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Iodocarbocyclization of α-iodocycloalkanones bearing an allenyl side chain: synthesis of spirocyclic cycloalkanones

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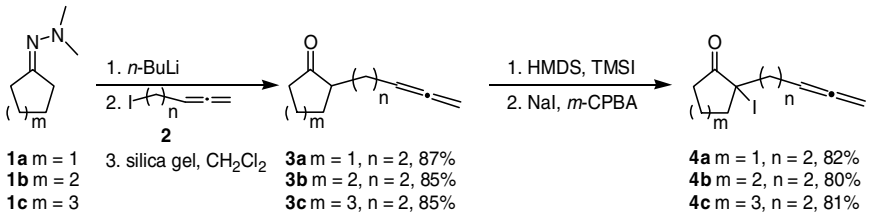
Abstract—$AlCl_3$/ICl-mediated iodocarbocyclizations of α-iodocycloalkanones bearing an allenyl side chain are described. Treatment of iodocycloalkanones **4a**–**i** with $AlCl_3$/ICl gave spirocyclic cycloalkanones **5a**–**i** and **6a**–**i** as a mixture of products.

Ionic iodocarbocyclization reactions involving intramolecular attack of a carbon nucleophile at a double bond activated by an electrophilic iodinating reagent are efficient processes to construct carbocyclic frameworks. Iodocarbocyclization involving 1,3-dicarbonyl compounds, such as 4-alkenyl and 4-alkynyl malonates, was extensively studied by Taguchi and co-workers.[1] The related ionic selenocarbocyclization of α-seleno ketones was investigated by Toru's group.[2] Free-radical atom-transfer cyclization of iodo substrates mediated with hexamethylditin[3] or other reagents[4] has also been reported. We have recently described the $AlCl_3$/ICl-mediated[5] and photo-induced[6] iodocarbocyclization of α-iodocycloalkanones. As an extension, we have investigated $AlCl_3$/ICl-mediated iodocarbocyclization of α-iodocycloalkanones bearing an allenyl side chain. Here, we report our preliminary results.

α-Iodocycloalkanones bearing an allenyl side chain were prepared according to conventional methods (Scheme 1). Deprotonation of hydrazones **1a**–**c** with *n*-BuLi followed by alkylation with allenylalkyl iodides **2** and hydrolysis gave cycloalkanones **3a**–**c**. Treatment of **3a**–**c** with chlorotrimethylsilane and hexamethyldisilazane gave the corresponding trimethylsilylenol ethers. Iodination of these TMS-enol ethers with a mixture of NaI and *m*-CPBA[7] afforded α-iodocycloalkanones **4a**–**c**. Preparation of compounds **4d**–**i** in Scheme 2 and Table 1 according to the same method was reported in our previous paper.[6]

Treatment of iodocycloalkanones **4a**–**f** with $AlCl_3$/ICl in CH_2Cl_2 at 0 °C gave **5a**–**f** as minor products and **6a**–**f** as major products (Scheme 2 and Table 1).[8] When the reactions were performed at −78 °C, compounds **5a**–**f** were obtained predominantly, and compounds **6a**–**f** were formed as minor products. For the formation of the seven-member-ring products, treatment of **4g**–**i** with $AlCl_3$/ICl in CH_2Cl_2 at both −78 °C and 0 °C gave compounds **5g**–**i** as major products and compounds **6g**–**i** as



Scheme 1.

