HETEROCYCLISATION OF 3-TRIFLUOROACETYLLACTAMS BY HYDRAZINES

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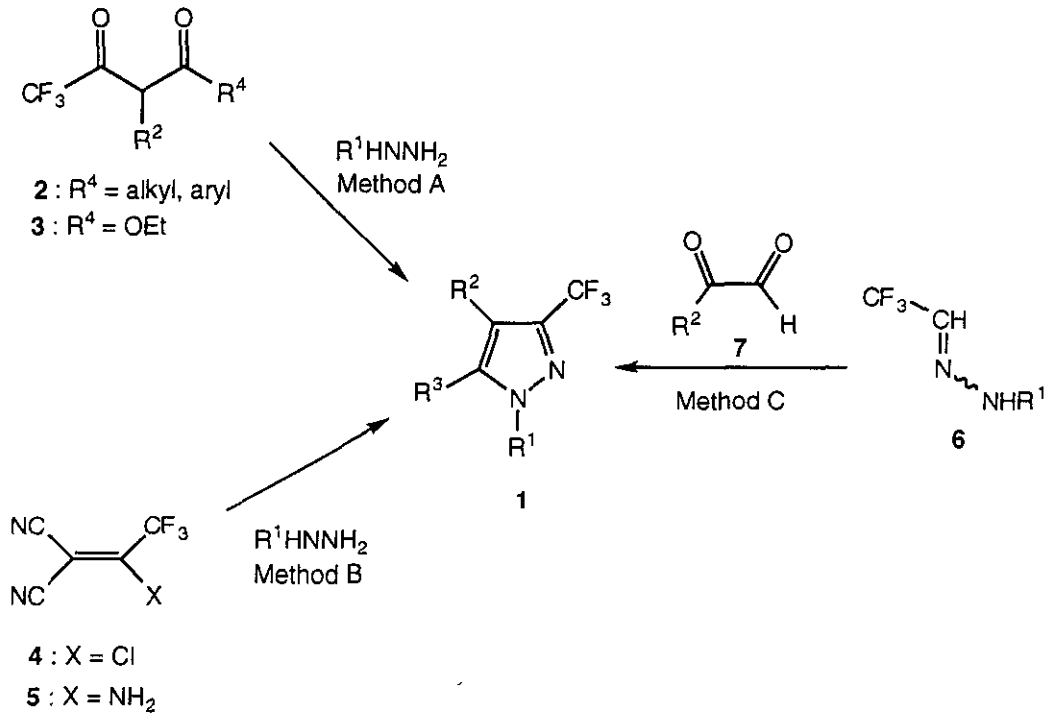
Dedicated to Prof. R. Huisgen on the occasion of his 75th birthday.

Abstract - 3-Trifluoroacetyllactams may heterocyclize with hydrazine or with its methyl or phenyl derivative either without ring opening to annelated trifluoromethylpyrazoles or by Ring Opening - Ring Closure (RORC) reaction to zwitterionic salts of 4-ω-alkylamino-5-hydroxy-3-trifluoromethylpyrazoles.

In view of their interesting biological activity as herbicides, antiulcer or cardiovasculary agents,[1a-c] trifluoromethylated pyrazoles (**1**) (R^1 = H, alkyl, aryl; R^2 = H, OH, CN, alkyl; R^3 = OH, NH_2, alkyl) constitute a target of choice for synthesis. While numerous papers[2] already deal with this class of compounds we want to describe a new approach starting from 3-trifluoroacetyllactams.

Scheme 1 briefly summarizes some previous principal synthetic methods of **1**. Heterocyclization of trifluoromethylated 1,3-dicarbonyl compounds (**2**, **3**) with hydrazines constitutes a general approach (Method A, Scheme 1),[3a-d] but there is a problem of regioselectivity in cyclizations with unsymmetrical starting compounds.[4] 3-Chloro- or 3-amino-4,4,4-trifluorocrotononitriles (**4**) and (**5**) react also with hydrazines[5a,b] to give **1** (Scheme 1, Method B). Other pyrazoles (**1**) can be prepared from hydrazones (**6**) of fluoral and glyoxal derivatives (**7**) (Scheme 1, Method C).[6]

Our method for **1** starts with the readily available 3-trifluoroacetyllactams and benzolactams.[7]



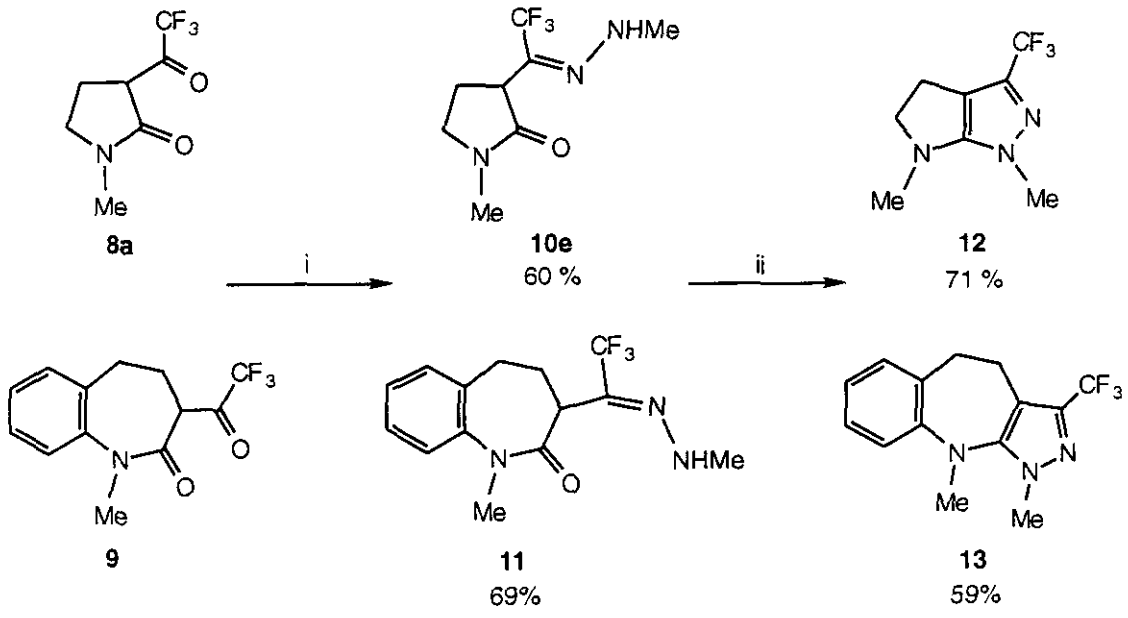
Scheme 1

As we communicated already, these compounds may cyclize with bis-nucleophiles[8a,b] without ring opening. Thus 3-trifluoroacetyl-1-methyl-2-pyrrolidone (**8a**) (TFANMP) and 3-trifluoroacetylbenzolactam (**9**) react with methylhydrazine to give the corresponding hydrazones (**10e**) and (**11**) which can be cyclized with phosphorus oxychloride to bicyclic *N*-methylpyrrolidinotrifluoromethylpyrazole (**12**) and to tricyclic benzazepinotrifluoromethyl-pyrazole (**13**) (Scheme 2).[8a]

Interestingly we have found that hydrazine or phenylhydrazine react mainly by the ring opening-ring closure (RORC) sequence and furnish the unusual zwitterionic pyrazole derivatives (**15**) rather than the postulated enehydrazines (**14**) (Scheme 3).

