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Synthesis of (2,2,2-trifluoroethyl) substituted pyridazin-3(2*H*)-ones and 1,5-dihydropyrrol-2-ones from α,β-unsaturated γ-lactones and hydrazines

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ABSTRACT

This paper presents the transformation of α,β-unsaturated γ-lactones into 2,2,2-trifluoroethyl substituted pyridazin-3(2*H*)-ones and 1,5-dihydropyrrol-2-ones starting from various hydrazines. The influence of the γ-lactone substitution (sulfanyl versus sulfonyl moiety) and the nature of the hydrazines (unsubstituted, alkyl- or aryl-substituted) on the outcome of the reaction were studied. All new heterocycles were characterized using 1D NMR, IR, MS and their data was compared with those of two reported X-ray diffraction structures. The two possible competitive pathways leading to pyridazin-3(2*H*)-ones and/or 1,5-dihydropyrrol-2-ones are discussed. *Ab initio* DFT calculations were also performed in order to rationalize several experimental results.

1. Introduction

The pyridazine and pyridazin-3-one family have attracted a great deal of attention due to the wide spectrum of their pharmaceutical and agrochemical activities. For example, 3-(alkylamino)pyridazine derivatives are well documented and exhibit anti-hypertensive or anti-depressant properties [1,2]. Pyridazin-3(2*H*)-ones also possess interesting synthetic versatility (precursors of 3-(alkylamino)pyridazines) and possible binding sites for interaction with various receptors. Therefore, these molecules have been used as positive inotropic agents for the treatment of congestive heart failure, potassium channel activators, antiasthmatics, an antihistaminic agent (Azelastine) and a phosphodiesterase inhibitor (Zordoverine) [3,4].

Pyridazin-3(2*H*)-ones have generally been prepared from γ-keto derivatives (acid or corresponding chloride, ester) [5], and various substituted hydrazines *via* dihydro intermediates, using multi-step sequence. γ-Lactones (saturated or α,β-unsaturated) have also been used as starting materials [6,7].

The introduction of fluorine-containing substituents into organic compounds is a very useful tool for changing their physical and chemical properties in order to improve their biological activity. This strategy is widely used in the search of new drugs. The increasing interest in fluorinated heterocycles (especially trifluoromethylated ones) [8–11] and the continuous need of new scaffolds for library syntheses prompted us to develop a general method for the preparation of new fluorine containing pyridazine and pyridazin-3-one derivatives, based on a building block strategy.

There are few syntheses of fluorinated pyridazin-3-ones reported so far, being mainly devoted to the preparation of 4-perfluoroalkyl substituted derivatives. Indeed, the general approach to 4-trifluoromethyl pyridazin-3(2*H*)-ones **1** ($R^2 = CF_3$) is based on a building block strategy starting from 4,4,4-trifluoro-1-phenylbut-2-en-1-one **2** [2], 2-trifluoromethyl γ-keto thioesters **3** [12], or more recently from 3,3,3-trifluoropyruvate **4** [13] and hydrazines (Scheme 1: Path A). Nevertheless, these methods suffer from several limitations such as multi-step sequences starting from commercially unavailable compounds (**2**, **3**), low-overall yields (**2**), substrate dependency (**3**) or incompatibility with additional functional groups reactive toward hydrazine (**4**).

The number of 4-perfluoroalkyl pyridazine-3(2*H*)-ones (longer than CF_3 group) are limited to the synthesis of 4-(1,2,2,2-tetrafluoroethyl)pyridazin-3(2*H*)-ones **1** ($R^2 = CH(F)CF_3$) [12], or 4-(1-ethylthio-2,2,2-trifluorethyl) derivatives **1** ($R^2 = CH(SEt)CF_3$) obtained by the sequence of a furan ring opening/ring closure of acylic γ-ketosemicarbazide [14] (Scheme 1: Path B).

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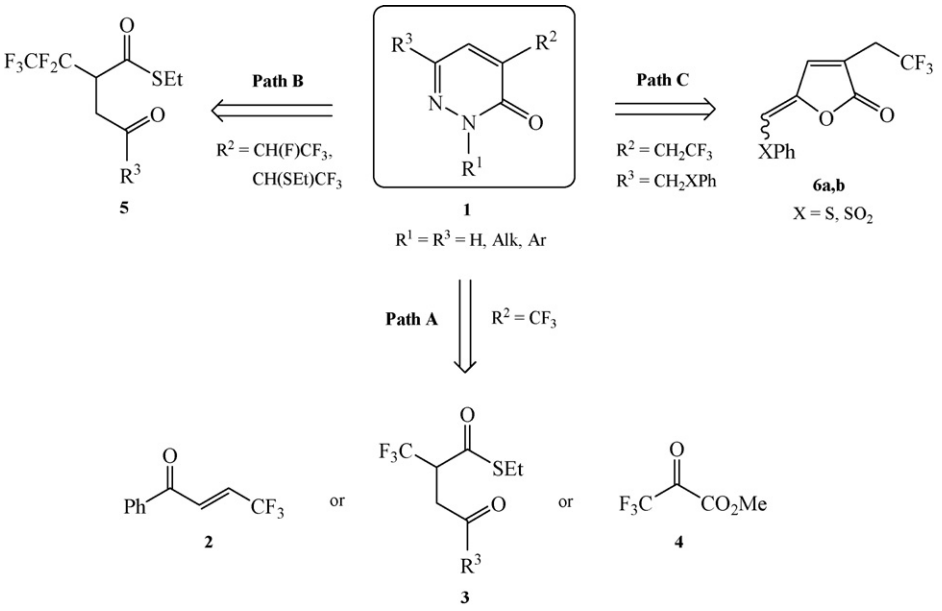


Scheme 1.

In order to increase structural diversity on the pyridazin-3-one nucleus, we were interested in preparing new 4-(2,2,2-trifluoroethyl) substituted derivatives **1** ($R^2 = CH_2CF_3$) starting from α,β-unsaturated γ-lactones **6a**,**b** and hydrazines (Scheme 1: Path C). The proposed strategy is based on a few results in the non-fluorinated γ-lactone series [15–17] as well as on our recent straightforward transformation of γ-lactones **6a**,**b** into γ-lactams **7** (Scheme 2) [18]. Furthermore, this method has the advantage of introducing either a phenylsulfanyl or a phenylsulfonyl group useful for further interesting transformations. To the best of our knowledge, there are no examples of a pyridazin-3(2*H*)-one bearing such substituents in the literature.

γ-Ketothioester **8** was prepared according to our reported procedure [19] starting from the corresponding perfluoroketene dithioacetal [20,21]. The treatment of **8** with non-nucleophilic diisopropylamine in diethyl ether led to α,β-unsaturated γ-lactone **6a** as a mixture of stereomers [19]. This compound was then easily transformed into sulfonyl derivative **6b** by oxidation with meta-chloroperbenzoïc acid (MCPBA). Finaly, γ-lactones **6a**,**b** were efficiently converted into 3-(2,2,2-trifluoroethyl) γ-lactams **7** (yields: 41–87%) in the presence of various substituted amines (Scheme 2) [18].

In this paper, we would like to report on a thorough investigation of heterocyclizations of compounds **6a**,**b** with hydrazines in order to prepare new pyridazin-3(2*H*)-ones. In particular, the influence of the lactone substitution (X = S, SO_2) and the nature of hydrazines on the outcome of the reaction were studied.

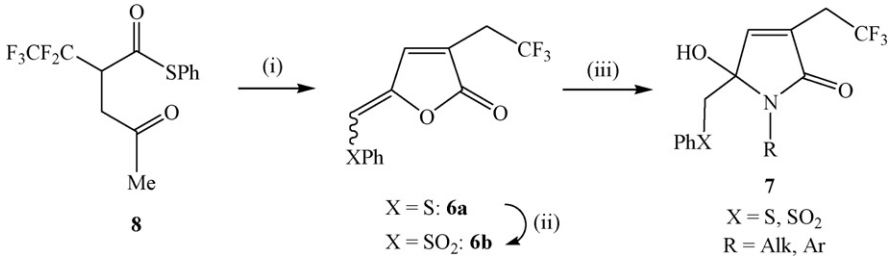
2. Results and discussion

In the first experiment, compound **6a** was treated with 5.0 equiv. of hydrazine hydrate in THF, for 16 h, at room temperature (Scheme 3: Method 1). The crude mixture was checked by ^{19}F NMR to confirm complete conversion of the starting material. At the end of the reaction, the solvent was evaporated *in vacuo* and the residue was purified by silica gel column chromatography affording the new pyridazin-3(2*H*)-one **9a** (yield: 21%) and γ-lactam **10a** (yield: 33%) (Table 1: entry 1).

