Aromatic Nucleophilic N,S- and N,O-Exchange Reactions of *N,N*-Dimethyl-2,4-bistrifluoroacetyl-1-naphthylamine with Various Thiols and Alcohols: A Facile Synthetic Method for Alkyl and Aryl 1-[2,4-Bis(trifluoroacetyl)naphthyl] Sulfides and Ethers

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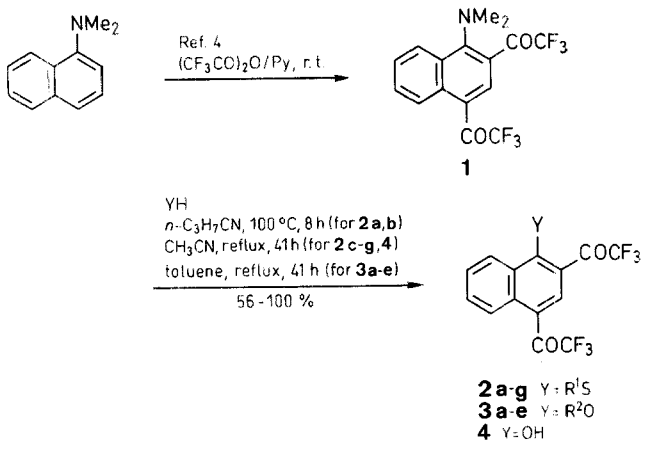
Aromatic nucleophilic N,S- and N,O-exchange reactions of *N,N*-dimethyl-2,4-bistrifluoroacetyl-1-naphthylamine (**1**) with various thiols and alcohols afford the corresponding 2,4-bistrifluoroacetyl-1-naphthyl sulfides **2** and ethers **3** in excellent yields. Hydrolysis of **1** to 1-naphthol derivative **4** is also described.

Activated aromatic compounds bearing good leaving groups such as halo, alkoxy, etc., are known to undergo aromatic nucleophilic substitution with various nucleophiles.[1-3] However, amino groups attached to aromatic rings are seldom replaced by nucleophiles. Recently we found that *N,N*-dimethyl-2,4-bistrifluoroacetyl-1-naphthylamine (**1**) reacts with various amines quite easily under mild conditions to afford the corresponding N,N-exchanged 1-naphthylamine derivatives in excellent yields.[4] As an extension of this work we have studied substitution at aromatic carbon atoms using thiols and alcohols. Expectedly, the N,S- and N,O- instead of N,N-exchange reactions proceeded very cleanly merely by heating, without the aid of catalysts, though sulfur and oxygen nucleophiles are considerably less reactive than the nitrogen analogues. We now wish to communicate a new facile synthetic method for various alkyl and aryl 1-[2,4-bis(trifluoroacetyl)naphthyl] sulfides and ethers starting from commercially available *N,N*-dimethyl-1-naphthylamine.

N,N-Dimethyl-2,4-bistrifluoroacetyl-1-naphthylamine **1**[4] was readily prepared by bistrifluoroacetylation of *N,N*-dimethyl-1-naphthylamine in almost quantitative yields. The N,S-exchange reactions of **1** with low boiling thiols (e.g., ethanethiol) was performed in a sealed tube with the use of butyronitrile as solvent at 100°C for 8 h to give alkyl and aryl 1-[2,4-bis(trifluoroacetyl)naphthyl] sulfides **2a, b** in fair yields (Method A).[5] In the case of other aliphatic thiols such as butanethiol, refluxing the mixture in acetonitrile afforded the desired sulfides **2c–f** in 56–100% yields (Method B). Aromatic thiols, for example, *p*-toluenethiol also reacted easily to give 83% yield of the corresponding sulfide **2g** by merely mixing them at higher temperatures (in refluxing toluene) (Table 1).



