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Facile Generation of Aziridines From The Reaction of α-Diazoamides With Tethered Oximino-Ethers

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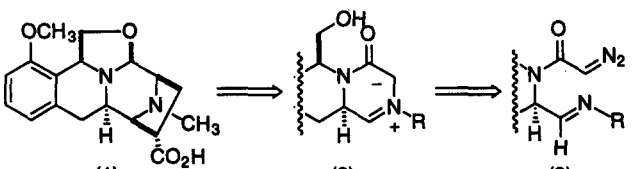
Abstract: In an attempt to prepare azomethine ylide intermediates for cycloaddition reactions with electron deficient olefins, oximino-ethers with tethered α-diazoamide moieties were reacted in the presence of metal catalyst. The reaction resulted in aziridine formation preferentially. Copyright © 1996 Elsevier Science Ltd

As part of an ongoing program directed toward the synthesis of complex alkaloids *via* tandem metallocarbenoid generation/ylide cycloaddition, we have investigated the reaction of α-diazoamides with tethered oximino-ethers as a preparative route to diazabicyclic[3.2.1]octane containing molecules. We wish to report our preliminary investigations regarding the selectivity of such a process.

Scheme 1



(1) (2) (3)

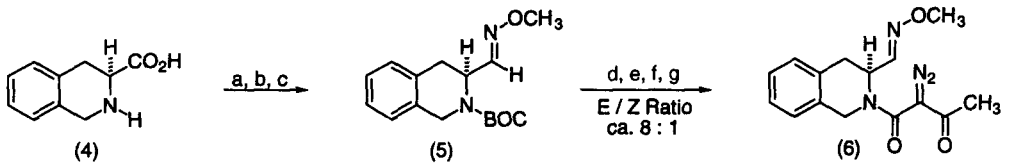
(-)-Quinocarcin

A metallocarbenoid pathway to the central diazabicyclo[3.2.1]octane core of quinocarcin[1a-m] can be envisioned to occur through the intermediacy of an azomethine ylide formed by attack of an imino-nitrogen upon an electrophilic metallocarbenoid center (**2, Scheme 1**). An oximino substituted tetrahydroisoquinoline system with a tethered diazoamide moiety (**3**) could be expected to generate the tricyclic azomethine ylide (**2**) *via* diazodecomposition in the presence of a suitable transition metal catalyst.[2] Trapping of the transient ylide with an electron poor olefin (acrylate or acrylonitrile) could occur regioselectively to provide a bridged-fused lactam which could function as an advanced intermediate for an attempted synthesis of quinocarcin (**1**).

In order to investigate the feasibility of this route, a simple tetrahydroisoquinoline model substrate was prepared and studied in this category of tandem cyclization /cycloaddition reactions. The preparation of a precursor for diazodecomposition studies began with commercially available tetrahydroisoquinoline acid (**4**) (**Scheme 2**). The BOC carbamate was utilized as a nitrogen blocking group after the trifluoroacetamide group was found to be incompatible with subsequent oxidative conditions. Oxidation (PCC), then oxamination[3] of the ensuing aldehyde occurred uneventfully to give oxime (**5**) as a mixture of *E* and *Z* isomers, predominately in the *E* configuration.[4] The crude oxime was deblocked and the resulting amino-oxime was acylated with diketene to provide the requisite β-ketoamide amenable to diazotization in excellent yield for the five step process. Diazo-

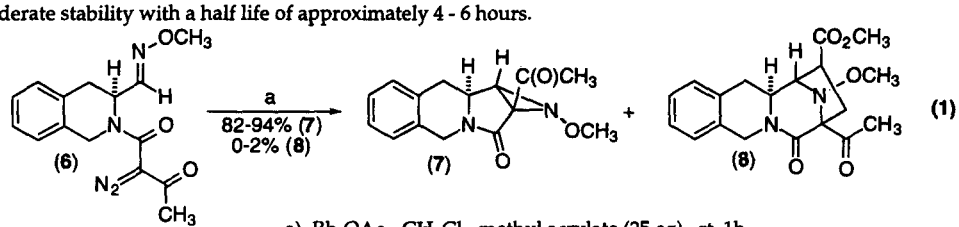
transfer to the activated methylene carbon was best accomplished with the Davies protocol (p-acetamidobenzenesulfonylazide, DBU) forming α-diazoamide (6) in excellent yield.[5]

Scheme 2[a]



[a]Key: (a) $(BOC)_2O$, NaOH (99%) (b) BH_3·THF (98%) (c) PCC, CH_2Cl_2 (81%) (d) NH_2OCH_3, pyridine, CH_3OH (86%) (e) TFA, CH_2Cl_2 (f) diketene, CH_2Cl_2 (88% for two steps) (g) $AcNHpPhSO_2N_3$, DBU, CH_3CN, 0°C (92%)

