AN UNUSUAL 2,6-DIALKOXYLATION OF QUINOLINE BY THE REACTION WITH ELEMENTAL FLUORINE AND ALCOHOL

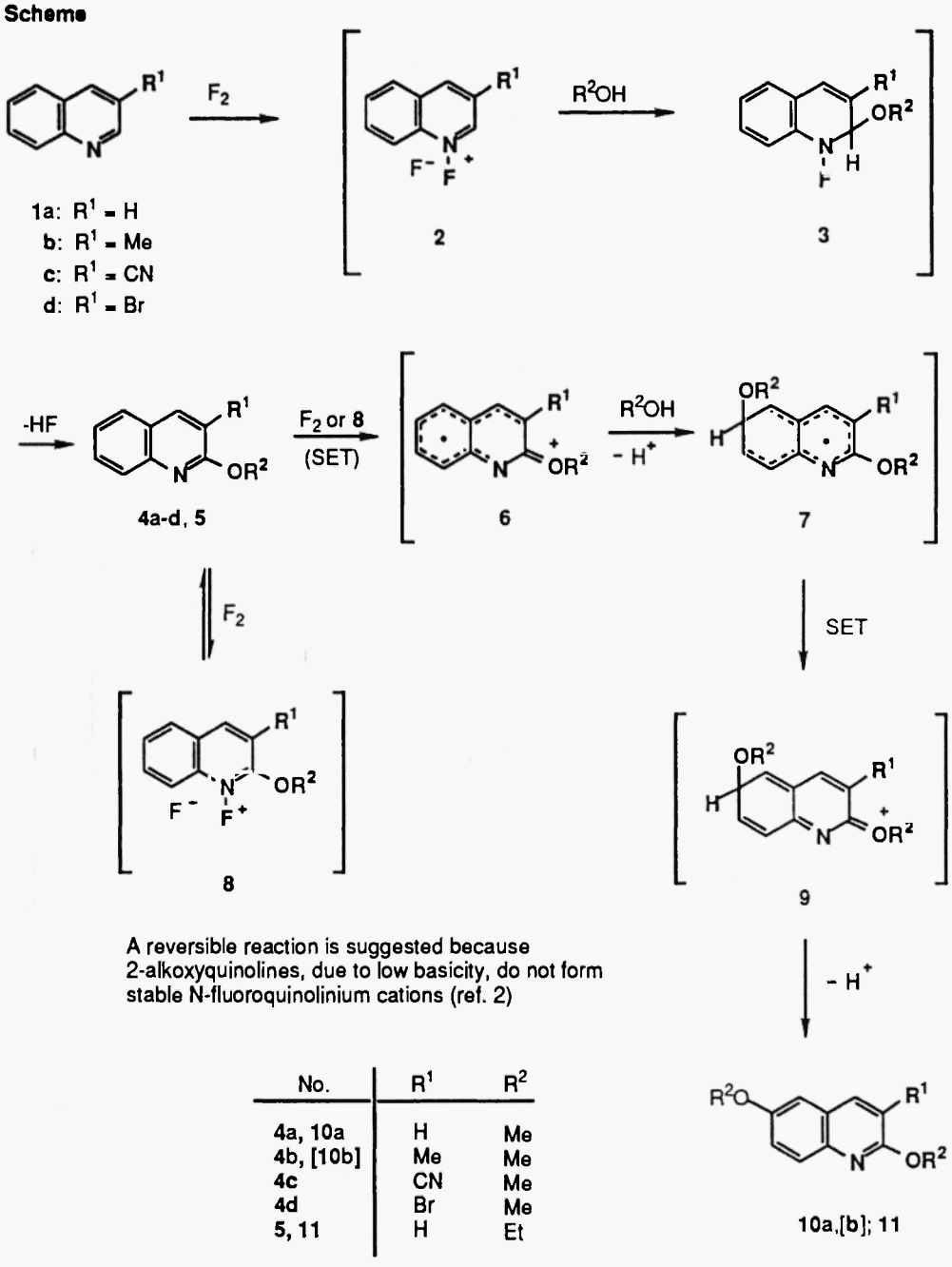
Alesia N. Parker and Lucjan Strekowski*
Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, USA

