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Origins of Selectivity in Brønsted Acid-Promoted Diazoalkane−Azomethine Reactions (The Aza-Darzens Aziridine Synthesis)

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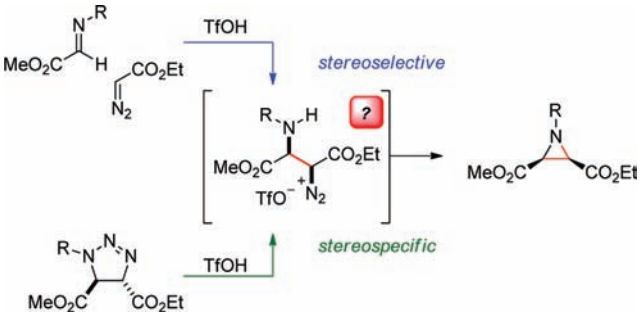
ABSTRACT

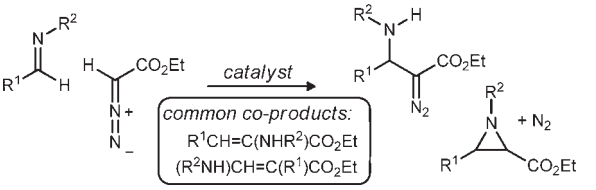


The mechanism of the Brønsted acid-catalyzed aza-Darzens reaction is explored by charting the stereochemical outcome of the triflic acid-promoted conversion of *trans*-triazolines to *cis*-aziridines. These experiments are consistent with the intermediacy of an α-diazonium-*β*-amino ester intermediate.

The addition of diazoalkanes to azomethines is a versatile reaction that can provide access to triazolines[1] and α-diazo-*β*-amino esters[2] atom economically, or glycolate Mannich[3] products and aziridines[4,5] (an aza-Darzens reaction, Scheme 1)[6] with loss of N_2. There are now numerous reports that the substrates can be activated by either Lewis acids[7,8] and/or redox-active metals,[9,10] and highly diastereo- and enantioselective variations are beginning to surface.[11] These highlights notwithstanding, a lack of mechanistic information has slowed the growing potential of this transformation, and in cases where a pathway to high stereoselectivity is realized, the appropriate (stereochemistry-determining) transition state to contemplate has not been identified with rigor.[12]

We hypothesized that the Brønsted acid-catalyzed aza-Darzens reaction and the Brønsted acid-promoted triazoline decomposition might mechanistically intersect at an

Scheme 1. General Outline of the Aza-Darzens Reaction



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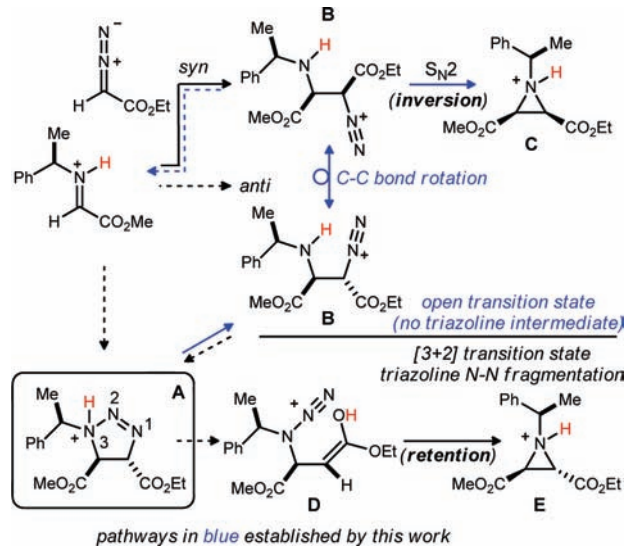

Figure 1. Mechanistic outline connecting aza-Darzens and triazoline decomposition reactions in the presence of Brønsted acid.

