

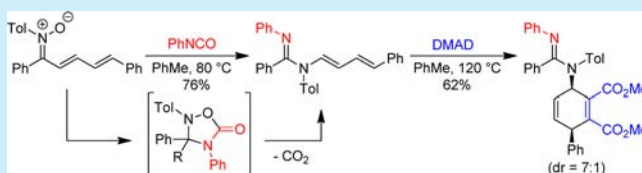
# Synthesis of *N*-Styrenyl Amidines from $\alpha,\beta$ -Unsaturated Nitrones and Isocyanates through CO<sub>2</sub> Elimination and Styrenyl Migration

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**S** Supporting Information

**ABSTRACT:** A mild, metal-free, and modular route for the preparation of *N*-styrenyl amidines from *N*-aryl- $\alpha,\beta$ -unsaturated nitrones and isocyanates has been developed that accesses an initial oxadiazolidinone intermediate that can undergo CO<sub>2</sub> elimination and styrenyl migration. The use of a migration event to install *N*-styrenyl amidine substituents circumvents a limitation of traditional Pinner-type methods for amidine synthesis that require the use of amine nucleophiles. The modularity of the nitron and isocyanate reagents provides access to a variety of differentially substituted *N*-styrenyl amidines. The scope and tolerance of the method are presented, and preliminary mechanistic data for the transformation are discussed.

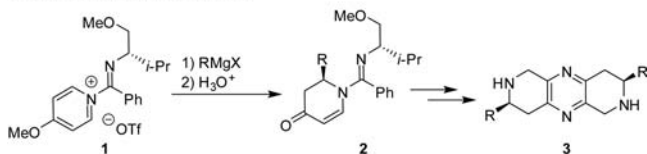


Amidines are important functional groups that are present in a variety of biologically active molecules and are commonly used as precursors to heterocyclic compounds.<sup>1–3</sup> Amidines are traditionally prepared by transformations related to the Pinner reaction that involve the addition of an amine to an activated nitrile or imidate moiety.<sup>4,5</sup> Due to the requirement of an amine nucleophile, these strategies make *N*-alkenyl amidines challenging to prepare; however, access to *N*-alkenyl amidines is synthetically appealing due to their potential for further functionalization. For example, Charette and co-workers previously showed that amidine **2** could be generated from pyridinium **1** through a Grignard addition (Scheme 1a).<sup>6</sup> This vinylogous amide functionality allowed for

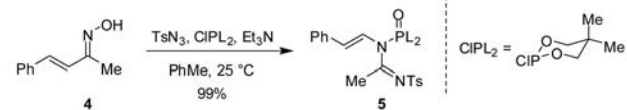
further synthetic manipulation of amidine **2** to result in the synthesis of barrenazine alkaloids **3**. Recently, Ashfeld and co-workers discovered a novel Staudinger ligation and Beckmann rearrangement cascade process for the synthesis of phosphoramidic acid ester-substituted amidines, which can be used to access *N*-alkenyl amidines such as **5** through a Beckman-like migration event.<sup>7</sup> As part of our program aimed at exploiting the reactivity of  $\alpha,\beta$ -unsaturated-*N*-aryl nitrones, we have discovered that *N*-styrenyl amidines **9** can be generated from nitron **6** via an oxadiazolidinone intermediate **8** that undergoes CO<sub>2</sub> elimination and styrenyl migration.<sup>8</sup> This transformation can be used to synthesize a variety of *N*-aryl-*N*-styrenyl amidines with a range of *N'*-substitution patterns due to the modularity of the nitron and isocyanate reagents. Herein we discuss the scope and tolerance of this new method for the rapid generation of *N*-styrenyl amidines from simple reagents under mild and metal-free conditions.

## Scheme 1. Synthesis of *N*-Alkenyl Amidines

a) Charette and coworkers, 2006



b) Ashfeld and coworkers, 2013



c) This work

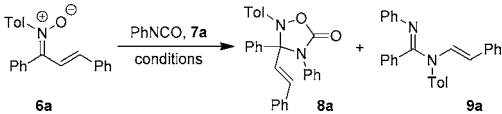


The synthesis of oxadiazolidinone **8a** was initially observed upon treatment of nitron **6a** with isocyanate **7a** at 80 °C in THF (Table 1, entry 1).<sup>9</sup> Surprisingly, when the same reagents were mixed in toluene and heated to 80 °C, amidine **9a** was isolated as the sole product in 90% yield (Table 1, entry 2).<sup>10</sup> Further screening of solvents showed that DCE also favored the exclusive formation of **9a** in slightly attenuated yield and mixtures of **8a** and **9a** could be isolated from reactions run in MeCN or DMSO (Table 1, entries 3–5). Increased reaction times in MeCN or DMSO led to the exclusive formation of **9a**.<sup>11</sup> Variation of reaction temperature affected both the chemoselectivity and efficiency of the process. While only **9a** was observed for reactions run in toluene from 60–100 °C, mixtures of **8a** and **9a** were observed at lower temperatures (Table 1, entries 2 and 6–9). The yield for the amidine

