An Expedient Preparation of 9-Fluorenylmethanol

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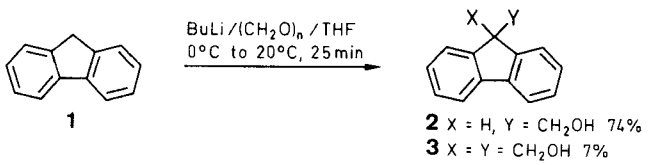
Lithiation of fluorene in tetrahydrofuran with butyllithium followed by reaction with paraformaldehyde provides a convenient one-pot preparation (~70% isolated yield) of 9-fluorenylmethanol. The yield of 9-fluorenylmethanol is critically dependent on stoichiometry and reaction times.

The 9-fluorenylmethyloxycarbonyl (Fmoc) group is becoming increasingly important as an amino protecting group in solid-phase peptide synthesis.[1,2] The 9-fluorenylmethyl ester (OFm) is also a useful base labile mode of protection for carboxylic acids.[3] 9-Fluorenylmethanol is the key component in the preparation of Fmoc amino acids, their derivatives, and OFm esters; the relatively high cost of this reagent has discouraged more widespread use of the milder [compared to the more established *t*-Boc (*tert*-butoxycarbonyl)-based methodology] Fmoc-based methodology.

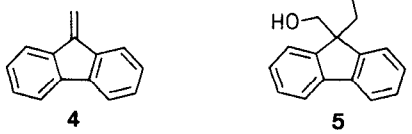
Previous syntheses of 9-fluorenylmethanol (**2**)[4-6] involve formylation of fluorene (**1**) with ethyl formate under basic conditions (sodium hydride/ethyl formate) to produce 9-fluorenecarboxaldehyde which is subsequently reduced (by a "cross-aldol alkylative cleavage" with formaldehyde[4,5] or using sodium borohydride[6]) to the alcohol. Problems with the instability and lachrymatory properties of the intermediate aldehyde, and the relatively complicated procedure for its isolation, prompted us to look for an alternative route to **2**. We now report that **2** may be prepared directly from fluorene in good yield and high purity.

It was felt that the most direct route to **2** would be reaction of a fluorenyl anion with paraformaldehyde. After some experimentation, it was found that treatment of a tetrahydrofuran solution of fluorene with butyllithium (BuLi) (1.0 equivalent, 0 °C, 3 minutes) followed by addition of paraformaldehyde to the orange solution (1.1 equivalents, 0 °C → room temperature, 30 minutes) and subsequent extractive workup provided a white solid. Analysis of the ^{1}H NMR spectrum of this material indicated that it was the expected alcohol **2** contaminated with a small amount of the diol **3** (7%). Recrystallization from hexanes/ethanol provided pure 9-fluorenylmethanol in 73% yield. The entire procedure requires only a few hours.



1

2 X = H, Y = CH_2OH 74%
3 X = Y = CH_2OH 7%



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It is necessary to quench the reaction just as the bright orange colour (presumably due to fluorenyllithium[7]) fades to a light peach colour (about 25 minutes after the addition of paraformaldehyde). Otherwise substantial amounts of dibenzofulvene (**4**) (which tends to form an insoluble polymer that seriously compromises the isolation of **2**) and alcohol **5** are formed. In fact, after 72 hours, none of the desired alcohol **2** remains. It is known that **2** undergoes base-induced elimination to fulvene **4**;[8] alcohol **5** may arise from addition of a fluorenylmethanol anion to the fulvene. Fortunately, the colour change is very distinct, and serves as a convenient signal to terminate the reaction.

The use of tetrahydrofuran as solvent is critical; only trace amounts of **2** were isolated when diethyl ether or *tert*-butyl methyl ether was used as solvent. Similarly, bases other than BuLi (such as lithium amide, sodium hydride, potassium *tert*-butoxide, and sodium amide) provided dismal results. Successful results were also obtained with methyllithium and lithium diisopropylamide; however, BuLi was deemed to be the base of choice because of convenience and cost.

Stoichiometry was also very important. An excess of base and paraformaldehyde lead to increased amounts of diol **3**. In fact, diol **3** was the major product formed with 2 equivalents of BuLi and 2 equivalents of paraformaldehyde.[9] Somewhat unexpectedly, when only 1 equivalent of BuLi was used in conjunction with excess (3 equivalents) paraformaldehyde, fulvene **4** became a major side product even with short (10–25 minutes) reaction times. Thus, it is necessary to use only 1 equivalent of BuLi and 1 equivalent of paraformaldehyde for optimal results.

