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SYNTHESIS OF A NEW SPIROCYCLIC γ-LACTAM DERIVATIVES FROM 3-HALOGENO-3-TRIFLUOROACETYL-1-METHYL-2-PYRROLIDINONES

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3-Bromo and 3-chloro-3-trifluoroacetyl-1-methyl-2-pyrrolidinones have been obtained by the halogenation reaction of the corresponding 3-trifluoroacetyl derivatives. These compounds were fully characterized as hydrates after simple filtration on silica gel. Reactions of 3-halogeno-3-trifluoroacetyl derivatives with benzathioamide and benzamidine lead to the formation of new spirocyclic γ-lactams in moderate yields and the corresponding product of the dehalogenation of the starting substance.

СИНТЕЗ НОВИХ СПІРОЦИКЛІЧНИХ ПОХІДНИХ γ-ЛАКТАМУ З 3-ГАЛОГЕНО-3-ТРИФЛУОРОАЦЕТИЛ-1-МЕТИЛ-2-ПІРОЛІДИНОНІВ

Жан-Філіп Буйон

3-Бромо- і 3-хлоро-3-трифлуороацетил-1-метил-2-піролідинони були отримані галогенуванням відповідних 3-трифлуороацетил похідних. Ці сполуки були охарактеризовані як гідрати після фільтрування через силікагель. Реакції 3-галогено-3-трифлуороацетил похідних з амідом тіобензойної кислоти і бензамідином приводять до утворення з помірними виходами нових спіроциклічних γ-лактамів та відповідного продукту дегалогенування вихідної речовини.

СИНТЕЗ НОВЫХ СПИРОЦИКЛИЧЕСКИХ ПРОИЗВОДНЫХ γ-ЛАКТАМА ИЗ 3-ГАЛОГЕНО-3-ТРИФТОРАЦЕТИЛ-1-МЕТИЛ-2-ПИРРОЛИДИНОНОВ

Жан-Филипп Буйон

3-Бром- и 3-хлор-3-трифторацетил-1-метил-2-пирролидиноны были получены галогенированием соответствующих 3-трифторацетил производных. Эти соединения были охарактеризованы как гидраты после фильтрования через силикагель. Реакции 3-галогено-3-трифторацетил производных с амидом тиобензойной кислоты и бензамидином приводят к образованию с умеренными выходами новых спироциклических γ-лактамов и соответствующего продукта дегалогенирования исходного вещества.

The increasing interest in trifluoromethylated heterocycles [1-3] and the need of new fluorinated scaffolds for parallel synthesis prompted us to investigate the application of 3-trifluoroacetyl-1-alkyl γ-lactams towards the synthesis of new heterocycles. It was previously shown that 3-trifluoroacetyl-1-methyl-2-pyrrolidinone (3-TFA-NMP) 1, obtained by β-trifluoroacetylation of the corresponding lactam [4], is an excellent versatile building block, especially as 1,3-bis-electrophile, for the preparation of a large variety of trifluoromethyl nitrogen-containing heterocycles such as pyrazole 2 (from methylhydrazine) [5], pyrimidine 3 (from benzamidine) [6], and benzoxazolidine or benzimidazolidine 4 (from 2-aminophenol or o-phenylenediamine) [7] (Scheme 1).

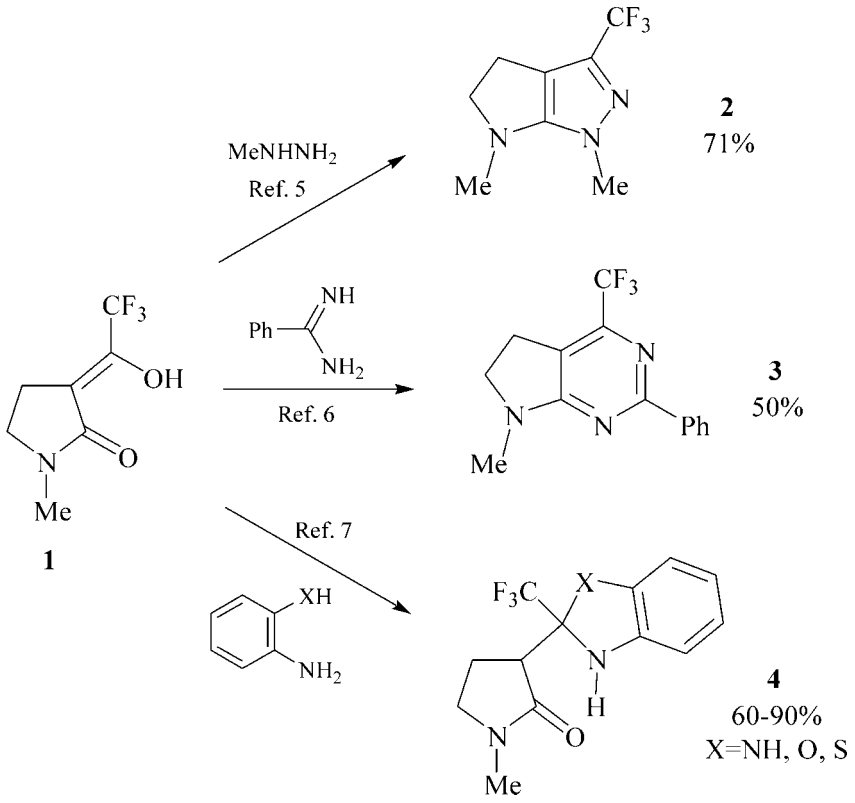
Moreover, 3-TFA-NMP 1 was also easily transformed into new spirocyclic heterocycles by Robinson annelation with α,β-unsaturated ketones (Scheme 2). Such reactions were general and efficient leading to various substituted spirocyclic cyclohexenones 5 in high yields [8, 9].

