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Intramolecular Aziridination: Decomposition of Diazoamides with Tethered Imino Bonds

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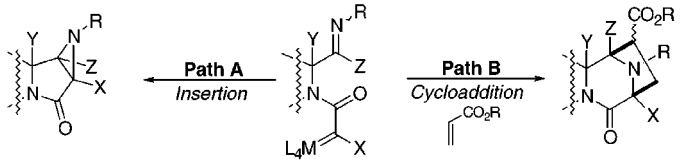
ABSTRACT



Of three possible mechanistic pathways, tethered oximino ethers react intramolecularly with diazoamides to produce a diazabicyclo[5.1.0]-hexane aziridine containing skeleton. Several acyclic and cyclic templates were synthesized and reacted with rhodium catalysts to prepare their corresponding annulated aziridines. Anomalous behavior was discovered with the piperidine template, resulting in an aziridination occurring during the attempted diazo-transfer reaction, rather than the catalyzed carbenoid reaction.

We recently reported one of the first examples of a novel *intramolecular* [2 + 1] cyclization pathway utilizing a rhodium-mediated metallocarbenoid intermediate to generate a cyclic substrate containing an aziridine.[1−3] It could be envisioned that the presence of a metallocarbenoid intermediate in proximity to an imino C═N moiety could lead to several reaction pathways resulting in the formation of medicinally relevant heterocycles. A [2 + 1] insertion/annulation of the putative ylide intermediate with the C═N bond of the imino group could be envisioned for Path A. Similarly, an aziridine might be available through a direct carbenoid insertion process, analogous to a carbene−alkene cyclopropanation reaction.[4] These similar pathways could lead to the formation of substituted diazabicyclo[3.1.0]-

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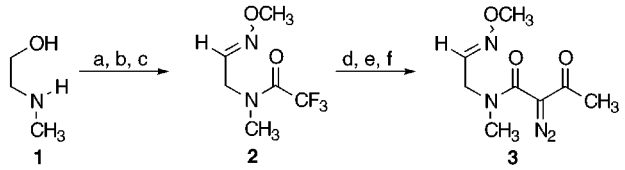
hexane-containing natural products, a critical structural feature of the mitomycin class of antineoplastic agents. Alternatively, Path B can be viewed operationally as formation of an azomethine ylide intermediate, followed by [1,3]-dipolar cycloaddition of a suitable dipolarophile leading to the formation of the 3,8-diazabicyclo[3.1.0]octane core, a substructure found in the potent antitumor, antibiotic compounds such as quinocarcin and naphthyridinomycin.

Herein, we wish to report our efforts directed toward the formation of aziridine-containing natural products utilizing Path A as a method for preparation of these highly bioactive natural products. Structural variation and process parameters will be the initial focus of this study. Toward that end, several structurally diverse substrates were examined, including acyclic, cyclic, and bicyclic diazoamides.

To facilitate this investigation, *N*-methylethanolamine (**1**) was protected as its trifluoromethyl amide (CF_3CO_2Et)[5] then oxidized (buffered PCC) to generate the corresponding aminoaldehyde (Scheme 1). The aldehyde was converted to

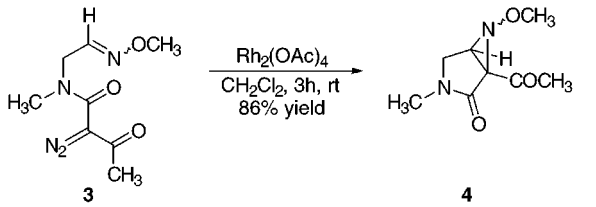
Scheme 1. Acyclic DiazoAmide Precursor



Key: a) $CF_3CO_2CH_2CH_3$, base, 92% b) PCC, NaOAc 85% c) NH_2OCH_3-HCl 87% d) NH_3-CH_3OH e) diketene 91% for 2 steps e) *p*-ABSA, DBU, 0°C 85%-92%

a mixture of oxime ether isomers (**2**) by exposure to methoxylamine hydrochloride in an alcoholic solvent (3.5:1, *E/Z* ratio). Deprotection occurred readily utilizing basic conditions for hydrolysis of the trifluoromethyl amide. The crude amine was then acetoacetylated in high yield by treatment with diketene. Conversion to diazoketoamide (**3**) was best accomplished by reaction with *p*-acetamidobenzenesulfonylazide[6] and DBU followed by rapid chromatographic purification.

