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Synthesis of medium-sized cyclic γ-haloketones by radical mediated ring-opening reaction of Lewis acid catalyzed (2+2)-cycloaddition products

Kiyosei Takasu,* Satoshi Nagao and Masataka Ihara*

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai 980-8578, Japan

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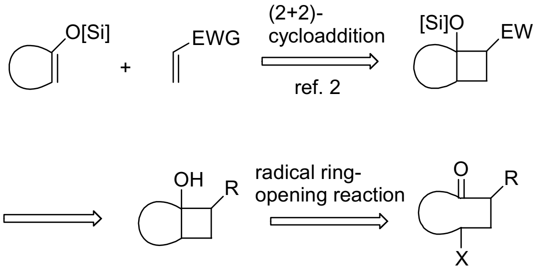
Abstract—Novel entry to synthesize medium-sized cycloalkanones is described. Thus, employment of catalytic (2+2)-cycloaddition for cyclic silyl enol ether followed by radical mediated ring-opening reaction provided medium-sized γ-halocycloalkanones.

Synthesis of medium-sized ring system is one of the challenging and intriguing issues in synthetic chemistry,[1] since there exist many natural products showing attractive biological activities. Among several approaches reported, ring cleavage reaction of bicyclic framework is one of the promising entries for the construction of medium-sized cyclic compounds. In this communication, we describe ring transformation reaction of cyclic silyl enol ethers into γ-halocycloalkanones by means of catalytic (2+2)-cycloaddition followed by radical cleavage reaction.

We recently reported Lewis acid catalyzed (2+2)-cycloaddition of silyl enol ethers and α,β–unsaturated esters to give substituted cyclobutanols in high yields.[2] As the extension of our findings, we envisaged the (2+2)-cycloadducts would be a potential precursor for medium-sized cycloalkanones by the cleavage of a ring fusion C–C bond (Scheme 1). There have been reported several methods for ring opening of cyclobutanols,[3] such as ionic C–C cleavage reaction,[4] radical mediated β-scission[5] and transition metal catalyzed reaction.[6] As the results of our preliminary examinations, radical mediated reaction has been selected for this project on account of good productivity in the desired reaction.



Scheme 1. Our strategy for formation of medium-sized cyclic ketones.

Bicyclic cyclobutanols **1a**–**f** as substrates for the ring cleavage reaction were prepared by our reported method with some modification. Namely, reaction of cyclic silyl enol ether **2a** with hexafluoroisopropyl acrylate in the presence of a catalytic amount of $EtAlCl_2$ gave bicyclo[4.2.0]octane **3a**. After reduction of ester *trans*-**3a**, **4a** was converted into **1a** by desilylation of tertiary alcohol, followed by TBDPS-protection of the resulted diol **5a** (Scheme 2). Substrate **1f**, which is a diastereomer of **1b** having opposite stereochemistry of siloxymethyl substituent, was prepared from *cis*-**3b** by the same sequence.

Next, radical reaction of **1a** was examined under several conditions to generate an alkoxyl radical (Table 1). The reaction would promote through radical fragmentation (atom transfer reaction) of alkoxyl radical, which would be generated from the corresponding hypoiodite.

Keywords: Medium-sized cycloalkanones; Ring-opening reaction; Cyclobutanols; Alkoxyl radicals; (2 + 2)-Cycloaddition.

* Corresponding authors. Tel.: +81 22 217 6887; fax: +81 22 217 6878; e-mail addresses: kay-t@mail.pharm.tohoku.ac.jp; mihara@mail.pharm.tohoku.ac.jp

