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# Synthesis and aromatic nucleophilic *N–N*, *N–S* and *N–O* exchange reactions of *N,N*-dimethyl-2-trifluoroacetyl-1-naphthylamine

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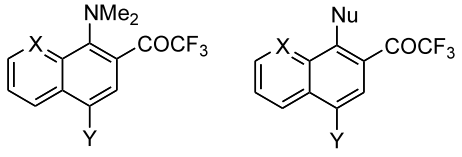
**Abstract**—We succeeded in the synthesis of *N,N*-dimethyl-2-trifluoroacetyl-1-naphthylamine (**10**) by the regioselective deacylation of *N,N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine with trifluoroacetic acid and water. The aromatic nucleophilic substitutions of **10** with various amines, thiols and alcohols proceeded cleanly to give the corresponding *N–N*, *N–S* and *N–O* exchanged products in moderate to excellent yields. 

Activated aromatic compounds with good leaving groups, such as halo and alkoxy groups, are well-known to undergo aromatic nucleophilic substitution reactions. However, amino groups attached to aromatic rings are seldom replaced by nucleophiles.[1–3] Previously, we have found that the dimethylamino group of 2,4-bis(trifluoroacetyl)-1-naphthylamines (**1**),[4,5] 2-trifluoroacetyl-4-halo-1-naphthylamines (**2a**,**b**)[6] and 5,7-bis(trifluoroacetyl)-8-quinolylamines (**3**)[7,8] was easily displaced with various nucleophiles (NuH), such as amines, thiols and alcohols, under mild conditions to give the corresponding $Me_2N$–Nu exchanged products (**4**–**6**) in excellent yields. Furthermore we succeeded in applying the amine–nucleophile exchange reaction to the efficient syntheses of fluorine-containing heterocyclic compounds[9] showing potential biological activities.[10–12] The important question raised by this finding is 'Are two units of an electron-withdrawing group the requirements for undertaking the present dimethylamino displacement reaction?' At the early stage we have already found that this type of $S_NAr$ reaction of *N,N*-dimethyl-4-trifluoroacetyl-1-naphthylamine (**8**), which was easily obtained by the monoacylation reaction of commercially available *N,N*-dimethyl-1-naphthylamine (**7**) with an equimolar amount of trifluoroacetic anhydride, could hardly take place to afford any substituted compounds (**9**).[4] However, studies on the replacement reaction of *N,N*-dimethyl-2-trifluoroacetyl-1-naphthylamine (**10**) have been much delayed by difficulties in the synthesis of **10**. Here, we report an efficient synthetic method for the desirable new substrate (**10**) and its aromatic nucleophilic *N–N*, *N–S* and *N–O* exchange reactions with various *N*-, *S*- and *O*-nucleophiles.




**1**: (X, Y)=(CH, $COCF_3$) **4**: (X, Y)=(CH, $COCF_3$)
**2a**: (X, Y)=(CH, Cl) **5a**: (X, Y)=(CH, Cl)
**2b**: (X, Y)=(CH, Br) **5b**: (X, Y)=(CH, Br)
**3**: (X, Y)=(N, $COCF_3$) **6**: (X, Y)=(N, $COCF_3$)

The direct mono(trifluoroacetylation) of **7** did not provide **10**, acylated at the 2-position, but another regioisomer **8**, acylated exclusively at the 4-position as mentioned above.[4] Therefore, we tried a new two-step synthesis of **10** via **1**, diacylated at both the 2- and

*Keywords*: regioselective deacylation; acid-catalyzed reaction; aromatic nucleophilic substitution; trifluoroacetylated naphthalenes; fluorine compounds.

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4-positions from **7**. The point is that deacylation is carried out after diacylation of **7**. By the use of trifluoroacetic acid together with water in refluxing acetonitrile, **1** underwent a regioselective deacylation reaction at the 4-position to yield the desired 2-monoacyl derivative (**10**) in 72% yield without any formation of the 4-monoacyl derivative (**8**). In the absence of water, treatment of **1** with trifluroracetic acid resulted in the formation of naphthoxazine (**14**).[13,14] Attempted deacylation reactions of **1** with other acids, such as hydrogen chloride, sulfuric acid and *p*-toluenesulfonic acid, ended in failure. Moreover, deacylation of the 2,4-diacyl derivatives (**4**: Nu = MeNH, $NH_2$, $PhCH_2CH_2S$, $PhCH_2CH_2O$, etc.) was also unsuccessful with the use of $CF_3CO_2H$ and $H_2O$.

