Cyclization of Some 2,3,5,6-Tetrafluorophenylhydrazine Derivatives. Use of Nuclear Overhauser Effect Measurements in Structural Assignment

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Treatment of *N*-(2,3,5,6-tetrafluorophenyl)-*N'*-thiobenzoylhydrazine and of *N*-benzoyl-*N'*-(2,3,5,6-tetrafluorophenyl)hydrazine with acetic anhydride and triethylamine proceed without rearrangement to give 4-acetyl-2-phenyl-5,6,8-trifluoro-4*H*-1,3,4-benzthiadiazine and -benzoxadiazine, respectively. Structures follow from ^{19}F n.m.r. and n.O.e. data.

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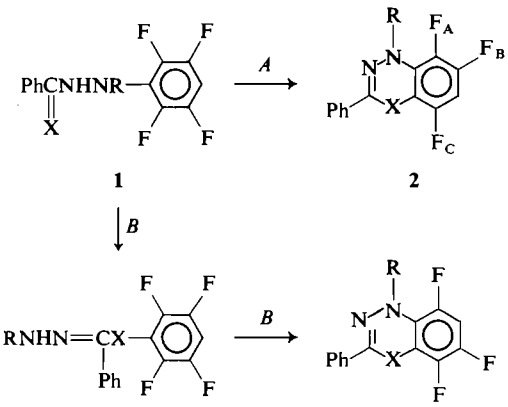
Le traitement de la *N*-(tétrafluoro-2,3,5,6 phényl) *N'*-thiobenzoyl hydrazine et de la *N*-benzoyl *N'*-(tétrafluoro-2,3,5,6 phényl) hydrazine par l'anhydride acétique et la triéthylamine se fait sans réarrangement; on obtient respectivement les acétyl-4 phényl-2 trifluoro-5,6,8 4*H*-benzothiadiazine-1,3,4 et la benzoxadiazine-1,3,4. On détermine les structures à partir des données de r.m.n. de ^{19}F et des données de e.O.n. [Traduit par le journal]

While cyclization of *N*-acetyl-*N*-(2,3,5,6-tetrafluorophenyl)-*N'*-thiobenzoylhydrazine (**1***b*) under basic conditions would be expected to yield 4-acetyl-2-phenyl-5,6,8-trifluoro-4*H*-1,3,4-benzothiadiazine (**2***b*) by direct nucleophilic displacement of an *ortho*-fluorine atom by the sulfur atom (path *A*) (1), an alternative (path *B*) involving a Smiles-type rearrangement (2) should also be considered. This would involve nucleophilic displacement of the acetyl-bearing nitrogen atom by the sulfur atom via a spirocyclic transition state, followed by nucleophilic displacement of an *ortho*-fluorine atom by the acetyl-bearing nitrogen atom to give compound (**3***b*). Similar considerations apply to the oxygen analog (**1***d*). These possible routes have been distinguished by recourse to ^{19}F n.m.r. and intramolecular nuclear Overhauser effect (n.O.e.) studies (3, 4).



a X = S; R = H
b X = S; R = $COCH_3$
c X = O; R = H
d X = O; R = $COCH_3$

Compound **1***a* was smoothly converted by reaction with acetic anhydride (Ac_2O) and triethylamine (NEt_3) into a compound $C_{15}H_9F_3N_2OS$, subsequently identified as **2***b*; it was shown that acetylation of **1***a* preceded ring closure although the intermediate **1***b* was not isolated. Hydrolysis of **2***b* gave **2***a*. Under slightly different conditions, **1***c* was converted to **2***d*, acetylation again preceding ring closure; satisfactory conditions for hydrolysis of **2***d* to **2***c* were not realized.

The ^{19}F n.m.r. and n.O.e. data for these compounds are set out in Table 1 and are seen to substantiate formulations **2***a*, *b*, and *d* (5). The *ortho* F,F coupling constants lie in the range 20–22 Hz, distinctly larger than the corresponding *para* and (in turn) *meta* values. The *ortho* H,F coupling constants are also somewhat larger than the corresponding *meta* values. The long range couplings between the N–H and F_A and F_B in **2***a* are of special interest since a similar effect is observable for H_A in the p.m.r. spectrum of 7-bromo-2-*p*-methoxyphenyl-4*H*-1,3,4-benzothiadiazine.[1] The ^{19}F chemical shifts are consistent with these structural assignments. Notably deacetylation of **2***b* to **2***a* results in a shift upfield

[1]The p.m.r. spectrum of this compound at 100 MHz in $CDCl_3$ shows a high-field aromatic proton absorption for the C-5 proton H_A as a doublet at δ 6.56 (J_{AB} = 9.0 Hz) which is further split by coupling with the N—H proton; this collapses to a sharp doublet on exchange with D_2O.

