

Partially Fluorinated Heterocyclic Compounds. Part VIII.¹

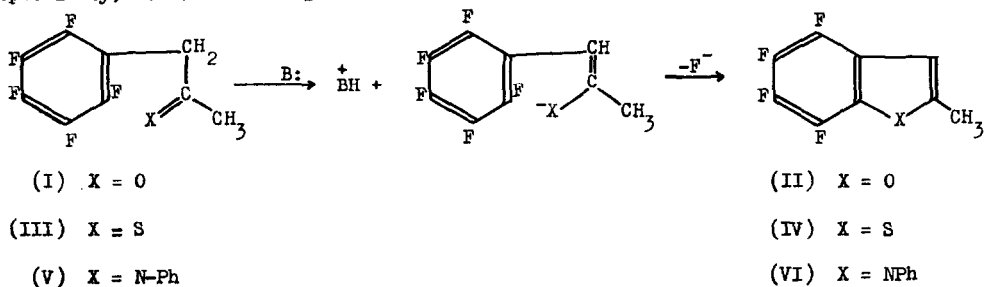
New Syntheses of Benzo[b]thiophen and Indole Derivatives.

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The synthesis of 4,5,6,7-tetrafluoro-2-methylbenzo[b]furan (II) by the reaction of sodium hydride with 2',3',4',5',6'-pentafluorophenylpropan-2-one (I) involving nucleophilic displacement of fluorine by oxygen, has been described recently (1). It suggested that base-catalysed reactions of the thioketone (III) and the Schiff's base (V) might lead to the formation of the benzo[b]thiophen and indole derivatives, (IV) and (VI) respectively, as outlined in Scheme 1:



Scheme 1

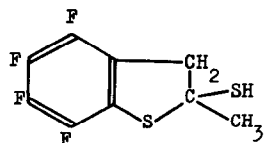
This paper describes the preparation of (IV) and (VI), though neither the thioketone (III), nor the Schiff's base (V) could be isolated for use according to Scheme 1.

Treatment of the ketone (I) with hydrogen sulphide and hydrogen chloride in 95% ethanol at 0° did not give the expected thioketone (III) (2). The product was 2',3',4',5',6'-pentafluorophenylpropan-2,2-dithiol (VII), m.p. 45-45.5° (56% yield). The structure of (VII) was deduced from its elemental analysis; by its mass spectrum (parent peak at mass 274); by its infra-red spectrum (complex weak absorption at 2530 cm.⁻¹ due to S-H); and by its ¹H n.m.r. spectrum (a solution in CCl₄ showed three absorptions with intensities in the ratio 3:2:2 at τ 8.19 [singlet due to CH₃] τ 7.30 [singlet due to two SH groups] and τ 6.62 [singlet due to -CH₂- which was a partially resolved triplet under high resolution due to coupling with two ortho fluorine atoms (3)] respectively).

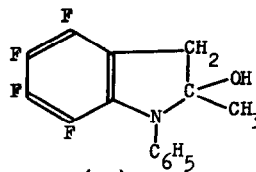
Treatment of the di-thiol (VII) with dry pyridine under reflux for 1 hr. gave 4,5,6,7-tetrafluoro-2-methylbenzo[b]thiophen (IV), m.p. $94.5 - 95.0^{\circ}$ (47% yield). However, the addition of a catalytic amount of solid KOH to the reaction mixture gave a significant increase in the yield of cyclised product (85%). The structure of (IV) was deduced from its elemental analysis; by its mass spectrum (parent peak at mass 220); and by n.m.r. spectroscopy. The ^{19}F n.m.r. spectrum of (IV) in CCl_4 showed four multiplets of equal intensity due to four fluorine atoms centred at 19.84, 16.00, 1.20 and 0.12 p.p.m. respectively, downfield from C_6F_6 as internal reference. The ^1H n.m.r. spectrum of (IV) in CCl_4 showed two absorptions with intensities in the ratio 3:1 at τ 7.42 (singlet due to CH_3) and τ 2.98 (multiplet due to $-\text{CH}=\text{}$, coupling with fluorine atoms).

