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Samarium (II) iodide-induced intermolecular coupling of α,β-unsaturated esters with ketones: reactions of methyl propiolate and ethyl buta-2,3-dienoate with cyclohexanone and its application to synthesis of a terpene carboxylic acid

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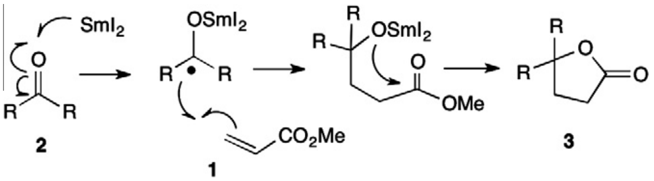
ABSTRACT

The reactions of methyl propiolate and ethyl buta-2,3-dienoate with cyclohexanone induced by SmI_2 occurred either at α- or β-position to yield different products depending on with or without a proton source. The synthesis of terpenic acid was demonstrated using this reaction.

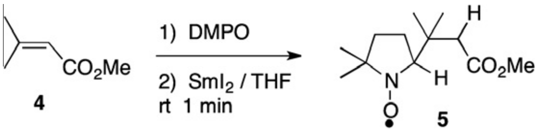
One-electron reductions induced by samarium (II) iodide are well known and documented.[1] These reactions are routinely used for many synthetic works and mechanistic studies are reported.[2] We have reported some results on the reductive cyclization.[3] Methyl acrylate (**1**) reacts with ketone **2** to form lactone **3**, which is an expected product in the well known reaction (Scheme 1).[4] Product **3** is thought to be derived from the coupling between a ketyl radical and an electron deficient olefin.

Recent reports have shown the selective conjugate reduction of the electron-deficient double bond followed by anionic (or possibly radical) addition to the carbonyl group.[5] Comparison of the half-wave potentials of α,β-unsaturated carbonyls with those of corresponding saturated carbonyl compounds has been extensively studied in electrochemistry.[6] The first waves of carbonyl groups, referred to as SCE., are −2.45 V (cyclohexanone), −2.25 V (methyl ethyl ketone), −1.8 V (propionaldehyde), −1.55 V (cyclohex-2-en-1-one), −1.50 V (acrolein), and −1.42 V (methyl vinyl ketone), respectively.[6] Therefore, the reduction of an α,β-unsaturated carbonyl moiety seems easier than that of an isolated ketone carbonyl group in electrochemical conception. About the ease of reduction of α,β-unsaturated carbonyl compounds, we have observed the formation of radical **5** from methyl 3-methylbut-2-enoate (**4**) induced by SmI_2 through radical trapping with DMPO using the ESR spectrum (Scheme 2). We reported these results as the first direct evidence of radical intermediates in SmI_2-induced reaction by ESR spectra.[7] The precise mechanism for a given reductive carbonyl-alkene coupling will depend on the specific combination of reactants and the respective redox potential and rates of reduction of each component by the lanthanide reagent.

We are interested in the reaction of propiolate (**6**) with cyclohexanone (**7**). Meanwhile, the results by Kim et al. reported that the coupling of cyclohexanone (**7**) with methyl propiolate (**6**) gave a sole product **9** in 74% yield (Scheme 3),[8] expected by the mechanism via ketyl radical as illustrated in Scheme 1. We have re-



Scheme 1. Reaction of methyl acrylate (**1**) with ketone **2**.



Scheme 2. Reaction of methyl 3-methylbut-2-enoate (**4**) with SmI_2 in the presence of DMPO.

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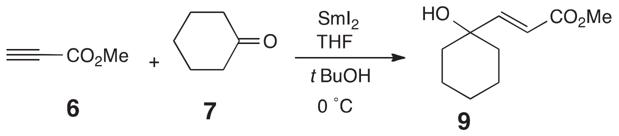
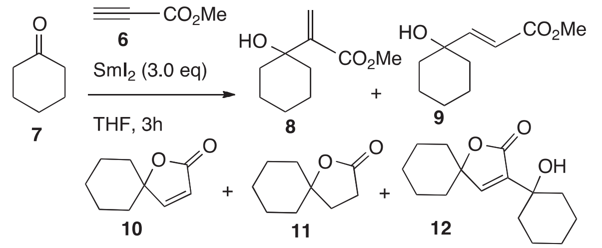


