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ScienceDirect
Journal of Fluorine Chemistry 129 (2008) 390–396
JOURNAL OF FLUORINE CHEMISTRY
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New method of preparation of C_2F_5Li and its reactions with cyclic imines and lactims: Synthesis of α-pentafluoroethyl proline

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Received 17 December 2007; received in revised form 23 January 2008; accepted 24 January 2008
Available online 6 February 2008

Abstract

Addition of pentafluoroethyllithium to cyclic imines leads to pentafluoroethyl substituted pyrrolidines, piperidines and azepanes while reaction of cyclic lactims gives rise to 2-pentafluoroethyl imines. Oxidative cleavage of 2-furyl-2-pentafluoroethyl pyrrolidine has been found to be an effective method for the preparation of a racemic α-pentafluoroethyl proline.

Keywords: Nucleophilic addition; Oxidative cleavage; Lewis acid; Cyclic imines; Pentafluoroethyl group; Azaheterocycles; α-Pentafluoroethyl proline

1. Introduction

Saturated nitrogen heterocycles are common feature of many natural alkaloids, modern medications and potent drug candidates [1]. Among them the most important are piperidine and pyrrolidine rings which are the object of continuous and numerous synthetic efforts [2].

On the other hand, it is well recognized that the introduction of perfluoroalkyl groups into organic molecules leads to the dramatic modification of their physico-chemical properties and biological activities, may significantly improve metabolic stability and is of powerful tool of modern drug design and drug discovery [3]. Among large number of outstanding applications of such organofluorine compounds in pharmaceutical field Efavirenz [4] and Celecoxib [5] can be mentioned as two recent prominent drugs used in the treatment of human diseases (HIV and arthritis correspondingly).

Organic molecules that combine in their structure piperidine and pyrrolidine fragments with perfluoroalkyl moieties take an important place in synthetic and medicinal chemistry for reasons mentioned above [6,7]. Of these fluorinated compounds, preparation of 2-perfluoroalkyl substituted aliphatic nitrogen heterocycles is attractive target [7]. Besides of their potential importance for medicinal chemistry and material science they may serve as potential fluorinated synthons for further functionalization, for example, as useful precursors for the synthesis of perfluoroalkyl containing analogues of natural α-amino acids [3,8]. To the best of our knowledge, mainly there are examples of trifluoromethylated derivatives described so far. Pentafluoroethyl derivatives of aliphatic nitrogen heterocycles are almost unexplored area despite the fact that in some test pentafluoroethyl analogues of biological active compounds show higher therapeutic affect compare with trifluoromethyl ones [9].

In this article we describe the successful synthesis of 2-pentafluoroethyl substituted cyclic amines and imines from cyclic imines and lactims respectively by reaction with pentafluoroethyllithium, easily generated from commercially available pentafluoroethane. Another notable synthetic application of this reaction is a key step in the synthesis of a promising amino acid α-pentafluoroethylproline.

2. Results and discussion

Earlier we have developed a convenient strategy for the generation of pentafluoroethyllithium based on the utilization of easily available and inexpensive pentafluoroethane [10]. On the other hand, we have a lot of experience in preparation of different 2-substituted cyclic imines. The latter can be produced

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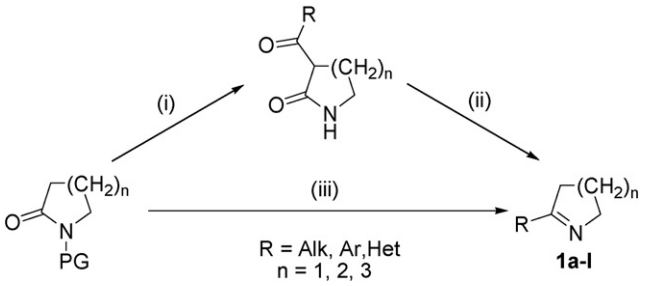
doi:10.1016/j.jfluchem.2008.01.013



Scheme 1. Synthesis of the starting imines **1**: (i) Claisen condensation with RCO_2Alk, then deprotection; (ii) decarboxylation with HCl (aq.) or (iii) reaction with RLi, then deprotection.

by Claisen condensation of *N*-protected cyclic amides with esters followed by simultaneous deprotection and decarboxylation in acidic media. Alternatively, this type of imines can be made by reaction of *N*-protected amides with readily available organolithium reagents (Scheme 1) [11]. 2-Substituted cyclic imines are very promising from the synthetic point of view and some examples of their transformations have been published recently [12].

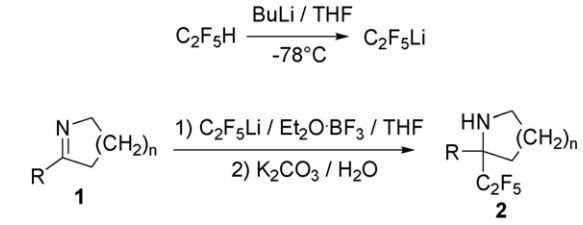
We suggested that reaction of pentafluoroethyllithium with these cyclic imines in the presence of a Lewis acid should proceed as an addition to imine C=N bond [13,14]. This approach opens up opportunities for the synthesis of 2-pentafluoroethyl substituted pyrrolidines, piperidines and azepanes, which are very interesting building blocks for potentially biologically active compounds.

