

MECHANISTIC STUDIES ON THE REACTIONS OF
BIS(ALKYLTHIO)CARBENES WITH VINYL ISOCYANATES

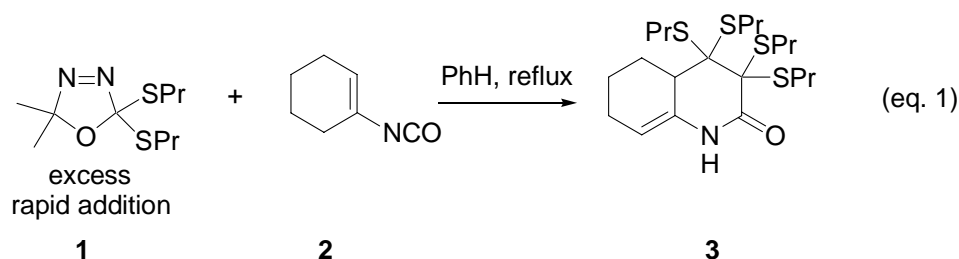
James H. Rigby,* Nancy A. Neale, and H. Bernhard Schlegel

Department of Chemistry, Wayne State University, Detroit, MI 48202-3489,
USA jhr@chem.wayne.edu

Abstract - Nucleophilic bis(alkylthio)carbenes demonstrate unique reactivity in their reactions with vinyl isocyanates. When a rapid addition of an excess amount of the oxadiazoline precursor (**1**) is reacted with vinyl isocyanate (**2**), a highly functionalized 2-pyridone (**3**) is produced. In an effort to further understand the mechanistic pathway followed by this reaction, *ab initio* methods are employed and experimental results support the proposed thermally induced [4+2] pathway of this reaction.

This paper is dedicated to A. I. Meyers on the occasion of his 70th birthday.

Due to the ubiquitous nature of partially reduced nitrogen heterocycles in alkaloids, the efficient synthesis of highly functionalized pyridones and pyrrolidones as synthetic intermediates continues to present a challenge in many total syntheses of natural products. These laboratories have demonstrated the versatility of the vinyl isocyanate function for the assembly of nitrogen heterocycles in a number of contexts.¹ Various pyridone adducts can be obtained using ester enolates, enamines^{2a} and benzyne^{2b} as electron rich, two-carbon reaction partners with vinyl isocyanates. Functionalized pyrrolidone intermediates can be constructed *via* [4+1] cycloadditions of vinyl isocyanates with 1,1-dipole equivalents such as alkyl isocyanides,^{3a} dimethoxycarbene,^{3b} chiral nucleophilic carbenes^{3c} and bis(alkylthio)carbenes.^{4a-c} Herein, we report studies on the reaction channel followed in the reaction of bis(propylthio)carbene precursor (**1**) with isocyanate (**2**) that produces the highly functionalized 2-pyridone (**3**) (eq. 1).



Tetrakis(propylthio)ethylene is an unavoidable dimeric byproduct of bis(propylthio)carbene additions to various substrates.⁵ This dimerization readily occurs and is normally competitive with the addition of the bis(propylthio)carbene species to a given electrophile. The nature of bis(propylthio)carbene is nucleophilic due to the lone pairs of the sulfur heteroatoms donating electron density into the empty *p*-orbital of the carbene center. This electron donation serves to stabilize the singlet form of the carbene, thereby accentuating its nucleophilicity. As a consequence, the overall reactivity of this species can be viewed as resembling a 1,1-dipole equivalent (Figure 1).

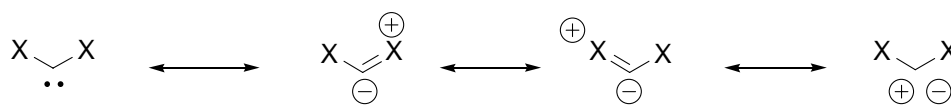
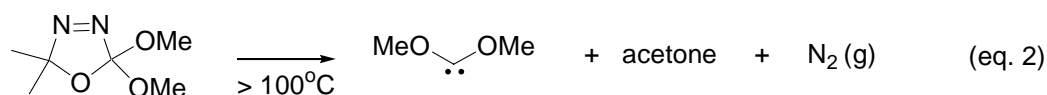