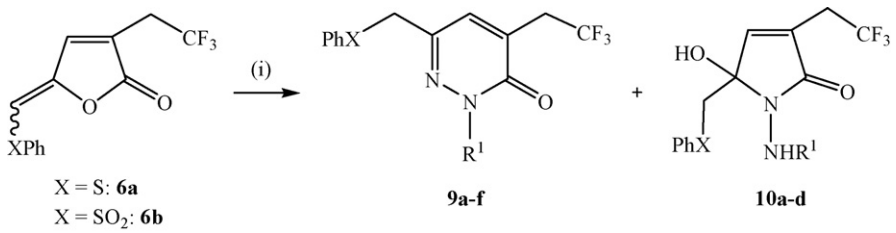
The transformation was then extended to various substituted hydrazines (R^1 = Me, Ph) or hydrazinium salts (R^1 = Et, *p*-MeC_6H_4) in order to study the influence of the R^1 substituent on the selectivity of the reaction. When hydrazinium derivatives were used, triethylamine was added as a base (Scheme 3: Method 2).

The reactions of **6a** with methylhydrazine (Method 1) and ethylhydrazinium oxalate (Method 2) proceeded smoothly providing only pyridazin-3(2*H*)-ones **9b** and **9c** in 61% and 57% yields, respectively (Scheme 3, Table 1: entries 2 and 3). In contrast, γ-lactone **6a** did not react with phenylhydrazine; only a very low conversion was observed by ^{19}F NMR of the crude mixture, even after reflux for 24 h (Table 1: entry 4). The carbonyl group seemed less reactive toward the poorly nucleophilic phenylhydrazine. A similar observation has been already done for the reaction of **6a** with aniline [18].

In order to increase the electrophilicity of the carbonyl function, the same transformations were performed with phenysulfonyl



Scheme 2. *Reagents and conditions*: (i) *i*Pr_2NH, Et_2O, rt; (ii) MCPBA, CH_2Cl_2, rt; (iii) RNH_2, Et_2O or THF, rt.



Scheme 3. *Reagents and conditions*: (i) Method 1: R^1NHNH_2 (2–5 equiv.), THF, rt, 16 h or Method 2: $R^1NHNH_2{\cdot}2HX$ (2 equiv.), Et_3N (4 equiv.), THF, rt, 16 h.

lactone **6b**. Indeed, we have already demonstrated that vinylogous conjugation with an electron-withdrawing substituent activates the carbonyl group thus facilitating the addition of less nucleophilic amines [18]. Reactions of hydrazine hydrate (R^1 = H, entry 5) or alkylhydrazines (R^1 = Me, Et: entries 6, 7) proceeded in the same manner affording new pyridazin-3(2*H*)-ones **9d–f** in moderate to good yields (Scheme 3, Table 1).

The behaviour of hydrazine hydrate with γ-lactone **6b** (Table 1: entry 5) was slightly different than it with sulfanyl analogue **6a** (entry 1). Indeed, the major reaction product of **6b** with hydrazine was the intermediate **11a** (Fig. 1) which appeared to be unstable and was decomposed into a complex mixture of products during its purification on silica gel column chromatography. Intermediate **11a** was characterized in the crude mixture by means of MS spectra and ^{19}F, ^1H and ^{13}C NMR. Nevertheless, pyridazin-3-one **9d** was isolated as pure compound in 22% yield. In order to increase the yield, we attempted performing a mild *in situ* dehydration of **11a** by addition of a dehydrating agent to the reaction mixture. However, magnesium sulphate or *p*-toluenesulfonic acid did not work (no conversion) whereas sulphuric acid or simple heating led to complete decomposition of **11a**.

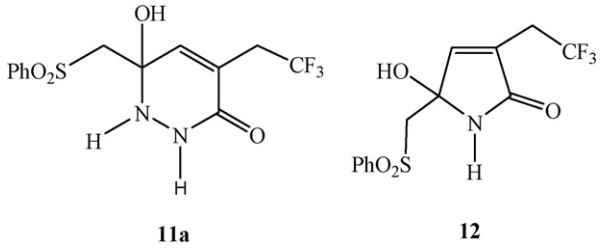


Fig. 1.

Table 1
Reactions of γ-lactones **6a**,**b** with hydrazines.

Entry	Substrate	X	Method[a]	R^1	Pyridazin-3-one[b]	γ-Lactam[b]
1	**6a**	S	1	H	**9a**: 21%	**10a**: 33%
2	**6a**	S	1	Me	**9b**: 61%	–
3	**6a**	S	2	Et	**9c**: 57%	–
4	**6a**	S	1	Ph[c]	–	–
5	**6b**	SO_2	1	H[d]	**9d**: 22%	–
6	**6b**	SO_2	1	Me	**9e**: 58%	–
7	**6b**	SO_2	2	Et	**9f**: 66%	**10b**: 7%
8	**6b**	SO_2	1	Ph	–	**10c**: 51%
9	**6b**	SO_2	2	*p*-MeC_6H_4	–	**10d**: 26%[e]

[a] Method 1: hydrazine (2–5 equiv.), THF, rt, 16 h; Method 2: hydrazinium salt (2 equiv.), Et_3N (4 equiv.), THF, rt, 16 h.
[b] Isolated yields.
[c] Very low conversion was obtained even at reflux for 24 h.
[d] The crude showed intermediate **11a** as the major product but it partially decomposed during silica gel chromatography.
[e] Lactam **10d** was accompanied by lactam **12** (~10%).

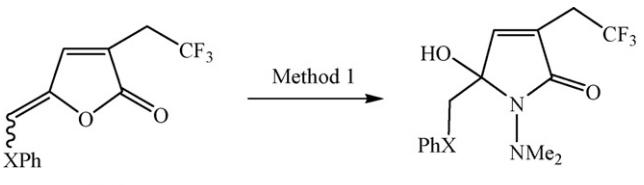
We then turned our attention to aryl substituted hydrazines. Reactions of the sulfonyl lactone **6b** with phenyl- and *p*-tolylhydrazines were selective providing γ-lactams **10c** and **10d** (Scheme 3, Table 1). Unfortunately, yields remained quite low (26–51%). It is worth noting that the reaction of **6b** with *p*-tolylhydrazine (entry 9) was accompanied by the formation of lactam **12** (~10%) (Fig. 1), probably due to N-N bond cleavage of lactam **10d**. This type of cleavage has been already observed in the literature in non-fluorinated heterocyclic chemistry [22] and also during the reaction of an α-pentafluoroethyl γ-carboxythioester with phenylhydrazine [23]. In order to confirm its structure, γ-lactam **12** (Fig. 1) was unambiguously prepared in 71% yield from compound **6b** and an aqueous solution of ammonia in THF at room temperature, according to our reported procedure [18].

This transformation was also applied to *N*,*N*-dimethylhydrazine in order to confirm the γ-lactam structure. No reaction was observed for γ-lactone **6a** whereas reaction of **6b** led exclusively to γ-lactam **10e** in 64% yield (Scheme 4). Again, these two heterocyclizations highlighted the strong reactivity difference between sulfanyl (X = S) and sulfonyl (X = SO_2) γ-lactones.

An important part of this work was to characterize the structure of the new pyridazin-3(2*H*)-ones **9a–f** and γ-lactams **10a–e**. First of all, NMR spectra (^{19}F, ^1H, ^{13}C), IR, MS and elemental analyses were in good agreement with the proposed structures. Nevertheless, this data was not sufficient to unambiguously confirm the precise skeleton of **9** and **10**. Therefore, we compared carefully selected NMR (δ_{19F}, $\delta_{H\text{-}5/H\text{-}4}$, $\delta_{C\text{-}2\ to\ C\text{-}6}$) and IR data ($\nu_{CO}$) of compounds **9** and **10** (Table 2) with those of **13** (for pyridazin-3(2*H*)-ones) and those of **14** (for γ-lactams) for which X-ray diffraction analyses were already obtained (Fig. 2) [14,18].

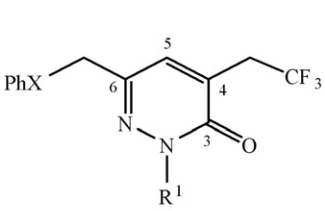
As shown in Table 2, the fluorine (δ_{19F}), olefinic proton ($\delta_{H\text{-}5/H\text{-}4}$) and carbon ($\delta_{C\text{-}2\ to\ C\text{-}6}$) chemical shifts of pyridazin-3(2*H*)-ones **9** and **13** and γ-lactams **10** and **14** are very similar respectively. Furthermore, infrared absorptions of the carbonyl group ($\nu_{C=O}$) are characteristic of a cyclic amide function. Therefore, we may reasonably assume that the structures **9**, **13** and **10**, **14** are very similar.

Reactions of lactones **6a**,**b** with substituted hydrazines appeared to be quite selective: alkylhydrazines gave mainly pyridazin-3-ones **9b**,**c**,**e**,**f** whereas arylhydrazines provided γ-lactams **10c**,**d**. To explain this selectivity, we proposed the mechanism depicted in Scheme 5.

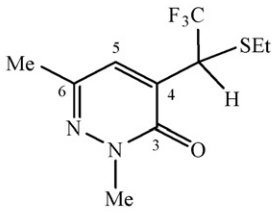


Scheme 4. *Reagents and conditions*: Method 1: Me_2NNH_2, THF, rt, 16 h.

