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Transition metal-free [2,3]-sigmatropic rearrangement in the reaction of sulfur ylides with allenoates†

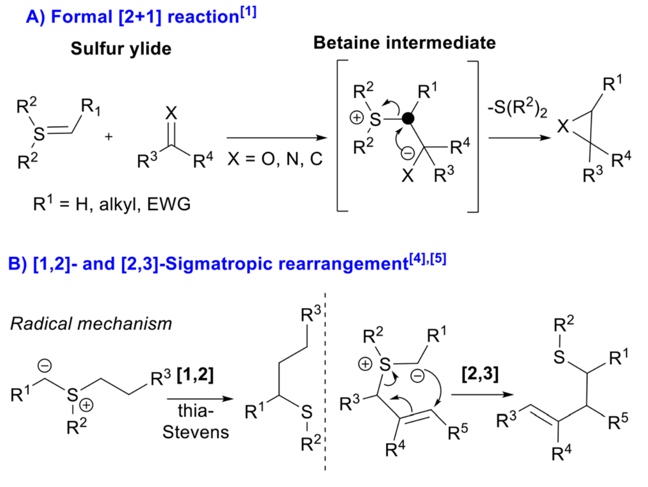
Miguel García-Castro, * Federico Moya-Utrera and Francisco Sarabia

An unprecedented transition metal free [2,3]-sigmatropic rearrangement involving stabilized sulfur ylides and allenoates has been thoroughly established. The scope and utility of this reaction have been extensively studied resulting in C–C bond formation under mild conditions with greater than 20 examples reported. A highlight of the work is the simple and fully operational process that does not involve the use of carbenes or the associated hazardous and sensitive reagents. The reaction can be performed at room temperature and using an open flask. Interestingly, the new C–C bond formation reaction is gram scalable, and the obtained isomers are readily separable, affording interesting building blocks that can be used in the preparation of complex molecules.

Introduction

Since the early days of organic chemistry, the reactivity of sulfur containing compounds has played a prominent role in the discipline.[1] Notably, the so-called sulfur ylides represent a very important class of chemical reagents first reported in the sixties, and the Corey–Chaykovsky reaction involving them has been extensively employed in organic synthesis.[2] Since then, the development of sulfur ylide chemistry has been exponential, expanding the utility of the chemistry in new ways for their preparation, as well as discovering new reactivities exhibited by them. To date, sulfur ylides have been mainly used to synthesize a plethora of cyclopropanes, oxiranes and aziridines,[3] exploiting their well-known ability to participate in the formation of three membered rings through the formation of a betaine intermediate in their reactions with α,β-unsaturated carbonyl compounds, carbonyl compounds and imines, respectively. The resulting betaine intermediate undergoes an intramolecular nucleophilic displacement, in what can be considered as a formal [2 + 1] cycloaddition reaction. On the other hand, quite more underexplored are the known [1,2]- and [2,3]-sigmatropic rearrangements, which are domino reactions involving sulfur ylide formation.[1,4] Furthermore, the examples reported for these modes of reactivity usually involve metal carbenoids, such as Doyle–Kirmse and thia-Sommelet–Hauser reactions (Scheme 1).[5,6]

However, recently the metal free version of the thia-Sommelet–Hauser reaction has been independently established by Biju and Tan groups,[7] involving only aromatic rings and requiring allyl or propargyl thioethers. Mechanistically, these reactions proceed through a benzyne intermediate and *in situ* formation of a sulfur ylide. It is worth mentioning that in this case, the [2,3]-sigmatropic rearrangement occurs just in the ylide itself, as the allyl or propargyl moiety provides the electrophilic α-carbon (Scheme 2A). On the other hand, allenoates have emerged in the last two decades as excellent reactive partners, able to participate in a vast number of reactions,



Scheme 1 Main pathways of reactivity in sulfur ylides.

