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1-Methyl-5-(trifluoromethyl)azafulvenium Methide, an Intermediate That Undergoes Reaction through "Unusual" *cis-exo*-1,3- and *trans-exo*-1,7-Cycloadditions

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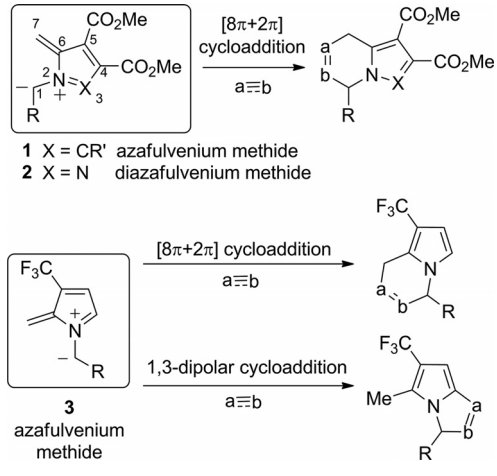
The generation and reactivity of a new 1-methyl-5-(trifluoromethyl)azafulvenium methide are described. Under microwave-induced pyrolysis conditions this intermediate could be trapped by dipolarophiles, acting either as a 4π or as an 8π dipole. Quantum chemical calculations carried out at the DFT level of theory allowed the rationalization of the results observed in the cycloaddition of 1-methyl-5-(trifluoromethyl)azafulvenium methide and *N*-substituted maleimides. The study revealed that for 1,7-cycloadducts the major products are obtained in the *trans* configuration through the unusual *exo*-cycloaddition mode, whereas for 1,3-cycloadducts the *cis* counterparts are obtained from this unexpected approach. In addition, under flash vacuum pyrolysis or conventional thermolysis conditions 1-methyl-5-(trifluoromethyl)azafulvenium methide undergoes an allowed suprafacial sigmatropic [1,8]H shift leading to the formation of 2-methyl-3-(trifluoromethyl)-1-vinyl-1*H*-pyrrole.

1. Introduction

Fluorinated compounds play an important role in medicinal chemistry because fluorine substitution in organic molecules often leads to improved metabolic stability, bioavailability, and protein–ligand interactions.[1] Furthermore, the polar and steric characteristics of fluorine have a remarkable effect upon physical and chemical properties such as acidity, lipophilicity, and polarity. Moreover, the influence of a CF_3 group on the physiological activity is usually associated with the increasing lipophilicity, leading to improvement of in vivo transport characteristics. The high electronegativity of the CF_3 group results in a quite different electron density distribution and significantly changes the reactivity of a molecule.

There are only a few examples of trifluoromethyl-containing pyrroles,[2] but some of these compounds have demonstrated important insecticidal action and mitochondrial uncoupling activity.[3] In addition to the participation of fluorinated groups, our interests also include the study of new versatile building blocks for particular syntheses, and in that context we have previously demonstrated that azafulvenium methides **1** and **3** and diazafulvenium methides **2** are good candidates for the synthesis of functionalized pyrroles and pyrazoles (Scheme 1).[4–7] These extended dipolar systems can, in principle, participate in cycloadditions either as 4π 1,3-dipoles or as 8π 1,7-dipoles. 5-Trifluoromethyl-azafulvenium methide derivatives **3** indeed participate in cycloaddition reactions as 1,3-dipoles and/or 1,7-dipoles, leading to new trifluoromethylpyrrole-annulated systems.[6]



Scheme 1. Cycloaddition of aza- and diazafulvenium methides.

Azafulvenium methide **3a**, generated from 2,2-dioxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **4a** by thermal extrusion of sulfur dioxide, showed high *site* selectivity in its reactions with strongly electron-deficient dipolarophiles such as *N*-

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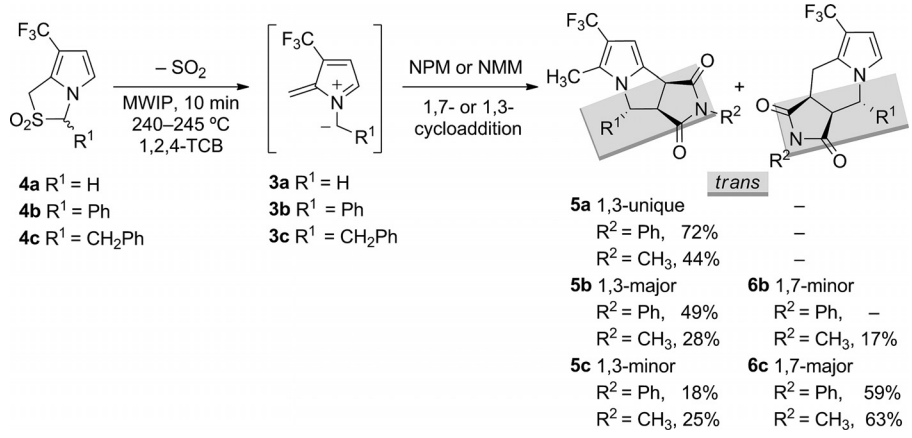


Scheme 2. Cycloaddition of azafulvenium methides **3** with *N*-substituted maleimides.[6]

methylmaleimide (NMM) and *N*-phenylmaleimide (NPM), leading exclusively to 1,3-cycloadducts **5a** (Scheme 2). However, use of 1-substituted azafulvenium methides **3b** and **3c** led to the competitive formation of both 1,3- and 1,7-cycloadducts. Azafulvenium methides bearing a phenyl group at C1 afford 1,3-cycloadducts as the major or only cycloaddition products, whereas 1-benzylazafulvenium methide **3c** leads to the preferential synthesis of 1,7-cycloadducts. These facts were explained by considering a combination of electronic and steric factors in a frontier molecular orbital (FMO) analysis.[6]

A thorough analysis of the products formed made another outstanding feature clear. Irrespective of the maleimide used, all the products formed, for R^1 other than H, exclusively had the *trans* configuration, which could be naturally expected as a consequence of the bulky character of the substituents but necessarily leads to the acceptance as standard of a type of reaction that has been extensively treated in advanced textbooks but barely described in experimental works.

For the particular case of the azafulvenium **3a**, bearing two identical H atoms on C^1, it is not possible to be sure either of any preferential orientation in the cyclization or of the stereoisomery. Therefore, we synthesized a particular azafulvenium compound that would allow the formation of both *cis* and *trans* structures, because of less constrained steric impediments, as well as both *endo* and *exo* cyclizations, as a result of the interplay between energy-stabilizing factors.

