Tetrahedron Letters No. 28, pp. 2675-2678, 1971. Pergamon Press. Printed in Great Britain.

A SIMPLE SYNTHESIS OF MONOFLUOROSTEARIC ACIDS

Nigel J. M. Birdsall [1]

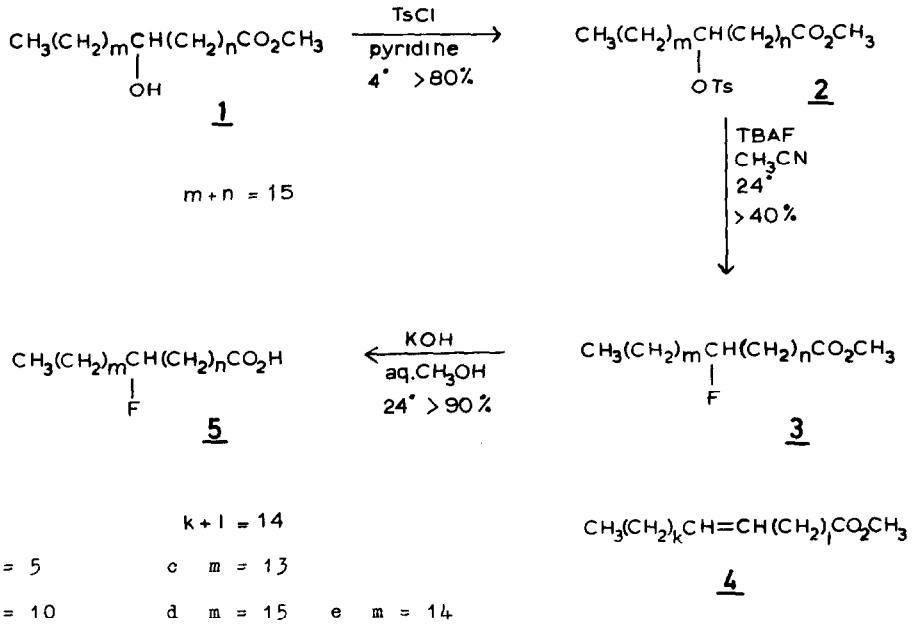
M.R.C. Molecular Pharmacology Unit, Hills Road, Cambridge, England.

(Received in Uk 21 May 1971; accepted in UK for publication 15 June 1971)

The preparation of fluorinated fatty acids [2,3] is complicated by the toxic and corrosive nature of the fluorinating agents employed [2-4]. Methyl 12-fluorostearate has been prepared in good yield using (2-chloro-1,1,2-trifluoroethyl) diethylamine [5] but there have been reports of undesired side reactions in the use of this reagent for the direct replacement of -OH by -F [6]. Nucleophilic displacement of a tosylate anion has been utilized in the preparation of primary fluoro compounds [7] and, using tetraalkylammonium fluorides in acetonitrile, for the synthesis of 3-fluoro sugars [8]. This latter displacement of an endo - sulphonyloxy group proceeds under relatively mild conditions.

This communication presents the extension of the latter reaction to the preparation of several fluorostearic acids and indicates its possible generality as a simple method for the introduction of a fluorine atom into the secondary position of an alkyl chain.

Methyl 12-tosyloxystearate 2a was obtained in good yield by the tosylation of methyl 12-hydroxystearate 1a. Displacement of the tosylate function by tetra n-butylammonium fluoride (TBAF) in acetonitrile proceeded readily at room temperature to give methyl 12-fluorostearate 3a which was isolated in 40% yield after several recrystallisations from methanol. The pmr spectrum[9] of 3a showed the CHF signal as a broad doublet (δ 4.39, J = 49.1 Hz) which on irradiation at δ 1.49 collapsed to a sharp doublet. The ^{19}F nmr spectrum [9] exhibited a multiplet which, on proton noise decoupling,



collapsed to a singlet 12.8 ppm upfield from an external standard of hexafluorobenzene. Pmr analysis of the crude reaction mixture indicated the presence of an unsaturated ester, which from the shape of the olefinic signal [10] at δ 5.32 was the trans isomer 4 [11].

Table I

Solvent [a]	Yield % [13] 2a	4	3a
CH_3CN	0	30	70
$(CH_3)_2CO$	25	25	50
DMF	0	45	30[b]
DMSO	0	55	20[b]
HMPT	0	100	0
$(CH_2OH)_2$	100	0	0
	90[c]	10	0

a 2a 0.25 mmole/5 ml solvent 2.0 equiv. TBAF, 24° 96h.
b 25% 1a present
c 100° 12h.