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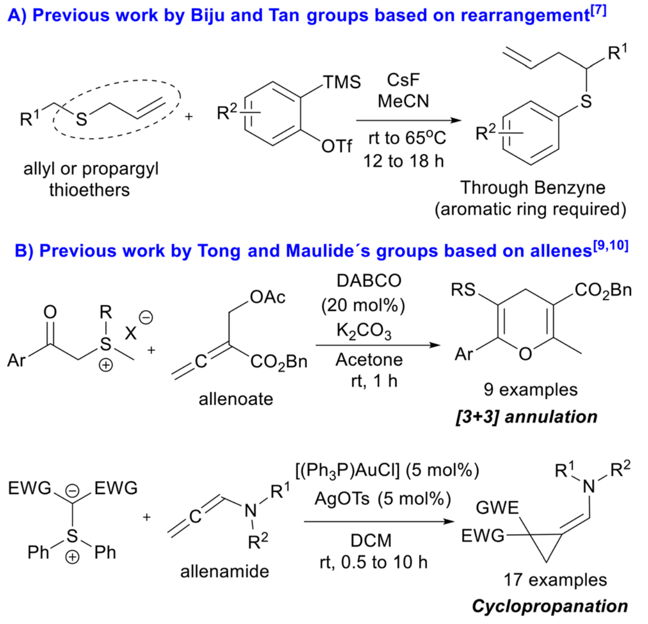
† Electronic supplementary information (ESI) available: All experimental details, including synthesis and characterization of all products reported in this study, NMR spectra of all products, High Resolution Mass spectrometry (HRMS) and elemental analysis. CCDC 2253009. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3ob00657c



Scheme 2 (A) Transition metal free [2,3]-sigmatropic rearrangement (thia–Sommelet–Hauser reaction) requiring special moieties. (B) Tong and Maulide's groups studied different reactions involving sulfur ylides and allenes.

mainly cycloaddition reactions.[8] Nevertheless, in the literature only one example in which their reactivities were explored with sulfur ylides is reported. In the reported example, Tong's group developed a DABCO-catalyzed [3 + 3] annulation of allenoates with sulfur ylides to deliver 9 examples of achiral 4*H*-pyrans.[9] Additionally, Maulide's group synthesized cyclopropanes using allenamide derivatives in the presence of cationic gold complexes and doubly stabilized sulfur ylides[10] (Scheme 2B).

Herein, we wish to report the first transition metal free [2,3]-sigmatropic rearrangement with non-aromatic partners as reagents and occurring between stabilized sulfur ylides and allenoates, without the need for employing carbene transfer reactions, photochemical conditions[11] or transition metals such as rhodium[12] (Fig. 1).

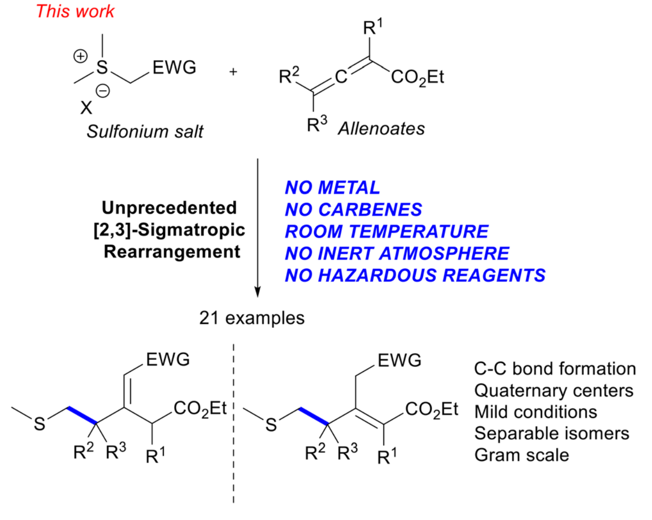


Fig. 1 Our unprecedented transition metal free [2,3]-sigmatropic rearrangement reaction involving sulfur ylides and allenoates.

