Aromatic Nucleophilic N-N, N-S and N-O Exchange Reactions: Efficient Synthesis of 5,7-Bis(trifluoroacetyl)-8-quinolylamines, Sulfides and Ethers

Etsuji Okada,* Norikado Tsukushi, Naofumi Shimomura

Department of Chemical Science and Engineering, Faculty of Engineering, Kobe University, Rokkodai-cho, Nada-ku, Kobe, 657-8501, Japan

Fax +81(78)8036206; E-mail: okada@appchem.chme.kobe-u.ac.jp

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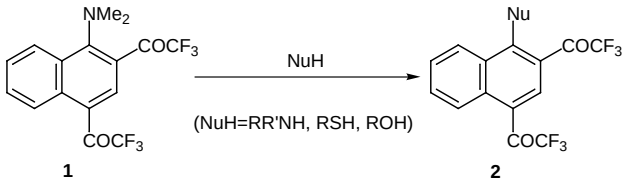
Abstract: Various 5,7-bis(trifluoroacetyl)-8-quinolylamines, sulfides and ethers were synthesized in excellent yields by aromatic nucleophilic N-N, N-S and N-O exchange reactions of *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine with amines, thiols and alcohols. Base-catalyzed cyclization of the resulting benzyl 8-quinolyl sulfide and subsequent dehydration gave fluorine-containing thieno[3,2-*h*]quinolines in high yields.

Key words: nucleophilic aromatic substitutions, fluorine compounds, quinolylamines, quinolyl sulfides, quinolyl ethers

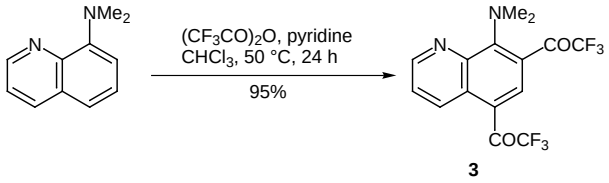
Activated aromatic compounds bearing good leaving groups such as halo-, alkoxy-, etc., are well known to undergo aromatic nucleophilic substitution with various nucleophiles.[1] However, amino groups attached to aromatic rings are seldom replaced by nucleophiles. Previously, we have found that *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**1**) reacts easily with various amines, thiols and alcohols under mild conditions to afford the corresponding N-N, N-S and N-O exchanged 2,4-bis(trifluoroacetyl)-1-naphthylamines, sulfides and ethers **2** in excellent yields, respectively (Scheme 1).[2] Up-to-lately we succeeded in extending the present S_NAr reaction to the less reactive *N*,*N*-dimethyl-2-trifluoroacetyl-4-halo-1-naphthylamines.[3] In recent years, considerable attention 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] Besides, quinolines are important heterocyclic systems, constituting the structure of many naturally occurring products and having interesting pharmacological properties as antimicrobial agents and antitumor drugs.[5]



Scheme 1

In this situation, we have very recently reported that *N*,*N*-dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine (**3**) undergoes a novel aromatic nucleophilic substitution with amines to give the corresponding 5,7-bis(trifluoroacetyl)-8-quinolylamines.[6] Herein, we report a full account of our systematic studies on this type of aromatic nucleophilic substitution including the new finding of the reactions of **3** with various thiols and alcohols, which are considerably less reactive than amines. Furthermore, we also present its application to the synthesis of fluorine-containing 2,3-dihydrothieno[3,2-*h*]quinoline **7** and thieno[3,2-*h*]quinoline **8**, which are greatly expected to show antibacterial,[7] antitumor[8] and antianaphylactic activities.[9]

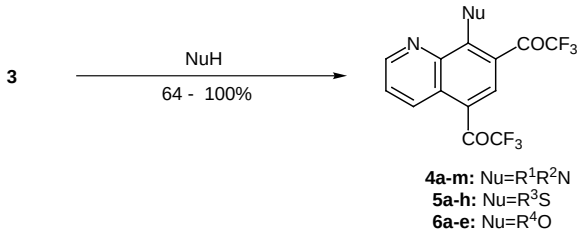
Starting material **3** was very easily prepared in 95% yield through the reaction of *N*,*N*-dimethyl-8-quinolylamine with trifluoroacetic anhydride in the presence of pyridine at 50 °C for 24 hours according to our method (Scheme 2).[10]



