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A SIMPLE AND EFFICIENT SYNTHETIC METHOD FOR FLUORINE-CONTAINING 7*H*-[1]BENZOTHIOPYRANO[3,2-*h*]-QUINOLINES

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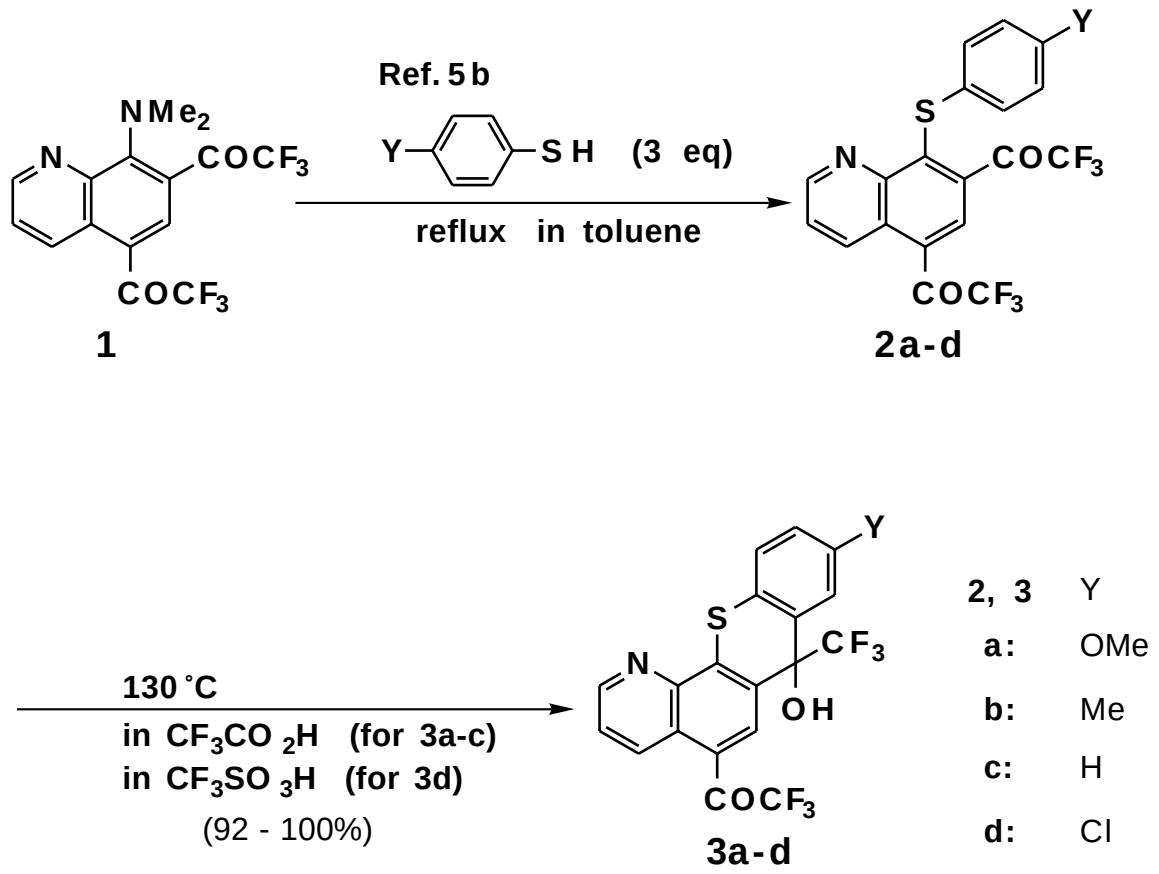
Abstract - Acid-catalyzed cyclization of 8-quinolyl aryl sulfides (**2**), prepared by aromatic nucleophilic nitrogen-sulfur exchange reaction of *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine (**1**) with *p*-substituted benzenethiols, afforded the corresponding fluorine-containing 7*H*-[1]benzothiopyrano[3,2-*h*]quinolines (**3 - 5**) in excellent yields.

