Organic Fluorine Compounds. Part XXXIX.[1] Reactions of α-Fluoro-β-keto-esters

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Ethyl 2,4-difluoroacetoacetate, ethyl ethoxalylfluoroacetate and the analogous benzyl ester gave the normal Wittig reaction with triethyl phosphonoacetate, whilst ethyl formylfluoroacetate gave a dimer of diethyl 4-fluoroprop-1-ene-1,3-dicarboxylate. Treatment of the sodio-enolate of ethyl formylfluoroacetate with acid chlorides gives 3-acyloxy-2-fluoroacrylates. The acyloxy-group of these compounds can be replaced easily by aromatic amines, and, furthermore, they can be employed for the synthesis of pyrimidines, *e.g.*, 5-fluorouracil.

FLUORINE atoms in α-fluoro-β-keto-esters inhibit enolisation [2] and for this reason ethyl ethoxalylfluoroacetate (I) reacts as a ketone both in the Reformatzky reaction [3] and with ethyl cyanoacetate.[4] It seemed interesting, therefore, to study the Wittig reaction of such fluorinated β-keto-esters. Machleidt and his co-workers have used the α-fluorinated ketones fluoroacetone and 1-chloro-3-fluoroacetone in Wittig reactions [5,6] and ethyl fluoroacetate has been shown to react with the Wittig reagents $Ph_3P{:}CHR$, to give the enol ethyl ethers of the α-fluoroketones $RCH_2{\cdot}CO{\cdot}CH_2F$.[7] Following Machleidt and his co-workers, we used triethyl phosphonoacetate (II) for the Wittig reaction. This reacted with ethyl 2,4-difluoroacetoacetate (III) to give diethyl 4-fluoro-3-fluoromethylprop-1-ene-1,3-dicarboxylate (IV), and with (I) afforded triethyl 3-fluoroprop-1-ene-1,2,3-tricarboxylate, (V);[4] the analogue of (I), prepared from benzyl fluoroacetate and diethyl oxalate, gave benzyl diethyl 4-fluoroprop-1-ene-1,2,3-tricarboxylate.

Since these esters are not very stable, no attempt was made to separate the *cis–trans* isomers which were possibly present. The instability is probably responsible for the fact that in the condensation of ethyl formylfluoroacetate (VI) with (II), a dimeride which could not be isolated in absolutely pure form was obtained and not the expected diethyl 3-fluoroprop-1-ene-1,3-dicarboxylate (VII). Diethyl prop-1-ene-1,3-dicarboxylate is itself dimerised by sodium ethoxide to ethyl 5-hydroxy-2,4-diethoxycarbonyl-1,4-dihydrophenyl acetate.[7a]

With acetyl chloride, the sodio-enolate of (VI) gives ethyl 3-acetoxy-2-fluoroacrylate (VIII; R = Me), which could not be obtained in a pure form; the solid phenyl analogue (VIII; R = Ph) proved fairly stable however. The corresponding enol methyl ether has been prepared before.[8]

$EtO_2C{\cdot}CO{\cdot}CHF{\cdot}CO_2Et$ (I)

$(EtO)_2P(O){\cdot}CH_2{\cdot}CO_2Et$ (II)

$CH_2F{\cdot}CO{\cdot}CHF{\cdot}CO_2Et$ (III)

$CH_2F{\cdot}C(=CH{\cdot}CO_2Et){\cdot}CHF{\cdot}CO_2Et$ (IV)

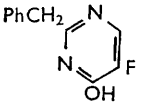
$EtO_2C{\cdot}C(=CH{\cdot}CO_2Et){\cdot}CHF{\cdot}CO_2Et$ (V)

$CHO{\cdot}CHF{\cdot}CO_2Et$ (VI)

$CH(=CH{\cdot}CO_2Et){\cdot}CHF{\cdot}CO_2Et$ (VII)

$RCO{\cdot}O{\cdot}CH{=}CF{\cdot}CO_2Et$ (VIII)

$ArNH{\cdot}CH{=}CF{\cdot}CO_2Et$ (IX)



(X)

The acetoxy-group in (VIII) is easily replaced by aromatic amines to give compounds of type (IX). The fluoroacrylates (VIII) can also be used for the synthesis of pyrimidines and, in this respect, have some advantages over the sodio-enolate of (VI). Thus, (VIII; R = Me) gave, with benzyl isothiouronium chloride

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2-(benzylthio)-5-fluoro-4-hydroxypyrimidine (X) (30%) which was converted to 5-fluorouracil. This is a variation of the usual method for the preparation of this important uracil derivative.

