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Synthesis and reactivity of new trifluoromethylated azacyanines starting from 3-(1-amino-2,2,2-trifluororoethylidene)pyrrolidin-2-ones†

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Summary — The trifluoromethylated enamines **4** and **5** obtained from 3-trifluoroacetyl-pyrrolidinone **1** and ammonia or methylamine, are good precursors for the synthesis of new 4-azapentamethine cyanines **8–10**. These 1,5-bis-electrophiles condense with ammonia or phenylhydrazine to give 5*H*-pyrrolo[2,3-*d*]pyrimidines **18**, **19**, pyrimidinone **20** and pyrrolo-[3,2-*f*]-1,2,4-triazepines **21**, **22**. The structure and configuration of all the heterocycles are confirmed by their NMR and UV/vis data and by comparison with analogous compounds.

enamine / pyrrolidin-2-one / 4-azacyanine / pyrimidine / pyrimidin-2-one / 1,2,4-triazepine

Résumé — Synthèse et réactivité des nouvelles azacyanines trifluorométhylées à partir des 3-(1-amino-2,2,2-trifluorométhylidène)pyrrolidin-2-ones. *Les énamines trifluorométhylées **4** et **5** qui sont obtenues à partir de la 3-trifluoroacétyl-pyrrolidone **1** et de l'ammoniac ou de la méthylamine, sont de bons précurseurs dans la synthèse des nouvelles 4-azapentaméthine cyanines **8–10**. Ces électrophiles 1,5 condensent avec l'ammoniac ou la phénylhydrazine pour donner les pyrrolo[2,3]pyrimidines **18** et **19**, la pyrimidone **20** ou les pyrrolidino[3,2-f]-1,2,4-triazépines **21** et **22**. Les structures et les configurations de ces hétérocycles sont confirmées par leurs spectres RMN et UV/vis mais aussi par comparaison avec des composés analogues.*

enamine / pyrrolidin-2-one / 4-azacyanine / pyrimidine / pyrimidin-2-one / 1,2,4-triazépine

Introduction

3-Trifluoroacetyl-lactam **1** and its homologues **2** and **3** are useful reagents for the synthesis of new trifluoromethylated heterocycles. To date they have been employed in heterocyclizations with bis-nucleophiles [1–5], in Robinson spiroannelations [6, 7] and in the preparation of 3-(2,2,2-trifluoroethylidene)lactams which underwent various 1,3-dipolar cycloadditions [8].

Now we report that the 3-trifluoroacetyl-pyrrolidinone **1** can be converted into enamines **4** and **5**, which are good precursors of new azacyanines and heterocycles such as 5*H*-pyrrolo[2,3-*d*]pyrimidines and pyrrolo-[3,2-*f*]-1,2,4-triazepines.

Results

Preparation of 3-(1-amino-2,2,2-trifluoroethylidene)-pyrrolidin-2-ones **4** *and* **5**

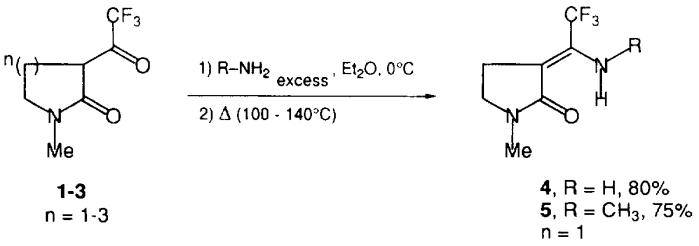
Enamines of trifluoromethylated β-ketoesters are usually obtained by reaction with amines followed by thermolysis of the intermediary ammonium salts [9, 10]. In our laboratory, we applied the same method to ethyl trifluoroacetoacetate to prepare ethyl 3-amino-4,4,4-trifluorocrotonate which turned out to be an excellent reagent for the synthesis of new trifluoromethylated heterocycles [11–13].

The treatment of 3-(trifluoroacetyl)pyrrolidone **1** with ammonia or methylamine produces the corresponding ammonium enolate which is then thermolyzed under reduced pressure to give the 3-(1-amino-2,2,2-trifluoroethylidene)pyrrolidin-2-ones **4** or **5** (scheme 1). Unfortunately, this reaction is limited to pyrrolidinone **1**. Indeed, no ammonium salts were formed with piperidinone **2** or azepinone **3**. We explain these observations by the difference in acidity of 3-trifluoroacetyl-lactams **1–3**.

The *Z* configuration of enamines **4** and **5** was assigned by comparison of the ^{13}C NMR data of **4**, **5** and pyrrolidinone **6**, for which the structure was determined by X-ray diffraction analysis [3]. As indicated in table I, the ^{13}C chemical shifts ($\delta_{C1,C5,C6}$) of **4** and **5** are very similar to those of pyrrolidinone **6** which exists as the *Z* stereoisomer only. Moreover, the carbon–hydrogen ($^3J_{C5,H8}$) and carbon–fluorine ($^4J_{C1,F}$) cou-

† Dedicated to Prof F Minisci.

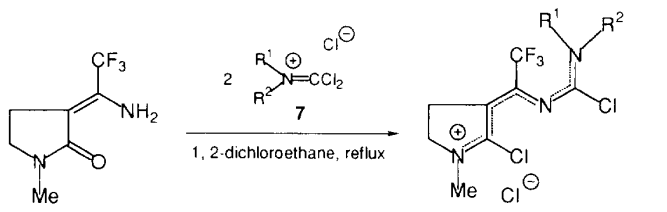
* Correspondence and reprints



1-3
n = 1-3

4, R = H, 80%
5, R = CH_3, 75%
n = 1

Scheme 1

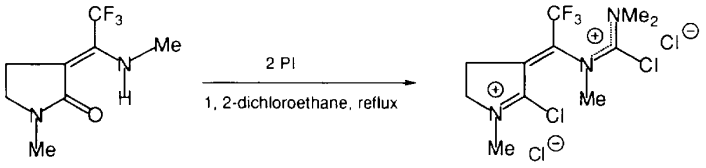


4

8 : $R^1 = R^2 =$ Me : 91 %

9 : $R^1 = R^2 =$ ⬠ : 80 %

Scheme 2



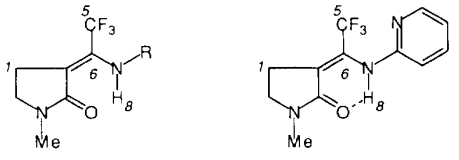
5

10
84 %

Scheme 3

pling constants of **4** and **5** are in good agreement with those of **6** and with the literature data [14]. It should be noted that we did not detect the other stereoisomer in solution at room temperature.

