Synthesis of Fluoro and Trifluoromethyl Derivatives of 2-Phenylquinolin-4-ol

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A *tert*-butoxide base-mediated cyclization of fluoro- and trifluoromethyl-substituted Schiff bases **12-19** produces 4-*tert*-butoxyquinolines **23-30** which are hydrolyzed to quinolin-4-ols **31-38**.

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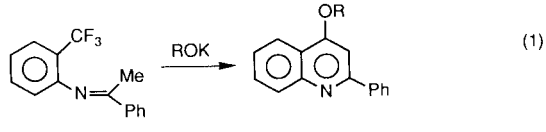
Recently we reported a base-mediated cyclization of Schiff bases derived from 2-trifluoromethylaniline and alkyl aryl or alkyl heteroaryl ketones, such as **1**, to give a quinoline derivative substituted with the base function in the 4 position [1]. With lithium alkylamide or dialkylamide reagents the cyclization provides an efficient entry into derivatives of quinolin-4-amine [2-5]. A similar approach has been adopted for the synthesis of substituted quinazolin-4-amines [6]. An analogous, alkoxide base-mediated cyclization has received little attention [1,2]. The reaction of **1** with potassium *tert*-butoxide gave 4-*tert*-butoxy-2-phenylquinoline (**2**) in a high yield, but the formation of 4-ethoxy-2-phenylquinoline (**3**) in the presence of either sodium or potassium ethoxide was inefficient (equation 1).



(1)

1

2: R = *t*-Bu (83%)
3: R = Et (25%)

In this paper we report the application of the *tert*-butoxide-mediated cyclization of Schiff bases to the preparation of fluoro and/or trifluoromethyl derivatives of 2-phenylquinolin-4-ol, such as **31-38** (Scheme I). This research was stimulated by the current immense interest in the synthesis of fluorinated heterocyclic compounds because many of them show biological activity. In particular, some fluoro-substituted derivatives of quinolin-4-ol are potent antimicrobial agents [7].

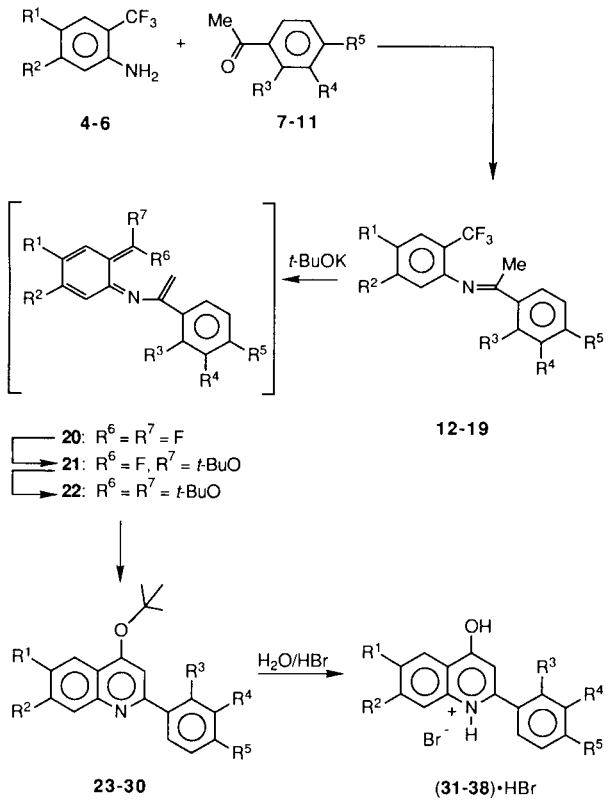
The starting azomethines **12-19** were obtained in a condensation reaction of 2-trifluoromethylanilines **4-6** with acetophenones **7-11**. Upon treatment with potassium *tert*-butoxide in tetrahydrofuran the azomethines **12-19** underwent cyclization to give the respective 4-*tert*-butoxyquinolines **23-30**. The cyclization involved the 2-trifluoromethyl group at the aniline portion of the azomethines, as observed for the reaction of **1** (equation 1), but other trifluromethyl and/or fluorine substituents were retained in the products. Yields were in the range of 52-92% for **23-28** and 29-36% for two 7-(trifluoromethyl)quinolines **29** and **30**. Fortunately in the latter two cases the balance material consisted of high molecular weight compounds and a large number of unidentified low molecular weight products, none of them major, which caused no problems with chromatographic purification of quinolines **29** and **30**. Efficient hydrolysis of 4-*tert*-butoxyquinolines **23-30** with hydrobromic acid completed this short and practical synthetic route to the desired derivatives of 2-phenylquinolin-4-ol, **31-38**. Quinolinols **31-38** were isolated as hydrobromide salts.