Benzothiopyranoquinolines and the related derivatives constitute an important class of heterocyclic compounds because of their interesting pharmacological properties such as antitumor,[1] analgesic,[2] and antiparasitic[3] activities. Besides, much attention in recent years has been paid to the development of new methodologies for the syntheses of many kinds of fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials showing interesting biological activities for their potential use in medicinal and agricultural scientific fields.[4] Recently, we have reported that *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine (**1**) undergoes a novel aromatic nucleophilic substitution with amines, thiols, and alcohols to give the corresponding N-N, N-S and N-O exchanged 5,7-bis(trifluoro-acetyl)-8-quinolylamines, sulfides, and ethers in excellent yields, respectively.[5] Later, we

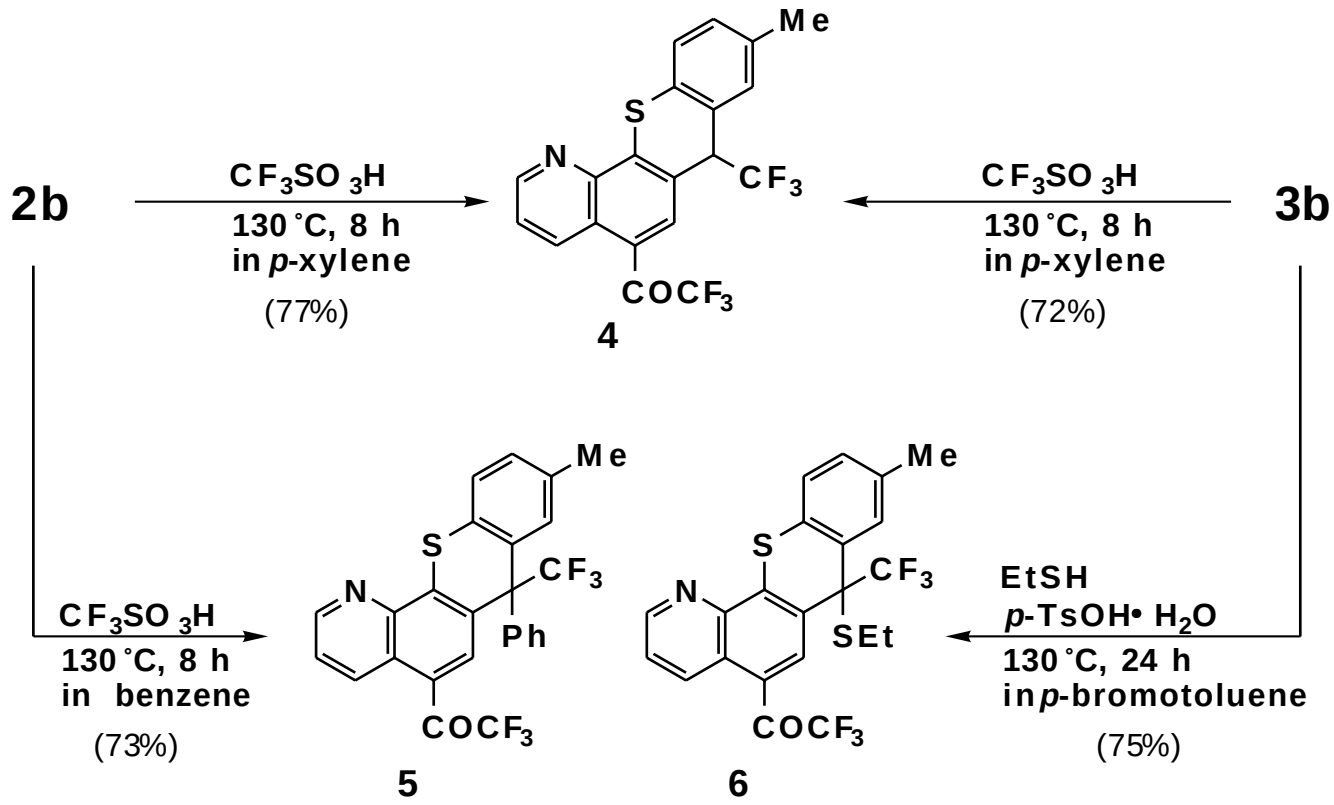
succeeded in applying this type of aromatic nucleophilic substitution to the simple syntheses of various CF_3-containing heterocycles having a quinoline skeleton.[6] In connection with these works, we now wish to report herein the facile synthesis of fluorine-containing 7*H*-[1]benzothiopyrano[3,2-*h*]quinolines (**3** - **6**) starting from trifluoroacetylated *N*,*N*-dimethyl-8-quinolylamine (**1**) and *p*-substituted benzenethiols. 5,7-Bis(trifluoroacetyl)-8-quinolyl aryl sulfides (**2a-d**) were obtained in over 93% yields by aromatic nucleophilic dimethylamino-arylthio exchange reaction of **1** with *p*-substituted benzenethiols in refluxing toluene (Scheme 1).[5b]



