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STEREOISOMERS OF PENTAFLUOROBENZALDEHYDE AND PENTAFLUOROACETOPHENONE PHENYLHYDRAZONES

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SUMMARY

The interaction of pentafluorobenzaldehyde or 2,3,4,5,6-pentafluoroacetophenone with phenylhydrazine leads to isomer mixtures of the corresponding phenylhydrazones. Stereochemical assignments are based upon spectral and chemical data.

INTRODUCTION

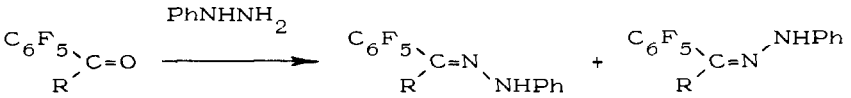
In a previous communication [1] we have reported syntheses of polyfluoroaromatic carbonyl phenylhydrazone compounds. As shown by the ^{19}F NMR spectra , single isomeric species were isolated in all cases . A sterically less strained E-configuration with trans-position of the C_6F_5 and PhNH groups was assigned for them . However the compounds obtained were transformed to indazoles by the intramolecular nucleophilic substitution of the ortho-fluorine (in DMFA , with anhydrous KF) . In all cases , except for decafluorobenzophenone phenylhydrazone containing a C_6F_5 ring in the cis-position to the PhNH group , the reaction required heating to 100-150°, which we explained by the conversion of E-isomer into the reactive Z-modification (cf [2,3]). This structural assignment is open to question and could be confirmed only by means of isolation and identification of both possible stereoisomers . The formation of isomeric mixtures in the condensation of aromatic carbonyl compounds with phenylhydrazine is reported [4-6] . The present

0022-1139/90/$3 50

paper will describe the results of detail investigations of the reactions of pentafluorobenzaldehyde and 2,3,4,5,6-pentafluoroacetophenone (I a,b) with phenylhydrazine .

RESULTS AND DISCUSSION

The treatment of compounds (I a,b) with phenylhydrazine leads to mixtures of stereoisomers of the phenylhydrazones (II) and (III) in ratio of ~8.1 and ~4:1 respectively. The same mixture of isomers (II b) and (III b) was also obtained by interaction of compound (Ib) with phenylhydrazine hydrochloride in aqueous ethanol in the presence of sodium acetate at 20° *.



I a,b II a,b (E) III a,b (Z)

a, R=H

b, R=Me

The E,Z-isomerism is confirmed by the analytical and spectral data . The major isomers were isolated individually and proved to be identical in their melting points and ^{1}H and ^{19}F NMR spectra to phenylhydrazones described in [1] . Separation of isomer mixtures by the highly efficient reversed-phase liquid chromatography allowed us to obtain the UV spectra of individual compounds (Fig. 1). The spectra of the predominant isomers are practically identical to those described in [1] . The UV spectra of isomeric phenylhydrazones formed in smaller amounts show a hypsochromic shift of the long-wave absorption band . We therefore conclude that these isomers have a sterically more strained and less coplanar Z-configuration (III a,b) (cf. [7,8]).

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* This reaction gives one isomer practically under the conditions described in [1] , i.e upon boiling of the reaction mixture .

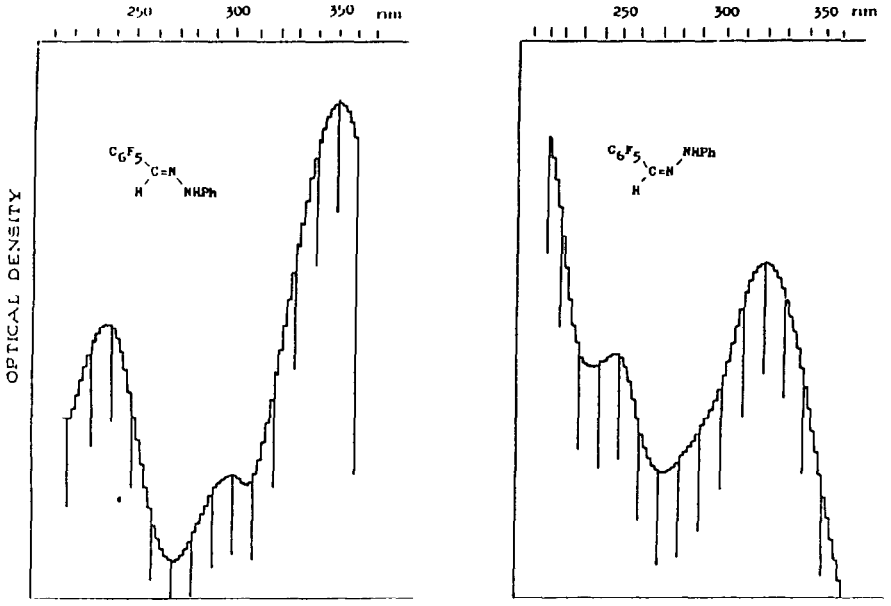


Fig. 1. The UV spectra of stereoisomers of pentafluorobenzaldehyde phenylhydrazone (spectra were recorded on a "Milichrom" for solution in 85% MeOH).

