A Facile and Convenient Synthetic Method for Fluorine-Containing Benz[*c*]acridines and Dihydrobenz[*c*]acridines from *N,N*-Dimethyl-1-naphthylamine

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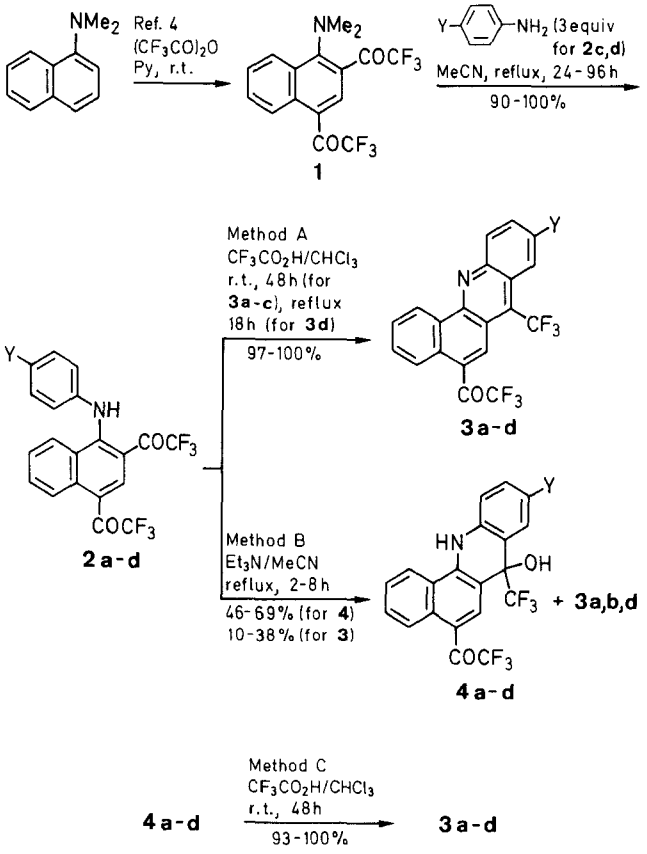
Aromatic nucleophilic nitrogen–nitrogen exchange reaction of *N,N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**1**) with *p*-substituted anilines gives the corresponding *N*-aryl-2,4-bis(trifluoroacetyl)-1-naphthylamines **2** in high yield. Acid-catalyzed cyclization of **2** affords selectively fluorine-containing benz[*c*]acridines **3** in almost quantitative yield, while the base-catalyzed cyclization gives fluorine-containing 7,12-dihydrobenz[*c*]acridines **4** in fair yield.

Recently much attention has been paid to the development of new methods for the synthesis of fluorine-containing heterocycles due to their potential importance in medicinal and agricultural scientific fields.[1-3] During our studies[4-7] on the novel nucleophilic substitutions at aromatic carbon atoms activated by a trifluoroacetyl group, it was found that *N,N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (**1**) can undergo various nitrogen–nitrogen exchange reactions. Namely, **1** reacted with various amines,[4] thiols[7] and alcohols[7] to give 2,4-bis(trifluoroacetyl)-1-naphthylamines, and the corresponding sulfides and ethers in excellent yields. As an extention of this work[4-7] the present study was undertaken to synthesize naphthalene-fused quinolines (benzacridines) and dihydroquinolines (dihydrobenzacridines) bearing trifluoromethyl groups. These fluorine-containing heterocycles are expected to show interesting biological activities and are hardly accessible by other methods.



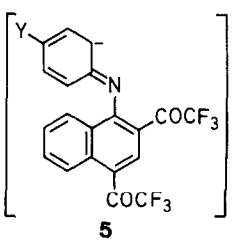
2–4	a	b	c	d
Y	OMe	Me	H	Cl

N-Aryl-2,4-bis(trifluoroacetyl)-1-naphthylamines **2a–d** were obtained in 90–100% yields by the aromatic nucleophilic dimethylamino–arylamino exchange reaction of **1**, which is prepared[4] by bistrifluoroacetylation of *N,N*-dimethyl-1-naphthylamine, with *p*-substituted anilines in refluxing acetonitrile for 24–96 h.

