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Selective Synthesis using ETFBO: A New Strategy for the Preparation of Hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one.

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Dedicated to Prof. Gustavo A. Argüello on the occasion of his 70th Anniversary

In this work, we report the regiospecific and stereoselective synthesis of novel pyrrolo thioxoimidazolidinones with promising biological activities due to the inherent pharmaceutical properties of thioxoimidazolidinone core. The reaction of different thioxoimidazolidinones with *trans*-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (ETFBO) yields bicyclic 1,3-diaza heterocycles bearing the trifluoromethyl (CF_3) moiety. Our investigation involved both depth experimental analysis and theoretical calculations to fathom out the mode of reaction of this building block and elucidate the underlying mechanism operating for the observed reactions. Remarkably, this unusual mechanism retained the ethanol moiety from the building block in the final products, deviating from conventional nucleophilic reactions reported in the literature.

Introduction

The synthesis of fluorinated compounds constitutes a field of research in medicinal chemistry in view of their applications in the pharmaceutical industry,[1,2] however, their synthesis in many cases is still challenging.[3] The most common fluorinated moieties introduced in an organic compound are the *gem*-difluor and trifluoromethyl groups.[4,5] Several organic compounds bearing these moieties are described in the literature and are linked to specific applications in chemical biology and catalysis.[6]

The introduction of a trifluoromethyl group modulates the physicochemical properties of molecules, which can improve their lipophilicity and stability.[7] Furthermore, the increasing use of fluorinated compounds in life science products constitutes a driving force in the development of regio- and stereoselective routes for the introduction of trifluoromethyl groups into aliphatic, as well as aromatic systems.[8] There are several mechanisms that facilitate the incorporation of a fluorinated group into an organic molecule and the best choice depends on the starting material. One of these possibilities is the use of a building block bearing the fluorinated moiety, which is fully incorporated in the synthesis and thus, increases the atom economy of the process.[9] For example, the *trans* 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (ETFBO, **1**), was first described by Gambaryan *et al*[10] in the 20th century, and it has been extensively used for the synthesis of several fluorinated organic compounds. Its utility results from the multiple functionalities of ETFBO, since it has a trifluoroacetyl α,β-unsaturated moiety together with an ethoxy substituted vinyl group. The latter can act as a dienophile in cycloaddition reactions with, for example, pyridinium N-ylides, C-arylnitrones and nitrile oxides to give indolizines, isoxazolidines and isoxazoles respectively.[11] In addition, the attack of different nucleophiles on the β-position of ETFBO has been extensively implemented due to the high electropositive character of this carbon. Different nucleophiles can be found in the literature, such as amines, alcohols, hydrazines, Grignard reagents, phosphines, etc., as it will be discussed in the next paragraphs. In most of the analyzed cases, the nucleophilic attack results in the elimination of the ethoxy group through an addition-elimination mechanism. Likewise, this position is susceptible to react with activated heterocycles in the presence of a catalyst through electrophilic aromatic substitution (EAS).[12]

In Figure 1, we illustrate notable examples of heterocyclic synthesis procedures in which ETFBO is employed. For instance, it has been used with vinyl amines (**2**) and hydrazides (**4**) to get pyridines (**3**)[13] and pyrazoles (**5**)[14] respectively. Furthermore, in our previous works, we found that the fluorinated building block **1** could be combined with thiazole **6**, yielding a fused bicyclic derivative **7** by means of an initial addition-elimination followed by intramolecular cyclization.[15] All of the reactions exemplified herein and some others[16–22] present a similar mechanism: at some stage of the reaction, ethanol is a leaving group. Few exceptions can be mentioned, for instance, when the reaction goes through a Diels-Alder mechanism where ETFBO participates as an electron-deficient diene to form six-membered heterocycles.[23] In contrast to the typical behavior well described in literature, in this work, the retention of the ethoxy group was observed when 2-thioxoimidazolidin-4-ones **8** was the nucleophilic substrate.

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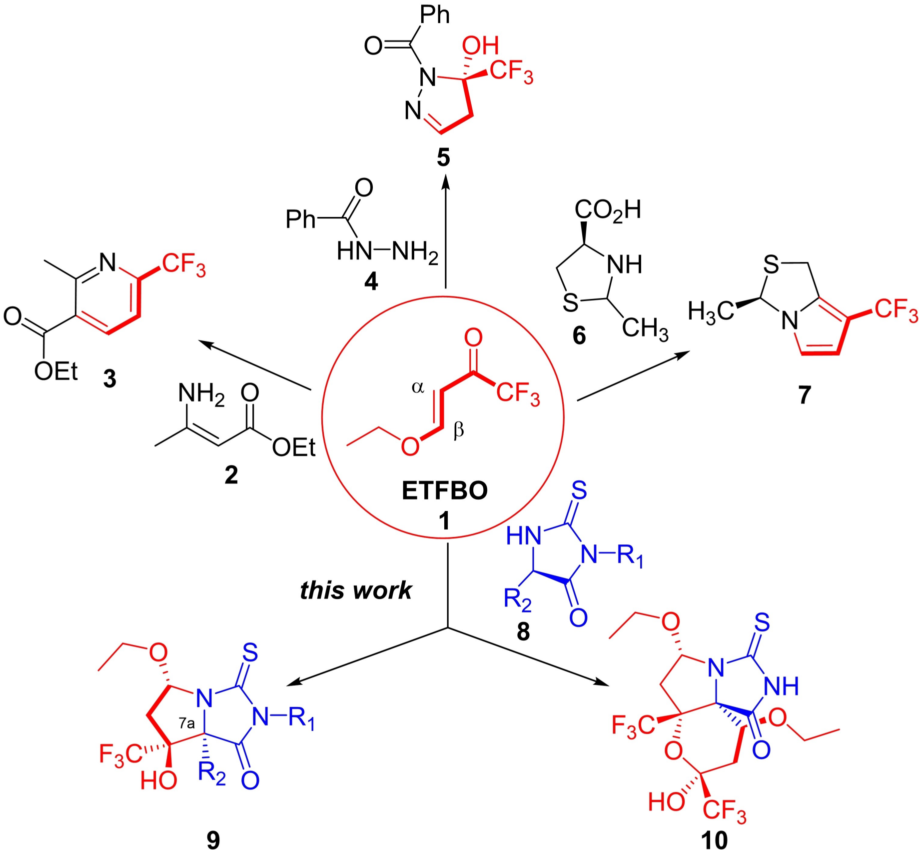


Figure 1. ETFBO as a building block in the synthesis with diverse reactants.

