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Synthesis of new 3-(2,2,2-trifluoroethyl)-5-hydroxy-5-(phenylsulfanyl- or phenylsulfonyl-methyl)-1,5-dihydropyrrol-2-ones starting from α,β-unsaturated γ-lactones and primary amines

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Abstract

The paper presents an efficient and straightforward transformation of α,β-unsaturated γ-lactones into 2,2,2-trifluoroethyl substituted γ-lactams, starting from a variety of primary amines. The structures of all new compounds were ascribed using 1D NMR (^{19}F, ^{1}H, ^{13}C), IR, MS. Selected ^{19}F, ^{13}C NMR and IR data of γ-lactams were compared to those of one which was characterized by X-ray diffraction analysis. The possible mechanism for the formation of γ-lactams is also presented.

Keywords: Fluorine; γ-Ketothioester; Heterocycle; γ-Lactam; 1,5-Dihydropyrrol-2-one

1. Introduction

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 γ-ketothioesters towards the synthesis of new heterocycles. It was already shown that S-ethyl 4-oxo-2-(pentafluoroethyl)-pentanethiocarboxylate **1** (R^1 = Me) or aryl substituted analogues (R^1 = Ar) are excellent versatile building blocks for the synthesis of a large variety of trifluoromethyl heterocycles such as γ-lactams, furans, pyrroles, pyridazines, pyridazin-3-ones [4–9]. The γ-ketothioesters **1** were easily obtained in two high yielding steps: substitution of vinylic fluoride of perfluoroketene dithioacetal [10] with potassium enolates of ketones and acidic hydrolysis of dithioacetal intermediates [5]. As it was previously reported, the treatment of γ-ketothioesters **1** with non-nucleophilic diisopropylamine in diethyl ether followed by addition of various primary amines led to α,β-unsaturated γ-lactams **2** as mixtures (∼50/50) of diastereomers (Scheme 1) [7].

More recently, the S-phenyl analogue **3** was easily transformed into the new α,β-unsaturated γ-lactone **4a** (as a mixture of stereomers) by simple treatment with diisopropylamine in ether (Scheme 2) [11].

Continuing our efforts directed toward synthesis of new fluorinated nitrogen-containing heterocycles, we decided to use γ-lactones **4a**, **4b** as precursors for the synthesis of γ-lactams bearing phenylsulfanyl- or phenylsulfonyl-methyl substituent. We report in the present paper on the full investigation of this transformation, especially the influence of the lactone substitution and the nature of the primary amine on the outcome of the reaction.

2. Results and discussion

In the first experiment, compound **4a** was treated with 1.2 equiv. of *n*-pentylamine in diethyl ether at room temperature for 30 h (Scheme 3: Method 1). The crude mixture was

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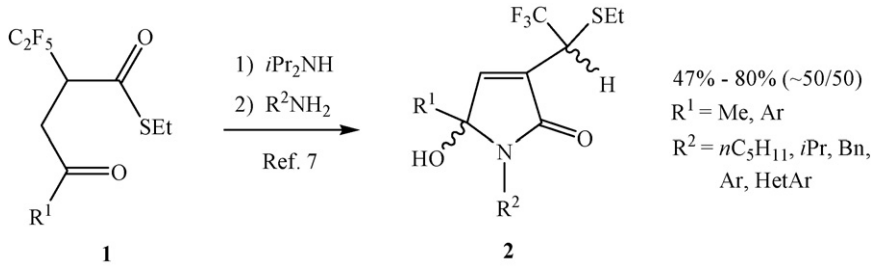
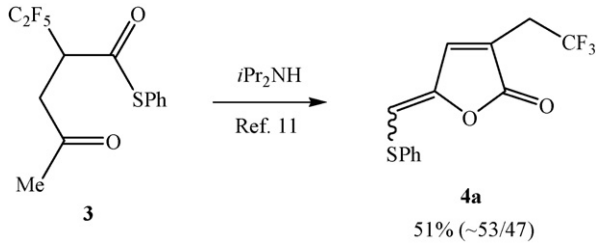


Scheme 1.

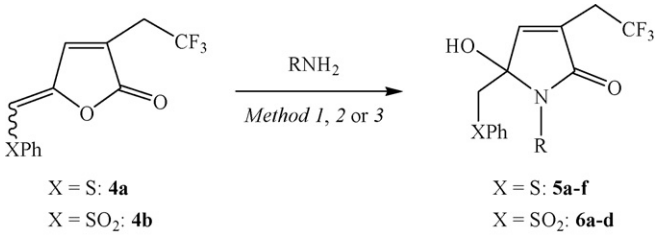


Scheme 2.

checked by ^{19}F NMR to confirm the complete conversion of the starting material. Without further treatment, the solvent was evaporated in vacuo then the residue was purified by silica gel column chromatography to give the new γ-lactam **5a** in 61% yield (Table 1: entry 1). The confirmation of the 1,5-dihydropyrrol-2-one structure will be discussed later.

The reaction was then successfully extended to others amines (Scheme 3). The transformation of **4a** was general and worked well (yields: 61–79%) with a wide variety of primary amines: linear (R = nC_5H_{11} and Bn: entries 1,2), branched (R = *i*Pr: entry 3) and functionalized amines bearing *N*,*N*-(dimethylamino) or hydroxyl groups (R = $(CH_2)_3NMe_2$, $(CH_2)_2OH$: entries 4, 5). It is worth noting that the reaction with 2-aminoethanol was chemoselective, as previously observed for other γ-lactam analogues [7]. Interestingly, the resulting heterocycle **5e** bears an additional nucleophilic hydroxyl group which could be used for further cyclisations.

Unfortunately, the reaction seemed to be more difficult with less nucleophilic amine such as aniline. Indeed, a very low yield of compound **5f** (conversion: <10%) was obtained using Method 1, even in boiling ether for 3 days. The conversion was slightly improved until 60% using boiling 1,4-dioxane as a solvent for 87 h (Scheme 3: Method 2). Nevertheless, we did not obtain a total conversion of the starting material, the yield remaining around 41% (Table 1: entry 6).



