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Synthesis of β-Halo-pyrrolidinones through a Tandem Sequence of 5-Endo Halolactamization and C−H Oxidative Functionalization

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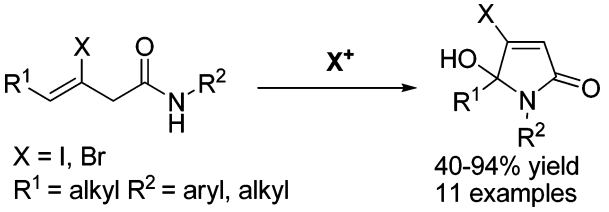
ABSTRACT



A tandem sequence of 5-*endo* halolactamization and direct C−H oxidative functionalization is described. A range of β-halo-pyrrolidinones can be efficiently synthesized using this method, making it an excellent approach for constructing natural products containing pyrrolidinones.

Halocyclization of unsaturated compounds, an important type of organic reaction, has been extensively investigated as a way to synthesize heterocyclic compounds, especially those that are biologically active.[1] In most cases, the cyclizations follow Baldwin's rules. Thus, closure of 3- to 7-membered rings often favors *exo*-trig and 6- to 7-*endo* processes, but not 3- to 5-*endo* processes. In addition, the regioselectivity of the reaction can be influenced by structural modifications; for example, substituents on the double bond can exert electronic effects that alter selectivity.

Numerous studies have examined 5-*exo* halocyclization, especially 5-*exo* iodolactonization of unsaturated carboxylic acids and amides.[2,3] In contrast, 5-*endo* halocyclization of these compounds is poorly understood because it is relatively uncommon. In particular, few studies have examined lactam formation through 5-*endo* halocyclization of unsaturated amides.[4] Li and co-workers described a 5-*endo* amidyl radical cyclization for the formation of unsaturated lactams; the reaction was promoted by vinylic

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iodine substitution.[5] The same researchers found ^{t}BuOCl/I_2 to be an efficient iodinating reagent for the synthesis of iminolactones.[6]

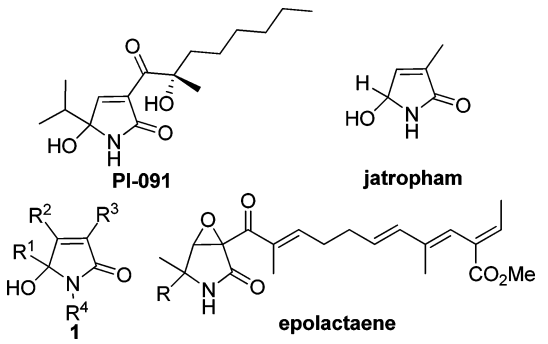
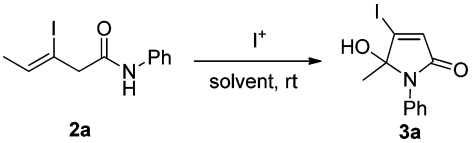


Figure 1. Examples of pyrrolidinone-containing natural products.

Our interest in novel approaches to natural product synthesis led us to wonder whether 5-*endo* amidyl cyclization could be combined with the oxidative functionalization[7] of C−H bonds. Many studies have examined the functionalization of such bonds adjacent to electron-rich tertiary amines or electron-poor amides; these reactions are catalyzed by Ru,[8] Fe,[9] Cu,[10] Rh,[11] Ir,[12] Pd,[13] and photoredox catalysts.[14] In addition, some studies have explored the oxidative functionalization of C−H bonds using nonmetal oxidants.[15]

Pyrrolidinone (**1**)[16] and its derivatives exhibit a wide range of potent biological activities, and that can easily be transformed into highly reactive *N*-acyliminium ions. These ions have historically been generated *in situ* by Lewis acid or Brønsted acid promoted elimination.[17] They have been used widely in the synthesis of alkaloid natural products (Figure 1).[18] Here we describe sequential 5-*endo* halolactamization and C−H oxidative functionalization for the synthesis of β-halo-pyrrolidinones. In our case, the reactions underwent halocyclization precesses rather than radical cyclization which has been reported previously in Li's pyrrolidinone synthesis.