All new compounds **12-19**, **23-30** and hydrobromides of **31-38** were characterized by spectral methods and gave satisfactory microanalysis results. In particular, a singlet for the C3-proton in the aromatic region of ^{1}H nmr spectra and a molecular ion peak in the mass spectra of all quinolines **23-38** were observed.

Finally, we wish to comment on a possible mechanism for cyclization of azomethines **12-19** to a quinoline system. The suggested mechanism (Scheme I) involves ionization of the starting azomethine at the methyl group. This is followed by elimination of fluoride from the 2-trifluoromethyl group of the resultant ionized azomethine to give 6-(difluoromethylene)-*N*-(1-arylvinyl)-2,4-cyclohexadien-1-imine, such as **20**. Intermediates of this type have been suggested previously to undergo a fast addition reaction with nucleophiles [1,8,9]. The elimination of fluoride from a new anionic intermediate gives a nucleophile-substituted unsaturated imine such as **21**. A similar addition/elimination pathway with **21** may give **22**. The electrocyclization of **22** followed by elimination of *tert*-butyl alcohol from the resultant dihydroquinoline intermediate is apparently the major pathway for the quinoline formation. The apparent fast addition reactions of alkoxide anion with **20** and **21** make these intermediates less likely to undergo electrocyclization.

The effect of steric hindrance in the alkoxide ion on the formation of a 4-alkoxyquinoline (equation 1) is consistent with this postulated mechanism [2]. The increased efficiency of quinoline formation in the presence of the *tert*-butoxide base in comparison to the reaction of the ethoxide base may reflect a decreased ability of the sterically con-

Scheme I



4-38	R^1	R^2	R^3	R^4	R^5
4	H	H	-	-	-
5	F	H	-	-	-
6	H	CF_3	-	-	-
7	-	-	F	H	H
8	-	-	H	F	H
9	-	-	H	H	F
10	-	-	H	CF_3	H
11	-	-	H	H	CF_3
12, 23, 31	H	H	F	H	H
13, 24, 32	H	H	H	F	H
14, 25, 33	H	H	H	H	F
15, 26, 34	H	H	H	H	CF_3
16, 27, 35	F	H	H	F	H
17, 28, 36	F	H	H	CF_3	H
18, 29, 37	H	CF_3	F	H	H
19, 30, 38	H	CF_3	H	H	CF_3

gested intermediate product, such as **22**, to undergo intermolecular reactions, including polymerization, which compete with the intramolecular electrocyclization reaction.

We have shown that yields of all quinolines **2**, **3** and **23-30** for the reactions conducted in tetrahydrofuran decrease about threefold with a concomitant increase in the formation of unidentified by-products when an alcohol (ethanol or *tert*-butyl alcohol) is used as the reaction medium. In addition, the rates for disappearance of the starting imines are slower in the alcohol solvents than in tetrahydrofuran. These results are also consistent with the postulated mechanism. In particular, the excess of *tert*-butanol would inhibit the formation of **22**, the key postulated intermediate product, by protonation of anionic precursors to **22**. This would facilitate side reactions and decrease efficiency of quinoline formation, as observed.

In summary, we have shown a useful extension of the previously published synthesis of substituted quinolin-4-amines to the preparation of sterically hindered 4-alkoxyquinolines. These two reactions appear to proceed by similar mechanistic pathways [1,2].

EXPERIMENTAL

All reagents were obtained from Aldrich. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use. Chromatography was conducted on a chromatotron with silica gel coated rotors. Melting points (Pyrex capillary) are not corrected. Unless otherwise stated, ^{1}H nmr spectra were obtained at 60 MHz at 25° in deuteriochloroform (**12-19, 23-30**) and deuterated dimethyl sulfoxide (hydrobromide salts of **31-38**) solutions with tetramethylsilane as an internal reference. Coupling constants smaller than 2 Hz are not reported. Electron impact mass spectra were obtained at 70 eV. Thermal dissociation of the hydrobromide salts of **31-38** directly in a mass spectrometer was used to obtain the spectra of free bases **31-38**.