In many other cases, ring opening of the lactam structure takes place (Scheme 3, Table 1).

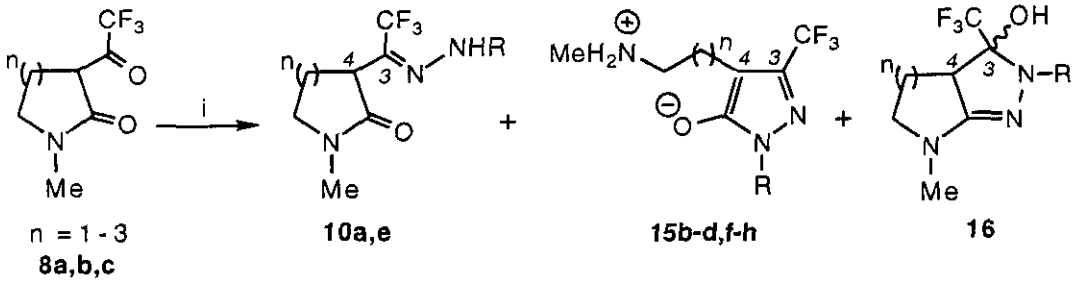
c



i : $MeHNNH_2$, $APTS_{(cat)}$, PhH, reflux ii : $POCl_3$, Py, CH_2Cl_2, 25°C or reflux

Scheme 2

In two cases (Entries **a,e**) hydrazones (**10a,e**) ould be isolated in good yields. Compound (**16**) was also present in trace amounts (Entry **e**).



n = 1 - 3
8a,b,c

10a,e

15b-d,f-h

16

i : $RHNNH_2$, $APTS_{(cat)}$, PhH or PhMe, reflux

Scheme 3

R	Entry	Lactam[7]	n	Yield **10** (%)	Yield **15** (%)	Yield **16** (%)
H	**a**	**8a**	1	74	-	-
	b	**8b**	2	-	59	-
	c	**8c**	3	-	73	-
Me	**d**[a)]	**8a**	1	-	72	-
	e[b)]	**8a**	1	60[c)]	-	4[d)]
	f	**8b**	2	-	73	-
	g	**8c**	3	-	59	-
Ph	**h**	**8a**	1	-	67	-

a) Lactam : 3 mmol, hydrazine : 1.5 eq., distillation; b) lactam : 25 mmol, hydrazine : 2.5 eq., chromatography on silica gel (ether/MeOH); c) mixture of hydrazone and enehydrazine (~90/10); d) mixture of diastereoisomers (~80/20).

Table 1

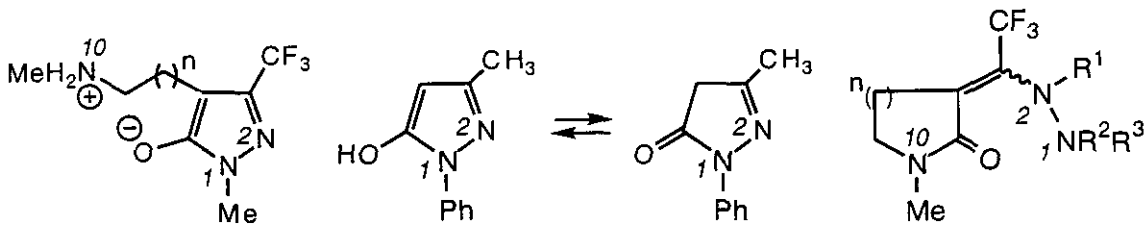
Spectroscopic characteristics of **10, 15, 16** and structure proof of **15**

^{13}C-Nmr spectra of **hydrazones** (**10a,e**) display a doublet at ~40 ppm ($^{1}J_{H}$ ~ 131-133 Hz) for the C-4 aliphatic carbon and a quartet between 128-150 ppm ($^{2}J_{F}$~30-32 Hz) for the C-3 hydrazone carbon. In the ir spectra both ν (C=O) at 1682 cm^{-1} and ν (C=N) at 1597 cm^{-1} can be observed.

Tetrahydropyrazolo[3,4-*b*]pyrrole (**16**) shows a doublet ($^{1}J_{H}$=126.8 Hz) at 41.0 ppm which is readily assigned to C-4 and a quartet ($^{2}J_{F}$=25.5 Hz) at 74.5 ppm typical of the sp3 carbon C-3. A strong ir absorption is observed at 1695 cm^{-1} for ν (C=N) and at 3200-3500 cm^{-1} for ν (OH).

The structure of the **zwitterionic pyrazole** (**15**) was elucidated based on ^{15}N- and ^{13}C- Nmr spectra for **15f,g**. Other compounds of this series are too insoluble for Nmr experiments. The nitrogen shifts of **15f,g** at -200 and -130 ppm are very close to those in 5-hydroxypyrazole (**17a**)[9] (Table 2).

Ene hydrazine structures (**14**) which we previously postulated[8a] must be discarded on the basis of ^{15}N-Nmr data. In fact, the chemical shifts observed in cyclic lactams (~ -267 ppm) are absent and there is a resonance at ~ -350 ppm.



Scheme 4

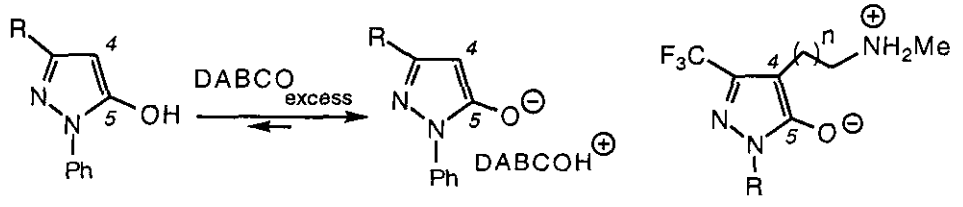
Compound[ref]	n	δN-1(ppm)	δN-2(ppm)	δN-10(ppm)	Nmr Solvent
15f	2	-201.4	-129.7	-349.0	CD_3OD,CH_3OD
15g	3	-200.8	-132.6	-348.4	CD_3OD
17a[9]	-	-191.7	-136.0	-	DMSO-d_6(major tautomer)
17b[9]	-	-187.5	-55.3	-	$CDCl_3$(major tautomer)
NMP[10]	-	-	-	-268.2	$CHCl_3$
2-Piperidinone[10]	-	-	-	-265.9	$CHCl_3$
$Me_2N^1N^2H_2$[10]	-	-322.8	-281.5	-	neat
MeHNNHMe[10]	-	-306.7	-306.7	-	neat
$EtN^{10}HMe$[10]	-	-	-	-352.0	-
EtNHMe.HCl[10]	-	-	-	-343.7	-

Table 2

Moreover, hydrazine ^{15}N chemical shifts (-280 to -320 ppm) are also absent. These features, however, do not permit unambiguously to choose between the covalent and zwitterionic forms of **15**. Both ring nitrogens in **15** are shielded which is in favour of a negatively charged oxygen on the ring, but δN-3 is in between a secondary amine and the corresponding

ammonium salt (Table 2). We excluded the pyrazol-5-one tautomer since the known **17b**[9] displays a signal δN-2 at -55.2 ppm which is absent in **15**.

