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Synthetic and Mechanistic Studies of the Aza-Retro-Claisen Rearrangement. A Facile Route to Medium Ring Nitrogen Heterocycles

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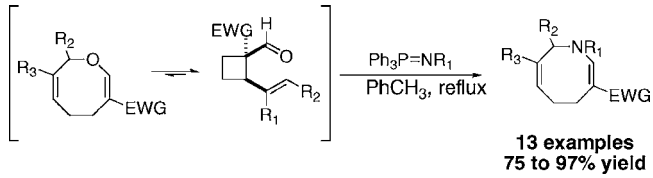
ABSTRACT



An efficient synthesis of medium-sized heterocyclic rings was achieved using a one-pot aza-Wittig/retro-aza-Claisen sequence of vinyl cyclobutanecarboxaldehydes derived from simple allylic carbonates. The use of various Staudinger reagents in the aza-Wittig reaction allows for a variety of *N*-substituted products to be obtained. The rearrangement is under thermodynamic control driven by relief of the cyclobutane ring strain and resonance stabilization of the resulting vinylogous amide/sulfonamide.

Heterocycles containing seven- or eight-membered rings are common structural elements in an array of natural products, many of which possess valuable biological activities.[1] A number of useful synthetic methods have been developed for the generation of medium ring nitrogen heterocycles,[2] including rearrangement of *N*-alkyl-2,3-divinyl and *N*-acyl-3-divinylaziridines,[3] 2-imino-3-vinyl-cyclopropanes,[4] and ring-closing metathesis (RCM).[5] The latter occasionally encounters problems with functional group compatibility and sluggish reaction rate.[6] Methods to prepare partially saturated eight-membered azacycles are much rarer.[6,7] We sought to extend our prior studies of the retro-Claisen reaction to develop an efficient and general route to medium size nitrogen-containing rings.[8] Our prior studies that examined the retro-Claisen rearrangement of vinylcyclopropane and vinylcyclobutane carboxaldehydes afforded a useful entry to highly substituted enantiomerically enriched oxepines and oxacenes culminating in the total synthesis of (+)-laurenyne (Figure 1).[8d]

(1) (a) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251–280. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1986**, *3*, 1–33. (c) Tsuda, M.; Kobayashi, J. *Heterocycles* **1997**, *46*, 765–794. (d) Matzanke, N.; Gregg, R.; Weinreb, S. *Org. Prep. Proced. Int.* **1998**, *30*, 1–52. (e) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201–6258.

(2) (a) Hassenruck, K.; Martin, H. D. *Synthesis* **1988**, *1988*, 569–586. (b) Shaw, R.; Anderson, M.; Gallagher, T. *Synlett* **1990**, *1990*, 584–586. (c) Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131–9166. (d) Furness, K.; Aube, J. *Org. Lett.* **1999**, *1*, 495–498. (e) Larock, R. C.; Tu, C.; Pace, P. *J. Org. Chem.* **1998**, *63*, 6859–6866.

(3) (a) Lindström, U., M.; Somfai, P. *Chem.—Eur. J.* **2001**, *7*, 94–98. (b) Pommelet, J. C.; Chuche, J. *Can. J. Chem.* **1976**, *54*, 1571–1581.

(4) Reissig, H.-U.; Böttcher, G.; Zimmer, R. *Can. J. Chem.* **2004**, *82*, 166–176.

(5) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446–452.

(6) Borer, B. C.; Deerenberg, S.; Bieraugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1994**, *35*, 3191–3194.

(7) (a) Chang, M.-Y.; Kung, Y.-H.; Ma, C.-C.; Chen, S.-T. *Tetrahedron* **2006**, *63*, 1339–1344. (b) Georg, G. I.; Guan, X. *Tetrahedron Lett.* **1992**, *33*, 17–20. Arata, Y.; Tanaka, K.; Yoshifuji, S.; Kanatomo, S. *Chem. Pharm. Bull.* **1979**, *27*, 981–983.