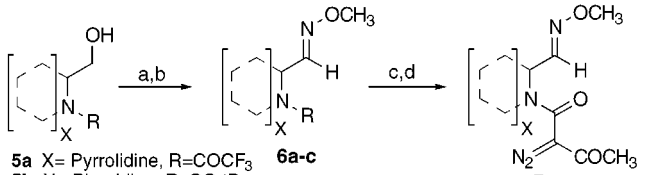
Allowing acyclic diazoamide (**3**) to react in the presence of rhodium acetate (2 mol %, rt) effected clean conversion to diazabicyclo[3.1.0]hexane (**4**) in excellent chemical yield (86%) as a 3.5:1 mixture, in favor of the exo-containing *N*-methoxyl group, in less than 3 h (acyclic diazodecomposition, eq 1). It was observed that this reaction could be catalyzed by copper $(acac)_2$ as well. Both catalytic reactions resulted in the formation of the same easily separable pair of bicyclic aziridine conformers.



(1)

With the successful completion of a simple acyclic analogue assured, attention turned to the synthesis of systems containing more complex cyclic ring systems such as those found in the mitomycins and higher homologues. To study the role of conformational effects on the diazodecomposition process, three additional substrates were prepared and examined for metal-mediated conversion to the aziridine-containing cyclic substrate. The cycloaddition precursors were prepared from commercially available amino acid or alcohol starting materials (Scheme 2).

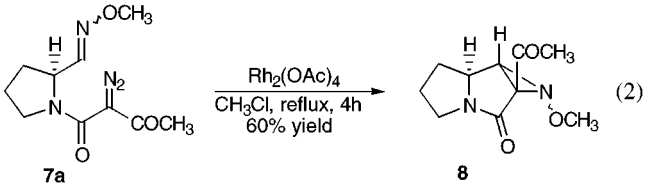
Scheme 2. Preparation of Cyclic DiazoAmides



Key: a) PCC, NaOAc or $(COCl)_2$, DMSO, TEA, 95% b) NH_2OCH_3-HCl 88% c) NH_3-CH_3OH or TFA d) diketene 94% for 2 steps e) *p*-ABSA, DBU, 0°C 92%

The same synthetic sequence, successful in preparing the acyclic diazoamide (**3**), was used to synthesize the diazopyrrolidine oxime, commencing with proline methanol. Pipecolic acid and isoquinoline-2-carboxylic acid were protected as the corresponding *tert*-butyl carbamates (BOC_2O), reduced with borane−THF complex, and then oxidized under Swern conditions to prepare the protected aminoaldehydes in excellent yield. All aldehydes were converted to a mixture of oxime ether isomers (**6a**−**c**) by exposure to methoxylamine hydrochloride in an alcoholic solvent (3−9:1, *E/Z* ratio). Deprotection of the *tert*-butyl carbamate occurred readily through brief exposure to TFA. The crude amines were acetoacetylated in high yield by treatment with diketene. Conversion to diazoketoamides (**7a**−**c**) was best accomplished utilizing Davies protocol under conditions determined for the formation of the acyclic diazoamide.

With the formation of pyrrolidine diazoamide (**7a**) secure, attention turned to a determination and optimization of conditions necessary for the aziridination process to occur. Addition of 2 mol % of rhodium acetate to a refluxing solution of diazoamide (**7a**) in chloroform resulted in the formation of the aziridine-containing pyrrolizidine (**8**) in good yield (aziridination of proline derivative, eq 2). The catalytic

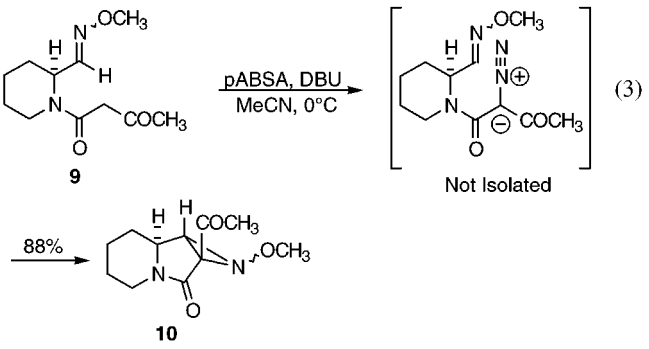


(2)

diazodecomposition reaction was found to be much slower than that of the acyclic diazoamide (**3**), while a number of

undetermined side products accompanied formation of the aziridinopyrrolizidine (**8**).

