ORGANIC
LETTERS

2010
Vol. 12, No. 10
2290−2293

# Carbon−Carbon Bond Formation and Pyrrole Synthesis via the [3,3] Sigmatropic Rearrangement of *O*-Vinyl Oxime Ethers

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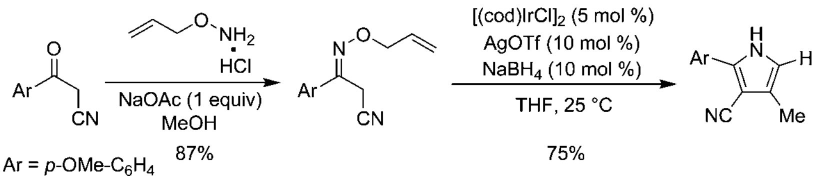
**Received March 19, 2010**

## ABSTRACT



**A new method for the synthesis of 2,4- and 2,3,4-substituted pyrroles in two or three steps from commercially available ketones and allyl hydroxylamine is described. An iridium-catalyzed isomerization reaction has been developed to convert *O*-allyl oximes to *O*-vinyl oximes, which undergo a facile [3,3] rearrangement to form 1,4-imino aldehyde Paal−Knorr intermediates that cyclize to afford the corresponding pyrroles. Optimization and examples of the isomerization and pyrrole formation are discussed.**

[3,3] Sigmatropic rearrangements, such as the Claisen and Fisher−Indole reactions, are powerful methods for forming new carbon−carbon bonds.[1] A less familiar example is the [3,3] rearrangement of *O*-vinyl oximes to give 1,4-imino carbonyl compounds. Trofimov and co-workers have shown that oximes can be added to acetylenes under strongly basic conditions to form *O*-vinyl oximes that rearrange to 1,4-imino carbonyl compounds and then participate in a Paal−Knorr cyclization and condensation sequence.[2] This transformation is an intriguing alternative approach to the synthesis of pyrroles because it uses the Paal−Knorr sequence without requiring the synthesis of 1,4-dicarbonyl compounds.[3,4] Unfortunately, the Trofimov reaction is limited in scope and efficiency. The strongly basic conditions limit functional group compatibility. While 2,3-substituted pyrroles can be accessed from acetylene and oximes which tolerate

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(1) (a) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991: Vol. 5, p 827. (b) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939. (c) Moody, C. J. *Adv. Heterocycl. Chem.* **1987**, *42*, 203. (d) Robinson, B. *Chem. Rev.* **1969**, *69*, 227. (e) Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 607. (f) Downing, R. S.; Kunkeler, P. J. In *The Fischer Indole Synthesis*; Sheldon, R. A., Bekkum, H., Eds.; Wiley-VCH: New York, 2001; p 178.

(2) For reviews of the Trofimov reaction see: (a) Mikhaleva, A. I.; Zaitsev, A. B.; Trofimov, B. A. *Russ. Chem. Rev.* **2006**, *75*, 797. (b) Trofimov, B. A. *Curr. Org. Chem.* **2002**, *6*, 1121. (c) Trofimov, B. A.; Mikhaleva, A. I. *Heterocycles* **1994**, *37*, 1193. (d) Trofimov, B. A. *Adv. Heterocycl. Chem.* **1990**, *51*, 177.