Results and Discussion

Despite the high reactivity of ETFBO as a building block, its reaction with heterocyclic nucleophiles (**8 a**–**c**) was highly regiospecific. This report covers a new synthetic route towards the preparation of novel conformationally constrained trifluoromethylated pyrrolo thioxoimidazolidinones (**9** and **10**).

First, the synthesis of ETFBO was straightforward, resulting in in high yield (98%), and just contained a few modifications from the literature procedure.[24] We previously demonstrated that the acylation reaction of vinyl ethyl ether exclusively afforded the *E* isomer of ETFBO.[16] In turn, while 2-thioxoimidazolidin-4-one (**8 a**) is commercially available, 5-benzyl-2-thioxoimidazolidin-4-one (**8 b**) and the 3-phenyl-analogue (**8 c**) were prepared from *L*-phenylalanine and thiourea or phenyl isothiocyanate, respectively; according to previous methodologies developed in our laboratory.[25] In such prior investigations, we performed the synthesis of several 1,3-diaza heterocycles studying their thermal and photochemical reactivity.[26,27] Recently, we have been focusing on these structures due to the fact that the imidazolidine core is attributed to many biological activities being a matter of interest in medicinal chemistry.[28–30] Accordingly, we reported the antioxidant properties and microbiological activities of a family of benzylidene imidazolidines.[31,32]

The reactions between ETFBO and the 2-thioxoimidazolidin-4-ones (**8 a**–**c**) were performed through MAOS (Microwave-Assisted Organic Synthesis). Initially, both reagents were mixed with triethylamine (TEA) that was added as a base. That is, the reactions were carried out in the absence of any solvent since the quantities of TEA and ETFBO, both liquids, provided a satisfactory medium to carry out the reaction. Although other bases such as pyridine, 2-methylpyridine or $NaHCO_3$ were used to produce the deprotonation of the 2-thiooxyimidazolidin-4-ones, none of them led to the formation of **9** and **10**.

Interestingly, apart from the bicyclic **9 a**, an intricate tricyclic compound **10** was identified. The structural analysis of **9 a** and **10** was very challenging due to the presence of several chiral centers. Consequently, single-crystal X-ray diffraction (SC-XRD) was a milestone for the unequivocal structure elucidation. The crystallographic structures for both compounds are illustrated in Figure 2, where it can be appreciated that each unit cell presents two enantiomeric structures. This finding is in agreement with the polarimetry studies ($\alpha_D^{25} = 0$, *c* 1.1, ACN), which undoubtedly reveal the racemic mixtures for both compounds.

From the crystallographic analysis, structural differences can be observed between the chiral centers of C7 in the bicyclic **9 a** and C6a in the tricyclic **10**; as this position plays a relevant role in the reaction mechanism, its configuration is discussed in more detail. Moreover, the relative position of the ethoxy in C5 and trifluoromethyl group is inverted when comparing compounds **9 a** and **10**, in other words, these moieties are on the same side for **9 a** (5*R*, 7*R* or 5*S*, 7*S*), while they are opposite for

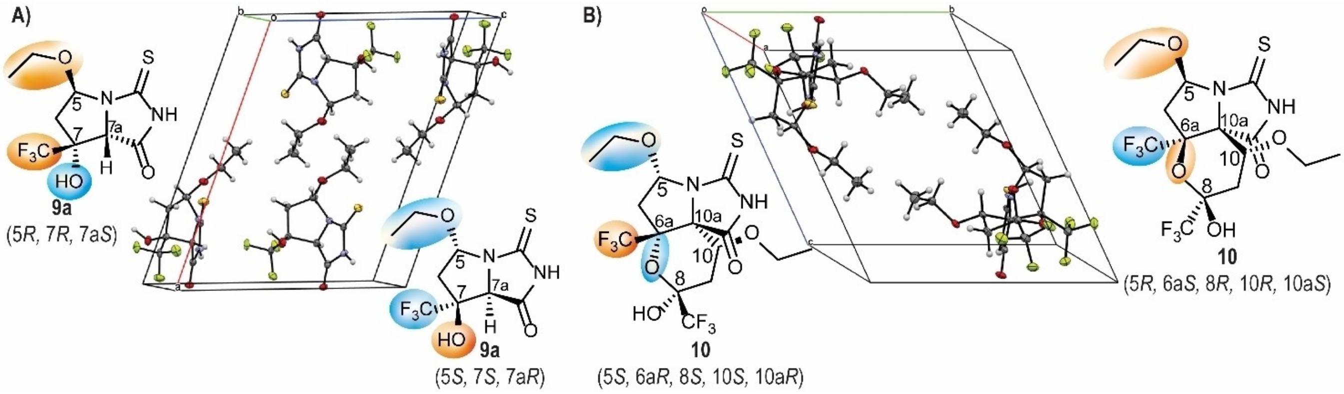
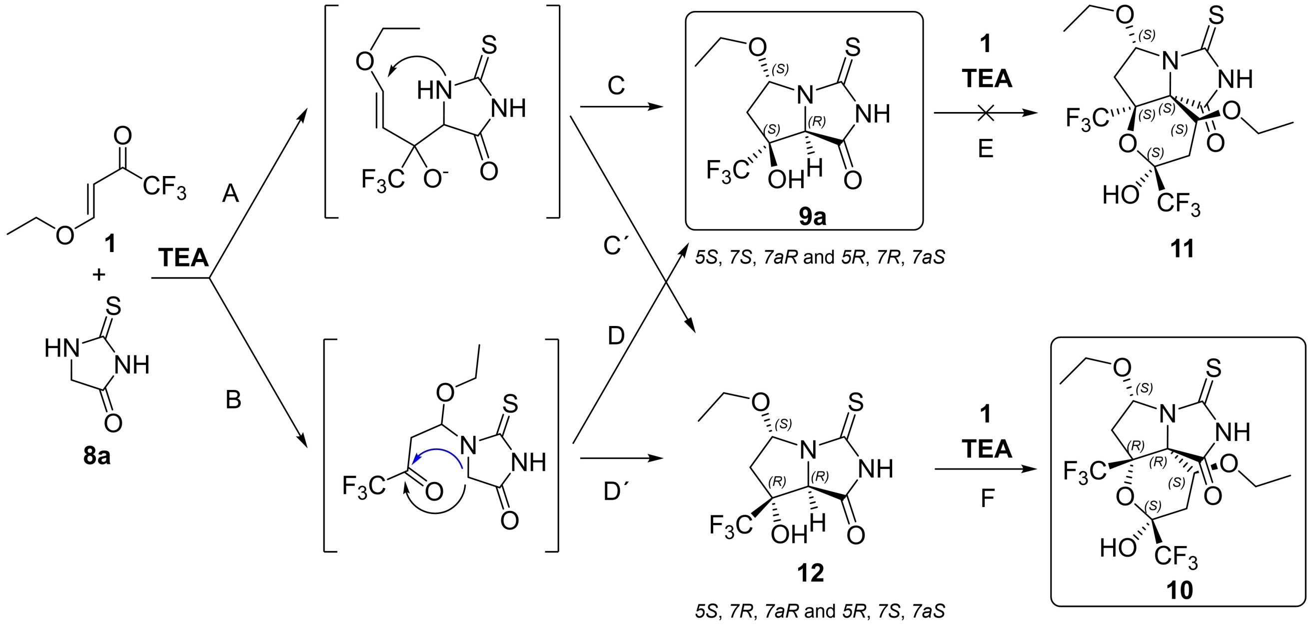