(8) (a) Boeckman, R. K., Jr.; Flann, C. J.; Poss, K. M. *J. Am. Chem. Soc.* **1985**, *107*, 4359–4362. (b) Boeckman, R. K., Jr.; Shair, M. D.; Vargas, J. R.; Stolz, L. A. *J. Org. Chem.* **1993**, *58*, 1295–1297. (c) Boeckman, R. K., Jr.; Reeder, M. R. *J. Org. Chem.* **1997**, *62*, 6456–6457. (d) Boeckman, R. K., Jr.; Zhang, J.; Reeder, M. R. *Org. Lett.* **2002**, *4*, 3891–3894.

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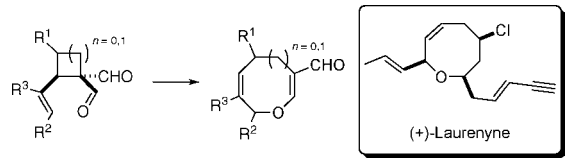
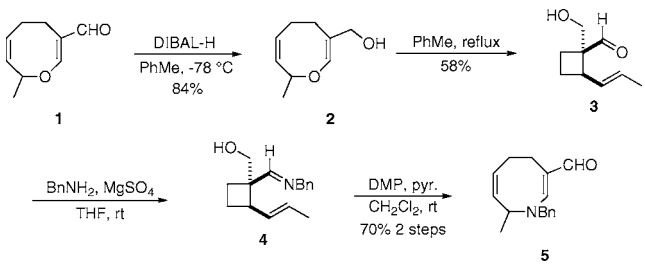


Figure 1. Retro-Claisen rearrangement to form oxacycles.

In order to explore the means for introduction of nitrogen, we first examined a stepwise process that was initiated by reduction of racemic oxacene **1** to the derived alcohol **2** (Scheme 1).[9] Upon heating, Claisen rearrangement was observed to provide aldehyde **3** with no evidence of the retro-Claisen isomer detectable by NMR (K_{eq} >20) in spite of the loss of vinylogous resonance stabilization by the electron-withdrawing group.

Scheme 1. Stepwise Aza-Retro-Claisen Rearrangement

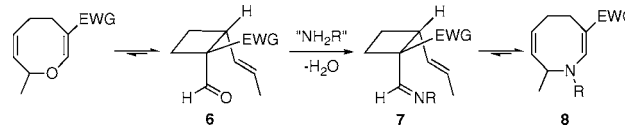


Condensation of aldehyde alcohol **3** with benzyl amine afforded aldimine alcohol **4**. Again **4** did not undergo aza-retro-Claisen rearrangement until after oxidation of **4** with Dess−Martin periodinane, which afforded the azocine aldehyde **5** directly at rt with no detectable cyclobutane aldehyde imine by NMR (K_{eq} >20). Although the shift in the equilibrium constant for interconversion of **4** and **5** owing to the combined effects of ring strain relief and additional resonance stabilization was expected, the apparent reduction in the kinetic barrier for interconversion of **4** and **5** relative to interconversion of **2** and **3** was not.

With the feasibility of the aza-retro-Claisen rearrangement via a stepwise sequence established, we turned our efforts to development of a one-pot procedure to avoid need for additional redox transformations.

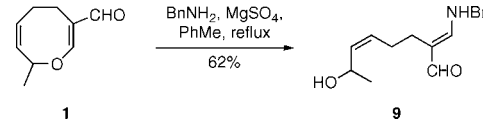
It has long been established that the equilibrium of the Claisen/retro-Claisen rearrangement can be perturbed by the introduction of electron-withdrawing/-donating substituents.[8a,10] By taking advantage of this phenomenon, we anticipated that conversion of **6** to imine **7** via condensation with a primary amine or amine equivalent would allow thermodynamically favored equilibration to the azocine **8** under the conditions required for conversion to **7** (Scheme 2).

Scheme 2. Potential One-Pot Aza-Retro-Claisen Rearrangement



Initially, the direct aza-retro-Claisen was attempted by treating racemic oxacene **1** with excess benzyl amine (or other primary amines) in the presence of $MgSO_4$ (Scheme 3).[11] Surprisingly, this led to preferential Michael addition−elimination resulting in ring cleavage, affording the acyclic hydroxy vinylogous formamide **9**.