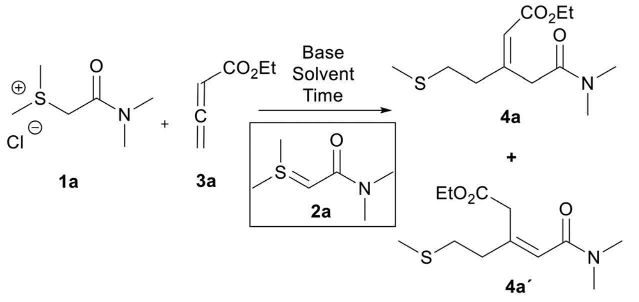
Results and discussion

Our interest in the chemistry of sulfur ylides, coupled with the scarcity of studies into their reactions with allenoates, prompted us to initiate this investigation.

Conceptually, the electrophilic carbon of allenoate should be attacked by the nucleophilic carbon of the sulfur ylide to obtain a betaine intermediate, which could convert to the corresponding cyclopropane derivatives. At first we studied the reaction between the *in situ* generated stabilized sulfur ylide **2a** and simple allenoate **3a**.

Importantly, we observed the formation of a mixture of two products, which, after separation and structural elucidation, were identified as **4a** and **4a′**. At the outset of our study, we first chose **1a** and **3a** as the standard substrates to identify the optimal reaction conditions, looking for reproducibility, full conversion and consistent results (Table 1). In order to optimize the reaction, we evaluated a diverse set of bases for the *in situ* formation of the sulfur ylide **2a** from the sulfonium salt

Table 1 Optimization of the reaction conditions for the reaction between sulfonium salt **1a** and simple allenoate **3a**[a]



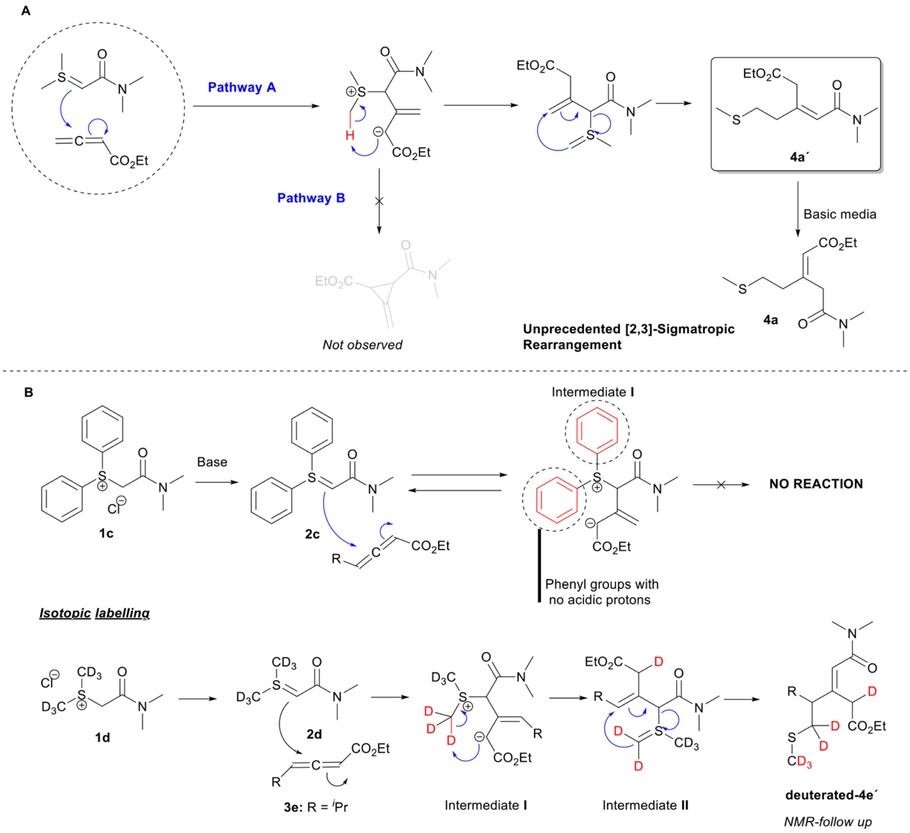
Entry[a]	Base[b]	Time[c]	Solvent	Yield[d] (%)
1	NaH	15 min	MeCN	NR
2	NaH	1 h	MeCN	NR
3	NaH	3 h	DMF	NR
4	NaOH	1.5 h	^{t}BuOH	NR
5	^{t}BuONa	1 h	^{t}BuOH	42
6[e]	NaOH	1 h	DCM/H_2O	NR
7[f]	^{t}BuOK	1 h	^{t}BuOH	69
8[g]	^{t}BuOK	1 h	^{t}BuOH	73
9[h]	^{t}BuOK	1 h	^{t}BuOH	74

