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PARTIALLY FLUORINATED HETEROCYCLIC COMPOUNDS
PART VII[1]. NEW SYNTHESES OF 4,5,6,7-TETRAFLUORO-2-METHYLBENZO[b]FURAN

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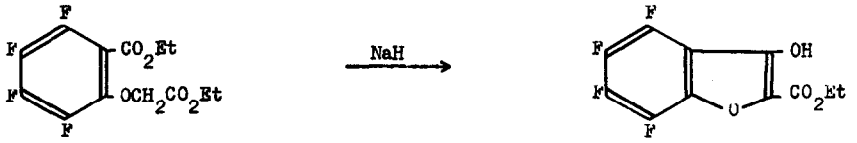
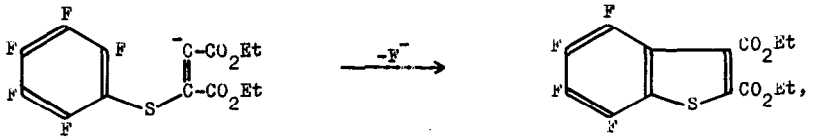
A recent Paper in this series described a conventional ring-cyclisation procedure for the formation of a partially fluorinated benzo[b]furan derivative (2):



However, we have also exploited the susceptibility of highly fluorinated aromatic compounds to nucleophilic replacement of fluorine by carbanions to prepare benzo[b]thiophen (3) and indole (4) derivatives, e.g.



but no unambiguous synthesis of a benzo[b]furan derivative proceeding by this mechanism has been described.

The present Paper describes two alternative synthetic routes to a benzo[b]furan derivative. both of which again exploit the nucleophilic replacement of fluorine, but in these cases the heteroatom is used as the nucleophile.

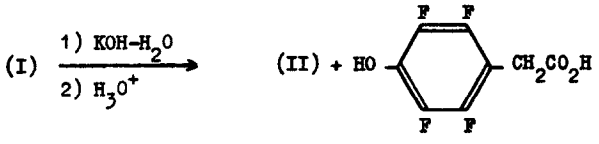
The starting material for these syntheses was diethyl 2,3,4,5,6-pentafluorophenylacetylmalonate(I) which was prepared in 91% yield by a standard reaction between 2,3,4,5,6-pentafluorophenylacetyl chloride (5) and diethyl ethoxymagnesium malonate (6). Compound (I) (b.p. 117-119°/0·05 mm) when treated with boiling sulphuric acid (30% v/v) for 1·5 hr gave 2',3',4',5',6'-pentafluorophenylpropan-2-one(II) m.p. 35·5-36·5° (82% yield). The structure of (II) was deduced from its elemental analysis; by its infra-red spectrum (a C=O stretch at 1720 cm^{-1}); and by its ^1H n.m.r. spectrum (a solution in CCl_4 showed two absorptions with

intensities in the ratio 3:2 at τ 7·76 [singlet due to CH_3-] and τ 6·21 [singlet due to -CH_2- which showed weak splitting due to coupling with ortho fluorine atoms (7)] respectively).

$$C_6F_5CH_2COCl + EtOMgCH(CO_2Et)_2 \longrightarrow C_6F_5CH_2COCH(CO_2Et)_2 \xrightarrow{H_3O^+} C_6F_5CH_2COCH_3$$

(I) (II)

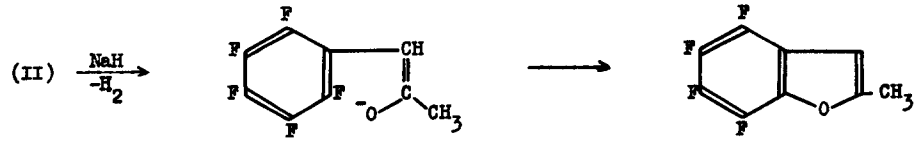
Treatment of (I) with boiling caustic potash solution for 2·5 hrs and acidification gave the ketone (II) (4% yield) and 2,3,5,6-tetrafluoro-4-hydroxyphenylacetic acid (III) m.p. 161-163° (96% yield). The structure of (III) was shown by its elemental analysis; by its mass spectral cracking pattern (a major fragment at mass 179 was due to $[HOC_6F_4CH_2]^+$); and by its ^{19}F n.m.r. spectrum (a solution in acetone showed two multiplets of equal intensity centred at 17·1 p.p.m. downfield and 0·07 p.p.m. upfield from C_6F_6 as internal reference due to two pairs of magnetically different fluorine atoms).



(III)

(III) was also produced by the treatment of ethyl 2,3,4,5,6-pentafluorophenylacetate (5) with aqueous alkali.

The first cyclisation reaction was carried out by treatment of the ketone (II) in tetrahydrofuran with sodium hydride at room temperature. After a rapid evolution of hydrogen, dry NN-dimethylformamide (D.M.F.) was added, the tetrahydrofuran removed by distillation and the D.M.F. solution heated under reflux for 4 hrs to give 4,5,6,7-tetrafluoro-2-methylbenso[b]-furan(IV) m.p. 59·5-60° (lit (8) 60·7-61°) (33% yield). In this reaction, cyclisation proceeds through the enolate anion by nucleophilic replacement of fluorine (Scheme 1).