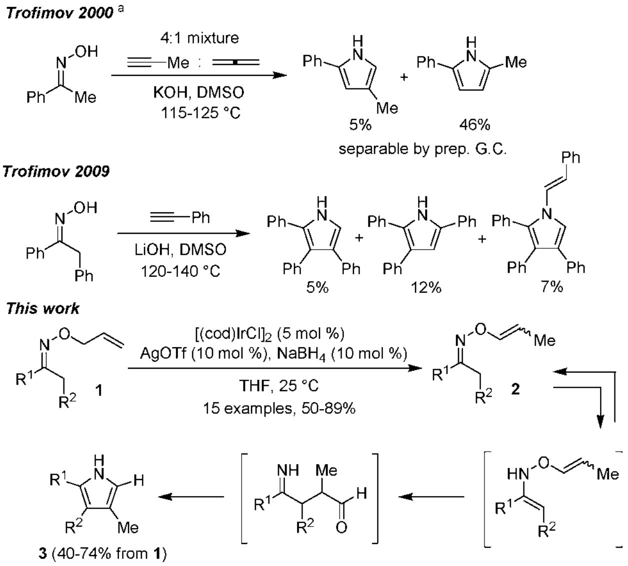
(3) For classic syntheses of pyrroles and reviews of the preparation of pyrroles, see: (a) Knorr, L. *Chem. Ber.* **1884**, *17*, 1635. (b) Paal, C. *Chem. Ber.* **1885**, *18*, 367. (c) Kostyanovsky, R. G.; Kadorkina, G. K.; Mkhitaryan, A. G.; Chervin, I. I.; Aliev, A. E. *Mendeleev Commun.* **1993**, 21. (d) Katritzky, A. R.; Ostercamp, D. L.; Yousaf, T. I. *Tetrahedron* **1987**, *43*, 5171. (e) Black, D. S. *Sci. Synth.* **2001**, *13*, 441. (f) Ferreira, V. F.; De Souza, M. C. B. V.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. G. *Org. Prep. Proced. Int.* **2001**, *33*, 411.

(4) For recent examples of pyrrole syntheses, see: (a) Rivero, M. R.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973. (b) Martin, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079. (c) Lu, Y.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 5430. (d) Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey, A. L.; Driver, T. G. *Org. Lett.* **2007**, *9*, 5191. (e) Milgram, B. C.; Eskildsen, K.; Richter, S. M.; Scheidt, W. R.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 3941. (f) Khalili, B.; Jajarmi, P.; Eftekhari-Sis, B.; Hashemi, M. M. *J. Org. Chem.* **2008**, *73*, 2090.

10.1021/ol100659q

the harsh reaction conditions,[5] the use of substituted alkynes is rare and gives regioisomeric mixtures of products in low yields (Scheme 1).[6] These limitations are regrettable given

**Scheme 1.** *O*-Vinyl Oximes as Precursors to Pyrroles

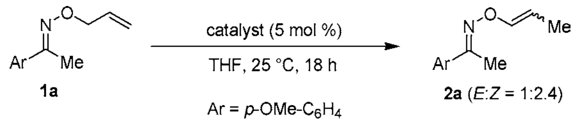


[a] Representative example.

the importance of substituted pyrrole architectures in medicinal and material target molecules.[7,8] To broaden the range of pyrroles accessible from the [3,3] sigmatropic rearrangement of *O*-vinyl oximes under more tolerant and efficient conditions, we have developed an alkene isomerization method to access *O*-vinyl oximes from easily prepared *O*-allyl oximes. Here we report the scope of this isomerization and the conversion of the *O*-vinyl oxime products to pyrroles with mild heating (Scheme 1). The overall method provides a simple, selective, and functional group tolerant synthesis of 2,4- and 2,3,4-substituted pyrroles in two or three steps from ketones and allyl hydroxylamine.

Alkene isomerization conditions for the conversion of *O*-allyl oximes to *O*-vinyl oximes were screened for allyl oxime **1a**. This substrate was synthesized by a condensation reaction between 4′-methoxyacetophenone and commericially available, allyl hydroxylamine. Initially, known allylic ether isomerization catalysts, such as [(Ph$_3$P)$_3$RhCl]/*n*-BuLi and [(coe)$_2$IrCl]$_2$/PCy$_3$/AgPF$_6$, were tested and shown to be ineffective for the desired transformation.[9,10] Instead, a 1:2:2 mixture of [(cod)IrCl]$_2$, NaBH$_4$, and AgOTf successfully catalyzed the conversion of **1a** to **2a** at 25 °C (Table 1, entries 1−3). Other common Ir(I) and Rh(I) catalyst precursors were screened under the isomerization conditions but were less efficient than [(cod)IrCl]$_2$ (Table 1, entries 3−6). The addition of phosphine ligands to the catalyst mixture and the removal of AgOTf also inhibited the reaction. Several reducing agents were screened and LiAlH$_4$ and NaBH$_4$ were found to give the highest yields of **2a** (Table 1, entries 3 and 7). A 2:1 ratio of the reducing reagent to the iridium dimer was required because larger concentrations of the reducing reagent provided small amounts of a side product produced by reduction of the allyl group to an *n*-propyl group.[11] THF and MeCN were determined to be optimal solvents for the isomerization. A significant decrease in yield