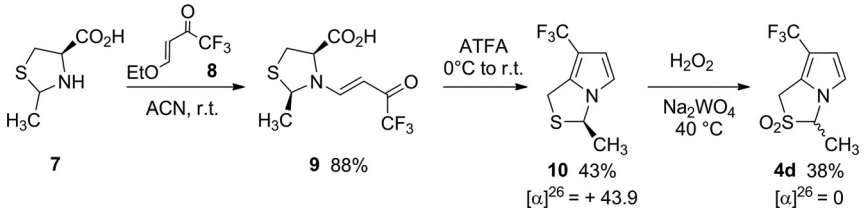
2. Results and Discussion

Synthesis of the 2,2-Dioxo-7-(trifluoromethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole

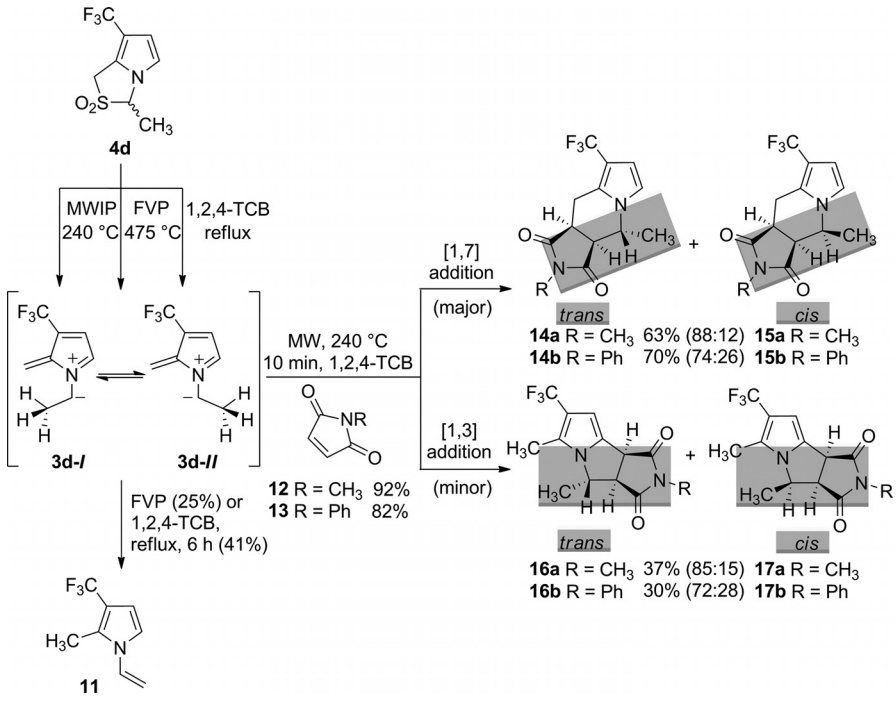
2,2-Dioxo-7-(trifluoromethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (**4d**), the precursor of the new 1-methyl-5-(trifluoromethyl)azafulvenium methide (**3d**), was prepared by a known general methodology (Scheme 3). The reaction between thiazolidine **7** and 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**8**) was diastereoselective, giving the expected 1-butenyl-thiazolidine **9** in 88% yield. Two rotamers were observed in the ^{1}H NMR and ^{13}C NMR spectra of this heterocycle recorded at ambient temperature, as previously observed for other 1-butenyl-thiazolidine derivatives.[5] Cyclization of thiazolidine **9** in the presence of trifluoroacetic anhydride gave 7-(trifluoromethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]-thiazole (**10**) in good yield as single enantiomer ($[\alpha]_D$ = +43.9). The stereochemistry of **10** was assigned by comparison with the structure of (*R*)-3-phenyl-7-(trifluoromethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole ($[\alpha]_D$ = +159), prepared by a similar synthetic methodology and possessing an absolute configuration that was determined by X-ray crystallography.[5a] Catalytic oxidation of thiazolidine **10** afforded sulfone **4d**, isolated as a racemic mixture, in good yield.

Generation and Reactivity of the 1-Methyl-5-(trifluoromethyl)azafulvenium Methide

2,2-Dioxo-7-(trifluoromethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **4d** was subjected to flash vacuum pyrolysis (FVP),



Scheme 3. Synthesis of 7-(trifluoromethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole 2,2-dioxide (**4d**).



Scheme 4. Reactivity of 5-(trifluoromethyl)azafulvenium methide **3d** genearated by FVP, MWIP, and conventional heating.

microwave induced pyrolysis (MWIP), and conventional heating to carry out the extrusion of sulfur dioxide, leading to the target azafulvenium methide **3d** (Scheme 4).

FVP or conventional thermolysis of **4d** in the absence of dipolarophiles led to the formation of *N*-vinylpyrrole **11** through an allowed suprafacial sigmatropic [1,8]H shift in the 8π 1,7-dipolar system of the azafulvenium methide **3d**, generated in situ (Scheme 4). Although azafulvenium methide **3d** exists in equilibrium as at least two conformers, only conformer **3d-*I*** bears hydrogen in the appropriate position to undergo the pericyclic reaction.

Under MWIP conditions, the azafulvenium methide **3d** was also generated, and it reacted with *N*-methylmaleimide (NMM, **12**) and *N*-phenylmaleimide (NPM, **13**) to give 1,7- and 1,3-cycloadducts. Notably, both 1,7-cycloadducts **14** and **15** and 1,3-cycloadducts **16** and **17** were obtained as mixtures of their *cis* and *trans* forms.

The structural assignment of cycloadducts **14**–**17** was based on one- (^{1}H, ^{13}C, ^{19}F) and two-dimensional HMQC, HMBC, and NOESY NMR spectra.

In particular, structural assignment of compounds **14** and **15** was supported by NOESY spectra. Relatively high-intensity cross-peaks between H-4 and H-9b and connectivity between the methyl group (at C-10) and H-3a were found; this is in agreement with the estimated distances between hydrogen atoms (Figure 1), thus establishing that compounds **14** have the *trans* configuration. On the other hand, no cross-peaks between H-4 and H-9b could be observed for the *cis* counterparts **15**.

The structures of compounds **16** and **17** were established mainly on the basis of the ^{1}H NMR spectra and the estimated dihedral angles between H-4 and H-3a (Figure 2). In fact, scalar coupling between these protons could not be

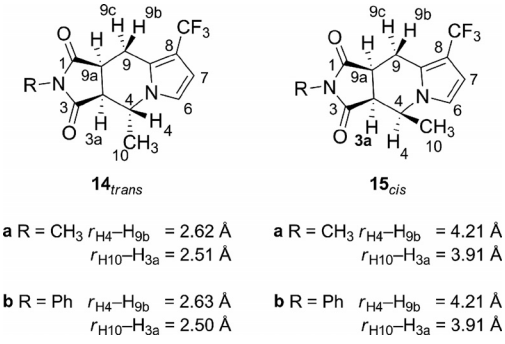


Figure 1. Estimated distances between hydrogen atoms in 8-(trifluoromethyl)-3a,4,9,9a-tetrahydro-1*H*-pyrrolo[3,4-*f*]indolizine-1,3(2*H*)-diones **14** and **15**.

detected for the major product, thus allowing us to establish that the azafulvenium **3d** reacts through 1,3-cycloaddition with *N*-phenyl- and *N*-methylmaleimide to afford mainly the *trans* stereoisomers **16**. Furthermore, in the ^{1}H NMR

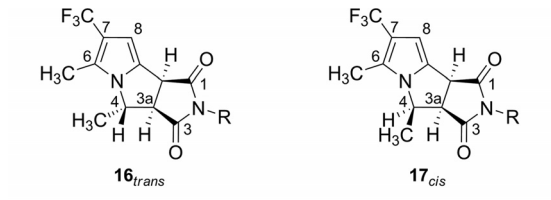


Figure 2. Estimated dihedral angles for 7-(trifluoromethyl)-3a,4-dihydropyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,8b*H*)-diones **16** and **17**.

spectra of the minor compounds, the coupling between H-4 and H-3a could be observed, thus allowing us to establish the *cis* configuration.

