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Generation and Reactivity of Aza-Oxyallyl Cationic Intermediates: Aza-[4 + 3] Cycloaddition Reactions for Heterocycle Synthesis

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Supporting Information

ABSTRACT: Aza-[4 + 3] cycloadditions of putative aza-oxyallyl cationic intermediates and cyclic dienes are reported. The intermediate is generated by the dehydrohalogenation of α-haloamides. The reaction is general to a variety of α-haloamides and is diastereoselective. Computational and experimental data suggest that an *N*-alkoxy substituent stabilizes the aza-oxyallyl cationic intermediate.

The [4 + 3] cycloaddition reaction of oxyallyl cationic intermediates (e.g., **2**, Figure 1) with dienes has been established as a premier method for the construction of seven-membered carbocycles **3**.[1] Our interest in the reactions of electrophilic nitrogen species led us to consider aza-oxyallyl cationic intermediates **7** for the synthesis of seven-membered azacycles **8**, a widely represented heterocycle in natural products, pharmaceuticals, peptidomimetics, and monomers for polymerization. This communication reports the design and generation of aza-oxyallyl cationic intermediates **7** and their aza-[4 + 3] cycloaddition with cyclic dienes.

The aza-oxyallylic cation has been primarily discussed in the context of the synthesis, reactions, and rearrangements of α-lactams **6**. Sheehan and Lengyl suggested that aza-oxyallyl cationic intermediates **7** could be relevant to the regioselectivity trends of the nucleophilic ring-opening reactions of α-lactams **6**.[2] Stang and Anderson proposed that the conversion of an alkylidene oxazirine **5** to an α-lactam **6** proceeds through an aza-oxyallylic cation **7**.[3] Tuscano and co-workers have computationally identified an aza-oxyallyl cationic transition state in their studies of the isomerization of an alkylidene oxazirine **5** to an α-lactam **6**.[4] Kikgugawa proposed an aza-oxyallyl cationic intermediate in the solvolysis of *N*-chloro-*N*-alkoxyphenylacetamides.[5] However, theoretical[6] and stereochemical[7] studies of the nucleophilic ring-opening reactions of alkyl-substituted α-lactams **6** and attempts to trap the proposed intermediate with alkene reactants have failed to provide any evidence of its involvement in these reactions.[8] The possibility of intercepting an aza-oxyallyl cationic intermediate in a [4 + 3] cycloaddition reaction led us to pursue studies of its generation and its reaction with dienes.

Base mediated dehydrohalogenation of α-haloketones **1** is a common method for the generation of oxyallylic cations **2**.[1] Similarly, a dehydrohalogenation of an α-haloamide **4** could provide the desired intermediate **7** *in situ*. The dehydrohalogenation of 2-bromo-*N*-benzylbutyramide (**9a**) in the presence of furan was studied. This reaction resulted in the recovery of the starting material, failing to provide the desired cycloadduct **10a** under a variety of conditions.

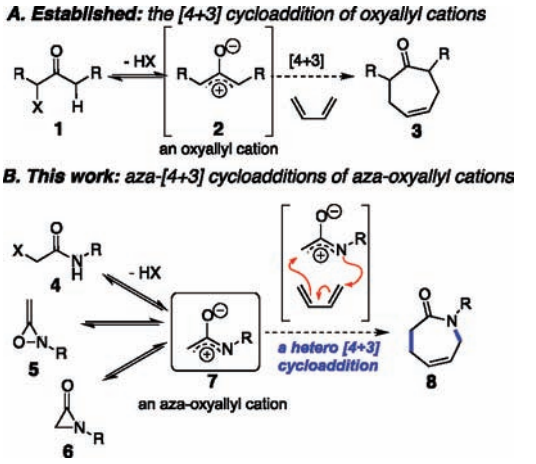

Figure 1. Aza-[4 + 3] cycloaddition reaction of aza-oxyallyl cations with dienes.

Oxygen,[9] nitrogen,[10] and sulfur[11] substituents are established to stabilize oxyallyl cationic intermediates[1a,b] and acyl nitrenium ions.[12] An *N*-alkoxy bromoamide[13] **9b** was prepared, and its dehydrohalogenation in the presence of furan was studied. Treatment of the α-bromohydroxamate **9b** to the Föhlisch conditions (CF_3CH_2OH/Et_3N)[14] in the presence of furan provided the desired cycloadduct **10b** in a 38% yield. The trifluoroethylether **11b** (56%) was formed as the major product of this reaction, presumed to be the result of solvolysis of the intermediate or the *N*-benzyloxyaziridinone.[5,10]

The choice of base and solvent was found to directly influence the yield of the cycloadduct. Changing the solvent from trifluoroethanol (TFE) to hexafluoroisopropanol (HFIP) significantly improved the yield of the cycloadduct **10b** and slowed the formation of the solvolysis product **11b** (*cf.* entry 2 with 3−6, Table 1).[15] Carbonate bases provided the desired product in comparable yields (entries 4−6, Table 1) to the reaction using triethylamine. The reaction could be effected in ether by using triethylamine with lithium perchlorate as a Lewis acid additive,[16] but these conditions also provided a methacrylamide as the major product from the elimination of the cationic intermediate or a transient α-lactam.