Continuing our efforts directed toward the development of versatile fluorinated building blocks and the synthesis of trifluoromethyl heterocycles, we studied new heterocyclizations from 3-halogeno-3-trifluoroacetyl-1-methyl-2-pyrrolidinone in order to prepare new type of spirocyclic compounds (Scheme 3).

We report in the present paper on the full investigation of the synthesis of 3-halogeno-3-trifluoroacetyl lactams and their reactions with mono- or bis-nucleophiles.

1. Halogenation reactions of 3-TFA-NMP

Among β-trifluoroacetyl carbonyl derivatives, 3-halogeno-3-trifluoroacetyl-1-alkyl- (or 1-aryl-) γ-lactams and their corresponding 4,4,4-trifluoroacetoacetamides are not reported so far. On the other hand, α-chloro-α-trifluoroacetyl-γ-butyrolactone [10] and ethyl 2-chloro [11-13] (or 2-bromo- [14, 15]) -4,4,4-tri-

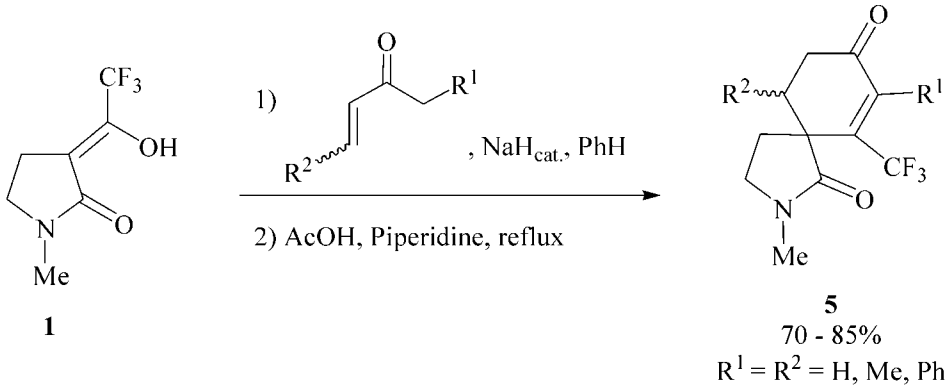


Scheme 1

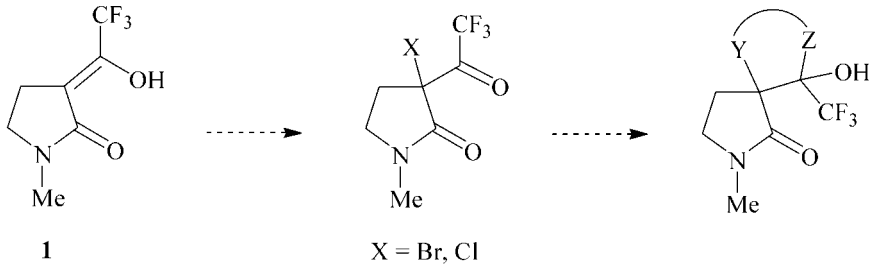
fluoroacetoacetate were prepared by halogenation of the corresponding dicarbonyl derivatives using chlorine, sulfuryl chloride or bromine, respectively.

In a first attempt, a mixture of 3-TFA-NMP 1, sulfuric acid and ice was treated at 0°C with bromine, without success. Indeed, the conversion was very low (<10%) and the hydrate of 1 was almost quantitatively recovered. Then, a solution of 1 and bromine in carbon tetrachloride was irradiated using 300 watts light for 1h at room temperature affording 83% yield of the brominated compound 6 (Scheme 4). It is worth noting that the light power was quite important as only 50% conversion was obtained after 12h using a 150 watts light.

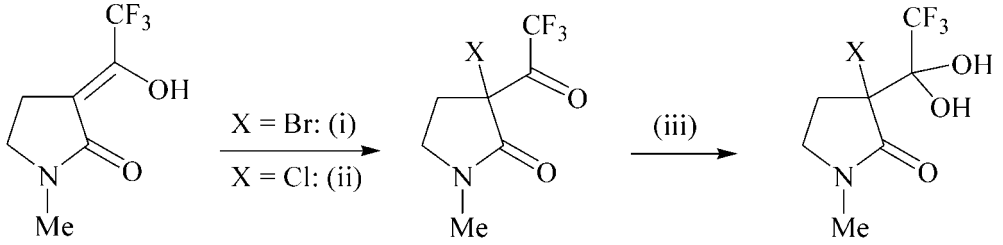
The 3-chloro-3-TFA-NMP 8 was obtained in high yield (93%) by addition of sulfuryl chloride to compound 1 and distillation under reduced pressure (Scheme 4).