[a] In all cases 1.0 equivalent of sulfonium salt **1a** was used. [b] In all cases 1.0 equivalent of base was used. NaOH was a 3 M aqueous solution. [c] Reactions were monitored by TLC. [d] NR means non-reproducible results.[14] Combined yield considering both formed products. [e] 5 M aqueous solution was used for a two phase method. [f] Addition of solid ^{t}BuOK to a solution of sulfonium salt in *tert*-butanol. [g] Addition of a 1 M *tert*-butanolic solution of ^{t}BuOK. [h] For scale-up: dropwise addition of allenoate for 2 h 30 min.

1a.[13] As a result, bases such as sodium hydride and 3 M aqueous NaOH solution were discarded due to non-reproducible results.[14] In contrast, potassium *tert*-butoxide in *tert*-butanol (entries 7–9, Table 1) proved to be the base of choice, providing compounds **4a** and **4a′** in a 73% combined yield.[15] The optimized procedure consisted of the addition of potassium *tert*-butoxide to sulfonium salt **1a**, and then, after stirring for 1 hour at room temperature, the addition of a solution of allenoate **3a** in *tert*-butanol in an open flask. We optimized the required time for completion of the reaction and we observed some variations depending on the nature of allenoates;[16] however, most reactions were completed after stirring for 3 hours at ambient temperature (Table 1).

Furthermore, we also evaluated a set of reactions where the sulfur ylide **2a** was isolated,[17] and reactions with allenoates were evaluated in four different solvents: dichloromethane, acetonitrile, tetrahydrofuran and *tert*-butanol, in order to answer two main questions: first, will avoiding the basic media generated with the *in situ* formation of sulfur ylide prevent the formation of two isomers, and second, will the nature of the solvents influence the course of the main reaction. Gratifyingly, first we were able to demonstrate that when using isolated sulfur ylide **2a**, the main reaction results in the formation of two separable isomers in the same proportion, and second, and quite interestingly, a variety of solvents can be used for the [2,3]-sigmatropic rearrangement, empowering the newly discovered methodology.

To rationalize the formation of these products, we propose a [2,3]-sigmatropic rearrangement from a transient sulfur ylide, which could be generated from the starting betaine intermediate (pathway A). It is somewhat expected that the outcome of the reaction was mainly represented by cyclopropanes (pathway B), but surprisingly and to our delight, we discovered that we obtained an easily separable mixture of compounds **4a** and **4a′** in an overall yield of 73% and in a ratio of 1 : 2, whose molecular structures were established by careful and extensive NMR and GC-MS analyses.[18] These structures reveal that a [2,3]-sigmatropic rearrangement could be operating and serves as a mechanistic explanation for the formation of the products. Accordingly, the nucleophilic carbon of the ylide attacks the electrophilic carbon of the allenoate, which stabilizes the negative charge due to the presence of the electron-withdrawing alkoxycarbonyl group in the α-position. Furthermore, this carbanion abstracts a proton from the methyl group attached to the sulfur atom, generating an unstable sulfur ylide that quickly triggers the formation of a new C–C bond and the breaking of C–S bond, representing a [2,3]-sigmatropic rearrangement, which results in the formation of both isomers due to the ability of the molecule to isomerize, which is facilitated by the acidic protons in the α-position of the ester (Scheme 3A).



