Synthesis of 3-(2,2,2-trifluoroethylidene)-lactams. First examples of 1,3-dipolar cycloaddition with diazomethane and *N*-methyl-α-phenylnitrone

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The preparation of 3-(2,2,2-trifluoroethylidene)-lactams 7–9 is accomplished by reduction of 3-trifluoroacetyl-substituted lactams 1–3 and subsequent dehydration of trifluoromethylated methanols 4–6. 1,3-Dipolar cycloadditions of compounds 7 with diazomethane and *N*-methyl-α-phenylnitrone give spirocyclic pyrazoline 11 and isoxazolidine 12. The structure of the latter heterocycle is confirmed by X-ray diffraction analysis and by comparison of ^{19}F and ^{13}C NMR data.

Introduction

Following our studies in heterocyclic chemistry, we demonstrated that 3-trifluoroacetyl-substituted lactams[1] are useful reagents for the synthesis of new trifluoromethylated pyrazoles,[2] pyrimidines,[3,4] oxazolidines,[5–7] imidazolidines[5–7] and thiazolidines.[5,7] Moreover, trifluoroacetylated lactams were used in Robinson annelation reactions to prepare new spirocyclic cyclohexenones which can be used as the starting materials for more complicated polycyclic systems.[8]

Now we report that 3-trifluoroacetyl-substituted lactams **1–3** can be employed for the synthesis of new 3-(2,2,2-trifluoroethylidene)-lactams **7–9** which should be good substrates for 1,3-dipolar cycloadditions.

To our best knowledge, 3-(2,2,2-trifluoroethylidene)-lactams **7–9** are still unknown in the literature although there are a few examples of their acyclic analogues — trifluoromethylated acrylic amides. They are generally obtained from 4,4,4-trifluorocrotonic esters or chlorides and an amine.[9,10] More peculiar methods are also reported: the reaction of cyclohexyl isocyanide with hexafluorobut-2-yne followed by acidic hydrolysis;[11] the perfluorination of pyridine in the presence of $KCo^{III}F_4$ followed by a subsequent hydrolysis of the 2-azahexa-2,4-diene intermediate.[12]

Results and discussion

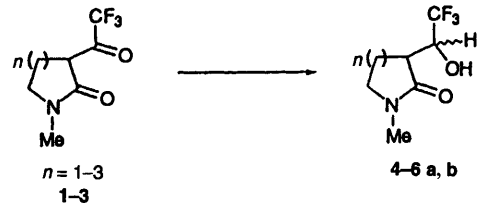
3-(2,2,2-Trifluoroethylidene)-lactams **7–9** are obtained from 3-trifluoroacetyl-substituted lactams **1–3** by using a two-step sequence, namely the reduction of the trifluoroacetyl function followed by dehydration of trifluoromethylated alcohols **4–6**.

Preparation of 3-(2,2,2-trifluoro-1-hydroxyethyl)-lactams 4–6

The reduction of the trifluoroacetyl function is usually carried out by means of lithium aluminium hydride[13] or by catalytic hydrogenation (Pd–C 5%, H_2).[14] For trifluoroacetylated 1,3-dicarbonyl compounds such as ethyl 4,4,4-trifluoroacetoacetate (ETFAA), sodium borohydride is generally employed.[15]

When we treated solutions of 3-trifluoroacetyl-substituted lactams **1–3** with sodium borohydride in dry methanol, the trifluoromethylated methanols **4–6** were obtained in good yield as a mixture of two diastereoisomers (Scheme 1, Table 1).

As indicated in Table 1, the yields of alcohols **4–6** are very similar, which means that there is no influence by the lactam ring-size. Moreover, the reduction is highly diastereoselective.



Scheme 1 *Reagents and conditions:* $NaBH_4$, MeOH, 0–25 °C

Table 1 Yield and selectivity of lactams **4–6**[a]

n	Yield **4–6** (%)	Compound	Selectivity (%)	$\delta(^{19}F)$
1	81	**4a**	95	−79.0
		4b	5	−77.7
2	83	**5a**	80	−76.2
		5b	20	−75.3
3	84	**6a**	95	−76.9
		6b	5	−75.6

[a] Selectivity: major/minor.

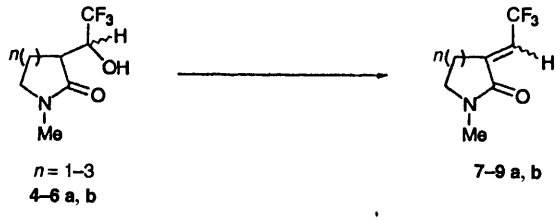
Although we did not determine the geometry of both diastereoisomers, it seems that the major isomers **4a**, **5a**, **6a** have the same relative configuration. Indeed, the ^{19}F NMR chemical shifts of compounds **4a**, **5a**, **6a** are more shielded than those of diastereoisomers **4b**, **5b**, **6b** (Table 1).

Preparation of 3-(2,2,2-trifluoroethylidene)-lactams 7–9

The dehydration of trifluoromethylated methanols is well known to be difficult. Thus, in the synthesis of 1,1,1-trifluoroalk-2-enes, the literature reports the use of concentrated phosphoric acid or its anhydride,[16] the flash pyrolysis of acetates or xanthates[17] and the treatment with chlorinating ($SOCl_2$, $POCl_3$) or brominating agents (PBr_3, HBr).[18]

The 4,4,4-trifluorocrotonic esters are generally obtained by using boric anhydride at high temperature[19] or by prior tosylation of the corresponding alcohol and subsequent elimination.[20]

For the preparation of lactams **7–9**, we employed chlorinating agents such as $SOCl_2$, PCl_5 or $POCl_3$, and thermolysis in the presence of phosphoric anhydride (Scheme 2, Table 2).



Scheme 2 *Reagents and conditions:* see Table 2

The chlorination of trifluoromethylated alcohol **4** gave poor to moderate yields of lactam **7** and was accompanied by a partial degradation of the starting material (Table 2). No trace of compound **7** was detected in the crude mixture when using thionyl chloride, whereas only a 22% yield was obtained with phosphorus pentachloride. There was some improvement when using a mixture of $POCl_3$ and pyridine. Finally, we found that the best method for dehydration of methanols **4–6** is thermolysis in the presence of an excess of diphosphorus pentoxide in a Büchi Kugelrohr apparatus. Under these conditions, yields of **7–9** are generally greater than 70% (Table 2).