Figure 2. Crystallographic structures of the true racemates for compounds A) **9a** and B) **10**. Deposition Numbers 2038635-1572325 (**9a**, **10**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

10 (5*R*, 6a*S* or 5*S*, 6a*R*). This finding allows us to interpret that **9a** and **10** do not share a common path.

The literature describes that due to the high reactivity of ETFBO, there is no need to add a base to perform the reaction synthesis.[33,34] Contrary to expectations, we did not observe the product formation without TEA. The TEA assists in the deprotonation of the 2-thioxoimidazolidinone (**8a**), so the addition of a base is crucial in this synthetic procedure. Thus, the formation of **9a** would occur either through the attack of the C5-anion of **8a** to the C=O group in ETFBO (*via* A, Scheme 1) or by means of the Michael addition of the NH of **8a** (*via* B, Scheme 1) to the ETFBO β-position. Considering that none of the intermediates was detected in the reaction crudes, both routes are equally possible as they could give rise to either bicyclic pyrrolo-imidazolidinones **9a** and **12** (see C, C', D, D' in Scheme 1). At this point, it is reasonable to propose that **9a** or **12** can react with a second ETFBO molecule to form the respective tricycles **11** and **10** (routes E and F, Scheme 1).

The mechanism proposed so far seems to be weakened by the fact that both compounds **11** and **12** were not detected under the careful analysis of the reaction crudes through GC-MS and HPLC. Therefore, to get more conclusive information about the mechanism that is actually operating here, other experiments were performed. First, carefully purified **9a** was mixed with ETFBO in TEA and after MW irradiation (90 °C, 15 min), neither **11** nor **10** was obtained. This fact would allow us to confirm that compound **10** does not arise from **9a**. Subsequently, compounds **8a** and ETFBO were mixed in TEA and different reactions were performed varying the molar ratio of the reagents but keeping the presence of base constant (Table 1, entries 2–5). In all reactions, a mixture of **9a** and **10**



Scheme 1. Proposed mechanism for the formation of bicyclic **9a** and tricyclic **10** products from **8a** and ETFBO.

Table 1. Synthetic conditions and yields of compounds **9 a** and **10**.[a]

Entry	Molar Equivalent			**9 a** (%)[b]	**10** (%)[b]
	8 a	ETFBO	TEA		
1	1.0	2.0	-	0	0
2	1.0	0.5	0.55	29	2
3	1.0	1.1	0.55	48	7
4	1.0	2.0	0.55	52	14
5	1.0	4.0	0.55	41	7

[a] Conditions: MW, 80 °C, 15 min. [b] yields determined by HPLC.

was obtained, even when the molar equivalent of ETFBO was one-half of the **8 a** moles (Table 1, entry 2).

Polymerization and hydrolysis of ETFBO have been reported previously,[35,36] and these processes are competitive pathways in our synthesis. It is established that the increase in reaction rates is uneven for both the formation of products and the polymerization, that is, there is a higher increase of the polymerization rate with the increase of the molar ratio. Moreover, as seen through the yields shown in Table 1, the rate of product formation is relatively low when the ratio of **8 a**:**1** is 1:0.5 (Table 1, entry 2) and steadily increases until the ratio reaches a value of 1:2 (Table 1, entry 4). Through these reactions, it was observed that the yield of the desired product decreased in the presence of a large excess of ETFBO (Table 1, entry 5). This fact can be rationalized by performing a kinetic analysis of the competitive reactions that ETFBO may undergo.

In order to tune the yield of the bicyclic **9 a**, a series of experiments were performed by maintaining the ratio of **8 a**:ETFBO:TEA at 1:2:0.55, and varying the temperatures and times of the microwave conditions, as shown in Table 2. From this screening, the best condition for the synthesis of **9 a** is at 80 °C and 20 min (Table 2, entry 2), where the highest yield reached was 68%. Neither higher temperatures nor longer irradiation times improved the amounts of recovered products (Table 2, entries 2–9). We also tried a two-step reaction, in which, in the first step, a mixture of ETFBO and TEA was heated under microwave irradiation (90 °C, 15 min), and for the second step, **8 a** was added, and the reaction mixture was heated (90 °C, 15 min). As a result, none of the products were formed.

