A Convenient and Facile Synthesis of Fluorine-Containing 1*H*-, 2*H*-Benz[*g*]indazoles and Naphthisoxazoles by Aromatic Nucleophilic *N*-*N* Exchange Reaction of *N*,*N*-Dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine with Hydrazines and Hydroxylamine

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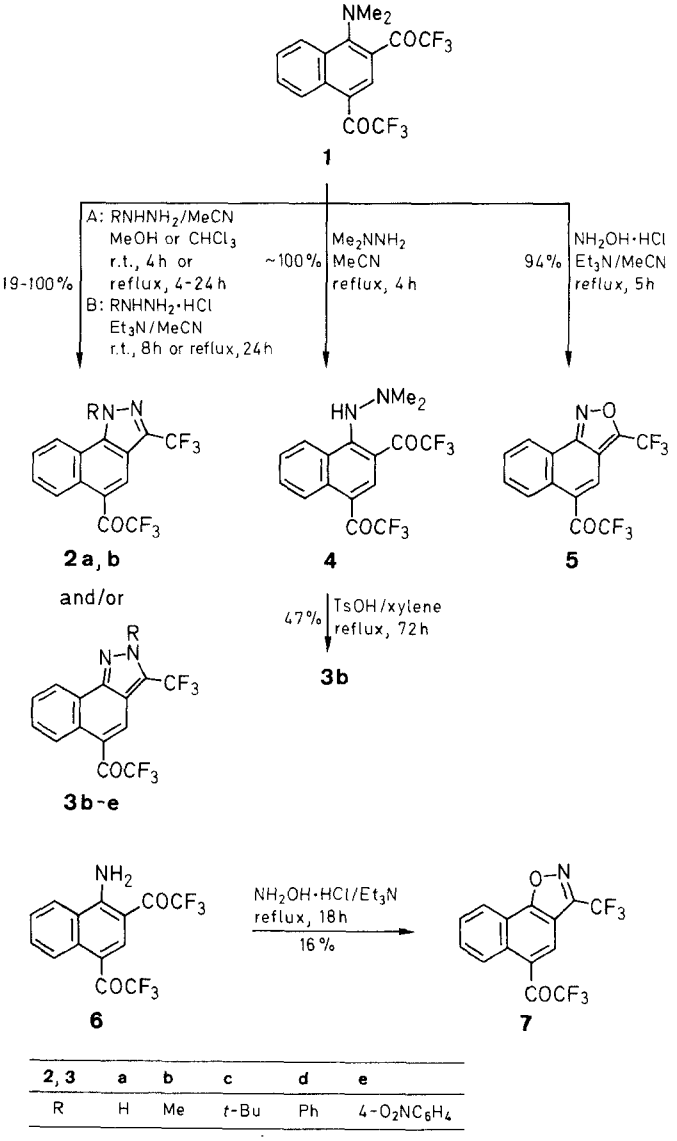
N,*N*-Dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**1**) undergoes an aromatic nucleophilic N–N exchange reaction with hydrazines followed by cyclocondensation to afford the corresponding fluorine-containing 1*H*- and 2*H*-benz[*g*]indazoles **2**, **3** in excellent yields. This reaction can be extended to the synthesis of 5-trifluoroacetyl-3-trifluoromethylnaphth[1,2-*c*]isoxazole (**5**) using hydroxylamine.

In our studies[1-3] on novel nucleophilic substitution reactions at aromatic carbon activated by trifluoroacetyl groups, it was found that *N*,*N*-dimethyl-2,4-bis-(trifluoroacetyl)-1-naphthylamine (**1**), which is readily prepared from *N*,*N*-dimethyl-1-naphthylamine and trifluoroacetic anhydride,[1] undergoes nitrogen–nitrogen exchange reactions with various amines[1] and amino acids.[3] This exchange reaction proceeds easily and cleanly under mild conditions to afford the corresponding nitrogen–nitrogen exchanged 2,4-bis(trifluoroacetyl)-1-naphthylamine derivatives in high yields. As an extension of this work, we used this type of aromatic nucleophilic substitution with bifunctional *N*-nucleophiles such as hydrazines and hydroxylamine, to prepare naphthalene-fused pyrazoles and isoxazoles bearing a trifluoromethyl group. The biological activities of these fluorine-containing heterocycles have attracted considerable attention in recent years due to their potential use in medicinal and agricultural science.[4-6]

