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Synthesis of 1,3-Diaryl-3-trifluoromethylcyclopropenes by Transition-Metal-Free Reaction of 2,2,2-Trifluoroacetophenone Tosylhydrazones with Alkynes: The Effect of the Trifluoromethyl Group

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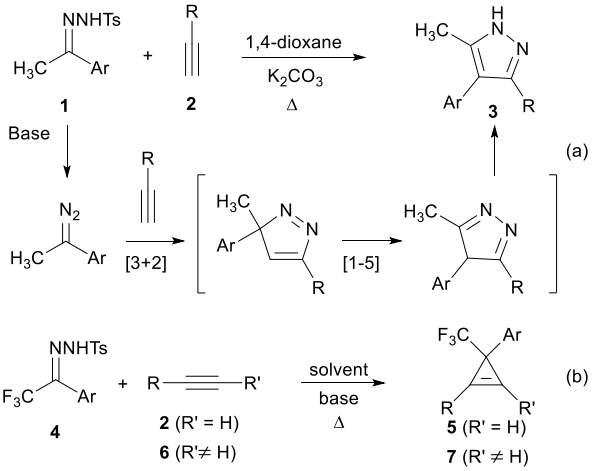
1,3-Diaryl-3-trifluoromethylcyclopropenes and 2-aryl- or 2-alkyl-1,3-diaryl-3-trifluoromethylcyclopropenes are prepared in a very simple way by reaction between 1,1,1-trifluoroacetophenone tosylhydrazones and terminal or internal alkynes respectively in a base promoted process that does not require the presence of any metal catalyst. The essential role of the trifluoromethyl group, which enables the formation of the cyclopropenes instead of the expected pyrazoles has been computationaly investigated, suggesting the participacion of a free carbene.

The synthesis of organic molecules containing trifluoromethyl substituents is a field of permanent interest in organic synthesis, due to the strong influence of the fluorinated rests on the physical, chemical and biological properties of the compounds.[1] In fact, trifluoromethylated molecules are of high interest in medicinal, agrochemical and materials chemistry. On the other hand, cyclopropenes, very strained carbocyclic compounds, are versatile intermediates in organic synthesis as a result of their high reactivity.[2,3] Therefore, trifluoromethyl substituted cyclopropenes might result in very interesting intermediates for the preparation of more complex trifluoromethyl-containing organic molecules. Various methodologies have been described for the synthesis of 3-trifluoromethylcyclopropenes with different substitution patterns, consisting in all cases in metal catalyzed cyclopropenation reactions between the corresponding trifluoromethyl diazo compounds and alkynes. [4,5]

We have recently reported the synthesis of 3,4,5- and 1,3,5-trisubstituted pyrazoles by reactions of tosylhydrazones of ketones with terminal alkynes, in the presence of a base.[6] In particular, with tosylhydrazones **1** derived from acetophenones, the 3,4,5-trisubstituted pyrazoles **3** are obtained as pure regioisomers (scheme 1, a). The mechanism proposed for this transformation involves the 1,3-dipolar cycloaddition of the diazo compound generated from the tosylhydrazone with the terminal alkyne followed by a [1,5]-sigmatropic rearrangement (scheme 1, a). With the aim to expand this methodology to the synthesis of the biologically relevant trifluoromethyl-substituted pyrazoles, the same reaction was studied starting from tosylhydrazones **4** derived from 2,2,2-trifluoroacetophenones.[7,8] Surprisingly, the expected pyrazoles were never detected, but instead, under the proper reaction conditions, the trisubstituted or tetrasubstituted 3-aryl-3-trifluoromethylcyclopropenes **5** or **7** were obtained as main product of the reaction (scheme 1, b).



Scheme 1: (a) Synthesis of trisubstituted pyrazoles by reaction of tosylhydrazones **1** with terminal alkynes. (b) Differential behavior observed for the trifluoromethylated tosylhydrazones **4** presented in this work.