Table 2. Microwave conditions and yields in the synthesis of **9 a** and **10**.[a]

Entry	Temp. (°C)	Time (min)	**9 a** (%)[b]	**10** (%)[b]
1	80	15	52	14
2	80	20	68	19
3	80	25	34	14
4	90	15	56	41
5	90	20	30	16
6	90	25	44	19
7	100	15	43	21
8	100	20	41	22
9	100	25	49	18

[a] molar ratio **8 a**:ETFBO (1:2). [b] yields determined by HPLC.

Regardless of all of the conditions explored and the fact that it was not possible to elude the competitive reaction that drives the formation of the tricyclic compound **10**, a new series of experiments were performed with the aim to shed light on the operating mechanism. For this, the ratio of the reagents **8 a** and ETFBO was set to 1:2 and the amount of TEA added was incremented from 0.55 until 3.00 (Table 3). As it can be seen, when the amount of base is increased, entries 1–3, the amount of tricyclic product **10** raises, indicating that the base actively participates in the formation of this intricate product. Whereas, when the amount of base is only 0.55 equivalents, the reaction proceeds more selectively towards the formation of the bicyclic **9 a**.

Addressing all these outstanding issues, we propose that the key intermediate in this mechanism must be highly reactive and unstable, which is formed *in situ* and susceptible to polymerization reactions. The compound that matches with these characteristics is presented in Scheme 2 as compound **13**, which was proposed by Vdovenko *et al.*[37] They established that ETFBO **1** (5×10^{-5} M) reacts easily with triethylamine ($k_{obs}=3.70\times10^{-2}\,\mathrm{L\,mol^{-1}s^{-1}}$) in aprotic solvents and alcohols, giving the appropriate enamino ketone (**15**) through the formation of the zwitterion **13**, followed by a subsequent de-ethylation. Despite this, we propose that in our reactions, where the reactants are highly concentrated due to the absence of solvent, a new reactive intermediate (**14**) could be formed, by self-reaction which could give the formation of both reaction products (**9 a** and **10**), Scheme 2.

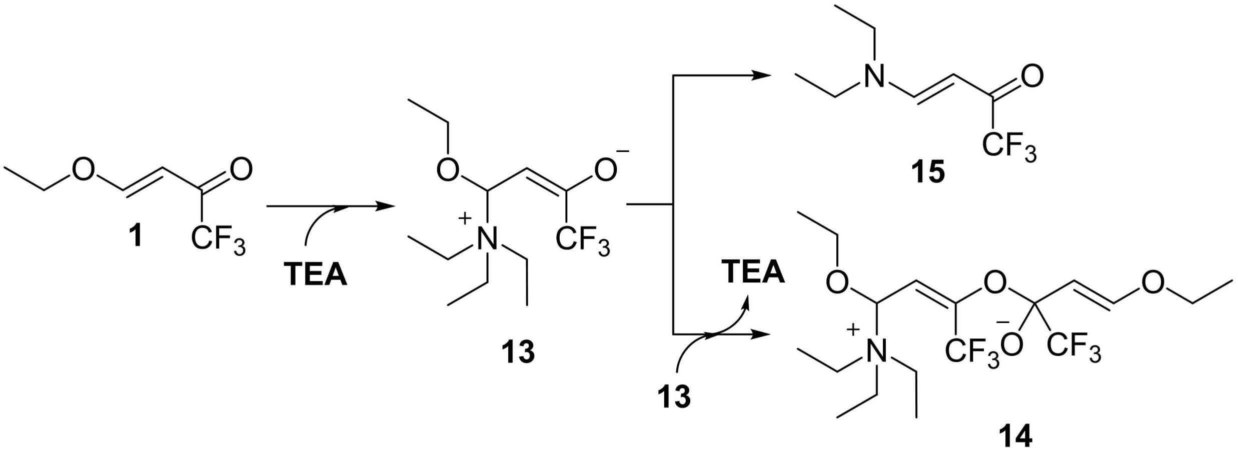
The proposal of this intermediate is supported by the following facts: regardless of the amount of initial ETFBO **1**, it is not possible to completely eliminate the formation of **10**. The presence of TEA is absolutely necessary, and the increase of it results in an increase in the amount of **10**. -no diastereomers of **9 a** and **10** were detected.

With this in mind, Scheme 3 presents a probable reaction mechanism that takes into consideration all of these experimental findings. The unassuming way of reaction would be through paths A–B–C–D/E, where the Vdovenko intermediate (**13**) initially reacts with **8 a** to generate **16**, which in turn would have an intramolecular cyclization to afford **17** and then easily achieve the main products of the reaction. However, this sequence of reactions fail due to both diastereomers (**9 a** and

Table 3. Molar ratio of TEA tested and yields obtained for compounds **9 a** and **10**.[a]

Entry	Molar Equivalent			**9 a** (%)[b]	**10** (%)[b]
	8 a	ETFBO	TEA		
1	1.0	2.0	0.55	68	19
2	1.0	2.0	1.0	48	39
3	1.0	2.0	2.0	41	45
4	1.0	2.0	3.0	45	42

[a] Conditions: MW, 80 °C, 15 min. [b] yields determined by HPLC.



Scheme 2. Highly reactive intermediates proposed by Vdovenko *et al*[37] (**13**) and here in this work (**14**).

12) should be obtained straightforwardly, nevertheless diastereomer **12** was not detected as it was stated above.