General Procedure for Preparation of Imines **12-19**.

A solution of an aniline **4-6** (12 mmoles), an acetophenone **7-11** (12 mmoles) and *p*-toluenesulfonic acid (15 mg) in toluene (50 ml) was heated under reflux for 15 hours with azeotropic removal of water and then concentrated under reduced pressure. Distillation on a Kugelrohr (105-125°/1.0 mmHg) gave an imine, **12-19**, as an oil.

N-[1-(2-Fluorophenyl)ethylidene]-2-(trifluoromethyl)aniline, **12**.

This compound was obtained in a 69% yield; ^{1}H nmr: δ 2.23 (d, J = 4 Hz, coupling with F, 3H), 6.70-8.15 (m, 8H); ms: m/z 145 (46), 266 (100), 281 (M^+, 34).

Anal. Calcd. for $C_{15}H_{11}F_4N$: C, 64.05; H, 3.94; N, 4.98. Found: C, 64.32; H, 3.96; N, 4.92.

N-[1-(3-Fluorophenyl)ethylidene]-2-(trifluoromethyl)aniline, **13**.

This compound was obtained in an 81% yield; ^{1}H nmr: δ 2.16 (s, 3H), 6.55-7.80 (m, 8H); ms: m/z 145 (48), 266 (100), 281 (M^+, 37).

Anal. Calcd. for $C_{15}H_{11}F_4N$: C, 64.05; H, 3.94; N, 4.98. Found: C, 64.15; H, 3.95; N, 4.95.

N-[1-(4-Fluorophenyl)ethylidene]-2-(trifluoromethyl)aniline, **14**.

This compound was obtained in an 80% yield; ^{1}H nmr: δ 2.18 (s, 3H), 6.60-8.10 (m, 8H); ms: m/z 145 (37), 266 (100), 281 (M^+, 34).

Anal. Calcd. for $C_{15}H_{11}F_4N$: C, 64.05; H, 3.94; N, 4.98. Found: C, 63.94; H, 3.95; N, 4.96.

2-(Trifluoromethyl)-*N*-[1-[4-(trifluoromethyl)phenyl]ethylidene]-aniline, **15**.

This compound was obtained in an 81% yield; ^{1}H nmr: δ 2.23

(s, 3H), 6.75-7.69 (m, 4H), 7.72 (d, J = 8 Hz, 2H), 8.07 (d, J = 8 Hz, 2H); ms: m/z 145 (69), 316 (100), 331 (M^+, 37).

Anal. Calcd. for $C_{16}H_{11}F_6N$: C, 58.01; H, 3.35; N, 4.23. Found: C, 58.24; H, 3.36; N, 4.20.

4-Fluoro-*N*-[1-(3-fluorophenyl)ethylidene]-2-(trifluoromethyl)-aniline, **16**.

This compound was obtained in a 73% yield; ^1H nmr: δ 2.19 (s, 3H), 6.60-7.80 (m, 7H); ms: m/z 95 (34), 163 (60), 204 (27), 284 (100), 299 (M^+, 37).

Anal. Calcd. for $C_{15}H_{10}F_5N$: C, 60.20; H, 3.37; N, 4.68. Found: C, 60.27; H, 3.37; N, 4.65.

4-Fluoro-2-trifluoromethyl-*N*-[1-[3-(trifluoromethyl)phenyl]ethylidene]aniline, **17**.

This compound was obtained in a 70% yield; ^1H nmr: δ 2.24 (s, 3H), 6.50-8.20 (m, 7H); ms: m/z 163 (44), 204 (22), 334 (100), 349 (M^+, 37).

Anal. Calcd. for $C_{16}H_{10}F_7N$: C, 55.02; H, 2.88; N, 4.01. Found: C, 54.70; H, 2.91; N, 3.90.

N-[1-(2-Fluorophenyl)ethylidene]-2,5-bis(trifluoromethyl)aniline, **18**.

This compound was obtained in a 70% yield; ^1H nmr: δ 2.25 (d, J = 4 Hz, coupling with F, 3H), 7.00-7.55 (m, 5H), 7.70-8.05 (m, 2H); ms: m/z 163 (31), 334 (100), 349 (M^+, 27).

Anal. Calcd. for $C_{16}H_{10}F_7N$: C, 55.02; H, 2.88; N, 4.01. Found: C, 55.13; H, 2.94; N, 3.91.

