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Domino Reactions That Combine an Azido-Schmidt Ring Expansion with the Diels–Alder Reaction

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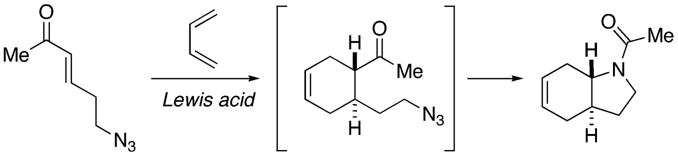
ABSTRACT



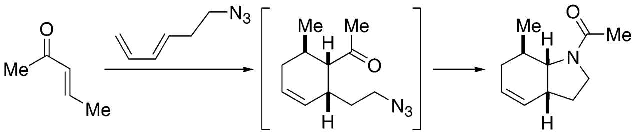
The combination of the intramolecular Schmidt reaction with the Diels–Alder reaction provides expedient access to a variety of heterocycles. Two different modes of reaction planning are presented. In one, the azide and ketone moieties necessary for the intramolecular Schmidt reaction originate on different molecules that are reacted and subsequently undergo a ring-adjustment step. Alternatively, an azido ketone can be used provided the ketone is deactivated by its presence in an enone.

Domino reactions, which result from the combination of multiple transformations in a single pot, are most valuable when they efficiently afford complex products from simple, readily available starting materials.[1] The design of an effective domino process involves control over the order of the various steps that make up the overall transformation. In seeking to develop streamlined heterocyclic syntheses using the azido-Schmidt reaction, we have begun to explore the combination of this useful ring expansion reaction with "strategy-level" C−C bond-forming processes such as the Diels−Alder reaction.

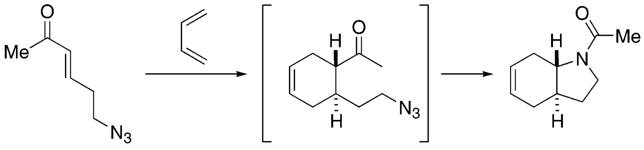
The azido-Schmidt reaction is the Lewis or protic acid-promoted reaction of an alkyl azide with a ketone, affording bicyclic lactam products.[2,3] In this work, we concentrated on rigging a domino sequence so that the azido-Schmidt reaction would react with ketones revealed in situ by a Lewis acid-promoted Diels−Alder reaction. Two conceptually different ways of timing the individual reactions are shown in Scheme 1. Since the intermolecular Schmidt reaction of azides is substantially less facile than the intramolecular version, one straightforward strategy is to segregate the ketone and azide on the dienophile and diene, respectively, and to use the Diels−Alder reaction bring the two pieces together (Scheme 1a). Only then should a subsequent intramolecular azido-Schmidt reaction take place.

Scheme 1

(a) Intermolecular Diels–Alder + intramolecular Schmidt reaction



(b) Enone deactivation method



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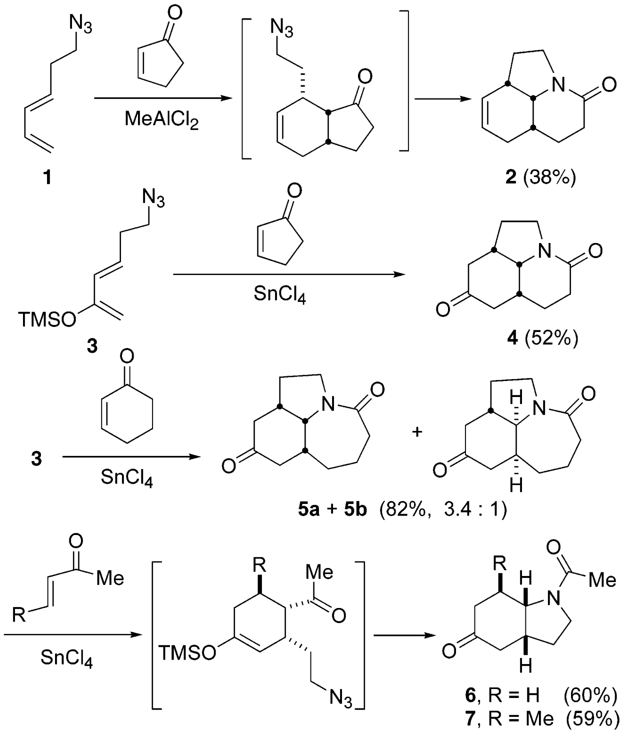
[1] For reviews of domino processes, see: (a) Ho, T.-L. *Tandem Reactions in Organic Synthesis*; Wiley: New York, 1992. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131−163. (c) Waldmann, H. *Organic Synthesis Highlights II*; Wiley-VCH: Weinheim, 1995; pp 193−202. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (e) Padwa, A. *Chem. Commun.* **1998**, 1417−1424. (f) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304−322.