Next we compared the ^{13}C-Nmr spectra of **19** (compound (**18**) was not available), and of its deprotonated form (**20**) (using DABCO as base), with **15** (Scheme 5). Table 3 shows that ^{13}C-Nmr values of the C-6 in **20** and **15** are almost identical which strongly suggests the presence of an oxyanion at C-5 in both structures. The values of C-4 show more variation which is probably due to the different substitution at this carbon in the model compound (**20**) and in **15**.



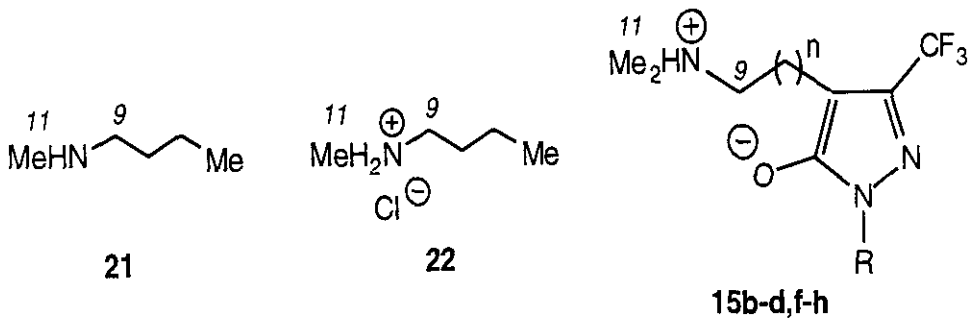
18, 19 **20** **15b-d,f-h**

Scheme 5

Compound[ref]	n	R	δC-4 (ppm)	δC-5 (ppm)	Nmr Solvent
18[9]	-	CF_3	85.7	153.8	DMSO-d_6
19[9]	-	Me	88.5	154.2	DMSO-d_6
20[9]	-	Me	85.4	159.7	DMSO-d_6
15b	2	H	96.1	162.5	CD_3OD
15c	3	H	94.9	160.3	DMSO-d_6
15d	1	Me	91.7	160.4	DMSO-d_6
15f	2	Me	95.5	162.1	CD_3OD
15g	3	Me	97.5	161.7	CD_3OD
15h	1	Ph	91.8	162.2	DMSO-d_6

Table 3

We have also measured the coupling constants $^1J_{C,H}$ in **21**, **22** and compared them with those of **15** (Scheme 7, Table 4). The values are almost identical which proves the existence of a protonated aminoalkyl side chain in **15**. Thus following the ^{15}N- and ^{13}C-Nmr arguments, the zwitterionic nature of **15** appears to be confirmed.



Scheme 6

Compound	n	R	$^1J_{C-11}$ (Hz)	$^1J_{C-9}$ (Hz)	Nmr Solvent
21	-	-	133.3	132.5	CD_3OD
22	-	-	142.8	142.7	CD_3OD
15d	1	Me	139.9	142.9	DMSO-d_6
15h	1	Ph	140.9	141.7	DMSO-d_6
15b	2	H	139.2	a)	CD_3OD
15f	2	Me	142.0	140.5	CD_3OD
15c	3	H	138.4	137.1	DMSO-d_6
15g	3	Me	142.1	139.8	CD_3OD

a) The triplet of the carbon C-9 is overlapped by the multiplet of CD_3OD.

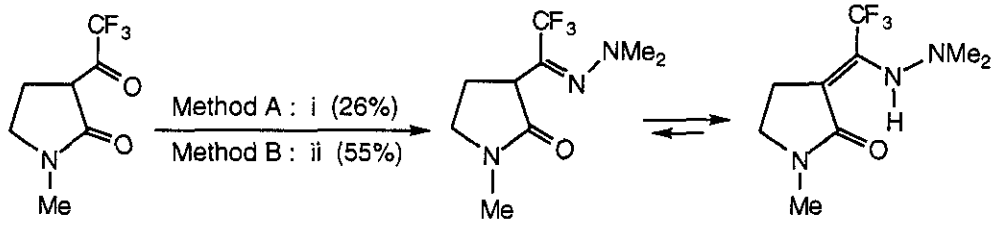
Table 4

Reaction of **8a** with 1,1-dimethylhydrazine or hydroxylamine.

N,N-Dimethylhydrazine reacts with **8a** at the more electrophilic ketocarbonyl group to give the expected hydrazone (**23a**) but the yield is low under standard conditions (Method A, Scheme 7); yet, it could be increased under harsher conditions (Method B, Scheme 7).

Nmr spectra reveal the existence of an equilibrium between the hydrazone (**23a**) and the tautomeric enehydrazine (**23b**) in the ratio 72/28.

The corresponding oxime (**24**) could also be prepared in a good yield (Scheme 8). Both *anti* and *syn* forms are present in the ratio of 90/10.