Scheme 2

First, we examined the reaction of **3** with various amines (Scheme 3, Table 1). Reactions of **3** with ammonia and aliphatic primary amines such as methyl-, ethyl-, benzyl- and *i*-propylamines took place very easily at room temperature within 1 hour to afford the desired 8-quinolylamine derivatives **4a**-**e** quantitatively (entries 1−5). Bulky *t*-butylamine also reacted cleanly to provide **4f** by merely elevating the reaction temperature (50 °C) and extending the reaction time (72 hours) (entry 6). The more functionalized *N*-allyl-8-quinolylamine derivative **4g** was easily synthesized in almost quantitative yield from **3** and allylamine (entry 7). In the case of propargylamine, for the sake of avoiding the formation of decomposed products, the reaction was performed at 0 °C to obtain the desired product **4h** cleanly (entry 8). While secondary amines showed lower reactivity than primary ones in the present reaction, pyrrolidine revealed considerable enhanced reactivity to afford **4i** in 100% yield (entry 9). Aromatic

amines such as *p*-substituted anilines underwent cleanly the desired dimethylamino-arylamino exchanges under slightly forced conditions to give the corresponding *N*-aryl-8-quinolylamine derivatives **4j-m** in over 82% yields (entries 10−13).



Scheme 3

Next, we attempted to carry out the N-S exchange reactions of **3** with various thiols (Table 2). Reactions of **3** with aliphatic thiols such as *n*-butanethiol, *n*-hexanethiol and benzyl mercaptan took place in refluxing acetonitrile within 24 hours to afford the desired alkyl 8-quinolyl sulfides **5b-d** quantitatively (entries 2−4). In the case of low boiling *n*-propanethiol, the reaction was performed with large amounts of reagent (20 equivalents), at a lower temperature (60 °C) and for an extended time (96 hours) to provide cleanly **5a** in 81% yield (entry 1). Aromatic thiols such as *p*-substituted benzenethiols also underwent easily the dimethylamino-arylthio exchanges under relatively mild conditions to give the corresponding aryl 8-quinolyl sulfides **5e-h** in over 93% yields (entries 5−8).

Further, the present aromatic nucleophilic substitutions were applied to alcohols (Table 3). In spite of the fairly low reactivities of alcohols, compared with the corresponding amines and thiols, the N-O exchange reaction of **3** with them, e.g. *n*-butyl, phenethyl and 2-phenoxyethyl alcohols, proceeded cleanly without the aid of base at reflux temperature in toluene to provide the corresponding 5,7-bis(trifluoroacetyl)-8-quinolylethers **6b**, **d**, **e** in high yields (entries 2, 4 and 5). In the cases of *n*-propyl and *i*-butyl alcohols, however, the desired N-O exchange reactions could barely proceed in refluxing toluene.[11] The at-

Table 1 Reaction of *N*,*N*-Dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine **3** with Amines

Entry	R^1R^2NH	Equiv	Temp. / °C	Time / h	Solvent	Product	Yield / %[a]
1	NH_3[b]	1	r.t.	0.5	MeCN	**4a**	100
2	$MeNH_2$[c]	1	r.t.	0.5	MeCN	**4b**	100
3	$EtNH_2$[d]	1	r.t.	1	MeCN	**4c**	100
4	$PhCH_2NH_2$	1	r.t.	0.5	MeCN	**4d**	100
5	*i*-$PrNH_2$	1	r.t.	1	MeCN	**4e**	100
6	*t*-$BuNH_2$	3	50	72	MeCN	**4f**	100
7	$CH_2{=}CHCH_2NH_2$	1	r.t.	1	MeCN	**4g**	98
8	$CH{\equiv}CCH_2NH_2$	1	0	2	MeCN	**4h**	100
9		1	r.t.	2	MeCN	**4i**	100
10	*p*-$MeOC_6H_4NH_2$	1	reflux	3	MeCN	**4j**	100
11	$C_6H_5NH_2$	1	reflux	12	MeCN	**4k**	100
12	*p*-$ClC_6H_4NH_2$	1	reflux	24	MeCN	**4l**	94
13	*p*-$NO_2C_6H_4NH_2$	5	reflux	96	PrCN	**4m**	82

[a]Isolated yields.
[b]Aq solution (28%) of ammonia was used.
[c]Aq solution (40%) of methylamine was used.
[d]Aq solution (70%) of ethylamine was used.