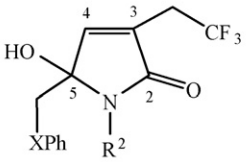
Table 2
Selected NMR and IR data for pyridazin-3-ones **9a–f**, **13** and γ-lactams **10a–e**, **14**.



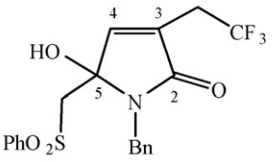
9a-f



13



10a-e



14

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Entry	X	R^1/R^2	Cpd[a]	δ_{19F} (ppm)	$\delta_{H\text{-}5/H\text{-}4}$ (ppm)	$\delta_{C\text{-}2}$ (ppm)	$\delta_{C\text{-}3}$ (ppm)	$\delta_{C\text{-}4}$ (ppm)	$\delta_{C\text{-}5}$ (ppm)	$\delta_{C\text{-}6}$ (ppm)	IR (ν_{CO}, cm^{-1})
1	S	H	**9a**	−64.8	7.44	–	161.0	132.9	127.5	145.5	1667
2	S	Me	**9b**	−64.8	7.2–7.4	–	159.6	132.0	127.0	143.6	1657
3	S	Et	**9c**	−64.8	7.1–7.3	–	159.0	132.0	127.4	143.5	1652
4	SO_2	H	**9d**[b]	−62.9	7.43	–	160.3	131.8	134.6	137.2 or 138.1	1667
5	SO_2	Me	**9e**	−64.8	7.38	–	159.5	131.9	132.4	137.5	1656
6	SO_2	Et	**9f**	−64.8	7.42	–	159.0	132.1	132.1	135.7	1670
7	–	–	**13**[c]	−68.1	7.20	–	158.5	135.3	130.1	143.9	1652
8	S	NH_2	**10a**[d]	−64.3	6.79	169.4	129.7	146.3	91.4	–	1651
9	SO_2	NHEt	**10b**	−65.1	7.10	167.2	[e]	143.2	86.7	–	–
10	SO_2	NHPh	**10c**	−65.1	7.2–7.3	167.6	[e]	145.3	87.6	–	1656
11	SO_2	NH*p*MeC_6H_4	**10d**	−65.0	7.30	167.5	128.6	143.7	86.9	–	1652
12	SO_2	NMe_2	**10e**	−65.1	7.09	165.9	129.2	142.2	86.6	–	1652
13	–	–	**14**[c]	−65.2	7.33	168.3	128.7	144.7	87.4	–	1682

[a] NMR solvent: $CDCl_3$.
[b] NMR solvent: DMSO-d_6.
[c] Structures determined by X-ray diffraction analysis [14,18].
[d] NMR solvent: CD_3COCD_3.
[e] Not visible.

Substituted hydrazines (R^1NHNH_2) possess two different reaction sites. Therefore, two competitive pathways can operate depending on the more nucleophilic centre of hydrazine. In the case of alkylhydrazines, the nitrogen atom bearing an alkyl group is more nucleophilic and attacks the carbonyl group of **6a**,**b** to give the acyclic intermediates **15** (Scheme 5: N-1 attack). Further cyclization of **15** followed by dehydration of **11** provides pyridazin-3-ones **9a–f**. It is worth noting that intermediates **11a** (R^1 = H) and **11b** (Scheme 6) were detected and characterized in the crude mixture. These reactions were observed for methyl- and ethylhydrazines; their selectivity was around 90% or higher (Table 1: entries 2, 3, 6, 7).

In the case of arylhydrazines, the unsubstituted amino group is more nucleophilic and attacks the carbonyl group of **6a**,**b** leading to acyclic intermediates **16** (Scheme 5: N-2 attack). γ-Ketosemicarbazides **16** then undergo cyclization into the corresponding γ-lactams **10a–e**. Such reactions were observed for phenyl- and *p*-tolylhydrazines (Table 1: entries 8 and 9).

According to the proposed mechanism, the behaviour of hydrazine hydrate with **6a**,**b** (Table 1: entries 1 and 5) remains difficult to explain. Indeed, pyridazin-3-ones **9a**,**d** and/or γ-lactam **10a** were obtained depending on substrate substitution (sulfanyl versus sulfonyl moiety).

We then tried to rationalize the experimental results using *ab initio* DFT calculations at the B3LYP 6–31G(d) theory level. It has already been mentioned that the energy of the LUMO is significantly lower in lactone **6b** compared to **6a** [18]. The first attack of any hydrazine derivative could occur either on C_2 (carbonyl lactone) or C_5. This is especially true in the case of **6b** where the strong electron withdrawing effect of the sulfone would decrease the electronic density on C_5, thus reinforcing its Michaël acceptor character. The charges and orbital coefficients in the LUMOs of **6a**,**b** were then

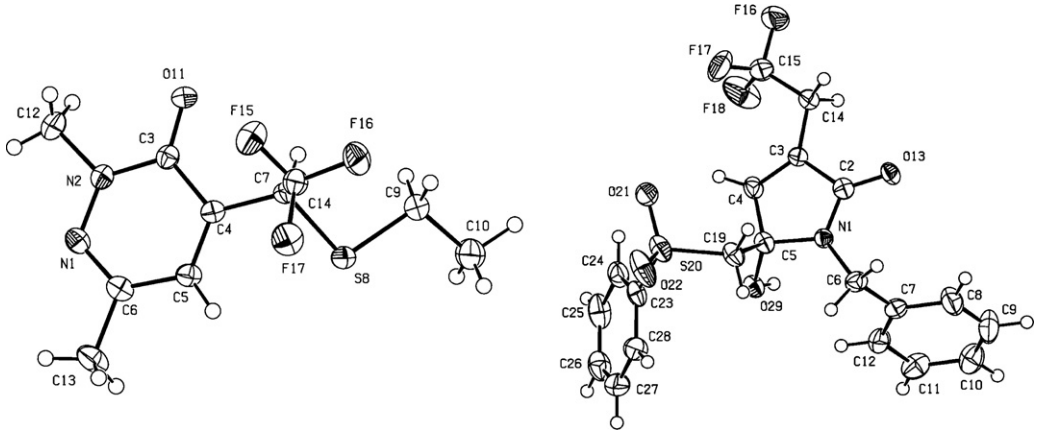
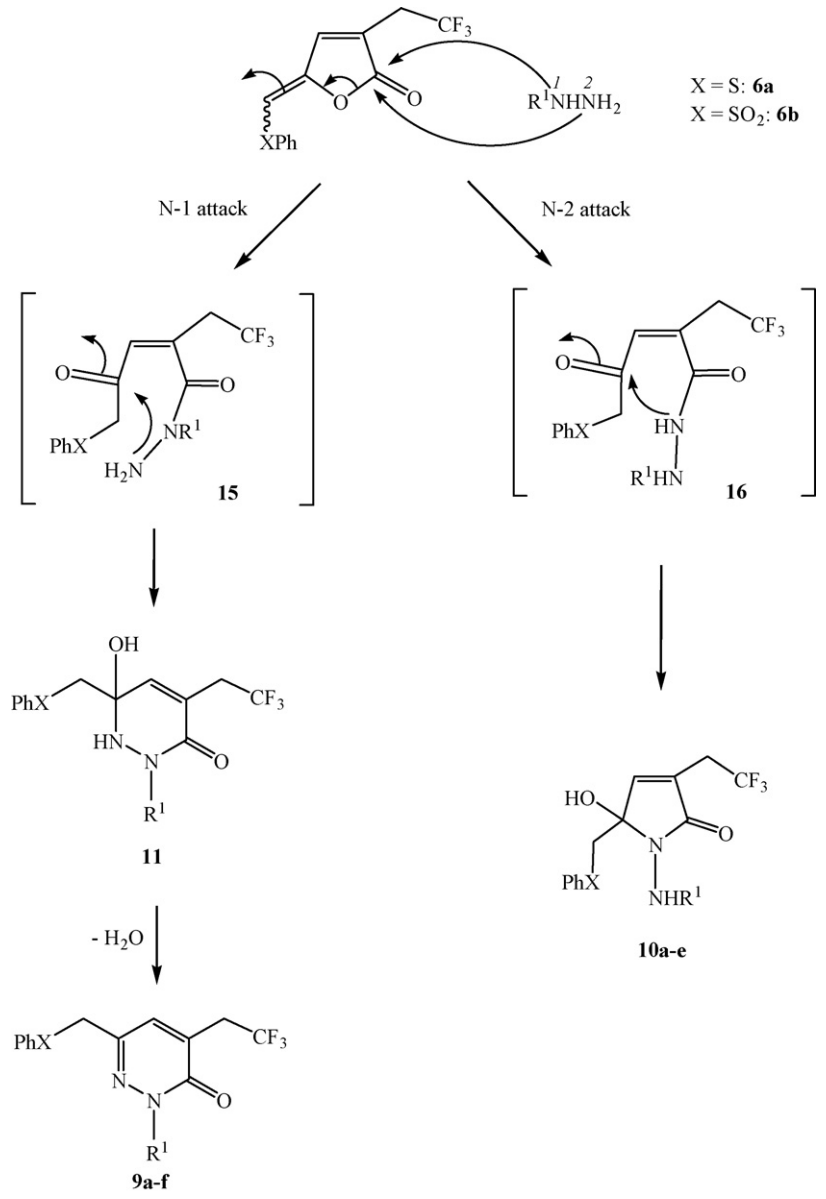
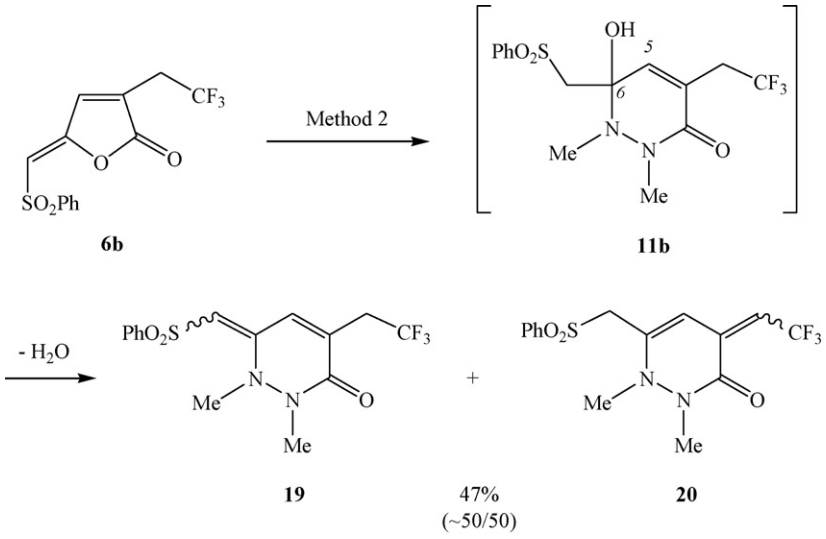