Theoretical Study

Quantum chemical calculations, carried out at the DFT level of theory (B3LYP functional), have been carried out in order to investigate the structure and preferred conformers of 1-methyl-5-(trifluoromethyl)azafulvenium methide **3d** in the gas phase (Figure 3). Full geometry optimizations were performed, followed by harmonic frequency calculations, at the same level of theory, which also allowed characterization of the nature of the stationary points. The geometrical counterpoise and dispersion corrections (gCP-D3) of Grimme et al. were added to all structures.[8a–8d] As described recently for the 1-benzyl-5-(trifluoromethyl)azafulvenium methide **3c**,[6b] **3d** can also exist in two different conformations, with conformer **3d-*II*** being slightly more stable than **3d-*I***, which has the methyl group pointing inward (15.9 kJ mol^{-1}).

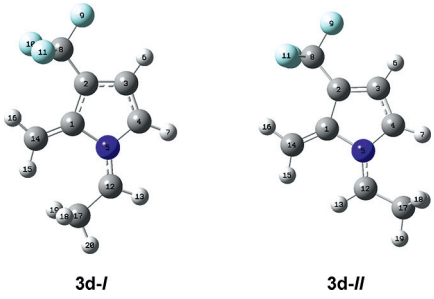


Figure 3. Optimized geometries of the two relevant conformers of 1-methyl-azafulvenium methide **3d** at the B3LyP[6-31+G(d,p)] level of theory.

We have previously reported that the $HOMO_{dipole}$–$LUMO_{dipolarophile}$ interaction is the dominant interaction in the cycloaddition reactions of trifluoromethyl azafulvenium methides **3a** and **3c** with strongly electron-deficient dipolarophiles such as DMAD and NPM.[6] The FMO analysis of the cycloaddition reactions of **3d**, summarized in Table 1, was also carried out. It was observed that the values of the HOMO and LUMO energies of azafulvenium methide **3a** are lower than those obtained for **3c** and **3d**, but with the $HOMO_{dipole}$–$LUMO_{dipolarophile}$ interaction still the dominant one.

In order to allow rationalization of the formation of *cis* and *trans* cycloadducts **14**–**17** from the cycloadditions between **3d** and N-substituted maleimides, quantum chemical calculations were carried out at the DFT level of theory (see the Supporting Information). The B3LYP functional, selected for this task, has been shown to be an effective method for modeling dipolar cycloadditions.[7,9] In this theoretical study, transition states resulting from the following reactions were considered: (i) *exo*-1,7-cycloaddition, (ii) *endo*-1,7-cycloaddition, (iii) *exo*-1,3-cycloaddition, and (iv) *endo*-1,3-cycloaddition. The activation energies corresponding to these transitions states and the synchronicities associated with the formation of the products are reported in Table 2.

Calculations showed that processes occur in a concerted manner but slightly asynchronously, with 1,3-cycloadditions being more polarized than 1,7-cycloadditions (Table 2). The computational results indicate that the formation of 1,7-cycloadducts has activation barriers (Table 2, Entries 1, 3, 6, and 8) lower than those observed for the formation of 1,3-cycloadducts (Table 2, Entries 10, 12, 13, and 15). The relative stabilities of the *cis*- and *trans*-1,7(1,3)-cycloadducts revealed that *cis* derivatives are calculated to be 10 kJ mol^{-1} less stable. On the other hand, calculations also indicate that 1,7-cycloadducts, identified as the major products, are around 8 kJ mol^{-1} more stable than their 1,3-counterparts.

From these data, we could conclude that 1,7-cycloadducts will be the major compounds to be obtained under both kinetic and thermodynamic control, which is in agreement with the experimental results.

The relevant *endo* or *exo* transition structures with the lower activation energies for each approach giving rise to the cycloaddition reaction of **3d-*II*** with **12** and **13** are summarized in Figure 4.

The formation of the *trans*-1,7-cycloadducts **14** could result either from the *endo*-1,7-cycloaddition of conformer **3d-*I*** through transition state ***t*-TS$_{endo}$1,7[*I*]** or from the *exo*-1,7-cycloaddition of conformer **3d-*II*** through transition state ***t*-TS$_{exo}$1,7[*II*]**, whereas the synthesis of the *cis*-1,7-cycloadducts **15** could result either from the *endo*-1,7-cycloaddition of conformer **3d-*II*** through transition state ***c*-TS$_{endo}$1,7[*II*]** or from the *exo*-1,7-cycloaddition of conformer **3d-*I*** through transition state ***c*-TS$_{exo}$1,7[*I*]** (Scheme 5).

Calculations showed that the lower-energy channel to the main products **14** is through ***t*-TS$_{exo}$1,7[*II*]**, about 22–24 kJ mol^{-1} lower in energy than ***t*-TS$_{endo}$1,7[*I*]** (Figure 5,

Table 1. Frontier orbital energies differences [eV] between **3d-*I***, **3d-*II***, **3c-*I***, or **3c-*II*** and different dipolarophiles at PM3, HF/6-31G(d), and B3LyP/6-31+G(d,p) theoretical levels.

	ΔE(I)[a] – ΔE(II)[b] PM3				HF/6-31G(d)				B3LyP/6-31+G(d,p)			
	3c-*I*	**3c-*II***	**3d-*I***	**3d-*II***	**3c-*I***	**3c-*II***	**3d-*I***	**3d-*II***	**3c-*I***	**3c-*II***	**3d-*I***	**3d-*II***
NMM (**12**)	1.96	1.92	1.94	1.90	5.08	4.98	4.18	4.01	3.46	3.38	3.48	3.41
NPM (**13**)	3.26	3.22	3.24	3.20	5.58	5.48	4.68	4.51	2.59	2.51	2.61	2.54

[a] ΔE(I) = $HOMO_{dipole}$ – $LUMO_{dipolarophile}$. [b] ΔE(II) = $HOMO_{dipolarophile}$ – $LUMO_{dipole}$.

Table 2. Activation energies[a] (ΔE_a, kJ mol^{-1}) and synchronicities[b] (Sy) associated with the formation of cycloadducts **14**–**17**, calculated relative to conformer **3d-*II*** and the corresponding maleimide.