To probe the subtle conformational effects that give rise to the surprising lack of reactivity found in the catalytic aziridination of pyrrolidine diazoamide **7a (**Scheme 1**)**, a ring-expanded analogue was prepared from pipecolic acid. *Surprisingly, it was found that exposure of ketoamide (**9**) to standard diazo-transfer conditions failed to produce the expected diazoamide (**7b**), rather it directly delivered the aziridinoindolizidine (**10**) in 88% isolated yield, also as a separable mixture of invertomers* (aziridination of piperidine derivative, eq 3).[7] The intermediate diazo oxime (**7b**) could

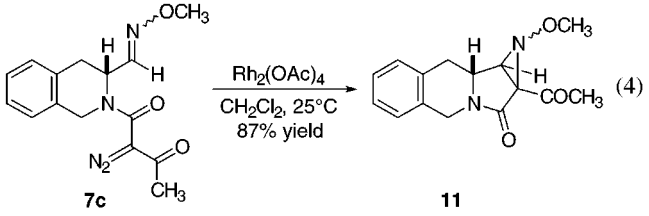


(3)

be observed in the crude NMR and IR spectra, but complete cyclization occurred prior to isolation.[8] This result is in direct contrast to the results seen previously, where rhodium catalysis was required to generate the aziridine, from the proposed metallocarbenoid intermediate. An attempt to prepare a similar diazoamide by an alternative route utilizing Padwa's diazomalonylchloride produced identical results.[9]

With the large disparate reactivity discovered between the acyclic and two cyclic substrates, a third derivative was prepared with two additional sp^2 centers. Isoquinoline carboxylic acid provided the additional rigidifying sp^2 centers through the facility of an aromatic ring at C4−C5 of the piperidine moiety. The addition of a benzene ring serves to restrict the conformational mobility of the two reactive moieties of isoquinoline (**7c**).

It was found that addition of a catalytic amount of rhodium acetate (2 mol %, room temperature, dichloromethane) resulted in the formation of the aziridinoisoquinoline (**11**) in excellent yield in approximately 20 min (aziridination of isoquinoline derivative, eq 4). Starting with a single diazo



(4)

oxime isomer (*E*) provided by chromatographic isolation of the diazotization products, the reaction produced a single N−O isomer. The cyclization adduct was unambiguously assigned through the facility of a single-crystal X-ray analysis.[10]

The reactivity profile of the isoquinoline series was similar to that found with the acyclic substrate, only one pair of N−O isomers being formed cleanly during the reaction. Reaction time is slower than that of the acyclic system but much faster than that of the pyrrolidine diazoamide. These results prompted us to investigate the thermal stability of the diazoamides of the acyclic, pyrrolidine, and isoquinoline series.

The acyclic analogue differs from all of the other examples in that the two reacting appendages are not constrained in a reactive conformation imposed by the rigid piperidine or isoquinoline template. Accordingly, this derivative showed a much greater thermal stability than either the isoquinoline or pipecolinic system. The acyclic diazoamide (**7a**) displayed a half-life of >10 days (as monitored by ^{1}H NMR). Surprisingly, pyrrolidine diazoamide (**7c)** was found to be remarkably resistant to any noncatalyzed cyclization conditions and showed no conversion to aziridine after 1 month at room temperature. Clean conversion was realized under thermal conditions by refluxing the diazoamide for 24−48 h in polar solvents. For comparison, it was found that the piperidine diazoamide could not be isolated at room temperature and was so reactive that at −78 °C it still formed an aziridine in 1−2 h. The isoquinoline diazoamide had a thermal half-life of about 4−6 h at room temperature. The speed of formation may suggest that the two reactive ends of the tether, the diazoamide and the oxime, are placed in close proximity in a highly reactive conformation, hastening aziridine formation.