2,5-Bis(trifluoromethyl)-*N*-[1-[4-(trifluoromethyl)phenyl]ethylidene]aniline, **19**.

This compound was obtained in a 69% yield; ^1H nmr: δ 2.26 (s, 3H), 7.05 (br s, 1H), 7.35-8.20 (m, 6H); ms: m/z 163 (37), 254 (19), 384 (100), 399 (M^+, 29).

Anal. Calcd. for $C_{17}H_{10}F_9N$: C, 51.13; H, 2.52; N, 3.51. Found: C, 51.21; H, 2.54; N, 3.48.

General Procedure for Preparation of Quinolines **23-30**.

Potassium *tert*-butoxide (1.12 g, 10 mmoles), tetrahydrofuran (35 ml) and a solution of an imine **12-19** (2 mmoles) in tetrahydrofuran (5 ml) were mixed in the given order under a nitrogen atmosphere, and then the mixture was heated under reflux for 2 hours. After cooling to 23° the mixture was quenched with water (0.25 ml), treated with hexanes (25 ml) and anhydrous sodium sulfate, filtered, and the solution was concentrated. Chromatography (hexanes/triethylamine, 9:1) gave a quinoline, **23-30**. Solid samples were crystallized from hexanes.

4-*tert*-Butoxy-2-(2-fluorophenyl)quinoline, **23**.

This compound was obtained as an oil, yield 92%; ^1H nmr (400 MHz): δ 1.68 (s, 9H), 7.19 (m, 1H), 7.32 (m, 1H), 7.39-7.52 (m and s at δ 7.45, 3H), 7.69 (t, J = 8 Hz, 1H), 8.07-8.13 (m, 2H), 8.20 (d, J = 8 Hz, 1H); ms: m/z 239 (100), 295 (M^+, 4).

Anal. Calcd. for $C_{19}H_{18}FNO$: C, 77.26; H, 6.14; N, 4.74. Found: C, 77.46; H, 6.15; N, 4.70.

4-*tert*-Butoxy-2-(3-fluorophenyl)quinoline, **24**.

This compound was obtained as an oil, yield 68%; ^1H nmr (400 MHz): δ 1.69 (s, 9H), 7.15 (m, 1H), 7.34 (s, 1H), 7.45-7.52 (m, 2H), 7.70 (t, J = 8 Hz, 1H), 7.80-7.86 (m, 2H), 8.09 (d, J = 8 Hz, 1H), 8.19 (d, J = 8 Hz, 1H); ms: m/z 239 (100), 295 (M^+, 4).

Anal. Calcd. for $C_{19}H_{18}FNO$: C, 77.26; H, 6.14; N, 4.74. Found: C, 77.09; H, 6.11; N, 4.72.

4-*tert*-Butoxy-2-(4-fluorophenyl)quinoline, **25**.

This compound had mp 74-75°, yield 74%; ^1H nmr (400 MHz): δ 1.68 (s, 9H), 7.20 (m, 2H), 7.33 (s, 1H), 7.47 (t, J = 8 Hz, 1H), 7.69 (t, J = 8 Hz, 1H), 8.04-8.09 (m, 3H), 8.18 (d, J = 8 Hz, 1H); ms: m/z 239 (100), 295 (M^+, 7).

Anal. Calcd. for $C_{19}H_{18}FNO$: C, 77.26; H, 6.14; N, 4.74. Found: C, 77.35; H, 6.19; N, 4.70.

4-*tert*-Butoxy-2-[4-(trifluoromethyl)phenyl]quinoline, **26**.

This compound had mp 114-116°, yield 69%; ^1H nmr (400 MHz): δ 1.69 (s, 9H), 7.37 (s, 1H), 7.50 (t, J = 8 Hz, 1H), 7.71 (t, J = 8 Hz, 1H), 7.78 (d, J = 8 Hz, 2H), 8.09 (d, J = 8 Hz, 1H), 8.18 (d, J = 8 Hz, 2H), 8.20 (d, J = 8 Hz, 1H); ms: m/z 289 (100), 345 (M^+, 3).

Anal. Calcd. for $C_{20}H_{18}F_3NO$: C, 69.55; H, 5.25; N, 4.05. Found: C, 69.62; H, 5.30; N, 4.03.

4-*tert*-Butoxy-6-fluoro-2-(3-fluorophenyl)quinoline, **27**.

