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Synthesis of 1,4-Enamino Ketones by [3,3]-Rearrangements of Dialkenylhydroxylamines

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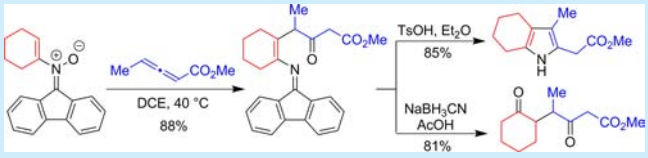
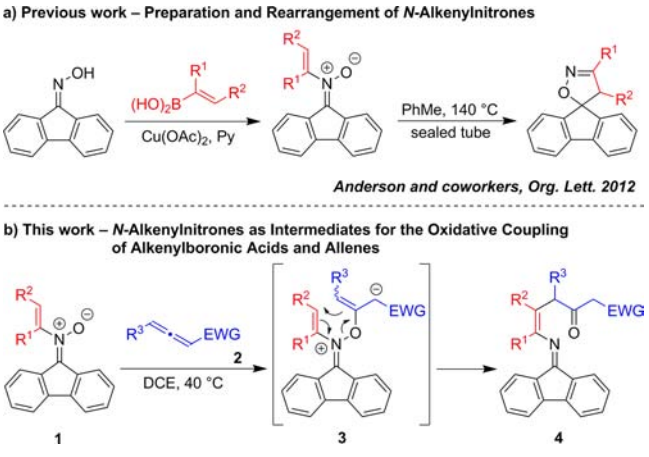
Supporting Information

ABSTRACT: The synthesis of 1,4-enamino ketones has been achieved through the [3,3]-rearrangement of dialkenylhydroxylamines generated from the addition of *N*-alkenylnitrones to electron-deficient allenes. The mild conditions required for this reaction, and the simultaneous installation of a fluorenyl imine *N*-protecting group as a consequence of the rearrangement, avoid spontaneous cyclization of the 1,4-enamino ketones to form the corresponding pyrroles and allow for the isolation and controlled divergent functionalization of these reactive intermediates. The optimization, scope, and tolerance of the new method are discussed with demonstrations of the utility of the products for the synthesis of pyrroles, 1,4-diones, and furans.



[3,3]-Rearrangements of dialkenylhydrazines and dialkenylhydroxylamines are important transformations that are employed as the key C−C bond forming steps in the Piloty−Robinson and Trofimov pyrrole syntheses.[1−3] Unfortunately, the conditions required to generate these intermediates and to achieve these transformations limit their scope and generality.[4−6] We surmised that dialkenylhydroxylamines could alternatively be accessed through the addition of an *N*-alkenylnitrone to an allene.[7,8] This route could then be used to circumvent limitations of the pyrrole syntheses mentioned above as well as provide access to isolable [3,3]-rearrangement products for divergent functionalization prior to heterocycle formation. Our recent discovery that *N*-alkenyl fluorenone oximes can be prepared by a copper-mediated C−N bond-forming reaction between fluorenone oxime and alkenyl boronic acids facilitated our study (Scheme 1a).[9] Herein, we describe the generation of dialkenylhydroxylamines **3** by the addition of *N*-alkenylnitrones **1** to activated allenes **2** and a subsequent spontaneous [3,3]-rearrangement to give 1,4-enamino ketones **4** (Scheme 1b). Isolation of these compounds with a fluorenone imine protecting group, installed as a consequence of the [3,3]-rearrangement, provided the opportunity for their straightforward conversion to tetrasubstituted pyrroles, 1,4-diones, and tetrasubstituted furans. Considered in sequence with our reported *N*-alkenylnitrone synthesis, this two-step procedure can be described as an oxime-mediated oxidative coupling of alkenyl boronic acids and allenes to form 1,4-diones and 1,4-dione derivatives.

Scheme 1. [3,3]-Rearrangement of Dialkenylhydroxylamines Generated from *N*-Alkenylnitrones



The synthesis of 1,4-enamino ketone **4a** was initially observed when *N*-cyclohexenylnitrone **1a** was treated with allenoate **2a** in toluene at 40 °C. A solvent screen showed that the preparation of **4a** was most efficient in 1,2-dichloroethane (DCE) but also occurred in dioxane, acetonitrile, DMF, and *t*-BuOH (Table 1, entries 1−6). Decomposition of the reaction mixture was observed at higher temperatures, but isolation of **4a** was possible in attenuated yields when the reaction was run at 25 °C (Table 1, entries 7−9). In addition to solvent and temperature, several acidic and basic additives were also tested to determine their effect on the synthesis of **4a**, but none improved the yield of the desired product.[10] The conditions described in Table 1, entry 5, were determined to be optimal conditions for the synthesis of **4a** and were used for further exploration of the scope of the method.[11]

