Aromatic Nucleophilic Nitrogen–Nitrogen Exchange Reaction of *N,N*-Dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine with Amino Acid Derivatives: A Facile Synthesis of Fluorine-Containing 1*H*-Benzo[*g*]indolines and 1*H*-Benzo[*g*]indoles

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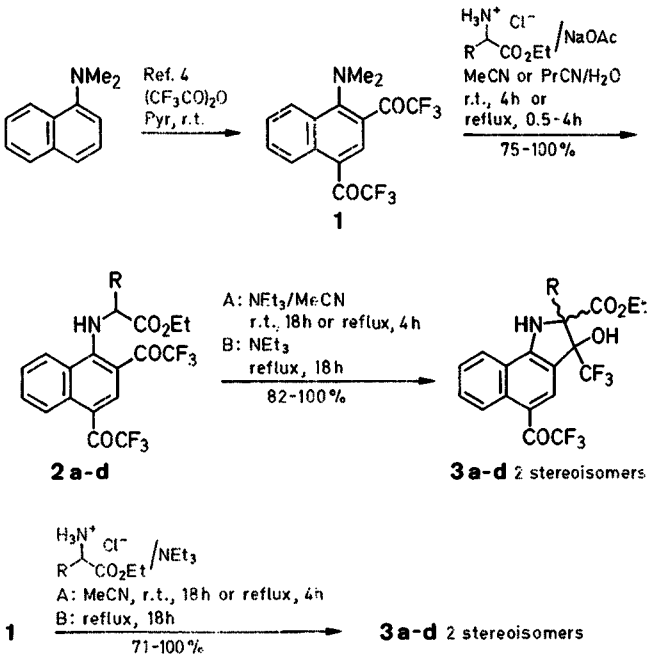
Aromatic nucleophilic nitrogen–nitrogen exchange reaction of *N,N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine **1** with some amino acid derivatives gives the corresponding *N*-[2,4-bis(trifluoroacetyl)-1-naphthyl]amino acid derivatives **2a–d** in excellent yields. Base-catalyzed cyclization affords fluorine-containing 1*H*-benzo[*g*]indolines (2,3-dihydro-1*H*-benzo[*g*]indoles) **3a–d** in high yields. Further conversion of **3a** into 1*H*-benzo[*g*]indoles **4**, **5** is also described.

Although activated aromatic compounds bearing good leaving groups such as halo, alkoxy, etc., are well-known to undergo aromatic nucleophilic substitution with various nucleophiles, amino groups attached to aromatic rings are seldom replaced by nucleophiles.[1–3] Recently we found that *N,N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine **1** reacts with various amines quite easily under mild conditions to give the corresponding nitrogen–nitrogen exchanged 1-naphthylamine derivatives in excellent yields.[4] In connection with this investigation, we now present a new aromatic nucleophilic nitrogen–nitrogen exchange reaction of **1** with amino acid derivatives and its application to the synthesis of 1*H*-benzo[*g*]indolines **3a–d** and -benzo[*g*]indoles **4**, **5**. These fluorine-containing heterocycles are expected to have interesting biological activities and have attracted much attention in recent years for their potential utility in medicinal and agricultural scientific fields.[5,6] The results are summarized in Table 1.

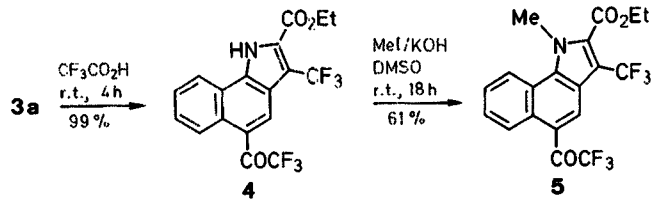
Aromatic nucleophilic nitrogen–nitrogen exchange reaction of substrate **1**, which can be easily prepared from commercially available *N,N*-dimethyl-1-naphthylamine and trifluoroacetic anhydride,[4] with ethyl glycinate hydrochloride proceeded readily at room temperature in the presence of sodium acetate in acetonitrile/water to give *N*-[2,4-(bistrifluoroacetyl)-1-naphthyl]glycine ethyl ester **2a** quantitatively. In the case of alanine and methionine ethyl ester hydrochlorides refluxing in the same solvent was required for completion of the reaction and afforded the corresponding amino acid derivatives **2b** and **2c** in 96% and 94% yield, respectively. Reaction of **1** with ethyl phenylglycinate hydrochloride and sodium acetate in refluxing acetonitrile/water for 4 h provided only 23% yield of the desired nitrogen–nitrogen exchanged product **2d**, and 1*H*-benzo[*g*]indoline **3d** was obtained as the major product in 71% yield. Both higher temperature (in refluxing butyronitrile/water) and shorter reaction time (for 0.5 h) were necessary in order to obtain **2d** in more excellent yields (75%) by suppressing subsequent cyclization to **3d** (20%).

