Friedel–Crafts Acylation of Fluorenes; Substituent Effects on Diacetylation

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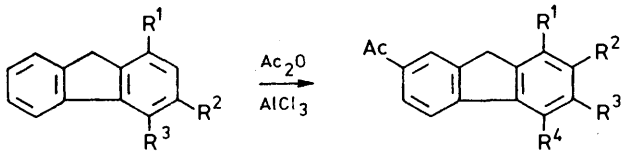
Several mono-substituted fluorenes have been diacetylated under Friedel–Crafts conditions, and the nature and position of some substituents were shown to have a profound influence on the resulting substitution pattern. Unambiguous structural assignment was facilitated by n.m.r. spectroscopy using lanthanide shift reagents.

It is well established that acylation of fluorene (1) proceeds exclusively at C-2, and that with this position blocked acylation will usually occur at the equivalent 7-position of the second benzenoid ring.[1-4] Moreover, diacetylation of (1) has been shown [5,6] to produce the expected 2,7-diacetyl derivative (7). In agreement with this latter work we have prepared (7) in 72% yield from fluorene (1) under Friedel–Crafts conditions.

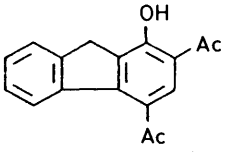
RESULTS AND DISCUSSION

Acylation of 1-methylfluorene (2) under similar conditions gave a 66% yield of a diacetyl derivative, which was shown to be exclusively the 2,7-diacetyl compound (9). Studies by Arene and Taylor [2] on the monoacylation of (2) have shown that steric hindrance precludes formation of the 2-acyl derivative, and favours acylation on the unsubstituted ring at C-7 to give (8). Less



(1) $R^1=R^2=R^3=H$
(2) $R^1=Me, R^2=R^3=H$
(3) $R^1=OMe, R^2=R^3=H$
(4) $R^2=Br, R^1=R^3=H$
(5) $R^3=Me, R^1=R^2=H$
(6) $R^3=F, R^1=R^2=H$

(7) $R^2=Ac, R^1=R^3=R^4=H$
(8) $R^1=Me, R^2=R^3=R^4=H$
(9) $R^1=Me, R^2=Ac, R^3=R^4=H$
(10) $R^1=OH, R^4=Ac, R^2=R^3=H$
(11) $R^1=OMe, R^4=Ac, R^2=R^3=H$
(12) $R^1=OAc, R^4=Ac, R^2=R^3=H$
(13) $R^2=Ac, R^3=Br, R^1=R^4=H$
(14) $R^2=Ac, R^4=Me, R^1=R^3=H$
(15) $R^1=Ac, R^4=F, R^2=R^3=H$



(16)

bulky electrophiles such as bromine or the nitronium ion did, however, yield the 2-substituted fluorenes, clearly demonstrating the enhanced reactivity of the alkylated ring.[2] From this work we infer that acylation of (2) initially takes place at C-7, followed by subsequent acylation at the more hindered 2-position.

The acetylation of 1-methoxyfluorene (3) under comparable conditions gave a mixture of products which showed evidence of extensive dealkylation, the resulting phenol being largely acetylated under the reaction conditions. Chromatographic separation of the major components of this mixture gave 6% of the 4,7-diacetyl-1-hydroxyfluorene (10) together with a mixture of 1-acetoxy- and 1-methoxy-derivatives which were not readily separated by either fractional recrystallization or repeated chromatography. Hydrolysis of the mixture gave a further quantity (15%) of the phenol (10) and 24% of the 4,7-diacetyl-1-methoxyfluorene (11). The n.m.r. spectrum of (11) showed typical splitting except for the downfield shift of the C-5 proton, induced by the anisotropic effect of the C-4 acetyl group. A pure sample of the acetate (12) was prepared by reacetylation of the phenol (10) and was shown to be identical with the second component of the chromatographed mixture. In addition, a small quantity (<5%) of 2,4-diacetyl-1-hydroxyfluorene (16) was isolated. Evidently the *para*-directing influence of the alkoxy-group in this instance, coupled perhaps with its bulk, is of sufficient importance to redirect acylation to the 4-position. Only trace amounts of 2-acetylated material could be discerned.

