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Regio-controlled Iodoaminocyclization Reaction of an Ambident Nucleophile Mediated by LiAl(O*t*-Bu)$_4$

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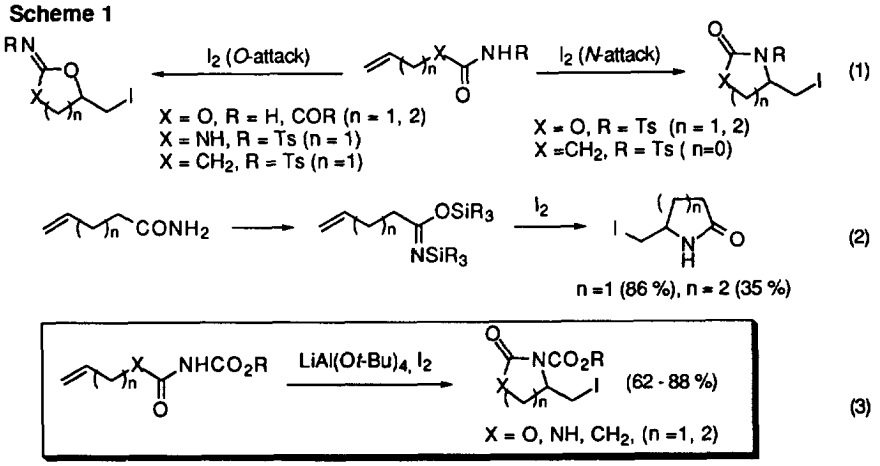
Abstract: A new and general method of iodine-mediated cyclization reactions of unsaturated carbamates, ureas and amides which gives *N*-cyclized products as a single regio-isomer was achieved. The present reaction proceeds in good yield through regio-control of an ambident nucleophile by LiAl(O*t*-Bu)$_4$, and the regio-control (*N*-attack vs *O*-attack) was also found to be remarkably affected by the additive employed.

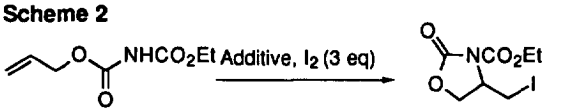
In the halocyclization reaction of olefinic compounds with an ambident nucleophile such as carbamate, urea and amide, *O*-cyclized products are generally obtained in preference to *N*-cyclized products.[1] As methods to get *N*-cyclized products in these substrates, the reactions of *N*-tosyl carbamates (n=1, 2) and amides (n=0) with lower pKa value,[2] or *N*,*O*-bistrimethylsilyl derivatives of 4-pentenamide have been reported (Scheme 1, Eq 1 and 2).[3] However, these methods based on the modification of substrates are quite limited as shown in Scheme 1; for example, the 5-membered ring forming reactions of *N*-tosyl amide (n=1, X=CH_2) or *N*-tosyl urea (n=1, X=NH) give *O*-cyclized products as the major isomers.[4] We report here the results of a new and general method of iodine-mediated cyclization reactions which give *N*-cyclized products as a single isomer with substrates (X=O, NH, CH_2, n=1,2, R=CO_2R) shown in Eq 3 of Scheme 1.[5] The present reaction proceeds in good yield through regio-control of an ambident nucleophile by LiAl(O*t*-Bu)$_4$, and the regio-control was also found to be remarkably affected by the additive employed.

Scheme 1



The reaction of *N*-ethoxycarbonyl allylcarbamate **1a** which can be more easily deprotected than the *N*-tosyl group has been investigated in the presence of various additives. Under usual conditions (I_2, NIS, or I_2-$NaHCO_3$), the *N*-cyclized product **2a** was not obtained or was formed in poor yield due to the low nucleophilicity of the nitrogen atom of **1a**. After a survey of basic reagents for the improvement of nucleophilicity, it was found that the reaction of **1a** in the presence of a relatively strong base such as NaH, *n*-BuLi or LiAl(O*t*-Bu)$_4$ proceeds in good yield to give *N*-cyclized product **2a** without the formation of any *O*-cyclized product.

Scheme 2

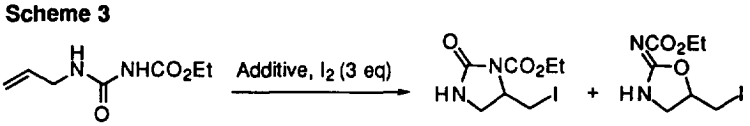


1a **2a**

Additive	Solvent	Yield (%)	Additive	Solvent	Yield (%)
none	Et_2O	0	Ti(O*t*-Bu)$_4$	toluene	58
NIS (instead of I_2)	Et_2O	0	NaH	THF	80
$NaHCO_3$	Et_2O	11	*n*-BuLi	THF	81
Zr(O*n*-Bu)$_4$	toluene	0	LiAl(O*t*-Bu)$_4$	toluene-THF	85
Al(O*t*-Bu)$_3$	toluene	29			