Base-catalyzed cyclization of amino acid derivatives **2a–d** into 1H-benzo[*g*]indolines **3a–d** with the use of triethylamine instead of sodium acetate proceeded readily at room temperature (18 h) or by heating at reflux temperatures for 4–18 h in 82–100% yield. Because the cyclization of alanine and methionine derivatives **2b, c** proceeded very slowly compared to glycinate **2a** and phenylglycinate **2d**, the reaction was carried out by refluxing them in triethylamine as solvent. Compounds **3a–d** could also be synthesized cleanly in a one-pot manner (71–100%) from **1** using triethylamine. Products **3a–d** were, in all cases, found to consist of two possible stereoisomers.[7] It seems that **3** is produced by deprotonation from the active *N*-methylene or *N*-methine carbon atom of **2** by triethylamine to give an intermediate carbanion, followed by intramolecular attack on the carbonyl carbon of the trifluoroacetyl group.



2, 3	R
a	H
b	CH_3
c	CH_2CH_2SMe
d	Ph

Treatment of benzoindoline derivative **3a** with trifluoroacetic acid at room temperature for 4 h caused dehydration to give benzoindole derivative **4** in nearly quantitative yield, which was then allowed to react with iodomethane in the presence of potassium hydroxide in dimethyl sulfoxide to afford the corresponding *N*-methylated compound **5** in 61% yield.



The structures of compounds **2–5** were confirmed by their spectral and analytical data (Table 2). The present procedure may be utilized as a facile and convenient synthetic method for fluorine-containing amino acids, naphthalene-fused pyrrolines and pyrroles which are difficultly accessible by other methods.[8] Extensive utilization of **1** as a useful synthetic intermediate for the preparation of various CF_3-containing compounds which have medicinal activities are now under investigation and will be presented elsewhere. Evaluation of biological activities for **2a–d** as well as **3a–d**, **4**, **5** is also in progress.

Nitrogen–Nitrogen Exchange Reaction of 1 with Amino Acid Derivatives; Typical Procedure:

A mixture of **1** (1.00 g, 2.75 mmol), ethyl glycinate hydrochloride (1.15 g, 8.26 mmol), and NaOAc (664 mg, 8.26 mmol) is suspended in MeCN (18 mL)/H_2O (2 mL), and this suspension is stirred at r.t. for 4 h. Most of the solvent is evaporated and CH_2Cl_2 (100 mL) is then added. The whole mixture is washed with H_2O (100 mL), and the organic layer is separated and dried (Na_2SO_4). Removal of the solvent under reduced pressure affords **2a**; yield: 1.16 g (100%); mp 134–135°C (*n*-C_6H_{14}/C_6H_6).

$C_{18}H_{13}F_6NO_4$	calc.	C 51.32	H 3.11	F 27.06	N 3.32
(421.3)	found	51.61	3.00	26.87	3.40

In the case of **2d**, the crude mixture (**2d** and **3d**) is chromatographed on a silica gel column, eluent: *n*-C_6H_{14}/C_6H_6 (3:2) for **2d**, C_6H_6/EtOAc (9:1) for **3d**.

Table 1. Compounds **2a–d**, **3a–d**, **4**, **5** Prepared

Substrate	Solvent	Temp.	Time (h)	Product[a]	Yield[b] (%)
1	MeCN/H_2O (9:1)	r.t.	4	**2a**	100
1	MeCN/H_2O (9:1)	reflux	4	**2b**	96
1	MeCN/H_2O (9:1)	reflux	4	**2c**	94
1	PrCN/H_2O (9:1)	reflux	0.5	**2d**	75[c]
2a	MeCN	r.t.	18	**3a**	91
2b	Et_3N	reflux	18	**3b**	100
2c	Et_3N	reflux	18	**3c**	82
2d	MeCN	reflux	4	**3d**	93
1	MeCN	r.t.	18	**3a**	100
1	Et_3N	reflux	18	**3b**	79
1	Et_3N	reflux	18	**3c**	71
1	MeCN	reflux	4	**3d**	86
3a	CF_3CO_2H	r.t.	4	**4**	99
4	DMSO	r.t.	18	**5**	61

[a] Products **3a–d** were mixtures of two stereoisomers.
[b] Yield of isolated products.
[c] Accompanied with **3d** (20%).

