Tetrahedron 69 (2013) 3646–3655

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis and thermal reactivity of 3-benzyl-7-trifluoromethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide

Walter José Peláez, Teresa M.V.D. Pinho e Melo *

Department of Chemistry, University of Coimbra, 3004-535 Coimbra, Portugal

ARTICLE INFO

Article history:
Received 21 January 2013
Received in revised form 28 February 2013
Accepted 5 March 2013
Available online 13 March 2013

Keywords:
Cycloadditions
Sigmatropic shifts
Dipoles
Azafulvenium methides
Trifluoromethylpyrroles
Flash vacuum pyrolysis
Microwave chemistry
DFT calculations

ABSTRACT

The generation and reactivity of 1-benzyl-5-trifluoromethyl-azafulvenium methide are described. Under microwave induced pyrolysis this intermediate could be trapped by dipolarophiles acting as a 4π as well as 8π dipole. It was observed that with dimethyl acetylenedicarboxylate the 1,3-dipolar cycloadduct was the major product whereas with *N*-substituted maleimides the major product results from the addition across the 1,7-position. FMO analysis of the cycloadditions corroborated the rationalization of the observed reactivity. Quantum chemical calculations carried out at the DFT level of theory allowed the rationalization of the stereoselectivity observed in the cycloaddition of 1-benzyl-5-trifluoromethyl-azafulvenium methide with *N*-substituted maleimides. The study revealed that *exo*-cycloaddition is the main reaction path for the 1,7-cycloaddition, while the *endo*-approach is the main mode of reaction leading to 1,3-cycloadducts. In addition, under flash vacuum pyrolysis or conventional thermolysis, 1-benzyl-5-trifluoromethyl-azafulvenium methide undergoes an allowed suprafacial sigmatropic [1,8]H shift leading to the efficient formation of 2-methyl-1-styryl-3-trifluoromethyl-1*H*-pyrrole.

1. Introduction

Fluorinated compounds play an important role in medicinal chemistry since fluorine substitution in organic molecules often leads to improved metabolic stability, bioavailability, and protein–ligand interactions.[1] The influence of the CF_3 group on physiological activity is usually concerned with the increasing lipophilicity, leading to the improvement of in vivo transport characteristics. The high electronegativity of the CF_3 group results in quite a different electron density distribution and significantly changes the reactivity of the molecules. There are only a few examples of trifluoromethyl-containing pyrroles,[2] however, some of these compounds have demonstrated important insecticidal action and mitochondrial uncoupling activity.[3]

We have previously demonstrated that 4,5-methoxycarbonyl-azafulvenium methides **1** and 4,5-methoxycarbonyl-diazafulvenium methides **2** are versatile building blocks for the synthesis of functionalized pyrroles and pyrazoles (Scheme 1).[4,5] These extended dipolar systems can, in principle, act as 4π 1,3-dipoles or as 8π 1,7-dipoles, although the typical reactivity is that expected for 1,7-dipoles. However, we have shown that 5-trifluoromethyl-azafulvenium methide derivatives **3** have a different reactivity pattern. In fact, these reactive intermediates participate in cycloaddition reactions as 1,3-dipoles and/or 1,7-dipoles, leading to new trifluoromethylpyrrole-annulated systems.[4h]

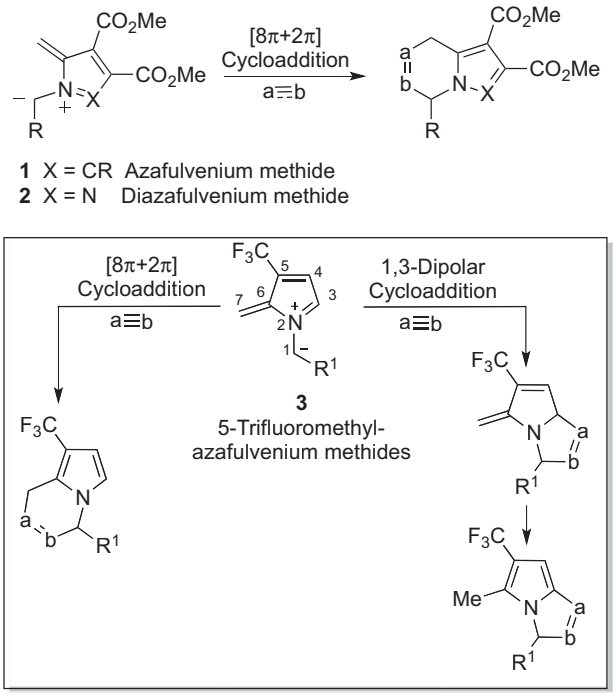
Azafulvenium methide **3a**, generated from 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide **4** by thermal extrusion of sulfur dioxide, showed *site* selectivity in the reaction with strong electron-deficient dipolarophiles such as dimethyl acetylenedicarboxylate (DMAD) and *N*-phenylmaleimide (NPM) leading exclusively to 1,3-cycloadducts **5** and **6**, respectively. However, in the cycloaddition of dipole **3a** with ethyl 3-phenylpropiolate, 1,7-cycloadduct **8** was also formed. Frontier molecular orbital (FMO) analysis of the cycloadditions was in agreement with the observed selectivity.[4h]

Azafulvenium methides also participate in other pericyclic reactions namely, sigmatropic [1,8]H shifts and 1,7-electrocyclizations giving vinylpyrroles.[4,6] In fact, we demonstrated that trifluoromethyl-azafulvenium methide **3b** is converted efficiently into *C*-vinylpyrrole **11** under thermolysis via 1,7-electrocyclization followed by a rearrangement. The generation of dipole **3b** in the presence of *N*-phenylmaleimide gives the corresponding 1,3-cycloadduct **12**, although the formation of *C*-vinylpyrrole **11** as a competitive reaction is also observed (Scheme 3).[4h]

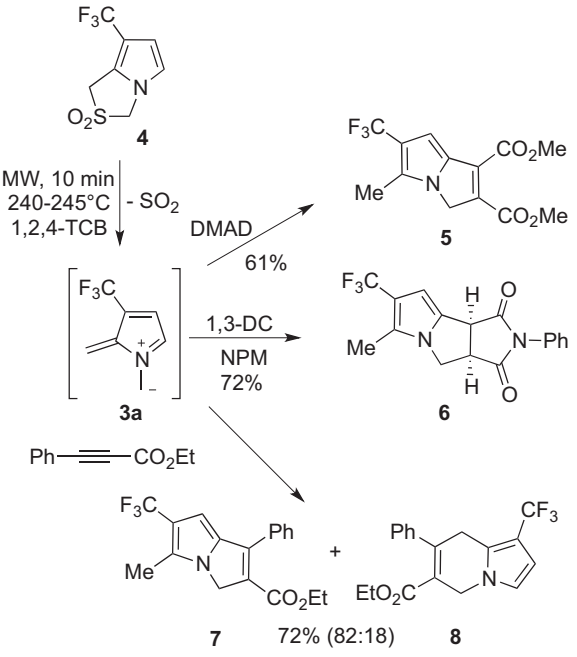
Herein, the chemistry of a new 5-trifluoromethyl-azafulvenium methide derivative was studied in order to better understand the chemistry of azafulvenium methides, in particular to know the structural features that allow these intermediates to participate in reactions with dipolarophiles as 1,3-dipoles and 1,7-dipoles. It was also our aim to evaluate the scope of this

* Corresponding author. E-mail address: tmelo@ci.uc.pt (T.M.V.D. Pinho e Melo).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.03.017



Scheme 1. Cycloaddition of aza- and diazafulvenium methides.



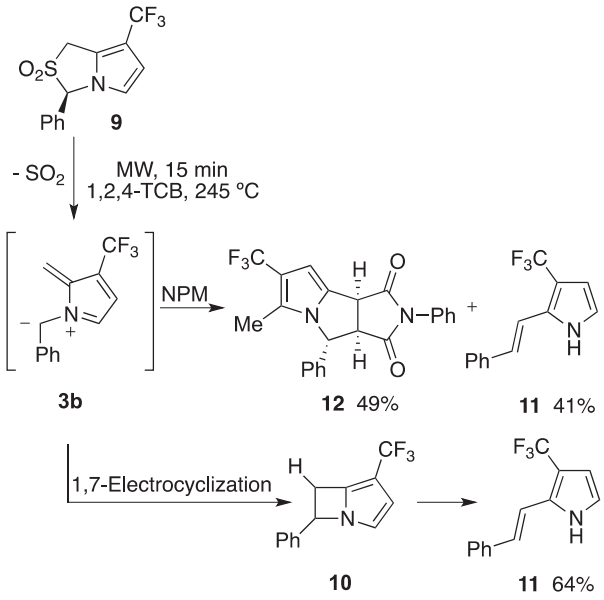
Scheme 2. Cycloaddition of azafulvenium methide **3a** with electron-deficient dipolarophiles.[4h]

synthetic approach to functionalized trifluoromethylpyrroles, including trifluoromethylpyrrole-annulated derivatives.

