2-FLUORO-1,3-PROPANEDIOL AND CHEMICAL TRANSFORMATIONS OF DERIVED COMPOUNDS*

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Ethyl 2-fluoro-3-hydroxypropionate (*I*) was reduced to 2-fluoro-1,3-propanediol (*II*) which was transformed into 1,3-di-*p*-toluenesulphonyloxy-2-fluoropropane (*III*). The action of allylmagnesium bromide on compound *III* gives 5-fluoro-6-*p*-toluenesulphonyloxy-1-hexene (*IV*) from which 5-fluoro-6-phthalimido-1-hexene (*VI*) and 5-fluoro-6-succinimido-1-hexene (*VII*) were prepared. Gabriel reaction of the ditosylate *III* affords either 2-fluoro-1-phthalimido-3-tosyloxypropane (*VIII*) or 1,3-diphthalimido-2-fluoropropane (*IX*). The tosylates *III* and *VIII* were transformed into 1,3-diiodo-2-fluoropropane (*X*) and 2-fluoro-1-iodo-3-phthalimidopropane (*XI*), respectively.

In our previous paper[1] we described the preparation of ethyl 2-fluoro-3-hydroxypropionate (*I*) and indicated some ways for the preparative utilization of this compound. Relatively good accessibility of ester *I* and the possibility of its reduction to 2-fluoro-1,3-propanediol (*II*) led us to a more detailed study of the preparation of diol *II*.

Taylor and Kent[2] prepared small amount of the crude diol *II* (identified as ditosylate *III*) by reduction of 2-fluoro-3-hydroxypropionaldehyde with lithium aluminium hydride in ether. However, when applying this procedure to the ester *I*, we found that a simultaneous reductive cleavage of the fluoro atom takes place, and we were not able to isolate either the diol *II* or the ditosylate *III*. We therefore tried milder reducing agents such as some borohydrides. Calcium borohydride prepared *in situ* in tetrahydrofuran solution was found to be the reagent of choice: using this reagent we obtained the diol *II* in 70% yield. Reduction with lithium borohydride gave only 45% yield whereas sodium borohydride was totally ineffective, though this reagent reduced successfully a similar grouping in 5-methylester of 4-fluoroglutamic acid[3]. The diol *II* was transformed into the ditosylate *III* by the action of *p*-toluenesulphochloride in pyridine. We further studied reactions of the compound *III* with some nucleophilic agents. When this compound was treated with allylmagnesium bromide, only one tosyl group reacted to give 5-fluoro-6-*p*-to-

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luenesulphonyloxy-1-hexene (*IV*) even when a fourfold molar excess of Grignard reagent was used; 5-fluoro-1,8-nonadiene (*V*) was not isolated. In order to obtain optimum yield of the olefin *IV* (40%), it was necessary to use at least two equivalents of the reagent; further increase in the ratio of the reactants did not affect the yield. The tosyl group in the compound *IV* reacted with potassium phthalimide giving 5-fluoro-6-phthalimido-1-hexene (*VI*); analogously, the reaction with sodium salt of succinimide led to 5-fluoro-6-succinimido-1-hexene (*VII*). Gabriel reaction between the ditosylate *III* and potassium phthalimide in dimethylformamide afforded high yields of phthalimido derivatives: according to the ratio of starting components, we prepared either 2-fluoro-1-phthalimido-3-*p*-toluenesulphonyloxypropane (*VIII*) or 1,3-diphthalimido-2-fluoropropane (*IX*). Exchange of the tosyloxy group for iodine using sodium iodide was also facile and gave good yields. The compound *III* was thus transformed into 1,3-diiodo-2-fluoropropane (*X*) whereas the tosylate *VIII* afforded 2-fluoro-1-iodo-3-phthalimidopropane (*XI*).