Cyclization of 2a–d with the Use of Triethylamine to 3a–d; Typical Procedure:

In Acetonitrile: To a solution of **2a** (1.00 g, 2.37 mmol) in MeCN (20 mL) is added Et_3N (252 mg, 2.5 mmol), and the mixture is stirred at r.t. for 18 h. Most of the solvent is evaporated and CH_2Cl_2 (100 mL) is then added. The whole mixture is washed with 1 N HCl (100 mL) and H_2O (100 mL), and the organic layer is separated and dried (Na_2SO_4). After removal of the solvent **3a** is obtained; yield: 914 mg (91%); mp 154–155°C (*n*-C_6H_{14}/$CHCl_3$).

$C_{18}H_{13}F_6NO_4$	calc.	C 51.32	H 3.11	F 27.06	N 3.32
(421.3)	found	51.44	3.12	26.80	3.28

In Triethylamine: A solution of **2c** (1.28 g, 2.58 mmol) in Et_3N (20 mL) is heated at reflux for 18 h with stirring. The mixture is then poured into ice-cold 1 N HCl (100 mL), and CH_2Cl_2 (100 mL) is added. The organic layer is separated, washed with H_2O (100 mL), and dried (Na_2SO_4). Evaporation of the solvent gives **3c**; yield: 1.05 g (82%); mp 169–170°C (*n*-C_6H_{14}/C_6H_6).

$C_{21}H_{19}NF_6O_4S$	calc.	C 50.91	H 3.87	F 23.01	N 2.83
(495.4)	found	50.67	3.67	23.31	2.76

Table 2. Physical and Spectral Data of Compounds **2a–d**, **3a–d**, **4**, **5**