Abstract: The one-step reaction produces 2,6-dimethoxyquinoline or 2,6-diethoxyquinoline in 30-35% yields. The postulated mechanistic pathway involves the intermediacy of a radical cation generated by single electron transfer from the initially formed 2-alkoxyquinoline to molecular fluorine or to 2-alkoxy-*N*-fluoroquinolinium cation.

The treatment of pyridines with elemental fluorine at low temperature generates the corresponding highly reactive *N*-fluoropyridinium cations, the subsequent reactions of which with basic/nucleophilic species provide useful synthetic routes to various substituted pyridines (**1**). The postulated mechanistic pathways of the latter reactions involve proton abstraction at position 2 to give an ylide/carbene, single electron transfer (SET) from the nucleophile to give a radical, and the addition reaction of the nucleophile to the position 2 of the *N*-fluoropyridinium cation. The addition reactions at position 4 have also been observed but are rare. This is due to the higher charge concentration at position 2 of the *N*-fluoropyridinium cation. In particular (2), *N*-fluoroquinolinium cation (**2** in Scheme) undergoes the addition reaction with methanol and then the resultant adduct **3** undergoes elimination of HF to give 2-methoxyquinoline (**4a**). Additional and previously unreported reactions of 3-methylquinoline (**1b**), 3-cyanoquinoline (**1c**), and 3-bromoquinoline (**1d**) with fluorine in methanol to furnish the respective 2-methoxyquinolines **4b-d** and the synthesis of 2-ethoxyquinoline (**5**) from quinoline in ethanol are also given in the Scheme. Although all these reactions produce a substantial amount of intractable tar, the one-step synthesis is experimentally simple and compounds **4a-d** and **5** (yields 40-60%) are the only major, low molecular weight products. Therefore, their isolation is also simple (3).

We noticed that the reactions of **1a** and **1b** are relatively efficient in the presence of **1.2-1.5** molar equivalents of elemental fluorine (-60 °C, 2h). With a greater excess of fluorine the yields of the corresponding alkoxyquinolines **4a,b** and **5** decreased and a new product was observed by GC-MS analysis in each case. These new products were identified as 2,6-dialkoxyquinolines **10a,b** and **11** (3,4) and they were the only major low molecular weight products after the mixtures had been allowed to stand at -20 °C for 12h. By contrast, a similar treatment of 3-cyanoquinoline (**1c**) or 3-bromoquinoline (**1d**) with excess fluorine (up to 5 equiv.) in methanol gave the respective 2-methoxyquinolines **4c,d** as the major products, and the corresponding dimethoxy derivatives were formed in less than 2% yield, as found by GC-MS analysis of the crude mixtures (5).

Scheme



No.	R^1	R^2
4a, 10a	H	Me
4b, [10b]	Me	Me
4c	CN	Me
4d	Br	Me
5, 11	H	Et

The one-step preparations of 2,6-dimethoxyquinoline (**10a**) and 2,6-diethoxyquinoline (**11**) (yields 30-35%) are of synthetic value (3,4). Analysis of the reaction leading to 2,6-dimethoxy-3-methylquinoline (**10b**) revealed rapid formation of 2-methoxy-3-methylquinoline (**4b**) followed by slow conversion of **4b** into **10b**. However, the decrease in **4b** was paralleled by a several-fold smaller increase in **10b**, which was in sharp contrast to the reactions of quinoline. Since the estimated yield of **10b** in the mixture was only 10%, no attempts were made to isolate this product in an analytically pure form. The low yield of **10b** is consistent with secondary transformations of methylquinolines **4b** and **10b** in the highly reactive environment of fluorine.