Considering the atractiveness of cyclopropenes as synthetic intermediates, the great interest of trifluoromethylated organic molecules, as well as the potential simplicity of this reaction, we carried out a study to establish the scope and synthetic usefulness of this particular transformation. Furthermore, the

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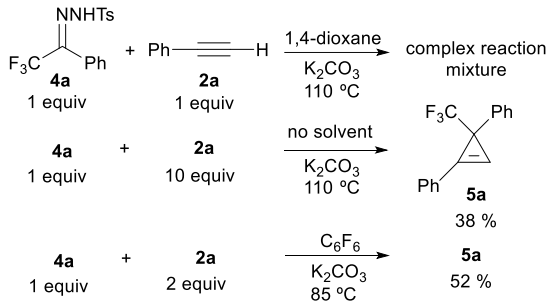
Electronic Supplementary Information (ESI) available: [Experimental procedures, characterization data and copies of the ^{1}H and ^{13}C NMR spectra for compounds **5** and **7**. Computational details, energy tables and cartesian coordinates for the stationary points represented in figure 1]. See DOI: 10.1039/x0xx00000x

differential behavior of the trifluoromethylated tosylhydrazones when compared with our previous results with the acetophenone derivatives, provided additional encouragement at the outset of this work.

Our initial experiments were conducted employing the tosylhydrazone of 2,2,2-trifluoroacetophenone **4a** and phenylacetylene, under the reaction conditions previously developed for the synthesis of 3,4,5-trisubstituted pyrazoles mentioned above (K_2CO_3 as base, 1,4-dioxane as solvent, at various temperatures). Formation of the pyrazole was never detected, and instead, a complex reaction mixture, suggesting the incorporation of molecules of solvent, probably through a C-H insertion process, was obtained.[9] To avoid the competitive reaction of the solvent, the same transformation was then attempted without solvent and under a large excess of the alkyne (10 equiv). Formation of the pyrazole was not detected either, but instead the cyclopropene **5a** was isolated in a promising 38 % yield. This preliminary result was noteworthy because it represented a differential behavior of the trifluoroacetophenone hydrazone **4a** when compared with the analogous non fluorinated tosylhydrazones. Additionally, although limited examples of the synthesis of 3-aryl-3-trifluoromethylcyclopropenes have been previously reported, those methods require the employ of transition metal catalysts.[4,10] For these reasons, we decided to invest some effort in order to find most convenient ways to achieve this transformation.



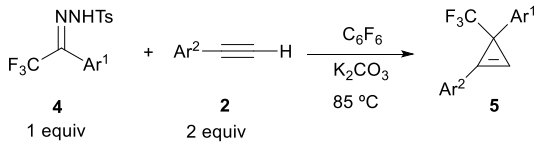
Scheme 2: Reaction of trifluoromethylated tosylhydrazone **4a** with phenylacetylene **2a**: Preliminary studies.

Indeed, after extensive experimentation, it was found that better results could be obtained by running the reaction employing hexafluorobenzene as solvent, at 85 ºC and with a 1: 2 ratio of both reagents. In this way the cyclopropene **5a** was isolated in a 52 % yield. Thus, the employment of an unreactive solvent under the reaction conditions turned out to be very important for the success of the cyclopropenation reaction. [9]

These reaction conditions were then applied to a set of tosylhydrazones **4** and terminal alkynes **2**. The results are summarized in table 1. As can be deduced from these data, the reaction is useful for the synthesis of an array of 1,3-diaryl-3-trifluoromethylcyclopropenes **5**. Unfortunately, the reaction is limited to aryl-substituted acetylenes, as alkyl-substituted alkynes failed to provide the expected cyclopropene.

In most cases the cyclopropenes **5** were obtained in moderate yields. However, it is worth noting that the scarce previous examples described of the synthesis of these cyclopropenes involve the presence of a transition metal,[4] and in some cases, the employment of a large excess of the alkyne.[4b] Moreover, those reactions are conducted from the isolated 1-(diazo-2,2,2-trifluoroethyl)arenes, which are usually prepared from the corresponding tosylhydrazones, but in really low yields.[8] Therefore, this simple methodology provides an advantageous procedure for the synthesis of 1,3-diaryl-3-trifluoromethylcyclopropenes **5**.