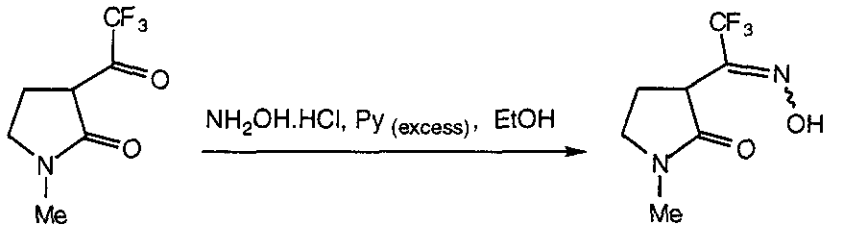
8a **23a** **23b**

(72 / 28) in $CDCl_3$

i : Me_2NNH_2 , $APTS_{(cat)}$, PhH, reflux

ii : 1) Me_2NNH_2 , 0° to 25 °C, 1 h ; 2) 80° - 100°C, 3 h

Scheme 7



8a

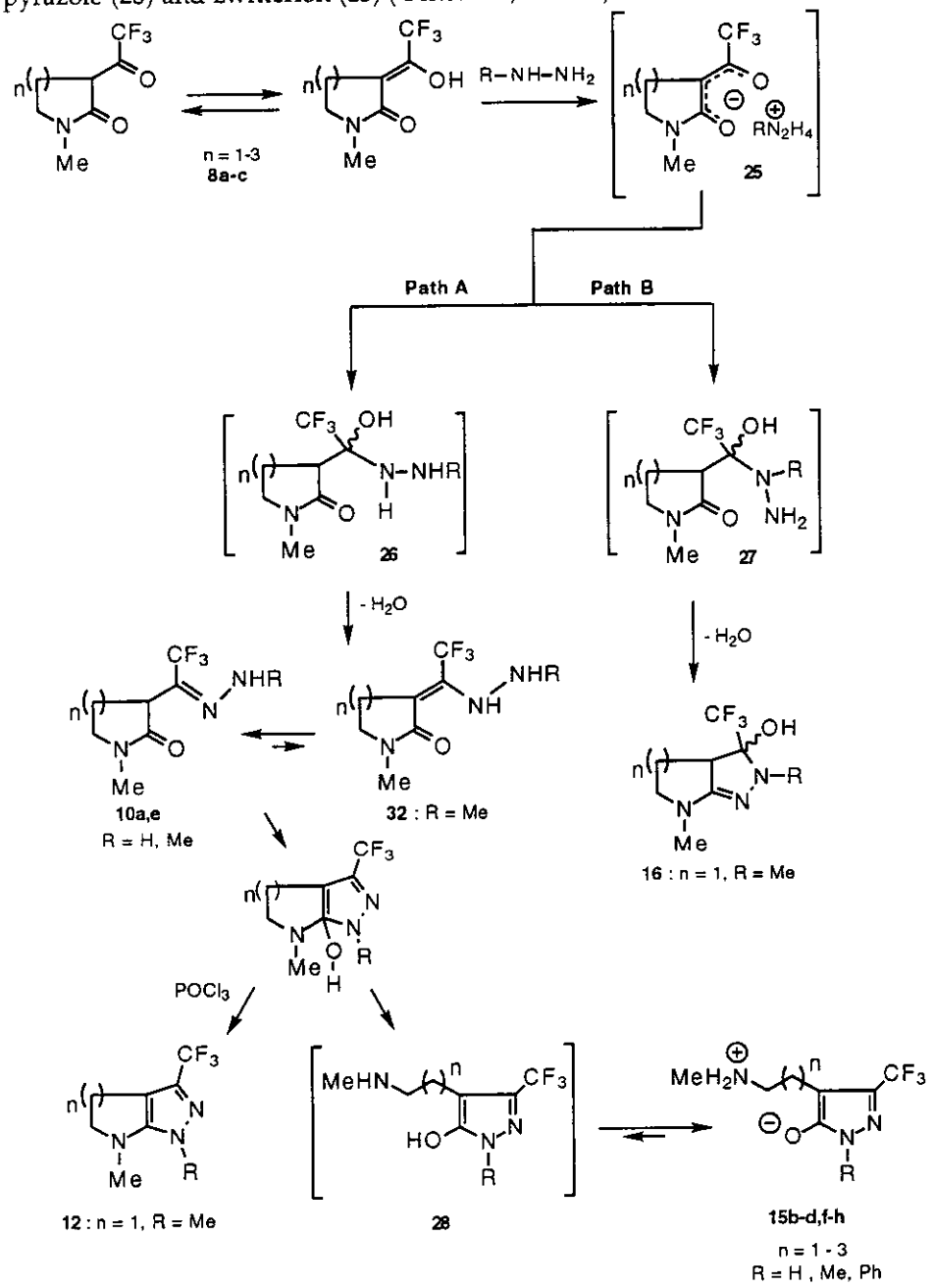
24
73 %
anti / syn : 90 / 10

Scheme 8

RORC-Mechanism of heterocyclizations

The first step consists apparently of a reaction acid-base whereby two possible enolates (**25**) are formed according to the ^{19}F-Nmr and a white precipitate occurs at 25°C. The primary enolate is unstable giving rise to hemiaminals (**26**) and (**27**). Similar observations have already been done while monitoring the reaction between ethyl trifluoroacetoacetate and ethylenediamines.[11] The adduct (**26**) then loses water to give hydrazone (**10**) and the corresponding tautomer (**32**). Their relative proportion depends on the nature of the solvent, the hydrazine substituent and the size of the lactam. These hydrazones can be isolated and **10e** is cyclized without lactam ring opening to **12** in the presence of $POCl_3$ (Scheme 2). Otherwise,

the internal attack at the lactam carbonyl leads to ring opening and formation of 5-hydroxypyrazole (**28**) and zwitterion (**15**) (Scheme 9, Path A).

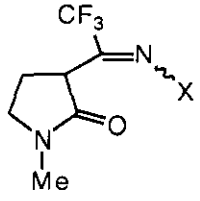


Scheme 9

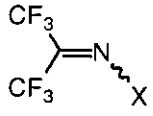
The regioisomeric hemiaminal (**27**) gives **16** (Scheme 9, Path B).

Geometry of hydrazones and ene hydrazines

Although generally hydrazones, as well as oximes, can exist in *E* and *Z* forms (called *anti* and *syn* isomers), we have generally detected only one form in solution. Most probably, the most stable configuration prevails or else there could be a rapid interconversion between the geometric isomers. In the case of oxime (**24**) we detected by the ^{19}F-Nmr both the *syn* and *anti* forms in solution . The δ^{19}F is -68.6 ppm belongs to the *anti* form and the signal at -64.8 ppm is obviously due to the *syn* form (Table 5). X-Ray analysis of the crystalline form proves this to be *anti* (Figure 1).



10a,e, 23a, 24



29, 30

Scheme 10

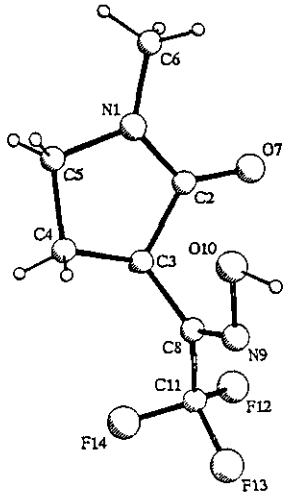


Figure 1

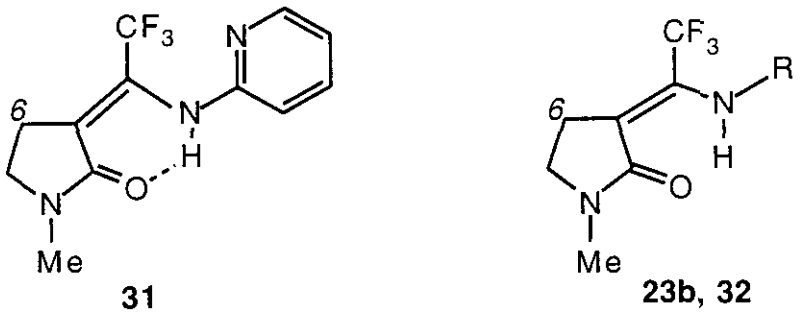
Compound	X	δ^{19}F (ppm)	NMR Solvent
10a[a)]	NH_2	-64.2	DMSO-d_6
10e[a)]	NHMe	-65.2	$CDCl_3$
23a[a)]	NMe_2	-65.5	$CDCl_3$
24[b)]	OH	-68.6 (anti)[c)]	$CDCl_3$
		-64.8 (syn)	$CDCl_3$
29[12]	NH_2	-66.7 (anti)	-
		-64.9 (syn)	-
30[12]	OH	-67.7 (anti)	-
		-65.6 (syn)	-

a) A single stereoisomer in solution; b) mixture of anti/syn stereoisomers (90/10);
c) configuration determined by X-ray diffraction.

Table 5

Similar $\delta^{19}F$ and $\Delta\delta^{19}F$ values were measured in the case of oxime (**30**) and hydrazone (**29**) of hexafluoroacetone.[12] Therefore we can suppose from the values $\delta^{19}F$ in **10a,e** and **23a** situated between -64.2 and -65.5 ppm that these hydrazones are present in the *syn* form.

Enehydrazines such as **23b** and **32** may also exist in two geometric forms but only one is detected in solution by the ^{19}F- and ^{13}C-Nmr. No crystalline sample was available for X-ray measurements, but the comparison with the known structure (**31**) indicates the Z form. By assuming the trifluoromethyl group in **23b, 31, 32** has the same structure relationship with the C-6 (Scheme 11) , the very similar values of δC-6 and $^{4}J_{C6,F}$ (Table 6) permit to conclude that the configuration is Z; this form moreover possesses a strong intramolecular hydrogen bond.

