1766 *J. Org. Chem.* **1999,** *64,* 1766−1767

Communications

Nucleophilic Carbenes in Synthesis. [1 + 4] Cycloaddition of Bis(alkylthio)carbenes with Vinyl Isocyanates

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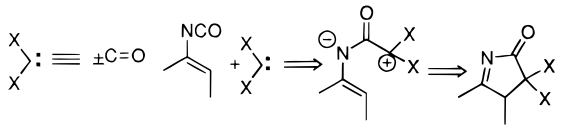
Received December 4, 1998

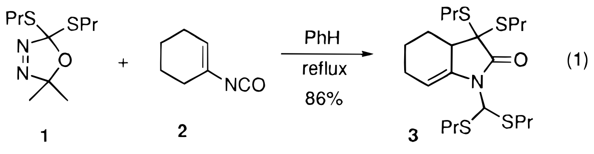
Carbene centers possessing donor substituents such as oxygen, nitrogen and sulfur frequently exhibit nucleophilic properties, in contrast to the well-established electrophilic character of dihalocarbenes.[1] This reactivity profile is believed to result from conjugative donation of electron density from the heteroatoms into the vacant p-orbital of the singlet state of the carbene. The nucleophilic character of these carbenes offers numerous opportunities for developing novel, synthetically useful transformations for the construction of functionally rich targets.

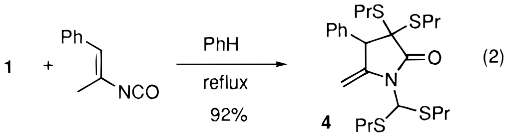


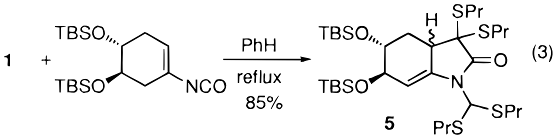
Recently, dimethoxycarbene was demonstrated to be a particularly useful carbonyl 1,1-dipole equivalent in [1 + 4] cycloaddition reactions with various vinyl isocyanate partners.[2] Subsequently, this process was exploited as the key strategy-level transformation in a total synthesis of the amaryllidaceae alkaloid tazettine.[3] We now wish to report that the corresponding dithiocarbene species can also participate in an efficient [1 + 4] cycloaddition with vinyl isocyanates; however, several intriguing differences have been noted between the chemistries of the two carbene series, both during and after the ring-forming event. While several dithiocarbenes have been reported previously, the chemistry observed for these reactive intermediates has been, for the most part, restricted to a very facile dimerization that is a characteristic reaction pathway available to most related species.[4] Recently, Warkentin and co-workers reported some interesting and synthetically useful chemistry for a mixed *S*,*O*-carbene.[5]

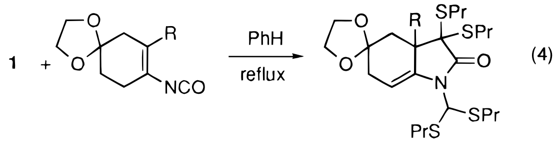
It was reasoned that dithiocarbenes should behave in a manner quite similar to that of the corresponding dioxy species in their reactions with isocyanates; however, it was also expected that the resultant dithioacetal function would offer a complementary range of post-cycloaddition functional group interchanges that would be of particular synthetic value.

Heating the readily available dithiooxadiazoline **1**[6] (2.5 equiv) in the presence of vinyl isocyanate **2** afforded the 2:1 adduct **3**[7] in excellent yield (eq 1). This result closely parallels observations made in the addition of dimethoxycarbene to isocyanate **2** except that considerably higher temperatures were required for efficient reaction with the oxygen-based carbene (80 vs 145 °C). The generality of this [1 + 4] cycloaddition process is illustrated by other examples depicted in eqs 2−4. Several salient features of the cyclization process emerge from these entries. For instance, a mixture of epimers resulted at the newly created bridgehead position in hydroindolone **5**[7] when remote stereogenic centers were present in the substrate. The capability, as shown in eq 4, of producing a quaternary carbon center during the ring-forming event to yield compound **7**[7] is also particularly noteworthy.









6, R=H (72%)
7, R=Me (47%)

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[1] For some leading references to nucleophilic carbenes, see: (a) Pole, D. L.; Sharma, P. K.; Warkentin, J. *Can. J. Chem.* **1996**, *74*, 1335. (b) Pole, D. L.; Warkentin, J. *Justus Liebigs Ann. Chem.* **1995**, 1907. (c) Arduengo, A. J., III; Dias, H. V. R.; Dixon, D. A.; Harlow, R. L.; Klooster, W. T.; Koetzle, T. F. *J. Am. Chem. Soc.* **1994**, *116*, 6812. (d) Ge, C.-J.; Jefferson, E. A.; Moss, R. A. *Tetrahedron Lett.* **1993**, *34*, 7549. (e) Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530. (f) Homberger, G.; Kirmse, W.; Lelgemann, R. *Chem. Ber.* **1991**, *124*, 1867. (g) Moss, R. A. *Acc. Chem. Res.* **1989**, *22*, 15. (h) Moss, R. A.; Wlostowski, M.; Shen, S.; Krogh-Jespersen, K.; Matro, A. *J. Am. Chem. Soc.* **1988**, *110*, 4443.

