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# 5-PERFLUOROALKYL BICYCLIC AMIDE ACETALS

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## SUMMARY

A new route to a novel class of bicyclic amide acetals, 5-perfluoroalkyl-4,6-dioxa-1-azabicyclo [3.3.0] octanes, is described. These compounds are prepared by the acid catalyzed dehydration of N,N-bis-(2-hydroxyethyl)-perfluoroalkylamides and are characterized by their lack of reactivity with a variety of electrophiles and nucleophiles relative to the very reactive 5-alkyl bicyclic amide acetals.

## INTRODUCTION

Alkyl-substituted bicyclic amide acetals (5-alkyl-4,6-dioxa-1-azabicyclo [3.3.0] octanes [1]) have been known for over a decade. These compounds have been prepared by either the addition of epoxides to $\Delta^2$-1,3-oxazolines [2] or the addition of 2,2'-iminodiethanols to aliphatic nitriles [3]. The bicyclic amide acetals prepared *via* these routes have been shown to be very reactive toward a variety of nucleophiles and electrophiles under fairly mild conditions [4]. Martini has reported [5] the reaction of fluoro-olefins and 2,2'-iminodiethanol which gives bicyclic amide acetals similar to those reported here. However, there was only limited data reported on the reactivity of these compounds with other reagents.

## RESULTS AND DISCUSSION

This report describes a new route to a class of bicyclic amide acetals, namely 5-perfluoro-4,6-dioxa-1-azabicyclo [3.3.0] octanes, 2, which differ substantially in reactivity from those previously reported.

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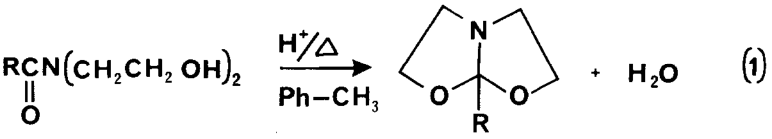
These compounds are synthesized in moderate yields by the acid catalyzed dehydration of perfluoroakylamide-diols, 1 (equation 1). Spectral data (IR, $^{1}$H NMR, $^{19}$F NMR, and $^{13}$C NMR) and elemental analysis [6] are



(1)

1a; $R=CF_3$

1b; $R=C_7F_{15}$

2a; $R=CF_3$

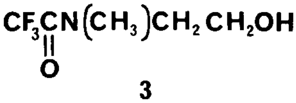
2b; $R=C_7F_{15}$

consistent with structure 2. This appears to be the first example of the preparation of such a ring system by a simple, intramolecular dehydration reaction.

The presence of the 5-perfluoroalkyl group significantly alters the reactivity of the ring system toward nucleophilic and electrophilic reagents relative to the previously reported 5-alkyl compounds. The reaction of 2 with an anhydride, carboxylic acid, aldehyde, phenol, or alkylating agent (under reaction conditions which gave high product yield with the analogous 5-alkyl compounds [4]) yields only unreacted starting materials. Compound 2 is alkylated on nitrogen only under rather harsh reaction conditions (110°, neat) affording the methyl sulfate salt in high yield.

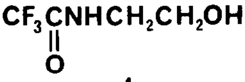
The electron withdrawing power of the perfluoroalkyl group, which enhances the electrophilicity of the amide carbonyl in 1, obviously plays a role in the formation of the bicyclc amide acetal 2; but other factors are also important. For example, the reaction of methyl trichloroacetate with 2,2'-iminodiethanol does not give the amide-diol but instead N-hydroxyethyl-2-oxazolidinone [7]. Since the corresponding reaction with methyl trifluoroacetate gives the amide-diol (1a) which can subsequently undergo a dehydrative 'double' cyclization reaction to 2a, the relatively poor leaving group ability of the perfluoroalkyl functionality is underscored [8].

The mechanism of the formation of 2 probably involves sequential attack of each hydroxyl oxygen atom on the electrophilic carbon atom adjacent to the fluorocarbon group in 1. However, attempts to form ring closure products from amides 3 and 4 under reaction conditions which gave 2 resulted in recovery of starting material.