EXPERIMENTAL

Triethyl Phosphonoacetate (II).—A mixture of triethyl phosphite (165 g.) and ethyl chloroacetate (121 g.) was heated under reflux for 1·5 hr. and the product (180 g., 80%) was isolated by fractionation, b. p. 134°/2 mm.[9]

Diethyl 4-Fluoro-3-fluoromethylprop-1-ene-1,3-dicarboxylate (IV).—The sodio-enolate of ethyl 2,4-difluoroacetoacetate (III) was prepared by the addition, at 0°, of ethyl fluoroacetate (10·6 g.) to a suspension of sodium hydride (2·4 g.; in light petroleum) in dibutyl ether (100 ml.) and warming the mixture to room temperature. After 4 hr., triethyl phosphonoacetate (11·2 g.) was added and the mixture was heated at 100° with stirring for 30 min.; after 12 hr., the mixture was poured into an equal volume of cold water. The organic layer was freed from the solvent (by distillation) and from the light petroleum which separated, and the product (6·5 g., 55%) was fractionated, b. p. 105°/1 mm. (lit.,[6] b. p. 97—99° 0·2 mm.) (Found: C, 50·9; H, 6·1; F, 16·4. Calc. for $C_{10}H_{14}F_2O_4$: C, 50·8; H, 5·9; F, 16·1%).

Triethyl 3-Fluoroprop-1-ene-1,2,3-tricarboxylate (V).—At a temperature of 20° and with stirring, ethyl fluoroacetate (10·6 g.) was added to a mixture of sodium hydride (4·8 g.), diethyl oxalate (15 g.), and dibutyl ether (100 ml.). After 12 hr., the liberated ethanol was removed from the ethyl ethoxyalfluoroacetate (I) by evaporation under reduced pressure. Triethyl phosphonoacetate (18 g.) was then added and the mixture heated at 100° for 1 hr. and then worked-up to give the *product* (8 g., 29%), b. p. 120—124°/0·6 mm. (Found: C, 51·9; H, 6·4; F, 7·3. $C_{12}H_{17}FO_6$ requires C, 52·2; H, 6·2; F, 6·9%).

Benzyl Diethyl 3-Fluoroprop-1-ene-1,2,3-tricarboxylate.—Benzyl fluoroacetate was prepared by heating, ethyl fluoroacetate (59·3 g.), benzyl alcohol (54 g.), and toluene-*p*-sulphonic acid (0·1 g.), until no more ethanol distilled off. The ester (57 g., 61%) boiled at 150—160° (35 mm.). Similarly, benzyl fluoroacetate (33·6 g.), diethyl oxalate (30g.), sodium hydride (9·6 g.), and triethyl phosphonoacetate (40 g.) were condensed in dibutyl ether (100 ml.). The *product* (20 g., 30%) boiled at 125°/0·02 mm. (Found: C, 60·4; H, 6·0; F, 6·0. $C_{17}H_{19}FO_6$ requires C, 60·3; H, 5·6; F, 5·6%).

Dimeride (?) *of Diethyl 3-Fluoroprop-1-ene-1,3-dicarboxylate* (VII).—Ethyl fluoroacetate (10·6 g.) was added dropwise, at 0°, to a suspension of sodium methoxide (5·4 g.) in toluene (80 ml.) and ethyl formate (14·8 g.). After 2 hr., triethyl phosphonoacetate (22·4 g.) was added and the reaction mixture stirred at 100° for 1 hr.; water was then added and the solution fractionated. The only product isolated was an *oil*, b. p. 170—175°/1 mm., which gave no carbonyl derivatives, but with ferric chloride produced a dark red colour [Found: C, 53·4; H, 6·6; F, 8·2. $(C_9H_{13}FO_4)_2$ requires C, 53·0; H, 6·4; F, 9·3%].

Ethyl 3-Acetoxy-2-fluoroacrylate (VIII; R = Me). At 0°, ethyl fluoroacetate (53 g.) was added dropwise to a suspension of sodium hydride (24 g.) in dibutyl ether (300 ml.) and ethyl formate (74 g.). After 12 hr. at room temperature, the liberated ethanol and the excess of ethyl formate was removed under reduced pressure (in some experiments the sodio-enolate was precipitated from the mixture). At a temperature not exceeding 20° and with vigorous stirring, acetyl chloride (39·5 g.) was added and, after 2 hr. at room temperature, the product was poured into water (250 ml.). The ester which boiled at 70° (0·6 mm.), could not be purified completely, but was suitable for all the reactions described later, $\nu_{max.}$ (liq.) 1775, 1735, 1690, 1650, and 1180 cm.$^{-1}$ (Found: C, 46·3; H, 5·6; F, 10·5. $C_7H_9FO_4$ requires C, 47·7; H, 5·1; F, 10·8%).