Keywords: Iodocarbocyclization; α-Iodocycloalkanones; Spirocyclic cycloalkanones.
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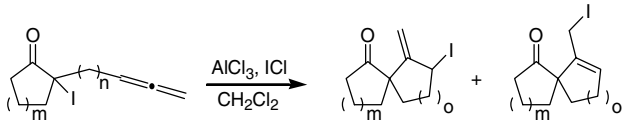


4a m = 1, n = 2
4b m = 2, n = 2
4c m = 3, n = 2
4d m = 1, n = 3
4e m = 2, n = 3
4f m = 3, n = 3
4g m = 1, n = 4
4h m = 2, n = 4
4i m = 3, n = 4

5a m = 1, o = 1 **6a** m = 1, o = 1
5b m = 2, o = 1 **6b** m = 2, o = 1
5c m = 3, o = 1 **6c** m = 3, o = 1
5d m = 1, o = 2 **6d** m = 1, o = 2
5e m = 2, o = 2 **6e** m = 2, o = 2
5f m = 3, o = 2 **6f** m = 3, o = 2
5g m = 1, o = 3 **6g** m = 1, o = 3
5h m = 2, o = 3 **6h** m = 2, o = 3
5i m = 3, o = 3 **6i** m = 3, o = 3

Scheme 2.

minor products. When the reactions were carried out at 30 °C, compounds **5g–i** were formed as minor products and compounds **6g–i** were obtained as major products (Table 2).

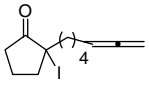
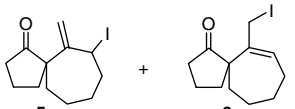
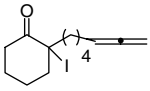
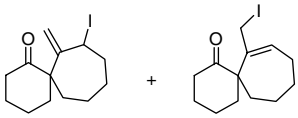
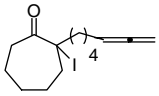
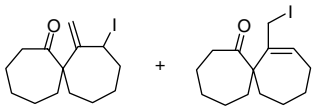
To rationalize these results, a plausible reaction mechanism shown in Scheme 3 was proposed. Upon treatment with $AlCl_3$, the iodoketone moiety in **4d** became transformed into dichloroaluminum enolate via intermediate complex **7**. During this reaction, ICl was generated and reacted with the allenyl group. At this point, addition of one extra equivalent of ICl increased the yield of the products. At −78 °C (entries 1–9) and 0 °C (entries

Table 1. Iodocarbocyclizations of α-iodocycloalkanones at 0 and −78 °C

Entry	α-Iodo cycloalkanones	Products	Yields at 0 °C (**5**:**6**)[a,b]	Yields at −78 °C (**5**:**6**)[a,b]
1	**4a**	**5a** + **6a**	83% (1:6)	85% (3:1)
2	**4b**	**5b** + **6b**	81% (1:7)	84% (4:1)
3	**4c**	**5c** + **6c**	85% (1:9)	87% (3:1)
4	**4d**	**5d** + **6d**	91% (1:8)	94% (5:1)
5	**4e**	**5e** + **6e**	91% (1:8)	92% (6:1)
6	**4f**	**5f** + **6f**	96% (1:9)	93% (6:1)
7	**4g**	**5g** + **6g**	72% (2:1)	74% (6:1)
8	**4h**	**5h** + **6h**	71% (3:1)	75% (6:1)
9	**4i**	**5i** + **6i**	75% (2:1)	73% (5:1)

[a] Direct addition of ICl to **4a–i** at the double bonds of the allenyl side chains also occurred to give some trace amount (3–5%) of side products.
[b] Ratio of the products was determined from the ^1H NMR spectra of products.