α-diazonium β-amino ester intermediate (**B**), as outlined in Figure 1.[13] Use of the Brønsted acid-catalyzed reaction to study the mechanism provides an advantage over Lewis acid/metal-catalyzed variants in that direct reaction of the diazoalkane with the latter can ultimately lead to an azomethine ylide intermediate, whose stereochemical fate might vary from catalyst to catalyst,[9,14] whereas protonation of the diazoalkane cannot lead to products of carbon−carbon bond formation. In this study, we report a series of isomerically enriched triazolines **1**−**4** and their stereospecific conversion to aziridines **5**−**6** consistent with mechanistic pathway **A** → **B** → **C**.

Our study commenced with the outline in Figure 1 and the hypothesis that relative stereochemistry could be used as a tool to probe the pathways described by consideration of a *trans*-triazoline (**A**) as a possible precursor to intermediate **B**. Fragmentation of the triazoline[15] core by Brønsted acid[16,17] could occur by protonation at oxygen, followed by amino diazonium ion (**D**) formation and ring closure to the *trans*-aziridinium salt (**E**). Alternatively, triazoline protonation at N3 in **A** would provide proper polarization for formation of alkyl diazonium intermediate **B**.[18]

The ester regioisomers of triazoline **A** and each *trans*-diastereomer were prepared by nonselective thermal cycloaddition of (*R*)-α-methyl benzyl azide[19] to ethyl methyl fumarate. The four isomers (**1**−**4**) could be separated by preparative HPLC to homogeneity (>98%). The use of both triazoline regioisomers was intentional so as to rely on coupling constants (instead of chemical shift alone) to assign aziridine stereochemistry. Assignment of the triazoline regioisomers was accomplished by a GOESY experiment to reveal long distance enhancements between the benzylic methine and both ethyl ester methyl (1.7%) and α-amino methine (2.2%) at C4 in **3** (Figure 2).[20]

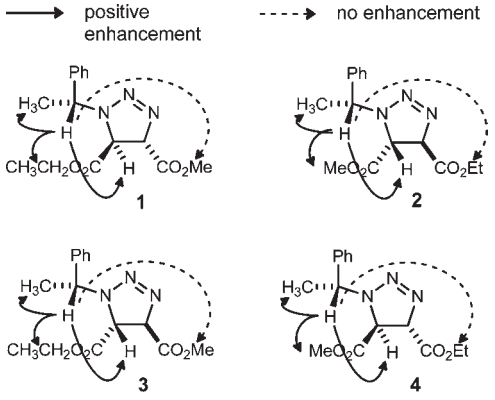

Figure 2. Selected GOESY enhancements.

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(13) Although they are not acid catalyzed, sulfonium ylide additions to carbonyl or azomethine have mechanistic considerations similar to those described here, and have been investigated extensively, including via computational methods. Leading references: (a) Lindvall, M. K.; Koskinen, A. M. P. *J. Org. Chem.* **1999**, *64*, 4596–4606. (b) Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747–5756. (c) Silva, M. a. A.; Bellenie, B. R.; Goodman, J. M. *Org. Lett.* **2004**, *6*, 2559–2562. (d) Robiette, R. *J. Org. Chem.* **2006**, *71*, 2726–2734.

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(15) Early studies, largely thermal triazoline decomposition: (a) Broeckx, W.; Overberg, N.; Samyn, C.; Smets, G.; L'Abbe, G. *Tetrahedron* **1971**, *27*, 3527–3534. (b) Huisgen, R.; Szeimies, G.; Möbius, L. *Chem. Ber.* **1966**, *99*, 475–490.