An analogous acylation of 3-bromofluorene (4) proceeded with some difficulty, a diacetyl derivative being formed only after extended reaction times. Chromatography of the resulting tar gave a single isolable product in only 12% yield, which was identified as the 2,7-diacetyl derivative (13). In this instance the directional influences of the substituent and that of the nucleus itself act in unison, although the bulk and deactivating influence of the halogen atom make entry of the homoanular acetyl group difficult.

4-Methylfluorene (5), which was prepared in excellent yield from fluorene-4-carboxylic acid [7] using an extension of the reductive silylation procedure of Benkeser *et al.*,[8] reacted under the same conditions as the parent compound to give a 94% yield of a mixture of the 2,7-diacetylfluorene (14) and a second diacetyl derivative in the ratio of 5 : 1, respectively. Repeated fractional recrystallisation of this mixture gave the major isomer (14). The minor component was not unambiguously identified owing to contamination with (14), but from the proton n.m.r. spectrum the structure was tentatively assigned as 1,7-diacetyl-4-methylfluorene.

4-Fluorofluorene (6) showed a marked tendency to

acylate at C-1 and in this instance the 1,7-diacetyl derivative (15), which was obtained in 37% yield, was the only product isolated. The formation of this derivative may be taken as evidence for the comparatively strong *para*-directing influence of the fluorene atom relative to the intrinsic directional influence of the fluorene nucleus, and in this context may be compared with the effect of the methoxy-group at C-1.

It is therefore evident that in suitable cases both the C-1 and C-4 positions of the fluorene nucleus may be selectively acetylated even in those situations where the 2-position remains vacant. A balance exists between the intrinsically electron rich C-2 and C-7 positions of the fluorene nucleus and the strength of the *ortho*/*para* directing character of the substituents present.

None of the reaction mixtures were exhaustively investigated for minor components and their presence is not therefore precluded.

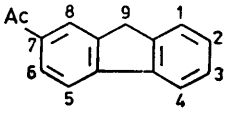
N.M.R. Spectra.—With the exception of compounds derived from 1-methoxyfluorene (3), unambiguous structural assignment of the diacetylfluorenes was not possible from the ^1H n.m.r. spectra owing to the complex aryl spin patterns. However, use was made of the carbonyl functions of the two acetyl groups as defined and singular sites in the structures for lanthanide ion attachment. Utilisation of the lanthanide shift reagent (LSR) Eu([$^2H_9$]fod)$_3$ as a structural probe, resulted in downfield shifts of the aryl-proton resonances in a quantitative manner according to their proximity to the acetyl groups. This provided large chemical-shift differences between aryl resonances and allowed easy assignment of individual protons by the simplification of spin patterns.

The Table shows the shift ratios relative to the methyl protons of the 7-acetyl group based on a *ca.* 1 : 0.9 molar ratio of substrate : Eu([$^2H_9$]fod)$_3$. There is excellent agreement between the shift ratio for similar protons in all compounds, 4-H, 5-H, 6-H, and 7-H, and also between similar protons for similar compounds, *i.e.* the methylene protons of compounds (7), (9), (13), and (14).

The larger shift of the 1-Me group in compound (9) relative to the 4-Me group in (14) is indicative of the proximity of the acetyl group and its attendant europium ion. Moreover, in compounds (9) and (13), where there are groups adjacent to the 2-acetyl moiety, there is a lower relative shift of the 2-acetyl protons, and of the 1-H in (13), which suggests steric hindrance of the LSR at the 2-position.

It is of note that in compound (15) the relative shift magnitudes of the 2-H, 6-H, 8-H, and more notably the methylene protons, indicate a preferred orientation of each carbonyl group in the LSR–substrate complex.

