

## Organic &amp; Supramolecular Chemistry

## Regioselectivity of [3 + 2] Cycloadditions of Heteroaryl Azides and Ethyl-Vinyl Ether

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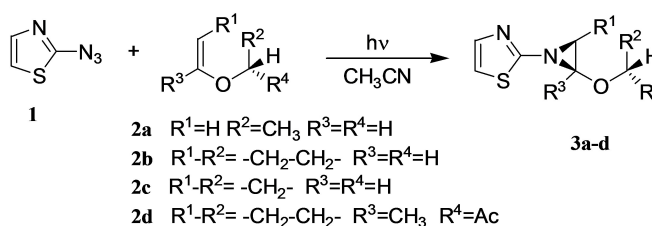
The reaction of ethyl vinyl ether with some heteroaryl azides in the presence of MnSO<sub>4</sub> affords some unexpected products. In the case of 2-azido-1,3-thiazole an imidate is formed, while 2-azidobenzothiophene gives an unprecedented 3,3a-dihydro-2H-8-thia-1-aza-cyclopenta[a]indene system, with loss of the

aromaticity of the benzothiophene ring. DFT calculations are performed to justify these structures. Selenophene -derived acyl azides on the contrary, afford in two cases *N*-heteroaryl carbamates, probably due to the reaction of an intermediate isocyanate and cleavage of the ether linkage.

## Introduction

Organic azides are valuable intermediates in many synthetic reactions.<sup>[1]</sup> Among them, the most important are 1,3 dipolar cycloaddition,<sup>[2]</sup> Staudinger reduction,<sup>[3]</sup> Curtius rearrangement,<sup>[4]</sup> and nitrene chemistry.<sup>[5]</sup> Some of these reactions have been widely used in the synthesis of pharmaceutically active compounds, like the tetrazole derived antihypertensive agent losartan,<sup>[6]</sup> or the azide analogue of the COX-2 inhibitor celecoxib.<sup>[7]</sup>

In our previous paper,<sup>[8]</sup> we found that 2-azido-1,3-thiazole **1** reacted photochemically with enol ethers **2a–d** to give, via the intermediate nitrene, aziridines **3a–d** in good yields (Scheme 1). Also, the aziridine moiety is involved in products like mitosanes and azinomycines,<sup>[9]</sup> with strong antibiotic and/or antitumour activity. As a development of this study intended to obtain the aziridines in enantioenriched forms, we have now found that various heteroaryl azides can react with ethyl vinyl



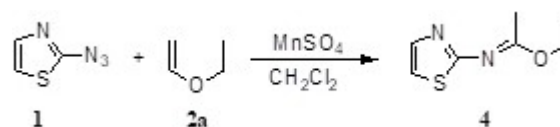
Scheme 1. Aziridination of enol ethers

ether in different conditions to give unusual and in some cases unprecedentedly obtained products.

## Results and Discussion

In preliminary tests, we found that the reaction of 2-azido-1,3-thiazole **1** with ethyl vinyl ether, besides the irradiation of the mixture, can be also catalyzed by transition metal complexes. In fact, when the reaction is carried out in the dark in the presence of Cu-bisoxazoline or Co-Salen chiral complexes, the corresponding aziridine is obtained with *ees* from low to moderate (to be published elsewhere). Surprisingly, when Mn(III) complexes were used (Mn-Salen or Mn-phtalocyanine) a completely different product is obtained, i.e. imidate **4**. On the contrary, the best yield was obtained simply by stirring under reflux in CH<sub>2</sub>Cl<sub>2</sub> the two reagents in the presence of a Mn(II) salt like MnSO<sub>4</sub> (Scheme 2).