Scheme 3 (A) Proposed mechanism for the formation of isomers **4a** and **4a′** through a novel [2,3]-sigmatropic rearrangement. (B) Experiments designed to prove the proposed mechanism.

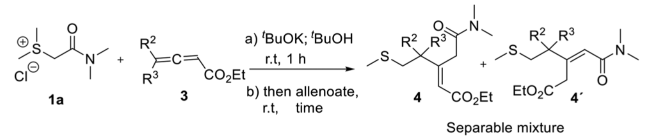
In order to demonstrate the proposed mechanism we devised two new sulfur ylides, derived from sulfonium salts **1c** and **1d**, respectively. Sulfonium salt **1c** contains two phenyl groups attached to the sulfur atom and lacks acidic protons, preventing the formation of a type II intermediate. Using **1c** in the standard reaction resulted in no reaction. On the other hand, the synthesis of deuterated sulfonium salt **1d** allowed us to realize the first isotopic studies by analyzing the ^{1}H-NMR spectra of the reaction products. In this case, we obtained deuterated compound **4e′**, supporting the formation of a transient ylide by deuterium abstraction of the betaine intermediate[19] (Scheme 3B).

While the formation of these products could be rationalized through a [2,3] sigmatropic rearrangement, the geometry of the resulting trisubstituted double bond, found in **4a** as in **4a′**, was justified according to Scheme 4. Thus, assuming a cisoid arrangement between the reactants as the preferred approach, in which the two polar groups are in an almost eclipsed orientation, the resulting betaine intermediate **A** should evolve to the transient sulfur ylide **B** by intramolecular deprotonation of the sulfonium salt by the basic carbanion located at the α-position of the ester. Intermediate **B** then should undergo a [2,3]-sigmatropic rearrangement to product **4a′** after rotation of the C–C bond allowing for the spatial approach of the nucleophilic carbon of the sulfur ylide to the double bond carbon. Two possible conformers (B′ and B″) could participate in the [2,3]-sigmatropic rearrangement, with the *Z*-isomer being the only possible product (**4a′**) in both cases. Finally, the basic conditions of the reaction mixture should promote an equilibrium isomerization of **4a′** to the thermodynamically favored **4a**, through intermediate C. In contrast, cyclopropane formation would require a high-energy conformer, whose carbanion and sulfonium groups are oriented in an antiperiplanar arrangement. The high barrier for ring closure establishes this process as the rate-determining step and, considering that betaine formation is reversible, makes this pathway non-productive.

Having determined the course of the reaction, we were prompted to study the scope of the reaction, in the first instance, by exploration of simple γ-substituted allenoates.

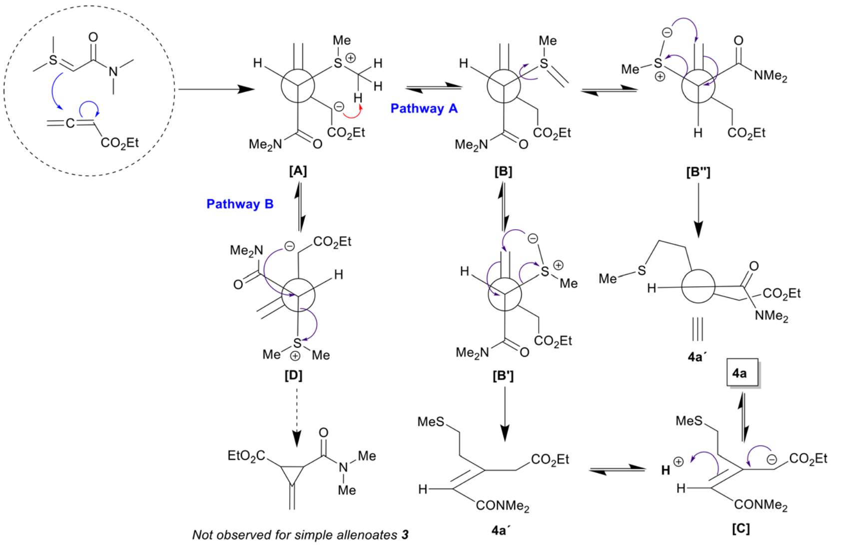
To our delight, compounds **4** and **4′** were obtained in moderate to good overall yields and as separable isomers (Table 2). Particularly relevant is the case of allenoate **3g**, which bears a geminal dimethyl group, in which compound **4g′** (entry 6, Table 2) was obtained in 57% yield, demonstrating that the