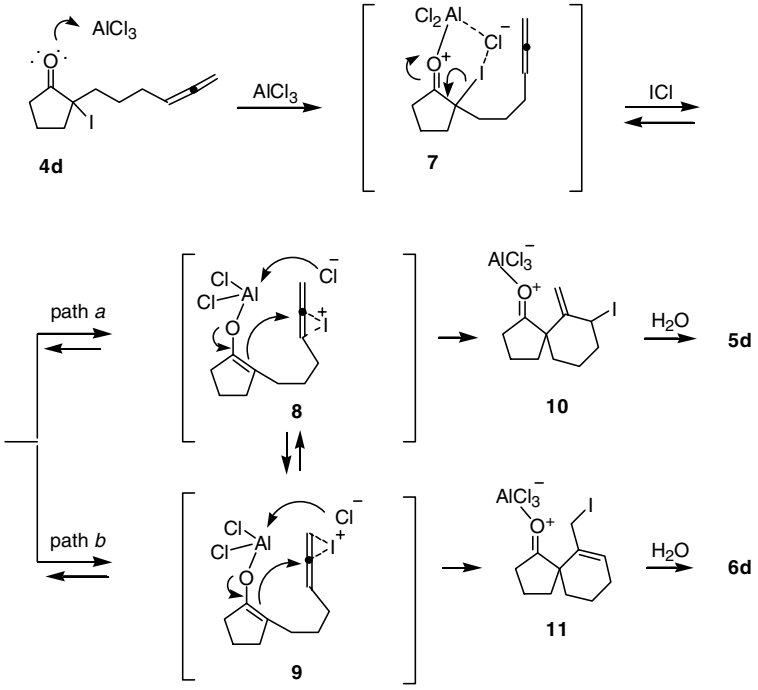
Table 2. Iodocarbocyclizations of α-iodocycloalkanones at 30 °C

Entry	α-Iodo cycloalkanones	Products	Yields at 30 °C (**5**:**6**)[a,b]
1	 **4g**	 **5g** + **6g**	67% (1:8)
2	 **4h**	 **5h** + **6h**	70% (1:5)
3	 **4i**	 **5i** + **6i**	69% (1:7)

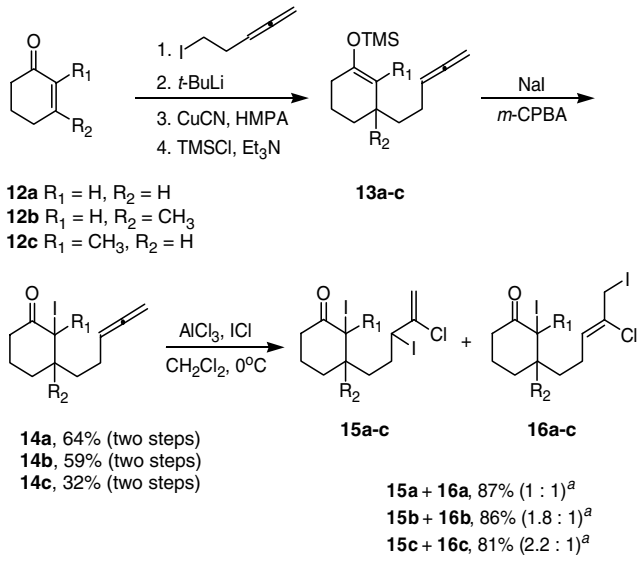
[a] Direct addition of ICl to **4g–i** at the double bonds of the allenyl side chains also occurred to give some trace amount (3–5%) of side products.
[b] Ratio of the products was determined from the ^{1}H NMR spectra of products.

7–9), ICl reacted preferentially at the more electron-rich inner double bonds of the allenyl side chain to form intermediate **8** (pathway a). Subsequent cyclization of **8** gave **10**. Aqueous workup afforded **5d** as the major product. At the 0 °C (entries 1–6, pathway b), complex **8** equilibrated to the more stable complex **9** with I^+ complexing at the terminal double bond. Subsequent cyclization of **9** gave **11**. Aqueous workup afforded **6d** as the major product. Pathway a seems to be a kinetically controlled process, whereas pathway b might be a thermodynamically controlled reaction. For the formation of the seven-member-ring products (entries 7–9), reactions at both 0 °C and −78 °C were all kinetically controlled, and afforded **5g–i** as major products. Only when the temperature of reaction was raised to 30 °C, the reactions (entries 1–3, Table 2) could become thermodynamically controlled, to give **6g–i** as the major products.

