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Facile 5-endo electrophilic cyclization of unsaturated amides with ^{t}BuOCl/I_2

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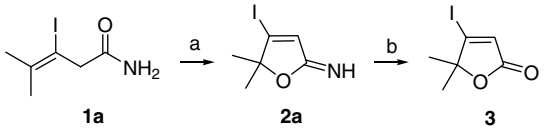
Abstract—5-Endo iodocyclization of various β,γ-unsaturated amides proceeded smoothly to give the corresponding conjugated iminolactones exclusively in satisfactory yields with the use of ^{t}BuOCl and I_2 as the reagents, which proved to be much advantageous over the conventional I_2/$NaHCO_3$.

Halocyclizations of unsaturated compounds have been well established to be an indispensable tool in the synthesis of heterocyclic compounds and continue to be actively pursued.[1,2] Among them, the most widely studied type of reaction is iodolactonization, especially 5-exo iodolactonization, which has found extensive application in natural product synthesis.[3] However, electrophilic cyclization in endo modes, especially in a 5-endo mode, is relatively uncommon. Bromolactonization of β,γ-unsaturated acids[4] often gave a mixture of the corresponding β-lactone and γ-lactone.[2d,5] As a comparison, iodolactonization showed better regioselectivity and β-iodo-γ-lactones could be obtained in moderate yields when β,γ-unsaturated acids were treated with I_2 and $NaHCO_3$.[5] However, this method suffered from an unwanted decarboxylative elimination process.[5] Changing the substrates from acids to the corresponding amides afforded the same lactone products in higher yield as reported by Hart and co-workers.[5] This methodology was then successfully applied to the total synthesis of natural products, such as antitumor antibiotic pleurotin,[6–8] demonstrating the great potential of 5-endo iodolactonization of unsaturated amides in organic synthesis. However, the above investigation[5–8] dealt mostly with 2-cyclohexene-1-carbamide derivatives, and examples other than those were rare.[9,10] Ganem and co-workers observed one example of efficient 5-endo iodolactonization with *N*-sulfonyl-substituted 3-pentenamide as an exception to the usual β-lactam formation.[9] Corey et al. reported the 5-endo cyclization of a trienamide by treatment with boron trifluoride etherate at low temperature to give the lactone product in only 15% yield.[10] Another reason that hinders the investigation of 5-endo cyclization is that the substrates, β,γ-unsaturated amides, can easily undergo isomerization under basic conditions. It is, therefore, of interest to systematically examine the behavior of 5-endo electrophilic cyclization of β,γ-unsaturated amides and to develop a convenient and general method to conduct such transformations. We report here that 5-endo electrophilic cyclization of unsaturated amides could be efficiently carried out by reaction with *tert*-butyl hypochlorite and iodine to afford unsaturated iminolactones.



1a **2a** **3** (1)

a: ^{t}BuOCl/I_2, rt, 2 h, 95%. b: HCl (3N), reflux, 5 h, 85%.

Our finding originated from our recent investigation on the 5-endo amidyl radical cyclization reactions promoted by terminal vinylic iodine substitution.[11] In an attempt to extend the scope of the amidyl radical cyclization, we synthesized the β,γ-unsaturated amide **1a**[12] with a β-iodine substituent. Substrate **1a** was then subjected to the treatment of ^{t}BuOCl (3 equiv) and I_2 (1 equiv) in the dark at room temperature (rt), hoping to get β- or γ-lactam as the amidyl radical cyclization product. The reaction was very clean and the starting material was all consumed within 2 h as indicated by TLC. After the usual work up with $Na_2S_2O_3$ (to remove

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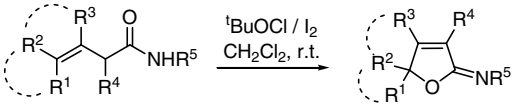
the excess I_2), the product was characterized to be iminolactone **2a** rather than the expected β- or γ-lactam (Eq. 1).

Apparently, iodolactonization occurred rather than amidyl radical cyclization. Moreover, the product was conjugated iminolactone rather than the usual iodolactone. This prompted us to check the reaction of **1a** under typical iodocyclization conditions (I_2 with or without excess K_2CO_3 or $NaHCO_3$). However, **1a** remained unchanged even at a prolonged time (24 h) at rt. Use of more potent reagent ICl also failed to give any product. Compound **2a** was quite stable towards aqueous NaOH or HCl solution at rt. When it was stirred in 3 N hydrochloric acid at reflux for 5 h according to the conventional method,[13] the corresponding butenolides **3** was obtained in 85% yield.

We then prepared a number of enamides **1b–m** and subjected them to treatment with ^{t}BuOCl and iodine. The results are summarized in Eq. 2 and Table 1. The reactions were very clean and all the starting enamides

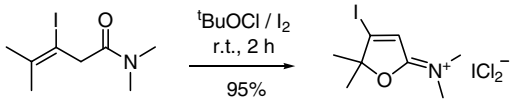


1a-m **2a-m** (2)

were consumed typically within 1 h. After work up with aqueous $Na_2S_2O_3$, the expected 5-endo cyclization product iminolactones were achieved in high yields for various γ,γ-dialkyl-substituted enamides while no 4-exo cyclization products could be detected. Substrates with an endocyclic or an exocyclic double bond led to the formation of the corresponding bicyclic iminolactones (Table 1, entries **c**, **k**, and **l**). Moreover, with the substrate **1e** having an electron-deficient C=C double bond, the reaction also proceeded smoothly to give the expected product **2e** in 83% yield (Table 1, entry **e**).

