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A Metallocarbenoid Approach to the Formation of Spirocyclic Ammonium Ylides Leading to the Preparation of Medium-Sized Azacane Rings

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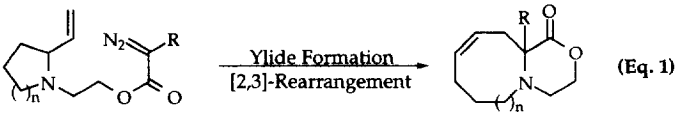
Abstract: A novel approach to azacyclooctene and azacyclononene containing substrates has been achieved *via* the intermediacy of a spirocyclic ammonium ylide derived from the diazodecomposition of a tethered α-diazoester moiety.

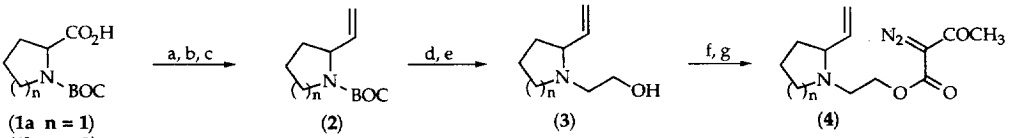


(Eq. 1)

As part of an ongoing program to apply diazodecomposition reactions in tandem with ylide formation / rearrangement reactions directed toward alkaloid syntheses, we have undertaken efforts to prepare simple eight- and nine-membered azacycles (**Eq. 1**). Prompted by the recent disclosure by Clark[1] relating to ring expansive [2,3]-rearrangements of spirocyclic ammonium ylides, we wish to report our efforts toward similar goals.[2]

Our general strategy involves the generation of spirocyclic ammonium ylides from the transition metal catalyzed decomposition of an α-diazoester moiety tethered to the nitrogen atom of 2-vinyl pyrrolidine or piperidine.[3] Rearrangement through the pendant vinyl group results in an overall three carbon expansion of the starting amine (i.e. pyrrolidine expands to azacyclooctene). This general process can function as an expedient route toward medium-sized nitrogen containing rings.[4]

SCHEME 1



(1a n = 1) **(1b n = 2)** **(2)** **(3)** **(4)**

a) BH_3-SMe_2, THF (90%) b) $(COCl)_2$, DMSO, Et_3N (85-88%) c) $Ph_3P{=}CH_2$, -78°C (82-86%) d) TFA, CH_2Cl_2 e) $BrCH_2CH_2OH$ iPr_2NEt, EtOAC, 60°C (2 steps, 70-80%) f) diketene, iPr_2NEt, CH_2Cl_2, 0°C (98%) g) MsN_3, Et_3N, H_2O, CH_3CN (86-99%)

First generation model substrates were prepared from commercially available BOC protected (L)-proline (n=1) or racemic pipecolic acid (n=2) (**Scheme 1**). Reduction of the starting acids, followed by Swern oxidation[5] produces the corresponding aldehydes which are olefinated *via* standard Wittig conditions to prepare the requisite vinyl appendage.[3] Deblocking of the t-butylcarbamate, followed by treatment with 2-bromoethanol affords the β-amino alcohol (**3**) in good yield. Acylation of the primary hydroxyl group with diketene and diazo- transfer to the activated methylene by action of mesyl azide produces the cyclization substrates **4a** or **4b** in good overall yield.[6] The diazodecomposition / rearrangement reactions of these substrates have been studied under a variety of conditions.

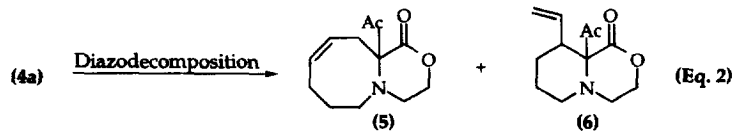


TABLE 1

Catalyst [a]	Solvent	Temperature [b]	Yield [c]	5 / 6 [d]
$Cu(acac)_2$	$ClCH_2CH_2Cl$	reflux	53%	2.5 / 1
$Cu(acac)_2$	PhH		33%	4 / 1
$Cu(acac)_2$	$PhCH_3$		62%	3 / 1
$Cu(hfacac)_2$	$ClCH_2CH_2Cl$		48%	2.5 / 1
$Cu(hfacac)_2$	PhH		62%	2.5 / 1
$Cu(hfacac)_2$	$PhCH_3$		70%	2.5 / 1