Table 2 Reaction of *N*,*N*-Dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine **3** with Thiols

Entry	R^3SH	Equiv	Temp. / °C	Time / h	Solvent	Product	Yield / %[a]
1	*n*-PrSH	20	60	96	MeCN	**5a**	81
2	*n*-BuSH	5	reflux	24	MeCN	**5b**	100
3	*n*-$C_6H_{13}SH$	5	reflux	24	MeCN	**5c**	100
4	$PhCH_2SH$	5	reflux	8	MeCN	**5d**	100
5	*p*-$MeOC_6H_4SH$	3	reflux	4	Toluene	**5e**	96
6	*p*-MeC_6H_4SH	3	reflux	4	Toluene	**5f**	98
7	PhSH	3	reflux	48	Toluene	**5g**	93
8	*p*-ClC_6H_4SH	3	reflux	8	Toluene	**5h**	95

[a]Isolated yields.

Table 3 Reaction of *N*,*N*-Dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine **3** with Alcohols[a]

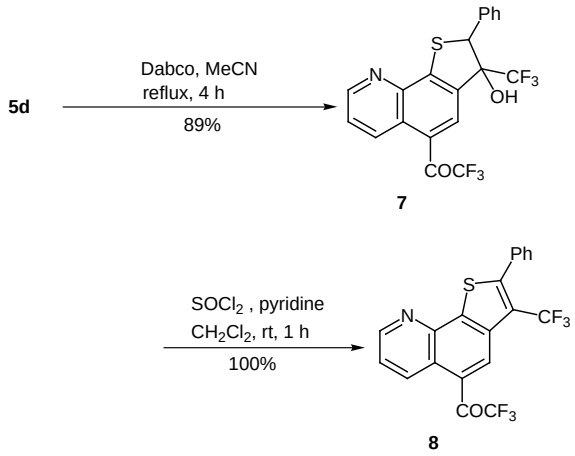
Entry	R^4OH	Equiv	Time / h	Solvent	Product	Yield / %[b]
1	*n*-PrOH	54	240	*n*-PrOH	**6a**	64
2	*n*-BuOH	10	168	Toluene	**6b**	81
3	*i*-BuOH	43	240	*i*-BuOH	**6c**	82
4	$PhCH_2CH_2OH$	10	96	Toluene	**6d**	71
5	$PhOCH_2CH_2OH$	20	168	Toluene	**6e**	77

[a] The reaction was carried out under reflux.
[b] Isolated yields.

tempted alcoholysis of **3** under reflux was successful and the desired ethers **6a**,**c** were prepared in 64−82% yields (entries 1 and 3). Either of the 5- or 7-trifluoroacetyl group of compounds (**5a-c** and **6b-d**) was found to exist as the hydrate form. It is of interest that the present N-O exchange reaction proceeded faster in less polar toluene than in butyronitrile. For instance, compound **3** was allowed to react with 5 equivalents of *n*-butyl alcohol at 110 °C for 48 hours and the following result was obtained: solvent/% conversion to **6b**; toluene / 49; butyronitrile / 30. These results were in a striking contrast to those obtained in the cases of dimethylamino-alkylthio exchange reactions in the present quinoline system.[12]

Moreover, we examined the differences in reactivities between the naphthalene system **1** and the quinoline one **3** in the present S_NAr reaction. Interestingly, in N-O exchange reaction naphthylamine **1** exhibited much higher reactivities than quinolylamine **3**,[13] in direct opposition to the cases of N-N[14] and N-S[15] exchanges.

Lastly, we set about the application of this type of aromatic nucleophilic substitution to the syntheses of fluorine-containing heterocycles having the quinoline skeleton. For example, as depicted in Scheme 4, base-catalyzed cyclization of benzyl 8-quinolyl sulfide **5d** with 1,4-diazabicyclo[2.2.2]octane (Dabco) proceeded in refluxing acetonitrile for 4 hours to yield 2,3-dihydrothieno[3,2-*h*]quinoline **7**, which was effectively converted into fluorine-containing thieno[3,2-*h*]quinoline **8** by formal dehydration (HO-Cl exchange and subsequent dehydrochlorination) with the use of thionyl chloride in the presence of pyridine.



Scheme 4

Thus, we succeeded in extending the novel aromatic nucleophilic substitutions of **3** with amines to those with thiols and alcohols and in providing an efficient synthetic method for various 5,7-bis(trifluoro-acetyl)-8-quinolylamines, sulfides and ethers, which are not easily accessible by other methods.[16] Further work is currently being continued in our laboratory.