On the other hand, paths A–F–G–H seem to be the most in agreement with the experimental results, since the proposed intermediate **18**, is capable of giving rise to the two products of the reaction. For this, we postulate that the anionic species of **18**, readily formed in the presence of TEA (at **C7a** and alpha at the carbonyl group), reacts intramolecularly by attacking the electron-deficient carbon of the vinyl ether moiety to generate the tricyclic product **10** or fragments by cleavage of the hemiacetal C–O bond to generate the bicycle **9a**. At this point, the intermediary **18** is crucial, since according to the relative stereochemistry of the chiral centers (*) formed in the cyclization of **19**, one or another of the products can be formed. If the stereochemistry of **C5** and **C7** is the same in both centers (both *R* or *S*), the intermediate **18** does not undergo the cyclization reaction, and under these reaction conditions it is unstable and fragments generating **9a**. Whereas if the stereocenters are different (*R/S* or *S/R*), the cyclization reaction does occur and **10** is obtained, as it is observed experimentally.

The experimental results obtained until here encourage us to evaluate, on the first stage, the relative population of the hypothetical mixture of diastereomers of **9a**/**12** and **10**/**11**. Thus, theoretical calculations with Gaussian09 program, using B3LYP and CAM–B3LYP functional methods (in combination with the 6–311+G(d,p) basis set), were performed.[38,39] The theoretical results, presented in Table 4, were performed according to the Boltzmann distribution in the gas phase and solution (TEA and acetone), respectively. These denote an unbalanced preference for one diastereoisomer, in agreement with the crystallographic data where a pure racemate of **9a** and **10** is observed, and compounds **11** and **12** are undetected. We can deduce that the steric and the electronic effects play an important role during the cyclization reaction from either intermediary **16** or **19**.

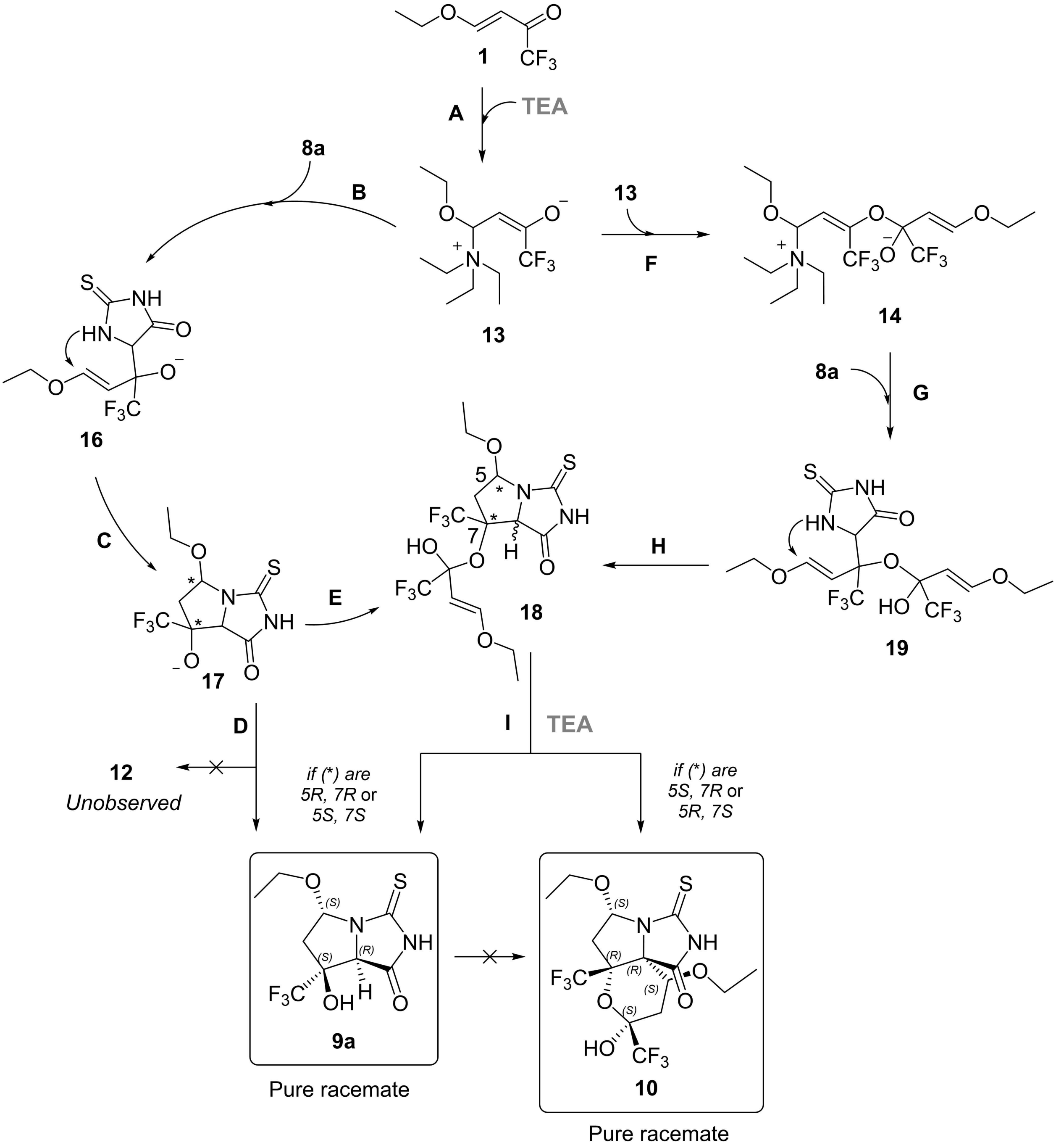
Continuing with quantum chemical calculations at the level of DFT theory (B3LYP/6-311+G(d,p)), we decided to explore the energetic requirements that led the key intermediate **18** to undergo cyclization or cleavage reactions to generate the experimentally detected products (compounds **10** and **9a**, respectively) and to explain why diastereomers **12** and **11** are not observed as reaction products. The gas-phase calculation results obtained using this approach are summarized in Scheme 4 and the reaction coordinates are shown in Figure 3.

