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Reactions of trifluoromethylated enamines with iminium chlorides and analogues. Synthesis of new 2-aza-1,3-dienes and pyridin-4-ones

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Summary — The trifluoromethylated enamines **1** and **2** condense with monochloromethyleneiminium chlorides, *N*,*N*-dimethylacetamide dimethylacetal and chloroiminium chlorides prepared from lactams and gaseous phosgene to give the new 2-aza-1,3-dienes **5a–c**, **6**, **13a–f**, **19a–c** and **20a–c** which then cyclize with sodium hydride to pyridin-4-ones **22** and **23a,b,e,f**.

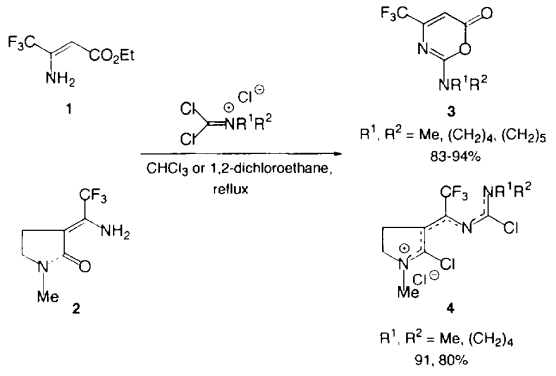
enamine / iminium chloride / 2-aza-1,3-diene / pyridin-4-one

Résumé — Réactions des énamines trifluorométhylées avec des chlorures d'iminium et des analogues. Synthèse de nouveaux 2-aza-1,3-diènes et pyridin-4-ones. Les énamines trifluorométhylées **1** et **2** se condensent avec des chlorures de monochlorométhylèneiminium, avec le diméthylacétal du *N*,*N*-diméthylacétamide et des chlorures de chloroiminium préparés à partir des lactames et du phosgène gazeux, pour donner les nouveaux 2-aza-1,3-diènes **5a–c**, **6**, **13a–f**, **19a–c** et **20a–c** qui se cyclisent ensuite avec l'hydrure de sodium en pyridin-4-ones **22** et **23a,b,e,f**.

énamine / chlorure d'iminium / 2-aza-1,3-diène / pyridin-4-one

Introduction

Following our studies on the synthesis of new fluorinated heterocycles, we focused our attention on the reactions of trifluoromethylated enamines such as ethyl 3-amino-4,4,4-trifluorocrotonate **1** [1] and 3-(1-amino-2,2,2-trifluoroethylidene)-1-methylpyrrolidin-2-one **2** [2a], which are easily prepared from trifluoroacetylated derivatives [1, 2b] and ammonia. As we reported previously, these enamines condense with dichloromethyleneiminium chlorides (PI) [3, 4] to give 1,3-oxazin-6-ones **3** [5] and 4-azapentamethine cyanines **4** [2a], respectively (scheme 1). Here we report the reactions of these enamines **1** and **2** with monochloromethyleneiminium chlorides, *N*,*N*-dimethylacetamide dimethylacetal and chloroiminium chlorides prepared from lactams and gaseous phosgene, and the subsequent cyclizations of amidines.



Scheme 1

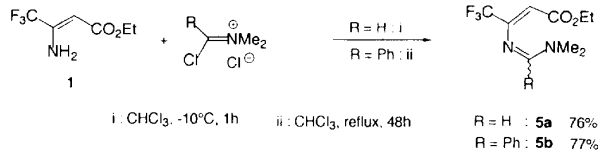
Results

Reactions with ethyl 3-amino-4,4,4-trifluorocrotonate **1**

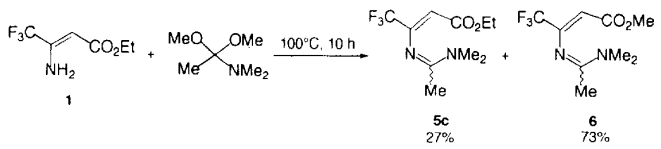
The Vilsmeier–Haack–Arnold salt was prepared from *N*,*N*-dimethylformamide and oxalyl chloride. It reacted with enamine **1**, at −10 °C, to furnish exclusively the formamidine **5a** (scheme 2). This selective *N*-acylation of **1** contrasts with ethyl or methyl 3-aminocrotonate and 3-aminocinnamate, which reacted with this iminium salt to give C-acylation products only [6].

* Correspondence and reprints

† Deceased 17 July 1996.



Scheme 2



Scheme 3

The condensation of enamine **1** with *N*,*N*-dimethylbenzamide chloride was performed in refluxing chloroform for 48 h to produce benzamidine **5b** in 77% yield (scheme 2). These 2-aza-1,3-dienes **5a,b** were characterized by ^{1}H, ^{13}C and ^{19}F NMR as only one stereomer in $CDCl_3$ solution. Their configuration will be discussed below.

We then tried to prepare the acetamidine **5c** starting from the *N*,*N*-dimethylacetamide chloride but without success. When the reaction was run at room temperature, we recovered more than 90% of the starting material after 24 h. In refluxing chloroform this amide chloride only underwent self-condensation to produce trimethine cyanine which was hydrolyzed to *N*,*N*-dimethylacetoacetamide [7] during the work-up. Fortunately, the reaction performed with *N*,*N*-dimethylacetamide dimethylacetal [8] at 100 °C furnished quantitatively the acetamidine as a mixture of ethyl and methyl esters **5c** and **6** (27:73) (scheme 3).

We then extended these condensations to chloroiminium chlorides prepared from lactams and gaseous phosgene. With only 1 equiv of these, ethyl 3-amino-4,4,4-trifluorocrotonate **1** was converted into the corresponding amidine in low yield (10–20%). Nevertheless, when phosgene was slowly introduced into the refluxed solution of enamine **1** and *N*-substituted lactams **7–12**, the cyclic amidines **13a–f** were obtained in moderate to good yield (scheme 4, table I).

Except entry for **e** in table I, the amidines **13a–f** were the only isolated products. The condensations were dependent on both the *N*-alkyl substitution and the stability of the chloroiminium chlorides [9]. From 1-methylpiperidin-2-one **11**, we obtained a low yield of amidine **13e** (15%) and we also isolated a less polar product (according to TLC) characterized as the pyrido[2,3-*b*]pyridone **14** (table I, entry **e**). This bicycle probably derived from the insertion of phosgene into the amidine **13e**. However when we heated **13e** in chloroform in the presence of this electrophile, the starting material was recovered quantitatively. Thus we presume that the pyrido[2,3-*b*]pyridone **14** was formed by the reaction of enamine **1** with the bis-electrophile **15** which was obtained from 1-methylpiperidin-2-one **11** and phosgene (scheme 5).

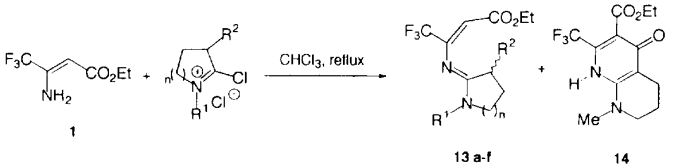
Table I. Reagents and yields for compounds **13a–f** and **14**.

Entry	*Lactam*	*n*	R^1	R^2	*Yield* ***13a–f*** *(%)*	*Yield* ***14*** *(%)*
a	**7**	1	Me	H	56	–
b	**8**	1	Et	H	45	–
c	**9**	1	Bn	H	86	–
d	**10**	1	Me	Me	41	–
e	**11**	2	Me	H	15	18
f	**12**	3	Me	H	79	–

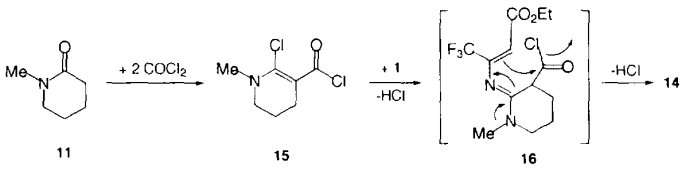
To obtain the related dehydrogenated amidine **18**, we prepared the 2-bromo-1-methylpyridinium salt **17**, by methylation of 2-bromopyridine with methyl triflate (yield 87%). The pyridinium salt **17** did not condense with ethyl crotonate **1** alone, even in refluxing 1,2-dichloroethane. When **17** was slowly added to a mixture of lithium hydride and enamine **1** in THF at 20 °C, it reacted exothermically to give the 2-imino-1-methylpyridine **18** in high yield (scheme 6).

Reactions with 3-(1-amino-2,2,2-trifluoroethylidene)-pyrrolidin-2-one **2**

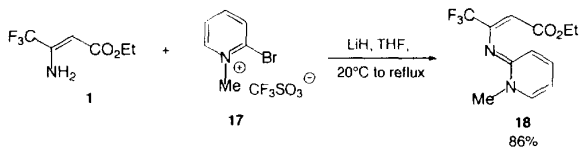
To compare the reactivity of enamino ester **1** with that of enamino lactam **2**, we reacted 3-(1-amino-2,2,2-trifluoroethylidene)pyrrolidin-2-one **2** with monochloromethyleneiminium chlorides and chloroiminium chlorides prepared from lactams and gaseous phosgene.



