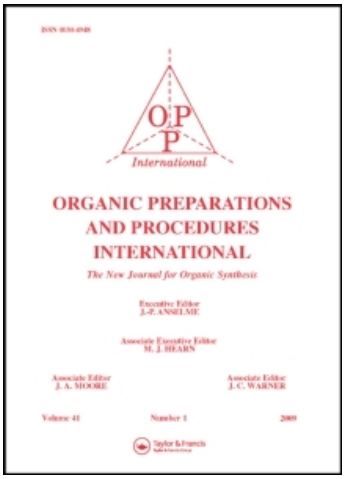

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A CONVENIENT PREPARATION OF 9*H*-FLUORENE-9-ACETIC ACID

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2. ^{13}C NMR (200 MHz, CF_3CO_2D) data: **2a** : δ 175.59 (C-4, C-6), 61.43 (OCH_3); **3a**: δ 175.49 (C-4), 174.09 (C-6), 61.37 (O-CH_3), 51.47 (N-CH_3); **9-OMe acridine**: δ 174.8 (C-9), 67.8 (O-CH_3); **N-Me-9-acridone**: δ 170.8 (C-9), 37.2 (N-CH_3)

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4. Diphenyl ether cannot be used as a co-solvent with the solvents mentioned, because of the poor solubility of **1** at low temperatures (<120°).

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A CONVENIENT PREPARATION OF 9*H*-FLUORENE-9-ACETIC ACID

Submitted by R. Richard Goehring
(12/03/93)

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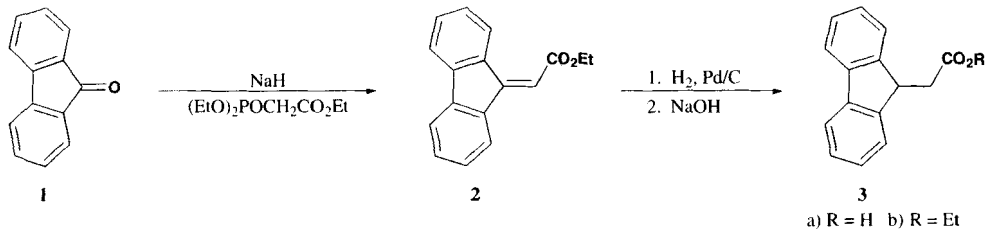
As part of a program for the synthesis of leukocyte recruitment inhibitors (leumedins)[1] we required substantial quantities of 9*H*-fluorene-9-acetic acid (**3a**). While **3a** is commercially available, we found the price to be prohibitively high.[2] A number of routes to **3a** have been described in the literature.[3] These include Reformatsky reaction with fluorenone (**1**),[3b,c] alkylation of diethyl malonate with 9-bromofluorene,[3d] alkylation of fluorene with glycolic acid,[3e] and ring opening of a cyclopropanone cyanohydrin.[3f] The preparation of **3a** from **1** held particular appeal due to analogs we had planned and the low cost of **1**. However, the Reformatsky-based approach proved to be undesirable due to modest yields, as well as synthetic incompatibility with other planned target molecules. We would like to describe a simple, high yielding alternate preparation of **3a** from fluorenone (**1**).



1 2 3

a) R = H b) R = Et

Wadsworth-Emmons (Horner) modification of the Wittig reaction[4] gave the unsaturated ester **2** cleanly and in excellent yield. Hydrogenation followed by saponification[5] gave the title compound in 84% overall yield from **1**. We feel this procedure is a significant improvement over those reported in the literature in terms of cost, yield and amenability to scale-up.

EXPERIMENTAL SECTION

Reagents and chemicals were purchased from common commercial suppliers and used without purification. Melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Boiling points are also uncorrected. IR spectra were recorded on a Perkin-Elmer Model 1625 FT-IR. ^{1}H NMR spectra were recorded on a Bruker AC-400 spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal reference.

