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Novel Intramolecular Reactivity of Oximes: Synthesis of Cyclic and Spiro-Fused Imines

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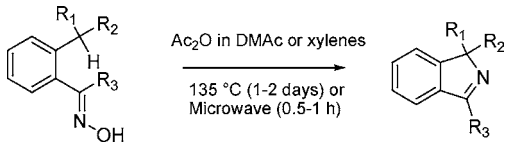
ABSTRACT



Under conventional heat (135–145 °C) or microwave irradiation and 1 equiv of acetic anhydride, ortho-substituted aryl-oximes undergo a novel sp^3 C–H activated cyclization to produce the corresponding isoindoles, and aliphatic oximes afford the corresponding dihydropyrroles. The cyclization occurs with various substrates in good yield (46–82%) leading to unique spiro-fused and cyclic imines. An initial mechanistic investigation suggests the reaction occurs via a nitrenium or vinyl nitrene intermediate.

Oximes are useful functional groups which can be easily prepared from the corresponding ketones.[1] They are known to undergo a number of transformations including Beckmann rearrangement to afford the corresponding amides,[2] Neber rearrangement to afford amino ketones,[3] reductions to the corresponding amine,[4] reductive coupling with a carbonyl moiety to provide amino alcohols, and enamide formation.[5] In addition, Narasaka and co-workers recently described the palladium- and copper-catalyzed cyclization of olefinic oxime derivatives to the corresponding dihydropyrroles.[6] We were recently interested in taking advantage of the reaction of oximes in the presence of acetic acid, acetic anhydride, and iron to afford the corresponding enamides.[7] Specifically, we required the preparation of acyl enamides from aryl-oximes having an aliphatic ortho substituent. As we started to investigate this transformation, we discovered the formation of a novel byproduct, a spiro-fused imine in which the nitrogen had formally inserted into the sp^3 C−H bond of the ortho aliphatic substituent (Scheme 1). Given the novelty of this transformation, we pursued a more detailed study of this reaction and have now developed a procedure which provides the C−H insertion product with good yield and selectivity. In this communication, we wish to report our results regarding this intriguing cyclization, including its

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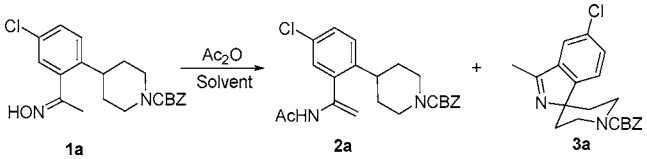
Scheme 1

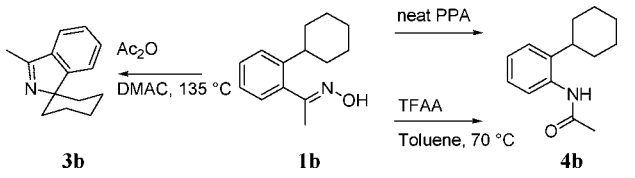


scope and limitations, as well as preliminary mechanistic insights of this novel reaction.

As we were exploring the reactivity of oxime **1a**, we initially observed that treating this compound with acetic anhydride, iron, and acetic acid at 70 °C for 17 h provided two main products: the expected enamide **2a** and a new cyclized product **3a**. In the presence of iron, varying AcOH and Ac_2O gave different ratios of enamide **2a** to spiro-imine **3a**. In the absence of iron, 40% of the desired spiro-imine was isolated with a 4:1 ratio of spiro to enamide while reacting the oxime in neat Ac_2O/pyridine.[7a] However, when the reaction was carried out with 3 equiv of acetic anhydride in refluxing toluene, only the acetate oxime was detected. In refluxing xylenes (135 °C), the cyclization proceeded in 58% assay yield and no enamide or Beckmann products were observed. Moreover, no cyclization occurred when the oxime was heated without additives at 135 °C. These experiments demonstrate that both acetic anhydride and high temperatures are necessary for this cyclization to occur.