The stereochemistry of 3-trifluoroethylidene-lactams **7–9** was assigned based on ^{19}F and ^{13}C NMR data (Table 3) and additional proof was obtained by establishing the configuration of spirocyclic isoxazolidine **12** by X-ray diffraction analysis (Fig. 1).

Following the ^{19}F NMR data (Table 3), one can observe that $\delta(^{19}F)$ of the major isomers **7a**, **8a**, **9a** is more shielded than in minor isomers **7b**, **8b**, **9b** and therefore they have probably the same configuration. We tentatively attributed to these major stereoisomers the *E* configuration for two reasons: first, the ^{13}C chemical shifts [Table 3: δ(C-1), (C-5), (C-7)] of compound **7a** are very similar to those of the pyrrolidinone **10** which was determined to be *Z* by X-ray diffraction analysis;[4,30] secondly, the carbon–hydrogen coupling constant [^3J(C-1,H-4) = 7–8 Hz] of isomer **7a** is in good agreement with the *E* configuration.[22]

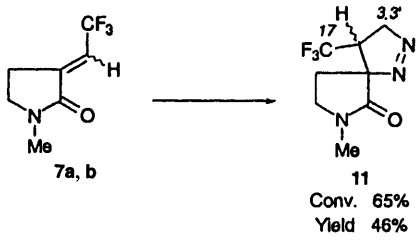
Table 2 Conditions and yield of lactams **7–9a,b**

n	Compound	Conditions	Yield **7–9a,b** (%)
1	**4a,b**	$SOCl_2$, pyridine, benzene, 25 °C; then reflux	—
		PCl_5, chlorobenzene, 25 °C; then reflux	22
		$POCl_3$, pyridine, benzene, reflux	56
		P_2O_5, thermolysis in a Kugelrohr apparatus	72
2	**5a,b**	P_2O_5, thermolysis in a Kugelrohr apparatus	84
3	**6a,b**	P_2O_5, thermolysis in a Kugelrohr apparatus	68

1,3-Dipolar cycloadditions

To our best knowledge, no 1,3-dipolar cycloaddition has been reported for trifluoromethylated vinyl lactams and acrylic amides. Nevertheless, there are a few examples with their analogues, such as 4,4,4-trifluorocrotonic esters and 3-methylenepyrrolidin-2-one. For example, some recent publications describe 1,3-dipolar cycloadditions between ethyl trifluorocrotonate and diazomethane, a nitrone or a nitrile oxide leading, respectively, to 4,5-dihydropyrazoles,[23] isoxazolidines[24] or 4,5-dihydroisoxazoles.[25] Moreover, cycloadditions of 5,5-dimethyl-3-methylenepyrrolidin-2-one with a nitrone or a nitrile oxide are reported to afford regioselectively spirocyclic isoxazolidines[26] or isoxazolines.[27]

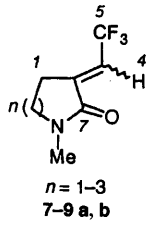
Reaction with diazomethane. Treatment of the pyrrolidinone **7** with an ethereal solution of diazomethane at 0 °C gives trifluoromethylated spirocyclic pyrazoline **11** in modest yield (Scheme 3). It is worth noting that we detected only one regio- and diastereo-isomer after purification by chromatography on silica gel.

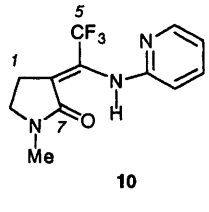


Scheme 3 *Reagents and conditions:* CH_2N_2, Et_2O, 0–25 °C

The regiochemistry of cycloadduct **11** was assigned based on its long-range ^1H–^{13}C couplings. Indeed, the value of the carbon–proton coupling constant [^3J(C-17, H-3) = 6.1 Hz; ^3J(C-17, H-3′) = 6.0 Hz] confirmed the regiochemistry of this 4,5-dihydro-3*H*-pyrazole **11**. It was not possible, however, to determine the *relative* configuration of compound **11** using NMR techniques. Nevertheless, based on X-ray diffraction analysis of compound **12** (Fig. 1) and on comparison of ^{13}C NMR data between compounds **11** and **12** [especially $\delta(^{19}F)$, δ(C-9), δ(C-17) and ^4J(C-9,F)] (Table 4), we favour for compound **11** the geometry (4*S*,5*S*) and (4*R*,5*R*) where the CF_3

Table 3 ^{19}F and ^{13}C NMR data of lactams **7–9**,[a] **10**[b]

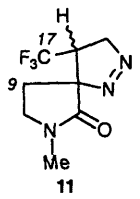




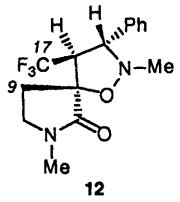
n	Compound (stereochemistry)	Selectivity (%)	$\delta(^{19}F)$	δ(C-1)	δ(C-5)	δ(C-7)
1	**7a** (*E*)	95	−61.4	21.8	122.9	165.7
	7b (*Z*)	5	−56.0			
2	**8a** (*E*)	95	−59.1	25.0	123.2	162.1
	8b (*Z*)	5	−57.6			
3	**9a** (*E*)	70	−61.1	26.6	122.8	169.7
	9b (*Z*)	30	−59.1			
	10 (*Z*)	100	−63.6	22.8	121.8	169.9

[a] Selectivity: major/minor. [b] The configuration of compound **10** was determined by X-ray diffraction analysis.

