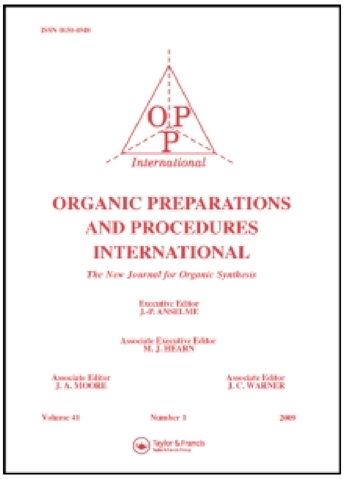

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A CONVENIENT SYNTHESIS OF DIFLUOROACETIC ACID

M. Cecilia Luz[a]; William P. Dailey[a]
[a] Department of Chemistry, University of Pennsylvania, Philadelphia, PA

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A CONVENIENT SYNTHESIS OF DIFLUOROACETIC ACID

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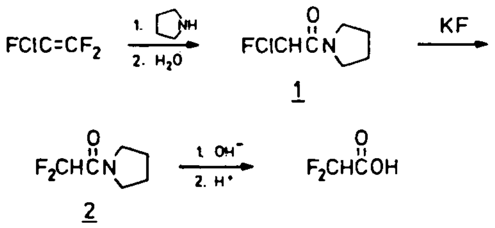
M. Cecilia Luz and William P. Dailey*

Department of Chemistry
University of Pennsylvania
Philadelphia, PA 19104-6323

In connection with another project, we required multi-gram quantities of difluoroacetic acid as a starting material. While both fluoroacetic and trifluoroacetic acid are relatively inexpensive commercially, difluoroacetic acid is very expensive. There are several syntheses which have been reported[1,2] but none is suitable for large scale production of difluoroacetic acid without using high pressure equipment. By making several modifications to previous syntheses, we have developed a procedure for producing multi-gram quantities of difluoroacetic acid from inexpensive, readily available starting materials using routine techniques.



Addition of pyrrolidine to chlorotrifluoroethylene occurs rapidly at 10°. This is in contrast to the addition of diethylamine[3] which requires higher temperatures and therefore a closed system. Hydrolysis of the crude reaction mixture with cold water yields the chlorofluoro amide 1 in 70% overall yield. This minor modification of a previous procedure[2] results in a much more convenient preparation of difluoroacetic acid. Replacement of chlorine by fluorine was accomplished using potassium fluoride in ethylene glycol to give the difluoroamide 2 in 87% yield.

Saponification of the amide and treatment with conc. sulfuric acid yields difluoroacetic acid in 70% yield.

EXPERIMENTAL SECTION

Proton nuclear magnetic resonance spectra were determined on a Bruker 250 Mhz spectrometer using deuterated chloroform as solvent. Infrared spectra were recorded using a Perkin-Elmer model 1430 Infrared Spectrometer. High resolution mass spectra were obtained on a VG 7070H mass spectrometer. Elemental Analyses were performed by Atlantic Microlabs, Inc. of Atlanta, Georgia.

2-Chloro-2-fluoroacetyl-1-pyrrolidine (1).- To a 500 ml 3-necked flask equipped with a magnetic stirrer, thermometer, gas dispersion tube and reflux condenser with a drying tube was added 150 ml of dry ether and 85 g (1.2 mol) of freshly distilled pyrrolidine. The flask was maintained at 10° using an ice bath and chlorotrifluoroethylene (114 g, 0.98 mol) was bubbled into the solution over the course of 2 hours. The clear colorless solution was added dropwise to 600 g of chopped ice. (Caution: HF is generated). The mixture was allowed to stir at room temperature for 2 hours and was extracted with ether (2 x 100 ml). The combined ethereal extracts were washed with a saturated NaCl solution and dried. Evaporation of the solvent and distillation of the residue under high vacuum gave 113.0 g of product (70%), bp. 75-80°/0.5 torr. IR (thin film): 1665 cm^{-1}. ^1H nmr ($CDCl_3$): δ 6.37 (d, J = 50 Hz, 1H), 3.55 (m, 4H), 1.90 ppm (m, 4H). High res. mass spectrum (m/e): C_6H_9ClFNO requires 165.0358, found 165.0357.

Anal. Calcd. for C_6H_9ClFNO: C, 43.52; H, 5.48; N, 8.46

Found: C, 43.11; H, 5.48; N, 8.23

2,2-Difluoroacetyl-1-pyrrolidine (2).- To a 500 ml round bottom flask was added 47.0 g (0.285 mol) of amide 1, 120 ml of dry diethylene glycol and 22.0 g (0.380 mol) of anhydrous KF. The flask was evacuated to 60 torr and slowly heated to 180°. The product distilled out of the flask as it was formed. The distillate was dissolved in 100 ml of ether, was washed with water (3 X 20 ml), was dried and concentrated. Redistillation of the product gave 37.0 g (87%) of clear colorless oil, bp. 95°/17 torr. IR (thin film): 1680 cm^{-1}. ^{1}H nmr: δ 5.98 (t, J = 53 Hz), 3.55 (m, 4H), 1.95 ppm (m, 4H). High res. mass spectrum (m/e): $C_6H_9F_2NO$ requires 149.0643; found 149.0652.

Anal. Calcd. for $C_6H_9F_2NO$: C, 48.32; H, 6.08; N, 9.39

Found: C, 48.28; H, 6.08; N, 9.30

2,2-Difluoroacetic Acid.- To a solution of 4.0 g (0.1 mol) of NaOH in 40 ml of water was added 15.0 g (0.1 mol) of amide 2. The amide dissolved almost immediately. The solution was evaporated to dryness and 30 ml of conc. sulfuric acid was added. The crude acid was distilled from the mixture, bp. 130-134°. Redistillation gave 6.7 g (70%) of difluoroacetic acid, bp. 133-134°, lit.[1] 133-134°.

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