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Vinyl Isocyanates in Synthesis. [4 + 2] Cycloaddition Reactions with Benzyne Addends

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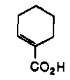
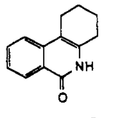
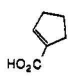
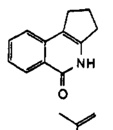
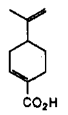
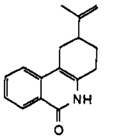
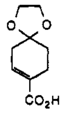
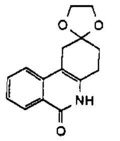
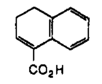
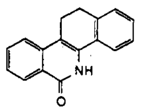
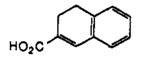
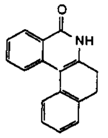
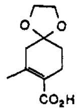
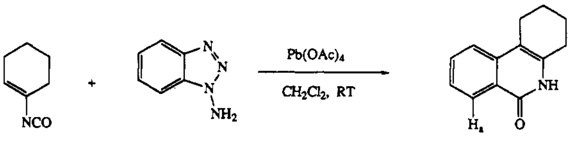
Summary: The net [4 + 2] cycloaddition of benzyne with various vinyl isocyanates to construct phenanthridinone and benzophenanthridinone products is disclosed. Generation of the benzyne is best accomplished by $Pb(OAc)_4$ oxidative decomposition of 1-aminobenzotriazole.

Sir: The hetero-Diels–Alder reaction in its various forms continues to play an important role in the synthesis of heterocyclic systems.[1] We have been interested recently in exploiting the unique reactivities afforded by the vinyl isocyanate function in developing efficient strategies for the total synthesis of alkaloids. In previous work, the utility of these readily available and reasonably stable functionalities has provided methods for the rapid assembly of extended polycyclic α-pyridone systems and 4-hydroxy-2-pyridone species.[2] The most notable feature of this chemistry has been the high level of convergency and experimental simplicity that normally characterizes the cyclization process.[3] We have been particularly intrigued with the notion of extending the vinyl isocyanate cyclization technology to the problem of direct construction of phenanthridinone and benzophenanthridinone ring systems by employing a "dienophilic" synthon for the benzo moiety.[4] The obvious choice for this synthetic equivalent would be a suitably generated benzyne.[5] The prospects for success of this conceptually novel approach into these important polycyclic heterocycles depends critically on the compatibility of the methodology employed for benzyne production with the relatively fragile isocyanate addend. We now report that a variety of vinyl isocyanate partners participate in a smooth cycloaddition reaction with benzyne that has been generated in situ by a $Pb(OAc)_4$-mediated oxidative decomposition of 1-aminobenzotriazole (2).[6] This experimentally convenient sequence provides direct access to phenanthridinone- and benzophenanthridinone-derived products in a convergent, one-step process. Equation 1 depicts the fundamentals of this methodology.

Table I. [4 + 2] Cycloadditions of Benzyne with Vinyl Isocyanates

entry	carboxylic acid	product[a]	yield,[b] %
1			58
2			40
3			50
4[c]			51
5[d]			46
6[e]			35
7[f]			0

[a] All compounds exhibit spectral (^1H NMR, ^{13}C NMR, IR) and analytical or HRMS data in agreement with the assigned structure. [b] Reported yields are not optimized. [c] Acid is prepared as in ref 10. [d] Acid prepared as in ref 11. [e] Acid prepared as in ref 12. [f] Acid prepared from Hagemann's ester.



(1)

1 2 3

In a typical procedure, a solution of 1.1 equiv of 1-aminobenzotriazole in CH_2Cl_2 was slowly added to a mixture of 1 equiv of isocyanate and a slight excess of $Pb(OAc)_4$ in CH_2Cl_2 at room temperature. Removal of insoluble inorganic byproducts by filtration of the reaction mixture after approximately 15 min and chromatographic purification of the resultant cycloadducts completed the process. All cycloadducts prepared in this fashion displayed a characteristic doublet (δ 8.40–8.45, J = 7–8 Hz) in the 300-MHz ^1H NMR spectra that was assigned to the aromatic peri proton H_a, which resonated nearly 1 ppm further downfield than the other aromatic signals. This

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[1] Boger, D. L.; Weinreb, S. N. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987.

[2] (a) Rigby, J. H.; Balasubramanian, N. *J. Org. Chem.* **1989**, *54*, 224. (b) Rigby, J. H.; Burkhardt, F. J. *Ibid.* **1986**, *51*, 1374. (c) Rigby, J. H.; Balasubramanian, N. *Ibid.* **1984**, *49*, 4569.

[3] For additional recent approaches to α-pyridones, see: (a) Winters, G.; Sala, A.; de Paoli, A.; Ferri, V. *Synthesis* **1984**, 1052. (b) Meth-Cohn, O.; Westwood, K. T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1173. (c) Earl, R. A.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1983**, *105*, 6991. (d) Overman, L. E.; Tsuboi, S.; Roos, J. P.; Taylor, G. F. *Ibid.* **1980**, *102*, 747.

[4] The ring systems generated by this process are the building blocks for a very wide variety of alkaloid structural classes. (a) Amaryllidaceae alkaloids: Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, pp 251–376. (b) Benzophenanthridine alkaloids: Simanek, V. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, pp 185–240.

[5] Phenyl isocyanate has been reported to give a [4 + 2] cycloadduct with benzyne in low yield: Sheehan, J. C.; Daves, G. D. *J. Org. Chem.* **1965**, *30*, 3247.

[6] (a) Hart, H.; Ok, D. *J. Org. Chem.* **1986**, *51*, 979. (b) Campbell, C. D.; Rees, C. W. *J. Chem. Soc. C* **1969**, 742.