Table 4 ^{19}F and ^{13}C NMR data of compounds **11**, **12**



11



12

Compound	$\delta(^{19}F)$	δ(C-9)	δ(C-17)	^4J(C-9,F)
11	−65.6	27.5	126.0	2.4
12	−67.0	25.0	125.6	2.5

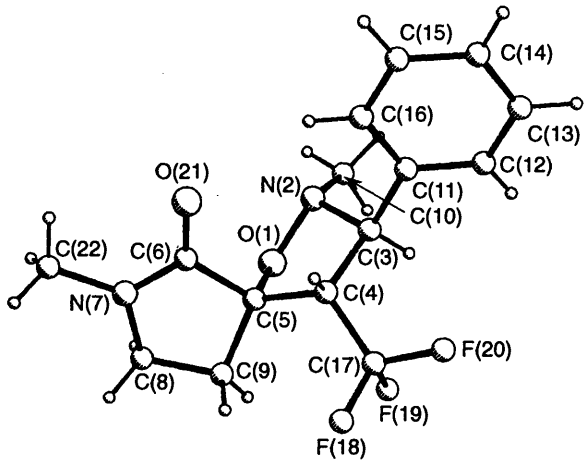
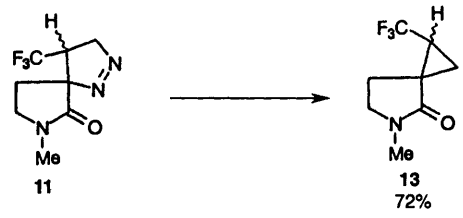


Fig. 1 View of compound **12** (PLUTO)[31]

group and the C-9 of the pyrrolidinone ring point in the same direction.

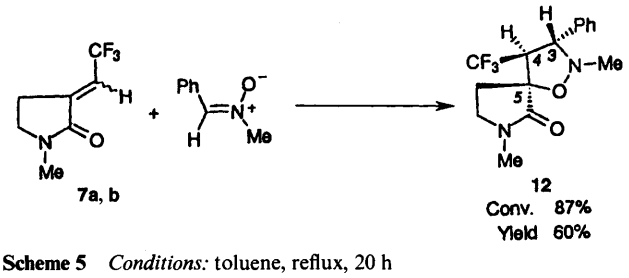
Since 4-trifluoromethylpyrazolines are known to decompose into cyclopropanes,[28] we thermolysed the heterocycle **11** and indeed obtained the 5-azaspiro[2,4]heptane **13** as a unique diastereoisomer (Scheme 4).



11 → **13** 72%

Scheme 4 *Conditions:* 160–170 °C, 12 h

Reactions with *N*-methyl-α-phenylnitrone. Cycloaddition between *N*-methyl-α-phenylnitrone[29] and 3-(trifluoroethylidene)pyrrolidin-2-one **7a,b** (more than 95% of the *E* configuration) afforded after 20 h, the isoxazolidine **12** in 60% yield (Scheme 5). The reaction is again regio- and stereo-selective.



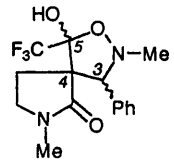
7a, b → **12** Conv. 87% Yield 60%

Scheme 5 *Conditions:* toluene, reflux, 20 h

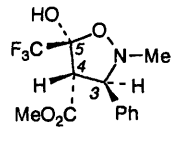
We note that we did not detect the other diastereoisomer after chromatography on silica gel.

First, we assigned the regiochemistry of 5-spiroisoxazolidine

Table 5 ^{13}C NMR data of heterocycles **14a,b** and **15**



14a, b

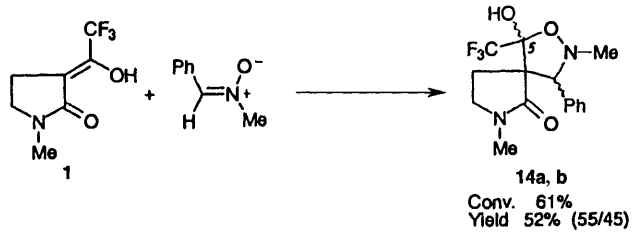


15

Compound	δ(C-3)	δ(C-4)	δ(C-5)	$\delta(CF_3)$
14a	76.1	59.2	101.1	121.9
14b	83.8	62.5	101.5	121.6
15	75.1	58.7	98.1	120.1

12 from its NMR data: the value of δ(C-5) = 82.0 indicates clearly that it carries the isoxazolidine ring oxygen. Also we found that the value of proton–proton coupling constant [^3J(H-3,H-4) = 9.4 Hz] strongly indicates the *trans* relationship between these two hydrogen atoms. The configuration of compound **12** was then determined by X-ray diffraction analysis as being (3*R**,4*S**,5*S**) (Fig. 1). Moreover, based on the well known '*cis*-stereospecificity' of 1,3-dipolar cycloadditions,[30] this confirms also the *trans* relationship between the trifluoromethyl group and the carbonyl function in the starting 3-(trifluoroethylidene)pyrrolidinone **7a**. Such diastereospecificity is not observed with 4,4,4-trifluorocrotonic esters[24,25] or 3-methylenepyrrolidin-2-one[27] which afford, in general, mixtures of regio- and diastereo-isomers.

In this context, we have also examined the 1,3-dipolar cycloaddition between the 3-(trifluoroacetyl)pyrrolidinone **1** (more than 95% of enol form in its *Z* configuration) and *N*-methyl-α-phenylnitrone (Scheme 6). Here, the isoxazolidine **14**



1 → **14a, b** Conv. 61% Yield 52% (55/45)

Scheme 6 *Conditions:* toluene, reflux, 25 h

is obtained as a mixture (55/45) of two diastereoisomers, **14a** and **14b**.

The structure of product **14a,b** was assigned by comparison of ^{13}C NMR data with the known cycloadduct analogue **15**[32] (Table 5). Indeed, ^{13}C NMR showed an hemiketal signal at δ(C-5) 101.1 (q, $^2J_{C,F}$ 32.5 Hz) for **14a** and δ(C-5) 101.5 (q, $^2J_{C,F}$ 31.6 Hz) for **14b**, which confirms the C-5 position of the trifluoromethyl group. These observations are in good agreement with the literature [compound **15**: δ(C-5) 98.1 (q, $^2J_{C,F}$ 33 Hz)].[32] Moreover, the chemical shifts [δ(C-3, C-4, CF_3)] of isoxazolidines **14a,b** and **15** are very similar (Table 5). These two arguments confirm the regiochemistry of cycloadducts **14a,b**, and consequently these heterocycles are diastereoisomers. Nevertheless, it was impossible to obtain suitable crystals and to determine their structure by X-ray diffraction analysis.