Table 1. Optimization of Reaction Conditions



entry	iodinating reagent (equiv)	solvent	time (h)	yield (%)
1	I_2/Na_2CO_3 (3)	CH_3CN/H_2O (1:1)	96	–[a]
2	ICl (3)	CH_3CN/H_2O (1:1)	1	21[b]
3	BPIT (3)	CH_3CN/H_2O (1:1)	96	trace
4	NIS (2)	CH_3CN/H_2O (1:1)	72	38
5	^{t}BuOCl/I_2 (3/2)	CH_3CN/H_2O (1:1)	15	58
6	**NIS (4)**	**CH_3CN/H_2O (1:1)**	**20**	**65**
7	NIS (6)	CH_3CN/H_2O (1:1)	10	63
8	^{t}BuOCl/I_2 (1/1)	CH_3CN/H_2O (1:1)	72	19
9	^{t}BuOCl/I_2 (3/3)	CH_3CN/H_2O (1:1)	15	67
10	^{t}BuOCl/I_2 (3/3)	H_2O	3	–[a]
11	^{t}BuOCl/I_2 (3/3)	THF	3	16
12	^{t}BuOCl/I_2 (3/3)	CH_2Cl_2	3	31
13	^{t}BuOCl/I_2 (3/3)	acetone	3	13
14	**^{t}BuOCl/I_2 (3/3)**	**CH_3CN**	**3**	**83**
15	NIS (4)	CH_3CN	96	19

[a] No product was identified by TLC. [b] The Cl-substituted product was formed in 34% yield.

In initial screening experiments, we selected **2a** and CH_3CN/H_2O as the reactant/solvent combination in order to determine optimal reaction conditions. First, we

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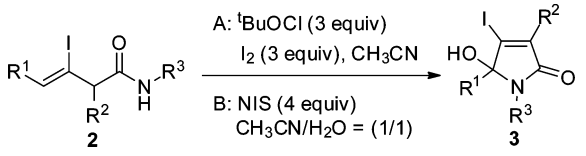
screened a series of iodinating reagents that included I_2/Na_2CO_3, ICl, $IPyBF_4$ (BPIT), NIS, and $^tBuOCl/I_2$ (Table 1, entries 1–5). While most showed no or poor activity, NIS and $^tBuOCl/I_2$ were moderately active. Then we examined the loading of NIS and $^tBuOCl/I_2$. Use of 4 equiv of NIS gave our desired pyrrolidinone **3a** in 65% yield (entry 6). No desired product was formed when water was employed as solvent (entry 10). Low yields of **3a** were obtained when CH_2Cl_2 and THF were used as solvents (entries 11, 12). In the presence of $^tBuOCl/I_2$ and commercial acetonitrile, **3a** was obtained in 83% yield (entry 14). NIS, however, gave only a 19% yield under similar conditions (entry 15).

Table 2. Formation of Iodo-pyrrolidinones **3**[a]

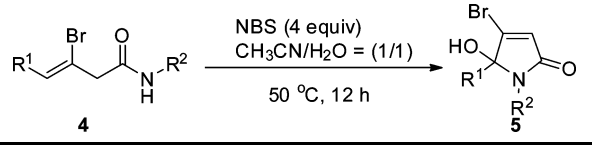


2 3

entry	R^1	R^2	R^3	yield (%)[b]
1	Me	H	Ph (**a**)	83 (65)
2	Me	H	Bn (**b**)	65 (80)
3	Me	H	*n*-Bu (**c**)	70 (76)
4	Me	H	*p*-$OMeC_6H_4$ (**d**)	45 (58)[c]
5	Me	H	*p*-$NO_2C_6H_4$ (**e**)	60 (40)
6	C_4H_9	H	Ph (**f**)	83 (82)
7	C_4H_9	H	Bn (**g**)	81 (94)
8	C_4H_9	H	*n*-Bu (**h**)	65
9	C_6H_{13}	H	Ph (**i**)	78
10	C_6H_{13}	H	Bn (**j**)	77
11	C_4H_9	Me	Ph (**k**)	51

[a] Method A: Substrate (1 equiv) was mixed with ^tBuOCl (3 equiv) and I_2 (3 equiv) at room temperature for 4 h in CH_3CN. Method B: Substrate (1 equiv) was mixed with NIS (4 equiv) at room temperature for 20 h in CH_3CN/H_2O (1:1). [b] Numbers in parentheses are the yields of **3** using method B. [c] The reaction was run for ca. 48 h.

