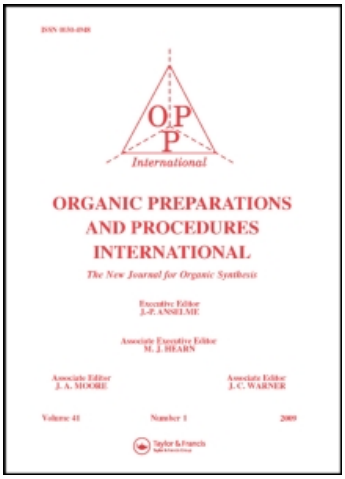

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN IMPROVED SYNTHESIS OF 3-NITROFLUORENE

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To cite this Article Moran, J. R. and Emmett, G.(1990) 'AN IMPROVED SYNTHESIS OF 3-NITROFLUORENE', Organic Preparations and Procedures International, 22: 5, 639 — 641
To link to this Article: DOI: 10.1080/00304949009356339
URL: http://dx.doi.org/10.1080/00304949009356339

AN IMPROVED SYNTHESIS OF 3-NITROFLUORENE

Submitted by (12/15/89)

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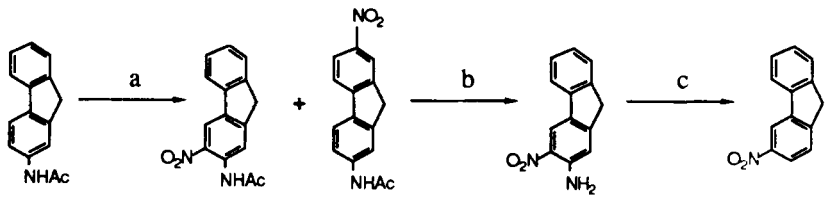
We have prepared gram-quantities of 3-nitrofluorene in three steps, from commercial materials in 20-25% yield, by modifying a previously reported procedure[1,2] that we were unable to reproduce. In view of the difficulty of preparing 3-substituted fluorenes[3a,b,c] and the recent interest in the mechanism of their carcinogenesis,[3c,4,5] we now report our procedure.

Nitration of 2-acetamidofluorene (1) as previously described,[1,2] with 1.6 equivalent of nitric acid at 52° produces a complex mixture containing several isomeric mononitro- and dinitro-2-acetamidofluorenes. We found that nitration with 1.0 equivalent of nitric acid at 25° gives, in nearly quantitative yield, a 2:1 mixture[7] of 2-acetamido-3-nitrofluorenene (2) and 2-acetamido-7-nitrofluorene (3) which could be used in the subsequent reaction without purification. The mixture of acetamidonitrofluorenes was deacylated in refluxing ethanolic HCl. 2-Amino-3-nitrofluorene (4) was isolated in 45% yield after removing the more basic isomer, 3, from the mixture by refluxing dilute HCl.



1 2 3 4 5

a) HNO_3, HOAc, 25°C.

b) HCl/EtOH(aq), reflux, 16 hrs; 0.75 N HCl, reflux.

c) t-BuONO, THF, reflux, 16 hrs.

In our hands, the previously described[1,2] reductive deamination of 2-amino-3-nitrofluorene using nitrous acid and ethanol gave 3-nitrofluorene (5) in less than 5% yield. In contrast, tert-butyl nitrite in refluxing THF afforded 3-nitrofluorene in 35-50% yield.[6a,b]

EXPERIMENTAL SECTION

General Methods. Melting points were determined with a Hoover capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were measured at 300.75 and 75.63 MHz, respectively, with a General Electric Nicolet NT-300 spectrometer. Chemical shifts are in parts per milion (δ) downfield from tetramethylsilane (δ = 0.00). Coupling constants (J) are in cycles per second (Hz). Infrared spectra were recorded on a Nicolet 60SX spectrophotometer. Frequencies are in reciprocal centimeters (cm^{-1}) and calibrated relative to the 1601.8 cm^{-1} absorbance of polystyrene. Ultraviolet spectra were obtained on a Varian Cary 2300 spectrophometer. Mass

spectra were recorded at 70 eV on a VG Micromass 70-70H double-focusing high-resolution spectrometer. **Caution:** *Nitrogen-substituted fluorenes are suspected carcinogens. Specifically, 2-acetamidofluorene is a potent liver carcinogen.*[8] *All operations must be performed in an efficient fume hood; safety glasses, disposable gloves and protective clothing should be used.*

