Synthesis of Pyrrolidine-2-ylidenes from Isoxazolines and Allenes

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Abstract: An addition and rearrangement reaction has been developed for the synthesis of pyrrolidine-2-ylidenes from N*H*-isoxazolines and electron-deficient allenes. This method generates pyrrolidine-2-ylidenes with a *gem*-dione at the 4-position via the rearrangement of a proposed *N*-alkenylisoxazoline intermediate. Reaction optimization and substrate scope are described, in addition to studies comparing the reactivity of the *gem*-dione and enaminone groups of the products. This method overcomes functional group tolerance limitations of alternative approaches and expands the scope of accessible pyrrolidine-2-ylidenes.

Introduction.

Pyrrolidine-2-ylidenes are *N*-heterocycles found in biologically active natural products such as plakoridine A, carzinophilin, azinomycin A, and batzelladine (Scheme 1A).[1-3] The enaminone functional group in these scaffolds has also been used as an intermediate in the synthesis of other pyrrolidine targets.[4] The most common method used for the synthesis of pyrrolidine-2-ylidenes is the olefination of lactams or thiolactams.[1a, 5] Additional synthetic approaches to these molecules include using intermolecular cycloaddition of enediones with imines, intramolecular cycloaddition of azides with enamines, cyclization via condensation, and titanium-catalyzed cyclization of ynamines in the presence of acyl cynanides (Scheme 1B).[6-10] While proven to be effective, these methods all have limitations that inhibit substrate compatibility and would be challenging to use to install a *gem*-dione at the 4-position of a pyrrolidine-2-ylidene as shown for **3** (Scheme 1D). Recently, we reported that gold-catalyzed *N*-alkenylation of isoxazolines with ynamides generates *N*-alkenylisoxazoline intermediates that undergo [3,3]-sigmatropic rearrangement to give 2-aminopyrrolines (Scheme 1C).[11] We wondered if this reactivity could be adapted for allenones to tolerate spectator ketone functionalities and used to prepare pyrrolidine-2-ylidenes with *gem*-dione functionalities. To the best of our knowledge, these compounds have not previously been reported and are poised to diversify SAR studies of pyrrolidine-2-ylidenes and provide new opportunities for derivatization. Herein we describe the synthesis of pyrrolidine-2-ylidenes **3** from N*H*-isoxazolines **1** and allenes **2** (Scheme 1D). This reaction occurs under neutral conditions to give highly functionalized pyrrolidine-2-ylidenes, which surprisingly exhibit a preference for reactivity at the *gem*-dione functionality prior to participating in more established reactions of enaminones. The scope of this method and investigation of the novel reactivity patterns of **3** are described below.

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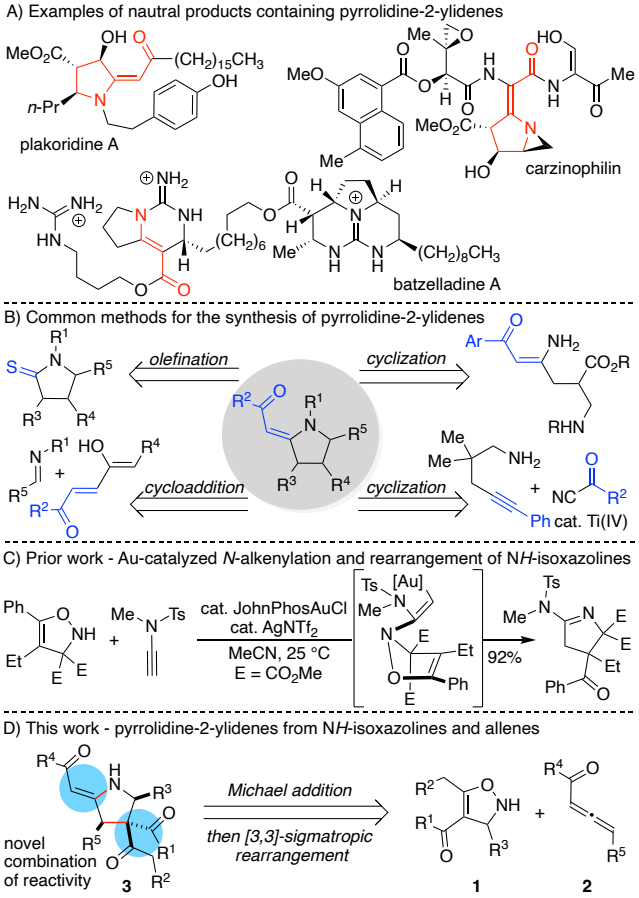
Scheme 1. Pyrrolidine-2-ylidenes – Targets and Synthesis



Results and Discussion.