Mps were determined on an electrothermal digital melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi EPI-G3 spectrophotometer. ^1H NMR spectra was obtained with a JEOL PMX 60SI instrument. Microanalyses 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). Reagents were obtained commercially and used without further purification except for *N*,*N*-dimethyl-8-quinolylamine, which was prepared from 8-quinolylamine and trimethylphosphate according to literature procedure.[17] Final purification of all products for microanalyses was done by recrystallization.

***N*,*N*-Dimethyl-5,7-bis(trifluoroacetyl)-8-quinolylamine (3)**
To a stirred solution of *N*,*N*-dimethyl-8-quinolylamine (1.72 g, 10 mmol) and pyridine (1.98 g, 25 mmol) in $CHCl_3$ (10 mL) was added dropwise trifluoroacetic anhydride (5.25 g, 25 mmol) with cooling, and stirring was continued at 50 °C for 24 h. The solvent was removed under reduced pressure, and EtOAc (100 mL) was added to the residue. The solution was washed with sat. Na_2CO_3 (200 mL), with 1N HCl (200 mL), thoroughly with H_2O (200 mL), and then dried (Na_2SO_4). The solvent was evaporated in vacuo and the crude product was chromatographed using *n*-hexane:EtOAc, 3:1 as eluent to give **3**; yield: 3.46 g (95%).

N-N Exchange Reaction of 3 with Amines; General Procedures
To a solution of **3** (1.10 g, 3 mmol) in MeCN (21 mL) were added the appropriate amines (3−15 mmol) and the mixture was stirred at 0 °C−reflux temperature for 0.5−96 h. The solvent was evaporated in vacuo to give the practically pure products **4a-l**. In the case of **4m**, PrCN was used as a solvent, and separation and purification were carried out by recrystallization from *n*-hexane/EtOAc (see Table 1).

N-S Exchange Reaction of 3 with Thiols; General Procedures
To a solution of **3** (1.10 g, 3 mmol) in MeCN (12 mL) were added the appropriate thiols (9−60 mmol) and the mixture was stirred at 60 °C−reflux temperature for 4−96 h. The solvent was evaporated in vacuo and the crude product was chromatographed using *n*-hex-

