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An efficient process for the bromolactamization of unsaturated acids

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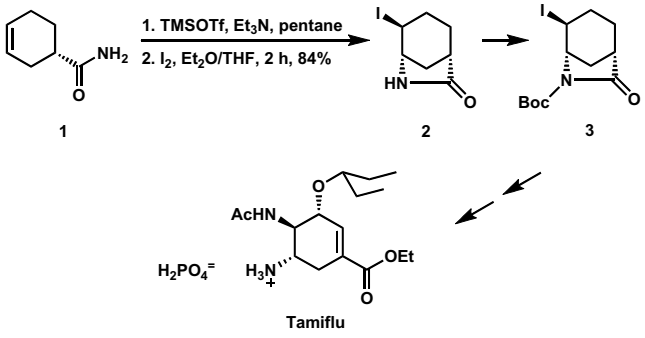
Abstract—Bromolactamization of the *N*-Boc derivatives of unsaturated amides using *N*-bromosuccinimide and lithium *t*-butoxide in tetrahydrofuran occurs smoothly to give excellent yields of bromo *N*-Boc α-lactams, which are valuable as synthetic intermediates.

Recently, we have reported an efficient and enantioselective synthesis of the antiflu agent oseltamivir phosphate (Tamiflu).[1] One of the key steps in that process is the Knapp iodolactamization of amide **1** to form γ-lactam **2**.[2,3] One drawback in that sequence for large-scale production stems from the use of trimethylsilyl triflate (TMSOTf), an expensive and moisture sensitive reagent. Herein we report a different and more practical process for lactamization.



In our synthesis of oseltamivir iodolactam **2** was transformed into the *N*-*t*-butoxycarbonyl (Boc) derivative **3** which greatly facilitates the remaining six steps in the synthesis. For this reason we investigated a more direct route to the *N*-Boc protected lactam **3** and the use of *N*-Boc-imides for halolactamization. Amide **1** was transformed into the corresponding isocyanate (**4**) which upon reaction with *t*-butyl alcohol gave the *N*-Boc-imide **5**.[4] Three examples of this process are shown in Table 1.

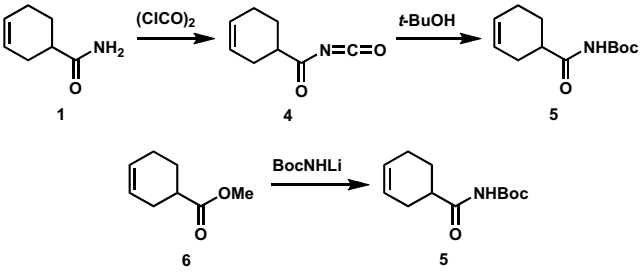
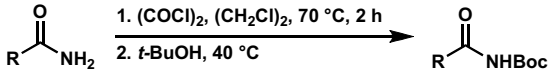
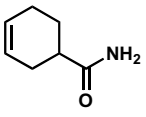
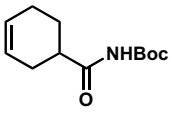
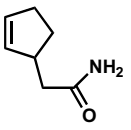
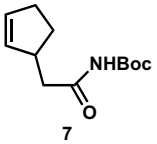
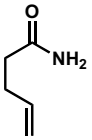
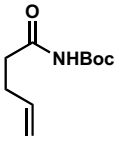


Table 1. Protection of amide



Entry	Substrate	Product	Time (h)	Yield (%)
1			1	83
	1	5		
2			2	78
		7		
3			4	71
		9		

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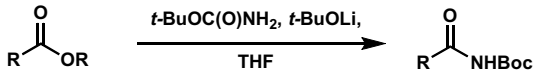
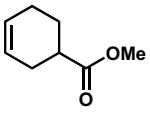
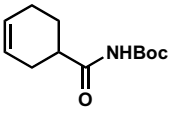
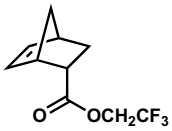
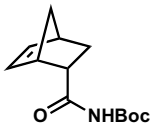
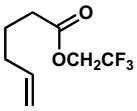
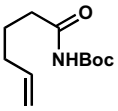
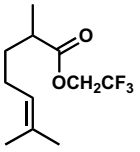
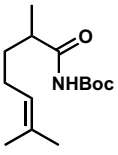
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.08.113

Table 2.