Fig. 2. X-ray diffraction analyses of compounds **13** and **14**.



Scheme 5. Proposed mechanism for the formation of compounds **9a–f** and **10a–e**.



Scheme 6. *Reagents and conditions*: Method 2: MeNHNHMe·2HCl, Et_3N, THF, rt, 16 h.

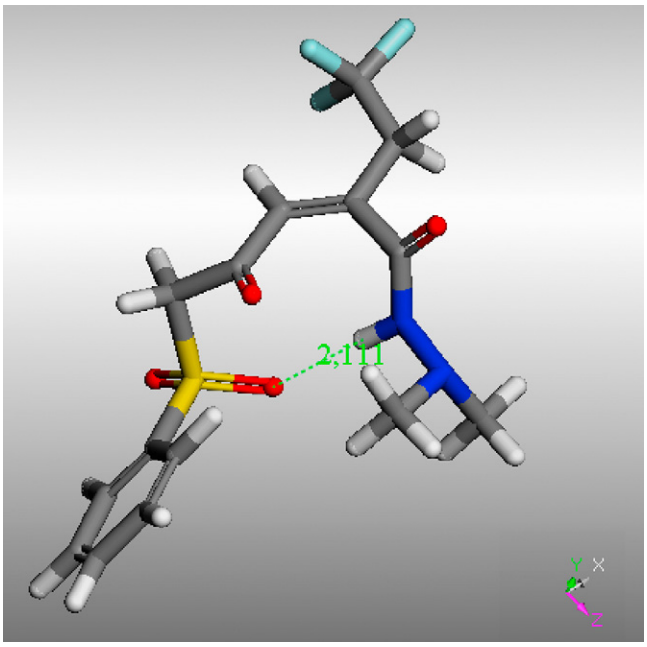


Fig. 3. Intermediate species **17** with a hydrogen bond.

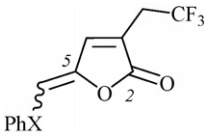
studied. The differences (Table 3) are in favour of an attack on C_2 in both cases assuming that the primary attack of the hydrazine derivative involves either a charge or an orbital control.

The most striking experimental result concerned the exclusive formation of the γ-lactam **10e** when **6a**,**b** were reacted with *N*,*N*-dimethylhydrazine (Scheme 4). Calculations on the postulated intermediate species **17** (Fig. 3) clearly revealed the formation of a hydrogen bond between an oxygen atom of the sulfone and the hydrogen atom of the Me_2NNH moiety. The H–O distance (around 210 pm) and the linear arrangement N–H–O observed are in good agreement with a strong hydrogen bond. This hydrogen bond would favour the proximity of the nitrogen atom connected to the carbonyl group and the other carbonyl (distance around 320 pm) and also increase the stability of intermediate **17**. Moreover, calculations performed on **18** (Fig. 4) showed longer S–H distance (around 430 pm) which is not in accordance with the formation of a hydrogen bond. Because both intermediates **17** and **18** are similar for an electronic point of view, this hydrogen bond could explain the transformation of **6b** into **10e** in a good yield whereas no conversion for **6a** into the corresponding γ-lactam was observed.

When γ-lactones **6a**,**b** were reacted with other hydrazines, the experimental results obtained were more difficult to explain. Competition, however, between intermediates **15** and **16** could be envisioned (Scheme 5). While formation of **16** would be favoured by the above-mentioned hydrogen bond, ease of ring closure might depend on the nature of the substituents connected to the terminal nitrogen atom. Calculation of the formation enthalpies of intermediates **15** and **16** shows that **16** is more stable than **15** when a sulfonyl group ($X = SO_2$) is present (a difference of 2.5 kcal mol^{-1} for $R^1 = Me$ and 10 kcal mol^{-1} for $R^1 = Ph$). The stability difference between **15** and **16** is less pronounced in the case of a sulfanyl group ($X = S$) (only 0.46 kcal mol^{-1} for $R^1 = Me$ and 0.65 kcal mol^{-1} for $R^1 = Ph$). The observed hydrogen bond in any intermediate **16** may explain this stability difference.

The charge densities on the nitrogen atoms of intermediates **15**–**18** were then calculated. When the electronic density on the terminal nitrogen atom of **15** is large enough (Table 4: entries 1 and 2), ring closure occurs through this intermediate and leads to the pyridazinone derivatives **9**. Alternatively, when this density is less important (Table 4: entry 3), ring closure involves the more stable intermediate **16** and leads to the γ-lactam derivatives **10**.

Table 3
Charges and MO coefficients in the LUMO on C_2 and C_5 of lactones **6a**,**b**.



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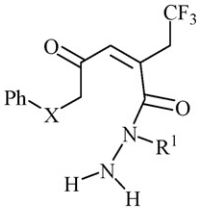
Lactone	Charge on C_2	Charge on C_5	MO coeff.[a] C_2	MO coeff.[a] C_5
6a (X = S)	0.58	0.42	0.27	0.21
6b ($X = SO_2$)	0.59	0.47	0.26	0.22

[a] The reported values take into account the 2p and 3p MO coefficients.

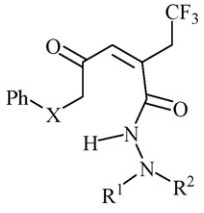
In order to better elucidate the proposed mechanism, the reaction of **6b** with symmetrical *N*,*N*′-dimethylhydrazine was performed under the same conditions (Scheme 6). Compound **11b** was unambiguously characterized in the crude mixture (this observation confirms our hypothesis concerning the selectivity of alkylhydrazines) but appeared to be not stable for a long reaction time or during purification. Nevertheless, NMR and MS (HRMS) data were in good agreement with the proposed structure. Characteristic signals of a 1,6-dihydropyridazin-3-one skeleton were observed in ^{13}C NMR (quaternary C-6 carbon at 84.7 ppm, olefinic CH-5 carbon at 134.2 ppm and carbonyl function at 161.3 ppm) and in the ^1H NMR spectra (olefinic H-5 proton at 6.26 ppm). During chromatography on silica gel, 1,6-dihydropyridazin-3-one **11b** underwent spontaneous transformation into its dehydrated derivatives containing exocyclic double bonds. Compounds **19** and **20** were isolated as a (~50/50) mixture, in 47% overall yield (Scheme 6). It was not possible to separate them by usual column chromatography. Their structures were in good agreement with IR, MS and NMR data, especially ^{19}F NMR spectra show a CF_3 group ($\delta = -65.0$ ppm, $^3J_{F,H} = 10.5$ Hz) identified as a triplet for **19** whereas the CF_3 group of **20** ($\delta = -58.3$ ppm, $^3J_{F,H} = 9.4$ Hz) appeared as a doublet. It is worth noting that compounds **19** and **20** were isolated as single isomers. Nevertheless, due to complicated ^1H spectra and several overlaps of ^1H signals, it was not possible to determine the configuration of their exocyclic double bonds by NOE experiments.

In conclusion, a new general synthesis of 2,2,2-trifluoroethyl pyridazin-3(2*H*)-ones **9** and 1,5-dihydropyrrol-2-ones **10** has been developed starting from α,β-unsaturated γ-lactones **6a**,**b** and hydrazines. Reaction selectivity depends on the nature of the

Table 4
Charges on the nitrogen atoms of postulated intermediates **15**–**18**.



15



16-18

.

