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Preparation of Highly Substituted 4-Aminopyridones via the Reaction of 2-Methylene Dihydrobenzimidazole with Vinyl Isocyanates

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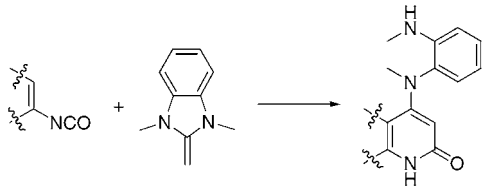
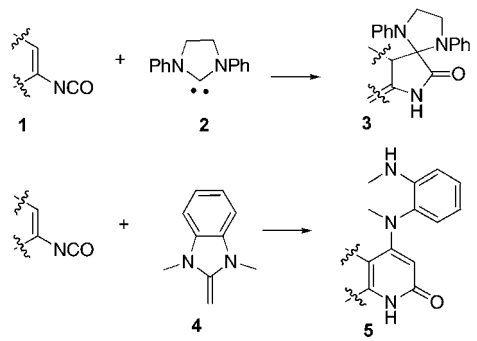
ABSTRACT



The rapid construction of highly substituted 4-aminopyridones was achieved employing an efficient cyclization between various vinyl isocyanates and 2-methylene dihydrobenzimidazole.

N,*N*-Dimethyl ketene aminals[1] have been used as 2π partners in inverse electron demand Diels−Alder reactions with a variety of electron-poor dienes,[2,3] tetrazines, and triazines.[4] The utility of these reactants was further illustrated in a [3 + 2] cycloaddition with methanesulfonyl azide.[5,6] We now disclose a simple, rapid, and efficient construction of 4-aminopyridones via a [4 + 2] cyclization of 2-methylene dihydrobenzimidazole (**4**) with various vinyl isocyanates (Scheme 1).

Scheme 1



Recently, our laboratory reported an efficient synthesis of functionalized hydroindolones through a powerful [4 + 1] cycloaddition of vinyl isocyanates and N-heterocyclic carbenes.[7] This process allowed for the facile construction of five-membered heterocycles, and a related transformation using ketene aminals was envisioned to deliver the corresponding six-membered ring system. Methods for the synthesis of the pyridone ring system have received considerable attention because it is an important substructure in a range of pharmaceutical agents.[8,9] Indeed, our laboratory has reported several approaches for constructing these heterocycles based on vinyl isocyanate cyclization chemistry.[10]

(1) Gruseck, U.; Heuschmann, M. *Chem. Ber.* **1987**, *120*, 2053−2064.
(2) Gruseck, U.; Heuschmann, M. *Tetrahedron Lett.* **1987**, *28*, 2681−2684.
(3) Heuschmann, M. *Chem. Ber.* **1988**, *121*, 39−49.
(4) Gruseck, U.; Heuschmann, M. *Tetrahedron Lett.* **1987**, *28*, 6027−6030.
(5) Quast, H.; Ivanova, S.; Peters, E.-M.; Peters, K.; Schnering, H. G. *Liebigs. Ann.* **1996**, 1541−1549.
(6) Quast, H.; Ach, M.; Kindermann, M. K.; Schindler, M. *Chem. Ber.* **1993**, *126*, 503−516.
(7) Rigby, J. H.; Wang, Z. *Org. Lett.* **2002**, *4*, 4289−4291.
(8) Girundon, M. F. *The Alkaloids*; The Chemical Society: London, 1977.
(9) Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*; Wiley: New York, 1977.

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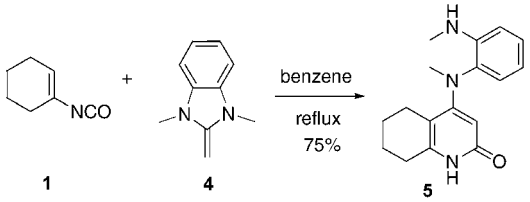
Numerous other laboratories have disclosed approaches to construct the pyridone moiety as well.[11] However, these approaches often require prolonged reaction times, harsh reaction conditions, or a strong base.