Imidates and cyclic imidates are synthesized in different ways.<sup>[10]</sup> Among these, three-component reaction of trichloroacetonitrile, alcohols and terminal alkynes,<sup>[11]</sup> electrophilic

Scheme 2. Reaction of **1** with **2a**. (1 mmol **1**, 12 mmol **2a**, 2 mmol MnSO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, reflux, 5 days, 64% yield)

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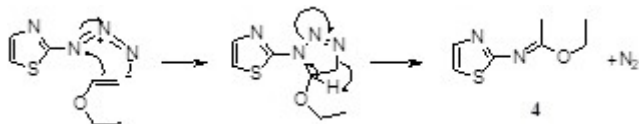
cyclization of 2-(1-alkynyl) benzamides,<sup>[12]</sup> chromium carbene chemistry,<sup>[13]</sup> and a modified Staudinger ligation.<sup>[14]</sup> In this latter case an aryl azide is involved, but the reaction requires the presence of a triarylphosphine moiety. On the contrary, in our and in some few other cases reported in the older literature<sup>[15,16]</sup> the azide reacts directly with enol ether to afford imidates like **4**. It must be noticed that in our experience the imidate is formed only when the metal (Mn (III) or Mn (II)) is present.

Imidate **4** was characterized by <sup>1</sup>HNMR, <sup>13</sup>CNMR and comparison with literature data.<sup>[17]</sup> A reasonable mechanism (Scheme 3) could involve an initial [1,3]-dipolar cycloaddition between the azide and the enol ether. The intermediate triazolone would undergo loss of nitrogen and 1,2 proton shift to give **4**.

We tested this hypothesis performing some calculations at DFT level on Gaussian 09.<sup>[18]</sup> We optimized the structure of **1** and **2a** at B3LYP/6-31G+(d,p) level. Compound **1** showed a total energy of  $-732.65416076$  H while ethyl vinyl ether had an energy of  $-232.45300117$  H. We followed both the approaches described in literature for the theoretical description of [1,3]-dipolar cycloadditions. The first approach, described by Houk and coworkers,<sup>[19]</sup> requires a superposition between HOMO and LUMO. To give a [1,3]-dipolar cycloaddition, a superposition between HOMO and LUMO has to be observed. The HOMO of **1** has been found at  $-0.24400$  H while the LUMO showed an energy of  $-0.06477$  H. Ethyl vinyl ether has the HOMO at  $-0.22845$  H and the LUMO at  $-0.00994$  H. The best interaction is obtained between the HOMO of the dipolarophile and the LUMO of the dipole. The atomic coefficients on these orbitals are reported in the Figure 1.

On the basis of these calculations the coupling has to occur between the nitrogen atom with an atomic coefficient of  $-0.25$  and the carbon atom with the atomic coefficient  $0.39$  and between the nitrogen atom with the atomic coefficient  $-0.22$  and the carbon atom with the atomic coefficient  $0.27$ . However, in this case, we do not obtain the triazolone depicted in the Scheme 3 but its regioisomer that cannot give the obtained product.

We tested another approach described some years later by Houk and coworkers.<sup>[20]</sup> In this case the energy of the transition states involved in the reaction has to be estimated and



Scheme 3. A possible mechanism for the formation of **4**.

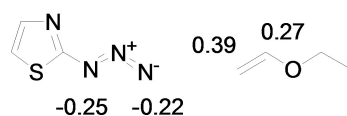


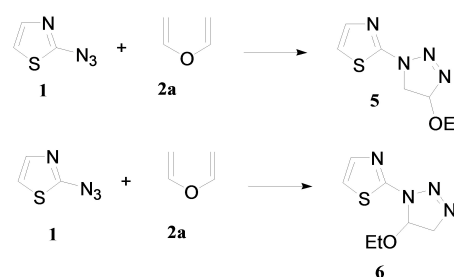
Figure 1. Atomic coefficients on suitable atoms on the LUMO of 2-azido-1,3-thiazole and the HOMO of ethyl vinyl ether.

compared. We estimated the energy of the transition states involved in the following [1,3]-dipolar cycloaddition reactions (Scheme 4).

The transition state of the reaction giving the triazolone **5** showed an energy of  $23.57$  kcal mol<sup>-1</sup> (ST1), while the transition state involved in the reaction between **1** and ethyl vinyl ether to give the triazolone **6** showed a transition state of  $15.51$  kcal mol<sup>-1</sup> (ST2) (Figure 2). On the basis of this results the expected triazolone can be obtained.