Searching of an appropriate Lewis acid to activate cyclic imines was the first step of our investigation. We found that boron trifluoride etherate is a simple and effective activator for this reaction. Other tested Lewis acids such as $TiCl_4$ and $AlCl_3$ were essentially ineffective in promoting the addition of pentafluoroethyllithium to the cyclic imine. This result coincide with addition of perfluoroalkyllithium generated from the halogen–metal exchange reaction of perfluoroalkyliodates to acyclic imine bond early developed by Uno [15]. Addition of the pentafluoroethyl group to the imine double bond of compounds **1a–l** proceed smoothly to afford the α-pentafluoroethylated heterocycles **2a–l** in reasonable yields (Table 1). In

Table 1
Reactions of C_2F_5Li generated from C_2F_5H and BuLi with cyclic imines via Scheme 2

Entry	Imine	Product	*n*	R	Yield[a] (%)
1	**1a**	**2a**	1	*tert*-Bu	65
2	**1b**	**2b**	1	Bu	58
3	**1c**	**2c**	1	Ph	52
4	**1d**	**2d**	1	3-CF_3–C_6H_4	49
5	**1e**	**2e**	1	4-F–C_6H_4	59
6	**1f**	**2f**	1	4-MeO–C_6H_4	55
7	**1g**	**2g**	1	2-Furyl	43
8	**1i**	**2i**	2	*tert*-Bu	48
9	**1j**	**2j**	2	Ph	59
10	**1k**	**2k**	3	*tert*-Bu	55
11	**1l**	**2l**	3	Ph	43

[a] The yields of 2-C_2F_5–2–R cyclic amines given after the purification by column chromatography.



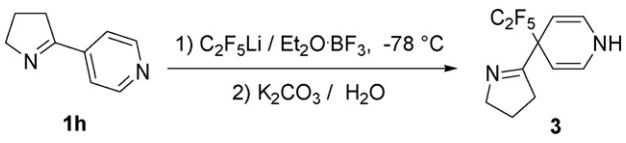
Scheme 2. Reaction of C_2F_5Li with cyclic imines.

contrast to observation of Uno and coworkers [13], the order of addition of the reagents has no influence on yields of the products. Probably, this is due to different nature of the reagent prepared by Li–Br exchange or by metalation of C_2F_5H with BuLi. In case Uno's method, 1 equiv. of LiBr or LiI salt was present in the system to form complex with the lithium reagent. Our technique permits to obtain a salt free lithium reagent (Scheme 2).

It is notable that five-, six- and seven-membered cyclic imines give very similar yields of the reaction products. The reaction is general, there is no significant dependence of the reaction yields on the nature of the substituent at the imine double bond. Even the presence of a bulky *tert*-butyl group at the imine function in case of **1a** did not lead to a significantly reduced yield.

An interesting result was obtained in the reaction of the 4-pyridyl substituted imine **1h**. Surprisingly, no addition to C=N imine bond was observed. Pentafluoroethyl reagent attacks 4-position of the pyridine ring to form dihydropyridine derivative **3**. Moreover, imine **3** is the only product of the reaction even if 2 equiv. of the organolithium reagent and boron trifluoride were used, allowing both nitrogen atoms in imine **1h** to coordinate BF_3. Although some details of the reaction deserve further study, we suggest that pentafluoroethyllithium react on more electrophilic and less sterically hindered position of the complex between the Lewis acid and more electron-donating pyrroline nitrogen atom. As well this direction for the attack of pentafluoroethyl anion on the pyridinium ring may be due to the stabilization of the transition state by delocalization of the negative charge generated in the ring by the attack (Scheme 3).

Our interest in further investigation of cyclic imines in the reaction with pentafluoroethyllithium led us to study lactim ethers. Cyclic lactim ethers (cyclic lactims) are useful building blocks for large variety of practically important organics [16]. The behavior of lactim ethers in reactions with various organometallics is a topic described in a number of publications [17]. It has been shown that lactims react easily with organolithium and organomagnesium reagents to give the corresponding imines or α,α-disubstituted amines depending on the stoichiometry and reactivity of the organometallic



Scheme 3. Reaction of C_2F_5Li with 4-(3,4-dihydro-2*H*-pyrrol-5-yl)pyridine.

Table 2
Reactions of C_2F_5Li generated from C_2F_5H and BuLi with lactims via Scheme 4

Entry	Product	*n*	Yield[a], % (^{19}F NMR data)	Yield[b], % (isolated)
1	**5a**	1	65	34
2	**5b**	2	83	62
3	**5c**	3	52	

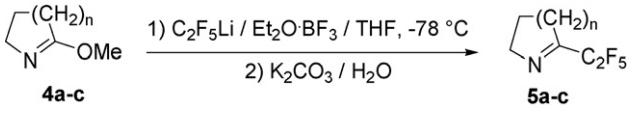
[a] The yields were determined with benzotrifluoride as internal standard.
[b] The yields given after the vacuum recondensation.

species. Usually, both types of the products are produced at the same time. In case of the most reactive organolithium and Grignard reagents α,α-disubstituted amines are the main products even with a large excess of lactim ether [18].

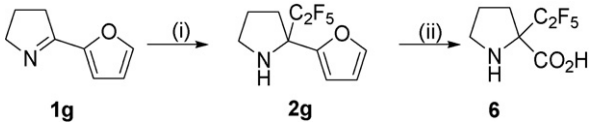
However, we found no reports of the addition of a perfluoroalkyllithium reagent to the lactim carbon–nitrogen double bond. As one would expect the pentafluoroethyllithium itself did not react with a cyclic lactim unless the lactim moiety is activated by a Lewis acid. We have tested several Lewis acids and have found that $TiCl_4$, $SnCl_4$ and $AlCl_3$ were essentially ineffective in promoting the addition of pentafluoroethyllithium to lactim. On the other hand, addition of pentafluoroethyllithium to cyclic lactim ether in the presence of boron trifluoride etherate occurred smoothly to afford the pentafluoroethyl imines **5a**–**c** in moderate yields (Table 2) (Scheme 4).