2. Results and discussion

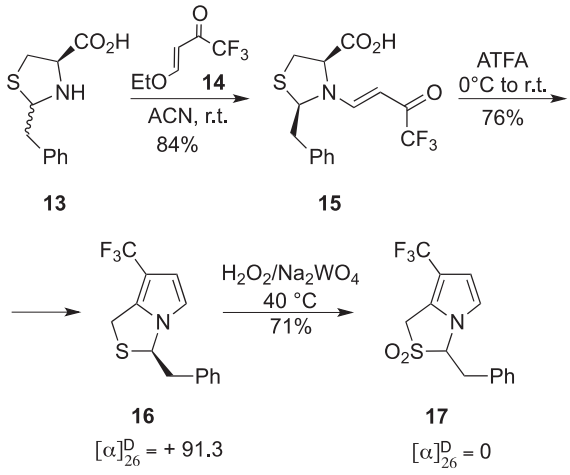
2.1. Synthesis of 7-trifluoromethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide

7-Trifluoromethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide **17**, the precursor of the new 1-benzyl-5-trifluoromethyl-azafulvenium



Scheme 3. Pericyclic reactions of azafulvenium methide **3b**.[4h]

methide, was prepared following a known general methodology (Scheme 4).[4h,6] The reaction of thiazolidine **13** with 4-ethyloxy-1,1,1-trifluorobut-3-ene-2-one (**14**) was diastereoselective, giving the expected 1-butenyl-thiazolidine **15** in 84% 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.[4h] Cyclization of thiazolidine **15** in the presence of trifluoroacetic anhydride gave 7-trifluoromethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **16** in good yield as single enantiomer ($[\alpha]_D$ +91.3). The stereochemistry of **16** 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, whose absolute configuration was determined by X-ray crystallography.[4h] Catalytic oxidation of thiazolidine **16** afforded sulfone **17** in good yield, isolated as a racemic mixture.

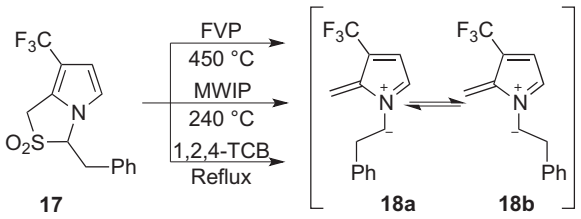


Scheme 4. Synthesis of 7-trifluoromethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide **17**.

2.2. Generation and reactivity of 1-benzyl-5-(trifluoromethyl) azafulvenium methide

7-Trifluoromethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide **17** was subjected to flash vacuum pyrolysis (FVP), microwave induced

pyrolysis (MWIP), and conventional heating to carry out the extrusion of sulfur dioxide leading to the target azafulvenium methide **18** (Scheme 5).



Scheme 5. Generation of azafulvenium methide **18** by FVP, MWIP, and conventional heating.

FVP or conventional thermolysis of **17** in the absence of dipolarophiles led to the efficient formation of *N*-styrylpyrrole **19** via an allowed suprafacial sigmatropic [1,8]-H shift in the 8π 1,7-dipolar system of the in situ generated azafulvenium methide **18** (Scheme 5). Although azafulvenium methide **18** exists in equilibrium of at least two conformers, only conformer **18a** bears a hydrogen in the appropriate position to undergo the pericyclic reaction (see below, theoretical calculations).

Under MWIP, azafulvenium methide **18** was also generated and trapped in cycloaddition reactions (Scheme 6). The reaction with DMAD gave a mixture of 1,3- and 1,7-cycloadducts **20** and **21** in 89:11 ratio, respectively. Under the same microwave induced reaction conditions, dipole **18** reacted with *N*-phenylmaleimide (NPM) and *N*-methylmaleimide (NMM) also giving 1,3- and 1,7-cycloadducts. However, the major products resulted from the addition across the 1,7-position, the selectivity opposite to the one observed with DMAD. It is important to note that cycloadducts **22** and **23** were obtained in a diastereoselective manner. Attempts to carry out the cycloaddition of azafulvenium methide **18** with ethyl 3-phenylpropiolate, only led to the formation of 2-methyl-1-styryl-3-trifluoromethyl-1*H*-pyrrole **19**, which was isolated in high yield (90%).

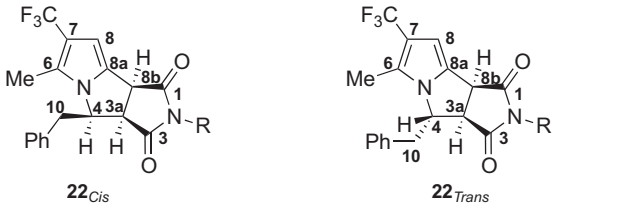


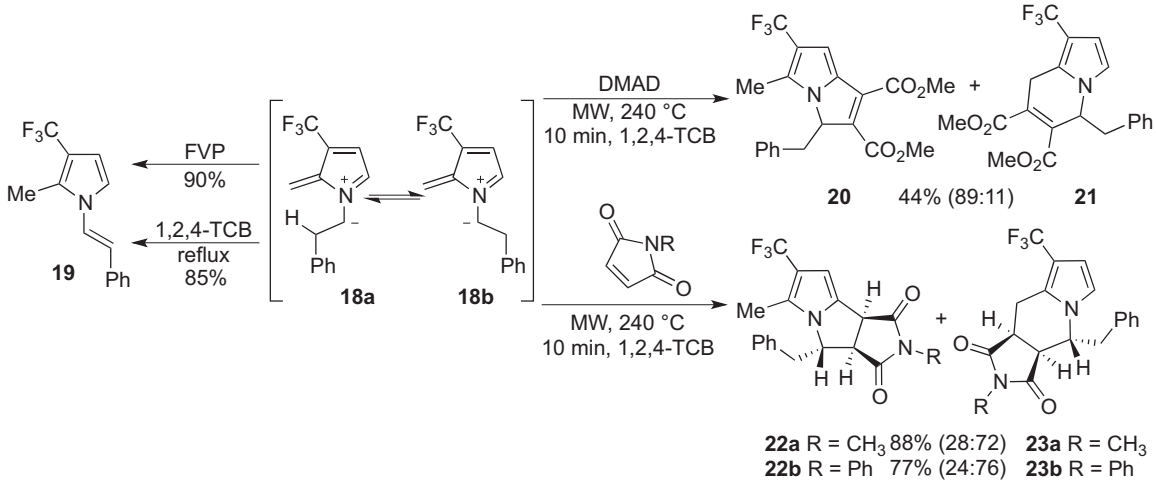
Fig. 1. Estimated dihedral angles for 3a,4-dihydropyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,8b*H*)-diones **22**.

to establish that the azafulvenium **18** reacts with *N*-phenyl- and *N*-methylmaleimide affording only the trans-stereoisomer. Furthermore, the ^{1}H NMR spectrum of a cis/trans mixture of a similar compound, bearing a methyl– instead of the benzyl– group, shows the major cycloadduct with the same coupling pattern and a minor cycloadduct, which was assigned as being the cis-isomer since the coupling between H4 and H3a could be observed.

The structural assignment of compounds **23** was supported by NOESY spectra. Relative high-intensity cross-peaks between H4 and H9b and connectivity between the methylene group (at C10) and H3a were found, which is in agreement with the estimated distances between hydrogen atoms (Fig. 2), establishing that compounds **23** have trans configuration.

2.3. 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 5-trifluoromethyl-azafulvenium methides **3a** and **18** in the gas phase (Fig. 3, Table S1). 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 azafulvenium methide **3a** was found to be planar. On the other hand, the results show that 5-trifluoromethyl-azafulvenium methide **18** can exist in two different conformers, conformer **18b** slightly more stable than conformer **18a** having the inward benzyl group (15.8 kJ mol^{-1}).



Scheme 6. Reactivity of 5-trifluoromethyl-azafulvenium methide **18**.

