Pergamon

Tetrahedron Letters 39 (1998) 2377–2380

TETRAHEDRON
LETTERS

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

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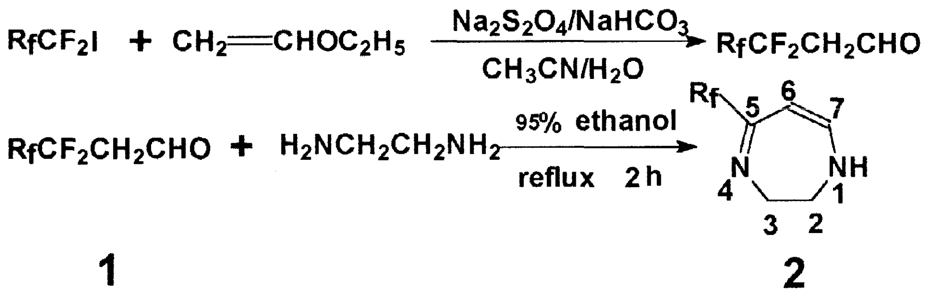
Received 23 October 1997; revised 2 December 1997; accepted 30 January 1998

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.

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 building blocks, are conveniently prepared[2] 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.



Scheme 1

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PII: S0040-4039(98)00261-5

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

Entry	Substrate	R_f	Product[4]	Yield (%)
1	1a	CF_3	2a	90[a]
2	1b	$ClCF_2$	2b	88[a]
3	1c	$BrCF_2$	2c	86[a]
4	1d	$Cl(CF_2)_4$	2d	92[b]
5	1e	$CF_3(CF_2)_4$	2e	94[b]

[a] Isolated yield based on R_fCF_2I.

[b] Isolated yield based on $R_fCF_2CH_2CHO$.

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 (3×40ml). The organic extracts were combined, washed with brine and dried over Na_2SO_4. The solvent was removed by distillation. The crude product was further purified by flash-chromatography using petroleum ether (bp: 60-90 ^{0}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 $H_2NCH_2CH_2CH_2NH_2$, $H_2NCH_2CH_2CH_2CH_2NH_2$, $HOCH_2CH_2OH$, $HOCH_2CH_2NH_2$ 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 ^{13}C 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 diffraction[6] 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** :

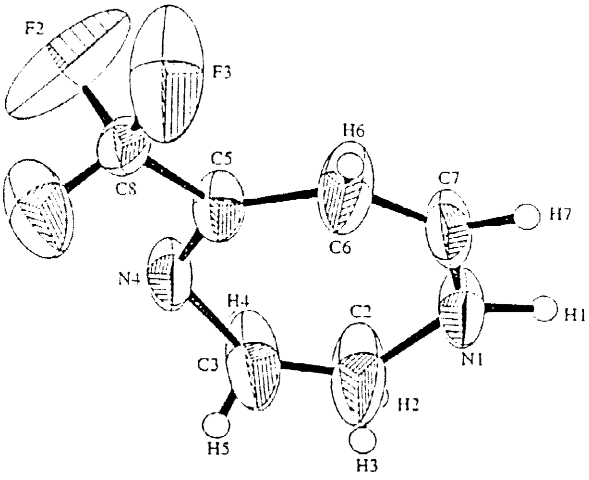
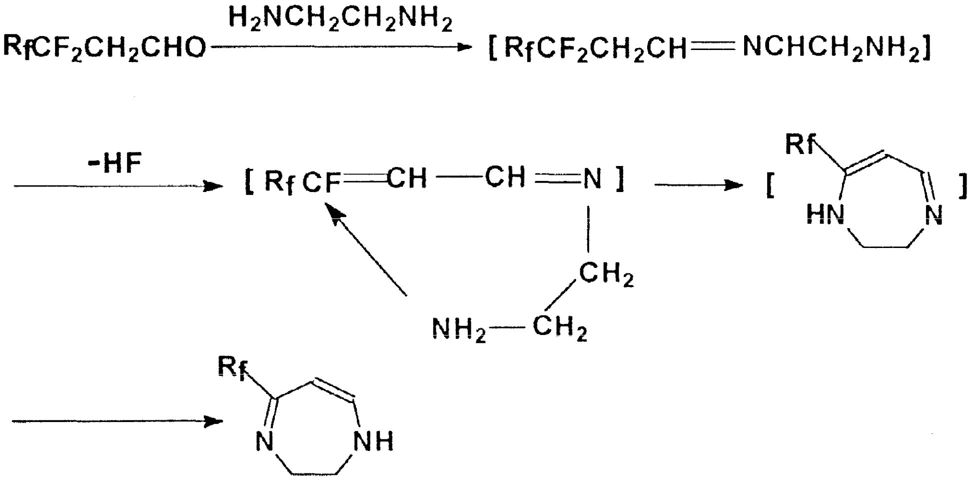


Figure 1: X-ray structure of compound 2a.

A possible reaction pathway was suggested:



Scheme 2

We thank Jie Shun and Xiang-Fu Kong of the X-ray Single Crystal Diffractometer Laboratory of Organometallic Chemistry for the X-ray crystal structure determination. We also thank the National Natural Science Foundation of China for financial support.

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4. All new compounds are fully characterized by spectral and elemental analyses. Data.for 2a: mp 176-177^{0}C ; UV (CH_3OH) nm^{-1} 327 ; ^{1}HNMR (300MHz, CD_3COCD_3), 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); ^{19}F NMR(56.4MHz, CD_3COCD_3) [CF_3COOH as standard, upfield positive] δ: -5.50 (s, 3F); ^{13}C NMR (300MHZ, CD_3COCD_3) 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) ν_{max} cm^{-1} 3230, 3070, 2994, 2911, 1628, 1555, 1320, 1135, 1095 ; MS m/z (%), 164 (M^+, 100), 136(M^+-NCH_2, 64), 116 (M^+-NCH_2-HF, 49); Anal. Calcd. for $C_6H_7F_3N_2$: 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) Å^3 , Dc=1.46g/cm^3 . Crystal dimensions 0.20×0.20×0.30mm. Data were measured at 293K on a Rigaku AFC7R diffractomer with graphite monochromated Mo-Kα radiation and a 12kW rotating anode generator.