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Diastereoselective 1,3-dipolar cycloadditions of new azomethine ylides derived from trifluorothioacetamides or cyanothioformamides

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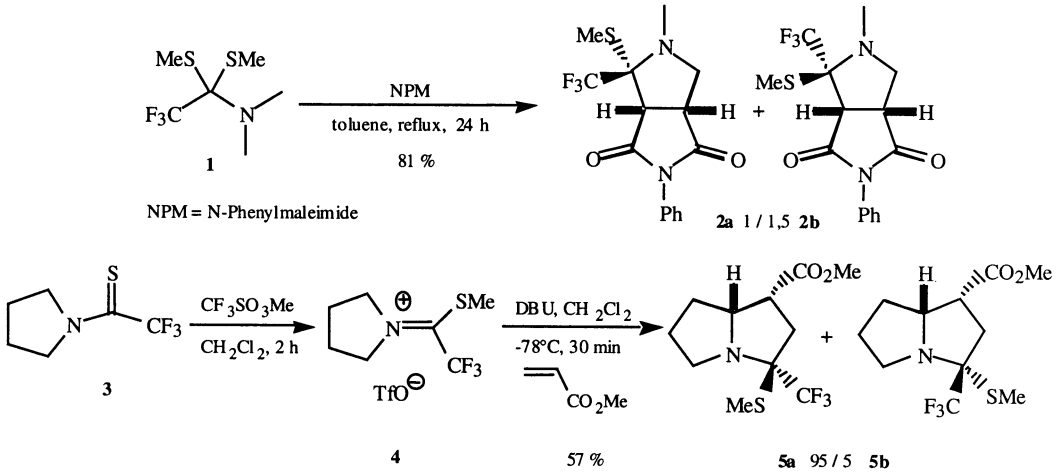
Abstract—Deprotonation of trifluoromethyl or cyano thioamidium salts generates new azomethine ylides which undergo cycloaddition to dipolarophiles with high diastereoselectivity. Epimerisation, hydrolysis and reduction of the new trifluoromethylated heterocycles are also described.

The selective synthesis of trifluoromethylated heterocycles from readily available synthons remains a challenge despite the biological and chemical potential[1] of these compounds. Generally, 1,3-dipolar cycloaddition of azomethine ylides with olefins is a very efficient method to prepare heterocycles as found in alkaloids[2] but this approach is little documented for the preparation of trifluoromethylated species. For example, the cycloaddition of bis-trifluoromethyl azomethine ylides with dimethyl acetylene dicarboxylate gives pyrrolines[3] while the cycloaddition of an azomethine ylide with a trifluoromethylated olefin leads to 3-trifluoromethyl pyrrolidines.[4]

Recently, we have reported on the generation of trifluoromethyl azomethine ylides either by heating α-trifluoromethyl thioaminal **1** or by deprotonation of trifluoromethyl thioamidium salts **4**. Both **1** and **4** were obtained from trifluorothioacetamides[5] (Scheme 1). While thioamidium salts have been used for the generation of azomethine ylides by the desilylation route,[6] our deprotonation approach is practical for reagents with electron-withdrawing groups in α position: these destabilise the thioamidium function and stabilise the formed 1,3-dipole. The resulting one-pot reaction allows access to new trifluoromethylated bicyclic alkaloid derivatives with high diastereoselectivity (Table 1).



Scheme 1.

Keywords: trifluoromethyl; thioamides; thioamidium salts; azomethine ylides; pyrrolizidines.
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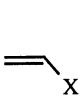
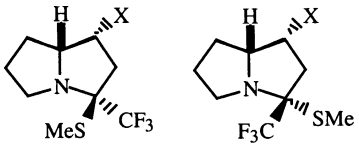
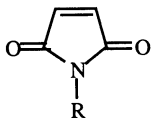
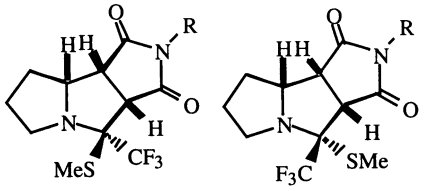
Table 1. Trifluoromethylated pyrrolizidines obtained from the trifluorothioacetamide **3** and dipolarophiles

Dipolarophiles	Pyrrolizidines	Ratio[a] a:b (Yields)
		
X=CO_2Me	5a:5b	95/5 (57%)
X=CN	6a:6b	96/4 (50%)
X=SO_2Ph	7a:7b	96/4 (63%)[b]
		
R=Me	8a:8b	88/12 (66%)
R=Ph	9a:9b	81/19 (55%)[c]

[a] Ratios have been determined from ^{19}F NMR spectra of the reaction mixture. Each diastereoisomers were isolated.
[b] Mixture of both isomers from which **7b** was detected.
[c] Mixture of both isomers; after recrystallisation, only **9a** was isolated.

1. Results and discussion

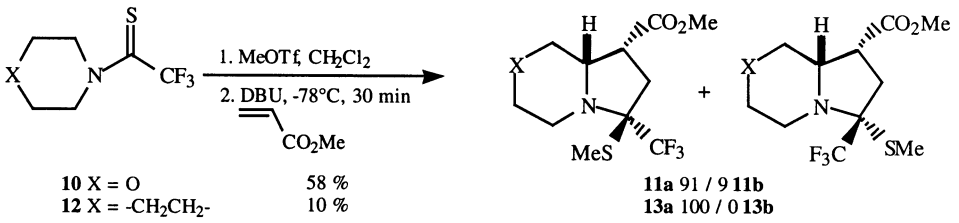
Whereas the *N*-tertiary trifluoroacetamides obtained by aminolysis of ethyl trifluoroacetate are rather inert, the corresponding thioamides can be smoothly transformed into the thioamidium salts or amide chlorides.[7] These useful reagents display increased reactivity due to the CF_3-substitution on the carbon of the iminium function and allow access to trifluoromethylated compounds. In this article, we report that α-captor thioamidium salts can be deprotonated by non-nucleophilic base such as DBU, to furnish azomethine ylides which undergo cycloaddition to olefins with high diastereoselectivity.

The results obtained from trifluorothioacetamide **3** derived from pyrrolidine[7a] are outlined in Scheme 1 and Table 1. Trifluoromethyl thioamidium salt **4** is obtained by alkylation of thioamide **3** with 1.1 equiv. of methyl triflate.[7a] The alkylation of trifluorothioacetamides is relatively slow and is best carried out in concentrated solution. The deprotonation step occurs at −78°C using 1.5 equiv. of DBU in the presence of different electron deficient olefins to produce 3-trifluoromethyl pyrrolizidines **5ab**–**9ab** with high diastereoselectivity. The ratio of the obtained isomers appears to depend upon the reactivity of the dipolarophile, i.e. very reactive dipolarophiles such as maleimides lead to a slight decrease in the ratio of the diastereoisomers.

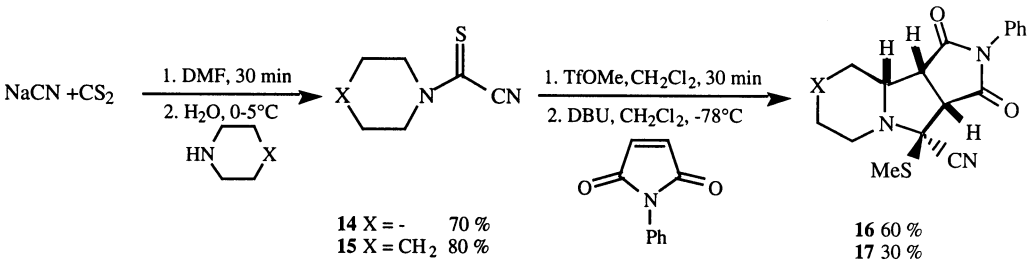
Scheme 2 shows the analogous cycloaddition of the morpholino derivative with methyl acrylate. The diastereoisomers **11a** and **11b** are obtained in a similar ratio as the pyrrolizidine derivatives.