Table 4 Physical and Spectral Data of Compounds **3–8**

Compound	Mp (°C) (Solvent)	Molecular Formula[a]	IR (KBr) υ (cm^{-1})	^1H NMR ($CDCl_3$/TMS) *J* (Hz)
3	145–146 (*n*-C_6H_{14}/EtOAc)	$C_{15}H_{10}F_6N_2O_2$ (364.2)	1687, 1663	3.49 (s, 6 H, CH_3), 7.54 (dd, 1 H, *J* = 4, 9, H-3), 8.60 (br s, 1 H, H-6), 8.78 (dd, 1 H, *J* = 2, 4, H-2), 9.38 (dd, 1 H, *J* = 2, 9, H-4)
4a	172–173 (*n*-C_6H_{14}/EtOAc)	$C_{13}H_6F_6N_2O_2$ (336.2)	3410, 3295, 1651	7.74 (dd, 1 H, *J* = 4, 9, H-3), 8.73 (br s, 1 H, H-6), 8.86 (dd, 1 H, *J* = 2, 4, H-2), 9.51 (dd, 1 H, *J* = 2, 9, H-4), 7.55–10.20 (br, 2 H, NH_2)
4b	175–176 (*n*-C_6H_{14}/EtOAc)	$C_{14}H_8F_6N_2O_2$ (350.2)	3125, 1675, 1633	3.21–4.23 (br, 3 H, CH_3), 7.70 (dd, 1 H, *J* = 4, 9, H-3), 8.68 (br s, 1 H, H-6), 8.89 (dd, 1 H, *J* = 2, 4, H-2), 9.51 (dd, 1 H, *J* = 2, 9, H-4), 10.07–11.79 (br, 1 H, NH)[b]
4c	120–121 (*n*-C_6H_{14})	$C_{15}H_{10}F_6N_2O_2$ (364.2)	3100, 1681, 1636	1.45 (t, 3 H, *J* = 7, CH_3), 3.64–5.06 (br, 2 H, CH_2), 7.66 (dd, 1 H, *J* = 4, 9, H-3), 8.70 (br s, 1 H, H-6), 8.85 (dd, 1 H, *J* = 2, 4, H-2), 9.51 (dd, 1 H, *J* = 2, 9, H-4), 10.19–11.67 (br, 1 H, NH)
4d	147–148 (*n*-C_6H_{14}/EtOAc)	$C_{20}H_{12}F_6N_2O_2$ (426.3)	3045, 1677, 1638	5.06–5.82 (br, 2 H, CH_2), 7.41 (s, 5 H, Ph), 7.63 (dd, 1 H, *J* = 4, 9, H-3), 8.69 (br s, 1 H, H-6), 8.84 (dd, 1 H, *J* = 2, 4, H-2), 9.50 (dd, 1 H, *J* = 2, 9, H-4), 10.63–11.66 (br, 1 H, NH)
4e	119–120 (*n*-C_6H_{14})	$C_{16}H_{12}F_6N_2O_2$ (378.3)	3095, 1684, 1638	1.45 (d, 6 H, *J* = 6, CH_3), 5.34–6.10 (br, 1 H, CH), 7.60 (dd, 1 H, *J* = 4, 9, H-3), 8.65 (br s, 1 H, H-6), 8.81 (dd, 1 H, *J* = 2, 4, H-2), 9.47 (dd, 1 H, *J* = 2, 9, H-4), 10.75–11.46 (br, 1 H, NH)
4f	140–141 (*n*-C_6H_{14})	$C_{17}H_{14}F_6N_2O_2$ (392.3)	3060, 1683, 1642	1.71 (s, 9 H, CH_3), 7.61 (dd, 1 H, *J* = 4, 9, H-3), 8.68 (br s, 1 H, H-6), 8.87 (dd, 1 H, *J* = 2, 4, H-2), 9.47 (dd, 1H, *J* = 2, 9, H-4), 11.27–11.83 (br, 1 H, NH)
4g	96–97 (*n*-C_6H_{14})	$C_{16}H_{10}F_6N_2O_2$ (376.3)	3090, 1686, 1643	4.13–6.43 (m, 5 H, $CH_2CH{=}CH_2$), 7.57 (dd, 1 H, *J* = 4, 9, H-3), 8.55 (br s, 1 H, H-6), 8.76 (dd, 1H, *J* = 2, 4, H-2), 9.36 (dd, 1 H, *J* = 2, 9, H-4), 10.07–11.77 (br, 1 H, NH)
4h	111 (dec) (*n*-C_6H_{14}/EtOAc)	$C_{16}H_8F_6N_2O_2$ (374.2)	3250, 3115, 1683, 1642	2.40 (t, 1 H, *J* = 2, CH), 4.92–5.37 (m, 2 H, CH_2), 7.69 (dd, 1 H, *J* = 4, 9, H-3), 8.73 (br s, 1 H, H-6), 8.88 (dd, 1 H, *J* = 2, 4, H-2), 9.54 (dd, 1 H, *J* = 2, 9, H-4), 10.42–10.82 (br, 1 H, NH)