It was found that acetonitrile as solvent gave the highest yield of 3a. (Table I). Substitution proceeded more slowly in acetone and there were increasing yields of 4 as the solvent basicity of the dipolar aprotic solvent increased [12]. Ethylene glycol did not appear to be a suitable solvent.

TABLE II

Compound [d]	Time Hr	Yield % [13] 4	3	Isolated yield 3	JHF gem Hz	mp[e] 3	mp[f] 5
2a	72	30	70	40	49.1	39.5-40[g]	76-7
2b	96	35	65	40	49.2	38.5-39	77.5-78
2c	60	15	85	55	49.6	39.5-40	75-76
2d	72	0	75[h]	70	49.5	43-4	89-90
2e	60	100	0	0			

d 2/CH_3CN + 2.0 equiv. TBAF/CH_3CN, 24°

e Recryst. 4 or 5 times (MeOH)

f Recryst 3 times (pet. ether 40/60)

g lit[4] mp. 39°

h 25% 1d present

i lit[2] mp 89-90°

The nucleophilic substitution reaction is also favoured by lower temperatures, necessitating longer reaction times, but the product yields are relatively unaffected by the concentration of TBAF.

Utilizing the optimum conditions, methyl 7-,4- and 2-tosyloxystearate, prepared in excellent yield from the hydroxyesters, gave 40-70% yields of the fluoroesters 2b, 2c and 2d respectively. (Table II). Displacement by fluoride of the mesyloxy group of methyl 12-mesyloxystearate gave 3a in yield comparable with that of tosylate displacement. Any group in the region of the tosyloxy group which increases the acidity of the vicinal proton causes elimination to take preference over substitution. For example, methyl 3-tosyloxystearate 3e and methyl threo 9, 10-ditosyloxystearate afforded predominantly elimination products. Hydrolysis of 3a - c to the fluorostearic acids 5a - c was accomplished in excellent yield by aqueous methanolic KOH, and 5d was obtained by acid hydrolysis of 3d[3].

The use of the fluorostearic acids and their derivatives as NMR lipid probes of model membrane systems will be reported elsewhere.

REFERENCES

1. Seconded from Roche Products, Welwyn Garden City, England.
2. F.L.M.Pattison and R.G.Woolford, J. Am. Chem. Soc., 77, 2308 (1957)
   F.L.M.Pattison, J.B.Stathers and R.G.Woolford, J. Am. Chem. Soc., 78, 2255(1956)
   R.E.A.Dear and F.L.M.Pattison. J. Am. Chem. Soc., 85, 622 (1963)
   H.Gershon and R.Parmegiani, J. Med. Chem., 10, 186 (1967)
   K.Fredenhagen and G.Cadenbach. Chem. Ber., 67, 928 (1934)
3. F.L.M.Pattison, R.L.Buchanan and F.H.Dean, Canad. J. Chem., 43, 1700 (1965)
4. For reviews of preparation of fluoro compounds see: F.L.M.Pattison and R.A.Peters, Handbook of Experimental Pharmacology,Springer-Verlag, XX/I, p. 387 (1966); F.L.M.Pattison, Toxic Fluorine Compounds Elsevier 1959
5. E.D.Bergmann and A.Cohen, Is. J. Chem., 3, 71 (1965)
6. L.H.Knox, E.Verlarde, S.Berger, D.Cuadrillo and A.D.Cross, J. Org. Chem., 29, 2187 (1964); K.R.Wood, D.Fisher and P.W.Kent, J. Chem. Soc.,1994 (1966)
7. H.Lettre and U.Wölcke, Ann. Chem., 708, 75 (1967)
8. A.B.Foster, R.Hems and J.M.Webber, Carbohyd. Res., 5, 292 (1967); J.S.Brimacombe, A.B.Foster, R.Hems and L.D.Hall, Carbohyd.Res. 8, 249 (1968) J.S.Brimacombe, P.A.Gent and J.H.Westwood, Carbohyd. Res., 12, 475 (1970)
9. The ^{1}H and ^{19}F nmr spectra of compounds in $CDCl_3$ were measured on a Varian XL-100/15 spectrometer. All new compounds gave satisfactory analyses.
10. E.Ucciani, R.Piantoni, Chem. Phys. Lipids, 2, 256 (1968)
11. There is probably a mixture of methyl Δ^{11} and Δ^{12} - trans octadecenoate resulting from the base-catalysed elimination of p-toluenesulphonic acid.
12. H.Normant, Angew Chem. Internat. Edit., 6, 1046 (1967)
13. The percentage yield of the compounds was obtained by integration of the pmr spectrum of the reaction product.