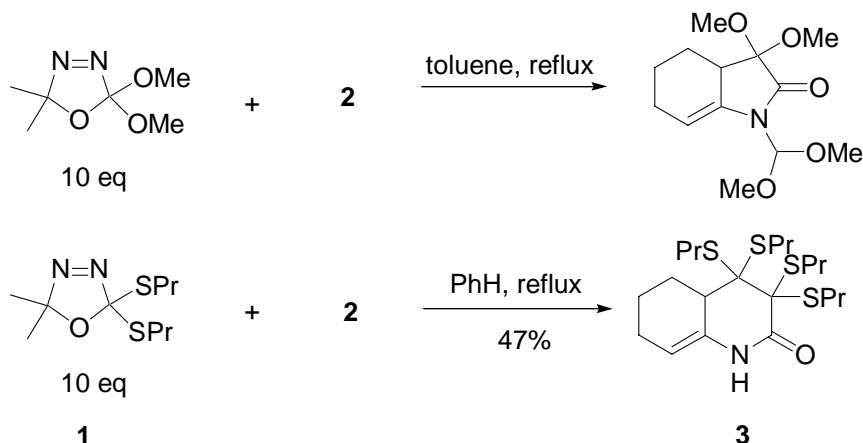
Figure 1. Nucleophilic carbenes as 1,1-dipole equivalents.

The most well studied nucleophilic carbene, dimethoxycarbene,⁶ has become readily available to the synthetic community *via* an oxadiazoline precursor, using methodology developed by Warkentin and coworkers (eq. 2).⁷

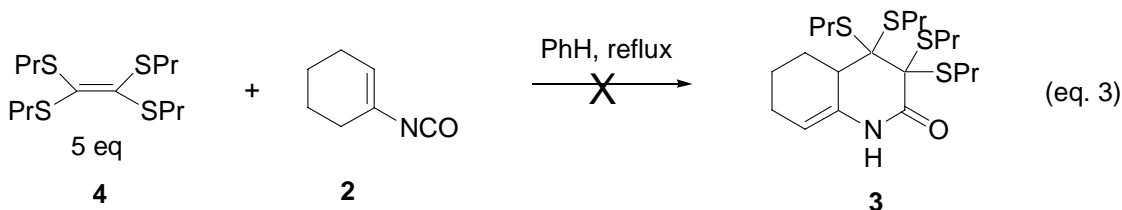


It has been investigated for its synthetic utility, specifically in [4+1] cycloadditions with vinyl isocyanates.^{3b,8} We recently reported the preparation of the related bis(alkylthio)carbene as well as cycloaddition studies of the corresponding carbene.⁴ These studies revealed several reactivity differences between the dioxo and dithio intermediates. The bis(propylthio)carbene will add to aryl isocyanates to produce isatin derivatives while the dimethoxycarbene will produce only hydantoin derivatives with this addend.^{4d,9} Excess dimethoxycarbene only participates in a [4+1] cycloaddition pathway with vinyl isocyanate (**2**) while excess bis(propylthio)carbene appears to undergo a very different reaction, leading to the 6-membered adduct (**3**) as the major product, Scheme 1.^{4a}

Scheme 1

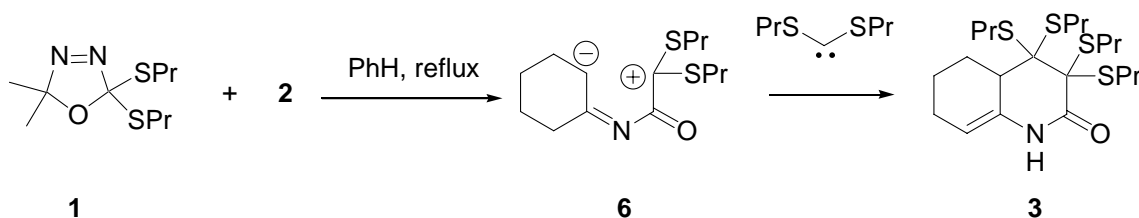


Originally, it was postulated that a [4+2] cycloaddition between the vinyl isocyanate and the dimer of the bis(propylthio)carbene (**4**) was taking place; however, a control experiment in which **4** was reacted with **2** in refluxing benzene did not lead to the expected [4+2] adduct (**3**) (eq. 3).^{4a}



