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Lewis Acid Promoted Hetero [2 + 2] Cycloaddition Reactions of Aldehydes with 10-Propynyl-9(10*H*)-acridone. A Highly Stereoselective Synthesis of Acrylic Acid Derivatives and 1,3-Dienes Using an Electron Deficient Variant of Ynamine

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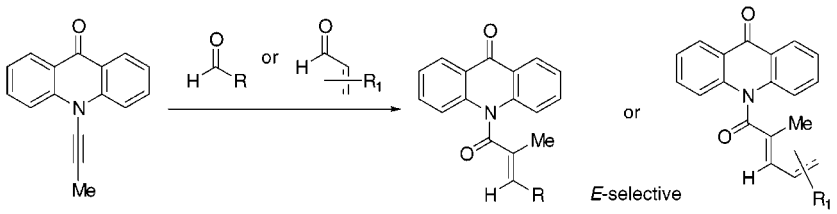
ABSTRACT



Reactivities of 10-propynyl-9(10*H*)-acridone toward various aldehydes in BF_3·Et_2O-promoted hetero [2 + 2] cycloaddition reactions are described here. This electron deficient variant of ynamine is more stable and easier to handle than most ynamines but possesses comparable reactivity. These reactions lead to a highly stereoselective synthesis of trisubstituted alkenes. A mechanistic model based on the stereochemical assignment is also described here. 10-Propynyl-9(10*H*)-acridone is also reactive toward α,β-unsaturated aldehydes and ketones. It provides hetero [2 + 2] products in reactions with α,β-unsaturated aldehydes but gives only the inverse demand [4 + 2] cycloadduct in a reaction with methyl vinyl ketone.

The synthetic significance of ynamines (**A**) in organic chemistry was firmly established by the work of many organic chemists more than 15 years ago.[2] However, since then there has been significantly less synthetic chemistry using ynamines, and it has become an area largely ignored by synthetic chemists.[2b,3] This lack of attention could be attributed to the difficulty in the preparation and handling of ynamines because of their high reactivity and sensitivity toward hydrolysis. Although ynol ethers (**B**, Figure 1) are relatively more stable, they are less reactive than ynamines, owing to the greater electronegativity of oxygen. Because

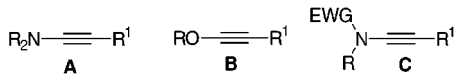


Figure 1.

(1) UMN Undergraduate Research Participant: 1998−1999. The recipient of 1998 Pharmacia-Upjohn and UMN Department of Chemistry Lando/NSF Program for Summer Research Fellowship.

(2) For reviews on chemistry of ynamines, see: (a) Ficini, J. *Tetrahedron* **1976**, *32*, 1448. (b) Himbert, G. *Methoden Der Organischen Chemie (Houben-Weyl)*; Kropf, H., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1993; pp 3267−3443.

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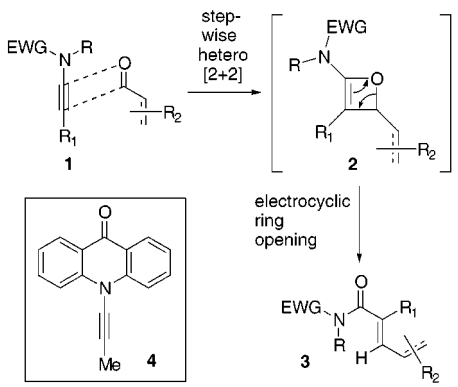
of our interest in heteroatom-substituted allenes[4] and alkynes, and in developing methodologies for synthesis of heterocycles,[5] we have been exploring the synthesis and reactivity of a class of ynamines that may combine the stability of ynol ethers with the reactivity of ynamines.

Specifically, this class includes electron deficient ynamines or ynamides (**C**) in which the nitrogen atom is substituted with an electron-withdrawing group. Reactivities of ynamides are almost unknown,[3a,c] although preparations and thermal stabilities of ynamides have been documented.[6,7] We report here the first reactivity study of an electron deficient ynamine toward aldehydes in hetero [2 + 2] cycloaddition reactions.