Similarly, N,O-exchange reaction of 1-naphthylamine derivative **1** with various alcohols proceeded cleanly in refluxing toluene to give the corresponding alkyl and aryl 1-[2,4-bis(trifluoroacetyl)-naphthyl] ethers **3** in excellent yields, although alcohols are considerably less reactive than thiols. The results are summarized in Table 2.[6] It is of interest that the present N,O-exchange reaction proceeds faster in less polar and lower boiling toluene than in butyronitrile. For instance, compound **1** was allowed to react with 1.1 equivalents of butanol at reflux temperature for 24 h and the following result was obtained: solvent/% conversion to **3b**; toluene = 50; butyronitrile = 20.

These results are in striking contrast to those obtained in the cases of N,N- and N,S-exchanges in the present naphthalene system.[7]

Furthermore, hydrolysis of **1** also proceeded easily even under neutral conditions in refluxing aqueous acetonitrile to afford 2,4-bistrifluoroacetyl-1-naphthol **(4)** in almost quantitative yield.

In order to evaluate some amino groups as leaving groups in the present exchange reactions, *N*-unsubstituted 2,4-bistrifluoroacetyl-1-naphthylamine, its *N*-methyl, *N*-*tert*-butyl, and *N*,*N*-dimethyl derivatives were allowed to react with 5 times molar amounts of butanethiol in refluxing acetonitrile. The results obtained are as follows: substrate/% conversion to **2c**; *N*-unsubstituted 2,4-bistrifluoroacetyl-1-naphthylamine = 0; its *N*-methyl derivative = 25; its *N*-*tert*-butyl derivative = 85; its *N*,*N*-dimethyl derivative **1** = 100. In this respect, *N*,*N*-dimethyl derivative **1** would be the best as a starting compound for the preparation of the title compounds **2** and probably for **3**.[8]

In conclusion, this is the first, general example of aromatic nucleophilic N,S- and N,O-exchange reactions[9,10] and may be utilized as a facile and convenient synthetic method for alkyl and aryl 1-[2,4-bis(trifluoroacetyl)naphthyl] sulfides and ethers, which are not accessible by other methods.[11] In addition, the present reaction can be applied to the syntheses of various naphthalene-fused heterocycles bearing trifluoromethyl group with the use of bifunctional reagents such as hydrazines and hydroxylamine. These results will be published in our forthcoming papers.

