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Cascade Iminium Ion Reactions for the Facile Synthesis of Quinolizidines. Concise Syntheses of (±)-Epilupinine and (−)-Epimyrtine

Shawn M. Amorde, Andrew S. Judd, and Stephen F. Martin*

Department of Chemistry and Biochemistry, The University of Texas, Austin, Texas 78712

sfmartin@mail.utexas.edu

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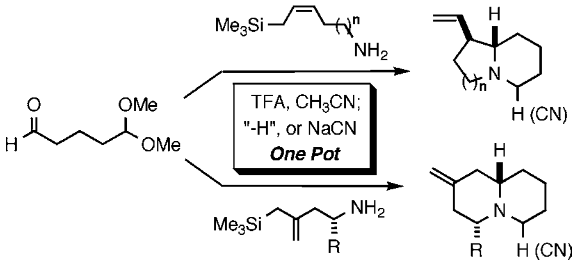
ABSTRACT



Several novel cascade processes have been designed and developed that involve sequential reactions of imines and iminium ions to form substituted quinolizidine ring systems in a single step from simple and readily available starting materials. The utility and promise of these cascade reactions is evident from their application to extraordinarily concise syntheses of the representative quinolizidine alkaloids (±)-epilupinine and (−)-epimyrtine.

Cascade reactions are powerful synthetic tools that involve sequential bond-forming events in which the product of one reaction is preprogrammed to be the starting material for the next one in a domino-like process.[1] Such methods enable the rapid assembly of complex molecular architectures in one-step procedures that are oftentimes efficient and environmentally friendly. Hence, there is an ongoing demand for new types of reaction cascades in the synthesis of natural products and other compounds having useful properties.

In the context of our longstanding interest in the design and development of useful tactics and strategies for alkaloid synthesis, we became intrigued with the challenge of combining different reactions to create useful domino reactions for forming nitrogen heterocycles. Because substituted indolizidines and quinolizidines are key structural subunits common to numerous families of alkaloids,[2] constructions leading to these ring systems have been of particular interest in our laboratories.[3] Imines are versatile intermediates that may serve both as electrophiles and nucleophiles in a diverse array of bond-forming reactions,[4] so we began a survey of

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[1] For reviews, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Padwa, A. *Pure Appl. Chem.* **2003**, *75*, 47. (c) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967.

[2] For a leading review of indolizidine and quinolizidine alkaloids, see: Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 625.

[3] (a) For some examples, see: Martin, S. F.; Yang, C. P.; Laswell, W. L.; Rüeger, H. *Tetrahedron Lett.* **1988**, *29*, 6685. (b) Martin, S. F.; Liao, Y.; Chen, H.-J.; Pätzel, M.; Ramser, M. N. *Tetrahedron Lett.* **1994**, *35*, 6005. (c) Martin, S. F.; Bur, S. K. *Tetrahedron* **1999**, *55*, 8905. (d) Reichelt, A.; Bur, S. K.; Martin, S. F. *Tetrahedron* **2002**, *58*, 6323. (e) Deiters, A.; Martin, S. F. *Org. Lett.* **2002**, *4*, 3243. (f) Deiters, A.; Chen, K.; Eary, C. T.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 4541.

[4] For reviews of *N*-alkyl iminium ions, see: (a) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857. (b) Kleinman, E. F.; Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; p 975. (c) Overman, L. E. *Aldrichim. Acta* **1995**, *28*, 107. (d) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311. For reviews of *N*-acyl iminium ions, see: (e) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (f) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