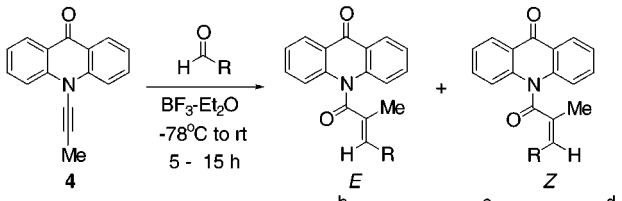
As shown in Scheme 1, hetero [2 + 2] cycloaddition reactions of the ynamide **1** with aldehydes could lead to an

Scheme 1



oxetene intermediate (**2**) that would undergo an electrocyclic ring opening to give alkene **3**.[2,8] In addition, if such a reaction can be rendered feasible with α,β-unsaturated aldehydes, then dienes (also shown as **3**) may also be prepared in a stereoselective manner. We elected to examine this reaction using the known electron deficient ynamine **4** which is a vinylogous ynamide.[9] Given the synthetic availability of **4** and its ease of handling [a stable crystalline solid],[10] it serves as an excellent model system for exploring reactivities of electron deficient ynamines.

Table 1



Entry	R[a]	LA (eq)	solvent[b]	product	yield[c]	ratio (*E* : *Z*)[d]
1	Me	0.25	toluene	**5**	78 %	≥95 : 5
2	Et	0.25	toluene	**6**	60	92 : 8
3	Et	0.25	CH_2Cl_2	**6**	55	95 : 5
4	Ph	0.10	toluene	**7**	67	≥94 : 6
5	Ph	0.25	CH_2Cl_2	**7**	91	≥95 : 5
6	*n*-hex	0.25	toluene	**8**	58	94 : 6
7	*n*-hex	0.25	CH_2Cl_2	**8**	70	≥95 : 5
8	$(CH_2)_4OTBS$[e]	0.25	CH_2Cl_2	**9**	53	≥95 : 5
9	*i*-Pr	0.25	CH_2Cl_2	**10**	61	95 : 5
10	*t*-Bu	0.25	CH_2Cl_2	**11**	64	95 : 5
11	C_6H_{11}	0.25	CH_2Cl_2	**12**	69	≥95 : 5

a) 2.0 eq of aldehydes were used. b) Anhydrous solvents distilled over CaH_2 were used. c) All yields are isolated yields. d) Ratios were determined by using ^1H and ^{13}C NMR. e) For preparation of the aldehyde see reference 11.

As shown in Table 1, the ynamide **4** was very reactive toward an array of aldehydes under Lewis acidic conditions to provide trisubstituted alkenes **5**−**12**[12]− in high yields as well as high *E* selectivities. These reactions were carried out in the presence of either 0.1 or 0.25 equiv of $BF_3{\cdot}Et_2O$ and proceeded with equal efficiency as well as stereoselectivity at −78 °C or room temperature. Dichloromethane was the better solvent from a solubility perspective, but toluene was a good solvent despite the reaction mixture being heterogeneous.

The configuration of the double bond was assigned by carrying out NOE experiments on alkene **5** and by obtaining an X-ray crystal structure of compound **7**. Assignments for other compounds in Table 1 were determined by ^1H NMR

(3) For recent examples, see: (a) Imbriglio, J.; Rainier, J. *Abstracts of Papers*, 217th National Meeting of the American Chemical Society, Anaheim, CA, Spring 1999; American Chemical Society: Washington, DC, 1999; ORGN-502. (b) Bernstein, R.; Foote, C. S. *Tetrahedron Lett.* **1998**, 7051. (c) Witulski, B.; Stengel, T. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 489. (d) Bloxham, J.; Dell, C. P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3055. (e) Padwa, A.; Gareau, Y.; Harrison, B.; Rodriguez, A. *J. Org. Chem.* **1992**, *57*, 3540.

(4) Wei, L.-L.; Xiong, H.; Douglas, C. J.; Hsung, R. P. *Tetrahedron Lett.* **1999**, 6903.

(5) (a) Hsung, R. P. *J. Org. Chem.* **1997**, *62*, 7904. (b) Hsung, R. P. *Heterocycles* **1998**, *48*, 421. (c) Granum, K. G.; Merkel, G.; Mulder, J. A.; Debbins, S. A.; Hsung, R. P. *Tetrahedron Lett.* **1998**, 9597. (d) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 690. (e) Degen, S. J.; Mueller, K. L.; Shen, H. C.; Mulder, J. A.; Golding, G. M.; Wei, L.-L.; Zificsak, C. A.; Hsung, R. P. *Bioorg. Med. Chem. Lett.* **1999**, 973. (f) Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Douglas, C. J.; McLaughlin, M. J.; Mulder, J. A.; Yao, L. J. *Org. Lett.* **1999**, *1*, 509. (g) Douglas, C. J.; Sklenicka, H. M.; Shen, H. C.; Golding, G. M.; Mathias, D. S.; Degen, S. J.; Morgan, C. D.; Shih, R. A.; Mueller, K. L.; Seurer, L. M.; Johnson, E. W.; Hsung, R. P. *Tetrahedron* **1999**, *55*, in press.