$HOCH_2CHFCO_2C_2H_5$

I

$CH_2{=}CHCH_2CH_2CHFCH_2X$

IV, X = OTs
V, X = $CH_2CH{=}CH_2$
VI, X = NPht

VII, X =

XCH_2CHFCH_2X'

II, X = X′ = OH
III, X = X′ = OTs
VIII, X = NPht, X′ = OTs
IX, X = X′ = NPht
X, X = X′ = I
XI, X = NPht, X′ = I

We also tried to alkylate diethyl malonate, formamidomalonate, acetamidomalonate and phthalimidomalonate with the compounds *III* and *X*. In contrast to the previous substitution reactions, during which the molecule of product retained the fluorine atom, efforts to obtain the desired fluoro esters in this way were unsuccessful, although reactions of this type were successfully carried out with 1,3-dibromopropane[4-6] and 1,3-ditosyloxypropane[7].

EXPERIMENTAL

The temperature data are not corrected. The melting points were determined on a Kofler block. Molecular sieve of the type Nalsit 4A (Dimitrov Chemical Works, Bratislava) was activated by heating to 350°C for 4 h. The IR-spectra were measured on a Perkin-Elmer 621 spectrophotometer.

2-Fluoro-1,3-propanediol (*II*)

A mixture of 95% sodium borohydride (38·4 g) and tetrahydrofuran (1 250 ml) was cooled to 0°C, anhydrous calcium chloride (97·2 g) was slowly added under stirring and the resulting slurry was stirred for 45 min without cooling. The mixture was then cooled to −10°C and a solution of the ester *I* (119 g) in tetrahydrofuran (100 ml) was added dropwise during 70 min. After stirring for 10 h at room temperature, the mixture was carefully decomposed with conc. HCl (115 ml)

at −20°C and stirred for 1 h without cooling. The precipitate was filtered, shaken for 30 min with tetrahydrofuran (200 ml) and again filtered. This procedure was repeated once more and the remaining cake was washed with tetrahydrofuran (2 × 50 ml). The combined filtrates were concentrated *in vacuo* to 250 ml and the precipitate which separated was filtered and washed with tetrahydrofuran (25 ml). The solvent was evaporated and the remaining oil was dissolved in methanol (250 ml) and shaken for 4 h with Dowex 50 X 8 (100−200 mesh, pre-washed with methanol) in order to remove the main portion of calcium ions. The exchange resin was filtered, washed with methanol, the filtrate evaporated, and the procedure was repeated once or twice more with a new portion of exchange resin till disappearance of Ca^{2+} ions. The residual boric acid was removed by evaporation with methanol (100 ml) and the deionised crude product was distilled *in vacuo*. Yield 63·8 g (70%) of a hygroscopic crystalline mass, b.p. 75−80°C/0·3 to 0·4 Torr. An analytical sample boiled at 121−122°C/16 Torr, m.p. 38−39°C. For $C_3H_7FO_2$ (94·09) calculated: 38·29% C, 7·51% H, 20·19% F; found: 38·55% C, 7·79% H, 20·46% F. IR-spectrum (liquid film): 3450 cm^{-1} (ν OH), 1060 cm^{-1} (ν C—O, primary alcohol).

1,3-Di-*p*-toluenesulphonyloxy-2-fluoropropane (*III*)

p-Toluenesulphonyl chloride (71 g) was added to a solution of the diol *II* (11·75 g) in pyridine (210 ml) at −10°C in the course of 25 min. The mixture was stirred at this temperature for 1 h, allowed to stand overnight at 0°C and then poured into a stirred mixture of conc. H_2SO_4 (56 ml) and ice (600 g) at a temperature lower than +3°C. The separated compound was filtered, ground under water, washed with water, dried *in vacuo* over P_2O_5, and recrystallized from ethanol (charcoal); yield 44 g (88%), m.p. 110−111°C (reported[2] m.p. 109°C).