Various haloamides underwent the aza-[4 + 3] cycloaddition with furan (Table 2). Monoalkyl substituted bromoamides (entries

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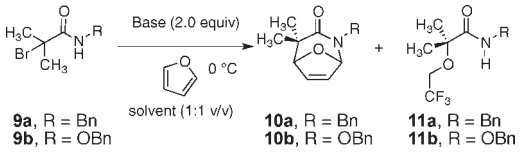
Table 1. Solvent, Base, and Substituent Effects on the Yield of the Aza-[4 + 3] Reaction of 9b with Furan



Entry	R	Solvent	Base	Yield[a] %
1	**Bn**	**TFE**	**Et_3N**	**no reaction**
2	OBn	TFE	Et_3N	38%[b]
3	OBn	HFIP	Et_3N	78%
4	OBn	HFIP	Cs_2CO_3	58%
5	OBn	HFIP	K_2CO_3	67%
6	OBn	HFIP	Na_2CO_3	74%
7	OBn	TFE	imidazole	decomp.
8	OBn	TFE	pyridine	no reaction
9	OBn	Et_2O	Et_3N, $LiClO_4$	See text

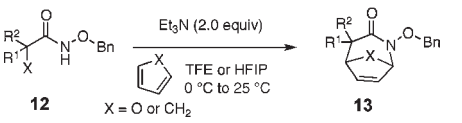
[a] Isolated yield of **10b**. [b] Provided a 56% yield of **11b**.

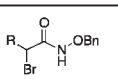
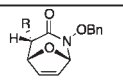
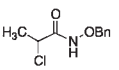
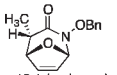
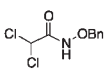
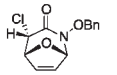
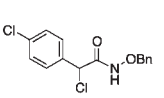
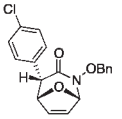
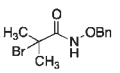
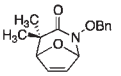
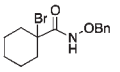
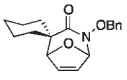
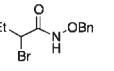
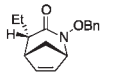
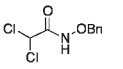
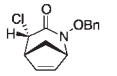
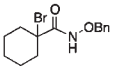
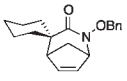
2−5) provided the highest yields of the cycloadduct. All monoaryl and monoalkyl haloamides (entries 2−5 and 7) selectively provided the *endo*-diastereoisomer (≥19:1).[17] In the case of entry 6, it was observed that the ratio of diastereoisomers at early conversion (≥19:1, endo:exo at *ca.* 40% conversion) was greater than at full conversion (2:1, endo:exo). Monoalkyl bromoamides reacted slower than aryl and dialkyl substituted haloamides. α-Chloroamides reacted slower than α-bromoamides (*cf.* entries 2 and 5). The bromoacetamide (X = Br, R^1 = R^2 = H, entry 1) was unreactive under these conditions, resulting in the recovery of the starting material. α-Chloromethoxyacetamide (R^1 = OCH_3) was found to be difficult to handle and resulted in decomposition during the cycloaddition reaction. Dialkyl substituted and aryl substituted haloamides provided the cycloadduct in moderate yields when run in HFIP (entries 8, 9, and 12). The aza-[4 + 3] cycloaddition of bromoamides with cyclopentadiene afforded the cycloadducts in comparable yields to the corresponding furan reactions (entries 10−12, Table 2) with less selectivity for the endo adduct.

A computational analysis of the isomerization of α-lactams **14** and **15** to their corresponding aza-oxyallylic cation was conducted at the B3LYP/6-31G* level of theory with a conductor polarized continuum model (cpcm)[18] for solvation in methanol (Figure 2).[19,20] No stationary point could be identified for the aza-oxyallylic cation (R = Et), which collapsed to the α-lactam **14** during the geometry minimization. Stationary points for both aza-allylic cation **16** (R = OCH_3) and the corresponding α-lactam **15** were located indicating a stabilizing effect of this group on the dipolar intermediate. The polarity of the medium had an effect on the depth of the well corresponding to the aza-oxyallylic cation **16** (cf. dashed line vs red line, Figure 2), consistent with the dipolar character of the intermediate.