2-Amino-3-nitrofluorene (4).- 2-Acetamidofluorene (1) (11.16 g, 50.0 mmol) was dissolved in glacial HOAc (200 mL) at 50°. The solution was cooled rapidly to 25° in a water bath over 3-5 min. Immediately before 1 could precipitate, conc. nitric acid (3.14 mL, 50.0 mmol) was added in one portion to the homogeneous solution. The mixture was stirred at 25° for 1 hr and diluted with water (750 mL). The bright yellow precipitate, a 2:1 mixture of 2 and 3,[7] was collected on a coarse fritted glass funnel, washed with water (25 mL) and pressed dry with a rubber dam. The damp solid was suspended in a mixture of EtOH (500 mL) and 12N HCl (33.3 mL) and refluxed for 16 hrs. The deep red solution was diluted with warm (ca. 50°) water (1.0 L) to give a suspension which was refluxed for 1 hr and filtered while hot. The collected red precipitate was suspended in 0.75 N HCl (666 mL) refluxed for 1 hr and filtered while hot. The collected solid was resuspended in 0.75 N HCl (666 mL) refluxed for 1 hr and filtered while hot. Finally, the collected solid was suspended in water (500 mL), refluxed for 30 min, filtered while hot and dried in vacuo to give 2-amino-3-nitrofluorene (4) (5.09 g, 45%) as a brick red solid with mp. 195-200°, lit.[1,2] mp. 206°, 201-202°. Crystallization from glacial acetic acid gave an analytical sample as red needles, mp. 201-202°. ^{1}H NMR (DMSO-d_6): δ 3.95 (s, 2H), 7.18 (s, 1H), 7.24 (ddd, J = 7.4 Hz, J = 7.4 Hz, J = 1.2 Hz, 1H), 7.32 (dd, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.46 (d, J = 7.4 Hz, 1H), 7.79 (d, J = 7.4 Hz, 1H), 8.36 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 36.14, 114.70, 115.80, 119.65, 124.93, 126.51, 126.98, 129.75, 130.37, 139.71, 141.98, 146.08, 151.84; IR (KBr): 3486, 3342, 1647, 1505, 1326, 1245; UV (EtOH): λ 441.5 (5050), 271.3 (31400); MS (m/z): Calcd for $C_{13}H_{10}N_2O_2$: 226.074228. Found: 226.0792.

3-Nitrofluorene (5).- tert-Butyl nitrite (40 mL, 33.08 g, 321 mmol) was added dropwise over 45 min to a solution of 2-amino-3-nitrofluorene (4) (25.34, 112 mmol) in THF (750 mL) at 25°. The solution was refluxed overnight, cooled and concentrated to dryness in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and flash chromatographed on silica gel [1 kg, toluene/cyclohexane (1:1)] to give 3-nitrofluorene (8.00 g, 34%) as a pale yellow solid, mp. 102-104°. An analytical sample crystallized from aqueous EtOH gave fine colorless needles, mp. 104.5-105.5°, lit.[1,2] mp. 105°, 105.5-106°. ^{1}H NMR ($CDCl_3$): δ 3.98 (s, 2H), 7.38 (ddd, J = 7.4 Hz, J = 6.5 Hz, J = 1.2 Hz, 1H), 7.44 (ddd, J = 7.4 Hz, J = 6.9 Hz, J = 0.7 Hz, 1H), 7.57 (dd, J = 6.5 Hz, J = 0.7 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.85 (dd, J = 6.9 Hz, J = 1.2 Hz, 1H), 8.17 (dd, J = 8.3 Hz, J = 2.0 Hz, 1H), 8.57 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 37.14, 114.87, 120.60, 121.79, 125.20, 125.34, 127.32, 128.23, 139.74, 143.23, 147.81, 150.07; IR (KBr): 1528, 1511, 1478, 1447, 1400, 1353, 1348, 1341, 1314, 1237, 1198, 1184, 828, 765, 734, 726; UV (EtOH): λ 334 (1660), 291.3 (11000), 258 (58300); MS(m/z): Calcd for $C_{13}H_9NO_2$: 211.063329. Found 211.0630.

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7. The ratio was deduced from integration of the resonances for 2 (8.941 ppm, H-4) and 3 (9.07 ppm, H-8) in nmr spectra of the unseparated reaction product in CDCl3.

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AN IMPROVED SYNTHESIS OF 4',5'-DIAMINOBENZO-15-CROWN-5

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Crown ether compounds first synthesized by Pedersen,[1] have been the focus of great deal of interest for the past twenty-five years because of the chemical and biological applications of their ion-binding capability, solvation and transport effects.[2] The molecular structure of the complexes has been studied by infrared, ^{1}H and ^{13}C NMR spectroscopy and X-ray crystallography.[3] Recently, crown ethers have also been employed to construct new compounds with extraordinary properties; ion channels were formed by the superposition of crown ether macrocycles in tetrakis(crown ether) substituted phthalocyanines;[4] bis(crown ether) Schiff-base,[5] quinoxaline,[6] and 2',2'-azobis(15-