We then tested the reaction with iodocycloalkanones **14a**, **b**[6] and **14c**[9] with a 3-substituted allenyl side chain (Scheme 4). To our surprise, none of these iodocycloalkanones could cyclize to the desired products. Only addition of ICl to the allenyl moiety on the side chain occurred to give compounds **15a–c** and **16a–c**. Apparently in the reactions of **4a–i** (Table 1), cyclization of dichloroaluminum enolates to iodonium moieties in **8** and **9** (Scheme 3) are faster than the addition of chloride ion to the iodonium moieties. Only trace amount (3–5%) of side products formed from the addition of ICl to the



Scheme 3.



[a]Ratio of the products was determined from the ^{1}H NMR spectra of products.

Scheme 4.

allenyl groups was detected (Table 1, entries 1–9). In the cases of **14a–c**, addition of chloride ion to the iodonium moieties became much faster than cyclization and afforded **15a–c** and **16a–c** as a mixture of products.

In summary, we have developed a convenient iodocarbocyclization reaction of α-iodocycloalkanones bearing an allenyl side chain. This reaction provides a new method to prepare spirocyclic ketones **5** and **6** bearing allylic iodide moieties. Selective formation of either **5** or **6** as the major product is achieved through controlling the reaction temperature. Furthermore, this ionic iodocarbocyclization reaction is complementary to our photo-cyclization method[6] reported earlier. This ionic cyclization occurred at the central carbon of the allene group whereas the photo-induced cyclization reacted at the proximal carbon of the allene group.

Acknowledgements

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8. A representative procedure for iodocarbocyclization: To a solution of compound **4a** (100 mg, 0.36 mmol) in CH_2Cl_2 (4.0 mL) was added $AlCl_3$ (70 mg, 0.54 mmol) at −78 °C, or 0 °C, or 30 °C. The mixture was stirred at −78 °C, or 0 °C, or 30 °C for 15 min. A solution of ICl in CH_2Cl_2 (1 M, 0.43 mL, 0.43 mmol) was added dropwise at −78 °C, or 0 °C, or 30 °C. The reaction mixture was stirred at −78 °C, or 0 °C, or 30 °C for 5 min and then quenched with H_2O (20 mL), saturated $Na_2S_2O_3$ solution (13 mL) and saturated $NaHCO_3$ solution (13 mL). The mixture was extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine and dried ($MgSO_4$). Concentration and silica gel column chromatography (EtOAc/hexane = 1:150) gave products **5a** and **6a** (80 mg, 83%) as a pale yellow liquid.

Data for **5a**: ^{1}H NMR (600 MHz, $CDCl_3$): 6.46–6.45 (m, 1H), 5.89 (d, $J = 1.9$ Hz, 1H), 4.08 (t, $J = 6.8$ Hz, 1H), 2.45–2.02 (m, 3H), 2.02–1.51 (m, 5H), 1.51–1.23 (m, 2H); IR($CHCl_3$): 2930, 2861, 1703, 1630 cm^{-1}; MS (EI) m/z: 276 (M^+, <1), 149 (32), 84 (100), 79 (16), 53 (16); HRMS (EI) m/z: calcd for $C_{10}H_{13}IO$: 276.0011, found: 276.0022. Data for **6a**: ^{1}H NMR (600 MHz, $CDCl_3$): 5.87 (t, $J = 6.4$ Hz, 1H), 4.16 (s, 2H), 2.58–2.22 (m, 4H), 2.16–1.74 (m, 4H), 1.74–1.23 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 220.8 (C), 130.5 (C), 130.3 (CH), 54.3 (C), 48.6 (CH_2), 38.0 (CH_2), 34.1 (CH_2), 29.6 (CH_2), 27.8 (CH_2), 20.6 (CH_2); IR($CHCl_3$): 2932, 2855, 1705, 1652 cm^{-1}; MS (EI) m/z: 276 (M^+, <1), 149 (32), 84 (100), 79 (16), 53 (16); HRMS (EI) m/z: calcd for $C_{10}H_{13}IO$: 276.0011, found: 276.0006.

9. Compound **14c** was prepared according to the procedure for the preparation of **14a**,**b**, which was reported in Ref. 6.