We followed the evolution of the triazolone **6** following the Scheme 3. The decomposition of the triazolone **6** to give **4** and nitrogen can be considered a concerted reaction with a transition state with an energy of  $23.57$  kcal mol<sup>-1</sup> (ST3) (Figure 2). Several years ago, a different hypothesis on the decomposition of the triazolone to give the corresponding oxime appeared (Scheme 5).<sup>[16]</sup>

We tested the presence of an intermediate of the type of **7** in our reaction. Our attempts failed. The compound **8** (Figure 3) did not exist. It did not represent a species at the minimum energy and evolved to the formation of the corresponding aziridine.



Scheme 4. Reactions used in B3LYP calculations.

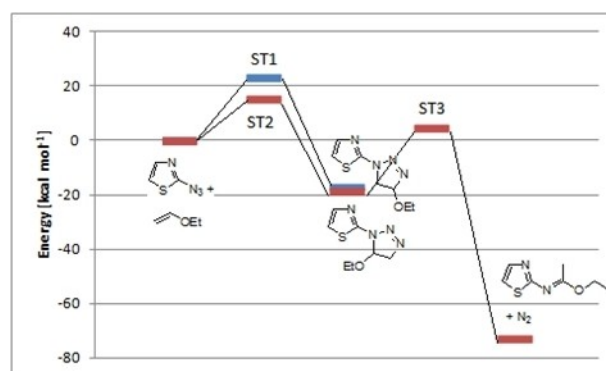
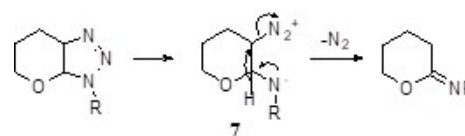


Figure 2. Transition states giving the triazolones **5** and **6**.



Scheme 5. Mechanism reported by Scheiner et al.

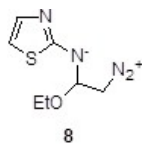
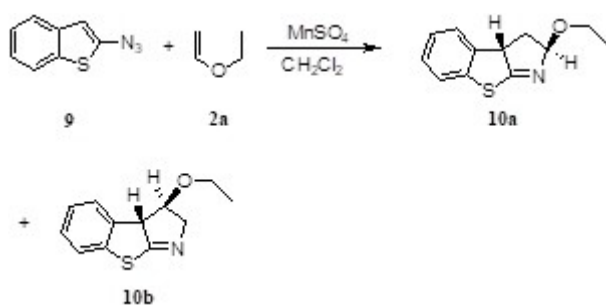


Figure 3. Possible intermediate in the conversion of **6** to **4**.

Analysis of global/local electrophilicities and nucleophilicities can be used in order to explain [1,3]-dipolar cycloaddition reactions.<sup>[21]</sup> We have optimized structures of **1** and **2a** and calculated respective indices. So, **1** is characterized by global electrophilicity which is equal to 1.54 eV. In consequence, in global electrophilicity scale, this compound should be treated as strongly electrophilic component. For comparison, global electrophilicity of **2a** is equal to 0.41 eV, and it should be considered as moderate electrophile. Subsequently, its global nucleophilicity is equal to 3.25 eV. Comparison of global electrophilicity values in reagent pair, show clearly that process **1** + **2a** should be interpreted as evidently polar cycloaddition. Additionally, analysis of local reactivity (*wk* for **1** and *nk* for **2a**) suggests that reaction course should be determined by attack of more nucleophilic center at terminal nitrogen atom of **1** on activated terminal position of nitroalkene **2a**.

When 2-azidobenzothiophene **9** was reacted with **2a** under reflux in CH<sub>2</sub>Cl<sub>2</sub> in the presence of MnSO<sub>4</sub>, two unusual regioisomeric products **10a** (major) and **10b** (minor) were obtained (Scheme 6), having a core 3,3a-dihydro-2H-8-thia-1-aza-cyclopenta[*a*]indene system. Either this system nor the simplest 4,5-dihydro-3aH-thieno[2,3-*b*]pyrrole system have never been described before in the literature.