Scheme 2



Scheme 3



1 X = Br: **6** (83%) X = Cl: **8** (93%) X = Br: **7** (100%) X = Cl: **9** (100%)

Scheme 4. Conditions and Reagents: (i): Br_2, hv, CCl_4, 1h, rt; (ii): SO_2Cl_2, 1h, rt; (iii): chromatography on silica gel.

As reported in the literature for trifluoromethylketones [16], lactams 6 and 8 underwent spontaneous partial hydration by air moisture exposure affording complicated ^1H and ^{13}C NMR spectra. This problem was solved by filtration of 6, 8 through silica gel column (eluent: diethyl ether) leading to the corresponding hydrates 7, 9 in quantitative yields (Scheme 4). These two new 2-pyrrolidinones are in good agreement with their NMR, IR and MS data (see experimental section).

2. Substitution and cyclization reactions of 3-halogeno-3-TFA-NMP

2-Aryl-4-trifluoromethylthiazoles bearing ester or amide function at the 5-position are well known in the literature because of their pharmaceutical and agrochemical activities (for recent applications, see references [17-19]). Moreover, it was also reported that α-chloro-α-trifluoroacetyl-γ-butyrolactone and ethyl 2-chloro (or 2-bromo-) -4,4,4-trifluoroacetoacetate are interesting precursors for the synthesis of trifluoromethyl nitrogen-containing heterocycles. Their reactions with thiourea gave 2-amino-4-trifluoromethylthiazoles which were sometimes accompanied with 2-amino-4-hydroxy-4-trifluoromethylthiazolidine derivatives depending on the reaction conditions [10, 15, 20, 21].

Ethyl 2-bromo-4,4,4-trifluoroacetoacetate was also reacted in the presence of various substituted 2-aminopyridines as 1,3-bis-nucleophiles, in order to prepare imidazo[1,2-a]pyridines as potential antiulcer agents, but there was only one example affording 74% yield of the desired heterocycle [22].

2.1. Substitution reactions with mono-nucleophiles

In order to check the halogen displacement, we performed several substitution reactions with monofunctionnalized nucleophiles such as primary amines and thiols. First, the 3-chloro lactam 8 was reacted with benzylamine and triethylamine in THF giving a complex mixture of fluorinated compounds. Among them, the N-benzyl trifluoroacetamide 10 [23] was isolated in 33% yield, resulting from a retro-Claisen type process (Scheme 5). This phenomenon seemed to be general with other primary amines and was already observed in the reactions of 1 with various o-phenylenediamines [7].

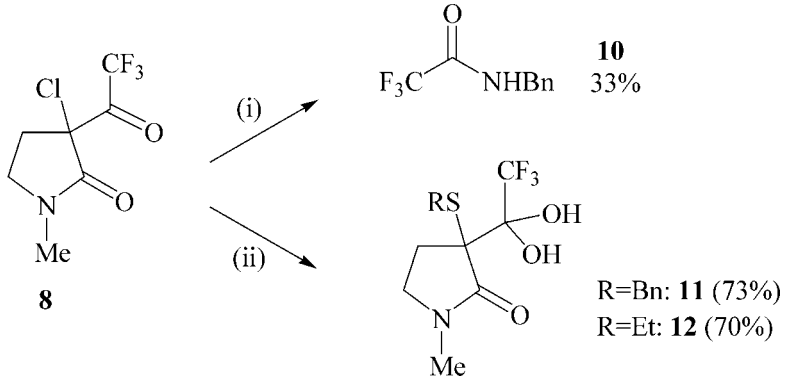
On the other hand, ethyl- and benzylthiols and compound 8 gave clean transformations (yields >70%) into the substitution products using the same reaction conditions (Scheme 5). The hydrates 11, 12 were obtained after silica gel chromatography (eluent: petroleum ether/ether 50:50). All NMR data, IR, MS and microanalyses are in good agreement with the proposed structures.

Once halogen substitution was checked, we were interested to investigate more complex cyclization using bifunctionnalized nucleophiles.

2.2. Cyclization reactions with bis-nucleophiles

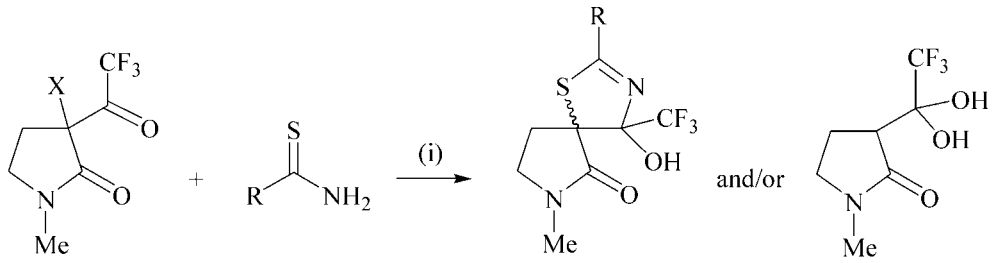
As it was mentioned in our small survey of the literature (see above), trifluoromethylated thiazoles and imidazo[1,2-a]pyridines exhibit interesting agrochemical [24] and antiulcer [22] activities, respectively. Therefore, we were interested to try new heterocyclizations with γ-lactams 6 and 8 in order to prepare spirocyclic analogues of such heterocycles.