4i	157–158 (*n*-C_6H_{14}/EtOAc)	$C_{17}H_{12}F_6N_2O_2$ (390.3)	1653	1.84–2.25 (m, 4 H, CH_2), 3.70–4.09 (m, 4 H, CH_2), 7.48 (dd, 1 H, *J* = 4, 9, H-3), 8.60–8.75 (m, 2 H, H-2, H-6), 9.30 (dd, 1 H, *J* = 2, 9, H-4)
4j	176–177 (*n*-C_6H_{14}/EtOAc)	$C_{20}H_{12}F_6N_2O_3$ (442.3)	3250, 1683	3.82 (s, 3H, OCH_3), 6.80–7.29 (m, 4 H_{arom}), 7.67 (dd, 1 H, *J* = 4, 9, H-3), 8.64 (br s, 1 H, H-6), 8.73 (dd, 1 H, *J* = 2, 4, H-2), 9.52 (dd, 1 H, *J* = 2, 9, H-4), 10.47–10.79 (br, 1 H, NH)
4k	192–193 (*n*-C_6H_{14}/EtOAc)	$C_{19}H_{10}F_6N_2O_2$ (412.3)	3270, 1683	7.03–7.51 (m, 5 H, Ph), 7.70 (dd, 1 H, *J* = 4, 9, H-3), 8.61 (br s, 1 H, H-6), 8.74 (dd, 1 H, *J* = 2, 4, H-2), 9.48 (dd, 1 H, *J* = 2, 9, H-4), 10.44–10.90 (br, 1 H, NH)
4l	184–185 (*n*-C_6H_{14}/EtOAc)	$C_{19}H_9ClF_6N_2O_2$ (446.7)	3235, 1687	6.96–7.44 (m, 4 H_{arom}), 7.67 (dd, 1 H, *J* = 4, 9, H-3), 8.60–8.75 (m, 2 H, H-2, H-6), 9.47 (dd, 1 H, *J* = 2, 9, H-4), 10.72–11.22 (br , 1 H, NH)
4m	201–202 (*n*-C_6H_{14}/EtOAc)	$C_{19}H_9F_6N_3O_4$ (457.3)	3170, 1685, 1502, 1340	7.27 (d, 2 H, *J* = 9, 2 H_{arom}), 7.79 (dd, 1 H, *J* = 4, 9, H-3), 8.21 (d, 2 H, *J* = 9, 2 H_{arom}), 8.65–8.89 (m, 2 H, H-2, H-6), 9.46 (dd, 1 H, *J* = 2, 9, H-4), 10.56–11.02 (br, 1 H, NH)[b]
5a	116–117 (*n*-C_6H_{14}/EtOAc)	$C_{16}H_{13}F_6NO_3S$[c] (413.3)	3350, 1736	0.78–1.83 (m, 5 H, CH_2CH_3), 3.11–3.52 (m, 2 H, SCH_2), 4.95–6.59 (br, 2 H, OH), 7.45–8.16 (m, 2 H, H-3, H-6), 9.00–9.43 (m, 2 H, H-2, H-4)[b]
5b	116–117 (*n*-C_6H_{14}/EtOAc)	$C_{17}H_{15}F_6NO_3S$[c] (427.4)	3310, 1744	0.70–1.84 [m, 7 H, $(CH_2)_2CH_3$], 1.86–6.33 (br, 2 H, OH), 3.16-3.56 (m, 2 H, SCH_2), 7.45-8.22 (m, 2H, H-3, H-6), 9.04–9.43 (m, 2 H, H-2, H-4)[b]
5c	96–97 (*n*-C_6H_{14}/EtOAc)	$C_{19}H_{19}F_6NO_3S$[c] (455.4)	3360, 1743	0.50–1.91 [m, 11 H, $(CH_2)_4CH_3$], 3.13–3.55 (m, 2 H, SCH_2), 5.25–6.48 (br, 2 H, OH), 7.45–8.20 (m, 2 H, H-3, H-6), 8.99–9.38 (m, 2 H, H-2, H-4)[b]
5d	124–125 (*n*-C_6H_{14}/EtOAc)	$C_{20}H_{11}F_6NO_2S$ (443.4)	1694	4.58 (s, 2 H, CH_2), 7.12 (s, 5 H, Ph), 7.57–7.85 (m, 1 H, H-3), 8.09 (br s, 1 H, H-6), 9.09–9.28 (m, 2 H, H-2, H-4)
5e	125–126 (*n*-C_6H_{14})	$C_{20}H_{11}F_6NO_3S$ (459.4)	1727, 1703	3.78 (s, 3 H, OCH_3), 6.83 (d, 2 H, *J* = 9, 2H_{arom}), 7.30 (d, 2 H, *J* = 9, 2 H_{arom}), 7.68 (dd, 1 H, *J* = 4, 9, H-3), 8.15 (br s, 1 H, H-6), 9.00 (dd, 1 H, *J* = 2, 4, H-2), 9.22 (dd, 1 H, *J* = 2, 9, H-4)
5f	114–115 (*n*-C_6H_{14})	$C_{20}H_{11}F_6NO_2S$ (443.4)	1722, 1685	2.32 (s, 3 H, CH_3), 7.02–7.36 (m, 4 H_{arom}), 7.72 (dd, 1 H, *J* = 4, 9, H-3), 8.22 (br s, 1 H, H-6), 9.05 (dd, 1 H, *J* = 2, 4, H-2), 9.27 (dd, 1 H, *J* = 2, 9, H-4)

