 103 (100%). - Analysis : calc. for $C_{10}H_9F_2NO_2$ (213.18) C 56.34, H 4.26; found C 56.63, H 4.24%.

2-Fluoro-3,3'-di(methoxy)prop-2-enanilide (23) : 9.1 g (81%). - Analysis : calc. for $C_{11}H_{12}FNO_3$ (225.22) C 58.66, H 5.37; found C 58.78, H 5.10%. - (*Z*) Isomer : mp 119.5 - 120.5 °C. ^{1}H-NMR : δ 7.68 (1 H, s, broad), 7.34 (1 H, t, *J* 2.3), 7.24 (1 H, t, *J* 8.1), 7.04 (1 H, ddd, *J* 8.1, 1.8, 0.7), 6.97 (1 H, d, *J* 21.3), 6.70 (1 H, ddd, *J* 8.1, 2.4, 0.7), 3.91 (3 H, s), 3.82 (3 H, s). - ^{19}F-NMR : δ -96.4 (1 F, dd, *J* 21, 4). - MS : 226 (M^+ + 1, 100%), 225 (M^+, 78%), 103 (77%). - (*E*) Isomer : mp 69 - 70 °C. - ^{1}H-NMR : δ 8.43 (1 H, s, broad), 7.42 (1 H, t, *J* 2.2), 7.23 (1 H, t, *J* 8.2), 6.99 (1 H, dm, *J* 7.5), 6.96 (1 H, d, *J* 8.9), 6.67 (1 H, dd, *J* 8.5, 2.2), 3.95 (3 H, s), 3.82 (3 H, s). - ^{19}F-NMR : δ -108.8 (1 F, dd, *J* 9, 1). - MS : 226 (M^+ + 1, 80%), 225 (M^+, 100%), 103 (78%).

3. 3-Fluoro-2-quinolones

A suspension of a *N*-(2-fluoro-3-methoxyacryloyl)-aniline (25 mmol) in 69% aqueous sulfuric acid (25 mL) was heated under stirring 5 h to 50 °C. The mixture was poured on crushed ice and the product collected by filtration. After washing with water (0.25 L) and drying, it was purified by crystallization or sublimation.

3-Fluoroquinol-2(1*H*)-one [1] : mp 239 - 241 °C.

3-Fluoro-6-(trifluoromethyl)quinol-2(1*H*)-one (2) : 4.7 g (81%); mp 202 - 204 °C (after sublimation). - ^{1}H-NMR : δ 12.7 (1 H, m), 8.14 (1 H, s), 8.01 (1 H, d, *J* 10.3), 7.83 (1 H, dm, *J* 8.9), 7.50 (1 H, d, *J* 8.8). - ^{19}F-NMR : δ 1.0 (3 F, s), -68.4 (1 F, dd, *J* 11, 5). - MS : 232 (M^+ +1, 25%), 231 (M^+, 100%). - Analysis : calc. for $C_{10}H_5F_4NO$ (231.15) C 51.96, H 2.18; found C 51.95, H 2.11%.

3,6-Difluoroquinol-2(1*H*)-one (4) : 4.0 g (89%); mp 251 - 253 °C (after sublimation). - ^{1}H-NMR : δ 12.4 (1 H, m), 7.86 (1 H, d, *J* 10.8), 7.53 (1 H, dd, *J* 9.2, 2.4), 7.4 (2 H, m). - ^{19}F-NMR : δ -59.4 (1 F, dt, *J* 5, 9), -69.0 (1 F, d, *J* 11). - MS : 181 (M^+, 14%), 153 (100%). - Analysis : calc. for $C_9H_5F_2NO$ (181.14) C 59.68, H 2.78; found C 59.91, H 3.09%.

3-Fluoro-6-methoxyquinol-2(1*H*)-one (6) : 4.0 g (83%); mp 246 - 248 °C (after sublimation). - ^{1}H-NMR : δ 12.13, s, broad), 7.82 (1 H, d, *J* 11.2), 7.28 (1 H, d, *J* 9.0), 7.21 (1 H, d, *J* 2.8), 7.14 (1 H, dd, *J* 9.0, 2.8), 3.78 (3 H, s). - ^{19}F-NMR : δ -70.4 (1 F, dd, *J* 11, 5). - MS : 194 (M^+ +1, 23%), 193 (M^+, 100%). - Analysis : calc. for $C_{10}H_8FNO_2$ (193.18) C 62.18, H 4.17; found C 62.34, H 4.23%.