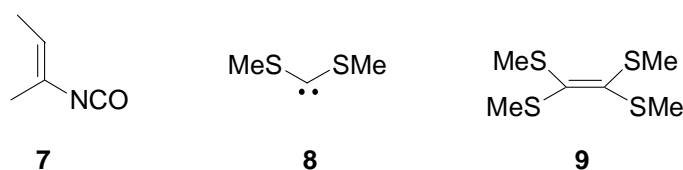
Lacking other visible alternative explanations for the formation of **3**, a novel [4+1+1] cycloaddition was suggested. One equivalent of carbene would add to **2** leading to a dipole intermediate (**6**). This dipole intermediate would exist long enough in solution to allow for a second addition of bis(propylthio)carbene to occur. Ring closure would then ensue yielding the adduct (**3**), Scheme 2.^{4a}

Scheme 2



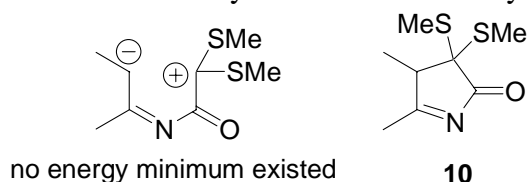
This explanation is certainly counter intuitive as it involved an intermolecular reaction occurring preferentially over an intramolecular reaction of the intermediate dipole (**6**).¹⁰

To further understand the reactivity differences between dimethoxycarbene and bis(propylthio)carbene, a computational approach was employed. Simplified versions of the vinyl isocyanate, the bis(propylthio)carbene and the tetrakis(propylthio)ethylene were used as model compounds for the computations. After initial computational studies, vinyl isocyanate (**7**), bis(alkylthio)carbene (**8**) and dimer (**9**) were found to be the best model candidates for the computational mechanistic studies.



All computations were performed using Gaussian 99 with the B3LYP functional and the 6-31g(d) basis set for both geometry optimization and frequency calculations.¹¹ The B3LYP/6-31g(d) level of theory has been demonstrated to be appropriate for nucleophilic carbene computations.¹² All computational results are on compounds, complexes and transition states in the gas phase.

The first concern about the proposed [4+1+1] mechanism materialized when several attempts to optimize the geometry of the proposed dipole intermediate (**6**) using the model equivalent, failed and structure (**10**) was the resultant energy minimum of the proposed dipole. The nature of the failure was the fact that the model dipole had no theoretical existence in an acyclic form under many initial conditions.



To further pursue this route, a search for a transition state of the [4+1] cycloaddition of optimized model compounds (**7**) and (**8**) using a quadratic synchronous transit route¹³ between starting materials and the closed optimized model (**10**) was attempted. A transition state was found, **11**, indicating the [4+1] reaction pathway is concerted in nature, providing additional support for the nonexistence of an intermediate dipole (Figure 2).

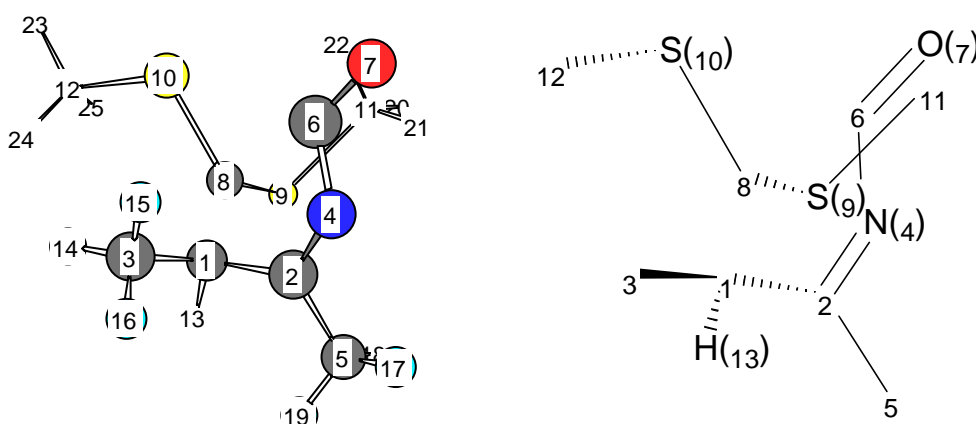


Figure 2. Transition state (**11**) of the [4+1] cycloaddition.