Table 2 Scope of the reaction with simple γ-substituted allenoates



Entry[a]	R^{3} [b]	Time[c]	Products (% yield)[d] [isomer ratio]
1[b]	Methyl (**3b**)	1 h	**4b**, **4b′** (68%) [1 : 1.3]
2	Ethyl (**3c**)	1 h	**4c**, **4c′** (65%) [1 : 1]
3	Propyl (**3d**)	1 h	**4d**, **4d′** (67%) [1.4 : 1]
4	Isopropyl (**3e**)	3 h	**4e**, **4e′** (54%) [1.3 : 1]
5	^{t}Butyl (**3f**)	1 h	**4f**, **4f′** (54%) [1 : 1.5]
6[b]	Methyl (**3g**)	12 h	**4g′** (57%)[e]
7	Phenyl (**3h**)	3 h	**4h**, **4h′** (40%) [2.3 : 1]
8	*p*-Chlorophenyl (**3i**)	1 h	**4i**, **4i′** (63%) [1 : 2.1]
9	*m*-Bromophenyl (**3j**)	3 h	**4j**, **4j′** (40%) [1.8 : 1]
10	*m*-Methoxyphenyl (**3k**)	3 h	**4k**, **4k′** (55%) [1 : 2]
11	Benzyl (**3l**)	2 h	**4l**, **4l′** (71%) [1 : 3]

[a] In all cases 1.0 equivalent of sulfonium salt **1a** and 1.0 equivalent of freshly prepared allenoate **3** were used. [b] In all cases R^{2} = H, except for entry 6, where R^{2} = methyl. [c] Stirring after the addition of allenoate. [d] Yield is given for pure compounds after separation using flash column chromatography. The overall yield is considered by taking both pure compounds together. [e] Only one isomer can be formed.



Scheme 4 Theoretical rationale of the reaction of **2a** with **3a** and justification of the stereochemical outcome.

rearrangement is possible despite the steric hindrance present at the allenoate moiety. The remaining examples show that there is no significant difference between the employment of aliphatic substituted allenoates **3b–f** (entries 1–5, Table 2) and aromatic substituted allenoates **3h–k** (entries 7–10, Table 2). The use of a benzyl group in the γ-position of the allenoate, compound **3l** (entry 11, Table 2), affords a mixture of compounds **4l** and **4l′** in a combined 71% yield, depicting the generality and robustness of the newly discovered synthetic methodology. In addition, compound **4f** could be isolated in the form of monocrystals and the subsequent X-ray analysis allowed for the unambiguous confirmation of the proposed structure of the product (Fig. 2).

In order to further explore the scope and limitations of the reaction, we decided to explore two important structural factors for the two reactants, the role of the electron-withdrawing group in the sulfonium salt and the use of more complex allenoates, such as the α,γ-substituted variants.[20]

To this aim, we tested the reaction employing the sulfur ylide **2b**, derived from sulfonium salt **1b**, where the electron-withdrawing group is an alkoxycarbonyl instead of an aminocarbonyl group, and allenoates **3(a, f and h)**. In these cases, the reactions proceeded in lower yields and the formation of product **4** dominated, which was ascribed to the lower reactivity of the sulfur ylide **2b** with respect to the amide-stabilized sulfur ylide (Scheme 5). For example, compounds **4m–o** were obtained in 20–30% *versus* the 50–70% yield obtained when sulfur ylide **2a** was used.

