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Short Note

2,3,5,6-Tetrafluoro-[*N*-(3-aminopropyl)-ε-caprolactam]-4-pyridine

Chadron M. Friesen [1,*], Nathan J. Weeks [2] and Scott T. Iacono [2,*]

[1] Department of Chemistry, Trinity Western University, 22500 University Drive, Langley, BC V2Y 1Y1, Canada
[2] Department of Chemistry & Chemistry Research Center, Laboratories for Advanced Materials, United States Air Force Academy, Colorado Springs, CO 80840, USA; nathan.weeks@afacademy.af.edu
* Correspondence: chad.friesen@twu.ca (C.M.F.); scott.iacono@afacademy.af.edu (S.T.I.)

Abstract: The title compound was synthesized at a near-quantitative yield using the nucleophilic aromatic substitution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) with perfluoropyridine (PFP). The purity and structure were determined by NMR (^{1}H, ^{13}C, ^{19}F), GC-EIMS, and single-crystal X-ray crystallography.

Keywords: organo-fluorine; pyridine; pentafluoropyridine; 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); nucleophilic aromatic substitution

1. Introduction

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) is known to be a very strong *N*-base yet has a low nucleophilicity. Its pK_a value is reported to be 24.33 [1]; however, it has been communicated in the past that the slow ring-opening of DBU can occur in the presence of water to form two possible products, either *N*-(3-aminopropyl) caprolactam or *N*-(3-aminopropyl)-2-piperidinecarboxylic acid [2–4]. In 2003, Brzezinski et al. reported reactions between chloropentafluorobenzene and strong *N*-bases such as DBN, DBU, TBD, and MTBD in polar aprotic solvents with water [5]. They concluded that the only pathway to lactams was first through the ring-opening of the *N*-bases followed by Meisenheimer complexes with chloropentafluorobenzene. They communicated that no complex could be detected by spectroscopic methods if chloropentafluorobenzene and strong *N*-bases are mixed without water molecules.

In our case, with pentafluoropyridine (PFP) rather than chloropentaflurobenzene, the pathway for reactivity with DBU is better described through its HOMO. The mechanism of the reaction proposed is shown in Scheme 1. The highest energy electrons on PFP occupy space delocalized over all the carbons except the 4-substituted carbon, leaving it more susceptible to nucleophilic attack by DBU [6]. Therefore, PFP is a more versatile starting material for nucleophilic aromatic substitution (SNAr) with DBU but has also shown a broad reactivity range with many *O*-, *N*-, *S*-, and *C*-nucleophiles through an exclusive attack at the 4-position [7,8]. For future work, using the PFP–DBU product, sequential additions to the 2,6-positions could be accomplished, leaving the 3,5-fluorines intact under specific solvent conditions. However, it is unknown whether the synthesis of these new *N*-substituted lactams can be used in polymerization due to the sterics, as reported by Puffr et al. [9]. Nonetheless, motivation for PFP incorporation into polymer frameworks remains due to several examples of their processing in polymers such as polyarylethers, fluorosilicones, dendrimers, and high-char-yield resins for demanding aerospace applications [10] as well as expanding the utility of hydrofluoroethers (HFEs) [11]. These unique polymeric materials have shown marked improvement over conventional state-of-the-art polymers in terms of their processability, mechanical strength, and compatibility with hybrid composites while retaining high temperature resistance. More recently, PFP was used for the mechanochemical synthesis of perfluoropolyalkylether (PFPAE) oligomers, which expands its utility for solvent-free polymerizations [12]. As an extension