TABLE 1. ^{19}F n.m.r. and n.O.e. data

Chemical shifts δ (p.p.m.)*		2*a*	2*b*	2*d*
F_A		82.25	54.08	52.84
F_B		54.27	50.92	55.16
F_C		36.54	36.28	57.06
Coupling constants (Hz)				
J_{AB}		21	20	22
J_{AC}		13	13	13
J_{BC}		2.5	2	0
J_{AH}		6	6	7
J_{BH}		10	9.5	10
J_{CH}		8.5	8	9
J_{AR}		3		
J_{BR}		1		
J_{CR}		0		
Nuclear Overhauser effect (%)				
Irradiate R proton(s); obsvd.	F_A	32	10	8
Irradiate C-7 proton; obsvd.	F_A	0	0	0
	F_B	22	21	23
	F_C	33	32	33

*Upfield from CF_3CCl_3.

for F_A, whereas F_B and F_C are barely affected; analogous shifts upfield for H_A occur on deacetylation of benzothiadiazines with no 5 substituent. The higher field positions of F_B and F_C in the benzoxadiazine **2***d* than in **2***b* are consistent with increased electron density in the ring, the smaller oxygen atom being capable of a greater resonance effect.

A large n.O.e. is observed for F_A when the N—H peak of **2***a* is irradiated, whereas F_B and F_C are unaffected. Saturation of the methyl protons of **2***b* produces a similar though smaller n.O.e. for F_A, while F_B and F_C are again unchanged. Large n.O.e. values are observed for F_B and F_C on saturation of the ring proton (at C-7) of **2***a* and **2***b*, while F_A is unaffected. Similar results are obtained for **2***d*.

Only structures **2***a*, *b*, and *d* are consistent with the above data and hence overall the above cyclization reactions must follow path *A* and not path *B*. Such n.O.e. measurements should continue to find use in confirming the course of substitution and cyclization reactions of polyfluoroaromatic compounds.

Experimental

^{19}F n.m.r. spectra were recorded on a Varian Associates DP-60 IL spectrometer in $CDCl_3$ solution at 56.4 MHz; results are given as p.p.m. (δ) upfield from 1,1,1-trichlorotrifluoroethane (internal standard). Proton magnetic resonance spectra were recorded on Varian Associates A-60 and T-60 spectrometers in $CDCl_3$ at 60 MHz; results are given as p.p.m. downfield from tetramethylsilane (internal standard). The presence of exchangeable protons was confirmed by use of D_2O. The procedure for n.O.e. measurements was essentially that described in ref. 4.

2,3,5,6-Tetrafluorophenylhydrazine was prepared from pentafluorobenzene and 100% hydrazine hydrate with minor modification of the published procedure and had m.p. 89–91 °C (lit. (6), m.p. 90–91.5 °C).

N-(2,3,5,6-Tetrafluorophenyl)-N′-thiobenzoylhydrazine (1a)

2,3,5,6-Tetrafluorophenylhydrazine (18.0 g, 0.1 mol) was added in portions to a stirred solution of carboxymethyl dithiobenzoate (7) (21.2 g, 0.1 mol) in aqueous 1 *M* KOH solution (100 ml) during 10 min; 1 *M* KOH was added as required to keep the p*H* at 10. The solution was then heated to 70 °C and allowed to cool to room temperature over 1 h. Dilute acetic acid was added till the p*H* reached 6. The solid was collected, washed, and dried. Crystallization from hexane gave the *thiohydrazide* **1***a* (17.1 g, 57%) as yellow needles, m.p. 90–92 °C; p.m.r. δ 9.35 (s, br 1H, exchangeable), 7.92 (s, br, 1H, exchangeable), 7.81–7.61 (m, 2H), 7.50–7.18 (m, 3H), and 7.00–6.25 (m, 1H).

Anal. Calcd. for $C_{13}H_8F_4N_2S$: C, 52.00; H, 2.67; N, 9.33. Found: C, 51.97; H, 2.68; H, 9.28.