Entry	Reaction	**TS** (through 1,7-Cycloaddition)	ΔE_a[a]	Sy[b]	Entry	Reaction	**TS** (through 1,3-Cycloaddition)	ΔE_a[a]	Sy[b]
	cis-					*cis-*			
1	**3d+12→15a**	*c*-TS$_{endo}$1,7[*II*]Me	6.5	0.875	9	**3d+12→17a**	*c*-TS$_{endo}$1,3[*I*]Me	19.5	0.741
2		*c*-TS$_{exo}$1,7[*I*]Me	32.8	0.781	10		*c*-TS$_{exo}$1,3[*II*]Me	19.0	0.718
3	**3d+13→15b**	*c*-TS$_{endo}$1,7[*II*]Ph	5.0	0.876	11	**3d+13→17b**	*c*-TS$_{endo}$1,3[*I*]Ph	21.9	0.745
4		*c*-TS$_{exo}$1,7[*I*]Ph	30.7	0.771	12		*c*-TS$_{exo}$1,3[*II*]Ph	19.5	0.729
	trans-					*trans-*			
5	**3d+12→14a**	*t*-TS$_{endo}$1,7[*I*]Me	27.4	0.806	13	**3d+12→16a**	*t*-TS$_{endo}$1,3[*II*]Me	12.8	0.679
6		*t*-TS$_{exo}$1,7[*II*]Me	5.8	0.819	14		*t*-TS$_{exo}$1,3[*I*]Me	21.3	0.734
7	**3d+13→14b**	*t*-TS$_{endo}$1,7[*I*]Ph	28.6	0.752	15	**3d+13→16b**	*t*-TS$_{endo}$1,3[*II*]Ph	15.0	0.684
8		*t*-TS$_{exo}$1,7[*II*]Ph	4.5	0.898	16		*t*-TS$_{exo}$1,3[*I*]Ph	19.5	0.736

[a] Computed at the B3LyP/6-31+G(d,p) + ZPVE level of theory by the approach and equations described previously.[10] Corrections for dispersion interactions and the BSSE are taken into account by the gCP-D3 method.[8] [b] For a perfectly synchronous reaction Sy = 1.

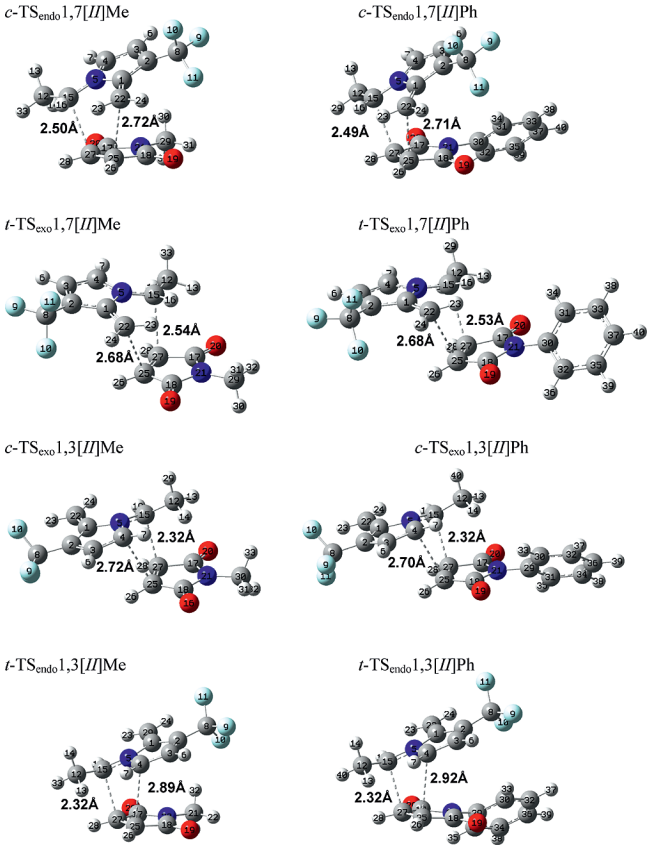


Figure 4. Geometries of transition states for the cycloaddition of azafulvenium methide **3d** with NPM and with NMM, calculated at the B3LyP[6-31+G(d,p)] level of theory.

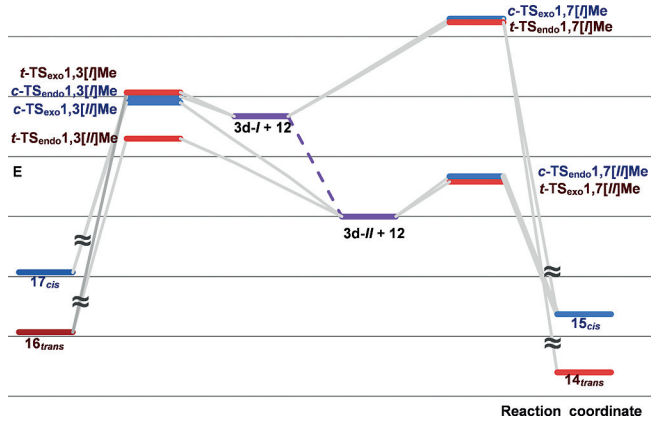
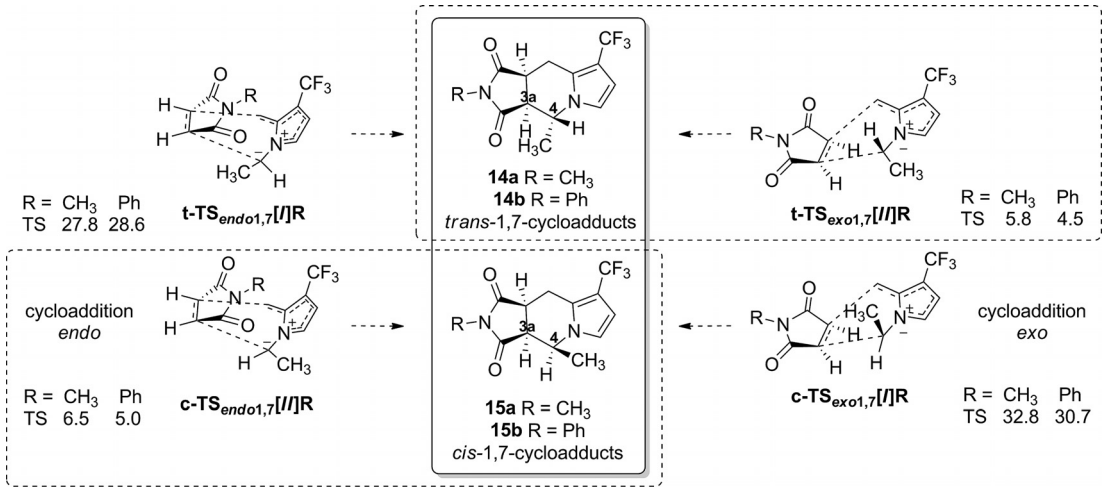


Figure 5. B3LyP[6-31+G(d,p)] energies (kJ mol^{-1}) calculated relative to conformer **3d-*II*** and NMM (**12**).