**Table 1.** Optimization of the *O*-Allyl Oxime Isomerization Catalyst



| entry | catalyst | yield (%)[a] |
|---|---|---|
| 1 | (Ph$_3$P)$_3$RhCl/*n*-BuLi | NR |
| 2 | [(coe)$_2$IrCl]$_2$/2PCy$_3$/2AgPF$_6$ | NR[b] |
| 3 | [(cod)IrCl]$_2$/2NaBH$_4$/2AgOTf | 85 |
| 4 | [(coe)$_2$IrCl]$_2$/2NaBH$_4$/2AgOTf | 53 |
| 5 | (cod)$_2$Rh(BF$_4$)/NaBH$_4$/AgOTf | 30 |
| 6 | [(coe)$_2$RhCl]$_2$/2NaBH$_4$/2AgOTf | NR |
| 7 | [(cod)IrCl]$_2$/2LiAlH$_4$/2AgOTf | 89 |

[a] Determined by using $^1$H NMR spectroscopy with CH$_2$Br$_2$ as a reference. [b] The reaction was done in THF and in 50:1 DCE:acetone.

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(5) For examples of the Trofimov reaction with acetylene, see: (a) Mikhaleva, A. I.; Trofimov, B. A.; Vasil'ev, A. N. *Zh. Org. Khim.* **1979**, *15*, 602. (b) Korostova, S. E.; Mikhaleva, A. I.; Vasil'tsov, A. M.; Trofimov, B. A. *Russ. J. Org. Chem.* **1998**, *34*, 911. (c) Trofimov, B. A.; Zaitsev, A. B.; Schmidt, E. Y.; Vasil'tsov, A. M.; Mikhaleva, A. I.; Ushakov, I. A.; Vashchenko, A. V.; Zorina, N. V. *Tetrahedron Lett.* **2004**, *45*, 3789. (d) Trofimov, B. A.; Schmidt, E. Y.; Zorina, N. V.; Senotrusova, E. Y.; Protsuk, N. I.; Ushakov, I. A.; Mikhaleva, A. I.; Meallet-Renault, R.; Clavier, G. *Tetrahedron Lett.* **2008**, *49*, 4362. (e) Schmidt, E. Y.; Mikhaleva, A. I.; Vasil'tsov, A. M.; Zaitsev, A. B.; Zorina, N. V. *ARKIVOC* **2005**, *7*, 11.

(6) For examples of regioisomeric mixtures of products obtained from the use of terminal alkynes in the Trofimov reaction see: (a) Petrova, O. V.; Sobenina, L. N.; Ushakov, I. A.; Mikhaleva, A. I.; Hyun, S. H.; Trofimov, B. A. *ARKIVOC* **2009**, *4*, 14. (b) Trofimov, B. A.; Tarasova, O. A.; Mikhaleva, A. I.; Kalinina, N. A.; Sinegovskya, L. M.; Henkelmann, J. *Synthesis* **2000**, 1585.

(7) For examples of the biological activity and medicinal application of pyrroles, see: (a) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*; John Wiley& Sons Inc.: Chichester, UK, 2009. (b) Barton, D. H. R.; Nakanishi, K.; MethCohn, O.; Kelly, J. W. *Comprehensive Natural Products Chemistry*; Pergamon Press: Oxford, UK, 1999. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Maryanoff, B. E.; Zhang, H.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (e) Saracoglu, N. *Top. Heterocycl. Chem.* **2007**, *11*, 1. (f) Zomax: McLeod, D. C. *Drug Intell. Clin. Pharm.* **1981**, *15*, 522. (g) Atorvastin (Lipitor): Roth, B. D. US4681893, 1987. (h) Muchowski, J. M. *Adv. Med. Chem.* **1992**, *4*, 181.

(8) For examples of pyrrole structures in material applications see: (a) Tshibaka, T.; Ulliel Roche, I.; Dufresne, S.; Lubell, W. D.; Skene, W. G. *J. Org. Chem.* **2009**, *74*, 9497. (b) Walczak, R. M.; Reynolds, J. R. *Adv. Mater.* **2006**, *18*, 1121.

