ORGANIC LETTERS

2002
Vol. 4, No. 25
4543−4546

Synthesis and Thermolysis of Heterocyclic 3-Aza-3-ene-1,5-diynes[1]

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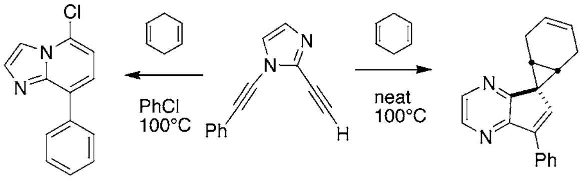
Received October 14, 2002

ABSTRACT



Simple, acyclic 3-aza-3-ene-1,5-diynes undergo an aza-Bergman rearrangement to a fleeting 2,5-didehydropyridine (2,5-ddp) intermediate that rapidly ring-opens to *β*-alkynylacrylonitrile products. In an effort to access longer-lived 2,5-ddp intermediates, we have prepared heterocyclic 3-aza-3-ene-1,5-diynes. The thermolysis of one such heterocyclic aza-enediyne does not afford products derived from trapping a 2,5-ddp intermediate but rather cyclopropanes that appear to arise from a carbene intermediate and a product that appears to be a trapping product from a 2,3-ddp intermediate.

The cyclization of the enediyne core of natural products such as calcheamicin γ_1,[1,2] esperamicin A_1,[3] and dynemicin A[4] generates diradical intermediates[5] that are capable of cleaving DNA,[6] and this DNA cleavage is the mechanism by which these compounds exert their potent cytotoxic effects.[7] One outstanding issue with this class of compounds is their relative lack of selectivity.[8] Much effort has been devoted to the design and synthesis of novel enediynes in which the diradical generation from an enediyne core might be triggered under conditions that could lead to cancer cell-specific cytotoxicity.[9] An alternative approach has recently emerged in which the core of the enediyne is modified by replacement of one carbon atom with a nitrogen to afford a 3-aza-3-ene-1,5-diyne moiety (Figure 1).[10] 3-Aza-3-ene-1,5-diynes have been predicted to have important advantages over the corresponding enediynes both in terms of the facility with which they undergo cyclization to afford diradicals[9] as well as the tunable reactivity of these diradicals toward target DNA cleavage in cancer cells.[11]

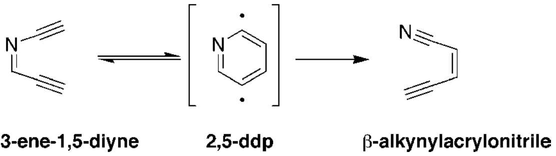


Figure 1. Aza-Bergman rearrangement of acyclic 3-aza-3-ene-1,5-diynes to afford fleeting 2,5-didehydropyridine diradical intermediates (**2,5-ddp**), which rapidly undergo a retro-aza-Bergman reaction to give *β*-alkynylacrylonitriles.

The aza-enediynes and their aza-Bergman cyclization products, 2,5-didehydropyridines (2,5-ddp), have been the

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[1] Portions of this work have previously been reported in the Ph.D. dissertation of Wendi M. David, The University of Texas at Austin, Austin, TX, 2000.

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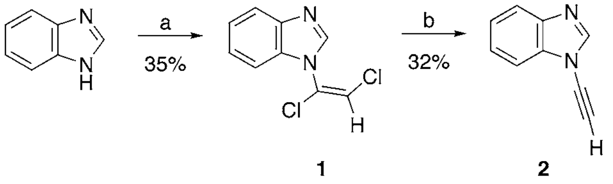
10.1021/ol027100p CCC: $22.00