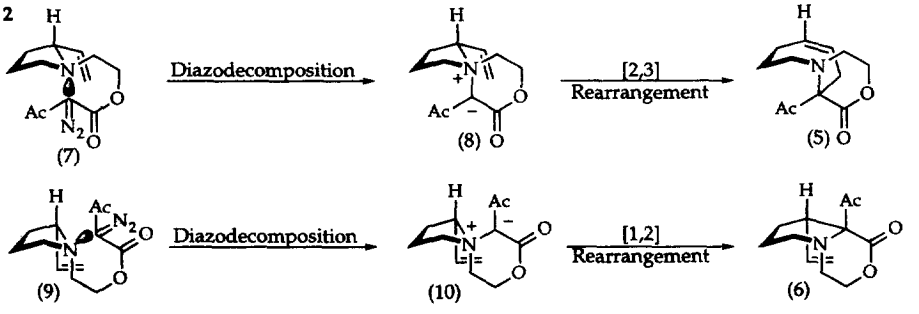
a) 15 mole% based on **4a** b) Slow addition (20 mg/1h) of the **4a** as a .01M solution to a refluxing solution of the catalyst in solvent c) Purified by column chromatography d) Some ratios based on GC-MS analysis of the crude reaction mixture

Initial studies focused upon the (L)-proline derived α-diazoester **4a** and results are shown in **Table 1** Early attempts at cyclization were made using rhodium based catalyst systems, but the reaction was observed to be sluggish, resulting in a complex mixture of products due to the extended reaction times.[4] Copper catalysis was found to be a superior alternative for effecting the desired rearrangements.[7] Decomposition of **4a** with several copper carboxylate catalysts yielded the expected azacyclooctene **5** along with a substantial amount of a product **6** presumably arising from a [1,2]-rearrangement (Stevens)[8] of the intermediate ylide (**Eq. 2**).[9] Azacyclooctene **5** displays a highly efficient transfer of chirality (97.5% e.e.)[10] from the acyclic α-diazoester **4a**, similar to the results found by Clark and West.

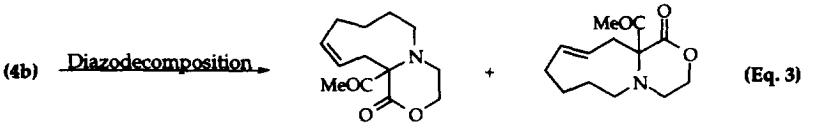
The appearance of a Stevens product was surprising in light of Clark's report[1a] that the [2,3]-rearranged product was formed exclusively in a similar all carbon case, although this may be attributed to lengthening of the tether, similar to the case presented by West.[11] Formation of the *cis* olefin in preference to the less stable *trans* isomer was found to be in accordance with results reported by Clark.[1a]

A proposed rationale involves the orientation of the nitrogen tether with respect to the pendant olefin. Amine **7** places the α-diazoester tether of the side chain *anti* to the pyrrolidine vinyl group. Attack of the axial lone pair to the electrophilic copper carbenoid center produces ylide **8**. Rearrangement through the proximal olefin gives the expected azacyclooctene **5**. An alternative, α-diazoester **9**, positions the side chain *syn* to the vinyl moiety. Ylide formation through this conformation produces intermediate **10** where the anion is improperly disposed to attack the pendant olefin. The ensuing shift occurs through the proline ring producing the Stevens product **6** instead of the bicyclic azacyclooctene **5**.

SCHEME 2



The racemic pipecolic homolog **4b** was synthesized via methodology determined during the preparation of the proline series. The piperidine α-diazoester was subjected to identical catalytic conditions as those used for the proline series. (**Table 2**). Copper mediated cyclization yielded the expected rearranged azacyclononenes in good overall yield. In contrast to the proline ylide, the piperidine ylide produced the [2,3]-rearrangement products (**11** and **12**)[12] to the complete exclusion of the Stevens product. However, with the larger piperidine ylide both the *cis* and *trans* azacyclononenes were produced in varying ratios (**Eq. 3**). Similar yields were obtained for the piperidine system as those found in the proline series.