Through conformational analysis, it was found that both diastereomers of **18** and their anions are stabilized by an intramolecular hydrogen bond formation (structures **20**(H–O=C) and **21**(H–OEt),) and depending on steric and electronic factors, a predilection towards cyclization is observed, Scheme 4. It was found that conformer **22** that bends its structure in an attempt to bring the nucleophilic site closer to the vinylic position for cyclization, gives rise a destabilizing distortion, requiring 60.7 kJ mol^{-1} more than the same process for its diastereomeric counterpart **24**, Scheme 4 paths A–B and

Table 4. Computational results of relative population of **9a**/**12** and **10**/**11**.[a,b]

Compound	Gas Phase[c]		TEA[d]		Acetone[e]	
	△E kJ mol^{-1}	%	△E kJ mol^{-1}	%	△E kJ mol^{-1}	%
9a	0.00	90.7	0.00	85.5	0.00	80.5
12	5.22	9.3	3.98	14.5	3.09	19.5
10	0.00	100.0	0.00	100.0	0.00	100.0
11	41.91	0.00	39.36	0.00	37.63	0.00

[a] For more details, see supporting information. [b] B3LYP and CAM–B3LYP functional methods[38,39] in combination with the 6–311+G(d,p) basis set. [c] Gas: $\varepsilon = 1.0000$, [d]TEA: $\varepsilon = 2.3832$, [e]Acetone: $\varepsilon = 20.7$ (Due to the NMR analysis).

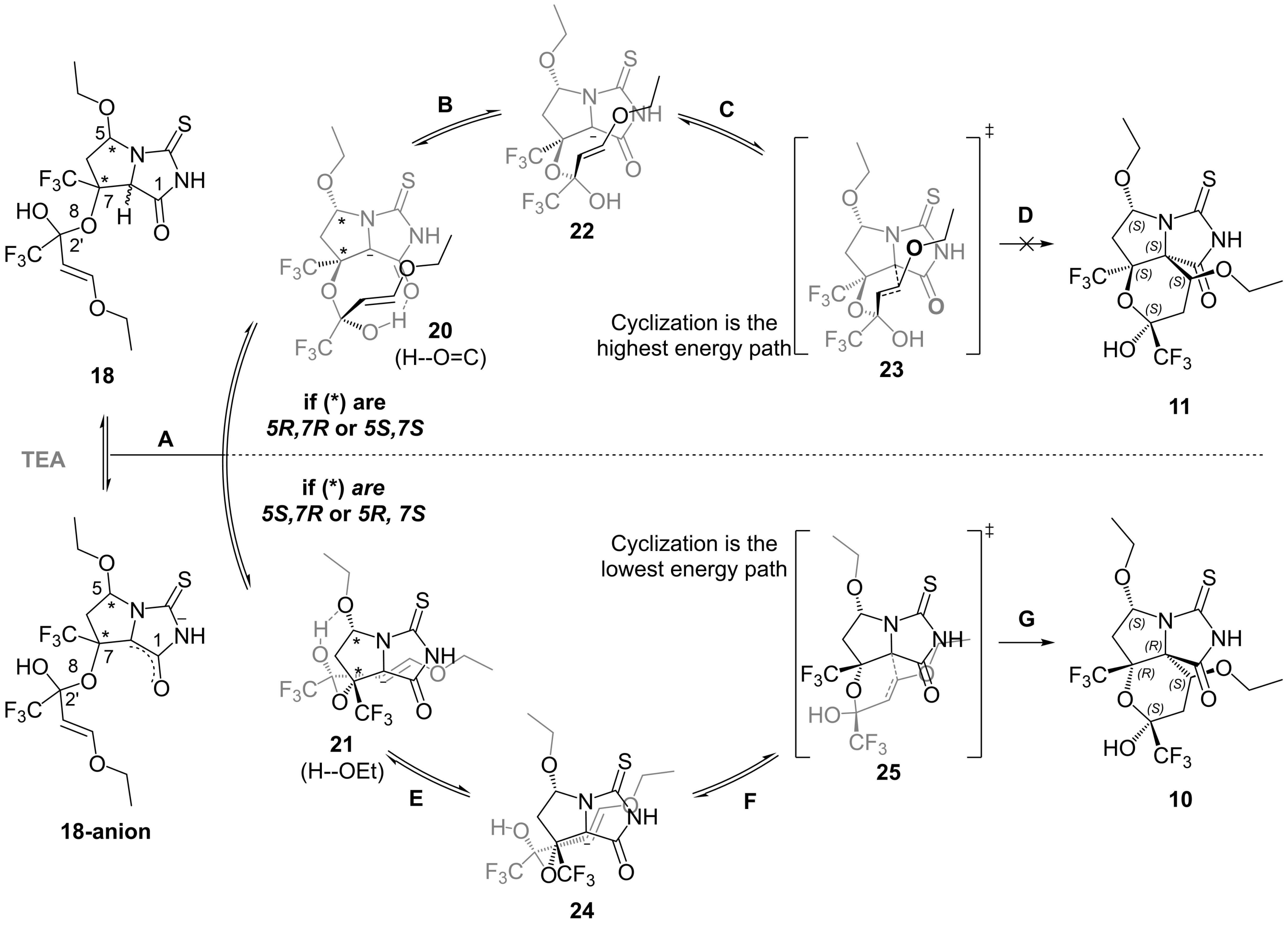


Scheme 3. Proposed reaction mechanisms for the synthesis of **9a** and **10** considering the possible reaction intermediates.

A–E, respectively. In turn, **22** additionally demands 62.6 kJ mol^{-1} more to afford the undetected compound **11** through the whole cyclization process, Scheme 4 paths A–B–C–D.

Nevertheless, the **21**(H–OEt) species, through the less stabilized intermediary **24**, performs the cyclization process over an entire potential energy surface (PES) of lower energy, requiring 48.3 kJ mol^{-1} less than its counterpart to successfully achieve the cyclization process to yield **10**, which is the detected product, Scheme 4 paths A–E–F–G.

On the other hand, calculations also explain how the detected compound **9a** is afforded by the hydrogen bond stabilized structure **20**(H–O=C) and subsequent cleavage of the O8–C2' bond, Figure 3 grey dashed line. Therefore, the energy required for the fragmentation process from **20**(H–O=C) is 86.7 kJ mol^{-1} less than the fragmentation process from **21**(H–OEt) for generating the hypothetical structure **12**. To sum up, all these theoretical results are conclusive and clearly explain why only **9a** and **10** are the products detected in these reactions.