Scheme 4

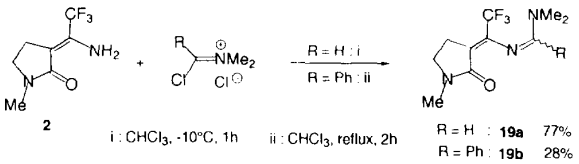


Scheme 5



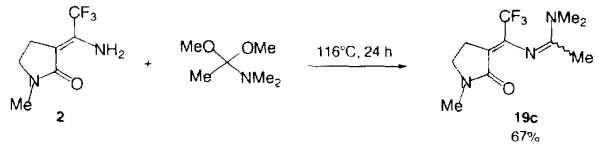
Scheme 6

The Vilsmeier salt and the *N*,*N*-dimethylbenzamide chloride were condensed with trifluoromethylated enamine **2** to give formamidine **19a** and benzamidine **19b** (scheme 7).



Scheme 7

The acetamidine **19c** was obtained when a mixture of enamine **2** and *N*,*N*-dimethylacetamide dimethylacetal was refluxed for 24 h (scheme 8). These amidines **19a–c** were isolated and characterized by ^{1}H, ^{13}C and ^{19}F NMR as having only one stereomer in $CDCl_3$ solution. Their configurations will be discussed below.



Scheme 8

The pyrrolidin-2-one **2** also reacted with chloroiminium chlorides prepared from lactams and gaseous phosgene to give the amidines **20a–c** in moderate to good yields (scheme 9, table II). No bicyclic product such as **14** was detected during the course of the reaction. From the reaction of **2**, we isolated the product **21**

Table II. Yields for compounds **20a–c** and **21**.

Entry	*n*	*Yield* **20a–c** *(%)*	*Yield* **21** *(%)*
a	1	32	15
b	2	47	–
c	3	56	–

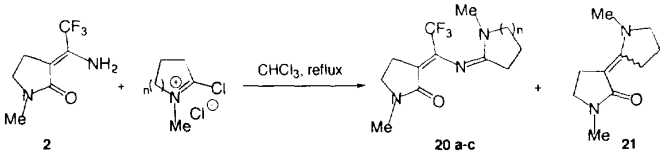
of the hydrolysis of trimethine cyanine, which derived from the dimerization of cyclic amide chloride [9].

Configuration of 2-aza-1,3-dienes

To determine the configuration of our 2-aza-1,3-dienes, we tried to obtain an X-ray diffraction analysis of one of the compounds in each series, but we could only obtain suitable crystals of the amidine **13c** and the pyrrolidin-2-one **20b**.

For amidines **5a–c** and **19a–c**, the configuration of $C_2{=}C_3$ is *Z* on the basis of the stereochemistry of the starting material. For compounds **5b** and **5c**, this was confirmed by the carbon–proton coupling constants ($^{3}J_{CF3\text{-}H2}$ = 5.0 and 4.9 Hz) which were in good agreement with the ^{13}C NMR data for **1** ($^{3}J_{CF3\text{-}H2}$ = 5.1 Hz) [10a,b] and with von Philipsborn [10c]. Moreover, for compounds **5b** and **5c**, the carbon–fluorine coupling constants ($^{3}J_{C2\text{-}F}$ = 3.6 and 3.6 Hz) had a typical value of 4 Hz which is in good agreement with *Z* configuration as described by Ourevitch [10d]. For compounds **19a–c**, we could not use von Philipsborn's and Ourevitch's methods [10c,d] because the $C_2{=}C_3$ double bonds were tetrasubstituted. Nevertheless, the *Z* configuration of $C_2{=}C_3$ was assigned by comparison of the ^{13}C NMR data of **2**, **19a–c** and one pyrrolidinone analogue for which the structure was determined by X-ray diffraction analysis [2a].

Unfortunately, we cannot assign the geometry of double bond $N_4{=}C_5$. Amidines generally prefer the *E* configuration [11, 12], as is the case for compound **13c** (fig 1) [13a]. However, the X-ray diffraction analysis of analogue **20b** shows the *Z* configuration for $N_4{=}C_5$ (fig 2) [13b]. If we compare the amidines with the same substituent R (table III: compounds **5a** and **19a**, **5b** and **19b**, **5c** and **19c**), it is worth noting that they have very similar values for the chemical shift δ_{C5} which means that they have the same configuration of $N_4{=}C_5$.



Scheme 9

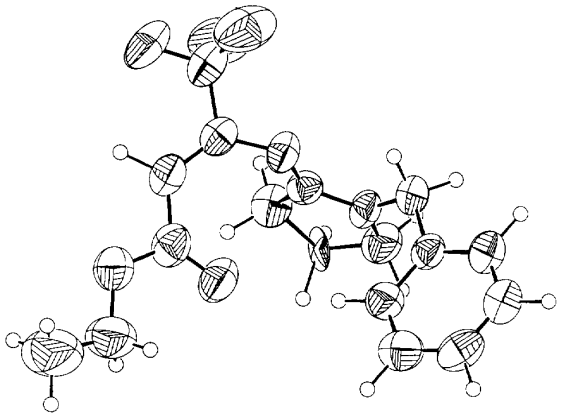


Fig 1. Stereoscopic view of compound **13c**.

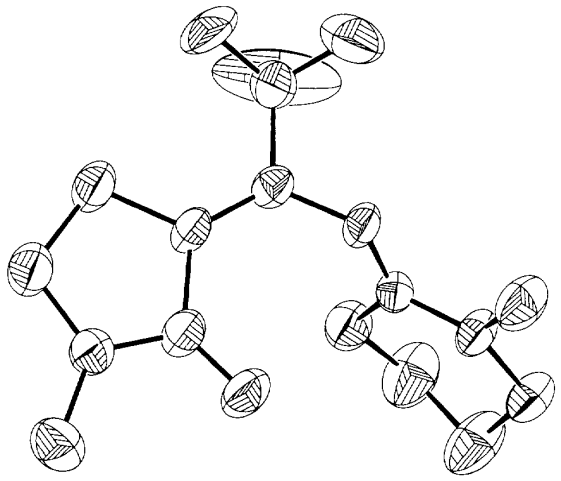
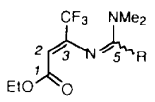


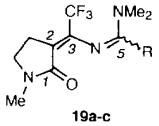
Fig 2. Stereoscopic view of compound **20b**.

For compounds **13a–f**, the *Z* configuration of the double bond C_2=C_3 is also given by the stereochemistry of enamine **1** which was determined by ^{15}N ($^3J_{N\text{-}H2}$ = 3.4 Hz) [10a] and ^{13}C NMR studies ($^3J_{CF3\text{-}H2}$ = 5.1 Hz) [10a,b]. The double bond N_4=C_5 of **13a–f** probably has the *E* configuration based on the X-ray diffraction analysis of **13c** (fig 1) and on the chemical shifts of carbons C_5 and C_6 (table IV). Consequently, we can assign the stereochemistry (*Z*,*E*) to 2-aza-1,3-dienes **13a–f**.

Table III. ^{13}C and ^{19}F NMR data for compounds **5a–c** and **19a–c**.



5a-c



19a-c

Compound	*R*	δ_{C1}	δ_{C2}	δ_{C3}	δ_{C5}	δ_{CF3}	$\delta_{^{19}F}$
5a	H	166.3	99.9	153.7	157.4	121.1	−72.4
5b	Ph	165.9	99.3	151.4	163.7	120.9	−71.2
5c	Me	165.5	97.5	150.5	160.9	120.8	−72.6
19a	H	167.9	113.6	143.5	156.6	121.9	−67.2
19b	Ph	168.1	114.7	140.7	163.3	121.7	−66.7
19c	Me	167.7	112.7	140.1	160.2	121.6	−67.5

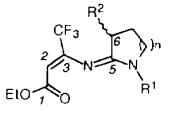
For compound **20b**, double bonds C_2=C_3 and N_4=C_5 both have the *Z* configuration [13b]. If we compare the carbon and fluorine chemical shifts (table IV: $\delta_{C1\text{-}C6}$, δ_{CF3}, $\delta_{^{19}F}$) of amidines **20a–c**, we see that they have very similar value. Thus, we assign the configuration (*Z*,*Z*) to 2-aza-1,3-dienes **20a** and **20c**.

Cyclization of amidines

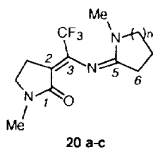
The amidines **5c**, **6**, **13** and **20** are good precursors for the synthesis of new trifluoromethylated pyridin-4-ones. With sodium hydride in *N*,*N*-dimethylformamide, acetamidines **5c** and **6** cyclized to 2-(dimethylamino)pyridin-4-one **22** in high yield (scheme 10). It is worth noting that we detected only the carbonyl form in $CDCl_3$ solution.

This reaction was then extended to amidines **13a,b,d–f** and we obtained the new bicyclic pyridin-4-ones **23a,b,e,f** in high yields (scheme 11, table V).

Table IV. ^{13}C and ^{19}F NMR data for compounds **13a–f** and **20a–c**.