Table 1. Aromatic Nucleophilic N,S-Exchange Reaction of **1** with Thiols

Product	R^1	Method	Yield[a] (%)	mp (°C) or bp (°C)/mbar	Molecular Formula[b]	IR (KBr or film) $\nu_{C=O}$ (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
2a	CH_2CH_3	A	72	53–54	$C_{16}H_{10}F_6O_2S$ (380.3)	1730	1.20 (t, 3H, J = 7, CH_3); 2.90 (q, 2H, J = 7, SCH_2); 7.63–7.83 (m, 2H, H-6, 7); 7.90 (s, 1H, H-3); 8.50–8.77 (m, 2H, H-5, 8)
2b	$(CH_2)_2CH_3$	A	80	160/7	$C_{17}H_{12}F_6O_2S$ (394.3)	1721	0.93 (t, 3H, J = 7, CH_3); 1.23–1.73 (m, 2H, SCH_2CH_2); 2.83 (t, 2H, J = 7, SCH_2); 7.50–7.60 (m, 2H, H-6, 7); 7.80 (s, 1H, H-3); 8.40–8.63 (m, 2H, H-5, 8)
2c	$(CH_2)_3CH_3$	B	100	160/7	$C_{18}H_{14}F_6O_2S$ (408.4)	1726	0.73–0.97 (m, 3H, CH_3); 1.20–1.76 (m, 4H, $SCH_2CH_2CH_2$); 2.90 (t, 2H, J = 7, SCH_2); 7.63–7.83 (m, 2H, H-6, 7); 7.90 (s, 1H, H-3); 8.50–8.77 (m, 2H, H-5, 8)
2d	$(CH_2)_4CH_3$	B	99	170/5	$C_{19}H_{16}F_6O_2S$ (422.4)	1743, 1722	0.77–1.70 [br m, 9H, $SCH_2(CH_2)_3CH_3$]; 2.90 (t, 2H, J = 7, SCH_2); 7.57–7.80 (m, 2H, H-6, 7); 7.70 (s, 1H, H-3); 8.47–8.70 (m, 2H, H-5, 8)
2e	$PhCH_2$	B	97	78–79	$C_{21}H_{12}F_6O_2S$ (442.4)	1730	4.00 (s, 2H, SCH_2); 6.80–7.12 (m, 5H, Ph); 7.48–7.82 (m, 2H, H-6, 7); 7.90 (s, 1H, H-3); 8.47–8.68 (m, 2H, H-5, 8)
2f	furfuryl	B	56	70–71	$C_{19}H_{10}F_6O_3S$ (432.3)	1752, 1711	4.30 (s, 2H, SCH_2); 5.67 (d, 1H, J = 3, H_α of furfuryl); 5.97 (dd, 1H, J = 2, H-β); 7.07 (d, 1H, J = 2, H-β'); 7.53–7.70 (m, 2H, H-6, 7); 7.92 (s, 1H, H-3); 8.43–8.60 (m, 2H, H-5, 8)
2g	4-$CH_3C_6H_4$	B[c]	83	91–92	$C_{21}H_{12}F_6O_2S$ (442.4)	1730	2.23 (s, 3H, CH_3); 6.93 (s, 4H_{arom}); 7.50–7.70 (m, 2H, H-6, 7); 7.97 (s, 1H, H-3); 8.47–8.63 (m, 2H, H-5, 8)

[a] Yield of isolated products.
[b] Satisfactory microanalyses obtained: C ±0.19, H ±0.16, F ±0.25.
[c] In refluxing toluene.

Table 2. Aromatic Nucleophilic N,O-Exchange Reaction of **1** with Alcohols

Product	R^2	Yield[a] (%)	mp (°C) or bp (°C)/mbar	Molecular Formula[b]	IR (KBr or film) $\nu_{C=O}$ (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
3a	$(CH_2)_2CH_3$	94	46–47	$C_{17}H_{12}F_6O_3$ (378.3)	1707	1.13 (t, 3H, J = 7, CH_3); 1.83–2.16 (m, 2H, CH_2CH_3); 4.10 (t, 2H, J = 7, OCH_2); 7.43–7.87 (m, 2H, H-6, 7); 8.23–8.40 (m, 2H, H-3, 8); 8.77 (dd, 1H, J = 2, 8, H-5)
3b	$(CH_2)_3CH_3$	~100	48–49	$C_{18}H_{14}F_6O_3$ (392.3)	1713	1.03 (t, 3H, J = 6, CH_3); 1.30–2.22 (m, 4H, OCH_2CH_2); 4.15 (t, 2H, J = 6, OCH_2CH_2); 7.48–7.93 (m, 2H, H-6, 7); 8.28–8.44 (m, 2H, H-3, 8); 8.85 (dd, 1H, J = 2, 8, H-5)
3c	$CH_2CH(CH_3)_2$	99	140/3	$C_{18}H_{14}F_6O_3$ (393.2)	1704	1.13 (d, 6H, J = 7, CH_3); 2.00–2.56 (m, 1H, CH); 3.90 (d, 2H, J = 7, OCH_2); 7.56–7.90 (m, 2H, H-6, 7); 8.26–8.43 (m, 2H, H-3, 8); 8.83 (dd, 1H, J = 2, 8, H-5)
3d	$PhCH_2CH_2$	81	83–84	$C_{22}H_{14}F_6O_3$ (440.3)	1715	3.20 (t, 2H, J = 7, OCH_2CH_2); 4.30 (t, 2H, J = 7, OCH_2CH_2); 7.20 (s, $5H_{arom}$); 7.36–8.00 (m, 3H, H-6, 7, 8); 8.37 (s, 1H, H-3); 8.73 (dd, 1H, J = 2, 8, H-5)
3e	$PhOCH_2CH_2$	74	91–92	$C_{22}H_{14}F_6O_4$ (456.3)	1730, 1713	4.27–4.53 (m, 4H, OCH_2CH_2); 6.70–7.43 (m, $5H_{arom}$); 7.50–7.90 (m, 2H, H-6, 7); 8.40–8.60 (m, 2H, H-3, 8); 8.77 (dd, 1H, J = 2, 8, H-5)