Once prepared, α-diazoamide-oxime (6) can be used to approximate the basic overall ring structure and substituents of a simple precursor to quinocarcin. In the initial reaction sequence, isoquinoline α-diazoamide (6) was exposed to dipolarophile methyl acrylate (**Eq. 1**), in the presence of catalytic dirhodium tetraacetate. Surprisingly, the expected cycloadduct (8) was obtained in only trace amounts (0-2%, variable), with the principle product isolated from the reaction assigned as aziridine (7) as a separable mixture of N-O epimers (82-94%, ~8:1).[6] *Remarkably, it was also found that α-diazoamide (6) was converted to the same mixture of products when reacted with catalyst at -78°C, or allowed to stand at room temperature without catalyst.* α-Diazoamide (6) was found to have moderate stability with a half life of approximately 4 - 6 hours.



a) Rh_2OAc_4, CH_2Cl_2, methyl acrylate (25 eq), rt, 1h

An X-ray structure determination of the aziridine (7) has been completed, showing that the α-aziridine is formed preferentially, with the aziridine hydrogen *syn* to the acetyl side chain and *anti* to the ring hydrogen (**Figure 1**). Padwa[7] reports a similar aziridination sequence as a minor reaction pathway and recently, Jacobsen[8] has shown the applicability of chiral aziridination of imines as a complementary procedure to Evans' olefin aziridination.[9a-e]

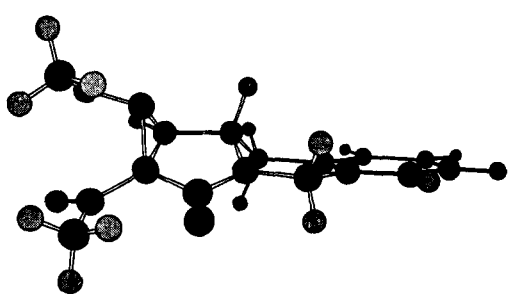
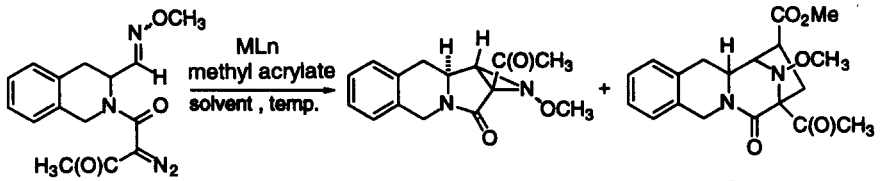


Figure 1: X-Ray Representation of isoquinoline metallocarbenoid insertion product (7).

Table 1. Catalyst Effect of Aziridination vs. Cycloaddition



6 7 8

catalyst	% catalyst [a]	solvent [b, d]	temp	tot. yield	7 [c]	8 [c]
$Rh_2(OAc)_4$	2-5 %	DCM,PhH,C_5H_{10},PhF,Freon10	RT	82-94%	100	0
$Rh_2(OAc)_4$	2-5 %	DCE,PhH,$PhCH_3$, PhF	reflux	80-88%	100	0
$Rh_2(OAc)_4$	2-5 %	DCM	-78°	90%	100	0
$Rh_2(hex)_4$	2-5 %	DCM , PhH	RT	86-87%	100	0
$Rh_2(cap)_4$	2-5 %	DCM , PhH	RT	86-87%	100	0
$Rh_2(pfb)_4$	2-5 %	DCM , PhH	RT	85%	100	0
$Rh_2(tfacam)_4$	2-5 %	DCM , PhH	RT	83%	100	0
$Cu(OTf)_2$	20%	DCM , PhH	RT	0%	0	0
$Cu(acac)_2$	20%	DCM , PhH	RT	85%	100	trace
$Cu(hfaca)_2$	20%	DCM , PhH	RT	80%	30	1

a) mole % catalyst based on diazoamide **6** b) All reactions: addition of the catalyst to a stirred 0.1 M solution of the diazoamide **6** in solvent with 25 eq. of acrylate at the indicated temperature c) some ratios are estimated from GC data of crude reaction mixtures d) all solvents shown are separate trials for each catalyst

A study was conducted to determine the efficacy of several rhodium and copper catalytic systems for the formation of 3,8-diazabicyclo[3.2.1]octane (**8**) in preference to the diazabicyclo[3.1.0]hexane (**7**) (**Table 1**). Thusfar, copper acetylacetonate and hexafluoroacetylacetonate are the only catalysts that have provided any of the cycloadduct, albeit in extremely low yield. Surprisingly, rhodium caprolactamate did not provide any of the cycloadduct, despite the elegant studies by Doyle and Padwa that suggest the caprolactamate may be the optimal catalyst for ylide formation/cycloaddition in preference to any other reactive mode.[10]

This sequence offers access to fused aziridine containing molecules that may prove useful as synthetic intermediates toward natural products such as the mitomycins.[11a-c] Current research in these labs involves the photolytic opening of the aziridine ring formed upon diazodecomposition to provide an alternate route for the preparation of azomethine ylide intermediates.[1h-k] Asymmetric induction utilizing chiral catalysis is also under investigation.

Although the origin of these reactivity differences remains unclear, extensive investigations are underway to determine the effect that conformation, catalyst, solvent, trapping agent and substitution of the diazo-containing carbon may have on the product formation and product ratio. This process is also being extended to other C=N species such as imines, hydrazones, silylimines, and sulfenimines.

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¶ Authors to whom questions regarding the X-Ray structure should be directed

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