Facile Ring Expansions of α-Halomethyl β-Keto Esters Mediated with SmI_2

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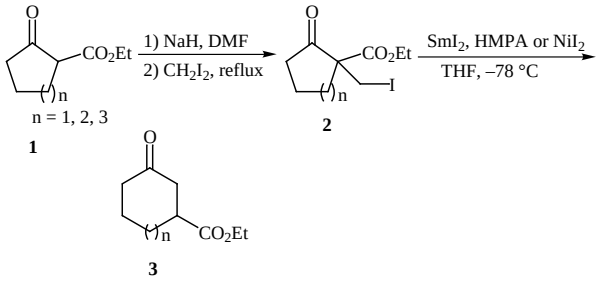
Abstract: Treatment of α-halomethyl β-keto esters with SmI_2 afforded their corresponding one-carbon expanded products with the aids of HMPA or NiI_2.

Key words: SmI_2, ring expansion, bicyclic compounds, β-keto esters, NiI_2

Ring expansion reactions give useful carbocyclic or heterocyclic intermediates in organic chemistry. Epoxide[1] and aziridines[2] were expanded to 5- or 6- membered heterocyclic compounds through cycloaddition or coupling reactions. Nitrogen or oxygen atom insertions in carbonyl derivatives are also well known to give the corresponding lactones[3] or lactams.[4] The ring expansions of many carbocyclic substrates have been also examined to result in one to three carbon-expanded products.[5] Especially, the carbon expanding reactions have been focussed to generate medium and large rings. For the synthetic utility, medium and larger rings have become important to explore and develop new avenues of approach to appropriately functionalized rings.[6] The general methods of medium and larger ring expansions have been studied by various groups. Most of them proceed via anionic procedure.[7] Recently, Dowd and his coworkers reported the radical procedure for the ring expansion using tin reagent.[8] Later, the mechanistic study of this free-radical reaction has been established.[9] Ring expansion reaction of cyclobutanone was reported via addition of diiodomethane.[10]

Samarium diiodide which is a strong one-electron donor have resulted in versatile synthetic utility in organic synthesis.[11, 12] Formation of a ketyl radical[13] of a ketone with SmI_2 and a radical or an anion of an alkyl halide with SmI_2[11] has been well known. In our earlier work,[14] we reported that functionalized cyclopropyl ketones underwent reductive ring opening with SmI_2 in the presence of proton source. On the supposition that formation of a cyclopropane intermediate by radical-radical coupling or through anion and then provides some interesting products by cleavage of cyclopropane, α-iodomethyl β-keto ester derivatives have been examined to react with SmI_2. Treatment of α-iodomethyl β-keto esters with SmI_2 in the presence of catalytic amount of NiI_2 in THF afforded one carbon-ring expanded products in good yields under mild reaction conditions at −78 °C in short reaction time.

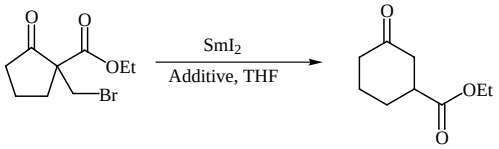
The α-iodomethyl β-keto ester derivatives **2** were readily synthesized by alkylation of commercially available β-keto esters with diiodomethane in the presence of NaH in DMF.[15] A typical experimental procedure is as follows. A THF solution of **2** (0.23 mmol) was diluted in THF (4.5 mL) and then slowly added to a SmI_2 solution (0.5 mmol in 5 mL THF) in the presence of NiI_2 (0.015 mmol) or HMPA (1.38 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for ca. 10 min and then quenched with a saturated NH_4Cl solution (5 mL). The product was extracted with ether, dried over $MgSO_4$, and then concentrated to give a crude product **3** which was purified by silica gel chromatography (silica gel: 230 − 400 mesh, ethyl acetate : *n*-hexane = 1: 5).[16]



Scheme 1

The additives of HMPA,[17] DMPU,[18] $Fe(DBM)_3$,[19] and NiI_2[20] are known as the activators in SmI_2 reactions. HMPA is well used, but not promising because it is highly toxic. Thus, these four activators are compared in this ring expansion reaction. The results are shown in Table 1.

Table 1 SmI_2 Mediated Ring Expansion Reaction with Additives

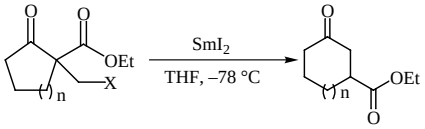


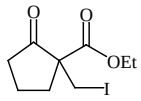
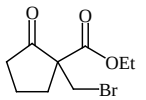
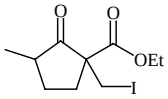
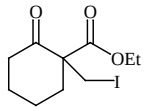
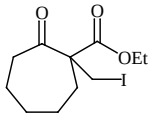
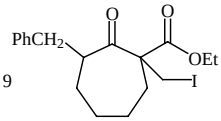
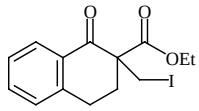
Run	SmI_2 (eq.)	Additives	(eq.)	Temp (°C)	Time(min)	Yield (%)[a]
1	2.15	HMPA	6.0	–78	10	85
2	2.15	DMPU	6.0	–20	30	85
3	2.15	$Fe(DBM)_3$	0.1	–20	180	76
4	2.15	NiI_2	0.1	–78	10	99

a) Yields were determined by ^1H NMR.