In contrast to reaction of the ordinary alkyllithium [17] addition of pentafluoroethyllithium to the lactims led to the α-pentafluoroethylimines **5** exclusively. Even if pentafluoroethyllithium was present in large excess (3 equiv.) no formation of α,α-disubstituted product was observed. Reasonable explanation of this fact should be an extraordinaire stability of an intermediate *hemi*-aminal arising from addition of C_2F_5Li to lactim carbon–nitrogen double bond under reaction temperature. The stability of the initial tetrahedral adducts between the organometallic reagent and carbonyl compounds at low temperatures as a result of the presence of electron-withdrawing perfluoroalkyl group are well documented [19]. Unfortunately, we have not succeeded to isolate seven-membered pentafluoroethylimine **5c** in pure form because of its extreme instability under usual work-up conditions. However, the compound **5c** was characterized by NMR.

Having in our hands a number of cyclic amines bearing C_2F_5 group we have developed an efficient and practical synthesis of α-pentafluoroethylproline. It is known, that substituted prolines are conformationally constrained amino acids which influence the conformation of the peptide backbone [20]. Among them the less investigated are the analogues of proline with a fluorinated group at α-position. In the literature only one synthesis of such proline has been described just recently [21]: the authors used a diastereoselective allylation reaction of ethyl trifluoropyruvate and (*R*)-phenylglycinol-based oxazolidines or imine (Scheme 5).



Scheme 4. Reaction of C_2F_5Li with lactims.



Scheme 5. Synthesis of α-pentafluoroethyl proline **6**: (i) C_2F_5Li, Et_2OBF_3, THF −78 °C, then H_2O, K_2CO_3, 71%; (ii) O_3, MeOH −78 °C 84% or $NaIO_4$, $RuCl_3$, $CH_3CN/CCl_4/H_2O$ 41%.

The key step of our approach to the synthesis of α-pentafluoroethylproline is the addition of C_2F_5Li in the presence of boron trifluoride to furylimine **1g** followed by oxidative cleavage of furyl group to carboxylic moiety. Chemoselective oxidative transformation of furyl ring of amine **2g** to the carboxylic group can be easily performed with ozone or using $NaIO_4$ with a catalytical amount of $RuCl_3$ to give target α-amino acid **5** in high yield. Thus, starting from commercial available and inexpensive *N*-vinylpyrrolidone the preparation of α-pentafluoroethylproline can be achieved in three synthetic steps without using any expensive reagent.

3. Conclusion

In conclusion, we have shown that addition of pentafluoroethyllithium to cyclic imines leads to pentafluoroethyl substituted pyrrolidines, piperidines and azepanes while the reaction of lactims gives rise to new 2-pentafluoroethyl five- and six-membered cyclic imines. We have developed a simple and convenient pathway to α-pentafluroethylproline—a prospective candidate for synthetic modification of biologically active peptides [22].

4. Experimental

4.1. General experimental procedures

NMR spectra were obtained on a Bruker DPX-200 (200.1 MHz for ^1H; 188.3 MHz for ^{19}F; 50.32 MHz for ^{13}C) or a Bruker AM-360 (360.1 MHz for ^1H; 90.5 MHz for ^{13}C) spectrometers, chemical shifts for ^1H NMR data are referenced internally to tetramethylsilane (0.0); chemical shifts for ^{13}C NMR data are referenced to corresponding $CDCl_3$ (77.2), $(CD_3)_2SO$ (39.5); chemical shifts for ^{19}F NMR data are referenced to $CFCl_3$ (0.0) or $PhCF_3$ (−63.90). High-resolution mass spectra (HRMS) were recorded using a Varian MAT CH7A instrument at 70 eV. Chemical ionization (CI) mass spectra (MS) were obtained with ammonia or isobutane as the reagent gas. Melting points are uncorrected. TLC was carried out on precoated silica plates (Merck $60F_{254}$) with UV light visualization. Flash chromatography was performed using MP Silica 60 (320–630 mesh) with the indicated solvents. All reactions were conducted in flame-dried or oven dried glassware under nitrogen atmosphere. Tetrahydrofuran and ether was distilled from sodium/benzophenone prior to use. All reagents were purchased from Aldrich unless otherwise stated. BuLi was a 2.5 M solution in hexane and was used without verification of its titre. The starting imines **1a**, **1h**, **1i** and **1k** were prepared by reaction of ethyl ester of the appropriate

carboxylic acids with *N*-vinylpyrrolidin-2-one, *N*-vinylcaprolactam or *N*-(diethoxymethyl)piperidin-2-one according to the described procedure [23]. Cyclic imines **1b–g**, **1j** and **1l** were obtained by the reaction of correspondinglithium compounds with *N*-vinylpyrrolidin-2-one, 1-(trimethylsilyl)caprolactam or 1-(trimethylsilyl)piperidin-2-one [24]. The lactim ethers were prepared from the corresponding lactams by the reaction with dimethyl sulfate [25].

4.2. General procedure for the reaction of cyclic imines with pentafluoroethyllithium

A pentafluoroethane (1.8 g, 15 mmol) was passed through solution of BuLi (4.8 ml of 2.5 M in hexane, 12 mmol) in THF (100 ml) at −85 to −80 °C. After 15 min a solution of the corresponding imine (10 mmol) in THF (15 ml) and BF_3 etherate (1.7 g, 12 mmol) was added subsequently. Then the reaction mixture was stirred for 6 h at −78 °C, quenched with water solution (50 ml) of K_2CO_3 (10 g). The organic phase was separated and the aqueous phase was extracted with ether (2× 20 ml). The combine extracts were dried over K_2CO_3, the solvents and excess of pentafluoroethane were evaporated at reduce pressure and the residue was purified by column chromatography on silica gel eluting with 15/1 mixture hexane/ethyl acetate afforded tagged amine.