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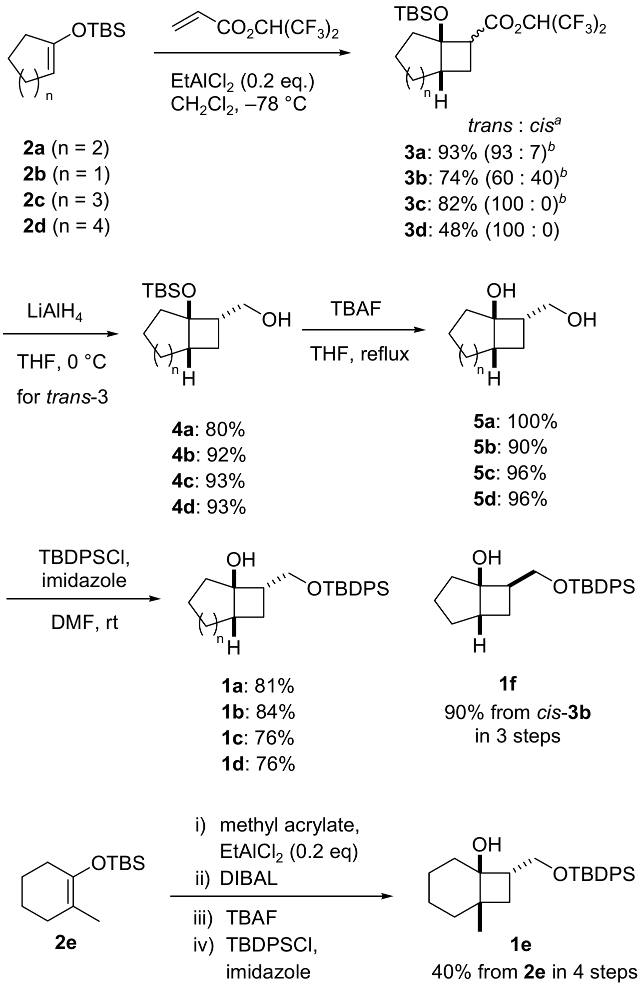


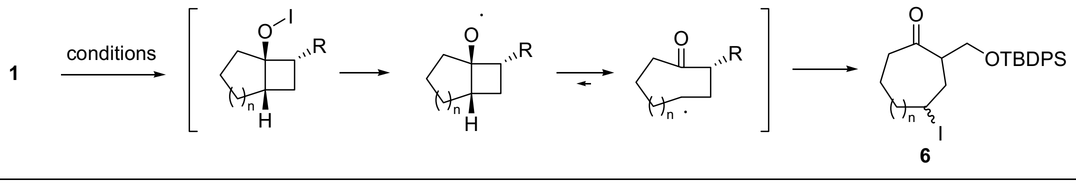
Scheme 2. [a]*trans*-isomer: α-ester, *cis*-isomer: β-ester. [b] See Ref. 2a.

Photoinduced reaction of **1a** in the presence of HgO (1 equiv) and I_2 (3 equiv) using high pressure Hg lump promoted the desired ring-opening reaction to furnish γ-iodocyclooctanone **6a** as a 1:1 mixture of two diastereomers in 24% yield (Table 1, entry 1).[7,8] Stereochemistry of both diastereomers were determined by NOE measurements. When using 3 equiv of HgO, chemical yield of **6a** was improved to 64% (Table 1, entry 2). When the radical reaction was carried out using $PhI(OAc)_2$, the desired ketone **6a** was obtained in high yields under whether photoirradiation or thermal conditions (Table 1, entries 3 and 4).[9] Irradiation of ultrasonic accelerated the radical reaction under the thermal conditions. The thermal reaction required less amount of reagents (iodine and hypervalent reagent) than photoreaction.

N-Iodo succinimide (NIS) as a source of iodonium cation instead of molecular iodine promoted the desired radical reaction to give **6a** in medium to good yield (Table 1, entries 5 and 6), although substrate **1a** was not completely consumed. Further exploration found addition of a catalytic amount of cuprous(I) iodide enhanced the reaction rate and improved chemical yields of **6a** without irradiation of ultrasonic (Table 1, entry 7)[10] Although the action mechanism of CuI in the radical ring-opening reaction is still unclear, we guess CuI accelerates the transformation of alcohol **1** into the corresponding hypoiodite. The reaction using NIS–CuI proceeded smoothly in toluene or cyclohexane (Table 1, entries 8 and 9). The optimized conditions (NIS–CuI) would be estimated as a rather convenient alternative for the radical β-scission reaction compared by the other conditions. On the other hand, only trace amount of the desired product was obtained under NBS–CuBr conditions.

Next, radical ring-opening reactions of alcohol **1b**–**1f** to synthesize medium-sized γ-iodocycloalkanones were examined under two conditions, such as NIS–CuI (condition A) and $PhI(OAc)_2$–I_2 (condition B). Reaction of

Table 1. Radical mediated ring-opening reaction of **1a** under various conditions