Acid-catalyzed cyclization of *N*-aryl-2,4-bis(trifluoroacetyl)-1-naphthylamines **2a–c** with trifluoroacetic acid proceeded easily even at room temperature in chloroform, to afford the corresponding 5-trifluoroacetyl-7-trifluoromethylbenz[*c*]acridines **3a–c** in almost quantitative yield. In the case of *p*-chloro derivative **2d** refluxing in the same solvent was necessary for completion of the reaction within moderate reaction time.

Base-catalyzed cyclization of **2a–d** using triethylamine proceeded also at reflux temperature in acetonitrile. Interestingly, in contrast to the case of acid-catalyzed cyclization, **2c** gave exclusively 7-hydroxy-5-trifluoroacetyl-7-trifluoromethyl-7,12-dihydrobenz[*c*]acridine (**4c**) in 62% yield. The other *p*-substituted derivatives **2a, b, d** afforded predominantly dihydroacridines **4a, b, d** (46–69% yield) together with some benzacridines **3a, b, d** (10–38% yield). Separation of **4** and **3** in these cases was performed by column chromatography on silica gel. In the case of the *p*-chloro derivative **2d**, a short reaction time (2 h) was necessary in order to suppress subsequent dehydration to **3d** and obtain **4d** in high yield. For example, prolonged (4 h) heating of **2d** provided **4d** and **3d** in 38% and 50% yield, respectively. The cyclization of **2d** to **4d** (or **3d**) did not proceed merely by refluxing in acetonitrile for 2 h without a catalyst. It is noteworthy that even a weak base such as triethylamine serves as an efficient catalyst for this cyclization. The cyclization presumably occurs by deprotonation from the nitrogen atom of **2** by triethylamine to give an intermediate anionic species **5**, followed by intramolecular nucleophilic attack on the carbonyl carbon of the trifluoroacetyl group.

Treatment of dihydrobenzacridines **4a–d** with trifluoroacetic acid at room temperature for 48 h in chloroform



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caused dehydration to give the benzacridines **3a–d** in excellent yield.

The structures of compounds **2–4** were determined from their ^{1}H-NMR and IR spectra and elemental analyses. As a representative case ^{13}C-NMR spectrum of dihydrobenzacridine **4c** showed a characteristic signal for 7-C bearing hydroxy and trifluoromethyl groups at $\delta = 70.3$ (q, $J_{C-F} = 29.7$ Hz).

Compounds **2** cannot be obtained from 1-chloro-2,4-bis(trifluoroacetyl)naphthalene, because bistrifluoroacetylation does not occurs on 1-chloronaphthalene. Accordingly, this method using the nitrogen–nitrogen exchange reaction and obtaining **3** or **4** by only three steps starting from *N,N*-dimethyl-1-naphthylamine presents a simple and convenient synthetic route to trifluoromethyl-containing benz[*c*]acridines and dihydrobenz[*c*]acridines. Evaluation of biological activities for **2a–d** as well as **3a–d** and **4a–d** is now in progress.

***N*-(4-Methoxyphenyl)-2,4-bis(trifluoroacetyl)-1-naphthylamine (2a); Typical Procedure:**

To a stirred solution of **1** (1.00 g, 2.75 mmol) in MeCN (20 mL) is added *p*-anisidine (373 mg, 3.03 mmol) and stirring is continued at reflux temperature for 24 h. The solvent is removed under reduced pressure and CH_2Cl_2 (100 mL) is added to the residue. This solution is washed with 2N HCl (100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure affords **2a**; yield: 1.21 g (100%). In the synthesis of **2c** and **2d** 3 mmol of aniline and