We first examined the *N–N* exchange reaction of **10** with various amines (Table 1). The reactions with aqueous ammonia and various aliphatic primary amines proceeded cleanly to produce *N–N* exchanged

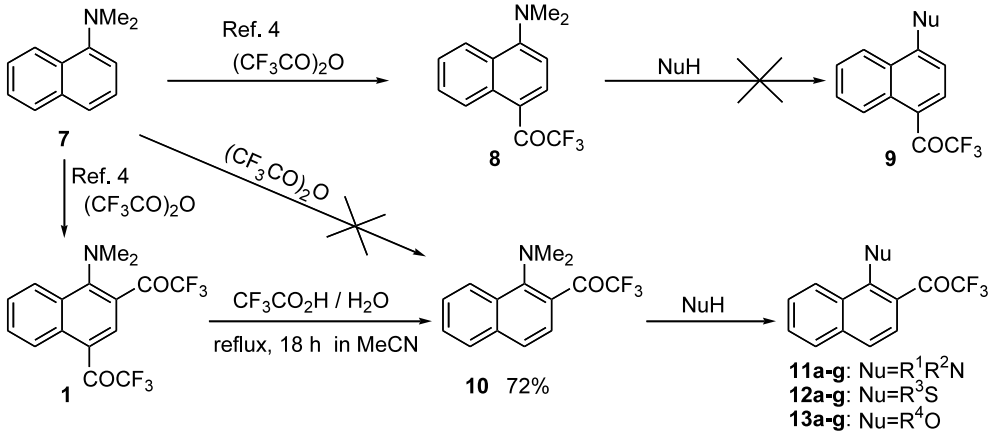
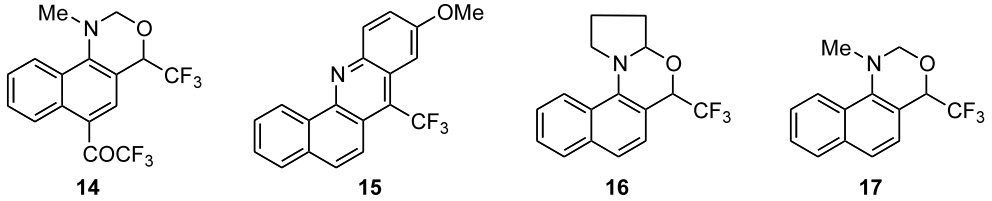