A catalytic amount of $Fe(DBM)_3$ works well, but the reaction time is long (180 min) and the yield is low (76%). Some data obtained from the reactions using catalytic amount of NiI_2 were added. The results obtained are summarized in Table 2.

Table 2 Ring Expansions of α-Iodomethyl β-Keto Esters with SmI_2[a]

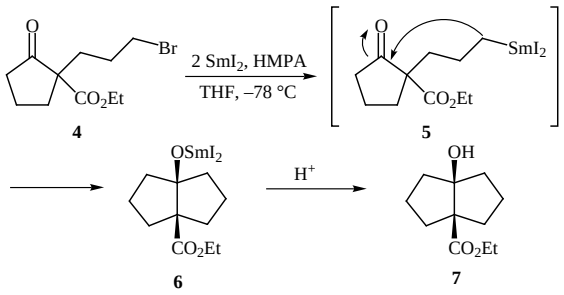


Run	Substrates	Additive	Time (min)	Yield (%)[a]
1		none	10	27
2		HMPA[b]	10	80
3		NiI_2 (10 mol%)	10	99[c]
4		NiI_2 (5 mol%)	10	87
5		HMPA	10	71
6		NiI_2 (5 mol%)	15	82[d]
7		HMPA	10	94
8		NiI_2 (5 mol%)	10	92
9		HMPA	10	87
10		HMPA	120	71

a) Isolated yields. b) The amount of HMPA is 6 eq. c) ^1H NMR yield. d) The ratio of the seven membered ring and the reduced alcohol is ca. 90: 10 by ^1H NMR.

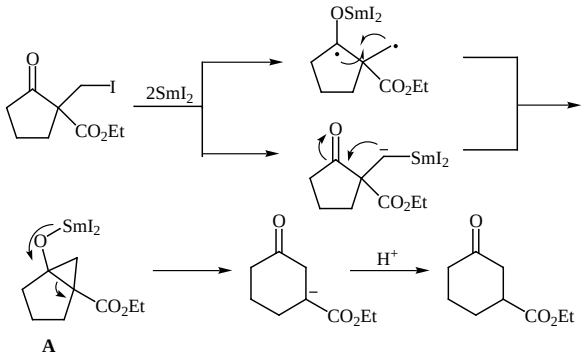
Without using an additive, the yield was low (run 1, 27%). In the most of reactions, the reduced side product of alcohol could not be obtained. But the ratio of the ring-expanded seven membered ring and the reduced alcohol was determined by ^1H NMR (ca. 90:10 in run 7). An acyclic α-halomethyl-β-ketoester did not give a chain extension product; only reduction occurred to give an alcohol.

It is noteworthy that under the same reaction conditions, ethyl(α-iodopropyl) pentyl β-keto ester **4** reacted with SmI_2 to afford a bicyclic compound **7** as shown in Scheme 2.



Scheme 2

Recently, a mechanism on the ring-expansion of α-bromomethyl benzocyclic β-keto ester with SmI_2 has been proposed.[21] Although the reaction mechanism is not clear, there are two possible pathways. The first is a radical pathway similar to the tin induced radical ring expansion.[8] Two equivalent of SmI_2 may generate the ketyl radical and the alkyl radical. The cyclopropane intermediate **A** is generated by coupling of two radicals each other. The intermediate **A** may rearrange to the product via cleavage of bicyclic C-C bond due to a cyclopropane C-C bond activation by CO_2Et group.[14] The other is an anionic pathway. The alkyl radical reduced to an anion of samarium Grignard type, which attack the cyclopropane intermediate like the case of Scheme 3. The present reaction may be widely available for constructing medium- and large-sized ring compounds and has an advantage that NiI_2 (0.05 equiv) is the better activator than HMPA in this reaction.



Scheme 3

Acknowledgement

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(15) For the synthesis of starting material **2**, see; Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565.
(16) Ethyl 3-oxocyclohexanone carboxylate, **3**: ^{1}H NMR (400MHz, $CDCl_3$, TMS) δ 1.21-1.25 (t, 3H), 1.71-1.82 (m, 2H), 2.01- 2.07 (m, 2H), 2.29-2.35 (m, 2H), 2.51-2.53 (m, 2H), 2.75-2.82 (m, 1H), 4.10-4.16 (q, 2H); ^{13}C NMR (100MHz, $CDCl_3$, TMS) δ 14.1, 24.4, 27.7, 40.9, 43.1, 43.2, 60.9, 173.7, 209.3. Ethyl 3-oxocycloheptanone carboxylate, **3**: ^{1}H NMR (400MHz, $CDCl_3$, TMS) δ 1.21-1.25 (t, 3H), 1.55-2.10 (m, 6H), 2.45-2.49 (m, 2H), 2.64-2.69 (m, 2H), 2.74-2.82 (m, 1H), 4.09-4.15 (q, 2H); ^{13}C NMR (100MHz, $CDCl_3$, TMS) δ 14.1, 23.9, 28.3, 33.2, 41.3, 43.9, 45.5, 60.9, 174.5, 212.2.
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