

N,N-Bis(difluoromethyl)anilines

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Abstract

N,N-Diformylanilines were prepared by the reaction of formanilide *N*-sodium derivatives with acetic–formic anhydride. Treatment of the *N,N*-diformylanilines with PCl_5 and POCl_3 solution led to *N,N*-bis(dichloromethyl)anilines, which were transformed to *N,N*-bis(difluoromethyl)anilines by reaction with anhydrous hydrogen fluoride in pentane solution.

Keywords: *N,N*-Diformylanilines; Acetic–formic anhydride; *N,N*-Bis(dichloromethyl)anilines; Hydrogen fluoride; *N,N*-Bis(difluoromethyl)anilines; NMR spectroscopy

1. Introduction

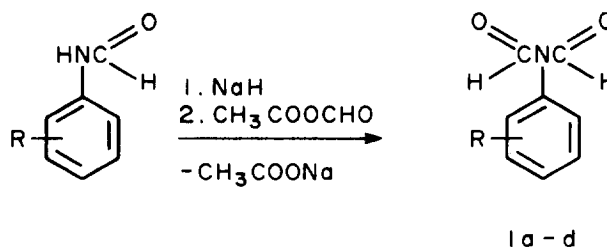
Aromatic compounds with $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{SCF}_3$ and $-\text{SCHF}_2$ substituents have attracted considerable attention because of their many uses as precursors for pharmacological preparations, as well as for pesticides, liquid crystals and dye syntheses [1]. Similar compounds with fluorinated nitrogen-containing groups are only known for $\text{ArN}(\text{CH}_3)\text{CF}_3$ [2] and $\text{ArN}(\text{CF}_3)_2$ [1,3,4]. Their applications are limited as yet, probably because there are still no reliable preparative methods for their synthesis. *N,N*-Bis-(difluoromethyl)-anilines have not been known previously.

The objective of this communication is to report the preparation of *N,N*-bis(difluoromethyl)anilines.

2. Results and discussion

N,N-Diformylanilines were chosen as starting substances. *N,N*-Diformylaniline as the only representative of this type of compound was synthesised by Allenstein et al. by heating formanilide with *N,N*-diformylacetamide [5]. However, a mixture of *N*-formylacetamide, initial formanilide and *N,N*-diformylaniline was actually formed in this reaction. It was then separated by fractionation in vacuo. The preparation of *N,N*-diformylacetamide is difficult and takes a lot of time.

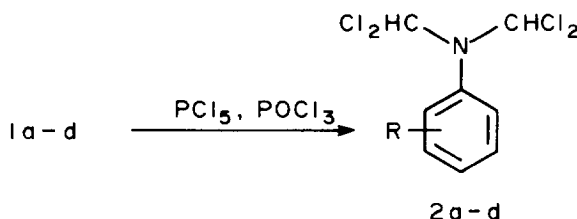
We have prepared *N,N*-diformylanilines **1a–d** by the interaction of the *N*-sodium derivatives of formanilides with acetic–formic anhydride.



R = H (a), 4-Cl (b), 3-CF₃ (c), 4-NO₂ (d)

N,N-Diformyl-3-trifluoromethylaniline is a liquid. All the other *N,N*-diformylanilines are colourless crystalline solids. The yields of compounds **1a–d**, their physical properties, elemental analyses and ¹H NMR data are listed in Table 1.

N,N-Diformylanilines **1a–d** were converted into *N,N*-bis(dichloromethyl)anilines **2a–d** by treatment with PCl_5 in POCl_3 solution.



The reaction is complete within 2 h at 80 °C. Compounds **2a–c** were purified by vacuum distillation. Compound **2d**, which can decompose on distillation, was dried in vacuo at 60 °C. The yields, physical properties, elemental analyses and ¹H NMR data are summarized in Table 2.