2-tert-Butyl-2-(pentafluoroethyl)pyrrolidine (**2a**). Colourless liquid, bp 67–79 °C (12 Torr), ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (9H, t, $^5J_{HF}$ = 1.7 Hz, $(CH_3)_3C$), 1.63–2.15 (4H, m), 2.98–3.15 (2H, m, CH_2N). ^{13}C NMR (90 MHz, $CDCl_3$): δ 25.8, 27.1 (3C, $(\mathbf{C}H_3)_3C$), 29.9, 39.7 (C_q, $(CH_3)_3\mathbf{C}$), 48.1 (CH_2NH), 72.9 (t, $^2J_{CF}$ = 19.7 Hz, $C_2F_5\mathbf{C}$), 119.6 (qt, $^1J_{CF}$ = 263.0 Hz, $^2J_{CF}$ = 32.4 Hz, $CF_3\mathbf{C}F_2$), 120.4 (tq, $^1J_{CF}$ = 287.7 Hz, $^2J_{CF}$ = 37.9 Hz, $\mathbf{C}F_3CF_2$). ^{19}F NMR (188 MHz, $CDCl_3$): δ −116.1, −114.7, −110.1, −108.6 (2F, AB-system, δ_A −118.25, δ_B −106.53, $^2J_{AB}$ = 274.1 Hz), −78.00 (3F, CF_3). EIMS 70 eV, *m/z* (rel. int.): 230 $[M-CH_3]^+$ (7), 188 $[M-C_4H_9]^+$ (100), 126 $[M-C_2F_5]^+$ (2), 111 $[M-CH_3, -C_2F_5]^+$ (4). HRMS (EI): calcd. for $C_9H_{13}F_5N$ ($M-CH_3$) 230.0968; found 230.0968.

2-Butyl-2-(pentafluoroethyl)pyrrolidine (**2b**). Colourless liquid, bp 68–70 °C (12 Torr), ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.78–0.84 (3H, m), 1.20–1.35 (4H, m), 1.45–1.88 (6H, m, incl. 1.52 (1H, bs, NH)), 1.97–2.10 (1H, m), 2.84–3.00 (2H, m, CH_2N). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6 (CH_3), 23.1, 25.4, 26.0, 31.2, 35.5, 47.6 (CH_2NH), 66.9 (t, $^2J_{CF}$ = 19.8 Hz, C_2F_5C), 117.5 (qt, $^1J_{CF}$ = 257.7 Hz, $^2J_{CF}$ = 33.8 Hz, $CF_3\mathbf{C}F_2$), 120.3 (tq, $^1J_{CF}$ = 288.2 Hz, $^2J_{CF}$ = 37.5 Hz, $\mathbf{C}F_3CF_2$). ^{19}F NMR (188 MHz, $CDCl_3$): δ −122.0, −120.5, −120.3, −118.9 (2F, AB-system, δ_A −121.18, δ_B −119.65, $^2J_{AB}$ = 274.1 Hz), −79.1 (3F, CF_3). EIMS 70 eV, *m/z* (rel. int.): 245 $[M]^+$ (21), 244 $[M-H]^+$ (16), 226 $[M-F]^+$ (13), 216 $[M-29]^+$ (24), 188 $[M-C_4H_9]^+$ (100), 126 $[M-C_2F_5]^+$ (68). HRMS (EI): calcd. for $C_{10}H_{16}F_5N$ 245.1203; found 245.1195.

2-(Pentafluoroethyl)-2-phenylpyrrolidine (**2c**). Colourless liquid, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.62–2.02 (2H, m), 2.26–2.40 (2H, m, incl. 2.30 (1H, s, NH)), 2.57–2.72 (1H, m), 2.98–3.27 (2H, m, CH_2N), 7.31–7.42 (3H, m, Ar-H), 7.54–7.58 (2H, m, Ar-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.5, 35.1, 46.5 (CH_2NH), 69.9 (t, $^2J_{CF}$ = 21.7 Hz, C_2F_5C), 116.2 (qt, $^1J_{CF}$ = 260.1 Hz, $^2J_{CF}$ = 34.3 Hz, CF_3CF_2), 120.0 (qt, $^1J_{CF}$ = 288.5 Hz, $^2J_{CF}$ = 37.9 Hz, CF_3CF_2), 127.3 (2C, s, Ar), 127.93 (Ar), 128.1 (2C, s, Ar), 139.2 (Ar). ^{19}F NMR (188 MHz, $CDCl_3$): δ −122.2, −120.8, −118.3, −116.8 (2F, AB-system, δ_A −122.63, δ_B −115.89, $^2J_{AB}$ = 274.9 Hz), −78.8 (3F, s, CF_3). EIMS 70 eV, *m/z* (rel. int.): 264 $[M-H]^+$ (4), 236 $[M-29]^+$ (18), 188 $[M-C_6H_5]^+$ (21), 146 $[M-C_2F_5]^+$ (100). CIMS NH_3, *m/z* (rel. int.): 266 $[M+H]^+$ (100), 146 $[M-C_2F_5]^+$ (16). HRMS (EI): calcd. for $C_{12}H_{11}F_5N$ (M−H) 264.0812; found 264.0807.