Scheme 3. Reagents and conditions—Method 1: Et_2O, rt, 30 h. Method 2: 1,4-dioxane, reflux, 87 h. Method 3: THF, rt, 16 h.

Therefore, we tried to increase the electrophilicity of the carbonyl function by transforming the sulfanyl into a sulfonyl moiety. Indeed, we may expect that the vinylogous conjugation with the electron-withdrawing sulfonyl group will activate the carbonyl making easier the nucleophilic addition of amine (see Scheme 5).

Lactone **4a** was oxidized into the corresponding sulfone **4b** (yield: 76%) by simple treatment with *m*-chloroperbenzoic acid (MCPBA, 3 equiv.) in dichloromethane, at room temperature (Scheme 4). The new heterocycle **4b** was obtained as a single stereomer after careful checking of the crude mixture by ^{19}F and ^{1}H NMR. The stereochemistry of compound **4b** was ascribed by ^{1}H–^{1}H NOE experiments. Irradiation of olefinic proton H_a at $\delta = 6.23$ ppm induced a 11% NOE on proton H_b. Moreover, irradiation of olefinic proton H_b at $\delta = 7.34$ ppm induced a 11% NOE on proton H_a and a 8% NOE on methylenic protons H_c, respectively (Fig. 1). These two observations confirmed the close relationship between H_a and H_b, which are in good agreement with the *Z* configuration between the phenylsulfonyl group and the lactone moiety. Similar results were already observed for a (*p*-chlorophenyl)sulfanyl analogue (Fig. 1) [11].

It was of interest to perform some molecular modeling calculations in order to find the most stable stereomer of **4b** and to try to quantify the difference of reactivity of the carbonyl groups of compounds **4a** and **4b**. The geometry of **4b** was first minimized at the molecular mechanics level using the CVFF force field as implemented in the Cerius2 package. The systematic variation of dihedral angles led to 361 stereomers,

Table 1
Preparation of new α,β-unsaturated γ-lactams **5** and **6**

Entry	Starting compound	R	Method[a]	Conversion (%)	γ-Lactam (%)[b]
1	**4a**	nC_5H_{11}	1	100	**5a** (61)
2	**4a**	Bn	1	100	**5b** (79)
3	**4a**	*i*Pr	1	100	**5c** (55)
4	**4a**	$(CH_2)_3NMe_2$	1	100	**5d** (63)
5	**4a**	$(CH_2)_2OH$	1	100	**5e** (68)
6	**4a**	Ph	2	60	**5f** (41)
7	**4b**	Bn	3	100	**6a** (76)
8	**4b**	*i*Pr	3	100	**6b** (60)
9	**4b**	$(CH_2)_2OH$	3	100	**6c** (79)
10	**4b**	Ph	3	100	**6d** (87)

[a] Method 1: Et_2O, rt, 30 h. Method 2: 1,4-dioxane, reflux, 87 h. Method 3: THF, rt, 16 h.
[b] Isolated yields.

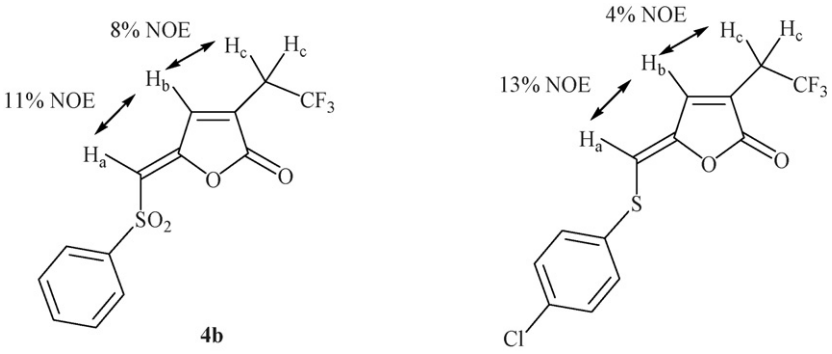
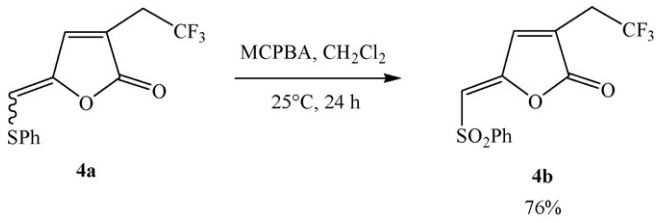


Fig. 1. Selected ^{1}H–^{1}H NOE for compound **4b** and a (*p*-chlorophenyl)sulfanyl analogue.



Scheme 4.

the most stable (57.23 kcal mol^{-1}) corresponding to the *Z* configuration of the exocyclic double bond (Fig. 2).

We also carried out molecular orbital calculations at the ab initio DFT (STO-6-31G**) level of theory. Energies of the LUMOs of **4a**, **4b** were computed (−0.0806 a.u. for **4a**, −0.1125 a.u. for **4b**). The energy of the LUMO is significantly lower in compound **4b** compared to **4a** showing that the electron-withdrawing effect of the sulfone increases the reactivity of the lactone carbonyl.

In a second set of experiments, the 5-(phenylsulfonylmethyl) γ-lactone **4b** was reacted with the same primary amines in order to compare the reactivity of **4a** and **4b**. The experimental procedure was slightly modified due to the very low solubility of sulfone derivative **4b** in diethyl ether; we used THF as a solvent, at room temperature, for 16 h (Scheme 3: Method 3). Using such conditions, no important differences were noticed for benzylamine, *i*-propylamine and 2-aminoethanol (Table 1: entries 7–9), the yields remaining around 60–79%. The reaction with aniline was more interesting as the new heterocycle **6d** was obtained in 87% yield after 16 h at room temperature (Table 1: entry 10). This result has to be compared with that of entry 6 (yield of **5f**: 41% after 87 h in boiling 1,4-dioxane) and seems to be in good agreement with the stronger electrophilic character of lactone function of **4b** as shown above using molecular orbital calculations.

