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Nucleophilic Carbenes in Organic Synthesis. Construction of Functionalized Hydroindolones *via* a Novel Reaction Pathway of Dimethoxycarbene

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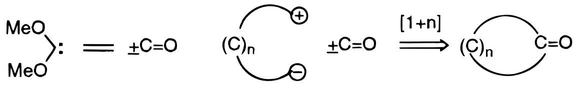
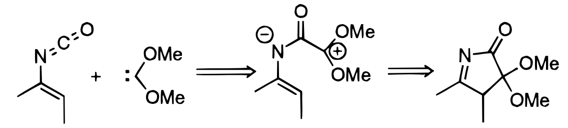
So-called nucleophilic carbenes are intriguing reactive intermediates that have attracted considerable attention in recent years due, in large measure, to their unusual reaction characteristics, which have been attributed to resonance stabilization of the singlet state by donor substituents.[1] It is noteworthy that, in spite of their attractive reactivity profiles, these species have rarely been employed in synthetic applications.[1] In this paper we report a novel reaction pathway between dimethoxycarbene and isocyanates that efficiently delivers structurally elaborate hydroindolone products.

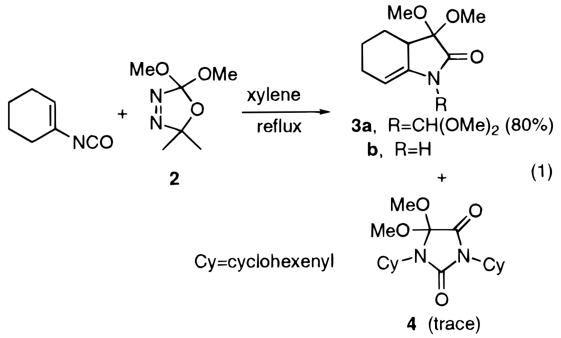
The [1 + *n*] cycloaddition represents an appealing method for ring construction that has been effectively deployed in a number of contexts,[2] and dimethoxycarbene (**1**), a typical nucleophilic carbene,[1g] offers the potential for serving as a novel example of a carbonyl 1,1-dipole equivalent, which are currently relatively rare species.[3,4] Typically these reactive intermediates have been generated by thermolysis of norbornadienone acetals[5] or by photolysis/thermolysis of dimethoxydiazirines.[1g,6] More recently, Warkentin has introduced the thermolysis of 2,2-dialkoxy-Δ^3-1,3,4-oxadiazolines (**2**) as a mild alternative method into these species.[7]



1

Vinyl isocyanates have recently been shown to be versatile "1,4-dipole" equivalents in various [2 + 4] and [1 + 4] cyclization protocols,[8] and it was envisioned that dimethoxycarbene, in combination with these substrates, could provide a new method for rapidly accessing highly functionalized pyrrolinone derivatives. To date, however, all reported reactions between nucleophilic carbenes and isocyanates have afforded only hydantoin-type products that have been produced by the addition of two isocyanate molecules to one equivalent of carbene.[5,7]





2

3a, R=CH(OMe)$_2$ (80%)
b, R=H

(1)

4 (trace)

We now report that vinyl isocyanates react with dimethoxycarbene through an entirely different reaction channel to afford 2:1 adducts in which one isocyanate combines with two carbene units in a carbocyclization event. Thus heating 1-isocyanatocyclohexene with excess carbene precursor **2** (3 equiv) in refluxing xylene afforded functionalized hydroindolone **3a**[9] in good yield accompanied by only a trace of the dimethoxyhydantoin **(4)**. The presence of the nitrogen substituent in **3a** is noteworthy. It is presumed that addition of the second equivalent of carbene occurs *via* a fast NH insertion subsequent to ring formation, since the 1:1 adduct **3b**[9] can be isolated in low yield when only a stoichiometric amount of **2** is employed in the reaction.

Structurally elaborate vinyl isocyanates have been found to be useful reaction partners in this new [1 + 4] process. For example, substituted systems such as **5** and **7** afford quite good yields of hydroindolone products **6** and **8**, respectively. The results in eq 3 are particularly noteworthy in that the Curtius rearrangement of the acyl azide intermediate as well as the cycloaddition can be performed in one operation by directly heating a mixture of acyl azide **7** and carbene precursor **2**. The successful reaction of acyl azide **7** also demonstrates that quaternary carbon centers can be generated with facility using this methodology. Acyclic isocyanates are also viable partners in this reaction process (eq 4). From these results, it is clear that the cyclization of dimethoxycarbene and vinyl isocyanates

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(1) (a) Pole, D. L.; Sharma, P. K.; Warkentin, J. *Can. J. Chem.* **1996**, *74*, 1335. (b) de Meijere, A.; Kozhushkov, S. I.; Yufit, D. S.; Boese, R.; Haumann, T.; Pole, D. L.; Sharma, P. K.; Warkentin, J. *Justus Liebigs Ann. Chem.* **1996**, 601. (c) Pole, D. L.; Warkentin, J. *Justus Liebigs Ann. Chem.* **1995**, 1907. (d) 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. (e) Win, W. W.; Kao, M.; Eiermann, M.; McNamara, J. J.; Wudl, F.; Pole, D. L.; Kassam, K.; Warkentin, J. *J. Org. Chem.* **1994**, *59*, 5871. (f) Moss, R. A. *Acc. Chem. Res.* **1989**, *22*, 15. (g) Moss, R. A.; Wlostowski, M.; Shen, S.; Krogh-Jespersen, K.; Matro, A. *J. Am. Chem. Soc.* **1988**, *110*, 4443.