Scheme 1

First, we examined the cyclization of **2** to 7*H*-[1]benzothiopyrano[3,2-*h*]quinolines (**3**) with the use of trifluoroacetic acid as an acid catalyst. The desired cyclization of *p*-methoxy derivative (**2a**) proceeded at 130 ˚C for 48 h in trifluoroacetic acid to afford the corresponding 5-trifluoroacetyl-7-trifluoromethyl-7-

hydroxy-9-methoxy-7*H*-[1]benzothiopyrano[3,2-*h*]quinoline (**3a**) in 92% yield. Similarly, 9-methyl and 9-unsubstituted derivatives (**3b**, **c**) were synthesized in excellent yields. In the case of *p*-chloro derivative (**2d**), however, even prolonged heating (96 h) resulted in the formation of **3d** in low yield (46%) with the recovery of **2d** (54%). Then, we tried to change trifluoroacetic acid for trifluoromethanesulfonic acid. Fortunately, the desired 9-chloro derivative (**3d**) was obtained in high yield (95%) and within extremely short time (0.5 h). Interestingly, as depicted in Scheme 2, when the CF_3SO_3H-catalyzed cyclization of **2b**

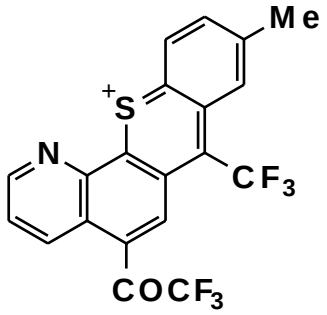


Scheme 2

was carried out with the use of *p*-xylene as a solvent, the *unexpected* reduced product (**4**) was selectively formed in 77% yield without any formation of the *expected* 7-hydroxy derivative (**3b**). Compound (**4**) was also found to be synthesized in 72% yield from **3b** under the same conditions. However, on the reaction of **2b** using benzene instead of *p*-xylene as a solvent, 7-phenyl derivative (**5**) was produced exclusively in 73% yield with the formation of neither **3b** nor **4**.[7]

Furthermore, 7-hydroxy derivative (**3b**) took place the HO-SEt exchange reaction with ethanethiol in the presence of *p*-toluenesulfonic acid to afford 7-ethylthio derivative (**6**) in 75% yield.[8]

A possible mechanism for the formation of benzothiopyranoquinolines (**4 - 6**) is as follows. 7-Hydroxy derivative (**3b**), which is formed by Friedel-Crafts type cyclization of **2b**, undergoes acid-catalyzed dehydration to produce the corresponding thiopyrylium (**7**). The cationic intermediate (**7**) presumably abstracts a hydride ion from the methyl group of *p*-xylene to give reduced form (**4**), on the other hand, **7** undergoes electrophilic attack on benzene ring to afford 7-phenyl derivative (**5**).[9] 7-Ethylthio derivative (**6**) would be certainly formed by the path *via* thiopyrylium (**7**) from **3b**.



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Thus, the present method provides a simple and efficient access to 7*H*-[1]benzothiopyrano[3,2-*h*]quinolines having both trifluoromethyl and trifluoroacetyl groups which are not easily obtained by other methods.

EXPERIMENTAL

All melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO A-302 spectrophotometer. ^{1}H-NMR spectra were obtained with JEOL PMX 60SI instrument using $CDCl_3$ as a solvent unless otherwise indicated. All chemical shifts are reported in ppm downfield from internal tetramethylsilane; coupling constants (J) are given in Hz. Elemental analyses were taken with a Yanaco CHN Corder MT-5 analyzer. Chromatographic separations were carried out on a silica gel column (Fuji Silysia Chemical BW-127ZH; 100-270 mesh). All reagents were obtained commercially and used without further purification. Final purification of all products for elemental analyses was done by recrystallization.

Synthesis of 5-Trifluoroacetyl-7-trifluoromethyl-7-hydroxy-7*H*-[1]benzothiopyrano-[*3,2-h*]quinolines (3a-d); General Procedure:

In CF_3CO_2H : A solution of **2a-c**[5b] (1 mmol) in CF_3CO_2H (4 mL) was placed in an ampoule and heated at 130 ˚C for 48 h. The acid was approximately removed under reduced pressure and EtOAc (50 mL) was added to the residue. This solution was washed with saturated solution of Na_2CO_3 (100 mL) and dried (Na_2SO_4). The solvent was evaporated and the crude product was chromatographed using *n*-

hexane/EtOAc (7:1) for **3b**, *n*-hexane/EtOAc (4:1) for **3c**, and *n*-hexane/EtOAc (3:1) for **3a** as eluent. For the synthesis of **3b**, the reaction time was 24 h.