This compound had mp 100-101°, yield 66%; ^1H nmr (400 MHz): δ 1.68 (s, 9H), 7.15 (m, 1H), 7.35 (s, 1H), 7.43-7.51 (m, 2H), 7.75-7.83 (m, 3H), 8.06 (m, 1H); ms: m/z 257 (100), 313 (M^+, 3).

Anal. Calcd. for $C_{19}H_{17}F_2NO$: C, 72.82; H, 5.47; N, 4.47. Found: C, 72.93; H, 5.46; N, 4.43.

4-*tert*-Butoxy-6-fluoro-2-[3-(trifluoromethyl)phenyl]quinoline, **28**.

This compound had mp 85-86°, yield 52%; ^1H nmr: δ 1.69 (s, 9H), 7.37 (s, 1H), 7.40-8.35 (m, 7H); ms: m/z 307 (100), 3.63 (M^+, 2).

Anal. Calcd. for $C_{20}H_{17}F_4NO$: C, 66.10; H, 4.71; N, 3.85. Found: C, 66.18; H, 4.76; N, 3.81.

4-*tert*-Butoxy-2-(2-fluorophenyl)-7-(trifluoromethyl)quinoline, **29**.

This compound had mp 78-80°, yield 36%; ^1H nmr (400 MHz): δ 1.70 (s, 9H), 7.21 (m, 1H), 7.34 (m, 1H), 7.46 (m, 1H), 7.54 (s, 1H), 7.65 (d, J = 8 Hz, 1H), 8.13 (m, 1H), 8.31 (d, J = 8 Hz, 1H), 8.41 (br s, 1H); ms: m/z 57 (27), 307 (100), 363 (M^+, 5).

Anal. Calcd. for $C_{20}H_{17}F_4NO$: C, 66.10; H, 4.71; N, 3.85. Found: C, 66.18; H, 4.75; N, 3.82.

4-*tert*-Butoxy-7-(trifluoromethyl)-2-[4-(trifluoromethyl)phenyl]-quinoline, **30**.

This compound had mp 129-131°, yield 29%; ^1H nmr (400 MHz): δ 1.71 (s, 9H), 7.46 (s, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.80 (d, J = 8 Hz, 2H), 8.20 (d, J = 8 Hz, 2H), 8.31 (d, J = 8.5 Hz, 1H), 8.40 (s, 1H); ms: m/z 57 (39), 357 (100), 413 (M^+, 3).

Anal. Calcd. for $C_{21}H_{17}F_6NO$: C, 61.01; H, 4.14; N, 3.38. Found: C, 61.29; H, 4.28; N, 3.31.

General Procedure for Preparation of Quinolinium Hydrobromides, **31-38•HBr**.

A mixture of a 4-*tert*-butoxyquinoline, **23-30** (0.5 mmole), a 95% ethanol (3 ml), and a 24% hydrobromic acid (0.25 ml) was heated under reflux for 1 hour. The mixture was then concentrated to 1 ml, treated with ether (1 ml), and refrigerated for 10 hours. The precipitated material was filtered and crystallized from a 95% ethanol to give a quinolinium hydrobromide, **31-38•HBr**.

4-Hydroxy-2-(2-fluorophenyl)quinolinium Hydrobromide, **31•HBr**.

This compound had mp 254-257°, yield 80%; ^{1}H nmr: δ 4.23 (a broad absorption for the quinolinium, C4-hydroxy, and water protons, also observed in the spectra reported below), 6.69 (s, 1H), 7.40-8.30 (m, 8H); ms: m/z 183 (26), 211 (82), 239 (M^+ for **31**, 100).

Anal. Calcd. for $C_{15}H_{10}FNO\cdot HBr$: C, 56.27; H, 3.46; N, 4.38. Found: C, 56.32; H, 3.48; N, 4.35.

4-Hydroxy-2-(3-fluorophenyl)quinolinium Hydrobromide Hemihydrate, **32·HBr·½H$_2$O**.

This compound had mp 256-259°, yield 85%; ^{1}H nmr: δ 4.70 (br s, see above), 6.94 (s, 1H), 7.40-8.30 (m, 8H); ms: m/z 183 (20), 211 (57), 239 (M^+ for **32**, 100).

Anal. Calcd. for $C_{15}H_{10}FNO\cdot HBr\cdot ½H_2O$: C, 54.73; H, 3.67; N, 4.25. Found: C, 54.95; H, 3.69; N, 4.23.