To confirm this structural assignment and clarify the routes of formation of indazoles from phenylhydrazones of compounds (I a,b) we kept mixtures of isomers (II) and (III) in DMFA in the presence of K_2CO_3* at different temperatures. At room temperature this procedure gave the products containing the corresponding indazole (IV a,b) and E-isomer (II a,b) in the ratio close to the isomer ratio of the starting mixture. This and the absence of cyclization of pure E-isomer in these conditions point to formation of indazole only from phenylhydrazone with Z-configuration. The conversion of E-isomer (II a,b) to indazole (IV a,b) can only be achieved under heating to 100° (Fig. 2.).

* The use of dry K_2CO_3 instead of KF (see [1]) results in increased rate of cyclization.

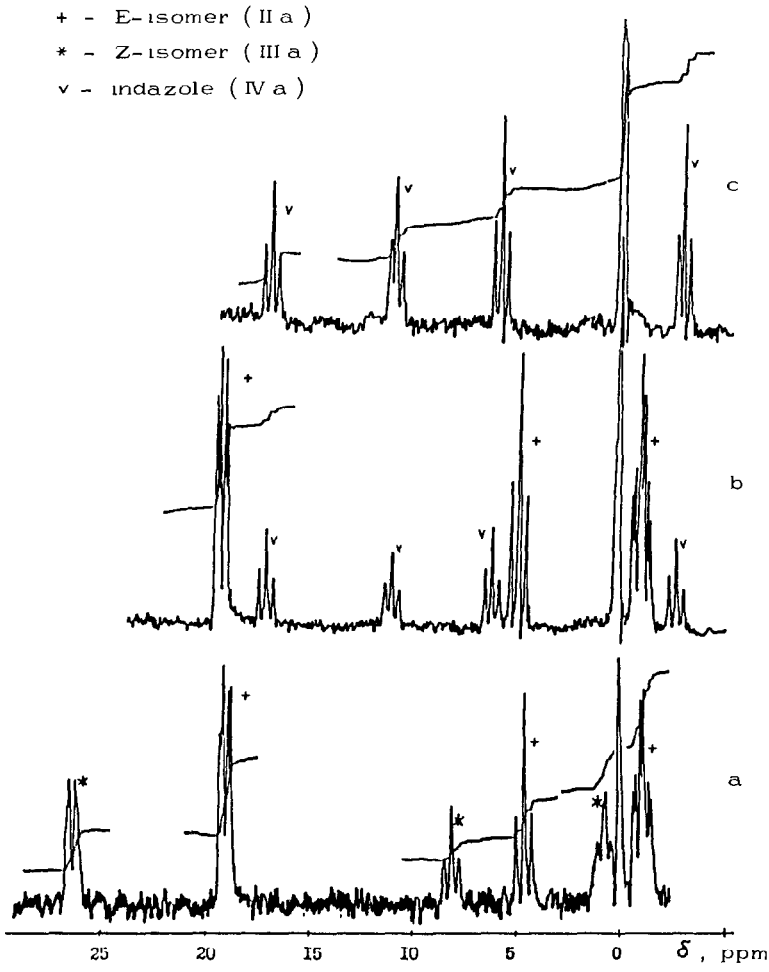
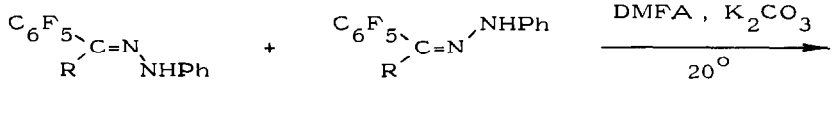
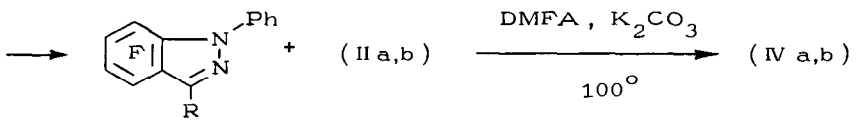


Fig. 2. The ^{19}F NMR spectra : a - the mixture (A) of isomers (II a) and (III a), b - this mixture after 1 h at 20° in DMFA with K_2CO_3, c - this mixture after 3 h at 100° in DMFA with K_2CO_3.



II a,b III a,b



IV a,b

a, R=H
b, R=Me

Thus the experimental data are in agreement with configurational assignment of stereoisomers of pentafluorobenzaldehyde and pentafluoroacetophenone phenylhydrazones made on the basis of their UV data and show the E ⟶ Z isomerization to be the intermediate stage in the synthesis of indazoles.

EXPERIMENTAL

^{19}F and ^{1}H NMR spectra were recorded on a "Varian A56/60A" spectrometer at the frequency of 56.4 and 60 MHz in THF and DMSO-d_6 respectively. Internal standards were hexafluorobenzene and hexamethyldisiloxane. Molecular weights were determined mass spectrometrically on GC/MS Finnigan Mat, model 8200.