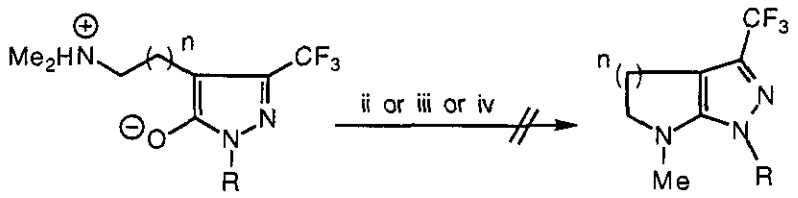


Scheme 11

Compound[ref]	R	δC-6 (ppm)	$^{4}J_{C6,F}$ (Hz)	Nmr Solvent
31[13]	$C_5H_4N_1$	22.8	2.3	$CDCl_3$
32	NHMe	20.9	2.2	$CDCl_3$
23b	NMe_2	21.8	2.4	$CDCl_3$

Table 6

Pyrrolidinopyrazole structures such as **12** (Scheme 2) appear to be new. Substituent effects so far precluded the generalisation of the cyclization of hydrazone (**10a**) and that of the zwitterions (**15b-d, f-h**) (Scheme 12).



15b-d,f-h

n = 1 - 3

R = H, Me, Ph

33

i : $SOCl_2$, Py, $CHCl_3$, 25°C to reflux

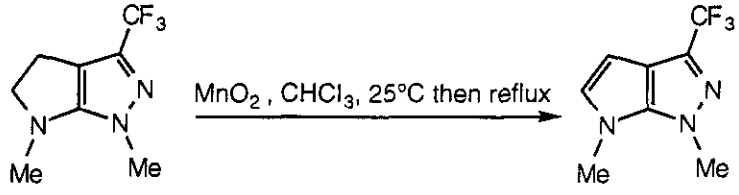
ii : $POCl_3$, Py, CH_2Cl_2, 25°C or reflux

iii : $POCl_3$, Py, reflux, 12 h

iv : PPA, 120-160°C, 10 h

Scheme 12

Compound (**12**) could be easily aromatized with manganese dioxide to **34** as the first trifluoromethylated pyrrolopyrazole derivative (Scheme 13).



12

34

68 %

Scheme 13

In conclusion, we have prepared a number of new trifluoromethylated pyrazoles either in a one-step procedure *via* a unique opening of the lactam ring or in two-step from the corresponding hydrazone and phosphorus oxychloride. The zwitterionic structure of pyrazoles (**15**) was confirmed by ^{15}N- and ^{13}C- Nmr measurements. We have also studied the geometry of hydrazones and enehydrazines. The cyclization could also be extended to 3-trifluoroacetyl-1-methylbenzolactams.[14]

EXPERIMENTAL

Melting points were taken using a Dr. Tottoli apparatus and are uncorrected. Ir and ms 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 AM 500 spectrometer at 500.13 MHz (^{1}H) and 125.77 MHz (^{13}C) or on 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 TMS signal was taken as internal reference for the ^{1}H and ^{13}C spectra, $CFCl_3$ for the ^{19}F spectra. The ^{15}N Nmr spectra[9] were run on a Bruker WR 250 spectrometer at 50 MHz, using 10 mm probes. The nitromethane signal was taken as external reference. The broad band decoupling was used for compound (**15f**) while the ^{15}N spectrum of **15g** was obtained from Distortionless Enhancement by Polarization Transfer (DEPT). Chemical shifts are in ppm on the δ scale and coupling constants J are given in Hz. The following abbreviations are used : s singlet, d doublet, t triplet, q quartet, qt quintet and m multiplet.

Hydrazines were commercially available and were distilled before use.

General procedure for hydrazine condensation.

A stirred solution of 3-trifluoroacetyllactam (**8a,b,c**)(10 mmol, 1 eq.), the corresponding hydrazine (10-50 mmol, 1-5 eq.) and a catalytic amount of *p*-toluenesulfonic acid (APTS) is refluxed during 5-24 h in toluene (50 ml), using a Dean-Stark apparatus. The solution is then cooled, diluted with ether and washed with water. The aqueous phase is extracted twice with ether. The combined organic phase is washed with brine, dried over $MgSO_4$ and evaporated. The residue is then chromatographed (compounds **10a,e; 15h; 16)** on silica gel (mixture of 80% pet. ether/20% ether for **10c** or 95% ether/5% *MeOH* for **10a, 15h, 16,**) or is distilled (compound **15d**) under reduced pressure. Compounds (**15b,c,f,g**) were obtained without purification.

Hydrazone of 1-methyl-3-trifluoroacetyl-2-pyrrolidone(**10a**).

mp 62-65°C. Ir(film) : 3419, 3192, 2944, 2883, 1682, 1620, 1407, 1298, 1109. Ms(m/z) : 210, 209, 193, 190, 152, 136, 123, 98, 69, 57, 42. ^{1}H Nmr (DMSO-d_6) : δ 1.9-2.1 (m, 1H), 2.2-2.4 (m, 1H), 2.75 (s, 3H), 3.3-3.5 (m, 2H), 3.9 (tm, 1H, J= 9.5 Hz), 7.5 (br s, NH_2). ^{13}C Nmr (DMSO-d_6) : δ 20.0 (tm, $^{4}J_F$ = 1.7 and $^{1}J_H$ = 133.3 Hz), 29.6 (q, $^{6}J_F$ = 1.3 and $^{1}J_H$ = 137.7 Hz), 39.6 (dm, $^{1}J_H$ = 131.6 Hz), 47.7 (tm, $^{5}J_F$ = 1.1 and $^{1}J_H$ = 144.3 Hz), 121.3 (qd, $^{1}J_F$ = 273.6 and $^{3}J_H$ = 5.8 Hz), 133.4 (qm, $^{2}J_F$ = 31.2 Hz), 171.4 (sm). ^{19}F Nmr (DMSO-d_6) : δ -64.2 (s). Anal. Calcd for $C_7H_{10}N_3OF_3$: C, 40.20; H, 4.82; N, 20.09. Found C,40.68; H, 4.54; N, 19.93.

Internal salt of 5-hydroxy-4-(3-methylaminopropyl)-3-trifluoromethylpyrazole (**15b**).

mp 201-202°C. Ir(KBr) : 3600, 3300-3100, 2992, 2961, 1680, 1618, 1579, 1473, 1419, 1130. Ms(m/z) : 224, 223, 204, 165, 163, 113, 69, 44. ^{1}H Nmr (CD_3OD) : δ 1.92 (q_t, 2H, J = 6.7 Hz), 2.60 (m, 2H), 2.71 (s, 3H), 2.97 (t, 2H, J = 6.7 Hz). ^{13}C Nmr (CD_3OD) : δ 18.8 (tm, $^{4}J_F$ = 1.2 and $^{1}J_H$ = 129.0 Hz), 27.9 (tm, $^{1}J_H$ = 128.6 Hz), 33.3 (q, $^{1}J_H$ = 139.2 Hz), 49.1 (m), 96.1 (sm, $^{3}J_F$ = 1.6 Hz), 123.9 (q, $^{1}J_F$ = 269.0 Hz), 140.1 (qm, $^{2}J_F$ = 35.2 Hz), 162.5 (sm). ^{19}F Nmr (CD_3OD) : δ -61.3 (s).