Table I. ^{13}C NMR data of pyrrolidinones **4–6**.



4,5

6

Lactam	*R*	δ_{C1}	δ_{C5}	δ_{C6}	$^3J_{C5,H8}$	$^4J_{C1,F}$
4	H	21.1	121.3	136.6	-	2.4
5	Me	22.2	121.6	139.8	10.6	2.6
6	-	22.8	121.8	135.0	8.4	2.3

Preparation of azacyanines **8–10**

Various azacyanines are already reported in the literature and so we will focus only on chlorinated 2-azapentamethine cyanines, which show the greatest similarity with our compounds **8–10**.

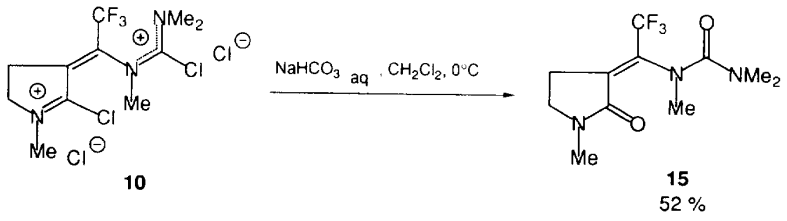
The 1,3,5-trichloro-2-azapentamethine cyanines are usually prepared using two procedures: the reaction of a nitrile with a phosgeniminium salt PI [15, 16], the acylation of a secondary amide with PI followed by thermolysis into 2-azabutadiene and the subsequent condensation of another phosgeniminium salt [17].

The 3-substituted 1,5-dichloro-2-azapentamethine cyanines are also obtained from vinyl isocyanates and 2 equivalents of phosgeniminium salt [18] whereas the 3,4-disubstituted analogs are synthesized by the reaction of silylated enamines and PI [19]. We employed a modification of this last method for the preparation of our trifluoromethylated azacyanines **8–10**.

A mixture of the stable primary enamine **4** and the phosgeniminium salt **7** was refluxed in dry 1,2-dichloroethane to give 3-trifluoromethyl-4-azapentamethine cyanines **8** and **9** (scheme 2). Moreover, the enamino pyrrolidinone **5** was condensed with 2 equivalents of PI to furnish the double salt **10** (scheme 3).

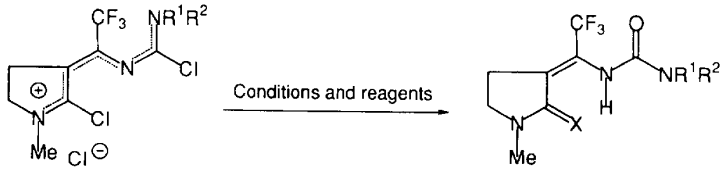
Characterization of azacyanines **8–10**

The trifluoromethylated azacyanines **8–10** are hygroscopic thick oils, soluble in chlorinated solvents. They are usually orange to brown. Their UV/vis spectra show a maximum between 364 and 370 nm (table II). Moreover, these azacyanines display a slightly lower λ_{max}



10 15 52 %

Scheme 4

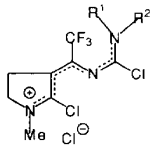


8,9 13,14,16,17

Scheme 5

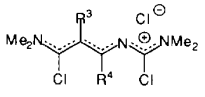
than the similar already known [19] compounds **11** and **12**, which indicates a weaker conjugation. This phenomenon can probably be explained by the increased rigidity of the chromophore due to the presence of a lactam ring.

Table II. UV/vis data of azacyanines **8–12**.



8 : $R^1 = R^2 = Me$

9 : $R^1 = R^2 =$ 



11,12

Compound [ref]	R^3	R^4	λ_{max} *(nm) (log ε)*	*Solvent*
8	–	–	368 (0.65)	$CHCl_3$
9	–	–	370 (0.49)	CH_2Cl_2
10	–	–	364 (1.16)	$CHCl_3$
11 [19]	Me	Ph	374	$CHCl_3$
12 [19]	Ph	Ph	382	$CHCl_3$

The azacyanines **8–10** are also characterized by hydrolysis, thiolysis and aminolysis. The treatment of **8–10** with an aqueous solution of $NaHCO_3$ gives the pyrrolidinones **13–15** in moderate to good yield (schemes 4 and 5, table III). As for **15**, one notes that there is no fragmentation into *N,N,N'*-trimethylurea or 3-(trifluoroacetyl)pyrrolidinone **1** as has been mentioned for the known analogues [19].

The thiolysis and aminolysis of azacyanine **8** are selective (scheme 5, table III). Thus when a mixture of **8** and triethylamine was saturated with a large excess of hydrogen sulfide (table III, entry **c**), the pyrrolidine-2-thione **16** was isolated and characterized unambiguously. Moreover, the treatment of **8** with a solution of aniline and triethylamine produced exclusively the 2-(phenylimino)pyrrolidine **17** (table III, entry **d**).

The thiolysis of azacyanine **8** is different from that of its analogues where only the bis-thioamides were obtained [20]. These results (table III, entries **c,d**) can be explained by the difference of reactivity between amide chloride and urea dichloride functions [21]. Indeed, the compounds **16** and **17** arise from the substitution of the more reactive chlorine with hydrogen sulfide or aniline followed by the basic hydrolysis of urea chloride during the work-up.

Table III. Conditions, reagents and yields for compounds **13**, **14**, **16** and **17**.