2-(Pentafluoroethyl)-2-[3-(trifluoromethyl) phenyl]pyrrolidine (**2d**). Colourless liquid, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.54–1.77 (1H, m), 1.84–2.00 (1H, m), 2.18–2.35 (2H, m, incl. 2.32 (1H, s, NH)), 2.58–2.74 (1H, m), 2.98–3.07 (1H, m), 3.17–3.29 (1H, m), 7.47 (1H, dd, $^3J_{HH}$ = 7.83 and 7.82 Hz, Ar-H), 7.58 (1H, m, $^3J_{HH}$ = 7.83 Hz, Ar-H), 7.75 (1H, d, $^3J_{HH}$= 7.82 Hz, Ar-H), 7.86 (1H, s, Ar-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.5, 35.6, 46.7 (CH_2NH), 69.9 (t, $^2J_{CF}$ = 21.7 Hz, C_2F_5C), 116.5 (qt, $^1J_{CF}$ = 260.1 Hz, $^2J_{CF}$ = 34.3 Hz, CF_3CF_2), 119.7 (qt, $^1J_{CF}$ = 288.2 Hz, $^2J_{CF}$ = 37.1 Hz, CF_3CF_2), 124.5 (t, $^1J_{CF}$ = 272.2 Hz, CF_3Ar), 124.8 (bs, Ar), 125.3 (q, $^3J_{CF}$ = 4.1 Hz, Ar), 129.0 (Ar), 131.1 (q, $^2J_{CF}$ = 32.2 Hz, Ar), 131.4 (Ar), 141.2 (Ar). ^{19}F NMR (188 MHz, $CDCl_3$): δ −122.2, −120.2, −118.1, −116.6 (2F, AB-system, δ_A −122.26, δ_B, −116.52, $^2J_{AB}$ = 274.9 Hz), −79.13 (3F, s, CF_3). EIMS 70 eV, *m/z* (rel. int.): 332 $[M-H]^+$ (2), 314 $[M-F]^+$ (5), 214 $[M-C_2F_5]^+$ (100). CIMS isobutan, *m/z* (rel. int.): 334 $[M+H]^+$ (100), 314 $[M-F]^+$ (11), 214 $[M-C_2F_5]^+$ (100). HRMS (EI): calcd. for $C_{13}H_{11}F_8N$ (M−H) 332.0685; found 332.0695.

2-(4-Fluorophenyl)-2-(pentafluoroethyl)pyrrolidine (**2e**). Colourless liquid, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.58–1.97 (2H, m), 2.18–2.31 (2H, m, incl. 2.28 (1H, s, NH)), 2.52–2.66 (1H, m), 2.94–3.25 (2H, m, CH_2N), 6.96–7.08 (2H, m, Ar-H), 7.48–7.55 (2H, m, Ar-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.6, 35.3, 46.6 (CH_2NH), 69.6 (t, $^2J_{CF}$ = 21.2 Hz, C_2F_5C), 111.2 (2C, d, $^2J_{CF}$ = 22.6 Hz, *m*-C_{Arom}), 116.7 (qt, $^1J_{CF}$ = 263.5 Hz, $^2J_{CF}$ = 33.9 Hz, CF_3CF_2), 119.8 (qt, $^1J_{CF}$ = 288.2 Hz, $^2J_{CF}$ = 36.7 Hz, CF_3CF_2), 129.7 (2C, d, $^3J_{CF}$ = 8.5 Hz, *o*-C_{Arom}), 135.4 (Ar), 162.9 (d, $^1J_{CF}$ = 247.2 Hz, Ar). ^{19}F NMR (188 MHz, $CDCl_3$): δ −122.2, −120.8, −118.3, −116.8 (2F, AB-system, δ_A −123.18, δ_B −115.89, $^2J_{AB}$ = 274.9 Hz), −78.8 (3F, s, CF_3). EIMS 70 eV, *m/z* (rel. int.): 282 $[M-H]^+$ (1), 164 $[M-C_2F_5]^+$ (100). CIMS isobutane, *m/z* (rel. int.): 284 $[M+H]^+$ (100), 188 $[M-C_6H_4F]^+$ (10), 164 $[M-C_2F_5]^+$ (100). HRMS (EI): calcd. for $C_{12}H_{10}F_6N$ (M−H) 282.0717; found 282.0726.

2-(4-Methoxyphenyl)-2-(pentafluoroethyl)pyrrolidine (**2f**). Colourless liquid, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.66–1.99 (2H, m), 2.23–2.36 (2H, m, incl. 2.34 (1H, s, NH)), 2.51–2.66 (1H, m), 3.01–3.26 (2H, m, CH_2N), 3.82 (3H, s, OCH_3), 6.86–6.94 (2H, m, Ar-H), 7.43–7.47 (2H, m, Ar-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.6, 34.9, 46.5 (CH_2NH), 55.2 (OCH_3), 69.5 (t, $^2J_{CF}$ = 21.4 Hz, C_2F_5C), 113.5 (2C, s, Ar), 115.4 (qt, $^1J_{CF}$ = 260.7 Hz, $^2J_{CF}$ = 33.9 Hz, CF_3CF_2), 120.0 (qt, $^1J_{CF}$ = 287.8 Hz, $^2J_{CF}$ = 36.9 Hz, $\mathbf{C}F_3CF_2$), 128.5 (2C, s, Ar), 130.9 (Ar), 159.3 ($\mathbf{C}_{Arom}$-OCH_3). ^{19}F NMR (188 MHz, $CDCl_3$): δ −122.0, −120.5, −118.4, −117.0 (2F, AB-system,

δ_A −122.70, δ_B −116.18, $^2J_{AB}$ = 271.2 Hz), −78.8 (3F, s, CF_3). EIMS 70 eV, *m/z* (rel. int.): 294 $[M-H]^+$ (2), 176 $[M-C_2F_5]^+$ (100), 133 $[M-162]^+$ (12). CIMS isobutane, *m/z* (rel. int.): 296 $[M+H]^+$ (100), 176 $[M-C_2F_5]^+$ (27). HRMS (EI): calcd. for $C_{12}H_{11}F_5N$ (M−H) 294.0917; found 294.0912.

