Fluorination of a bicyclic ketolactam with sulfur tetrafluoride

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Abstract

1-Azabicyclo[5.3.0]decane-5,10-dione has been prepared and fluorinated using sulfur tetrafluoride at different temperatures. Whereas the carbonyl ketone was fluorinated at room temperature, the amidic C—N bond remained essentially untouched even at 160 °C for 24 h. The resulting difluorobicyclic lactam was reduced to the corresponding bicyclic tertiary amine which proved to be more stable than the hydrocarbon analog.

Introduction

Interest in polyfluoro analogs [1] led us to synthesise 1-azabicyclo-[5.3.0]decane (**1**) [2], and now to consider partially fluorinated derivatives of **1** that could be more stable and be subjected to exhaustive-type fluorinations more efficiently. In this context, the work of Speckamp [3] on cationic cyclisations was appealing: cyclic imides can be reduced regioselectively to give alkoxylactams **3a** which in turn can be converted into the highly reactive α-acyliminium ion **3b** under acid catalysis (Scheme 1). In the presence of an internal nucleophile, intramolecular bond formation will take place furnishing a bicyclic ketolactam. In this approach the starting materials are mostly easily accessible, the route is relatively short and the cyclised material contains carbonyl functions capable of being converted to difluoromethylene groups. It might also be possible to use fluorinated cyclic imides [4] as a way of accessing more highly fluorinated derivatives.

Results

To evaluate this route as a way to construct partially fluorinated fused 7/5 ring systems, the first goal was to synthesize 1-azabicyclo[5.3.0]decane-5,10-dione (**2**) following the Speckamp *et al.* protocol [5], and to explore the efficacy of sulfur tetrafluoride (SF_4) fluorinations on the carbonyl groups

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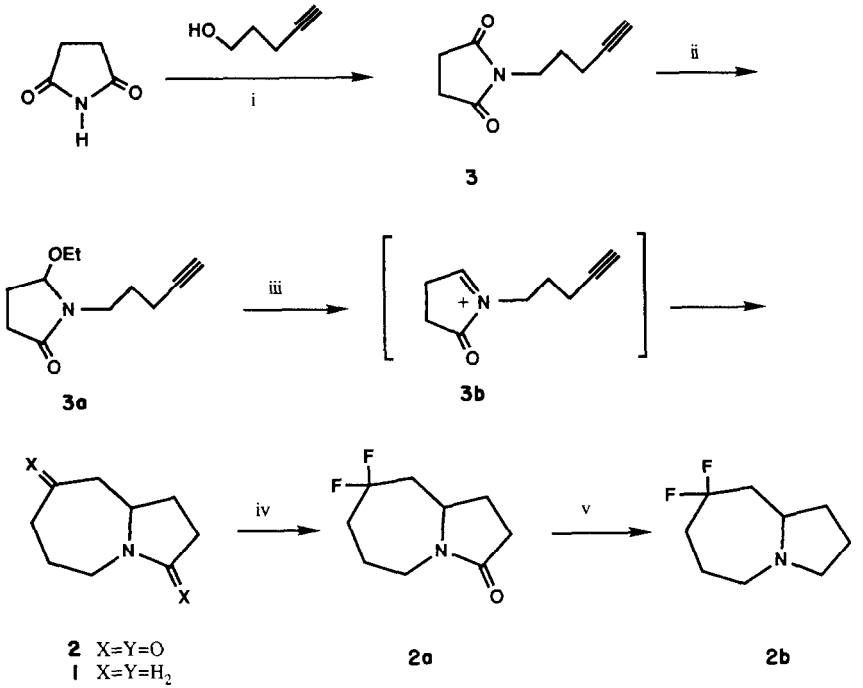

Scheme 1. Reagents: i. PPh_3, EtOOC-N=N-COOEt; ii. $NaBH_4$, HCl, EtOH; iii. HCO_2H; iv. SF_4/HF; v. $LiAlH_4$.

of this molecule. The route to the ketolactam **2** is outlined in Scheme 1. 4-Pentyn-1-ol [6], prepared in 72% yield, was condensed with succinimide in a Mitsunobu fashion [7] in 50% yield to give the N-substituted imide **3**. Following the Speckamp *et al.* protocol [5], compound **3** was reduced to **3a** and cyclised (via **3b**) producing the bicyclic ketolactam **2** in 61% overall yield from **3**. No signs of the fused 6/6-ring isomer were found.