(2) For some recent examples, see: (a) Pearson, W. H.; Bergmeier, S. C.; Degan, S.; Lin, K.-C.; Poon, Y.-F.; Schkeryantz, J. M.; Williams, J. P. *J. Org. Chem.* **1990**, *55*, 5719. (b) Padwa, A.; Norman, B. H. *Tetrahedron Lett.* **1988**, *29*, 3041. (c) Bäckvall, J. E.; Renko, Z. D.; Byström, S. E. *Ibid.* **1987**, *28*, 4199. (d) Pearson, W. H.; Celebuski, J. E.; Poon, Y.-F.; Dixon, B. R.; Glans, J. H. *Ibid.* **1986**, *27*, 6301.

(3) For examples of other 1,1-dipole equivalents, see: (a) (Sulfur ylides) Trost, B. M.; Melvin, L. S. *Sulfur Ylides, Emerging Synthetic Intermediates*; Academic Press: New York, 1975. (b) (Alkylidene carbenes) Krageloh, K.; Anderson, G. H.; Stang, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 6015. (c) (Carbon monoxide) Sigman, M. S.; Kerr, C. E.; Eaton, B. E. *J. Am. Chem. Soc.* **1993**, *115*, 7545. (d) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (e) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050.

(4) Isocyanides are also useful 1,1-dipole equivalents: (a) Rigby, J. H.; Qabar, M. *J. Am. Chem. Soc.* **1991**, *113*, 8975. (b) Curran, D. P.; Liu, H. *Ibid.* **1991**, *113*, 2127. (c) Morel, G.; Marchand, E.; Foucaud, A.; Toupet, L. *J. Org. Chem.* **1990**, *55*, 1721. (d) VanWagenen, B. C.; Cardellina, J. H. *Tetrahedron Lett.* **1989**, *30*, 3605. (e) Morel, G.; Marchand, E.; Foucaud, A.; Toupet, L. *J. Org. Chem.* **1989**, *54*, 1185. (f) Westling, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1987**, *109*, 590. (g) Westling, M.; Smith, R.; Livinghouse, T. *J. Org. Chem.* **1986**, *51*, 1159.

(5) (a) Hoffmann, R. W.; Steinbach, K.; Dittrich, B. *Chem. Ber.* **1973**, *106*, 2174. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 529. (c) Lemal, D. M.; Gosselink, E. P.; McGregor, S. D. *J. Am. Chem. Soc.* **1966**, *88*, 582.

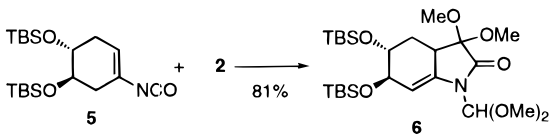
(6) (a) Ge, C.-S.; Jefferson, E. A.; Moss, R. A. *Tetrahedron Lett.* **1993**, *34*, 7549. (b) Moss, R. A.; Shen, S.; Wlostowski, M. *Ibid.* **1988**, *29*, 6417. (c) Moss, R. A.; Fan, H.; Hadel, L. M.; Shen, S.; Wlostowska, J.; Wlostowski, M.; Krogh-Jespersen, K. *Ibid.* **1987**, *28*, 4779.

(7) (a) Couture, P.; Terlouw, J. K.; Warkentin, J. *J. Am. Chem. Soc.* **1996**, *118*, 4214. (b) Kassam, K.; Pole, D. L.; El-Saidi, M.; Warkentin, J. *Ibid.* **1994**, *116*, 1161. (c) El-Saidi, M.; Kassam, K.; Pole, D. L.; Tadey, T.; Warkentin, J. *Ibid.* **1992**, *114*, 8751.

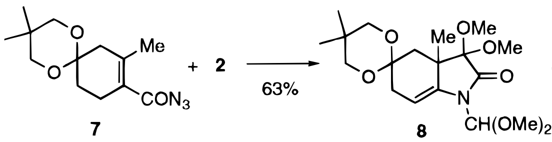
(8) (a) Rigby, J. H.; Qabar, M.; Ahmed, G.; Hughes, R. C. *Tetrahedron* **1993**, *49*, 10219. (b) Rigby, J. H.; Qabar, M. *J. Org. Chem.* **1989**, *54*, 5852. (c) Rigby, J. H.; Holsworth, D. D.; James, K. *Ibid.* **1989**, *54*, 4019. (d) Rigby, J. H.; Balasubramanian, N. *Ibid.* **1989**, *54*, 224.

(9) 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.