In the reaction of *N*-ethoxycarbonyl *N'*-allylurea **1b**, a remarkable additive effect on the regio-control of the ambident nucleophile was observed as shown in Scheme 3: that is, the reaction in the presence of I_2-$NaHCO_3$ gave *O*-cyclized product **3b** as a single isomer, while the use of *n*-BuLi or LiAl(O*t*-Bu)$_4$ gave *N*-cyclized product **2b** in good yield and with almost complete regio-selectivity. The use of NaH which gave a good result in the reaction of **1a**, resulted in a mixture of **2b** and **3b** in a ratio of 2:1.[6]

Scheme 3



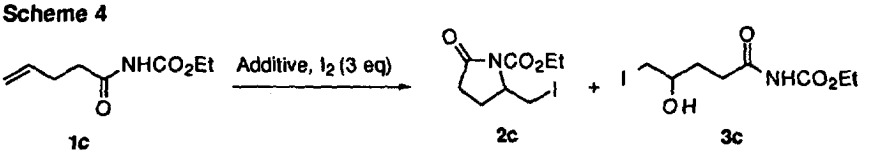
1b **2b** **3b**

Additive	Solvent	Yield (%)	
$NaHCO_3$	Et_2O	0	77
t-BuOK	toluene	0	18
NaH	THF	45	21
n-BuLi	THF	88	trace
LiAl(O*t*-Bu)$_4$	toluene-THF	88	0

This additive effect on the regio-control of the ambident nucleophile was also found in the reaction of *N*-ethoxycarbonyl 4-pentenamide **1c** (Scheme 4). The reaction of **1c** in the presence of $NaHCO_3$-I_2 gave iodohydrin **3c** as the sole product without the formation of any lactam **2c**. The iodohydrin **3c** was formed even under anhydrous conditions using NaH and, in this case, a mixture of **2c** and **3c** was obtained in a ratio of **2c**/**3c** = 3.6. Thus, **3c** may be formed through iodocyclization by *O*-attack of amide-carbonyl and subsequent hydrolysis of the iminoether intermediate, but not by intermolecular addition of I_2 and H_2O to

the double bond. Similar to **1b**, the use of *n*-BuLi or LiAl(O*t*-Bu)$_4$ was the most effective to give *N*-cyclized product **2c** in 68 % or 69 % yield as a single regio-isomer, respectively.

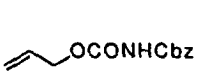
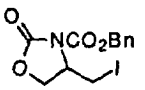
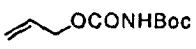
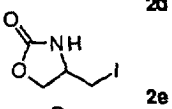
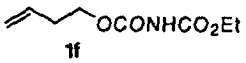
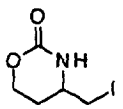
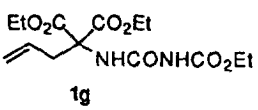
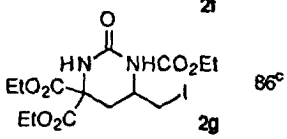
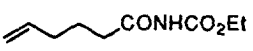
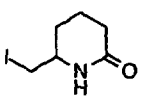
Scheme 4



1c **2c** **3c**

Additive	Solvent	Yield (%)	
$NaHCO_3$	Et_2O	0	53
NaH	THF	51	14
n-BuLi	THF	68	0
LiAl(O*t*-Bu)$_4$	toluene-THF	69	0

Table. Iodoaminocyclization Reaction in the Presence of LiAl(O*t*-Bu)$_4$[a]

Entry	1	Temp.	Time (h)	2	Yield (%)[b]
1	 **1d**	rt	24	 **2d**	79
2	 **1e**	rt	24	 **2e**	68
3	 **1f**	rt	20	 **2f**	73
4	 **1g**	0 °C	20	 **2g**	86[c]
5	 **1h**	0 °C	24	 **2h**	62[d]

[a] Iodoaminocyclization: **1** (0.5 mmol), 1M THF solution of LiAl(O*t*-Bu)$_4$ (0.5 ml), I_2 (1.5 mmol), toluene (6 ml). [b] Isolated yield. [c] The reaction at rt gave a mixture of **2g** and dealkoxycarbonylated product of **2g**. [d] In this case, the use of THF gave a better yield than that of toluene.

In the presence of LiAl(O*t*-Bu)$_4$, the iodoaminocyclization reaction of various substrates was further examined (Table).[7,8] The reaction of *N*-Cbz or *N*-Boc derivatives **1d** and **1e** which can be easily deprotected in comparison with *N*-ethoxycarbonyl derivative **1a** also proceeded in good yields to give *N*-cyclized products **2d** and **2e**, respectively (Entries 1, 2). In the case of **1e**, *N*-unsubstituted cyclic carbamate **2e** was obtained through iodocyclization and subsequent loss of the Boc group (Entry 2). This method can be applied to the 6-membered ring forming reaction. Thus, the reaction of **1f**, **1g** and **1h** gave *N*-cyclized products **2f**, **2g** and **2h**[3] as a single regio-isomer (Entries 3-5). Although the mechanism has