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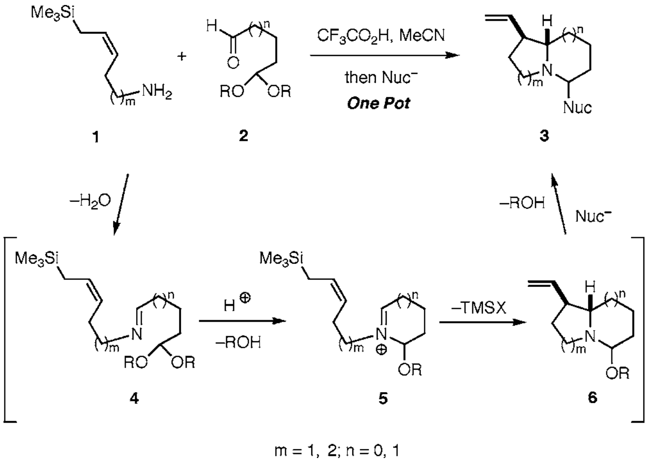
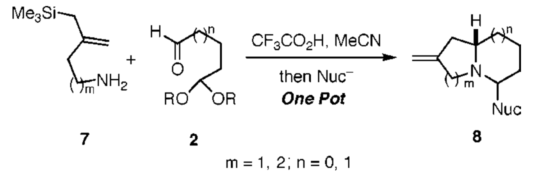
procedures by which these modes of reactivity might be sequenced in novel ways for preparing heterocycles with bridgehead nitrogen atoms.

Toward this goal, we envisioned a sequence of reactions that commenced with condensation of the amino allylsilane **1** with the monoprotected dialdehyde **2** to generate the imine **4** (Scheme 1). Although several reaction manifolds are available to **4**, acid-catalyzed cyclization of **4** would furnish **5** that could in turn undergo cyclization via addition of the allylsilane moiety to the iminium ion to provide **6**.[4a,5] Ionization of the *N*,*O*-acetal group of **6** in situ would generate another iminium ion that could be trapped with a number of nucleophiles to deliver the fused bicyclic amines **3** in a *single chemical operation in which four new bonds and two rings are formed from three different components.* A simple modification of this cascade of reactions would involve use of a branched allylsilane **7** in place of the linear **1** to give the related bicyclic amines **8** (Scheme 2).

Scheme 1. Cascade Reaction Sequence



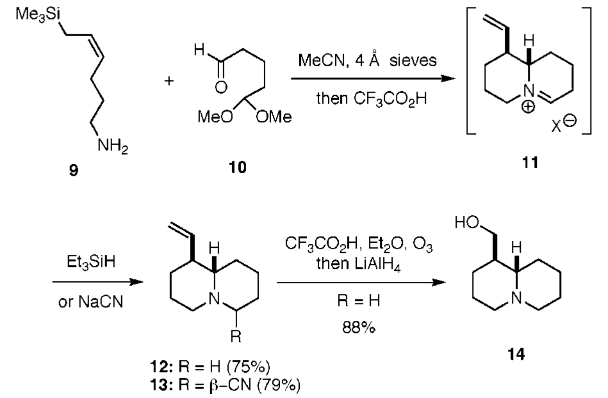
Scheme 2. Cascade Reaction Scope



Although the individual reactions outlined in Schemes 1 and 2 are precedented,[6] they have never before been orchestrated in a single domino process. We now report some preliminary results that illustrate the exceptional utility of such cascade reactions for the rapid construction of quinolizidines and alkaloids derived therefrom.

To establish the underlying feasibility of the plan depicted in Scheme 1, (*Z*)-6-(trimethylsilyl)-4-hexenylamine (**9**)[7] was first condensed with the monoprotected dialdehyde **10** (Scheme 3).[8] Without isolation the resultant imine was treated with trifluoroacetic acid to initiate two acid-catalyzed cyclizations leading to the putative iminium ion **11** that was reduced in situ with triethylsilane to deliver the quinolizidine **12** as a single diastereomer in 75% overall yield from **9**. The high level of stereoselectivity in the second cyclization step of the cascade to give a trans relationship of the hydrogen atoms at the newly created stereocenters is noteworthy. Compound **12** is a known intermediate in a previous synthesis of (±)-epilupinine (**14**),[9] but we developed an improved protocol for effecting this conversion. In the event, ozonolysis of the trifluoroacetate salt of **12**, followed by reduction of the intermediate ozonide furnished (±)-epilupinine in 88% yield.[10]

Scheme 3. Synthesis of (±)-Epilupinine



We have also briefly explored the feasibility of trapping the iminium ion with other nucleophiles in order to expand the versatility of this methodology. In preliminary experiments, we were unable to identify conditions under which **11** would react with allylsilane. However, we did discover that **11** could be trapped with cyanide ion to give the amino nitrile **13** as a single diastereomer (73%).