Several *N*-alkenylnitrones were tested under the optimized reaction conditions to determine the scope of the transformation (Table 2). Cycloalkenylnitrone substituents were discovered to be particularly amenable to the preparation of imine-protected 1,4-enamino ketones **4**, and cyclohexenyl, cycloheptenyl, and cyclooctenyl groups were well-tolerated by the transformation (Table 2, entries 1−3). *N*-Cyclopentenylnitrones were also efficient substrates, but enamino ketone **4d** was sensitive to

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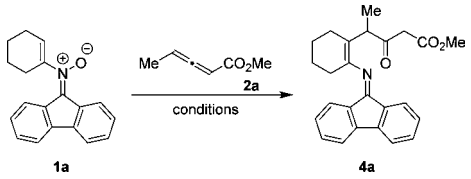
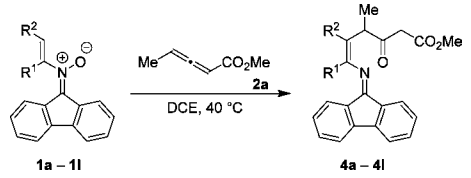
Table 1. Optimization of the Addition of *N*-Alkenylnitrone 1a to Allenoate 2a and Rearrangement to 4a

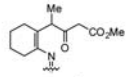
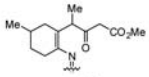
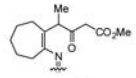
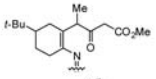
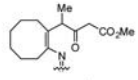
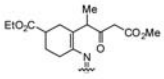
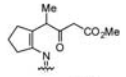
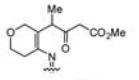
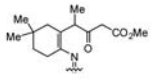
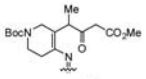
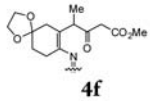
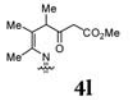


entry	solvent	temp (°C)	yield[a] (%)
1	PhMe	40	63
2	dioxane	40	65
3	MeCN	40	80
4	DMF	40	54
5	DCE	40	89
6	*t*-BuOH	40	72
7	DCE	80	dec
8	DCE	60	56
9	DCE	25	66

[a]Determined by ^{1}H NMR spectroscopy using CH_2Br_2 as a reference: **1a** (1 equiv), **2a** (3−4 equiv), 0.1 M, 18 h.

Table 2. Scope of *N*-Alkenylnitrone Reagent



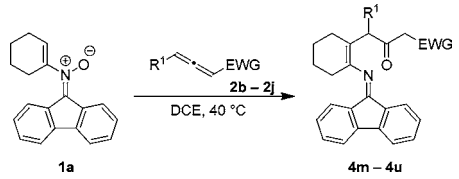
entry	4	yield (%)[a]	entry	4	yield (%)[a]
1	 **4a**	88	7	 **4g**	94
2	 **4b**	60	8	 **4h**	67
3	 **4c**	68	9	 **4i**	57
4	 **4d**	30	10	 **4j**	78
5	 **4e**	63	11	 **4k**	77
6	 **4f**	92	12	 **4l**	64

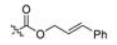
[a]Percent isolated yield. Conditions: **1** (1 equiv), allenoate **2a** (3−4 equiv), 0.1 M in DCE, 40 °C, 18−24 h.

purification on silica gel (Table 2, entry 4). Substituted cyclohexenylnitrones with alkyl, ester, and ketal substituents smoothly underwent the addition and rearrangement to give enamino ketones **4e−i** (Table 2, entries 5−9). Monosubstituted enamino ketones **4g−i** were isolated as 1:1 mixtures of diastereomers. Gratifyingly, nitrones with heterocyclic substituents such as **1j** and **1k** were also well-tolerated (Table 2, entries 10 and 11), and nitrone **1l** with a linear alkenyl group gave the corresponding product **4l** in good yield. These examples describe the generality of the method for the synthesis of imino-protected, 1,4-enamino ketones and offer an alternative route to enamine displacements of α-halogenated ketones or oxidative couplings of enamines and silyl enol ethers for the preparation of monoenamino-functionalized 1,4-diones.[12−14]

In addition to the nitrones discussed above, the scope of the allene component of the transformation was tested to determine the range of the method for installing the ketone fragment of the products. As shown in Table 3, when methyl allenoates with

