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Inverse demand [4+2] cycloaddition reactions of allenamides: reactivity scopes of an electron deficient variant of allenamines

Lin-Li Wei, Hui Xiong, Christopher J. Douglas † and Richard P. Hsung *

Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, USA

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Abstract

The synthesis and reactivity of a series of new allenamides are described. These electron deficient variants of allenamines are more stable than allenamines but possess comparable reactivity. Particularly, oxazolidinone and imidazolidinone substituted allenamides undergo efficient inverse demand [4+2] cycloaddition reactions with heterodienes, leading to unique pyranyl heterocycles. The reactivity differences between various allenamides containing different substitution patterns around the nitrogen atom are illustrated.

Allenes are among the most versatile synthons in organic synthesis, and are involved in a diverse array of reactions.[1] Important subgroups of allenes are those containing heteroatom substitutions such as allenol ethers and allenamines (Fig. 1). The electron donating ability of the oxygen or nitrogen atom renders them even more synthetically attractive because of the electronic bias imposed by the heteroatoms, allowing regioselective transformation of these molecules. However, the extent of synthetic applications of allenol ethers and allenamines has remained limited, especially in the case of allenamines.[1] This lack of attention could be attributed to the difficulty in preparation and handling of allenamines due to their high reactivity and sensitivity towards hydrolysis. While allenol ethers are relatively more stable, they are less reactive than allenamines, owing to the greater electronegativity of oxygen.

Because of our interest in developing methodologies for the synthesis of heterocycles,[2] we have been exploring the synthesis and reactivity of a new class of heteroatom-substituted allenes that may

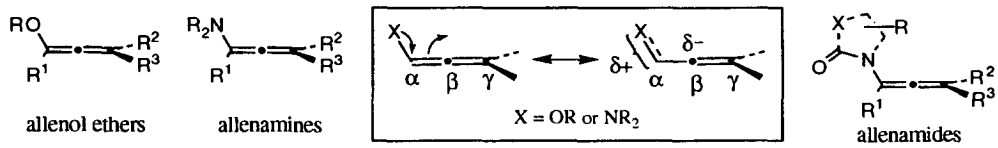

Figure 1.

* Corresponding author.

† UMN Undergraduate Research Participant: 1998–1999.

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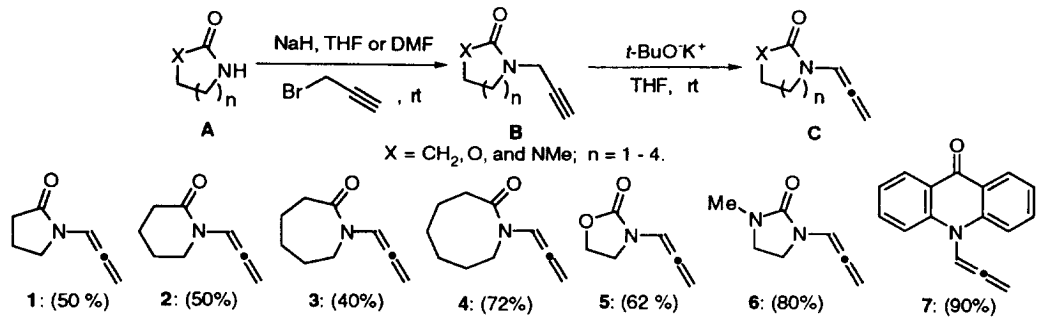
combine the stability of allenol ethers with the reactivity of allenamines. Specifically, they are electron deficient allenamines in which the nitrogen atom contains an electron withdrawing group (Fig. 1). While allenamines are the least studied among heteroatom-substituted allenes, allenamides are even more rare.[1] Since the preparations of 1,2-propadienyl-2-pyrrolidinone by Dickinson[3] and *N*-trichloroacetamido-1,2-diene by Overman,[4] the most common electron deficient allenamines are those in which the nitrogen atom is part of the hetero-aromatic system prepared for medicinal purposes.[5,6] Palladium catalyzed cross-couplings[7] and other cyclization or cycloaddition reactions[8] using electron deficient allenamines have also been reported. We report here preparations of some new allenamides and the first studies of their reactivity towards heterodienes in inverse demand [4+2] cycloaddition reactions.