Finally, more complex allenoates **5** were tested in order to expand the reaction scope and to afford structurally complex products. Thus, we explored the reaction between sulfonium salt **1a** and allenoates **5(a–h)** under the previously optimized conditions, to afford products **6(a–c, e, g)** in moderate to good yields as separable mixtures of isomers (Table 3).

Particularly interesting is the study of this reaction using allenoates bearing different groups in the α-position, with the consideration that they should exhibit higher reactivities, for example, the allyl (**5e**) and propargyl (**5g**) groups. However, the

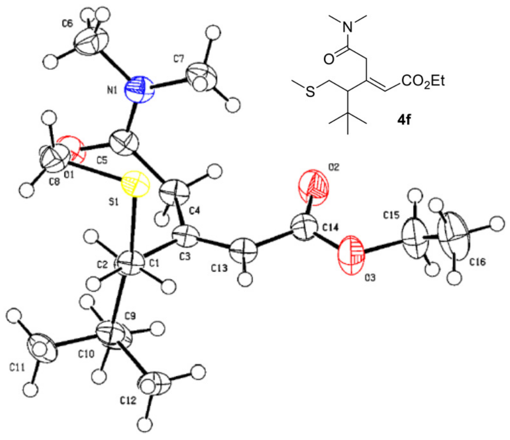
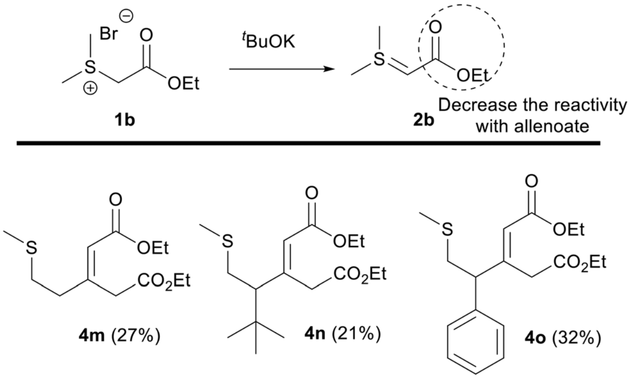
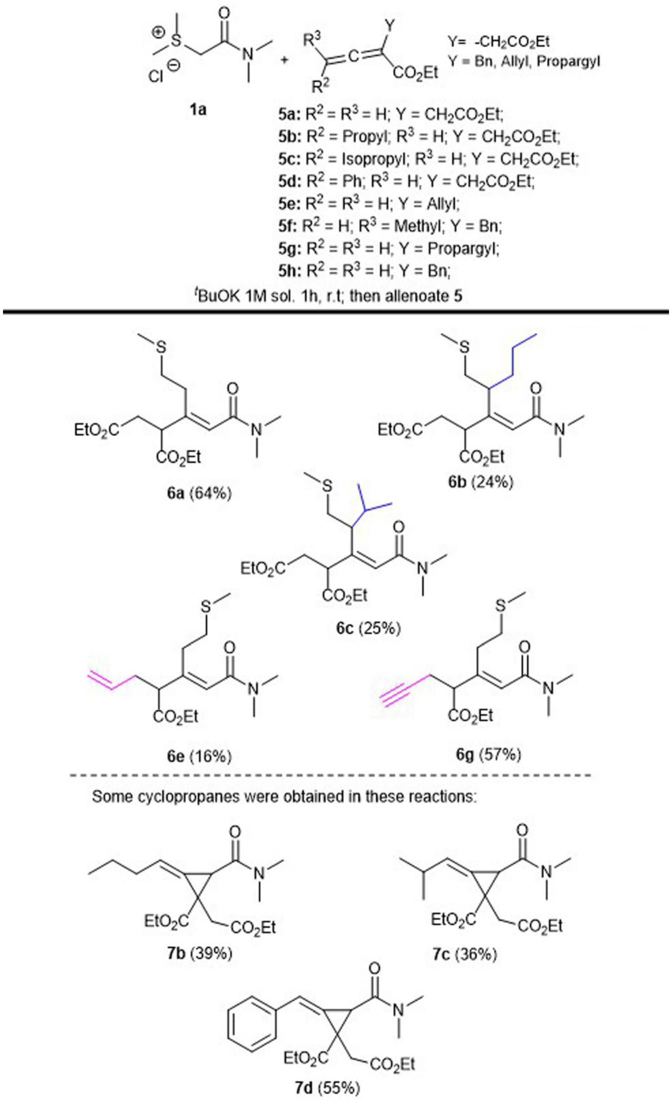