Table 1: Synthesis of 1,3-diaryl-3-trifluoromethylcyclopropenes 5 by reaction of tosylhydrazones 4 with terminal alkynes.



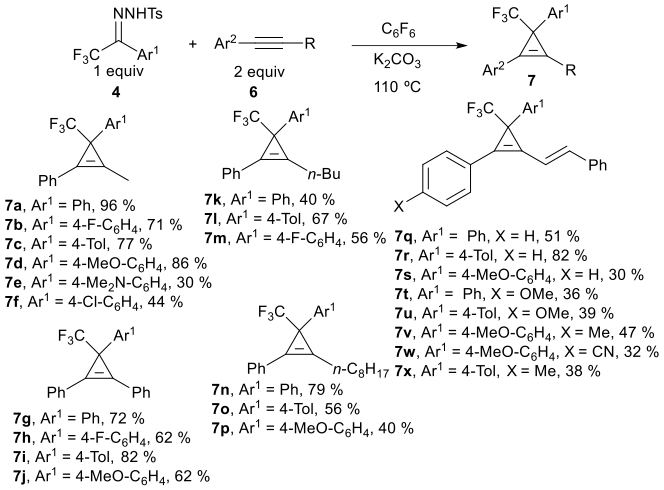
Compound	Ar^1	Ar^2	Yield[a] %
5a	Ph	Ph	52
5b	Ph	4-Tol	30
5c	Ph	4-F-C_6H_4	31
5d	Ph	4-F_3C-C_6H_4	51
5e	Ph	4-Cl-C_6H_4	40
5f	Ph	3-Thiophenyl	30
5g	4-F-C_6H_4	Ph	96
5h	4-F-C_6H_4	4-F_3C-C_6H_4	56
5i	4-F-C_6H_4	4-F-C_6H_4	63
5j	4-F-C_6H_4	4-Cl-C_6H_4	47
5k	4-MeO-C_6H_4	Ph	61
5l	4-Tol	Ph	47
5m	4-MeO-C_6H_4	4-Cl-C_6H_4	47

[a] Isolated yields after column chromatography.

We next turned out our attention to the reactions with disubstituted alkynes **6**, which would lead to the obtention of totally substituted 3-triflurometylcyclopropenes **7**. Indeed, under similar reaction conditions than those reported for the terminal alkynes, the cyclopropenes were again the main reaction product. Noteworthy, the yields were generally higher than those reported for the terminal alkynes (Scheme 3). The reaction was compatible with diarylacetylenes and also with aryl alkyl disubstituted alkynes giving rise to 1,2,3-triaryl and 1,3-diaryl-2-alkylcyclopropenes respectively. Finally, the reaction could be achieved with conjugated en-ynes, to provide the 1-vinylcyclopropenes **7q-x**,[11] which are appealing structures with particularly interesting ring opening chemistry.[12] Noteworthy, in these reactions, the process takes place exclusively through the triple bond of the en-yne, leaving the double bond untouched.

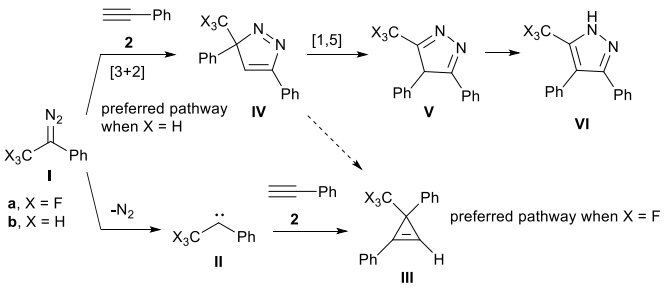
The different chemical behavior observed for the tosylhydrazones derived from acetophenones **1** and trifluoroacetophenones **4** in the reactions with terminal alkynes (scheme 1) is really intriguing. Assuming that the first step in every reaction will be the base promoted thermal decomposition of the tosylhydrazone to give the diazo compound **I** (scheme 4), there are various possible reaction pathways that might lead to the formation of either the