3-Fluoro-8-methylquinol-2(1*H*)-one (8) : 7.8 g (88%); mp 208 - 209 °C. - ^{1}H-NMR (D_3CCOCD_3) : 7.72 (1 H, d, *J* 10.7), 7.53 (1 H, d, broad, *J* 7.8), 7.40 (1 H, d, broad, *J* 7.4), 7.18 (1 H, t, *J* 7.6), 2.58 (3 H, s). - ^{19}F-NMR : δ -69.4 (dd, *J* 10, 4). - MS : 178 (M^+ + 1, 100%), 148 (10%). - Analysis : calc. for $C_{10}H_8FNO$ (177.18) C 67.79, H 4.55; found C 67.92, H 4.56%.

3-Fluoro-8-phenylquinol-2(1*H*)-one (10) : 5.5 g (92%); mp 161 - 162 °C (without further purification). - ^{1}H-NMR : 10.59 (1 H, s), 7.98 (1 H, d, *J* 10.6), 7.70 (1 H, dm, *J* 7.5), 7.5 (5 H, m), 7.39 (1 H, dm, *J* 7.2), 7.33 (1 H, t, *J* 7.5). - ^{19}F-NMR : δ -70.8 (1 F, d, *J* 11). - Analysis : calc. for $C_{15}H_{10}FNO$ (239.25) C 75.30, H 4.21; found C 75.03, H 4.07%.

3,8-Difluoroquinol-2(1*H*)-one (12) : 3.8 g (84%; mp 230.5 - 232.5 °C (after sublimation. - ^{1}H-NMR : δ 12.39 (1 H, s), 7.92 (1 H, dd, *J* 10.5, 1.3), 7.48 (1 H, d, *J* 7.9), 7.39 (1 H, dd, *J* 10.9, 8.1), 7.21 (1 H, td, *J* 7.9, 5.0). - ^{19}F-NMR : δ -68.5 (1 F, d, *J* 10), -69 (1 F, m). - MS : 182 (M^+ + 1, 27%), 181 (M^+, 100%). - Analysis : calc. for $C_9H_5F_2NO$ (181.14) C 59.68, H 2.78; found C 59.65, H 2.83%.

3-Fluoro-7-methyl- and 3-Fluoro-5-methylquinol-2(1*H*)-one (14a and **14b** in the ratio of 55 : 45) : 3.7 g (83%), melting around 175 °C.- ^{1}H-NMR : δ 12.3 (0.45 H, m), 12.2 (0.55 H, m), 7.93 (0.45 H, d, *J* 11.9), 7.82 (0.55 H, d, *J* 11.1), 7.54 (0.55 H, d, *J* 7.9), 7.37 (0.45 H, t, *J* 7.7), 7.19 (0.45 H, d, *J* 8.2), 7.13 (0.55 H, s), 7.1 (1 H, s), 2.47 (0.45 × 3 H, s), 2.37 (0.55 × 3 H, s). - ^{19}F-NMR : δ -70.2 (0.45 F, dd, *J* 12, 5), -72.3 (0.55 F, dd, *J* 11, 5). - Analysis : calc. for $C_{10}H_8FNO$ (177.18) C 67.79, H 4.55; found C 67.83, H 4.49%.

3-Fluoro-7-(trifluoromethyl)quinol-2(1*H*)-one (16a) : 2.4 g (41%; mp 223 - 225 °C. - ^{1}H-NMR : δ 12.57 (1 H, s, broad), 7.99 (1 H, d, *J* 10.6), 7.88 (1 H, d, *J* 7.9), 7.63 (1 H, s), 7.54 (1 H, dm, *J* 7.9). - ^{19}F-NMR : δ -0.1 (3 F, s), -66.4 (1 F, d, *J* 11). - MS : 232 (M^+ + 1, 9%), 231 (M^+, 100%). - Analysis : calc. for $C_{10}H_5F_4NO$ (231.15) C 51.96, H 2.18; found 51.97, H 2.14%.