$CF_3C(=O)N(CH_3)CH_2CH_2OH$

3



$CF_3C(=O)NHCH_2CH_2OH$

4

It is also interesting to note the unusually facile hydrolysis of amide-diol 1 to the carboxylate-ammonium salt 5. Addition of water to an NMR sample of 1 in acetone-*d*-6 results in the immediate appearance of signals consistent with the initial formation of 5 [9]. Independent

$$R_fCO\bar{O}\ \overset{+}{N}H_2(CH_2CH_2OH)_2$$

5

experiments [10] also indicate some hydrolytic instability of 3; however, 4 appears to be more stable toward hydrolysis. Experiments to rationalize this behavior in terms of an internally assisted hydrolysis mechanism are under consideration.

## EXPERIMENTAL

The $^1H$ and $^{13}C$ NMR spectra were recorded on either a Varian XL-100 or XL-200 instrument and are reported in $\delta$ units from the internal standard tetramethylsilane. The IR spectra were obtained using either a Perkin-Elmer 137 or 283 spectrophotometer.

### N,N-Bis-(2-hydroxyethyl)trifluoroacetamide (1a)

Methyl trifluoroacetate (25.6 g, 200 mmol) was added dropwise to an ice-bath cooled, stirred solution of 2,2'-iminodiethanol (21.0 g, 200 mmol) in 150 mL tetrahydrofuran. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Removal of volatiles in vacuo left 39.8 g (100%) of 1a as a light yellow liquid: IR (neat) 1667 $cm^{-1}$; NMR [$(CD_3)_2SO$] 3.22-39 (m, 8H), 5.6 (s, 2H). This material was used without further purification.

### N,N-Bis-(2-hydroxyethyl)perfluorooctanamide (1b)

Methyl perfluorooctanoate (conveniently prepared by refluxing perfluorooctanoic acid in excess trimethylorthoformate) was reacted with 2,2'-iminodiethanol in a manner analogous to the preparation of 1a. Compound 1b was isolated in quantitative yield as a slightly yellow, viscous liquid: IR (neat) 1667 $cm^{-1}$; NMR [$(CD_3)_2CO$] 3.6-3.92 (m, 8H), 4.27 (s, 2H). This material was used without further purification. It should be noted that the starting acid (3M FC-26) contains some branching in the alkyl chain; no attempt was made at any stage to obtain a pure straight chain $C_7F_{15}$ carboxylic acid.

### 5-Trifluoromehtyl-4,6-dioxa-1-azabicyclo [3.3.0] octane (2a)

A mixture of compound 1a (19.2 g, 95.0 mmol), 6 drops conc. $H_2SO_4$, and 200 mL toluene was refluxed into a Dean-Stark trap for 43 h. Approx. 2 mL water was collected. The reacton mixture was cooled, washed with 150 mL sat. $NaHCO_3$ solution followed by 100 mL brine, and dried over $MgSO_4$. The toluene was removed in vacuo and 2a (10.1 g, 58%) was isolated as a low melting solid by vacuum distillation: bp 47°C (0.03 mm); IR (neat) no hydroxyl or carbonyl absorptions; $^{13}C$ NMR ($CDCl_3$) 121.80 ($-\underline{C}F_3$, $J_{C-F}$ = 285.1), 117.79 ($CF_3\underline{C}N$, $J_{C-F}$ = 34.8), 66.45 ($O\underline{C}H_2CH_2$), 52.29 ($CH_2\underline{C}H_2N$); $^1H$ NMR ($CDCl_3$) 4.10 (dt, 2H), 3.39 (dt, $^2J$ = -10.7, 1H), 3.08 (dt, $^2J$ = -10.7 1H) [11]. Analysis: Found: C, 39.0; H, 4.5; N, 7.5; F, 30.5%. $C_6H_4O_2NF_3$ requires C, 39.3; H, 4.4; N, 7.6; F, 31.1%.