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Table 1
N,N-Diformylanilines $\text{RC}_6\text{H}_4\text{N}(\text{CHO})_2$ **1a–d**

Product	R	Yield (%)	M.p. (°C) (solvent for cryst.) or b.p. (°C/Torr)	Formula	Elemental microanalyses: found/calculated (%)			¹ H NMR (CD ₃ CN/HMDS) (δ ppm)
					C	H	N	
1a	H	56	64–65 (CCl ₄ /ether)	C ₈ H ₇ NO ₂	<u>64.65</u> 64.42	<u>4.76</u> 4.72	<u>9.20</u> 9.39	7.05–7.42 (m, 5H, CH arom.); 8.99 (s, 2H, CHO)
1b	4-Cl	67.5	100–101 (CCl ₄ /hexane)	C ₈ H ₆ ClNO ₂	<u>52.64</u> 52.34	<u>3.13</u> 3.30	<u>7.57</u> 7.63	7.13–7.18, 7.42–7.47 (dm, 4H, CH arom.); 8.95 (s, 2H, CHO)
1c	3-CF ₃	64	98–100 (0.04)	C ₉ H ₆ F ₃ NO ₂	<u>49.75</u> 49.78	<u>2.85</u> 2.78	<u>6.56</u> 6.44	7.20–7.80 (m, 4H, CH arom.); 9.03 (s, 2H, CHO)
1d	4-NO ₂	73	117–119 (glym/CCl ₄)	C ₈ H ₆ N ₂ O ₄	<u>49.28</u> 49.49	<u>3.02</u> 3.16	<u>14.50</u> 14.43	7.40–7.45, 8.23–8.29 (dm, 4H, CH arom.); 8.99 (s, 2H, CHO)

It should be mentioned that *N,N*-bis(dichloromethyl)-aniline (**2a**) has been obtained by Allenstein and Sille by treatment of *N,N*-diformylaniline (**1a**) with PCl₅ in petroleum ether [6]. However, the melting point of this compound given in Ref. [6] as 75 °C differs from that found by us at 41–42 °C.

N-methyl- and *N*-ethyl-bis(difluoromethyl)amines were obtained by treatment of the corresponding bis(dichloromethyl)amines with antimony(III) fluoride in the absence of solvent [7]. When we tried to fluorinate *N,N*-bis(dichloromethyl)aniline with SbF₃ or SbF₅ in the presence of catalytic amounts of SbCl₅ at 40–50 °C with the simultaneous distillation of the reaction products in vacuo, we obtained a mixture of C₆H₅N(CHF₂)₂, C₆H₅N(CHO)(CHF₂) and C₆H₅NHCHF₂. The yield of this mixture did not exceed 10%. In the ¹⁹F NMR spectrum of this mixture there were three groups of signals at δ = –90.5, –94.5 and –103.2 ppm, which correspond to the –N(CHF₂)₂, –N(CHO)(CHF₂) and –NHCHF₂ substituents with intensities of 14:1:3 on fluorination with SbF₃/SbCl₅ or 4:1:2 on fluorination with SbF₅.

Table 2
N,N-Bis(dichloromethyl)anilines $\text{RC}_6\text{H}_4\text{N}(\text{CHCl}_2)_2$ **2a–d**

Product	R	Yield (%)	M.p. (°C) or b.p. (°C/Torr)	Formula	Elemental microanalyses: found/calculated (%)				¹ H NMR (CDCl ₃ /HMDS) (δ ppm)
					C	H	N	Cl	
2a	H	91.5	41–42 100–101 (0.05)	C ₈ H ₇ Cl ₄ N	<u>37.28</u> 37.10	<u>2.48</u> 2.52	<u>5.72</u> 5.41	<u>55.36</u> 54.76	7.31 (s, 2H, CHCl ₂); 7.45–7.60 (m, 5H, CH arom.)
2b	4-Cl	94	122–123 (0.05)	C ₉ H ₆ Cl ₅ N				<u>59.90</u> 60.04	7.17 (s, 2H, CHCl ₂); 7.30–7.50 (m, 4H, CH arom.)
2c	3-CF ₃	79	96–97 (0.05)	C ₉ H ₆ Cl ₄ F ₃ N				<u>42.93</u> 43.37	7.22 (s, 2H, CHCl ₂); 7.55–7.72 (m, 4H, CH arom.)
2d	4-NO ₂	97.5	75–76	C ₈ H ₆ Cl ₄ N ₂ O ₂				<u>45.97</u> 46.67	7.35 (s, 2H, CHCl ₂); 7.55–7.72 (m, 4H, CH arom.)