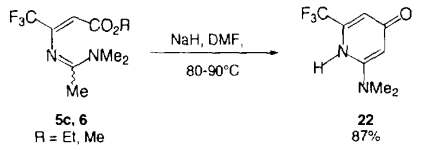


13 a-f

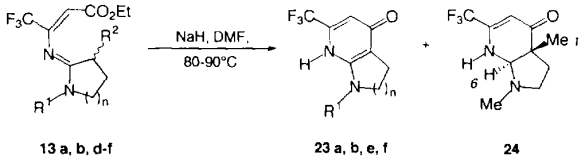


20 a-c

Compound	*n*	R^1	R^2	δ_{C1}	δ_{C2}	δ_{C3}	δ_{C5}	δ_{C6}	δ_{CF3}	$\delta_{^{19}F}$
13a	1	Me	H	165.3	99.4	152.1	164.8	27.4	120.7	−72.3
13b	1	Et	H	165.3	99.3	152.1	163.9	27.8	120.8	−72.5
13c	1	Bn	H	165.5	100.4	152.1	164.7	28.0	121.1	−72.4
13d	1	Me	Me	166.2	97.1	151.9	169.5	34.9	121.0	−71.6
13e	2	Me	H	165.2	97.6	150.0	159.8	25.7	120.6	−72.3
13f	3	Me	H	165.0	96.9	150.0	165.4	28.8	120.4	−72.5
20a	1	Me	H	167.4	114.0	141.1	164.6	27.5	121.6	−67.2
20b	2	Me	H	168.2	113.6	140.0	160.2	26.6	122.1	−67.2
20c	3	Me	H	168.3	112.9	140.5	165.5	27.9	122.1	−67.4



Scheme 10

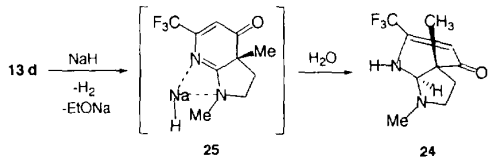


Scheme 11

Table V. Reagents and yields for compounds **23a,b,e,f** and **24**.

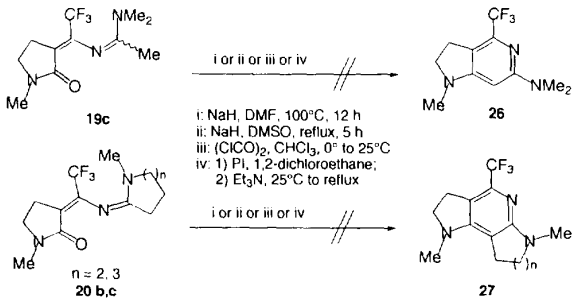
Entry	*n*	R^1	R^2	*Amidine*	*Yield* **23a,b,e,f** *(%)*	*Yield* **24** *(%)*
a	1	Me	H	**13a**	89	–
b	1	Et	H	**13b**	81	–
d	1	Me	Me	**13d**	–	19
e	2	Me	H	**13e**	60	–
f	3	Me	H	**13f**	86	–

The cyclizations of compounds **13c** and **13d** were very different. The *N*-benzyl-amidine **13c** gave only degradation products. From the 1,3-dimethyl derivative **13d**, we obtained only low yields (19%) of pyridin-4-one **24**, which was formed probably from the hydride reduction of the expected pyridin-4-one **25** (scheme 12). The *E* configuration of this unique isomer was determined using ^{13}C NMR data: the carbon–proton coupling constant ($^3J_{C1\text{-}H6}$ = 11 Hz) was in good agreement with a *trans* arrangement (scheme 11, table V).



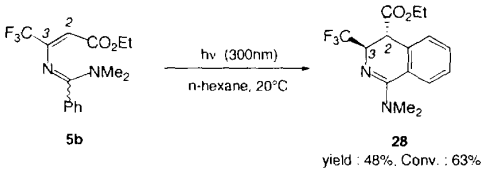
Scheme 12

We also attempted to cyclize the acetamidine **19c** and the bicyclic derivatives **20b,c** using basic conditions. Unfortunately, the starting material was always quantitatively recovered or only degradation products were obtained (i and ii in scheme 13). Attempts to activate the lactam function as its chloride also failed (iii and iv in scheme 13) because of the lower reactivity of **19c** and **20b,c**.



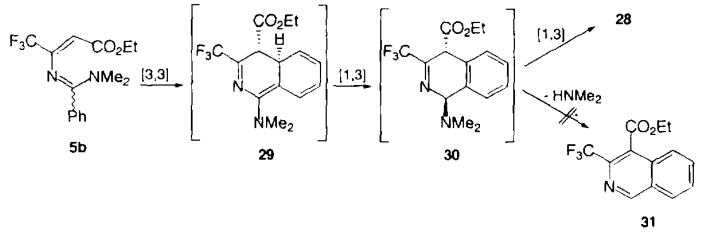
Scheme 13

We also studied the photochemical cyclization of benzamidine **5b**. When a hexane solution of **5b** was irradiated at 300 nm for 7 days, we obtained the dihydroisoquinoline **28** (yield: 48%) as only one diastereomer and the starting amidine **5b** (scheme 14). From the proton–proton coupling constant of **28** ($^3J_{H2\text{-}H3}$ = 7.5 Hz), we reasonably proposed a *trans* relationship between the trifluoromethyl group and the ethoxycarbonyl function.



Scheme 14

To explain the formation of heterocycle **28**, we propose first the [3,3]electrocyclic rearrangement in a conrotatory mechanism to give intermediate **29**, which then undergoes two consecutive [1,3]sigmatropic migrations with retention of configuration. Surprisingly, the intermediate **30** does not eliminate dimethylamine to produce the isoquinoline **31** (scheme 15).



Scheme 15

Conclusion

We have prepared a number of new trifluoromethylated 2-aza-1,3-dienes in a one-step procedure starting from enamines **1** and **2** and monochloromethyleneiminium chlorides, *N,N*-dimethylacetamide dimethylacetal and chloroiminium chlorides prepared from lactams and gaseous phosgene. We assigned the stereochemistry (*Z,E*) to amidines **13a–f** and (*Z,Z*) to bicyclic products **20a–c** on the basis of X-ray diffraction analyses of **13c** and **20b** and ^{13}C NMR data. The cyclizations of **5c**, **6** and **13a,b,e,f** into new pyridin-4-ones **22** and **23a,b,e,f** were achieved in high yield using sodium hydride in DMF. We also performed the photochemical cyclization of benzamidine **5b**.

Experimental section

Melting points were prepared 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 $CDCl_3$ or CD_3OD. 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 sextet, s_p septet and m multiplet. Flash chromatography was run using silica-gel Merck 60 (0.040–0.060 mm) and the distillations were run in a Büchi Kugelrohr GKR 50 apparatus.

Amides and lactams are commercially available and were distilled over calcium hydride before use. Chlorinated solvents (dichloromethane, chloroform and 1,2-dichloroethane) and diethyl ether were dried over phosphorus hemipentoxide and sodium/benzophenone, respectively.

General procedure for the reaction of the Vilsmeier–Haack–Arnold salt

To a solution of oxalyl chloride (1.1 equiv, 11 mmol) in chloroform (10 mL), at −20 °C, was added a solution of DMF (1.2 equiv, 12 mmol) in chloroform (5 mL) for 1 h. The temperature was allowed to reach 0 °C (30 min). A solution of enamine **1** or **2** (1.0 equiv, 10 mmol) in chloroform (10 mL) at −10 °C was added. The mixture was stirred at 0 °C for 30 min then the temperature was allowed to reach 20 °C and maintained for 1 h. The crude product was neutralized with an aqueous solution of potassium hydroxide 2 N (12 mL) until pH 8 then extracted three times with ether (3 × 50 mL). The organic phase was washed with water (20 mL) and brine (30 mL) then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized in hexane to give the amidine **5a** or **19a**.

- *Ethyl 3-{[(dimethylamino)methylidene]amino}-4,4,4-trifluorobut-2-enoate* **5a**

The reaction of enamine **1** (2.75 g, 15 mmol) gave the amidine **5a** (2.65 g, 76%) as colorless needles.

mp = 47–48 °C.

IR (KBr): ν 3 000–2 900, 1 710, 1 640, 1 600, 1 300, 1 190, 1 130, 1 080.

^1H NMR ($CDCl_3$): δ 1.26 (t, 3H, J = 7.1), 3.06 (s, 3H), 3.08 (s, 3H), 4.12 (q, 2H, J = 7.1), 5.66 (s, 1H), 7.58 (s, 1H).

^{13}C NMR ($CDCl_3$): δ 13.6 (qt, J = 126.8, J = 1.5), 34.0 (qdq, J = 138.2, J = 4.7, J = 3.2), 39.9 (qdq, J = 138.0, J = 4.2, J = 3.4), 59.6 (tq, J = 147.1, J = 3.4), 99.9 (dq, J = 164.0, J_F = 3.6), 121.1 (qd, J_F = 277.6, J = 5.0), 153.7 (qd, J_F = 30.8, J = 10.0), 157.4 (dm, J = 181.0), 166.3 (t, J = 3.0).

^{19}F NMR ($CDCl_3$): δ −72.4 (s).

MS: m/z 238 (M^+), 193, 150, 123, 97, 72, 44.

Anal calc for $C_9H_{13}N_2O_2F_3$: C, 45.38; H, 5.50; N, 11.76. Found: C, 45.11; H, 5.76; N, 11.82.

- *3-({1-[(Dimethylamino)methylidene]amino}-2,2,2-trifluoroethylidene)-1-methylpyrrolidin-2-one* ***19a***

The reaction of enamine **2** (0.97 g, 5 mmol) gave the amidine **19a** (0.96 g, 77%) as an oil.

IR ($CHCl_3$): ν 3 005, 2 931, 2 883, 1 669, 1 637, 1 605, 1 425, 1 404, 1 379, 1 182.