In CF_3SO_3H : A solution of **2d**[5b] (464 mg, 1 mmol) in CF_3SO_3H (4 mL) was placed in an ampoule and heated at 130 ˚C for 0.5 h. Following work-up was carried out in a similar manner as above and the crude product was chromatographed using *n*-hexane/EtOAc (4:1) as an eluent to afford **3d**.

3a: yield 92%; mp 190-191 ˚C (hexane/EtOAc); IR (KBr) 3425, 1695 cm^{-1}; ^{1}H-NMR ($CD_3CN/CDCl_3$) 9.33 (dd, 1H, J=2, 9, H-4), 9.03-8.96 (m, 2H, H-2, H-6), 7.88-7.44 (m, 3H, H-3, $2H_{arom}$), 7.16-6.97 (m, $1H_{arom}$), 5.64 (br s, 1H, OH), 3.91 (s, 3H, OCH_3). Anal. Calcd for $C_{20}H_{11}NO_3F_6S$: C, 52.29; H, 2.41; N, 3.05. Found: C, 52.30; H, 2.48; N, 2.98.

3b: yield 95%; mp 212-213 ˚C (hexane/EtOAc); IR (KBr) 3395, 1698 cm^{-1}; ^{1}H-NMR ($CD_3CN/CDCl_3$) 9.32 (dd, 1H, J=2, 9, H-4), 9.03-8.93 (m, 2H, H-2, H-6), 7.89-7.16 (m, 4H, H-3, H-8, H-10, H-11), 4.92-3.24 (br, 1H, OH), 2.44 (s, 3H, CH_3). Anal. Calcd for $C_{20}H_{11}NO_2F_6S$: C, 54.18; H, 2.50; N, 3.16. Found: C, 54.11; H, 2.62; N, 3.11.

3c: yield 100%; mp 206-207 ˚C (hexane/EtOAc); IR (KBr) 3490, 1690 cm^{-1}; ^{1}H-NMR 9.28 (dd, 1H, J=2, 9, H-4), 9.01-8.91 (m, 2H, H-2, H-6), 8.20-7.90 (m, $1H_{arom}$), 7.84-7.28 (m, 4H, H-3, $3H_{arom}$), 5.29-3.77 (br, 1H, OH). Anal. Calcd for $C_{19}H_9NO_2F_6S$: C, 53.15; H, 2.11; N, 3.26. Found: C, 53.26; H, 2.17; N, 3.32.

3d: yield 95%; mp 188-189 ˚C (hexane/EtOAc); IR (KBr) 3500, 1700 cm^{-1}; ^{1}H-NMR ($CD_3CN/CDCl_3$) 9.27 (dd, 1H, J=2, 9, H-4), 9.00-8.90 (m, 2H, H-2, H-6), 8.18-7.25 (m, 4H, H-3, H-8, H-10, H-11), 5.92-4.96 (br, 1H, OH). Anal. Calcd for $C_{19}H_8NO_2ClF_6S$: C, 49.21; H, 1.74; N, 3.02. Found: C, 49.20; H, 2.03; N, 2.92.

Synthesis of 5-Trifluoroacetyl-7-trifluoromethyl-9-methyl-7*H*-[1]benzothiopyrano-[3,2-h]quinoline (4); General Procedure:

To a solution of **2b** or **3b** (1 mmol) in *p*-xylene (4 mL) was added CF_3SO_3H (300 mg, 2 mmol) and the mixture was stirred at 130 ˚C for 8 h. After removal of the solvent under reduced pressure EtOAc (50 mL)

was added to the residue. This solution was washed with saturated solution of Na_2CO_3 (100 mL) and dried (Na_2SO_4). The solvent was evaporated and the crude product was chromatographed using *n*-hexane/EtOAc (30:1) as an eluent to afford **4**.