Scheme 6. Reaction of **9** with **2a** (0.85 mmol **9**, 10 mmol **2a**, 1.7 mmol MnSO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, reflux, 3 days, yield **10a** 47% yield **10b** 32%).

Table 1. COSY correlations between protons on **10a**.

Proton	Correlates with
H <sub>a</sub>	H <sub>e</sub> , H <sub>f</sub>
H <sub>b</sub>	H <sub>e</sub> , H <sub>f</sub>
H <sub>c</sub>	H <sub>d</sub> , CH <sub>3</sub>
H <sub>d</sub>	H <sub>c</sub> , CH <sub>3</sub>
H <sub>e</sub>	H <sub>a</sub> , H <sub>b</sub> ; H <sub>f</sub>
H <sub>f</sub>	H <sub>a</sub> , H <sub>b</sub> , H <sub>e</sub>

Due to the novelty of these products, a careful NMR analysis was performed. 2D-COSY experiment allowed the assignment of all the protons of **10a** and **10b** (Figure 4 and 5, Table 1, and Supplementary Material).

Furthermore, a NOESY experiment, which excluded a correlation between protons H<sub>a</sub> and H<sub>b</sub> (see Figure 5 for all the correlations) allowed to establish the right *trans* configuration between these protons.

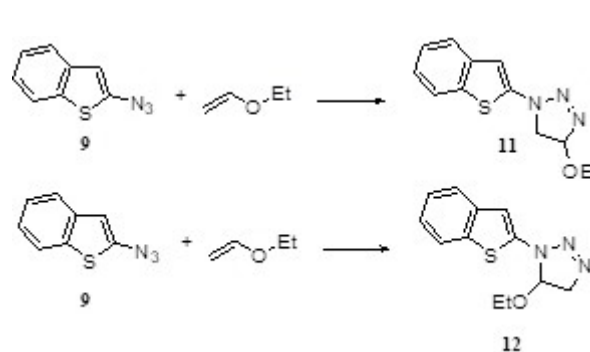
Furthermore, in the minor regioisomer **10b** a NOESY experiment showed only a weak correlation between the two protons marked on Scheme 6, allowing to establish a *trans* configuration between these protons (Figure 6).

We tested also in this case the formation of two regioisomeric triazolines through a [1,3]-dipolar cycloaddition of the azide **9** to ethyl vinyl ether (Scheme 7).

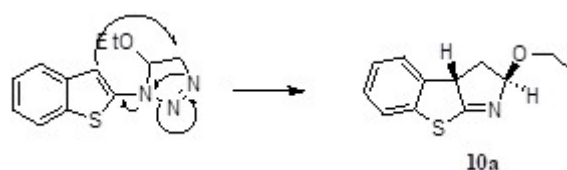
The formation of the triazoline **12** is favored. In fact, while the transition state of the reaction between the azide and ethyl vinyl ether to give **11** showed an energy of 19.65 kcal mol<sup>-1</sup> (ST1), the transition state of the reaction to obtain the triazoline **12** showed an energy of 13.98 kcal mol<sup>-1</sup> (ST2) (Figure 7). The Scheme 8 showed a possible evolution of the triazoline **12**.

The conversion of the triazoline **12** into the product can occur in a single step reaction depicted in the Scheme 8 where the calculated transition state is 40 kcal mol<sup>-1</sup> (ST3).<sup>[22]</sup>