[a] Yield of isolated products.
[b] Satisfactory microanalyses obtained: C ±0.25, H ±0.23, F ±0.16.

Melting and boiling points are uncorrected. Boiling points refer to oven temperature of Kugelrohr distillation. IR spectra were recorded on a Hitachi Model EPI-G3 grating spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL PMX-60 SI spectrometer.

N,S-Exchange Reaction of 1 with Thiols; Typical Procedures:

Method A: *Ethyl 1-[2,4-Bis(trifluoroacetyl)naphthyl] Sulfide* (**2a**): A mixture of **1** (1 g, 2.75 mmol), ethanethiol (1.708 g, 27.5 mmol)[12] and butyronitrile (10 mL) is placed in an ampoule and heated at 100 °C for 8 h. The solvent is removed under reduced pressure and the crude mixture is chromatographed on a silica gel column (5 × 20 cm; 200 mesh) using hexane/benzene (7:3) as eluent to give **2a**; yield: 753 mg (72%).

$C_{16}H_{10}F_6O_2S$	calc.	C 50.53	H 2.65	F 29.97
(380.3)	found	50.57	2.51	29.96

Method B: *Butyl 1-[2,4-Bis(trifluoroacetyl)naphthyl] Sulfide* (**2c**): To a stirred solution of butanethiol (2.48 g, 27.5 mmol)[12] in CH_3CN (10 mL) is added **1** (1 g, 2.75 mmol) and the mixture is refluxed for 41 h. After removal of the solvent *in vacuo*, the crude mixture is purified by chromatography on a silica gel column (200 mesh, 5 × 20 cm) using hexane/benzene (1:1) as eluent to give **2c**; yield: 1.12 g (~100%).

$C_{18}H_{14}F_6O_2S$	calc.	C 52.94	H 3.46	F 27.91
(408.4)	found	52.75	3.49	28.16

The following eluents are used: hexane/benzene (7:3) for **2d, g** and the same (1:1) for **2b, e, f**.

N,O-Exchange Reaction of 1 with Alcohols, Butyl 1-[2,4-Bis(trifluoroacetyl)naphthyl] Ether (3b); Typical Procedure:

To a stirred solution of butanol (1020 mg, 13.75 mmol) in toluene (10 mL) is added **1** (1.02 g, 2.75 mmol) and the mixture is refluxed for 41 h. The solvent is then removed at reduced pressure to give practically pure product **3b**; yield: 1.08 g (~100%).

$C_{18}H_{14}F_6O_3$	calc.	C 55.11	H 3.60	F 29.06
(392.3)	found	55.23	3.48	29.16

In the cases of products **3d** and **3e**, separation and purification are carried out by column chromatography on silica gel using hexane/benzene (3:2) and benzene as eluents, respectively.

Hydrolysis of 1 in CH_3CN/H_2O; 2,4-Bistrifluoroacetyl-1-naphthol (4):

To a stirred solution of **1** (1 g, 2.75 mmol) in CH_3CN (5 mL) is added water (5 mL) and the mixture is refluxed (bath temperature, 85 °C) for 41 h. Most of the solvent is evaporated and CH_2Cl_2 (50 mL) is then added. The mixture is washed with water, and the organic layer is separated and dried (Na_2SO_4). Removal of the solvent and purification by column chromatography on silica gel (5 × 20 cm; 200 mesh) using CH_2Cl_2 as eluent afford pure **4**; yield: 898 mg (97%); mp 110–111 °C.

