

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

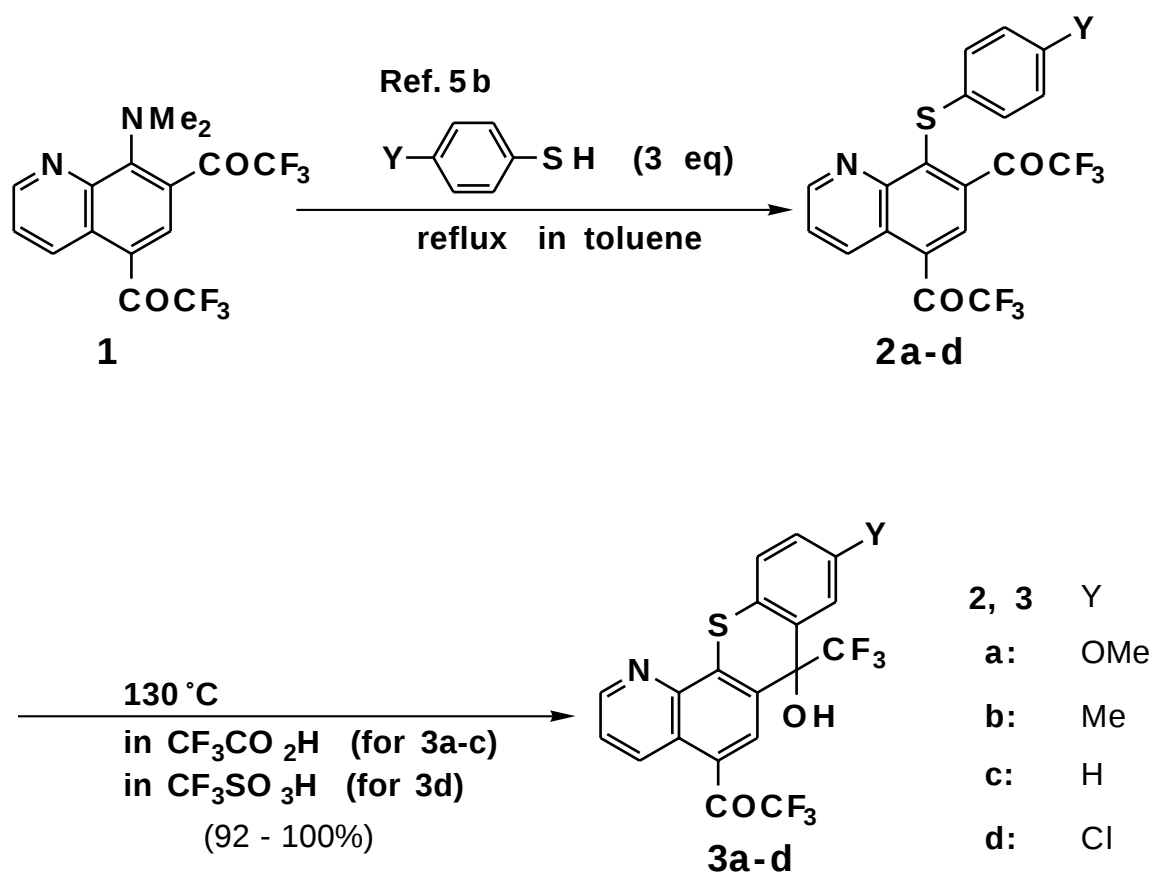
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**Abstract** - Acid-catalyzed cyclization of 8-quinolyl aryl sulfides (**2**), prepared by aromatic nucleophilic nitrogen-sulfur exchange reaction of *N,N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine (**1**) with *p*-substituted benzenethiols, afforded the corresponding fluorine-containing 7H-[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,<sup>1</sup> analgesic,<sup>2</sup> and antiparasitic<sup>3</sup> 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.<sup>4</sup> 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(trifluoroacetyl)-8-quinolylamines, sulfides, and ethers in excellent yields, respectively.<sup>5</sup> Later, we