Entry	Postulated intermediates	Charge on N–C═O	Charge on NH_2	Charge on NR^1R^2
1	**15**: X = S, $R^1 = Me$	−0.31	−0.57	–
2	**15**: $X = SO_2$, $R^1 = Me$	−0.31	−0.57	–
3	**16**: $X = SO_2$, $R^1 = H$, $R^2 = Ph$	−0.53	–	−0.50
4	**17**: $X = SO_2$, $R^1 = R^2 = Me$	−0.51	–	−0.25
5	**18**: X = S, $R^1 = R^2 = Me$	−0.47	–	−0.25

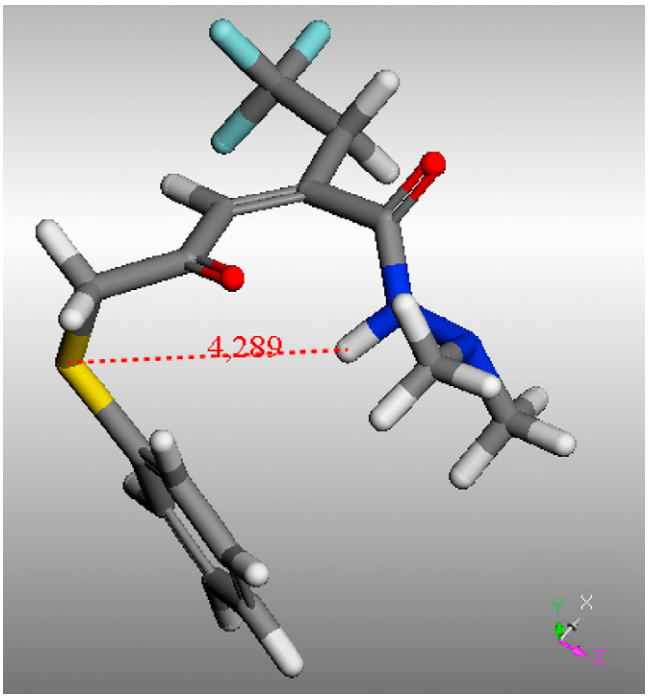


Fig. 4. Intermediate species **18** without a hydrogen bond.

hydrazine substituent: alkylhydrazines (R^1 = Me, Et) afforded mainly pyridazin-3-ones **9** whereas arylhydrazines (R^1 = Ph, *p*-MeC_6H_4) provided γ-lactams **10**. Further transformations of these new heterocycles **9** and **10** are under investigation.

3. Experimental

IR spectra were recorded on a FT-IR PerkinElmer PARAGON 500. ^{1}H NMR (250 MHz), ^{19}F NMR (235 MHz) and ^{13}C NMR (63 MHz) spectra were recorded, in $CDCl_3$ as a solvent unless otherwise specified, on a Bruker AC250 Instrument spectrometer. Tetramethylsilane (^{1}H NMR: δ = 0.00 ppm) or $CHCl_3$ (^{1}H NMR: δ = 7.27 ppm; ^{13}C NMR: δ = 77.00 ppm) or $CFCl_3$ (^{19}F NMR: δ = 0.00 ppm) were used as internal standards for ^{1}H, ^{13}C or ^{19}F spectra. 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 performed with silica gel (63–200 mesh, Normasil Prolabo, Fontenay-sous-bois, France). Mass spectra (MS) were recorded on a Thermo Finnigan, LCQ Advantage Max, Electrospray Ionisation, Source heater T = 220 °C, cone voltage = 33 V. 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. DFT calculations were carried out with the Gaussian-03 suite of programs [24] implemented on a P575 IBM cluster. We used the three parameters hybrid function of Becke [25] and the correlation function of Lee et al. (B3LYP) [26] with the 6–31G(d) basis set for any element. Formation enthalpies have been calculated after a frequency calculation in order to be sure that the geometry found corresponds to a stationary point and to achieve the zero point correction.

3.1. General procedure for the reactions of lactones 6a,b and hydrazines (Method 1)

The mixture of lactone **6a** or **6b** (1.0 mmol) and hydrazine (hydrazine hydrate: 5 equiv., *N*-methyl-, *N*,*N*-dimethyl- or *N*-phenylhydrazine: 2 equiv.) in THF (5 mL) was stirred for 16 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 residue was purified by silica gel column chromatography (eluent: mixture of petroleum ether and ethyl acetate) to give the corresponding pyridazin-3(2*H*)-ones **9a**,**b**,**d**,**e** and/or γ-lactams **10a**,**c**,**e** (Schemes 3 and 4, Table 1). For lactams **10a**,**c**, pure analytical samples were obtained by recrystallization from a mixture of pentane and ethyl acetate.

3.2. Typical procedure for the reactions of lactones 6a,b and hydrazinium salts (Method 2)

Triethylamine (0.90 g, 8.8 mmol) was added to a solution of ethylhydrazinium oxalate (0.26 g, 4.4 mmol) in THF (8 mL). After 15 min stirring, a solution of lactone **6a** (0.63 g, 2.2 mmol) in THF (2 mL) was added. The reaction mixture was then stirred for 16 h at room temperature. After the completion of the reaction (checked by ^{19}F NMR of the crude mixture), the precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent: mixture (90:10) of petroleum ether and ethyl acetate) giving 0.41 g (yield: 57%) of pure pyridazin-3(2*H*)-one **9c** (Scheme 3, Table 1: entry 3).

3.3. Reaction of lactone 6a with hydrazine (Scheme 3, Table 1: entry 1, Method 1)

6-(Phenylsulfanylmethyl)-4-(2,2,2-trifluoroethyl)-pyridazin-3(2*H*)-one (**9a**). It was purified on silica gel, eluting with a mixture (60:40) of petroleum ether and ethyl acetate. Yield: 21%. Oil. ^{1}H NMR ($CDCl_3$, δ ppm): 3.44 (qd, $^3J_{H,F}$ = 10.5, $^4J_{H,H}$ = 1.0 Hz, 2H, CH_2CF_3), 3.99 (s, 2H, CH_2S), 7.2–7.4 (m, 5H, Ph), 7.44 (m, 1H, =CH), 11.4 (brm, 1H, NH). ^{19}F NMR ($CDCl_3$, δ ppm): −64.8 (t, $^3J_{F,H}$ = 10.5 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 32.5 (q, $^2J_{C,F}$ = 31.2 Hz, CH_2CF_3), 37.6 (s, CH_2S), 125.1 (q, $^1J_{C,F}$ = 277.0 Hz, CF_3), 127.5 (s, CH), 129.2 (s, 2 × CH Ph), 131.1 (s, 2 × CH Ph), 132.8 (s, CH), 132.9 (q, $^3J_{C,F}$ = 2.9 Hz, CCH_2CF_3), 133.2 (s, C_q Ph), 145.5 (s, C_q, C=N), 161.0 (s, C=O). IR (film, cm^{-1}): 3227, 2924, 1667, 1613. MS (ESI): m/z = 301 [M+1], 283 [M+1−H_2O]. HRMS (ESI): calcd. for $C_{13}H_{12}F_3N_2OS$ m/z 301.0622, found 301.0615.

1-(*N*-Amino)-3-(2,2,2-trifluoroethyl)-5-hydroxy-5-(phenylsulfanylmethyl)-1,5-dihydropyrrol-2-one (**10a**). It was purified by chromatography on silica gel, eluting with a mixture (60:40) of petroleum ether and ethyl acetate. Recrystallization from a mixture of pentane and ethyl acetate. Yield: 33%. Solid. m.p. 139 °C. ^{1}H NMR (CD_3COCD_3, δ ppm): 3.12 (qm, $^3J_{H,F}$ = 10.4 Hz, 1H, $CH_AH_BCF_3$), 3.19 (qm, $^3J_{H,F}$ = 10.4 Hz, 1H, $CH_AH_BCF_3$), 3.56 (m, 2H, CH_2S), 3.98 (brs, 2H, NH_2), 5.6 (brm, 1H, OH), 6.79 (s, 1H, =CH), 7.2–7.4 (m, 5H, Ph). ^{19}F NMR (CD_3COCD_3, δ ppm): −64.3 (t, $^3J_{F,H}$ = 10.4 Hz). ^{13}C NMR (CD_3OD, δ ppm): 30.5 (q, $^2J_{C,F}$ = 31.6 Hz, CH_2CF_3), 39.7 (s, CH_2S), 91.4 (s, C_q, COH), 126.7 (q, $^1J_{C,F}$ = 275.9 Hz, CF_3), 127.9 (s, CH Ph), 129.7 (q, $^3J_{C,F}$ = 2.9 Hz, CCH_2CF_3), 130.1 (s, 2 × CH Ph), 131.4 (s, 2 × CH Ph), 137.0 (s, C_q Ph), 146.3 (s, =CH), 169.4 (s, CO). IR (KBr, cm^{-1}): 3311, 2935, 1698, 1651, 1617. MS (ESI): m/z = 301 [M+1−H_2O]. HRMS (ESI): calcd. for $C_{13}H_{13}F_3N_2NaO_2S$ m/z 341.0548, found 341.0559.