Internal salt of 5-hydroxy-4-(4-methylaminobutyl)-3-trifluoromethylpyrazole (**15c**).

mp 143-145°C. Ir(KBr) : 3350, 3205, 2966, 2954, 1664, 1579, 1509, 1474, 1263, 1122. Ms(m/z) : 238, 237, 199, 198, 166, 165, 145, 137, 69, 57, 44. ^{1}H Nmr (DMSO-d_6; 500 MHz; 40°C) : δ 1.4-1.5 (m, 4H), 2.2-2.3 (m, 2H), 2.38 (s, 3H), 2.70 (t, 2H, J = 5.9 Hz), 5.0-7.0 (br m, NH and NH_2). ^{13}C Nmr (DMSO-d_6; 500 MHz; 40°C) : δ 20.4 (tm, $^{1}J_H$ = 125.7 Hz), 25.2 (tm, $^{1}J_H$ = 124.6 Hz), 28.4 (tm, $^{1}J_H$ = 126.6 Hz), 33.9 (q, $^{1}J_H$ = 138.4 Hz), 49.0 (tm, $^{1}J_H$ = 137.1 Hz), 94.9 (sm), 123.4 (q, $^{1}J_F$ = 268.7 Hz), 137 7 (qm, $^{2}J_F$ = 34.0 Hz), 160.3 (sm). ^{19}F Nmr (DMSO-d_6) : δ - 59.6 (s).

Internal salt of 4-(2-methylaminoethyl)-5-hydroxy-1-methyl-3-trifluoromethylpyrazole (**15d**).

mp 138-139°C. Ir(KBr) : 3400-3200, 3029, 2827, 1688, 1602, 1471, 1253, 1151, 1032, 926, 739. Ms(m/z): 224, 223, 204, 184, 177, 123, 111, 101, 69, 44. ^{1}H Nmr (DMSO-d_6) : δ 2.54 (s, 3H), 2.62 (tm, 2H, J = 5.3 Hz), 3.04 (tm, 2H, J = 5.6 Hz), 3.33 (s, 3H), 3.5-4.5 (br s, NH_2). ^{13}C Nmr (DMSO-d_6) : δ 20.5 (tm, $^{4}J_F$ = 1.3 and $^{1}J_H$ = 127.1 Hz), 32.1 (q, $^{1}J_H$ = 139.9 Hz), 32.7 (q, $^{1}J_H$ = 138.9 Hz), 49.5 (tm, $^{1}J_H$ = 147.9 Hz), 91.7 (st, $^{3}J_F$ = 1.5 and $^{2}J_H$ = 6.2 Hz), 123.4 (q, $^{1}J_F$ = 269.6 Hz), 135.5 (qm, $^{2}J_F$ = 34.3 Hz), 160.4 (sm). ^{19}F Nmr (DMSO-d_6) : δ - 60.0 (s).

N-Methylhydrazone of 1-methyl-3-trifluoroacetyl-2-pyrrolidone (**10e**) .

Oil. Ir(film) : 3302, 2952, 2937, 1682, 1597, 1504, 1407, 1370, 1176. Ms(m/z) : 224, 223, 204, 151, 125, 123, 117, 103, 98, 69, 57, 42. ^{1}H Nmr ($CDCl_3$; 500 MHz) : δ 2.2-2.3 (m, 1H), 2.3-2.4 (m, 1H), 2.84 (s, 3H), 3.01 (d, 3H, J = 4.0 Hz), 3.37 (ddd, 1H, J = 9.5, 8.1 and 6.7 Hz), 3.45 (ddd, 1H, J = 9.6, 8.7 and 4.7 Hz), 3.74 (dd, 1H, J = 9.4 and 8.2 Hz), 7.21 (br s, NH). ^{13}C Nmr ($CDCl_3$; 500 MHz) : δ 20.4 (tm, $^{4}J_F$ = 1.6 and $^{1}J_H$ = 136.5 Hz), 29.7 (q, $^{1}J_H$ = 138.6 Hz), 37.8 (qd, $^{1}J_H$ = 136.6 and $^{2}J_H$ = 4.0 Hz), 40.2 (dm, $^{1}J_H$ = 132.2 Hz), 47.9 (tm, $^{5}J_F$ = 1.2 and $^{1}J_H$ = 143.9 Hz), 121.4 (qd, $^{1}J_F$ = 272.7 and $^{3}J_H$ = 4.2 Hz), 128.0 (qm, $^{2}J_F$ = 32.2 Hz), 171.6 (sm). ^{19}F Nmr ($CDCl_3$) : δ - 65.2 (s).

1-[1-(*N'*-Methylhydrazyl)-2,2,2-trifluoroethylidene]-1-methyl-2-pyrrolidone (32).

Selected chemical shifts of ^{13}C Nmr ($CDCl_3$; 500 MHz) : δ 20.9 (q, ^4J_F = 2.2 Hz), 29.7, 46.2, 120.6. ^{19}F Nmr ($CDCl_3$) : δ - 62.3 (s). This compound contains about 10% of (**10e**).

2,7-Dimethyl-3-hydroxy-3-trifluoromethyl-2,7(*H*)-3,4,5,6-tetrahydropyrazolo[3,4-*b*]pyrrole (16).

Major diastereoisomer : mp 50-53°C. Ir(KBr) : 3500-3200, 2915, 2875, 1695, 1498, 1430, 1400, 1260, 1175. Ms(m/z) : 224, 223, 204, 195, 180, 126, 103, 98, 69, 43. ^1H Nmr ($CDCl_3$) : δ 2.1-2.6 (m, 2H), 2.82 (s, 3H), 3.0-3.5 (m, 2H), 3.88 (s, 3H), 4.51 (q, 1H, ^4J_F = 4.7 Hz), 6.3 (br s, OH). ^{13}C Nmr ($CDCl_3$) : δ 18.6 (tm, ^4J_F = 1.3 and ^1J_H = 137.3 Hz), 29.7 (q, ^1J_H = 138.4 Hz), 41.0 (dm, ^3J_F = 1.6 and ^1J_H = 126.8 Hz), 47.6 (tm, ^1J_H = 143.3 Hz), 57.9 (qm, ^1J_H = 137.1 Hz), 74.5 (qm, ^2J_F = 25.5 Hz), 124.7 (qm, ^1J_F = 281.0 Hz), 171.7 (sm).^{19}F Nmr ($CDCl_3$) : δ - 71.0 (d, ^4J_H = 8.3 Hz). Anal. Calcd for $C_8H_{12}N_3OF_3$: C, 43.05; H, 5.42; N, 18.83. Found C, 43.43; H, 5.24; N, 18.59.

Minor diastereoisomer : selected chemical shifts of ^1H Nmr ($CDCl_3$) : δ 2.86 (s, 3H), 3.93 (s, 3H). ^{13}C Nmr ($CDCl_3$) : δ 20.5, 40.2, 47.2, 57.2, 172.0. ^{19}F Nmr ($CDCl_3$) : δ - 68.2 (d, ^4J_H = 7.4 Hz).