Scheme 3. Reaction of methyl propiolate (**6**) with cyclohexanone (**7**) induced by $\mathrm{SmI_2}$ reported by Kim et al.[8]

Table 1

$\mathrm{SmI_2}$-induced reaction of methyl propiolate (**6**) with cyclohexanone (**7**) studied by us



Entry[a]	Additives	Temp (°C)	Ratio(GC–MS)				
			8	9	10	11	12
1[b]	None	0	0	0	0	0	100
2		rt	15	7	0	0	78
3	^{t}BuOH	0	32	27	13	16	27
4[c]	(3 equiv)	rt	40	14	10	26	10

[a] A solution of 1 mmol of **6** and **7** in THF (10 mL) was added into $\mathrm{SmI_2}$ (3 mmol).

[b] Isolation yield: **12** (48%).

[c] Isolation yield: **8** (23%), **9** (8%), **11** (19%), and **12** (5%).

peated this reaction and found that compound **8** was also produced as well as **9** and other products (Table 1) (vide infra).[9] Thus, we have studied the reactions using propiolate and allenic ester with cyclohexanone induced by $\mathrm{SmI_2}$ under different conditions in detail and demonstrated the utility of this reaction to a synthesis of the natural product.

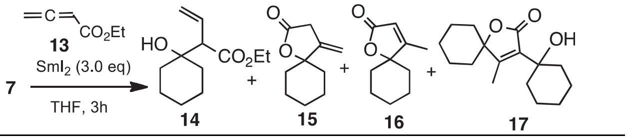
Cyclohexanone (**7**) was subjected to reaction with methyl propiolate (**6**), the results of which were shown in Table 1. The products were isolated and their structures were characterized. The ratio was determined by GC-MS to see the product distribution. Five products were formed depending on the conditions as shown in Table 1. The spectroscopic data of compound **8** indicated the presence of hydroxy (3500 cm^{-1}) and ester (1710 cm^{-1}) groups as well as an exomethylene (δ 5.77, 6.16) establishing its structure.[10] This compound **8** may be formed by the attack at the α-position of propiolate to cyclohexanone.

While compound **9** had an α,β-unsaturated ester [δ 6.07 (d, J = 15.6 Hz), 7.04 (d, J = 15.6 Hz)] moiety as well as a hydroxy (3450 cm^{-1}) group.[11] It must be derived by the attack at the β-position of propiolate to cyclohexanone (Fig 2). This product **9** is the same as that reported by Kim and co-workers.[8] However, **9** was not a sole product. Compound **10**[12] (1775, 1750 cm^{-1}) is unsaturated lactone derived from further cyclization of compound **9**, with *Z*-stereochemistry. Compound **11**[12] is saturated lactone (1770 cm^{-1}), formed by reduction of compound **10**. Compound **12**[12] is noteworthy, because this compound came from the attack of the anion produced at the α-position of the propiolate moiety regardless of before or after cyclization to **10** (vide infra). This compound clearly shows that the β-position of methyl propiolate worked as a radical and that the α-position worked as an anion.[13]

Because the radical formed from methyl propiolate (**6**) is similar to allenic ester (Fig. 2), and ethyl buta-2,3-dienoate (**13**) is considered to be 'exomethylene acrylate', we are interested in the reaction of **13** with **7** induced by $\mathrm{SmI_2}$.

Table 2

Reaction of ethyl buta-2,3-dienoate (**13**) with cyclohexanone (**7**) induced by $\mathrm{SmI_2}$

