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[4 + 1] Cycloaddition of N-Heterocyclic Carbenes with Vinyl Isocyanates

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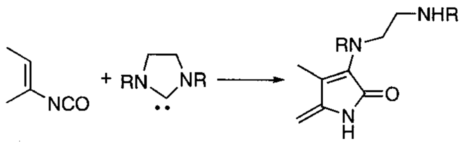
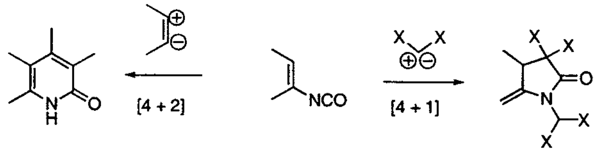
ABSTRACT



N-Heterocyclic carbenes have been found to undergo [4 + 1] cycloaddition with various vinyl isocyanates to afford functionalized hydroindolone products.

Vinyl isocyanates have emerged as powerful building blocks for the preparation of highly substituted five- and six-membered nitrogen heterocycles.[1] These readily available cummulenes have been shown to react smoothly with “1,2-dipoles” such as enamines,[2] ester enolates,[3] and benzynes[4] to deliver structurally complex pyridone-based products. More recently, “1,1-dipole” equivalents such as isocyanides[5] and O- and S-based nucleophilic carbenes[6] have been employed to assemble functionally rich hydroindolone products with excellent efficiency via the corresponding [4 + 1] cycloaddition process (Scheme 1).

Scheme 1



N-Heterocyclic carbenes have been the subject of numerous studies ever since Wanzlick first reported their interesting properties in 1962.[7,8] One of the most notable contemporary applications of these species is as a useful ligand for a variety of metal-based catalysts.[9]

We now wish to disclose that these strongly nucleophilic carbenes can also undergo a net [4 + 1] cycloaddition with vinyl isocyanates, but with several noteworthy differences when compared to other carbene addition pathways.[1−6] In previous studies, various oxygen- and sulfur-substituted oxadiazolines were thermalized to produce the carbene species in the presence of the isocyanate, which immediately underwent reaction to afford the cycloadduct. However, in the current study, thermal decomposition of 2-trichloromethyl-1,3-imidazolidines,[10] which are readily available from condensation of vicinal diamines and chloral, was found to be the method of choice for carbene production. One advantage of this method is that innocuous chloroform is the only byproduct of the process, thus avoiding potentially reactive bases and cation precursors typically used for making N-heterocyclic carbenes.[8] Another noteworthy feature of this protocol is that the labile isocyanate function is generated

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[8] For some recent reviews of this chemistry, see: (a) Arduengo, A. J. *Acc. Chem. Res.* **1999**, *32*, 913. (b) Herrmann, W. A.; Köchen, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2162.
[9] Herrman, W. A. *Angew. Chem.. Int. Ed.* **2002**, *41*, 1290.
[10] (a) Wanzlick, H. W.; Schrikora, E. *Chem. Ber.* **1961**, *94*, 2389. (b) For a variation on this theme, see: Schonberg, A.; Singer, E.; Stephan, W. *Chem. Ber.* **1987**, *120*, 1589.

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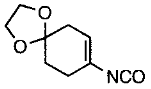
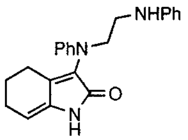
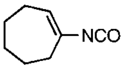
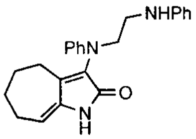
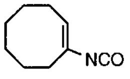
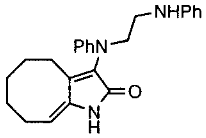
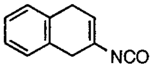
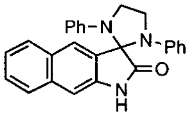
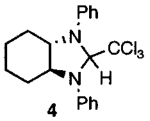
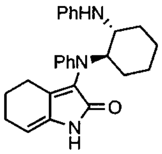
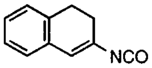
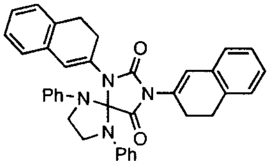
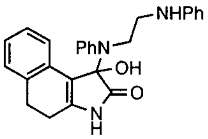
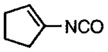
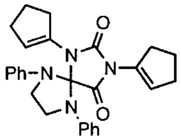
Table 1. Reaction between VinyI Isocyanates and N-Heterocyclic Carbenes[a]