Scheme 4. Mutually exclusive and independent pathways that can be followed by **18** towards the formation of **10**. Reaction mechanism paths calculated at DFT (B3LYP/6-311+G(d,p)) theory level.

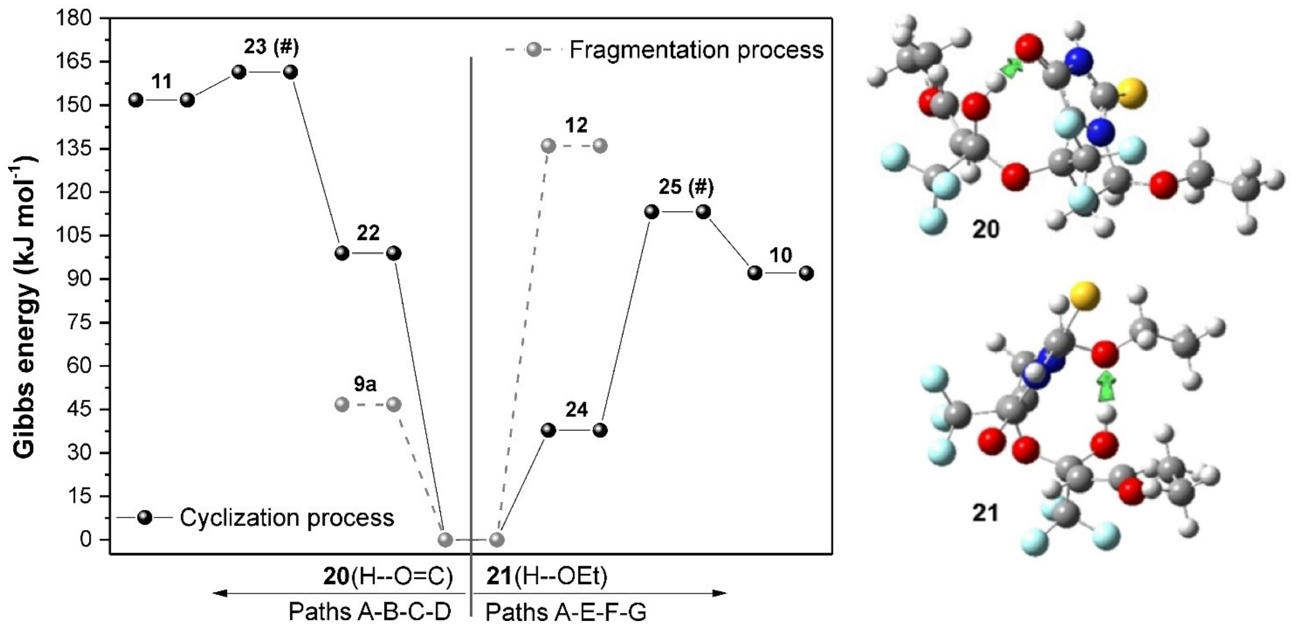


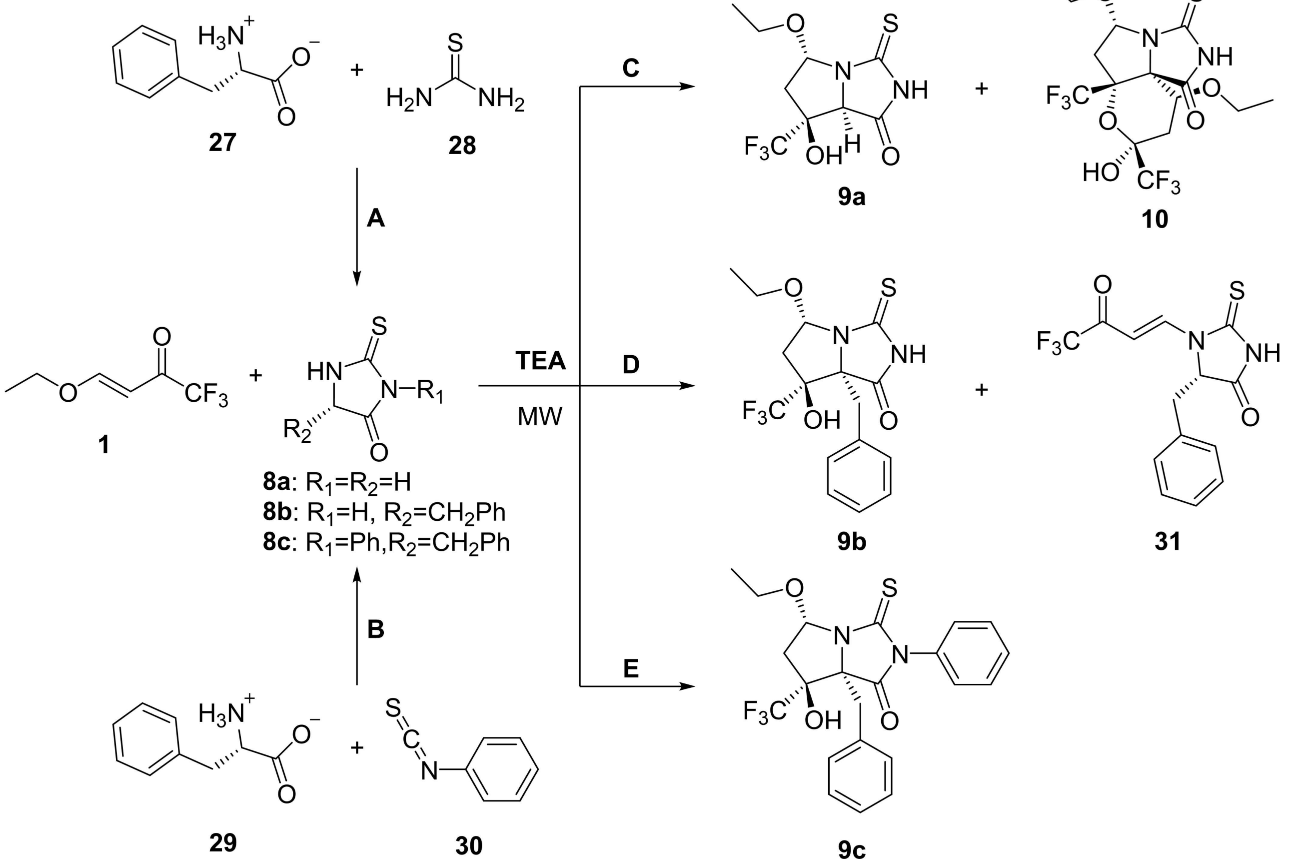
Figure 3. Reaction coordinates of the different reaction paths of Scheme 4 for any of the hydrogen bond stabilized structures (**20** or **21**) at DFT (B3LYP/6-311+G(d,p)) level.