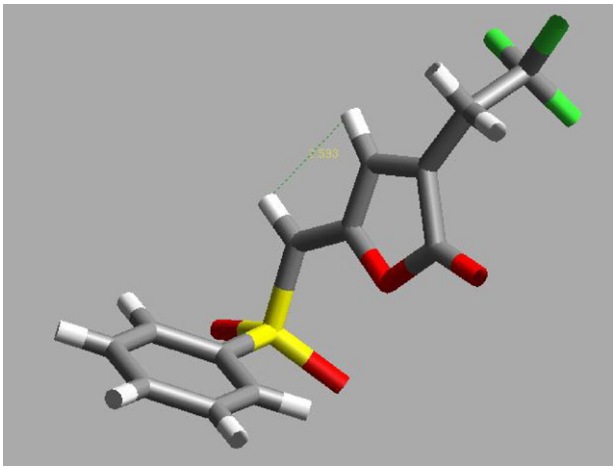


Fig. 2. Most stable stereomer of compound **4b**.

An important problem was to confirm the structure of the new trifluoromethylated heterocycles **5a–f** and **6a–d**. 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 **5** and **6**. Nevertheless, those data were not sufficient to ascribe unambiguously the α,β-unsaturated γ-lactam moiety. So, we decided first to compare carefully selected NMR and IR data of compounds **5a–f** and **6a–d** (Table 2), then to compare the selected data with those of **6a** for which we have obtained X-ray diffraction analysis (Fig. 3).

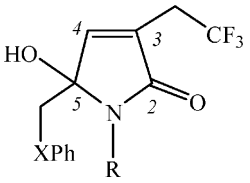
As you can see in Table 2, the fluorine chemical shift (δ_{19F}), the chemical shift of olefinic proton ($\delta_{H\text{-}4}$) and all ^{13}C chemical shifts of γ-lactam skeleton ($\delta_{C\text{-}2}$, $\delta_{C\text{-}3}$, $\delta_{C\text{-}4}$, $\delta_{C\text{-}5}$) and the characteristic infrared absorption of cyclic amide function ($\nu_{C=O}$) are very similar to each other and to γ-lactam **6a** (determined by X-ray diffraction analysis). Therefore, we may reasonably assume that those structures are almost the same.

The X-ray structure of **6a** had two independent molecules in the asymmetric part of the unit cell. Selected bond lengths (Å) mean values over the 2 independent molecules: N(1)–C(2) = 1.343(6), C(2)–C(3) = 1.490(6), C(3)–C(4) = 1.324(6), C(4)–C(5) = 1.510(6), C(5)–N(1) = 1.473(6), C(5)–O(29) = 1.403(6), C(2)–O(13) = 1.231(5). The two independent molecules differ only by the orientation of the aromatic groups: the torsion angles being N(1)–C(6)–C(7)–C(8) = 112(1)°, C(19)–S(20)–C(23)–C(24) = −105(1)° in molecule 1 comparing to, respectively, 84(1)° and −11(1)° in molecule 2. Intermolecular hydrogen bonds are observed between the O–H and C=O: the geometry is as follows:

	O–H (Å)	H···O (Å)	O···O (Å)	O–H···O (Å)
O29–H29···O13	0.84(2)	2.32(2)	2.691(7)	114.3(1)
O129–H129···O113	1.00(2)	1.72(2)	2.695(6)	163.7(1)

O(13): 0.5 − *x*, *y* − 0.5, 0.5 − *z*; O(113): 1.5 − *x*, 0.5 + *y*, 0.5 − *z*

Table 2
Selected NMR and IR data for γ-lactams **5** and **6**



X=S: **5a-f**
X=SO_2: **6a-d**

Entry	R: Cpd[a]	δ_{19F} (ppm)	δ_{H-4} (ppm)	δ_{C-2} (ppm)	δ_{C-3} (ppm)	δ_{C-4} (ppm)	δ_{C-5} (ppm)	IR ($\nu_{C=O}$, cm^{-1})
1	nC_5H_{11}: **5a**	−65.2	6.62	168.2	129.7 (q)	143.9	90.7	1688
2	Bn: **5b**	−65.2	6.72	170.6	130.1 (q)	145.6	92.2	1682
3	*i*Pr: **5c**	−65.2	6.58	167.6	130.7 (q)	143.3	90.9	1689
4	$(CH_2)_3NMe_2$: **5d**	−65.5	6.69	168.4	127.8 (q)	144.3	90.1	1698
5	$(CH_2)_2OH$: **5e**	−65.2	6.67	169.4	128.8 (q)	145.5	90.1	1682
6	Ph: **5f**	−65.1	6.65	167.7	129.3 (q)	144.4	92.0	1690
7	Bn: **6a**[b]	−65.2	7.33	168.3	128.7 (q)	144.7	87.4	1682
8	*i*Pr: **6b**	−65.2	7.26	167.4	129.6 (q)	143.4	87.8	1693
9	$(CH_2)_2OH$: **6c**	−65.2	7.26	168.7	128.4 (q)	145.0	86.7	1694
10	Ph: **6d**	−65.0	7.2–7.3	167.4	128.4 (q)	144.6	88.4	1695

[a] NMR solvent: $CDCl_3$.
[b] Structure confirmed by X-ray diffraction analysis.

The formation of α,β-unsaturated γ-lactams **5** and **6** may be explained by the mechanism depicted in Scheme 5. Owing to the electrophilicity of γ-lactone function, the first step could be a nucleophilic attack of primary amine on carbonyl group followed by ring opening leading to the corresponding unsaturated γ-ketoamide **7**.

This intermediate could then cyclize into the desired α,β-unsaturated γ-lactam **5** or **6**. This hypothesis was supported by two features: on the one hand, non-fluorinated analogues of **7** were used as key intermediates in 1,5-dihydropyrrol-2-one synthesis [13,14]; on the other hand, the same type of cyclization was already observed for the formation of fluorinated analogues [7].

