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Samarium(II) iodide-induced tandem reductive coupling-Dieckmann condensation reaction: one-step synthesis of bicyclic oxacyclopentanecarboxylate from bis-α,β-unsaturated esters

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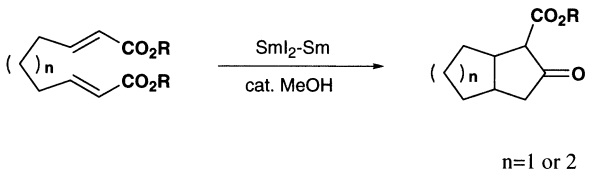
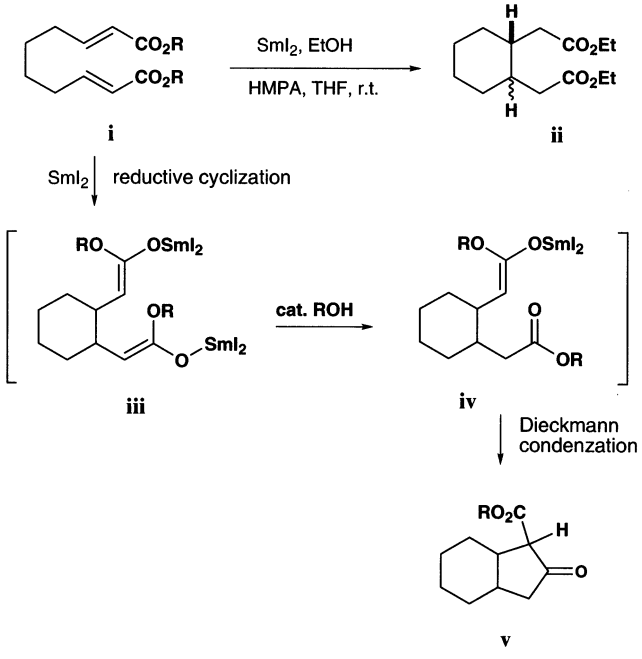
Abstract—The tandem cyclization of bis-α,β-unsaturated esters with SmI_2-Sm–THF in the presence of catalytic amount of methanol was found to stereoselectively provide bicyclo[4.3.0]nonan-8-ones and bicyclo[3.3.0]octan-3-ones.

Numerous efforts have been made to produce bicyclic cyclopentanones, not only in consideration of their abundance in nature, but also their usefulness as versatile synthetic building blocks. The tandem reductive coupling-Dieckmann condensation reaction has been found quite useful as a one-step process for effectively producing oxacyclopentanecarboxylates from α,β-unsaturated esters. Electrohydrodimerization[1] and metal (Yb or Na)-induced cyclization[2] of cinnamate derivatives are methods generally applied for this purpose but to our knowledge none has been shown to produce in an intramolecular manner bicyclic oxacyclopentanecarboxylate. The authors have established an effective method for the SmI_2-induced tandem cyclization of bis-α,β-unsaturated ester to afford bicyclo[4.3.0]octan-8-ones and bicyclo[3.3.0]nonan-3-ones (Scheme 1).[3]



Scheme 1.



Scheme 2.

Keywords: samarium and compounds; radicals and radical reactions; annulation; cyclopentanones.

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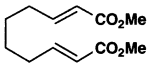
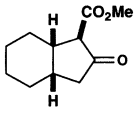
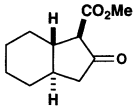
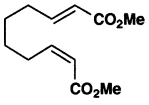
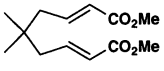
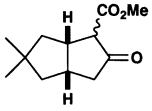
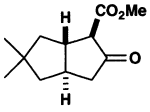
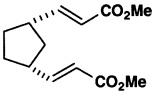
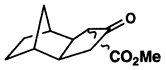
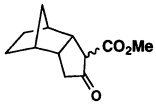
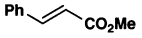
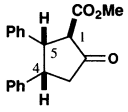
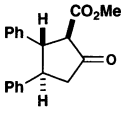
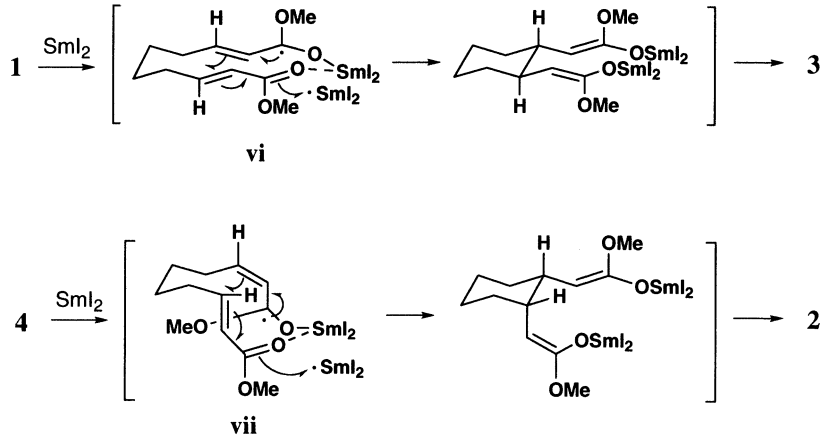
The reaction of bis-α,β-unsaturated ester **i** (R = Et) with SmI_2–HMPA in the presence of an adequate proton source gives intramolecular reductive coupling product **ii** according to Inanaga but formation of bicyclic oxacyclopentanecarboxylate **v** is not described (Scheme 2).[4] Appropriate reaction conditions should make possible Dieckmann condensation subsequent to the intramolecular reductive coupling of **i**. That is, quantitative restrictions on the proton source may bring about transformation of bis-α,β-unsaturated ester **i** to bicyclic keto ester **v** possibly via **iii** and **iv**, and the α-keto ester **v** thus obtained should serve as a new proton source.