pyrazole **VI** or the cyclopropane **III** (scheme 4). Thus, the diazocompound **I** could undergo a 1,3-dipolar cycloaddition, to provide the 3*H*-pyrazole **IV**, that may evolve, after the [1,5]-sigmatropic rearrangement to the 1*H*-pyrazole **VI**. This is indeed the case of the previously studied system **Ib** (X = H).[6a] Alternatively, from **IV**, the formation of the cyclopropene might then occur upon nitrogen extrusion, probably through a ring opening / ring closing pathway. A second possible reaction pathway might consist on the decomposition of the diazo compound **I**, to give the carbene **II**, which would react with the alkyne to provide directly the cyclopropene **III**. Obviously, for this reaction pathway to operate, the decomposition of the diazo compound **I** by loss of nitrogen, must be favored towards the 1,3-dipolar cycloaddition with the alkyne.



Scheme 3: Synthesis of 2-substituted-1,3-diaryl-3-trifluoromethylcyclopropenes **7** by reaction of tosylhydrazones **4** with internal alkynes.

In order to understand the different outcomes of the reactions, and therefore the dramatic influence of the trifluoromethyl group, we carried out some DFT computational studies starting from **Ia** (X = F) and **Ib** (X = H).‡



Scheme 4: Possible reaction pathways for the formation of 1*H*-pyrazoles **VI** and cyclopropenes **III**.

First of all, the two possibilites for the first step were computed for both models **Ia** and **Ib**. For the trifluoromethyl series **Ia** we found that the decomposition of the diazo compound to give carbene **IIa** is favoured towards the 1,3-dipolar cycloaddition with phenylacetylene by 2.3 kcal·mol^{-1}. An activation free energy value of 28.7 kcal·mol^{-1} was obtained for the diazo compound decomposition. In contrast, for **IIb**, the 1,3-dipolar cycloaddition that leads to the formation of the 3*H*-pyrazole **IV** is preferred by 3.1 kca·mol^{-1}. Interestingly, these results are consistent with the experimental observations. According to our calculations, the effect of the trifluoromethyl substitution affects both in 1,3-dipolar cycloaddition and in the carbene formation by nitrogen release. There is a remarkable difference on the activation free energies for the dipolar cycloaddition ($\Delta\Delta G^{act}$ = 3.3 kcal·mol^{-1}) between both systems, which features a higher barrier for the trifluoromethylated system. Additionally, the trifluoro substituted diazo compound **Ia** features a lower free energy of activation for the carbene generation than **Ib** ($\Delta\Delta G^{act}$ = 2.1 kcal·mol^{-1}). Thus, considering that the generation of the carbene **IIa** is the favoured pathway when X = F, the formation of the trifluoromethylcyclopropene **III** must take place by reaction of the free carbene with the alkyne. This process takes place through a concerted and very early transition state with a relative low energy barrier (ΔG^{act} = 7.4 kcal·mol^{-1}). Thus, the diazo compound decomposition is the rate limiting step for this process.

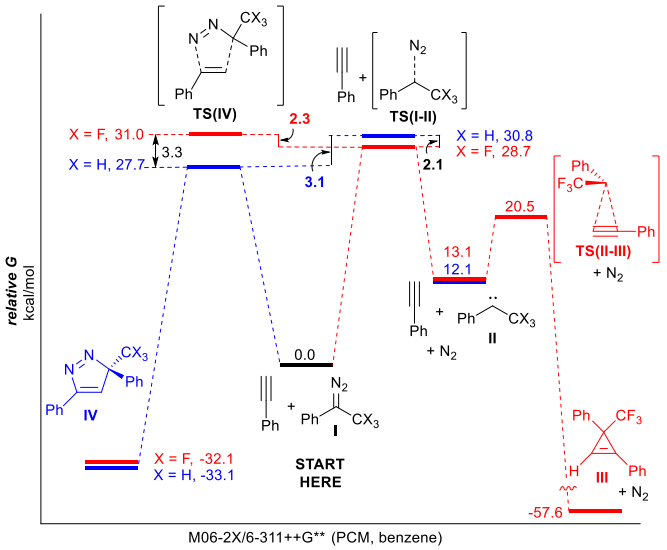


Figure 1. Calculated reaction pathways for the formation of cyclopropenes **III** and 3*H*-pyrazoles **IV** by reaction of phenylacetylene with (1-diazo-2,2,2-trifluoroethyl)benzene **Ia** (X = F) and 1-diazoethylbenzene **Ib** (X = H).