Internal salt of 5-hydroxy-1-methyl-4-(3-methylaminopropyl)-3-trifluoromethylpyrazole (15f).

mp 215°C. Ir(KBr) : 3450-3300, 2985, 2944, 1652, 1560, 1526, 1466, 1292, 1102. Ms(m/z) : 238, 237, 218, 206, 194, 179, 69, 58, 44. ^1H Nmr (CD_3OD) : δ 1.91 (q_t, 2H, J = 6.6 Hz), 2.58 (m, 2H), 2.72 (s, 3H), 2.96 (t, 2H, J = 6.5 Hz), 3.59 (s, 3H). ^{13}C Nmr (CD_3OD) : δ 19.1 (tm, ^4J_F = 1.6 and ^1J_H = 127.2 Hz), 27.9 (tm, ^1J_H = 128.6 Hz), 32.7 (q, ^1J_H = 138.9 Hz), 33.3 (qt, ^1J_H = 142.0 and ^2J_H = 2.2 Hz), 49.0 (tm, ^1J_H = 140.5 Hz), 95.5 (sm, ^3J_F = 1.4 Hz), 123.9 (q, ^1J_F = 268.6 Hz), 138.1 (qm, ^2J_F = 35.7 Hz), 162.1 (sm). ^{19}F Nmr (CD_3OD) : δ - 61.4 (s). ^{15}N Nmr (CD_3OD and CH_3OD) : δ - 129.7 (q, ^3J_F = 2.5 Hz), - 201.4 (s), -349.0 (s). Anal. Calcd for $C_9H_{14}N_3OF_3$: C, 45.67; H, 5.95; N, 17.71. Found C, 45.77; H, 5.73; N, 17.85.

Internal salt of 4-(4-methylaminobutyl)-5-hydroxy-1-methyl-3-trifluoromethylpyrazole (15g).

mp 210-212°C. Ir(KBr) : 3500-3300, 2933, 2909, 2870, 1636, 1561, 1498, 1459, 1277. Ms(m/z) : 252, 251, 212, 182, 179, 177, 139, 111, 69, 44. ^1H Nmr (CD_3OD) : δ 1.5-1.7 (m, 4H), 2.3-2.4 (m, 2H), 2.66 (s, 3H), 2.96 (t, 2H, J = 6.6 Hz), 3.49 (s, 3H). ^{13}C Nmr (CD_3OD) : δ 22.1 (tm, ^4J_F = 1.2 and ^1J_H = 126.7

Hz), 26.1 (tm, $^{1}J_{H}$ = 125.9 Hz), 28.4 (tm, $^{1}J_{H}$ = 126.2 Hz), 32.7 (q, $^{1}J_{H}$ = 138.7 Hz), 33.6 (qt, $^{1}J_{H}$ = 142.1 and $^{2}J_{H}$ = 2.7 Hz), 50.1 (tm, $^{1}J_{H}$ = 139.8 Hz), 97.5 (sm, $^{3}J_{F}$ = 1.0 Hz), 124.2 (q, $^{1}J_{F}$ = 268.6 Hz), 138.1 (qt, $^{2}J_{F}$ = 34.6 and $^{3}J_{H}$ = 4.3 Hz), 161.7 (sm). ^{19}F Nmr (CD_3OD) : δ - 61.0 (s). ^{15}N Nmr (CD_3OD) : δ -132.6 (q, $^{3}J_{F}$ = 2.3 Hz), -200.8 (s), - 348.4 (s). Anal. Calcd for $C_{10}H_{16}N_3OF_3$: C, 47.80; H, 6.42; N, 16.72. Found C, 48.04; H, 6.37; N, 16.76.

Internal salt of 4-(2-methylaminoethyl)-5-hydroxy-1-phenyl-3-trifluoromethylpyrazole (**15h**).
mp 181-183°C. Ir(KBr) : 3500-3300, 3060, 2963, 2803, 1599, 1579, 1509, 1485, 1285, 1125. Ms(m/z) : 286, 285, 266, 242, 173, 123, 77, 44. ^{1}H Nmr (DMSO-d_6; 500 MHz; 30 °C) : δ 2.55 (d, 3H, J = 1.2 Hz), 2.65 (dd, 2H, J = 5.3 and 5.1 Hz), 3.05 (dd, 2H, J = 5.1 and 5.0 Hz), 7.11 (tt, 1H, J = 7.8 and 1.0 Hz), 7.35 (ddd, 2H, J = 7.9, 7.6 and 0.6 Hz), 8.02 (dd, 2H, J = 7.8 and 0.7 Hz), 10.9 (br s, NH_2). ^{13}C Nmr (DMSO-d_6; 500 MHz; 30 °C) : δ 20.0 (ttq, $^{1}J_{H}$ = 127.5, $^{2}J_{H}$ = 1.9 and $^{4}J_{F}$ = 1.5 Hz), 31.8 (q, $^{1}J_{H}$ = 140.9 Hz), 49.5 (tm, $^{1}J_{H}$ = 141.7 Hz), 91.8 (sm, $^{3}J_{F}$ = 1.6 Hz), 119.4 (ddd, $^{1}J_{H}$ = 161.5, $^{3}J_{H}$ = 7.1 and 5.2 Hz), 122.7 (q, $^{1}J_{F}$ = 270.2 Hz), 123.9 (dt, $^{1}J_{H}$ = 160.0 and $^{3}J_{H}$ = 7.8 Hz), 128.3 (dd, $^{1}J_{H}$ = 159.6 and $^{3}J_{H}$ = 8.6 Hz), 137.8 (qdd, $^{2}J_{F}$ = 33.5, $^{3}J_{H}$ = 2.3 and 2.1 Hz), 140.5 (sm, $^{4}J_{F}$ = 1.3 Hz), 162.2 (sdd, $^{3}J_{H}$ = 4.4 and 4.0 Hz). ^{19}F Nmr (DMSO-d_6) : δ -60.4 (s). Anal. Calcd for $C_{13}H_{14}N_3OF_3$: C, 54.74; H, 4.95; N, 14.73. Found C, 54.64; H, 4.93; N, 14.84.

Reaction of *N,N*-dimethylhydrazine with TFANMP (Scheme 7, method B : ii).
N,N-dimethylhydrazine (0.50 ml, 6.6 mmol) is added to TFANMP (**8a**) (0.59 g, 3 mmol) at 0°C. The temperature is allowed to reach 25°C (1 hour) then the mixture is heated at 80-100°C during 3 h. The crude product is chromatographed on silica gel (eluent : 95% ether/ 5% MeOH) to give a mixture (72/28) of hydrazone (**23a**) and ene hydrazine (**23b**) (yield : 55%).

N,N-Dimethylhydrazone (**23a**) of 1-methyl-3-trifluoroacetyl-2-pyrrolidone. bp 45-50°C/0.2 mm Hg. Ir($CHCl_3$) : 2965, 2877, 1695, 1504, 1438, 1353, 1133, 1020, 915, 705. Ms(m/z) : 237, 195, 168, 138, 122, 99, 98, 69, 60, 44. ^{1}H Nmr ($CDCl_3$) : δ 2.22 (ddd, 2H, J = 7.6, 7.6 and 0.9 Hz), 2.69 (s, 6H), 2.85 (s, 3H), 3.38 (tm, 2H, J = 7.4 Hz), 4.31 (tm, 1H, J = 9.5 Hz). ^{13}C Nmr ($CDCl_3$) : δ 21.9 (tm, $^{4}J_{F}$ = 2.0 and $^{1}J_{H}$ = 136.1 Hz), 29.9 (q, $^{1}J_{H}$ = 138.5 Hz), 40.9 (dm, $^{1}J_{H}$ = 133.0 Hz), 47.2 (tm, $^{5}J_{F}$ = 1.6 and $^{1}J_{H}$ =

143.1 Hz), 48.1 (qq, ^1J_H = 136.6 and ^3J_H = 4.9 Hz), 120.7 (qd, ^1J_F = 278.1 and ^3J_H = 6.7 Hz), 149.6 (qm, ^2J_F = 30.8 Hz), 170.8 (sm). ^{19}F Nmr ($CDCl_3$) : δ -65.5 (s).