Entry	*Cyanine*	R^1	R^2	*Conditions and reagents*	*Cpd*	*X*	*Yield (%)*
a	**8**	Me	Me	$NaHCO_3$ aq, $CHCl_3$ or CH_2Cl_2, 0 °C	**13**	O	73
b	**9**	$(CH_2)_4$			**14**	O	51
c	**8**	Me	Me	H_2S, Et_3N, CH_2Cl_2, 0 °C	**16**	S	31
d	**8**	Me	Me	$PhNH_2$, Et_3N, CH_2Cl_2, reflux	**17**	NC_6H_5	63

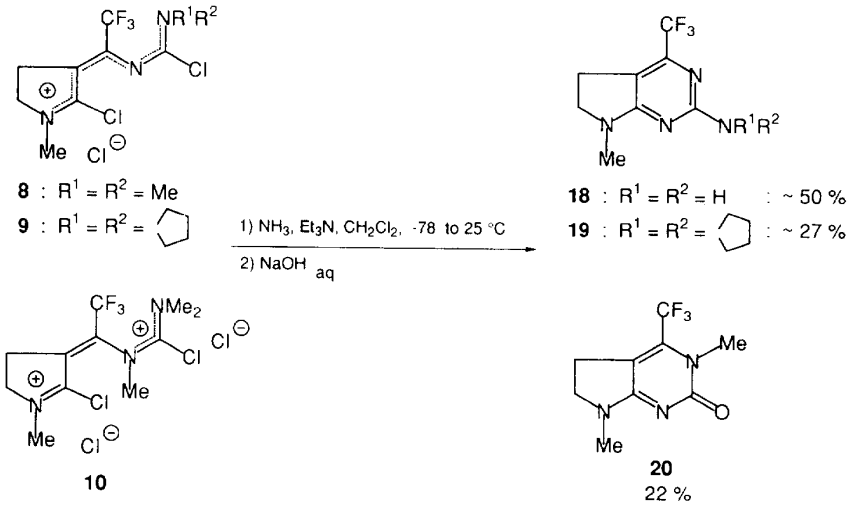
The *Z* configuration of pyrrolidinones **13–15** was assigned based on the chemical shift of carbon 1 (δ_{C1} = 22–23 ppm) and the carbon–fluorine coupling constant ($^4J_{C1,F}$ = 2.4–3.1 Hz) as was observed for the enamines **4** and **5** (table I). One notes a small difference of δ_{C1} between heterocycles **16** and **17** (δ_{C1} = 25.3 ppm and δ_{C1} = 24.3 ppm respectively).

Cyclization of azacyanines **8–10** *with nucleophiles*

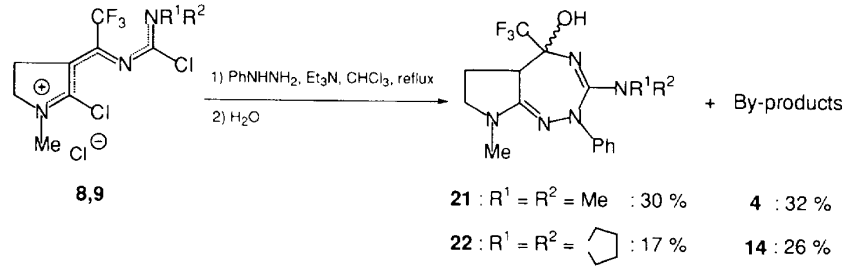
Heterocyclizations of 4-azapentamethine cyanines **8–10** with 1,1- or 1,2-bis-nucleophiles constitute an easy access to new trifluoromethylated 5*H*-pyrrolo[2,3-*d*]-pyrimidines and pyrrolo[3,2-*f*]-1,2,4-triazepines.

• *Reaction with ammonia*

The treatment of azacyanines **8**, **9** and **10** with a large excess of ammonia in the presence of triethylamine gives respectively pyrimidines **18**, **19** and pyrimidinone **20** in moderate yields (scheme 6).



Scheme 6



Scheme 7

The expected (dimethylamino)pyrimidine **18** (R^1 = R^2 = Me) could not be isolated; instead the pyrimidine **18** (R^1 = R^2 = H) was formed by the transamination reaction and was unambiguously characterized by ^1H and ^{13}C NMR. This process was probably favored by the weak solubility of **18**. Pyrimidine **19** (27%) was accompanied by pyrrolidinone **14** (43%). These compounds could not be separated. In contrast no transamination was detected for **19**.

It is worth mentioning that 5*H*-pyrrolo[2,3-*d*]pyrimidine **19** and 2*H*-pyrrolo[2,3-*d*]pyrimidin-2-one **20** are not accessible by condensation of 3-(trifluoroacetyl)pyrrolidin-2-one **1** with guanidine or urea [22].

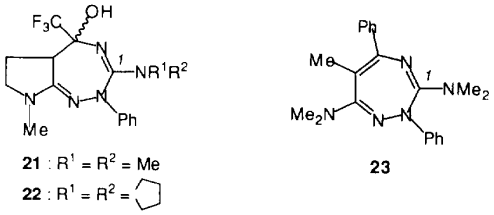
• *Reaction with phenylhydrazine*

A solution of 4-azapentamethine cyanine **8** or **9**, triethylamine and phenylhydrazine was refluxed for 6 h to produce new triazepines **21** and **22** in moderate yields (scheme 7). The by-products **4** and **14** were also characterized unambiguously. They arise respectively from a fragmentation process and from the hydrolysis of azacyanine **9**.

The structure of the pyrrolo[3,2-*f*]-1,2,4-triazepines **21** and **22** was assigned by comparison of their ^{13}C NMR data (especially δ_{C12}) with those of analogue **23** [23] which was determined by X-ray diffraction analysis [24]. As indicated in table IV, the chemical shifts δ_{C1} of **21**, **22** and **23** are very similar.

It is worth noting that only one regioisomer was formed. This regioselectivity can be explained by the substitution of the more reactive chlorine by the terminal nitrogen of phenylhydrazine followed by cyclization on the urea chloride moiety. Nevertheless, the triazepine intermediates add one molecule of water during the work-up to give the 5-hydroxy-1,2,4-triazepines **21** and **22**. Such a spontaneous hydration process has previously been reported in the literature for 4-(trifluoromethyl)pteridines [25, 26].

Table IV. ^{13}C, ^{19}F NMR data and diastereoselectivity of triazepines **21–23**.



Compound [ref]	δ_{C12} *(ppm)*	δ_{19F} *(ppm)*	*Diastereoselectivity (%)*
21a	154.8	−79.7	80
21b	[a]	−72.6	20
22a	153.0	−79.9	70
22b	154.1	−73.5	30
23 [23]	154.7	–	–

[a] Invisible.