The first attempt was performed with thiourea and 2-bromo derivative 6 under usual conditions (EtOH, reflux) [15], without success (Scheme 6, Table 1: entry 1). Although total conversion of 6 was observed, the hydrate of 1 was the main isolated product (yield: 63%) accompanied with very small amounts of others fluo-



8 **10** 33% R=Bn: **11** (73%) R=Et: **12** (70%)

Scheme 5. Conditions and Reagents: (i): $BnNH_2$, Et_3N, THF;(ii): RSH, Et_3N, THF then chromatography on silica gel.



Scheme 6. Conditions and Reagents: (i): EtOH reflux, 1h-24h.

rinated compounds. The formation of hydrate could be explained by a dehalogenation reaction of 6 followed by hydration of 1 during silica gel chromatography. The same observation was made for 3-chloro derivative 8 in more drastic conditions (Table 1: entry 2).

More interesting was the reaction with benzthioamide (Scheme 6, Table 1: entry 3). Indeed, the mixture of 8 and benzthioamide was refluxed for 10h in EtOH solution giving the spirocyclic lactam 13 (18% yield) as a mixture (71:29) of diastereomers and the hydrate of 1 (36% yield). Unfortunately, the conversion remained almost unchanged even after reflux for 48h. The confirmation of spirocyclic structure will be discussed later.

In a second set of experiments, we turned our attention to the heterocyclizations with benzamidines or synthetic equivalents. First, taking into account the easy transformation of ethyl 2-bromo-4,4,4-trifluoroacetoacetate into imidazo[1,2-a]pyridine [22], the compound 8 was reacted with 2-aminopyridine in boiling ethanol. Unfortunately, the conversion was very low (<15%) and no final product was detected in the crude mixture by ^{19}F NMR and GC-MS.

Then, benzamidine was chosen as a model for nitrogen-containing 1,3-bis-nucleophiles. A mixture of 8 and benzamidine (obtained by neutralisation of its hydrochloride salt) was refluxed in ethanol for 15h leading to 30% conversion. Small amounts of the desired product 14 was detected in the crude mixture by ^{19}F NMR (δ_{CF3} = -77.1 ppm as a singulet) and GC-MS (m/z = 313 [M^+]). In order to increase conversion and yield of 14, a mixture of 8 and benzamidine was heated without solvent at 100°C for 3h (Scheme 7). The spirolactam 14, as only one diastereomer (even in the crude mixture), was isolated in 25% yield accompanied with a small quantity of the starting material (conversion ~ 90%).

An important problem was to confirm the structure of the new trifluoromethylated spirocyclic heterocycles. First of all, all NMR spectra (^{19}F, ^{1}H, ^{13}C), IR, MS and elemental analysis are in good agreement with the structures of 13 and 14. Moreover, we decided to compare carefully selected NMR and IR data of compounds 7, 9, 11 and spirocyclic heterocycles 13, 14. As shown in Table 2, selected ^{13}C NMR data ($\delta_{C2\text{-}C5}$) and IR ($\nu_{C=O}$) data confirmed the γ-lactam skeleton. The chemical shifts of carbon C-3 and C-6 are also in good agreement with an aliphatic quaternary spirocyclic junction (for C-3) and with a trifluoromethyl hemiaminal function (for C-6: quartet, $^{2}J_{C,F}$ ~ 30 Hz), respectively.

The regiochemistry of compound 13 was proposed based on the structure of 4-hydroxy-4-trifluoromethylthiazolines 15, already described in the literature [15, 25-28] (Table 2). In addition, to our best knowledge, the other regioisomer 16 was never reported so far.

In conclusion, this study extends the field of synthetic applications of 3-trifluoroacetyl-γ-lactams. 3-Trifluoroacetyl-1-methyl-2-pyrrolidinone 1 was easily converted into its new 3-bromo- and 3-chloro derivatives 6 and 8, in good yields. The compound 8 was an interesting precursor for the synthesis of new 3-alkylsulfanyl-2-pyrrolidonones 11, 12 and spirocyclic γ-lactams 13 and 14. Unfortunately, the yields of such heterocycles remained low.