1-[1-(*N',N'*-Dimethylhydrazyl)-2,2,2-trifluoroethylidene]-1-methyl-2-pyrrolidone (23b).
Selected chemical shifts of ^{1}H Nmr ($CDCl_3$) : δ 2.45 (s, 6H), 2.7-2.8 (m, 2H), 2.83 (d, 3H, J = 0.7 Hz), 3.35 (m, 2H), 8.3 (br s, NH). ^{13}C Nmr ($CDCl_3$) : δ 21.8, 29.6, 46.6, 47.7, 120.7, 121.5, 139.1, 170.4. ^{19}F Nmr ($CDCl_3$) : δ -63.3 (s).

Reaction of hydroxylamine with TFANMP.
A solution of **8a** (5 mmol, 0.98 g), hydroxylamine hydrochloride (6 mmol, 0.42 g) and a large excess of pyridine (32 ml), in ethanol (15 ml), is refluxed during 6 h. After evaporation of solvent, the residue is diluted with ether (20 ml), washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil is then chromatographed on silica gel (eluent : 95% ether/5% MeOH) to give 0.77 g (yield : 73%) of a white solid which is recrystallised in pet. ether/AcOEt.

Oxime of 1-methyl-3-trifluoroacetyl-2-pyrrolidone(24). Major isomer : mp 129-132°C. Ir(KBr) : 3200, 3085, 2921, 2887, 1681, 1647, 1507, 1403, 1310, 1190, 980. Ms(m/z) : 211, 210, 193, 191, 136, 116, 99, 69, 42. X-ray : monoclinic, P1 21/a1, a = 9.685(3) Å, b = 7.128(2) Å, c = 13.572(4) Å, β = 99.78(2)°, V = 923.3(5) Å^3, Z = 4. ^{1}H Nmr ($CDCl_3$) : δ 2.3-2.4 (m, 2H), 2.90 (s, 3H), 3.4-3.6 (m, 2H), 3.73 (tm, 1H, J = 8.3 Hz), 10.8 (br s, OH). ^{13}C Nmr ($CDCl_3$) : δ 20.9 (ttd, ^4J_F = 1.2, ^1J_H = 136.5, ^2J_H = 3.8 and 3.2 Hz), 29.3 (q, ^1J_H = 138.5 Hz), 38.6 (dm, ^1J_H = 131.6 Hz), 47.3 (ttq, ^1J_H = 143.3, ^2J_H = 3.1 and ^3J_H = 1.6 Hz), 120.4 (qd, ^1J_F = 273.6 and ^3J_H = 4.5 Hz), 144.9 (qd, ^2J_F = 31.9 and ^2J_H = 4.0 Hz), 170.0 (sm). ^{19}F Nmr ($CDCl_3$) : δ -68.6 (s). Anal. Calcd for $C_7H_9N_2O_2F_3$: C, 40.00; H, 4.32; N, 13.33. Found C, 40.33; H, 4.16; N, 13.22. Minor isomer : ^{19}F Nmr ($CDCl_3$) : δ -64.8 (s).

Cyclisation of hydrazone (10e) by means of $POCl_3$.
Phosphoryl oxychloride (0.23 ml) is added slowly to a solution of hydrazone (**10e**) (0.56 g, 2.5 mmol) and pyridine (0.8 ml) in dichloromethane (5 ml). The mixture is stirred for 2 h at 25°C. The solution is then cooled and hydrolysed with saturated aqueous NH_4Cl (~10 ml). The

aqueous phase is extracted with dichloromethane (2 x 30 ml). The combined organic phase is washed with brine, dried over $MgSO_4$ and evaporated. The residue is chromatographed on silica gel (eluent : 50% pet. ether/50% ether) to give 0.36 g (yield : 71%) of pyrazole (**12**).

2,3-Dihydro-1,6-dimethyl-4-trifluoromethylpyrrolo[2,3-*c*]pyrazole (**12**). mp 31-35°C. Ir(KBr) : 2970, 2958, 2876, 1576, 1561, 1435, 1419, 1389, 1244, 1163, 1118, 1079. Ms(m/z) : 206, 205, 204, 190, 186, 163, 93, 69. ^1H Nmr ($CDCl_3$) : δ 2.81 (t, 2H, J = 7.9 Hz), 2.82 (s, 3H), 3.76 (t, 2H, J = 7.9 Hz), 3.78 (s, 3H). ^{13}C Nmr ($CDCl_3$) : δ 22.0 (tt, ^1J_H = 136.2 and ^2J_H = 3.0 Hz), 36.2 (q, ^5J_F = 1.6 and ^1J_H = 140.4 Hz), 37.8 (qt, ^1J_H = 136.2 and ^3J_H = 2.6 Hz), 64.5 (ttq, ^1J_H = 141.5, ^2J_H = 4.8 and ^3J_H = 2.4 Hz), 108.1 (sm, ^3J_F = 2.1 Hz), 121.3 (q, ^1J_F = 268.2 Hz), 134,5 (qm, ^2J_F = 37.9 Hz), 157.7 (sm, ^4J_F = 1.5 Hz). ^{19}F Nmr ($CDCl_3$) : δ -62.5 (s). Anal. Calcd for $C_8H_{10}N_3F_3$: C, 46.83; H, 4.91; N, 20.48. Found C, 46.82; H, 4.81; N, 20.12.

Oxidation of pyrazole (**12**) with MnO_2.

A solution of pyrazole (**12**) (0.31 g, 1.5 mmol) and manganese dioxide (0.39 g, 4.5 mmol) in chloroform (3 ml) is stirred 12 h at room temperature then refluxed during 3 h. After filtration over celite and evaporation under reduced pressure, the crude product is chromatographed on silica gel (eluent : 30% pet. ether/70% CH_2Cl_2) and recrystallised in the same solvent to give 0.21 g (68 %) of pyrazole (**34**).

1,6-Dimethyl-3-trifluoromethylpyrrolo[3,2-*d*]pyrazole (**34**).

mp 150-152 °C. Ir(KBr) : 3097, 1615, 1526, 1439, 1423, 1247, 1158, 1106, 899. Ms(m/z) : 204, 203, 202, 184, 134, 107, 93. ^1H Nmr ($CDCl_3$) : δ 3.65 (s, 3H), 3.93 (s, 3H), 5.94 (dm, 1H, J = 2.9 Hz), 6.42 (dm, 1H, J = 3.2 Hz). ^{13}C Nmr ($CDCl_3$) : δ 33.3 (qd, ^6J_F = 1.8, ^1J_H = 139.4 and ^3J_H = 1.6 Hz), 36.8 (q, ^6J_F = 1.8 and ^1J_H = 140.3 Hz), 95.4 (dd, ^1J_H = 178.1 and ^2J_H = 7.6 Hz), 114.0 (sm, ^3J_F = 1.8 Hz), 121.8 (q, ^1J_F = 267.8 Hz), 129.17 (q, ^2J_F = 38.9 Hz), 129.24 (ddq, ^1J_H = 184.9, ^2J_H = 9.0 and ^3J_H = 3.3 Hz), 143.4 (sm). ^{19}F Nmr ($CDCl_3$) : δ -61.8 (s). Anal. Calcd for $C_8H_8N_3F_3$: C, 47.30; H, 3.97; N, 20.68. Found C, 46.99; H, 3.81; N, 20.24.

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