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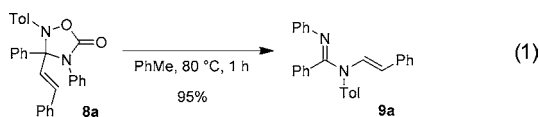
Table 1. Optimization of Amidine Synthesis



entry	solvent	<i>t</i> (°C)	yield (%) <sup>a</sup>	8a/9a <sup>a</sup>
1	THF	80	80	only 8a
2	PhMe	80	90	only 9a
3	DCE	80	83	only 9a
4	MeCN	80	81 <sup>b</sup>	3:1 <sup>b</sup>
5	DMSO	80	40 <sup>c</sup>	3:1 <sup>c</sup>
6	PhMe	100	77	only 9a
7	PhMe	60	88	only 9a
8	PhMe	40	74	1:2
9	PhMe	25	49	1:2

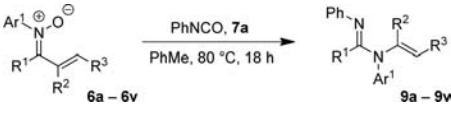
<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy using CH<sub>2</sub>Br<sub>2</sub> as a reference: 6a (1 equiv), 7a (2 equiv), 0.1 M, 18 h. <sup>b</sup>36 h, 75%, only 9a. <sup>c</sup>36 h, 59%, only 9a.

synthesis was optimal for reaction temperatures between 60 and 80 °C but decreased at both higher and lower temperatures. When oxadiazolidinone 8a was dissolved in toluene and heated to 80 °C, amidine 9a was isolated in almost quantitative yield (eq 1). This experiment correlated with the longer reaction time results determined for MeCN and DMSO, as well as the reaction temperature data for toluene, and suggested that 8a is an intermediate along the pathway for conversion of 6a to 9a. With optimal conditions for the preparation of *N*-styrenyl amidine 9a in hand, the scope of the method was further examined.



The synthesis of *N*-styrenyl amidines 9 from *N*-aryl- $\alpha,\beta$ -unsaturated nitrones 6 and phenylisocyanate 7a was shown to tolerate a variety of different substitution patterns on the nitron component of the reaction mixture.<sup>12,13</sup> As shown in Table 1, nitrones with both electron-rich and electron-deficient aryl groups at the R<sup>3</sup>-position gave the corresponding amidines in high yield (Table 2, entries 1–7). Tolerance for functionalizable groups such as nitro and halogen substituents, as well as substitution at the 2-, 3-, and 4-positions of the arene, broadened the synthetic applicability of the method. In addition to arenes, furanyl and styrenyl groups were also tolerated at the R<sup>3</sup>-position and were smoothly converted to the corresponding *N*-(2-vinylfuran) and *N*-dienyl amidines 9h and 9i, respectively (Table 2, entries 8–9). Arene substitution at the R<sup>1</sup>-position was shown to be more sensitive to electronic effects than the R<sup>3</sup>-position. *p*-Tolyl substituted nitron 6j gave amidine 9j in an attenuated yield, while *p*-CF<sub>3</sub>-substituted 6k proceeded smoothly to give 9k (Table 2, entries 10–11). When a *p*-OMe-substituted arene was tested at the R<sup>1</sup>-position only a trace amount of product was observed.<sup>14</sup> In contrast to these limitations, H, Me, and styrenyl groups were well-tolerated at the R<sup>1</sup>-position and gave amidines 9l–9n in good yields (Table 2, entries 12–14). The R<sup>2</sup>-position of the nitron can be substituted with a methyl group as illustrated for 9o and indicated that the scope of the amidine synthesis also includes  $\beta$ -substituted styrenyl groups (Table 2, entry 15). In addition to

Table 2. Scope of Nitron Reagent for Amidine Synthesis

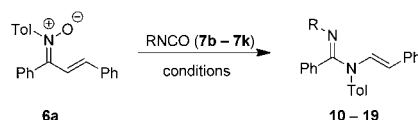


entry	9	yield (%) <sup>a</sup>	entry	9	yield (%) <sup>a</sup>
1		91	12		82
2		77	13		80
3		92	14		82
4		87	15		79
5		83	16		88
6		89	17		83
7		77	18		75
8		84	19		73
9		76	20		75
10		51	21		78
11		73	22		80

<sup>a</sup>% Isolated yield. Conditions: 6 (1 equiv), isocyanate 7a (2 equiv), 0.1 M in PhMe, 80 °C, 18 h.

changing the substituents on the carbon chain of the nitron, the *N*-aryl substituents were also varied. This functionality tolerated halogen, 3-OMe, 3,5-Me<sub>2</sub>, vinyl, and naphthyl substitution patterns all in good yield (Table 2, entries 16–22).<sup>15</sup> The results described in Table 2 showcase the generality of the method for the synthesis of a range of *N*-styrenyl amidines from a variety of  $\alpha,\beta$ -unsaturated nitrones.