3.4. Reaction of lactone 6a with methylhydrazine (Scheme 3, Table 1: entry 2, Method 1)

6-(Phenylsulfanylmethyl)-4-(2,2,2-trifluoroethyl)-2-methyl-pyridazin-3(2*H*)-one (**9b**). It was purified by chromatography on silica gel, eluting with a mixture (60:40) of petroleum ether and ethyl acetate. Yield: 61%. Oil. ^{1}H NMR ($CDCl_3$, δ ppm): 3.42 (qd, $^3J_{H,F}$ = 10.6, $^4J_{H,H}$ = 1.0 Hz, 2H, CH_2CF_3), 3.66 (s, 3H, NCH_3), 3.95 (s, 2H, CH_2S), 7.2–7.4 (m, 6H, Ph + =CH). ^{19}F NMR ($CDCl_3$, δ ppm):

−64.8 (t, $^3J_{F,H}$ = 10.6 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 32.9 (q, $^2J_{C,F}$ = 31.0 Hz, CH_2CF_3), 37.8 (s, CH_2S), 40.3 (s, NCH_3), 125.2 (q, $^1J_{C,F}$ = 277.2 Hz, CF_3), 127.0 (s, CH), 129.0 (s, 2 × CH Ph), 131.2 (s, 2 × CH Ph), 131.3 (s, CH), 132.0 (q, $^3J_{C,F}$ = 2.7 Hz, CCH_2CF_3), 133.4 (s, C_q Ph), 143.6 (s, C=N), 159.6 (s, C=O). IR (film, cm^{-1}): 3444, 2927, 1657, 1613, 1487. MS (ESI): *m/z* = 315 [M+1], 206 [M+1-SPh]. HRMS (ESI): calcd. for $C_{14}H_{14}F_3N_2OS$ *m/z* 315.0779, found 315.0781.

3.5. Reaction of lactone 6a with ethylhydrazine (Scheme 3, Table 1: entry 3, Method 2)

6-(Phenylsulfanylmethyl)-4-(2,2,2-trifluoroethyl)-2-ethylpyridazin-3(2*H*)-one (**9c**). Method 2 was used but the reaction mixture was refluxed for 60 h. The compound was purified by chromatography on silica gel, eluting with a mixture (90:10) of petroleum ether and ethyl acetate. Yield: 57%. Oil. ^{1}H NMR ($CDCl_3$, δ ppm): 1.14 (t, $^3J_{H,H}$ = 7.2 Hz, 3H, CH_3), 3.37 (q, $^3J_{H,F}$ = 10.6 Hz, 2H, CH_2CF_3), 3.90 (s, 2H, SCH_2), 4.01 (q, $^3J_{H,H}$ = 7.2 Hz, 2H, NCH_2), 7.1–7.3 (m, 6H, Ph + =CH). ^{19}F NMR ($CDCl_3$, δ ppm): −64.8 (t, $^3J_{F,H}$ = 10.6 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 13.3 (s, CH_3), 32.9 (q, $^2J_{C,F}$ = 31.1 Hz, CH_2CF_3), 37.8 (s, CH_2S), 47.1 (s, NCH_2), 125.2 (q, $^1J_{C,F}$ = 277.2 Hz, CF_3), 127.4 (s, CH), 129.0 (s, 2 × CH Ph), 131.0 (s, CH), 131.3 (s, 2 × CH Ph), 132.0 (q, $^3J_{C,F}$ = 2.6 Hz, CCH_2CF_3), 133.3 (s, C_q Ph), 143.5 (s, C_q C=N), 159.0 (s, C=O). IR (film, cm^{-1}): 2980, 2937, 1660, 1652, 1614, 1538, 1440. MS (ESI): *m/z* = 351 [M+Na], 329 [M+1]. HRMS (ESI): calcd. for $C_{15}H_{16}F_3N_2OS$ *m/z* 329.0935, found 329.0930.

3.6. Reaction of lactone 6b with hydrazine (Scheme 3, Table 1: entry 5, Method 1)

6-(Phenylsulfonylmethyl)-4-(2,2,2-trifluoroethyl)-pyridazin-3(2*H*)-one (**9d**). It was purified by chromatography on silica gel, eluting with a mixture (30:70) of petroleum ether and ethyl acetate. Yield: 22%. Solid. m.p. 264 °C. ^{1}H NMR (DMSO-d_6, δ ppm): 3.56 (q, $^3J_{H,F}$ = 10.9 Hz, 2H, CH_2CF_3), 4.72 (s, 2H, CH_2SO_2), 7.43 (s, 1H, =CH), 7.6–7.8 (m, 5H, Ph), 13.3 (brs, 1H, NH). ^{19}F NMR (DMSO-d_6, δ ppm): −62.9 (t, $^3J_{F,H}$ = 10.9 Hz). ^{13}C NMR (DMSO-d_6, δ ppm): 31.9 (q, $^2J_{C,F}$ = 29.9 Hz, CH_2CF_3), 59.7 (s, CH_2SO_2), 125.8 (q, $^1J_{C,F}$ = 277.0 Hz, CF_3), 128.0 (s, 2 × CH Ph), 129.4 (s, 2 × CH Ph), 131.8 (q, $^3J_{C,F}$ = 2.9 Hz, CCH_2CF_3), 134.6 (s, 2C, CH Ph + CH=), 137.2 (s, C_q), 138.1 (s, C_q), 160.3 (s, C=O). IR (KBr, cm^{-1}): 3222, 2994, 2904, 1667, 1610, 1416, 1366. MS (ESI): *m/z* = 333 [M+1]. HRMS (ESI): calcd. for $C_{13}H_{12}F_3N_2O_3S$ *m/z* 333.0521, found 333.0525.

6-(Phenylsulfonylmethyl)-4-(2,2,2-trifluoroethyl)-6-hydroxy-1,6-dihydropyridazin-3(2*H*)-one (**11a**). The compound **11a** was characterized in the crude mixture but it decomposed partly during silica gel chromatography. Selected ^{1}H NMR data (DMSO-d_6, δ ppm): 3.96 (m, 2H, CH_2CF_3), 4.05 (m, 1H, $CH_AH_BSO_2$), 4.13 (m, 1H, $CH_AH_BSO_2$), 6.99 (s, 1H, =CH), 7.7–8.1 (m, 5H, Ph). ^{19}F NMR (DMSO-d_6, δ ppm): −63.1 (t, $^3J_{F,H}$ = 11.1 Hz). Selected ^{13}C NMR data (DMSO-d_6, δ ppm): 32.7 (q, $^2J_{C,F}$ = 28.6 Hz, CH_2CF_3), 59.3 (s, CH_2SO_2), 87.2 (s, C_q, COH), 126.9 (s, 2 × CH Ph), 127.6 (s, CH Ph), 129.4 (s, 2 × CH Ph), 133.6 (s, CH=), 134.2 (s, C_q Ph), 171.0 (s, C=O). IR (KBr, cm^{-1}): 1667, 1610. MS (ESI): *m/z* = 445 [M+THF+Na], 423 [M+THF+1].

3.7. Reaction of lactone 6b with methylhydrazine (Scheme 3, Table 1: entry 6, Method 1)

6-(Phenylsulfonylmethyl)-4-(2,2,2-trifluoroethyl)-2-methyl-pyridazin-3(2*H*)-one (**9e**). It was purified by chromatography on silica gel, eluting with a mixture (40:60) of petroleum ether and ethyl acetate. Yield: 58%. Solid. m.p. 146 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 3.46 (q, $^3J_{H,F}$ = 10.5 Hz, 2H, CH_2CF_3), 3.60 (s, 3H, NCH_3), 4.30 (s, 2H, CH_2SO_2), 7.38 (s, 1H, =CH), 7.53 (m, 2H Ph), 7.67 (m, 1H Ph), 7.75 (dm, $^3J_{H,H}$ = 8.3 Hz, 2H Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −64.8 (t, $^3J_{F,H}$ = 10.5 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 33.0 (q, $^2J_{C,F}$ = 31.2 Hz, CH_2CF_3), 40.6 (s, NCH_3), 60.9 (s, CH_2SO_2), 125.0 (q, $^1J_{C,F}$ = 277.3 Hz, CF_3), 128.4 (s, 2 × CH Ph), 129.3 (s, 2 × CH Ph), 131.9 (q, $^3J_{C,F}$ = 2.7 Hz, CCH_2CF_3), 132.4 (q, $^4J_{C,F}$ = 1.5 Hz, CH=), 134.3 (s, CH Ph), 135.6 (s, C_q), 137.5 (s, C_q), 159.5 (s, C=O). IR (KBr, cm^{-1}): 2974, 2928, 1656, 1611, 1537, 1446. MS (ESI): *m/z* = 347 [M+1], 315. HRMS (ESI): calcd. for $C_{14}H_{14}F_3N_2O_3S$ *m/z* 347.0677, found 347.0668.