[2] (a) Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635−1637. (b) Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **2000**, *122*, 7226−7232.

10.1021/ol047809r CCC: $27.50

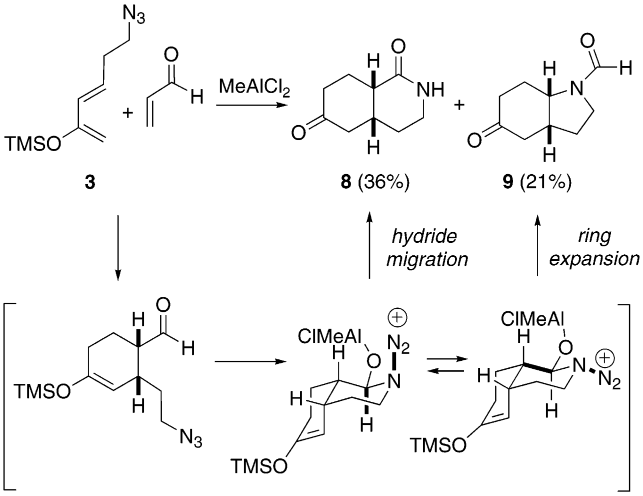
Scheme 2



A less obvious method works by "deactivating" the ketone functionality prior to Diels−Alder cycloaddition (Scheme 1b). We have shown that enones rarely undergo even intramolecular azido-Schmidt reactions.[4] Thus, an azide attached to an α,β-unsaturated ketone will be reluctant to attack the carbonyl group until conjugation has been eliminated by the Diels−Alder reaction. In the example shown, premature azido-Schmidt reaction is also less likely due to the presence of an *E* double bond between the ketone and azide. In this letter, we describe how both approaches allow for efficient, single-step syntheses of a variety of complex heterocycles.[5]

Some representative examples of the domino intermolecular Diels−Alder/intramolecular Schmidt reactions as exemplified in Scheme 1a are shown in Scheme 2.[6] Initial investigations using the unactivated azido diene **1** afforded modest yields of cyclic lactams such as **2**, but as expected, better results were obtained using the more electron-rich silyloxydiene **3**. Of a limited set of Lewis acids examined, the best results so far were obtained using the aluminum- or tin-based reagents in DCM from −78 °C → room temperature. It is worth noting that these reactions provide a highly efficient synthesis of natural productlike skeleta such as pyrroloisoquinolone (**2**, **4**), azepinoindolone (**5a**, **5b**), and the cis-fused perhydroindole (**6**, **7**) with good yields and high diastereoselectivity. The relative stereochemistry of each isolated heterocycle was confirmed by NOESY studies, which show that the domino reaction proceeds through an *endo*-selective Diels−Alder reaction followed by stereoselective Schmidt ring expansion. It is interesting to note that reaction of **3** with acrolein gave both decahydroisoquinoline (**8**) and perhydroindole (**9**) products, which result from hydride migration or ring expansion, respectively (Scheme 3).

Scheme 3



proposed antiperiplanar migration shown (darkened bonds)

The enone deactivation method shown in Scheme 1b was first examined using acylic azido enones **10** or **11**,[7] which readily undergo tandem Diels−Alder/Schmidt reactions when reacted with variously substituted dienes using MeAlCl$_2$ as a Lewis acid in DCM from 0 °C → room temperature (Scheme 4). The products **12**−**16** are *trans*-hexahydroindoles that would otherwise require a *trans*-enamide dienophile (and subsequent ring closure) for their direct synthesis. It should be noted that these hexahydroindoles are stereochemically and constitutionally complementary to those obtained using the first strategy (cf. **6** and **7** in Scheme 2 with **12**−**16**). Although **10** and **11** worked nicely in the above examples, reaction of these enones with 1,3-cyclohexadiene afforded only Diels−Alder adduct (**17** and **18**), presumably due to the rigid trans disposition of the azide and ketone functionalities in this product.

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(3) (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965−8966. (b) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449−10459.