Although Dickinson's preparation of 1,2-propadienyl-2-pyrrolidinone (**1**) was carried out in a one-pot procedure,[3] we found a two-step protocol that proved to be more general for our purposes. As shown in Scheme 1, pure propargyl amides (**B**) were first obtained from the corresponding lactams, 2-oxazolidinone, or *N*-methyl-2-imidazolidinone (**A**). Subsequent isomerization of these propargyl amides (**B**) was induced by using *t*-BuOK in anhydrous THF at ambient temperature, leading to the desired allenamides (**C**). By using this two-step sequence, Dickinson's allenamide **1** as well as other new allenamides **2–6** were obtained in very good overall yields (for two steps) (Scheme 1).[9]



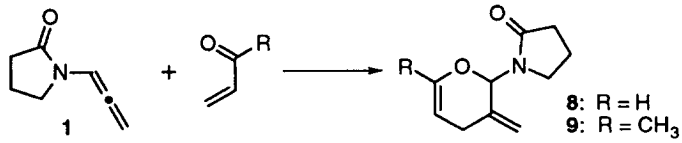
Scheme 1.

It is noteworthy that further isomerization to ynamides was not observed in the preparation of **1–6**, although base-induced isomerization of propargyl amines to ynamines is known.[10] In contrast, the known vinylogous allenamide **7**[11] could also be prepared in 90% overall yield from acridone under the same reaction conditions (anhydrous DMSO was used as solvent in the isomerization), but further isomerization to the corresponding vinylogous ynamide readily occurred if the reaction was not carefully monitored. These allenamides are stable, and compounds **5** and **6** are crystalline solids. The stabilities of these allenamides, compared to those of allenamines, suggest a more delocalized nitrogen lone pair with reduced ability for donating towards the allene moiety.

Since chemistry of allenamides is not well known, we proceeded to investigate their reactivity in inverse demand [4+2] cycloaddition reactions with heterodienes because of our interest in pyranyl heterocycles.[2] Dickinson's allenamide **1** was used as a model compound to examine the reactivity of allenamides towards heterodienes such as acrolein and methyl vinyl ketone (MVK) under various thermal and Lewis acidic conditions. These results are summarized in Table 1.

When the allenamide **1** was heated with 2 equiv. of acrolein or MVK in anhydrous CH_3CN at 80°C for 64 h, the corresponding cycloadducts **8** and **9** were isolated in modest yields of 27 and 31%, respectively (entries 1 and 2).[9] Cycloadducts **8** and **9** are the only regioisomers found in these reactions, and similar cycloadducts have been reported from reactions of allenol ethers[12] and allenamines.[13] A range of Lewis acids was then explored to enhance the reactivity of **1** (entries 3–9). $ZnCl_2$ (0.1 equiv.) appears to be the best Lewis acid, while CH_3CN appears to be the best solvent, leading to the desired cycloadduct **8** and

Table 1
Reactions of the allenamide **1**



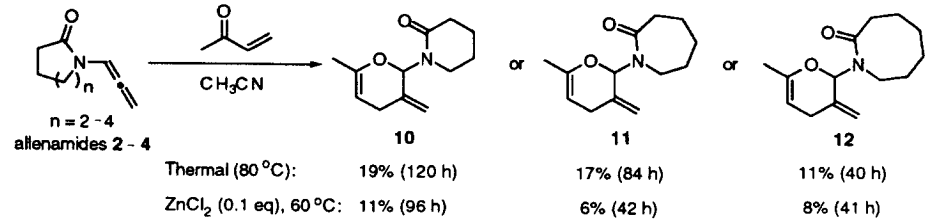
Entry	R	Lewis acid	equivalent	solvent[a]	temperature	time	yield[b]
1	H	-	-	CH_3CN	80 °C	64 h	27 %
2	CH_3	-	-	CH_3CN	80	64	31
3	H	Et_2AlCl	1.0 eq	toluene	-15 °C to rt	19	<5
4	H	$TiCl_4$	1.0	CH_2Cl_2	-15 °C to rt	19	<5
5	H	$ZnCl_2$[c]	1.0	CH_2Cl_2	-15 °C to rt	19	7
6	H	$ZnCl_2$	0.3	THF	rt	20	~5
7	H	$ZnCl_2$	0.06	THF	0 °C to rt	15	<5
8	H	$ZnCl_2$[d]	0.1	CH_3CN	60 °C	46	42
9	CH_3	$ZnCl_2$	0.1	CH_3CN	60 °C	62	40

a) All solvents used were anhydrous, and all glassware was washed with an amine base and flame-dried. Reactions in entries 1-2 and 8-9 were carried out in a sealed reaction vessel. b) All yields are isolated yields. c) For entries 5-7, $ZnCl_2$ was added as an anhydrous solid. d) For entries 8-9, 1.0 M $ZnCl_2$ solution in ether was used.