In conclusion, this study extends the field of synthetic applications of γ-ketothioesters **1** and **3**. The compound **4a** and its oxidized analogue **4b** were easily converted into the new α,β-unsaturated γ-lactams **5a–f** and **6a–d**. The scope of this method was exemplified by the preparation of heterocycles bearing different types of substituents (R = alkyl, aryl, functionalized chain). The γ-lactams **5**, **6** show interesting features (conjugated amide system, hemiaminal function, phenylsulfanyl- or phenylsulfonylmethyl substituent) useful for further transformations. These aspects of new synthetic application are under investigation.

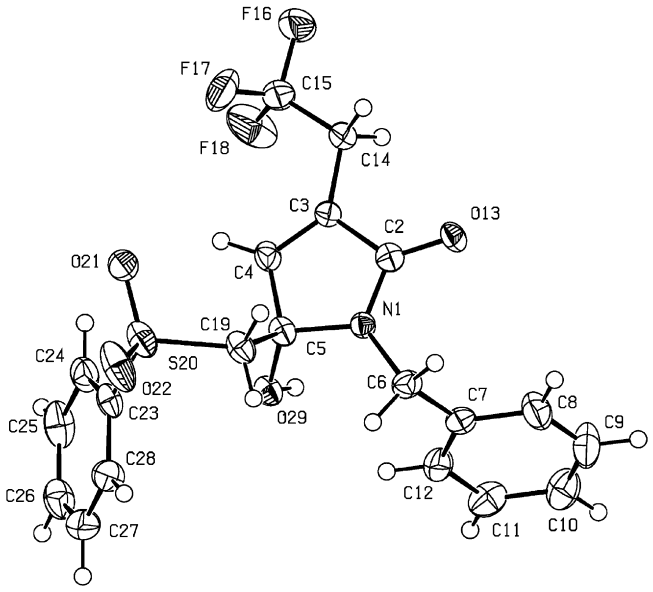


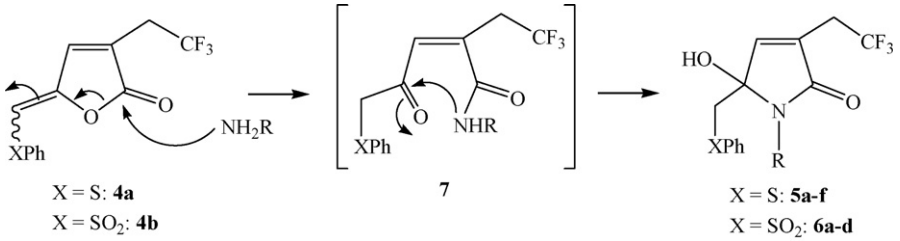
Fig. 3. View and atom labelling of compound **6a** [12].

3. Experimental

IR spectra were recorded on a FT-IR Perkin Elmer PARAGON 500. ^1H (250 MHz), ^{19}F (235 MHz) and ^{13}C (63 MHz) NMR spectra were recorded, in $CDCl_3$ as solvent, on a Bruker AC250 Instrument spectrometer. The abbreviations for the multiplicity of the proton and carbon signals are as follows: s singlet, d doublet, t triplet, q quartet, m multiplet, C_q quaternary carbon. Column chromatography was conducted with silica gel (63–200 mesh, Normasil Prolabo, Fontenay-sous-bois, France). GC–MS analyses were performed using a Navigator (Finigan) instrument (flame ionization detector, in electronic impact mode) with the following temperature program: 5 min at 40 °C then 5 °C min^{-1}, from 40 to 150 °C. High Resolution Mass Spectra (HRMS) were recorded with a Q-TOF Micromass Instrument in the positive ESI (CV = 30 V) mode. Melting points were recorded on a Bücchi apparatus and are uncorrected. Molecular mechanics calculations were carried out with the Cerius2 package (Accelrys Co). Ab initio DFT calculations were carried out with Gaussian-98 using 4 processors on an IBM cluster [15].

3.1. Procedure for the synthesis of lactone *4b*

To a solution of compound **4a** (1.70 g, 5.94 mmol) in dichloromethane (25 mL) was added a solution of



Scheme 5.

m-chloroperbenzoic acid (MCPBA, 3.11 g, 17.8 mmol) in dichloromethane (10 mL), at room temperature. The mixture was stirred for 24 h at this temperature. The reaction mixture was cooled at 4 °C for 2 h then *m*-chlorobenzoic acid was precipitated and filtered off. The filtrate was washed with saturated aqueous solution (2 mL × 20 mL) of sodium hydrogenocarbonate then with water (2 mL × 15 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by silica gel column chromatography (eluent:mixture (60:40) of petroleum ether and ethyl acetate) to give the desired lactone **4b** (1.37 g, yield: 76%) (Scheme 4).

*3.1.1. 5-(Phenylsulfonylmethylene)-3-(2,2,2-trifluoroethyl)-5H-furan-2-one (**4b**)*

Solid. mp 119–120 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 3.28 (qd, $^3J_{H,F}$ = 10.7, $^4J_{H,H}$ = 1.3 Hz, 2H, CH_2CF_3), 6.23 (s, 1H, $CHSO_2$), 7.34 (m, 1H, =CH), 7.59 (m, 2H, 2 × CH Ph), 7.68 (m, 1H, CH Ph), 8.05 (dm, $^3J_{H,H}$ = 8.2 Hz, 2H, 2 × CH Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −65.1 (t, $^3J_{F,H}$ = 10.7 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 30.4 (q, $^2J_{C,F}$ = 32.8 Hz, CH_2CF_3), 113.6 (s, $CHSO_2$), 124.3 (q, $^1J_{C,F}$ = 277.0 Hz, CF_3), 128.2 (s, 2 × CH Ph), 128.4 (q, $^3J_{C,F}$ = 2.9 Hz, CCH_2CF_3), 129.4 (s, 2 × CH Ph), 134.2 (s, CH Ph), 140.2 (s, =CH), 140.6 (s, C_q Ph), 152.4 (s, C_q, $CCHSO_2$), 166.2 (s, CO). IR (KBr, cm^{-1}): 1806, 1644, 1624, 1448, 1324. HRMS: calcd. for $C_{13}H_{10}F_3O_4S$ *m/z* 319.0252, found 319.0240. Formula: $C_{13}H_9F_3O_4S$: calcd. C 49.1, H 2.9, S 10.1; found C 49.3, H 2.8, S 10.2.