The exclusive 6-regioselectivity in the formation of **10a** and **11** (and, apparently, for **10b**) is not consistent with a nucleophile (alcohol) addition reaction to the *N*-fluoroquinolinium cation **8** derived from **4a** or **5**. Such a reaction followed by elimination of HF (as shown for **1** in Scheme) would produce 2,4-, 2,5- or 2,7-dialkoxyquinoline, none of which was found in the corresponding crude mixture. On the other hand, the reaction does appear to involve an electrophilic intermediate because the presence of an electron withdrawing bromo or cyano substituent in the quinoline strongly inhibits the formation of a dialkoxy derivative (5).

These results can be explained in terms of an initial SET pathway in which the quinoline **4a**, **5** (electron donor) undergoes a reaction with elemental fluorine or *N*-fluoropyridinium cation **8** derived from **4a**, **5** (electron acceptor) to generate a radical cation 6. This reaction would be inhibited by electron-withdrawing substituents, as observed (5). The subsequent nucleophilic addition of alcohol with the electrophilic intermediate **6** would take place at position 6 because the resultant radical 7 is highly conjugated. The alternative addition to the position 8 to give a similarly conjugated radical is less likely for steric reasons. The subsequent SET of 7 would generate a well-stabilized cation **9**. Deprotonation of **9** is suggested to give the observed product **10**a, **11**.

Due to the high reactivity of elemental fluorine the mechanisms of its reactions with organic molecules are extremely difficult to study, and the literature is abundant with various mechanistic speculations. The many simplistic explanations reported in the early literature have recently been reexamined in favor of SET pathways (6). One major reason is that fluorine is the most electronegative element and, as such, it is a powerful electron acceptor. Evidence has been also been accumulating that *N*-fluoropyridinium cations are excellent electron acceptors as well (7,8).

Acknowledgment

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References and Notes

(1) For a review, see: L. Strekowski and A.S. Kiselyov, Adv. Heterocycl. Chem. *62*, 1 (1995)

(2) D. Hebel and S. Rozen, J. Org. Chem. *56*, 6298 (1991)

(3) **Caution:** *Elemental fluorine is a strong oxidant and a corrosive material. All operations must be conducted with fluorine diluted with argon or nitrogen and under an efficient hood.* Molecular fluorine diluted with argon (1:9) was obtained from Air Products and Chemicals, Inc. The experimental set-up consisted of a standard glass flask, all-Teflon connectors and tubing, and all all-glass flow meter to estimate the amount of fluorine passed through the mixture. Occasionally, the amount of fluorine was estimated by passing the gas through the mixture in the flask and then collecting argon under a glass cylinder filled with water.

In the preparation of **4a-d**, **5** a solution of **1** (3 mmol) and elemental fluorine (1.5-4.5 mmol) in anhydrous MeOH or EtOH (10 mL) was allowed to stand at -70 °C to -60 °C for 2h, after which time a TLC analysis (silica gel, hexanes/AcOEt, 4:1) showed the absence of **1**. Any excess of fluorine was removed by bubbling nitrogen through the mixture and, at the same time, the temperature was allowed to rise to 0 °C. The brown solution was treated with an aqueous saturated solution of $NaHCO_3$ (2 mL) and then extracted with ether (3 x 20 mL). The extract was diluted with pentanes (5 mL) to facilitate drying ($MgSO_4$) and concentrated on a rotary evaporator. Flash chromatography of

the residue (silica gel, hexanes/AcOEt, 9:1) followed by Kugelrohr distillation (140-150 °C/0.5 mmHg) gave an analytically pure 2-methoxyquinoline **4,5**: Compound **4b**, an oil; **4c**, mp 78-79 °C (from pentanes/ether, 19:1) [reported mp 74 °C: H. Wojahn and H. Kramer, Arch. Pharm. *276*, 291 (1938)]; **4d**, an oil; **5**, an oil [M.T. Bogert and C.E. May, J. Am. Chem. Soc. *31*, 507 (1909)].