It is worth noting that this result is quite different from that reported for ethyl 4,4,4-trifluoroacetoacetate and *N*-methyl-α-phenylnitrone, which give exclusively one diastereoisomer.[32]

Conclusions

3-(2,2,2-Trifluoroethylidene)-lactams **7–9a,b** were obtained from 3-trifluoroacetyl-substituted lactams **1–3** by using a reduction–dehydration sequence. We attribute the *E* configuration to their major stereoisomers. Moreover, the 3-(2,2,2-

trifluoroethylidene)pyrrolidinone **7a,b** turned out to be a useful reagent for 1,3-dipolar cycloadditions with diazomethane and *N*-methyl-α-phenylnitrone. The structure of trifluoromethylated pyrazoline **11** and isoxazolidines **14a,b** was assigned by comparison of their ^{13}C NMR data, whereas the configuration of spirocyclic isoxazolidine **12**, was determined by X-ray diffraction analysis.

Experimental

Mps were taken using a Dr Tottoli apparatus and are uncorrected. IR and mass spectra were measured on a Perkin-Elmer 1710 and a Finnigan Mat TSQ 70 apparatus, respectively. The 1 H, ^{13}C and ^{19}F NMR spectra were run on a Bruker AM500 spectrometer at 500.13 MHz (^{1}H) and 125.77 MHz (^{13}C) or with Varian VXR-200 and Gemini-200 spectrometers at 200 MHz (^{1}H), 188.2 MHz (^{19}F) and 50.3 MHz (^{13}C), using 5 mm probes. The tetramethylsilane (TMS) signal was taken as internal reference for ^{1}H and ^{13}C spectra, while $CFCl_3$ was used as an internal reference for the ^{19}F spectra. The ^{13}C NMR spectra were obtained from proton-coupled or proton-noise-decoupled spectra. In coupled spectra, many signals were observed as multiplets due to long-range coupling to fluorine; *J*-values for these multiplets are marked with an asterisk. For compounds **6a,b**, **11**, **13** unambiguous assignments were obtained by use of the two-dimensional ^{1}H–^{13}C heteronuclear chemical-shift correlation spectroscopy.[33,34] For the ^{1}J connectivities, we have assumed an average one-bond carbon–proton coupling constant of ~135 Hz [fixed delays durations: $\Delta_1 = \frac{1}{2}$ ($^{1}J_{CH}$) = 3.6 ms $\Delta_2 = \frac{1}{4}$ ($^{1}J_{CH}$) = 1.8 ms]. For the long-range ^{1}H–^{13}C connectivities, we have chosen averaged ^{13}C–^{1}H coupling constants of ~12.5 Hz [fixed delays: $\Delta_1 = \frac{1}{2}$ ($^{n}J_{CH}$) = 40 ms; $\Delta_2 = \frac{1}{4}$ ($^{n}J_{CH}$) = 20 ms]. The two-dimensional data were submitted to a Lorentz–Gauss transformation[33,34] in the t_1 dimension and to a sinusoidal multiplication[33,34] in the t_2 dimension prior to Fourier transformation ('power' spectrum calculation in all cases). We have also used the double-quantum filtered correlation spectroscopy (DQF-COSY)[33,35] to verify or to assign some of the ^{1}H resonances. The DQF-COSY experiments have been acquired using the TPPI (time-proportional phase incrementation)[33,34,36] and transformed in the phase-sensitive mode.[33,34,36] Chemical shifts are in ppm on the δ scale and coupling constants *J* are given in Hz. The following abbreviations are used: qt, quintet; sx, sextet and sp, septet. Light petroleum refers to the fraction with distillation range 40–60 °C.

General procedure for the preparation of compounds 4–6

To a cooled solution (0 °C) of distilled 3-trifluoroacetyl-substituted lactams **1**, **2** or **3** (10 mmol, 1 mol equiv.) in dry methanol (20 cm^3), was added sodium borohydride (10–15 mmol, 1.0–1.5 mol equiv.) in several portions. The temperature was maintained at 0 °C for 30 min, then was allowed to rise to ambient (1 h). After dilution with diethyl ether (50 cm^3) and hydrolysis with aq. NH_4Cl (15 cm^3) and 1 mol dm^{-3} HCl (3 cm^3) until pH = 6, the mixture was extracted twice with diethyl ether (2 × 50 cm^3). The combined organic phase was then washed with brine (30 cm^3), dried over $MgSO_4$, and evaporated. The crude product was purified by recrystallization (for **4**), by distillation using a Kugelrohr apparatus (for **5**) or by chromatography on silica gel (for **6**).

Preparation of 1-methyl-3-(2,2,2-trifluoro-1-hydroxyethyl)-pyrrolidin-2-one 4. The reaction of 1-methyl-3-(trifluoroacetyl)-pyrrolidin-2-one **1** (19.50 g, 100 mmol) with $NaBH_4$ (3.78 g, 100 mmol) gave, after recrystallization from diethyl ether–light petroleum (60:40), the title compound **4** (15.96 g, 81%) as a mixture (95/5) of two diastereoisomers.

Major diastereoisomer **4a**: mp 65–67 °C, $\delta_H(CDCl_3)$ 1.8–2.0 (1 H, m), 2.2–2.4 (1 H, m), 2.6–3.0 (1 H, m), 2.91 (3 H, s), 3.3–3.5 (2 H, m), 4.09 (1 H, qd, J_F 10.2, *J* 6.2) and 6.39 (OH, br s); $\delta_C(CDCl_3)$ 21.9 (t, *J* 133.6, $*J_F$ 2.0), 29.3 (q, *J* 138.9, $*J_F$ 1.4), 39.6 (d, *J* 131.1, $*J_F$ 1.6), 47.5 (t, *J* 143.2, $*J_F$ 1.3), 72.1 (dq, *J* 147.4, J_F 31.1), 124.1 (qdd, J_F 280.9, *J* 7.9 and 3.6) and 174.7 (s); $\delta_F(CDCl_3)$ −79.0 (d, *J* 6.5); ν_{max}(KBr)/cm^{-1} 3400–3200, 2972, 2956, 2896, 1665, 1506, 1476, 1410 and 1276; *m/z* (EI) 198, 197 (M^+), 177 (M^+ − HF), 128 (M^+ − CF_3), 99, 98, 69 (CF_3^+) and 44 (Found: C, 42.45; H, 5.1; N, 7.0. $C_7H_{10}F_3NO_2$ requires C, 42.64; H, 5.11; N, 7.10%).