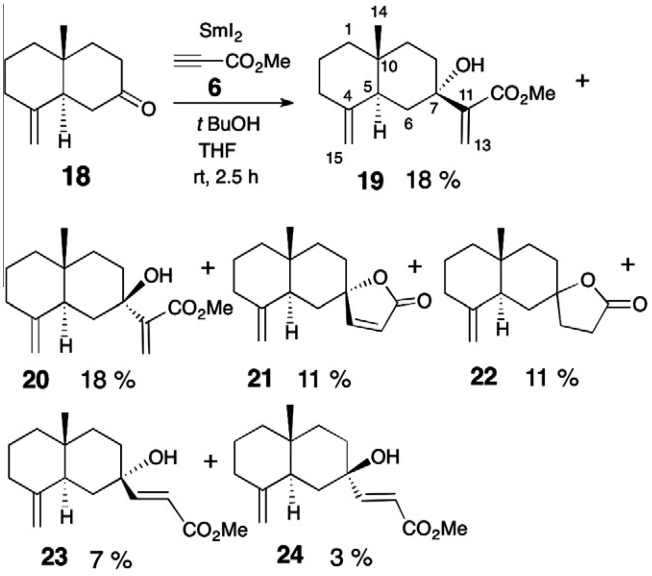


Entry[a]	Additives	Temp (°C)	Ratio(GC–MS)			
			14	15	16	17
1[b]	None	0	96	0	4	–
2		rt	62	2	22	14
3[c]	^{t}BuOH	0	49	32	16	3
4	(2 equiv)	rt	30	0	67	3

[a] A solution of 1 mmol of **7** and **13** in THF (10 mL) was added into $\mathrm{SmI_2}$ (3 mmol).

[b] Isolation yield: **14** (68%) and **16** (3%).

[c] Isolation yield: **14** (49%), **15** (32%), **16** (16%), and **17** (1.5%).



Scheme 4. Reaction of ketone **18** with methyl propiolate (**6**).

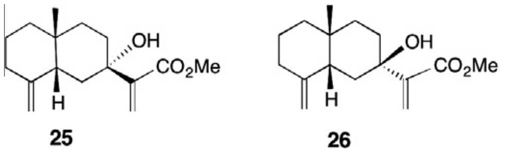


Figure 1. The cis diastereoisomers.

Ethyl butane-2,3-dienoate (**13**) and cyclohexanone (**7**) were reacted with 3 equivalents of $\mathrm{SmI_2}$ in THF at 0 °C or at rt as shown in Table 2. The product ratio indicates that compound **14**,[12] derived by the α-attack of allenic ester was the major product (Table 2, entry 1). But, with a proton source at rt (entry 4), the ratio of **16**[12] predominated. Again compound **17**[12] was formed as a result of the α-attack of the anion produced at the α-position of allenic ester, although the ratio was not high. Thus, the α-attack predominated without additive, and the β-attack was the main reaction with a proton source. It is because an anion is quenched by a proton source and a radical reaction should be a main course.

We demonstrate now the application of this reaction to the synthesis of a natural product. The partial structure having α-methylene-β-hydroxyester derivative is a complicated target to