(11) cis **(12) trans** **(Eq. 3)**

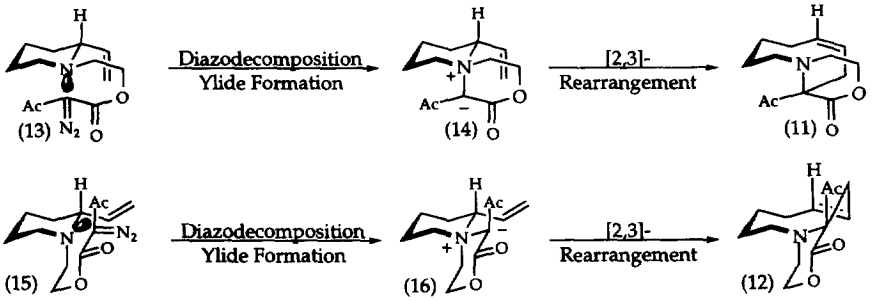
Table 2

Catalyst [a]	Solvent	Temperature [b]	Yield [c]	cis / trans [d]
$Cu(acac)_2$	$ClCH_2CH_2Cl$	reflux	65%	3.5 / 1
$Cu(acac)_2$	PhH		39%	3 / 2
$Cu(acac)_2$	$PhCH_3$		53%	5 / 1
$Cu(hfacac)_2$	$ClCH_2CH_2Cl$		53%	2 / 1
$Cu(hfacac)_2$	PhH		65%	2 / 1
$Cu(hfacac)_2$	$PhCH_3$		65%	5 / 1

a) 15 mole% based on **4b** b) Slow addition (20 mg/1h) of **4b** as a .01M solution to a refluxing solution of the catalyst in solvent c) Purified by column chromatography d) Some ratios based on GC-MS analysis of the crude reaction mixture

Vedjes[4] and others have shown in analogous acyclic ammonium ylides derived from 2-vinyl-piperidine, that diequatorial substitution resulting in axial attack at the nitrogen lone pair provides the major product of the reaction (**Scheme 3**). Assuming a chair orientation for the piperidine ring, the low energy conformer positions the tether in an equatorial manner (**13**). Attack of the axial lone pair produces ylide **14** which further rearranges through the olefin to give the *cis* azacyclononene **11**. Conformer **15** places the diazo-tether in an axial position which can form ylide **16**. Intermediate **16** is similar to the vinylpiperidine systems shown by Vedejs[4] to give the *trans* azacyclononene **12**.

SCHEME 3



The effectiveness of these tandem ylide formation / rearrangement reactions suggests a possible approach to medium azacycloalkene containing natural products. In addition, the resulting morpholinone ring can be envisioned as a protected amino acid.[13] This methodology could be employed to synthesize larger cyclic amino acids that could prove useful in peptide mimic design.[14] Current efforts are directed toward employing the same methodology toward small

nitrogen-containing ring systems which can undergo a strain accelerated rearrangement to form expanded heterocyclic rings.[15]

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9. Olefin geometry assigned on the basis of selected spectroscopic data for the *cis* azacyclooctene **5**: ^{1}H (250MHz, $CDCl_3$) δ= 5.8, 5.6 *J*= 10.2Hz (-HC=CH- From selective decoupling) 1.95(s, 3H) ^{13}C(62.5MHz, C_6D_6) δ= 200.8, 167.8, 133.9, 126.9 IR(cm^{-1}) 1729, 1709 MS(EI, 70ev) 223(M+), 180 Stevens product **6**: ^{1}H (250MHz, C_6D_6) δ=6.2, 5.1, 5.05 *J*= 1.8, 10, 17.2 (H_2C=CH-) 2.07(s, 3H) ^{13}C(62.5MHz, C_6D_6) δ= 204.5, 172.5, 137.7, 117.4 IR(cm^{-1}) 1730, 1709 MS(EI, 70ev) 223(M^+), 180.
10. Enantiomeric excesses determined using Pirkle Type 1A, chiral phase HPLC with 95 : 5 hexane : isopropanol.
11. West, F.G.; Naidu, B.N. *J. Am. Chem. Soc.* **1994**, *116*, 8420.
12. Although **11** and **12** were difficult to separate chromatographically, coupling constants were found by NMR to be 9.9Hz (dd) and 19.0Hz (dd) respectively. A mixture of **11** and **12** was hydrogenated (H_2, Pd/C, EtOH, 1 atm, 96%) to yield a single compound with the following spectral characteristics: ^{1}H NMR (250MHz, $CDCl_3$) δ= 3.91 (ddd, *J*=3.7, 10.7, 11.9Hz, 1H) 3.63 (ddd, *J*=1.4, 3.4, 10.7Hz, 1H) 2.83 (ddd, *J*=3.4, 11.7, 13.1Hz, 1H) 2.55-2.33 (m, 2H) 2.06 (ddd, *J*=1.4, 3.5, 11.7Hz, 1H) 2.02 (s, 3H) 1.69-0.9 (m, 12H) ^{13}C NMR (62.5MHz, $CDCl_3$) δ= 203.9, 168.2, 79.1, 68.4, 46.4, 43.1, 29.9, 27.9, 27.4, 26.5, 20.8, 20.2, 19.4 IR(cm^{-1}) 1729, 1710 MS(EI, 70ev) 239(M^+), 180.
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