DMFA was dried over molecular sieves 4A and 9A.

The highly efficient reversed-phase liquid chromatography with concurrent recording of the UV spectra was performed on "Milichrom" instrument. Column: 02x62 mm, L.Chromosorb C18.5 μm. Eluent - 85% MeOH, flow rate 100 μL/min. Detector - 330 and 360 nm for the mixture (II a, III a), 290 and 310 nm for the mixture (II b, III b).

Pentafluorophenylhydrazones

1. A solution of 1.08 ml of freshly distilled phenylhydrazine in 5 ml of ethanol was added dropwise to 1.98 g of aldehyde (I a) in 5 ml of ethanol. The mixture was stirred for 15 min and treated with water. The solid was filtered off, washed with petroleum ether to give the product (2.79 g, 98%), shown to be a ~8:1 mixture of the isomers (II a) and (III a). ^{1}H NMR, δ, ppm: 6.48-7.52 (Ph, CH), 7.88 (CH)*, 9.74 (NH) and 10.88 (NH)*. ^{19}F NMR, δ, ppm: -1.2*, 0.5, 4.4*, 8.0, 19.0* and 26.2.

This product was washed with ethanol and dried to give 2.20 g (77%) of E-isomer (II a), m.p. 159.5-160.5° (lit. [1] 157-159.5°). The filtrate was then poured into water and the precipitate was filtered off to give 0.5 g a mixture (A) of isomers (II a) and (III a) in the ratio of ~9:4. Mass spectral data of the product (A) are identical to these of E-isomer (II a). The UV spectrum recorded on "Milichrom" exhibits bands at 250 and 320 nm.

2. A solution of ketone (I b, 2.10 g), phenylhydrazine hydrochloride (1.45 g) and sodium acetate (0.82 g) in ethanol (60 ml) and water (20 ml) was allowed to stand for 24 h at room temperature. The mixture was treated as in exp.1 to give 2.80 g (93%) of the mixture (B) containing, as shown by ^{19}F and ^{1}H NMR spectroscopy, isomers (II b) and (III b) in the ratio of ~7:3. ^{1}H NMR (DMSO-d_6), δ, ppm: 2.26 (Me), 6.64-7.34 (Ph), 9.06 (NH) and 9.61 (NH)*. ^{1}H NMR (CCl_4), δ, ppm: 2.10 (Me)*, 2.28 (Me) and 6.70-7.50 (Ph, NH) (cf. [5]). ^{19}F NMR, δ, ppm: -0.7*, 1.3, 5.7*, 8.3, 20.4* and 24.3. Found: C, 55.72; H, 3.25; F, 31.08, N, 9.25%. $C_{14}H_9F_5N_2$ requires C, 56.00; H, 3.02; F, 31.64, N 9.33%. The UV spectrum of Z-isomer (III b): 268 and 306 nm.

E-isomer (III b) was isolated by recrystallization from petroleum ether (b.p. 40-70°). The yield was 44%, m.p. 104-106°; in [1] m.p. 104-105.5°.

3. 10 mmol of ketone (I b) and 10 mmol of phenylhydrazine were heated for 1 h at 100° to give the mixture (3.13 g) containing isomers (II b) and (III b) in the ratio of ~4:1.

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* The signals of E-isomer.

Cyclization of phenylhydrazones

1. 0.42 g of dried potassium carbonate was added to a stirred solution of the mixture (A) in 14 ml of DMFA at room temperature. After 1 h the mixture was poured into water with HCl and extracted with ether. The dried ($MgSO_4$) extract was filtered and evaporated to give the mixture (0.41 g) of E-isomer (II a) and indazole (IV a) with a correct ^{19}F NMR spectrum [1] in the ratio of ~ 11:5.

2. 0.29 g of a mixture (A) and 0.29 g of anhydrous potassium carbonate in 10 ml of DMFA were heated for 3 h at ~ 100° and treated as in exp. 1 to yield 0.28 g of indazole (IV a) as shown by ^{19}F NMR spectrum.

3. 0.30 g of a mixture (B), 0.30 g of anhydrous potassium carbonate in 10 ml of DMFA were stirred for 4 h at 20°, treated as in exp.1. This gave 0.30 g of the product containing E-isomer (II b) and indazole (IV b) in the ratio of ~ 3:1.

4. 0.60 g of E-isomer (II b) or a mixture (B) and 0.60 g of anhydrous potassium carbonate in 20 ml of DMFA were stirred for 7 h at ~ 100°, then treated as in exp.1. The residue was washed with ethanol to give 0.39 g (65%) of indazole (IV b) with a correct m.p. [1].

5. 0.30 g of E-isomer (II a,b) and 0.30 g of anhydrous potassium carbonate in 10 ml of DMFA were kept for 5-9 h at 20°, then treated as in exp.1 to yield the starting compound (II a,b).

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