subject of numerous computational studies.[12] These computational studies have confirmed our earlier observation[10] that 2,5-ddp intermediates derived from the aza-Bergman cyclization of simple, acyclic 3-aza-3-ene-1,5-diynes undergo an extremely facile retro-aza-Bergman ring-opening reaction to afford β-alkynylacrylonitrile products (Figure 1). Significantly, the only report of a product derived from trapping the elusive 2,5-ddp intermediate has come from studies of the aza-Bergman cyclization reaction. Chen and co-workers[11] reported the detection of miniscule amounts of pyridine product by GC/MS in the thermolysis of an acyclic aza-enediyne under acidic conditions. One approach to produce longer-lived diradical intermediates involves the rearrangement of “skipped” 4-aza-3-ene-1,6-diynes, which we have shown are effective, pH-dependent DNA cleavage agents.[13] An alternative approach to longer-lived 2,5-ddp intermediates has been proposed in which the carbon−nitrogen double bond of the 3-aza-3-ene-1,5-diyne moiety is incorporated into an amide or amidine functional group[12a] such that retro-Bergman ring opening of the corresponding 2,5-ddp intermediate is disfavored. We have explored a variant of this approach in which the carbon−nitrogen double bond of the 3-aza-3-ene-1,5-diyne functionality is incorporated into a five-membered heterocycle. This approach has the advantage of enforcing the cis geometry of the N- and C-alkynyl groups of the aza-enediyne required for aza-Bergman cyclization. Here we report the synthesis of these previously unknown heterocyclic 3-aza-3-ene-1,5-diynes. Under thermolysis conditions in the presence of 1,4-cyclohexadiene, one such heterocyclic 3-aza-3-ene-1,5-diyne affords products that arise from reactive intermediates produced from profound molecular rearrangements that may proceed from the aza-Bergman-retro-aza-Bergman cascade.

The synthesis of heterocyclic 3-aza-3-ene-1,5-diynes requires the construction of a potentially unstable N-alkynyl heterocycle. While there are reports of other N-alkynyl aromatic heterocycles,[14] no N-alkynyl benzimidazoles or imidazoles have been reported. To generate an alkyne moiety at the nitrogen of a benzimidazole ring, we investigated the elimination of a N-dichloroalkene precursor in a model system (Scheme 1). Addition of trichloroethylene to the anion derived from benzimidazole afforded chloroenamine **1**, which when treated with *n*-BuLi gave *N*-ethynylbenzimidazole **2** in modest yield.

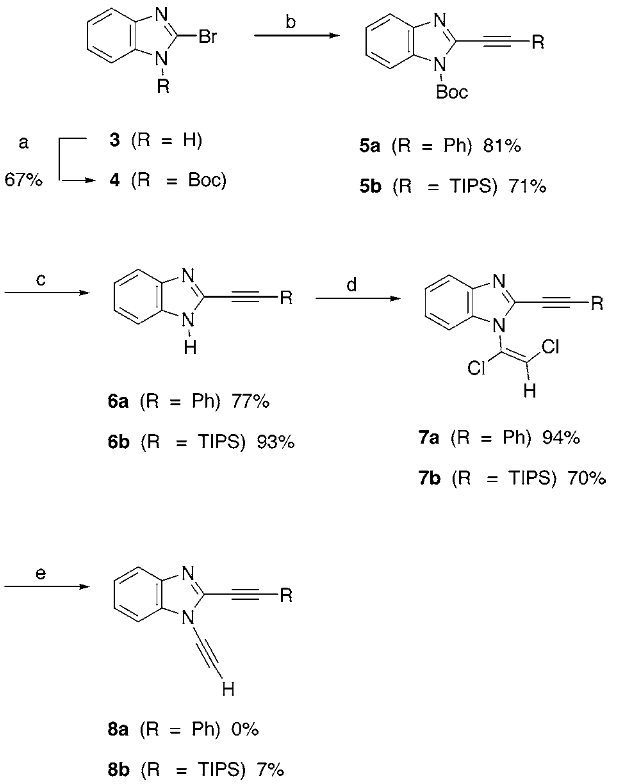
Scheme 1. Preparation of *N*-Ethynylbenzimidazole[a]



[a] Reaction conditions: (a) NaH, DMF, 60 °C, then $Cl_2C{=}CHCl$, rt. (b) *n*-BuLi, −78 °C.

When this same approach was undertaken with benzimidazoles bearing an alkyne substituent at the 2-position, difficulties were encountered. Addition of trichloroethylene to 2-alkynylbenzimidazoles proceeded well, although the addition required more forcing conditions in the case of 2-(2-triisoproplsilylethynyl)benzimidazole (Scheme 2). Elimina-

Scheme 2[a]



[a] Reaction conditions: (a) $(Boc)_2O$, Et_3N, DMF/MeCN. (b) Phenylacetylene (for **9a**) or (triisopropylsilyl)acetylene (for **9b**), $Pd(OAc)_2$, PPh_3, Et_3N. (c) TFA, CH_2Cl_2. (d) NaH, DMF, 50 °C (for **11a**) or KH, DMF, 50 °C (for **11b**), then $Cl_2C{=}CHCl$, rt. (e) *n*-BuLi, −78 °C.