Study to clarify conditions for the tandem cyclization reaction indicated 1.5 equiv. of SmI_2, 1.5 equiv. of Sm and trace amount of alcohol in THF effective for this purpose and olefin geometry in substrates and HMPA as an additive to affect the stereochemistry of the

Table 1. SmI_2-induced tandem reductive coupling-Dieckmann condensation of bis-α,β-unsaturated esters[a]

Entry	Esters	Additive	Conditions		Products		Yield[b] (ratio)[c]
			Temp. (°C)	Time			
1	 **1**	none	r.t.	3 h	 **2**	 **3**	63% (**2**:**3**=1:12)[d]
2	**1**	none	50°C	1.5 h	**2**	**3**	78% (**2**:**3**=1:21)
3	**1**	HMPA[e]	r.t.	5 min	**2**	**3**	39% (**2**:**3**=1:2)
4	 **4**	none	50°C	1.5 h	**2**	**3**	76% (**2**:**3**=14:1)
5	 **5**	none	0°C	15 min	 **6**		62%
6	**5**	HMPA[e]	r.t.	5 min	**6**	 **7**	41% (**6**:**7**=4:5)[d]
7	 **8**	none	r.t.	17 h	 **9**	 **10**	49% (**9**:**10**=9:1)[d]
8	 **11**	none[f]	r.t.	2.5 h	 **12**	 **13**	47% (**12**:**13**=3:1)[d]
9	**11**	HMPA[g]	r.t.	5 min	**12**	**13**	70% (**12**:**13**=1:2)

a) Reactions were conducted at 0.33 mmol scale. b) Isolated yield. c) Determined by ^1H NMR (400 or 300 MHz) analysis. d) Compounds **2** and **3**, and **9** and **10** were inseparable. Compounds **6** and **7**, and **12** and **13** were separable. e) 6.6 equiv of HMPA and 2.2 equiv of SmI_2 were used. f) 0.75 equiv of SmI_2 and 0.75 equiv of Sm were used. g) 3.3 equiv of HMPA and 1.1 equiv of SmI_2 were used.



Scheme 3.

cyclized products, as evident from Table 1. On treating bisenoate **1**,[5] whose double bonds have the *E* configuration, with SmI_2–Sm[6] in THF in the presence of a trace amount of methanol at room temperature, (1*R**,6*S**,7*R**)-7-methoxycarbonylbicyclo[4.3.0]nonan-8-one (**3**)[7] having a *trans* ring juncture was obtained as the main product along with a small amount of *cis* isomer **2** (**2**:**3** = 1:12) (entry 1). Higher reaction temperature (50°C) improved the value of the ratio of **3**/**2** (**2**:**3** = 1:21) and yield (entry 2).[8] HMPA addition enhanced the reaction rate, though considerably decreased the ratio of **3**/**2** (entry 3). Reaction of **4**,[9] the *E*,*Z*-isomer of **1**, with SmI_2–Sm gave *cis* isomer **2**[10] as the major product, **2**:**3** = 14:1 in good yield (entry 4). This tandem cyclization was found useful for establishing a bicyclo[3.3.0]octane ring system. The cyclization of **5**[11] with SmI_2–Sm in THF proceeded to completion within 15 min at 0°C with only *cis* isomer **6**[12] formation (entry 5). The presence of HMPA resulted in the warped *trans* isomer **7**[13] formation, in addition (entry 6). The severely strained **7** was not synthesized from the corresponding *trans* cyclopentane diester, methyl 2-{(1*R**,2*R**)-2-[(methoxycarbonyl)methyl]-4,4-dimethylcyclopentyl}acetate, by typical conditions for Dieckmann condensation such as sodium methoxide in toluene or in DMSO. Reaction of bisenoate **8**[5] with SmI_2–Sm provided tricyclic keto esters **9**[14] and **10**,[15] each possessing a *cis* ring juncture, in moderate yield. Intermolecular cyclization of methyl cinnamate (**11**) with SmI_2–Sm in THF and SmI_2 in THF–HMPA gave *cis* isomer **12**[16] and *trans* isomer **13**[1c] as major products, respectively, the former being in contrast to electrohydrodimerization and metal-induced coupling of **11** which mainly provide *trans* isomer **13**.[1,2]