^1H NMR ($CDCl_3$): δ 2.88 (s, 3H), 2.9–3.1 (m, 2H), 3.02 (s, 3H), 3.03 (s, 3H), 3.37 (tm, 2H, J = 7.1), 7.38 (s, 1H).

^{13}C NMR ($CDCl_3$): δ 22.9 (tm, J = 134.5, J_F = 3.3), 29.7 (q, J = 137.7), 33.9 (qm, J = 138.0), 39.8 (qqd, J = 137.9, J = 3.4, J = 3.2), 45.7 (tm, J = 140.5, J_F = 1.7), 113.6 (sm, J_F = 1.8), 121.9 (qdd, J_F = 277.3, J = 10.8, J = 7.7), 143.5 (qm, J_F = 31.0), 156.6 (dm, J = 183.7), 167.9 (sm).

^{19}F NMR ($CDCl_3$): δ −67.2 (t, J = 3.4).

MS: m/z 249 (M^+), 180, 178, 109, 69, 44.

Anal calc for $C_{10}H_{14}N_3OF_3$: C, 48.19; H, 5.66; N, 16.86. Found: C, 47.82; H, 5.65; N, 16.52.

General procedure for the reaction of N,N-dimethylbenzamide chloride

To a solution of oxalyl chloride (1.7 equiv, 17 mmol) in chloroform (10 mL), at 0 °C, was added a solution of *N,N*-dimethylbenzamide (1.7 equiv, 17 mmol) in chloroform (5 mL). The temperature was allowed to reach 25 °C (1 h) and then a solution of enamine **1** or **2** (1.0 equiv, 10 mmol) in chloroform (5 mL) was added. The mixture was refluxed for 2–48 h. After cooling at 0 °C, the crude was neutralized with an aqueous solution of potassium hydroxide 2 N (10 mL) until pH 8–9 and then extracted three times with chloroform (3 × 50 mL). The organic phase was washed with water (20 mL) and brine (30 mL) then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: ether/hexane, 50:50) to give the amidine **5b** or **19b** as yellow oils.

- *Ethyl 3-{[(dimethylamino)phenylmethylidene]amino}-4,4,4-trifluorobut-2-enoate* **5b**

The reaction of enamine **1** (0.92 g, 5 mmol) gave the amidine **5b** (1.21 g, 77%).

bp = 145–150 °C/0.2 mmHg.

IR (film): ν 2 960, 2 920, 1 700, 1 570, 1 395, 1 275, 1 170, 1 125.

UV/vis (MeCN, conc 5 × 10^{-5} mol·L^{-1}): λ_{max} 312, A 0.44, ε 8800.

^1H NMR ($CDCl_3$): δ 1.18 (t, 3H, J = 7.1), 2.84 (s, 3H), 3.22 (s, 3H), 4.04 (q, 2H, J = 7.1), 5.25 (s, 1H), 7.3 (m, 5H).

^{13}C NMR ($CDCl_3$): δ 13.8 (qt, J = 127.2, J = 2.6), 37.8 (q, J = 139.5), 39.3 (q, J = 139.3), 59.1 (tq, J = 147.2,

J = 4.4), 99.3 (dq, J = 165.0, J_F = 3.6), 120.9 (qd, J_F = 278.1, J = 4.9), 127.8 (dm, 2C, J = 159.6), 128.3 (dt, 2C, J = 162.3, J = 6.2), 129.5 (dtt, J = 161.7, J = 6.2, J = 2.0), 132.5 (sm), 151.4 (q, J_F = 31.8), 163.7 (sm), 165.9 (t, J = 3.1).

^{19}F NMR ($CDCl_3$): δ −71.2 (s).

MS: m/z 314 (M^+), 286, 269, 241, 226, 199, 183, 123, 95, 77, 69.

Anal calc for $C_{15}H_{17}N_2O_2F_3$: C, 57.32; H, 5.45; N, 8.91. Found: C, 57.28; H, 5.67; N, 8.99.

• *3-{1-[α-(Dimethylamino)benzylideneamino]-2,2,2-trifluoroethylidene}-1-methylpyrrolidin-2-one* **19b**

The reaction of enamine **2** (0.97 g, 5 mmol) gave the amidine **19b** (0.46 g, 28%).

bp = 70–80 °C/0.03 mmHg.

IR ($CHCl_3$): ν 3 010, 2 940, 2 880, 1 680, 1 610, 1 595, 1 575, 1 400, 1 280.

^{1}H NMR ($CDCl_3$): δ 2.5–2.6 (m, 2H), 2.79 (s, 3H), 3.08 (tm, 2H, J = 6.3), 3.1–3.3 (m, 6H), 7.2–7.3 (m, 5H).

^{13}C NMR ($CDCl_3$): δ 22.7 (tm, J = 136.6, J_F = 2.7), 29.7 (qm, J = 137.6, J_F = 1.8), 38.7 (q, J = 138.2), 45.9 (tm, J = 140.8, J_F = 1.5), 114.7 (sm, J_F = 1.7), 121.7 (qm, J_F = 277.9), 127.3 (dm, 2C, J = 161.9), 128.1 (dm, 2C, J = 162.6), 128.6 (dm, J = 162.8), 133.7 (sm), 140.7 (qm, J_F = 31.1), 163.3 (sm), 168.1 (sm).

^{19}F NMR ($CDCl_3$): δ −66.7 (t, J = 3.0).

MS: m/z 325 (M^+), 281, 256, 153, 136, 107, 89, 84, 77.

General procedure for the reaction of N,N-dimethylacetamide dimethylacetal

A mixture of enamine **1** or **2** (1.0 equiv, 5.0 mmol) and *N*,*N*-dimethylacetamide dimethylacetal (1.5 equiv, 7.5 mmol) was heated (100 or 116 °C) for 10–24 h. The crude was evaporated under reduced pressure and chromatographed on silica gel (eluent: ether/hexane, 50:50) to give the amidine **5c**, **6** or **19c**.

The reaction of enamine **1** (0.92 g, 5 mmol) gave a colorless oil (1.23 g, 100%) as a mixture (27:73) of ethyl and methyl esters **5c** and **6**.

Mixture of esters **5c** and **6**: bp = 80–85 °C/0.3 mmHg.

IR (film): ν 2 930, 1 710, 1 600, 1 410, 1 390, 1 280, 1 160, 1 120.

MS: m/z 252 (M^+ of **5c**), 238 (M^+ of **6**), 207, 194, 179, 162, 137, 123, 111, 96, 69.

• *Ethyl 3-{[1-(dimethylamino)ethylidene]amino}-4,4,4-trifluorobut-2-enoate* **5c**

^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H, J = 7.1), 1.93 (s, 3H), 3.07 (s, 6H), 4.10 (q, 2H, J = 7.1), 5.62 (s, 1H).

^{13}C NMR ($CDCl_3$): δ 13.3 (qt, J = 127.1, J = 2.6), 14.5 (q, J = 129.6), 37.0 (qm, J = 138.5), 59.8 (tq, J = 147.1, J = 4.4), 97.5 (dq, J = 164.7, J_F = 3.5), 120.8 (qd, J_F = 277.9, J = 4.9), 150.5 (q, J_F = 30.8), 160.9 (sm), 165.5 (t, J = 3.0).

^{19}F NMR ($CDCl_3$): δ −72.58 (s).

Anal calc for $C_{10}H_{15}N_2O_2F_3$: C, 47.62; H, 5.99; N, 11.11. Found: C, 47.84; H, 5.77; N, 11.21.

• *Methyl 3-{[1-(dimethylamino)ethylidene]amino}-4,4,4-trifluorobut-2-enoate* **6**

^{1}H NMR ($CDCl_3$): δ 1.93 (s, 3H), 3.06 (s, 6H), 3.63 (s, 3H), 5.59 (s, 1H).

^{13}C NMR ($CDCl_3$, proton-noise-decoupled spectrum): δ 14.6, 36.9, 49.9, 96.8 (q, J_F = 3.5), 120.7 (q, J_F = 278.0), 150.9 (q, J_F = 30.8), 161.2, 165.9.

^{19}F NMR ($CDCl_3$): δ −72.62 (s).

• *3-{1-[1-(Dimethylamino)ethylidenamino]-2,2,2-trifluoroethylidene}-1-methylpyrrolidin-2-one* **19c**

The reaction of enamine **2** (0.97 g, 5 mmol) gave the amidine **19c** (0.88 g, 67%) as an oil.

IR (film): ν 2 933, 2 883, 1 685, 1 608, 1 501, 1 445, 1 421, 1 398, 1 278.

^{1}H NMR ($CDCl_3$): δ 1.91 (s, 3H), 2.86 (s, 3H), 2.94 (tq, 2H, J = 6.8, J_F = 3.3), 3.04 (s, 6H), 3.36 (tm, 2H, J = 6.6).

^{13}C NMR ($CDCl_3$): δ 15.1 (q, J = 128.8), 22.4 (tq, J = 133.4, J_F = 3.3), 29.3 (qm, J = 137.6, J_F = 1.4), 37.4 (q, 2C, J = 137.0), 45.7 (tm, J = 140.8, J_F = 1.7), 112.7 (sm, J_F = 1.6), 121.6 (q, J_F = 277.7), 140.1 (qt, J_F = 31.0, J = 3.7), 160.2 (sm), 167.7 (sm).