Table. Compounds **2–4** Prepared

Product	Method	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b]	IR (KBr)[c] ν(cm^{-1})			^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)
					OH	NH	C=O	
2a	–	100	171–172 (hexane/benzene)	$C_{21}H_{13}F_6NO_3$ (441.3)	–	3280–2690	1695 1644	3.78 (s, 3H, OCH_3), 6.70–7.20 (m, 5H$_{arom}$), 7.43–7.87 (m, 2H$_{arom}$), 8.60 (s, 1H, H-3), 8.70 (d, 1H, J = 8, H-5), 12.10 (br s, 1H, NH)
2b	–	90	182–183 (hexane/benzene)	$C_{21}H_{13}F_6NO_2$ (425.3)	–	3270–2675	1695 1656	2.33 (s, 3H, CH_3), 6.78–7.17 (m, 5H$_{arom}$), 7.40–7.83 (m, 2H$_{arom}$), 8.55 (s, 1H, H-3), 8.80 (d, 1H, J = 8, H-5), 12.05 (br s, 1H, NH)
2c	–	93	132–133 (hexane/benzene)	$C_{20}H_{11}F_6NO_2$ (411.3)	–	3270–2765	1694 1662	6.88–8.00 (m, 8H$_{arom}$), 8.60 (s, 1H, H-3), 8.95 (d, 1H, J = 8, H-5), 11.6–12.3 (br, 1H, NH)
2d	–	98	184–185 (hexane/benzene)	$C_{20}H_{10}ClF_6NO_2$ (445.8)	–	3260–2760	1693 1661	6.83–7.27 (m, 5H$_{arom}$), 7.77–7.81 (m, 2H$_{arom}$), 8.57 (s, 1H, H-3), 8.85 (d, 1H, J = 8, H-5), 11.6–12.1 (br, 1H, NH)
3a	A C	98 100	179–180 (hexane/benzene)	$C_{21}H_{11}F_6NO_2$ (423.3)	–	–	1716	3.92 (s, 3H, OCH_3), 7.27–7.72 (m, 4H$_{arom}$), 8.02 (d, 1H, J = 10, H-11), 8.40 (dd, 1H, J = 3, 6, H-1), 8.82 (s, 1H, H-6), 9.25 (dd, 1H, J = 3, 6, H-4)
3b	A C	100 95	166–167 (hexane/$CHCl_3$)	$C_{21}H_{11}F_6NO$ (407.3)	–	–	1719	2.49 (s, 3H, CH_3), 7.27–7.70 (m, 3H$_{arom}$), 7.77–8.03 (m, 2H$_{arom}$), 8.22 (dd, 1H, J = 3, 6, H-1), 8.67 (s, 1H, H-6), 9.10 (dd, 1H, J = 3, 6, H-4)
3c	A C	100 100	148–149 (hexane/benzene)	$C_{20}H_9F_6NO$ (393.3)	–	–	1716	7.30–8.30 (m, 7H$_{arom}$), 8.68 (s, 1H, H-6), 9.03 (dd, 1H, J = 3, 6, H-4)
3d	A C	97 93	160–161 (hexane/$CHCl_3$)	$C_{20}H_8ClF_6NO$ (427.8)	–	–	1730	7.43–7.83 (m, 3H$_{arom}$), 7.86–8.39 (m, 3H$_{arom}$), 8.68 (s, 1H, H-6), 9.11 (dd, 1H, J = 3, 6, H-4)
4a[e]	B	62	195–196 ($CHCl_3$/EtOAc)	$C_{21}H_{13}F_6NO_3$ (441.3)	3560	3440	1676	3.77 (s, 3H, OCH_3), 5.07 (s, 1H, OH), 6.83–7.33 (m, 3H$_{arom}$), 7.46–7.87 (m, 2H$_{arom}$), 8.00–8.33 (m, 1H, H-1), 8.4–8.8 (br, 2H, H-6 and NH), 8.83–9.17 (m, 1H, H-4)[f]
4b[e]	B	69	250–251 ($CHCl_3$/EtOAc)	$C_{21}H_{13}F_6NO_2$ (425.3)	3570	3410	1667	2.38 (s, 3H, CH_3), 5.19 (s, 1H, OH), 7.24 (s, 2H$_{arom}$), 7.59–7.76 (m, 3H$_{arom}$), 8.20–8.43 (m, 1H, H-1), 8.57–8.87 (m, 2H, H-6 and NH), 8.95–9.20 (m, 1H, H-4)[f]
4c[e]	B	62	217–218 ($CHCl_3$/EtOAc)	$C_{20}H_{11}F_6NO_2$ (411.3)	3555	3460	1698	5.07 (s, 1H, OH), 6.93–7.93 (m, 6H$_{arom}$), 8.03–8.67 (m, 1H, H-1), 8.4–8.8 (br, 2H, H-6, NH), 8.87–9.17 (m, 1H, H-4)[f]
4d[e]	B	46	214–215 ($CHCl_3$/EtOAc)	$C_{20}H_{10}ClF_6NO_2$ (445.8)	3565	3400	1663	5.39 (s, 1H, OH), 7.26–7.86 (m, 5H$_{arom}$), 8.13–8.39 (m, 1H, H-1), 8.63 (s, 1H, H-6), 8.76–9.16 (m, 2H, H-4, NH)[f]

