Preliminary Note

A new one-pot synthesis of 1,2,3,4-tetrafluoroacridines and some 7-substituted derivatives [1]

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Abstract

1,2,3,4-Tetrafluoroacridine (**1a**) and a range of 7-substituted analogues can be synthesised by heating pre-formed Schiff bases (*E*)-$C_6F_5CH{=}NC_6H_4R$-*p* (**3**) (from $C_6F_5CHO + H_2NC_6H_4R$-*p*) with the parent aniline $H_2NC_6H_4R$-*p* (1:1 molar ratio) or by heating a mixture of the aldehyde C_6F_5CHO and the aniline $H_2NC_6H_4R$-*p* (R = H, OMe, Me Bu^t, F, Cl and Br) (1:2 molar ratio) in toluene or 1,2-dichlorobenzene under reflux. The mechanism has been deduced through the isolation in certain reactions of *ortho*-substituted Schiff bases 2-(*p*-$RC_6H_4NH)C_6F_4CH{=}NC_6H_4R$-*p* (**6**) (R = Cl or Br), which on acid catalysis (by *p*-$RC_6H_4NH_3^+F^-$) undergo ring-closure with elimination of the aniline *p*-$RC_6H_4NH_2$. Except where R = F, Cl or Br, substantial amounts of the corresponding 3-anilino-1,2,4-trifluoroacridines **5** are also formed; these arise via sequential *para*- and *ortho*-substitution of fluorine in the pentafluorophenyl moiety of the Schiff bases. The synthesis is capable of extension to other fluorinated aromatic aldehydes, e.g. the formation of 1-fluoro-7-methoxyacridine (**9**) from 2,6-difluorobenzaldehyde and *p*-anisidine.

1,2,3,4-Tetrafluoroacridine (**1a**) was first synthesised in 1966 from pentafluorophenylmagnesium bromide [2] via a modification of the Lehmstedt–Tanasescu rearrangement [3, 4] leading to 1,2,3,4-tetrafluoroacridin-9-one; certain derivatives were also prepared. Of more relevance to the present work were reports (i) in 1971 that treatment of methyl pentafluorophenyl ketone with aniline afforded 3-anilino-1,2,4-trifluoro-9-methylacridine (**2**) [5] (Scheme 1), a method which was extended later to derivatives of aniline [6]; and (ii) in 1977 that the acridine **1a** could be prepared from pentafluorobenzaldehyde and the Grignard reagent PhNHMgBr [7] (Scheme 2).

In 1990, during a study of Schiff bases of the type $C_6F_5CH{=}NAr$ (**3**), Flowers and DeFigueredo of this department observed that when the aldehyde

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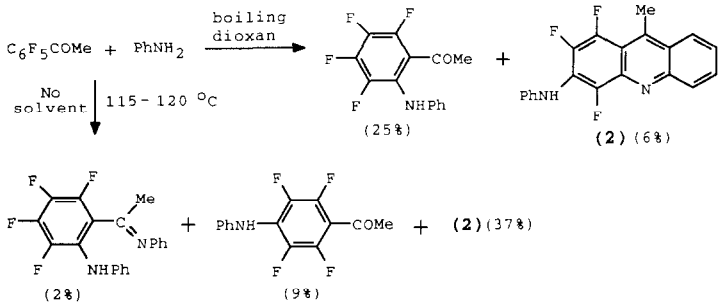
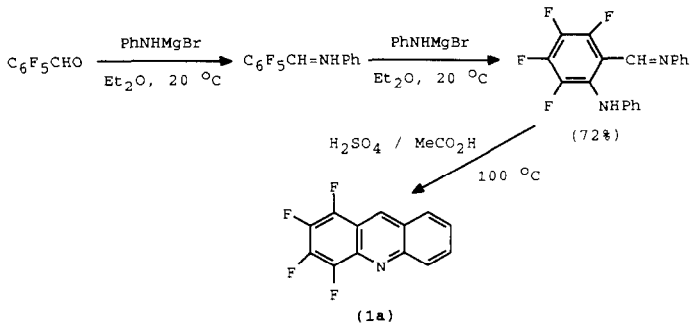
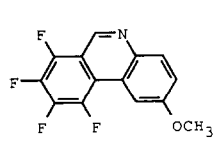


Scheme 1.