At this point, our computational approach was shedding no new light on the reactivity differences between the dimethoxycarbene and the bis(propylthio)carbene. It was apparent that there was no theoretical evidence of the existence of an intermediate dipole, which would allow for the second addition of a bis(alkylthio)carbene leading to a 6-membered adduct. However, a parallel computational

study on the formation of the model carbene dimer (**9**) was leading back to the original postulation of the mechanism for the formation of the adduct (**3**), namely the [4+2] pathway involving dimer (**4**) as the 2π component and vinyl isocyanate (**2**) as the 4π partner.

It was found that conformations (**9a**) and (**9b**) of the model dimer existed and these were optimized, (Figure 3).

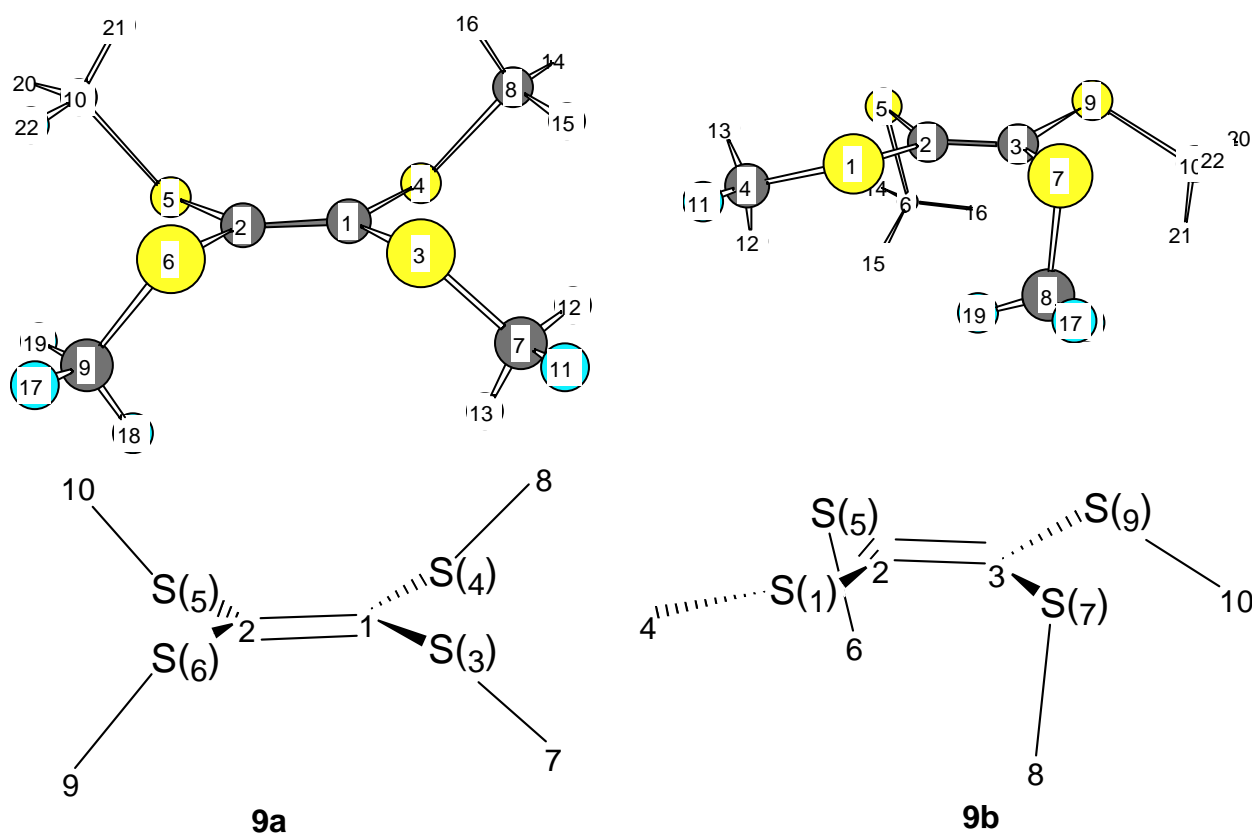
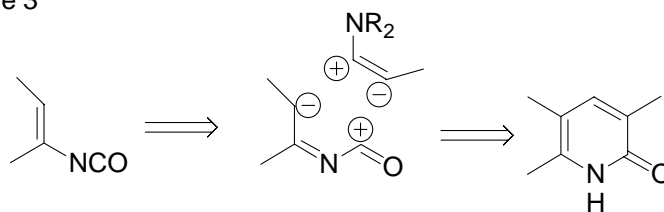