*3.2. Typical procedures for the synthesis of γ-lactams **5** and **6***

3.2.1. Method 1

The mixture of lactone **4a** (140 mg, 0.50 mmol) and *i*-propylamine (36 mg, 0.60 mmol, 1.2 equiv.) in diethyl ether (5 mL) was stirred 30 h at room temperature. After the completion of the reaction (checked by ^{19}F NMR of the crude mixture), the solvent was evaporated in vacuo and the crude product was purified by silica gel column chromatography (eluent:mixture (75:25) of petroleum ether and ethyl acetate) to give the desired lactam **5c** (94 mg, yield: 55%) (Scheme 3, Table 1: entry 3).

3.2.2. Method 2

Method 1 was used to prepare the lactam **5f** except that diethyl ether, at room temperature, for 30 h was replaced by boiling 1,4-dioxane for 87 h. The crude mixture was checked by ^{19}F NMR and showed a conversion of only 60%. Silica gel column chromatography was used to obtain pure lactam **5f** (78 mg, yield: 41%) (Scheme 3, Table 1: entry 6).

3.2.3. Method 3

Method 1 was used to prepare the lactams **6a–d** except that diethyl ether, at room temperature, for 30 h was replaced by THF, at room temperature, for 16 h (Scheme 3, Table 1: entries 7–10).

*3.2.3.1. 3-(2,2,2-Trifluoroethyl)-5-hydroxy-5-(phenylsulfanylmethyl)-1-(n-pentyl)-1,5-dihydropyrrol-2-one (**5a**).* It was purified by chromatography on silica gel, eluting with a mixture (50:50) of cyclohexane and diethyl ether. Yield: 61%. Oil. ^{1}H NMR ($CDCl_3$, δ ppm): 0.81 (t, $^3J_{H,H}$ = 7.5 Hz, 3H, CH_3), 1.22 (m, 4H, 2 × CH_2), 1.35 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 2.98 (q, $^3J_{H,F}$ = 10.7 Hz, 2H, CH_2CF_3), 3.19 (d, $^2J_{H,H}$ = 14.0 Hz, 1H, CH_AH_BS), 3.41 (d, $^2J_{H,H}$ = 14.0 Hz, 1H, CH_AH_BS), 6.62 (s, 1H, CH=), 7.2–7.4 (m, 5H, Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −65.2 (t, $^3J_{F,H}$ = 10.7 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 14.0 (s, CH_3), 22.3 (s, CH_2), 28.7 (s, CH_2), 29.4 (s, CH_2), 29.8 (q, $^2J_{C,F}$ = 31.6 Hz, CH_2CF_3), 39.3 (s, CH_2), 40.7 (s, CH_2), 90.7 (s, C_q, COH), 125.3 (q, $^1J_{C,F}$ = 276.4 Hz, CF_3), 127.2 (s, C_q Ph), 129.2 (s, 2 × CH Ph), 129.7 (q, $^3J_{C,F}$ = 2.9 Hz, CCH_2CF_3), 130.4 (s, 2 × CH Ph), 135.2 (s, C_q Ph), 143.9 (s, =CH), 168.2 (s, CO). IR (film, cm^{-1}): 3332, 1688, 1657, 1585, 1140. GC–MS: *m/z* = 373 [M^+], 355. HRMS: calcd. for $C_{18}H_{23}F_3NO_2S$ *m/z* 374.1402, found 374.1405.

*3.2.3.2. 1-Benzyl-3-(2,2,2-trifluoroethyl)-5-hydroxy-5-(phenylsufanylmethyl)-1,5-dihydropyrrol-2-one (**5b**).* It was purified by chromatography on silica gel, eluting with a mixture (77:23) of petroleum ether and ethyl acetate. Yield: 79%. Solid. mp 128–129 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 2.66 (brs, 1H, OH), 3.09 (d, $^2J_{H,H}$ = 14.1 Hz, 1H), 3.12 (q, $^3J_{H,F}$ = 10.8 Hz, 2H, CH_2CF_3), 3.33 (d, $^2J_{H,H}$ = 14.1 Hz, 1H), 4.46 (d, $^2J_{H,H}$ = 15.6 Hz, 1H), 4.54 (d, $^2J_{H,H}$ = 15.6 Hz, 1H), 6.72 (s, 1H, =CH), 7.2–7.4 (m, 10H, 2 × Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −65.2 (t, $^3J_{H,F}$ = 10.8 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 30.4 (q, $^2J_{C,F}$ = 31.9 Hz, CH_2CF_3), 41.6 (s, CH_2), 43.2 (s, CH_2), 92.2 (s, C_q, COH), 126.8 (q, $^1J_{C,F}$ = 276.3 Hz, CF_3), 127.6 (s, CH Ph), 128.3 (s, CH Ph), 129.2 (s, 2 × CH Ph), 129.4 (s, 2 × CH Ph), 130.0 (s, 2 × CH Ph), 130.1 (q, $^3J_{C,F}$ = 3.0 Hz, CCH_2CF_3), 131.1 (s, 2 × CH Ph), 137.4 (s, C_q Ph), 139.0 (s, C_q Ph), 147.6 (s, CH=), 170.6 (s, CO). IR (KBr, cm^{-1}): 3329, 3091, 2924, 1682, 1652, 1440, 1259. GC–MS: *m/z* = 393 [M^+],

375, 284, 110, 91. Formula: $C_{20}H_{18}F_3NO_2S$: calcd. C 61.1, H 4.6, N 3.6; found C 61.2, H 4.8, N 3.3.