**Table 3. Scope of Isocyanate Reagent for Amidine Synthesis**



entry	R	conditions <sup>a</sup>	no.	yield (%) <sup>b</sup>
1	7b, <i>p</i> -OMe(C <sub>6</sub> H <sub>4</sub> )	A	10	51
2	7c, <i>p</i> -CF <sub>3</sub> (C <sub>6</sub> H <sub>4</sub> )	A	11	45
3	7d, <i>p</i> -I(C <sub>6</sub> H <sub>4</sub> )	A	12	75
4	7e, <i>p</i> -F(C <sub>6</sub> H <sub>4</sub> )	A	13	72
5	7f, 1-naphthyl	A	14	83
6	7g, 2-Br(C <sub>6</sub> H <sub>4</sub> )	A	15	66
7	7h, <i>p</i> -Cl(C <sub>6</sub> H <sub>4</sub> )SO <sub>2</sub>	A	16	61
8	7i, Fmoc	B	17	64
9	7j, Bn	C	18	75
10	7k, allyl	C	19	84

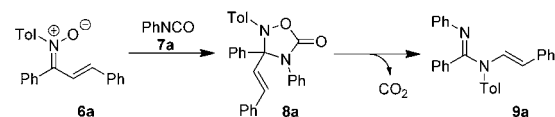
<sup>a</sup>Conditions A: **6a** (1 equiv), **7b–7g**, **7i** (2–4 equiv), 0.1 M in PhMe, 80 °C, 18 h. Conditions B: **6a** (1 equiv), **7h** (4 equiv), 0.1 M in DCE, 80 °C, 18 h. Conditions C: **6a** (1 equiv), **7j–7k** (4 equiv), 0.1 M in PhMe, 80 °C, 18 h, then AlCl<sub>3</sub> (10 mol %), 25 °C, 4–18 h. <sup>b</sup>% Isolated yield.

In addition to exploring the scope of the nitron component of the amidine synthesis, the tolerance for the isocyanate reagent was also investigated. As shown in Table 3, several aryl isocyanates smoothly underwent the addition and rearrangement with **6a** to give *N*-styrenyl amidines **10–15** (Table 3, entries 1–6). These transformations were more efficient for halogen-substituted aryl and naphthyl isocyanates **7d–7f** than 4-OMe- and 4-CF<sub>3</sub>-substituted aryl isocyanate reagents **7b–7c**. To our delight, the scope of the amidine synthesis included not only aryl isocyanates but also sulfonyl-, carbamate-, and alkyl-substituted reagents (Table 3, entries 7–10). While sulfonyl-isocyanate **7h** underwent the amidine synthesis when subjected to standard reaction conditions, improved yields were observed for Fmoc isocyanate **7i** when the transformation was run in DCE. Benzyl and allyl isocyanate reagents required the addition of 10 mol % AlCl<sub>3</sub> to facilitate CO<sub>2</sub> elimination and styrenyl migration from the corresponding oxadiazolidinones. Addition of this Lewis acid rapidly provided the desired products **18** and **19** in good yield. Having determined the generality of the method for the preparation of *N*-styrenyl amidines, we next examined the mechanism of the transformation.

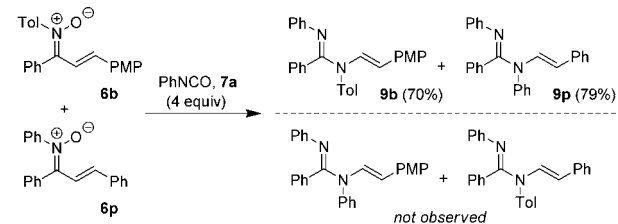
A proposed mechanism for the synthesis of *N*-styrenyl amidine **9a** from *N*-aryl nitron **6a** is illustrated in Scheme 2. The addition of nitron **6a** to isocyanate **7a** gives heterocycle **8a**, which can then undergo a subsequent CO<sub>2</sub> elimination and styrenyl migration to give **9a**. The intermediacy of oxadiazolidinone **8a** in the synthesis of **9a** is supported by the independent conversion of **8a** to **9a** as illustrated in eq 1. In order to gain a better understanding of the CO<sub>2</sub> elimination and styrenyl group migration steps, we decided to test two other product-based mechanistic experiments. As shown in Scheme 2b, no crossover products were observed when the