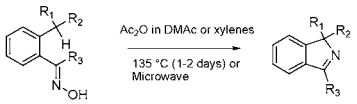
A survey of the relevant literature revealed a single example by Lansbury and co-workers[8] who reported that 7-alkyl-1-indanone oximes undergo C−H bond insertion when treated with polyphosphoric acid at 130 °C.[9] The authors speculated that a very strained system prevented the Beckmann rearrangement from occurring which led to the observed product via an alternate pathway. Interestingly, subjecting compound **1a** under these conditions provided only the Beckmann product (Scheme 2). In addition, the use

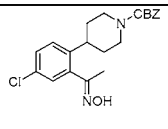
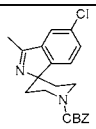
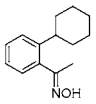
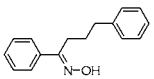
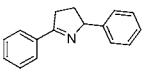
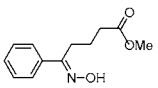
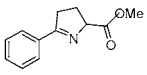
Scheme 2



of trifluoroacetic anhydride in toluene at 70 °C also only led to the Beckmann product. However, treating oxime **1b** with 1 equiv of Ac_2O cleanly afforded the spiro-imine. This reaction constitutes an interesting complement to the known metal-catalyzed C−H amination reactions.[10]

Table 1. Cyclization of Oximes



entry	cyclization	yield (%)
1	 **1a**  **3a**	82 (19h)[a] 78 (30 min)[b]
2	 **1b**  **3b**	78 (27 h)[a]
3	 **1c**  **3c**	68 (30 min)[b]
4	 **1d**  **3d**	0[a, b]
5	 **1e**  **3e**	62 (17min)[b]
6	 **1f**  **3f**	61 (17 min)[b]

[a] Conventional heat at 135 °C. [b] Microwave at 240 °C.

The optimization of the reaction conditions with oxime **1a** was undertaken as well as investigation of the scope and limitations. Various high-boiling solvents (dimethylacetamide (DMAC), xylenes, dichlorobenzene) worked equally well with no observable rate difference. We then examined the effect of the activating anhydrides in the best two solvents. Although yields were moderate, the reaction was promoted with phthalic, benzoic, and succinic anhydrides. Acetic anhydride in DMAC or xylene was the most efficient protocol.

A full equivalent of acetic anhydride is needed for the reaction to proceed to completion: 0.5 equiv only afforded

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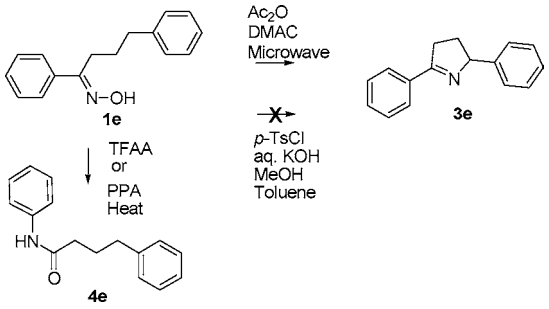
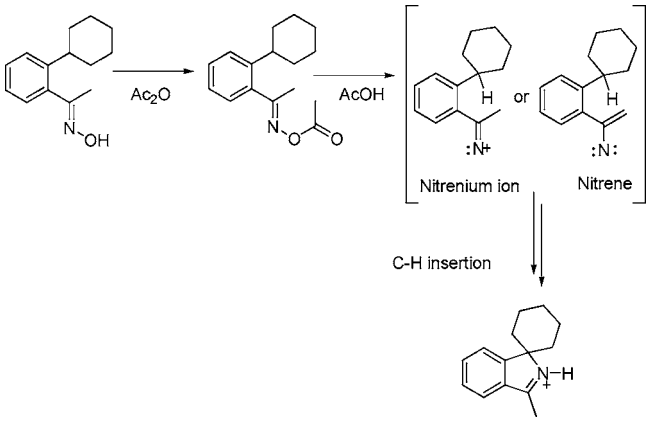
(9) Mittel and co-workers failed in trying to carry out such a cyclization in refluxing acetic and sulfuric acid: Mittell, I. *Ber.* **1931**, *64B*, 71.