As described above, the formation of compound **10** would occur by removal of the acidic hydrogen of **C7a** in the intermediate **18**. As a consequence, the replacement of that hydrogen by a suitable substituent would allow to obtain exclusively derivatives of **9**. This fact was corroborated by preparing and employing 5-benzyl-2-thioxoimidazolidin-4-one derivatives (**8 b**–**c**) as starting material where a total absence of tricyclic derivatives was observed, Scheme 5. It is important to note that, as previously reported, 5-benzyl analogs can be dehydrogenated to yield a benzylidene analog **26**,[25] the ratio of ETFBO, temperature and time employed in this new set of reactions was adjusted to avoid the formation of this byproduct. Particularly, 5-benzyl-2-thioxoimidazolidin-4-ones (**8 b**) gave two products: the bicyclic compound **9 b** and another derivative with a trifluoro-oxobuten moiety **31**. Thus, the former was obtained with an acceptable yield (41%), and the latter was formed at 21% of yield. Compound **31** is structurally comparable to those described in the literature obtained through an addition-elimination mechanism at the β-position of ETFBO **1** of primary or secondary amines with subsequent elimination of ethanol,[37] generated in this case due to steric factors produced by the bulky benzyl fragment at C5 position.

Closely related to **9 b**, the compound **9 c** was generated as the main product from 5-benzyl-3-phenyl-2-thioxoimidazolidin-4-ones (**8 c**). In this case, a higher temperature (100 °C) was needed for the substrate conversion in good yield (72%), Scheme 3. The assignment of the stereochemical centers was made by comparison with the structure of **9 a** through the similarities of the ^{1}D and ^{2}D NMR spectra and whose absolute configuration was determined by SC-XRD. It is important to note that compounds **9 a**–**c** are obtained by the mechanism proposed in Scheme 3, since under the reaction conditions employed and through the intermediate **14**, the products obtained have retention of the ethanol moiety. Here again, theoretical results presented in Table 5, were performed on the relative population of the hypothetical mixture of **C7a** diastereomers (**9 a**–**c** and **9 a'**–**c'**) in the gas phase and solution (TEA and acetone), respectively. These denote an unbalanced preference for the diastereoisomer presented in the Scheme 5, confirming that steric and the electronic effects play an important role during the cyclization reaction.

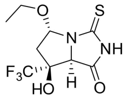
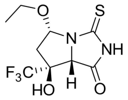
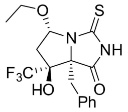
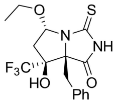
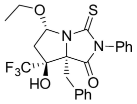
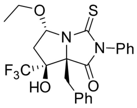
Conclusions

From a simple building block, ETFBO **1**, and 2-thioxoimidazolidinone **8 a**, we were able to prepare trifluoromethylated bicycles which allowed us to gain fundamental knowledge regarding the reactivity of 1,3-heterocycles. The synthetic route described in these studies is an efficient process due to its high atom



Scheme 5. Obtention of trifluoromethylated pyrrolo thioxoimidazolidinones **9 b**–**c**. The yields were determined by GC-MS. **a**: MW, 190 °C, 15 min; **b**: reflux, water:acetone (1 : 1), 2.5 h; **c**: MW, 80 °C, 20 min; **d**: MW, 80 °C, 20 min; **e**: MW, 100 °C, 15 min.

Table 5. Population in gas and solution phase of compounds **9 a–c** and their **C7a** diastereomers **9 a'–c'**.[a,b]

Compound	Gas Phase[c]		TEA[d]		Acetone[e]	
	ΔE kJ mol^{-1}	%	ΔE kJ mol^{-1}	%	ΔE kJ mol^{-1}	%
 **9a**	00.00	99.9996	00.00	99.9995	00.00	99.9992
 **9a'**	30.37	00.0004	29.66	00.0005	28.58	00.0008
 **9b**	00.00	99.9998	00.00	99.9994	00.00	99.9992
 **9b'**	32.77	00.0002	29.97	00.0006	28.58	00.0008
 **9c**	00.00	99.9999	00.00	99.9997	00.00	99.9992
 **9c'**	34.18	00.0001	31.47	00.0003	28.58	00.0008

[a] For more details, see supporting information. [b] B3LYP and CAM–B3LYP functional methods[38,39] in combination with the 6–311 + G(d,p) basis set. [c] Gas: ε = 1.0000, [d] TEA: ε = 2.3832, [e] Acetone: ε = 20.7 (Due to the NMR analysis).

economy with unusual mechanism involving conservation of the ethoxy moiety. Moreover, through tailoring the reaction conditions we were able to get the aliphatic heterocycle **9 a** in good yield. Besides the experimental evidence, we employed theoretical calculations which shed light on why it is not possible to avoid the formation of the intricate compound **10**. For the best of our knowledge, and through an exhaustive search over derivatives with the hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one core, the derivatives presented in this work have not yet been described. In a recent publication, only some trifluoromethylated imidazolidine derivatives are described but employing a different building block.[40] Moreover, there are no subsequent publications describing preparation of trifluoromethyl derivatives on the imidazolidinone ring.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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