Unfortunately, the seven-membered cyclic thioamide **12** reacts with methyl acrylate to furnish a complex mixture from which only cycloadduct **13** is isolated in 10% yield.

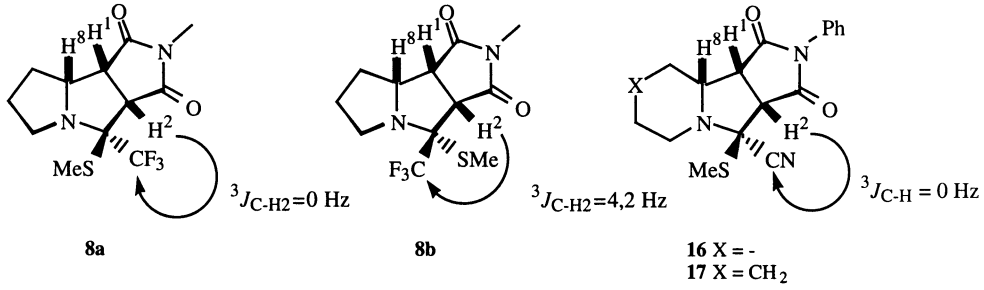
When readily accessible cyanothioformamides[8] **14** or **15** are used as ylide precursors, the cycloadditions with *N*-phenylmaleimide lead respectively to diastereoisomer **16** or **17**. These can be purified by chromatography on neutral alumina but are unstable at room temperature (Scheme 3). In contrast, the *N*,*N*-dimethylphenylthioformamidium salt does not react in the same conditions. Thus, the electron-withdrawing groups facilitate the deprotonation of the destabilisated thioamidium salts. Furthermore, we do not observe elimination of methylthiol, leading to the formation of the corresponding enamines, which always arise after



Scheme 2.



Scheme 3.

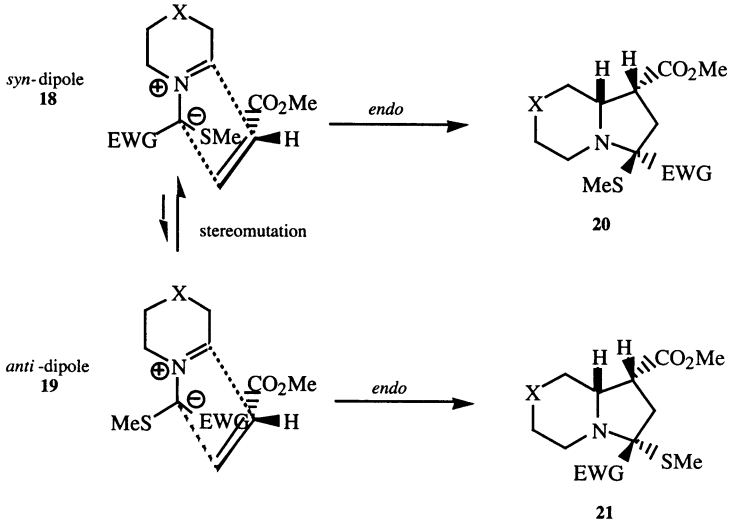


Scheme 4.

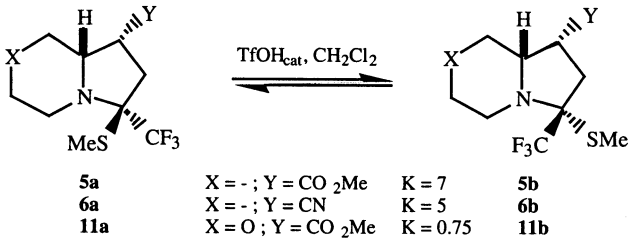
cycloaddition of azomethine ylides produced by desilylation.[6] Clearly, the stabilisation by the electron-withdrawing substituents (CF_3 or CN) of the thioaminal carbon is responsible for this enhanced stability.[11]

The structure and the stereochemistry of the cycloadducts has been assigned based upon their ^1H, ^{13}C and ^{19}F NMR data and by their correlation with the structure of morpholino derivative **11a** unambiguously established by X-ray analysis.[9] The ^{13}C NMR spectra show the presence of the carbon bound to nitrogen and bearing only one hydrogen (δ=64.0±4.4 ppm), of the methylsulfide (δ=12.6±2.8 ppm) and of the CF_3 group (δ=126.8±2.6 ppm). The ^1H data confirm the presence of the methylsulfide group (δ=2.23±0.26 ppm) and of one hydrogen H^8 α to the nitrogen atom and coupled with three protons (δ=3.62±0.47 ppm). The ^{13}C NMR spectrum of **8b** shows a coupling constant $^3J_{CF3-H2}$ of 4.2 Hz (Scheme 4). Taking into account the absence of this coupling constant $^3J_{CF3-H2}$ in **8a**, these results are indicative of a *trans* (**8a**) and a *cis* (**8b**) relationship between the CF_3 group and the proton H2. By comparison, no coupling constant $^3J_{CN-H2}$ is detected in the spectra of products **16** and **17** which suggests a *trans* relationship between the cyano group and the proton H2.

As mentioned earlier, the cycloaddition of these new azomethine ylides with dipolarophiles is highly diastereoselective. The regiochemistry obtained with dissymetric dipolarophiles indicates that the reaction is controlled by $HOMO_{dipole}$–$LUMO_{dipolarophile}$ interactions. Qualitatively, the largest orbital coefficient of the HOMO of the dipole appears to be on the carbon bearing the electron-



Scheme 5.



Scheme 6.

withdrawing group (CF_3 or CN). This result agrees with the effect of substituents on the magnitude of the orbital coefficients.[10] The stereochemistry could be rationalised either by preferred kinetic formation of *syn*-EWG dipole **18** followed by *endo* dipolarophile addition or by thermodynamic control presuming that the *anti*-dipole **19** is in equilibrium with the more stable *syn*-dipole **18** (Scheme 5). We have observed that with maleimides, the ratio of cycloadducts obtained in the series of trifluoromethyl azomethine ylides is lower than with less reactive dipolarophiles (Table 1). Furthermore, the ylides bearing a cyano group, which stabilises the dipole stronger than the CF_3 group, lead exclusively to a single diastereoisomer (Scheme 3). Both of these observations suggest a possible stereomutation to the more stable *syn*-dipole **18** before the cycloaddition. This was recently confirmed by theoretical study of reaction between trifluoromethyl thiomethyl azomethine ylide and acrylonitrile.[12] Calculations revealed that the *endo* attack to *syn*-dipole **18** is 1.0 kcal/mol more favourable than for the *anti*-dipole **19**. Moreover, *endo* approach is favored over the *exo* attack mode in the range of 3.5–4.3 kcal/mol.