Entry	Substrate	Product	Temperature (°C)	Time (h)	Yield (%)
1	 **6**	 **5**	−20 to 23	8	83
2[a]		 **10**	0–23	12	64
3[a]		 **11**	0–23	12	68
4[a]		 **12**	0–23	12	86

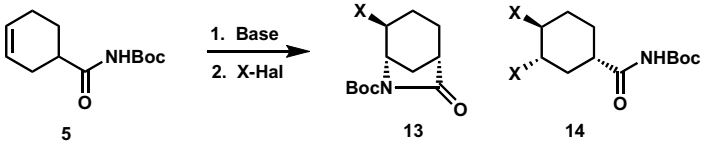
[a] 2 equiv *t*-BuOLi was used.

Alternatively, the reaction of ester **6** with the lithio derivative of *t*-butylcarbamate[5] provided Boc-imide **5** directly. Examples of this route are shown in Table 2.

A representative procedure for the synthesis of **5** by the process outlined in Table 2 is given herein.[6]

A number of conditions were screened for the halolactamization of Boc-imide **5** using the lithio derivative of the imide and various halogenating agents. The results are summarized in Table 3. Bromine was not a satisfactory reagent since the major product was found to be the vicinal dibromide **14** (X = Br) (Table 3, entries 4 and 5). Iodine on the other hand did provide the *trans*-iodo lactam (**13**, X = I). However, the best conditions were those outlined in entry 7 which involved *t*-BuOLi as the base and *N*-bromosuccinimide (NBS) as the brominating agent and afforded the desired bromolactam **13** (X = Br) in 94% yield. When these conditions were applied to a number of other unsaturated *N*-Boc imides the expected bromolactams were obtained in the yields shown in Table 4. The process was highly efficient

Table 3.

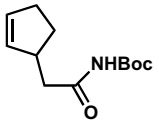
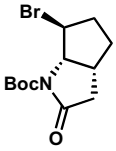
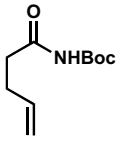
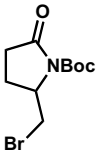
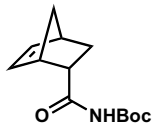
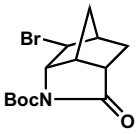
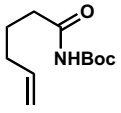
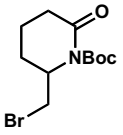
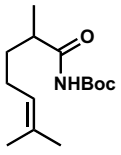
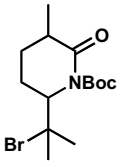


5 **13** **14**

Entry[a]	Base	X-Hal	Solvent	Temperature (°C), time (h)	Yield (**13**, **14**) (%)
1	*n*-BuLi	I_2	THF	0–23, 12	60[b], 0
2	*n*-BuLi	Br_2	THF	−20, 1.5	66, 15
3	*n*-BuLi	NBS	THF	−20, 4	72, 0
4	*n*-BuLi	Br_2	Et_2O	−20, 4	0, 91
5	*t*-BuOLi	Br_2	Et_2O	−20, 4	0, 95
6	*t*-BuOLi	Br_2	THF	−20 to 0, 2	72, 27
7	*t*-BuOLi	NBS	THF	−20 to 0, 2	94, 0

[a] For entry 1, X = I, for entries 2–8, X = Br.
[b] 30% starting material was recovered.

Table 4. Bromolactamization of Boc-imides

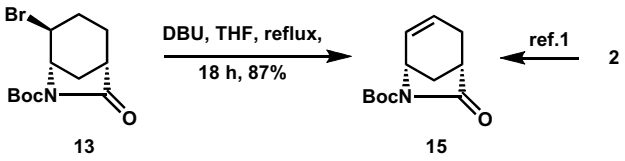
Entry	Substrate	Product	Temp (°C)	Time (h)	Yield (%)
1	 7	 16	−20 to 0	4	92
2	 9	 17	−20 to 0	4	93
3	 10	 18	−20 to 0	4	84
4	 11	 19	−20 to 23	12	54[a]
5	 12	 20	−20 to 0	8	73

[a] 39% of starting material was recovered.