(6) (a) Novikov, M. S.; Khlebnikov, A. F.; Kostikov, R. R. *J. Org. Chem. USSR* **1991**, *27*, 1576. (b) Tikhomirov, D. A.; Eremeev, A. V. *Chem. Heterocycl. Compd.* **1987**, *23*, 1141. (c) Balsamo, A.; Macchia, B.; Macchia, F.; Rossello, A. *Tetrahedron Lett.* **1985**, 4141. (d) Janousek, Z.; Collard, J.; Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 917.

(7) Joshi, R V.; Xu, Z.-Q.; Ksebati, M. B.; Kessel, D.; Corbett, T. H.; Drach, J. C.; Zemlicka, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1089.

(8) For a related account using ynamines, see: Fuks, R.; Viehe, H. G. *Chem. Ber.* **1970**, *103*, 564.

(9) (a) Katritzky, A. R.; Ramer, W. H. *J. Org. Chem.* **1985**, *50*, 852. (b) Rádl, S.; Kovárová, L. *Collect. Czech. Chem. Commun.* **1991**, *56*, 2413. (c) Reisch, J.; Salehi-Artimani, R. A. *J. Heterocycl. Chem.* **1989**, *26*, 1803. (d) Mahamoud, A.; Galy, J. P.; Vincent, E. J. *Synthesis* **1981**, 917.

(10) We prepared compound **4** from acridone in two high-yielding steps (89% overall). Deprotonated acridone was propargylated with propargyl bromide in THF, and a subsequent isomerization of the terminal alkyne to the ynamide **4** was carried out by using KOH in DMSO at room temperature. Also see ref 9a.

(11) Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236.

(12) All new compounds are identified and characterized by ^1H NMR, ^{13}C NMR, FTIR, and LRMS (see Supporting Information).

correlations. The $\Delta\delta$ values for olefinic protons of the *E* and *Z* isomers are within the range of 0.2−0.4 ppm, although in several cases (entries 1, 4, 6, and 10) the *Z* isomer was not observed.

The stereoselectivity observed here is likely a kinetic selectivity based on our preliminary experiments as well as related precedents.[8] When ynamide **4** was reacted with cyclohexylcarboxaldehyde at −80 °C for 3 h, the only observed isomer was *E*-**12**, and no *Z* isomer was seen after 35% conversion.

A working model (Spartan Program AM1) was proposed on the basis of the stereochemical assignment (Figure 2).