The structural assignment of cycloadducts **20**–**23** was based on one-dimensional NMR spectra (^{1}H, ^{13}C, ^{19}F) and two-dimensional HMQC, HMBC, and NOESY spectra.

In particular, structures of compounds **22** were established mainly on the basis of the ^{1}H NMR spectra and the estimated dihedral angle between H4 and H3a (Fig. 1). In fact, scalar coupling between these protons could not be detected, allowing us

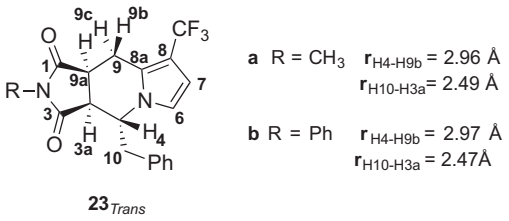


Fig. 2. Estimated distances between hydrogen atoms for 3a,4,9,9a-tetrahydro-1*H*-pyrrolo[3,4-*f*]indolizine-1,3(2*H*)-diones **23**.

dipole have the highest orbital coefficients, indicating that the 1,3-cycloaddition should be favored over the 1,7-cycloaddition (Fig. 5). This is in agreement with the selectivity observed experimentally in the cycloaddition of **18** with DMAD. However, with *N*-substituted maleimides, the 1,7-cycloadducts became the major products, and no cycloaddition was observed with ethyl 3-phenylpropiolate. Thus, in the case of azafulvenium methide **18**, bearing an additional benzyl group at C1, the selectivity can only be explained considering a combination of electronic and steric factors.

In order to be able to rationalize the stereoselective synthesis of *trans*-cycloadducts (**22** and **23**) from the cycloaddition of aza-

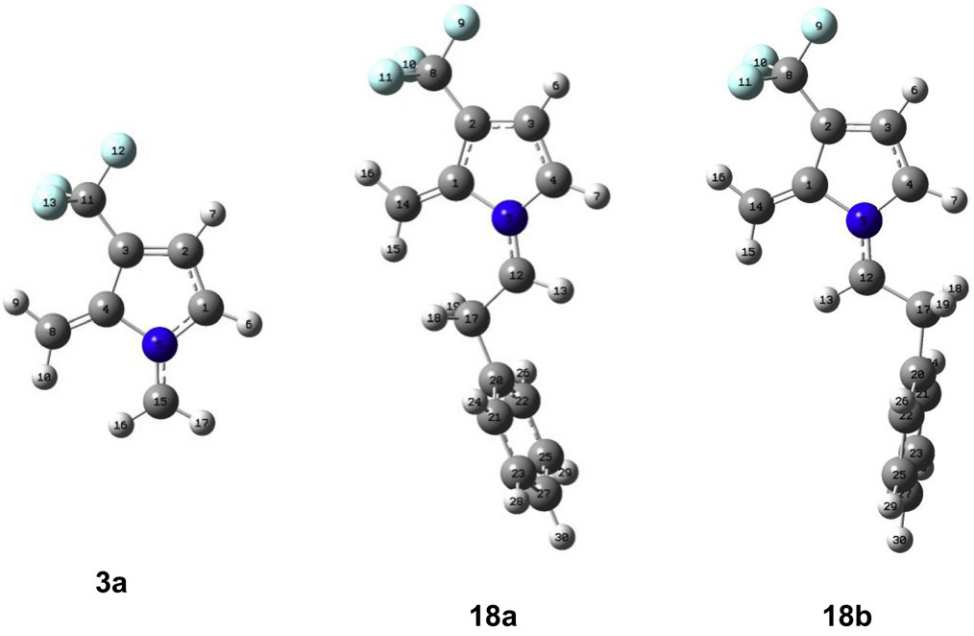


Fig. 3. Optimized geometries of 5-trifluoromethyl-azafulvenium methide (**3a**) and of the two relevant conformers of 1-benzyl-5-trifluoromethyl-azafulvenium methide (**18**), at B3LyP(6-31+G(d,p)) level of theory.

We have previously reported that the frontier molecular orbital (FMO) analysis of the cycloaddition reactions of trifluoromethyl-azafulvenium methide **3a** indicated that the HOMO$_{dipole}$–LUMO$_{dipolarophile}$ is the dominant interaction for strong electron-deficient dipolarophiles such as DMAD and NPM. In the HOMO dipole controlled reaction, the C1 and C3 reactive sites of dipole **3a** have the highest orbital coefficients indicating that the 1,3-cycloaddition should take place exclusively as observed experimentally. For the less-activated dipolarophiles such as ethyl 3-phenylpropiolate, the LUMO$_{dipole}$–HOMO$_{dipolarophile}$ interaction must also be considered. The LUMO of the azafulvenium methide **3a** is characterized by having the C1 and C7 reactive sites with the highest orbital coefficients, favoring the 1,7-cycloaddition. This rationalization explains the formation of both 1,3-cycloadduct and 1,7-cycloadduct in the reaction of azafulvenium methide **3a** with ethyl 3-phenylpropiolate (Scheme 2).[4h]

FMO analysis of the cycloaddition reactions of **18a** and **18b**, summarized in Fig. 4 and Table 1, has been carried out. The values of the HOMO and LUMO energies of azafulvenium methide **3a** are lower than the corresponding values obtained for azafulvenium methide **18**. Nevertheless, HOMO$_{dipole}$–LUMO$_{dipolarophile}$ is still the dominant interaction for strong electron-deficient dipolarophiles. Analyzing the HOMO$_{dipole}$ controlled cycloaddition of azafulvenium methide **18**, we found that the C1 and C3 reactive sites of the fulvenium methide **18** with *N*-substituted maleimides, quantum chemical calculations were carried out at the DFT level of theory (see Supplementary data). The B3LYP functional, selected for this task, has been shown to be an effective method for modeling dipolar cycloadditions.[7] 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 are reported in Table 2. The optimized geometries of relevant transition structures for the cycloaddition of azafulvenium **18b** and maleimides are presented in Fig. 6.

Calculations carried out to estimate the relative stability of the *cis*- and *trans*-1,7(1,3)-cycloadducts revealed that the *cis*-derivatives, which were not detected, are around 17 kJ mol^{-1} less stable. On the other hand, calculations also indicate that *trans*-1,7-cycloadducts **23**, identified as the major products, are around 8 kJ mol^{-1} more stable than the *trans*-1,3-counterparts **22**.

In this analysis of the cycloaddition of azafulvenium methide **18** with maleimides, the two conformers **18a** and **18b** were considered. The synthesis of the *trans*-1,7-cycloadducts **23** could only result from the *endo*-1,7-cycloaddition of conformer **18a** through transition state TS$_{endo}$1,7[**18a**] or from the *exo*-1,7-cycloaddition of conformer **18b** through transition state TS$_{exo}$1,7[**18b**] (Scheme 7).

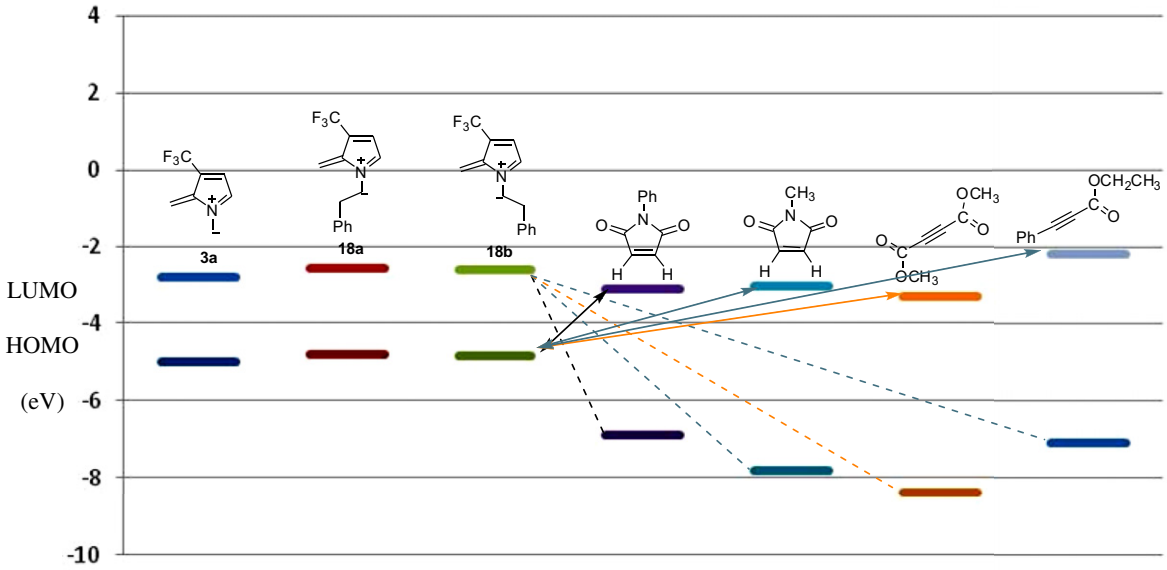


Fig. 4. Relative energies (eV) for dipoles **3a** and **18** and different dipolarophiles [B3LyP/6-31+G(d,p)].