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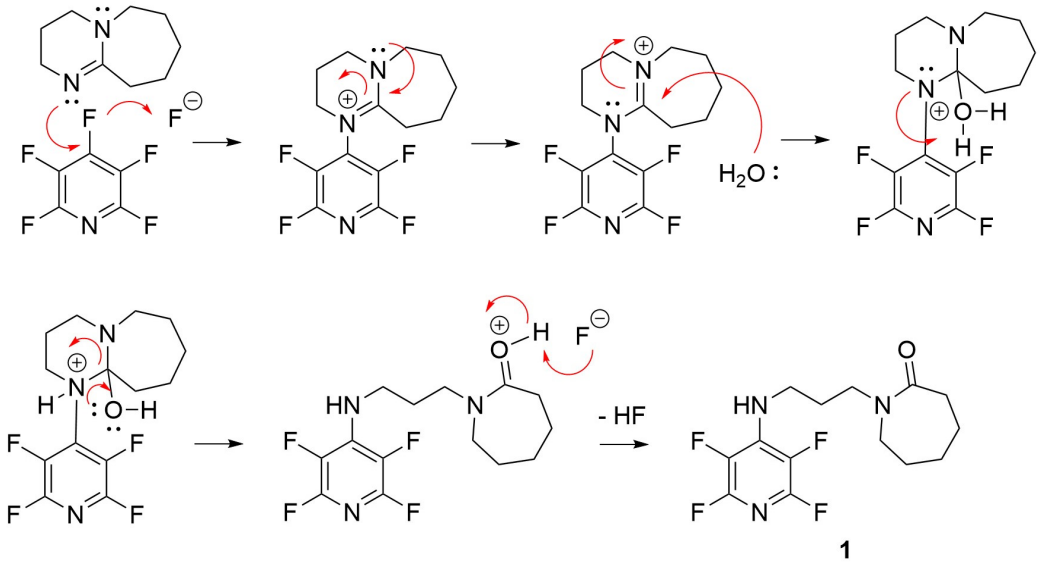
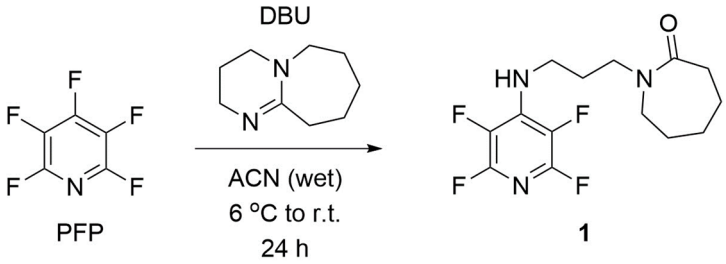
of this work, we report the detailed synthesis and structural characterization of a 2,3,5,6-tetrafluoro-[*N*-(3-aminopropyl)-ε-caprolactam]-4-pyridine (**1**), as a new type of monomer for SNAr polymerizations.



Scheme 1. Suggested mechanism of the attack of DBU onto a PFP and its ring-opening with water.

2. Results and Discussion

The synthesis of 2,3,5,6-tetrafluoro-*N*-[(propyl)caprolactam]-4-pyridinamine (**1**) was accomplished by the nucleophilic aromatic substitution of pentafluoropyridine (PFP) by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 2). For the analysis, the product was analyzed by ^{19}F NMR, showing the regio-selective quantitative conversion of the F_4 (δ −130 ppm) from PFP to, exclusively, a set of equivalent $F_{2,6}$ multiplets at δ −98.0-(−88.2 ppm) and −165.5-(−153.9 ppm), respectively. There was a small trace of what is believed to be HF_2^- at a chemical shift of −151.9 ppm in "wet" acetonitrile, which has been reported by Wilson and Christi [13]. Both ^{1}H- and ^{13}C-NMR helped in determining the structure of the PFP–DBU product as the ring-opened DBU lactam. However, the crystal structure was the true determining factor to fully verify the exact structure. After the product was purified and dried, the appearance was a very light tan solid with a 49% overall isolated yield. GC-EIMS confirmed the purity to be >99% with an observed molecular ion at $[M]^+$ at m/z = 319.



Scheme 2. Synthesis of compound **1** using PFP and DBU.

Crystals suitable for single-crystal X-ray diffraction were obtained by the dissolution of **1** in absolute ethanol in a scintillation vial with slow evaporation of the solvent. The molecular structure of **1** (Figure 1) shows the expected 2,3,5,6-tetrafluoropyridine group attached via an amino-*N*-propyl linkage to the seven-membered lactam ring.