The addition of N*H*-isoxazolines to allenones to generate *N*-alkenylisoxazolines and synthesize pyrrolidines was initially investigated with **1a** and **2a** (Table 1). N*H*-Isoxazoline **1a** was prepared as reported by Zhang and coworkers.[12] As described in our previous work, the addition of *N*-hydroxyenamines to allenoates can be achieved in the presence of a mild base to initiate a sigmatropic rearrangement.[13] When a mixture of isoxazoline **1a** and allene **2a** in CH_2Cl_2 was treated with either K_2CO_3 or quinoline, the desired addition and rearrangement product **3a** was observed in good yield (Table 1, entries 1 – 2). Surprisingly, removal of the base additive led to a small increase in yield for **3** and optimal conditions for the synthesis of **3a** were determined to be simply a 2:3 mixture of **1a**:**2a** in CH_2Cl_2 (Table 1, entry 9). The reaction was shown to be tolerant of other solvents and different concentrations but worked best as a 0.05 M solution (Table 1 entries 4 – 9). In analogy to our previous work,[11,14] we propose *N*-alkenylisoxazoline **4a** (or related tautomers) as the intermediate in this process that can undergo rearrangement through a boat transition state to form pyrrolidine **3a** with the illustrated relative stereochemistry.

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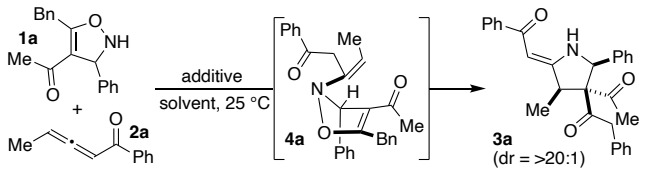
Table 1. Optimization of the Synthesis of Pyrrolidine-2-ylidenes from Isoxazoline 1a and Allene 2a



Entry[a]	Additive	Solvent	[**1a**] M	% Yield[b]
1	K_2CO_3	CH_2Cl_2	0.1	80
2	quinoline	CH_2Cl_2	0.1	86
3	--	CH_2Cl_2	0.1	89
4	--	MeOH	0.1	76
5	--	THF	0.1	69
6	--	EtOAc	0.1	78
7	--	acetone	0.1	51
8[c]	--	CH_2Cl_2	0.05	85
9[c,d]	--	CH_2Cl_2	0.05	90

Conditions: **1a** (1 equiv), **2a** (2 equiv), additive (2 equiv), 25 °C, 1 h. [b] Determined by ^{1}H NMR spectroscopy. CH_2Br_2 used as an internal standard. [c] 3 h, [d] **2a** (1.5 equiv).

With optimal conditions in hand, the scope of the reaction was investigated by varying the substituents on the allene and the N*H*-isoxazoline. As shown in Scheme 2, allenes with alkyl- and aryl ketone functional groups smoothly underwent conversion to **3a** – **3c** with N*H*-isoxazoline **1a**. A somewhat attenuated yield was observed for **3c** presumably due to the lower electrophilicity of **2c**. Branched alkyl groups were also tolerated at the 3-position of the allene as shown for **3d**. To interrogate the effect of substituents on the N*H*-isoxazoline, the procedure by Zhang and coworkers[12] was expanded to prepare N*H*-isoxazolines **1b** – **1f**. N*H*-Isoxazolines with aryl- and heteroaryl groups adjacent to the N-atom were tolerated to give **3e** – **3h**. When the acyl group of **1a** was changed to a furanyl substituent, pyrrolidines **3i** – **3j** were prepared in good yield. More significant changes to the structure of the substrates required additional changes in reaction conditions. For example, allenoate **2e** gave **3k** in only 42% yield and dr = 10:1 under the optimal conditions shown in Table 1 but gave **3k** in 75% yield with dr = >20:1 when treated with **1a** in MeOH and H_2O. These protic conditions were also tested for a mixture of **1a** and **2a** but shown to be inferior to the optimized conditions determined in Table 1. The structure and relative stereochemistry of **3** was confirmed with an X-ray crystal structure of **3l**.[15] N*H*-Isoxazolines **1g** – **1i** were prepared from the corresponding azetidine nitrones[11] but did not form the corresponding pyrrolidines under standard conditions. In contrast, when **1g** – **1i** were treated with allene **2a** in the presence of catalytic $Sc(OTf)_3$, pyrrolidines **3m** – **3o** were formed in moderate yield. With several examples of pyrrolidine-2-ylidenes **3** in hand, the reactivity of these compounds was evaluated.