Minor diastereoisomer **4b**: selected $\delta_H(CDCl_3)$ 3.01 (3 H, s), 4.55 (1 H, qd, J_F 10.0, *J* 6.3) and 5.10 (OH, br s); $\delta_F(CDCl_3)$ −77.7 (d, *J* 7.8).

Preparation of 1-methyl-3-(2,2,2-trifluoro-1-hydroxyethyl)-piperidin-2-one 5. The reaction of 1-methyl-3-(trifluoroacetyl)-piperidin-2-one **2** (1.25 g, 6.0 mmol) with $NaBH_4$ (0.34 g, 9.0 mmol) gave, after distillation using a Kugelrohr apparatus, the title compound **5** (1.05 g, 83%) as a mixture (80/20) of two diastereoisomers.

Major diastereoisomer **5a**: bp 90–95 °C/0.03 mmHg, $\delta_H(CDCl_3$; 500 MHz) 1.59 (1 H, dddd, *J* 12.6, 12.5, 12.2 and 3.4), 1.72–1.84 (1 H, m), 1.92–1.98 (2 H, m), 2.55 (1 H, ddd, *J* 11.3, 8.9 and 6.1), 2.94 (3 H, s), 3.2–3.4 (2 H, m), 4.09 (1 H, qd, *J* 8.8, J_F 7.1) and 6.6 (OH, br s); $\delta_C(CDCl_3)$ 21.2 (t, *J* 131.6), 22.6 (t, *J* 131.3, $*J_F$ 2.5), 34.6 (qd, *J* 139.2 and 2.4, $*J_F$ 1.3), 41.5 (d, *J* 128.7, $*J_F$ 1.3), 49.2 (t, *J* 140.3), 71.2 (dq, *J* 146.6, J_F 30.3), 124.4 (qddd, J_F 282.2, *J* 6.5, 4.0 and 3.9) and 170.6 (s); $\delta_F(CDCl_3)$ −76.2 (d, *J* 7.1); ν_{max}(film)/cm^{-1} 3500–3100, 2952, 2877, 1624, 1507, 1470, 1452, 1406 and 1269; *m/z* (EI) 212, 211 (M^+), 191 (M^+ − HF), 163, 142 (M^+ − CF_3), 112, 98, 69 (CF_3^+) and 44 (Found: C, 45.3; H, 5.9; N, 6.5. $C_8H_{12}F_3NO_2$ requires C, 45.50; H, 5.73; N, 6.63%).

Minor diastereoisomer **5b**: selected $\delta_H(CDCl_3$; 500 MHz) 2.02–2.08 (2 H, m), 2.63 (1 H, ddd, *J* 8.8, 8.4 and 1.8), 2.92 (3 H, s), 4.74 (1 H, qd, J_F 8.2, *J* 2.5) and 5.0–5.2 (OH, br m); $\delta_C(CDCl_3$; decoupled spectrum) 20.0, 21.5 (J_F 1.9), 34.9, 42.5, 49.5, 68.5 (J_F 30.4), 125.4 (J_F 283.0) and 169.2; $\delta_F(CDCl_3)$ −75.3 (d, *J* 7.9).

Preparation of 1-methyl-3-(2,2,2-trifluoro-1-hydroxyethyl)-azepan-2-one 6. The reaction of 1-methyl-3-(trifluoroacetyl)-azepan-2-one **3** (1.20 g, 5.4 mmol) with $NaBH_4$ (0.20 g, 5.4 mmol) gave, after chromatography on silica gel [eluent: diethyl ether–light petroleum (70:30)], the title compound **6** (1.02 g, 84%) as a mixture (95/5) of two diastereoisomers.

Major diastereoisomer **6a**: mp 75–77 °C, $\delta_H(CDCl_3$, 500 MHz) 1.49 (1 H, ttdd, *J* 11.5, 11.1, 3.7 and 2.8), 1.66 (1 H, tt, *J* 11.7 and 11.6), 1.72–1.82 (2 H, m), 1.88 (1 H, d, *J* 14.2), 1.96 (1 H, dqt, *J* 13.6 and 4.1), 2.88 (1 H, ddd, *J* 10.7, 2.9 and 2.7), 2.98 (3 H, s), 3.16 (1 H, dddd, *J* 15.4, 5.2, 2.7 and 0.8), 3.68 (1 H, ddd, *J* 15.4, 11.6 and 1.6), 3.99 (1 H, qd, J_F 7.7, *J* 3.5) and 6.5 (OH, br m); $\delta_C(CDCl_3$, 126 MHz) 25.6 (t, *J* 125.8), 27.7 (t, *J* 126.0), 28.3 (t, *J* 136.4, $*J_F$ 1.0), 34.7 (qdd, *J* 138.8, 4.2 and 4.0, $*J_F$ 1.4), 40.0 (d, *J* 125.3, $*J_F$ 1.3), 49.9 (t, *J* 138.6), 74.5 (dq, *J* 144.4, J_F 30.3), 124.8 (qddd, J_F 284.1, *J* 4.9, 1.8 and 1.6) and 175.7 (s); $\delta_F(CDCl_3)$ −76.9 (d, *J* 7.6); ν_{max}(KBr)/cm^{-1} 3500–3100, 2953, 2936, 2895, 1632, 1498 and 1404; *m/z* (EI) 226, 225 (M^+), 205 (M^+ − HF), 156 (M^+ − CF_3), 127, 112, 98, 69 (CF_3^+) and 42 (Found: C, 48.0; H, 6.2; N, 6.1. $C_9H_{14}F_3NO_2$ requires C, 48.00; H, 6.27; N, 6.22%).

Minor diastereoisomer **6b**: selected $\delta_H(CDCl_3$, 500 MHz) 3.00 (3 H, s), 4.53 (1 H, q, J_F 9.1); selected $\delta_C(CDCl_3$, 126 MHz) 69.5 (J_F 29.8); $\delta_F(CDCl_3)$ −75.6 (d, *J* 6.4).