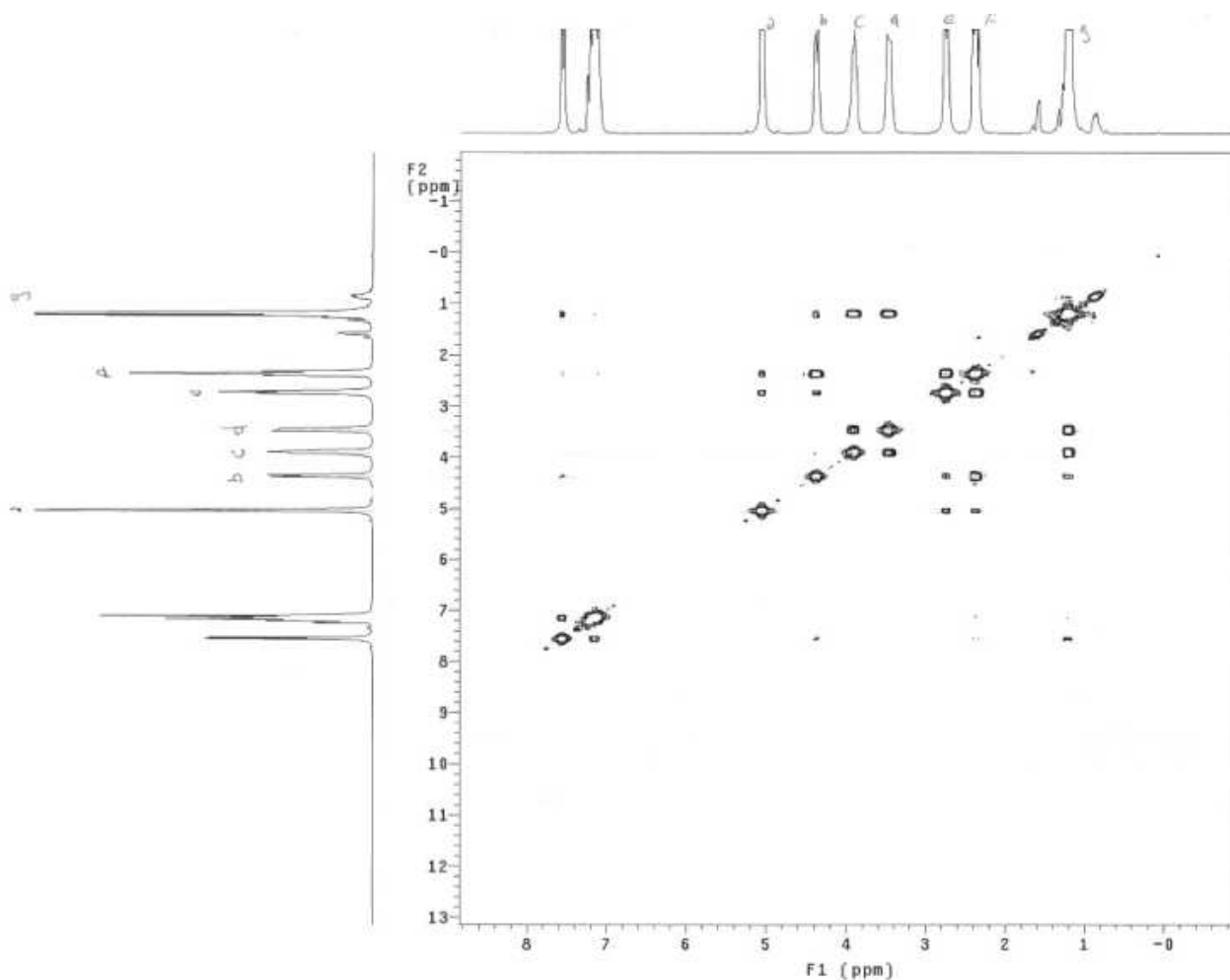
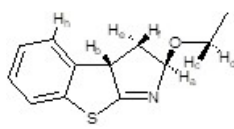
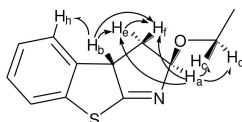
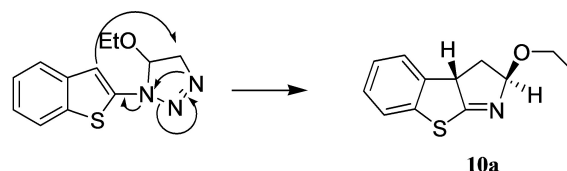
Examples of aziridine formation from triazolines derived via [3+2]-cycloaddition was recently described.<sup>[23,24]</sup> Anyway, at this moment several mechanism should be considered regarding to [3+2]-cycloaddition reaction: a) non-polar mechanisms (synchronical mechanism or stepwise, biradical mechanism,<sup>[24]</sup> b) polar mechanisms<sup>[25]</sup> (one step-two stage mechanism), stepwise zwitterionic mechanism<sup>[26]</sup>. Formation of zwitterions in the course of reactions involving organic azides has been recently reported.<sup>[27]</sup>