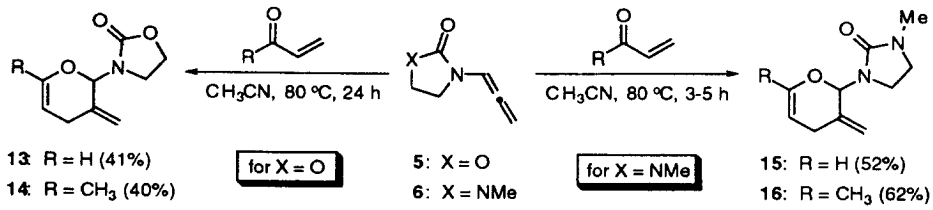
9 in 42 and 40% yields, respectively (entries 8 and 9). Thermal assistance at 60°C was still required to achieve optimal reactivity. Although several other Lewis acids such as BF_3–Et_2O, $NaClO_4$–H_2O, $InCl_3$, and $MgBr_2$–Et_2O were also examined (not shown in the Table), no desired products were isolated in these attempts, and severe decomposition of the starting allenamide **1** occurred. It is noteworthy that these are the first reported cycloaddition reactions of allenamides or any electron deficient allenamines.

Having established the reactivity of the allenamide **1** in inverse demand [4+2] cycloadditions, we turned our attention to the effect of ring size of the lactam moiety on the reactivity of allenamides. As shown in Scheme 2, it is evident that allenamides **2**–**4**, with larger lactam ring size than the allenamide **1**, were much less reactive than **1** under the same reaction conditions. Reactions of **2**–**4** with MVK provided cycloadducts **10**–**12** in yields ranging from 11 to 19% when heated at 80°C, while the yields were even lower (8–11%) when 0.1 equiv. of $ZnCl_2$ was used. The low yields obtained for the allenamide **2** could be due to the fact that it is relatively less stable than compounds **1**, **3**, and **4**. Nevertheless, these reactivity differences suggest that the larger and more flexible lactam rings in allenamides **2**–**4** could allow increased delocalization of the nitrogen lone pair than that of **1**, thereby reducing the ability to push electron density towards the allene moiety and diminishing their reactivity. In addition, the allenamide **7** was not reactive under any of the reaction conditions described above, suggesting that the nitrogen lone pair of **7** is strongly delocalized into the acridone moiety. Detailed calculations are currently being pursued.

Having found the superior reactivity of the allenamide **1** containing a five-membered lactam ring, we compared the reactivity of **1** with those of allenamides **5** and **6** containing either an oxazolidinone or imidazolidinone moiety. Under thermal conditions, the allenamide **5** was more reactive than **1**, and its reaction with acrolein and MVK provided the cycloadducts **13** and **14** in 41 and 40% yields, respectively, in a much shorter reaction time. However, the allenamide **6** was the most reactive among the three allenamides, providing the cycloadducts **15** and **16** in good yields in 3–5 h (Scheme 3).



Scheme 2.



Scheme 3.

When 0.05 equiv. of $ZnCl_2$ was used, the reaction of **5** with acrolein was complete in 7 h at 60°C, leading to **13** in 46% yield. However, under several Lewis acidic conditions, decomposition of the allenamide **6** occurred, leading to the desired cycloadducts **15** or **16** in low yields (10–30%). These differences again suggest that the reactivity can be correlated with the extent of delocalization of the electron lone pair on the nitrogen atom. It is also noteworthy that allenamides **5** and **6** are the best examples for combining the stability of allenol ethers and reactivity of allenamines since both are more reactive than allenol ether under thermal conditions.[12]

We have described here the first reactivity of some new allenamides in inverse demand [4+2] cycloaddition reactions. These electron deficient variants of allenamines are more stable than allenamines without compromising their reactivities. We are currently exploring synthetic applications involving these allenamides.

Acknowledgements

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