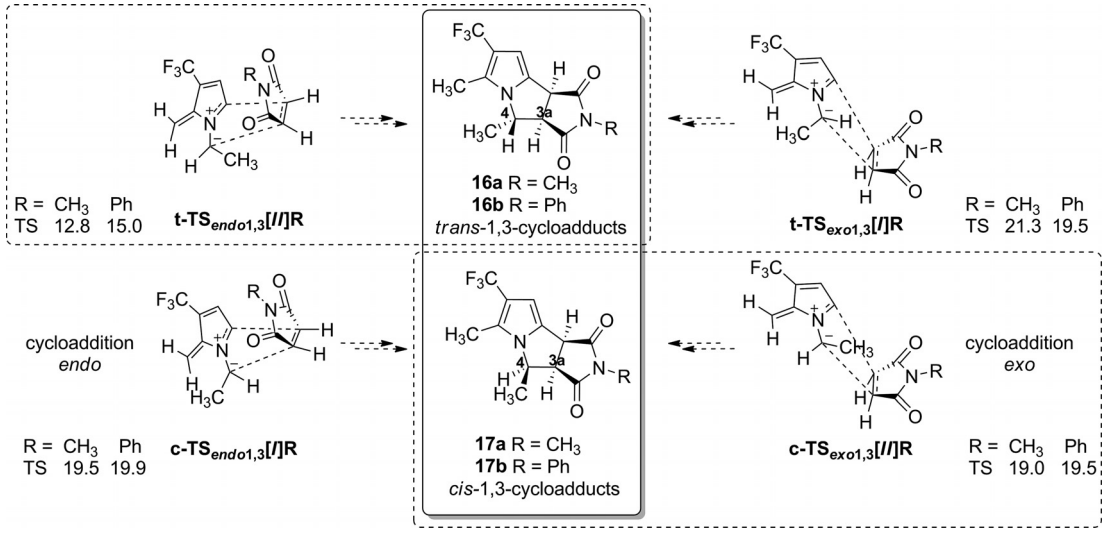
Table 2), whereas the lower energy channel to compounds **15** is through ***c*-TS$_{endo}$1,7[*II*]**, about 25–26 kJ mol^{-1} lower in energy than ***c*-TS$_{exo}$1,7[*I*]**. These results allowed us to conclude that compounds **15** are obtained through *endo*-1,7-cycloaddition, as has always been thought, whereas compounds **14** are obtained through the "unusual" *exo*-1,7-cycloaddition of conformer **3d-*II***.

The possible mechanism pathways relating to the cycloadditions of **3d** with maleimides leading to 1,3-cycloadducts are shown in Scheme 6. The *trans*-1,3-cycloadducts **16** could be produced through *endo*-cycloaddition of conformer **3d-*II*** through transition state ***t*-TS$_{endo}$1,3[*II*]** or as the result of the *exo*-cycloaddition of conformer **3d-*I*** through transition state ***t*-TS$_{exo}$1,3[*I*]**. On the other hand, *cis*-1,3-cycloadducts **17** could be obtained through *endo*-cycloaddition of conformer **3d-*I*** through transition state ***c*-TS$_{endo}$1,3[*I*]** or as the result of the *exo*-cycloaddition of **3d-*II*** through transition state ***c*-TS$_{exo}$1,3[*II*]**.

The results of the quantum chemical calculations demonstrate that the synthesis of heterocycles **16** is achieved through *endo-1,3-cycloaddition* through transition state ***t*-TS$_{endo}$1,3[*II*]**, with an energy barrier about 3–8 kJ mol^{-1} lower in energy than the *exo*-cycloaddition, whereas *cis*-heterocycles **17** are obtained through *exo-1,3-cycloaddition* through transition state ***c*-TS$_{exo}$1,3[*II*]** (Table 2), this being only 0.5 kJ mol^{-1} lower in energy than ***c*-TS$_{endo}$1,3[*I*]** and about 5 kJ mol^{-1} higher than the energy barrier required for the major products, which are the *trans*-1,3-cycloadducts.



Scheme 5. 1,7-Cycloaddition of azafulvenium methide **3d** with NMM (**12**) and with NPM (**13**).



Scheme 6. 1,3-Cycloaddition of azafulvenium methide **3d** with NMM (**12**) and NPM (**13**).

Calculations on specific NBO donor–acceptor interactions in the transition states were performed in order to shed light into the *endo* or *exo* preference in each cycloaddition.

Calculation on ***t*-TS$_{endo}$1,3[*II*]Me** and ***t*-TS$_{exo}$1,3[*I*]Me**, which lead to the major products **14a** and **16a**, show effective energy interactions between the N5–C15 two-center bond (BD), the C12–C15 two-center bond (BD), the C4 lone pair (LP), and the N5–C15 two-center antibonding orbital (BD*), all with the σ antibonding orbital (σ*) of C25–C27, favoring the formation of ***t*-TS$_{endo}$1,3[*II*]Me** by about 4 kJ mol^{-1}. Moreover, NBO calculation on the transition states ***t*-TS$_{endo}$1,7[*I*]Me** and ***t*-TS$_{exo}$1,7[*II*]Me** also showed the same kind of effective energy interactions favoring the formation of ***t*-TS$_{endo}$1,7[*I*]Me** by about 17.3 kJ mol^{-1}.

On the other hand, NBO calculations for the TSs that lead to the minor products (compounds **15a** and **17a**) show that for ***c*-TS$_{endo}$1,3[*I*]Me** and ***c*-TS$_{exo}$1,3[*II*]Me** there are effective energy interactions between the N5–C15 two-center bond (BD), C1–C22 two-center bond (BD), the C15–H16 two-center bond (BD) and the N5–C15 two-center antibonding orbital (BD*), all with the σ antibonding orbital (σ*) of C25–C27, favoring the formation of ***c*-TS$_{exo}$1,3[*II*]Me** by about 17.4 kJ mol^{-1}. Moreover, NBO calculation on the transition states ***c*-TS$_{endo}$1,7[*II*]Me** and ***c*-TS$_{exo}$1,7[*I*]Me** also showed the same kind of effective energy interactions, favoring the formation of ***c*-TS$_{exo}$1,7[*I*]Me** by about 29 kJ mol^{-1}.

It is important to note that in the case of 1,7-cycloadditions the NBO stabilization of the *trans*-*endo* and *cis*-*exo* modes is not large enough to compensate for the energy barrier, thus driving the reaction through the ***t*-TS$_{exo}$1,7[*II*]Me** and ***c*-TS$_{endo}$1,7[*II*]Me** transition states (Entries 1, 2, 5, and 6, Table 2). This means that steric factors override the orbital interactions in those cycloadditions. Similar results are obtained when the analysis is performed on the possible transitions states that produce the *N*-phenyl derivatives **14b** and **15b**.

Nevertheless, for 1,3-cycloadditions that lead to the *trans*-**16b** and *cis*-**17b** counterparts, one difference is found.

The NBO interaction between the N5–C15 two-center antibonding orbital (BD*) with the σ antibonding orbital (σ*) of C25–C27 does not exist for the two *exo*-TSs.