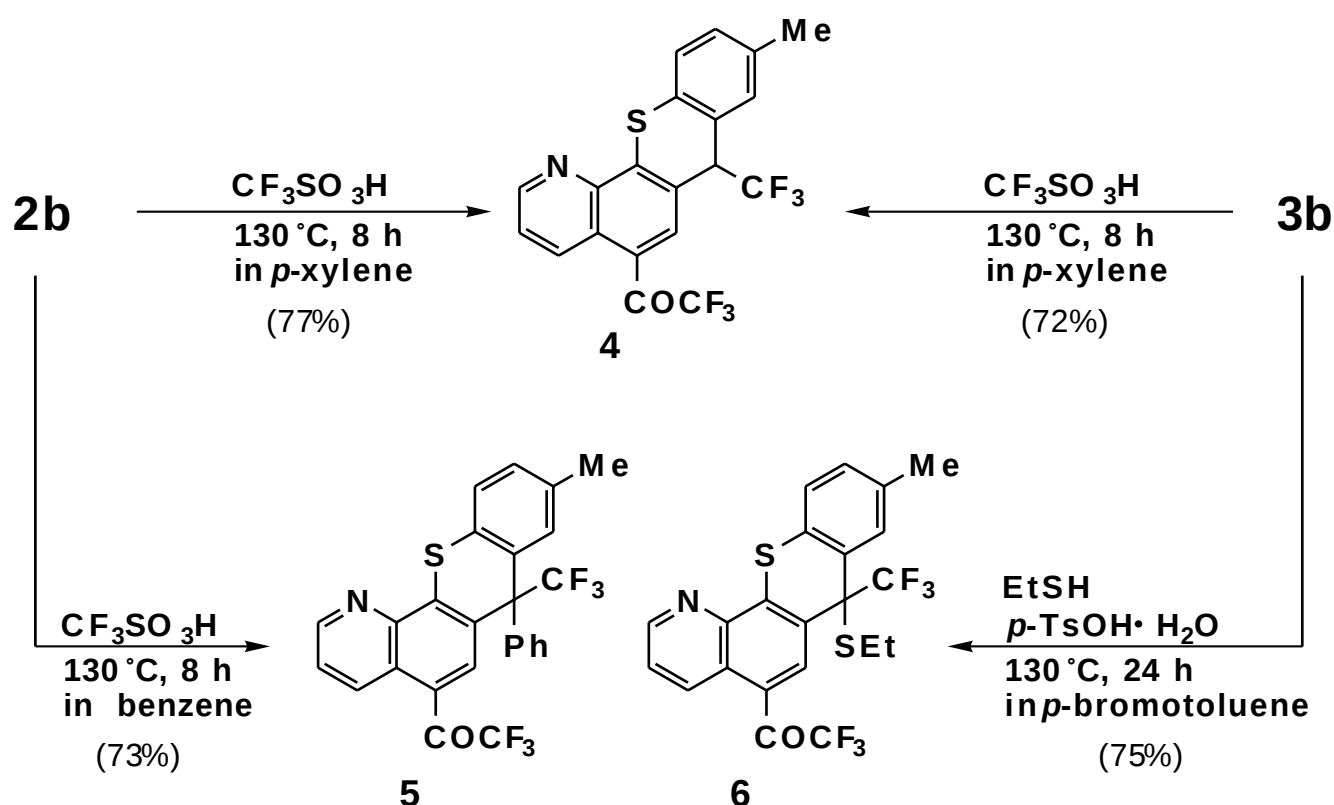
succeeded in applying this type of aromatic nucleophilic substitution to the simple syntheses of various CF<sub>3</sub>-containing heterocycles having a quinoline skeleton.<sup>6</sup> In connection with these works, we now wish to report herein the facile synthesis of fluorine-containing 7*H*-[1]benzothiopyrano[3,2-*h*]quinolines (**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).<sup>5b</sup>



**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<sub>3</sub>SO<sub>3</sub>H-catalyzed cyclization of **2b**

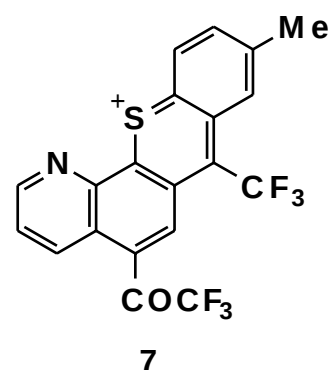


**Scheme 2**

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**.<sup>7</sup>

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.<sup>8</sup>

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**).<sup>9</sup> 7-Ethylthio derivative (**6**) would be certainly formed by the path *via* thiopyrylium (**7**) from **3b**.