## Scheme 2. Proposed Mechanism and Mechanistic Experiments

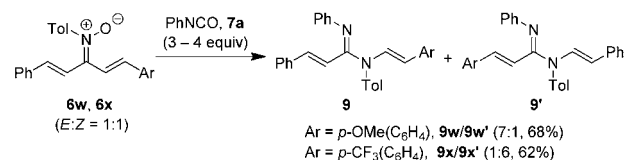
### a) Proposed Mechanism



### b) Crossover Experiment



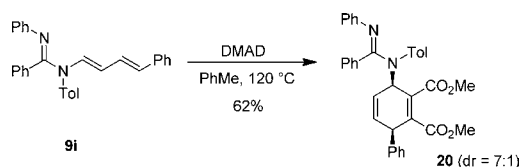
### c) Competition Experiment



addition and rearrangement of **6b** with **7a** was run in the presence of **6p**. This experiment suggests that solvent-separated intermediates are not involved in the CO<sub>2</sub> elimination and migration process. A competition experiment was also designed to probe whether the geometry of the nitron or the electronic nature of the styrenyl group affected the migratory aptitude of the substrate. As shown in Scheme 2c, a distinct electronic effect was observed when dibenzylidene acetone derived nitrones **6w** and **6x** were treated with **7a**. The *p*-OMe-substituted styrenyl group of **6w** migrated in preference to the unsubstituted styrenyl group, while the unsubstituted styrenyl group of **6x** migrated in preference to the *p*-CF<sub>3</sub>-substituted styrenyl group. These results indicate that the reactive intermediate that precedes the migration must exhibit electrophilic character at the *N*-atom derived from the nitron and that the styrenyl group migrates as a nucleophilic species. Since both **6w** and **6x** were subjected to the reaction conditions as 1:1 mixtures of *E/Z* isomers, these results further suggest that the geometry of the nitron does not affect the migratory preference of the nitron substituents. This result is in contrast to the Beckman-type rearrangement, observed by Ashfeld and co-workers for the synthesis of *N*-phosphoramidate-substituted amidines from oximes, sulfonyl azides, and chlorophosphites.<sup>7</sup>

To test the synthetic utility of the enamine functionality of the *N*-alkenyl amidines, we decided to use dienyl amidine **9i** as a cycloaddition substrate. As shown in Scheme 3, this compound smoothly undergoes a [4 + 2] cycloaddition reaction with dimethylacetylene dicarboxylate (DMAD) to give the cycloadduct **20**. This experiment illustrates the use of

## Scheme 3. Functionalization of *N*-Dienyl Amidine **9i**



the amidine synthesis described above as a simple method for accessing functionalizable amidines that can be easily converted to more complicated compounds through the reactivity of the enamine functionality. The fact that compound **20** is structurally similar to cyclohexene nucleoside analogues suggests that these transformations may be applicable to a variety of medicinal targets.<sup>16</sup>

In summary, we have discovered a new method for the synthesis of *N*-styrenyl amidines by the addition of  $\alpha,\beta$ -unsaturated nitrones to isocyanates. This transformation provides a new route to *N*-alkenyl amidines which are challenging to access by traditional methods for amidine synthesis. Preliminary mechanistic studies suggest that this transformation proceeds through an initial cycloaddition of a nitrone to an isocyanate to form an oxadiazolidinone followed by a subsequent CO<sub>2</sub> elimination and styrenyl migration. Ongoing studies in our lab are aimed at expanding the scope of the migratory alkenyl group through a better understanding of the mechanism for CO<sub>2</sub> elimination and migration, as well as developing synthetic applications that exploit *N*-styrenyl amidines as synthetic intermediates.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(10) Structural assignment of **9a** was verified by X-ray crystallography: CCDC 1004695.

(11) When the transformation was run in THF for 36 h, only **8a** was observed. The THF did not contain an inhibitor.

(12) Nitrones **6a–6m** and **6o–6v** were prepared as a >95:5 mixture of *E/Z* isomers and separated by chromatography to give only the *E*-isomer. See ref 8b and the Supporting Information for details. Nitrone **6n** was prepared as a 4:1 mixture of *E/Z* isomers as described in: Hood, T. S.; Huels, C. B.; Yang, J. *Tetrahedron Lett.* **2012**, *53*, 4679.

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(14) No starting material was recovered, no evidence of aryl migration was observed, and only decomposition products were isolated.

(15) *N*-Aryl- $\alpha,\beta$ -unsaturated nitrones with *ortho*-substitution on the *N*-aryl substituent were not tolerated by our Cu-mediated nitrone synthesis (see ref 12) and are not accessible by other methods.

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