The pyrrolo[3,2-*f*]-1,2,4-triazepines **21** and **22** were obtained as mixtures of diastereomers. Although the geometry was not determined by X-ray diffraction analysis, it seems that the major isomers **21a** and **22a** have the same relative configuration. Indeed, the ^{19}F chemical shifts of **21a** and **22a** are more shielded than those of **21b** and **22b** (table IV).

Conclusion

The trifluoromethylated enamines **4** and **5** were obtained by condensation of ammonia or methylamine and thermolysis of their ammonium salts. They are good precursors for the preparation of three new azacyanines **8–10** which were characterized by UV/vis spectroscopy and by chemical transformations. The cyclizations of azacyanines **8–10** with bis-nucleophiles such as ammonia and phenylhydrazine gave new trifluoromethylated pyrimidines **18** and **19**, pyrimidinone **20** and triazepines **21** and **22**. The structure of these heterocycles was confirmed by comparison of ^{19}F and ^{13}C NMR data with their analogues.

The scope of these cyclizations and the reactions of enamines **4** and **5** with other iminium salts and acid chlorides remain to be studied.

Experimental section

Melting points were taken using a Dr Tottoli apparatus and are uncorrected. IR (ν in cm^{-1}), UV/vis (λ_{max} in nm) and mass spectra (electronic impact) were measured on a Perkin-Elmer 1710, VARIAN Cary 210 and a Finnigan Mat TSQ 70 apparatus, respectively. CHN-Analyses were measured at the Microanalysis Laboratory of London University. The ^1H, ^{13}C and ^{19}F NMR spectra (δ in ppm, J in Hz) were run on Varian VXR-200 and Gemini-200 spectrometers at 200 MHz (^1H), 188.2 MHz (^{19}F) and 50.3 MHz (^{13}C), using 5-mm probes. The samples were dissolved in $CDCl_3$. The TMS signal was taken as internal reference for ^1H and ^{13}C spectra, while $CFCl_3$ was used as an internal reference for the ^{19}F spectra. ^{13}C NMR spectra were obtained from proton-coupled or proton noise-decoupled spectra. The following abbreviations are used: s singlet, brs broad singlet, d doublet, t triplet, q quartet, q_t quintet, s_x sextuplet, s_p septuplet and m multiplet. Flash chromatography was run using silica gel Merck 60 (0.040–0.060 mm) whereas distillations were carried out in a Büchi Kugelrohr GKR 50 apparatus.

Triethylamine, aniline and phenylhydrazine are commercially available and were distilled before use. The chlorinated solvents (dichloromethane, chloroform and 1,2-dichloroethane) and diethyl ether were dried over phosphorus hemipentoxide and sodium respectively.

General procedure for compounds **4** *and* **5**

A solution of 3-(1-hydroxy-2,2,2-trifluoroethylidene)pyrrolidin-2-one **1** (100 mmol, 1 equiv) in dry ether (200 mL) was saturated with a large excess of amine (ammonia or methylamine), at −78 °C. The temperature was allowed to reach 20 °C (1 h) and the volatiles were evaporated under reduced pressure to give the corresponding ammonium salt as a white solid.

This salt was then heated under reduced pressure (100–120 °C/0.1 mmHg) for 2 h. The crude product was purified by distillation or by chromatography on silica gel to furnish enamines **4** and **5**.

• *3-(1-Amino-2,2,2-trifluoroethylidene)-1-methylpyrrolidin-2-one* **4**

Reaction of pyrrolidinone **1** (19.5 g, 100 mmol) with ammonia gave the corresponding salt. This ammonium salt was then decomposed (100–110 °C/0.1 mmHg) into the enamine **4** which was purified by distillation (120–130 °C/0.02 mmHg) to furnish a white solid (15.5 g, 80%); mp = 93–95 °C.

IR (KBr): ν 3 305, 3 271, 2 987, 2 894, 1 670, 1 589, 1 505, 1 392.

^1H NMR: δ 2.8–2.9 (m, 2H), 2.92 (s, 3H), 3.43 (t, 2H, J = 7.7), 5.6–5.9 (brs, NH_2).

^{13}C NMR: δ 21.1 (tm, J = 135.4, J_F = 2.4), 29.5 (q, J = 137.4), 46.9 (tm, J = 141.2, J_F = 1.4), 100.6 (sm), 121.3 (q, J_F = 276.1), 136.6 (q, J_F = 33.1), 171.1 (sm).

^{19}F NMR: δ −69.6 (s).

MS: m/z 194 (M^+), 175 (M^+-F), 137 (M^+-3F), 125 (M^+-CF_3), 123, 98, 69 (CF_3^+).

Anal calc for $C_7H_9N_2OF_3$: C, 43.30; H, 4.67; N, 4.43. Found: C, 43.72; H, 4.51; N, 4.29.

• *3-(1-Methylamino-2,2,2-trifluoroethylidene)-1-methylpyrrolidin-2-one* **5**

Reaction of pyrrolidinone **1** (9.75 g, 50 mmol) with methylamine gave the corresponding salt. This ammonium salt was then decomposed (110–120 °C/0.1 mmHg) into the enamine **5** which was purified by chromatography on silica gel (eluent: CH_2Cl_2/petroleum ether 80:20) to furnish a colorless solid (7.80 g, 75%); mp = 43–45 °C.

IR (KBr): ν 3 278, 3 238, 2 933, 2 889, 1 656, 1 650, 1 503, 1 448, 1 407, 1 293.

^1H NMR: δ 2.8–3.0 (m, 5H), 2.87 (s, 3H), 3.35 (tm, 2H, J = 6.8), 8.1 (brs, NH).

^{13}C NMR: δ 22.2 (tm, J = 135.4, J_F = 2.6), 29.4 (q, J = 138.0), 30.9 (qdm, J = 137.7, J = 3.5, J_F = 2.2), 46.6 (tm, J = 141.0, J_F = 2.1), 101.0 (sm, J_F = 3.2), 121.6 (qdd, J_F = 278.1, J = 10.6, J = 1.3), 139.8 (qm, J_F = 30.8), 171.4 (sm).

^{19}F NMR: δ −62.5 (s).

MS: m/z 208 (M^+), 188 (M^+-HF), 168 (M^+-2HF), 148 (M^+-3HF), 139, 136, 124, 98, 69 (CF_3^+).