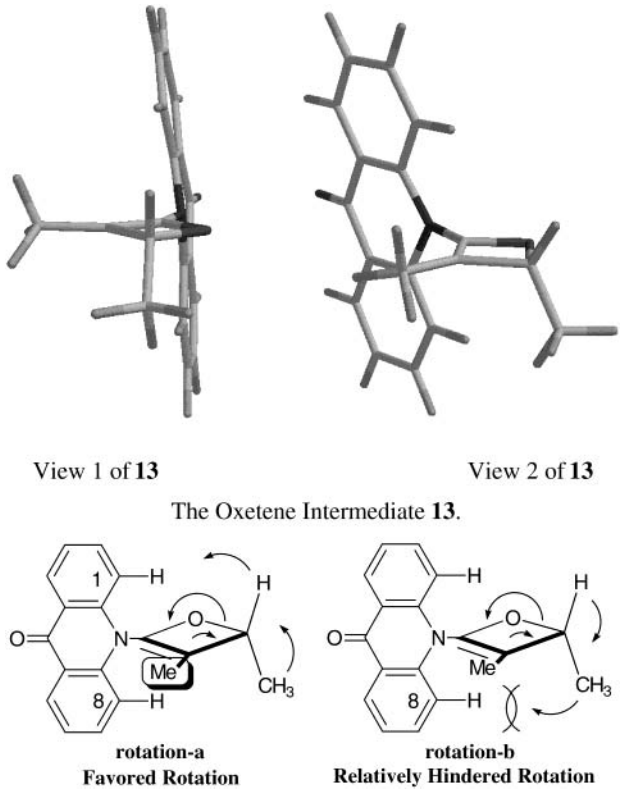


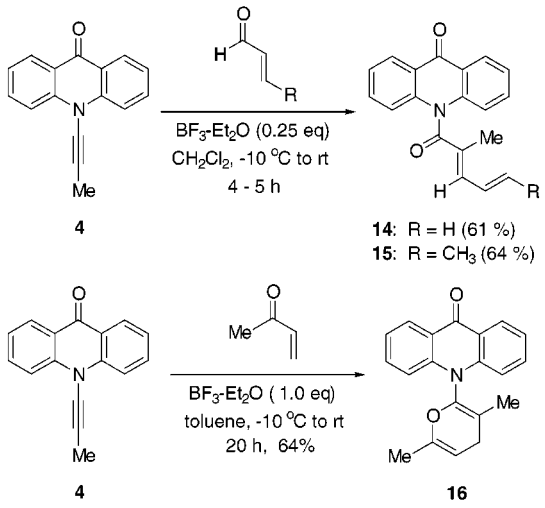
Figure 2. A working model for the observed stereoselectivity.

Two rotations for the ring opening are possible for the oxetene intermediate **13** (rotation **a** and rotation **b**). The most stable conformation of **13** indicates that the acridone moiety is nearly orthogonal to the plane of the oxetene ring (Views 1 and 2), providing the least steric interaction with the adjacent Me group (*circled*, the original propargyl methyl of **4**).

In addition, the model shows that the acridone moiety is not completely eclipsed with the H and CH_3 groups (View 1). This is mechanistically intriguing because without this slight bias, there would be no bias in the rotation during the electrocyclic ring opening. As a result, rotation **a** should be more favored, thereby leading to the major *E* isomer. On the other hand, rotation **b** is less favored because of the steric hindrance between the proton at C-8 of acridone and the rotating methyl group. This model suggests the significance of the acridone moiety of ynamide **4** as well as the adjacent methyl group.

We also examined reactions of **4** with α,β-unsaturated aldehydes and ketones. Under the same reaction conditions, ynamide **4** reacted with α,β-unsaturated aldehydes to give dienes **14** and **15**[12] in excellent yields as well as stereoselectivities via the hetero [2 + 2] pathway (Scheme 2). In

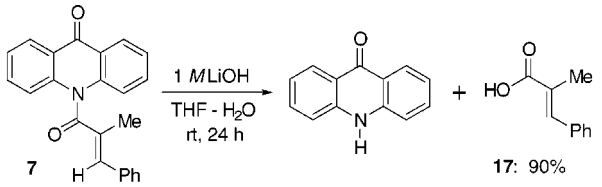
Scheme 2



contrast, hetero [4 + 2] cycloadduct **16** was obtained in 64% yield as the only product when MVK was used. It was also observed that the reaction with MVK was much slower and 1.0 equiv of $BF_3{\cdot}Et_2O$ was necessary to drive the reaction to completion. Compounds **14**−**16** represent unique synthetic building blocks for further transformation. We are currently exploring the mechanistic details behind these two diverse reaction pathways.

The acridone moiety of alkenes **5**−**12** could be removed and recovered efficiently under mild basic conditions. For example, treatment of the alkene **7** with LiOH at room temperature afforded hydrolysis product **17** in 90% yield with no observable isomerization, and acridone was recovered in ≥90% after simple acid−base workup (Scheme 3). Hence,

Scheme 3



the acridone moiety of ynamide **4** essentially serves as an auxiliary in this stereoselective olefination reaction.

We have described here the first studies of reactivities of an electron deficient variant of ynamine in hetero [2 + 2]

and [4 + 2] cycloaddition reactions. An in-depth mechanistic model for the [2 + 2] reaction has been proposed. This study demonstrates a significant principle that with improved stability over ynamines, ynamides should maintain comparable reactivities, leading to stereoselective and synthetically useful preparations of trisubstituted alkenes and dienes under Lewis acidic conditions. We are currently exploring other synthetic applications involving various ynamides.

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Supporting Information Available: Experimental procedures and ^{1}H NMR spectral and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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