The experimental and computational data support a mechanism where dehydrohalogenation of the haloamide **12** generates an aza-oxyallyl cationic intermediate *i* that reacts as a dienophile in the aza-[4 + 3] cycloaddition reaction (Scheme 1). An electron-donating group (OBn) is essential for permitting the aza-[4 + 3] cycloaddition to take place and was computationally found to stabilize the proposed intermediate. Aryl substituents accelerate the overall rate of conversion. Much like the all-carbon [4 + 3] cycloaddition with cyclic dienes, the aza-[4 + 3] cycloaddition

Table 2. Evaluation of the Substrate Scope of the Aza-[4 + 3] Reaction of Various Halo-Benzyloxyamides 12 with Furan or Cyclopentadiene[a]



entry	solvent reaction time	substrate	product dr (endo:exo)[b]	yield[c]
1 2 3 4	TFE 16 h		 dr ≥19:1 (endo:exo)	R = H (0 %) R = Me (67 %) R = Et (86 %) R = *t*-Bu (54 %)
5	TFE 48 h		 dr ≥19:1 (endo:exo)	78 %
6	TFE 72 h		 dr = 2:1 (endo:exo)	73 %
7	TFE 1 h		 dr ≥19:1 (endo:exo)	52 %
8	HFIP 30 min			78 %
9	HFIP 30 min			65 %
10	TFE 16 h		 dr = 3:1 (endo:exo)	85 %
11	TFE 16 h		 dr = 8:1 (endo:exo)	64 %
12	HFIP 30 min			81 %

[a] Conditions: solvent was furan or cyclopentadiene (1:1 v/v, 0.25 M) at 0 to 25 °C with Et_3N (2.0 equiv). Diastereoisomeric ratio (dr) was determined from crude ^{1}H NMR analysis. [b] ≥ 19:1 dr indicates that the minor diastereoisomer was not detected. [c] Isolated yield of both diastereoisomers, **13**.

demonstrates a preference for the formation of the *endo* cycloadduct. The observation that the diastereoisomeric ratio of cycloadducts (entry 6, Table 2) was high at early conversion and that the purified *endo*-adduct isomerized to a *ca.* 1:1 ratio of diastereoisomers (**13**-*endo* to **13**-*exo*, R = Cl, Scheme 1) under the reaction conditions suggests that there is a kinetic preference for the *endo*-cycloadduct. The precise nature of this diastereoselectivity is currently under further investigation.

In summary, *N*-benzyloxy α-haloamides react under basic conditions with cyclic dienes to provide bicyclic lactams in good yield and with diastereoselectivity. Computational and experimental data support that this reaction proceeds through an aza-oxyallyl cationic intermediate. The *N*-alkoxy substituent was essential for this reaction, and computational analysis revealed that it acts to stabilize the cationic intermediate. Studies focused

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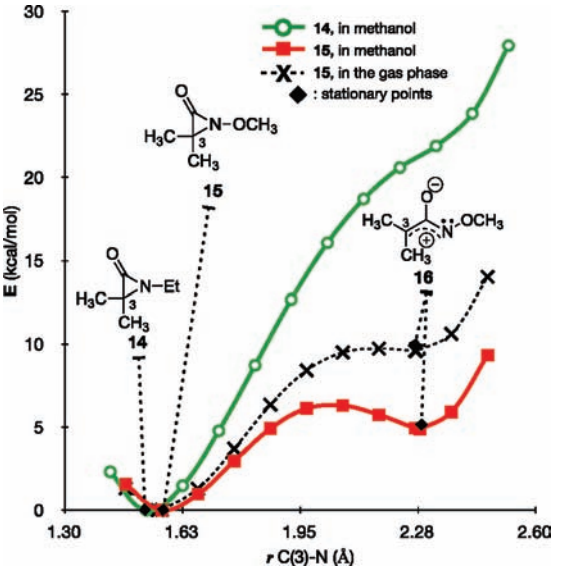
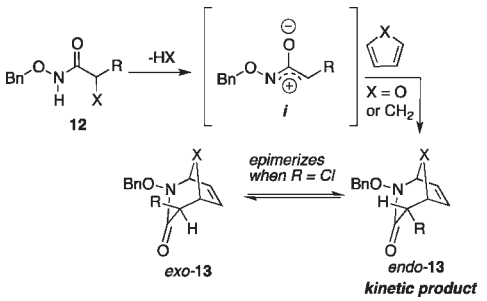


Figure 2. Relaxed potential energy scans along the C(3)−N(1) coordinate of α-lactams **14** and **15** (10−13 steps at 0.1 Å intervals) at a B3LYP/6-31G* level of theory. Green line/○ = **14** in methanol, red line/■ = **15** in methanol; dashed-line/× = **15** in the gas phase. Stationary points are indicated by ◆.

Scheme 1. Proposed Mechanism for the Aza-[4 + 3] Cycloaddition Reaction with Furan (X = O) and Cyclopentadiene (X = CH_2)



on the detailed mechanistic aspects, the synthetic scope, and the applications of this reaction are underway.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, tabulated characterization data, complete ref 19, tabulated computational data, and copies of ^{1}H and ^{13}CNMR spectra for all new compounds are provided in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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