The relatively stable 2-methylene dihydrobenzimidazole (**4**) was prepared using a precedure reported by Quast.[5] A variety of substituted and functionalized vinyl isocyanates were used in this study to probe the scope and versatility of the reaction. The vinyl isocyanates were generated easily and cleanly through a Curtius rearrangement of the corresponding vinyl acyl azides. The production of pyridone (**5**)[12] is a typical example of this protocol (Scheme 2).

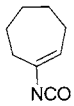
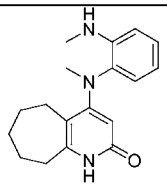
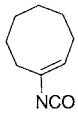
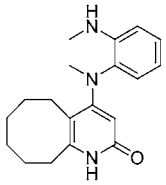
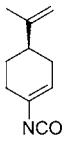
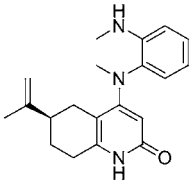
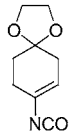
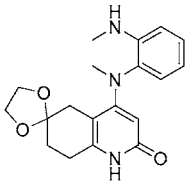
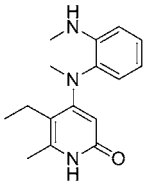
Scheme 2



As shown in Table 1, several acyclic and cyclic substituted 4-amino pyridones were obtained through this process. One benefit of this procedure is that the reaction required only 2 h to reach completion, while the reaction between conventional enamines and vinyl isocyanates required reaction times of at least 2 days to obtain reasonable yields and often required much harsher reaction conditions as well. The observations reported herein further confirm the strong nucleophilicity of ketene aminals in comparison to other enamines.

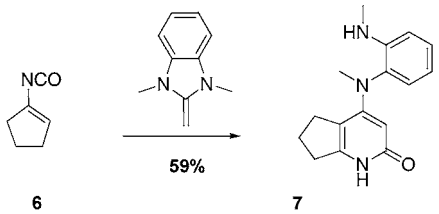
The result in entry 5, Table 1, is particularly noteworthy in that acyclic isocyanates are often problematic reaction partners in other cyclizations. Indeed, few enamines are known to successfully engage acyclic isocyanates in productive reaction.[10] Another distinctive feature of this process is that the enamide function was obtained instead of the cyclic aminal moiety. This allows for direct transformation into various synthetically useful compounds, whereas the aminal would require additional processing.

Table 1. Reaction between Vinyl Isocyanates and *N*,*N*-Dimethyl Ketene Aminal (**4**)

Entry	Isocyanate	Product[13]	Yield[12] (%)
1			72
2			74
3			65
4			60
5			55

The successful formation of pyridone **7** (59%)[12] through reaction of cyclopentene isocyanate with **4** is another significant outcome of this study (Scheme 3). Conventional

Scheme 3



enamines provided this pyridone in very modest yield, and reactions with other 2π partners failed completely to deliver pyridone products.

Another important difference between the current reaction and previous enamine/isocyanate cyclizations is the ability

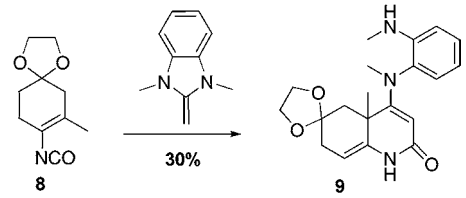
(10) (a) Rigby, J. H.; Holsworth, D. D.; James, J. *J. Org. Chem.* **1989**, *54*, 4019−4020. (b) Rigby, J. H.; Burkhardt, F. J. *J. Org. Chem.* **1986**, *51*, 1374−1376. (c) Rigby, J. H.; Balasubramanian, N. *J. Org. Chem.* **1989**, *54*, 224−228. (d) Rigby, J. H.; Qabar, M. *J. Org. Chem.* **1989**, *54*, 5852−5853. (e) Rigby, J. H.; Balasubramanian, N. *J. Org. Chem.* **1984**, *49*, 4569−4571.

