J. Chem. Research (S),
1997, 76–77
J. Chem. Research (M),
1997, 0530–0555

One-pot Synthesis of 1,2,3,4-Tetrafluoroacridines from Pentafluorobenzaldehyde[1]

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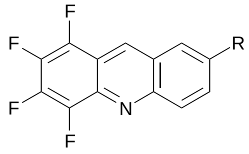
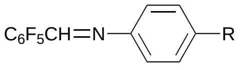
1,2,3,4-Tetrafluoroacridines (accompanied in certain cases by their 3-arylamino derivatives) have been prepared in one-pot fashion (*via* formation *in situ* of the corresponding Schiff bases) by heating pentafluorobenzaldehyde with a 2 molar equivalence of aniline, *para*-substituted anilines 4-$RC_6H_4NH_2$ (R = OMe, Me, Bu^t, F, Cl, Br) or 3,5-dimethylaniline in boiling *o*-dichlorobenzene.

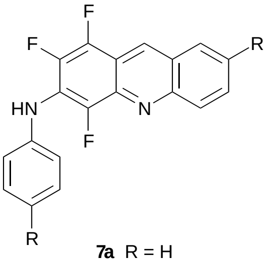
It seems that 1,2,3,4-tetrafluoroacridine (**1a**) was first synthesised in the early 1960s from bromobenzene *via* a low-yield, laborious, multi-step synthesis based on a modified Lehmstedt–Tanasescu rearrangement.[2] Since this route involved both 1,2,3,4-tetrafluoro-9(10*H*)-acridone and 9-chloro-1,2,3,4-tetrafluoroacridine as intermediates, it possessed potential as a source of several other derivatives of 1,2,3,4-tetrafluoroacridine; however, this opportunity seems not to have been pursued, although the development of other routes to 1,2,3,4-tetrafluoro-9(10*H*)-acridone (electrochemical oxidation of 2-amino-3,4,5,6-tetrafluorobenzophenone; KF-driven cyclization of 2′-amino-2,3,4,5,6-pentafluorobenzophenone) was undertaken, and this led to the synthesis of octafluoro-9(10*H*)-acridone.[3,4] Of more relevance to the work described in detail[1] here are reports concerning fluorinated acridones from Russian researchers in the 1970s, notably that (*i*) thermal treatment of methyl pentafluorophenyl ketone with aniline affords, *inter alia*, 3-anilino-1,2,4-trifluoro-9-methylacridine[5] (a reaction extended later to derivatives of aniline[6]) and (*ii*) the preparation of 1,2,3,4-tetrafluoroacridine (**1a**) from pentafluorobenzaldehyde and the Grignard reagent PhNHMgBr.[7]



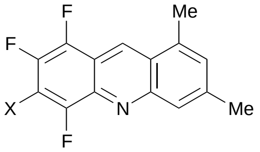
1a R = H
b R = OMe
c R = Me
d R = Bu^t
e R = F
f R = Cl
g R = Br



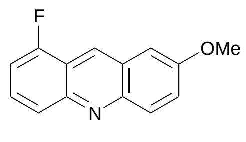
4a R = H
b R = OMe
c R = Me
d R = Bu^t
e R = F
f R = Cl
g R = Br



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



11a X = F
b X = 3, 5-$Me_2C_6H_3NH$



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The work reported here stemmed from a serenedipitous discovery, made during mass spectrometric studies on fluorinated Schiff bases,[8,9] that condensation of pentafluorobenzaldehyde with *p*-anisidine under forcing conditions yields 4-methoxy-*N*-(pentafluorobenzylidene)aniline (**4b**) contaminated with, *inter alia*, a product of molecular formula $C_{14}H_7F_4NO$. Having shown by X-ray crystallographic analysis[12] that the by-product was 1,2,3,4-tetrafluoro-7-methoxyacridine (**1b**), the generality of the pentafluorobenzaldehyde–primary arylamine reaction as a route to 1,2,3,4-tetrafluoroacridines carrying no 9-substituent has been probed.

We have established that 1,2,3,4-tetrafluoroacridine (**1a**) and a range of 7-substituted analogues (**1b–g**) can be produced by heating pre-formed Schiff bases (*E*)-$C_6F_5CH{=}NC_6H_4R$-*p* (**4a–g**) (from $C_6F_5CHO + H_2NC_6H_4R$-*p*) with the parent aniline $H_2NC_6H_4R$-*p* (1:1 molar ratio) or a 1:2 molar 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) in boiling toluene or, preferably, 1,2-dichlorobenzene. Except where R = Bu^t, F, Cl or Br, substantial amounts of the corresponding 3-anilino-1,2,4-trifluoroacridines (**7a–e**) are also formed.

Inter alia, 1,2,3,4-tetrafluoro-6,8-dimethylacridine (**11a**) and its 3-(3,5-dimethylanilino) derivative (**11b**) can be obtained by heating pentafluorobenzaldehyde with 2 molar equivalence of 3,5-dimethylaniline at 180 °C in *o*-$C_6H_4Cl_2$, while 1-fluoro-7-methoxyacridine (**12**) is produced under similar conditions from 2,6-difluorobenzaldehyde and *p*-anisidine — a conversion which heralds numerous extensions envisioned for this new acridine ring synthesis.

The formation of 1,2,3,4-tetrafluoroacridines **1a–g** is best rationalized in terms of intramolecular ring closure of 2-arylamino derivatives of Schiff bases **4a–g** generated *in situ via ortho*-S_NAr attack on those Schiff bases by the arylamines involved.

The ^{19}F NMR spectra of tetrafluoroacridines **1a–g** and **11a** are unexpectedly simple (four equally intense 17 Hz triplets under routine operating conditions, with digital resolution of 1.6 Hz/point).

Techniques used: UV, MS, NMR (^{1}H, ^{19}F, ^{13}C)

References: 18

Tables: 4 (yields, mps, elemental analyses and spectrsopic data for products of thermal reactions between C_6F_5CHO and arylamines)

Schemes: 4

Received, 11th November 1996; Accepted, 18th November 1996
Paper E/6/07642D

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