Scheme 3. Unexpected Ring Cleavage



To obtain the desired regioselectivity during conversion of **1** to imine **8**, we sought to increase the nucleophilicity of the amine via use of the related Staudinger imino-phosphoranes facilitating kinetic formation of the imine **8** via elimination of triphenylphosphine oxide.[12] Staudinger reagents are readily accessible via reaction of alkyl or aryl azides with triphenylphosphine under mild heating.[12]

The *N*-benzyl Staudinger reagent (≥2 equiv), generated in situ from BnN_3 and Ph_3P in $PhCH_3$ at reflux, was treated with oxacene **1** until conversion to **11** was complete (∼14 h). Because the resulting azocine imine **11** proved to be unstable to purification, we effected direct hydrolysis of the reaction mixture with aq NaOAc buffer (pH = 4) at rt, affording azocine aldehyde **5** in 82% yield after chromatography.[13]

The precise sequence of events by which oxacene **1** is transformed to **5** could not be readily ascertained as multiple independent pathways can be envisioned for the sequential Staudinger/aza-Claisen−retro-Claisen process, all of which afford azocine **5** after hydrolysis (Scheme 4). Use of excess Staudinger reagent apparently drives the formation of the diimine **10** or the azocine imine **11** ensuring complete conversion to **5** after hydrolysis.

To further test the scope and functional group compatibility of the aza-retro-Claisen rearrangement, a series of variously substituted vinyl cyclobutanecarboxaldehydes/oxacenes were

(9) We described a single example of azepine formation by rearrangement of the *N*-benzyl imine of (1*S*,2*S*)-1-hydroxymethyl-2-((*E*)-propen-1-yl)cyclopropane carbaldehyde after oxidation.[8b]

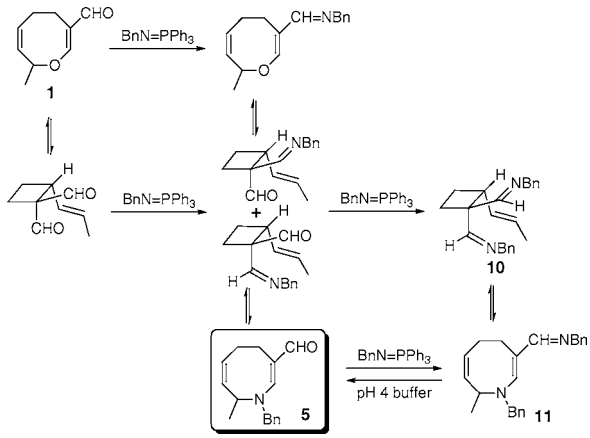
(10) Rhoads, S. J.; Cockroft, R. D. *J. Am. Chem. Soc.* **1969**, *91*, 2815–2816.

(11) All materials employed in these studies were racemic although we have previously described routes to such enantiomerically enriched starting materials.[8]

(12) (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635–646. (b) Staudinger, H.; Hauser, E. *Helv. Chim. Acta* **1921**, *4*, 861–886.

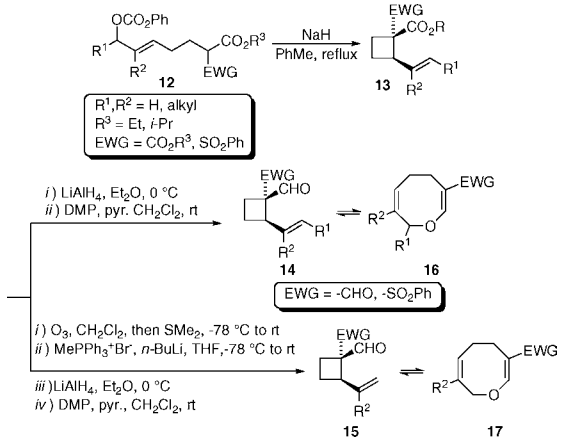
(13) Ono, M.; Tamura, S. *Chem. Pharm. Bull.* **1982**, *30*, 1453–1462.

Scheme 4. Potential One-Pot Aza-Retro-Claisen Rearrangement Pathways to Azocine **5**



prepared using variations of our previously described general route (Scheme 5).[8c,11] The sequences were designed to rapidly access a diversity of substitution rather than providing an optimal route to any individual example. Beginning with allylic carbonates **12**, these sequences afforded the cyclobutanecarboxaldehydes **14** and **15** and/or the oxacenes **16** and **17** in 15−53% combined overall yield (~70−80%/step unoptimized) depending upon the magnitude of K_{eq} for the individual cases at rt.