Anal calc for $C_8H_{11}N_2OF_3$: C, 46.16; H, 5.33; N, 13.46. Found: C, 45.96; H, 5.21; N, 13.17.

General procedure for compounds **8–10**

To a suspension of iminium salt (10.5 mmol, 2.1 equiv) in dry 1,2-dichloroethane (10 mL), pyrrolidinone **4** or **5** (5 mmol, 1.0 equiv) was added in several portions. The mixture was refluxed until the end of hydrochloric acid release, then it was cooled and evaporated. The azacyanine **8**, **9** or **10** was washed three times with dry ether (3 × 10 mL), dried under reduced pressure and stored under argon.

• *2-Chloro-3-{1-[(chlorodimethylamino)methylideneamino]-2,2,2-trifluoroethylidene}-1-methyl-4,5-dihydro-3H-pyrrol-1-ium chloride* **8**

Reaction of pyrrolidinone **4** (5.82 g, 30 mmol) with phosgeniminium salt (PI) (10.23 g, 63 mmol) gave the azacyanine **8** (9.25 g, 91%) as an orange oil.

IR (CCl_4): ν 2 956, 1 650, 1 625, 1 428, 1 367, 1 316, 1 161.

UV/vis ($CHCl_3$, conc 5.5 × 10^{-4} mol.L^{-1}): λ_1 281, A_1 1.4, ε_1 2500; λ_2 368, A_2 0.36, ε_2 655.

^1H NMR: δ 3.29 (s, 3H), 3.32 (s, 3H), 3.4–3.5 (m, 2H), 3.46 (s, 3H), 4.30 (tm, 2H, J = 7.2).

^{13}C NMR: δ 20.8 (tm, J = 136.7, J_F = 1.6), 31.9 (q, J = 143.9), 35.8 (qq, J = 141.6, J = 3.1), 37.6 (qq,

J = 139.7, J = 3.0), 51.9 (tm, J = 149.7), 106.6 (m, J_F = 2.3), 118.5 (q, J_F = 275.6), 143.8 (q, J_F = 38.1), 151.8 (m), 165.5 (m).

^{19}F NMR: δ −71.4 (s).

• *2-Chloro-3-{1-[(chloropyrrolidino)methylidene-amino]-2,2,2-trifluoroethylidene}-1-methyl-4,5-dihydro-3H-pyrrol-1-ium chloride* **9**

Reaction of pyrrolidinone **4** (0.78 g, 4.0 mmol) with *N*-pyrrolidinophosgeniminium salt (1.58 g, 8.4 mmol) gave the azacyanine **9** (1.17 g, 80%) as an orange-brown oil.

IR ($CHCl_3$): ν 2 979, 2 958, 2 886, 1 698, 1 648, 1 621, 1 368, 1 321.

UV/vis (CH_2Cl_2, conc 1.04 × 10^{-3} mol.L^{-1}): λ_1 270, A_1 2.1, ε_1 2000; λ_2 370, A_2 0.51, ε_2 490.

^{1}H NMR: δ 2.0–2.2 (m, 4H), 3.4–3.5 (m, 2H), 3.47 (s, 3H), 3.6–3.9 (m, 4H), 4.30 (m, 2H).

^{13}C NMR: δ 21.9 (tm, J = 136.8, J_F = 3.2), 24.7 (tm, J = 132.8), 33.1 (q, J = 143.5), 48.7 (tm, J = 147.4), 52.8 (tm, J = 150.0, J_F = 1.4), 107.0 (m, J_F = 1.7), 119.1 (qm, J_F = 275.3), 145.0 (qm, J_F = 38.2), 150.2 (m, J_F = 1.5), 166.1 (m).

^{19}F NMR: δ −71.0 (s).

• *2-Chloro-3-(1-{[(chlorodimethylamino)methyl-idene]methylammonio}-2,2,2-trifluoroethylidene)-1-methyl-4,5-dihydropyrrol-1-ium chloride* **10**

Reaction of pyrrolidinone **5** (1.04 g, 5.0 mmol) with phosgeniminium salt (PI) (1.71 g, 10.5 mmol) gave the azacyanine **10** (1.48 g, 84%) as an orange oil.

IR ($CHCl_3$): ν 2 949, 1 741, 1 654, 1 461, 1 408, 1 359, 1 302, 1 181, 1 143.

UV/vis ($CHCl_3$, conc 5.12 × 10^{-4} mol.L^{-1}): λ_{max} 364, A 0.59, ε 1157.

^{1}H NMR: δ 3.38 (s, 6H), 3.3–3.6 (m, 2H), 3.49 (s, 3H), 3.53 (s, 3H), 3.7–3.8 (m, 2H).

^{13}C NMR (proton noise decoupled spectrum): δ 28.1 (q, J_F = 2.1), 33.7, 39.3, 42.7 (2C), 55.7, 106.8 (q, J_F = 1.9), 119.8 (q, J_F = 289.7), 131.8 (q, J_F = 38.0), 150.1, 161.3.

^{19}F NMR: δ −71.5 (s).

General procedure for compounds **13–15**

A solution of azacyanine **8**, **9** or **10** (5 mmol, 1 equiv) in chloroform (15 mL) was treated at 0 °C with a saturated aqueous solution of $NaHCO_3$ (25 mL). The mixture was extracted twice with chloroform (2 × 50 mL). The organic phase was then dried over $MgSO_4$ and concentrated under reduced pressure. The crude was recrystallized (for **13** and **14**) or chromatographed on silica gel (for **15**).

• *1-Methyl-3-[1-(3,3-dimethylureido)-2,2,2-trifluoro-ethylidene]pyrrolidin-2-one* **13**

Hydrolysis of azacyanine **8** (1.02 g, 3 mmol) then recrystallization in cyclohexane gave the pyrrolidin-2-one **13** (0.58 g, 73%) as a colorless solid; mp = 107–109 °C.

IR (CCl_4): ν 3 240, 2 930, 1 698, 1 679, 1 501, 1 406, 1 290, 1 189, 1 097, 910.

^{1}H NMR: δ 2.94 (s, 3H), 3.01 (s, 6H), 2.9–3.1 (m, 2H), 3.45 (tm, 2H, J = 6.6), 9.8 (brs, NH).