We have found that the best conditions for the cycloaddition require an excess of DBU (1.5 equiv.) over methyl triflate (1.1 equiv.). When the cycloadditions employing thioamides **3** or **10** are carried out overnight with 1.2 equiv. of methyl triflate and 1.1 equiv. of DBU, the ratio of the diastereoisomers is gradually eroded; from 95/5 to 10/70 in the case of **5** and from 91/9 to 40/30 for **11**, respectively. By monitoring the reactions by ^{19}F NMR, we have observed that this isomerisation occurs within the cycloadducts.

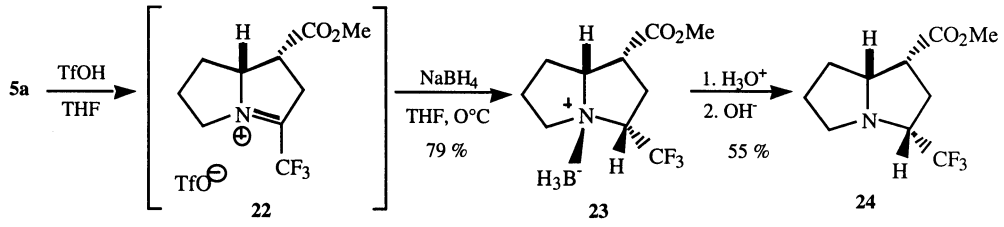
This epimerisation could be due to traces of triflic acid generated by the excess of methyl triflate. To substantiate this proposal, compounds **5a**, **6a** or **11a** and their isomer **5b**, **6b** or **11b** were treated with a catalytic amount of triflic acid in dichloromethane. In each case, epimerisation was observed and the equilibrium was determinated by ^{19}F NMR (Scheme 6). In the case of pyrrolizidines **5** and **6** which exist in a bent conformation, the major diastereoisomers **5b** and **6b** are the ones in which the steric interaction with CF_3 group is minimised, cycloadduct **6b** being more stable than **6a**.[12] The cycloadducts **11a** and **11b** have the five-membered ring in the envelope conformation with the six-membered ring in a chair. This conformation decreases steric repulsion between substituents; the equilibrium constant is thus closer to unity.

The difference between both diastereoisomers from each cycloaddition is clearly located in the stereogenic carbon bearing both methylsulfide and trifluoromethyl groups; it has been already demonstrated by NMR analysis.

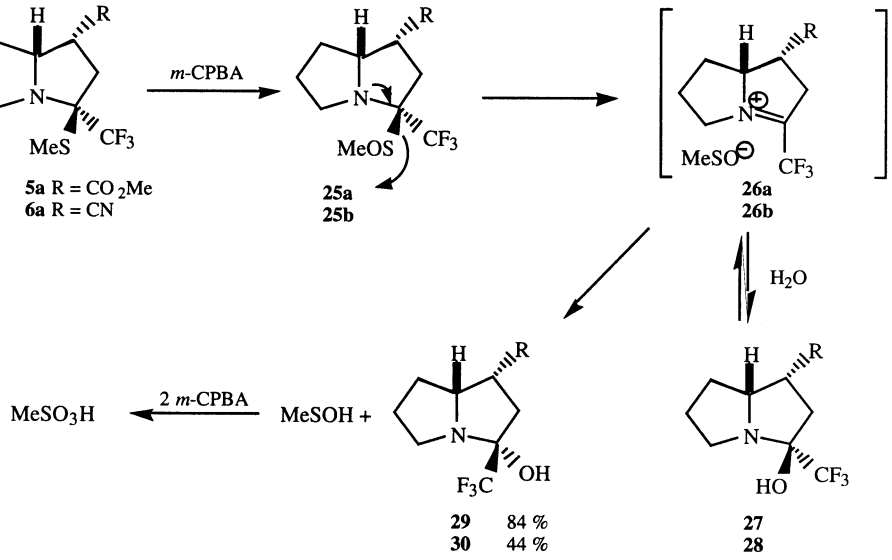
The epimerisation reaction appears to proceed via iminium intermediate **22** (Scheme 7). This iminium salt can be generated in situ by reacting **5a** with 1.5 equiv. of triflic acid in THF. Subsequent trapping of the intermediate by $NaBH_4$ at 0°C gives rise to aminoborane **23** which is isolated and purified by chromatography on silica gel or by distillation. The pyrrolizidine alkaloid **24** can then be liberated from its borane salt by an initial acidic treatment followed by a basic work-up in 55% overall yield (Scheme 7). That an iminium intermediate is involved in this reaction is demonstrated by the lack of reactivity of pyrrolizidine **5a** with $NaBH_4$ in the absence of triflic acid. The stereochemistry of **24** deduced from NMR data and MM2 calculations shows that the hydride attack on iminum **22** occurs from the less-hindered face of bicyclic system.

The hydrolysis of pyrrolizidines **5a** or **6a** is also possible under triflic acid catalysis. However, this method is less efficient than their reaction with three equivalents of *m*-chloroperbenzoic acid (*m*-CPBA 70–75%). Under these optimised conditions, α-trifluoromethylated hemiaminals **29** or **30** are obtained as single diastereoisomers (Scheme 8). These hemiaminals are crystalline and stable at room temperature, a property which can be ascribed to the electron-withdrawing effect of the α-trifluoromethyl substituent.

A mechanistic pathway which may explain these results is as follows (Scheme 8): the thioethers **5a** and **6a** undergo oxidation to unstable sulfoxides **25a**–**b** which dissociate into an iminium intermediate **26a**–**b**. These probably add water from the less hindered face to generate initially hemiaminal **27** and **28**. Upon isomerisation under these acidic conditions, the thermodynamically preferred diastereoisomers **29** and **30** are then produced. The sulfenic acid by-product is further oxidised to sulphonic acid. Presumably, the sulfoxide group in **25** is not oxidised to the sulphone before elimination. Indeed, if the sulphone group was generated, then one equivalent of *m*-CPBA should furnish a mixture of the starting pyrrolizidines **5a** or **6a**,



Scheme 7.



Scheme 8.

the products of first oxidation (sulfoxide **25** or **26**) and the hemiaminal **29** or **30**. In fact, the reaction of **5a** with 1 equiv. of *m*-CPBA gives rise to starting pyrrolizidine **5a** and the hemiaminal **29**.

In order to determinate the stereochemistry of **29** and **30**, we have studied the variation of the chemical shift of the hydroxy function in ^{1}H NMR in $CDCl_3$ in presence of different amounts of DMSO-d_6. The OH proton of **29** does not exhibit a deshielding in presence of DMSO-d_6. This result can be rationalised by the existence of an intramolecular hydrogen bond between the hydroxy and the ester group. The X-ray diffraction analysis of **29** confirms this *cis* relationship and shows the intramolecular hydrogen bond.[9]

In contrast, the OH proton of **30** gives a peak at 2.74 ppm in $CDCl_3$. In the presence of DMSO-d_6, a wide deshielding is obtained (6.50 ppm with 10% of DMSO-d_6) due to intermolecular hydrogen bonding between hydroxy group and DMSO. Intramolecular hydrogen bond between the hydroxy group and the linear cyano function is not possible and by analogy, we assume that **26** has the same stereochemistry as **29** by comparison based on their ^{19}F, ^{1}H and ^{13}C characteristic peaks.

In conclusion, we have shown that novel azomethine ylides could be efficiently produced, under mild conditions, from trifluorothioacetamides. Their subsequent reaction with a variety of dipolarophiles leads to a range of interesting heterocycles with high diastereoselectivity. Moreover, the intermediates thioaminals are useful synthons for further elaboration into interesting alkaloid structures.