Lanthanide shift ratio [a] (relative to the 7-Ac protons)



Compound	1-H	2-H	3-H	4-H	5-H	6-H	8-H	2-Ac	7-Ac	CH_2	4-Me
(7)	0.88		0.79	0.31	0.31	0.79	0.88	1	1	0.21	
(9)			0.49	0.25	0.32	0.80	0.96	0.74	1	0.25	0.58 [b]
(13)	0.41			0.23	0.29	0.79	0.89	0.67	1	0.15	
(14)	0.84		0.81		0.31	0.78	0.87	0.98	1	0.23	0.23
(15)		0.57	0.29		0.37	0.97	0.77	0.97 [c]	1	1.04	

[b] Based on molar ratios of *ca.* 1 : 0.9 for substrate : Eu([$^2H_9$]fod)$_3$; average shift for 7-Ac protons at this molar ratio *ca.* +4.5 p.p.m. [b] 1-Me group. [c] 1-Ac group.

EXPERIMENTAL

The i.r. spectra were measured as dispersions in Nujol using a Perkin-Elmer 157 spectrophotometer. N.m.r. spectra were determined on a Perkin-Elmer R32 90 MHz instrument using solutions in $CDCl_3$ or [$^2H_6$]DMSO with $SiMe_4$ as internal reference.

2,7-Diacetylfluorene (7).—Fluorene (1) (36.5 g, 0.22 mol) was acetylated with an excess of acetic anhydride following the procedure of Sulzberg and Cotter [6] to give 39.48 g (72%) of the 2,7-diacetyl derivative (7), m.p. (acetone) 176—177 °C (lit., m.p.[5] 183—184 °C; m.p.[6] 178—179 °C).

2,7-Diacetyl-1-methylfluorene (9).—Acetic anhydride (28.5 ml, 0.30 mol) was added during 90 min to a stirred, cooled suspension of anhydrous aluminium chloride (74.5 g, 0.56 mol) in dry 1,2-dichloroethane (90 ml) and the resulting solution added dropwise to a stirred solution of 1-methylfluorene (2) (15 g, 0.084 mol) in dry 1,2-dichloroethane (90 ml) at room temperature. After completion of the addition the mixture was refluxed for 90 min, during which time most of the solvent was distilled off. The thick residue was poured into ice–HCl and the cream solid which separated was filtered off and recrystallised from acetone to give the product (8.2 g, 66%), m.p. 162 °C; $\nu_{max.}$ (mull) 1 670 (C=O) cm^{-1}; $\delta(CDCl_3)$ 2.50 (3 H, s), 2.60 (6 H, s), 3.72 (2 H, s), and 7.60—8.04 (5 H, complex m) (Found: C, 81.7; H, 6.2; $C_{18}H_{16}O_2$ requires C, 81.8; H, 6.1%).

4,7-Diacetyl-1-methoxyfluorene (11).—The complex formed from acetic anhydride (5.65 ml, 0.06 mol) and anhydrous aluminium chloride (15.2 g, 0.117 mol), prepared as above, was added during 45 min to a solution of 1-methoxyfluorene (3) (3 g, 0.015 mol) in 1,2-dichloroethane (20 ml) at 0 °C and the product stirred at reflux (bath temperature < 120 °C) for 90 min, during which time most of the solvent was removed. The dark solution was diluted with ice–water (400 ml) and the acidified mixture extracted with chloroform leaving a small insoluble residue. Elution of this residue from Kieselgel 60 using chloroform gave a white crystalline material of R_F 0.1 ($CHCl_3$, SiO_2) which was recrystallised from ethanol to give 4,7-diacetyl-1-hydroxyfluorene (10) (240 mg, 6%), m.p. 243—244 °C; $\nu_{max.}$ (mull) 3 170 (OH), 1 660 (C=O); δ([$^2H_6$]DMSO) 2.60 (3 H, s, MeCO), 2.63 (3 H, s, MeCO), 3.85 (2 H, s, CH_2),

6.90 (1 H, d, J 8.7 Hz, 2-H), 7.83 (1 H, d, J 8.7 Hz, 3-H), 7.91 (1 H, dd, 6-H), 8.16 (1 H, br s, 8-H), and 8.39 (1 H, d, J 8.0 Hz, 5-H); 1 exchangeable H (Found: C, 76.9; H, 5.4; $C_{17}H_{14}O_3$ requires C, 76.7; H, 5.3%).