### 5-Perfluoroheptyl-4,6-dioxa-1-azabicyclo [3.3.0] octane (2b)

A mixture of compound 1b (30.8 g, 62.0 mmol), 5 drops conc. $H_2SO_4$, and 200 mL toluene was refluxed into a Dean-Stark trap for 96 h. Approx. 1 mL water was collected. The reaction mixture was cooled, washed with 150 mL sat. $NaHCO_3$ solution followed by 100 mL brine, and dried over $MgSO_4$. The toluene was removed in vacuo and 2b (15.5 g, 52%) was isolated by vacuum distillation: bp 65-86$^{o}$C (0.075 mm); IR (neat) no hydroxy or carbonyl absorptions; $^{13}$C NMR (CDCl3) 104-120 (CF multiplets, not assigned), 66.7 ($O\underline{C}H_2CH_2$), 52.5 ($CH_2\underline{C}H_2N$); $^{19}$F NMR showed peaks typical of a perfluoroheptyl group; $^{1}$H NMR ($CDCl_3$) 4.10 (dt, $^{3}J$ = 6.7, 5.7, 2H), 3.38 (dt, $^{2}J$ = -10.5, $^{3}J$ = 6.7, 1H), 3.05 (dt, $^{2}J$ = -10.5, $^{3}J$ = 5.7, 1H) [11].

## Reaction of 2a with succinic anhydride

A mixture of 2a (1.83 g, 10.0 mmol) and succinic anhydride (1.00 g, 10.0 mmol) was heated with stirring at 140 ± 5°C for 2 h under a positive $N_2$ atmosphere. The reaction mixture was cooled and dissolved in 25 mL $CHCl_3$ and the resulting solution added to 300 mL $Et_2O$. This solution was slightly cloudy (unreacted anhydride) but no polymer precipitated. The ether was removed *in vacuo* and Freon 113 was added to the residue and then filtered. The filtrate was concentrated *in vacuo*; the residue had an IR spectrum indicative of unreacted 2a.

## Reaction of 2a with acetic acid

A mixture of 2a (1.83 g, 10.0 mmol) and acetic acid (3.0 g, 50 mmol) was heated with stirring for 2 h at 120°C under a positive $N_2$ atmosphere. An NMR spectrum of the crude reaction mixture showed only peaks consistent with unreacted starting materials.

## Reaction of 2a with propionaldehye

A solution of 2a (1.83 g, 10.0 mmol), freshly distilled propionaldehyde (0.58 g, 10 mmol), and 20 mL toluene was heated at 70°C for 4 h under a positive $N_2$ atmosphere. The volatiles were removed *in vacuo* and an NMR spectrum of the residue showed only peaks consistent with unreacted 2a.

## Reaction of 2b with phenol

A mixture of 2b (1.94 g, 4.00 mmol) and phenol (0.38 g, 4.0 mmol) was heated at 120°C for 3.5 h under a positive $N_2$ atmosphere. A NMR spectrum of the crude reaction mixture showed only peaks consistent with unreacted starting materials.

Reaction of 2b with dimethylsulfate

A solution of 2b (0.97 g, 2.0 mmol) and dimethylsulfate (0.25 g, 2.0 mmol) was heated in the absence of solvent at 100-110°C. In approx. 1 h a white solid formed which was cooled, washed with $CHCl_3$, and air dried. The $^1H$ NMR of this material was consistent with the N-methylated product, 1-methyl-5-perfluoroheptyl-4,6-dioxa-1-azoniabicyclo [3.3.0] octane methyl sulfate: yield, 1.0 g (85%); mp 195-200°C (d); $^1H$ NMR $[(CD_3)_2SO]$ 4.73 (dt, $^3J = 8, 6$, 2H), 4.44 (dt, $^2J = -12$, $^3J = 6$, 1H), 4.11 (dt, $^2J = -12$, $^3J = 8$, 1H), 3.67 (s, 3H), 3.42 (s, 3H) [11].

## ACKNOWLEDGEMENT

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9 Initially, triplets at $\delta$ 3.34 and 3.90 are observed, indicative of formation of 5. Further reaction of 5 with solvent gives signals consistent with formation of either a Schiff base or an oxazolidine.

10 These experiments consisted of stirring an acetone-water solution of 3 and 4 at room temperature for ten days followed by NMR and IR analysis of the reaction mixtures.

11 The assignments are in good agreement with those reported for 5-methyl-4,6-dioxa-1-azabicylco [3.3.0] octane and its methyl sulfate salt, M. Anteunis, J. Gelan and R. Van Canwenberghe, Org. Magn. Reson., 6 (1974) 362.