Experimental section

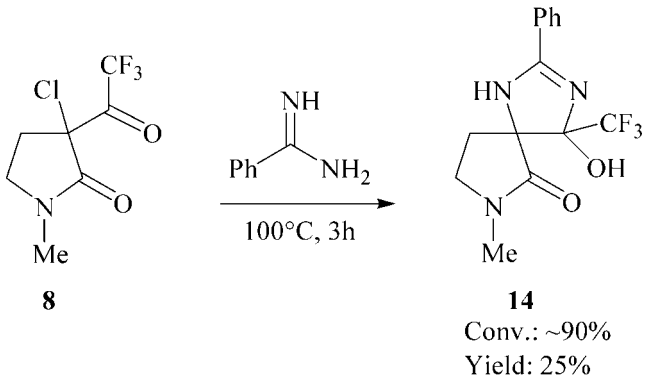
Melting points were taken using a Dr Tottoli apparatus and are uncorrected. IR (ν in cm^{-1}) and mass spectra (electronic impact) were measured on a Perkin-Elmer 1710, and a Finnigan Mat TSQ 70 apparatus, respectively. Microanalyses were measured at the University of Rouen on a ThermoQuest EA1110

Table 1

Reactions of lactones 6, 8 with thiourea and benzthioamide

Entry	Starting material	R	Duration (h)	Conversion (%)	Spirolactam (%)*	Hydrate of 1 (%)*
1	6	NH_2	1	100**	-	63
2	8	NH_2	18	100**	-	48
3	8	Ph	10	80**	13 (18)***	36

* Isolated yield.
** Small amount of other fluorinated compounds were detected in the crude mixture by ^{19}F NMR.
*** Mixture (71:29) of diastereomers.



8 **14**

Conv.: ~90%

Yield: 25%

Scheme 7

CHNS-O apparatus. The ^{1}H, ^{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 (^{1}H), 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 ^{1}H 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 spectra. The following abbreviations are used: s singlet, brs broad singlet, d doublet, t triplet, q quartet and m multiplet. Flash chromatography was run using silica gel Merck 60 (0.040-0.060 mm).

Sulfuryl chloride, triethylamine and benzthioamide are commercially available and were distilled before use. THF and ethanol were dried over Na and distilled before use. Benzamidine was obtained by neutralisation of benzamidine hydrochloride with an aqueous solution of potassium hydroxide 1N (until pH = 8-9) and extraction (3 times) with dichloromethane.

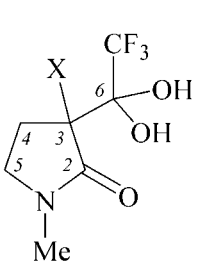
Preparation of compound (6) (Scheme 4)

Bromine (4.79 g, 30 mmol) was added to a solution of lactam 1 (5.85 g, 30 mmol) in carbon tetrachloride (18 mL), at room temperature under argon atmosphere. The resulting mixture was irradiated using 300 watts light for 1h. The conversion of the starting material was monitored by ^{19}F NMR. After evaporation of solvent, the residue was purified by distillation under reduced pressure (94-95°C/0.1 mm Hg) to give 6.82 g (yield: 83 %) of the compound 6 (red oil). In order to avoid spontaneous partial hydration of the trifluoroacetyl function, compound 6 was filtered through silica gel (eluent: diethyl ether) affording the corresponding hydrate 7 in quantitative yield. All analyses were performed on hydrate derivative.

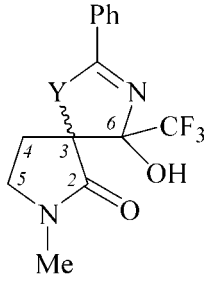
White solid. mp 105-106°C. ^{1}H NMR ($CDCl_3$, δ ppm): 2.47 (dd, $^{2}J_{H,H}$ = 14.5, $^{3}J_{H,H}$ = 6.0 Hz, 1H, CH_AH_BCBr), 2.8-3.0 (m, 1H, CH_AH_BCBr), 2.96 (s, 3H, NMe), 3.33 (m, 1H, CH_AH_BNMe), 3.52 (m, 1H, CH_AH_BNMe), 4.04 (brs, 1H, OH), 7.49 (brs, 1H, OH). ^{19}F NMR ($CDCl_3$, δ ppm): -79.7 (s). ^{13}C NMR ($CDCl_3$, δ ppm): 30.5 (q, $^{1}J_{C,H}$ = 139.6, $^{6}J_{C,F}$ = 1.5 Hz, NMe), 32.7 (tm, $^{1}J_{C,H}$ = 137.7, $^{4}J_{C,F}$ = 2.3 Hz, CH_2CBr), 46.5 (tm, $^{1}J_{C,H}$ = 143.5, $^{5}J_{C,F}$ = 1.1 Hz, CH_2NMe), 57.1 (s, CBr), 94.4 (q, $^{2}J_{C,F}$ = 32.2 Hz, CCF_3), 121.9 (qd, $^{1}J_{C,F}$ = 287.8, $^{3}J_{C,H}$ = 9.3 Hz, CF_3), 172.2 (s, CO). IR (KBr, cm^{-1}): 3327, 2949, 2894, 1673, 1503, 1449, 1417, 1314. MS (EI): m/z = 294 [M+2], 292 [M+], 275, 273, 223, 194, 176, 98, 69.