Table 1
Frontier orbital energies (eV) for **3a** and **18** and different dipolarophiles at AM1, PM3, HF/6-31G(d), and B3LyP/6-31+G(d,p) theoretical level

	HOMO				LUMO			
	AM1	PM3	HF/6-31G(d)	B3LyP/6-31+G(d,p)	AM1	PM3	HF/6-31G(d)	B3LyP/6-31+G(d,p)
3a	−7.83	−8.19	−6.15	−5.00	−1.24	−1.44	1.40	−2.81
18a	−7.64	−8.02	−6.08	−4.82	−1.19	−1.43	1.65	−2.56
18b	−7.67	−8.07	−6.12	−4.86	−1.18	−1.42	1.59	−2.60
NPM	−11.61	−11.49	−11.52	−6.87	−1.25	−1.22	1.51	−3.10
NMM	−10.51	−10.18	−11.06	−7.81	−1.14	−1.23	1.55	−3.03
DMAD	−11.96	−11.83	−11.72	−8.40	−0.51	−0.36	3.01	−3.30
Ethyl 3-phenyl-propiolate	−9.68	−9.72	−8.94	−7.09	−0.67	−0.66	2.25	−2.20

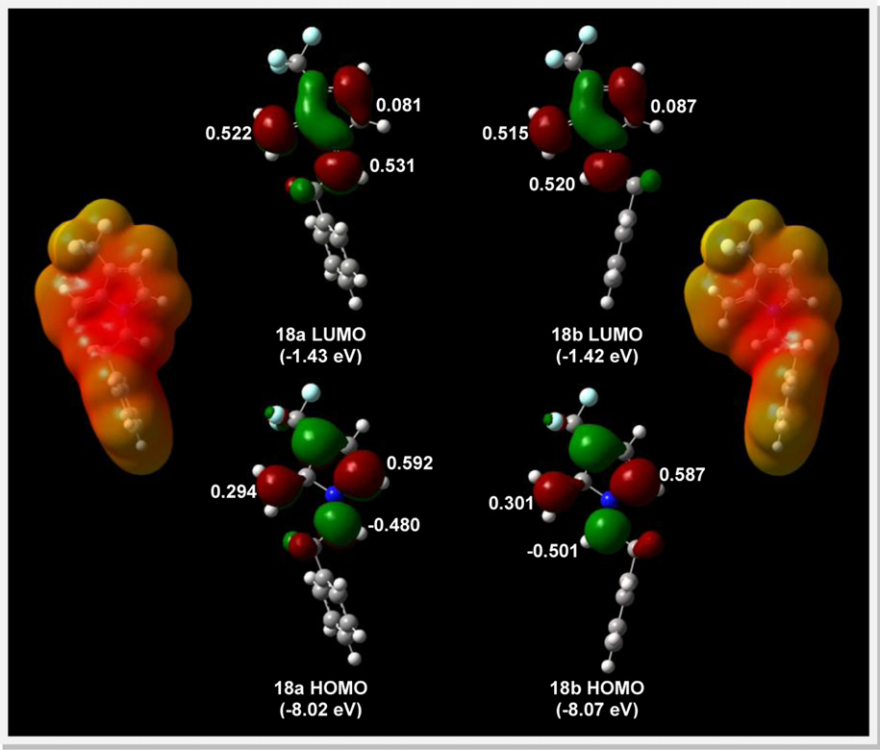


Fig. 5. Surface of electron density, isosurface of HOMO and LUMO of **18a**,**b** and calculated MO coefficients (PM3) at the reactive sites C1, C3, and C7 are also presented.

Table 2
Transition state energies at B3LyP/6-31+G(d,p) theoretical level, calculated relative to conformer **18b** and the corresponding maleimide

1,7-Cycloaddition	B3LyP/6-31+G(d,p) kJ mol^{-1}	1,3-Cycloaddition	B3LyP/6-31+G(d,p) kJ mol^{-1}
TS$_{exo}$1,7[**18b**]Me	5.14	TS$_{exo}$1,3[**18a**]Me	19.40
TS$_{endo}$1,7[**18a**]Ph	24.78	TS$_{endo}$1,3[**18b**]Ph	12.40
TS$_{endo}$1,7[**18a**]Me	25.84	TS$_{endo}$1,3[**18b**]Me	8.93
TS$_{exo}$1,7[**18b**]Ph	3.49	TS$_{exo}$1,3[**18a**]Ph	18.00

barrier, relative to the conformer **18b** for this 1,3-cycloaddition. In addition, NBO calculation on the transition states TS$_{endo}$1,7[**18a**] and TS$_{exo}$1,7[**18b**], also showed the same kind of effective energy interactions between the N_5—C_{26} two-center bond (BD), the C_1—C_{37} two-center bond (BD), as well as the N_5—C_{26} two-center antibonding (BD*), all with the π antibonding orbital (π*) of C_{40}—C_{42} favoring the formation of TS$_{endo}$1,7[**18a**] by about 9 kJ mol^{-1} (Fig. 5). Nevertheless, this effective stabilization in the *endo*-cycloaddition

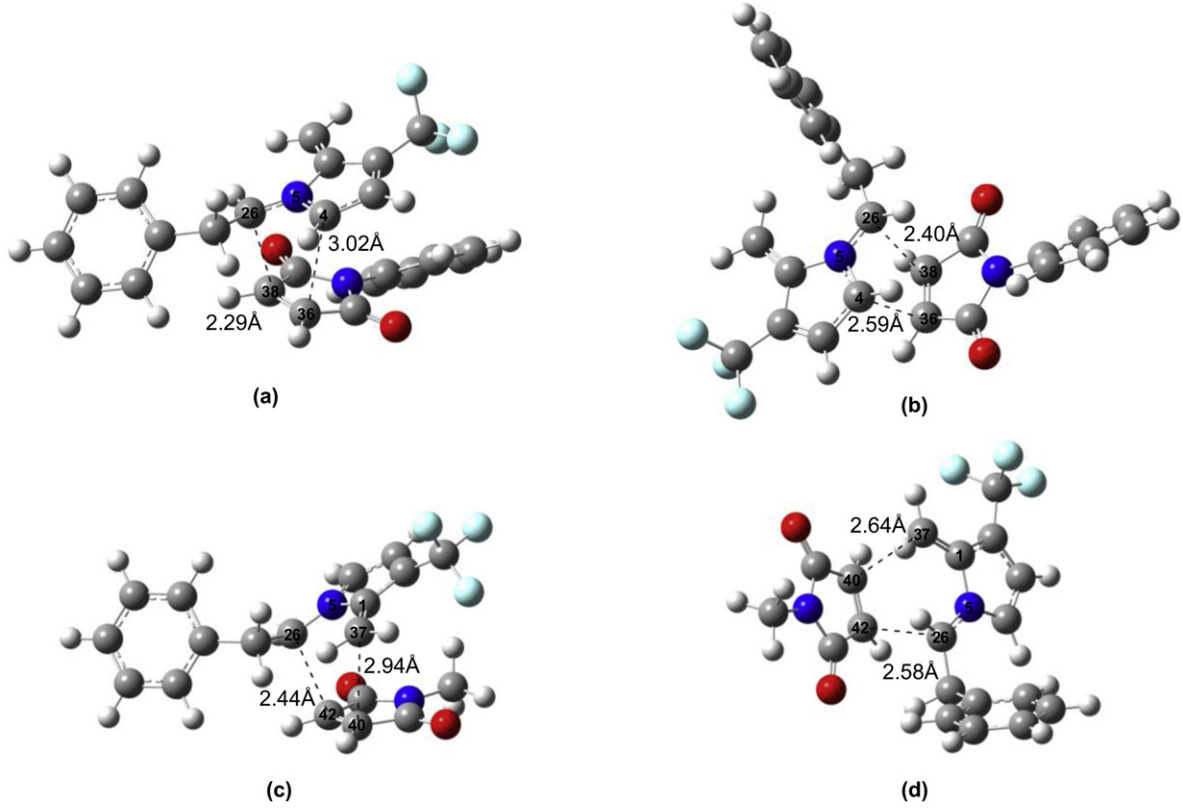


Fig. 6. Geometries of transition states for the cycloaddition of azafulvenium methide **18b** with NPM, TS$_{endo}$1,3 (a) and TS$_{exo}$1,3 (b), and with NMM, TS$_{endo}$1,7 (c) and TS$_{exo}$1,7 (d), calculated at B3LyP(6-31+G(d,p)) level of theory.