(11) For other pyridone syntheses, see: (a) Overman, L. E.; Tsuboi, S.; Roos, J. P.; Taylor, G. F. *J. Am. Chem. Soc.* **1980**, *102*, 747−754. (b) Saunte, F.; Serckx-Ponci, B.; Hesbain-Frisque, A.-M.; Ghosez, L. *J. Am. Chem. Soc.* **1982**, *104*, 1428−1430. (c) Winters, G.; Sala, A.; DePaoli, A.; Ferri, V. *Synthesis* **1984**, 1052. (d) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T. *J. Org. Chem.* **1999**, *64*, 2038−2049. (e) Alberola, A.; Calvo, L. A.; Ortega, A. G.; Ruiz, M. C.; Yustos, P.; Granda, G.; Garcia-Rodriguez, E. *J. Org. Chem.* **1999**, *64*, 9493−9498. (f) Carles, L.; Narkunan, K.; Penlou, S.; Rousset, L.; Bouchu, D.; Ciufolini, M. A. *J. Org. Chem.* **2002**, *67*, 4304−4308. (g) Savarin, C. G.; Murry, J. A.; Dormer, P. G. *Org. Lett.* **2002**, *4*, 2071−2074.

(12) All new compounds exhibit spectral (^{1}H NMR, ^{13}C NMR, IR) and analytical (HRMS) data fully consistent with the assigned structures.

to construct quaternary carbon centers during the ring-forming process as exemplified by the successful preparation of **9**,[12] albeit in modest yield (Scheme 4). This represents a

Scheme 4

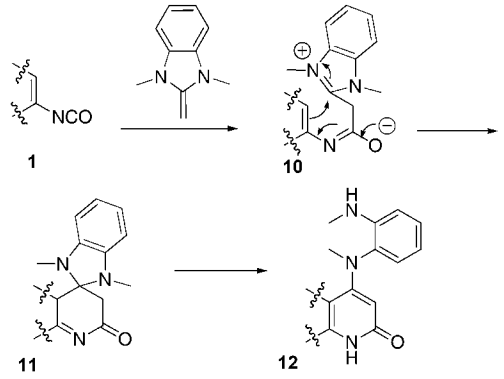


reaction channel that is without precedent in our previous six-membered heterocycle synthetic work[10] but has been observed in certain [4 + 1] cyclizations with carbenes.[14]

The putative mechanism of this cyclization is depicted in Scheme 5. Treatment of isocyanate **1** with 2-methylene dihydrobenzimidazole (**4**) would result in the formation of zwitterionic iminium intermediate **10**. This species could then undergo cyclization to aminal **11**, which is then further transformed into the observed pyridone **12** via tautomerization and elimination.[15]

In summary, the nucleophilicity[16] of 2-methylene dihydrobenzimidazole has been shown to be superior to conventional enamines in reactions with vinyl isocyanates. The ability of this *N*,*N*-dimethyl ketene aminal to deliver 4-aminopyridones rapidly and efficiently offers an attractive alternative approach to this class of heterocycles.

Scheme 5



Further work is currently underway to explore the utility of *N*,*N*-dimethyl ketene aminals for the synthesis of biologically significant compounds that possess a pyridone core structure.

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

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

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(13) Standard conditions: a solution of acyl azide (1 equiv) in benzene or acetonitrile was refluxed for 1 h and then cooled to 0 °C. A solution of 2-methylene dihydrobenzimidazole in benzene or acetonitrile was added, and the reaction was stirred at room temperature for 30 min and then refluxed for 2 h, concentrated, and purified by column chromatography.

(14) (a) Rigby, J. H.; Laurent, S. *J. Org. Chem.* **1999**, *64*, 1766−1767. (b) Rigby, J. H.; Laurent, S.; Dong, W.; Danca, M. D. *Tetrahedron*, **2000**, *56*, 10101−10111.

(15) Hydrolysis of the enamides has been problematic, but studies continue in this direction.

(16) For studies on the nucleophilicity of these species, see: Kuhn, N.; Bohnen, H.; Kruetzberg, J.; Blaser, D.; Boese, R. *J. Chem. Soc., Commun.* **1993**, 1136.