3-Fluoro-5-(trifluoromethyl)quinol-2(1*H*)-one (16b) : 1.8 g (31%); mp 246 - 248 °C. - ^{1}H-NMR : δ 12.74 (1 H, s, broad), 7.73 (1 H, dd, *J* 11.4, 1.2), 7.6 (3 H, m). - ^{19}F-NMR : δ 2.8 (3 F, s), -64.8 (1 F, d, *J* 11). - MS : 232 (M^+ +1, 4%), 231 (M^+, 100%). - Analysis : calc. for $C_{10}H_5F_4NO$ (231.15) C 51.96, H 2.18; found C 51.60, H 2.19%.

3-Fluoro-7-nitro- and 3-Fluoro-5-nitroquinol-2(1*H*)-one (18a and **18b** in the ratio of 45 : 55); 0.31 g (5%); impure, tan material. - ^{1}H-NMR : δ 12.9 (0.55 H, m), 12.7 (0.45 H, m), 8.18 (0.55 H, d, *J* 12.5), 8.16 (0.45 H, d, *J* ~ 2.3), 8.04 (0.45 H, d, *J* 10.5), 8.03 (0.45 H, dd, *J* 8.6, 2.3), 7.98 (0.55 H, dd, *J* 5.4, 3.5), 7.91 (0.45 H, d, *J* 8.8), 7.71 (0.55 H, d, *J* 5.4), 7.69 (0.55 H, d, *J* 3.5). - ^{19}F-NMR : δ -64.0 (0.45 F, dd, *J* 11, 5), -64.1 (0.55 F, dd, *J* 12, 5).

7-Chloro- and 5-Chloro-3-fluoroquinol-2(1*H*)-one (20a and **20b** in the ratio of 55 : 45) : 4.2 g (85%); melting around 230 °C. - ^{1}H-NMR : δ 12.59 (0.45 H, s, broad), 12.39 (0.55 H, s, broad), 7.92 (0.45 H, d, *J* 10.9), 7.89 (0.55 H, d, *J* 10.8), 7.68 (0.55 H, d, *J* 8.4), 7.49 (0.45 H, t, *J* 7.9), 7.37 (0.45 H, d, *J* 7.7), 7.34 (0.55 H, d, *J* 1.9), 7.32 (0.45 H, d, *J* 8.3), 7.28 (0.55 H, dd, *J* 8.4, 1.9). - ^{19}F-NMR : δ -67.1 (0.45 F, d, *J* 11), -69.7 (0.55 F, d, *J* 11). - Analysis : calc. for $C_9H_5F_3ClFNO$ (197.60) C 54.71, H 2.55; found C 53.61, H 2.70%; second, identical sample : found C 55.87, H 2.84%.

3,7-Difluoroquinol-2(1*H*)-one (22a) : 4.0 g (88%; mp 249 - 251 °C (without further purification). - ^{1}H-NMR: δ 12.41 (1 H, s, broad), 7.91 (1 H, d, *J* 11.2), 7.72 (1 H, dd, *J* 8.9, 6.1), 7.13 (1 H, td, *J* 8.9, 2.4), 7.08 (1 H, dd, *J* 10.3, 2.4). - ^{19}F-NMR : δ -49.7 (1 F, symm. m), -72.1 (1 F, dt, *J* 11, 5). - MS : 182 (M^+ + 1, 20%), 181 (M^+, 100%). - Analysis : calc. for $C_9H_5F_2NO$ (181.14) C 59.68, H 2.78; found C 59.67, H 2.89%.

3-Fluoro-7-methoxyquinol-2(1*H*)-one (24a) : 3.6 g (75%); mp 220 - 221 °C (after sublimation). - ^{1}H-NMR : δ 12.2 (1 H, m), 7.80 (1 H, d, *J* 11.2), 7.56 (1 H, d, *J* 8.6), 6.9 (2 H, m), 3.80 (3 H, s). - ^{19}F-NMR : δ -75.3 (1 F, d, *J* 11). - MS : 193 (M^+, 100%), 178 (15%), 150 (66%). - Analysis : calc. for $C_{10}H_8FNO_2$ (193.18) C 62.18, H 4.17; found C 62.24, H 4.24%.

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