The scope of these imine cascade reactions was then broadened in a process related to that outlined in Scheme 2. Thus, 3-(methyltrimethylsilyl)-3-butenylamine (**15**)[11] and **10** were first condensed, and trifluoroacetic acid and NaCN were

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[5] For examples of related cyclizations, see: (a) Cellier, M.; Gelas-Mialhe, Y.; Husson, H. P.; Perrin, B.; Remuson, R. *Tetrahedron*: *Asymmetry* **2000**, *11*, 3913 and references therein. (b) Agami, C.; Comesse, S.; Kadouri-Puchot, C. *J. Org. Chem.* **2002**, *67*, 2424 and references therein.

[6] (a) Grieco, P. A.; Fobare, W. F. *J. Chem. Soc.*, *Chem. Commun.* **1987**, 185. (b) Doedens, R. J.; Meier, G. P.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 685. (c) Bowman, W. R.; Stephenson, P. T.; Young, A. R. *Tetrahedron* **1996**, *52*, 11445. (d) Pearson, W. H.; Mi, Y. *Tetrahedron Lett.* **1997**, *38*, 5441. (e) Clark, R. B.; Pearson, W. H. *Org. Lett.* **1999**, *1*, 349. (f) An, D. K.; Duncan, D.; Livinghouse, T.; Reid, P. *Org. Lett.* **2001**, *3*, 2961. (g) Furman, B.; Dziedzic, M. *Tetrahedron Lett.* **2003**, *44*, 8249.

[7] Wasserman, H. H.; Vu, C. B.; Cook, J. D. *Tetrahedron* **1992**, *48*, 2101.

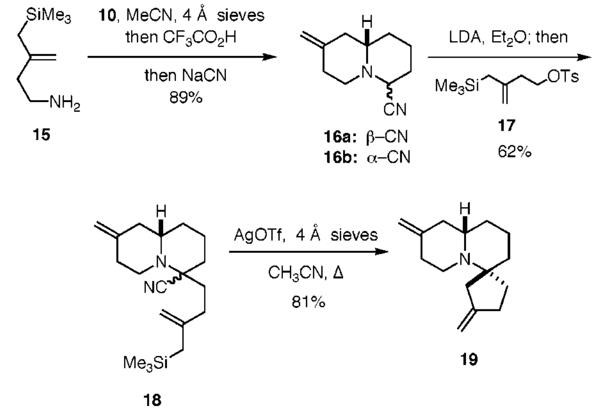
[8] Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.

[9] Pandey, G.; Reddy, G. D.; Chakrabarti, D. *J. Chem. Soc.*, *Perkin Trans.1* **1996**, 219.

[10] ^{1}H and ^{13}C NMR spectral data for synthetic **14** were consistent with those reported. See: Ma, S.; Ni, B. *Eur. J. Chem.* **2004**, *10*, 3286.

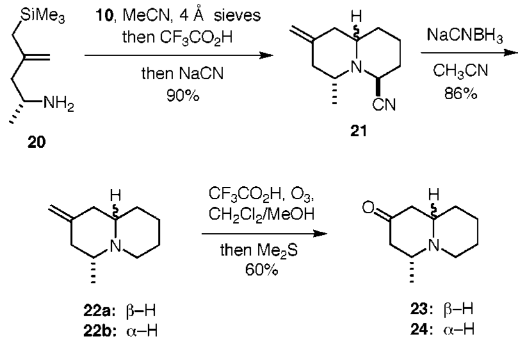
then added sequentially to furnish an epimeric mixture (88:12) of the amino nitriles **16a** and **16b** (Scheme 4).[12] Bicyclic amino nitriles as **16a,b** may be useful intermediates in the synthesis of more complex molecular architectures[13] as evidenced by the facile transformation of this mixture into the spirocyclic tricycle **19**. Thus, deprotonation of **16a**,**b** with LDA followed by alkylation of the carbanion with the tosylate **17**[14] gave **18**. Subsequent exposure of **18** to AgOTf generated an iminium ion that underwent efficient cyclization via addition of the allylsilane to give **19** as a single diastereomer in accord with the principles of stereoelectronic control.[15] The relative stereochemistry of the spiro and bridgehead centers in **19** was assigned on the basis of NOE correlations observed in a GOESY experiment.