^{19}F NMR ($CDCl_3$): δ −67.5 (t, J = 3.6).

MS: m/z 263 (M^+), 244, 219, 194, 192, 123, 101, 56.

General procedure for the reaction of N-substituted lactams with gaseous phosgene

Gaseous phosgene (4–5 equiv, 40–50 mmol) was first condensed in a graduate gas ampoule and then slowly introduced in a refluxed solution of enamine **1** or **2** (1 equiv, 10 mmol) and *N*-substituted lactams **7**–**12** (4–5 equiv, 40–50 mmol) in chloroform (20 mL). The mixture was then refluxed for 1–2 h. After cooling, the crude was hydrolyzed with water (10 mL) and neutralized with an aqueous solution of potassium hydroxide 2 N (15 mL) until pH 8–9 and then extracted three times with chloroform (3 × 50 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: ether/hexane, 50:50) to give the cyclic amidines **13a–f** or **20a–c**, the pyridin-4-one **14** and the pyrrolidin-2-one **21**.

Reaction with the enamine ***1***

• *Ethyl-4,4,4-trifluoro-3-[(1-methylpyrrolidin-2-ylidene)amino]but-2-enoate* ***13a***

The reaction of enamine **1** (4.60 g, 25 mmol) with 1-methylpyrrolidin-2-one **7** (12.40 g, 125 mmol) and phosgene (9.0 mL, 125 mmol) gave the pyrrolidine **13a** (3.70 g, 56%) as a colorless oil.

IR (film): ν 2 980, 2 880, 1 720, 1 650, 1 440, 1 280, 1 170, 1 130.

^{1}H NMR ($CDCl_3$): δ 1.25 (t, 3H, J = 7.1), 2.00 (qt, 2H, J = 7.5), 2.47 (t, 2H, J = 7.5), 2.98 (t, 3H, J = 0.7), 3.46 (t, 2H, J = 7.5), 4.12 (q, 2H, J = 7.1), 5.66 (q, 1H, J_F = 0.4).

^{13}C NMR ($CDCl_3$): δ 13.2 (qt, J = 127.2, J = 2.4), 18.4 (tqt, J = 132.3, J = 2.1), 27.4 (tt, J = 133.2, J = 3.5), 30.2 (q, J = 138.1), 50.8 (tm, J = 141.2), 58.9 (tq, J = 147.1, J = 4.5), 99.4 (dq, J = 164.1, J_F = 3.5), 120.7 (qd, J_F = 277.6, J = 4.6), 152.1 (qd, J_F = 31.1, J = 1.9), 164.8 (sm), 165.3 (t, J = 3.6).

^{19}F NMR ($CDCl_3$): δ −72.3 (s).

MS: m/z 264 (M^+), 245, 219, 195, 191, 177, 149, 123, 99, 69.

Anal calc for $C_{11}H_{15}N_2O_2F_3$: C, 50.00; H, 5.72; N, 10.60. Found: C, 50.26; H, 5.72; N, 10.68.

• *Ethyl 3-[(1-ethylpyrrolidin-2-ylidene)amino]-4,4,4-trifluorobut-2-enoate* **13b**

The reaction of enamine **1** (4.60 g, 25 mmol) with 1-ethylpyrrolidin-2-one **8** (14.20 g, 125 mmol) and phosgene (9.0 mL, 125 mmol) gave the pyrrolidine **13b** (3.13 g, 45%) as a yellow oil.

IR (film): ν 2 980, 2 940, 2 880, 1 720, 1 630, 1 280, 1 170, 1 130, 1 030.

^{1}H NMR ($CDCl_3$): δ 1.18 (t, 3H, J = 7.2), 1.25 (t, 3H, J = 7.1), 1.99 (qt, 2H, J = 7.1), 2.47 (t, 2H, J = 7.1), 3.45 (t, 2H, J = 7.1), 3.46 (q, 2H, J = 7.2), 4.12 (q, 2H, J = 7.1), 5.65 (q, 1H, J_F = 0.4).

^{13}C NMR ($CDCl_3$): δ 10.6 (qt, J = 127.4, J = 3.4), 13.3 (qt, J = 127.1, J = 2.6), 18.6 (tqt, J = 134.0, J = 3.3), 27.8 (tt, J = 133.7, J = 3.1), 38.1 (tq, J = 138.0, J = 3.5), 48.0 (tm, J = 143.4), 58.9 (tq, J = 146.6, J = 4.5), 99.3 (dq, J = 164.6, J_F = 3.5), 120.8 (qd, J_F = 278.3, J = 4.8), 152.1 (q, J_F = 30.7), 163.9 (sm), 165.3 (td, J = 2.9, J = 1.2).

^{19}F NMR ($CDCl_3$): δ −72.5 (s).

MS: m/z 278 (M^+), 233, 209, 205, 191, 163, 137, 97, 69.

Anal calc for $C_{12}H_{17}N_2O_2F_3$: C, 51.80; H, 6.16; N, 10.07. Found: C, 51.82; H, 6.21; N, 9.91.

• *Ethyl 3-[(1-benzylpyrrolidin-2-ylidene)amino]-4,4,4-trifluorobut-2-enoate* **13c**

The reaction of enamine **1** (3.30 g, 18 mmol) with 1-benzylpyrrolidin-2-one **9** (12.80 g, 72 mmol) and phosgene (5.3 mL, 72 mmol) gave, after chromatography and recrystallization in hexane, the pyrrolidine **13c** (5.23 g, 86%) as a white solid.

mp = 95–96 °C.

IR (KBr): ν 2 980, 2 930, 2 880, 1 710, 1 630, 1 470, 1 430, 1 290.

^{1}H NMR ($CDCl_3$): δ 1.26 (t, 3H, J = 7.1), 1.97 (qt, 2H, J = 7.4), 2.54 (t, 2H, J = 7.4), 3.33 (t, 2H, J = 7.4), 4.15 (q, 2H, J = 7.1), 4.61 (s, 2H), 5.71 (q, 1H, J_F = 0.4), 7.33 (m, 3H), 7.35 (m, 2H).

^{13}C NMR ($CDCl_3$): δ 13.7 (qt, J = 127.2, J = 2.6), 18.8 (tqt, J = 133.9, J = 3.1), 28.0 (tt, J = 134.0, J = 2.6), 47.5 (tt, J = 138.9, J = 4.3), 48.2 (tqt, J = 142.4, J = 3.2), 59.4 (tq, J = 147.2, J = 4.4), 100.4 (dq, J = 164.9, J_F = 3.4), 121.1 (qd, J_F = 278.2, J = 5.0), 127.2 (dtt, J = 160.6, J = 6.2, J = 2.0), 128.0 (dt, J = 159.3, J = 5.1), 128.4 (ddd, J = 160.9, J = 6.8, J = 1.8), 136.5 (t, J = 4.8), 152.1 (q, J_F = 30.9), 164.7 (sm), 165.5 (t, J = 3.2).

^{19}F NMR ($CDCl_3$): δ −72.4 (s).

MS: m/z 340 (M^+), 295, 271, 267, 252, 225, 91, 65.

Anal calc for $C_{17}H_{19}N_2O_2F_3$: C, 59.99; H, 5.63; N, 8.23. Found: C, 59.78; H, 5.33; N, 8.02.

X-ray [13a]: monoclinic, $P2_1/c$, a = 11.999(4) Å, b = 12.359(4) Å, c = 12.555(4) Å, β = 111.11(4)°, V = 1 736.9(9) Å^3, Z = 4.

• *Ethyl-3-[(1,3-dimethylpyrrolidin-2-ylidene)amino]-4,4,4-trifluorobut-2-enoate* **13d**

The reaction of enamine **1** (1.83 g, 10 mmol) with 1,3-dimethylpyrrolidin-2-one **10** (5.65 g, 50 mmol) and phosgene (3.7 mL, 50 mmol) gave the pyrrolidine **13d** (1.14 g, 41%) as a yellow oil.

IR (film): ν 2 980, 2 940, 2 820, 1 710, 1 625, 1 400, 1 280, 1 170, 1 130.

^{1}H NMR ($CDCl_3$): δ 1.06 (d, 3H, J = 7.2), 1.25 (t, 3H, J = 7.1), 1.63 (ddt, 1H, J = 12.5, J = 7.3, J = 5.0), 2.26 (ddt, 1H, J = 12.5, J = 8.4, J = 8.3), 2.97 (d, 3H, J = 0.6), 3.00 (m, 1H), 3.45 (dd, 2H, J = 8.4, J = 7.3), 4.10 (q, 2H, J = 7.1), 5.55 (s, 1H).

^{13}C NMR ($CDCl_3$): δ 13.6 (qt, J = 127.0, J = 2.5), 16.2 (q, J = 126.5), 27.4 (t, J = 131.0), 31.2 (q, J = 138.6), 34.9 (d, J = 135.6), 49.4 (t, J = 141.6), 59.1 (tq, J = 142.7, J = 4.5), 97.1 (dq, J = 164.6, J_F = 3.4), 121.0 (qd, J_F = 278.4, J = 5.2), 151.9 (q, J_F = 30.8), 166.2 (t, J = 3.6), 169.5 (sm).

^{19}F NMR ($CDCl_3$): δ −71.6 (s).

MS: m/z 278 (M^+), 233, 206, 205, 191, 163, 137, 113, 94, 69.