$C_{14}H_6F_6O_3$	calc.	C 50.02	H 1.80	F 33.91
(336.2)	found	50.26	1.74	33.87

IR (KBr): ν = 3140 (OH); 1714, 1670 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 7.43–7.93 (m, 2H, H-6, 7); 8.37–8.50 (br, 2H, H-3, 8); 8.80 (dd, 1H, J = 2,8 Hz, H-5); 13.20 (s, 1H, OH).

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(1) Bunnett, J.F., Zahler, R.E. *Chem. Rev.* **1951**, *49*, 273.
(2) Zoltewicz, J.A. *Top. Curr. Chem.* **1975**, *59*, 33.
(3) de Vargas, E.B., de Rossi, R.H. *J. Org. Chem.* **1984**, *49*, 3978.
(4) Hojo, M., Masuda, R., Okada, E. *Tetrahedron Lett.* **1987**, 28, 6199.
(5) Rection of **1** in acetonitrile with ethanethiol and propanethiol in sealed tube was not complete at 80 °C for 8 h. Prolongation of reaction time (30 h) at the same temperature caused increased decomposition of products. Accordingly, both higher temperature (in butyronitrile at 100 °C) and shorter reaction time (8 h) were necessary in order to obtain the desired N-S exchanged products **2a, b** in higher yields.
(6) The N-O exchange reaction of **1** with low boiling alcohols (e.g., EtOH) and phenols (e.g., *p*-methoxyphenol) proceeded with difficulty. Attempted reactions in a sealed tube at high temperatures failed due to much decomposition of the products.
(7) N,N-exchange reaction (80 °C, 0.5 h) of **1** with pyrrolidine (3 equiv) did not take place in toluene. However, replacing toluene by butyronitrile as solvent allowed the conversion of **1** to *N*-(2,4-bistrifluoroacetyl-1-naphthyl)pyrrolidine (70%). Similarly, N,S-exchange reaction (reflux, 24 h) of **1** with phenylmethanethiol (1.1 equiv) proceeded easier in butyronitrile (conversion to **2e**, 70%) than in toluene (50%).
(8) This observed decreasing order of efficiency as leaving groups, Me_2N > *t*-BuNH > MeNH > NH_2, is due to the decreasing order of bulkiness. This result strongly suggests that relief of the steric strain imposed on the intermediate Meisenheimer type complex would be a driving force of the present interesting substitution at aromatic carbon atoms.

(9) There is only one example reporting that 2,4-dinitrophenylpiperidine undergoes N,O-exchange reaction in MeOH in the presence of NaOMe to form 2,4-dinitroanisol:
Bunnett, J.F., Garst, R.H. *J. Org. Chem.* **1968**, *33*, 2320.

(10) There are only a few reports on the hydrolysis of *N*-2,4-dinitrophenyl derivatives of piperidine, morpholine and imidazole to 2,4-dinitrophenol in the presence of NaOH:
Bernasconi, C.F., Schmid, P. *J. Org. Chem.* **1967**, *32*, 2953.
de Vergas, E.B., de Rossi, R.H., Veglia, A.V. *J. Org. Chem.* **1986**, *51*, 1976.
Ref. 3.

(11) 2,4-Bistrifluoroacetylation of 1-naphthol, 1-naphthyl ethers and sulfides by trifluoroacetic anhydride did not proceed at all under forced conditions. Furthermore, compounds **2–4** are not obtainable by halogen-sulfur and halogen-oxygen exchanges of 1-halo-2,4-bistrifluoroacetylnaphthalenes with thiols, alcohols and water because of difficulty in preparing the substrates.

(12) Although the use of 1–2 times molar amount of reagents also allows the present exchange reaction, fairly long reaction times are necessary for completion of the reaction leading to product decomposition and low yields.