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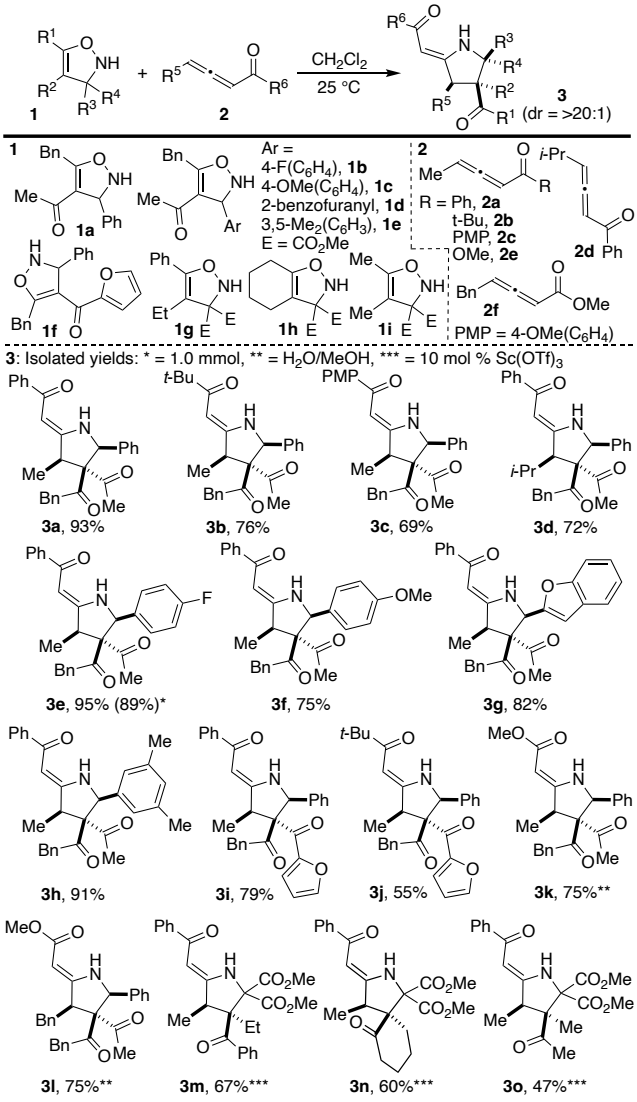
Scheme 2. Scope of the Synthesis of Pyrrolidine-2-ylidenes



Investigations into the reactivity of pyrrolidine-2-ylidenes **3** focused on interrogating the effect of the carbonyl functionalities decorating these molecules. Initial attempts at reducing the enaminone with hydride reagents and hydrogenation were met with a lack of reactivity or the formation of alternative product mixtures (Scheme 3A). Further analysis showed that treatment of **3a** with base leads to the formation of **5a** as a single diastereomer. The relative stereochemistry of **5a** was confirmed by X-ray crystal structure analysis.[15] While a variety of bases such as NaH and KO*t*-Bu were shown to trigger this reactivity, DBU was determined to be optimal for the synthesis of **5a** from **3a**. This reaction was general for several pyrrolidine-2-ylidenes **3** as illustrated by successful formation of **5b** – **5e** but no reaction was observed for **3m** – **3o**, which do not have *gem*-diketone functionalities at the 4-position of the heterocycle (Scheme 3B). A proposed mechanism for this reaction is shown in Scheme 3C. Either an intramolecular or a DBU-facilitated acyl migration could form intermediate **6a**,[16] which could be converted to **5a** via