General procedure for the preparation of compounds 7–9

A mixture of 3-(2,2,2-trifluoro-1-hydroxyethyl)-substituted lactams **4**, **5** or **6** (4 mmol, 1 mol equiv.) and diphosphorus pentoxide (8–12 mmol, 2–3 mol equiv.) was thermolysed under reduced pressure (0.01–0.03 mmHg), using a Büchi Kugelrohr apparatus, to give 3-(2,2,2-trifluoroethylidene)-substituted lactams **7**, **8** or **9** as a mixture of two stereoisomers.

Preparation of 1-methyl-3-(2,2,2-trifluoroethylidene)pyrrolidin-2-one 7. The thermolysis of the 3-(2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-2-one **4** (0.79 g, 4 mmol) and diphosphorus pentoxide (1.70 g, 12 mmol) gave the title compound **7** (0.52 g, 72%) as a mixture (95/5) of two stereoisomers.

Major stereoisomer **7a**: bp 40–50 °C/0.01 mmHg, $\delta_H(CDCl_3)$ 2.9–3.1 (2 H, m), 3.03 (3 H, s), 3.53 (2 H, dd, *J* 6.3 and 6.2) and 6.47 (1 H, qdd, J_F 8.4, *J* 3.2 and 3.0); $\delta_C(CDCl_3)$ 21.8 (tdt, *J* 136.1, 7.1 and 3.5), 29.8 (q, *J* 139.2, $*J_F$ 1.5), 46.3 (t, *J* 143.5), 116.5 (dqt, *J* 170.0, J_F 35.3, *J* 4.1), 122.9 (qdt, J_F 270.0, *J* 3.6 and 1.9), 142.1, $*J_F$ 5.0) and 165.7 (s); $\delta_F(CDCl_3)$ −61.4 (dt, *J* 7.6 and 3.6); ν_{max}(film)/cm^{-1} 2947, 2935, 2897, 1699, 1652, 1504, 1360, 1269 and 1122; *m/z* (EI) 180, 179 (M^+), 159 (M^+ − HF), 136, 108, 89, 69 (CF_3^+) and 42 (Found: C, 47.0; H, 4.8; N, 7.9. $C_7H_8F_3NO$ requires C, 46.93; H, 4.50; N, 7.82%).

Minor stereoisomer **7b**: $\delta_F(CDCl_3)$ −56.0 (dt, *J* 8.6 and 3.4).

Preparation of 1-methyl-3-(2,2,2-trifluoroethylidene)piperidin-2-one 8. The thermolysis of the 3-(2,2,2-trifluoro-1-hydroxyethyl)piperidin-2-one **5** (0.47 g, 2.3 mmol) and diphosphorus pentoxide (0.63 g, 4.6 mmol) gave the title compound **8** (0.36 g, 84%) as a mixture (95/5) of two stereoisomers.

Major stereoisomer **8a**: bp 125–130 °C/0.03 mmHg, $\delta_H(CDCl_3)$ 1.93 (2 H, m), 2.7–2.8 (2 H, m), 3.07 (3 H, s), 3.43 (2 H, dd, *J* 5.9 and 5.8) and 6.83 (1 H, q, J_F 8.9); $\delta_C(CDCl_3)$ 21.4 (tdd, *J* 130.8, 4.5 and 3.7), 25.0 (t, *J* 130.6, $*J_F$ 1.3), 35.7 (qdd, *J* 139.2, 1.8 and 1.7), 49.5 (t, *J* 140.2), 122.2 (dqt, *J* 170.2, J_F 34.6, *J* 4.0), 123.2 (qdt, J_F 271.0, *J* 3.8 and 1.6), 140.4 (s, $*J_F$ 5.2) and 162.1 (s); $\delta_F(CDCl_3)$ −59.1 (d, *J* 7.6); ν_{max}(film)/cm^{-1} 2942, 2875, 1682, 1635, 1500, 1406, 1366, 1319 and 1269; *m/z* (EI) 194, 193 (M^+), 173 (M^+ − HF), 165, 145, 126, 122, 96, 69 (CF_3^+) and 44 (Found: C, 50.0; H, 5.3; N, 7.3. $C_8H_{10}F_3NO$ requires C, 49.74; H, 5.22; N, 7.25%).

Minor stereoisomer **8b**: $\delta_F(CDCl_3)$ −57.6 (d, *J* 7.2).

Preparation of 1-methyl-3-(2,2,2-trifluoroethylidene)azepan-2-one 9. The thermolysis of the 3-(2,2,2-trifluoro-1-hydroxyethyl)azepan-2-one **6** (0.45 g, 2.0 mmol) and diphosphorus pentoxide (0.57 g, 4.0 mmol) gave the title compound **9** (0.28 g, 68%) as a mixture (70/30) of two stereoisomers.

Major stereoisomer **9a**: bp 105–110 °C/0.01 mmHg, $\delta_H(CDCl_3)$ 1.6–2.0 (4 H, m), 2.5–2.6 (2 H, m), 3.04 (3 H, s), 3.3–3.4 (2 H, m) and 6.00 (1 H, q, J_F 8.4); $\delta_C(CDCl_3)$ 25.6 (t, *J* 129.4), 26.6 (t, *J* 130.6), 34.6 (qdd, *J* 138.7, 3.8 and 3.7, $*J_F$ 1.7), 49.5 (t, *J* 137.6), 119.1 (dqt, *J* 168.1, J_F 34.6, *J* 4.8), 122.8 (qd, J_F 271.5, *J* 3.7), 151.1 (s, $*J_F$ 5.2) and 169.7 (s); ν_{max}(film)/cm^{-1} 2939, 2868, 1648, 1639, 1489, 1434, 1400, 1367, 1285 and 1169; *m/z* (EI) 208, 207 (M^+), 187 (M^+ − HF), 159, 138 (M^+ − CF_3), 108, 95, 69 (CF_3^+) and 44 (Found: C, 52.2; H, 5.9; N, 6.6. $C_9H_{12}F_3NO$ requires C, 52.17; H, 5.84; N, 6.76%).

Minor stereoisomer **9b**: selected $\delta_H(CDCl_3)$ 2.3–2.4 (2 H, m), 3.07 (3 H, s) and 5.69 (1 H, q, J_F 7.6); $\delta_F(CDCl_3)$ −59.1 (d, *J* 7.8).