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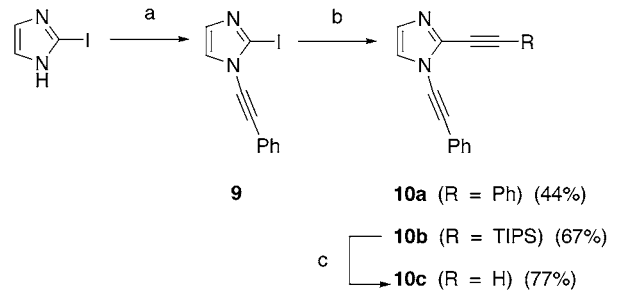
tion of the resulting chloroenamine **7a** did not afford any of the desired aza-enediyne. In this case, only products corresponding to addition of butyllithium to the 2-alkynyl substituent were identified by ^{1}H NMR of the crude reaction mixture. While a low yield of the desired aza-enediyne **8b** was isolated from the elimination of chloroenamine **7b**, the difficulty in purifying this material from side products, combined with the low yield, led us to investigate alternative approaches to heterocyclic aza-enediynes.

For aza-enediynes incorporating the imidazole heterocycle, an approach similar to that described above involving building the 2-alkyne arm, followed by the N-alkyne group, was initially attempted; however, the yields of the desired heterocyclic aza-enediyne were low. In contrast, the alternative approach wherein the N-alkynyl substituent is introduced first, followed by the 2-alkynyl substituent on the imidazole nucleus, was fruitful (Scheme 3). Introduction of the phenylethynyl substitution could be accomplished in moderate yield to give *N*-alkynylimidazole **9**. Palladium-mediated coupling of **9** with either phenylacetylene or (triisopropylsilyl)acetylene afforded the imidazole-based heterocyclic aza-enediynes **10a** and **10b**. Deprotection of **10b** afforded an additional heterocyclic aza-enediyne **10c**.

Scheme 3[a]

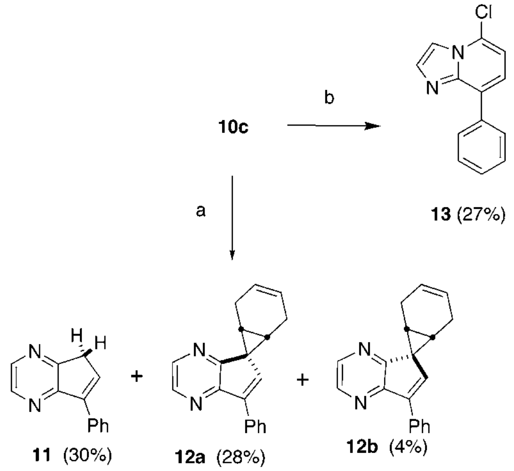


[a] Reaction conditions: (a) NaH, THF, then phenyl(phenylethynyl)iodinium tosylate (29%). (b) Phenylacetylene (for **10a**) or (triisopropylsilyl)acetylene (for **10b**), Pd(PPh$_3$)$_4$, CuI, Et$_3$N, rt. (c) TBAF, THF, −78 °C.

The heterocyclic aza-enediynes **10a**−**c** were isolated as stable oils or solids. Heating a solution of **10a** in chlorobenzene containing an excess of 1,4-cyclohexadiene (1,4-chd) at 150 °C led to the slow disappearance of **10a.** After 2 days, no **10a** remained by TLC. The reaction mixture was analyzed by mass spectrometry, which demonstrated the formation of a compound ($m/z = 270$) corresponding to the addition of two hydrogen atoms to **10a**. However, attempts to isolate this compound from the complex reaction mixture were not successful.

Thermolysis of the heterocyclic aza-enediyne **10c** proceeded under milder conditions than for **10a**. Heating a solution of **10c** in neat 1,4-chd at 100 °C for 2 days led to the formation of two major products: the cyclopentapyrazine **11** (30%) and the related cyclopropane **12a** (28%) (Scheme 4). The structure of cyclopropane **12a** was determined by X-ray crystallographic analysis, which confirmed the stereochemical arrangement about the cyclopropane ring. A small amount of a third product **12b** (4%) was also isolated, which from MS and ^{1}H NMR analysis appears to be the stereoisomer of **12a** in which the cyclohexenyl ring is syn to the pyrazine nitrogen.

Scheme 4[a]



[a] Reaction conditions: (a) Neat 1,4-cyclohexadiene, 100 °C, 2 days. (b) Chlorobenzene, 1,4-cyclohexadiene (20 equiv), 100 °C, 24 h.