Fluorination of *N,N*-bis(dichloromethyl)aniline with anhydrous hydrogen fluoride at –10 °C did not lead to *N,N*-bis(difluoromethyl)aniline and a mixture of C₆H₅N(CHO)(CHF₂) and C₆H₅NHCHF₂ in a ratio of 1:3 was obtained.

Treatment of C₆H₅N(CHO)₂ with sulphur tetrafluoride in anhydrous HF solution at 40–90 °C or with sulphur tetrafluoride in the presence of potassium fluoride at 150 °C, as described for *N*-ethyl-*N*-formylaniline in Ref. [8], caused resinification and decomposition. Better results were achieved by treatment of *N,N*-bis(dichloromethyl)anilines with SF₄ in the presence of KF at 40–50 °C. After vacuum distillation, the mixture obtained in ca. 85% yield contained, as judging from the ¹⁹F NMR spectrum, *N,N*-bis(difluoromethyl)aniline as the main product. However, the mixture included about 15% of impurities which could not be separated.

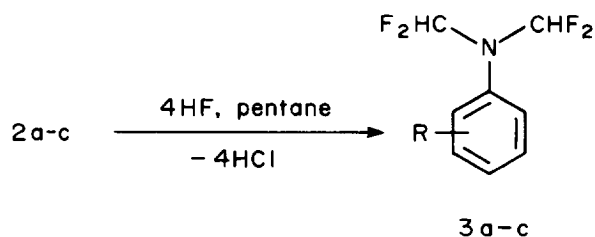
Our attempt to fluorinate *N,N*-bis(dichloromethyl)aniline with *py*·*n*HF in hexane solution at ambient temperature gave pure *N,N*-bis(difluoromethyl)aniline in ca. 20% yield instead. The low yield may be attributed to the solubility of

Table 3
N,N-Bis(difluoromethyl)anilines $\text{RC}_6\text{H}_4\text{N}(\text{CHF}_2)_2$ **3a–c**

Product	R	Yield (%)	B.p. (°C/Torr)	Reaction temperature	Formula	Elemental microanalyses: found/calculated (%)		^1H NMR (CDCl ₃ /HMDS) (δ ppm)	^{19}F NMR (CDCl ₃ /CCl ₃ F) (δ ppm)
						C	H		
3a	H	79	43–45 (0.3)	–30 to +5	$\text{C}_8\text{H}_7\text{F}_4\text{N}$	49.34 49.75	3.26 3.65	6.51 (m, 2H, CHF ₂); 7.30–7.47 (m, 5H, CH arom.)	–90.88 (m, 4F, CHF ₂)
3b	4-Cl	72.5	61–63 (0.15)	–5 to +30	$\text{C}_8\text{H}_6\text{ClF}_4\text{N}$	42.12 42.21	2.66 2.66	6.43 (m, 2H, CHF ₂); 7.20–7.40 (m, 4H, CH arom.)	–91.07 (m, 4F, CHF ₂)
3c	3-CF ₃	64	72–74 (15)	–20 to +30	$\text{C}_9\text{H}_6\text{F}_7\text{N}$	41.45 41.39	2.39 2.31	6.48 (m, 2H, CHF ₂); 7.40–7.60 (m, 4H, CH arom.)	–91.06 (m, 4F, CHF ₂); –63.26 (s, 3F, CF ₃)

the reaction product in $\text{py} \cdot n\text{HF}$ and its decomposition in the presence of HF.

As a result, we have concluded that it is better to fluorinate compounds **2a–d** in an inert non-polar solvent in which both starting substances and reaction products can dissolve, hydrogen fluoride being insoluble. Thus, we have accomplished the conversion of the *N,N*-bis(dichloromethyl)anilines **2a–c** to *N,N*-bis(difluoromethyl)anilines **3a–c** by treatment of compounds **2a–c** with a small excess of anhydrous hydrogen fluoride in pentane solution at -5°C to -30°C . To complete the reaction, the temperature was increased to 0°C to $+30^\circ\text{C}$ depending on the substituent in the benzene ring. Thus the low concentration of reaction products in hydrogen fluoride was ensured.