[2] Rigby, J. H.; Cavezza, A.; Ahmed, G. *J. Am. Chem. Soc.* **1996**, *118*, 12848.

[3] Rigby, J. H.; Cavezza, A.; Heeg, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 3664.

[4] (a) Benati, L.; Calestani, G.; Nanni, D.; Spagnolo, P.; Volta, M. *Tetrahedron* **1997**, *53*, 9269. (b) Benati, L.; Calestani, G.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Chem. Commun.* **1995**, 1999. (c) Bittner, S.; Moradpour, A.; Krief, P. *Synthesis* **1989**, 132. (d) Nakayama, J. *Sulfur Rep.* **1985**, *4*, 159. (e) Nakayama, J.; Seki, E.; Hoshino, M. *J. Chem. Soc., Perkin Trans. 1* **1978**, 468. (f) Cohen, T. Ouellette, D.; Daniewski, W. M. *Tetrahedron Lett.* **1978**, 5063. (g) Nitsche, M.; Seebach, D.; Beck, A. K. *Chem. Ber.* **1978**, *111*, 3644. (h) Obata, N. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2187. (i) Nakayama, J.; Fujiwara, K.; Hoshino, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3567. (j) Nakayama, J. *Synthesis* **1975**, 168. (k) Hartzler, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 4379. (l) Carlson, R. M.; Helquist, P. M. *Tetrahedron Lett.* **1969**, 173. (m) Seebach, D. *Angew. Chem., Intl. Ed. Engl.* **1967**, *6*, 443. (n) Schöllkopf, U.; Wiskott, E. *Justus Liebigs Ann. Chem.* **1966**, 694, 44. (o) Lemal, D. M.; Banitt, E. H. *Tetrahedron Lett.* **1964**, 245.

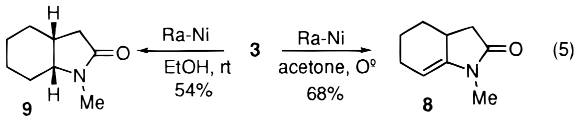
[5] (a) Er, H.-T.; Pole, D. L.; Warkentin, J. *Can. J. Chem.* **1996**, *74*, 1480. (b) For the apparent preparation of another bis(alkylthio)oxadiazoline, see: Warkentin, J. In *Advances in Carbene Chemistry*; Brinker, U., Ed.; JAI Press: 1998; Vol. 2, p 263.

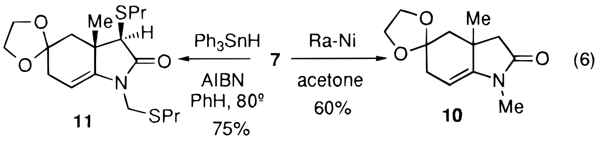
[6] Prepared by a variation of the Warkentin procedure: Couture, P.; Terlouw, J. K.; Warkentin, J. *J. Am. Chem. Soc.* **1996**, *118*, 4214.

[7] This compound exhibited spectral (^{1}H NMR, ^{13}C NMR, IR, MS) and analytical (combustion analysis and/or HRMS) data in complete accord with the assigned structure.

10.1021/jo9823801 CCC: $18.00

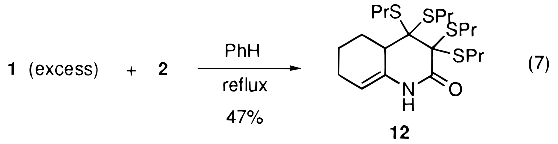
One of the more appealing features of this chemistry is the range of synthetically useful post-cycloaddition manipulations that are available with the dithiocarbene adducts, many of which are not easily achieved in the corresponding dialkoxy series. An obvious potential advantage of the current methodology is the expectation that reductive desulfurization would afford functionalized hydroindolones at oxidation levels found in many alkaloid targets such as in the lycorine, crinine, and erythrina families. Equations 5 and 6 illustrate this point. Of particular significance is the ability to control the desulfurization process to produce either the enamide **8**[7] or the fully reduced system **9**[7] depending on the conditions employed.[8]