2. Experimental

The ^{1}H NMR spectra were recorded on Varian Gemini-200 (200 MHz), Gemini-300 (300 MHz) and Brucker AM 500 (500 MHz) spectrometers using tetramethylsilane (TMS) as internal standard. The ^{13}C NMR spectra were recorded on Varian Gemini-200 (50 MHz) and Gemini-300 (75 MHz) spectrometers using $CDCl_3$ as reference. The ^{19}F NMR spectra were recorded on a Varian Gemini 300 (282 MHz) using $CFCl_3$ as the external standard (δ are given in ppm and J in Hz). IR were recorded on a Nicolet-205-FT and a Bio-Rad FTS 135 apparatus. Mass spectra were recorded on a Varian Matt 44S and a Finnigan-Mat TSQ-70 apparatus and elemental analysis were carried out at University College London, London, UK. Melting points were determined with a Buchi apparatus in capillaries and are uncorrected. Column chromatography was performed with Merck silica gel 60 (70–230 mesh ASTM) or Aldrich neutral alumina (150 mesh). All reaction solvents were dried and distilled according to standard procedures. Dichloromethane (Fluka p.a.) was washed with concentrated H_2SO_4 and water, dried over $CaCl_2$ and distilled on P_2O_5 prior to use for cycloaddition reactions.

2.1. Synthesis of thioamides

Trifluorothioacetamides **3**, **10** and **12** are prepared from the corresponding amides by thionation with P_4S_{10} as described recently.[7a] Cyanothioformamides **14** and **15** are synthesised by this modified procedure:[8]

CS_2 (0.1 mol) was added dropwise to a suspension of NaCN (0.1 mol) in DMF (30 ml) during 10 min. The brown mixture was stirred for 30 min at room temperature. Diethyl ether (100 ml) was added to the mixture under vigorous agitation and the brown precipitate was filtered and washed with diethyl ether (3×30 ml). This sodium salt was added to a cooled solution (0–5°C) of the amine (0.1 mol) and water (200 ml). The reaction was immediate and furnished a bright yellow precipitate which was collected by filtration and washed with water. The thioamide was recrystallised from ethanol/hexane.

2.1.1. *N*-Pyrrolidine cyanothioformamide (14). Yield: 70%. Mp: 36°C. ^{1}H NMR ($CDCl_3$) δ: 2.16 (m, 4H); 3.75 (m, 2H); 4.00 (m, 2H) ppm. RN: 28345-19-9.

2.1.2. *N*-Piperidine cyanothioformamide (15). Yield: 80%. Mp: 36–37°C. ^{1}H NMR ($CDCl_3$) δ: 1.78 (m, 6H); 4.04 (m, 2H); 4.11 (m, 2H) ppm. RN: 62025-88-1.

2.2. Cycloaddition reaction: general procedure

Methyl triflate (1.1 equiv.) was added to a solution of thioamide (1 g) dissolved in dry CH_2Cl_2 (1 ml), in a dry apparatus under an argon atmosphere. The mixture was stirred for 2 h in the case of trifluorothioacetamides, or for 30 min in the case of cyanothioformamides. Dry CH_2Cl_2 (40 ml) was added to the mixture via canula followed by the dipolarophile (1.5 equiv.). The mixture was cooled to −78°C and then dry DBU (1.5 equiv.) was added at once via a syringe. The mixture was stirred at this temperature for 30 minutes. The reaction mixture was then washed with HCl (1 M) and water. The organic phase was dried (Na_2SO_4) and evaporated. The cycloadducts were separated and purified by chromatography on silica gel or on neutral alumina.

2.3. Epimerisation reaction: general procedure

One drop of triflic acid was added to a solution of the cycloadduct in dry CH_2Cl_2 (5 ml). The reaction was monitored by ^{19}F NMR or by TLC. When the reaction has reached equilibrium, the mixture was washed with $NaHCO_3$ solution (1%). The organic phase was dried (Na_2SO_4) and evaporated. Both isomers were separated by chromatography on silica gel.

2.3.1. Methyl 3-(methylthio)-3-(trifluoromethyl)pyrrolizidine-1-carboxylate (5). Compound **5a**. Colourless oil. Yield: 54%. IR (neat): 2954; 1740 (C=O); 1438; 1259–1152 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: 70.4 (s) ppm. ^{1}H NMR ($CDCl_3$) δ: 28–2.05 (m, 4H, $-_2CH_2-$); 2.15 (q, J_{H-F}=1.1 Hz, 3H, $-SCH_3$); ~2.15 (1H, hidden by methyl group at 2.15, CF_3CCH_2-); 2.78 (dd, ^2J=13.6 Hz, ^3J=9.6 Hz, 1H, CF_3CCH_2-); 2.91–3.08 (m, 2H, NCH_2-); 3.38 (dd, ^3J=9.6, 9.2 Hz, 1H, MeOCOC*H*–); 3.71 (s, 3H, OCH_3); 3.86 (ddd, ^3J=9.4, 9.2, 6.0 Hz, 1H, NC*H*–) ppm. ^{13}C NMR ($CDCl_3$) δ: 13.20 (SCH_3); 26.56 ($-CH_2CH_2-$); 26.92 ($-CH_2CH_2-$); 36.58 (CF_3CCH_2); 43.47 (MeOCO*C*H); 47.15 (J_{C-F}=2.4 Hz, NCH_2); 51.53 (OCH_3); 66.38 (N*C*H); 76.22 (J_{C-F}=28.7 Hz, CF_3C-); 125.72 (J_{C-F}=282.5 Hz, CF_3-); 172.71 (MeO*C*O) ppm. MS (*m*/*e*): 283 (M^+); 264; 236; 177; 167; 69. Anal. calcd for $C_{11}H_{16}F_3NO_2S$: C: 46.64, H: 5.69, N: 4.94%. Found: C: 46.23, H: 5.61, N: 5.06%.

Compound **5b**. Colourless oil. Yield: 3%. IR (neat): 2955; 1740 (C=O); 1438; 1299–1156 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −76.5 (s) ppm. ^{1}H NMR ($CDCl_3$) δ: 1.35–2.06 (m, 4H, $-CH_2CH_2-$); 2.28 (q, J_{H-F}=1.3 Hz, 3H, $-SCH_3$); 2.53 (dd, ^2J=14.4 Hz, ^3J=8.7 Hz, 1H, CF_3CCH_2-); 2.67 (dd, ^2J=14.4 Hz, ^3J=9.5 Hz, 1H, CF_3CCH_2-); 2.97 (ddd, ^2J=11.8 Hz, ^3J=8.5, 4.6 Hz, 1H, NCH_2-); 3.34–3.48 (m, 2H, MeOCOC*H*–and NCH_2-); 3.72 (s, 3H, OCH_3); 3.81 (ddd, ^3J=11.1, 8.3, 5.8 Hz, 1H, NC*H*–) ppm. ^{13}C NMR ($CDCl_3$) δ: 14.47 (SCH_3); 26.54 ($-CH_2CH_2-$); 27.66 ($-CH_2CH_2-$); 35.84 (CF_3CCH_2); 42.63 (MeOCO*C*H); 47.77 (NCH_2); 51.50 (OCH_3); 68.40 (N*C*H); 75.90 (J_{C-F}=28.8 Hz, CF_3C-); 126.00 (J_{C-F}=282.7 Hz, CF_3-); 172.19 (MeO*C*O) ppm.