3.8. Reaction of lactone 6b with ethylhydrazine (Scheme 3, Table 1: entry 7, Method 2)

6-(Phenylsulfonylmethyl)-4-(2,2,2-trifluoroethyl)-2-ethyl-pyridazin-3(2*H*)-one (**9f**). It was purified by chromatography on silica gel, eluting with a mixture (50:50) of petroleum ether and ethyl acetate and recristallization from pentane/CH_2Cl_2. Yield: 66%. Solid. m.p. 133 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 1.08 (t, $^3J_{H,H}$ = 7.2 Hz, 3H, CH_3), 3.47 (q, $^3J_{H,F}$ = 10.5 Hz, 2H, CH_2CF_3), 3.99 (q, $^3J_{H,H}$ = 7.2 Hz, 2H, NCH_2), 4.32 (s, 2H, CH_2SO_2), 7.42 (s, 1H, =CH), 7.53 (dd, $^3J_{H,H}$ = 7.4, $^3J_{H,H}$ = 7.2 Hz, 2H, Ph), 7.66 (tm, $^3J_{H,H}$ = 7.4 Hz, 1H, Ph), 7.73 (dm, $^3J_{H,H}$ = 7.2 Hz, 2H, Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −64.8 (t, $^3J_{F,H}$ = 10.5 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 13.1 (s, CH_3), 33.0 (q, $^2J_{C,F}$ = 31.3 Hz, CH_2CF_3), 47.4 (s, NCH_2), 60.9 (s, CH_2SO_2), 125.1 (q, $^1J_{C,F}$ = 277.4 Hz, CF_3), 128.4 (s, 2 × CH Ph), 129.3 (s, 2 × CH Ph), 132.1 (m, =CH + CCH_2CF_3), 134.2 (s, CH Ph), 135.7 (s, C_q), 137.3 (s, C_q), 159.0 (s, C=O). IR (KBr, cm^{-1}): 2989, 2928, 1670, 1613, 1584, 1529, 1449. MS (ESI): *m/z* = 383 [M+Na], 361 [M+1]. HRMS (ESI): calcd. for $C_{15}H_{16}F_3N_2O_3S$ *m/z* 361.0834, found 361.0837.

1-(*N*-Ethylamino)-3-(2,2,2-trifluoroethyl)-5-hydroxy-5-(phenylsulfonylmethyl)-1,5-dihydro-pyrrol-2-one (**10b**). Yield: 7%. This compound was partly purified by chromatography on silica gel, eluting with a mixture (50:50) of petroleum ether and ethyl acetate giving a mixture (90:10) of pyridazinone **9f** and γ-lactam **10b**. Selected ^{1}H NMR data ($CDCl_3$, δ ppm): 3.0–3.2 (m, 4H, $NHCH_2$ + CH_2CF_3), 7.10 (s, 1H, =CH), 7.91 (dm, $^3J_{H,H}$ = 7.2 Hz, 2H, Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −65.1 (t, $^3J_{F,H}$ = 10.5 Hz). Selected ^{13}C NMR data ($CDCl_3$, δ ppm): 13.3 (s, CH_3), 30.3 (q, $^2J_{C,F}$ = 31.3 Hz, CH_2CF_3), 46.1 (s, $NHCH_2$), 60.0 (s, CH_2SO_2), 86.7 (s, C_q, COH), 127.9 (s, 2 × CH Ph), 129.3 (s, 2 × CH Ph), 139.7 (s, C_q Ph), 143.2 (s, =CH), 167.2 (s, C=O).

3.9. Reaction of lactone 6b with phenylhydrazine (Scheme 3, Table 1: entry 8, Method 1)

1-(*N*-Phenylamino)-3-(2,2,2-trifluoroethyl)-5-hydroxy-5-(phenylsulfonylmethyl)-1,5-dihydro-pyrrol-2-one (**10c**). It was purified by chromatography on silica gel, eluting with a mixture (60:40) of petroleum ether and ethyl acetate. Recrystallization from a mixture of pentane and ethyl acetate. Yield: 51%. Solid. m.p. 172 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 3.17 (qm, $^3J_{H,F}$ = 10.4 Hz, 2H, CH_2CF_3), 3.55 (d, $^2J_{H,H}$ = 14.2 Hz, 1H, $CH_AH_BSO_2$), 3.88 (d, $^2J_{H,H}$ = 14.2 Hz, 1H, $CH_AH_BSO_2$), 4.05 (brs, 1H, OH or NH), 5.95 (brs, 1H, NH or OH), 6.86 (dm, $^3J_{H,H}$ = 7.8 Hz, 2H Ph), 6.93 (t, $^3J_{H,H}$ = 7.4 Hz, 1H Ph), 7.2–7.3 (m, 3H, 2H Ph + =CH), 7.61 (dd, $^3J_{H,H}$ = 7.8, $^3J_{H,H}$ = 7.3 Hz, 2H Ph), 7.72 (t, $^3J_{H,H}$ = 7.4 Hz, 1H Ph), 7.92 (d, $^3J_{H,H}$ = 7.4 Hz, 2H Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −65.1 (t, $^3J_{F,H}$ = 10.4 Hz). ^{13}C NMR (CD_3COCD_3, δ ppm): 30.2 (q, $^2J_{C,F}$ = 31.3 Hz, CH_2CF_3), 60.6 (s, CH_2SO_2), 87.6 (s, C_q, COH), 114.3 (s, CH Ph), 121.0 (s, CH Ph), 126.8 (q, $^1J_{C,F}$ = 275.9 Hz, CF_3), 129.0 (s, 2 × CH Ph), 129.5 (s, 2 × CH Ph), 130.0 (s, 2 × CH Ph), 134.6 (s, 2 × CH Ph), 141.7 (s, C_q Ph), 145.3 (s, =CH), 149.0 (s, C_q Ph), 167.6 (s, CO). IR (KBr, cm^{-1}): 3320, 1690, 1656, 1499. MS (ESI): *m/z* = 449 [M+Na], 427 [M+1], 409 [M+1−H_2O]. HRMS (ESI): calcd. for $C_{19}H_{17}F_3N_2NaO_4S$ *m/z* 449.0759, found 449.0760.

3.10. Reaction of lactone 6b with p-tolylhydrazine (Scheme 3, Table 1: entry 9, Method 2)

1-(*N*-(*p*-Tolyl)amino)-3-(2,2,2-trifluoroethyl)-5-hydroxy-5-(phenylsulfonylmethyl)-1,5-dihydropyrrol-2-one (**10d**). It was purified by chromatography on silica gel, eluting with a mixture (20:80) of petroleum ether and ethyl acetate. Lactam **10d** was accompanied by lactam **12** (~10%). Yield: 26%. Oil. ^{1}H NMR ($CDCl_3$, δ ppm): 2.23 (s, 3H, CH_3), 3.09 (q, $^3J_{H,F}$ = 10.0 Hz, 2H, CH_2CF_3), 3.54 (d, $^2J_{H,H}$ = 14.3 Hz, 1H, $CH_AH_BSO_2$), 3.86 (d, $^2J_{H,H}$ = 14.3 Hz, 1H, $CH_AH_BSO_2$), 4.37 (brs, 1H, OH or NH), 5.98 (brs, 1H, NH or OH), 6.72 (d, $^3J_{H,H}$ = 8.0 Hz, 2H tolyl), 6.98 (d, $^3J_{H,H}$ = 8.0 Hz, 2H tolyl), 7.30 (s, 1H, =CH), 7.5–7.6 (m, 2H Ph), 7.6–7.7 (m, 1H Ph), 7.88 (d, $^3J_{H,H}$ = 7.9 Hz, 2H Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −65.0 (t, $^3J_{F,H}$ = 10.0 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 20.5 (s, CH_3), 30.0 (q, $^2J_{C,F}$ = 32.0 Hz, CH_2CF_3), 59.7 (s, CH_2SO_2), 86.9 (s, C_q, COH), 124.9 (q, $^1J_{C,F}$ = 275.3 Hz, CF_3), 114.0 (s, 2 × CH Ar), 128.0 (s, 2 × CH Ar), 128.6 (q, $^3J_{C,F}$ = 3.3 Hz, CCH_2CF_3), 129.5 (s, 2 × CH Ar), 129.7 (s, 2 × CH Ar), 131.2 (s, C_q Ar), 134.4 (s, CH Ph), 139.4 (s, C_q Ar), 143.7 (s, =CH), 144.0 (s, C_q Ar), 167.5 (s, CO). IR (film, cm^{-1}): 3430, 2925, 2854, 1779, 1652, 1449. MS (ESI): *m*/*z* = 423 [M+1−H_2O]. HRMS (ESI): calcd. for $C_{20}H_{18}F_3N_2O_3S$ (M+1−H_2O) *m*/*z* 423.0990, found 423.0986.