N-Unsubstituted 1*H*-benz[*g*]indazole derivative **2a** was obtained in 100% yield from the reaction of **1** with hydrazine hydrate in refluxing acetonitrile for 4 h.[7] Treatment of **1** with methylhydrazine at room temperature in acetonitrile gave quantitatively a mixture of the two regioisomers (**2b** and **3b**) in a ratio of about 1:4. Interestingly, this ratio is very solvent-dependent. In methanol, the ratio changes to 1:1 (yield: 79%). Repeated recrystallization of this mixture from hexane/benzene gave pure isomer **2b**, having mp 168–169 °C. In contrast, the reaction in refluxing chloroform afforded regioselectively 2*H*-benz[*g*]indazole **3b** in a quantitative yield.[7,8] Compound **3b** was independently synthesized in 47% yield, by heating **4** with *p*-toluenesulfonic acid in refluxing xylene for 72 h. *tert*-Butylhydrazine hydrochloride reacted with **1** at room temperature for 8 h in the presence of triethylamine to afford solely **3c** in 92% yield.

Likewise, arylhydrazines gave 2-aryl-2*H*-benz[*g*]indazoles **3d,e** regioselectively and in excellent yields (Table 1).[7] The exclusive formation of 2*H*-regioisomers **3** is probably due to steric hindrance by the *tert*-butyl and aryl groups toward the attacking nitrogen atom.

The possibility that the reaction proceeds *via* the prior formation of a hydrazone at the 2-trifluoroacetyl group followed by an intramolecular N–N exchange to give the cyclized product seems unlikely, since the reaction of **1**



2, 3	a	b	c	d	e
R	H	Me	*t*-Bu	Ph	4-$O_2NC_6H_4$

Table 1. Benz[*g*]indazoles **2** and **3** Prepared from **1** and Hydrazines[7]

Solvent	Additive	Temperature	Time (h)	Product	Yield[a] (%)
MeCN	none	reflux	4	**2a**	100
MeCN	none	r.t.	4	**2b/3b**	19/81[b]
MeOH	none	r.t.	4	**2b/3b**	39/40[b]
$CHCl_3$	none	reflux	18	**3b**	100
MeCN	Et_3N	r.t.	8	**3c**	92
MeCN	none	reflux	24	**3d**	100
MeCN	Et_3N	reflux	24	**3e**	83

[a] Yield of isolated products.
[b] Product ratios were determined from integrated ^{1}H-NMR spectra.