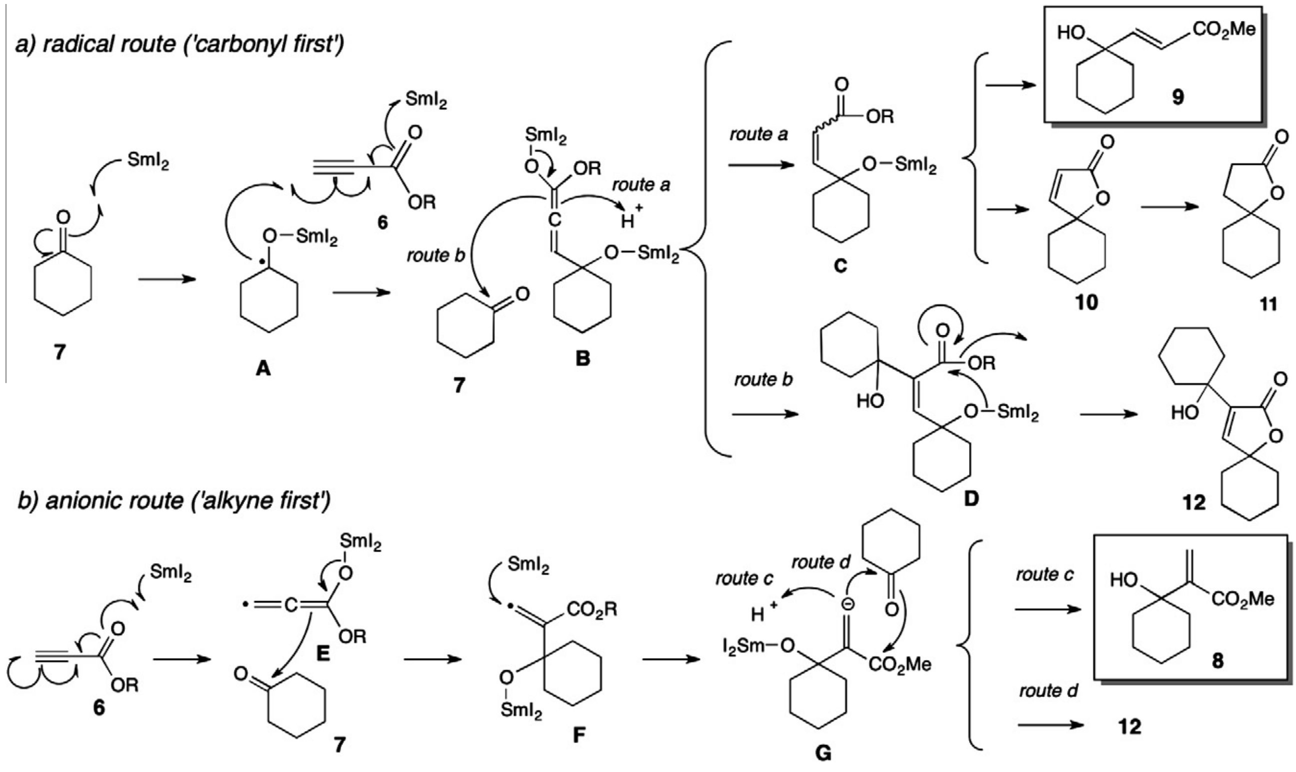
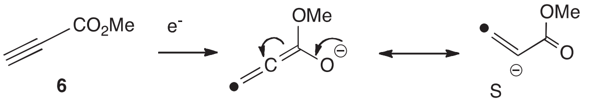


Figure 2. Mechanisms for the reaction in Table 1.



Scheme 5. Bifunctional synthon **S** derived from methyl propiolate (**6**).

construct. It takes several steps to reach such a partial structure. Now, we attempt the reaction between known bicyclic ketone **18**[14] and methyl propiolate (**6**) with SmI_2 in the presence of ^{t}BuOH as a proton source. The product composition was shown in Scheme 4 and the desired product **19**[15] was isolated in 18% yield. Its stereoisomer **20**[12] was also isolated in 18%, as well as **21**–**24**.[12] The cis-fused isomer of **18** was similarly treated to give both **25** and **26** (Fig. 1).[12] The spectroscopic data of four isomeric products, **19**, **20**, **25**, and **26**, were compared to each other. By comparison of the spectral data with those of the natural product,[16] compound **19** was concluded to be the natural product.

The mechanism is shown in Figure 2 for these cross coupling reactions. In the case of propiolate, the attack at the β-position should occur by radical coupling between ketyl radical **A** and **6** (radical route). The intermediate **B** can take a proton giving **C** (route a) or attack cyclohexanone forming **D** (route b). Each produces **9**, **10**, **11**, and **12**, respectively.

Compound **8** is produced by an aldol-type carbon–carbon bond formation. The radical anion **E** attacks the carbonyl group of **7** at the α-position to form **F**. The radical is further reduced by SmI_2 to afford an anion **G**, which is protonated by ^{t}BuOH (anionic route).

These results suggest that methyl propiolate (**6**) can be considered as a bifunctional synthon in which the α- and β-positions both act as anion equivalents (Scheme 5). Especially the formation of compound **8** strongly indicates the formation of the species **F**. Preferential reduction of electron deficient olefin was observed using ESR by radical trapping experiments.[7] Compound **12** was formed by the attack at both α- and β-positions of α,β-unsaturated carbonyl compound **6**.

In conclusion, the carbon–carbon bond forming reaction by one-electron reduction using SmI_2 starts from not only the reduction of the ketone giving ketyl radical (**A**) (to **9**, **10**, and **11** (via **B** and **C**) or to **12** (via **B** and **D**) (carbonyl first route in Fig. 2)), but also reduction of the α,β-unsaturated carbonyl moiety giving an anion radical (**E**) (to **8** (via **F** and **G**, route c) or to **12** (via **F** and **G**, route d) (alkyne first route in Fig. 2)). These depend on the reaction conditions and compete with each other.[7] This reaction was successfully applied to the synthesis of natural product **19** in one step.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.120.