^{13}C NMR: δ 22.2 (tm, J = 136.5, J_F = 2.5), 29.3 (q, J = 139.3), 35.9 (qq, J = 138.1, J = 3.3), 46.3 (tm, J = 143.3, J_F = 1.3), 118.3 (sm, J_F = 2.6), 120.6 (qd, J_F = 276.4, J = 1.4), 133.0 (qd, J_F = 35.6, J = 1.7), 155.9 (sm), 168.9 (sttq, J = 2.8, J = 2.8, J = 2.8).

^{19}F NMR: δ −63.6 (s).

MS: m/z 265 (M^+), 221 (M^+-NMe_2), 201, 193 (M^+-$CONMe_2$), 72, 69 (CF_3^+).

Anal calc for $C_{10}H_{14}N_3O_2F_3$: C, 45.28; H, 5.32; N, 15.84. Found: C, 45.17; H, 5.25; N, 15.61.

• *1-Methyl-3-{1-[(pyrrolidin-1-ylcarbonyl)amino]-2,2,2-trifluoroethylidene}pyrrolidin-2-one* **14**

Hydrolysis of azacyanine **9** (0.91 g, 2.5 mmol) then recrystallization in a mixture chloroform/petroleum ether gave the pyrrolidin-2-one **14** (0.37 g, 51%) as a colorless solid; mp = 81–83 °C.

IR (KBr): ν 3 193, 2 956, 1 693, 1 668, 1 505, 1 411, 1 368, 1 290, 1 181.

^{1}H NMR: δ 1.8–2.0 (m, 4H), 2.94 (s, 3H), 2.9–3.0 (m, 2H), 3.4–3.5 (m, 6H), 9.8 (brs, NH).

^{13}C NMR: δ 22.6 (tqt, J = 136.4, J_F = 2.6, J = 2.5), 25.3 (tm, J = 136.5), 29.6 (q, J = 138.7), 45.7 (tm, J = 142.2), 46.5 (tm, J = 144.1, J_F = 1.5), 117.9 (sm, J_F = 2.1), 120.7 (qdt, J_F = 271.8, J = 7.7, J = 1.6), 132.7 (qdm, J_F = 35.6, J = 4.2), 153.7 (m), 168.8 (ttq, J = 3.2, J = 3.2, J = 3.2).

^{19}F NMR: δ −63.5 (dd, J = 4.2, J = 3.3).

MS: m/z 291 (M^+), 220 (M^+-pyrrolidine), 193 (M^+-C_4H_8NCO), 160, 113, 98, 71, 69 (CF_3^+).

Anal calc for $C_{12}H_{16}N_3O_2F_3$: C, 49.48; H, 5.54; N, 14.43. Found: C, 49.35; H, 5.47; N, 14.23.

• *1-Methyl-3-[1-(1,3,3-trimethylureido)-2,2,2-tri-fluoroethylidene]pyrrolidin-2-one* **15**

Hydrolysis of azacyanine **10** (1.55 g, 4.4 mmol) then chromatography on silica gel (eluent: MeOH/AcOEt, 5:95) gave the pyrrolidin-2-one **15** (0.64 g, 52%) as a yellow oil.

IR (film): ν 2 935, 2 894, 1 695, 1 669, 1 495, 1 461, 1 405, 1 377, 1 288, 1 128.

^{1}H NMR: δ 2.82 (s, 6H), 2.95 (s, 3H), 3.08 (s, 3H), 2.9–3.1 (m, 2H), 3.45 (tm, 2H, J = 6.5).

^{13}C NMR: δ 22.8 (tm, J = 135.0, J_F = 2.5), 29.9 (q, J = 138.5, J_F = 1.9), 37.8 (qq, J = 137.6, J = 3.2, J_F = 1.8), 38.5 (q, J = 139.6, J_F = 2.1), 45.3 (tm, J = 142.4, J_F = 1.1), 121.6 (qq, J_F = 279.7, J = 1.8), 132.9 (qm, J_F = 34.0), 133.4 (m, J_F = 2.6), 161.4 (m), 164.0 (m).

^{19}F NMR: δ −64.7 (m).

MS: m/z 279 (M^+), 234 (M^+-NMe_2), 207 (M^+-$CONMe_2$), 178, 102, 72, 58, 44.

Anal calc for $C_{11}H_{16}N_3O_2F_3$: C, 47.31; H, 5.77; N, 15.05. Found: C, 47.25; H, 5.70; N, 14.82.

Thiolysis of azacyanine **8**

• *1-Methyl-3-[1-(3,3-dimethylureido)-2,2,2-trifluoro-ethylidene]pyrrolidine-2-thione* **16**

A solution of azacyanine **8** (2.46 g, 7.3 mmol) in dry dichloromethane (25 mL) was saturated with a large excess of hydrogen sulfide at 0 °C. After 30 min, a solution of triethylamine (2.21 g, 21.9 mmol) in dry dichloromethane (10 mL) was added. The mixture was stirred at room temperature for 1 h then diluted with ether (15 mL) to precipitate the triethylammonium hydrochloride. After filtration and evaporation of the volatiles, the crude product was chromatographed on silica gel (eluent: ether/petroleum ether, 90:10) to give the pyrrolidine-2-thione **16** (0.64 g, 31%) as a yellow solid; mp = 98–101 °C.

IR (CCl_4): ν 3 100, 2 932, 1 695, 1 650, 1 494, 1 311, 1 271, 1 186, 782.

^{1}H NMR: δ 2.9–3.2 (m, 2H), 3.05 (s, 6H), 3.28 (s, 3H), 3.73 (tm, 2H, J = 7.0), 11.3 (brs, NH).

^{13}C NMR: δ 25.3 (tm, J = 136.7, J_F = 3.1), 35.1 (q, J = 140.4), 36.3 (qqd, J = 138.2, J = 3.1, J = 1.3), 53.6 (tm, J = 144.3, J_F = 1.3), 121.2 (qd, J_F = 277.6, J = 7.8), 125.4 (sm, J_F = 2.7), 134.6 (qm, J_F = 34.5), 156.4 (sm), 190.3 (sm).

^{19}F NMR: δ −63.9 (s).

MS: m/z 281 (M^+), 237 (M^+-NMe_2), 209 (M^+-$CONMe_2$), 208, 72, 69 (CF_3^+), 44.