Table 2

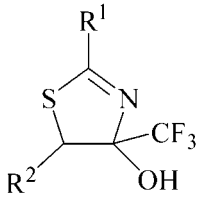
Selected chemical shifts and IR data of compounds 7, 9, 12-14



7, 9, 11



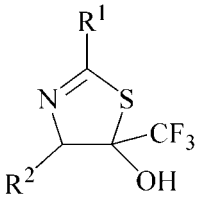
13, 14



15

$R^1 = NH_2$, Ar

R^2 = H, CO_2R



16

$R^1 = NH_2$, Ar

R^2 = H, Alk, Ar

Entry	X	Y	Cpd*	δ_{19F}	δ_{C-2}	δ_{C-3}	δ_{C-4}	δ_{C-5}	δ_{C-6}	ν_{CO} (cm^{-1})
1	Br	-	7	-79.7	172.2	57.1	32.7	46.5	94.4	1673
2	Cl	-	9	-80.3	171.5	64.9	31.8	46.3	94.6	1675
3	SBn	-	11	-80.2	173.0	53.4	29.2	46.4	96.6	1666
4a	-	S	13a**	-78.0	172.1	63.4	29.7	46.4	104.9	1682
4b	-	S	13b***	-77.7	173.5	67.9	26.0	45.8	103.7	1682
5	-	NH	14****	-77.1	168.0	89.5	26.8	44.7	87.7	-

* NMR solvent: $CDCl_3$, δ (ppm).
** Major diastereomer.
*** Minor diastereomer.
**** NMR solvent: CD_3COCD_3, δ (ppm).

Preparation of compound (8) (Scheme 4)

Sulfuryl chloride (SO_2Cl_2, 8.10 g, 60 mmol) was added dropwise to lactam 1 (9.75 g, 50 mmol), at room temperature under argon atmosphere. The resulting mixture was then stirred at this temperature for 1h. After evaporation of the excess of chlorinating reagent, the crude was purified by distillation under reduced pressure (98- 99°C/0.4 mm Hg) giving 10.65 g (yield: 93 %) of the 3-chlorolactam 8 (colourless oil). This compound 8 was filtered through silica gel (eluent: diethyl ether) affording the corresponding hydrate 9 in quantitative yield. All analyses were performed on hydrate derivative.

White solid. mp 91-92°C. ^{1}H NMR ($CDCl_3$, δ ppm): 2.40 (dd, $^2J_{H,H}$ = 14.1, $^3J_{H,H}$ = 5.9 Hz, 1H, CH_AH_BCCl), 2.8-2.9 (m, 1H, CH_AH_BCCl), 2.98 (s, 3H, NMe), 3.38 (m, 1H, CH_AH_BNMe), 3.59 (m, 1H, CH_AH_BNMe), 3.69 (brs, 1H, OH), 7.63 (brs, 1H, OH). ^{19}F NMR ($CDCl_3$, δ ppm): -80.3 (s). ^{13}C NMR ($CDCl_3$, δ ppm): 30.4 (q, $^1J_{C,H}$ = 140.2, $^6J_{C,F}$ = 1.6 Hz, NMe), 31.8 (tm, $^1J_{C,H}$ = 137.9, $^4J_{C,F}$ = 2.4 Hz, CH_2CCl), 46.3 (tm, $^1J_{C,H}$ = 143.7, $^5J_{C,F}$ = 1.2 Hz, CH_2NMe), 64.9 (s, CCl), 94.6 (q, $^2J_{C,F}$ = 32.1 Hz, CCF_3), 121.9 (qdd, $^1J_{C,F}$ = 287.7, $^3J_{C,H}$ = 9.2, $^3J_{C,H}$ = 2.2 Hz, CF_3), 171.5 (s, CO). IR (KBr, cm^{-1}): 3331, 2947, 2903, 1675, 1504, 1447, 1418, 1315. MS (EI): m/z = 249 [M+2], 247 [M$^+$], 230, 228, 194, 178, 131, 69. Formula: $C_7H_9ClF_3NO_3$: calcd. C 33.95, H 3.66, N 5.66; found C 34.03, H 3.60, N 5.49.

Reaction of compound (8) with benzylthiol (Scheme 5)

To a mixture of benzylthiol (0.37 g, 3 mmol) and triethylamine (0.30 g, 3 mmol) in THF (5 mL), at 0°C under argon atmosphere, was added a solution of 3-chlorolactam 8 (0.69 g, 3 mmol) in THF (5 mL). After stirring for 12h at room temperature, the crude mixture was filtered then concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a mixture (50:50) of petroleum ether and diethyl ether affording 0.73 g (yield: 73%) of the hydrated compound 11.