2.3.2. 3-(Methylthio)-3-(trifluoromethyl)pyrrolizidine-1-carbonitrile (6). Compound **6a**. Colourless crystals. Yield: 48%. Mp: 40–42°C. IR (KBr): 2953; 2245 (CN); 1214–1117 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −71.5 (s) ppm. ^{1}H NMR ($CDCl_3$) δ: 1.77–2.30 (m, 4H, $-CH_2CH_2-$); 2.20 (q, J_{H-F}=1.2 Hz, 3H, $-SCH_3$); 2.54 (dd, ^2J=14.5 Hz, ^3J=8.4 Hz, 1H, CF_3CCH_2-); ~2.84 (1H, hidden by the proton at 2.86, NCH_2-); 2.86 (dd, ^2J=14.5 Hz, ^3J=4.3 Hz, 1H, CF_3CCH_2-); 3.03 (m, 1H, NCH_2-); 3.15 (ddd, ^3J=8.4, 6.3, 4.3 Hz, 1H, *H*C–CN); 3.61 (ddd, ^3J=9.0, 6.3, 6.3 Hz, 1H, NC*H*–) ppm. ^{13}C NMR ($CDCl_3$) δ: 13.54 (SCH_3); 25.23 ($-CH_2CH_2-$); 27.08 ($-CH_2CH_2-$); 29.57 (–HCCN)); 42.46 (CF_3CCH_2); 44.30 (NCH_2); 65.70 (N*C*H); 72.62 (J_{C-F}=30.2 Hz, CF_3C-); 118.97 (–*C*N); 125.09 (J_{C-F}=282.9 Hz, CF_3-) ppm. MS (*m*/*e*): 250 (M^+); 231; 203; 134; 92; 69. Anal. calcd for $C_{10}H_{13}F_3N_2S$: C: 47.99, H: 5.24, N: 11.19%. Found: C: 48.21, H: 5.19, N: 11.24%.

Compound **6b**. Colourless oil. Yield: 2%. IR (neat): 2951; 2236 (CN); 1286–1085 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −75.7 (s) ppm. ^{1}H NMR ($CDCl_3$) δ: 1.92–2.10 (m, 4H, $-CH_2CH_2-$); 2.30 (q, J_{H-F}=1.1 Hz, 3H, $-SCH_3$); 2.70 (dd, ^2J=14.1 Hz, ^3J=2.7 Hz, 1H, CF_3CCH_2-); 2.82 (dd, ^2J=14.1 Hz, ^3J=7.9 Hz, 1H, CF_3CCH_2-); 2.88–2.94 (m, 1H, NCH_2-); 3.26–3.37 (m, 2H, NCH_2- and *H*C–CN); 3.91 (ddd, ^3J=7.6, 7.6, 4.1 Hz, 1H, NC*H*–) ppm. ^{13}C NMR ($CDCl_3$) δ: 14.63 (SCH_3); 28.21 ($-CH_2CH_2-$); 29.15 ($-CH_2CH_2-$); 30.21 (–HCCN)); 38.48 (CF_3CCH_2); 46.83 (NCH_2); 67.15 (N*C*H); 75.32 (J_{C-F}=30.2 Hz, CF_3C-); 119.20 (–*C*N); 125.58 (J_{C-F}=282.7 Hz, CF_3-) ppm.

2.3.3. 3-(Methylthio)-1-phenylsulphonyl-3-(trifluoromethyl)pyrrolizidine (7). Yield: 63% of a mixture of both diastereoisomers (**7a**/**7b**: 96/4) as a colourless oil which is unstable at room temperature. IR (neat): 2979; 1447; 1308–1097 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −70.1 (s, **7a**) and −76.7 (s, **7b**) ppm. ^{1}H NMR ($CDCl_3$) δ (**7a**): 1.78–2.15 (m, 4H, $-CH_2CH_2-$); 2.10 (s, 3H, $-SCH_3$); 2.25–2.39 (m, 1H, CF_3CCH_2-); 2.79 (dd, ^2J=13.0 Hz, ^3J=10.5 Hz, 1H, CF_3CCH_2-); 2.86–3.17 (m, 2H, NCH_2-); 3.90 (ddd, ^3J=9.0, 8.3, 6.3 Hz, 1H, NC*H*–); 4.01 (ddd, ^3J=10.5, 8.3, 7.5 Hz, 1H, *H*CSO_2Ph); 7.58–7.92 (m, 5H, –Ph) ppm. ^{13}C NMR ($CDCl_3$) δ (**7a**): 12.96 (SCH_3); 25.65 ($-CH_2CH_2-$); 26.74 ($-CH_2CH_2-$); 36.31 (CF_3CCH_2-)); 47.12 (NCH_2); 62.35 (H*C*SO_2Ph); 65.08 (N*C*H); 75.95 (J_{C-F}=29.0 Hz, CF_3C-); 125.35 (J_{C-F}=282.8 Hz, CF_3-); 127.76; 129.30; 133.78; 139.78 ppm. MS (*m*/*e*): 318 (M^+−SMe); 188; 175; 156; 141; 77.

2.3.4. 2-Methyl-4-(methylthio)-4-(trifluoromethyl)-pyrrolo[3,4-α]pyrrolizidine (8). Compound **8a**. Colourless oil. Yield: 58%. IR (neat): 2986–2850; 1782 (C=O); 1708 (C=O); 1435; 1291–1118 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −68.1 (s) ppm. ^{1}H NMR ($CDCl_3$) δ: 1.89–2.25 (m, 4H, $-CH_2CH_2-$); 2.31 (q, J_{H-F}=1.4 Hz, 3H, $-SCH_3$); 2.73 (td, ^2J=9.0 Hz, ^3J=9.0, 6.1 Hz, 1H, NCH_2-); 2.98 (m, 1H, NCH_2-); 2.99 (s, 3H, NCH_3); 3.19 (dd, ^3J=7.8, 7.5 Hz, 1H, $-CF_3CCHCHCH-$); 3.70 (d, ^3J=7.8 Hz, 1H, $-CF_3CCHCHCH-$); 3.74 (1H, hidden by the proton at 3.70, NC*H*–) ppm. ^{13}C NMR ($CDCl_3$) δ: 13.84 (SCH_3); 22.95 ($-CH_2CH_2-$); 25.08 (NCH_3); 26.62 ($-CH_2CH_2-$); 42.58 (NCH_2); 43.81 ($CF_3CCHCHCH$); 57.50 ($CF_3CCHCHCH$); 65.45 (N*C*H); 75.99 (J_{C-F}=30.8 Hz,

CF_3C–); 124.19 (J_{C-F}=282.8 Hz, CF_3–); 173.01 (C=O); 174.89 (C=O) ppm. MS (*m/e*): 289 (M^+−F); 261; 176. Anal. calcd for $C_{12}H_{15}F_3N_2O_2S$: C: 46.75, H: 4.90, N: 9.09%. Found: C: 46.14, H: 4.83, N: 8.78%.