Anal calc for $C_{12}H_{17}N_2O_2F_3$: C, 51.80; H, 6.16; N, 10.07. Found: C, 51.77; H, 6.18; N, 9.96.

• *Ethyl-4,4,4-trifluoro-3-[(1-methylpiperidin-2-ylidene)amino]but-2-enoate* **13e**

The reaction of enamine **1** (2.75 g, 15 mmol) with 1-methylpiperidin-2-one **11** (9.45 g, 75 mmol) and phosgene (5.4 mL, 75 mmol) gave the piperidine **13e** (0.63 g, 15%) as a colorless oil and the pyridin-4-one **14** (0.82 g, 18%) as an yellow oil.

IR (film): ν 2 950, 2 880, 1 710, 1 600, 1 405, 1 350, 1 285, 1 170.

^{1}H NMR ($CDCl_3$): δ 1.25 (t, 3H, J = 7.1), 1.70 (qt, 2H, J = 6.1), 1.85 (qt, 2H, J = 6.1), 2.37 (t, 2H, J = 6.1), 3.02 (t, 3H, J = 0.7), 3.33 (t, 2H, J = 6.1), 4.11 (q, 2H, J = 7.1), 5.59 (q, 1H, J_F = 0.4).

^{13}C NMR ($CDCl_3$): δ 13.5 (qt, J = 126.8, J = 2.6), 19.5 (tqt, J = 130.4, J = 4.3), 22.6 (tqt, J = 129.6, J = 4.3), 25.7 (t, J = 125.8), 36.5 (qt, J = 137.9, J = 1.7), 49.5 (ts_x, J = 138.9, J = 2.6), 58.8 (tq, J = 146.8, J = 4.4), 97.6 (dq, J = 164.5, J_F = 3.4), 120.6 (qd, J_F = 277.7, J = 4.8), 150.0 (q, J_F = 30.6), 159.8 (sm), 165.2 (t, J = 3.0).

^{19}F NMR ($CDCl_3$): δ −72.3 (s).

MS: m/z 278 (M^+), 233, 205, 163, 137, 69.

Anal calc for $C_{12}H_{17}N_2O_2F_3$: C, 51.80; H, 6.16; N, 10.07. Found: C, 51.69; H, 6.09; N, 9.91.

• *Ethyl 8-methyl-2-(trifluoromethyl)-1,4,5,6,7,8-hexahydro-1,8-naphthyridine-3-carboxylate* **14**

mp = 44–45 °C.

IR (KBr): ν 3 500, 2 950, 1 660, 1 610, 1 560, 1 400, 1 320, 1 250.

^{1}H NMR ($CDCl_3$): δ 1.38 (t, 3H, J = 7.2), 1.91 (tt, 2H, J = 6.2, J = 5.5), 2.68 (t, 2H, J = 6.3), 3.19 (s, 3H), 3.36 (t, 2H, J = 5.5), 4.38 (q, 2H, J = 7.2), 11.6 (brs, NH).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.2 (qt, J = 127.4, J = 2.6), 19.7 (t, J = 130.8), 19.8 (t, J = 130.8), 35.7 (qt, J = 137.7, J = 1.6), 49.0 (t, J = 137.9), 61.6 (tq, J = 148.5, J = 4.4), 98.4 (dq, J = 4.1, J_F = 1.7), 102.6 (dqt, J = 6.3, J = 5.9), 121.3 (q, J_F = 275.2), 145.4 (q, J_F = 34.4), 156.2 (sm, J_F = 1.4), 163.4 (dt, J = 4.5, J = 2.5), 169.2 (t, J = 2.9).

^{19}F NMR ($CDCl_3$): δ −64.3 (s).

MS: m/z 304 (M^+), 258, 230, 205, 201, 181, 121, 58.

Anal calc for $C_{13}H_{15}N_2O_3F_3$: C, 51.32; H, 4.97; N, 9.21. Found: C, 51.45; H, 4.90; N, 9.20.

• *Ethyl 4,4,4-trifluoro-3-[(1-methylazepan-2-ylidene)amino]but-2-enoate* **13f**

The reaction of enamine **1** (2.20 g, 12 mmol) with 1-methylazepan-2-one **12** (7.60 g, 60 mmol) and phosgene (4.4 mL, 60 mmol) gave the azepane **13f** (2.77 g, 79%) as a colorless oil.

IR (film): ν 2 940, 2 860, 1 710, 1 600, 1 450, 1 400, 1 350, 1 280, 1 170.

^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H, J = 7.1), 1.6 (m, 6H), 2.45 (m, 2H), 3.11 (s, 3H), 3.45 (m, 2H), 4.10 (q, 2H, J = 7.1), 5.60 (s, 1H).

^{13}C NMR ($CDCl_3$): δ 13.4 (qt, J = 126.7, J = 2.5), 23.3 (t, J = 128.2), 26.9 (t, J = 127.7), 28.1 (t, J = 130.4), 28.8 (t, J = 126.5), 37.3 (qt, J = 138.1, J = 3.8), 52.0 (t, J = 136.0), 58.6 (tq, J = 146.6, J = 4.5), 96.9 (dq, J = 164.3, J_F = 3.5), 120.4 (qd, J_F = 277.4, J = 4.9), 150.0 (q, J_F = 30.6), 165.0 (t, J = 3.1), 165.4 (sm).

^{19}F NMR ($CDCl_3$): δ −72.5 (s).

MS: m/z 292 (M^+), 247, 223, 219, 177, 151, 96, 69.

Anal calc for $C_{13}H_{19}N_2O_2F_3$: C, 53.42; H, 6.55; N, 9.58. Found: C, 53.38; H, 6.61; N, 9.46.

Reaction with enamine **2**

• *1-Methyl-3-{1-[(1-methylpyrrolidin-2-ylidene)-amino]-2,2,2-trifluoroethylidene}pyrrolidin-2-one* **20a**

The reaction of enamine **2** (0.97 g, 5 mmol) with 1-methylpyrrolidin-2-one **7** (2.48 g, 25 mmol) and phosgene (1.8 mL, 25 mmol) gave the pyrrolidin-2-one **20a** (0.44 g, 32%) as a colorless oil and the pyrrolidin-2-one **21** [9] (0.32 g, 15%) as a yellow oil.

IR ($CHCl_3$): ν 3 000, 2 930, 2 885, 1 685, 1 645, 1 500, 1 408, 1 280, 1 160.

^{1}H NMR ($CDCl_3$): δ 1.96 (tt, 2H, J = 7.4, J = 7.2), 2.42 (t, 2H, J = 7.8), 2.87 (d, 3H, J = 1.4), 2.9–3.0 (m, 2H), 2.96 (s, 3H), 3.36 (tq, 2H, J = 6.9, J = 1.1), 3.42 (t, 2H, J = 7.0).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.8 (ttt, J = 133.4, J = 3.2, J = 3.1), 22.3 (tqt, J = 135.9, J_F = 3.4, J = 3.2), 27.5 (t, J = 133.3), 29.2 (q, J = 137.8), 30.6 (q, J = 137.4), 45.5 (tm, J = 142.5, J_F = 1.7), 50.9 (ttq, J = 141.1, J = 3.1, J = 3.0), 114.0 (tm, J = 6.7, J_F = 1.7), 121.6 (q, J_F = 277.1), 141.1 (qt, J_F = 30.8, J = 3.7), 164.6 (sm), 167.4 (sm).

^{19}F NMR ($CDCl_3$): δ −67.2 (t, J = 3.4).

MS: m/z 275 (M^+), 256, 206, 205, 135, 86, 84, 69.

• *1-Methyl-3-{1-[(1-methylpiperidin-2-ylidene)-amino]-2,2,2-trifluoroethylidene}pyrrolidin-2-one* **20b**

The reaction of enamine **2** (0.97 g, 5 mmol) with 1-methylpiperidin-2-one **11** (3.15 g, 25 mmol) and phosgene (1.8 mL, 25 mmol) gave the pyrrolidin-2-one **20b** (0.68 g, 47%) as a yellow solid.

mp = 114–116 °C.

IR (KBr): ν 2 958, 2 937, 2 888, 1 674, 1 600, 1 519, 1 472, 1 404, 1 366.

^{1}H NMR ($CDCl_3$): δ 1.6–1.7 (m, 2H), 1.81 (tt, 2H, J = 5.8, J = 5.6), 2.2–2.6 (m, 2H), 2.86 (s, 3H), 2.9–3.0 (m, 2H), 3.01 (s, 3H), 3.29 (t, 2H, J = 5.6), 3.34 (t, 2H, J = 7.3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.7 (tqt, J = 130.1, J = 4.0), 23.0 (tqt, J = 135.8, J_F = 3.2, J = 3.1), 23.4 (ttt, J = 129.2, J = 4.5, J = 3.7), 26.6 (t, J = 129.2), 29.9 (q, J = 137.7), 37.3 (qt, J = 137.5, J = 1.7), 46.3 (tm, J = 142.2, J_F = 1.7), 50.3 (tqt, J = 141.2, J = 3.2, J = 3.1), 113.6 (tm, J = 2.7, J_F = 1.6), 122.1 (q, J_F = 278.3), 140.0 (qt, J_F = 30.7, J = 3.6), 160.2 (sm), 168.2 (sm).

^{19}F NMR ($CDCl_3$): δ −67.3 (t, J = 2.5).

MS: m/z 289 (M^+), 270, 269, 220, 218, 149, 98, 69.