White solid. mp 89-91°C. ^{1}H NMR ($CDCl_3$, δ ppm): 1.87 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 6.8 Hz, 1H, CH_AH_BCS), 2.6-2.9 (m, 1H, CH_AH_BCS), 2.91 (s, 3H, NMe), 3.28 (m, 1H, CH_AH_BNMe), 3.50 (m, 1H, CH_AH_BNMe), 4.01 (d, $^2J_{H,H}$ = 11.3 Hz, CH_AH_BS), 4.08 (brs, 1H, OH), 4.30 (d, $^2J_{H,H}$ = 11.3 Hz, CH_AH_BS), 7.2-7.4 (m, 5H, Ph), 7.5-7.8 (brm, 1H, OH). ^{19}F NMR ($CDCl_3$, δ ppm): -80.2 (s). ^{13}C NMR ($CDCl_3$, δ ppm): 29.2 (tm, $^1J_{C,H}$ = 136.4, $^4J_{C,F}$ = 2.4 Hz, CH_2CS), 30.0 (q, $^1J_{C,H}$ = 139.2 Hz, NMe), 35.6 (tm, $^1J_{C,H}$ = 144.4 Hz, CH_2S), 46.4 (tm, $^1J_{C,H}$ = 142.5 Hz, CH_2NMe), 53.4 (s, CS), 96.6 (q, $^2J_{C,F}$ = 31.0 Hz, CCF_3), 122.5 (qd, $^1J_{C,F}$ = 288.1, $^3J_{C,H}$ = 9.1 Hz, CF_3), 127.3 (dm, $^1J_{C,H}$ = 159.7 Hz, CH Ph), 128.5 (dm, $^1J_{C,H}$ = 159.6 Hz, 2 x CH Ph), 129.3 (dm, $^1J_{C,H}$ = 159.5 Hz, 2 x CH Ph), 136.0 (s, C_q Ph), 173.0 (sm, $^4J_{C,F}$ = 1.1 Hz, CO). IR (KBr, cm^{-1}): 3308, 3259, 3031, 2958, 2883, 1666, 1602, 1498, 1456, 1417, 1265. MS (EI): m/z = 335 [M$^+$], 248, 220, 213, 195, 126, 91, 77, 69. Formula: $C_{14}H_{16}F_3NO_3S$: calcd. C 50.14, H 4.81, N 4.18; found C 50.20, H 5.00, N 4.12.

Reaction of compound (8) with ethanethiol (Scheme 5)

The same procedure described for compound 11 was used to prepare the 2-pyrrolidinone 12 (yield: 70% after chromatography on silica gel). Oil. ^{1}H NMR ($CDCl_3$, δ ppm): 1.25 (t, 3H, $^3J_{H,H}$ = 7.4 Hz, SCH_2CH_3), 2.0-2.6 (m, 2H, CH_2CH_2NMe), 2.7-2.8 (m, 2H, SCH_2CH_3), 2.93 (s, 3H, NMe), 3.31 (m, 1H, CH_AH_BNMe), 3.52 (m, 1H, CH_AH_BNMe), 4.1 (brs, 1H, OH), 7.5-7.7 (brm, 1H, OH). ^{19}F NMR ($CDCl_3$, δ ppm): -80.5 (s). ^{13}C NMR ($CDCl_3$, δ ppm): 14.2 (qm, $^1J_{C,H}$ = 137.8 Hz, SCH_2CH_3), 28.2 (tm, $^1J_{C,H}$ = 137.5 Hz, SCH_2CH_3), 29.3 (tm, $^1J_{C,H}$ = 136.4, $^4J_{C,F}$ = 2.4 Hz, CH_2CH_2NMe), 30.3 (q, $^1J_{C,H}$ = 139.4 Hz, NMe), 46.0 (tm, $^1J_{C,H}$ = 142.5 Hz, CH_2NMe), 53.2 (s, CS), 96.7 (q, $^2J_{C,F}$ = 31.0 Hz, CCF_3), 122.2 (qm, $^1J_{C,F}$ = 288.1 Hz, CF_3), 172.8 (sm, $^4J_{C,F}$ = 1.1 Hz, CO). IR (film, cm^{-1}): 3305, 3260, 2958, 2883, 1666, 1265. MS (EI): m/z = 273 [M$^+$], 248, 235, 213, 195, 128.

Reaction of compound (8) with benzthioamide (Scheme 6, Table 1: entry 3)

To a solution of 3-chlorolactam 8 (0.92 g, 4 mmol) in dry ethanol (8 mL) was added portionwise benzthioamide (0.82 g, 6 mmol). The resulting mixture was refluxed for 10h. After evaporation of the solvent under reduced pressure, the crude was diluted with CH_2Cl_2 (15 mL) then washed with water (10 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a mixture (15:85) of petroleum ether and diethyl ether affording 0.24 g (yield: 18%) of spirolactam 13 as a mixture (71:29) of diastereomers, 0.31 g (yield: 36%) of hydrate of 1 and 0.18 g (conversion: 80%) of 8.

Oil. IR (film, cm^{-1}): 3179, 3052, 2987, 1682, 1600, 1576, 1448, 1436, 1407. MS (EI): m/z = 331 [M+1], 330 [M$^+$], 261, 227, 205, 144, 130, 98, 77, 69.