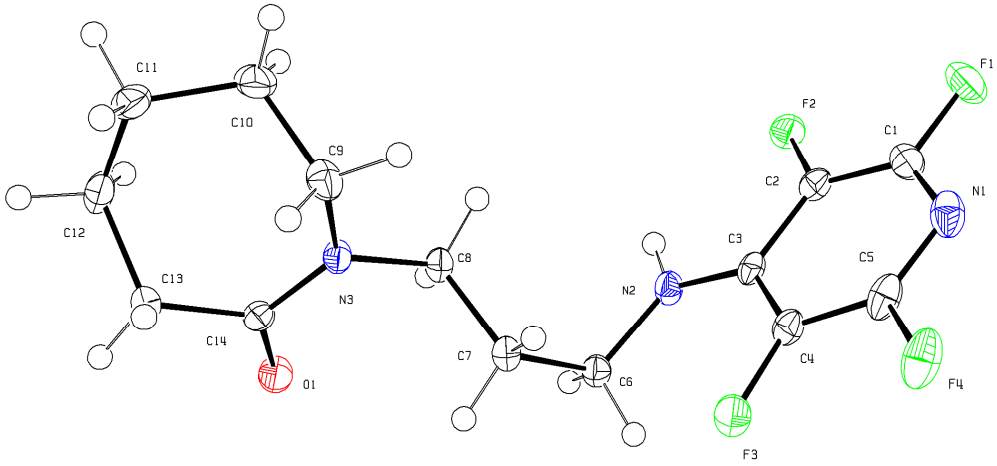


Figure 1. Molecular structure of **1** with thermal ellipsoids shown at the 50% probability.

3. Materials and Methods

Chemicals and solvents were purchased at the reagent grade through commercial suppliers: perfluoropyridine (SynQuest), 1,8-diazabicyclo[5.4.0]undec-7-ene (Acros Organics), and silica gel (Sorbtech, porosity: 60 A, particle size: 40–63 um, bulk density: 0.4–0.6 g/mL, pH range: 6.5–7.5). ^{1}H, ^{13}C{^{1}H}, and ^{19}F NMR spectra were recorded on a Jeol 500 MHz spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (acetonitrile-d_3 δ 1.94), carbon (acetonitrile-d_3, C{D} multiplet and septet, respectively for δ 118.26 and 1.32 ppm), and fluorine (C_6F_6 δ −164.9) was used as a reference. Data are reported as follows: chemical shift, multiplicity (s = singlet, m = multiplet), coupling constants (Hz), and integration. Gas chromatography mass spectrometry (GC-MS) analyses were performed on an Agilent 7890 gas chromatograph coupled to an Agilent 5975C electron impact mass spectrometer. The GC method for analysis started with a 2 min solvent delay at 90 °C followed by a 15 °C/min heating to 325 °C, holding for 5 min. The column was a ZB-5 HT, length 30 m, internal diameter (ID) 0.25 mm, film thickness = 0.25 um. The helium column flow rate was 37.1 cm/s. Front inlet temperature was 250 °C with a pressure of 9.95 psi with a flow rate of 24 mL/min and a septum purge of 3 mL/min.

*3.1. Synthesis of 2,3,5,6-Tetrafluoro-N-[(propyl)caprolactam]-4-pyridinamine (**1**)*