Table 2. Physical and Spectral Data of Compounds **2–5** and **7**

Compound	mp (°C)[a] (solvent)	Molecular Formula[b]	IR (KBr)[c] ν(cm^{-1}) NH	C=O	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS)[e] δ, C-9b
2a	247–248 (benzene/EtOAc)	$C_{14}H_6F_6N_2O$ (332.2)	3260	1710	7.43–7.73 (m, 2H, H-7, H-8), 8.28–8.65 (m, 3H, H-4, H-6, H-9), 13.41–14.58 (br, 1H, NH)[f]	141.5[f]
2b	168–169 (hexane/benzene)	$C_{15}H_8F_6N_2O$ (346.2)	–	1715	4.53 (s, 3H, NCH_3), 7.56–7.73 (m, 2H, H-7, H-8), 8.29–8.46 (m, 2H, H-4, H-9), 8.78 (dd, 1H, J = 3, 7, H-6)	139.0, 139.8[f]
3b	151–152 (hexane/benzene)	$C_{15}H_8F_6N_2O$ (346.2)	–	1707	4.27 (s, 3H, NCH_3), 7.46–7.67 (m, 2H, H-7, H-8), 8.24 (s, 1H, H-4), 8.37–8.58 (m, 2H, H-6, H-9)	146.1
3c	138–139 (hexane/benzene)	$C_{18}H_{14}F_6N_2O$ (388.3)	–	1700	1.86 (s, 9H, $C(CH_3)_3$), 7.49–7.64 (m, 2H, H-7, H-8), 8.38 (s, 1H, H-4), 8.44–8.65 (m, 2H, H-6, H-9)	144.2
3d	154–155 (hexane/benzene)	$C_{20}H_{10}F_6N_2O$ (408.3)	–	1706	7.36–7.76 (br m, 7H, H-7, H-8, C_6H_5), 8.34 (s, 1H, H-4), 8.46–8.64 (m, 2H, H-6, H-9)	146.9
3e	178–179 (hexane/benzene)	$C_{20}H_9F_6N_3O_3$ (453.3)	–	1713	7.54–7.90 (m, 4H, H-7, H-8, $2H_{arom}$), 8.28–8.65 (m, 5H, H-4, H-6, H-9, $2H_{arom}$)	147.7
4	127–128 ($CHCl_3$)	$C_{16}H_{12}F_6N_2O_2$ (378.3)	3313	1695, 1653	2.63 (s, 6H, $N(CH_3)_2$), 7.20–7.70 (m, 3H, H-6, H-7, H-8), 7.8–8.5 (br, 1H, NH), 7.97 (s, 1H, H-3), 8.92 (dd, 1H, J = 2, 8, H-5)	–
5	79–80 (hexane)	$C_{14}H_5F_6NO_2$ (333.2)	–	1725	7.59–7.86 (m, 2H, H-7, H-8), 7.99 (s, 1H, H-4), 8.16–8.62 (m, 2H, H-6, H-9)	155.6
7	105–106 (hexane)	$C_{14}H_5F_6NO_2$ (333.2)	–	1717	7.49–7.82 (m, 2H, H-7, H-8), 8.26–8.66 (m, 3H, H-4, H-6, H-9)	165.0

[a] Uncorrected.
[b] Satisfactory microanalyses obtained: C ±0.39, H ±0.27, F ±0.28, N ±0.28; exception: **7**, N +0.54.
[c] Recorded on a Hitachi Model EPIG3 grating spectrophotometer.
[d] Measured using a JEOL PMX-60SI spectrometer.
[e] Recorded on a JEOL FX-90Q spectrometer.
[f] In acetone-d_6.

with *N,N*-dimethylhydrazine gave the exchange product **4** quantitatively[7] and the corresponding hydrazone could not be detected.

The structures of compounds **2a** and **3c–e** were determined on the basis of their ^{1}H- and ^{13}C-NMR spectra. The ^{1}H-NMR spectral data of the naphthalene-ring protons (H-4, -6 and -9) for the **3**-isomers are different than those of the **2**-isomers. In the ^{13}C-NMR spectra, the signal of the naphthalene-ring carbon (C-9b) bearing nitrogen occurs more downfield for **3** (δ = 144.2–147.7) than for **2** (δ = 139.0–141.5).

Hydroxylamine hydrochloride was also successfully used as a nucleophile in reaction with **1** to give 5-trifluoroacetyl-3-trifluoromethylnaphth[1,2-*c*]isoxazole **(5)** in high yield.[7] Its possible regioisomer, the naphth[2,1-*d*]isoxazole derivative **7** was prepared in low yield by heating 2,4-bis(trifluoroacetyl)-1-naphthylamine **(6)**[1] with hydroxylamine hydrochloride in refluxing triethylamine for 18 h.[9,10] ^{13}C-NMR spectrometry enabled discrimination between these two isomers. The nitrogen-substituted carbon (C-9b) of **5** appeared at δ = 155.6, while the oxygen-substituted carbon (C-9b) of **7** gave a signal at δ = 165.0.

The present method is experimentally simple, convenient and useful for the synthesis of CF_3-containing benz[*g*]indazoles and naphthisoxazoles which are not easily obtained by other methods.[11] Evaluation of biological activities for **2–5** and **7** is now under way.

5-Trifluoroacetyl-3-trifluoromethyl-1*H*-benz[*g*]indazoles and -2*H*-benz[*g*]indazoles 2, 3; Typical Procedure:

Method A (*in the cases of hydrazine monohydrate, methyl- and phenylhydrazines*): To a stirred solution of **1** (1.00 g, 2.75 mmol) in $CHCl_3$ (20 mL) is added methylhydrazine (164 mg, 3.57 mmol) and the mixture is refluxed for 18 h. After removal of the solvent **3b** is obtained; yield: 957 mg (100%).