Compound **8b**. Colourless solid. Yield: 8%. IR (KBr): 2965; 1780 (C=O); 1704 (C=O); 1434; 1285–1107 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −71.8 (s) ppm. ^1H NMR ($CDCl_3$) δ: 1.64–2.20 (m, 4H, $-CH_2CH_2-$); 2.26 (q, J_{H-F}=2.0 Hz, 3H, $-SCH_3$); 2.88 (ddd, ^2J=11.0 Hz, ^3J=8.6, 4.8 Hz, 1H, NCH_2-); 3.01 (s, 3H, NCH_3); 3.32 (ddd, ^2J=11.0 Hz, ^3J=8.2, 6.6 Hz, 1H, NCH_2-); 3.45 (dd, ^3J=9.1, 9.0 Hz, 1H, $-CF_3CCHCHCH-$); 3.86 (ddd, ^3J=9.1, 9.0, 6.2 Hz, 1H, NC*H*–); 3.91 (d, ^3J=9.0 Hz, $-CF_3CCHCHCH-$) ppm. ^{13}C NMR ($CDCl_3$) δ: 15.30 (SCH_3); 24.90 (NCH_3); 26.42 ($-CH_2CH_2-$); 27.64 ($-CH_2CH_2-$); 45.36 ($CF_3CCHCHCH$); 45.67 (NCH_2); 56.25 ($CF_3CCHCHCH$); 66.12 (N*C*H); 76.70 (J_{C-F}=32.1 Hz, CF_3C–); 125.00 (J_{C-F}=286.8 Hz, CF_3–); 172.83 (C=O); 175.54 (C=O) ppm.

2.3.5. 2-Phenyl-4-(methylthio)-4-(trifluoromethyl)-pyrrolo[3,4-α]pyrrolizidine (9). Yield: 55% of a mixture of both diastereoisomers (**9a/9b**: 81/19) from which **9a** was isolated after recrystallisation from petroleum ether/ethyl acetate. **9a**: colourless solid. Mp: 104–106°C. ^{19}F NMR ($CDCl_3$) δ: −67.9 (s, **9a**) and −69.9 (s, **9b**) ppm. ^1H NMR ($CDCl_3$) δ: 1.93–2.17 (m, 4H, $-CH_2CH_2-$); 2.35 (q, J_{H-F}=1.3 Hz, 3H, $-SCH_3$); 2.73–2.85 (m, 1H, NCH_2-); 2.90–3.00 (m, 1H, NCH_2-); 3.37 (dd, ^3J=8.0, 7.7 Hz, 1H, $-CF_3CCHCHCH-$); 3.83 (m, 1H, NC*H*–); 3.85 (d, ^3J=8.0 Hz, 1H, $-CF_3CCHCHCH-$); 7.23–7.50 (m, 5H, –Ph) ppm. ^{13}C NMR ($CDCl_3$) δ: 14.00 (SCH_3); 22.91 ($-CH_2CH_2-$); 26.75 ($-CH_2CH_2-$); 42.98 (NCH_2); 44.01 ($CF_3CCHCHCH$); 57.69 ($CF_3CCHCHCH$); 65.97 (N*C*H); 76.49 (J_{C-F}=30.5 Hz, CF_3C–); 124.45 (J_{C-F}=283.2 Hz, CF_3–); 126.26; 128.70; 129.00; 131.72; 172.05 (C=O); 174.01 (C=O) ppm. MS (*m/e*): 370 (M^+); 323; 271; 176; 91; 77; 69. Anal. calcd for $C_{17}H_{17}F_3N_2O_2S$: C: 55.13, H: 4.63, N: 7.56%. Found: C: 55.47, H: 4.84, N: 7.05%.

2.3.6. Methyl 6-(methylthio)-6-trifluoromethylperhydropyrrolo[2,1-*c*][1,4]oxazine-8-carboxylate (11). Compound **11a**. Colourless crystals. Yield: 53%. IR (KBr): 2984–2843; 1747 (C=O); 1433; 1296–1151 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −71.8 (s) ppm. ^1H NMR ($CDCl_3$) δ: 2.26 (q, J_{H-F}=1.2 Hz, 3H, $-SCH_3$); ~2.27 (1H, hidden by the methyl at 2.26, CF_3CCH_2-); 2.80–2.89 (m, 2H, CF_3CCH_2- and NCH_2-); 2.99 (broad d, ^2J=11.2 Hz, 1H, NCH_2-); 3.20 (dd, ^3J=9.3, 5.1 Hz, 1H, MeOCOC*H*–); 3.25 (dd, ^2J=10.4 Hz, ^3J=10.2 Hz, 1H, $-NCHCH_2O-$); 3.32 (ddd, ^3J=10.2, 9.3, 2.5 Hz, 1H, NC*H*–); 3.46 (dt, ^2J=11.3 Hz, ^3J=2.7 Hz, 1H, $-OCH_2CH_2N-$); 3.70 (s, 3H, $-OCH_3$); 3.80 (dd, ^2J=11.3 Hz, ^3J=3.1 Hz, 1H, $-OCH_2CH_2N-$); 4.04 (broad d, ^2J=10.4 Hz, 1H, $-NCHCH_2O-$) ppm. ^{13}C NMR ($CDCl_3$) δ: 14.22 (SCH_3); 34.39 (CF_3CCH_2); 41.16 (MeOCO*C*H); 47.56 (NCH_2); 51.85 (OCH_3); 60.52 (N*C*H); 65.72 ($-OCH_2CH_2N-$); 69.29 ($-OCH_2CHN-$); 77.47 (J_{C-F}=29.9 Hz, CF_3C–); 125.54 (J_{C-F}=283.2 Hz, CF_3–); 171.86 (MeO*C*O) ppm. MS (*m/e*): 299 (M^+); 264; 252; 220; 192; 162; 69. Anal. calcd for $C_{11}H_{16}F_3NO_3S$: C: 44.14, H: 5.39, N: 4.68, S: 10.71%. Found: C: 44.34, H: 5.44, N: 4.65, S: 10.48%.

Compound **11b**. Colourless oil. Yield: 5%. IR (neat): 2958–2856; 1737 (C=O); 1451; 1290–1051 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −70.2 (s) ppm. ^1H NMR ($CDCl_3$) δ: 2.14 (s, 3H, $-SCH_3$); 2.48 (dd, ^2J=15.1 Hz, ^3J=9.7 Hz, 1H, CF_3CCH_2-); 2.70–2.80 (m, 2H, CF_3CCH_2- and NCH_2-); 2.99 (dd, ^2J=10.4 Hz, ^3J=10.4 Hz, 1H, $-NCHCH_2O-$); 3.11–3.21 (m, 2H, MeOCOC*H*– and NCH_2-); 3.33 (ddd, ^2J=11.3 Hz, ^3J=11.1, 2.8 Hz, 1H, $-OCH_2CH_2N-$); 3.48 (tm, ^3J=10.4 Hz, 1H, NC*H*–); 3.70 (s, 3H, $-OCH_3$); 3.83 (broad dd, ^2J=11.1 Hz, ^3J=3.2 Hz, 1H, $-OCH_2CH_2N-$); 3.94 (dd, ^2J=10.4 Hz, ^3J=3.0 Hz, 1H, $-NCHCH_2O-$) ppm. ^{13}C NMR ($CDCl_3$) δ: 9.84 (SCH_3); 34.24 (CF_3CCH_2); 40.82 (MeOCO*C*H); 44.60 (NCH_2); 51.72 (OCH_3); 59.52 (N*C*H); 66.63 ($-OCH_2CH_2N-$); 69.85 ($-OCH_2CHN-$); 76.90 (J_{C-F}=25.5 Hz, CF_3C–); 126.79 (J_{C-F}=294.9 Hz, CF_3–); 172.59 (MeO*C*O) ppm.