(9) For related syntheses of allyl vinyl ethers which undergo subsequent Claisen rearrangements, see: (a) Wang, K.; Bungard, C. J.; Nelson, S. G. *Org. Lett.* **2007**, *9*, 2325. (b) Nelson, S. G.; Bungard, C. J.; Wang, K. *J. Am. Chem. Soc.* **2003**, *125*, 13000. (c) Schmidt, B. *Synlett* **2004**, *9*, 1541. (d) Tanaka, K.; Okazaki, E.; Shibata, Y. *J. Am. Chem. Soc.* **2009**, *131*, 10822, and references cited within.

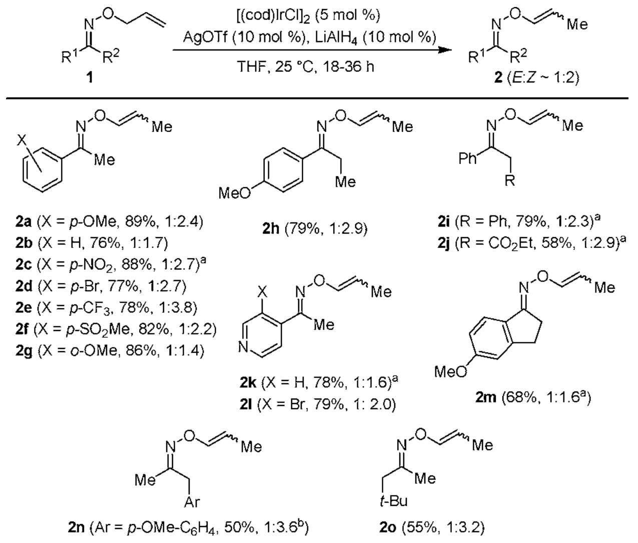
(10) For examples of allylic ether isomerizations see: (a) Tanaka, K. *Compr. Organomet. Chem. III* **2007**, *10*, 71. (b) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224. (c) Boons, G.-J.; Isles, S. *J. Org. Chem.* **1996**, *61*, 4262.

(11) See the Supporting Information for full characterization of the *O-n*-propyl oxime reduction product.

was observed when the reaction was run in toluene and only starting material was observed when the reaction was run in $CH_2Cl_2$. On the basis of these results, the optimal catalytic conditions for substrate screening were determined to be 5 mol % $[(cod)IrCl]_2$, 10 mol % $NaBH_4$ or $LiAlH_4$, and 10 mol % AgOTf in THF.

A variety of *O*-vinyl oxime ethers[12] were synthesized in good yield from the corresponding *O*-allyl oxime ethers, using the isomerization conditions determined in Table 1 (Scheme 2). The predominantly *E*-*O*-allyl oxime substrates used for these reactions were selected to illustrate the functional group tolerance of the isomerization and were prepared by simple allyl hydroxylamine condensations with the corresponding ketones.[13] Both electron-poor and electron-rich aryl oximes, as well as pyridyl-substituted substrates, were tolerated under the isomerization conditions. Alkyl, aryl, and ester functional groups were also allowed at the enolizable position of the allyl oximes. The preference for $NaBH_4$ or $LiAlH_4$ as a reducing agent was related to functional group compatibility. The *O*-vinyl oxime products of the isomerizations were isolated with vinyl *E*:*Z* ratios of approximately 1:2 and favored a cis-relationship between the *O*-substituent and the enolizable carbon atom.[14] Overall, the results in Scheme 2 show that the iridium-catalyzed alkene isomerization is a mild, general, and efficient method for the synthesis of *O*-vinyl oximes that uses simple starting materials and provides a facile entry into the study of *O*-vinyl oximes as precursors to pyrroles.