The main reactivity difference between the CH_3 and the CF_3 containing diazo compounds relays on the higher activation energy of the 1,3-dipolar cycloaddition with the CF_3-derived diazo compound **Ia**. The geometries of the transition states are quite similar for models **a** and **b**, and no relevant steric influence should be expected due to the presence of the slightly bulkier fluorine atoms (figure 2, a). Nevertheless, a possible explanation for the different behavior observed could be found by analysis of the energies of the frontier orbitals involved in the 1,3-dipolar cycloaddition. The presence of the CF_3 substituent lowers substantially the energy of the HOMO of the diazo compound. Considering in both cases a dominant HOMO(dipole)-LUMO(dipolarophile) interaction, the stabilization of the HOMO of the diazo compound in **Ia** justifies its lower reactivity in the 1,3-dipolar cycloaddition. Finally, the ability of the free carbene **II** to participate in the cyclopropenation reaction is enabled by its kinetic stability,

derived from the lack of hydrogen atoms at the α- position, and also by the election of an unreactive solvent as hexafluorobenzene.

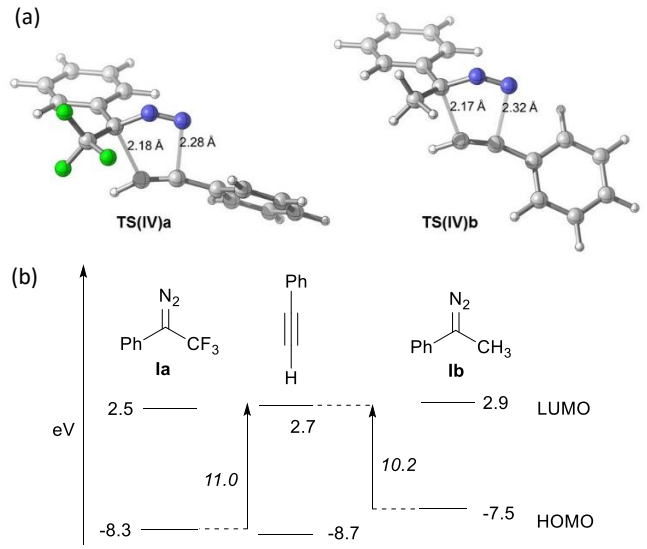


Figure 2: Figure 2. (a) Transition structures **TS(IV)** obtained for the 1,3-dipolar cycloadditions of phenylacetylene with the 1-(diazo-2,2,2-trifluoroethyl)benzene **Ia** and 1-diazoethylbenzene **Ib** respectively obtained at the M06-2X/6-311++G** level. (b) Representation of the energies of the Frontier Orbitals responsible for the main interactions in the 1,3-dipolar cycloaddition. Frontier Orbital Energies (eV) have been obtained from a single point HF/6-311G** calculation on the geometries optimized at the M06-2X/6-311++G** level.

In summary, we have described a straightforward synthesis of 1,3-diaryl-3-trifluoromethylcyclopropenes by reaction of tosylhydrazones with alkynes, without the need of any catalyst. The presence of the trifluoromethyl group is essential for the differential behavior of the 1-diazo-2,2,2-trifluoroethyl)benzene derivatives, which is due to a combination of their lower reactivity in 1,3-dipolar cycloadditions with alkynes and their higher tendency to generate a carbene upon nitrogen loss. These results might stimulate the development of other transition metal-free transformations based on these free carbenes.

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Notes and references

‡ The calculations were conducted employing the Density Functional Theory, with the M06-2X hybrid functional[13] and the 6-311++G** basis set employing the Gaussian 09 package. Solvation effects considering benzene as the solvent were applied on the gas phase optimized structures through the IEF-PCM at the same level of theory. See ESI for details.

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