Fig. 2 X-ray structure of compound **4f**.



Scheme 5 Changing the EWG on sulfur ylides affects dramatically the yield of the reaction.

Table 3 Scope and limitations of the reaction with complex α,γ-substituted allenoates



corresponding products **6e** and **6g** were obtained in low to moderate yields (16 and 57%, respectively) and also as a separable mixture of isomers in the case of the allyl derivative, and in the propargyl case, surprisingly only one isomer was afforded opening up the possibility of generating any desired carbon skeleton with different patterns of substitution using the appropriate corresponding allenoates.

However, it is important to point out that in several reactions using complex allenoates, we isolated in moderate to good yields the corresponding cyclopropane derivatives as the main products; for example, compounds **7b**, **7c** and **7d** were obtained in 39, 36 and 55% yields, respectively, along with the corresponding rearrangement products (**6b** and **6c** in 24 and 25% yields, respectively). These results demonstrate that the initially expected outcome of these reactions resulting in the formation of cyclopropyl derivatives is operative when additional groups are included in the allenoate moiety. These observations offer the opportunity for further exploration of complex allenoates with sulfur ylides. Furthermore, we could isolate other reaction products in specific reactions employing allenoate **5f** and **5h**, affording diverse complex products[21] (Table 3).

We envision that the present methodology can be further applied to the total synthesis of natural products and complex molecules. In fact, during the preparation of this manuscript, a related reaction based on Baldwin's work[4] was proposed by Fürstner's group for the total synthesis of the marine natural product scabrolide A.[22]

Conclusions

In conclusion, we have systematically explored the reactivity between stabilized sulfur ylides and allenoates, discovering a novel and simple method to synthesize interesting scaffolds through a new carbon–carbon bond formation *via* a [2,3]-sigmatropic rearrangement which does not require transition metals or carbene formation, a very important feature of this reaction. Currently, the synthesized compounds are being tested in biological screenings. Further exploitation of this new methodology in the synthesis of natural products is currently in progress.

Author contributions

All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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14 See the ESI† for unexpected results due to highly observed reactivity on allenoate patterns.

15 Either adding solid ^{t}BuOK over a *tert*-butanolic solution of sulfonium salt or adding a commercially available 1 M *tert*-butanolic solution of ^{t}BuOK.

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17 We used an earlier modified protocol previously used in our labs, consisting of reacting the sulfonium salt with NaH in acetonitrile at room temperature followed by stirring for 3 hours, in the presence of two drops of H_2O. The reaction mixture was filtered and concentrated in a rotavapor, affording a freshly prepared sulfur ylide. F. Sarabia, F. Martín-Gálvez, M. García-Castro, S. Chammaa, A. Sánchez-Ruiz and J. F. Tejón-Blanco, *J. Org. Chem.*, 2008, **73**, 8979–8986.

18 Structural determination was realized by a combination of GC-MS and deep NMR analysis. And finally, X-ray diffraction was employed for crystalline products.

19 See the ESI† for additional information regarding mechanistic studies.

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21 Those structures were not clearly defined, and they are currently under further elucidation studies.

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