Interestingly, the thermolysis of heterocyclic aza-enediyne **10c** in chlorobenzene containing excess 1,4-chd afforded a different product, imidazo[1,2-*a*]pyridine **13** (Scheme 4). The structure of **13** was determined from NOESY, COSY, and HMBC NMR experiments, as well as by comparison of the one-dimensional ^{1}H NMR with that reported for the parent 8-phenylimidazo[1,2-*a*]pyridine system.[15] In neither of the thermolysis reactions of **10a** were products corresponding to direct trapping of the putative 2,5-ddp intermediate isolated.

The profound molecular rearrangements leading from heterocyclic aza-enediyne **10c** to the trapping products **11**, **12a**,**b**, and **13** are unprecedented. The formation of cyclopropane-containing products **12a**,**b** is strongly suggestive of the formation of the carbene intermediate **C** (Figure 2). Triplet state hydrogen atom abstraction by **C** from 1,4-chd can also rationalize the formation of the reduced product **11**. Semiempirical calculations (PM3) indicate that the favored triplet state of **C** is more stable than **10a** by 10.1 kcal/mol. While the origin of the putative intermediate **C** is not known, a possible route involves the aza-Bergman reaction of **10a** leading to a 2,5-ddp intermediate (**A**) that undergoes retro-aza-Bergman reaction to afford a cyclic cumulene intermediate **B**. Intermediate **B** may cyclize to afford the carbene **C** or undergo an alternative cyclization to afford 2,3-ddp intermediate **D**, trapping of which may give rise to the observed product **13**. Although the reaction scheme shown in Figure 2 is only hypothetical, the interesting solvent effect on the product distribution in the trapping reactions provides

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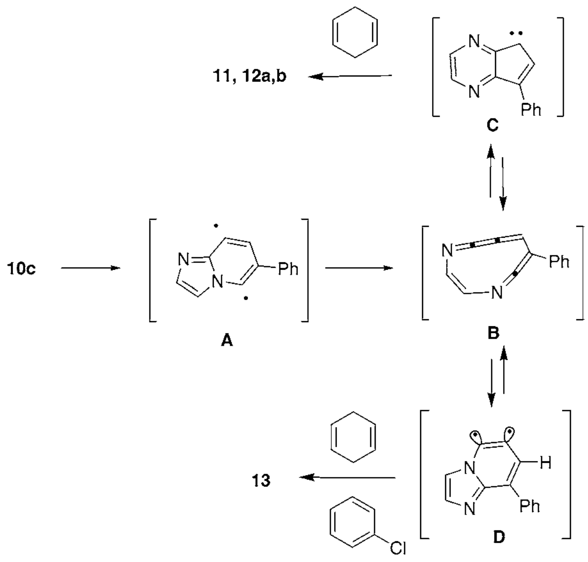

Figure 2. Proposed pathway for the conversion of heterocyclic 3-aza-3-ene-1,5-diyne **10c** to the trapped products **11**, **12a**,**b**, and **13** that involves an aza-Bergman cyclization to a 2,5-didehdyropyridine (**A**) followed by rapid retro-aza-Bergman reaction to a strained cumulene (**B**) that leads to carbene (**C**) and 2,3-didehydropyridine **(D**) intermediates.

some support for this proposal. The stabilization of carbene **C** through interaction with the chlorobenzene solvent[16] may result in a lifetime that is sufficiently long to allow rearrangement to diradical **D**.

In conclusion, the preparation of heterocyclic 3-aza-3-ene-1,5-diynes has enabled the exploration of their thermal chemistry. Despite our expectation that these heterocyclic aza-enediynes would undergo aza-Bergman cyclization to afford 2,5-ddp intermediates of sufficient reactivity for trapping with hydrogen atom donors such as 1,4-chd, thermolysis of these aza-enediynes affords products that are apparently derived from rearranged carbene and diradical intermediates. These results further highlight the difference between the Bergman reaction of enediynes and the chemistry of the 3-aza-3-ene-1,5-diyne system. The apparently simple replacement of a single carbon in the enediyne framework results in profound differences in reactivity and has led to the discovery of unprecedented rearrangements. From the results presented here, it is clear that these aza-enediynes represent a fertile area for further study. The mechanistic, synthetic, and biological implications of these results are currently under investigation.

Acknowledgment. Partial support for this work was provided by the Robert Welch Foundation.

Supporting Information Available: Experimental details of the synthesis and spectroscopic characterization of compounds **1**−**13** and X-ray crystallographic data for **12a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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