Having obtained the bicyclic ketolactam **2**, it was then necessary to establish if both carbonyl oxygens could be replaced stepwise with *gem*-difluoro groups. The reagent of choice was SF_4, which has a broad scope and is effective with virtually all carbonyl compounds [8]. For ketones, this reaction usually works well in relatively mild conditions and gives good yields. However, little is known regarding the behavior of lactams or imides [9] towards SF_4. Amide groups react with difficulty, and the course of the reaction seems to be dependent on the presence or absence of N–H bonds on the amide [8]. With amides lacking an N–H bond, the C–N bond may or may not be broken. In consequence, SF_4 fluorination of **2** could give much needed information regarding the behavior of amides in general, and bicyclic lactams in particular.

1-Azabicyclo[5.3.0]decane-5,10-dione (**2**) was treated with SF_4 in the presence of HF at different temperatures, the results obtained being displayed in Table 1. Comparison between the ^1H NMR bridgehead proton [δ 3.65–3.95

TABLE 1

SF_4/HF fluorination of 1-azabicylco[5.3.0]decane-5,10-dione (**2**)

Solvent	Temp. (°C)	Time (h)	Yield of **2a** (%)
CH_2Cl_2	20	24	46
CH_2Cl_2	100	20	51
CH_2Cl_2	160	24	50

ppm for **2** versus δ 3.70–4.20 ppm for **2a**] and IR lactam C=O absorption [ν 1680 cm^{-1} for **2** versus ν 1665 cm^{-1} for **2a**] indicated the continued presence of the 7/5 ring system in **2a**. Thus, the carbonyl ketone was easily fluorinated at room temperature but the amidic C–N bond remained essentially untouched even at 160 °C for 24 h. In all cases, the only isolated product was the difluoro bicyclic lactam **2a** in yields of *c.* 50%.

1-Azabicyclo[5.3.0]decane (**1**) is thermally unstable. To evaluate the stability of a partially fluorinated analog, the difluorolactam **2a** was reduced to the corresponding bicyclic tertiary amine **2b**. This was done efficiently in 74% yield by treatment with lithium aluminum hydride in tetrahydrofuran at room temperature. Whereas **2b** could be easily purified via vacuum transfer, the parent heterobicycle **1** decomposed when this technique was applied to it. However, on prolonged exposure to ambient temperatures, **2b** turned gradually yellow. This observation is in good agreement with the fact that increased fluorine substitution on a given molecule increases its stability.

Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 instrument. NMR spectra were recorded on a Perkin-Elmer R12B spectrometer (^1H) at 60 MHz, (^{19}F) at 56.4 MHz or on a Perkin-Elmer R14 instrument (^1H) at 100.1 MHz. Unless noted, the solvent used was $CDCl_3$; $SiMe_4$ was used as internal standard for ^1H NMR spectra, ^{19}F NMR spectra have been quoted in ppm upfield from $CFCl_3$. All mass spectra were obtained on a Kratos MS 80 mass spectrometer using a DS 55 data processing unit; only selected ions are reported. TLC was carried out using Kieselgel 60 F_{254} (Merck) silica-gel-precoated 0.25 mm plates. Column chromatography was carried out on either activated alumina 100 mesh or silica-gel Kieselgel 60, 70–230 mesh, type 7734 (Merck). Solutions of organic compounds isolated by extraction were dried over anhydrous magnesium sulfate and concentrated at reduced pressure on a rotary evaporator.