Pentafluoropyridine (1.11 g, 6.57 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.00 g, 6.56 mmol) in "wet" reagent-grade acetonitrile (15 mL) [14] where combined at 6 °C (refrigerated) in a 50 mL round-bottomed flask, equipped with a magnetic stir bar and air-cooled condenser under nitrogen. The reagents were allowed to stir and warm to room temperature for 24 h. The reaction was monitored by GC/EIMS until there was no increase in products. After the reaction, the 50 mL round-bottomed flask was transferred to a rotary evaporator to remove most of the solvent to form a tacky, viscous liquid (2.164 g). The viscous liquid was loaded on a 4 cm (diameter) × 3 cm (height) silica gel plug and rinsed with additional acetonitrile, since TLC determined that the desired product could be easily eluted by acetonitrile, leaving undesired materials on the silica gel plug. Finally, the eluted product was placed on a rotary evaporator to remove most of the acetonitrile with a final drying in a vacuum oven (20.9 mm Hg at 49 °C), affording a light tan solid (1.032 g, 49%). ^{1}H NMR (CD_3CN, 500 MHz) δ 6.5 (br, N-H, 1H), 3.40 (t, ^{3}J = 7 Hz, 2H), 3.38 (t, ^{3}J = 6 Hz, 2H), 3.33 (m, 2H), 2.46 (m, 2H), 1.71 (m, 2H), 1.69 (m, 2H), 1.59 (m, 2H), 1.58 (m, 2H); ^{13}C{^{1}H} NMR (CD_3CN, 126 MHz) δ 177.0 (1C, C=O), 144.3 (dm, 2,6-position, ^{1}J = 230 Hz, 2C), 138.4 (m, ipso, 1C), 131.4 (ddm, 3,5-position, ^{1}J = 246 Hz, ^{2}J = 32 Hz, 2C), 49.3 (1C), 44.3 (1C), 40.8 (1C), 36.7 (1C), 29.6 (1C), 28.3 (1C), 28.2 (1C), 23.3 (1C) ^{19}F NMR (CD_3CN, 471 MHz) δ −98.0 (m, 2,6-position, 2F), −165.5 (m, 3,5-position, 2F); GC–EIMS (70 eV) *m/z* (% relative intensity) 319 ([M]$^{+}$, 17), 185 (5), 179 (39), 177 (6), 154 (27), 153 (7), 141 (5), 140

(27), 139 (5), 138 (13), 132 (12), 128 (8), 127 (100), 126 (20), 114 (25), 112 (19), 100 (7), 99 (36), 98 (32), 85 (11), 84 (16), 82 (8), 70 (23), 69 (15), 67 (6), 57 (10), 56 (19), 55 (27), 44 (28), 43 (18), 42 (17), 41 (26), see Supplementary Materials.

3.2. Single-Crystal XRD Determination

The single-crystal X-ray diffraction studies were carried out on a Rigaku Synergy-I single crystal diffractometer equipped with a Cu K_α radiation source (λ = 1.542 Å) and a Bantam HyPIX-3000 direct photon counting detector. A 0.18 × 0.14 × 0.09 mm^3 translucent yellowish-green rectangular prism crystal was mounted on a Cryoloop with Paratone-N oil. Data were collected in a nitrogen gas stream at 100.00 (3) K using ω scans. Crystal-to-detector distance was 40 mm using an exposure time of 0.2 s with a scan width of 0.50°. Data collection was 99.80% complete to 69.351° in θ. A total of 14,769 reflections were collected. A total of 2680 reflections were found to be symmetry independent, with an R_{int} of 0.0257. Indexing and unit cell refinement indicated a primitive orthorhombic lattice. The space group was found to be $P2_1/n$. The data were integrated using the CrysAlisPro software program (Rigaku Oxford Diffraction, 2020, 1.171.43.90) and scaled using an empirical absorption correction implemented in the SCALE 3 ABSPACK software program as well as a numerical absorption correction based on Gaussian integration over a multifaceted crystal model. Solution by direct methods (SHELXT-2018/2) produced a complete phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2019/3). All carbon-bonded hydrogen atoms were placed using a riding model with their positions constrained relative to their parent atom using the appropriate HFIX command in SHELXL.

Supplementary Materials: The following supporting information is available online: ^{1}H, ^{19}F, ^{13}C NMR spectra and GC-MS for **1**.

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Data Availability Statement: CCDC 2327461 contains the supplementary crystallographic data for **1**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44-1223-336033.

Conflicts of Interest: The authors declare no conflicts of interest.

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