Scheme 2.

C_6F_5CHO and *p*-anisidine were heated together in n-butyl acetate under reflux, the Schiff base expected [$C_6F_5CH{=}NC_6H_4OMe$-*p* (**3b**)] was contaminated with another product. On the basis of elemental analysis and NMR (^1H and ^{19}F) and mass spectral data, this by-product was thought to be 7,8,9,10-tetrafluoro-2-methoxyphenanthridine (**4**) [8]. We have repeated their work and, using X-ray crystallography, shown this compound to be the structural 'ring' isomer 1,2,3,4-tetrafluoro-7-methoxyacridine (**1b**) [9]. Note that NMR and mass spectral data do not allow isomers **4** and **1b** to be differentiated.



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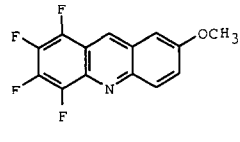


(1b)

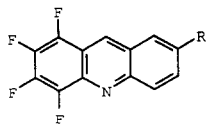
We have synthesised a range of 7-substituted-1,2,3,4-tetrafluoroacridines (**1a–1g**) by heating pre-formed Schiff bases of the type $C_6F_5CH{=}NC_6H_4R$-*p* (**3**) (*E*-isomers according to X-ray crystallography [9]) with the parent aniline (1:1 molar ratio), or by heating a mixture of the aldehyde C_6F_5CHO and anilines $H_2NC_6H_4R$-*p* (1:2 molar ratio) in boiling inert solvents (toluene or 1,2-dichlorobenzene) for 66–70 h (see Table 1).

TABLE 1

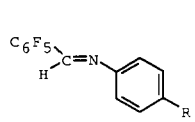
Reaction of *para*-substituted anilines with Schiff bases **3** (1:1 molar ratio; method A) and with pentafluorobenzaldehyde (2:1 molar ratio; method B)

R in p-$RC_6H_4NH_2$	Method	Temp. (°C)	Products isolated (%)[e]		Crude product ratio[g]				
			1	**5**	**1**	**5**	**3**	**6**	**7**
OMe[a]	A	179[c]	30	30	42	55	3	0	0[h]
OMe[a]	B	111[d]	32	9[f]	32	10	38	0	20
OMe[a]	B	179[c]	19	21	32	68	0	0	0
H[b]	B	179[c]	48	21	55	34	8	0	3
Me[b]	B	179[c]	39	15	58	30	4	0	8
Bu^t[b]	B	179[c]	46	0	73	18	3	0	6
F[b]	B	179[c]	66	0	91	4	4	0	1
Cl[a]	B	179[c]	52	0	69	0	10	20	1
Br[b]	B	179[c]	36	0	44	0	21	34	1

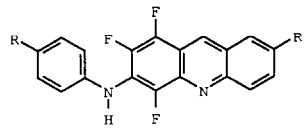
[a]Product work-up by dry-column flash chromatography.
[b]Product work-up by sublimation.
[c]Boiling 1,2-dichlorobenzene.
[d]Boiling toluene.
[e]Based on reactant Schiff base **3** or C_6F_5CHO.
[f]The Schiff bases **3b** (32%) and **7b** (7%) were also isolated.
[g]Ratios determined by ^{19}F NMR spectroscopy.
[h]Trace amount observed.