1,3-Dipolar cycloadditions

Reaction with diazomethane: preparation of 7-methyl-4-trifluoromethyl-1,2,7-triazaspiro[4,4]non-1-en-6-one 11. To a cooled solution (0 °C) of the 3-(2,2,2-trifluoroethylidene)pyrrolidin-2-one **7** (0.90 g, 5 mmol) in diethyl ether (5 cm^3) was added an ethereal solution of diazomethane (5 M; 20 cm^3, 100 mmol). The temperature was allowed to reach 25 °C and the mixture was maintained at room temperature for 3 h. After evaporation of volatiles, the crude mixture was chromatographed on silica gel [eluent: diethyl ether, then methanol–diethyl ether (5:95)] to furnish the *spirocyclic pyrrolidinone* **11** (0.51 g, 46%) as an oil, $\delta_H(CDCl_3$; 500 MHz) 2.33 (1 H, dd, *J* 13.7 and 6.8), 2.49 (1 H, ddd, *J* 13.8, 8.7 and 8.6), 2.82 (3 H, s), 3.07 (1 H, dqd, *J* 10.3, J_F 10.1, *J* 4.9), 3.39 (1 H, ddd, *J* 9.5, 9.0 and 1.8), 3.81 (1 H, ddd, *J* 9.2, 8.8 and 7.1) and 4.65–4.80 (2 H, m); $\delta_C(CDCl_3$; 126 MHz) 25.0 (t, *J* 136.6, $*J_F$ 2.5), 29.9 (q, *J* 139.0), 40.1 (dqtd, *J* 139.1, J_F 28.6, *J* 1.9 and 1.8), 47.0 (t, *J* 144.6), 78.1 (tqd, *J* 144.9, J_F 1.7, *J* 1.5), 96.8 (dq, *J* 5.1, J_F 3.3), 125.6 (qtd, J_F 278.3, *J* 6.1 and 6.0) and 168.1 (s); $\delta_F(CDCl_3)$ −67.0 (d, *J* 10.1); ν_{max}(film)/cm^{-1} 2934, 2892, 1708, 1560, 1501, 1436, 1408, 1304 and 1185; *m/z* (EI) 222, 221 (M^+), 193 (M^+ − N_2), 192, 172, 144, 124, 122, 98, 67 and 42 (Found: C, 43.2; H, 4.6; N, 18.8. $C_8H_{10}F_3N_3O$ requires C, 43.44; H, 4.56; N, 18.99%).

Thermolysis of pyrazoline 11: preparation of 5-methyl-4-oxo-1-trifluoromethyl-5-azaspiro[2,4]heptane 13. The pyrazoline **11** (0.33 g, 1.5 mmol) was heated under argon (160–170 °C) for 12 h. After cooling, the crude was purified by chromatography on silica gel [eluent: AcOEt–light petroleum (60:40)] to give the oily heterocycle **12** (0.21 g, 72%) as one diastereoisomer, $\delta_H(CDCl_3)$ 1.13 (1 H, dd, *J* 5.9 and 5.5), 1.39 (1 H, ddd, *J* 5.8, 4.3 and 1.0), 2.0–2.2 (2 H, m), 2.3–2.5 (1 H, m), 2.91 (3 H, s) and 3.4–3.6 (2 H, m); $\delta_C(CDCl_3)$ 14.5 (t, *J* 165.5, $*J_F$ 2.9), 22.1 (t, *J* 135.1, $*J_F$ 1.6), 23.2 (dq, *J* 167.2, J_F 36.6), 30.0 (q, *J* 138.2), 46.5 (t, *J* 142.6), 97.0 (s), 125.5 (qdd, J_F 271.5, *J* 6.0 and 4.0) and 172.9 (s); $\delta_F(CDCl_3)$ −63.6 (d, *J* 7.6); ν_{max}(film)/cm^{-1} 2934, 2886, 1698, 1505, 1439, 1407, 1311 and 1140; *m/z* (EI) 194, 193 (M^+), 192, 173 (M^+ − HF), 172, 136, 124 (M^+ − CF_3), 110, 69 (CF_3^+), 67 and 42 (Found: C, 49.85; H, 5.3; N, 7.5. $C_8H_{10}F_3NO$ requires C, 49.74; H, 5.22; N, 7.25%).

Reactions with *N*-methyl-α-phenylnitrone: general procedure for the preparation of compounds 13 and 14. A mixture of pyrrolidin-2-one **7** or **1** (5 mmol, 1 mol equiv.) and *N*-methyl-α-phenylnitrone (5 mmol, 1 mol equiv.) in dry toluene (5 cm^3) was refluxed for 20–25 h. After evaporation of the mixture, the crude residue was chromatographed on silica gel to give the isoxazolidine **12** or **14**.

Preparation of 2,7-dimethyl-6-oxo-3-phenyl-4-trifluoromethyl-1-oxa-2,7-diazaspiro[4,4]nonane 12. The reaction of 3-(2,2,2-trifluoroethylidene)pyrrolidin-2-one **7** (0.90 g, 5 mmol) and *N*-methyl-α-phenylnitrone (0.68 g, 5 mmol) gave, after chromatography on silica gel [eluent: diethyl ether–light petroleum (80:20), then methanol–diethyl ether (5:95)] and recrystallization from a mixture of AcOEt–light petroleum, the *title compound* **12** (0.94 g, 60%) as one diastereoisomer, mp 106–108 °C; $\delta_H(CDCl_3$; 500 MHz) 2.17 (1 H, dd, *J* 13.9 and 5.9), 2.41 (1 H, ddd, *J* 14.0, 8.6 and 8.5), 2.44 (3 H, s), 2.88 (3 H, s), 3.17 (1 H, ddd, *J* 9.2, 9.0 and 1.1), 3.46–3.53 (1 H, m), 3.54 (1 H, d, *J* 9.4), 3.86 (1 H, dq, *J* 9.5, J_F 9.3), 7.26 (1 H, d, *J* 7.1), 7.30 (2 H, ddd, *J* 7.7, 6.8 and 1.6) and 7.58 (2 H, dd, *J* 7.5 and 0.9); $\delta_C(CDCl_3$; 126 MHz) 27.5 (t, *J* 135.0, $*J_F$ 2.4), 30.0 (q, *J* 138.5, $*J_F$ 1.1), 42.5 (q, *J* 136.1), 46.0 (t, *J* 143.9), 57.5 (dq, *J* 136.7, J_F 26.1), 75.2 (d, *J* 137.6, $*J_F$ 2.0), 82.0 (s, $*J_F$ 1.4), 126.0 (qdd, J_F 278.7, *J* 5.5 and 5.4), 128.5 (3 C, d, *J* 159.8), 128.6 (d, *J* 160.1), 136.3 (s) and 171.4 (s); $\delta_F(CDCl_3)$ −65.6 (d, *J* 9.8); ν_{max}(KBr)/cm^{-1} 3054, 3004, 2994, 2968, 2868, 1698, 1498, 1463, 1436, 1405 and 1389; *m/z* (EI) 315, 314 (M^+), 242, 200, 172, 134, 118, 77 ($C_6H_5^+$) and 42 (Found: C, 57.2; H, 5.3; N, 8.9. $C_{15}H_{17}F_3N_2O_2$ requires C, 57.32; H, 5.45; N, 8.91%).