Entry	Conditions	Solvent	Temp (°C)	Time (h)	% Yield of **6a**[d]
1	HgO (1 equiv), I_2 (3 equiv), *hv*	Benzene	rt	6.0[b]	24
2	HgO (3 equiv), I_2 (3 equiv), *hv*	Benzene	rt	2.0[c]	64
3	$PhI(OAc)_2$ (2 equiv), I_2 (3 equiv), *hv*	Benzene	rt	2.0[c]	81
4	$PhI(OAc)_2$ (1.4 equiv), I_2 (1.4 equiv), ultrasonic	Cyclohexane/benzene[a]	45	0.5[c]	74
5	NIS (1.2 equiv)	CH_2Cl_2	Reflux	8.5[b]	50
6	NIS (1.2 equiv)	Cyclohexane/benzene[a]	Reflux	5.0[b]	70
7	NIS (1.2 equiv), CuI (0.1 equiv)	Cyclohexane/benzene[a]	Reflux	2.0[c]	80
8	NIS (1.2 equiv), CuI (0.1 equiv)	Toluene	95	1.0[c]	60
9	NIS (1.2 equiv), CuI (0.1 equiv)	Cyclohexane	Reflux	3.5[c]	84

[a] Cyclohexane–benzene = 10:1.

[b] Starting material was still remained at the time.

[c] Reaction was stopped after **1** was completely consumed.

[d] Compound **6a** was obtained as a ca. 1:1 diastereomeric mixtures in all entries.

Table 2. Synthesis of 7 to 10-membered γ-iodocycloalkanones by radical mediated ring-opening reaction

Entry	Substrate	Conditions[a]	Product	% Yield
1	**1b**	A	**6b**	88[b]
2	**1b**	B	**6b**	92[b]
3	**1c**	A	**6c**	30[c]
4	**1c**	B	**6c**	76[d]
5	**1d**	A	**6d**	3[d]
6	**1d**	B	**6d**	62[d]
7	**1e**	A	**6e**	Trace[e]
8	**1f**	B	**6b**	79[b]

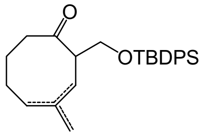
[a] (Condition A) NIS (1.2 equiv), CuI (0.1 equiv), toluene, 95 °C, (condition B) $PhI(OAc)_2$ (1.4 equiv), I_2 (1.4 equiv), cyclohexane/benzene (10:1), 45 °C, sonication.

[b] Products were obtained as ~1:1 diastereomeric mixtures.

[c] As ~9:1 diastereomeric mixtures.

[d] As ~4:1 diastereomeric mixtures.

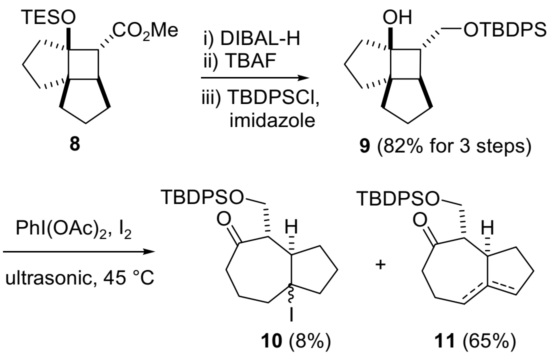
[e] Compound **7e** was obtained as a mixture of isomers.



7e

bicyclo[3.2.0]heptanol **1b** under the condition A in toluene provided γ-iodocycloheptanone **6b** in 88% yield as a 1:1 mixture of diastereomers (Table 2, entry 1). However, reaction of alcohol **1c** and **1d** under condition A resulted in poor productions of **6** and a lot of unknown by-products formed (Table 2, entries 3 and 5). On the other hand, reaction of **1b–d** under condition B afforded the corresponding **6b–d** in 62–92% yield (Table 2, entries 2, 4 and 6). In the reaction of **1e**, which possesses methyl substituent at the position of ring juncture, trace amount of desired product **6e** but dehydrohalogenated product **7e** was obtained as a mixture of regioisomeric olefins under condition A. No significant effect of the stereochemistry of α-substituent of **1** was observed in the radical ring-opening reaction. Thus, the reaction of **1f** afforded **6b**, which is the same product from diastereomer **1b**, in 79 % yield as a 1:1 diastereomeric mixture (Table 2, entry 8 vs Table 1, entry 4).

Radical ring-opening reaction of tricyclic compound **9** which was prepared from intramolecular (2+2)-cycloaddition product **8**[2a] was further investigated. As expected, the desired β-scission reaction promoted under the condition B to furnish iodobicyclo[5.3.0]decanones **10** and bicyclo[5.3.0]decenones **11** as inseparable mixtures in 8% and 65% yields, respectively. **11** could be obtained by the elimination reaction of **10** (Scheme 3).