3. Conclusion

The synthesis of 3-methyl-2,2-dioxo-7-(trifluoromethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole and the generation of a new 1-methyl-5-(trifluoromethyl)azafulvenium methide by thermal extrusion of sulfur dioxide are described. This new and reactive azafulvenium methide intermediate undergoes different reactions. The higher selectivity of 5-(trifluoromethyl)azafulvenium methide for the formation of 1,3-cycloadducts, in relation to 1-benzyl- or 1-methyl-5-(trifluoromethyl)azafulvenium methides, indicates that a combination of electronic and steric factors determines the outcome of the cycloaddition. Nevertheless, whereas the 1-benzyl derivative affords only *trans* cycloadducts, in this article we have demonstrated that both *cis* and *trans* counterparts can be experimentally obtained when the skeleton has a suitable substituent.

In addition, calculations showed that cycloadditions occur in a concerted manner but slightly asynchronously, with 1,3-cycloadditions being more polarized than 1,7-cycloadditions. The study also conclusively revealed that the unusual *exo*-cycloaddition is the main reaction mode for the *trans*-1,7- and *cis*-1,3-cycloadducts, counter to mainstream opinion, whereas the *endo* approach is the main mode of reaction leading to *cis*-1,7- and *trans*-1,3-cycloadducts, in agreement with the mainstream view.

Experimental Section

General: Microwave reactions were carried out in a CEM Focused Synthesis System Discover S-Class microwave reactor with 10 mL microwave tubes. The reaction temperatures were measured by infrared surface detector during microwave heating. Thiazolidine[11] **7**, 1-butenyl-thiazolidine **9**, 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **10**, and 2,2-dioxo-7-(trifluoromethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **4d** were prepared by modifying a procedure described in the literature.[5]

^{19}F NMR spectra were recorded with an instrument operating at 376 MHz. ^{1}H NMR spectra were recorded with an instrument operating at 400 MHz. ^{13}C NMR spectra were recorded with an instrument operating at 100 MHz. Chemical shifts are expressed in parts per million relative to internal tetramethylsilane (TMS), and coupling constants (*J*) are in Hertz. Infrared spectra (IR) were recorded with a Fourier Transform spectrometer (FTIR). Mass spectra were recorded under electron impact (EI) or electrospray ionization (ESI) conditions. High-resolution mass spectra (HRMS) were obtained with an electron impact (EI) or electrospray (ESI) TOF mass spectrometer. Melting points were determined in open glass capillaries and are uncorrected. Thin-layer chromatography (TLC) analyses were performed with precoated silica gel plates. Flash column chromatography was performed with silica gel 60 as the stationary phase.

(2*S*,4*R*)-2-Methyl-3-[(*E*)-4,4,4-trifluoro-3-oxobut-1-enyl]thiazolidine-4-carboxylic Acid (9): A solution of 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**8**, 4.28 g, 25.4 mmol) in acetonitrile (15 mL) was added dropwise to a solution of thiazolidine-4-carboxylic acid **7** (3.95 g, 26.8 mmol) in acetonitrile (110 mL) at room temperature. After stirring for 10 min, the solution was heated at 60 °C for 24 h. The reaction mixture was then filtered, and the solvent was removed in vacuo. Diethyl ether (120 mL) and water (120 mL) were added, and the two layers were separated. The aqueous phase was extracted with diethyl ether (2 × 120 mL), the combined organic phases were dried (Na_2SO_4), and the solvent was removed in vacuo. The resulting pale orange oil was purified by column chromatography [hexane, hexane/ethyl acetate (9:1)] to give **9** as a solid (6.4 g, 88.5%).

Data for 9: M.p. 120–122 °C (amorphous solid, from hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): Two conformers, major: δ = 8.85 (d, J = 12.7 Hz, 1 H), 5.30 (d, J = 12.7 Hz, 1 H), 5.05 (d, J = 19.2 Hz, 1 H), 4.78 (br. s, 1 H), 3.48 (br. s, 2 H), 1.66 (d, J = 19.2 Hz, 3 H); minor: δ = 8.85 (d, J = 12.7 Hz, 1 H), 5.47 (d, J = 12.7 Hz, 1 H), 5.05 (d, J = 19.2 Hz, 1 H), 4.60 (br. s, 1 H), 3.48 (br. s, 2 H), 1.66 (d, J = 19.2 Hz, 3 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –76.11 ppm. IR (KBr): $\tilde{\nu}$ = 3400–2800 (broad), 3120, 2994, 2941, 1732, 1646, 1558, 1468, 1384, 1263, 1191, 1141, 1088, 983, 899, 794, 717, 601 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_9H_{11}F_3NO_3S$ $[M + H]^+$ 270.04062; found 270.04091.

(*R*)-3-Methyl-7-(trifluoromethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (10): Trifluoroacetic anhydride (6.00 g, 28.5 mmol) was added dropwise under nitrogen at 0 °C to a stirred solution of **9** (6.39 g, 23.7 mmol) in dry dichloromethane (100 mL). After the mixture had been stirred at 0 °C for 1 h and at room temperature for 7 h, the solvent was removed in vacuo. The resulting brown oil was purified by flash chromatography [hexane, hexane/ethyl acetate (9:1)] to give the corresponding (*R*)-3-methyl-7-(trifluoromethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (**10**) as a white solid (2.13 g, 43%).

Data for 10: Oil. $[\alpha]_D^{26}$ = +43.9 (c = 1.1 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.60 (d, J = 2.8 Hz, 1 H), 6.45 (d, J = 2.8 Hz, 1 H), 5.47 (q, J = 6.2 Hz, 1 H), 4.15 (m, 2 H), 1.76 (d, J = 6.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.0 (q, J_{CC-CF3} = 3.7 Hz), 124.0 (q, J_{CF3} = 266.3 Hz), 114.2, 111.4 (q, J_{CC-CF3} = 2.9 Hz), 106.4 (q, J_{C-CF3} = 37.4 Hz), 59.3, 28.1, 23.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –55.39 ppm. IR (KBr): $\tilde{\nu}$ = 3100, 2980, 2930, 1732, 1670, 1590, 1485, 1440, 1379, 1256, 1110, 1033, 999, 949, 722, 684 cm^{-1}. MS (EI): m/z (%) = 208(1) $[M + 1]^+$, 207(9) $[M]^+$, 192 (16), 175 (96), 174 (100), 148 (33), 106 (27), 105 (9). HRMS (EI-TOF): calcd. for $C_8H_8F_3NS$ $[M]^+$: 207.0330; found 207.0331.

3-Methyl-2,2-dioxo-7-(trifluoromethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (4d): A solution of (*R*)-3-methyl-7-(trifluoromethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (**10**, 0.207 g, 1 mmol) in ethyl acetate (3 mL) was treated with $Na_2WO_4{\cdot}2H_2O$ (1 M in water, 5 μL), $C_6H_5PO_3H_2$, (1 M in water, 5 μL), $CH_3N[(CH_2)_7CH_3]_3Cl$ (1 M in methanol, 5 μL), and aqueous H_2O_2 (33%, 13 mmol). This mixture was vigorously stirred at 50 °C. After 2 d, a new load of catalysts and H_2O_2 was added, and the system was stirred again for 2 more days at 40 °C. The reaction mixture was washed with aqueous sodium bisulfite (10% w/v), and the aqueous phase was extracted with ethyl acetate. The organic phase was then dried with anhydrous Na_2SO_4, and the solvent were evaporated off. The resulting pale yellow oil was purified by column chromatography [hexane, hexane/ethyl acetate (9:1), hexane/ethyl acetate (1:1)] to give sulfone **4d** as a white solid (0.091 g, 38%).