A possible mechanistic interpretation of this proposed reaction sequence could involve several different pathways from one initial intermediate. Formation of a fleeting or stable diazoamide is followed by (1) the intramolecular cyclization to the azomethine ylide (**12**) formed after addition of catalytic metal or (2) a direct carbenoid C═N insertion process analogous to intramolecular cyclopropanation. A plausible mechanism for the noncatalyzed process could involve the intermediacy of a [2 + 3]-dipolar cycloadduct between the diazo group and the pendant oxime to produce a triazole intermediate (**13**) which spontaneously collapses with concomitant loss of nitrogen to form the aziridines **4**, **8**, or **11**[11] (Scheme 3). Support for the triazole intermediate with diazoamide (**7c**) is provided through the observation of a pyrazole intermediate in a related olefin-containing sub-

(5) Curphey, T. J. *J. Org. Chem.* **1979**, *44*, 2805.

(6) Davies, H. M. L.; Cantrell, W. R.; Romines, K. R.; Baum, J. S. In *Organic Synthesis*; Meyers, A. I., Ed.; 1991; Vol. 70, p 93.

(7) Aziridine nitrogen bearing electronegative heteroatoms possess high barriers to inversion, see: (a) Schurig, V., Leyrer, U. *Tetrahedron: Asymmetry* **1990**, *1*, 865. (b) Atkinson, R. S., Williams, P. J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 205. (c) Kost D., Raban, M. *J. Am. Chem. Soc.* **1982**, *104*, 2960. The products of systems in this study show no tendency to interconvert N−O stereochemistry.

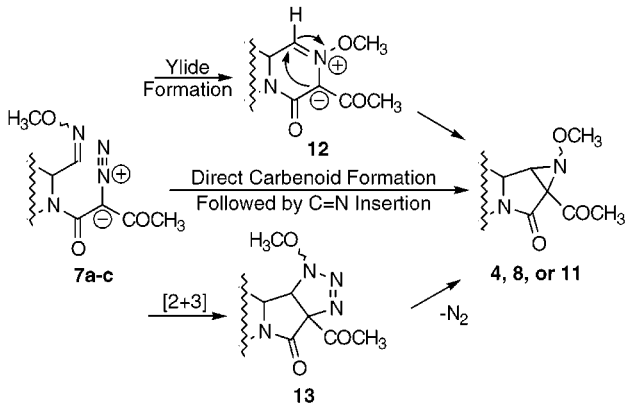
(8) The trans relationship at the bridgeheads was assigned by the small coupling constant between the two bridgehead protons and with analogy to compound **10**.

(9) Marino, J. P.; Osterhout, M. H.; Price, A. T.; Sheehan, S. M.; Padwa, A. *Tetrahedron Lett.* **1994**, *35*, 849.

(10) The structure was confirmed by X-ray crystallographic analysis. The coordinates have been deposited with the Cambridge Crystallographic Database.

(11) A similar pathway has been suggested for the spontaneous formation of triazoles. Hunig, S.; Kraft, P. *Heterocycles* **1995**, *40*, 639.

Scheme 3. Proposed Aziridination Mechanism



strate.[12] Experiments designed to determine the overall steric and electronic requirements for these cyclization reactions are ongoing in this lab.

Conclusions. The utilization of carbenoid intermediates for the intermolecular aziridination of C═N bonds has recently matured into a valuable synthetic method. This study demonstrates for the first time that intramolecular metallocarbenoid addition can be accomplished, thus providing efficient access to novel heterocyclic systems.[13] Many of these types of products can serve as advanced intermediates for synthesis utilizing the potential reactive nature of the aziridine moiety as a departure point for further elaboration. Current investigations are aimed at further functionalization of the aziridine-containing substrates as well as the application of asymmetric catalysis to provide a route to chiral aziridines.

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Supporting Information Available: Full characterization for compounds **1**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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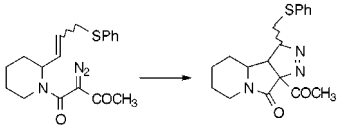
(12) We have observed an analogous cycloaddition with a similarly disposed olefin to produce a simple pyrazole. This structure was confirmed by X-ray crystallography. Weekly, R. M. Masters Thesis, Ohio University, 1997. See also: Doyle, M. P.; Kalinin, A. V. *J. Org. Chem.* **1996**, *61*, 2179. Doyle, M. P.; Dorow, R. L.; Tamblyn, W. H. *J. Org. Chem.* **1982**, *47*, 4059.



(13) For a related approach to the mitomycins, see (a) Jones, G. B.; Moody, C. J. *Chem. Commun.*. **1988**, 1009. (b) Jones, G. B.; Moody, C. J.; Padwa, A.; Kassir, J. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, *1*, 1721.