*3.2.3.3. 3-(2,2,2-Trifluoroethyl)-5-hydroxy-5-(phenylsulfanylmethyl)-1-(i-propyl)-1,5-dihydropyrrol-2-one (**5c**).* It was purified by chromatography on silica gel, eluting with a mixture (75:25) of petroleum ether and ethyl acetate. Yield: 55%. Yellow oil. ^{1}H NMR ($CDCl_3$, δ ppm): 1.35 (d, $^3J_{H,H}$ = 6.8 Hz, 3H, CH_3), 1.37 (d, $^3J_{H,H}$ = 6.8 Hz, 3H, CH_3), 2.96 (q, $^3J_{H,F}$ = 10.7 Hz, 2H, CH_2CF_3), 3.14 (d, $^2J_{H,H}$ = 13.6 Hz, 1H, CH_AH_BS), 3.42 (d, $^2J_{H,H}$ = 13.6 Hz, 1H, CH_AH_BS), 3.68 (sept, $^3J_{H,H}$ = 6.8 Hz, 1H, $CHMe_2$), 3.90 (brs, 1H, OH), 6.58 (s, 1H, CH=), 7.2–7.3 (m, 5H, Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −65.2 (t, $^3J_{F,H}$ = 10.7 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 20.2 (s, CH_3), 20.6 (s, CH_3), 29.5 (q, $^2J_{C,F}$ = 31.6 Hz, CH_2CF_3), 40.9 (s, CH_2), 44.0 (s, CH), 90.9 (s, C_q, COH), 125.2 (q, $^1J_{C,F}$ = 276.4 Hz, CF_3), 127.0 (s, CH Ph), 129.2 (s, 2 × CH Ph), 130.1 (s, 2 × CH Ph), 130.7 (q, $^3J_{C,F}$ = 3.1 Hz, CCH_2CF_3), 135.4 (s, C_q Ph), 143.3 (s, CH=), 167.6 (s, CO). IR (film, cm^{-1}): 3334, 1689, 1659, 1584, 1359, 1140. GC–MS: *m/z* = 345 [M$^+$], 327. HRMS: calcd. for $C_{16}H_{19}F_3NO_2S$ *m/z* 346.1089, found 346.1081.

*3.2.3.4. 3-(2,2,2-Trifluoroethyl)-5-hydroxy-5-(phenylsulfanylmethyl)-1-[3-(N,N-dimethylamino)-propyl]-1,5-dihydropyrrol-2-one (**5d**).* It was purified by chromatography on silica gel, eluting with a mixture (50:50) of petroleum ether and ethyl acetate. Yield: 63%. Yellow oil. ^{1}H NMR ($CDCl_3$, δ ppm): 1.5 (m, 2H, $CH_2CH_2NMe_2$), 2.00 (s, 6H, NMe_2), 2.1–2.3 (m, 1H, $CH_AH_BNMe_2$), 2.4–2.5 (m, 1H, $CH_AH_BNMe_2$), 2.7–2.9 (m, 2H, $CH_2CH_2CH_2NMe_2$), 2.94 (qd, $^3J_{H,F}$ = 10.7 Hz, $^4J_{H,H}$ = 1.1 Hz, 1H, $CH_AH_BCF_3$), 3.09 (qd, $^3J_{H,F}$ = 10.7 Hz, $^4J_{H,H}$ = 1.1 Hz, 1H, $CH_AH_BCF_3$), 3.16 (d, $^2J_{H,H}$ = 13.7 Hz, 1H, CH_AH_BS), 3.34 (d, $^2J_{H,H}$ = 13.7 Hz, 1H, CH_AH_BS), 6.69 (m, 1H, CH=), 7.1–7.3 (m, 5H, Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −65.5 (t, $^3J_{F,H}$ = 10.7 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 23.1 (s, $CH_2CH_2CH_2$), 29.4 (q, $^2J_{C,F}$ = 31.0 Hz, CH_2CF_3), 37.7 (s, CH_2NMe_2), 41.0 (s, $CH_2CH_2CH_2NMe_2$), 43.6 (s, NMe_2), 57.7 (s, CH_2S), 90.1 (s, C_q, COH), 125.2 (q, $^1J_{C,F}$ = 276.4 Hz, CF_3), 126.7 (s, CH Ph), 128.9 (s, 2 × CH Ph), 130.3 (s, 2 × CH Ph), 127.8 (q, $^3J_{C,F}$ = 2.9 Hz, CCH_2CF_3), 135.8 (s, C_q Ph), 144.3 (s, CH=), 168.4 (s, CO). IR (film, cm^{-1}): 3382, 2932, 1698, 1659, 1260, 1139. GC–MS: *m/z* = 388 [M$^+$], 370. Formula: $C_{18}H_{23}F_3N_2O_2S$: calcd. C 55.7, H 5.9, N 7.2, S 8.3, found C 55.6, H 5.9, N 7.2, S 8.3.

*3.2.3.5. 1-(2-Hydroxyethyl)-3-(2,2,2-trifluoroethyl)-5-hydroxy-5-(phenylsulfanymethyl)-1,5-dihydro-pyrrol-2-one (**5e**).* It was purified by chromatography on silica gel, eluting with a mixture (60:40) of petroleum ether and ethyl acetate. Yield: 68%. Yellow solid. mp 88–89 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 2.9–3.0 (m, 4H, CH_2CF_3 + CH_2N), 3.26 (d, $^2J_{H,H}$ = 14.0 Hz, CH_AH_BS), 3.39 (d, $^2J_{H,H}$ = 14.0 Hz, 1H, CH_AH_BS), 3.5–3.6 (m, 2H, CH_2OH), 6.67 (m, 1H, =CH), 7.2–7.3 (m, 5H, Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −65.2 (tm, $^3J_{F,H}$ = 11.0 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 29.9 (q, $^2J_{C,F}$ = 31.6 Hz, CH_2CF_3), 40.1 (s, CH_2), 41.5 (s, CH_2), 61.1 (s, CH_2OH), 90.1 (s, C_q, COH), 125.1 (q, $^1J_{C,F}$ = 276.4 Hz, CF_3), 127.4 (s, CH Ph), 128.8 (q, $^3J_{C,F}$ = 2.9 Hz, CCH_2CF_3), 129.1 (s, 2 × CH Ph), 130.6 (s, 2 × CH Ph), 135.0 (s, C_q Ph), 145.5 (s, CH=), 169.4 (s, CO). IR (KBr, cm^{-1}): 3455, 3092, 1682, 1631, 1218. HRMS: calcd. for $C_{15}H_{17}F_3NO_3S$ *m/z* 348.0881, found 348.0890.