Table 3. Formation of Bromo-pyrrolidinones **5**[a]



4 5

entry	R^1	R^2	yield (%)
1	C_4H_9	Ph (**a**)	40[b]
2	Me	Ph (**b**)	36[b,c]
3	Me	Bn (**c**)	58
4	Me	*n*-Bu (**d**)	63

[a] Substrate (1 equiv) was mixed with NBS (4 equiv) at 50 °C for 10 h n CH_3CN/H_2O (1:1). [b] The derivative with a bromo substitution at the *para* position of the phenyl group was obtained. [c] 20% of the starting material was recovered.

We next studied the scope and limitation of the halolactamization/C–H oxidative functionalization reaction sequence. Under the optimized conditions, the *N*-phenyl, benzyl, and *n*-butyl substrates **2a**–**2k** gave iodo-pyrrolidinones **3a**–**3k** in moderate-to-excellent yields using both methods (Table 2). Intriguingly, substrates containing either an electron-donating or -withdrawing group at the *para* position gave low yields of iodo-pyrrolidinones. The molecular structure of **3e** was determined by X-ray crystallography (Figure 2).

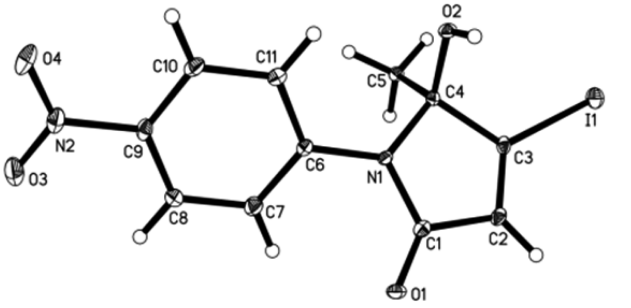
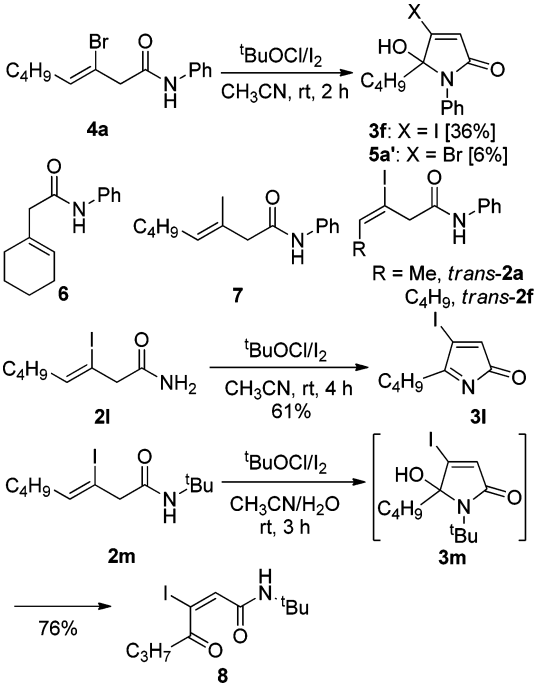


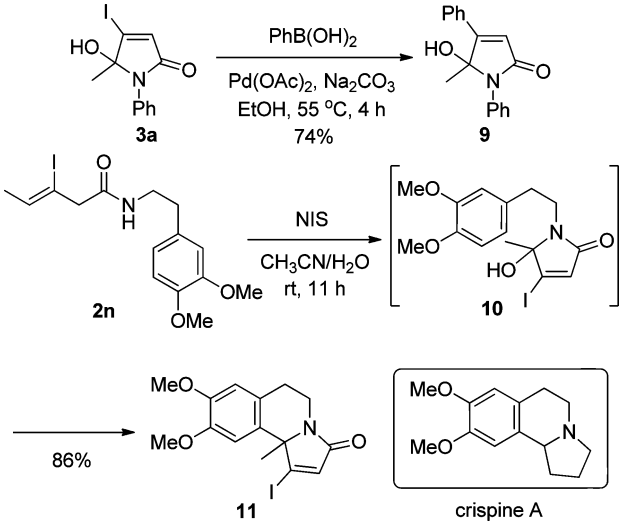
Figure 2. X-ray structure of **3e**.