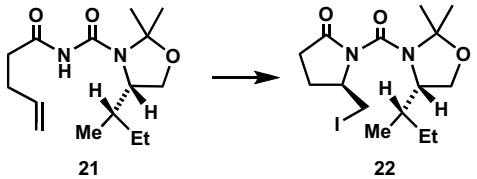
for the formation of γ-lactams (Table 4, entries 1–3) but somewhat less so for δ-lactams (Table 4, entries 4 and 5).[7]

The use of sodium hydride as base, as has been chosen in the one case reported earlier,[3a] afforded greatly inferior results for the bromolactamization of *N*-Boc-imides as compared with *t*-BuOLi as base, in our experience.

Treatment of the *N*-Boc bromolactam **13** with 1,8-diazabicycloundecene (DBU) in THF at reflux for 18 h provided the unsaturated lactam **15** (87% yield), a key intermediate for the synthesis of oseltamivir.[1] The new bromolactamization process described herein is both more practical and convenient than the Knapp protocol employed by us originally.[1] The operational effectiveness of the new method and also the route to oseltamivir that we have developed has been substantiated by the successful preparation of oseltamivir by Harvard junior undergraduates in a one-semester course in intermediate organic synthesis (under the guidance of Dr. Ahmindra Jain).



There are some other examples that indicate the utility of the halolactamization process to effect asymmetric induction. For example, diastereoselective iodolactamization of chiral substrates such as **21** which contain a chiral controller group occurs with good stereocontrol.[8]



References and notes

1. Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310.
2. Knapp, S.; Levorse, A. T. *J. Org. Chem.* **1988**, *53*, 4006.
3. For some other applications of halolactamization, see: (a) Boeckman, R. K., Jr.; Connell, B. T. *J. Am. Chem. Soc.* **1995**, *117*, 12368; (b) Fujita, M.; Kitagawa, O.; Suzuki, T.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7330; Review on lactam formation: (c) Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681–13736.
4. Martín, A.; Pérez-Martin, I.; Suárez, E. *Org. Lett.* **2005**, *7*, 2027.
5. Love, B.; Kormendy, M. F. *J. Org. Chem.* **1963**, *28*, 3421.
6. *Procedure for the preparation of N-boc-imide* **5**: To a solution of ester **6** (70 mg, 0.5 mmol) and *tert*-butylcarbamate (59 mg, 0.5 mmol) in THF (2 mL) was added *t*-BuOLi (1.0 M in THF, 1.0 mL, 1.0 mmol) at −20 °C over 30 min. The solution was allowed to warm to 23 °C, stirred at that temperature for 8 h, and treated with saturated aqueous NH_4Cl (3 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3×5 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane–EtOAc, 5:1) to give the desired Boc-imide **5** (84 mg, 75%) as a colorless solid.
7. *Representative procedure for the preparation of* 4-*bromo*-7-*oxo*-6-*aza*-*bicyclo*[3.2.1]*octane*-6-*carboxylic acid tert-butyl ester* (**13**): To a solution of Boc-imide **5** (0.25 mmol) in THF (1.5 mL) was added dropwise a solution of *t*-BuOLi (1.0 M in THF, 0.25 mL, 0.25 mmol) at −20 °C over 10 min. After stirring for an additional 20 min, the solution was shielded from light and NBS (52 mg, 0.27 mmol) in THF (0.5 mL) was added dropwise over 30 min. The resulting solution was allowed to warm to 0 °C. After 2 h at 0 °C, the reaction mixture was treated with saturated $NaHSO_3$ (1 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3×3 mL). The combined organic extracts were washed with water (1 mL), dried ($MgSO_4$), filtered, and concentrated and in vacuo. The residue was purified by flash column chromatography (*n*-hexane–EtOAc, 5:1) to give the desired lactam **13** (72 mg, 94%) as a colorless solid.
8. Shen, M.; Li, C. *J. Org. Chem.* **2004**, *69*, 7906–7909.