2-(2-Furyl)-2-pentafluoroethylpyrrolidine (**2g**). Colourless liquid, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.69–2.04 (2H, m), 2.25–2.42 (2H, m), 2.51 (1H, s, NH), 2.96–3.19 (1H, m), 2.98–3.27 (2H, m, CH_2N), 6.34–6.38 (2H, m, Furyl), 7.40–7.41 (1H, m, Furyl). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.7, 32.5, 46.5 (CH_2NH), 66.9 (t, $^2J_{CF}$ = 22.9 Hz, C_2F_5**C**), 115.6 (qt, $^1J_{CF}$ = 259.6 Hz, $^2J_{CF}$ = 34.5 Hz, CF_3**C**F_2), 119.7 (qt, $^1J_{CF}$ = 287.6 Hz, $^2J_{CF}$ = 36.8 Hz, **C**F_3CF_2), 108.4 (C_q, Furyl), 110.6 (2C, s, Furyl), 142.8 (1C, s, Furyl). ^{19}F NMR (188 MHz, $CDCl_3$): δ −123.7, −122.3, −120.8, −119.4 (2F, AB-system, δ_A −125.00, δ_B −120.34, $^2J_{AB}$ = 270.3 Hz), −80.6 (3F, s, CF_3). EIMS 70 eV, *m/z* (rel. int.): 255 $[M]^+$ (4), 254 $[M-H]^+$ (17), 236 $[M-F]^+$ (12), 136 $[M-C_2F_5]^+$ (100). HRMS (EI): calcd. for $C_{12}H_{11}F_5N$ (M−H) 255.0812; found 255.0807.

2-tert-Butyl-2-(pentafluoroethyl)piperidine (**2i**). Colourless liquid, ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.03 (9H, t, $^5J_{HF}$ = 1.3 Hz, $(CH_3)_3C$), 1.46–1.73 (6H, m, incl. 1.70 (1H, bs, NH)), 1.87–1.91 (1H, m), 2.89–3.03 (2H, m, CH_2N). ^{13}C NMR (90 MHz, $CDCl_3$): δ 20.9, 23.8 (3C, (**C**$H_3)_3$C), 24.2, 26.3, 40.0 (C_q, $(CH_3)_3$**C**), 41.9 (CH_2NH), 62.6 (t, $^2J_{CF}$ = 18.3 Hz, C_2F_5**C**), 121.6 (qt, $^1J_{CF}$ = 266.7 Hz, $^2J_{CF}$ = 33.9 Hz, CF_3**C**F_2), 120.9 (tq, $^1J_{CF}$ = 288.6 Hz, $^2J_{CF}$ = 38.4 Hz, **C**F_3CF_2). ^{19}F NMR (188 MHz, $CDCl_3$): δ −111.0, −109.5, −108.7, −107.2 (2F, AB-system, δ_A −111.17, δ_B −107.77, $^2J_{AB}$ = 286.2 Hz), −76.7 (3F, CF3). EIMS 70 eV, *m/z* (rel. int.): 244 $[M-CH_3]^+$ (37), 202 $[M-C_4H_9]^+$ (100), 174 $[M-85]^+$ (10). HRMS (EI): calcd. for $C_{10}H_{15}F_5N$ ($M-CH_3$) 244.1125; found 244.1122.

2-Phenyl-2-(pentafluoroethyl)piperidine (**2j**). Colourless liquid, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25–1.53 (3H, m), 1.68–1.74 (1H, m), 1.99–2.13 (1H, m, incl. 2.13 (1H, bs, NH)), 2.50–2.73 (2H, m), 2.88–2.95 (1H, m), 7.30–7.56 (5H, m, Ar-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.7, 26.0, 28.2 (bs, CH_2(Cq)C_2F_5), 40.8 (CH_2NH), 63.1 (t, $^2J_{CF}$ = 20.7 Hz, C_2F_5C), 116.1 (qt, $^1J_{CF}$ = 260.5 Hz, $^2J_{CF}$ = 34.3 Hz, CF_3CF_2), 120.0 (tq, $^1J_{CF}$ = 288.4 Hz, $^2J_{CF}$ = 37.2 Hz, CF_3CF_2). ^{19}F NMR (188 MHz, $CDCl_3$): δ −121.8, −123.3, −123.5, −125.0 (2F, AB-system, δ_A −124.12, δ_B −122.66, $^2J_{AB}$ = 277.6 Hz), −77.7 (3F, CF_3). EIMS 70 eV, *m/z* (rel. int.): 278 $[M-H]^+$ (14), 260 $[M-F]^+$ (5), 160 $[M-C_2F_5]^+$ (100), 104 $[M-175]^+$ (11). HRMS (EI): calcd. for $C_{13}H_{13}F_5N$ (M−H) 278.0968; found 278.0971.