**Table 1.** *N–N*, *N–S* and *N–O* exchange reactions of **10** with various nucleophiles [NuH (*a* equiv)][a]




| Entry | NuH | *a* (equiv.) | Solvent | Temp. (°C) | Time (h) | Product | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | $NH_3$ | 10 | PrCN | 100[c] | 72 | **11a** | 95 |
| 2 | $MeNH_2$ | 5 | MeCN | 80[c] | 24 | **11b** | 81 |
| 3 | $EtNH_2$ | 5 | MeCN | 80[c] | 72 | **11c** | 93 |
| 4 | $PhCH_2NH_2$ | 3 | MeCN | Reflux | 48 | **11d** | 100 |
| 5 | *i*-$PrNH_2$ | 5 | MeCN | 80[c] | 72 | **11e** | 100 |
| 6 | *t*-$BuNH_2$ | 10 | PrCN | 110[c] | 336 | **11f** | 73 (27) |
| 7 | *p*-$MeOC_6H_4NH_2$ | 10 | BuCN | Reflux | 48 | **11g**/**15** | 78/22 |
| 8 | Pyrrolidine | 5 | PrCN | Reflux | 72 | **16** | 84 |
| 9 | EtSH | 20 | Mesitylene | 150[c] | 72 | **12a** | 59 |
| 10 | *n*-BuSH | 20 | Mesitylene | 150[c] | 72 | **12b** | 82 |
| 11 | $PhCH_2SH$ | 3 | Toluene | Reflux | 72 | **12c** | 86 |
| 12 | *p*-$MeOC_6H_4SH$ | 3 | Toluene | Reflux | 72 | **12d** | 89 |
| 13 | *p*-$MeC_6H_4SH$ | 3 | Toluene | Reflux | 72 | **12e** | 84 |
| 14 | PhSH | 3 | Toluene | Reflux | 72 | **12f** | 90 |
| 15 | *p*-$ClC_6H_4SH$ | 3 | Toluene | Reflux | 120 | **12g** | 92 |
| 16 | EtOH | 10 | Mesitylene | 150[c] | 168 | **13a**/**17** | 63/17 (15) |
| 17 | *n*-PrOH | 10 | Mesitylene | 150[c] | 72 | **13b**/**17** | 59/3 (26) |
| 18 | *n*-BuOH | 10 | Mesitylene | Reflux | 96 | **13c** | 96 |
| 19 | *i*-BuOH | 20 | Xylene | Reflux | 240 | **13d**/**17** | 57/19 |
| 20 | $PhCH_2OH$ | 5 | Xylene | Reflux | 72 | **13e**/**17** | 74/9 |
| 21 | $PhCH_2CH_2OH$ | 5 | Mesitylene | Reflux | 24 | **13f** | 85 |
| 22 | $PhOCH_2CH_2OH$ | 5 | Mesitylene | Reflux | 24 | **13g**/**17** | 70/10 |

[a] Reaction was carried out on a 0.5 mmol scale in 1.8 mL of solvent.
[b] Values in parentheses are the recovery of the substrate (**10**).
[c] The reaction was carried out in a sealed tube.

compounds (**11a–f**)[15] in 73–100% yields by simply allowing them to stand at high temperatures (entries 1–6). Aromatic amines, for example, *p*-anisidine, also reacted in refluxing valeronitrile within 48 h to afford the desired diarylamines (**11g**) in 78% yield with the formation of benzacridines (**15**) as a by-product (entry 7). The reaction with secondary amines, pyrrolidine, also occurred cleanly under reflux in butyronitrile and provided naphthoxazines (**16**) in 84% yield with no formation of the dimethylamino–pyrrolidinyl exchanged product (entry 8).[13] Next, the *N–S* exchange reactions of **10** with various thiols were carried out. The reactions with ethanethiol and butanethiol were performed in a sealed tube with the use of mesitylene as the solvent at 150°C for 72 h to give the desired alkyl 1-naphthyl sulfides (**12a**,**b**)[15] in 59 and 82% yields, respectively (entries 9 and 10). High boiling benzyl mercaptan easily reacted in refluxing toluene to afford **12c** in 86% yield (entry 11). The monoacyl derivative (**10**) showed much higher reactivity than expected for aromatic thiols to provide aryl 1-naphthyl sulfides **12d–g** in high yields (entries 12–15). Finally, we attempted to accomplish the *N–O* exchange reactions with alcohols. The reactions of **10** with butanol and phenethyl alcohol proceeded cleanly in refluxing mesitylene to give the desired alkyl 1-naphthyl ethers **13c**,**f** in excellent yields (entries 18 and 21). While other alcohols such as ethyl, propyl, *i*-butyl, benzyl and phenoxyethyl alcohols also reacted without any bases at reflux temperatures to afford the corresponding ethers (**13a**,**b**,**d**,**e**,**g**)[15] in moderate to good yields, naphthoxazines (**17**) were produced in 3–19% yields and the starting material (**10**) was also recovered in some cases (entries 16, 17, 19, 20, and 22). Unfortunately, the dimethylamino–aryloxy exchange reaction of **10** with phenols was not successful. As expected, the 2-monoacyl derivative (**10**) showed considerably less reactivity than the 2,4-diacyl derivative (**1**). However, it was very surprising that 2-monoacylated **10** exhibited a very much higher reactivity than 4-monoacylated **8**. Although the reason for the great difference in reactivity between the two monoacylated compounds (**8** and **10**) is not clear at the present moment, it is probably due to the force magnitude of the relief from the steric strain imposed in the intermediate Meisenheimer type complex as well as the transmission distance of the inductive effect of a trifluoroacetyl group.