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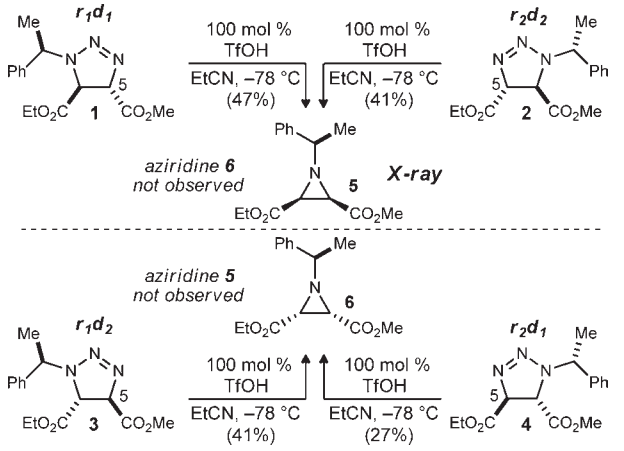
(20) Complete details, including ^{1}H NMR spectra for crude reaction mixtures, are provided in the Supporting Information. Additional control experiments are provided as well.

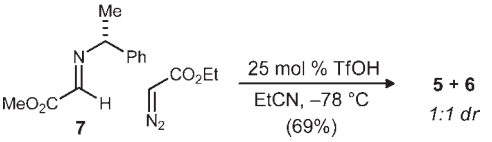
Since our intent was to study the selectivity of triazoline conversion under kinetic control, we adopted the use of 100 mol % of TfOH with otherwise identical conditions to the Brønsted acid-catalyzed aza-Darzens (EtCN, −78 °C),[4b] taking care to stop short of full conversion. These reactions provided only the aziridine and α-diazo-*β*-amino ester (essentially the mass balance of the reactions in Scheme 2) upon reaction quench.[20] The latter is the ring-opened isomer of **A**, which did not react further under these conditions. Importantly, each reaction provided only the *cis*-aziridine ($^3J_{HH}$ = 6.7 Hz).[20] Crystallographic data were obtained for one of the two *cis*-aziridines (**5**), thereby allowing the assignment of relative configuration necessary to determine the stereochemical changes in each case.

Scheme 2. Stereochemical Outcome of the Brønsted Acid-Promoted Fragmentation of Chiral Triazolines to *cis*-Aziridines



As the results in Scheme 2 detail, Brønsted acid-promoted conversion of triazoline to aziridine is a stereospecific process with inversion of configuration at C5 in each case (Figure 1, **A** → **B** → **C**). If an amino diazonium intermediate **D** were formed instead, formation of the *trans*-aziridine would be expected. Formation of **C** via **D** would require rotation to the s-*cis* conformer prior to cyclization. Since the s-*trans* → s-*cis* conversion is presumably uphill energetically, it would be reasonable to expect that at least one case among **1**−**4** would provide some evidence of the *trans*-aziridine if this pathway was operative. Finally, fragmentation to **B** is consistent with the behavior of unsubstituted triazolines.[16]

Scheme 3. Nonselective Brønsted Acid-Catalyzed Diazoester Addition to Chiral Nonracemic Imine **7**



Comparison was next made to the aza-Darzens reaction of imine **7** bearing the α-methyl benzyl amine substituent (Scheme 3).[4b] This allowed us to determine that retro-Mannich reaction of **B** is not operative, since the triflic acid-catalyzed addition of ethyl diazoacetate to imine **7** is nonselective (1:1 dr). Formation of the diazonium addition product (**B**) is therefore irreversible under the conditions of triazoline fragmentation.

Taken together, these findings validate the stereochemical integrity of intermediate **B** and establish its reluctance to undergo retro-Mannich to diazo and iminium. Furthermore, we provide a basis for developing stereochemical models in enantioselective azomethine−diazo alkane additions catalyzed by chiral Lewis acids. These experiments may have broader use as tools to investigate mechanisms, particularly in cases where *cis*-diastereoselection is observed in aziridine synthesis[21] (and selective *trans*-diastereomer degradation is not operative).[1,22]

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Supporting Information Available. Preparation and analytical data for all new compounds, X-ray data for **5**, and stacked plots of spectroscopic data for crude reaction mixtures. This material is available free of charge via the Internet at http://pubs.acs.org.

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