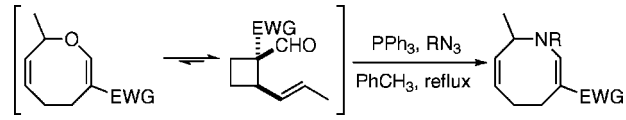
Scheme 5. General Sequence for Preparation of Cyclobutanecarboxaldehyde/Oxacene Substrates

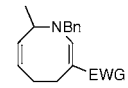
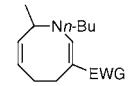
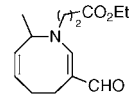
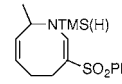
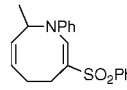


Having demonstrated the feasibility of a one-pot sequence to form azocine **5**, the scope of nitrogen substitution was investigated (Table 1). A variety of azides[14] were converted to the respective Staudinger reagents in situ and reacted with oxacenes **1** and **14** (EWG = SO_2Ph, $R_1 = CH_3$, $R_2 = H$). As shown in Table 1, the scope of the nitrogen substitution proved to be broad. Benzylic, primary, and functionalized primary alkyl, aryl, and trialkylsilyl are tolerated, affording the expected

(14) Alvarez, M. T.; Miho, T. *Synthesis* **1997**, *4*, 413–414.

Table 1. Evaluation of Scope: Azide Component



entry	azide (RN_3)	time(h)	product[a]		EWG	yield(%)[b]
1	$PhCH_2N_3$	14		**5**	CHO	82
2		36		**20**	SO_2Ph	86
3	*n*-BuN_3	12		**18**	CHO	88
4		36		**21**	SO_2Ph	88
5	$EtO_2C(CH_2)_2N_3$	14		**19**	CHO	87
6	$TMSN_3$	48		**22** **24**	SO_2Ph SO_2Ph	91[c]
7	PhN_3	48		**23**	SO_2Ph	75

[a] For entries 1, 3, and 5 the intermediate formyl imines were hydrolyzed with pH = 4 NaOAc buffer. [b] Yields based on isolated products after purification by chromatography. [c] Isolated as **24**, the N−H azocine.

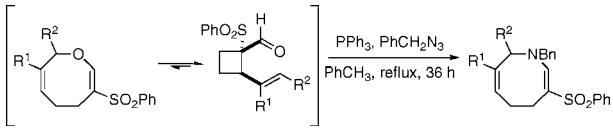
N-substituted azocine products **5**, **18**, and **19** (EWG = CHO) and **20**−**23** (EWG = SO_2Ph) in 75−91% yield. Particularly noteworthy is the successful use of $TMSN_3$ as a Staudinger precursor.[15] Typically removal of N-protecting groups such as that present in **19** (mild base) proceeds readily.[16] Desilylation of **22** (N-TMS) occurs during chromatographic purification affording **24** (N−H), providing ready access to N-unsubstituted azocines, if desired, minimizing the need for protection/deprotection steps.

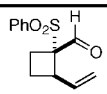
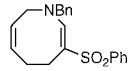
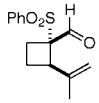
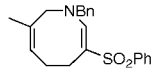
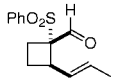
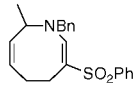
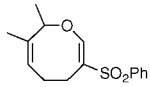
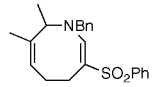
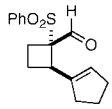
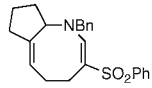
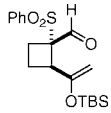
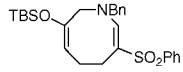
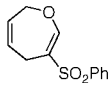
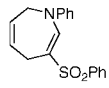
We also examined the olefin substitution pattern for the vinyl cyclobutanecarboxaldehydes. For these studies, we employed a sulfone as the electron-withdrawing group (EWG), eliminating the need for the acid hydrolysis required when employing a formyl group as the EWG. The unsubstituted azocine **25** was readily accessible as depicted in Table 2. Methyl substitution at the C_7 and C_8 positions of the oxacene, respectively, gave products **26** and **20** in excellent yield. Disubstitution was also well-tolerated, affording the dimethyl azocine **27** in 92% yield, prompting us to explore the possibility of producing bicyclic azocines from an appropriate cycloalkenyl-substituted cyclobutane. To our delight the rearrangement afforded the desired [5,8]-bicyclic azocine **28** in 76% yield. A silyl enol ether was also employed to determine whether heteroatom substitution was also tolerated under the standard reaction conditions. As hoped, the rearrangement proceeded smoothly to afford the cyclic enol ether **29** in 88% yield. As would be expected, the one-pot aza-retro-Claisen sequence readily affords azepines from