Scheme 7. [1,3]-dipolar cycloaddition between **9** and ethyl vinyl ether.



Scheme 8. Conversion of **12** into **10a**.

Figure 4.  $^1\text{H}$ NMR COSY of **10a**.Figure 5. Protons on **10a**.Figure 6. NOESY correlations among the protons on **10a**.Scheme 9. Reaction of selenophene-2-carbonyl azide **13** with **2a** (1 mmol **13**, 24 mmol **2a**, 2 mmol  $\text{MnSO}_4$ ,  $\text{CH}_2\text{Cl}_2$ , reflux, 4 days, 22% yield)

aziridine presumably derived from insertion of the intermediate nitrene into the double bond of **2a**, as described in our previous paper.<sup>[8]</sup>

To our surprise, when the reaction was performed on 5-methyl selenophene-2-carbonyl azide **15**, a completely different product was obtained, the *N*-heteroaryl carbamate **16** (Scheme 10). Also in this case, this product was carefully characterized by GC-MS and NMR spectroscopy. The molecular peak at  $m/z$  233 in the MS spectrum, the presence of a broad singlet at  $\delta = 7.54$  ppm which accounts for an amide proton, and the set of signals for the ethoxy group in the  $^1\text{H}$ NMR spectrum are in agreement for the proposed structure.

Having in our laboratory the availability of some selenophene derived acyl azides, we decided to investigate also on these compounds their reactivity in the same conditions.

The reaction of selenophene-2-carbonyl azide **13** with **2a** under reflux in  $\text{CH}_2\text{Cl}_2$  in the presence of  $\text{MnSO}_4$  afforded, although in low yield (22%) aziridine **14** (Scheme 9). This

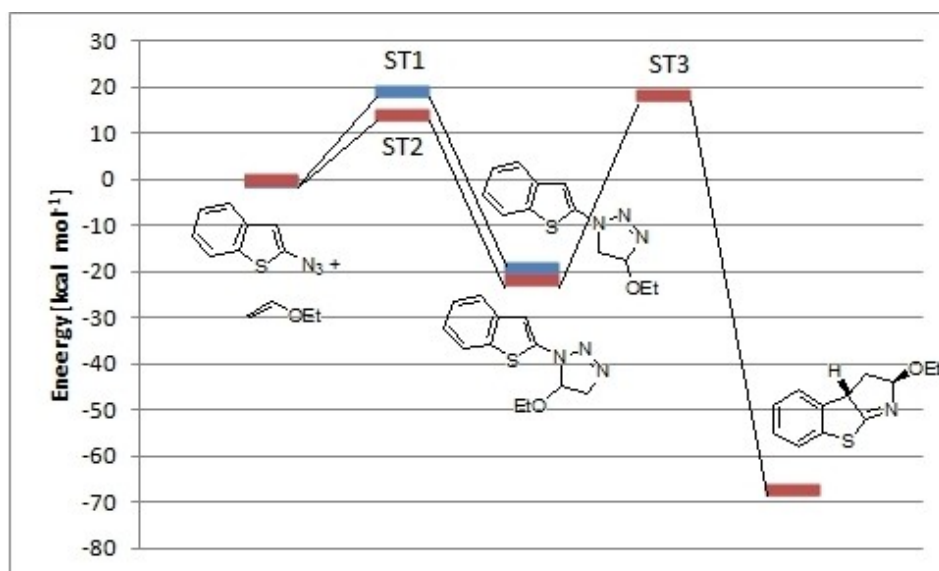
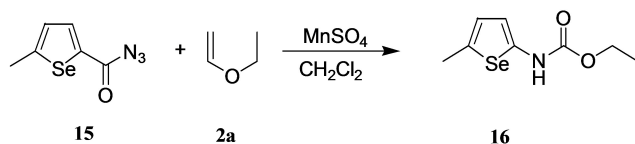