2-tert-Butyl-2-(pentafluoroethyl)azapane (**2k**). Colourless liquid, ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.06 (9H, t, $^5J_{HF}$ = 1.7 Hz, $(CH_3)_3C$), 1.46–1.50 (4H, m), 1.71–1.74 (2H, m), 1.82 (1H, bs, NH), 1.94–2.00 (2H, m), 2.90–2.93 (2H, m, CH_2N). ^{13}C NMR (90 MHz, $CDCl_3$): δ 25.7, 27.7 (3C, t, $^4J_{CF}$ = 3.8 Hz, (**C**$H_3)_3$C), 30.4, 31.6, 33.7, 42.0 (C_q, $(CH_3)_3$**C**), 45.8 (CH_2NH), 69.3 (t, $^2J_{CF}$ = 17.4 Hz, C_2F_5**C**), 119.8 (qt, $^1J_{CF}$ = 267.9 Hz, $^2J_{CF}$ = 33.5 Hz, CF_3**C**F_2), 120.1 (tq, $^1J_{CF}$ = 288.1 Hz, $^2J_{CF}$ = 38.0 Hz, **C**F_3CF_2). ^{19}F NMR (188 MHz, $CDCl_3$): δ −113.5, −112.0, −111.8, −110.3 (2F, AB-system, δ_A −112.7, δ_B −111.2, $^2J_{AB}$ = 282.7 Hz), −76.7 (3F, CF_3). EIMS 70 eV, *m/z* (rel. int.): 258 $[M-CH_3]^+$ (72), 216 $[M-C_4H_9]^+$ (100), 154 $[M-C_2F_5]^+$ (15). HRMS (EI): calcd. for $C_{11}H_{17}F_5N$ ($M-CH_3$) 258.1281; found 258.1273.

2-Pentafluoroethyl-2-phenylazapane (**2l**). Colourless liquid, ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.34–1.56 (4H, m), 1.64–1.80 (2H, m), 2.01 (1H, bs, NH), 2.32–2.39 (1H, m), 2.51–2.58 (1H, m), 2.81–2.87 (1H, m), 3.10–3.17 (1H, m), 7.33–7.41 (3H, m, Ar-H), 7.59–7.61 (2H, m, Ar-H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 23.8, 30.7, 34.1, 34.8 (bs, **C**H_2(C_q)C_2F_5), 44.5 (CH_2NH), 66.8 (t, $^2J_{CF}$ = 19.8 Hz, C_2F_5**C**), 117.6 (qt, $^1J_{CF}$ = 263.0 Hz, $^2J_{CF}$ = 33.8 Hz, CF_3**C**F_2), 120.6 (tq, $^1J_{CF}$ = 288.6 Hz, $^2J_{CF}$ = 37.2 Hz, **C**F_3CF_2). ^{19}F NMR (188 MHz, $CDCl_3$): δ −117.0, −118.5, −120.4, −121.9 (2F, AB-system, δ_A −122.55, δ_B −116.36, $^2J_{AB}$ = 275.0 Hz), −77.6 (3F, CF_3). EIMS 70 eV, *m/z* (rel. int.): 293 $[M]^+$ (4), 292 $[M-H]^+$ (12), 264 $[M-CH_2NH]^+$ (11), 236 $[M-C_3H_6NH]$ (35), 174 $[M-C_2F_5]^+$ (100), 105 $[M-188]^+$ (24). HRMS (EI): calcd. for $C_{14}H_{16}F_5N$ 293.1203; found 293.1192.

4-(3,4-Dihydro-2H-pyrrol-5-yl)-4-(pentafluoroethyl)-1,4-dihydropyridine (**3**). Yellow crystals, mp 117–119 °C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.79–1.94 (2H, m), 2.56–2.64 (2H, m), 3.82–3.89 (2H, m, CH_2N), 4.65 (2H, d, $^3J_{HH}$ = 7.5 Hz, C–CH_{vinyl}), 5.51 (1H, bs, NH), (2H, dd, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 4.9 Hz, HN-CH_{vinyl}). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.6, 33.8, 48.9 (t, $^2J_{CF}$ = 22.0 Hz, C_2F_5**C**), 60.5 (CH_2N), 92,7 (2C, CH-vinyl), 114.1 (qt, $^1J_{CF}$ = 260.2 Hz, $^2J_{CF}$ = 32.9 Hz, CF_3**C**F_2), 119.6 (qt, $^1J_{CF}$ = 289.1 Hz, $^2J_{CF}$ = 37.2 Hz, **C**F_3CF_2), 127.8 (2C, HN-CH-vinyl), 177.3 (C_q=N). ^{19}F NMR (188 MHz, $CDCl_3$): δ −121.0 (2F, CF_2), −78.8 (3F, CF_3). EIMS 70 eV, *m/z* (rel. int.): 266 $[M]^+$ (10), 198 $[M-C_4H_6N]^+$ (68), 147 $[M-C_2F_5]^+$ (100), 129 $[M-137]^+$ (21). HRMS (EI): calcd. for $C_{11}H_{11}F_5N_2$ 266.08424; found 266.08344.

4.3. General procedure for the reaction of cyclic lactims with pentafluoroethyllithium

A pentafluoroethane (1.8 g, 15 mmol) was passed through solution of BuLi (4.8 ml of 2.5 M in hexane, 12 mmol) in THF (100 ml) at −85 to −80 °C. After 15 min a solution of the corresponding lactims (10 mmol) in THF (15 ml) and BF_3 etherate (1.7 g, 12 mmol) was added subsequently. Then the reaction mixture was stirred for 6 h at −78 °C, was quenched by slow addition of 1N aqueous HCl (50 ml) and the organic solvents were removed at reduce pressure. The residue was quenched with water solution (50 ml) of K_2CO_3 (10 g). The aqueous phase was extracted with ether (3× 20 ml). The combine extracts were dried over K_2CO_3, the ether was evaporated at normal pressure. The residue was purified by bulb-to-bulb recondensation under vacuum afforded corresponding pentafluoroethylimines.