Calculations showed that the lower energy channel to obtain the main product is through TS$_{exo}$1,7[**18b**], about 20 kJ mol^{-1} lower in energy than TS$_{endo}$1,7[**18a**] (Fig. 7, Table 2). This result allowed us to conclude that compounds **23** are obtained via *exo*-1,7-cycloaddition of conformer **18b**.

The possible mechanism pathways regarding the cycloadditions of azafulvenium methides **18** with maleimides leading to *trans*-1,3-cycloadducts are shown in Scheme 8. The *trans*-1,3-cycloadducts **22** could be produced only via *endo*-cycloaddition of conformer **18b** through transition state TS$_{endo}$1,3[**18b**] or as the result of the *exo*-cycloaddition of conformer **18a** through transition state TS$_{exo}$1,3 [**18a**].

The results of the quantum chemical calculations demonstrate that the stereoselective synthesis of heterocycles **22** is achieved via *endo-1,3-cycloaddition* through transition state TS$_{endo}$1,3[**18b**] (Fig. 7, Table 2).

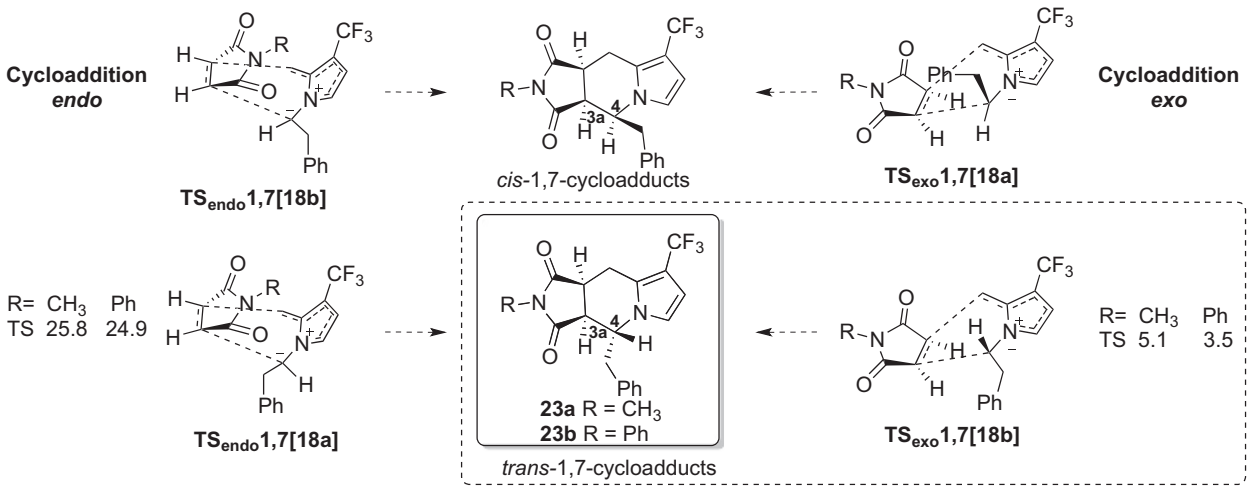
Calculations on specific NBO donor—acceptor interactions in the transition states TS$_{endo}$1,3[**18b**] and TS$_{exo}$1,3[**18a**], showed that there were effective energy interactions between the N_5—C_{26} two-center bond (BD), the C_4 lone pair of electrons (LP) as well as the N_5—C_{26} two-center antibonding (BD*), all with the π antibonding orbital (π*) of C_{36}—C_{38} favoring the formation of TS$_{endo}$1,3[**18b**] by about 13 kJ mol^{-1} according to the results obtained on the energy was not large enough to compensate the large energy barrier through this reaction path, which means that the steric factors play an important role in this cycloaddition (Fig. 6).

3. Conclusion

The generation and reactivity of 1-benzyl-5-trifluoromethyl-azafulvenium methide were described. This reactive intermediate undergoes sigmatropic [1,8]H shift to give the corresponding *N*-styrylpyrrole and participates in cycloaddition reactions with DMAD and *N*-substituted maleimides to afford trifluoromethyl-pyrrole-annulated derivatives resulting from the addition across the 1,3- and 1,7-positions.

The higher selectivity of 5-trifluoromethyl-azafulvenium methide for the formation of 1,3-cycloadducts when compared with 1-benzyl-5-trifluoromethyl-azafulvenium methide, bearing an additional benzyl group at C1, indicates that a combination of electronic and steric factors determines the outcome of the cycloaddition. FMO analysis of the cycloadditions corroborated this observation.

Quantum chemical calculations were carried out at the DFT level of theory in order to be able to rationalize the stereoselective synthesis of *trans*-1,3-cycloadducts and *trans*-1,7-cycloadducts from the cycloaddition of 1-benzyl-5-trifluoromethyl-



Scheme 7. 1,7-Cycloaddition of azafulvenium methide **18** with NMM and NPM.

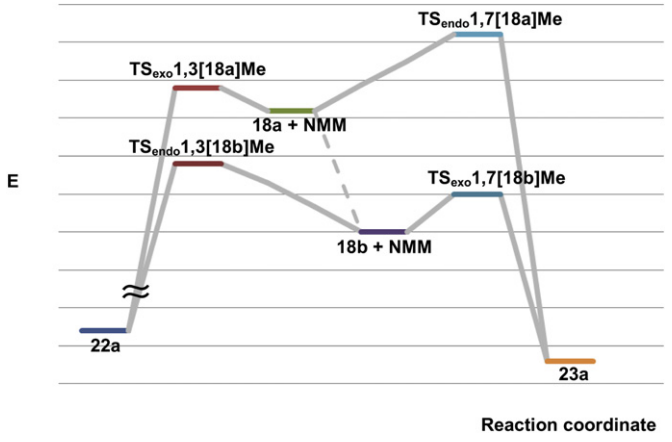


Fig. 7. B3LyP(6-31+G(d,p)) energy (kJ mol^{-1}) calculated relative to conformer **18b** and NMM.

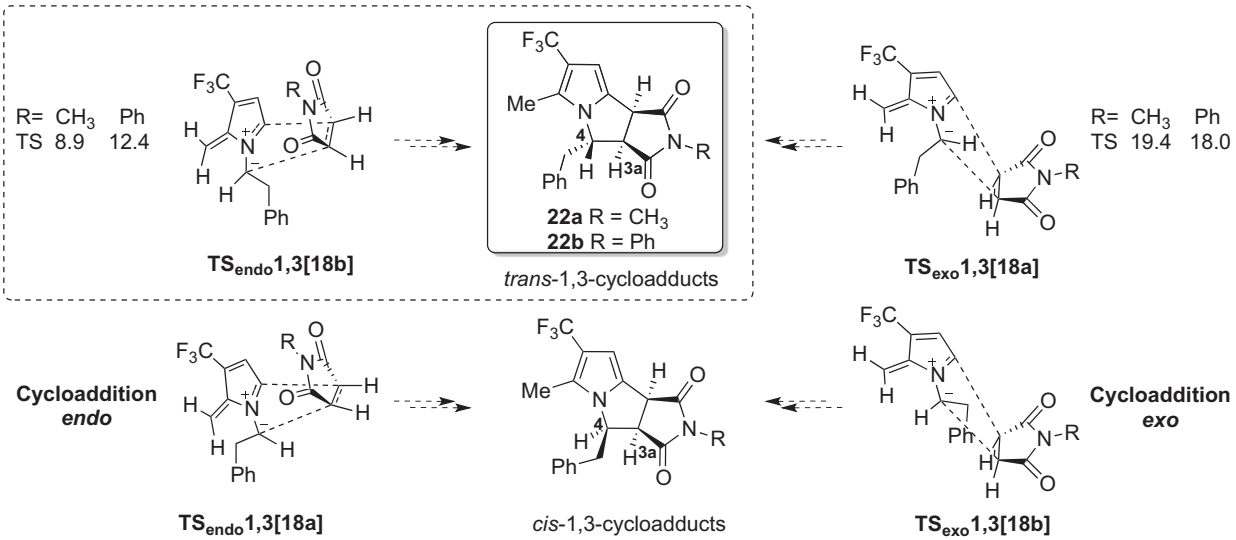
azafulvenium methide with *N*-substituted maleimides. The study revealed that *exo*-cycloaddition is the main reaction path for the 1,7-cycloaddition, while the *endo*-approach is the main mode of reaction leading to 1,3-cycloadducts.