Evaporation of the dried chloroform extracts gave a dark oily residue which was chromatographed on Kieselgel 60, eluting with chloroform, to give two fractions, one of R_F 0.6 and the other of R_F 0.55. The former, after recrystallisation from ethanol, gave a white solid (200 mg), m.p. 183—184 °C, shown to be 2,4-diacetyl-1-hydroxyfluorene (16); $\nu_{max.}$ (mull) 1 680 and 1 645 (C=O) cm^{-1}; $\delta(CDCl_3)$ 2.62 (3 H, s, MeCO), 2.67 (3 H, s, MeCO), 3.80 (2 H, s, CH_2), 7.36 (4 H, m, 6-, 7-, and 8-H), 7.95 (1 H, s, 3-H), and 8.18 (1 H, dd, J 8 and 3.5 Hz, 5-H) (Found: C, 76.5; H, 5.4; $C_{17}H_{14}O_3$ requires C, 76.7; H, 5.3%).

The second fraction (1.74 g), m.p. 114—140 °C, was shown by n.m.r. to be a mixture of methoxy- and acetoxy-derivatives which were only partially separated by fractional recrystallisation and/or chromatography.

Hydrolysis with 2.5M sodium hydroxide at room temperature for 1 h gave pure 4,7-diacetyl-1-methoxyfluorene (11) (1.04 g, 24%), which after recrystallisation from ethanol had m.p. 147—148 °C; $\nu_{max.}$ (mull) 1 675 (C=O) cm^{-1}; $\delta(CDCl_3)$ 2.60 (3 H, s, MeCO), 2.66 (3 H, s, MeCO), 3.76 (2 H, s, CH_2), 3.90 (3 H, s, OMe), 6.77 (1 H, d, J 8.6 Hz, 2-H), 7.68 (1 H, d, J 8.6 Hz, 3-H), 7.82 (1 H, br d, J 8.2 Hz, 6-H), 8.01 (1 H, br s, 8-H), and 8.32 (1 H, d, J 8.2 Hz, 5-H) (Found: C, 77.35; H, 5.95; $C_{18}H_{16}O_3$ requires C, 77.1; H, 5.75%).

From the alkali-soluble fraction 0.61 g (15%) of a phenol, shown by m.p. and mixed m.p. to be identical with 4,7-diacetyl-1-hydroxyfluorene (10) was isolated. Acetylation of (10) gave the acetate (12), m.p. 154 °C after recrystallisation from ethanol; $\nu_{max.}$ (mull) 1 755 (acetate C=O), and 1 695, 1 675 (ketone C=O); $\delta(CDCl_3)$ 2.38 (3 H, s, $MeCO_2$), 2.60 (3 H, s, MeCO), 2.68 (3 H, s, MeCO), 3.79 (2 H, s, CH_2), 7.10 (1 H, d, J 8.4 Hz, 2-H), 7.61 (1 H, d, J 8.4 Hz, 3-H), 7.83br (1 H, d, J 8.4 Hz, 6-H), 8.02 (1 H, br s, 8-H), and 8.12 (1 H, d, J 8.4 Hz, 5-H) (Found: C, 74.05; H, 5.35; $C_{19}H_{16}O_4$ requires C, 74.0; H, 5.25%).

This acetate was shown to be a component of the mixture isolated by chromatography by comparison of their n.m.r. spectra.

3-Bromo-2,7-diacetylfluorene (13).—Acetylation of 3-bromofluorene [9] (4) (12.2 g, 0.05 mol) by the procedure given for the 1-methyl analogue above gave essentially the monoacetyl derivative with (13) as a minor component. Increasing the reflux time to 10 h, however, gave a tar which was chromatographed on silica gel (eluting with chloroform) to give a buff solid. This was recrystallised from acetone to give 3-bromo-2,7-diacetylfluorene (13) (2.0 g, 12%), m.p. 145 °C, $\nu_{max.}$ (mull) 1 680 (C=O) cm^{-1}; $\delta(CDCl_3)$ 2.62 (3 H, s, Me), 2.67 (3 H, s, Me), 3.87 (2 H, s, CH_2), and 7.62—8.12 (5 H, complex m) (Found: C, 62.0; H, 4.25; Br, 24.45; $C_{17}H_{13}BrO_2$ requires C, 62.0; H, 4.0; Br, 24.3%).