Figure 3. Optimized conformations of the model dimer (**9a**) and (**9b**).

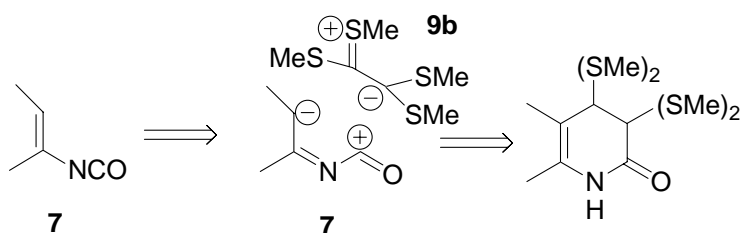
Upon inspection of Figure 2, **9b** is a more polarized dimer with a dipole moment of 3.8 Debye compared to the 0.20 Debye dipole moment of **9a**. One face of **9b** is sterically unhindered whereas both faces of **9a** are equally hindered. Furthermore, there is only 0.13 kcal/mol free energy difference between these two conformations. These results seem to indicate that this tetrakis(alkylthio)dimer has a conformation that could be viewed as mimicking a 1,2-dipole equivalent.

Enamines have served as particularly useful electron-rich 1,2-dipole equivalents in their additions to vinyl isocyanates (Scheme 3)¹ and **9b** could be, in principle, visualized as an electron-rich 1,2-dipole equivalent in a [4+2] reaction with **7** (Scheme 4) as well.

Scheme 3



Scheme 4



Application of Frontier Molecular Orbital Theory to these model compounds indicates that the HOMO of the polarized dimer (**9b**) with the LUMO of the model vinyl isocyanate (**7**) is the favored frontier orbital interaction in the [4+2] cycloaddition (Figure 4).

