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Synthesis of 5-Per(poly)fluoroalkyl-2,3-dihydro-1,4-diazepines

Quan-Fu Wang^a, Bin Hu^b, Bing-Hao Luo^a and Chang-Ming Hu^a*

^a Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

^b College of Pharmacy, Shanghai Medical University, Shanghai, China.

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Abstract: a series of 5-per(poly)fluoroalkyl-2,3-dihydro-1,4-diazepines were synthesized from α -per(poly)fluoroalkyl aldehydes and ethylenediamine. A possible reaction pathway was suggested. © 1998 Elsevier Science Ltd. All rights reserved.

Regioselective replacement of hydrogen by fluorine or fluoroalkyl on a heterocyclic system might have a profound influence on the biological and physical properties of such molecules.¹ As a result, considerable efforts have been devoted in recent years to the development of methodologies for the synthesis of fluorine-containing compounds. α -Per(poly)fluoroalkyl aldehydes, as one of the important fluorine-containing bilding blocks, are conveniently prepared² and have been utilized to synthesize various aromatic heterocyclics.³ However, little work has been done on the synthesis of seven membered none aromatic rings.

Our continuing research showed that ethylenediamine could be used as a dinucleophile to react with α -per(poly)fluoroalkyl aldehydes. As a result, new kinds of compounds, 5-per(poly)fluoroalkyl-2,3-dihydro-1,4-diazepines, were obtained in high yields. The results are shown in table 1.



Entry	Substrate	R _f	Product ⁴	Yield (%)
1	la	CF ₃	2a	90ª
2	16	ClCF ₂	2b	88ª
3	1c	BrCF ₂	2c	86ª
4	ld	Cl(CF ₂) ₄	2d	92 ^b
5	le	CF ₃ (CF ₂) ₄	2e	94 ^b

Table 1: Preparation of 5-per(poly)fluoroalkyl-2,3-dihydro-1,4-diazepines.

^a Isolated yield based on R_fCF₂I.

^b Isolated yield based on R_fCF₂CH₂CHO.

A typical procedure was as follows:

Compound 1 (10mmol) and ethylenediamine (20mmol) were dissolved in 40ml 95% ethanol. After refluxing at 80°C for about 2h, the mixture was cooled, poured into 50ml ice water and extracted with diethyl ether (3×40 ml). The organic extracts were combined, washed with brine and dried over Na₂SO₄. The solvent was removed by distillation. The crude product was further purified by flash-chromatography using petroleum ether (bp: 60-90 °C) and ethyl acetate as eluants (2:1 by volume).

The length of the per(poly)fluoroalkyl chain and the presence of ω -chlorine or bromine showed little effect on the reaction and all of the substrates afforded product 2 in nearly the same yield.

Whether the α -fluoroalkyl aldehydes were isolated or used directly in the next reaction has little effect on the finial product and yields.

When other dinucleophiles such as $H_2NCH_2CH_2CH_2NH_2$, $H_2NCH_2CH_2CH_2CH_2CH_2NH_2$, $HOCH_2CH_2OH$, $HOCH_2CH_2NH_2$ and $HSCH_2CH_2NH_2$ were used instead of $H_2NCH_2CH_2NH_2$, none of them produced the corresponding ring products.

Dihydrodiazepines take up a half-chair conformation with atoms N(4)-C(7), N(1) coplanar and atoms C(2, 3) staggered.⁵ The electrons delocalize among N(4)-C(7) and N(1), thus the position of the hydrogen needed to be clarified. The ¹³C spectrum of compound 2a (see reference 4) showed that it was a pure compound, not a mixture of two isomers. The crystal structure of compound 2a by X-ray diffraction⁶ showed that the hydrogen is attached to the nitrogen which is far away from the fluoroalkyl substituent.

The conformation of compound 2a is shown in Figure 1 :



Figure 1: X-ray structure of compound 2a.

A possible reaction pathway was suggested:





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4. All new compounds are fully characterized by spectral and elemental analyses. Data for 2a: mp 176-177°C ; UV (CH₃OH) nm⁻¹ 327; ¹HNMR (300MHz, CD₃COCD₃), δ : 6.92 (d, J=9Hz,1H), 4.84 (d, J=9Hz,1H), 4.03 (s, 2H), 3.93 (broad, NH. exchangable singlet), 3.41 (s, 2H); ¹⁹F NMR(56.4MHz, CD₃COCD₃) [CF₃COOH as standard, upfield positive] δ : -5.50 (s, 3F); ¹³C NMR (300MHZ, CD₃COCD₃) δ : 49.42, 56.91, 85.61, 122.60 (q, ¹J_{CF}=3.7 ppm), 147.27, 158.80 (q, ²J_{CF}=0.4ppm); IR(KBr) v_{max} cm⁻¹ 3230, 3070, 2994, 2911, 1628, 1555, 1320, 1135, 1095 ; MS m/z (%), 164 (M⁺, 100), 136(M⁺-NCH₂, 64), 116 (M⁺-NCH₂-HF, 49); Anal. Calcd. for C₆H₇F₃N₂: C, 43.90; H, 4.27; N, 17.07; F, 34.76. Found: C, 43.79; H, 4.03; N, 17.53; F, 34.84.

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6. X-ray data for compound 2a: $C_6H_7F_3N_2$, M=164.13, orthorhombic, a=11.855(4), b=7.829(3), c=8.059(2) Å , V=748.0(8) Å³ , Dc=1.46g/cm³ . Crystal dimensions $0.20 \times 0.20 \times 0.30$ mm. Data were measured at 293K on a Rigaku AFC7R diffractomer with graphite monochromated Mo-K α radiation and a 12kW rotating anode generator.