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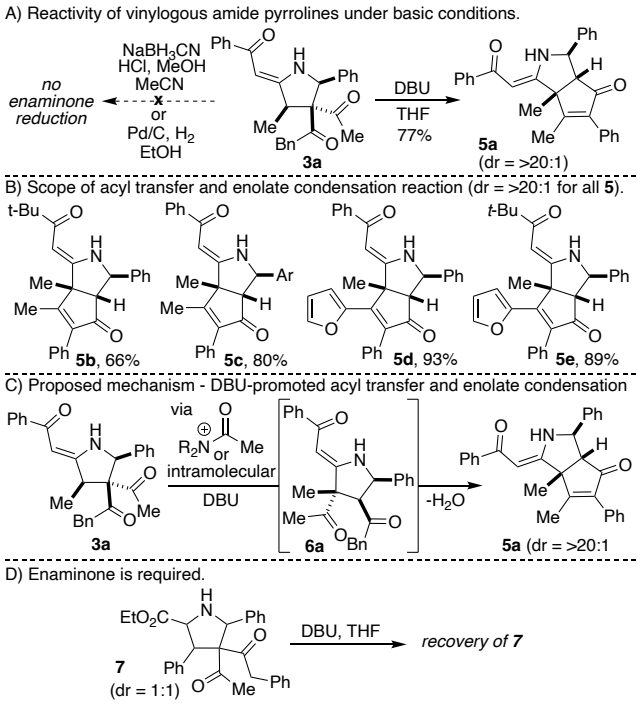
enolization at the benzyl ketone followed by addition to the adjacent acyl group and elimination of H_2O. No crossover products were observed when a mixture of **3b** and **3i** were subjected to reaction conditions supporting the absence of solvent separated fragments during the acyl transfer. Independent synthesis of a diastereomeric mixture of **7** via dipolar cycloaddition[17] followed by treatment with DBU also did not form the analogous fused pyrrolidine suggesting that the enaminone functionality of **3** is required for initial acyl transfer (Scheme 3D). These studies identified the *gem*-diketone of **3** to be activated by the vinylogous amide towards preferential rearrangement to fused pyrrolidines **5**.

Scheme 3. Conversion of 3 to Fused Pyrrolidines 5



Having discovered that the *gem*-diketone functionality dominates the reactivity of **3** under basic conditions, we next considered the reactivity of **3** after removal of the acyl group at the 4-position. As shown in Scheme 4A, deacylation of **3a** with NaOMe gave **8a** in good yield and high diastereoselectivity.[18] This compound smoothly underwent sodium cyanoborohydride reduction to give **9a** in good yield albeit with low diastereoselectivity.[19] Cyclization of **8a** with acrylate gave **10a** in moderate yield and high diastereoselectivity.[20] While these reactions have previously been reported with other heterocyclic enaminones, these are to the best of our knowledge the first examples with spectator ketone substituents in the 4-position. Further following the trend that the vinylogous amide of **3** reacts as expected in the absence of a *gem*-diketone in the 4-position, fused-pyrrolidine **5a** was also shown to smoothly undergo reduction to **11a** with $NaBCNH_3$ (Scheme 4B).[19] Taken together these investigations demonstrate the synthetic utility of **3a** and how the *gem*-diketone can be used as a reactivity controlling element.

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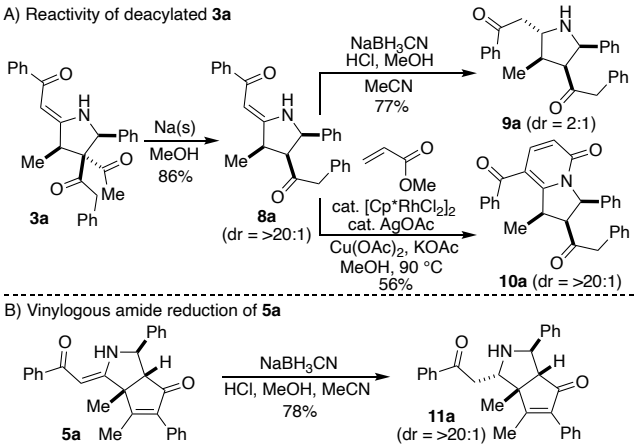
Scheme 4. Reactivity of Deacylated Pyrrolidine-2-ylidenes



Conclusion

In summary, we have discovered a conjugate addition and [3,3]-sigmatropic rearrangement reaction to form pyrrolidine-2-ylidenes from N*H*-isoxazolines and allenes. This transformation occurs under mild conditions that tolerate carbonyl functionalities that are not compatible with other approaches to these heterocycles. Further studies also identified an unusual reactivity pattern of these compounds where the *gem*-dione preferentially undergoes acyl migration and cyclization under basic conditions. Removal of this functional group, then provides access to known reductions and cyclizations of enaminones. This work expands chemical space of accessible pyrrolidine-2-ylidenes and showcases new reactivity patterns of pyrrolidine-2-ylidenes with *gem*-dione functional groups.

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Keywords

pyrrolidine-2-ylidene, sigmatropic rearrangement, enaminone, *gem*-dione

Author Contributions

The manuscript was written through contributions of all authors.

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Supporting Information

Experimental details and spectral data (PDF).

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15. Deposition numbers 2373332 (for **3l**) and 2370375 (for **5a**), contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.
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