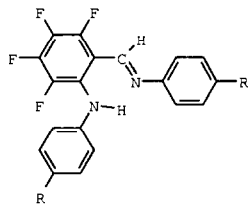
(**1**) **a**, R = H
b, R = OMe
c, R = Me
d, R = Bu^t
e, R = F
f, R = Cl
g, R = Br



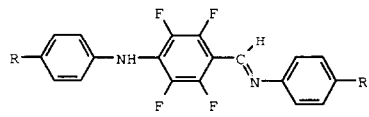
(**3**) **a**, R = H
b, R = OMe
c, R = Me
d, R = Bu^t
e, R = F
f, R = Cl
g, R = Br



(**5**) **a**, R = H
b, R = OMe
c, R = Me
d, R = Bu^t
e, R = F
f, R = Cl
g, R = Br



(**6**) **a**, R = H
b, R = OMe
c, R = Me
d, R = Bu^t
e, R = F
f, R = Cl
g, R = Br

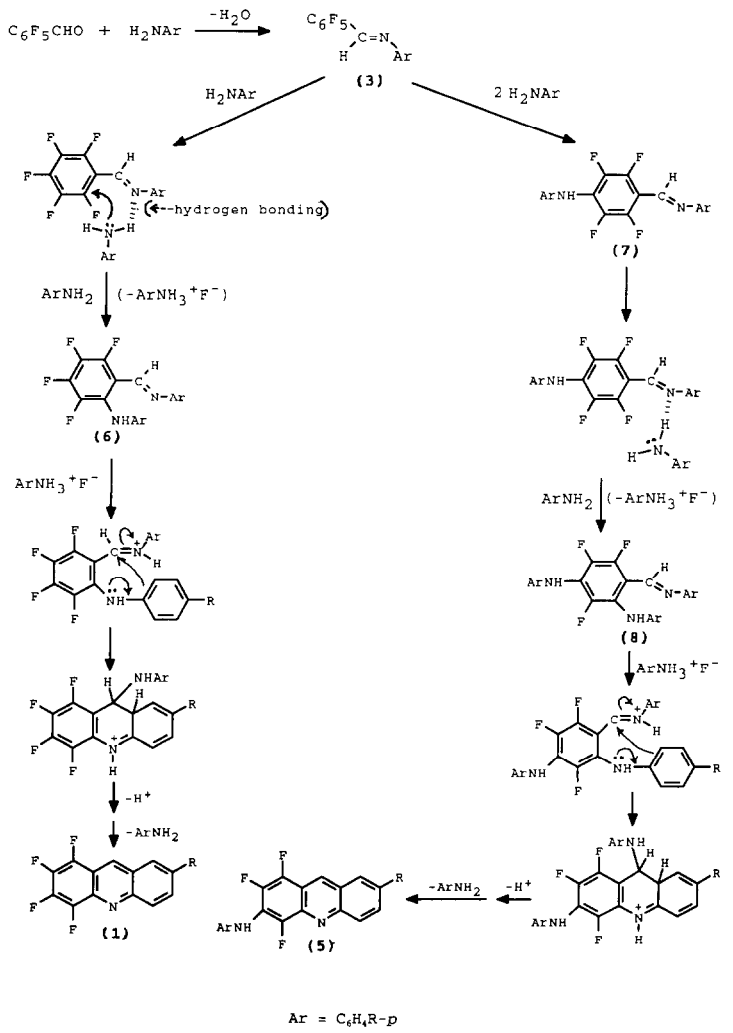


(**7**) **a**, R = H
b, R = OMe
c, R = Me
d, R = Bu^t
e, R = F
f, R = Cl
g, R = Br

Crude product ratios observed for the reactions carried out at 179 °C indicate that the relative yields of the tetrafluoroacridines **1** and the 3-anilino-1,2,4-trifluoroacridines **5** depend on the nucleophilicity/base strength of the aniline employed. Thus, the 3-anilino-1,2,4-trifluoroacridine **5b** is the major product from *p*-anisidine, and appreciable amounts of the corresponding substituted trifluoroacridines **5a**, **5c** and **5d** are formed from aniline and its 4-alkyl derivatives. However, with anilines which contain *para* halogen (F, Cl or Br), substituted acridines **5e–5g** are formed in low yield or not at all. At lower temperature (111 °C) with *p*-anisidine, formation of the 3-anilino-1,2,4-trifluoroacridine **5b** is less favoured than at 179 °C.