Thus, we succeeded in the synthesis of *N*,*N*-dimethyl-2-trifluoroacetyl-1-naphthylamine (**10**) by the regioselective deacylation of *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**1**) with trifluoroacetic acid–water, and also in the performance of aromatic nucleophilic substitutions of **10** with various amines, thiols and alcohols. Studies are now in progress to elucidate the mechanism of this reaction, together with the development of simple synthetic methods for various naphthalene-fused heterocycles having a single trifluoromethyl group by the extension to bifunctional nucleophiles. These results will be published elsewhere in our forthcoming papers.

**Experimental procedure for the synthesis of 10**: To a solution of **1** (5.45 g, 15 mmol) in MeCN (27 mL) were added $CF_3CO_2H$ (11.6 mL, 150 mmol) and $H_2O$ (13.5 mL, 750 mmol) and the mixture was stirred under reflux for 18 h. After removing the solvent, $CH_2Cl_2$ (200 mL) was added to the residue. The solution was washed with aq. $Na_2CO_3$ (2200 mL) and with $H_2O$ (2200 mL), dried over $Na_2SO_4$, and concentrated under vacuum. The resulting mixture was chromatographed on silica gel using hexane–AcOEt (23:2) as the eluent to give **10** (2.89 g, 72%). Compound **10**: bp 100°C/3 mmHg (oven temp.); $^1$H NMR ($CDCl_3/CD_3CN$): $\delta$ 8.23–8.02 (m, 1H, H-3), 7.92–7.33 (m, 5H, H-4, -5, -6, -7, -8), 2.95 (s, 6H, $CH_3$); IR (KRS-5): 1716 cm$^{-1}$. Anal. calcd for $C_{14}H_{12}F_3NO$: C, 62.92; H, 4.53; N, 5.24. Found: C, 62.70; H, 4.80; N, 5.09%.

## Acknowledgements

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15. Compound **11a**: mp 139–140°C (hexane/$CHCl_3$); $^1$H NMR ($CDCl_3/CD_3CN$): $\delta$ 9.20–7.25 (br, 2H, NH), 8.13–7.92 (m, 1H, H-8), 7.71–7.27 (m, 4H, H-3, -5, -6, -7), 6.92 (d, 1H, $J=9$ Hz, H-4); IR (KBr): 3450, 3315, 1648, 1640 cm$^{-1}$. Anal. calcd for $C_{12}H_8F_3NO$: C, 60.26; H, 3.37; N, 5.86. Found: C, 60.39; H, 3.41; N, 5.69%.

Compound **12a**: bp 90°C/3 mmHg (oven temp.); $^1$H NMR ($CDCl_3$): $\delta$ 8.89–8.56 (m, 1H, H-3), 8.04–7.26 (m, 5H, H-4, -5, -6, -7, -8), 2.84 (q, 2H, $J=7$ Hz, $CH_2$), 1.16 (t, 3H, $J=7$ Hz, $CH_3$); IR (KRS-5): 1732 cm$^{-1}$. Anal. calcd for $C_{14}H_{11}F_3OS$: C, 59.15; H, 3.90. Found: C, 58.93; H, 3.76%.

Compound **13a**: bp 85°C/3 mmHg (oven temp.); $^1$H NMR ($CDCl_3$): $\delta$ 8.38–8.08 (m, 1H, H-3), 7.98–7.38 (m, 5H, H-4, -5, -6, -7, -8), 4.15 (q, 2H, $J=7$ Hz, $CH_2$), 1.53 (t, 3H, $J=7$ Hz, $CH_3$); IR (KRS-5): 1704 cm$^{-1}$. Anal. calcd for $C_{14}H_{11}F_3O_2$: C, 62.69; H, 4.13. Found: C, 62.63; H, 4.14%.