Compound[a]	mp (°C)[b] (solvent)	Molecular Formula[c]	IR (KBr)[d] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J (Hz)
2a	134–135 (*n*-C_6H_{14}/C_6H_6)	$C_{18}H_{13}F_6NO_4$ (421.3)	3303–2276, 1739, 1697, 1648, 1617, 1603, 1595, 1540	1.33 (t, 3H, J = 7, $CO_2CH_2CH_3$); 4.33 (q, 2H, J = 7, $CO_2CH_2CH_3$); 4.63 (d, 2H, J = 5, $NHCH_2$); 7.50–8.20 (m, 3H$_{arom}$); 8.60 (s, 1H, H-3); 8.97 (dd, 1H, J = 2, 8, H-5); 10.93–11.33 (br, 1H, NH)
2b	108–109 (*n*-C_6H_{14})	$C_{19}H_{15}F_6NO_4$ (435.3)	3336–2284, 1743, 1674 (sh), 1619, 1601, 1579, 1531	1.23 (t, 3H, J = 7, $CO_2CH_2CH_3$); 1.73 (d, 3H, J = 7, $CHCH_3$); 4.17 (q, 2H, J = 7, $CO_2CH_2CH_3$); 4.66–5.13 (m, 1H, $NHCH$); 7.17–8.07 (m, 3H$_{arom}$); 8.50 (s, 1H, H-3); 8.93 (dd, 1H, J = 2, 8, H-5); 10.56 (d, 1H, J = 8, NH)
2c	70–71 (*n*-C_6H_{14})	$C_{21}H_{19}F_6NO_4S$ (495.4)	3355–2309, 1743, 1704, 1670, 1619, 1601, 1583, 1530	1.23 (t, 3H, J = 7, $CO_2CH_2CH_3$); 2.07 (s, 3H, SCH_3); 2.20–2.77 (m, 4H, $CH_2CH_2SCH_3$); 4.15 (q, 2H, J = 7, $CO_2CH_2CH_3$); 4.87–5.22 (m, 1H, $NHCH$); 8.10–7.10 (m, 3H$_{arom}$); 8.47 (s, 1H, H-3); 8.90 (dd, 1H, J = 2, 8, H-5); 10.40 (d, 1H, J = 8, NH)
2d	134–135 (*n*-C_6H_{14}/C_6H_6)	$C_{24}H_{17}F_6NO_4$ (497.4)	3361–2283, 1757, 1690, 1674, 1615, 1604, 1578, 1536	1.17 (t, 3H, J = 7, $CO_2CH_2CH_3$); 4.10 (q, 2H, J = 7, $CO_2CH_2CH_3$); 5.83 (d, 1H, J = 8, $NHCH$); 7.10–7.96 (m, 8H$_{arom}$); 8.50 (s, 1H, H-3); 8.87 (dd, 1H, J = 2, 8, H-5); 11.50 (d, 1H, J = 8, NH)
3a	154–155 (*n*-C_6H_{14}/$CHCl_3$)	$C_{18}H_{13}F_6NO_4$ (421.3)	3400, 3300, 1721, 1654, 1606, 1581, 1558, 1511	1.33 (t, 3H, J = 7, $CO_2CH_2CH_3$); 4.26 (q, 2H, J = 7, $CO_2CH_2CH_3$); 4.90 (s, 1H, H-2); 6.13 (s, 1H, NH or OH); 7.10–7.67 (m, 4H, 3H$_{arom}$, NH or OH); 8.18 (s, 1H, H-4); 8.87–9.03 (m, 1H, H-6)
3b	178–179 ($CHCl_3$)	$C_{19}H_{15}F_6NO_4$ (435.3)	3360 (sh), 1730, 1675, 1625, 1596, 1574, 1526	1.20 (t, 3H, J = 7, $CO_2CH_2CH_3$); 1.83 (q, 3H, J_{H-F} < 2, CCH_3); 4.13 (q, 2H, J = 7, $CO_2CH_2CH_3$); 6.43 (s, 1H, NH or OH); 7.33–8.00 (m, 4H, 3H$_{arom}$, NH or OH); 8.20 (s, 1H, H-4); 9.10 (dd, 1H, J = 2, 8, H-6)
3c	169–170 (*n*-C_6H_{14}/C_6H_6)	$C_{21}H_{19}F_6NO_4S$ (495.4)	3360 (sh), 1730, 1678, 1628, 1596, 1574, 1526	1.33 (t, 3H, J = 7, $CO_2CH_2CH_3$); 2.13 (s, 3H, SCH_3); 2.40–2.90(m, 4H, $CH_2CH_2SCH_3$); 4.23 (q, 2H, J = 7, $CO_2CH_2CH_3$); 6.17 (s, 1H, NH or OH); 7.13–7.97 (m, 4H, 3H$_{arom}$, NH or OH); 8.13 (s, 1H, H-4); 8.97 (dd, 1H, J = 2, 8, H-6)
3d	183–184 (C_6H_6/EtOAc)	$C_{24}H_{17}F_6NO_4$ (497.4)	3395, 3368, 1713, 1683, 1628, 1578, 1521	1.13 (t, 3H, J = 7, $CO_2CH_2CH_3$); 4.17 (q, 2H, J = 7, $CO_2CH_2CH_3$); 6.03 (s, 1H, NH or OH); 6.37 (s, 1H, NH or OH); 7.23–7.93 (m, 8H$_{arom}$); 8.23 (s, 1H, H-4); 9.07 (dd, 1H, J = 2, 8, H-6)
4	223–224 (C_6H_6/EtOAc)	$C_{18}H_{11}F_6NO_3$ (403.3)	3316, 1704, 1691, 1604, 1574, 1539	1.37 (t, 3H, J = 7, $CO_2CH_2CH_3$); 4.37 (q, 2H, J = 7, $CO_2CH_2CH_3$); 7.37–7.50 (m, 2H, H-7, H-8); 8.37–8.77 (m, 3H, H-4, H-6, H-9); 13.66 (s, 1H, NH)
5	128–129 (*n*-C_6H_{14}/C_6H_6)	$C_{19}H_{13}F_6NO_3$ (417.3)	1720, 1708, 1604, 1565, 1530	1.43 (t, 3H, J = 7, $CO_2CH_2CH_3$); 4.33 (s, 3H, NCH_3); 4.46 (q, 2H, J = 7, $CO_2CH_2CH_3$); 7.49–7.69 (m, 2H, H-7, H-8); 8.42–8.79 (m, 3H, H-4, H-6, H-9)

[a] In the case of compounds **3a–d**, physical and spectral data for either of two stereoisomers are shown.
[b] Uncorrected, measured by capillary.
[c] Satisfactory microanalyses obtained: C ±0.30, H ±0.20, F ±0.30, N ±0.08.
[d] Recorded on a Hitachi Model EPI-G3 grating spectrophotometer.
[e] Measured using a JEOL PMX-60SI spectrometer.