Our success in transforming vinyl iodide **2** into iodo-pyrrolidinones through sequential 5-*endo* halolactamization and C–H oxidative functionalization prompted us to further investigate the use of vinyl bromide **4** as the substrate (Table 3). The bromo-pyrrolidinones **5** were obtained in moderate-to-good yields when the reaction temperature was increased to 50 °C. When *N*-phenyl amides were used as substrates, the products could be further

Scheme 1. Miscellaneous Alkenyl Amide Reactions



Scheme 2. Application of Vinyl Iodo Amides



converted to the *para*-bromo-substituted derivatives **5a** and **5b** in moderate yields. Running the reactions at room temperature gave only trace amounts of the desired products.

Using vinyl bromide **4a** as a substrate gave the unseparated products **3f** and bromo-pyrrolidinone **5a′** in 36% and 6% yield. For comparison, we repeated the above reaction conditions using compounds **6** and **7** as the substrates (Scheme 1). These gave rise to messy reactions with ^{t}BuOCl/I_2, and no identifiable products could be isolated. Our results indicate that the halogen atom in **2** does not act simply as a substituent but plays a crucial role in the reaction. When *trans*-**2a** or **2f** was employed as the substrate in the reaction with ^{t}BuOCl/I_2, the reaction was sluggish and the substrate decomposed after prolonged stirring. Using the *N*-hydrogen substituted substrate **2l** gave the corresponding compound **3l** in moderate yield. When the substrate was an *N*-*tert*-butyl-substituted amide, the product **8** was obtained in good yield. Using a substrate with a more crowded structure led to the cyclic intermediate **3m**.

The halo-pyrrolidinones can be used as synthetic intermediates as illustrated in Scheme 2. The presence of the vinylic halogen makes possible numerous cross-coupling reactions catalyzed by transition metals. To demonstrate that the compounds prepared with our method can

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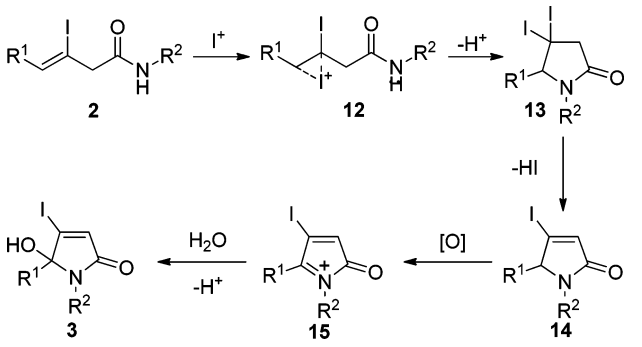
Scheme 3. Proposed Mechanism for Formation of **3**



function as intermediates, **3a** was subjected to standard Suzuki coupling conditions,[19] and the corresponding coupling product **9** was obtained in good yield. Applying the Pictet–Spengler condensation reaction to **10** allowed the construction of a second ring in one step and afforded compound **11**, which contains the core structure of the alkaloid crispine A.[20]

We propose the mechanism for the formation of **3** in Scheme 3. First, electrophilic attack by I^+ on the olefin gives iodonium species **12**. Then, closure through the amide nitrogen gives the lactam **13**. Elimination of hydrogen iodide generates enamide **14**, which undergoes allylic oxidative functionalization to yield intermediate **15**. Quenching the functionalization with water affords iodo-pyrrolidinone **3**.

In summary, we have developed a practical, efficient, and rapid process for the synthesis of halo-pyrrolidinones. These products readily undergo cross-coupling reactions or Pictet–Spengler condensation to afford useful synthetic intermediates.

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Supporting Information Available. Detailed experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all products, and X-ray crystallographic data for **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.