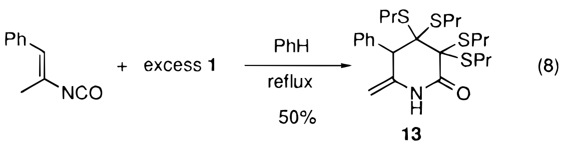


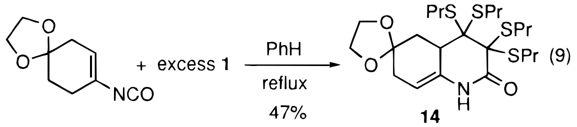


In an effort to improve the efficiency of the cycloaddition process, an experiment was performed in which a large excess of oxadiazoline **1** (10 equiv) was added rapidly to a solution of vinyl isocyanate **2** in refluxing benzene. Remarkably, under these conditions the reaction followed an unanticipated pathway to deliver an alternative 2:1 adduct **12**,[7] in good yield.

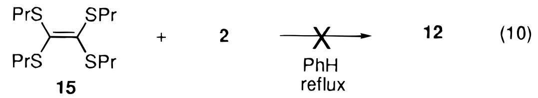
Several features of this product are quite unusual when compared to adducts from the "normal" reaction channel. Most notable is the apparent addition of 2 equiv of carbene to the isocyanate prior to ring formation, a process that leads to a six-membered lactam product. Furthermore, unlike the examples in equations 1−4, no carbene addition occurred at the amide N−H bond. This is apparently not an isolated event, since the observations depicted in eq 7 seem to apply whenever a large excess of oxadiazoline is *rapidly* decomposed in the presence of an isocyanate reaction partner (i.e., eqs 8 and 9).

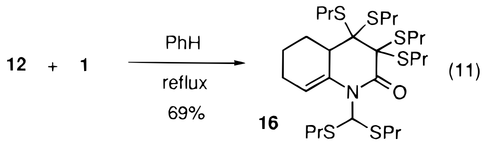




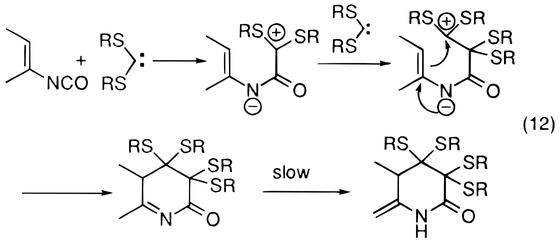


A possible rationale for these observations that would satisfy each of the novel features of the reaction is that the carbene generated under these conditions rapidly dimerizes to **15**, which then undergoes a thermal [4 + 2] cycloaddition with the isocyanate to deliver the observed product. Somewhat related cyclizations between electron-rich alkenes and vinyl isocyanates have been achieved previously, but pyridone products (via heteroatom elimination) have normally resulted.[9] The absence of N−H insertion in the final product is also consistent with this pathway since the initial dimerization event would exhaust most of the supply of carbene needed for subsequent insertion. In the event, heating preformed dimer **15** with isocyanate **2** in refluxing benzene did not afford any of the anticipated adduct **12** (eqs 10 and 11). Furthermore, in a companion experiment, adduct **12** was exposed to excess oxadiazoline in refluxing benzene to afford N−H insertion product **16**[7] in good yield. In concert, these two observations clearly suggest the possible involvement of a rapid set of multiple carbene additions that precede the key ring-forming step.





In light of these latter developments, it is believed that the abnormal 2:1 adducts arise from the very rapid production of a large amount of carbene that is present in sufficient quantities to competitively add a second equivalent of reactive intermediate to the initial dipolar 1:1 adduct prior to ring closure (eq 12). In addition, the absence of N−H insertion in these products could be due to a slow *N*-acylimine−enamide tautomerization in the six-membered ring series. In contrast, this isomerization process appears to be quite fast in the related hydroindolone system, thus facilitating N−H insertion. The initially formed imine species in the six-membered ring series cannot undergo N−H insertion and serves to "protect" the amide from reaction during the relatively short lifetime of the carbene. Further investigation of this intriguing double addition pathway is currently underway.[10]



In conclusion, dithiocarbenes have been found to react smoothly with vinyl isocyanates to afford a variety of interesting adducts that are amenable to useful functional group interchange to afford building blocks for alkaloid synthesis.

Acknowledgment. The authors wish to thank the National Science Foundation for their generous support of this research.

Supporting Information Available: Typical experimental conditions for cycloadditions and ^{1}H NMR data for **4**, **5**, **7**, and **13**.

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[9] (a) Fuks, R. *Tetrahedron* **1970**, *26*, 2161. (b) Rigby, J. H. Balasubramanian, N. *J. Org. Chem.* **1989**, *54*, 224.

[10] It should be noted that *no* 2:1 adducts of the type shown in eqs 7−9 could be identified under similar conditions using the corresponding dimethoxycarbene precursor.