not yet been clarified, in the reaction of **1e-1h**, the formation of dealkoxycarbonylated products was also observed depending on the reaction conditions and the structure of starting materials **1** (Scheme 4, Entries 2-5 in Table). For example, prolonged reaction time brought about an increase in such dealkoxycarbonylated products and, generally, 6-membered ring products **2f-2g** are easily dealkoxycarbonylated as compared with 5-membered products **2a-2d**. The best yield in each reaction obtained under optimized conditions at present is shown in the Table. The effect of $LiAl(O\textit{t}\text{-}Bu)_4$ should be noted; that is, in the reaction of **1h**, the use of *n*-BuLi which gave good results in the reaction of carbamate **1a**, urea **1b** and amide **1c** (Scheme 1-3), resulted in the formation of a complex mixture.

In conclusion, we have succeeded in the development of a new and general method of iodine-mediated cyclization reactions which give *N*-cyclized products through regio-control of an ambident nucleophile such as carbamates, urea and amides by $LiAl(O\textit{t}\text{-}Bu)_4$.

References and Notes

1. (a) Corey, E. J.; Fleet, G. W. J.; Kato, M. *Tetrahedron Lett.* **1973**, 3963-3966. (b) Hirama, M.; Uei, M. *Tetrahedron Lett.* **1982**, *23*, 5307-5310. For reviews of halocyclization: (c) Bartlett, P. A. "*Asymmetric Synthesis*", Ed. Morrison, J. D. Academic Press, Orland, **1984**, Vol 3, Part B, p411. (d) Gardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321-3408.
2. (a) Biloski, A. J.; Wood, R. D.; Ganem B. *J. Am. Chem. Soc.* **1982**, *104*, 3233-3235. (b) Hirama, M.; Iwashita, M.; Yamazaki, Y.; Ito, S. *Tetrahedron Lett.* **1984**, 4963-4964.
3. Knapp, S.; Levorse, A. *J. Org. Chem.* **1988**, *53*, 4006-4014.
4. See ref. 18 in 2a. We also found that the reaction of *N*-tosyl-*N'*-allylurea in the presence of I_2 and $NaHCO_3$ gave a mixture of *O*- and *N*-cyclized products in a ratio of 2 : 1.
5. The preparation of 5-membered lactam through iodocyclization of unsaturated thioimidate was reported. (a) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Heterocycles*, **1987**, *26*, 359-362. (b) Takahata, H.; Takamatsu, T.; Mozumi, M.; Chen, Y-S.; Yamazaki, T.; Aoe, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1627-1629.
6. **2b**: white crystals; mp 158-160 °C; IR (KBr) 3259, 1719, 1709; ^{1}H-NMR ($CDCl_3$) δ 1.35 (3H, t, *J* = 7.1 Hz), 3.31 (1H, ddd, *J* = 1.1, 3.2, 9.9 Hz), 3.39 (1H, dd, *J* = 8.8, 9.9 Hz), 3.50 (1H, dd, *J* = 2.7, 9.9 Hz), 3.62 (1H, t, *J* = 9.3 Hz), 4.28-4.42 (3H, m), 6.26 (1H, br); ^{13}C-NMR ($CDCl_3$) δ: 8.0, 14.3, 43.2, 55.0, 62.8, 151.5, 155.6.
   3b: white crystals; mp 101-103 °C; IR (KBr) 3367, 1655, 1631; ^{1}H-NMR ($CDCl_3$) δ 1.29 (3H, t, *J* = 7.1 Hz), 3.31 (1H, dd, *J* = 8.6, 10.4 Hz), 3.44 (1H, dd, *J* = 4.0, 10.4 Hz), 3.62 (1H, dd, *J* = 6.4, 9.8 Hz), 3.97 (1H, dd, *J* = 8.7, 9.8 Hz), 4.14 (2H, q, *J* = 7.1 Hz), 4.84 (1H, m), 8.40 (1H, br); ^{13}C-NMR ($CDCl_3$) δ: 4.9, 14.3, 48.3, 61.5, 76.1, 164.1, 166.7.
7. Typical procedure of iodoaminocyclization: 1M THF soution of $LiAl(O\textit{t}\text{-}Bu)_4$ (0.5 ml, 0.5 mmol) which was prepared from $LiAlH_4$ and *t*-BuOH in THF, was added to a solution of **1a** (86.5 mg, 0.5 mmol) in toluene (6 ml) under argon atmosphere at rt. After the mixture was stirred for 30 min, I_2 (381 mg, 1.5 mmol) was added, and then the reaction mixture was stirred for 24 h at rt. The mixture was poured into aqueous $Na_2S_2O_3$ solution and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane / AcOEt = 5) gave **2a** (127 mg, 85 %).
8. Carbamates **1a**, **1f**, ureas **1b**, **1g**, and amides **1c**, **1h** could be easily prepared through the reaction of ethoxycarbonyl isocyanate with alchols, amines, and Grignard reagents, respectively.

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