In conclusion, 9-fluorenylmethanol (**2**) may be conveniently prepared by lithiation/hydroxymethylation of fluorene with the appropriate choice of base (BuLi), solvent (tetrahydrofuran), stoichiometry (1 equivalent of base, paraformaldehyde), and reaction time (25 minutes or as indicated by the colour change). We have used this procedure in our laboratory over the past few years to prepare 1 g to 100 g batches of **2**.

THF was distilled from Na/benzophenone ketal. Fluorene was obtained from Aldrich Chemical Co. and recrystallized twice from hexanes; paraformaldehyde was dried in vacuo at r.t. for 12 h just before use. BuLi was titrated using the dibromoethane method of Gilman.[10]

9-Fluorenylmethanol (2):
To a cold (0 °C) stirred solution of fluorene (**1**; 20.0 g, *0.120 mol*) in anhydr. THF (500 mL) under an atmosphere of Ar was added BuLi (1.65 M in hexanes, 73 mL, 0.120 mol) via syringe over 5 min. After another 3 min, $(CH_2O)_n$ (3.96 g, 0.132 mol) was added in one

portion via a solid addition tube and the ice bath was removed. After 25 min, the bright orange solution faded to a light peach. Sat. aq $NaHCO_3$ (200 mL) was then added to quench the reaction. The mixture was diluted with Et_2O (200 mL) and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (2 × 75 mL), dried ($MgSO_4$), and concentrated to afford a white solid (23.8 g). Recrystallization from hexanes (1050 mL)/EtOH (18 mL) provided 13.5 g of **2** as long white needles. The mother liquor affords a further 3.9 g of **2** after recrystallization from EtOH (70 mL)/H_2O (80 mL). The combined product was homogeneous by GC and TLC, and its 250 MHz ^1H NMR spectrum was free of extraneous signals;[11] yield: 17.4 g (74%); mp 99–100 °C (Lit.[4] mp 100–101 °C).

^1H NMR (250 MHz, $CDCl_3$/TMS): δ = 3.97 (B of AB_2, 2H, J_{AB} = 6.2 Hz[12], CH_2), 4.07 (A of AB_2, 1H, J_{AB} = 6.2 Hz, CH), 7.30 (dd, 2H, J = 0.7, 7.2, 7.2 Hz), 7.38 (ddd, 2H, J = 0.7, 7.2, 7.2 Hz), 7.58 (dd, 2H, J = 0.7, 7.2 Hz, $H_{4,5}$), 7.75 (dd, 2H, J = 0.7, 7.2 Hz, $H_{1,8}$).

^{13}C NMR (50 MHz, $^1CDCl_3$/TMS): δ = 50.26, 64.93, 119.98, 124.74, 127.00, 127.50, 141.45, 144.40.

Prolonged reaction times led to formation of dibenzofulvene **(4)** and the previously unreported alcohol **5** (3–10% yield); 9-(fluoren-9-ylmethyl)-9-hydroxymethylfluorene **(5)**: mp 183–184 °C.

$C_{28}H_{22}O$ (374.1)	calc.	C 89.81	H 5.92
	found	89.60	6.26

MS (EI): m/z (%) = 374 (20, M^+), 178 (64), 165 (100).

IR (KBr): ν = 3400 cm^{-1} (O–H).

^1H NMR (250 MHz, $CDCl_3$/TMS): δ = 2.79 (d, 2H, J = 6 Hz, $HCC\underline{H}_2C$), 3.27 (t, 1H, J = 6 Hz, $C\underline{H}CH_2$), 3.87 (s, 2H, CH_2O), 6.64 (dd, 2H, J = 1.1, 7 Hz), 7.01 (ddd, 2H, J = 1.1, 7, 7 Hz), 7.18 (dd, 2H, J = 7, 7 Hz), 7.36 (ddd, 2H, J = 1.5, 7, 7 Hz), 7.43 (ddd, 2H, J = 1.5, 7, 7 Hz), 7.53 (d, 2H, J = 7 Hz), 7.58 (dd, 2H, J = 1.5, 7 Hz), 7.79 (dd, 2H, J = 1.5, 7 Hz).

^{13}C NMR (63 MHz, $CDCl_3$/TMS): δ = 39.07, 44.28, 70.17, 119.18, 120.49, 124.49, 124.86, 126.53, 127.34, 128.04, 140.44, 141.53, 147.14, 148.17.

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