Table 3. Scope of Allene Reagent



entry	2	R^1	EWG	yield (%)[a]
1	**2b**	*n*-Bu	CO_2Me	**4m** (81)
2	**2c**	*i*-Pr	CO_2Me	**4n** (89)
3	**2d**	Bn	CO_2Me	**4o** (94)
4	**2e**	Me	CO_2Ph	**4p** (80)
5	**2f**	Me		**4q** (89)
6	**2g**	Me		**4r** (85)
7	**2h**	Me		**4s** (77)
8	**2i**	Me	SO_2Ph	**4t** (75)
9	**2j**	Me		**4u** (84)

[a]Percent isolated yield. Conditions: **1a** (1 equiv), **2** (3−4 equiv), 0.1 M in DCE, 40 °C, 18−24 h.

isopropyl, butyl, and benzyl substituents were treated with nitrone **1a**, enamino ketones **4m−o** were isolated in good yield (Table 3, entries 1−3). These results suggest that the cascade rearrangement is tolerant of various substitution patterns at this position. Several different allenoates, including phenyl, styrenyl, allyl, and propargyl esters, smoothly underwent addition and rearrangement with **1a** (Table 3, entries 4−7). In addition, allenes with alternative electron-withdrawing groups, such as sulfonyl and Weinreb amide functionalities, were equally effective substrates for the preparation of functionalized 1,4-enamino ketones (Table 3, entries 8 and 9).

A proposed mechanism for the conversion of mixtures of *N*-alkenylnitrones and allenes to 1,4-enamino ketones is illustrated in Scheme 2a. Addition of nitrone **1a** to electron-deficient allene **2a** could form intermediate **3a**, which could then undergo a [3,3]-rearrangement to form azallenium **5a** and a subsequent proton transfer to form **4a**.[15] Alternatively, a [3 + 2]-cycloaddition to form exomethylene isoxazoline **6a** could also predicate a [3,3]-rearrangement to form azepine **7a** (Scheme 2b). A subsequent retro-Mannich reaction could then cleave the azepine to form **4a**.[16] The pathway illustrated in Scheme 2b,

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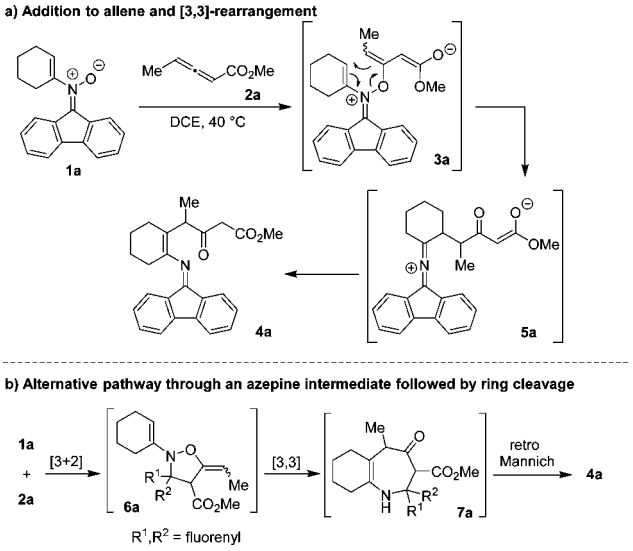
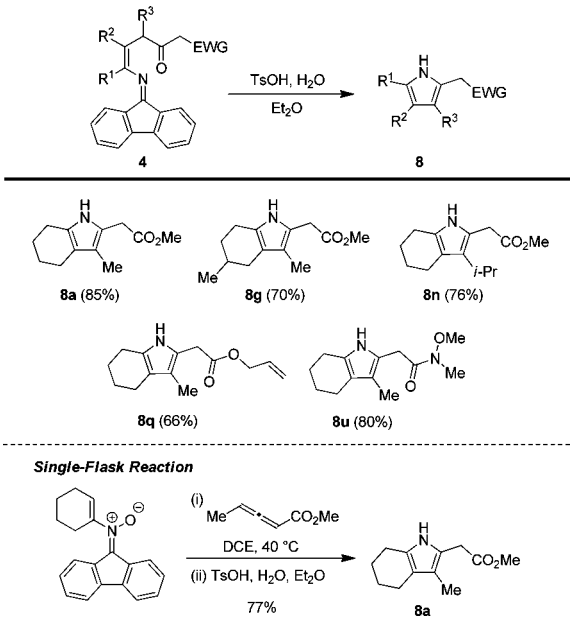
Scheme 2. Proposed Mechanism



however, seems less likely than the pathway illustrated in Scheme 2a due to the sterically hindered and electronically deactivated fluorenyl imine which would be unlikely to undergo a [3 + 2]-cycloaddition.[17]