2-(Pentafluoroethyl)-3,4-dihydro-2H-pyrrole (**4a**). Colourless liquid, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.94–2.10 (2H, m), 2.72–2.80 (2H, m), 4.02–4.14 (2H, m, CH_2N). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.8, 34.0 (bs, **C**H_2-C_q-C_2F_5), 62.4 (CH_2N), 110.8 (qt, $^1J_{CF}$ = 252.6 Hz, $^2J_{CF}$ = 38.4 Hz, CF_3**C**F_2), 118.9 (tq, $^1J_{CF}$ = 286.2 Hz, $^2J_{CF}$ = 35.7 Hz, **C**F_3CF_2), 166.3 (t, $^2J_{CF}$ = 27.44 Hz, C_2F_5**C**). ^{19}F NMR (188 MHz, $CDCl_3$): δ

−118.2, (2F, CF_2), −83.4 (3F, CF_3). EIMS 70 eV, *m/z* (rel. int.): 201 $[M]^+$ (71), 173 $[M-C_2H_4]^+$ (66), 132 $[M-CF_3]^+$ (49), 82 $[M-C_2F_5]^+$ (50), 54 $[C_4H_6]^+$ (100). CIMS NH_3, *m/z* (rel. int.): 218 $[M+NH_3]^+$ (2), 216 $[M+NH]^+$ (2), 202 $[M+H]^+$ (100), 178 $[M-23]^+$ (12). HRMS (EI): calcd. for $C_7H_8F_5N$ 201.0577; found 201.0568.

2-(Pentafluoroethyl)-2,3,4,5-tetrahydropyridine (**4b**). Colourless liquid, ^1H NMR (360 MHz, $CDCl_3$): δ 1.62–1.68 (2H, m), 1.73–1.80 (2H, m), 2.30–2.33 (2H, m), 3.79–3.82 (2H, m, CH_2N). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.3, 21.1, 24.1 (bs, $\mathbf{C}H_2C_qC_2F_5$), 49.7 (CH_2N), 110.6 (qt, $^1J_{CF}$ = 255.1 Hz, $^2J_{CF}$ = 36.6 Hz, $CF_3\mathbf{C}F_2$), 119.1 (tq, $^1J_{CF}$ = 286.4 Hz, $^2J_{CF}$ = 36.4 Hz, $\mathbf{C}F_3CF_2$), 160.2 (tq, $^2J_{CF}$ = 25.9 Hz, $^3J_{CF}$ = 0.8 Hz, $C_2F_5\mathbf{C}$). ^{19}F NMR (188 MHz, $CDCl_3$): δ −120.5, (2F, CF_2), −82.7 (3F, CF_3). EIMS 70 eV, *m/z* (rel. int.): 187 $[M]^+$ (100), 159 $[M-CH_2N]^+$ (76), 90 $[M-97]^+$ (26), 68 $[M-C_2F_5]^+$ (16). HRMS (EI): calcd. for $C_6H_6F_5N$ 187.04204; found 187.04158.

4.4. 2-(Pentafluoroethyl)proline (*5*)

4.4.1. Method A, ozonolysis

Ozone was passed through a solution of the amine 2 g (1.28 g, 5 mmol) in methanol (75 ml) at −78 °C. When blur color was appeared the reaction was stopped and excess of ozone was removed by oxygen stream. Evaporation of the solvent gave the crude product as yellowish solid which was purified by washing with dichloromethane.

4.4.2. Method A, oxidation with $RuCl_3$

To a solution of sodium periodate (8.5 g, 40 mmol) in a mixed solvent carbon tetrachloride/acetonitrile/water (3/3/2, 60 ml) was added an aqueous solution of $RuCl_3 \cdot xH_2O$ (0.05 g, 0.5 mmol). After stirring reaction mixture for 15 min at r.t. a solution of the amine 2 g (1.28 g, 5 mmol) in carbon tetrachloride (5 ml) was added in one portion. After a further 15 min, the reaction mixture was diluted with water (100 ml) and extracted with ethyl acetate (3× 30 ml). The combined organic extracts were washed with brine, filtered through celite and evaporated in vacuum. The crude product was purified by precipitation from alkali water solution by adding of 1N aqueous HCl to pH 5.5.

White crystals, mp 168–169 °C, ^1H NMR (200 MHz, D_2O): δ 1.64–1.98 (2H, m), 2.32–2.61 (2H, m), 3.23–3.37 and 3.75–3.85 (2H, m, CH_2N), 8.16 (1H, bs, NH). ^{13}C NMR (90 MHz, D_2O): δ 22.1, 34.7, (bs, $\mathbf{C}H_2C_qC_2F_5$), 47.2 (CH_2N), 72.8 (t, $^2J_{CF}$ = 23.6 Hz, $C_2F_5\mathbf{C}$), 115.6 (qt, $^1J_{CF}$ = 260.5 Hz, $^2J_{CF}$ = 34.7 Hz, $CF_3\mathbf{C}F_2$), 119.8 (tq, $^1J_{CF}$ = 287.8 Hz, $^2J_{CF}$ = 37.2 Hz, $\mathbf{C}F_3CF_2$), 167.2 (CO_2). ^{19}F NMR (188 MHz, $CDCl_3$): δ −115.0, −113.5, −113.3, −111.8 (2F, AB-system, δ_A −114.20, δ_B −112.60, $^2J_{AB}$ = 281.0 Hz), −78.7 (3F, CF_3). EIMS 70 eV, *m/z* (rel. int.): 233 $[M]^+$ (3), 216 $[M-F]^+$ (28), 188 $[M-CO_2H]^+$ (100). HRMS (EI): calcd. for $C_7H_8F_5NO_2$ 233.0475; found 233.0471.

Acknowledgment

The authors thank the Deutsche Forschungsgemeinschaft (436 RUS 113/812/0-1) for financial support of this work.

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