Acridines **1** and **5** are thought to be formed via the *ortho*- and *para*-substituted Schiff bases **6** and **7** respectively, with the latter then undergoing further substitution to give the 2,4-bis-anilino Schiff bases (**8**) (Scheme 3).

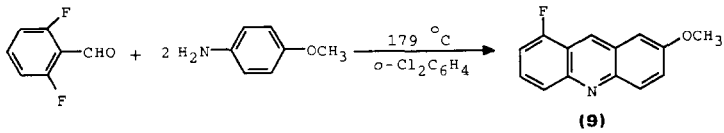
The following observations are pertinent to our conclusions. (i) In the reactions involving 4-chloro- and 4-bromo-aniline, appreciable amounts of the *ortho*-substituted Schiff bases **6f** and **6g** were formed (both were isolated and characterised spectroscopically). When 2,6-dimethylaniline was treated with C_6F_5CHO, acridines were not formed and the reaction stopped at the substituted Schiff base stage. (ii) A reaction between 3,5-dimethylaniline and pre-formed 7-bromo-1,2,3,4-tetrafluoroacridine **1g** [2:1 molar ratio] under standard ring-closure conditions (179 °C/68 h; boiling 1,2-dichlorobenzene) gave no 3-(3,5-dimethylanilino)-7-bromo-1,2,4-trifluoroacridine, and hence



Scheme 3.

nucleophilic displacement of the *para* fluorine must have occurred at the Schiff base stage. The identification (^{19}F NMR spectroscopy) of small amounts of the *para*-substituted Schiff bases **7** in the crude product mixtures from most reactions studied confirms this deduction. In fact, at 111 °C with *p*-anisidine, an appreciable amount of the *para*-substituted Schiff base **7b** was present in the crude mixture. This was separated by dry-column flash chromatography and fully characterised.

Thus, substitution of fluorine in the Schiff bases **3** can occur either at positions *ortho* or *para* to the imino substituent (CH=NAr). Except with highly nucleophilic anilines (e.g. *p*-anisidine and 3,5-dimethylaniline), substitution occurs more readily in the hindered *ortho* position, presumably due



(9)

Scheme 4.

to a hydrogen-bonding interaction between the imino nitrogen and an amino hydrogen in the attacking aniline (Scheme 3).

The seemingly slow cyclisations of the *ortho*-substituted Schiff bases **6f** and **6g** relative to those of **6a** to **6e** is possibly due to low concentrations of the salts p-$XC_6H_4NH_3^+F^-$ (X = Cl or Br) available to catalyse ring-closure. The anilines p-$XC_6H_4NH_2$ (X = Cl or Br) were the weakest bases of all the anilines employed, and hence their hydrofluoride salts would be the most prone to loss of HF in the open reaction vessels used to date.

The acridine synthesis described has been extended successfully to a range of fluorinated aldehydes, as exemplified by the reaction of 2,6-difluorobenzaldehyde with p-anisidine to give a 25% yield (not optimised) of analytically pure 1-fluoro-7-methoxyacridine **9** (Scheme 4).

Acridines **1**, **5** and **9** all gave satisfactory elemental analyses, and the spectral data (^1H, ^{13}C, ^{19}F NMR; MS) were consistent with the structures proposed. X-Ray crystallographic structure determinations have also been carried out on acridines **1a**, **1b**, **1e** and **5c** [9].

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References

1 Presented as a poster (P24) at the *10th Eur. Symp. Fluorine Chem.*, Padua, Italy, 20–25 September, 1992; see A.J. Adamson, R.E. Banks and A.E. Tipping, *J. Fluorine Chem.*, *58* (1992) 300.
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