The crystallographic data are as follows: $C_{15}H_{17}F_3N_2O_2$, M_r = 314.31, monoclinic, *C*2/*c*, *a* = 21.486(2), *b* = 9.504(1), *c* = 15.971(1) Å, β = 113.03(1)°, *V* = 3001.4(3) Å^3, *Z* = 8, D_x = 1.39 g cm^{-3}. Crystals were obtained by slow evaporation from a light petroleum–acetone mixture. Parallelepiped crystals with dimensions 0.20 × 0.32 × 0.40 mm. Lattice parameters refined using 30 reflections in the range 25° ⩽ 2θ ⩽ 60°. Huber four-circle diffractometer and Rigaku rotating anode, graphite-monochromatized Cu-Kα radiation (λ = 1.5418 Å) were used. 2716 Measured reflections, with $\sin\theta/\lambda \leqslant 0.60$ Å^{-1}; $-25 \leqslant h \leqslant 23$, $0 \leqslant k \leqslant 11$, $0 \leqslant l \leqslant 17$, 2470 with $I \geqslant 2.0\sigma(I)$. A standard reflection (1 5 3) was checked every 50 reflections, no significant deviation was observed. Structure was solved by direct methods using SHELXS86.[37] All H-atoms from difference Fourier synthesis. Anisotropic least-squares refinement (SHELXL93)[38] using *F*; H isotropic with common refined temperature factor (*U* = 0.068 Å^2). 252 Parameters. Extinction coefficient = 0.0075(3). $w = 1/(\sigma^2(F_o)^2 +$

$0.0534P^2 + 1.76P$), $R = 0.039$, wR_2 (all data) = 0.11, $S = 1.12$. Final maximum shift-to-error = 0.001. Maximum and minimum heights in final difference Fourier synthesis = 0.25 and -0.16 e Å^{-3}. Atomic scattering factors were from ref. 39. Complete X-ray data have been deposited with the Cambridge *Crystallo*graphic Data Centre.†

Preparation of 3,7-dimethyl-1-hydroxy-6-oxo-4-phenyl-1-trifluoromethyl-2-oxa-3,7-diazaspiro[4,4]nonane 14. The reaction of 3-(trifluoroacetyl)pyrrolidin-2-one **1** (more than 95% of enol form in its *Z* configuration, 0.98 g, 5 mmol) and *N*-methyl-α-phenylnitrone (0.68 g, 5 mmol) gave, after chromatography on silica gel [eluent: diethyl ether–light petroleum (90:10), then methanol–diethyl ether (5:95)], the title compound **14** (0.86 g, 52%) as a mixture (55/45) of two diastereoisomers, and the hydrate of the 3-(trifluoroacetyl)pyrrolidin-2-one (0.42 g, 39%) was also recovered.

Major diastereoisomer **14a**: mp 133–134 °C, $\delta_H(CDCl_3)$ 1.6–1.7 (1 H, m), 2.32 (1 H, dd, *J* 12.8 and 5.5), 2.78 (3 H, s), 2.90 (3 H, s), 2.7–3.0 (2 H, m), 4.48 (1 H, s), 7.3–7.4 (5 H, m) and 8.39 (OH, br s); $\delta_C(CDCl_3)$ 21.4 (t, *J* 136.0, J_F 3.3), 29.8 (q, *J* 139.3), 45.4 (qd, *J* 136.9 and 6.1), 45.8 (t, *J* 144.3), 59.2 (s), 76.1 (d, *J* 140.9), 101.1 (q, J_F 32.5), 121.9 (qd, J_F 286.5, *J* 1.9), 127.3 (d, *J* 159.8), 128.6 (ddd, *J* 161.0, 7.1 and 1.9), 129.1 (dt, *J* 161.4 and 6.9), 132.3 (s) and 172.7 (s); $\delta_F(CDCl_3)$ −77.7 (s); ν_{max}(KBr)/cm^{-1} 3130, 3061, 3035, 2974, 2946, 2893, 1674, 1503, 1456, 1442, 1410 and 1308; *m/z* (EI) 330 (M^+), 297, 200, 136, 134, 118, 91; 77 ($C_6H_5^+$) and 42 (Found: C, 54.4; H, 5.3; N, 8.5. $C_{15}H_{17}F_3N_2O_3$ requires C, 54.54; H, 5.19; N, 8.48%).

Minor diastereoisomer **14b**: mp 153–154 °C, $\delta_H(CDCl_3)$ 2.25 (1 H, dd, *J* 12.1 and 5.0), 2.41 (3 H, s), 2.60 (3 H, s), 2.5–2.8 (2 H, m), 2.93 (1 H, dd, *J* 9.3 and 7.8), 3.75 (1 H, s), 7.3–7.4 (5 H, m) and 7.84 (OH, br s); $\delta_H(CDCl_3$; decoupled spectrum) 26.8 (J_F 3.2), 29.3, 43.1, 45.8, 62.5, 83.8, 101.5 (q, J_F 31.6), 121.6 (q, J_F 285.3), 128.3, 128.5, 129.6, 132.6 and 172.5; $\delta_F(CDCl_3)$ −79.7 (s); ν_{max}(KBr)/cm^{-1} 3400–3100, 3070, 3035, 3004, 2963, 2919, 2881, 1669, 1503, 1456, 1410 and 1316.

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