Benzindazole derivative **3d** is purified by silica gel column chromatography (hexane/benzene, 1:2).

Method B (*in the cases of tert-butyl- and p-nitrophenylhydrazine hydrochlorides*): To a suspension of *p*-nitrophenylhydrazine hydrochloride (730 mg, 3.85 mmol) and Et_3N (389 mg, 3.85 mmol) in MeCN (20 mL) is added **1** (1.00 g, 2.75 mmol), and this mixture is refluxed for 24 h. The solvent is then removed under reduced pressure and CH_2Cl_2 (100 mL) is added to the residue. This solution is washed with H_2O (200 mL) and dried (Na_2SO_4). The solvent is evaporated, and the crude mixture is chromatographed on a silica gel column (5 × 15 cm; 200 mesh; hexane/benzene, 2:3) to give **3e**; yield: 1033 mg (83%).

***N,N*-Dimethyl-*N'*-[2,4-bis(trifluoroacetyl)-1-naphthyl]hydrazine 4:**

To a stirred solution of **1** (1.00 g, 2.75 mmol) in MeCN (20 mL) is added *N,N*-dimethylhydrazine (198 mg, 3.30 mmol) and stirring is continued while refluxing for 4 h. Removal of the solvent under reduced pressure affords **4**; yield: 1038 mg (100%).

Synthesis of 2*H*-Benz[*g*]indazole Derivative 3b from 4:
A solution of **4** (600 mg, 1.59 mmol) and *p*-toluenesulfonic acid monohydrate (91 mg, 0.53 mmol) in xylene (8 mL) is refluxed for 72 h with stirring. The solvent is removed *in vacuo* to afford the crude mixture, which is chromatographed on a silica gel column (3 × 15 cm; 200 mesh; benzene) to give **3b**; yield: 259 mg (47%).

5-Trifluoroacetyl-3-trifluoromethylnaphth[1,2-*c*]isoxazole (5):
To a suspension of hydroxylamine hydrochloride (211 mg, 3.03 mmol) and Et_3N (306 mg, 3.03 mmol) in MeCN (20 mL) is added **1** (1.00 g, 2.75 mmol), and stirring is continued while refluxing for 5 h. The solvent is removed *in vacuo* and CH_2Cl_2 (100 mL) is added to the residue. The solution is washed with H_2O (200 mL), dried (Na_2SO_4), and concentrated to afford the naphthisoxazole derivative **5**; yield: 861 mg (94%).

5-Trifluoroacetyl-3-trifluoromethylnaphth[2,1-*d*]isoxazole (7):
To a stirred suspension of hydroxylamine hydrochloride (765 mg, 11.01 mmol) in Et_3N (20 mL) is added 2,4-bis(trifluoroacetyl)-1-naphthylamine **(6)** (1846 mg, 5.51 mmol), and this mixture is refluxed 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 (200 mL), and dried (Na_2SO_4). Removal of the solvent gives a crude mixture of **6** and **7**, which is chromatographed on a silica gel column (5 × 15 cm; 200 mesh; EtOAc) to furnish **7**; yield: 293 mg (16%).

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(7) Although the reaction of **1** with hydrazine hydrate, methylhydrazine (in $CHCl_3$), *N,N*-dimethylhydrazine, arylhydrazines and hydroxylamine hydrochloride proceeded even at room temperature, some starting material was recovered; elevated temperature were necessary to complete these reactions.
(8) It is not certain at present why the product distribution is solvent-dependent. Further investigations are now in progress.
(9) Prolonged reaction times caused decomposition of the products.
(10) Compound **7** is probably produced by prior formation of the oxime of **6** at the 2-trifluoroacetyl group, followed by an intramolecular N–O exchange reaction. It is thought that the ketoxime formation takes precedence over N–N exchange due to the low ability of NH_2 as a leaving group compared to Me_2N.[1]
(11) Compounds **2–5** cannot be obtained by reaction of 1-chloro- or 1-methoxy-2,4-bis(trifluoroacetyl)naphthalene with hydrazines and hydroxylamine, because of difficulty in bis-trifluoroacetylation of 1-chloro- and 1-methoxynaphthalenes with trifluoroacetic anhydride.