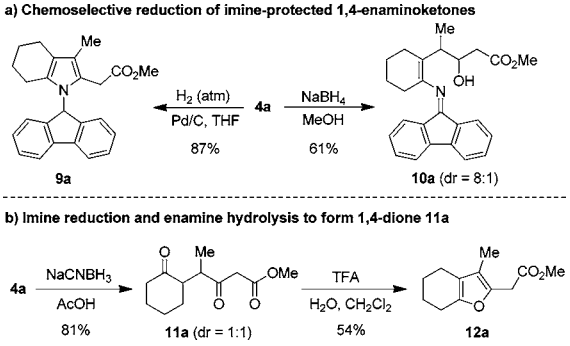
With several 1,4-enamino ketone products in hand, we decided to investigate the reactivity of these unusual imino-protected intermediates. Hydrolysis conditions were tested to remove the fluorenone imine and assess the use of these compounds for the preparation of highly substituted pyrroles. A mixture of *p*-toluenesulfonic acid (TsOH) and H_2O in ether was determined to be optimal for removal of the fluorenone imine from **4a** and the synthesis of tetrasubstituted pyrrole **8a** (Scheme 3). These conditions were tolerated by a variety of 1,4-enamino ketones **4** and provided tetrasubstituted pyrroles with cyclohexyl, $-CH_2CO_2R$, and Weinreb amide functional groups.[18] The hydrolysis of **4a** can also be performed as a two-step, single-flask process with the addition and rearrangement reaction providing direct conversion of *N*-alkenylnitrone **1a** to tetrasubstituted pyrrole **8a** in good yield. Pyrroles with 2-CH_2CO_2R groups have previously been prepared by the treatment of α-aminated ketones with β-ketoesters.[19] The transformation described above provides a simple, alternative route to these compounds through an oxime-mediated coupling of an alkenyl boronic acid and an electron-deficient allene.

Scheme 3. Hydrolysis of Imine-Protecting Group To Give Tetrasubstituted Pyrroles



To further pursue the use of imino-protected 1,4-enamino ketones **4** as synthetic intermediates, we also screened conditions for chemoselective reductions. As shown in Scheme 4,

Scheme 4. Synthetic Diversification of Isolated 1,4-Enamino Ketones by Selective Reduction Methods



hydrogenation of fluorenone imine **4a** with Pd/C gave a fluorenyl amine which cyclized to the corresponding *N*-fluorenylpyrrole **9a**. In contrast, reduction of **4a** with $NaBH_4$ gave δ-hydroxyenamine **10a**. To our delight, a $NaCNBH_3$ reduction of **4a** in acetic acid gave 1,4-dione **11a**, which could also be subsequently converted to tetrasubstituted furan **12a**.[20] These experiments imply that [3,3]-rearrangements of dialkenylhydroxylamines, triggered by the addition of *N*-alkenylnitrones to allenes, can provide rapid access to 1,4-diones and their derivatives. These transformations provide alternative routes to oxidative enolate couplings and Stetter reactions to access these challenging fragments.[21,22]

In summary, we have discovered a new method for the generation of dialkenylhydroxylamines through the addition of *N*-alkenylnitrones to electron-deficient allenes and the synthesis of 1,4-enamino ketones by a subsequent spontaneous [3,3]-rearrangement. This new route to dialkenylhydroxylamines has a broader scope than the Trofimov reaction, and the mild reaction conditions allow for the isolation of a novel fluorenylimine-protected 1,4-enamino ketone intermediate. Simple functionalization methods have been shown to be effective for the conversion of these compounds to pyrroles, 1,4-diones, and furans. Ongoing work in our laboratory is focused on controlling the stereochemistry of these rearrangements and further exploring the synthetic utility of the imino-protected enamino ketone rearrangement products.

■ 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.

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(9) Mo, D.-L.; Wink, D. J.; Anderson, L. L. *Org. Lett.* **2012**, *14*, 5180.

(10) See the Supporting Information for an expanded optimization table.

(11) Preparation of **4a** can be achieved in attenuated yield (40 − 50%) from the corresponding oxime through a two-step, single-flask, Chan–Lam coupling followed by the addition of **2a**.

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(18) We chose to demonstrate the utility of enamino ketones **4** by converting a representative set of examples to pyrroles **8**. The hydrolysis and condensation process appeared to be general.

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