4-Acetyl-2-phenyl-5,6,8-trifluoro-4H-1,3,4-benzothiadiazine (2b)

A mixture of **1***a* (3.0 g, 0.01 mol), NEt_3 (20 ml), and Ac_2O (20 ml) was boiled under reflux for 2 h, cooled, and poured into water. The solid was collected, washed, and dried. Crystallization from ethanol or hexane gave the *thiadiazine* **2***b* (3.1 g, 91%) as buff needles, m.p. 127–128 °C; i.r. (KBr) 1710 cm^{-1} (C=O); p.m.r. δ 8.13–7.92 (m, 2H), 7.62–7.43 (m, 3H), 7.33–6.77 (m, 1H), and 2.50 (s, 3H).

Anal. Calcd. for $C_{15}H_9F_3N_2OS$: C, 55.90; H, 2.80; F, 17.70. Found: C, 56.05; H, 2.84; F, 17.68.

In a separate experiment, a mixture of **1***a* (2.0 g), NEt_3 (15 ml), and ethanol (15 ml) was refluxed for 5 h. Evaporation *in vacuo* and crystallization from benzene–hexane gave the *1:1 adduct* or salt of **1***a* and NEt_3 as buff needles, m.p. 106–108 °C; p.m.r. δ 9.64 (s, br, 2H, exchangeable), 8.24–8.00 (m, 2H), 7.41–7.17 (m, 3H), 6.75–6.10 (m, 1H), 2.72 (q, 6H), and 1.05 (t, 9H).

Anal. Calcd. for $C_{19}H_{23}F_4N_3S$: C, 56.86; H, 5.74; N, 10.47. Found: C, 56.77; H, 5.85; N, 10.47.

Decomposition of the 1:1 adduct with boiling ethanol – concentrated HCl regenerated **1***a*, m.p. and mixture m.p. 90–91 °C; identity was confirmed by i.r. spectral correlation.

*2-Phenyl-5,6,8-trifluoro-4H-1,3,4-benzothiadiazine (**2a**)*

A mixture of **2***b* (2.0 g), ethanol (30 ml), and concentrated HCl (20 ml) was refluxed for 1 h, cooled, and the solid was collected. Crystallization from ethanol gave the *4H-thiadiazine* **2***a* (1.4 g, 80%) as yellow needles, m.p. 107–108 °C.

Anal. Calcd. for $C_{13}H_7F_3N_2S$: C, 55.71; H, 2.50. Found: C, 55.77; H, 2.53.

*N-Benzoyl-N'-(2,3,5,6-tetrafluorophenyl)hydrazine (**1c**)*

Benzoyl chloride (2.8 g, 0.02 mol) was added dropwise to a stirred solution of 2,3,5,6-tetrafluorophenylhydrazine (3.6 g, 0.02 mol) and NEt_3 (5 ml) in dry ether (50 ml) at −78 °C. Stirring was continued for 2 h at −78 °C and the mixture was then allowed to warm to room temperature. Solvent was removed *in vacuo* and the solid was washed well with ice-cold water. Crystallization from aqueous methanol gave the *hydrazide* **1***c* (4.2 g, 75%) as needles, m.p. 176 °C.

Anal. Calcd. for $C_{13}H_8F_4N_2O$: C, 54.93; H, 2.82; N, 9.86. Found: C, 54.80; H, 2.87; N, 9.83.

*4-Acetyl-2-phenyl-5,6,8-trifluoro-4H-1,3,4-benzoxadiazine (**2d**)*

A mixture of **1***c* (1.0 g), NEt_3 (5 ml), Ac_2O (5 ml), and dimethylformamide (15 ml) was boiled under reflux for 4 h, cooled, and poured into dilute acetic acid. The solid was filtered off, washed, and dried. Crystallization from hexane gave the *oxadiazine* **2***d* (0.6 g, 65%) as needles, m.p. 144–145 °C; i.r. 1700 cm^{-1} (C=O).

Anal. Calcd. for $C_{15}H_9F_3N_2O_2$: C, 58.82; H, 2.94. Found: C, 58.62; H, 2.85.

In a separate experiment, a mixture of **1***c* (1.0 g), NEt_3 (2 ml), NaOH (0.4 g), and dimethylformamide (20 ml) was refluxed for 4 h. Isolation as above gave a yellow gum which contained **1***c* and at least four other materials, none of which was fluorescent (t.l.c.).

Attempted hydrolysis of **2***d* gave dark gums.

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