4-Methylfluorene (5).—A mixture of fluorene-4-carboxylic acid [7] (10.4 g, 0.05 mol), trichlorosilane (40.5 g, 0.3 mol), and dry acetonitrile (40 ml) was refluxed for 1 h, cooled to below 15 °C, and maintained below this temperature during the dropwise addition of tri-n-propylamine (18.8 g) with stirring. The product was heated to reflux for a further 16 h, cooled, and diluted to 450 ml with anhydrous ether. After removal of the insoluble hydrochloride by filtration, the filtrate was evaporated *in vacuo* and the residual brown oil refluxed for 1 h with methanol (25 ml). A solution of potassium hydroxide (28 g) in aqueous methanol (60 ml; 1 : 3) was slowly added to the cooled mixture, and the resulting suspension refluxed overnight. After cooling and dilution with water the product was extracted into chloroform and the extracts washed with 2N hydrochloric acid and water, dried, and evaporated. Recrystallisation of the residue from ethanol gave 4-methylfluorene (6.70 g, 75%), m.p. 71—72 °C (lit.,[10] m.p. 71—72 °C).

2,7-Diacetyl-4-methylfluorene (14).—Acetylation of 4-methylfluorene (5) (5 g) by the procedure outlined above for the 1-methyl homologue afforded, after recrystallisation from ethanol a mixture of diacetyl derivatives (6.16 g, 94%), m.p. 134—155 °C. N.m.r. showed this to be a 5 : 1 mixture of the 2,7-diacetyl derivative (14) and a second isomer (thought to be the 1,7-diacetyl compound), respectively. Repeated fractional recrystallisation from acetone gave pure 2,7-diacetyl-4-methylfluorene (1.88 g), m.p. 167—168 °C; $\nu_{max.}$ (mull) 1 675 (C=O) cm^{-1}; $\delta(CDCl_3)$ 2.60 (6 H, s, MeCO), 2.70 (3 H, s, Me), 3.86 (2 H, s, CH_2), and 7.68—8.02 (5 H, complex m) (Found: C, 81.75; H, 6.4; $C_{18}H_{16}O_2$ requires C, 81.8; H, 6.1%).

4-Fluorofluorene (6).—Zinc dust (30 g) was added to a mixture of 4-fluorofluorenone (5.2 g, 0.026 mol), ethanol (145 ml), and ammonia (d 0.880, 30 ml) and the mixture stirred at reflux for 90 min and filtered hot. Dilution of the filtrate with water (1 l) gave 4-fluorofluoren-9-ol (4.51 g), m.p. 154 °C, which was dissolved in propionic acid (150 ml) and red phosphorus (10 g) and hydriodic acid (12 g) added. This mixture was stirred at reflux overnight, filtered, and the filtrate poured into water. The fluorene was extracted into chloroform and the extracts washed with bisulphite solution and water and dried. Evaporation gave an oil which crystallised from aqueous methanol to give 4-fluorofluorene (2.85 g, 59%), m.p. 38—39 °C (lit.,[11] m.p. 39 °C).

1,7-Diacetyl-4-fluorofluorene (15).—4-Fuorofluorene (6) (2.85 g) was acetylated by the procedure outlined above for 1-methylfluorene to give, after recrystallisation from acetone, 1,7-diacetyl-4-fluorofluorene (15) (1.4 g, 37%), m.p. 177—178 °C; $\nu_{max.}$ (mull) 1 680 (C=O) cm^{-1}; $\delta(CDCl_3)$ 2.62 (6 H, s, Me), 4.27 (2 H, s, CH_2), 7.15 (1 H, dd, J_{HH} 9 and J_{HF} 9 Hz, 2-H), and 7.78—8.12 (4 H, complex m) (Found: C, 76.3; H, 4.75; $C_{17}H_{13}FO_2$ requires C, 76.1; H, 4.9%).

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