Table 4 (continued)

Compound	Mp (°C) (Solvent)	Molecular Formula[a]	IR (KBr) υ (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) *J* (Hz)
5g	134–135 (*n*-C_6H_{14}/EtOAc)	$C_{19}H_9F_6NO_2S$ (429.3)	1722, 1688	7.31 (s, 5 H, Ph), 7.72 (dd, 1 H, *J* = 4, 9, H-3), 8.25 (br s, 1 H, H-6), 9.04 (dd, 1 H, *J* = 2, 4, H-2), 9.27 (dd, 1 H, *J* = 2, 9, H-4)
5h	123–124 (*n*-C_6H_{14})	$C_{19}H_8ClF_6NO_2S$ (463.8)	1716, 1697	7.26 (s, 4 H_{arom}), 7.72 (dd, 1 H, *J* = 4, 9, H-3), 8.29 (br s, 1 H, H-6), 9.03 (dd, 1 H, *J* = 2, 4, H-2), 9.23 (dd, 1 H, *J* = 2, 9, H-4)
6a	97–98 (*n*-C_6H_{14}/EtOAc)	$C_{16}H_{11}F_6NO_3$ (379.3)	1695	1.06 (t, 3H, *J* = 7, CH_3), 1.80–2.16 (m, 2 H, CH_2), 5.07 (t, 2 H, *J* = 7, OCH_2), 7.72 (dd, 1 H, *J* = 4, 9, H-3), 8.48 (br s, 1 H, H-6), 9.06 (dd, 1 H, *J* = 2, 4, H-2), 9.41 (dd, 1 H, *J* = 2, 9, H-4)
6b	88–89 (*n*-C_6H_{14}/EtOAc)	$C_{17}H_{15}F_6NO_4$[c] (411.3)	3340, 1698	0.89–2.29 [m, 7 H, $(CH_2)_2CH_3$], 4.63–6.58 (br, 2 H, OH), 4.76–5.23 (m, 2 H, OCH_2), 7.55–7.83 (m, 1 H, H-3), 8.46–8.76 (m, 1 H, H-6), 8.97–9.16 (m, 1 H, H-2), 9.24–9.52 (m, 1 H, H-4)[b]
6c	83–84 (*n*-C_6H_{14}/EtOAc)	$C_{17}H_{15}F_6NO_4$[c] (411.3)	3395, 1703	1.00–1.26 (m, 6 H, CH_3), 1.95–2.73 (m, 1 H, CH), 3.83–5.47 (br, 2 H, OH), 4.61–4.90 (m, 2 H, OCH_2), 7.56–7.86 (m, 1 H, H-3), 8.46–8.68 (m, 1 H, H-6), 8.96–9.09 (m, 1 H, H-2), 9.20–9.55 (m, 1 H, H-4)[b]
6d	93–94 (*n*-C_6H_{14}/EtOAc)	$C_{21}H_{15}F_6NO_4$[c] (459.3)	3360, 1699	3.05–4.94 (br, 2 H, OH), 3.16–3.51 (m, 2 H, CH_2), 4.98–5.44 (m, 2 H, OCH_2), 7.29–7.82 (m, 6 H, H-3, Ph), 8.46–8.68 (m, 1 H, H-6), 8.97–9.14 (m, 1 H, H-2), 9.22–9.48 (m, 1 H, H-4)[b]
6e	133–134 (*n*-C_6H_{14}/EtOAc)	$C_{21}H_{13}F_6NO_4$ (457.3)	1698	4.40 (t, 2 H, *J* = 4, $PhOC\underline{H}_2$), 5.42 (t, 2 H, *J* = 4, OCH_2), 6.73–7.47 (m, 5 H, Ph), 7.67 (dd, 1 H, *J* = 4, 9, H-3), 8.45 (br s, 1 H, H-6), 9.00 (dd, 1 H, *J* = 2, 4, H-2), 9.33 (dd, 1 H, *J* = 2, 9, H-4)
7	135–136 (*n*-C_6H_{14}/EtOAc)	$C_{20}H_{11}F_6NO_2S$ (443.4)	3230, 1696	3.01–3.89 (br, 1 H, OH), 5.38 (s, 1 H, H-2), 7.21–7.79 (m, 6 H, H-7, Ph), 8.28 (br s, 1 H, H-4), 8.91 (dd, 1 H, *J* = 2, 4, H-8), 9.31 (dd, 1 H, *J* = 2, 9, H-6)
8	152–153 (EtOAc)	$C_{20}H_9F_6NOS$ (425.4)	1697	7.45–7.87 (m, 6 H, H-7, Ph), 8.77 (br s, 1 H, H-4), 9.01 (dd, 1 H, *J* = 2, 4, H-8), 9.27 (dd, 1 H, *J* = 2, 9, H-6)

[a]Satisfactory microanalyses were obtained: C±0.34, H±0.36, N±0.29.
[b]In $CD_3CN/CDCl_3$.
[c]Compounds (**5a**–**c** and **6b**–**d**) were found to exist as monohydrate form.

ane:EtOAc, 3:1 for **5a-d** and *n*-hexane:EtOAc, 2:1 for **5e-h,** as eluent. In the cases of **5e-h**, toluene was used as a solvent (see Table 2).