[a] Yield of isolated products.

[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.24, Cl ±0.24, F ±0.29, N ±0.29; exception: **2a**, N +0.42.

[c] Recorded on a Hitachi Model EPI-G3 grating spectrophotometer.

[d] Measured using a JEOL PMX-60SI spectrophotometer.

[e] Byproducts are for **4a**: **3a** 38%, for **4b**: **3b** 19%, for **4d**: **3d** 10%, **2d** (recovery) 32%.

[f] Solvents used; $CD_3CN/CDCl_3$ for **4a–c**: CD_3CN for **4d**.

p-chloroaniline, respectively, are used to 1 mmol of **1**. The following reaction time applies; 24 h for **2b**, 48 h for **2c** and 96 h for **2d**.

9-Methoxy-5-trifluoroacetyl-7-trifluoromethylbenz[*c*]acridine (3a); Typical Procedure:

Method A: To a solution of **2a** (1.32 g, 3 mmol) in $CHCl_3$ (10 mL) is added CF_3CO_2H (10 mL), and this solution is stirred at r.t. for 48 h. The mixture is washed with an ice-cold aq 10% Na_2CO_3 (100 mL) and H_2O (200 mL), extracted with CH_2Cl_2 (200 mL), and dried (Na_2SO_4). The solvent is evaporated to give the benzacridine **3a**; yield: 1.24 g (98%).

9-Methoxy-5-trifluoroacetyl-7-trifluoromethylbenz[*c*]acridine (3a) and 7-Hydroxy-9-methoxy-5-trifluoroacetyl-7-trifluoromethyl-7,12-dihydrobenz[*c*]acridine (4a); Typical Procedure:

Method B: To a stirred solution of **2a** (1.21 g, 2.74 mmol) in MeCN (20 mL) is added Et_3N (277 mg, 2.74 mmol) and the mixture is refluxed for 8 h. The solvent is removed under reduced pressure and the crude mixture is chromatographed on a silica gel column (3 × 20 cm; 200 mesh) using benzene/EtOAc (19:1) and hexane/benzene (1:1) as eluent to afford **4a** [yield: 750 mg (62%)] and **3a** [yield: 440 mg (38%)].

The following eluents are used; benzene/EtOAc (19:1) for **4b, d** and hexane/benzene (1:1) for **3b, d**. The following reaction time applies; 8 h for **4b**, 4 h for **4c** and 2 h for **4d**.

^{13}C-NMR of **4c** (DMSO-d_6/TMS): δ = 70.3 (q, J_{CF} = 29.7 Hz), 109.4(s), 115.3(s), 116.3(d), 117.3 (q, J_{CF} = 294.2 Hz), 118.3(s), 121.8(s), 122.9(d), 123.1(d), 124.4 (q, J_{CF} = 256.3 Hz), 125.7(d), 126.8(d), 128.4(d), 130.1(d), 130.6(d), 132.2(s), 136.3(d), 136.7(s), 141.2(s), 178.3 (q, J_{CF} = 30.5 Hz).

Dehydration of 4a to 3a; Typical Procedure:

Method C: To a solution of **4a** (1.21 g, 2.74 mmol) in $CHCl_3$ (10 mL) is added CF_3CO_2H (10 mL), and this solution is stirred at r.t. for 48 h. The mixture is washed with an ice-cold aq 10% Na_2CO_3 (100 mL) and H_2O (200 mL), extracted with CH_2Cl_2 (200 mL), and dried (Na_2SO_4). The solvent is evaporated to give benzacridine **3a**; yield: 1.17 g (100%).

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