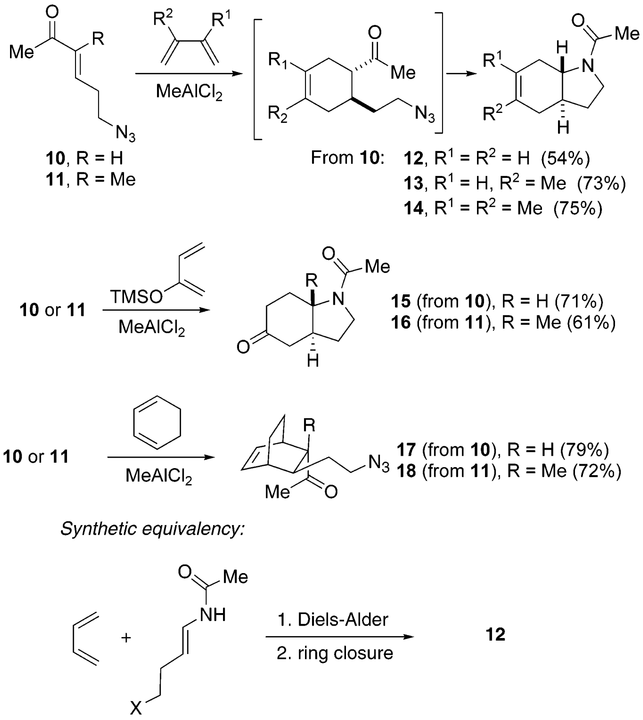
(4) Reddy, D. S.; Judd, W. R.; Aubé, J. *Org. Lett.* **2003**, *5*, 3899−3902.

(5) A single example of an intramolecular variant of an analogous reaction to that shown in Scheme 1b was published in the context of a total synthesis of stenine: Golden, J. E.; Aubé, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4316−4318. To our knowledge, this is the only example of a tandem process involving any variation of the Schmidt reaction prior to the present work.

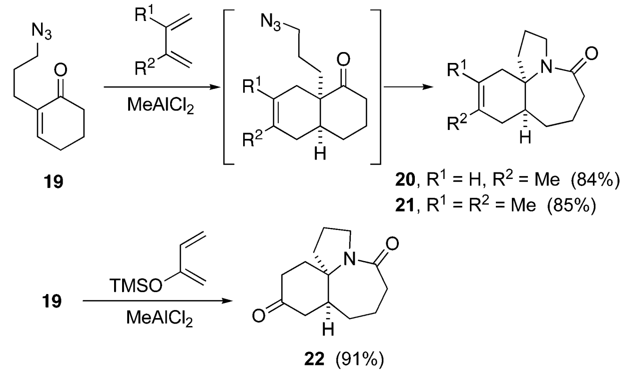
(6) There are many examples of domino reactions involving the Diels−Alder reaction (see reviews listed in ref 1). Some recent examples include: (a) Akai, S.; Tanimoto, K.; Kita, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 1407−1410. (b) Sabitha, G.; Reddy, E. V.; Fatima, N.; Yadav, J. S.; Krishna, K. V. S. R.; Kunwar, A. C. *Synthesis* **2004**, 1150−1154. (c) Tietze, L. F.; Rackelmann, N.; Mueller, I. *Chem. Eur. J.* **2004**, *10*, 2722−2731. (d) Tietze, L. F.; Rackelmann, N. *Z. Naturforsch. B: Chem. Sci.* **2004**, *59*, 468−477. (e) Yadav, J. S.; Reddy, B. V. S.; Narsimhaswamy, D.; Lakshmi, P. N.; Narsimulu, K.; Srinivasulu, G.; Kunwar, A. C. *Tetrahedron Lett.* **2004**, *45*, 3493−3497. (f) Raw, S. A.; Taylor, R. J. K. *J. Am. Chem. Soc.* **2004**, *126*, 12260−12261.

(7) All azides and other starting materials were prepared using standard methods; see Supporting Information for details. All azides should be used with caution!

Scheme 4



Scheme 5



Finally, the cyclic azido enone **19**[7] readily underwent domino Diels–Alder/Schmidt reactions to give homopyrrolo-[2,1-*j*]quinolin-5-ones (**20**–**22**) in excellent yields as outlined in Scheme 5. The structure of **22** was confirmed by X-ray crystallographic analysis.

In summary, we have investigated two conceptually different ways to combine the azido-Schmidt ring expansion with the Diels–Alder reaction. These experiments highlight the potential of the azido-Schmidt reaction when enhanced by its combination with other Lewis acid-promoted processes. In particular, we note the diversity of ring systems and substitution types obtained using these one-pot methods. Importantly, this concept can be extended to encompass other Lewis acid-promoted reactions such as the Mukaiyama aldol and Sakurai reactions; our preliminary work in these areas will be submitted for publication in due course. Future work will apply these reactions to both target- and diversity-oriented synthesis projects.

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Supporting Information Available: Experimental procedures and characterization of compounds (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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