4. Experimental section

4.1. General

Microwave reactions were carried out in a microwave reactor CEM Focused Synthesis System Discover S-Class using 10 mL microwave tubes. The reaction temperatures were measured by infrared surface detector during microwave heating. Thiazolidine **13**,[8] 1-butenyl-thiazolidine **15**, 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **16**, and 7-trifluoromethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide **17** were prepared by modifying a procedure described in the literature.[5]

^{19}F NMR spectra were recorded on an instrument operating at 376 MHz. ^{1}H NMR spectra were recorded on an instrument operating at 400 MHz. ^{13}C NMR spectra were recorded on an instrument



Scheme 8. 1,3-Cycloaddition of azafulvenium methide **18** with NMM and NPM.

operating at 100 MHz. Chemical shifts are expressed in parts per million (ppm) relative to internal tetramethylsilane (TMS), and coupling constants (*J*) are in hertz (Hz). Infrared (IR) spectra were recorded on a Fourier transform spectrometer (FTIR). Mass spectra were recorded under electron impact (EI) or electrospray ionization (ESI). High-resolution mass spectra (HRMS) were obtained on 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 using precoated silica gel plates. Flash column chromatography was performed with silica gel 60 as the stationary phase.

4.2. (2*R*,4*R*)-2-Benzyl-3-[(*E*)-4,4,4-trifluoro-3-oxobut-1-enyl] thiazolidine-4-carboxylic acid (15)

A solution of 4-ethyloxy-1,1,1-trifluoro-3-buten-2-one (3.24 g, 19.3 mmol) in acetonitrile (10 mL) was added dropwise to a solution of thiazolidine-4-carboxylic acid **13** (4.73 g, 21.2 mmol) in acetonitrile (90 mL) at room temperature. After stirring for 10 min, the solution was heated at 60 °C for 24 h. Then the reaction mixture was filtered and the solvent was removed in vacuum. Diethyl ether (120 mL) and water (120 mL) were added and the two layers separated. The aqueous phase was extracted with diethyl ether (2×120 mL) and the combined organic phases were dried ($MgSO_4$) and the solvent removed in vacuum. The resulting pale yellow oil was purified by column chromatography [hexane, hexane/ethyl acetate (7:3), then hexane/ethyl acetate (1:1)] to give **15** as a solid (5.60 g, 84%).

*4.2.1. Data for **15**.* Mp 184–185 °C (amorphous solid, from hexane/ethyl acetate). ^{19}F NMR (376 MHz, DMSO-d_6): δ −74.99. ^{1}H NMR (400 MHz, DMSO-d_6): two conformers. Major: δ 8.15 (d, J=12.7 Hz, 1H), 5.64 (d, J=12.7 Hz, 1H), 5.43 (m, 1H), 5.08 (d, J=6.5 Hz, 1H), 3.27 (m, 2H), 3.12 (m, 2H). Minor: δ 8.23 (d, J=12.4 Hz, 1H), 5.35 (m, 1H), 5.32 (d, J=12.4 Hz, 1H), 4.94 (d, J=5.1 Hz, 1H), 3.27 (m, 2H), 3.01 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): two conformers. Major: δ 175.7 (q, J_{CO-CF_3}=31.6), 171.0, 153.4, 136.5, 129.9, 128.3, 126.9, 117.5 (q, J_{CF_3}=292.0), 90.5, 67.9, 65.5, 38.3, 30.8. Minor: δ 175.5 (q, J_{CO-CF_3}=31.6), 169.0, 152.2, 136.6, 130.0, 128.2, 126.9, 117.4 (q, J_{CF_3}=291.25), 90.1, 69.7, 63.8, 42.8, 31.4. IR (KBr, cm^{-1}): 3300–2700 br, 3031, 2933, 1724, 1659, 1558, 1456, 1383, 1283, 1265, 1137, 1100, 787, 699. HRMS (ESI-TOF): calculated $C_{15}H_{15}F_3NO_3S$ [M^++H]: 346.07072. Found: 346.07193.

4.3. (*R*)-3-Benzyl-7-trifluoromethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (16)

To a stirred solution of *N*-(unsaturated ketone) thiazolidine-4-carboxylic **15** (5.87 g, 17.0 mmol) under nitrogen in dry dichloromethane (140 mL), trifluoroacetic anhydride (4.28 g, 20.4 mmol) was added dropwise at 0 °C. After stirring at 0 °C for 1 h and at room temperature for 7 h, the solvent was removed in vacuum. The resulting brown oil was purified by flash chromatography [hexane, hexane/ethyl acetate (9:1)] to give the corresponding (*R*)-3-benzyl-7-trifluoromethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **16** as a white solid (3.66 g, 76%).

*4.3.1. Data for **16**.* Mp 40–41 °C (amorphous solid). $[\alpha]_D^{26}$ +91.3 (*c*, 1.1 $CHCl_3$). ^{19}F (376 MHz, $CDCl_3$): δ −55.58. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.26 (m, 1H), 3.74 (d, J=13.7 Hz, 1H), 3.92 (d, J=13.7 Hz, 1H), 5.60 (m, 1H), 6.41 (d, J=2.5 Hz, 1H), 6.48 (d, J=2.5 Hz, 1H), 7.10 (m, 2H), 7.29 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.3, 134.6 (q, J_{CC-CF_3}=3.8 Hz), 129.8, 128.6, 127.6, 124.0 (q, J_{CF_3}=265.6 Hz), 115.1, 111.3, 106.2 (q, J_{C-CF_3}=36.7 Hz), 65.0, 44.8, 27.8. IR (KBr, cm^{-1}): 3112, 3031, 2922, 1587, 1485, 1454, 1437, 1393, 1374, 1258, 1224, 1171, 1103, 1030, 978, 751, 698. MS (EI): 283(M^+, 5%), 250(10%), 236(3%), 192(100%), 148(33%), 135(5%), 104(7%), 91(12%). HRMS (EI-TOF): calculated $C_{14}H_{12}F_3NS$ [M^+]: 383.0643. Found: 383.0647.

4.4. 3-Benzyl-7-trifluoromethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide (17)

A solution of (*R*)-3-benzyl-7-trifluoromethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **16** (0.567 g, 2 mmol) in ethyl acetate (3 mL) was charged with $Na_2WO_4 \cdot 2H_2O$ (1 M solution in water, 45 μL), $C_6H_5PO_3H_2$ (1 M solution in water, 45 μL), $CH_3N[(CH_2)_7CH_3]_3Cl$ (1 M solution in methanol, 45 μL), and aqueous 35% H_2O_2 (75 mmol). This mixture was vigorously stirred at 40 °C. After 3 days, a new load of catalysts and H_2O_2 was added and stirred again for three more days at 40 °C. The reaction mixture was washed with 10% (w/v) aqueous sodium bisulfite and the aqueous phase was extracted with ethyl acetate. The organic phase was then dried over anhydrous Na_2SO_4 and the solvent evaporated off giving a pale yellow oil which was purified by column chromatography [hexane, hexane/ethyl acetate (9:1), hexane/ethyl acetate (8:2)] to give sulfone **17** as a white solid (0.448 g, 71%).