Ethyl 3-Benzoyloxy-2-fluoroacrylate (VIII; R = Ph).—By the method described in the preceding experiment, benzoyl chloride (70 g.) was added to the sodio-enolate of ethyl formylfluoroacetate, prepared from ethyl fluoroacetate (54 g.). The product (94 g., 79%) formed *plates*, m. p. 54° (from n-hexane); $\nu_{max.}$ (KBr) 1750, 1675, 1630, 1600, 1150, 1130, and 705 cm.$^{-1}$ (Found: C, 60·4; H, 4·4; F, 7·4. $C_{12}H_{11}FO_4$ requires C, 60·5; H, 4·6; F, 8·0%).

Ethyl 3-Anilino-2-fluoroacrylate (IX; Ar = Ph). A mixture of (VIII; R = Me) (8·8 g.), aniline (9·3 g.), acetic acid (1 g.), and methanol (40 ml.) was heated under reflux for 10 min. and diluted cautiously with water, until the solution became turbid. Further cooling and scratching of the solution gave a solid product which recrystallised from cyclohexane or methylcyclohexane as white *plates* (7 g., 70%), m. p. 100°. $\nu_{max.}$ (KBr) 3300, 1700, 1660, 1630, 1600, 1100, and 745 cm.$^{-1}$ (Found: C, 63·0; H, 5·8; F, 9·1; N, 6·9. $C_{11}H_{12}FNO_2$ requires C, 63·2; H, 5·7; F, 9·1; N, 6·7%).

Ethyl 3-(β-Naphthylamino)-2-fluoroacrylate (IX; Ar = β-$C_{10}H_7$). The fluoroacrylate (VIII; R = Me) (4·4 g.) was condensed with β-naphthylamine (7·1 g.) in ethanol (50 ml.). The product which separated crystallised from methylcyclohexane or ethanol as *plates* (5·5 g., 84%), m. p., 156°. $\nu_{max.}$ (KBr) 3300, 1700, 1650,1600, 1100, and 740 cm.$^{-1}$ (Found: C, 69·3; H, 5·3; F, 7·3; N, 5·8. $C_{15}H_{14}FNO_2$ requires C, 69·5; H, 5·4; F, 7·3; N, 5·4%).

Ethyl 3-(p-Methoxyanilino)-2-fluoroacrylate (IX; Ar = *p*-MeO·C_6H_4).—A mixture of ethyl 3-acetoxy-2-fluoroacrylate (4·4 g.), *p*-anisidine (6 g.), and a little methanol was heated under reflux for 5 min. and then diluted with warm water (10 ml.) and cooled slowly. The product crystallised from aqueous methanol (85%) as *plates* (4·2 g., 70%), m. p., 154° (Found: C, 60·6; H, 5·9; F, 7·7; N, 5·9. $C_{12}H_{14}FNO_3$ requires C, 60·3; H, 5·9; F, 8·0; N, 5·9%). *p-N*-Acetylanisidine, m. p. 130°, was isolated from the mother-liquor.

2-(Benzylthio)-5-fluoro-4-hydroxypyrimidine (X).—A mixture of ethyl 3-acetoxy-2-fluoroacrylate (1·8 g.), freshly prepared sodium methoxide (1·8 g.), benzylisothiouronium chloride (3 g.), and methanol (50 ml.) was heated under reflux for 2 hr. After 12 hr., the methanol was distilled off and the aqueous extract of the residue was acidified with hydrochloric acid. The *product* recrystallised from ethyl acetate as needles (0·7 g., 30%), m. p. 222° (lit.,[10] m. p. 216—218°) (Found: C, 56·1; H, 4·0; F, 7·8. Calc. for $C_{11}H_9FN_2OS$: C, 55·9; H, 3·8; F, 8·1%).

5-Fluorouracil.—Hydrolysis of the foregoing product with conc. hydrochloric acid gave a 40% yield of 5-fluorouracil, m. p. 282°, [(lit.[11] m. p. 282—283° (decomp.)]. Its infrared spectrum showed peaks at 1675, 1590, 1530, 1450, 1270, 1250, 710, and 670 cm.$^{-1}$.

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