3-(2,2,2-Trifluoroethyl)-5-hydroxy-5-(phenylsulfonylmethyl)-1,5-dihydropyrrol-2-one (**12**) (Fig. 1). The compound **12** was obtained in small amounts (~10%) in the reaction of **6b** and *p*-tolylhydrazine. In order to confirm its structure, **12** was unambiguously prepared (0.24 g, yield: 71%) from lactone **6b** (1.0 mmol) and NH_4OH (1.2 mmol, 1.2 equiv.) in THF (4 mL) at room temperature for 16 h, according to a previously reported procedure [18]. The compound **12** was purified by chromatography on silica gel, eluting with a mixture (20:80) of petroleum ether and ethyl acetate. Recrystallization from a mixture of pentane and ethyl acetate. Solid. m.p. 171 °C. ^{1}H NMR (CD_3COCD_3, δ ppm): 2.90 (brs, 1H, OH or NH), 3.18 (q, $^3J_{H,F}$ = 11.1 Hz, 2H, CH_2CF_3), 3.84 (d, $^2J_{H,H}$ = 14.8 Hz, 1H, $CH_AH_BSO_2$), 3.90 (d, $^2J_{H,H}$ = 14.8 Hz, 1H, $CH_AH_BSO_2$), 5.66 (brs, 1H, OH or NH), 7.16 (m, 1H, CH=), 7.63 (dd, $^3J_{H,H}$ = 7.8, $^3J_{H,H}$ = 7.5 Hz, 2H Ph), 7.71 (m, 1H, Ph), 7.96 (dm, $^3J_{H,H}$ = 7.1 Hz, 2H Ph). ^{19}F NMR (CD_3COCD_3, δ ppm): −64.4 (t, $^3J_{F,H}$ = 11.1 Hz). ^{13}C NMR (CD_3COCD_3, δ ppm): 29.6 (q, $^2J_{C,F}$ = 31.3 Hz, CH_2CF_3), 62.7 (s, CH_2SO_2), 85.4 (s, C_q, COH), 126.6 (q, $^1J_{C,F}$ = 275.9 Hz, CF_3), 129.1 (s, 2 × CH Ph), 129.3 (q, $^3J_{C,F}$ = 3.3 Hz, CCH_2CF_3), 129.8 (s, 2 × CH Ph), 134.4 (s, CH Ph), 142.2 (s, C_q Ph), 147.1 (s, =CH), 169.8 (s, CO). IR (KBr, cm^{-1}): 3450, 3093, 2994, 2944, 1722, 1450. MS (ESI^-): *m*/*z* = 334 [M−1], 316 [M−1−H_2O]. HRMS (ESI^+): calcd. for $C_{13}H_{12}F_3NNaO_4S$ *m*/*z* 358.0337, found 358.0339.

3.11. Reaction of lactone 6b with N,N-dimethylhydrazine (Scheme 4, Method 1)

1-(*N*,*N*-Dimethylamino)-3-(2,2,2-trifluoroethyl)-5-hydroxy-5-(phenylsulfonylmethyl)-1,5-dihydropyrrol-2-one (**10e**). It was purified by chromatography on silica gel eluting with a mixture (40:60) of petroleum ether and ethyl acetate. Yield: 64%. m.p. 132 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 2.82 (s, 6H, NMe_2), 3.04 (qd, $^3J_{H,F}$ = 10.6, $^4J_{H,H}$ = 1.5 Hz, 2H, CH_2CF_3), 3.27 (d, $^2J_{H,H}$ = 14.1 Hz, 1H, $CH_AH_BSO_2$), 4.00 (d, $^2J_{H,H}$ = 14.1 Hz, 1H, $CH_AH_BSO_2$), 4.3 (brs, 1H, OH), 7.09 (m, 1H, CH=), 7.59 (tm, $^3J_{H,H}$ = 7.5 Hz, 2H Ph), 7.70 (tm, $^3J_{H,H}$ = 7.5 Hz, 1H Ph), 7.94 (dm, $^3J_{H,H}$ = 7.1 Hz, 2H Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −65.1 (t, $^3J_{F,H}$ = 10.6 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 29.5 (q, $^2J_{C,F}$ = 32.0 Hz, CH_2CF_3), 45.2 (s, NMe_2), 60.1 (s, CH_2SO_2), 86.6 (s, C_q, COH), 125.0 (q, $^1J_{C,F}$ = 276.6 Hz, CF_3), 128.0 (s, 2 × CH Ph), 129.2 (q, $^3J_{C,F}$ = 2.9 Hz, CCH_2CF_3), 129.4 (s, 2 × CH Ph), 134.3 (s, CH Ph), 139.6 (s, C_q Ph), 142.2 (s, CH=), 165.9 (s, CO). IR (KBr, cm^{-1}): 3402, 2935, 1710, 1652, 1586. MS (ESI): *m*/*z* = 379 [M+1], 361 [M+1−H_2O]. HRMS (ESI): calcd. for $C_{15}H_{18}F_3N_2O_4S$ *m*/*z* 379.0939, found 379.0934.

3.12. Reaction of lactone 6b with N,N′-dimethylhydrazine (Scheme 6, Method 2)

Reaction of **6b** (0.22 mmol) with *N*,*N*′-dimethylhydrazine dihydrochloride (2 equiv.) in the presence of triethylamine (4 equiv.) gave the intermediate **11b** which was slowly and spontaneously dehydrated into a mixture (~50:50) of compounds **19** and **20**.

6-(Phenylsulfonylmethyl)-4-(2,2,2-trifluoroethyl)-6-hydroxy-1,2-dimethyl-1,6-dihydro-pyridazin-3-one (**11b**). This compound was characterized in the crude mixture. Oil. ^{1}H NMR ($CDCl_3$, δ ppm): 2.54 (s, 3H, NMe), 2.76 (s, 3H, NMe), 3.32 (q, $^3J_{H,F}$ = 10.4 Hz, 2H, CH_2CF_3), 3.37 (d, $^2J_{H,H}$ = 14.4 Hz, 1H, $CH_AH_BSO_2$), 3.77 (d, $^2J_{H,H}$ = 14.4 Hz, 1H, $CH_AH_BSO_2$), 6.26 (s, 1H, =CH), 7.59 (ddm, $^3J_{H,H}$ = 7.5 Hz, $^3J_{H,H}$ = 7.5 Hz, 2H Ph), 7.69 (tm, $^3J_{H,H}$ = 7.4 Hz, 1H Ph), 7.92 (dm, $^3J_{H,H}$ = 8.1 Hz, 2H Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −65.7 (t, $^3J_{F,H}$ = 10.4 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 32.5 (q, $^2J_{C,F}$ = 30.9 Hz, CH_2CF_3), 32.8 (s, NMe), 33.8 (s, NMe), 58.0 (s, CH_2SO_2), 84.7 (s, C_q, COH), 125.1 (q, $^1J_{C,F}$ = 275.0 Hz, CF_3), 125.8 (s, CH Ph), 128.0 (s, 2 × CH Ph), 129.3 (s, 2 × CH Ph), CCH_2CF_3 not visible, 134.2 (s, CH=), 140.6 (s, C_q Ph), 161.3 (s, CO). MS (ESI): *m*/*z* = 401 [M+Na], 379 [M+1], 361 [M+1−H_2O].

The mixture (~50:50) of **19** and **20** was purified by chromatography on silica gel eluting with ethyl acetate. It was not possible to separate them. Yield: 47%. Oil. IR (film, cm^{-1}): 2923, 2853, 1732, 1633, 1532, 1463. MS (ESI): *m*/*z* = 383 [M+Na], 361 [M+1]. HRMS (ESI): calcd. for $C_{15}H_{16}F_3N_2O_3S$ *m*/*z* 361.0834, found 361.0842.

6-(Phenylsulfonylmethylidene)-4-(2,2,2-trifluoroethyl)-1,2-dimethyl-1,6-dihydropyridazin-3-one (**19**) (selected data). ^{1}H NMR ($CDCl_3$, δ ppm): 3.33 (s, 3H, NMe), 3.40 (q, $^3J_{H,F}$ = 10.5 Hz, 2H, CH_2CF_3), 3.47 (s, 3H, CON*Me*), 5.14 (s, 1H, $CHSO_2$), 7.0–7.4 (m, 5H, Ph), 8.38 (s, 1H, =CH). ^{19}F NMR ($CDCl_3$, δ ppm): −65.0 (t, $^3J_{F,H}$ = 10.5 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 33.2 (q, $^2J_{C,F}$ = 30.9 Hz, CH_2CF_3), 34.6 (s, NMe), 41.0 (s, CON*Me*), 95.6 (s, $CHSO_2$), 129.8 (s, CH=), 145.6 (s, C_q, =C–N), 157.6 (s, CO).

6-(Phenylsulfonylmethyl)-4-(2,2,2-trifluoroethylidene)-1,2-dimethyl-1,4-dihydropyridazin-3-one (**20**) (selected data). ^{1}H NMR ($CDCl_3$, δ ppm): 3.06 (s, 3H, NMe), 3.28 (s, 3H, CON*Me*), 4.05 (s, 2H, CH_2SO_2), 5.83 (s, 1H, =CH), 6.08 (q, $^3J_{H,F}$ = 9.4 Hz, 1H, $CHCF_3$), 7.0–7.4 (m, 5H, Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −58.3 (d, $^3J_{F,H}$ = 9.4 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 34.2 (s, NMe), 40.4 (s, CONMe), 59.2 (s, CH_2SO_2), 107.6 (s, CH=), 109.6 (m, $CHCF_3$) 137.6 (s, C_q, =C–N), 158.7 (s, CO).

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