In an attempt to prepare the Schiff's base (V), the ketone (I) was heated under reflux with excess aniline in the presence of anhydrous zinc chloride. The only product which was isolated, however, was N-phenyl-4,5,6,7-tetrafluoro-2-methylindole (VI) m.p. $116-117^{\circ}$ (<10% yield). The yield of (VI) was increased by the addition of aniline hydrobromide to the reaction mixture and in a typical experiment, heating a mixture of the ketone (I), aniline hydrobromide, anhydrous zinc chloride and aniline in the molar ratio 1:1.3:2.6:55 under reflux for 2 hr. gave the indole derivative (VI) in 47% yield. The structure of (VI) was shown by its elemental analysis and mass spectrum (parent peak at mass 279); and by n.m.r. spectroscopy. The ^{19}F n.m.r. spectrum of (VI) in CCl_4 showed four magnetically different fluorine atoms centred at 10.55 p.p.m., and 1.50 p.p.m. downfield and 4.90 p.p.m. and 7.45 p.p.m. upfield from C_6F_6 as internal reference. The ^1H n.m.r. spectrum of (VI) in CCl_4 had three areas of absorption with intensities in the ratio 3:1:5 at τ 7.80 (singlet due to CH_3), τ 3.64 (multiplet due to $-\text{CH}=\text{}$, coupling with fluorine atoms) and τ 2.6 (multiplet due to C_6H_5) respectively.

The formation of the benzo[b]thiophen and indole derivatives, (IV) and (VI) could have occurred through the intermediacy of the thioketone (III) and the Schiff's base (V) respectively, the cyclisation being promoted by pyridine (and by KOH) in the former case and by aniline in the latter case, in accordance with Scheme 1 outlined above. However, the formation of the five-membered ring before the overall elimination of either H_2S (e.g. from (VIII)) in the case of the benzo[b]thiophen, or of H_2O (e.g. from (IX)) in the case of the indole, should also be considered.



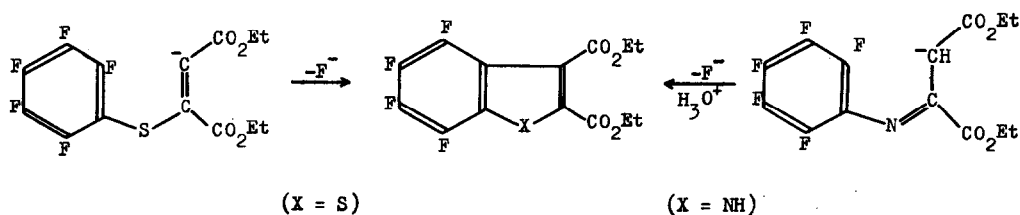
(VIII)



(IX)

The exact role of the KOH in the formation of the sulphur heterocycle is not fully understood, and it is not easy to see why a base should remove hydrogen from a α - CH_2 -group in preference to the hydrogen of the S-H group in (VIII). The overall elimination of H_2O from (IX) under the reaction conditions employed (Lewis acids present) remains a distinct possibility however. It is not possible to distinguish unambiguously between the two alternative mechanisms for the two cyclisation reactions on the present evidence.

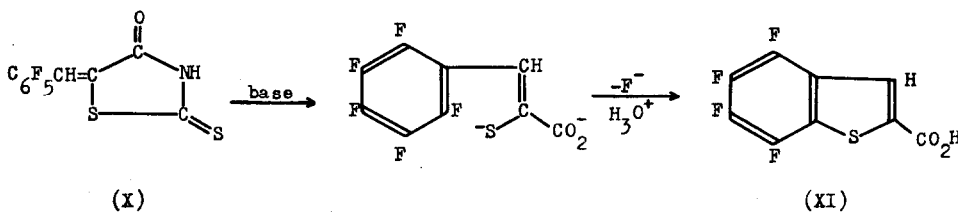
The syntheses of partially fluorinated benzo[b]thiophen and indole derivatives by nucleophilic displacement of fluorine by carbanions have been reported (4,5) e.g.



(X = S)

(X = NH)

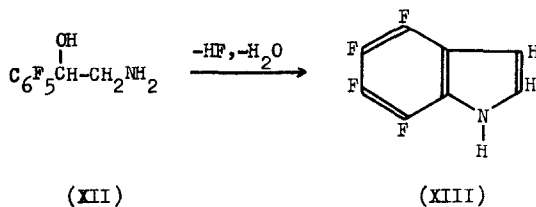
More recently the formation of such ring systems by the nucleophilic replacement of fluorine by sulphur (6) and by nitrogen (7) have been reported. The base-catalysed decomposition of the rhodanine derivative (X) was used to prepare the benzo[b]thiophen derivative (XI):



(X)

(XI)

and Russian workers described the formation of 4,5,6,7-tetrafluoroindole (XIII) in excellent yield by heating compound (XII) in *N,N*-dimethylformamide at reflux temperature:



In the former reaction, the function of the base was to promote hydrolysis at carbonyl- and thiocarbonyl-carbon atoms. In the latter reaction, as in the synthesis of the indole derivative (VI) described in this paper, there remains the uncertainty whether H₂O is eliminated before or after the cyclisation step.

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