Anal calc for $C_{10}H_{14}N_3SOF_3$: C, 42.70; H, 5.02; N, 14.94. Found: C, 42.65; H, 4.67; N, 14.78.

Aminolysis of azacyanine **8**

• *3-[1-(3,3-Dimethylureido)-2,2,2-trifluoroethylidene]-1-methyl-2-(phenylimino)pyrrolidine* **17**

To a solution of aniline (1.62 g, 17.4 mmol) and triethylamine (2.64 g, 26.1 mmol) in dry dichloromethane (15 mL) was added a solution of azacyanine **8** (2.94 g, 8.7 mmol) in dichloromethane (10 mL). The mixture was refluxed for 4 h. After cooling and hydrolysis with an aqueous solution (1 N) of potassium hydroxide (7 mL), the mixture was extracted twice with dichloromethane (2 × 70 mL), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was chromatographed on silica gel (eluent: ether/petroleum ether, 60:40) to give the pyrrolidine **17** (1.86 g, 63%) as a colorless solid; mp = 125–126 °C.

IR ($CHCl_3$): ν 3 419, 3 024, 3 009, 2 933, 2 878, 1 681, 1 661, 1 631, 1 591, 1 510, 1 489, 1 370.

^{1}H NMR: δ 2.48 (s, 3H), 2.93 (s, 6H), 2.9–3.0 (m, 2H), 3.38 (tm, 2H, J = 7.0), 6.84 (dd, 2H, J = 8.2, J = 1.3), 6.98 (tm, 1H, J = 7.4), 7.24 (ddm, 2H, J = 8.0, J = 7.9), 11.7 (brs, NH).

^{13}C NMR: δ 24.3 (tm, J = 135.7, J_F = 2.4), 35.88 (q, J = 138.4), 35.92 (qq, J = 137.9, J = 3.3), 51.7 (tm, J = 141.1, J_F = 1.4), 121.1 (qd, J_F = 275.4, J = 1.2), 121.3 (sm, J_F = 3.0), 121.4 (ddd, J = 160.6, J = 7.8, J = 7.5), 121.9 (dt, J = 161.9, J = 7.8), 128.1 (dd, J = 160.1, J = 7.9), 130.6 (qdd, J_F = 34.5, J = 4.0, J = 3.8), 147.3 (st, J = 8.0), 154.4 (sm), 156.4 (sm).

^{19}F NMR: δ −62.3 (s).

MS: m/z 340 (M^+), 296 (M^+-NMe_2), 271 (M^+-CF_3), 268 (M^+-$CONMe_2$), 77, 72, 58, 44, 43.

Anal calc for $C_{16}H_{19}N_4OF_3$: C, 56.46; H, 5.63; N, 16.46. Found: C, 56.56; H, 5.58; N, 16.34.

General procedure for compounds **18–20**

A cooled solution (0 °C) of azacyanine **8**, **9** or **10** (5 mmol, 1 equiv) in dry dichloromethane (10 mL) was saturated with a large excess of ammonia. The mixture was stirred under an Ar atmosphere at room temperature for 3–10 h then diluted with dichloromethane (50 mL) and hydrolyzed with an aqueous solution (1 N) of sodium hydroxide (7 mL). The aqueous phase was extracted three times with dichloromethane (3 × 50 mL) then the organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. For heterocycles **19** and **20**, the crude product was chromatographed on silica gel (eluent: mixture of ether/methanol). For the pyrimidine **18** which precipitated in the crude mixture, the solid was filtered, washed with water (15 mL) then with dichloromethane (2 × 15 mL) and dried under reduced pressure.

• *7-Methyl-4-(trifluoromethyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-2-amine* **18**

Reaction of azacyanine **8** (3.79 g, 11.2 mmol) with ammonia gave, without purification, the pyrimidine **18** (50%) contaminated by another product which was difficult to characterize. The heterocycle **18** has previously been prepared using another method: see ref [2] for satisfactory spectroscopic data.

• *7-Methyl-2-pyrrolidino-4-(trifluoromethyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine* **19**

Reaction of azacyanine **9** (1.17 g, 3.2 mmol) with ammonia then chromatography on silica gel (eluent: ether/methanol, 93:7) gave, according to the NMR data, a non-separable mixture of pyrimidine **19** (27%) and pyrrolidinone **14** (43%).

^{1}H NMR: δ 1.8–2.0 (m, 4H), 2.7–2.8 (m, 2H), 2.91 (s, 3H), 3.4–3.6 (m, 6H).

^{13}C NMR (proton noise-decoupled spectrum): δ 21.9 (q, J_F = 2.4), 25.1 (2C), 34.0 (q, J_F = 1.2), 46.1 (2C), 46.7 (q, J_F = 1.2), 102.1 (q, J_F = 2.5), 120.9 (q, J_F = 276.4), 135.2 (q, J_F = 32.4), 159.73, 159.79.

^{19}F NMR: δ −68.8 (s).

• *3,7-Dimethyl-4-(trifluoromethyl)-3,5,6,7-tetrahydro-2H-pyrrolo[2,3-d]pyrimidin-2-one* **20**

The reaction of azacyanine **10** (0.89 g, 2.5 mmol) with ammonia gave, after chromatography on silica gel (eluent: ether/methanol, 95:5), the pyrimidinone **20** (0.13 g, 22%) as a colorless solid; mp = 78–80 °C.

IR (KBr): ν 2 953, 2 886, 1 673, 1 592, 1 519, 1 438, 1 327, 1 127.

^{1}H NMR: δ 3.0–3.2 (m, 2H), 3.06 (s, 3H), 3.45 (q, 3H, J_F = 1.4), 3.68 (tm, 2H, J = 7.1).

^{13}C NMR (proton noise-decoupled spectrum): δ 23.0 (q, J_F = 3.5), 30.5, 39.6 (q, J_F = 1.3), 50.5 (q, J_F = 2.1), 110.6 (q, J_F = 3.2), 120.0 (q, J_F = 275.1), 133.8 (q, J_F = 35.3), 158.1 (q, J_F = 1.5), 166.1.

^{19}F NMR: δ −62.2 (t, J = 4.4).