*4.4.1. Data for **17**.* Mp 110–111 °C (amorphous solid). $[\alpha]_D^{26}$ 0.0 (*c*, 1.0 $CHCl_3$). ^{19}F (376 MHz, $CDCl_3$): δ −56.13. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.15 (dd, J_1=14.6 Hz, J_2=4.8 Hz, 1H), 3.59 (dd, J_1=14.6 Hz, J_1=8.0 Hz, 1H), 4.04 (d, J=15.5, 1H), 4.37 (d, J=15.5 Hz, 1H), 5.16 (dd, J_1=8.0 Hz, J_2=4.8 Hz, 1H), 6.34 (d, J=2.8 Hz, 1H), 6.41 (d, J=2.8 Hz, 1H), 7.15 (m, 2H), 7.34 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.7, 129.8, 129.2, 128.3, 123.2 (q, J_{CF_3}=266.3 Hz), 121.4 (q, J_{CC-CF_3}=3.9), 119.1, 111.8 (q, J_{C-CF_3}=37.4 Hz), 75.5, 49.8, 37.3, 135.3, 134.6 (q, J_{CC-CF_3}=3.8 Hz), 129.8, 128.6, 127.6, 124.0 (q, J_{CF_3}=265.6 Hz), 115.1, 111.3, 106.2 (q, J_{C-CF_3}=36.7 Hz), 65.0, 44.8, 27.8. IR (KBr, cm^{-1}): 3169, 3093, 3037, 2981, 2963, 2950, 1600, 1484, 1457, 1438, 1400, 1330, 1262, 1175, 1133, 973, 749, 719, 697. MS (EI): 315(M^+, 3%), 251(89%), 250(80%), 236(33%), 232(9%), 182(9%), 174(4%), 167(7%), 154(3%), 148(3%), 113(4%), 104(100%), 78(9%). HRMS (EI-TOF): calculated $C_{14}H_{12}F_3NO_2S$ [M^+]: 315.0541. Found: 315.0542.

4.5. Synthesis of 2-methyl-1-styryl-3-trifluoromethyl-1*H*-pyrrole (19)

Flash vacuum pyrolysis. Pyrolysis of the 3-benzyl-7-trifluoromethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide (**17**) (107.2 mg, 0.34 mmol) at 450–475 °C and 1×10^{-5} to 2×10^{-5} mbar onto a surface cooled at −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 a pre-oven, which heated the sample at 70–80 °C.]. The pyrolysate was allowed to warm to room temperature and removed from the cold finger with dichloromethane. The solvent was removed in vacuum and the pyrolysate was recrystallized from a mixture of hexane/ethyl acetate to give 2-methyl-1-styryl-3-trifluoromethyl-1*H*-pyrrole **19**, in high yield as a white solid (76.9 mg, 90%).

Conventional heating. A suspension of 7-trifluoromethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide **17** (50.5 mg, 0.16 mmol) in 1,2,4-trichlorobenzene (1 mL) was heated at reflux under dry nitrogen for 6 h. After cooling to room temperature, the pyrolysate was purified by column chromatography [hexane, hexane/ethyl acetate (9:1)] to give 2-methyl-1-styryl-3-trifluoromethyl-1*H*-pyrrole **19**, which was isolated in high yield as a white solid (34.2 mg, 85%).

*4.5.1. Data for 1H-pyrrole **19**.* Mp 76–77 °C (amorphous solid). ^{19}F (376 MHz, $CDCl_3$): δ −54.93. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 6.38 (d, J=2.8 Hz, 1H), 6.66 (d, J=14.3 Hz, 1H), 6.96 (d, J=2.8 Hz, 1H), 7.26 (d, J=14.3 Hz, 1H), 7.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 129.0, 128.0, 127.4, 126.3, 124.4(q, J_{CF_3}=266.3 Hz), 123.5, 119.5, 116.9, 113.0 (q, J_{C-CF_3}=35.4 Hz), 107.9 (q, J_{CC-CF_3}=2.9 Hz), 10.5.

IR (KBr, cm^{-1}): 3115, 3085, 3028, 2981, 2929, 1655, 1587, 1495, 1440, 1268, 1098, 1019, 934, 750, 722, 688. MS (EI): 251(M^+, 81%), 250(100%), 236(22%), 232(11%), 181(20%), 167(15%), 148(6%), 104(42%), 103(10%), 77(8%). HRMS (EI-TOF): calculated $C_{14}H_{12}F_3N$ [M^+]: 251.0922. Found: 251.0917.

4.6. General procedure for cycloadditions under MWIP conditions

A suspension of 7-trifluoromethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide **17** (53.6 mg, 0.17 mmol) and dipolarophile (1.2–4.0 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.

*4.6.1. Dimethyl 3-benzyl-5-methyl-6-trifluoromethyl-3H-pyrrolizine-1,2-dicarboxylate (**20**) and dimethyl 5-benzyl-1-trifluoromethyl-5,8-dihydroindolizine-6,7-dicarboxylate (**21**).* Isolated as an 89:11 mixture (determined by ^{1}H NMR), 44% yield.

*4.6.1.1. Data for **20**.* ^{19}F (376 MHz, $CDCl_3$): δ −55.37. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.38 (dd, J_1=14.6 Hz, J_2=4.4 Hz, 1H), 3.46 (dd, J_1=14.6 Hz, J_2=4.6 Hz, 1H), 3.81 (s, 3H), 3.84 (s, 3H), 5.26 (m, 1H), 6.26 (s, 1H), 6.78 (d, J=3.7 Hz, 2H), 7.17 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 162.6, 135.6, 134.0, 131.7, 129.9 (q, J_{CC-CF_3}=3.7 Hz), 129.3, 128.5, 127.4, 123.9 (q, J_{CF_3}=267.0 Hz), 116.6 (q, J_{C-CF_3}=36.0 Hz), 102.0 (q, J_{CC-CF_3}=2.9 Hz), 63.7, 52.8, 52.3, 37.2, 11.52.

*4.6.1.2. Data for **21**.* ^{19}F (376 MHz, $CDCl_3$): δ −55.07. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.08 (dd, J_1=13.5 Hz, J_2=3.3 Hz, 1H), 3.23 (dd, J_1=13.5 Hz, J_2=4.6 Hz, 1H), 3.79 (s, 3H), 3.89 (s, 3H), 3.92 (m, 2H), 5.34 (m, 1H), 6.42 (d, J=2.6 Hz, 1H), 6.64 (d, J=2.6 Hz, 1H), 6.65 (br s, 2H), 7.17 (m, 3H)., HRMS (ESI-TOF): mixture of compounds **20** and **21**: calculated $C_{20}H_{19}F_3NO_4$ [M^++H]: 394.12589. Found: 394.12607.

*4.6.2. 4-Benzyl-2,6-dimethyl-7-trifluoromethyl-3a,4-dihydropyrrolo[3,4-a]pyrrolizine-1,3(2H,8bH)-dione (**22a**) and 4-benzyl-2-methyl-8-trifluoromethyl-3a,4,9,9a-tetrahydro-1H-pyrrolo[3,4-f]indolizine-1,3(2H)-dione (**23a**).* Isolated as a 28:72 mixture (determined by ^{1}H NMR), 88% yield.

*4.6.2.1. Data for **22a**.* ^{19}F (376 MHz, $CDCl_3$): δ −55.17. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.89 (s, 3H), 3.06 (dd, J_1=14.2 Hz, J_2=4.2 Hz, 1H), 3.12 (dd, J_1=14.2 Hz, J_2=5.3 Hz, 1H), 3.43 (d, J=7.4 Hz, 1H), 3.61(d, J=7.4 Hz, 1H), 5.00 (t, J=4.6 Hz, 1H), 6.10 (s, 1H), 6.80 (d, J=6.6 Hz, 2H), 7.25 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.07, 174.30, 134.3, 129.5, 129.0, 127.8, 127.6, 124.0 (q, J_{CC-CF_3}=3.7 Hz), 124.0 (q, J_{CF_3}=266.7 Hz), 116.2 (q, J_{C-CF_3}=35.5 Hz), 99.9(q, J_{CC-CF_3}=3.7 Hz), 53.1, 25.4, 59.1, 43.5, 41.1, 10.8.

*4.6.2.2. Data for **23a**.* ^{19}F (376 MHz, $CDCl_3$): δ −54.55. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.83 (s, 3H), 2.98 (dd, J_1=15.8 Hz, J_1=7.2 Hz, 1H), 3.20 (dd, J_1=9.2 Hz, J_2=3.8 Hz, 1H), 3.26 (m, 1H), 3.37(dd, J_1=13.4 Hz, J_2=5.2 Hz, 1H), 3.52(d, J=15.8 Hz, 1H), 3.76 (dd, J_1=13.4 Hz, J_2=6.1 Hz, 1H), 4.31 (m, 1H), 6.24 (d, J=2.6 Hz, 1H), 6.62 (d, J=2.6 Hz, 1H), 7.34 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 175.5, 136.2, 129.6, 129.0, 127.4, 126.4 (q, J_{C-C-CF_3}=3.67 Hz), 124.1(q, J_{C-C-CF_3}=266.8 Hz), 117.27, 111.6 (q, J_{C-C-CF_3}=36.4 Hz), 105.9 (q, J_{C-C-CF_3}=2.9 Hz), 56.2, 42.5, 39.4, 34.5, 25.1, 22.2.