4-Hydroxy-2-(4-fluorophenyl)quinolinium Hydrobromide Hemihydrate, **33·HBr·½H$_2$O**.

This compound had mp 273-275°, yield 80%; ^{1}H nmr: δ 3.43 (br s, see above), 6.51 (s, 1H), 7.30-8.20 (m, 8H); ms: m/z 183 (27), 211 (56), 239 (M^+ for **33**, 100).

Anal. Calcd. for $C_{15}H_{10}FNO\cdot HBr\cdot ½H_2O$: C, 54.73; H, 3.67; N, 4.25. Found: C, 54.60; H, 3.72; N, 4.23.

4-Hydroxy-2-[4-(trifluoromethyl)phenyl]quinolinium Hydrobromide, **34·HBr**.

This compound had mp 315-316°, yield 88%; ^{1}H nmr (400 MHz): δ 4.65 (br s, see above), 6.89 (s, 1H), 7.61 (t, J = 8 Hz, 1H), 7.91 (t, J = 8 Hz, 1H), 8.00 (d, J = 8 Hz, 1H), 8.04 (d, J = 8 Hz, 2H), 8.14 (d, J = 8 Hz, 2H), 8.25 (d, J = 8 Hz, 1H); ms: m/z 261 (50), 289 (M^+ for **34**, 100).

Anal. Calcd. for $C_{16}H_{10}F_3NO\cdot HBr$: C, 51.91; H, 2.99; N, 3.78. Found: C, 52.07; H, 3.06; N, 3.76.

6-Fluoro-2-(3-fluorophenyl)-4-hydroxyquinolinium Hydrobromide Hemihydrate, **35·HBr·½H$_2$O**.

This compound had mp 309-310°, yield 88%; ^{1}H nmr (400 MHz): δ 4.13 (br s, see above), 6.68 (s, 1H), 7.49 (m, 1H), 7.65-7.85 (m, 5H), 7.96 (m, 1H); ms: m/z 229 (40), 257 (M^+ for **35**, 100).

Anal. Calcd. for $C_{15}H_9F_2NO\cdot HBr\cdot ½H_2O$: C, 51.89; H, 3.19; N, 4.03. Found: C, 51.97; H, 3.21; N, 4.02.

6-Fluoro-4-hydroxy-2-[3-(trifluoromethyl)phenyl]quinolinium Hydrobromide, **36·HBr**.

This compound had mp 299-301°, yield 68%; ^{1}H nmr: δ 3.95 (br s, see above), 6.68 (s, 1H), 7.60-8.30 (m, 7H); ms: m/z 279 (22), 290 (21), 307 (M^+ for **36**, 31), 308 (100).

Anal. Calcd. for $C_{16}H_9F_4NO\cdot HBr$: C, 49.50; H, 2.59; N, 3.61. Found: C, 49.36; H, 2.62; N, 3.60.

2-(2-Fluorophenyl)-4-hydroxy-7-(trifluoromethyl)quinolinium Hydrobromide, **37·HBr**.

This compound had mp 248-251°, yield 61%; ^{1}H nmr: δ 3.67 (br s, see above), 6.40 (s, 1H), 7.40-8.50 (m, 7H); ms: m/z 208 (26), 251 (21), 279 (50), 306 (100), 307 (M^+ for **37**, 86).

Anal. Calcd. for $C_{16}H_9F_4NO\cdot HBr$: C, 49.50; H, 2.59; N, 3.61. Found: C, 49.38; H, 2.54; N, 3.57.

4-Hydroxy-7-(trifluoromethyl)-2-[4-(trifluoromethyl)phenyl]quinolinium Hydrobromide Hemihydrate, **38·HBr·½H$_2$O**.

This compound had mp 255-257°, yield 80%; ^{1}H nmr (400 MHz): δ 3.80 (br s, see above), 6.66 (s, 1H), 7.67 (d, J = 8 Hz, 1H), 7.99 (d, J = 8 Hz, 2H), 8.12 (d, J = 8 Hz, 2H), 8.18 (s, 1H), 8.31 (d, J = 8 Hz, 1H); ms: m/z 329 (43), 357 (M^+ for **38**, 100).

Anal. Calcd. for $C_{17}H_9F_6NO\cdot HBr\cdot ½H_2O$: C, 45.65; H, 2.48; N, 3.13. Found: C, 45.65; H, 2.49; N, 3.10.

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