MS: m/z 233 (M^+), 218, 198, 183, 164, 149, 123, 109, 71, 69 (CF_3^+).

General procedure for compounds **21** *and* **22**

A mixture of phenylhydrazine (5 mmol, 1 equiv) and triethylamine (15 mmol, 3 equiv) in dry chloroform (5 mL) was added dropwise, at room temperature and under an Ar atmosphere, to a solution of azacyanine **8** or **9** (5 mmol, 1 equiv) in chloroform (5 mL). The mixture was refluxed for 6–7 h. After evaporation of the solvent, the oil was treated with water (20 mL) and extracted three times with dichloromethane (3 × 70 mL). The organic phase was then washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The triazepine **21** or **22** was chromatographed on silica gel (eluent: ether then ether/methanol, 95:5).

• *3-(Dimethylamino)-8-methyl-2-phenyl-5-(trifluoromethyl)-2,5,5a,6,7,8-hexahydropyrrolo[3,2-f]-1,2,4-triazepin-5-ol* **21**

Reaction of azacyanine **8** (2.72 g, 8 mmol) with phenylhydrazine (1.08 g, 8 mmol) and triethylamine (2.43 g, 24 mmol) gave, after chromatography on silica gel (eluent: ether then ether/methanol, 95:5), the triazepine **21** (0.85 g, 30%) as a mixture (80:20) of diastereoisomers and the enamine **4** (0.50 g, 32%).

Major diastereoisomer **21a**: mp = 133–134 °C.

IR (KBr): ν 3 302, 2 966, 2 868, 1 683, 1 648, 1 614, 1 593, 1 489, 1 417, 1 328, 1 166.

^{1}H NMR: δ 2.4–2.6 (m, 2H), 2.62 (s, 6H), 2.96 (s, 3H), 3.52 (t, 1H, J = 8.4), 3.83 (td, 1H, J = 9.5, J = 5.9), 4.28 (dd, 1H, J = 11.9, J = 8.3), 5.08 (brs, OH), 7.0–7.5 (m, 5H).

^{13}C NMR: δ 26.0 (tm, J = 135.6, J_F = 1.6), 32.3 (qd, J = 138.9, J = 1.8, J_F = 1.7), 35.6 (qq, J = 137.5, J = 3.4), 55.8 (dm, J = 128.9), 57.1 (tm, J = 140.4), 78.2 (qm, J_F = 29.9), 121.8 (ddd, J = 159.5, J = 6.9, J = 6.0), 123.5 (qd, J_F = 288.1, J = 9.0), 124.0 (dt, J = 161.6, J = 7.2), 128.9 (ddd, J = 160.4, J = 7.6, J = 1.1), 145.0 (tm, J = 8.3), 154.8 (septet, J = 2.5), 165.5 (m).

^{19}F NMR: δ −79.7 (s).

MS: m/z 355 (M^+), 310 (M^+-Me_2NH), 267, 218, 151, 136, 119, 108, 93, 77, 69 (CF_3^+), 44.

Anal calc for $C_{16}H_{20}N_5OF_3$: C, 54.08; H, 5.67; N, 19.71. Found: C, 54.14; H, 5.30; N, 20.03.

Minor diastereoisomer **21b**: selected ^{1}H NMR data: δ 2.58 (s, 6H), 2.92 (s, 3H), 4.70 (brs, OH); selected ^{13}C NMR data: δ 22.9, 32.4, 35.9, 54.3, 85.6; ^{19}F NMR: δ −72.6 (s).

• *8-Methyl-2-phenyl-3-pyrrolidino-5-(trifluoromethyl)-2,5,5a,6,7,8-hexahydropyrrolo[3,2-f]-1,2,4-triazepin-5-ol* **22**

Reaction of azacyanine **9** (2.00 g, 5.5 mmol) with phenylhydrazine (0.74 g, 5.5 mmol) and triethylamine (1.67 g, 16.5 mmol) gave, after chromatography on silica gel (eluent: ether then ether/methanol, 95:5), the triazepine **22** (0.36 g, 17%) as a mixture (70:30) of diastereoisomers and the pyrrolidin-2-one **14** (0.42 g, 26%).

Major diastereoisomer **22a**: mp = 120–123 °C.

IR (KBr): ν 3 300-3 150, 3 063, 3 035, 2 977, 2 954, 2 880, 1 681, 1 602, 1 498, 1 463, 1 405, 1 383, 1 291.

^{1}H NMR: δ 1.6–2.0 (m, 4H), 2.3–2.7 (m, 2H), 2.97 (s, 3H), 3.0–3.2 (m, 2H), 3.3–3.7 (m, 3H), 3.7–3.9 (m, 1H), 4.14 (dd, 1H, J = 13.0, J = 8.1), 4.92 (brs, OH), 6.9–7.5 (m, 5H).

^{13}C NMR: δ 25.0 (tm, J = 132.7), 25.9 (tm, J = 136.4, J_F = 1.4), 32.2 (qd, J = 137.7, J = 1.8, J_F = 1.5), 44.9 (tm, J = 141.6), 55.6 (dm, J = 129.2), 57.1 (tm, J = 142.8), 78.1 (qm, J_F = 29.5), 121.6 (ddd, J = 160.4, J = 7.7, J = 7.3), 123.5 (qd, J_F = 288.1, J = 8.8), 123.7 (dt, J = 161.8, J = 7.4), 128.7 (dd, J = 160.1, J = 8.2), 144.9 (tm, J = 8.6), 153.0 (m), 165.4 (sm).

^{19}F NMR: δ −79.9 (s).

MS: m/z 381 (M^+), 310 (M^+-pyrrolidine), 267, 168, 98, 85, 83, 77, 47.

Anal calc for $C_{18}H_{22}N_5OF_3$: C, 56.69; H, 5.81; N, 18.36. Found: C, 56.51; H, 5.76; N, 18.19.

Minor diastereoisomer **22b**: selected ^{1}H NMR data: δ 2.94 (s, 3H), 4.02 (m, 1H), 4.55 (brs, OH); ^{13}C NMR (proton noise-decoupled spectrum): δ 25.2, 25.6, 32.6, 45.2, 54.0, 57.2, 85.2, 123.8, 129.5, 124.4, 127.9, 145.4, 154.1, 162.9; ^{19}F NMR: δ −73.5 (s).

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