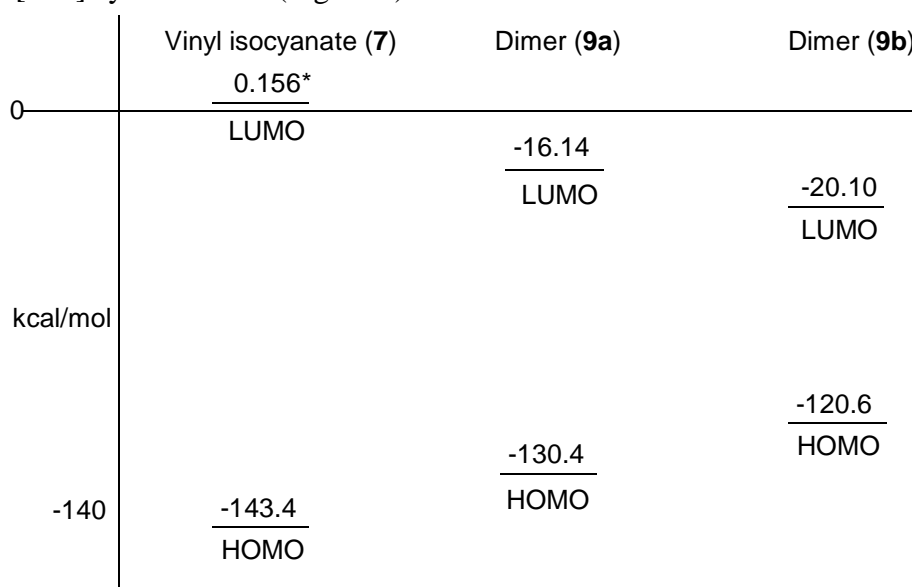
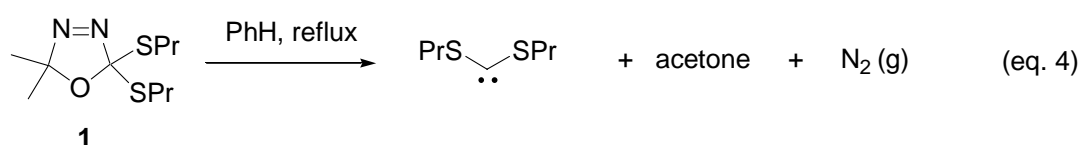
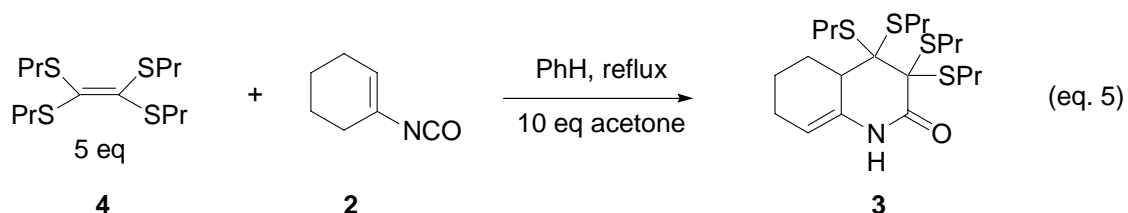


Figure 4. Frontier molecular orbitals of model compounds.
*unscaled energies used for comparison

In light of the computational results, it stood to reason that the direct [4+2] mechanism was the most reasonable reaction pathway. However, a previous control experiment appeared not to support this contention. Upon closer examination of the control experiment, it was realized that the original experiment did not represent a true simulation of the original reaction conditions. Indeed, the precursor to the bis(propylthio)carbene is oxadiazoline derivative (**1**), which, upon thermolysis, releases one equivalent of acetone and nitrogen gas along with the carbene (eq. 4).



However, the original control experiment was performed with 5 equivalents of **4** with **2** in refluxing benzene in the absence of acetone. In light of the apparent dipolar nature of **4**, a more accurate set of conditions would include 10 equivalents of acetone (eq. 5).



This experiment was performed and it resulted in the production of **3** in a 44% yield. This result is virtually identical to that of the original cycloaddition, thus strongly supporting the involvement of a thermally induced [4+2] cycloaddition. As a result of the insights afforded by the computational results, solvent effects are of critical importance in this [4+2] cycloaddition. Indeed, the polarizability of solvents has significant effects on the rate of normal and inverse electron demand Diels-Alder reactions, where a nonsynchronous mechanism is proposed.¹⁴ Thus, the [4+2] cycloaddition of **4** with **2** was investigated in refluxing acetonitrile ($\epsilon_{\text{MeCN}}=36.44$, $\epsilon_{\text{acetone}}=21.01$, $\epsilon_{\text{PhH}}=2.28$)¹⁵ and the reaction yielded 63% of the expected product (**3**).

Conclusion

The [4+2] cycloaddition between tetrakis(propylthio)ethylene (**4**) and the vinyl isocyanate (**2**) is a rapid, efficient and clean route to a highly functionalized 2-pyridone synthetic intermediate (**3**). Dimer (**4**) is readily available as a byproduct of bis(propylthio)carbene additions to electrophiles and the utility of this unavoidable dimer byproduct has been demonstrated. This report further illustrates the versatility of bis(alkylthio)carbenes in their reactions with vinyl isocyanates. Studies on synthetic applications of bis(alkylthio)carbenes continue in these laboratories.

Furthermore, one must be confident that a control experiment is truly a control. However, this report is a classic example of theory leading one to the correct experimental investigation and an application of the true scientific method.

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