(15) Tsuge, O.; Kanemasa, S.; Matsuda, K. *J. Org. Chem.* **1984**, *49*, 2688–2691.

(16) Boeckman, R. K., Jr; Jackson, P. F.; Sabatucci, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 2191–2192.

Table 2. Evaluation of Scope: Olefin Substitution



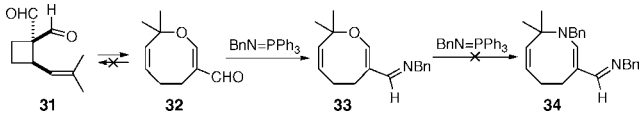
entry	substrate		product	yield(%)[a]
1		**25**		88
2		**26**		88
3		**20**		86
4		**27**		92
5		**28**		76
6		**29**		88
7		**30**		97[b,c]

[a] Yields based on isolated products after chromatography. [b] For entry 7, related oxepine sulfone used as starting material. [c] For entry 7, phenyl azide used in preparation of the Staudinger reagent.

the respective vinylcyclopropanecarboxaldeydes, for example, providing **30** in 97% yield.

One limitation in the scope of the aza-retro-Claisen rearrangement encountered thus far involves use of terminally disubstituted olefins (Scheme 6). Although the Claisen/retroClaisen equilibrium apparently strongly favors oxacenecarboxaldehye **32** over the vinylcyclobutane **31**,[17] exposure to 2 equiv of a Staudinger reagent consumed only 1 equiv, affording the oxacene **33**, which failed to undergo the subsequent Claisen/retro-Claisen rearrangement intended to provide the desired *gem*-dimethyl-substituted azocine **34**.

Scheme 6[a]

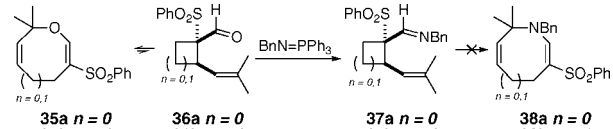


31 **32** **33** **34**

[a] All reactions employed 3 equiv of Staudinger reagent at 0.2 M concentration in $PhCH_3$ at reflux for 48 h.

In the case of vinylcyclopropane/oxepine **36a**/**35a** and cyclobutanecarboxaldehyde/oxacene **36b**/**35b** bearing a sulfone as the EWG, the equilibrium lies completely (>95% by NMR) toward oxepine **35a** and vinylcyclobutane **36b** at rt. However, upon treatment of **35a**/**35b** and **36a**/**36b** with excess benzyl Staudinger reagent, the only products observed were **37a** and **37b** with the latter isolated in 71% yield (Scheme 7). These results suggest that the presence of the combination of *syn* geminal and nitrogen substituents in **37a** and **37b**, thermodynamically disfavors the aza-retro-Claisen rearrangement even at elevated temperatures.

Scheme 7[a]



35a *n* = 0 **35b** *n* = 1 **36a** *n* = 0 **36b** *n* = 1 **37a** *n* = 0 **37b** *n* = 1 **38a** *n* = 0 **38b** *n* = 1

[a] All reactions employed 3 equiv of Staudinger reagent at 0.2 M in $PhCH_3$ at reflux for 48 h.

In summary, we have described a practical method for preparing medium sized *N*-heterocycles through a one-pot aza-retro-Claisen rearrangement sequence. The rearrangement sequence proceeds under mild conditions and appears quite general and compatible with a variety of substituents at nitrogen and carbon.

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Supporting Information Available: Full characterization data and NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Reactions heated at reflux in PhMe for 72 h with no change. The temperature was then increased to 180 °C. Heating for 18 h using a sealed tube afforded **33** with some slight decomposition by ^1H NMR.