*3.2.3.6. 3-(2,2,2-Trifluoroethyl)-5-hydroxy-5-(phenylsulfanylmethyl)-1-phenyl-1,5-dihydropyrrol-2-one (**5f**).* It was purified by chromatography on silica gel, eluting with a mixture (75:25) of petroleum ether and ethyl acetate. Yield: 41% (conversion: 60%). Yellow oil. ^{1}H NMR ($CDCl_3$, δ ppm): 3.0 (m, 2H, CH_2CF_3), 3.11 (d, $^2J_{H,H}$ = 13.9 Hz, 1H, CH_AH_BS), 3.32 (d, $^2J_{H,H}$ = 13.9 Hz, 1H, CH_AH_BS), 6.65 (m, 1H, CH=), 7.1–7.4 (m, 10H, 2 × Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −65.1 (t, $^3J_{F,H}$ = 9.5 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 29.7 (q, $^2J_{C,F}$ = 31.6 Hz, CH_2CF_3), 40.2 (s, CH_2S), 92.0 (s, C_q, COH), 121.8 (q, $^1J_{C,F}$ = 278.1 Hz, CF_3), 126.5 (s, 2 × CH Ph), 127.0 (s, CH Ph), 127.3 (s, CH Ph), 129.1 (s, 4 × CH Ph), 129.3 (q, $^3J_{C,F}$ = 2.8 Hz, CCH_2CF_3), 130.1 (s, 2 × CH Ph), 134.6 (s, C_q Ph), 135.0 (s, C_q Ph), 144.4 (s, CH=), 167.7 (s, CO). IR (film, cm^{-1}): 3296, 2925, 1690, 1656, 1598, 1392, 1263, 1102. GC–MS: *m/z* = 379 [M$^+$], 361. HRMS: calcd. for $C_{19}H_{17}F_3NO_2S$ *m/z* 380.0932, found 380.0926.

*3.2.3.7. 1-Benzyl-3-(2,2,2-trifluoroethyl)-5-hydroxy-5-(phenylsulfonylmethyl)-1,5-dihydropyrrol-2-one (**6a**).* It was purified by chromatography on silica gel, eluting with a mixture (65:35) of petroleum ether and ethyl acetate. Yield: 76%. White solid. mp 158 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 3.04 (d, $^2J_{H,H}$ = 14.6 Hz, 1H), 3.17 (qd, $^3J_{H,F}$ = 10.4, $^4J_{H,H}$ = 1.7 Hz, 2H, CH_2CF_3), 3.52 (d, $^2J_{H,H}$ = 14.6 Hz, 1H), 4.32 (d, $^2J_{H,H}$ = 15.6 Hz, 1H), 4.73 (d, $^2J_{H,H}$ = 15.6 Hz, 1H), 7.26 (m, 5H, Ph), 7.33 (m, 1H, =CH), 7.56 (tm, $^3J_{H,H}$ = 7.6 Hz, 2H Ph), 7.69 (tm, $^3J_{H,H}$ = 7.5 Hz, 1H Ph), 7.7–7.8 (m, 2H Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −65.2 (t, $^3J_{F,H}$ = 10.4 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 29.6 (q, $^2J_{C,F}$ = 31.8 Hz, CH_2CF_3), 41.8 (s, CH_2Ph), 61.4 (s, CH_2SO_2), 87.4 (s, C_q, COH), 125.0 (q, $^1J_{C,F}$ = 277.0 Hz, CF_3), 127.5 (s, CH Ph), 127.8 (s, 2 × CH Ph), 127.9 (s, 2 × CH Ph), 128.6 (s, 2 × CH Ph), 128.7 (q, $^3J_{C,F}$ = 2.9 Hz, CCH_2CF_3), 129.1 (s, 2 × CH Ph), 133.9 (s, CH Ph), 137.2 (s, C_q Ph), 139.8 (s, C_q Ph), 144.7 (s, =CH), 168.3 (s, CO). IR (KBr, cm^{-1}): 3205, 1682, 1586. MS: *m/z* = 426 [M + 1], 408 [M + 1-H_2O]. Formula: $C_{20}H_{18}F_3NO_4S$: calcd. C 56.5, H 4.2, N 3.3, S 7.5, found C 56.7, H 4.3, N 3.3, S 7.5.

*3.2.3.8. X-ray crystal structure determination of compound **6a** (Fig. 3).* $C_{20}H_{18}F_3NO_4S$, Mr = 425.41, monoclinic, $P2_1/n$ (Nr 14), a = 17.888(5), b = 11.188(3), c = 19.344(6) Å, β = 97.22(2)°, V = 3841(2) Å^3, Z = 8, Dx = 1.47 g cm^{-3}. A total of 19587 reflections were collected at 120 K using a MAR345 image plate detector and Mo Kα radiation (λ = 0.71069 Å). A 5451 independent reflections (R_{int} = 0.044, $2\Theta_{max}$ = 47.6°). The structure was solved by direct methods with SHELXS-97 [16] and refined by least square using F^2 values and anisotropic thermal parameters for non-hydrogen atoms with SHELXL-97 [16]. There are two independent molecules in the asymmetric part of the unit cell. The second molecule was labelled by adding 100 to the labels of the first one (represented at Fig. 3). The H

atoms of the OH groups were located by Fourier-difference synthesis and included in the refinement with a common isotropic temperature factor. The other H atoms were calculated with afix. The final R values are $R = 0.087$ for 4896 observed reflections and $wR_2 = 0.235$ all data. The data have been deposit with the Cambridge Crystallographic Data Centre (Nr CCDC631439).