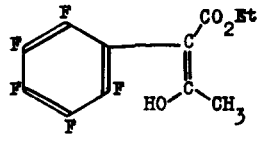


(IV)

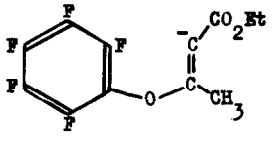
Scheme 1

The benso[b]furan derivative (IV) had been prepared previously (8) by a series of

reactions which initially involved the reaction between hexafluorobenzene and the sodio derivative of ethyl acetoacetate to give 3-ethoxycarbonyl-4,5,6,7-tetrafluoro-2-methylbenzo-[b]furan(V). Hydrolysis and decarboxylation of this compound using aqueous alkali gave (IV). The Russian workers proposed that the cyclisation reaction involved nucleophilic replacement of fluorine by oxygen in an intermediate formulated (VI), though other workers (9) have suggested carbanionic replacement of fluorine through an intermediate (VII).



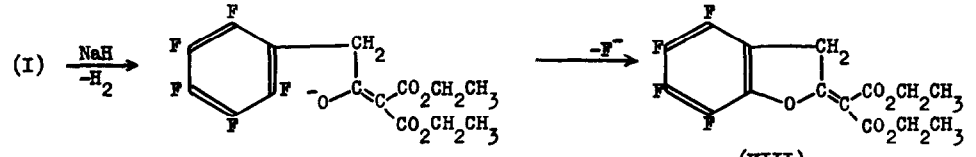
(VI)



(VII)

The work presented in this Paper, together with the observation (10) that the reaction between the pentafluorophenate anion and ethyl tetrolate under conditions identical with those used before to prepare (V) did <u>not</u> give (V), suggests that (VI) rather than (VII) is involved in that cyclisation reaction.

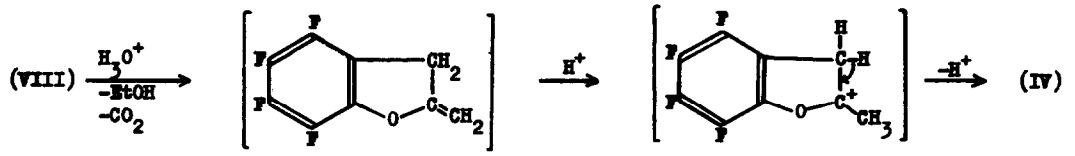
In the second cyclisation reaction, (I) was treated with sodium hydride in tetrahydrofuran, the solvent then replaced by D.M.F. and the mixture finally heated under reflux for 3 hrs to give (VIII) b.p. 104-107°/0·01-0·05 mm., m.p. 27-28·5° (16% yield). The final purification was accomplished by means of thick layer chromatography on Kieselgel GF_{254} using $CHCl_3/CCl_4$(3:1) as solvent. The structure of (VIII) was deduced by elemental analysis and n.m.r. spectroscopy. The ^{19}F n.m.r. spectrum of a solution of (VIII) in CCl_4 showed three multiplets with intensities in the ratio 1:2:1 due to four fluorine atoms centred at 15·0 p.p.m. and 0·8 p.p.m. downfield and 1·9 p.p.m. upfield from C_6F_6 as internal reference respectively. The ^1H n.m.r. spectrum of (VIII) in CCl_4 showed two non-equivalent protons at τ 2·93 (singlet showing signs of splitting) and τ 5·08 (singlet) due to the 3-H protons; four protons at τ 5·70 (quartet) due to overlapping by two $-CH_2-$ groups from two ethyl groups; and six protons at τ 8·68 (triplet) due to overlapping by two CH_3- groups from two ethyl groups.



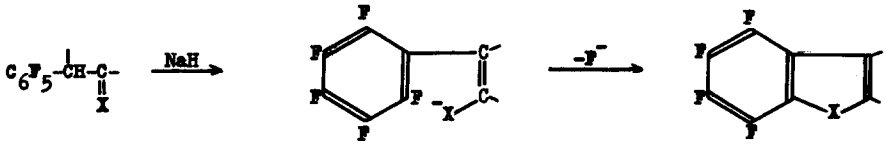
(VIII)

When (VIII) was heated with sulphuric acid (50% v/v) for 2·5 hrs, 4,5,6,7-tetrafluoro-2-

methylbenso[b]furan (IV) was again formed (94% yield):



The simple hydride ion promoted cyclisation of 2',3',4',5',6'-pentafluorophenylpropan-2-one to the partially fluorinated benso[b]furan compound (IV) (Scheme 1) now suggests the possibility of extending the scope of this reaction to prepare partially fluorinated benso[b]-thiophen and indole derivatives. This possibility is outlined in Scheme 2:



X = S; N-Ph etc. Scheme 2.

Acknowledgment

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