Data for 4d: M.p. 70–71 °C (amorphous solid). $[\alpha]_D^{26}$ = 0.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79 (d, J = 2.4 Hz, 1 H), 6.53 (d, J = 2.4 Hz, 1 H), 4.98 (q, J = 6.6 Hz, 1 H), 4.40 (br. s, 2 H), 1.80 (d, J = 6.6, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):

δ = 123.2 (q, J_{CF3} = 266.3 Hz), 121.1 (q, J_{CC-CF3} = 3.7 Hz), 117.2, 111.8 (q, J_{C-CF3} = 38.2 Hz), 109.7 (q, J_{CC-CF3} = 2.2 Hz), 70.8, 49.6, 14.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –56.07 ppm. IR (KBr): $\tilde{\nu}$ = 3145, 2994, 2941, 1602, 1481, 1438, 1411, 1384, 1338, 1263, 1229, 1178, 1130, 998, 741, 550 cm^{-1}. MS (EI): *m*/*z* (%) = 239 (5) $[M]^+$, 176 (9), 175 (100), 174 (70), 156 (6), 148 (16), 133 (5), 127 (4), 106 (26). HRMS (EI-TOF): calcd. for $C_8H_8F_3NO_2S$ $[M]^+$: 239.0228; found 239.0234.

Synthesis of 2-Methyl-3-(trifluoromethyl)-1-vinyl-1*H*-pyrrole (11)

Flash Vacuum Pyrolysis: Pyrolysis of 3-methyl-2,2-dioxo-7-(trifluoromethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (**4d**, 76.2 mg, 0.33 mmol) at 450–475 °C and 1×10^{-5} to 2×10^{-5} mbar onto a surface cooled to –196 °C over a period of 1 h gave a colorless pyrolysate. [The rate of volatilization of the starting material was controlled by the use of an oven, which heated the sample at 70–80 °C]. After cooling to room temperature the pyrolysate was removed from the cold finger with dichloromethane and the solvent was removed in vacuo to give 2-methyl-3-(trifluoromethyl)-1-vinyl-1*H*-pyrrole (**11**) as an oil (14.2 mg, 25%).

Conventional Heating: A suspension of 3-methyl-2,2-dioxo-7-(trifluoromethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (**4d**, 79.4 mg, 0.33 mmol) in 1,2,4-trichlorobenzene (1 mL) was heated at reflux under dry nitrogen for 6 h. After cooling to room temperature, the mixture was purified by flash chromatography (hexane) to remove 1,2,4-trichlorobenzene, followed by elution with ethyl acetate/hexane. The solvent was removed in vacuo to give 2-methyl-3-(trifluoromethyl)-1-vinyl-1*H*-pyrrole (**11**) as an oil (32.7 mg, 41%).

Data for 2-Methyl-3-(trifluoromethyl)-1-vinyl-1*H*-pyrrole (11): Oil. ^{1}H NMR (400 MHz, $CDCl_3$): 6.90 (d, *J* = 2.7 Hz, 1 H), 6.86 (dd, J_1 = 18.8 Hz J_2 = 8.8 Hz, 1 H), 6.34 (d, *J* = 2.7 Hz, 1 H), 5.21 (d, *J* = 15.6 Hz, 1 H), 4.87 (d, *J* = 8.7 Hz, 1 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.9, 128.6 (q, J_{CC-CF3} = 3.7 Hz), 124.4 (q, J_{CF3} = 266.3 Hz), 116.2, 112.7 (q, J_{CCF3} = 35.2 Hz), 107.7 (q, J_{CC-CF3} = 2.9 Hz), 101.8, 10.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –54.95 ppm. MS (EI): *m*/*z* (%) = 176 (15) $[M + 1]^+$, 175 (100) $[M]^+$, 174 (58), 160 (45), 156 (33), 148 (71), 140 (53), 136 (25), 106 (35), 79 (13). HRMS (EI-TOF): calcd. for $C_8H_8F_3N$ $[M]^+$ 175.0609; found 175.0612.

General Procedure for Cycloadditions Under MWIP Conditions: A suspension of 3-methyl-2,2-dioxo-7-(trifluoromethyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (**4d**, 59.0 mg, 0.25 mmol) and a dipolarophile (1.0–1.5 equiv.) in 1,2,4-trichlorobenzene (0.5 mL or 1 mL) was irradiated in the microwave reactor at the temperature and for the time indicated in each case. After cooling to room temperature, the mixture was purified by flash chromatography (hexane) to remove 1,2,4-trichlorobenzene, followed by elution with hexane/ethyl acetate to obtain the corresponding cycloadducts.

Data for *trans*-(3a,4,9a)-2,4-dimethyl-8-(trifluoromethyl)-3a,4,9,9a-tetrahydro-1*H*-pyrrolo[3,4-*f*]indolizine-1,3(2*H*)-dione (**14a**) and *cis*-(3a,4,9a)-2,4-dimethyl-8-(trifluoromethyl)-3a,4,9,9a-tetrahydro-1*H*-pyrrolo[3,4-*f*]indolizine-1,3(2*H*)-dione (**15a**), isolated as an 88:12 mixture (determined by ^{1}H NMR), 66% yield.

Data for 14a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.65 (d, *J* = 2.8 Hz, 1 H), 6.26 (d, *J* = 2.8 Hz, 1 H), 4.29 (m, 1 H), 3.55 (dd, J_1 = 15.7, J_2 = 2.6 Hz, 1 H), 3.37 (m, 1 H), 3.27 (dd, J_1 = 9.0, J_2 = 4.6 Hz, 1 H), 2.98 (dd, J_1 = 15.7, J_2 = 6.8 Hz, 1 H), 2.83 (s, 3 H), 1.82 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6, 175.3, 126.4 (q, J_{CC-CF3} = 3.7 Hz), 124.1 (q, J_{CF3} = 266.5 Hz), 118.6, 111.5 (q, J_{C-CF3} = 36.1 Hz), 106.0 (q, J_{CC-CF3} = 2.9 Hz), 49.9, 45.4, 39.3, 25.1, 21.8, 15.7 ppm. ^{19}F (376 MHz, $CDCl_3$): δ = –54.61 ppm.

Data for 15a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.60 (d, *J* = 2.8 Hz, 1 H), 6.26 (d, *J* = 2.8 Hz, 1 H), 4.60 (m, 1 H), 3.90 (dd, J_1 = 9.0, J_2 = 3.4 Hz, 1 H), 3.40 (dd, J_1 = 9.0, J_2 = 3.3 Hz, 1 H), 3.32 (m, 1 H), 3.18 (dd, J_1 = 15.4, J_2 = 6.9 Hz, 1 H), 2.92 (s, 3 H), 1.61 (d, *J* = 7.1 Hz, 3 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –54.52 ppm.