In the preparation of 2,6-dialkoxyquinolines **10** and **11** a solution of **1** (3 mmol) was treated with elemental fluorine (5 mmol) at -78 °C followed by standing of the resultant solution at -20 °C for 12h and then workup as described above.

10a: yield 35%, mp 149-150 °C (from pentanes/ether, 19:1) [reported mp 88-90 °C, apparently, an impure sample: R.R. Holmes, J. Conrady, J. Guthrie and R. McKay, J. Am. Chem. Soc. *76*, 2400 (1954)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3H), 4.04 (s, 3H), 6.88 (d, J = 9 Hz, 1H), 7.05 (d, J = 3 Hz, 1H), 7.28 (dd, J = 9 and 3 Hz, 1H), 7.76 (d, J = 9 Hz, 1H), 7.89 (d, J = 9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.3, 55.5, 106.2, 113.1, 121.0, 125.7, 128.5, 137.7, 142.0, 156.0, 161.5.

[**10b**]: MS m/z 174 (40), 188 (50), 202 (50), 203 (100 , M^+). In comparison to ^{1}H NMR spectra of **10a** and **11** the ^{1}H NMR spectrum of crude compound **10b** gave chemical shifts for the corresponding aromatic protons within 0.1 ppm and a virtually identical coupling pattern.

11: yield 30%, mp 102-104 °C from pentanes/ether, 19:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (t, J = 7 Hz, 3H), 1.46 (t, J = 7 Hz, 3H), 4.11 (q, J = 7 Hz, 2H), 4.49 (q, J = 7 Hz, 2H), 6.85 (d, J = 9 Hz, 1H), 7.02 (d, J = 3 Hz, 1H), 7.27 (dd, J = 9 and 3 Hz, 1H), 7.72 (d, J = 9 Hz, 1H), 7.85 (d, J = 9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 14.8, 61.5, 63.7, 107.0, 113.3, 121.2, 125.5, 128.4, 137.6, 141.9, 155.3, 160.8.

The reported yields correspond to analytically pure compounds. Quinoline derivatives **4b-4d, 10a**, and **11a** gave good results of elemental analysis (C, ±0.2; H, ±0.1; N, ±0.2).

(4) Due to the large difference between mp of our sample of **10a** and that reported for the compound synthesized by an independent cumbersome method (see footnote 3 above), our compound **10a** was subjected to x-ray crystallographic analysis. In crystal, the 2-methoxy group is syn to the quinoline nitrogen atom and anti relative to the 6-methoxy group. The molecule lies on a crystallographic inversion center located midway between C4a and C8a.

(5) The 2-methoxyquinoline **4c** or **4d** was still present after the mixture containing excess fluorine (5 equiv.) was allowed to stand at -20 °C for 24h.

(6) L. German and S. Zemskov, eds., New Fluorinating Agents in Organic Synthesis, Springler-Verlag, Berlin, 1989.

(7) A.S. Kiselyov, L. Strekowski and V.V. Semenov, J. Heterocycl. Chem. *30*, 329 (1993), and references cited therein.

(8) An alternative mechanistic pathway to **10, 11** would involve the intermediacy of radical RO$^\bullet$ that would be formed as follows:

$$ROH \xrightarrow{F_2} ROF \rightleftharpoons RO^\bullet + F^\bullet$$

The radical RO$^\bullet$ would undergo the reaction with cation radical 6 to give adduct 9 directly. We do not favor this alternative because (i) although the formation of methyl hypofluorite MeOF by the reaction of MeOH and XeF_2 has been postulated [D.F. Shellhamer, C.M. Curtis and D.R. Hollingsworth, Tetrahedron Lett. *31*, 2157 (1982)], it has never been shown that this reagent can be generated from MeOH and F_2 and (ii) the postulated reagent MeOF is highly unstable at extremely low temperatures, far below -20 °C used in the synthesis of **10, 11**. By the same token a direct electrophilic alkoxylation of **4, 5** [ROF ↔ RO^+F^-] appears to be unlikely.

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