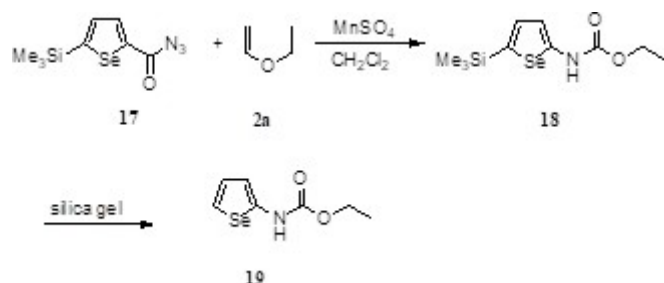
Figure 7. Transition states giving the triazolines 11 and 12.



Scheme 10. Reaction of 5-methyl selenophene-2-carbonyl azide 15 with 2a (3 mmol 15, 36 mmol 2a, 6 mmol  $\text{MnSO}_4$ ,  $\text{CH}_2\text{Cl}_2$ , reflux, 7 days, 23% yield)

Furthermore, comparison of  $^1\text{H}$ NMR data of compound 19 (see below) with an analogous compound (dodecyl *N*-(2-selenophenyl)carbamate) reported in the literature,<sup>[28]</sup> furnishes an ulterior confirmation of this structure.

An analogous behavior was observed when the reaction was performed on 5-trimethylsilyl selenophene-2-carbonyl azide 17. In this case, however, the expected product 18 cannot be isolated because it tends to desilylate upon purification on silica gel to give directly the carbamate 19 (Scheme 11). The



Scheme 11. Reaction of 5-trimethylsilyl selenophene-2-carbonyl azide 17 with 2a (3 mmol 17, 36 mmol 2a, 6 mmol  $\text{MnSO}_4$ ,  $\text{CH}_2\text{Cl}_2$ , reflux, 3 days, 20% yield)

intermediate 18 can however be detected by GC-MS ( $m/z = 291$ ) in the crude mixture.

From a mechanistic point of view, it is not easy to explain what happens in these two latter cases. Assuming that an isocyanate is formed as an intermediate, the reaction of this compound with an alcohol to give carbamates is a well-documented reaction in organic chemistry. In our case, instead, the reaction would be between an isocyanate and an ether, with subsequent cleavage of the ether linkage, and, to the best of our knowledge, this would be the first case reported.

All the results are summarized in Table 2 with respect to the reaction times and yields. In all the cases, the reactions were performed under refluxing anhydrous dichloromethane in the presence of powdered 4 Å molecular sieves.

## Conclusion

In this work we have reported an unusual reactivity of some heteroaryl azides with ethyl vinyl ether, which gives rise to some unexpected products. In our opinion, the most remarkable result is the difference of reactivity between 2-azido-1,3-thiazole and 2-azidobenzothiophene. In this latter case, in fact,

Table 2. The reactions of the azides with ethyl vinyl ether.

Azide	Reaction time [h]	Product	Yield [%] <sup>[a]</sup>
1	120	4	64
9	72	10a	47
		10b	32
13	96	14	22
15	168	16	23
17	72	18	Traces
		19	20

[a] After chromatographic purifications.

the obtained product shows a loss of aromaticity of the benzothiophene ring, giving rise to an unprecedented 3,3a-dihydro-2H-8-thia-1-aza-cyclopenta[a]indene system.

## Supporting Information Summary

The Supporting Information Section contains the Experimental Section, the GC-MS analysis of the reaction products, and the collection of NMR spectra.

## Acknowledgements

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

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

**Keywords:** azide · carbamate · density functional calculations · imidate · rearrangement

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