One-Pot Synthesis of 3a–d from 1 and Amino Acid Derivatives; Typical Procedure:

In Acetonitrile: To a suspension of ethyl glycinate hydrochloride (1.15 g, 8.25 mmol) and Et_3N (837 mg, 8.27 mmol) in MeCN (20 mL) is added **1** (1.00 g, 2.75 mmol), and stirring is continued at r.t. for 18 h. The solvent is then removed *in vacuo* and CH_2Cl_2 (100 mL) is added to the residue. This solution is washed with H_2O (100 mL), dried (Na_2SO_4), and evaporated to give the practically pure product **3c**; yield: 1.16 g (100%).

In Triethylamine: To a stirred suspension of methionine ethyl ester hydrochloride (1.177 g, 5.51 mmol) in Et_3N (20 mL) is added **1** (1.0 g, 2.75 mmol), and this mixture is heated at reflux for 18 h. The mixture is then poured into ice-cold 1 N HCl (100 mL), and CH_2Cl_2 (100 mL) is added. The organic layer is separated, washed with H_2O (100 mL), and dried (Na_2SO_4). Removal of the solvent affords **3c**; yield: 967 mg (71%).

2-Ethoxycarbonyl-3-trifluoromethyl-5-trifluoroacetyl-1*H*-benzo[*g*]indole (4):

Benzindoline derivative **3a** (300 mg, 0.71 mmol) is dissolved in trifluoroacetic acid (3 mL), and this solution is stirred at r.t. for 4 h. To the mixture is added EtOAc (50 mL), and the mixture is washed with an ice-cold aq. 10% Na_2CO_3 (50 mL), water (50 mL), and dried (Na_2SO_4). The solvent is removed *in vacuo* to give benzindole derivative **4**; yield: 284 mg (99%); mp 223–224°C (C_6H_6/EtOAc).

$C_{18}H_{11}F_6NO_3$	calc.	C 53.61	H 2.75	F 28.27	N 3.47
(403.3)	found	53.55	2.59	28.15	3.50

2-Ethoxycarbonyl-1-methyl-3-trifluoromethyl-5-trifluoroacetyl-1*H*-benzo[*g*]indole (5):

Benzindole derivative **4** (202 mg, 0.50 mmol) and powdered KOH (34 mg, 0.6 mmol) are dissolved in DMSO (6 mL). To the solution is added MeI (710 mg, 5.0 mmol), and the mixture is stirred at r.t. for 18 h. The mixture is washed with water (200 mL), extracted with CH_2Cl_2 (100 mL), and dried (Na_2SO_4). The solvent is evaporated, and the crude mixture is chromatographed on silica gel column (3 × 15 cm; 200 mesh) using *n*-C_6H_{14}/C_6H_6 (1:4) as eluent to give **5**; yield: 127 mg (61%); mp 128–129°C (*n*-C_6H_{14}/C_6H_6).

$C_{19}H_{13}F_6NO_3$	calc.	C 54.69	H 3.14	F 27.32	N 3.36
(417.3)	found	54.93	3.13	27.02	3.36

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(7) Proportions of the two stereoisomers could not be estimated exactly; furthermore, extensive overlap of the signals did not allow individual assignments. Attempts to fractionate two isomers by TLC were unsuccessful. However, the two stereoisomers could be readily separated by recrystallization of the mixtures from the solvents listed in Table 2. The stereochemistry is not determined at present.
(8) 2,4-Bis(trifluoroacetylation) of 1-chloro- and 1-methoxynaphthalenes with trifluoroacetic anhydride did not proceed even under forced conditions. Accordingly, compounds **2**–**5** are not obtainable by chloro-nitrogen and oxygen-nitrogen exchange reactions of 1-chloro- and 1-methoxy-2,4-bis(trifluoroacetyl)naphthalenes with amino acids.