Anal calc for $C_{13}H_{18}N_3OF_3$: C, 53.97; H, 6.27; N, 14.52. Found: C, 54.07; H, 6.04; N, 14.47.

• *1-Methyl-3-{1-[(1-methylazepan-2-ylidene)amino]-2,2,2-trifluoroethylidene}pyrrolidin-2-one* **20c**

The reaction of enamine **2** (0.97 g, 5 mmol) with 1-methylazepan-2-one **12** (3.17 g, 25 mmol) and phosgene (1.8 mL, 25 mmol) gave the pyrrolidin-2-one **20c** (0.85 g, 56%) as a yellow solid.

mp = 95–96 °C.

IR (KBr): ν 2 984, 2 936, 2 885, 2 860, 1 676, 1 596, 1 511, 1 402, 1 316, 1 278.

^{1}H NMR ($CDCl_3$): δ 1.4–1.8 (m, 6H), 2.2–2.7 (m, 2H), 2.85 (s, 3H), 2.94 (tq, J = 6.9, J_F = 3.4), 3.09 (s, 3H), 3.34 (t, 2H, J = 6.8), 3.4–3.7 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.0 (tqt, J = 135.8, J_F = 3.2, J = 3.0), 24.2 (t, J = 128.9), 27.9 (t, J = 126.9), 28.9 (t, J = 128.9), 29.7 (t, J = 127.0), 29.9 (q, J = 137.6), 38.2 (qt, J = 137.6, J = 3.9), 46.2 (tm, J = 142.2, J_F = 1.7), 52.7 (t, J = 141.1), 112.9 (tm, J = 6.4, J_F = 1.6), 122.1 (q, J_F = 277.9), 140.5 (qt, J_F = 31.0, J = 3.6), 165.5 (sm), 168.3 (sm).

^{19}F NMR ($CDCl_3$): δ −67.4 (dd, J = 5.3, J = 2.7).

MS: m/z 303 (M^+), 284, 234, 220, 205, 177, 98, 69.

Anal calc for $C_{14}H_{20}N_3OF_3$: C, 55.44; H, 6.65; N, 13.85. Found: C, 55.31; H, 6.62; N, 13.72.

Reaction of enamine **1** *and 2-bromo-1-methylpyridinium triflate* **17**

• *Preparation of 2-bromo-1-methylpyridinium triflate* **17**

Methyl triflate (6.2 mL, 55 mmol) was added to a solution of 2-bromopyridine (1 equiv, 50 mmol) in dry ether (50 mL), at 20 °C. The mixture was stirred at room temperature for 1 h. The white solid was then filtered, washed with ether (30 mL) and dried under reduced pressure to give the triflate **17** (14.0 g, 87%).

• *Preparation of ethyl 4,4,4-trifluoro-3-[(1-methyl-1,2-dihydropyridin-2-ylidene)amino]but-2-enoate* **18**

Lithium hydride (0.25 g, 30.0 mmol) was added to a solution of enamine **1** (2.75 g, 15.0 mmol) in THF (25 mL), at 20 °C. The pyridinium salt **17** (5.60 g, 22.5 mmol) was then added in several portions until the end of hydrogen release (1 h). The mixture was slowly refluxed during 1.5 h then cooled, hydrolyzed with water (20 mL) and extracted twice with ether (2 × 50 mL). The organic phase was washed with brine (30 mL), dried over $MgSO_4$ and concentrated. The residue was then chromatographed on silica gel (eluent: ether) to give the pyridine **18** (3.53 g, 86%) as a yellow solid; mp = 65–66 °C.

IR (KBr): ν 2 990, 2 920, 1 690, 1 640, 1 590, 1 540, 1 280, 1 190.

^{1}H NMR ($CDCl_3$): δ 1.14 (t, 3H, J = 7.1), 3.58 (s, 3H), 4.03 (q, 2H, J = 7.1), 5.67 (s, 1H), 6.10 (td, 1H, J = 6.8, J = 1.4), 6.54 (ddd, 1H, J = 9.1, J = 1.4, J = 0.8), 7.12 (ddd, 1H, J = 9.1, J = 6.8, J = 1.8), 7.23 (ddd, 1H, J = 6.8, J = 1.8, J = 0.8).

^{13}C NMR ($CDCl_3$): δ 13.3 (qt, J = 126.5, J = 2.5), 39.2 (qd, J = 141.6, J = 4.3), 58.7 (tq, J = 147.6, J = 3.9), 96.6 (dq, J = 163.4, J_F = 3.4), 106.1 (dddd, J = 171.8, J = 9.9, J = 4.1, J = 1.8), 114.3 (dd, J = 166.9, J = 6.5), 121.1 (qd, J_F = 278.1, J = 5.1), 136.0 (dd, J = 162.4, J = 8.2), 137.6 (dm, J = 180.5), 149.9 (q, J_F = 30.3), 154.9 (sm), 165.0 (t, J = 2.8).

^{19}F NMR ($CDCl_3$): δ −72.3 (s).

MS: m/z 274 (M^+), 229, 202, 201, 181, 159, 133, 131, 109, 93, 78.

Anal calc for $C_{12}H_{13}N_2O_2F_3$: C, 52.56; H, 4.78; N, 10.21. Found: C, 52.49; H, 4.88; N, 10.30.

General procedure for the cyclizations of amidines ***5c, 6*** *and* ***13a,b,d–f***

Sodium hydride (2 equiv, 20 mmol) was added to a solution of amidine **5c**, **6** or **13a,b,d–f** (1 equiv, 10 mmol) in *N,N*-dimethylformamide at 20 °C. The mixture was slowly heated at 80–90 °C until the end of hydrogen release (30–45 min). The crude was diluted with ether (50 mL), hydrolyzed with water (10 mL), neutralized with an aqueous solution of potassium hydroxide 2 N (5 mL) until pH 7–8 and then extracted three times with ether (3 × 50 mL). The organic phase was washed with brine (30 mL), dried over $MgSO_4$ and concentrated. The residue was distilled under reduced pressure and recrystallized or chromatographed on silica gel (eluent: ether/hexane, 50:50) to give the cyclic pyridin-4-one **22** or **23a,b,e,f** and the pyrrolo[2,3-*b*]pyridin-4-one **24**.

• *2-(Dimethylamino)-6-(trifluoromethyl)pyridin-4(1H)-one* ***22***

The cyclization of a mixture of amidines **5c** and **6** (5.34 g, 22 mmol) gave after chromatography, the pyridin-4-one **22** (3.93 g, 87%) as a colorless oil.

IR (film): ν 3 500–3 000, 1 610, 1 510, 1 400, 1 300, 1 170, 1 120, 1 020.

^{1}H NMR ($CDCl_3$): δ 3.00 (s, 6H), 6.02 (d, 1H, J = 1.8), 6.48 (d, 1H, J = 1.8), 8.2 (brs, NH).

^{13}C NMR ($CDCl_3$): δ 37.7 (qq, J = 137.4, J = 3.6), 94.2 (dd, J = 161.5, J = 3.5), 99.9 (dqd, J = 168.7, J_F = 3.3, J = 3.2), 121.5 (qd, J_F = 274.8, J = 3.0), 146.3 (q, J_F = 34.0), 160.7 (sp, J = 3.0), 166.5 (dd, J = 3.7, J = 2.5).

^{19}F NMR ($CDCl_3$): δ −69.1 (s).

MS: m/z 206 (M^+), 191, 177, 163, 115, 93, 69, 58.

Anal calc for $C_8H_9N_2OF_3$: C, 46.61; H, 4.40; N, 13.59. Found: C, 46.50; H, 4.33; N, 13.65.

• *1-Methyl-6-(trifluoromethyl)-1,2,3,7-tetrahydro-4H-pyrrolo[2,3-b]pyridin-4-one* ***23a***

The cyclization of amidine **13a** (5.33 g, 20 mmol) gave after distillation under reduced pressure and recrystallization in hexane, the pyridin-4-one **23a** (3.92 g, 89%) as a colorless solid.

bp = 90 °C/0.06 mmHg; mp = 141 °C.

IR (KBr): ν 3 600–3 000, 1 660, 1 630, 1 600, 1 580, 1 520, 1 405, 1 320, 1 280, 1 120.

^{1}H NMR ($CDCl_3$ + CD_3CN): δ 2.89 (s, 3H), 2.91 (t, 2H, J = 8.3), 3.50 (t, 2H, J = 8.3), 6.44 (s, 1H), 8.3 (brs, NH).

^{13}C NMR ($CDCl_3$ + CD_3CN): δ 22.2 (tt, J = 134.5, J = 2.7), 31.8 (qt, J = 137.2, J = 1.1), 51.6 (ts_x, J = 142.0, J = 3.5), 101.0 (dqt, J = 166.3, J_F = 3.8, J = 1.9), 108.5 (sm, J_F = 1.3), 121.7 (qd, J_F = 273.8, J = 3.1), 145.3 (q, J_F = 33.1), 158.0 (q, J = 2.6), 165.7 (s_x, J = 3.1).

^{19}F NMR ($CDCl_3$ + CD_3CN): δ −68.2 (s).

MS: m/z 218 (M^+), 217, 197, 177, 149, 131, 104, 91, 77.

Anal calc for $C_9H_9N_2OF_3$: C, 49.55; H, 4.16; N, 12.84. Found: C, 49.61; H, 4.12; N, 12.97.