Stereoselectivity in intramolecular tandem cyclization of **1** and **4** in THF (entries 2 and 4) can be explained as due to generation of favored cyclic transition structures **vi** and **vii** enforced by chelation, as shown in Scheme 3.

In a typical experiment, a suspension of Sm (151 mg, 1.00 mmol) and 1,2-diiodoethane (141 mg, 0.500 mmol) in THF (3.3 mL) was sonicated for 1 h at room temperature under an argon atmosphere. The mixture, following addition of a solution of bis-α,β-unsaturated ester **1** (75.3 mg, 0.333 mmol) and methanol (40 μg) in THF (2 mL) was stirred for 1.5 h at 50°C and the reaction was terminated with few drops of 30% hydrogen peroxide and 1N HCl. The mixture was then diluted with ether, washed with saturated $NaHCO_3$ and saturated $Na_2S_2O_3$, dried and concentrated. The crude product was purified by silica gel column chromatography to give keto ester **3** (51.0 mg, 78% yield) which contained a small amount of **2** (**2**:**3** = 1:21).

In summary, the authors established an effective and direct one-step process for obtaining bicyclo[4.3.0]nonan-8-ones and bicyclo[3.3.0]octan-3-ones from simple bis-α,β-unsaturated esters using one electron transfer reagent SmI_2 in the presence of methanol in trace amount. By these mild conditions, the use of strongly basic conditions for the Dieckmann condensation is avoided and good to excellent stereocontrol over newly formed ring junctures in the product is possible.

Acknowledgements

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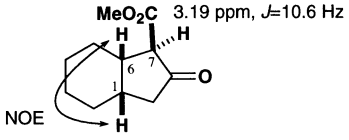
8. It is likely that the resulting Sm(III) species is reduced back to Sm(II) species by the proportionality of oxidation states with Sm metal. Reaction of **1** with 3 equiv. of SmI_2 in THF in the presence of a trace amount of methanol at 50°C gave **3** as the main product in similar yield, but the value of the ratio of **3**/**2** (**2**:**3**=1:15) was worse than that obtained by SmI_2–Sm treatment.
9. Bisenoate **4** was prepared from cyclohexene in three steps: (1) O_3, CH_2Cl_2, −78°C then Ph_3P; (2) $Ph_3P{=}CHCO_2Me$ (1.2 equiv.), CH_2Cl_2, rt; (3) $(PhO)_2P(O)CH_2CO_2Me$,[17] NaH, THF, −78°C to rt.
10. Relative configurations of **2** were elucidated by NOE experiment and coupling constants in ^1H NMR.



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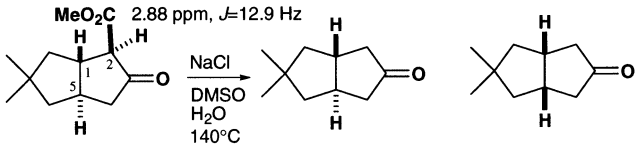
13. Configurations of ring junctures in **7** was elucidated based on the ^{13}C NMR analysis of **14** derived from **7** by decarbomethoxylation with NaCl, DMSO and H_2O at 140°C.[18] The ^{13}C NMR spectrum of **14** indicated six signals, while that of **15**[11] from **6**, seven signals. ^{13}C NMR (100 MHz, $CDCl_3$) of **14**: δ 32.1, 41.8, 44.0, 44.2, 48.3, 220.4; ^{13}C NMR (100 MHz, $CDCl_3$) of **15**: δ 28.4, 29.8, 38.7, 40.8, 44.9, 48.9, 220.9. The relative configuration of C1–C2 in **7** was derived based on the coupling constant of C2–H (2.88 ppm), J=12.9 Hz, in ^1H NMR.



7 **14** **15**

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16. Stereochemistries of C1, C4 and C5 in **12** were found based on chemical transformation and ^1H NMR. Relative configuration of C1 and C5 were determined based on coupling constants of C1–H (3.82 ppm), J=11.6 Hz. These of C4 and C5 were clarified based on the transformation of **12** to known *meso* 3,4-diphenyl-1-cyclopentanone[19] by decarbomethoxylation with NaCl, DMSO and H_2O at 140°C.
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