2.3.7. Methyl 3-(methylthio)-3-trifluoromethyloctahydropyrrolo[1,2-*a*]azepine-1-carboxylate (13). Compound **13**. Colourless liquid. Yield: 10%. IR (neat): 2930; 1742 (C=O); 1438; 1259–1163 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −73.8 (s) ppm. ^1H NMR ($CDCl_3$) δ: 1.36–1.75 (m, 6H, $-CH_2CH_2CH_2-$); 2.15 (q, J_{H-F}=1.3 Hz, 3H, $-SCH_3$); 2.29 (dd, ^2J=13.4 Hz, ^3J=6.6 Hz, 1H, CF_3CCH_2-); 2.71 (dd, ^2J=13.4 Hz, ^3J=12.3 Hz, 1H, CF_3CCH_2-); 2.75 (1H, hidden by the proton at 2.71, NCH_2-); 3.23 (ddd, ^3J=12.3, 6.6, 6.5 Hz, 1H, MeOCOC*H*–); 3.42 (ddd, ^2J=9.3 Hz, ^3J=9.2, 3.3 Hz, 1H, NCH_2-); 3.61 (ddd, ^3J=12.3, 9.2, 6.5 Hz, 1H, NC*H*–); 3.70 (s, 3H, $-OCH_3$) ppm. ^{13}C NMR ($CDCl_3$) δ: 13.64 (SCH_3); 25.20 ($-CH_2CH_2CH_2-$); 26.60 ($-CH_2CH_2CH_2-$); 29.37 ($-CH_2CH_2CH_2-$); 31.90 ($NCHCH_2$); 33.38 (CF_3CCH_2); 44.30 (MeOCO*C*H); 47.26 (NCH_2); 51.73 ($-OCH_3$); 64.83 (N*C*H–); 77.64 (J_{C-F}=30.0 Hz, CF_3C–); 125.82 (J_{C-F}=284.0 Hz, CF_3–); 172.03 (MeO*C*O) ppm. MS (*m/e*): 311 (M^+); 264; 204; 148; 69.

2.3.8. 4-(Methylthio)-2-phenyl-4-cyano-pyrrolo[3,4-α]-pyrrolizidine (16). Compound **16**. Colourless gum which is unstable at room temperature. Yield: 60%. IR (KBr): 2950; 1720 (C=O); 1500; 1383; 1191 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.98–2.16 (m, 4H, $-CH_2CH_2-$); 2.43 (s, 3H, $-SCH_3$); 3.10 (m, 2H, NCH_2-); 3.64 (t, ^3J=8.8 Hz, 1H, $-CF_3CCHCHCH-$); 3.85 (d, ^3J=8.8 Hz, 1H, $-CF_3CCHCHCH-$); 4.02 (m, 1H, NC*H*–); 7.28–7.49 (m, 5H, –Ph) ppm. ^{13}C NMR ($CDCl_3$) δ: 14.09 (SCH_3); 25.80 ($-CH_2CH_2-$); 26.11 ($-CH_2CH_2-$); 46.08 ($CF_3CCHCHCH$); 48.81 (NCH_2); 60.00 ($CF_3CCHCHCH$); 65.94 (N*C*H); 70.07 (NC–*C*–); 115.02 (–*C*N); 126.21; 129.01; 129.28; 131.15; 172.10 (C=O); 174.06 (C=O) ppm. MS (*m/e*): 327 (M^+); 300; 280; 133; 26.

2.3.9. 2-Methyl-4-cyano-4-(methylthio)-pyrrolo[3,4-α]-indolizidine (17). Compound **17**. Colourless solid which is unstable at room temperature. Mp: 60–61°C. Yield: 30%. IR (KBr): 2944; 1718 (C=O); 1500; 1387; 1195 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.27–2.18 (m, 6H, $-CH_2CH_2CH_2-$); 2.49 (s, 3H, $-SCH_3$); ~2.49 (1H, hidden by the methyl group at 2.49, NCH_2-); 3.15 (ddd, ^3J=11.0, 8.4, 2.6 Hz, 1H, NC*H*–); 3.28 (dm, ^2J=10.6 Hz, 1H, NCH_2-); 3.44 (dd, ^3J=8.4, 8.0 Hz, 1H, $-CF_3CCHCHCH-$); 3.62 (d, ^3J=8.0 Hz, 1H, $-CF_3CCHCHCH-$); 7.27–7.49 (m, 5H, –Ph) ppm. ^{13}C NMR ($CDCl_3$) δ: 15.69 (SCH_3); 23.64

(–$CH_2CH_2CH_2$–); 24.48 (–$CH_2CH_2CH_2$–); 28.30 (–$CH_2CH_2CH_2$–); 45.67 ($CF_3CCHCHCH$); 47.48 (NCH_2); 54.10 ($CF_3CCHCHCH$); 60.24 (NCH); 72.49 (NC–C–); 113.07 (–CN); 126.27; 128.63; 129.05; 131.56; 171.82 (C=O); 173.38 (C=O) ppm. MS (*m/e*): 341 (M^+); 314; 294; 267; 246; 194.

2.4. Reduction of the pyrrolizidine 5a by treatment successive with triflic acid and $NaBH_4$

2.4.1. Amino borane of methyl 3-(trifluoromethyl)pyrrolizidine-1-carboxylate (23). Triflic acid (0.465 ml, 5.30 mmol) was added via a syringe to a cooled (0°C) solution containing the pyrrolizidine **5a** (1.0 g, 3.53 mmol) in dry THF (5 ml). The mixture was stirred at 0°C for 10 min. Dry THF (10 ml) was then added to the mixture followed by $NaBH_4$ (0.4 g, 10.60 mmol) at 0°C. The mixture was stirred for an additionnal 15 min. Water (10 ml) was added to the mixture and the product was extracted with CH_2Cl_2 (3×10 ml). The organic phase was washed with a saturated solution of $NaHCO_3$ and with water and dried ($MgSO_4$). The solvent was evaporated and the product was purified by chromatography on silica gel (eluent: CH_2Cl_2) to afford **23** (0.7 g, 79%) as a colourless solid. Mp: 51°C. Bp: 110°C/5×10^{-3} mm Hg. IR (KBr): 2991–2957; 2395–2282 (B–H); 1741 (C=O); 1476–1300; 1278–1132 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −65.5 (d, $^3J_{F-H}$=7.4 Hz) ppm. ^1H NMR ($CDCl_3$) δ: 1.48–2.27 (m, 7H, –CH_2CH_2– and BH_3); 2.30–2.49 (m, 2H, CF_3CHCH_2–); 3.19 (m, 1H, NCH_2–); 3.34–3.49 (m, 2H, NCH_2– and MeOCOCH–); 3.74 (s, 3H, OCH_3); 3.96 (m, 1H, CF_3CH–); 4.12 (ddd, ^3J=9.5, 9.5, 6.7 Hz, 1H, NCH–) ppm. ^{13}C NMR ($CDCl_3$) δ: 25.10 (–CH_2CH_2–); 27.25 (–CH_2CH_2–); 28.93 (CF_3CHCH_2); 42.84 (MeOCOCH); 52.12 (OCH_3); 58.08 (NCH_2); 70.47 (J_{C-F}=31.0 Hz, CF_3CH–); 77.81 (NCH); 123.60 (J_{C-F}=280.6, CF_3–); 170.15 (MeOCO) ppm. MS (*m/e*): 251 (M^+); 237; 222; 168; 69. Anal. calcd for $C_{10}H_{17}BF_3NO_2$: C: 47.84, H: 6.83, N: 5.58%. Found: C: 47.67, H: 6.79, N: 5.48%.