• *1-Ethyl-6-(trifluoromethyl)-1,2,3,7-tetrahydro-4H-pyrrolo[2,3-b]pyridin-4-one* ***23b***

The cyclization of amidine **13b** (1.34 g, 4.8 mmol) gave after chromatography the pyridin-4one **23b** (0.90 g, 81%) as a yellow solid.

mp = 100–101 °C.

IR (KBr): ν 3 500–3 000, 2 975, 2 920, 1 650, 1 585, 1 520, 1 420, 1 330, 1 175.

^{1}H NMR (CD_3OD): δ 1.15 (t, 3H, J = 7.2), 2.89 (t, 2H, J = 8.5), 3.39 (q, 2H, J = 7.2), 3.47 (t, 2H, J = 8.5), 6.52 (s, 1H).

^{13}C NMR (CD_3OD): δ 12.3 (qt, J = 126.6, J = 3.0), 23.2 (tt, J = 134.9, J = 2.5), 40.7 (tq, J = 136.8, J = 4.5), 49.9 (t, J = 140.8), 102.3 (dq, J = 165.9, J_F = 4.0), 110.2 (sm, J_F = 1.2), 123.4 (qd, J_F = 273.5, J = 2.5), 147.0 (q, J_F = 33.1), 160.2 (q, J = 2.5), 166.9 (qt, J = 2.6).

^{19}F NMR (CD_3OD): δ −67.9 (s).

MS: m/z 232 (M^+), 217, 203, 197, 183, 177, 128, 101, 91.

Anal calc for $C_{10}H_{11}N_2OF_3$: C, 51.73; H, 4.77; N, 12.06. Found: C, 51.67; H, 4.80; N, 11.93.

• *1,3a-Dimethyl-6-(trifluoromethyl)-1,2,3,3a,7,7a-hexahydro-4H-pyrrolo[2,3-b]pyridin-4-one* ***24***

The cyclization of amidine **13d** (1.06 g, 3.8 mmol) gave after chromatography and recrystallization in a mixture of ether and hexane, the pyridin-4-one **24** (0.17 g, 19%) as a yellow solid.

mp = 113 °C.

IR (KBr): ν 3 600–3 100, 2 970, 2 930, 2 870, 1 610, 1 360, 1 300, 1 280, 1 165.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.07 (s, 3H), 1.96 (ddd, 1H, J = 12.2, J = 10.0, J = 8.5), 2.12 (dd, 1H, J = 12.2, J = 6.4), 3.00 (s, 3H), 3.41 (dd, 1H, J = 10.0, J = 8.5), 3.59 (td, 1H, J = 10.0, J = 6.4), 4.52 (qd, 1H, J_F = 3.3, J = 2.6), 5.41 (s, 1H).

^{13}C NMR (CD_3OD): δ 12.8 (qdt, J = 129.0, J = 11.0, J = 5.0), 31.5 (qd, J = 138.8, J = 1.1), 36.3 (t, J = 134.0), 47.2 (sm), 51.1 (t, J = 143.6), 75.4 (dd, J = 141.5, J = 8.3), 112.1 (ddq, J = 168.6, J = 4.7, J_F = 4.6), 123.5 (qdd, J_F = 271.5, J = 4.3, J = 1.8), 138.9 (qd, J_F = 32.1, J = 4.2), 174.5 (sm).

^{19}F NMR (CD_3OD): δ −71.0 (d, J = 3.3).

MS: m/z 234 (M^+), 219, 217, 205, 157, 137, 96, 82, 69.

Anal calc for $C_{10}H_{13}N_2OF_3$: C, 51.28; H, 5.59; N, 11.96. Found: C, 51.47; H, 6.15; N, 12.05.

• *8-Methyl-7-(trifluoromethyl)-1,4,5,6,7,8-hexahydro-1,8-naphthyridin-4-one* ***23e***

The cyclization of amidine **13e** (0.50 g, 1.8 mmol) gave after chromatography the pyridin-4-one **23e** (0.25 g, 60%) as a yellow oil.

IR (film): ν 3 500–3 000, 2 950, 2 860, 1 620, 1 525, 1 410, 1 330, 1 270, 1 170.

^{1}H NMR (CD_3OD): δ 1.86 (tt, 2H, J = 6.7, J = 5.6), 2.64 (t, 2H, J = 6.7), 3.05 (s, 3H), 3.24 (t, 2H, J = 5.6), 6.47 (s, 1H).

^{13}C NMR (CD_3OD): δ 21.5 (tqt, J = 129.4, J = 4.6), 21.6 (tt, J = 129.4, J = 3.7), 36.9 (qt, J = 137.0, J = 1.7), 50.5 (t, J = 137.9), 99.3 (dq, J = 165.7, J_F = 3.4), 106.3 (sm, J_F = 1.3), 123.5 (qd, J_F = 279.7, J = 2.7), 145.6 (q, J_F = 33.6), 159.3 (s_x, J = 3.3), 162.2 (q, J = 2.4).

^{19}F NMR (CD_3OD): δ −68.7 (s).

MS: m/z 232 (M^+), 217, 203, 177, 157, 105, 91, 74, 58.

Anal calc for $C_{10}H_{11}N_2OF_3$: C, 51.73; H, 4.77; N, 12.06. Found: C, 51.80; H, 5.00; N, 12.09.

• *9-Methyl-2-(trifluoromethyl)-1,5,6,7,8,9-hexahydro-4H-pyrido[2,3-b]azepin-4-one* **23f**

The cyclization of amidine **13f** (1.17 g, 4.0 mmol) gave after chromatography the pyridin-4-one **23f** (0.85 g, 86%) as a yellow oil.

IR (film): ν 3 500–3 000, 2 940, 2 860, 1 610, 1 575, 1 500, 1 405, 1 330, 1 170.

^{1}H NMR ($CDCl_3$): δ 1.81 (m, 4H), 2.76 (t, 2H, J = 5.6), 3.04 (s, 3H), 3.29 (t, 2H, J = 5.2), 6.50 (s, 1H).

^{13}C NMR ($CDCl_3$): δ 22.4 (t, J = 127.7), 23.1 (tqt, J = 128.8, J = 5.0), 26.5 (tt, J = 127.0, J = 3.3), 39.3 (qt, J = 137.2, J = 3.2), 52.5 (t, J = 137.5), 102.5 (dq, J = 165.5, J_F = 3.0), 114.0 (tq, J = 4.7, J_F = 1.0), 121.6 (qd, J_F = 274.5, J = 2.8), 142.6 (q, J_F = 34.5), 162.6 (sm), 163.7 (sm, J_F = 1.4).

^{19}F NMR ($CDCl_3$): δ −69.1 (s).

MS: m/z 246 (M^+), 231, 217, 203, 197, 190, 183, 176.

Anal calc for $C_{11}H_{13}N_2OF_3$: C, 53.66; H, 5.32; N, 11.38. Found: C, 53.60; H, 5.40; N, 11.25.

Photochemical cyclization of benzamidine **5b** *to ethyl 1-(dimethylamino)-3-(trifluoromethyl)-3,4-dihydroisoquinoline-4-carboxylate* **28**

A solution of benzamidine **5b** (0.63 g, 2.0 mmol) in dry n-hexane (25 mL) was irradiated (300 nm) at room temperature for 1 week. After evaporation of solvent, the crude was chromatographed on silica gel (eluent: ether/hexane, 30:70) to give the starting material (0.15 g, conversion: 63%) and the dihydroisoquinoline **28** as a white solid (0.30 g, yield: 48%), as only *trans* diastereomer.

mp = 83–84 °C.

IR (KBr): ν 2 990, 2 950, 2 880, 1 730, 1 620, 1 600, 1 390, 1 330, 1 260.

^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H, J = 7.1), 2.92 (s, 6H), 3.87 (d, 1H, J = 7.5), 4.26 (q, 2H, J = 7.1), 4.51 (qd, 1H, J_F = 7.5, J = 7.3), 7.19 (dd, 1H, J = 7.1, J = 2.0), 7.3 (m, 2H), 7.53 (dd, 1H, J = 6.6, J = 2.2).

^{13}C NMR ($CDCl_3$): δ 13.9 (qt, J = 127.3, J = 2.7), 40.2 (qq, J = 136.9, J = 4.0), 43.7 (dtdq, J = 134.6, J = 2.7, J = 2.0, J_F = 1.7), 59.9 (dqd, J = 142.5, J_F = 27.7, J = 4.9), 61.5 (tq, J = 148.0, J = 4.5), 124.5 (sm), 125.6 (qdd, J_F = 281.5, J = 7.3, J = 3.0), 126.8 (ddd, J = 161.0, J = 6.7, J = 3.1), 127.3 (d, J = 159.3), 127.5 (dd, J = 162.4, J = 7.7), 130.7 (dd, J = 162.0, J = 7.7), 134.6 (tdd, J = 6.4, J = 4.6, J = 2.0), 163.2 (sm), 171.1 (dt, J = 10.8, J = 3.0).

^{19}F NMR ($CDCl_3$): δ −74.5 (d, J = 7.5).

MS: m/z 314 (M^+), 285, 241, 171, 157, 143, 128, 91, 69, 44.

Anal calc for $C_{15}H_{17}N_2O_2F_3$: C, 57.32; H, 5.45; N, 8.91. Found: C, 56.96; H, 5.37; N, 8.82.

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