[7] The vinyl isocyanates described in this paper were conveniently prepared from the corresponding α,β-unsaturated carboxylic acid via a modified Curtius procedure: Weinstock, J. *J. Org. Chem.* **1961**, *26*, 3511. Alternately, the isocyanate could be prepared directly from the acid by employing commercial diphenyl phosphorazidate (DPPA): Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

[8] Employing lead tetraacetate from a freshly opened bottle appears to be crucial to the success of these reactions as is the use of freshly prepared isocyanate.

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proton is positioned within the deshielding cone of the adjacent pyridone carbonyl group and is diagnostic for the formation of the phenanthridinone system.

Table I presents some of the phenanthridinone products rendered readily available via this methodology. Entries 4 and 5 are particularly significant in terms of their application to alkaloid synthesis. Appropriate modifications of these examples could be envisioned to lead to rapid construction of target natural products such as lycorine[4a] and chelidonine,[4b] respectively. In general these cycloaddition reactions proceeded without complications on a range of substrates; however, steric hindrance appears to suppress bond formation as evidenced by the failure of the isocyanate derived from the α,β-unsaturated acid depicted in entry 7 to undergo cycloaddition with benzyne under these conditions. This particular substrate is of interest since it could represent a potentially attractive model for entry into the crinine-type amaryllidaceae alkaloids.

It is noteworthy that during the course of this investigation a number of other conditions for mild benzyne generation were examined in detail and found to be, in general, inferior to the 1-aminobenzotriazole oxidation method for the application at hand.[9] A detailed mechanistic scenario for the process reported herein is obscure at this point. Benzynes are well known to participate in [4 + 2] cycloaddition processes with a wide range of diene addends[6,9] and our experience to date indicates that vinyl isocyanates tend to react in a polar, step-wise fashion with most reaction partners to yield net [4 + 2] products.[2] In this regard it is interesting to note that in some reactions studied to date, trace quantities of a possible β-lactam species (ν_{max} 1790 cm^{-1}) have been observed in crude reaction mixtures and pathways involving sequential [2 + 2] cycloaddition–rearrangement steps, although unlikely, cannot be rigorously excluded at this juncture.[13,14] Efforts to shed light on the mechanistic subtleties of these reactions are currently underway in our laboratory as is the application of the methodology to alkaloid total synthesis.

Acknowledgment. We thank the National Science Foundation (CHE-8719185) for their generous support of this work.

Supplementary Material Available: Experimental details and full spectroscopic and physical characterization of all new products (3 pages). Ordering information is given on any current masthead page.

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[9] For other methods of benzyne preparation, see: Bryce, M. R.; Vernon, J. M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1981; Vol. 28, pp 183–229.

[10] Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.

[11] Vebrel, J.; Carrie, R. *Bull. Soc. Chim. Fr.* **1982**, 161.

[12] Holmer, H. L.; Trevoy, L. W. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 300.

[13] Chlorosulfonyl isocyanate is known to react with dienes in a sequence involving initial [2 + 2] cycloaddition followed by rearrangement. (a) Moriconi, E. J.; Meyer, W. C. *J. Org. Chem.* **1971**, *36*, 2841. (b) Haug, T.; Lohse, F.; Metzger, K.; Batzer, H. *Helv. Chim. Acta* **1968**, *51*, 2069.

[14] Benzoazetinone species have been identified as transients in other reactions, but isolation of these unstable materials has been achieved only under select circumstances: (a) Bashir, N.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1973**, 868. (b) Olofson, R. A.; Vander Meer, R. K.; Hoskin, D. H.; Bernheim, M. Y.; Stournas, S.; Morrison, D. S. *J. Org. Chem.* **1984**, *49*, 3367.

Synthesis of α′-Acyloxy Enones from Enones Using Manganese(III) Acetate in Combination with Manganese(II) Carboxylates or Carboxylic Acids

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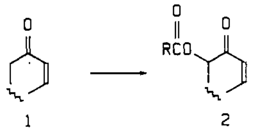
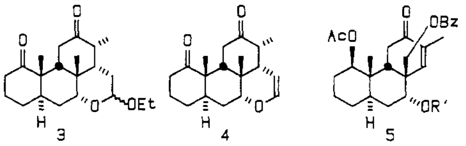
Summary: The oxidation of enones using manganese(III) reagents prepared from manganese(III) acetate in the presence of various carboxylic acids or manganese(II) salts of these carboxylic acids provided a convenient synthesis of α′-acyloxy enones.

Sir: In the course of devising an enantioselective route to the quassinoids,[1] we required an effective procedure for the α′-oxidation of enones 1 to α′-acyloxy enones 2 as shown in Scheme I. Previously, we experienced difficulty with the simultaneous C-2 and C-11 oxidation[2] of a bis(enolate) derived from the tetracyclic diketones 3 and 4 in Scheme II to either a bis(α-ketol) or a bis(diosphenol) as well as difficulty with other multistep procedures[3] that would effect these oxidations. We next considered the sequential oxidation of the C-2 and C-11 positions in which application of manganese(III) acetate[4,5] would effect the C-11 oxidation of the tricyclic enone 5 in Scheme II. After finding that this C-11 oxidation process was compatible with a limited range of C-1 protecting groups[2] such as the C-1β acetate in 5, we questioned whether we could dif-

Scheme I



Scheme II



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[1] Polonsky, J. *Fortsch. Chem. Org. Naturst.* **1973**, *30*, 101; **1985**, *47*, 221.

[2] Gross, R. S.; Kawada, K.; Kim, M.; Watt, D. S. *Synth. Commun.*, in press.