5-Fluoro-6-*p*-toluenesulphonyloxy-1-hexene (*IV*)

A solution of ditosylate *III* (20·1 g) in tetrahydrofuran (120 ml) was added dropwise in the course of 30 min to a solution of Grignard reagent[8] prepared from allyl bromide (12·2 g; 8·7 ml) and magnesium (7 g) in ether (120 ml). The mixture was refluxed under stirring for 1 h. and, after standing overnight, poured into a mixture of an aqueous solution (100 ml) of ammonium chloride (22 g) and ice (200 g). The aqueous layer was extracted twice with 50 ml of ether (after slight acidification with acetic acid), the ethereal solution was washed with a 5% solution of sodium bicarbonate, with water, and dried with calcium chloride. The solvents were evaporated and the residue distilled giving 5·4 g (40%) of an oil, b.p. 127−137°C/0·2 Torr which solidified. Crystallization from light petroleum (b.p. 50−70°C) afforded an analytical sample as needles, melting at 34°C. For $C_{13}H_{17}FO_3S$ (272·3) calculated: 57·33% C, 6·29% H, 6·98% F, 11·77% S; found: 57·50% C, 6·34% H, 7·10% F, 11·81% S. IR-spectrum (tetrachloromethane): 3080, 1643, 993, 919 cm^{-1} (vinyl group); 1378, doublet at 1192, 1181 cm^{-1} (ν SO_2); 1600, 1496 cm^{-1} (phenyl group).

5-Fluoro-6-phthalimido-1-hexene (*VI*)

A mixture of olefin *IV* (19 g), potassium phthalimide (12·9 g), sodium iodide (4·7 g) and dimethylformamide (100 ml) was heated under stirring at 120−125°C for 3 h. The resulting neutral solution was cooled, poured into ice-cold water (500 ml) and set aside for 3 days in a refrigerator. The separated compound was filtered, ground under water, washed with water and dried *in vacuo* over P_2O_5, giving thus 14·6 g (84%) of the crude product, m.p. 48−50°C, which contained traces of phthalimide. After recrystallization from light petroleum (b.p. 50−70°C) (charcoal) the melting point rose to 57°C. For $C_{14}H_{14}FNO_2$ (247·3) calculated: 68·00% C, 5·71% H, 7·68% F, 5·66% N;

found: 67·84% C, 5·47% H, 7·55% F, 5·71% N. IR-spectrum (tetrachloromethane): 3080, 1642, 993, 917 cm^{-1} (vinyl group): 1777, 1722 cm^{-1} (ν C=O); 1613, 1469, doublet at 722, 713 cm^{-1} (phenyl group).

5-Fluoro-6-succinimido-1-hexene (*VII*)

Succinimide (5·4 g) was added to a solution of sodium (1·26 g) in ethanol (40 ml), the mixture was stirred for 10 min and evaporated to dryness *in vacuo*. The residue was suspended in dimethylformamide (30 ml), and the olefin *IV* (14·9 g) in dimethylformamide (50 ml) was added. The mixture was heated at 110°C for 2 h, evaporated *in vacuo* (40°C, 0·2 Torr), the residue shaken with dichloromethane (50 ml) and water (20 ml) and the aqueous layer extracted twice with dichloromethane (50 ml). The combined extracts were washed with water (2 × 15 ml), dried with molecular sieve and concentrated to a small volume. A compound, m.p. 208–214°C, separated (2·0 g) during this process; it was not studied further. Distillation of the filtrate afforded 4·2 g (38·5%) of the compound *VII*, b.p. 95–100°C/0·15 Torr. An analytical sample had b.p. 100 to 105°C/0·2 Torr, n_D^{20} 1·4832. For $C_{10}H_{14}FNO_2$ (199·2) calculated: 60·29% C, 7·12% H, 9·54% F, 7·03% N; found: 60·03% C, 7·00% H, 9·72% F, 7·03% N. IR-spectrum (tetrachloromethane): 3078, 1642, 994, 917 cm^{-1} (vinyl group); 1783, 1715 cm^{-1} (ν C=O).