N,N-Bis(dichloromethyl)-4-nitroaniline (**2d**) is poorly soluble in pentane and other non-polar solvents, which is why *N,N*-bis(difluoromethyl)-4-nitroaniline could not be obtained by the above method. Its concentration in the reaction mixture was established by ^{19}F NMR spectrum as ca. 40%.

N,N-Bis(difluoromethyl)anilines **3a–c** are colourless liquids which are hydrolyzed by atmospheric moisture and which decompose when stored in a glass vessel. The yields of compounds **3a–c**, their boiling points, temperatures of reaction, elemental analyses, ^{19}F and ^1H NMR data are summarized in Table 3.

The ^{19}F NMR spectrum of the $-\text{N}(\text{CHF}_2)_2$ group in these compounds is the $\text{A}_2\text{A}_2'$ part of a six-spin system $\text{A}_2\text{A}_2'\text{XX}'$, the ^1H NMR spectrum being the XX' part of this system. The spin–spin coupling constants have been determined for compounds **3a–c** as $J_{\text{F-H}} = 60\text{--}61$ Hz and $J_{\text{F-F}} = 7\text{--}7.5$ Hz. The

chemical shifts to the centres of corresponding multiplets are listed in Table 3.

In conclusion, a suitable method has been found for fluorinating some unstable, hydrogen fluoride-sensitive substances. The feature of the method is the treatment of such compounds with HF in a non-polar solvent in which HF is not soluble.

3. Experimental details

^1H and ^{19}F NMR spectra were recorded on either a Varian Gemini-200 (188.18 MHz) or a Bruker WP-200 (200 MHz) spectrometer, using HMDS and CCl₃F as internal standards, respectively, and CDCl₃ and CD₃CN as solvents. THF was freshly distilled from sodium benzophenone ketyl immediately prior to use. DME and ether were distilled from LiAlH₄.

3.1. *N,N*-Diformylanilines **1a–d**. General procedure

A solution or suspension of the corresponding *N*-formylaniline (50 mmol) in anhydrous THF or DME was added dropwise to a stirred suspension of NaH (1.34 g, 55 mmol) in THF or DME (50 ml). The mixture was stirred at ambient temperature for 30 min and the precipitate was filtered off and washed with the solvent under an inert dry atmosphere. A solution of acetic–formic anhydride (5 g, 55 mmol) in anhydrous Et₂O (50 ml) was added to the vigorously stirred filtrate and the mixture was stirred for 1 h at r.t. The precipitate was filtered off and the filtrate evaporated in vacuo. The residue was recrystallized to give **1a**, **b**, **d**, or distilled in vacuo to give **1c**. In the case of **1a** the residue was dissolved in CCl₄ (20 ml) and Et₂O (5 ml) and the mixture cooled to -60°C . The precipitate was filtered off and pentane (10 ml) added to the filtrate. The mixture was cooled again and the additional **1a** collected.

3.2. *N,N*-Bis(dichloromethyl)anilines **2a–d**. General procedure

A mixture of *N,N*-diformylaniline **1a–d** (20 mmol), PCl_5 (9.36 g, 45 mmol) and POCl_3 (5 ml) was stirred at 80 °C for 2 h. POCl_3 was evaporated and the residue distilled in vacuo to give **2a–c** or stored in vacuo (0.05 mmHg, 60 °C, 3 h) to give **2d**.

3.3. *N,N*-Bis(difluoromethyl)anilines **3a–c**. General procedure

Anhydrous HF (2.4 g, 120 mmol) was condensed into a Teflon vessel containing 20 ml of pentane. A solution of **2a–c** (20 mmol) in pentane (20 ml) was added dropwise to this mixture at –30 °C with stirring. After 5 min, the mixture

was slowly allowed to warm to the temperature cited in Table 3 and stirred until the gaseous products had escaped. The pentane layer was separated, concentrated in vacuo and distilled in vacuo from the quartz flask.

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