As a comparison, the typical iodolactonization procedure (I_2, $NaHCO_3$, THF–H_2O, rt) was also tested on enamides **1a–m**. It turned out that no reaction could be observed for enamides **1a–e**. With **1f–m**, iminolactones **2f–m** rather than the corresponding β-iodo-γ-lactones were again formed. However, the reactions proceeded sluggishly and even after 24 h there were, more or less, always some amount of the starting materials that remained or isomerized to their conjugated forms as indicated by ^{1}H NMR monitoring.

We also used *N*,*N*-dimethyl-substituted enamide **4** as the substrate (Eq. 3). Treatment of **4** with ^{t}BuOCl/I_2 at rt for 1 h afforded salt **5**, whose structure was unambiguously characterized by its X-ray diffraction analysis (Fig. 1). Again, no reaction occurred when **4** was treated with I_2/$NaHCO_3$ in aqueous THF. Surprisingly, the hydrolysis of **5** to the corresponding butenolide **3** turned out to be unsuccessful. When **5** was treated with aqueous HCl or NaOH solution at ambient temperature, either no reaction occurred or it simply decomposed, while no pure **3** could be isolated.



4 **5** (3)

When 3-butenamide or 3-pentenamide was employed, the reaction was rather complicated. This was probably because the competing amidyl radical reactions[11] also occurred when the C=C double bond was mono- or di-substituted.

Based on the above results, a plausible mechanism could be drawn for the formation of **2**. The combination of ^{t}BuOCl with I_2 generated ^{t}BuOI and ICl.[14] Since ICl did not react with **1a**, the active iodination reagent had to be ^{t}BuOI. Electrophilic iodocyclization of amide **1a** with ^{t}BuOI gave the intermediate β-iodoiminolactone, which then underwent fast HI elimination to afford the conjugated iminolactone **2a**.

The above results reveal that the formation of conjugated iminolactones rather than iodolactones is of generality. Once the imine is stabilized by conjugation with the C=C bond, its hydrolysis becomes difficult. The formation of iodolactones in the reactions of

Table 1. Reactions of **1a–m** with ^{t}BuOCl and I_2

Entry	R^1	R^2	R^3	R^4	R^5	Yield (%)[a]
a	Me	Me	I	H	H	95
b	Me	Et	I	H	H	88
c	$(CH_2)_5$		I	H	H	76
d	Me	Me	I	H	Bn	90
e	Me	Me	CO_2Et	H	Ph	83
f	Me	Me	Me	H	H	85
g	Me	Me	Me	H	Bn	95
h	Me	Me	Me	H	Ph	85
i	Me	Me	Me	Me	Bn	83
j	Me	Me	Bu	H	Ph	85
k	$(CH_2)_5$		Me	H	Ph	66
l	Me	$(CH_2)_4$		H	Bn	80
m	Me	Me	H	H	Ph	66[b]

[a] Isolated yield based on **1**.
[b] The reaction was performed at 0 °C.

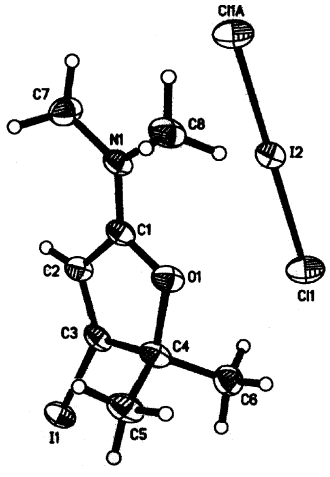


Figure 1. ORTEP drawing of compound **5**.

2-cyclohexenyl-1-carbamide systems reported in the literature[5–8] should be attributed to the formation of the rigid [3,2,1] ring system which prevented the HI elimination. As a result, the hydrolysis of the iminium ion readily occurred to afford the iodolactones. The results have also demonstrated that the combination of ^{t}BuOCl and I_2 is a much more powerful reagent than the usual I_2/$NaHCO_3$ for efficient 5-endo iodocyclization of unsaturated amides. Moreover, the easy isomerization of β,γ-unsaturated amides was successfully inhibited because ^{t}BuOCl/I_2 is acidic.

The above detailed investigation constitutes a facile entry to the 5-endo iodocyclization reactions of unsaturated amides. The product conjugated iminolactones **2** can be readily converted to the corresponding butenolides (such as **3**) or to hydroxylamines,[15] both of which serve as important building blocks in organic synthesis. Moreover, along with the easy preparation of ^{t}BuOCl from NaClO and ^{t}BuOH,[16] the advantage of ^{t}BuOCl/I_2 over the conventional I_2/$NaHCO_3$ could also be utilized to conduct other types of electrophilic iodolactonization.[17]

Acknowledgments

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17. Typical procedure for 5-endo iodocyclization of enamides **1**. *tert*-Butyl hypochlorite (0.071 mL, 0.63 mmol) was added to a dichloromethane (4.2 mL) solution of iodine (55 mg, 0.21 mmol) and **1a** (50 mg, 0.21 mmol) at rt. The mixture was stirred in the dark at rt for 2 h. The resulting mixture was then treated with an excess of aqueous $Na_2S_2O_3$. The two phases were separated and the aqueous phase was extracted with dichloromethane (10 mL × 3). The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the crude product was purified by flash chromatography on silica gel with hexane–ethyl acetate (1:1, v:v) as the eluent to afford the pure product **2a** as a yellowish oil. Yield: 47 mg (95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (6H, s), 5.62 (1H, br), 6.42 (1H, s). ^{13}C NMR ($CDCl_3$) δ 169.8, 130.9, 122.8, 92.7, 25.7. EIMS: *m/z* (rel intensity) 237 (M^+, 40), 222 (100), 110 (46), 43 (26). HRMS calcd for C_6H_8NOINa ($M+Na^+$): 259.9554. Found: 259.9543.