*1-Azabicyclo[5.3.0]decane-5,5-difluoro-10-one (**2a**)*

SF_4 (5 cm^3) was slowly distilled into a nickel autoclave (50 cm^3 capacity) at −78 °C, containing a solution of 1-azabicyclo[5.3.0]decane-5,10-dione

(**2**) [5] (1.53 g, 9 mmol), dichloromethane (10 cm^3) and hydrogen fluoride (5 cm^3). This was sealed and shaken at room temperature for 24 h; it was then recooled to −78 °C when the contents were poured into a plastic beaker. After the volatile material had evaporated, water (100 cm^3) was then added slowly and the mixture extracted with dichloromethane (2×75 cm^3). The organic layer was washed with saturated sodium bicarbonate solution (50 cm^3) and brine (50 cm^3), dried and concentrated to give a dark brown solid (1.15 g, 68% recovery). Sulfur was first removed from the crude product by filtration through a column (silica gel, dichloromethane). The column was then eluted with ethanol and the ethanolic solution concentrated. The residual brown solid was purified further by sublimation *in vacuo*. At 130 °C/ 0.1 mmHg, 1-azabicyclo[5.3.0]decane-5,5-difluoro-10-one (**2a**) (0.74 g, 46% yield) was obtained as white crystals; m.p. 88–91 °C. Analysis: Found: C, 57.00; H, 7.00; F, 20.35; N, 7.10%. $C_9H_{13}F_2NO$ requires: C, 57.13; H, 6.93; F, 20.08; N, 7.40%. IR (cm^{-1}): 1665 (lactam C=O). MS (*m/z*): 189 (100, M^+); 174 (25); 124 (23); 110 (35); 69 (51). ^1H NMR δ: 1.4–2.6 (10H, m, CH_2); 3.50 (2H, t, J=4.7 Hz, CH−N); 3.70–4.20 (1H, m, CH) ppm. ^{19}F NMR δ: 85 and 96 (AB quartet, J=245.6 Hz, CF_2) ppm.

*5,5-Difluoro-1-azabicyclo[5.3.0]decane (**2b**) (nc)*

Lithium aluminum hydride (0.181 g, 4.8 mmol) was added carefully to a solution of 1-azabicyclo[5.3.0]decane-5,5-difluoro-10-one (**2a**) (0.141 g, 0.75 mmol) in THF (10 cm^3). The suspension was then stirred continuously for 4 h at room temperature before it was quenched by sequential addition of water (0.15 cm^3), 4 M sodium hydroxide (0.15 cm^3) and water (0.45 cm^3). The granular precipitate thus formed was filtered off and washed with diethyl ether (15 cm^3). The filtrate was dried and concentrated to yield the title compound (**2b**) (0.096 g, 74% yield) as a pale yellow liquid which was further purified via vacuum transfer at 0.05 mmHg to give a volatile colorless liquid. Analysis: Found: C, 62.00; H, 8.90; N, 7.90%. $C_9H_{15}F_2N$ requires: C, 61.69; H, 8.63; N, 7.99%. MS (*m/z*): 175 (28, M^+); 110 (30); 96 (100); 83 (38); 28 (51). ^1H NMR δ: 1.3–2.8 (13H, m, CH_2, CH, CH−N); 2.85–3.40 (2H, m, CH−N) ppm. ^{19}F NMR δ: 80.5 and 84.8 (AB quartet, J=238.13 Hz, CF_2) ppm.

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References

1 R. G. Plevey, R. W. Rendell and J. C. Tatlow, *J. Fluorine Chem.*, *21* (1982) 413; K. Yokoyama, K. Yamanouchi and T. Suyama, *Life Chem. Rep.*, *2* (1983) 35.

2 G. B. Hammond and R. G. Plevey, *Org. Prep. Proced. Int.*, *23* (1991) 741.
3 W. N. Speckamp, *Recl. Trav. Chem. Pays-Bas*, *100* (1981) 345.
4 M. S. Hadley, F. D. King and R. T. Martin, *Tetrahedron Lett.*, *24* (1983) 91.
5 H. E. Schoemaker, T. Boer-Terpstra, J. Dijkink and W. N. Speckamp, *Tetrahedron*, *36* (1980) 143.
6 O. Mitsunobu, *Synthesis*, (1981) 1.
7 M. C. Whitting, *Org. Synth. Coll. Vol.*, *IV* (1963) 755.
8 G. A. Boswell, Jr., W. C. Ripka, R. M. Scribner and C. W. Tullock, *Org. React.*, *21* (1974) 1.
9 R. J. De Pasquale, *J. Org. Chem.*, *43* (1978) 1727.