4: yield 77% (from **2b**), 72% (from **3b**); mp 173-174 ˚C (hexane/EtOAc); IR (KBr) 1690 cm^{-1}; ^{1}H-NMR 9.20 (dd, 1H, J=2, 9, H-4), 8.89 (dd, 1H, J=2, 4, H-2), 8.11 (br s, 1H, H-6), 7.66-6.96 (m, 4H, H-3, H-8, H-10, H-11), 4.93 (q, 1H, J_{HF}=9, H-7), 2.36 (s, 3H, CH_3). Anal. Calcd for $C_{20}H_{11}NOF_6S$: C, 56.21; H, 2.59; N, 3.28. Found: C, 55.94; H, 2.87; N, 3.18.

Synthesis of 5-Trifluoroacetyl-7-trifluoromethyl-9-methyl-7-phenyl-7*H*-[1]benzothio-pyrano[3,2-*h*]quinoline (5): A mixture of **2b** (443 mg, 1 mmol), CF_3SO_3H (300 mg, 2 mmol), and benzene (4 mL) was placed in an ampoule and heated at 130 ˚C for 8 h. After removal of the solvent under reduced pressure EtOAc (50 mL) was added to the residue. This solution was washed with saturated solution of Na_2CO_3 (100 mL) and dried (Na_2SO_4). The solvent was evaporated and the crude product was chromatographed using *n*-hexane/EtOAc (30:1) as an eluent to afford **5** (368 mg, 73%) (mixture of two stereoisomers): mp 71-72 ˚C (hexane); IR (KBr) 1691 cm^{-1}; ^{1}H-NMR 9.36 (dd, 1H, J=2, 9, H-4), 9.04 (dd, 1H, J=2, 4, H-2), 7.79-6.83 (m, 10H, H-3, H-6, H-8, H-10, H-11, Ph), 2.36 (s, 1.5H, CH_3), 2.21 (s, 1.5H, CH_3). Anal. Calcd for $C_{26}H_{15}NOF_6S$: C, 62.03; H, 3.00; N, 2.78. Found: C, 61.84; H, 3.32; N, 2.65.

Synthesis of 7-Ethylthio-5-trifluoroacetyl-7-trifluoromethyl-9-methyl-7*H*-[1]benzothio-pyrano[3,2-*h*]quinoline (6): A mixture of **3b** (443 mg, 1 mmol), ethanethiol (75 mg, 1.2 mmol), *p*-TsOH・H_2O (228 mg, 1.2 mmol), and *p*-bromotoluene (8 mL) was placed in an ampoule and heated at 130 ˚C for 24 h. After removal of the solvent under reduced pressure EtOAc (50 mL) was added to the residue. This solution was washed with saturated solution of Na_2CO_3 (100 mL) and dried (Na_2SO_4). The solvent was evaporated and the crude product was chromatographed using *n*-hexane/EtOAc (15:1) as an eluent to afford **6** (366 mg, 75%): mp 189-190 ˚C (hexane); IR (KBr) 1690 cm^{-1}; ^{1}H-NMR 9.62-9.33 (m, 2H, H-4, $1H_{arom}$), 9.02 (dd, 1H, J=2, 4, H-2), 8.32 (br s, 1H, H-6), 7.72 (dd, 1H, J=4, 9, H-3), 7.49-7.30 (m, $2H_{arom}$), 2.47 (s, 3H, CH_3), 2.26 (q, 2H, J=7, $C\underline{H}_2CH_3$), 1.10 (t, 3H, J=7, $CH_2C\underline{H}_3$). Anal. Calcd for

$C_{22}H_{15}NOF_6S_2$: C, 54.21; H, 3.10; N, 2.87. Found: C, 54.42; H, 3.24; N, 2.52.

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7. When toluene was used as a solvent instead of benzene and *p*-xylene [at 130 ˚C for 8 h in the presence of CF_3SO_3H (2 eq)], both reduced product (**4**) and 7-(*p*-tolyl) derivative (**5**: *p*-tolyl in place of Ph) were produced in 11% and 70% yields, respectively.
8. In order to obtain 7-ethylthio derivative (**6**) exclusively, *p*-bromotoluene was superior to toluene as a solvent. For example, the reaction of **3b** with ethanethiol (1.2 eq) in toluene at 130˚C for 24 h in the presence of *p*-TsOH・H_2O (1.2 eq) gave **6** in 61% yield with 20% yield of reduced product (**4**) as a by-product.
9. Although *p*-xylene has higher electron density of the aromatic ring than benzene and toluene, it may not act as a nucleophile, but as a hydrogen donor in the present reaction. This seems to be attributed to the steric hindrance of the methyl substituent.[7]