N-O Exchange Reaction of 3 with Alcohols; General Procedures
To a solution of **3** (1.10 g, 3 mmol) in toluene (12 mL) was added the appropriate alcohols (30−162 mmol) and the mixture was stirred at reflux temperature for 96−240 h. The solvent was evaporated in vacuo and the crude product was chromatographed using *n*-hexane:EtOAc, 3:1 for **6d**,**e** and *n*-hexane:EtOAc, 2:1 for **6a-c,** as eluent. In the cases of **6a** and **6c**, *n*-propyl and *i*-butyl alcohols were used as solvents, respectively (see Table 3).

5-Trifluoroacetyl-3-trifluoromethyl-3-hydroxy-2-phenyl-2,3-dihydrothieno[3,2-*h*]quinoline (7)
To a solution of **5d** (1.33 g, 3 mmol) in MeCN (12 mL) was added Dabco (1.01 g, 9 mmol) and the mixture was stirred at reflux temperature for 4 h. Most of the solvent was evaporated and EtOAc (50 mL) was then added. The whole mixture was washed with 1N HCl (100 mL) and H_2O (100 mL), and the organic layer was separated and dried (Na_2SO_4). The solvent was evaporated in vacuo and the crude mixture was chromatographed using *n*-hexane:EtOAc, 9:1 as eluent to give **7**; yield: 1.18 g (89%).

Dehydration of 7 to 8
To a stirred solution of **7** (1.33 g, 3 mmol) and pyridine (0.48 g, 6 mmol) in CH_2Cl_2 (24 mL) was added dropwise thionyl chloride (0.71 g, 6 mmol) with cooling, and stirring was continued at room temperature for 1 h. After evaporation of most the solvent, EtOAc (50 mL) was added. The whole mixture was washed with sat. Na_2CO_3 (100 mL) and H_2O (100 mL), and the organic layer was separated and dried (Na_2SO_4). The solvent was evaporated in vacuo and the crude mixture was chromatographed using *n*-hexane:EtOAc, 4:1 as eluent to give **8**; yield: 1.28 g (100%).

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(11) For example, reaction of **3** with *n*-propyl alcohol (20 equiv) in refluxing toluene for 168 h afforded the desired product **6a** in only 17% yield and substrate **3** was recovered in 83% yield.
(12) Me_2N-SBu-*n* exchange reaction (110 °C, 4 h) of **3** with *n*-butanethiol (3 equiv) did not take place in toluene. However, replacing toluene with butyronitrile as solvent allowed the conversion of **3** to **5b** (78%). As for dimethylamino-arylthio exchange, e.g., in the reaction of **3** with 3 equivalents of *p*-toluenethiol at 110 °C for 2 h, the solvent effect bore some resemblance to that of N-O exchange (solvent /% conversion to **5f**; toluene / 92; butyronitrile / 85). There was little difference in the reactivities attributed to changing the solvents in N-N exchange reaction of **3** with amines.
(13) For example, naphthylamine **1** and quinolylamine **3** were allowed to react with 5 equivalents of *n*-butyl alcohol in refluxing toluene for 24 h: substrate /% conversion to *n*-butyl 1-[2,4-bis-(trifluoroacetyl)naphthyl] ether **2** (Nu = *n*-BuO) and **6b**; **1** / 93; **3** / 41.
(14) Naphthylamine **1** and quinolylamine **3** were allowed to react with equimolar amounts of benzylamine at r.t. for 5 min in MeCN: substrate /% conversion to *N*-benzyl-2,4-bis(trifluoroacetyl)-1-naphthylamine **2** (Nu = $PhCH_2NH$) and **4d**; **1** / 59; **3** / 99.
(15) Naphthylamine **1** and quinolylamine **3** were allowed to react with 3 equivalents of *n*-butanethiol for 8 h in refluxing MeCN: substrate /% conversion to *n*-butyl 1-[2,4-bis(trifluoroacetyl)-naphthyl] sulfide **2** (Nu = *n*-BuS) and **5b**; **1** / 38; **3** / 83.
(16) 5,7-Bis(trifluoroacetylation) of 8-quinolyl sulfides and ethers by trifluoroacetic anhydride did not proceed at all under forced conditions. Furthermore, compounds **5a-h** and **6a-e** are not obtainable by halogen-sulfur and halogen-oxygen exchanges of 8-halo-5,7-bis(trifluoroacetyl)quinolines with thiols and alcohols because of difficulty in preparing the substrates.
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