2-Fluoro-1-phthalimido-3-*p*-toluenesulphonyloxypropane (*VIII*)

A mixture of ditosylate *III* (8·06 g), potassium phthalimide (3·70 g) and dimethylformamide (50 ml) was stirred at 65°C for 2 h. The neutral mixture was cooled, poured into ice-cold water (800 ml) and shaken thoroughly. After standing for 3 days at 0°C, the separated compound was filtered, washed with water and dried in a dessicator; yield 7·2 g (96%), m.p. 120–127°C. Two recrystallizations from ethanol afforded and analytical sample, m.p. 135–139°C. For $C_{18}H_{16}$.FNO_5S (377·4) calculated: 57·28% C, 4·27% H, 5·03% F, 3·71% N, 8·49% S; found: 57·50% C, 4·17% H, 4·75% F, 3·93% N, 8·44% S.

1,3-Diphthalimido-2-fluoropropane (*IX*)

A mixture of ditosylate *III* (403 mg), potassium phthalimide (185 mg) and dimethylformamide (5 ml) was stirred at 60–70°C for 1·5 h, then another portion of potassium phthalimide (185 mg) was added and the mixture was heated for another 4 h at the same temperature. After cooling, the residual alkalinity was neutralized by addition of 1 drop of conc. HCl, the reaction mixture was poured into water (50 ml) under shaking and allowed to stand in an ice bath for 3 h. The separated product was filtered, washed with water and dried in a dessicator; yield 220 mg (62·5%). For analysis the compound was recrystallized twice from aqueous acetone, m.p. 218–225°C (sintering at 190°C). For $C_{19}H_{13}FN_2O_4$ (352·3) calculated: 64·77% C, 3·71% H, 5·39% F, 7·95% N; found: 64·95% C, 3·80% H, 5·40% F, 7·92% N. IR-spectrum (Nujol mull): 1770, 1723 cm^{-1} (ν C=O); 1611, 1464, doublet at 725, 717 cm^{-1} (phenyl group).

1,3-Diiodo-2-fluoropropane (*X*)

A solution of the compound *III* (47·6 g) and sodium iodide (71 g) in acetone (400 ml) was refluxed for 16 h under protection from light. After cooling, the separated salts were filtered off, washed with ether and the filtrate evaporated *in vacuo*. The oily residue was diluted with dichloromethane (60 ml), washed subsequently with water (20 ml), saturated sodium thiosulphate solution (2 × 5 ml), and water (2 × 20 ml), and dried with a molecular sieve. Distillation afforded 32·5 g (87·3%) of the diiodide *X*, b.p. 31–34°C/0·2 Torr. An analytical sample boiled at 32–33°C/0·2 Torr and had n_D^{20} 1·6098. For $C_3H_5FI_2$ (313·9) calculated: 6·04% F; found: 6·17% F.

2-Fluoro-1-iodo-3-phthalimidopropane (*XI*)

A stirred solution of the tosyl derivative *VIII* (3·8 g) and NaI (3·0 g) in acetone (25 ml) was refluxed for 20 h. After cooling, the separated sodium *p*-toluenesulphonate was filtered, washed with acetone and the filtrate evaporated *in vacuo*. The remaining oil was dissolved in ethyl acetate (50 ml) and washed successively with water (10 ml), saturated sodium thiosulphate solution (5 ml) and water (2 × 10 ml). The solution was dried with a molecular sieve and evaporated *in vacuo*, affording 3·2 g (96%) of product, m.p. 92—95°C, which contained traces of the unreacted tosylate *VIII* (melting between 120—130°C). Recrystallization from benzene (7 ml) gave 2·6 g (78%) of crystals, m.p. 93—95°C. An analytical sample melted at 93—95°C (benzene). For $C_{11}H_9FINO_2$ (333·1) calculated: 39·66% C, 2·72% H, 5·72% F, 4·20% N; found: 39·89% C, 3,00% H, 5·99% F, 4·29% N. IR-spectrum (Nujol mull): 1775, 1716 cm^{-1} (ν C=O); 1608, 1465, doublet at 725, 714 cm^{-1} (phenyl group).

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