2.4.2. Methyl 3-(trifluoromethyl)pyrrolizidine-1-carboxylate (24). Triflic acid (0.465 ml, 5.30 mmol) was added via a syringe to a cooled (0°C) solution containing the pyrrolizidine **5a** (1.0 g, 3.53 mmol) in dry THF (5 ml). The mixture was stirred at 0°C for 10 min. Dry THF (10 ml) was then added to the mixture followed by $NaBH_4$ (0.4 g, 10.60 mmol) at 0°C. The mixture was stirred at room temperature for an additional 15 min and then acidified to pH 1–2 with HCl (5%). The THF was removed under reduced pressure and the residue was stirred for another 10 min. Water (10 ml) was added and the mixture was extracted with diethyl ether (3×5 ml). The aqueous phase was basified to pH 9–10 at 0°C with NaOH (10%) and extracted with diethyl ether (4×5 ml). The combined ether layers were washed with water and dried (Na_2SO_4). The solvent was evaporated and the product was purified by chromatography on silica gel (eluent: CH_2Cl_2) to afford **24** (0.5 g, 59%) and a small amount of aminoborane **23**. **24**: colourless liquid. **IR** (neat): 2962; 1739 (C=O); 1285–1129 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −71.1 (d, $^3J_{F-H}$=7.5 Hz) ppm. ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.37–2.02 (m, 4H, –CH_2CH_2–); 2.22 (ddd, $^2J_{2-2'}$=13.2 Hz, $^3J_{2-1}$=8.3 Hz, $^3J_{2-3}$=6.7 Hz, 1H, CF_3CHCH_2–); 2.56 (m, 2H, CF_3CHCH_2– and NCH_2–); 2.92 (m, 1H, NCH_2–); 3.02 (ddd, $^3J_{1-8}$=8.3 Hz, $^3J_{1-2}$=8.3 Hz, $^3J_{1-2'}$=8.1 Hz, 1H, MeOCOCH); 3.25 (ddq, $^3J_{3-2'}$=10.2 Hz, $^3J_{3-2}$=6.7 Hz, $^3J_{H-F}$=7.9 Hz, 1H, CF_3CH); 3.45 (ddd, $^3J_{8-1}$=8.3 Hz, $^3J_{8-7}$=8.3 Hz, $^3J_{8-7'}$=6.6 Hz, 1H, NCH–); 3.71 (s, 3H, –OCH_3) ppm. ^{13}C NMR ($CDCl_3$) δ: 25.95 (–CH_2CH_2–); 26.58 (–CH_2CH_2–); 29.12 (CF_3CHCH_2); 43.91 (MeOCOCH); 47.45 (NCH_2); 51.64 (OCH_3); 61.12 (J_{C-F}=30.0 Hz, CF_3CH–); 68.90 (NCH); 125.42 (J_{C-F}=279.1 Hz, CF_3–); 172.99 (MeOCO) ppm. MS (*m/e*): 237 (M^+); 222; 168; 158; 141. Anal. calcd for $C_{10}H_{14}F_3NO_2$: C: 50.63 H: 5.95, N: 5.90%. Found: C: 50.45, H: 5.83, N: 5.75%.

2.5. Reaction of pyrrolizidines 5a and 6a with *m*-CPBA: general procedure

m-CPBA (3 equiv., 70–75%) was slowly added to a cooled (0°C) solution of pyrrolizidine **5a** or **6a** and CH_2Cl_2 (15 ml). The mixture was stirred at room temperature for 4 h. Additional CH_2Cl_2 (35 ml) was added and the mixture was washed with saturated Na_2CO_3 solution (2×20 ml) and once with water. The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The hemiaminal was purified by chromatography on silica gel.

2.5.1. Methyl 3-hydroxy-3-(trifluoromethyl)pyrrolizidine-1-carboxylate (29). 29: colourless crystals which can be recrystallised from cooled cyclohexane. Mp: 31–33°C. Yield: 84%. IR (neat): 3390; 2959; 1707 (C=O); 1215–1155 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −82.3 (s) ppm. ^1H NMR ($CDCl_3$) δ: 1.30–1.86 (m, 4H, –CH_2CH_2–); 2.40 (d, ^2J=14.0 Hz, 1H, $CF_3C(OH)CH_2$–); 2.68 (m, 2H, $CF_3C(OH)CH_2$– and NCH_2–); 3.19 (dd, $^3J_{1-8}$=8.1, 8.1 Hz, 1H, MeOCOCH); 3.35 (ddd, $^2J_{/}$=10.0, 10.0, 7.0 Hz, 1H, NCH_2–); 3.77 (s, 3H, –OCH_3); 4.07 (dd, ^3J=14.7, 8.1 Hz, 1H, NCH–); 5.53 (s, 1H, –OH) ppm. ^{13}C NMR ($CDCl_3$) δ: 28.29 (–CH_2CH_2–); 28.88 (–CH_2CH_2–); 39.83 (CF_3CHCH_2); 43.38 (NCH_2); 44.19 (MeOCOCH); 52.50 (OCH_3); 68.65 (NCH); 90.14 (J_{C-F}=31.1 Hz, $CF_3CH(OH)$–); 124.33 (J_{C-F}=283.6 Hz, CF_3–); 177.53 (MeOCO) ppm. MS (*m/e*): 253 (M^+); 235; 222; 184; 176; 139; 69. Anal. calcd for $C_{10}H_{14}F_3NO_3$: C: 47.43 H: 5.57, N: 5.53%. Found: C: 47.23, H: 5.38, N: 5.35%.

2.5.2. 3-Hydroxy-3-(trifluoromethyl)pyrrolizidine-1-carbonitrile (30). Compound **30**. Colourless crystals which can be recrystallised from hexane. Mp: 90–92°C. Yield: 44%. IR (KBr): 3389; 2956; 2249 (CN); 1285–1037 cm^{-1}. ^{19}F NMR ($CDCl_3$) δ: −83.1 (s) ppm. ^1H NMR ($CDCl_3$) δ: 1.95–2.15 (m, 4H, –CH_2CH_2–); 2.47 (d, ^2J=13.8 Hz, 1H, $CF_3C(OH)CH_2$–); 2.74 (dd, ^2J=13.8 Hz, ^3J=7.9 Hz, 1H, $CF_3C(OH)CH_2$–); 2.74 (s, 1H, –OH); 2.75 (1H, hidden by the protons at 2.74, NCH_2–); 3.25 (m, 2H, NCH_2– and NC–CH); 3.91 (dd, ^3J=13.5, 7.0 Hz, 1H, NCH–) ppm. ^{13}C NMR ($CDCl_3$) δ: 27.95 (–CH_2CH_2–); 29.44 (–CH_2CH_2–); 30.28 (NC–CH); 41.04 ($CF_3C(OH)CH_2$); 43.96 (NCH_2); 66.57 (NCH); 90.03 (J_{C-F}=31.7 Hz, $CF_3C(OH)$–); 119.95 (–CN); 123.77 (J_{C-F}=284.1 Hz, CF_3–) ppm. MS (*m/e*): 220 (M^+); 203; 167; 151; 139; 109; 98. Anal. calcd for $C_9H_{11}F_3N_2O$: C: 49.09 H: 5.04, N: 12.72%. Found: C: 48.70, H: 5.00, N: 12.12%.

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