HRMS (ESI-TOF): Mixture of compounds **14a** and **15a**: calcd. for $C_{13}H_{14}F_3N_2O_2$ $[M + H]^+$ 287.10019; found 287.10060.

Data for *trans*-(3a,4,8b)-2,4,6-trimethyl-7-(trifluoromethyl)-3a,4-dihydropyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,8b*H*)-dione (**16a**) and *cis*-(3a,4,8b)-2,4,6-trimethyl-7-(trifluoromethyl)-3a,4-dihydropyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,8b*H*)-dione (**17a**), isolated as an 85:15 mixture (determined by ^{1}H NMR), 37% yield.

Data for 16a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.22 (s, 1 H), 4.73 (t, *J* = 6.3 Hz, 1 H), 4.30 (d, *J* = 7.6 Hz, 1 H), 3.54 (d, *J* = 7.5 Hz, 1 H), 2.96 (s, 3 H), 2.29 (s, 3 H), 1.52 (d, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 174.4, 124.4, 124.2 (q, J_{CC-CF3} = 3.7 Hz), 124.0 (q, J_{CF3} = 266.8 Hz), 115.9 (q, J_{C-CF3} = 36.7 Hz), 100.3 (q, J_{CC-CF3} = 2.9 Hz), 56.0, 55.0, 43.3, 25.5, 22.9, 10.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –55.23 ppm.

Data for 17a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.27 (s, 1 H), 4.70 (t, *J* = 5.3 Hz, 1 H), 4.15 (d, *J* = 8.7 Hz, 1 H), 4.07 (d, *J* = 9.1 Hz, 1 H), 3.00 (s, 3 H), 2.31 (s, 3 H), 1.54 (d, *J* = 6.5 Hz, 3 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –55.12 ppm.

HRMS (ESI-TOF): Mixture of compounds **16a** and **17a**: calcd. for $C_{13}H_{14}F_3N_2O_2$ $[M + H]^+$ 287.10019; found 287.10020.

Data for *trans*-(3a,4,9a)-4-methyl-2-phenyl-8-(trifluoromethyl)-3a,4,9,9a-tetrahydro-1*H*-pyrrolo[3,4-*f*]indolizine-1,3(2*H*)-dione (**14b**) and *cis*-(3a,4,9a)-4-methyl-2-phenyl-8-(trifluoromethyl)-3a,4,9,9a-tetrahydro-1*H*-pyrrolo[3,4-*f*]indolizine-1,3(2*H*)-dione (**15b**), isolated as a 74:26 mixture (determined by ^{1}H NMR), 70% yield.

Data for 14b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 3 H), 6.92 (d, *J* = 7.3 Hz, 2 H), 6.70 (d, *J* = 2.7 Hz, 1 H), 6.33 (d, *J* = 2.7 Hz, 1 H), 4.33 (m, 1 H), 3.66 (d, *J* = 15.5 Hz, 1 H), 3.50 (m, 1 H), 3.37 (dd, J_1 = 9.1, J_2 = 4.1 Hz, 1 H), 3.01 (dd, J_1 = 15.5, J_2 = 6.8 Hz, 1 H), 1.87 (d, *J* = 6.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 174.4, 131.5, 129.3, 129.0, 126.5, 125.0 (q, J_{CC-CF3} = 3.7 Hz), 124.1 (q, J_{CF3} = 266.3 Hz), 116.7, 111.5 (q, J_{C-CF3} = 36.4 Hz), 105.8 (q, J_{CC-CF3} = 2.9 Hz), 50.2, 45.8, 39.8, 22.5, 15.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –54.38 ppm.

Data for 15b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 3 H), 7.04 (d, *J* = 7.4 Hz, 2 H), 6.63 (d, *J* = 2.6 Hz, 1 H), 6.29 (d, *J* = 2.6 Hz, 1 H), 4.75 (m, 1 H), 3.54 (d, *J* = 12.9 Hz, 1 H), 3.48 (m, 1 H), 3.27 (dd, J_1 = 9.1, J_2 = 2.7 Hz, 1 H), 3.23 (dd, J_1 = 15.6, J_2 = 7.0 Hz, 1 H), 1.62 (d, *J* = 6.9 Hz, 1 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –54.33 ppm.

HRMS (ESI-TOF): Mixture of compounds **14b** and **15b**: calcd. for $C_{18}H_{16}F_3N_2O_2$ $[M + H]^+$ 349.11584; found 349.11536.

Data for *trans*-(3a,4,8b)-4,6-dimethyl-2-phenyl-7-(trifluoromethyl)-3a,4-dihydropyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,8b*H*)-dione (**16b**) and *cis*-(3a*R*,4*R*,8b*S*)-4,6-dimethyl-2-phenyl-7-(trifluoromethyl)-3a,4-dihydropyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,8b*H*)-dione (**17b**), isolated as a 72:28 mixture (determined by ^{1}H NMR), 30% yield.

Data for 16b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (m, 3 H), 7.23 (d, *J* = 7.6 Hz, 2 H), 6.29 (s, 1 H), 4.82 (m, 1 H), 4.43 (d, *J* = 7.7 Hz, 1 H), 3.71 (d, *J* = 7.5 Hz, 1 H), 2.32 (s, 3 H), 1.55 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 173.2, 131.5, 129.3, 129.0, 127.4, 126.4, 124.4 (q, J_{CC-CF3} = 3.7 Hz), 124.0 (q, J_{CF3} = 267.0 Hz), 116.0 (q, J_{C-CF3} = 35.5 Hz), 100.5 (q, J_{CC-CF3} = 2.9 Hz), 56.1, 55.2, 43.4, 22.7, 10.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ –55.21 ppm.

Data for 17b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 3 H), 7.25 (d, J = 7.5 Hz, 2 H), 6.33 (s, 1 H), 4.78 (m, 1 H), 4.36 (d, J = 8.9 Hz, 1 H), 4.23 (t, J = 9.2 Hz, 1 H), 2.34 (s, 3 H), 1.60 (d, J = 6.7 Hz, 3 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –55.10 ppm.

HRMS (ESI-TOF): Mixture of compounds **16b** and **17b**: calcd. for $C_{18}H_{16}F_3N_2O_2$ $[M + H]^+$ 349.11584; found 349.11568.

Computational Study: All calculations were performed with the Gaussian09 program system.[12] Transition-state theory was used to evaluate the energy of the different channels. The transition states were characterized by the presence of one negative frequency and the internal reaction coordinate (IRC) method was applied to verify that the correct states were connected. Grimme's gCP-D3 webservice was used for the BSSE and dispersion correction.[8b–8d]

Supporting Information (see footnote on the first page of this article): ^{19}F, ^{1}H, and ^{13}C NMR spectra for all new compounds and theoretical calculation results. Cartesian coordinates [Å] obtained from the B3LyP[6-31+G(d,p)] calculations. This material is available free of charge through the internet at http://pubs.acs.org.

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