HRMS (ESI-TOF): mixture of compounds **22a** and **23a**: calculated $C_{19}H_{18}F_3N_2O_2$ [M^++H]: 363.13254. Found: 363.13149.

*4.6.3. 4-Benzyl-6-methyl-2-phenyl-7-trifluoromethyl-3a,4-dihydropyrrolo[3,4-a]pyrrolizine-1,3(2H,8bH)-dione (**22b**) and 4-benzyl-2-phenyl-8-trifluoromethyl-3a,4,9,9a-tetrahydro-1H-pyrrolo[3,4-f]indolizine-1,3(2H)-dione (**23b**).* Isolated as a 24:76 mixture (determined by ^{1}H NMR), 77% yield.

*4.6.3.1. Data for **22b**.* Mp 135–136 °C (amorphous solid). ^{19}F (376 MHz, $CDCl_3$): δ −55.21. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 3.10 (dd, J_1=14.3 Hz, J_2=5.2 Hz, 1H), 3.18 (dd, J_1=14.3 Hz, J_2=4.0 Hz, 1H), 3.52 (d, J=7.49 Hz, 1H), 3.79 (d, J=7.49 Hz, 1H), 5.11 (m, 1H), 6.17 (s, 1H), 6.82 (d, J=6.1 Hz, 2H), 7.17 (d, J=7.37 Hz, 2H), 7.25 (d, J=6.3 Hz, 2H), 7.40 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 176.2, 134.3, 131.4, 129.5, 129.3, 129.1, 129.0, 128.1, 127.9, 126.3, 124.3 (q, J_{C-C-CF_3}=3.6 Hz), 124.0 (q, J_{CF_3}=267.0 Hz), 116.5 (q, J_{C-CF_3}=36.1 Hz), 100.6 (q, J_{C-C-CF_3}=2.9 Hz), 43.6, 53.3, 59.3, 41.0, 10.9. MS (EI): 424(M^+, 13%), 333(12%), 187(7%), 186(100%), 173(2%), 166(7%), 117(8%), 91(8%). HRMS (EI-TOF): calculated $C_{24}H_{19}F_3N_2O_2$ [M^+]: 424.1398. Found: 424.1399.

*4.6.3.2. Data for **23b**.* Mp 94–95 °C (amorphous solid). ^{19}F (376 MHz, $CDCl_3$): δ −54.42. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.00(dd, J_1=15.5 Hz, J_2=6.8 Hz, 1H), 3.31(dd, J_1=9.2 Hz, J_2=3.2 Hz, 1H), 3.39 (m, 1H), 3.46 (dd, J_1=13.0 Hz, J_2=5.9 Hz, 1H), 3.68 (d, J=15.5 Hz, 1H), 3.83 (dd, J_1=13.0 Hz, J_2=10.5 Hz, 1H), 4.37(m, 1H), 6.33 (d, J=2.7 Hz, 1H), 6.72(d, J=2.7 Hz, 1H), 6.91(d, J=7.3 Hz, 2H), 7.37 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 174.6, 136.2, 131.4, 129.7, 129.4, 129.1(x2), 127.5, 126.5, 126.4 (q, J_{C-C-CF_3}=3.67 Hz), 124.1 (q, J_{C-C-CF_3}=266.6 Hz), 117.3, 111.6 (q, J_{C-C-CF_3}=36.4 Hz), 106.0 (q, J_{C-C-CF_3}=2.9 Hz), 56.4, 42.7, 39.9, 34.3, 23.0. MS (EI): 424(M^+, 43%), 333(18%), 187(8%), 186(100%), 174(5%), 166(9%), 117(23%), 91(9%). HRMS (EI-TOF): calculated $C_{24}H_{19}F_3N_2O_2$ [M^+]: 424.1398. Found: 424.1399.

4.7. Computational study

All calculations were performed with the Gaussian09 program system.[9] 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 reactions coordinate (IRC) method was applied to verify that the correct states were connected.

Acknowledgements

Thanks are due to FCT (PEst-C/QUI/UI0313/2011), FEDER, COMPETE, and QREN for financial support. W.J.P. acknowledges the National Scientific and Technical Research Council (CONICET) of Argentina for the Post-Doctoral fellowship and Ana Julieta Pepino for the assistance in the theoretical study.

Supplementary data

^{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. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.03.017.

References and notes

1. Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827–856.
2. (a) Muzalevskiy, V. M.; Shastin, A. V.; Balenkova, E. S.; Haufe, G.; Nenajdenko, V. G. *Synthesis* **2009**, *23*, 3905–3929; (b) Saijo, R.; Hagimoto, Y.; Kawase, M. *Org. Lett.* **2010**, *12*, 4776–4779; (c) Saijo, R.; Kawase, M. *Tetrahedron Lett.* **2012**, *53*, 2782–2785.

3. (a) Black, B. C.; Hollingworth, R. M.; Ahammadsahib, K. Y.; Kukel, C. D.; Donovan, S. *Pestic. Biochem. Physiol.* **1994**, *50*, 115–128; (b) Zanatta, N.; Schneider, J. M. F. M.; Schneider, P. H.; Wouters, A. D.; Bonacorso, H. G.; Martins, M. A. P.; Essjohann, L. A. *J. Org. Chem.* **2006**, *71*, 6996–6998; (c) Dou, G.; Shi, C.; Shi, D. *J. Comb. Chem.* **2008**, *10*, 810–813; (d) Uno, H.; Inoue, K.; Inoue, T.; Fumoto, Y.; Ono, N. *Synthesis* **2001**, 2255–2258; (e) Fitzgerald, J. P.; Nanda, H.; Fitzgerald, P.; Yee, G. T. *J. Org. Chem.* **2000**, *65*, 2222–2224; (f) Funabiki, K.; Ishihara, T.; Yamanaka, H. *J. Fluorine Chem.* **1995**, *71*, 5–7; (g) Zanatta, N.; Wouters, A. D.; Fantinnel, L.; da Silva, F. M.; Barichello, R. *Synlett* **2009**, 755–758; (h) Korotaev, V. Yu; Barkov, A. Yu; Kotovich, I. V.; Sosnovskikh, V. Ya *J. Fluorine Chem.* **2012**, *138*, 42–47.
4. (a) Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Rocha Gonsalves, A. M. d'A.; McNab, H. *Tetrahedron Lett.* **2004**, *45*, 3889–3893; (b) Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Rocha Gonsalves, A. M. d'A.; Paixão, J. A.; Matos Beja, A.; Ramos Silva, M. *J. Org. Chem.* **2005**, *70*, 6629–6638; (c) Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Nunes, C. M. *Tetrahedron* **2007**, *63*, 1833–1841; (d) Soares, M. I. L.; Pinho e Melo, T. M. V. D. *Tetrahedron Lett.* **2008**, *49*, 4889–4893; (e) Soares, M. I. L.; Lopes, S. M. M.; Cruz, P. F.; Brito, R. M. M.; Pinho e Melo, T. M. V. D. *Tetrahedron* **2008**, *64*, 9745–9753; (f) Pereira, N. A. M.; Serra, A. C.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2010**, 6539–6543; (g) Pereira, N. A. M.; Fonseca, S. M.; Serra, A. C.; Pinho e Melo, T. M. V. D.; Burrows, H. D. *Eur. J. Org. Chem.* **2011**, 3970–3979; (h) Nunes, C. M.; Ramos Silva, M.; Matos Beja, A.; Fausto, R.; Pinho e Melo, T. M. V. D. *Tetrahedron Lett.* **2010**, *51*, 411–414.
5. (a) Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Rocha Gonsalves, A. M. d'A. *Tetrahedron Lett.* **2006**, *47*, 791–794; (b) Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Nunes, C. M.; Paixão, J. A.; Matos Beja, A.; Ramos Silva, M. *J. Org. Chem.* **2007**, *72*, 4406–4415.
6. (a) Druzhinin, S. V.; Balenkova, E. S.; Nenajdenko, V. G. *Tetrahedron* **2007**, *63*, 7753–7808; (b) Andrew, R. J.; Mellor, J. M. *Tetrahedron* **2000**, *56*, 7267–7272.
7. Ess, H.; Houk, K. N. *J. Phys. Chem. A.* **2005**, *109*, 9542–9553.
8. Soloway, H.; Kipnis, F.; Ornfelt, J.; Spoerri, P. E. *J. Am. Chem. Soc.* **1948**, *70*, 1667–1668.
9. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Ioslowski, J.; Fox, D. J. *Gaussian 09, Revision B.01*; Gaussian: Wallingford, CT, 2010.