Major diastereomer 13a: ^{1}H NMR ($CDCl_3$, δ ppm): 2.4-2.5 (m, 1H, $CH_AH_BCH_2NMe$), 2.8-3.0 (m, 1H, $CH_AH_BCH_2NMe$), 2.97 (s, 3H, NMe), 3.1-3.5 (m, 2H, CH_2NMe), 3.8 (brs, 1H, OH), 7.4-7.6 (m, 3H, Ph), 7.88 (dm, $^3J_{H,H}$ = 6.8 Hz, 2H, Ph). ^{19}F NMR ($CDCl_3$, δ ppm): -78.0 (s). ^{13}C NMR ($CDCl_3$, δ ppm): 29.7 (tm, $^1J_{C,H}$ = 134.9, $^4J_{C,F}$ = 2.6 Hz, CH_2CH_2NMe), 30.0 (q, $^1J_{C,H}$ = 139.6 Hz, NMe), 46.4 (tm, $^1J_{C,H}$ = 143.7, $^5J_{C,F}$ = 1.8 Hz, CH_2NMe), 63.4 (s, C_q, CCO), 104.9 (q, $^2J_{C,F}$ = 29.4 Hz, CCF_3), 122.9 (q, $^1J_{C,F}$ = 288.3 Hz, CF_3), 128.0 (dm, $^1J_{C,H}$ = 161.5 Hz, 2 x CH Ph), 128.2 (dm, $^1J_{C,H}$ = 161.5 Hz, 2 x CH Ph), 131.2 (s, C_q Ph), 132.4 (dm, $^1J_{C,H}$ = 161.7 Hz, CH Ph), 171.0 (s, C_q), 172.1 (s, C_q).

Minor diastereomer 13b: selected ^{1}H NMR ($CDCl_3$, δ ppm): 2.92 (s, 3H, NMe). ^{19}F NMR ($CDCl_3$, δ ppm): -77.7 (s). Selected ^{13}C NMR ($CDCl_3$, δ ppm): 26.0 (tm, $^1J_{C,H}$ = 134.7 Hz, CH_2CH_2NMe), 30.1 (q, $^1J_{C,H}$ = 139.5 Hz, NMe), 45.8 (tm, $^1J_{C,H}$ = 142.7 Hz, CH_2NMe), 67.9 (s, C_q), 103.7 (q, $^2J_{C,F}$ = 28.7 Hz, CCF_3), 123.0 (q, $^1J_{C,F}$ = 288.1 Hz, CF_3), 132.1 (s, C_q Ph), 131.6 (dm, $^1J_{C,H}$ = 161.4 Hz, CH Ph), 168.9 (s, C_q), 173.5 (s, C_q).

Reaction of compound (8) with benzamidine (Scheme 7)

A mixture of 3-chlorolactam 8 (0.92 g, 4 mmol) and benzamidine (0.48 g, 4 mmol) was heated at 100°C for 3h. After cooling, the crude was diluted with CH_2Cl_2 (10 mL), washed with an aqueous solution of NaOH 0.1M (5 mL) then water (5 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a mixture (10:90) of petroleum ether and diethyl ether affording 0.31 g (yield: 25%) of spirolactam 14 as only one diastereomer and 99 mg (conversion: ~ 90%) of 8.

Oil. ^{1}H NMR ($CDCl_3$, δ ppm): 2.41 (m, 1H, $CH_AH_BCH_2NMe$), 2.91 (s, 3H, NMe), 3.02 (dd, $^2J_{H,H}$ = 13.6, $^3J_{H,H}$ = 6.4 Hz, 1H, $CH_AH_BCH_2NMe$), 3.29 (dd, $J_{H,H}$ = 9.4, $J_{H,H}$ = 9.3 Hz, 1H, CH_AH_BNMe), 3.43 (m, 1H, CH_AH_BNMe), 7.41 (dd, $^3J_{H,H}$ = 7.7, $^3J_{H,H}$ = 7.6 Hz, 2H Ph), 7.52 (t, $^3J_{H,H}$ = 7.4 Hz, 1H Ph), 7.99 (d, $^3J_{H,H}$ = 7.7 Hz, 2H Ph). ^{19}F NMR ($CDCl_3$, δ ppm): -77.1 (s). ^{13}C NMR (CD_3COCD_3, δ ppm): 26.8 (tm, $^1J_{C,H}$ = 135.7 Hz, CH_2CH_2NMe), 30.6 (q, $^1J_{C,H}$ = 138.7 Hz, NMe), 44.7 (tm, $^1J_{C,H}$ = 144.7 Hz, CH_2NMe), 87.7 (q, $^2J_{C,F}$ = 29.8 Hz, CCF_3), 89.5 (sm, C_q, CCO), 123.9 (q, $^1J_{C,F}$ = 284.6 Hz, CF_3), 126.3 (t, $^2J_{C,H}$ = 7.9 Hz, C_q Ph), 128.4 (dd, $^1J_{C,H}$ = 162.1, $^2J_{C,H}$ = 7.6 Hz, 2 x CH Ph), 128.9 (ddd, $^1J_{C,H}$ = 162.7, $^2J_{C,H}$ = 7.3, $^2J_{C,H}$ = 6.3 Hz, 2 x CH Ph), 132.6 (dt, $^1J_{C,H}$ = 161.7, $^2J_{C,H}$ = 7.6 Hz, CH Ph), 166.7 (sm, C_q), 168.0 (sm, C_q). IR (film, cm^{-1}): 3250, 3051, 2985, 1675, 1605, 1550. MS (EI): m/z = 313 [M^+], 295, 244, 77, 69.

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