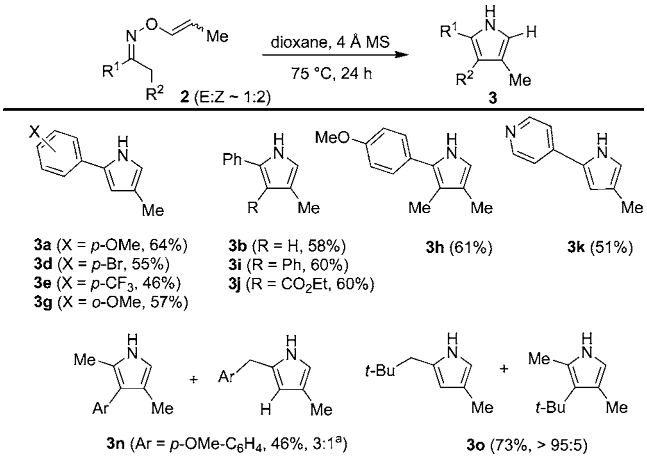
**Scheme 2.** Isomerization of *O*-Allyl Oximes to *O*-Vinyl Oximes



[a] $NaBH_4$ was used instead of $LiAlH_4$. [b] DIBAL-H was used instead of $LiAlH_4$.

Several *O*-vinyl oximes prepared in Scheme 2 were tested as precursors to 1,4-imino aldehyde Paal−Knorr intermediates and pyrroles.[15] As shown in Scheme 3, conversion of *O*-vinyl oximes to 2,4- and 2,3,4-substituted pyrroles was achieved by mild heating in the presence of molecular sieves.[16] The pyrroles were isolated in good yield after the three-step sequence involving [3,3] rearrangement, cyclization, and dehydration.[17] Pyrrole formation was sensitive to solvent choice and substrate concentration: a 0.4 M dioxane solution afforded optimal yields. Electron-donating substitutents on the aryl ring of the acetophenone-derived oximes favored pyrrole formation (**3a** vs **3e**) but substitution at the α-carbon had little effect on the efficiency of the transformation (**3h**, **3i**, and **3j**). For substrates derived from dialkyl ketones, the pyrrole synthesis favored enamine formation at the more enolizable α-carbon atom for **2n** and the most sterically accessible position for **2o**. The transformation of *O*-vinyl oximes to pyrroles was monitored by $^1H$ and $^{13}C$

**Scheme 3.** Conversion of *O*-Vinyl Oximes to Pyrroles



[a] Regioselectivity ratio.

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(12) (a) For the base-mediated synthesis of benzophenone-derived *O*-vinyl oximes from alkynes see: Zaitsev, A. B.; Vasil'tsov, A. M.; Schmidt, E. Y.; Mikhaleva, A. I.; Morozova, L. V.; Afonin, A. V.; Ushakov, I. A.; Trofimov, B. A. *Tetrahedron* **2002**, *58*, 10043. (b) For the base-mediated synthesis of *O*-vinyl oximes with enolizable oximes, see: Trofimov, B. A.; Mikhaleva, A. I.; Vasil'tsov, A. M.; Schmidt, E. Y.; Tarasova, O. A.; Morozova, L. V.; Sobenina, L. N.; Preiss, T.; Henkelmann, J. *Synthesis* **2000**, 1125.

(13) *O*-allyl oxime **1m** was synthesized by a substitution reaction between the corresponding oxime and allyl bromide.

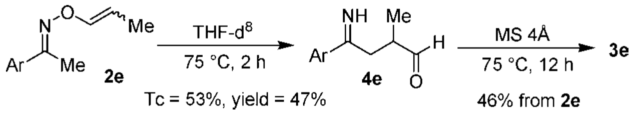
(14) Oxime and vinyl isomers were identified by $^1H-^1H$ nOe experiments. The minor *Z*-*O*-allyl oxime isomer of the starting material was not observed as unreacted starting material; therefore, it is likely that isomerization to the *E*-oxime isomer occurs with isomerization of the allyl group to the vinyl group.

(15) For examples of cascade processes involving the Stetter reaction or oxidative enolate coupling with the Paal−Knorr reaction, see: (a) Szakal-Quin, G.; Graham, D. G.; Millington, D. S.; Maltby, D. A.; McPhail, A. T. *J. Org. Chem.* **1986**, *51*, 621. (b) Lee, C. K.; Lee, I.-S. H.; Noland, W. E. *Heterocycles* **2007**, *71*, 419. (c) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465. (d) Braun, R. U.; Müller, T. J. J. *Synthesis* **2004**, *14*, 2391. (e) Periasamy, M.; Srinivas, G.; Seenivasaperumal, M. *J. Chem. Res.* **2004**, 270.