Scheme 3.

In summary, we have demonstrated the synthesis of medium ring-sized γ-iodocycloalkanones from bicyclo[n.2.0] compounds, which were readily prepared by Lewis acid catalyzed (2 + 2)-cycloaddition from cyclic silyl enol ethers and α,β–unsaturated esters. From the outset of this paper and our preceding results, combination of the (2 + 2)-cycloaddition and radical mediated ring-opening reaction would be a new method for two-carbon ring-enlargement of cycloalkanones.

Acknowledgements

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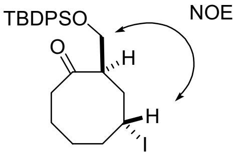
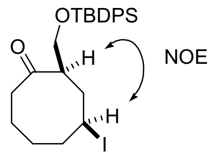
7. Procedure for photoinduced ring-opening reaction using HgO-I_2: A mixture of **1a** (23 mmol, 58 μmol), HgO (37 mg, 0.17 mmol) and I_2 (47 mg, 0.18 mmol) in degassed benzene (3.8 mL) was irradiated for 2 h, with Pyrex-filtered light (400 W Hg lump) under Ar atmosphere. After the resulting mixture was filtered through Celite, the filtrate was diluted with Et_2O. The organic layer was successively washed with 5% aq sodium thiosulfate and water, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel PTLC (AcOEt/hexane = 1:9) to give *trans*-**6a** (10 mg, 32%) and *cis*-**6a** (10 mg, 32%).

8. Spectral data for γ-iodocyclooctanone **6a**. *trans*-**6a**: colourless oil, IR (neat) ν 2930, 2856, 1697, 1427, 1113, 739, 802 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.58 (m, 4H), 7.47–7.35 (m, 6H), 4.60–4.51 (m, 1H), 3.86 (dd, 1H, J = 5.8, 10.2 Hz), 3.73 (dd, 1H, J = 6.6, 10.2 Hz), 2.89–2.79 (m, 1H), 2.70–2.60 (m, 1H), 2.60–2.51 (m, 1H), 2.51–2.38 (m, 2H), 2.00–1.42 (m, 6H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 135.5, 135.4, 133.0, 132.9, 129.7, 127.7, 127.6, 64.2, 53.2, 41.1, 37.2, 37.0, 33.0, 28.4, 27.3, 26.9, 19.3; LRMS *m*/*z* 463 (M^+−57); HRMS calcd for $C_{21}H_{24}IO_2$ Si (M^+–C_4H_9): 463.0590; found: 463.0574. *cis*-**6a**: colourless oil, IR (neat) ν 2932, 2858, 1703, 1427, 1111, 739, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.57 (m, 4H), 7.48–7.34 (m, 6H), 4.44–4.34 (m, 1H), 3.69 (dd, 2H, J = 2.8, 6.0 Hz), 2.78–2.51 (m, 3H), 2.43–2.33 (m, 1H), 2.30–2.15 (m, 2H), 1.99–1.48 (m, 5H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.9, 135.5, 135.4, 132.8, 132.7, 129.8, 129.7, 127.7, 65.6, 56.5, 40.6, 40.5, 36.9, 31.6, 27.1, 26.8, 25.1, 19.3; LRMS *m*/*z* 463 (M^+−57); HRMS calcd for $C_{21}H_{24}IO_2Si$ (M^+−C_4H_9): 463.0590; found: 463.0584; Selected NOEs of *trans*-**6a** and *cis*-**6a** were shown in the following chart.



trans-**6a**



cis-**6a**

9. Procedure for ring-opening reaction under $PhI(OAc)_2$–I_2 conditions: A mixture of **1a** (20 mg, 51 μmol), $PhI(OAc)_2$ (23 mg, 71 μmol) and I_2 (18 mg, 69 μmol) in cyclohexane/benzene (3 mL/0.3 mL) was maintained at 45 °C for 30 min with ultrasonic irradiation. Work-up and purification were carried out as the similar manner as above to give **6a** (20 mg, 74%) as a mixture of diastereomers.
10. Procedure for ring-opening reaction under NIS–CuI conditions: A mixture of **1a** (17 mg, 44 μmol), NIS (12 mg, 52 μmol) and CuI (0.9 mg, 4.7 μmol) in cyclohexane (2.9 mL) was refluxed for 3.5 h. Work-up and purification were carried out as the similar manner as above to give **6a** (19 mg, 84%) as a mixture of diastereomers.