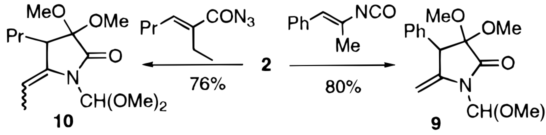
S0002-7863(96)02784-9 CCC: $12.00



(2)

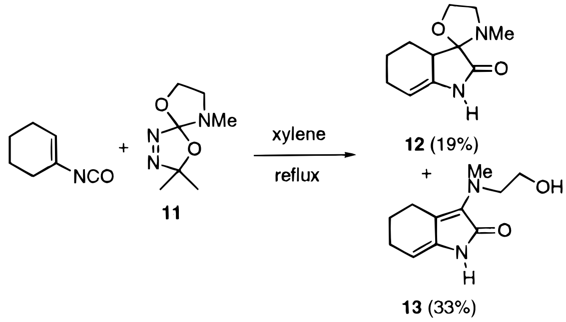


(3)



(4)

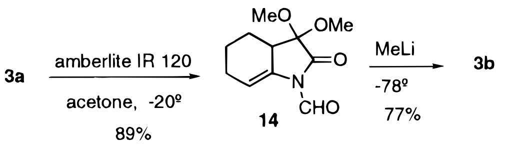
is a general process with significant potential for organic synthesis applications.



(5)

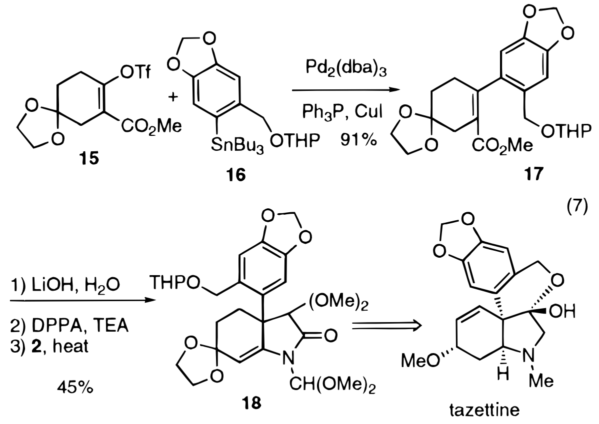
Interestingly, the mixed N/O-substituted carbene species derived from oxadiazoline **11**[7a] initially provided a complex mixture of products when heated for an extended period at 100 °C with the parent cyclohexenyl isocyanate in toluene. However, performing the same reaction in refluxing xylene resulted in a mixture of products from which hydroindolones **12** and **13** could be isolated in modest yields (eq 5). It is noteworthy that both of these adducts arise from 1:1 addition processes. This observation is in contrast to the reaction pathway typically followed by dimethoxycarbene as described above.

The synthetic utility of the hydroindolones isolated from these reactions is critically dependent on the ability to selectively manipulate one of the two quite similar dimethoxy acetal functions present in the products. Preferential removal of the nitrogen substitution without jeopardizing the protected isatin-like carbonyl function is particularly desirable. This can be achieved in high yield as outlined in eq 6.



(6)

To illustrate the utility of dimethoxycarbene-based [1 + 4] cyclization in complex synthesis, rapid entry has been achieved into an advanced intermediate that could be employed in the synthesis of the Amaryllidaceae alkaloid, tazettine,[10] or the related mesembrine alkaloids (eq 7).[11] Palladium-mediated coupling[12] between the readily available vinyl triflate **15** (from the corresponding *β*-ketoester[13]) and the arylstannane **16**[9] (from the known bromide[14]) afforded ester **17**[9] in high yield. Routine ester saponification and Curtius rearrangement of the corresponding acyl azide gave the vinyl isocyanate intermediate, which upon heating in the presence of excess oxadiazoline **2** afforded the hydroindolone **18**[9] in 45% overall yield (58% for the cycloaddition step). It is noteworthy that efforts to effect a similar transformation using a wide range of insertion reactions, including isocyanide cyclization,[4a] failed, demonstrating that dimethoxycarbene-based [1 + 4] cyclization is an advance over existing technology in this area. With compound **18** in hand, routes to a number of alkaloid targets can be envisioned, and these are being pursued at this time.



(7)

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Supporting Information Available: Typical experimental procedures and complete spectroscopic data for all new compounds (12 pages). See any current masthead page for ordering and Internet access instructions.

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[10] (a) Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E. *J. Am. Chem. Soc.* **1970**, *92*, 5538. (b) Tsuda, Y.; Ukai, A.; Isobe, K. *Tetrahedron Lett.* **1972**, *31*, 3153. (c) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1980**, *102*, 2838. (d) Abelman, M. M.; Overman, L. E.: Tran, V. D. *Ibid.* **1990**, *112*, 6959. (e) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1994**, *59*, 5662.

[11] Stevens, R. V. In *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley: New York, 1977; Vol. 3, pp 443−53.

[12] (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V.; Roth, G. P. *Tetrahedron Lett.* **1991**, *32*, 4243.

[13] Pariza, R. J.; Kuo, F.; Fuchs, P. L. *Synth. Commun.* **1983**, *13*, 243.

[14] Alexander, B. H.; Gertler, S. I.; Oda, T. A.; Brown, R. T.; Ihndris, R. W.; Beroza, M. *J. Org. Chem.* **1960**, *25*, 626.