Dibenzofulvenecarboxylic Acid, Ethyl Ester (2).- Under a blanket of argon, sodium hydride (60 wt%, 10.00 g, 0.250 mol) was placed in a 500 mL flask, washed with hexanes (3 x 25 mL), and suspended in anhydrous THF (100 mL). To this magnetically stirred suspension was added dropwise a solution of triethylphosphonoacetate (56.60 g, 0.250 mol) in THF (50 mL) at such a rate that gas evolution was not excessively vigorous (*ca.* 25 min). After the addition was complete, the mixture was stirred at room temperature for 1 hr to afford a clear, nearly colorless solution of the phosphonate anion. To this was added dropwise a solution of fluorenone (**1**) (39.60 g, 0.220 mol) in THF (100 mL) and rinsed in with a second portion of THF (50 mL). The reaction mixture was stirred at room temperature for 1 hr, heated to reflux for 2 hrs, and cooled to room temperature. After diluting with Et_2O and H_2O (400 mL, each) the layers were separated and the aqueous phase extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product. Recrystallization from hexanes gave 51.65 g (94%) of **2** as yellow needles, mp. 75-76°, lit.[3b] mp. 77°; R_f = 0.61 (SiO_2, 10% EtOAc/hexanes, UV); ^{1}H NMR ($CDCl_3$): δ 1.38 (t, 3H, J = 7.1Hz), 4.32 (quart, 2H, J = 7.1Hz), 6.72 (s, 1H), 7.20-7.42 (m, 4H), 7.55-7.68 (m, 3H), 8.89 (d, 1H, J = 7.8Hz); IR (KBr): 2972, 1709, 1638, 1598, 1438, 1374, 1200, 1167, 1035, 781, 735 cm^{-1}.

9*H*-Fluorene-9-acetic Acid, Ethyl Ester (3b).- A mixture of unsaturated ester **2** (50.00 g, 0.200 mol) and 5% Pd/C (1.00 g) in EtOAc (400 mL) was hydrogenated at 40-45 psi of H_2 for 3 hr. Filtration through Celite and evaporation of the solvent *in vacuo* gave 50.10 g (99%) of product as a colorless oil. This material was used directly in the next step. An analytical sample could be obtained by bulb-

to-bulb distillation, bp. 106-112°/0.10 mm Hg, lit.[3c] bp. 214°/12 mm Hg; R_f = 0.47 (SiO_2, 10% EtOAc/hexanes, UV); ^1H NMR ($CDCl_3$): δ 1.26 (t, 3H, J = 7.1Hz), 2.78 (d, 2H, J = 7.2Hz), 4.25 (quart, 2H, J = 7.1Hz), 4.43 (t, 1H, J = 7.2Hz), 7.26-7.34 (m, 2H), 7.35-7.42 (m, 2H), 7.50 (d, 2H, J = 7.2Hz), 7.75 (d, 2H, J = 7.5Hz); IR (film): 2980, 1733, 1449, 1370, 1221, 1156, 1028, 743 cm^{-1}.

9*H*-Fluorene-9-acetic Acid (3a).- To a solution of ester **3b** (47.20 g, 0.188 mol) in 95% EtOH (200 mL) was added 5*M* aqueous NaOH (50 mL, 0.250 mol). The resulting mixture was stirred at room temperature for 30 min, heated to reflux for 1 hr, cooled to room temperature and poured into a mixture of H_2O (100 mL) and Et_2O (300 mL). The layers were separated and the aqueous phase washed with Et_2O (2 x 50 mL). The aqueous phase was cooled in an ice bath and acidified to pH 1 with conc. HCl. The resulting solid was collected by filtration and dried at room temperature *in vacuo* overnight to give 38.04 g (90%) of pure product as a white solid, mp. 131-133°, lit.[3d] mp. 131.5-132.5°; R_f = 0.66 (SiO_2, 10% MeOH/CH_2Cl_2, UV); ^1H NMR ($CDCl_3$): δ 2.88 (d, 2H, J = 7.1Hz), 4.44 (t, 1H, J = 7.1Hz), 7.30-7.37 (m, 2H), 7.38-7.45 (m, 2H), 7.57 (d, 2H, J = 7.2Hz), 7.77 (d, 2H, J = 7.5Hz); IR (KBr): 3438, 3016, 2923, 1701, 1450, 1425, 1245, 925, 743 cm^{-1}.

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5. When the order of these operations is reversed (saponification followed by hydrogenation), the overall yield for these two steps drops from 89% to 69%.

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