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. <sup>1</sup>H-NMR spectra were obtained with JEOL PMX 60SI instrument using CDCl<sub>3</sub> 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<sub>3</sub>CO<sub>2</sub>H :** A solution of **2a-c**<sup>5b</sup> (1 mmol) in CF<sub>3</sub>CO<sub>2</sub>H (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<sub>2</sub>CO<sub>3</sub> (100 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). 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<sub>3</sub>SO<sub>3</sub>H** : A solution of **2d**<sup>5b</sup> (464 mg, 1 mmol) in CF<sub>3</sub>SO<sub>3</sub>H (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<sup>-1</sup>; <sup>1</sup>H-NMR (CD<sub>3</sub>CN/CDCl<sub>3</sub>) 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<sub>arom</sub>), 7.16-6.97 (m, 1H<sub>arom</sub>), 5.64 (br s, 1H, OH), 3.91 (s, 3H, OCH<sub>3</sub>). Anal. Calcd for C<sub>20</sub>H<sub>11</sub>NO<sub>3</sub>F<sub>6</sub>S: 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<sup>-1</sup>; <sup>1</sup>H-NMR (CD<sub>3</sub>CN/CDCl<sub>3</sub>) 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<sub>3</sub>). Anal. Calcd for C<sub>20</sub>H<sub>11</sub>NO<sub>2</sub>F<sub>6</sub>S: 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<sup>-1</sup>; <sup>1</sup>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<sub>arom</sub>), 7.84-7.28 (m, 4H, H-3, 3H<sub>arom</sub>), 5.29-3.77 (br, 1H, OH). Anal. Calcd for C<sub>19</sub>H<sub>9</sub>NO<sub>2</sub>F<sub>6</sub>S: 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<sup>-1</sup>; <sup>1</sup>H-NMR (CD<sub>3</sub>CN/CDCl<sub>3</sub>) 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<sub>19</sub>H<sub>8</sub>NO<sub>2</sub>ClF<sub>6</sub>S: 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-7H-[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<sub>3</sub>SO<sub>3</sub>H (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<sub>2</sub>CO<sub>3</sub> (100 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). 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<sup>-1</sup>; <sup>1</sup>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<sub>HF</sub>=9, H-7), 2.36 (s, 3H, CH<sub>3</sub>). Anal. Calcd for C<sub>20</sub>H<sub>11</sub>NOF<sub>6</sub>S: 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-7H-[1]benzothio-pyrano[3,2-*h*]quinoline (5):** A mixture of **2b** (443 mg, 1 mmol), CF<sub>3</sub>SO<sub>3</sub>H (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<sub>2</sub>CO<sub>3</sub> (100 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). 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<sup>-1</sup>; <sup>1</sup>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<sub>3</sub>), 2.21 (s, 1.5H, CH<sub>3</sub>). Anal. Calcd for C<sub>26</sub>H<sub>15</sub>NOF<sub>6</sub>S: 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-7H-[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<sub>2</sub>O (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<sub>2</sub>CO<sub>3</sub> (100 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). 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<sup>-1</sup>; <sup>1</sup>H-NMR 9.62-9.33 (m, 2H, H-4, 1H<sub>arom</sub>), 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<sub>arom</sub>), 2.47 (s, 3H, CH<sub>3</sub>), 2.26 (q, 2H, J=7, CH<sub>2</sub>CH<sub>3</sub>), 1.10 (t, 3H, J=7, CH<sub>2</sub>CH<sub>3</sub>). Anal. Calcd for

C<sub>22</sub>H<sub>15</sub>NOF<sub>6</sub>S<sub>2</sub>: 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<sub>3</sub>SO<sub>3</sub>H (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<sub>2</sub>O (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.<sup>7</sup>