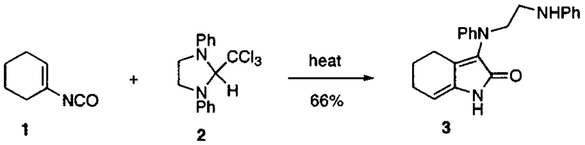
entry	vinyl isocyanate	carbene precursor	product[b]		yield (%)[c]
1	 **5**	2		**11**	57
2	 **6**	2		**12**	55
3	 **7**	2		**13**	52
4	 **8**	2		**14**	51
5	1	 **4**		**15**	65
6	 **9**	2		**16**	71 (**16**/**17**=1/0.6)
				**17**	
7	 **10**	2		**18**	70

[a] Standard conditions: a solution of acyl azide (1 equiv) and carbene precursor (2 equiv) in xylene (ca. 0.05 M) was heated at 80 °C for 2 h and then refluxed for 16 h. The resulting solution was directly chromatographed on silica gel (hexane, then EtOAc/hexane). [b] Reference 11. [c] Isolated yield based on the acyl azide.

in situ via thermolysis of the readily available acyl azide simultaneous to carbene production.

Scheme 2 depicts a typical cycloaddition reaction in this series. Inspection of the hydroindolone **3**[11] reveals several of the novel features of the current transformation as compared to the reaction channel followed by other carbene additions to vinyl isocyanates. The most significant of these differences from a synthetic perspective is the absence of any carbene N−H insertion products; a 1:1 adduct is

Scheme 2



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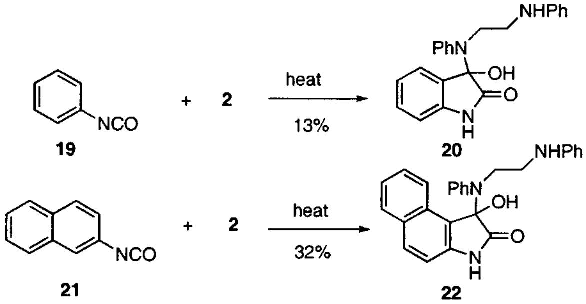
[11] All new compounds exhibit spectral (^{1}H NMR, ^{13}C NMR, IR) and analytical (HRMS and/or elemental analysis) data fully consistent with the assigned structure.

produced in every case examined to date. This observation is in stark contrast to the 2:1 adducts (carbene:isocyanate) that prevailed in virtually all other reactions of this genre.[1] This result was unanticipated in light of the strong basicity of the N-heterocyclic carbene species[12] and may be reflective of the enhanced steric hindrance in the vicinity of the carbene center in these intermediates relative to the corresponding O- and S-based carbenes employed previously in related reactions.[13] Another distinction of the present reaction is the production of the enamide rather than the alternative aminal function in most instances. This outcome is attractive because the enamide can participate directly in subsequent, synthetically useful bond forming transformations, whereas the aminal would require processing prior to undergoing chemistry.[14]

Other examples of this cyclization process are compiled in Table 1. Observations of note include the exclusive formation of an aromatized aminal adduct (entry 4) and the production of the corresponding hydantoin with cyclopentene isocyanate (entry 7). The former may arise from a rapid dehydrogenation of the intermediate adduct, and it is known that hydantoins are the major products of the reactions of aryl isocyanates with most nucleophilic carbenes.[15] A significant exception to this trend is seen with bis(alkylthio)-carbenes,[16] which participate in a [4 + 1] cyclization. Thus, the current result represents only the second major exception to normal reactivity trends in this area.

Even more intriguing was the isolation of hemiaminal **17**[11] from the reaction of **9** with **2** (entry 6). At this juncture it is unclear how this novel product arises, but related materials were found to be the major isolable products on the reaction of both phenyl and naphthyl isocyanates with the carbene (Scheme 3). A possible explanation for the production **17**, **20**,[11] and **22**[11] is the trapping of the intermediate iminium ion with adventitious water present in the reaction mixture. Further support for this notion comes from the isolation of a small quantity of hydrated carbene from these reactions. The regioselectivity of the ring formation (**21** to **22**) is fully consistent with the reactivity patterns in naphthalene.[17]

Scheme 3



In summary, the addition of N-heterocyclic carbenes to vinyl isocyanates proceeds effectively to deliver highly functionalized hydroindolone products. These transformations complement the previously disclosed O- and S-based carbene additions in several synthetically significant ways. The means of generating the carbenes is also important in that it precludes the use of reagents and precursors that could react with cycloaddition partners.

Further work is currently underway to more fully establish the scope and limitations of this novel reaction and to apply it to alkaloid total synthesis.

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Note Added after ASAP. Acknowledgment and Supporting Information paragraphs were printed incorrectly in the version posted ASAP November 6, 2002. The corrected version was posted November 11, 2002.

Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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