Scheme 4. Synthesis and Applications of Amino Nitriles



We then turned our attention to applying a cascade in which a branched allylsilane is employed as a reaction partner to a facile, enantioselective synthesis of the quinolizidine alkaloid (−)-epimyrtine (**23**) (Scheme 5). Toward this end, (*R*)-1-methyl-3-(methyltrimethylsilane)-3-butenylamine (**20**)[16] and the aldehyde **10** were first condensed to give an imine that was then treated sequentially with trifluoroacetic acid and NaCN to give a mixture of diastereomeric amino nitriles **21** in excellent yield (Scheme 5). Subsequent reduction of **21** with NaCNBH$_3$ provided a mixture (95:5) of epimeric quinolizidines **22a**,**b**. When the exocyclic olefin in the trifluoroacetate salt of **22a**,**b** was cleaved by ozonolysis, an inseparable mixture (95:5) of (−)-epimyrtine (**23**) and (+)-myrtine (**24**) was obtained.[17]

Scheme 5. Synthesis of (−)-Epimyrtine



In summary, we have discovered and developed several novel cascade reactions that involve iminium ions to form quinolizidines in excellent overall yields. Although the precise mechanistic pathway involved in these processes is not yet known, their utility and promise is evident from their application to extraordinarily concise syntheses of the representative quinolizidine alkaloids (±)-epilupinine and (−)-epimyrtine. Further applications of these domino-like reactions to the syntheses of more complex alkaloids are under active investigation, the results of which will be reported in due course.

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Supporting Information Available: Experimental procedures for preparing **12**, **14**, **21**, and **23**, comparison of ^{1}H and ^{13}C NMR data for **14** and **23** with literature data, and copies of ^{1}H NMR spectra of **14**, **23**, and all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] (a) Gramain, J. C.; Remuson, R. *Tetrahedron Lett.* **1985**, *26*, 327. (b) Burfeindt, J.; Patz, M.; Mueller, M.; Mayr, H. *J. Am. Chem. Soc.* **1998**, *120*, 3629.

[12] The products **16a** and **16b** were readily separable by flash chromatography. The ratio of the two compounds appears to be thermodynamic as **16b** equilibrated to a mixture (88:12) of **16a** and **16b** upon standing in CD$_3$CN or upon heating in the presence of basic alumina.

[13] Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359.

[14] Rubiralta, M.; Diez, A.; Miguel, D.; Remuson, R.; Gelas-Mialhe, Y. *Synth. Commun.* **1992**, *22*, 359.

[15] (a) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289. (b) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688. (c) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Organic Chemistry Series, Vol. 1; Pergamon Press: New York, 1983.

[16] Monfray, J.; Gelas-Mialhe, Y.; Gramain, J.-C.; Remuson, R. *Tetrahedron Lett.* **2003**, *44*, 5785.

[17] ^{1}H and ^{13}C NMR spectral data for synthetic **23** and **24** and the specific rotation for **23** were consistent with those reported. See: (a) Slosse, P.; Hootele, C. *Tetrahedron* **1981**, *37*, 4287. (b) Gardette, D.; Gelas-Mialhe, Y.; Gramain, J.-C.; Perrin, B.; Remuson, R. *Tetrahedron*: *Asymmetry* **1998**, *9*, 1823. (c) Davis, F. A.; Zhang, Y.; Anilkumar, G. *J. Org. Chem.* **2003**, *68*, 8061.