*3.2.3.9. 3-(2,2,2-Trifluoroethyl)-5-hydroxy-5-(phenylsulfonylmethyl)-1-(i-propyl)-1,5-dihydropyrrol-2-one (**6b**).* It was purified by chromatography on silica gel, eluting with a mixture (55:45) of petroleum ether and ethyl acetate. Yield: 60%. White solid. mp 128 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 1.35 (d, $^3J_{H,H}$ = 6.9 Hz, 3H, CH_3), 1.39 (d, $^3J_{H,H}$ = 6.9 Hz, 3H, CH_3), 3.06 (q, $^3J_{H,F}$ = 10.5 Hz, 2H, CH_2CF_3), 3.25 (d, $^2J_{H,H}$ = 14.1 Hz, 1H, $CH_AH_BSO_2$), 3.66 (sept, $^3J_{H,H}$ = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.80 (d, $^2J_{H,H}$ = 14.1 Hz, 1H, $CH_AH_BSO_2$), 7.26 (s, 1H, =CH), 7.61 (dd, $^3J_{H,H}$ = 7.7, $^3J_{H,H}$ = 7.7 Hz, 2H, 2 × CH Ph), 7.7–7.8 (m, 1H, CH Ph), 7.93 (dm, $^3J_{H,H}$ = 7.7 Hz, 2H, 2 × CH Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −65.2 (t, $^3J_{F,H}$ = 10.5 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 20.0 (s, CH_3), 20.2 (s, CH_3), 29.3 (q, $^2J_{C,F}$ = 31.8 Hz, CH_2CF_3), 43.8 (s, $CH(CH_3)_2$), 61.4 (s, CH_2SO_2), 87.8 (s, C_q, COH), 125.1 (q, $^1J_{C,F}$ = 276.4 Hz, CF_3), 128.0 (s, 2 × CH Ph), 129.2 (s, 2 × CH Ph), 129.6 (q, $^3J_{C,F}$ = 2.9 Hz, CCH_2CF_3), 134.0 (s, CH Ph), 140.0 (s, C_q Ph), 143.4 (s, =CH), 167.4 (s, CO). IR (KBr, cm^{-1}): 3286, 1693, 1656, 1362, 1310. GC–MS: m/z = 377 [M$^+$], 194, 141, 77. HRMS: calcd. $C_{16}H_{18}F_3NO_4S$ m/z 378.0987, found 378.0986.

*3.2.3.10. 1-(2-Hydroxyethyl)-3-(2,2,2-trifluoroethyl)-5-hydroxy-5-(phenylsulfonylmethyl)-1,5-dihydropyrrol-2-one (**6c**).* It was purified by chromatography on silica gel, eluting with ethyl acetate. Yield: 79%. Oil. ^{1}H NMR ($CDCl_3$, δ ppm): 3.14 (m, 4H, $CH_2CF_3 + CH_2$), 3.50 (d, $^2J_{H,H}$ = 14.6 Hz, 1H, $CH_AH_BSO_2$), 3.81 (m, 2H), 3.90 (d, $^2J_{H,H}$ = 14.6 Hz, 1H, $CH_AH_BSO_2$), 7.23 (s, 1H, =CH), 7.58 (dd, $^3J_{H,H}$ = 7.3, $^3J_{H,H}$ = 7.0 Hz, 2H, 2 × CH Ph), 7.69 (m, 1H, CH Ph), 7.88 (dm, $^3J_{H,H}$ = 7.9 Hz, 2H, 2 × CH Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −65.2 (t, $^3J_{F,H}$ = 10.7 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 29.6 (q, $^2J_{C,F}$ = 32.0 Hz, CH_2CF_3), 41.6 (s, CH_2N), 60.4 (s, CH_2), 60.6 (s, CH_2), 86.7 (s, C_q, COH), 125.0 (q, $^1J_{C,F}$ = 276.4 Hz, CF_3), 127.9 (s, 2 × CH Ph), 128.4 (q, $^3J_{C,F}$ = 2.9 Hz, CCH_2CF_3), 129.4 (s, 2 × CH Ph), 134.3 (s, CH Ph), 139.4 (s, C_q Ph), 145.0 (s, =CH), 168.7 (s, CO). IR (film, cm^{-1}): 3418, 1694, 1660, 1448, 1260. MS: m/z = 380 [M + 1], 362 [M + 1-H_2O], 308, 223. HRMS: calcd. $C_{15}H_{16}F_3NNaO_5S$ m/z 402.0599, found 402.0602.

*3.2.3.11. 3-(2,2,2-Trifluoroethyl)-5-hydroxy-5-(phenylsulfonylmethyl)-1-phenyl-1,5-dihydropyrrol-2-one (**6d**).* It was purified by chromatography on silica gel, eluting with a mixture (70:30) of petroleum ether and ethyl acetate. Yield: 87%. Solid. mp 130 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 3.06 (q, $^3J_{H,F}$ = 10.4 Hz, 2H, CH_2CF_3), 3.23 (d, $^2J_{H,H}$ = 14.3 Hz, 1H, $CH_AH_BSO_2$), 3.53 (d, $^2J_{H,H}$ = 14.3 Hz, 1H, $CH_AH_BSO_2$), 4.51 (brs, 1H, OH), 7.2–7.3 (m, 6H, Ph + =CH), 7.45 (m, 2H, 2 × CH Ph), 7.58 (tt, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.3 Hz, 1H, CH Ph), 7.71 (m, 2H, 2 × CH Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −65.0 (t, $^3J_{F,H}$ = 10.4 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 29.4 (q, $^2J_{C,F}$ = 31.7 Hz, CH_2CF_3), 60.5 (s, CH_2SO_2), 88.4 (s, C_q, COH), 125.0 (q, $^1J_{C,F}$ = 276.4 Hz, CF_3), 126.2 (s, 2 × CH Ph), 127.3 (s, CH Ph), 127.6 (s, 2 × CH Ph), 128.4 (q, $^3J_{C,F}$ = 2.9 Hz, CCH_2CF_3), 128.9 (s, 2 × CH Ph), 129.0 (s, 2 × CH Ph), 133.8 (s, CH Ph), 133.9 (s, C_q Ph), 139.6 (s, C_q Ph), 144.6 (s, =CH), 167.4 (s, CO). IR (KBr, cm^{-1}): 3381, 1695, 1598, 1501, 1370, 1263. MS: m/z = 412 [M + 1], 394 [M + 1-H_2O]. HRMS: calcd. $C_{19}H_{17}F_3NO_4S$ m/z 412.0830, found 412.0825.

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