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10. *Compound* **8**: Oil; FTIR: 3500, 1710, 1620 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.16 (1H, d, *J* = 0.6 Hz), 5.77 (1H, d, *J* = 0.6 Hz), 3.78 (3H, s), 3.64 (1H, s), 1.5-1.9 (8H, m), 1.22 (2H, m); ^{13}C NMR (75 MHz, CDCl$_3$) δ 21.6 (CH$_2$ × 2), 25.6 (CH$_2$), 36.1 (CH$_2$ × 2), 51.8 (OCH$_3$), 71.9 (C), 123.4 (CH$_2$), 146.3 (C), 168.2 (C); MS (EI) *m*/*z* 184 [M$^+$], 156, 152, 141, 124, 109 (base), 96, 81, 68, 55; HRMS (EI) Found *m*/*z* 184.1086 [M$^+$]. C$_{10}$H$_{16}$O$_3$ requires 184.1099.
11. *Compound* **9**: Oil; FTIR: 3450, 1720, 1650 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.04 (1H, d, *J* = 15.6 Hz), 6.07 (1H, d, *J* = 15.6 Hz), 3.74 (3H, s), 1.20–1.90 (10H, m); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.4 (C), 155.1 (CH$_2$), 117.8 (CH$_2$), 71.6 (C), 51.6 (OCH$_3$), 37.0 (CH$_2$ × 2), 25.2 (CH$_2$), 21.5 (CH$_2$ × 2); MS (CI) *m*/*z* 185 [M+H]$^+$, 167, 153 (base); HRMS (CI) Found *m*/*z* 185.1193 [M+H]$^+$. C$_{10}$H$_{17}$O$_3$ requires 185.1177.
12. See Supplementary data.
13. Similar results were reported by Kagan et al.: Machrouhi, F.; Hamann, B.; Namy, J.-L.; Kagan, H. B. *Synlett* **1996**, 633–634.
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15. *Compound* **19**: IR (FT) 3520, 1715 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 6.20 (1H, d, *J* = 0.5 Hz, H-13), 5.84 (1H, d, *J* = 0.5 Hz, H-13), 4.70 (1H, d, *J* = 1.6 Hz, H-15), 4.37 (1H, d, *J* = 1.6 Hz, H-15), 3.80 (3H, s, OCH$_3$), 3.46 (1H, s, OH), 2.39 (1H, br d, *J* = 12.3 Hz, H-5), 2.31 (1H, br d, *J* = 12.6 Hz, H-3), 2.06 (1H, td, *J* = 12.6, 6.0 Hz, H-3), 1.84 (1H, td, *J* = 12.6, 4.0 Hz, H-8), 1.76 (1H, td, *J* = 12.6, 3.4 Hz, H-9), 1.73 (1H, m, H-6), 1.70 (1H, m, H-8), 1.66 (1H, t, *J* = 12.3 Hz, H-6), 1.59-1.64 (2H, m, H-2), 1.45 (1H, br d, *J* = 12.9 Hz, H-1), 1.39 (1H, td, *J* = 12.9, 5.5 Hz, H-1), 1.31 (1H, ddd, *J* = 12.6, 4.1, 2.3 Hz, H-9), 0.73 (3H, s, H-14); ^{13}C NMR (150 MHz, CDCl$_3$) δ 168.2 (CO), 150.7 (C-4), 146.4 (C-11), 123.4 (C-13), 105.1 (C-15), 72.9 (C-7), 52.0 (OCH$_3$), 43.8 (C-5), 41.3 (C-1), 36.9 (C-3), 35.9 (C-9), 35.6 (C-10), 34.4 (C-6), 31.4 (C-8), 23.5 (C-2), 15.5 (C-14); MS (EI) *m*/*z* 264 [M$^+$], 246 (base), 231, 187, 171, 123, 93, 43; HRMS (EI) Found *m*/*z* 264.1718, Calcd for C$_{16}$H$_{24}$O$_3$, 264.1726.
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