(10) (a) For a review: Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518 and references herein. (b) Wehn, P. M.; Du Bois, J. *Org. Lett.* **2005**, *7* (21), 4685. (c) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126* (47), 15378. (d) Fiori, K. W.; Fleming, J. J.; Du Bois, J. *Angew. Chem., Int. Ed.* **2004**, *43* (33), 4349.

Scheme 3



Scheme 4



32% yield of product. We also observed that as the number of equivalents of acetic anhydride was increased beyond 2.0 the yield decreased.[11]

A screen of bases (pyridine, potassium carbonate, Hunig's base, KO-*t*-Bu, imidazole, DBU) and acids (acetic acid and camphorsulfonic acid) at temperatures between 70 and 135 °C did not lead to improved reaction conditions. High temperatures were still required for the reaction to proceed as well as long reaction time.

The cyclization was studied under microwave conditions using the same solvent and amount of acetic anhydride. This modification allowed for a more concentrated media (1 mmol in 3 mL). Under microwave irradiation (240 °C), the cyclization was complete in 30 min with a clean reaction profile and good yield (78%). Therefore, the cyclized product can be obtained in 1−2 days by thermal treatment or in 0.5 h using microwaves.

With the optimized protocol, the scope of the reaction was studied by cyclizing various oximes. These oximes are readily obtained from their corresponding ketone using known protocols (Table 1).[1] Oximes **1a**−**c** with a cyclohexyl or a cyclopentyl group in ortho positions were cyclized in efficient yields. However, no desired product was isolated in the case of the trifluorooxime **1d**.[12]

Of interest, aliphatic oximes **1e** and **1f** efficiently cyclized to the corresponding dihydropyrrole. For substrate **1e**, no enamide or Beckmann rearrangement products were observed while reacting the substrate with 1 equiv of Ac_2O. However, when **1e** was submitted to TFAA or neat PPA, only formation of the Beckmann product was observed with no trace of dihydropyrrole (Scheme 3).

One of the possible mechanisms for this cyclization could involve a radical pathway. However, radical promoters such as samarium diiodide, AIBN, and triethylborane did not provide the desired cyclized product. Moreover, the use of a BHT additive in the cyclization did not affect the yield of cyclization.

The O-acylated oxime intermediate was detected by HPLC/MS and by NMR, and it was also possible to isolate this product after treatment with Ac_2O. When this isolated oxime-acetate was heated alone or in the presence of acetic anhydride, no cyclized product was observed. However, when the oxime-acetate was heated in the presence of acetic acid, the spiro compound was observed. From these experiments, we concluded that the oxime-acetate is an intermediate on the reaction pathway and acetic acid generated from the acetate formation was essential to the cyclization. Moreover, the enamide was not an intermediate on the reaction pathway: no cyclized product was generated when the enamide was treated with acetic anhydride and acetic acid.

A possible mechanism could involve the formation of a nitrenium ion or a vinyl nitrene,[13] which then inserts into the proximal C−H bond (Scheme 4).

In summary, a novel reactivity of oximes was uncovered and investigated. With 1 equiv of acetic anhydride at 135 °C or under microwave irradiation, ortho-substituted aryl-oximes undergo a novel sp^3 C−H activated cyclization to produce the corresponding isoindoles in good yields. Moreover, the obtained products are highly attractive building blocks. The proposed mechanism involves C−H insertion of the nitrenium ion derived from the oxime-acetate intermediate. Further work to better understand the course of the reaction as well as the use as key intermediates for the synthesis of biologically active compounds is presently underway.

Acknowledgment. We thank Vicky Vydra and Thomas Novak from Merck Research Laboratories for their help performing the high-resolution mass spectrometry analysis and X-ray analysis.

Supporting Information Available: Experimental details and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The formation of two other side products was also observed. Treating pure isolated spiro with acetic anhydride at 135 °C also led to these side products which were identified as the acylated products of the spiro, which gives further option to functionalize the spiro imine.

(12) In the case of the formation of unsubstituted isoindole (using, for instance, ethanone, 1-(2-methylphenyl), or oxime), only oxidized products were obtained. The desired products are reported to be relatively unstable and easily oxidized. Veber, D. F.; Lwowski, W. *J. Am. Chem. Soc.* **1964**, *86*, 4152.

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