(16) *E*:*Z* mixtures of the *O*-vinyl oximes were used for the synthesis of pyrroles.

(17) Less than 5% of **2** and the corresponding ketone were isolated with the pyrrole products. The remainder of the starting material is most likely converted into a highly colored polymeric material that remains physisorbed to silica gel.

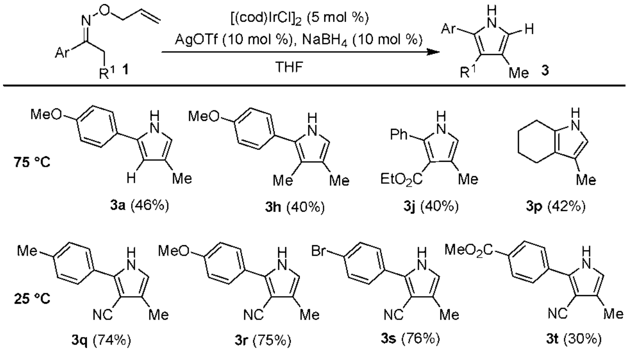
**Scheme 4.** Observation of Paal−Knorr Intermediate by $^{1}$H and $^{13}$C NMR Spectroscopy



NMR spectroscopy to observe the 1,4-imino carbonyl intermediate: the [3,3] rearrangement of **2e** occurs between 2 and 4 h at 75 °C (Scheme 4) to give imino aldehyde **4e**. The subsequent cyclization and condensation that are necessary to form **3e** requires an additional 10−12 h of heating in the presence of molecular sieves.

A one-flask procedure for the conversion of *O*-allyl oximes to pyrroles was tested for comparison to the two-step procedure. *O*-Allyl oximes **1a**, **1h**, and **1j** were subjected to isomerization reaction conditions for 12 h and then heated to 75 °C for 24 h (Scheme 5). The isolated yields from these transformations corresponded to the sum of the yields from the two-step procedure. No deleterious effect was observed due to the presence of the iridium catalyst during pyrrole formation. The one-flask procedure also allowed for an extension of the method to include substrates such as **1p**, which were slow to isomerize at 25 °C.

**Scheme 5.** Conversion of *O*-Allyl Oximes to Pyrroles



Although a clear electronic trend for pyrrole formation was not established in Scheme 3, cyano-substitution at the enolizable α-carbon of *O*-vinyl oximes was shown to dramatically favor the [3,3] rearrangement and subsequent Paal−Knorr reaction. When subjected to the iridium-catalyzed isomerization conditions at 25 °C, cyano-substituted *O*-allyl oxime substrate **1q** gave the corresponding pyrrole in a one-flask procedure in 74% yield (Scheme 5). Further investigation showed that this reactivity was consistent for several cyano-substituted acetophenones and that electron-donating groups on the aryl ring facilitated the reaction. These results suggest that pyrrole formation is particularly facile for these substrates.

In summary, we have shown that *O*-vinyl oximes can be synthesized from *O*-allyl oximes by an iridium-catalyzed isomerization reaction and that *O*-vinyl oximes can be thermally converted to pyrroles. Cyano-substituted *O*-allyl oximes have also been identified as substrates that are particularly amenable to this reaction sequence and can be directly converted to the corresponding pyrroles at 25 °C. This new isomerization reaction provides reliable and reproducible access to a variety of *O*-vinyl oximes as well as facile entry into subsequent [3,3] rearrangements and use in the preparation of 2,4- and 2,3,4-substituted pyrroles in a two- or three-step procedure from commericially available starting materials. Future work will concentrate on expanding the scope and controlling selectivity of the isomerization reaction and pyrrole synthesis. Isolation and study of the reaction intermediates will also be targeted to explore the breadth of the transformation.

**Acknowledgment.** We would like to thank Profs. T. G. Driver (UIC) and D. J. Wardrop (UIC) for insightful discussions and chemicals. We would also like to thank Mr. Furong Sun (UIUC) for mass spectrometry data and the University of Illinois at Chicago for funding.

**Supporting Information Available:** Experimental procedures, expanded optimization tables, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100659Q