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Alkylation-Annulation of Halo Esters with Organometallic Reagent/SmI_2 Couple Leading to Cycloalkanols: A Facile Cyclopropanol Synthesis from a 3-Halo Ester

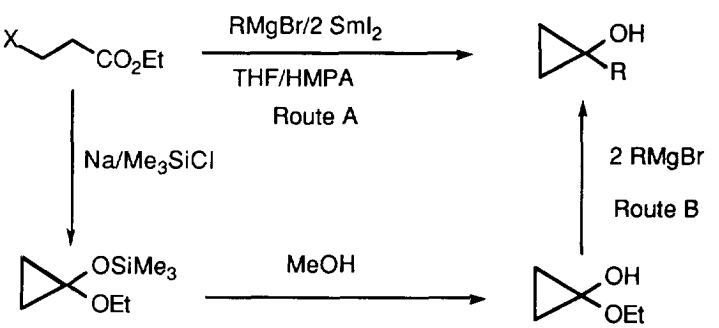
Shin-ichi Fukuzawa,* Hideki Furuya, and Teruhisa Tsuchimoto†

Department of Applied Chemistry, Chuo University, Kasuga, Bunkyo-ku, Tokyo 112, Japan

Abstract: Transformation of a 3-halo ester to cyclopropanols has been accomplished in excellent yields under mild conditions employing a coupled reagent of samarium(II) diiodide with organometallic reagents. 5- and 6-Halo esters were also transformed into cyclopentanols and cyclohexanols, respectively, in low to moderate yields. The reaction with a 4-halo ester gave 2,2-disubstituted tetrahydrofuran as a major product that resulted from double alkylation followed by cyclization; a substituted cyclobutanol was formed in poor yield.

Introduction

Samarium(II) diiodide (SmI_2) has proven to be superior to other reducing agents during intramolecular reductive cyclization of halo-substituted alkenes, ketones and esters.[1-2] The cycloalkanol synthesis by the SmI_2 induced intramolecular Barbier reaction attracted us because we felt that if this reaction was applied to 3-halo ketones, synthetically important cyclopropanols would be easily prepared.[3] However, 3-halo ketones were not readily available. We tried to prepare a 3-halo ketone by direct alkylation of a commercially available 3-bromo ester with an organometallic reagent (e.g., Grignard reagent) under various conditions, but the product was the halo-substituted tertiary alcohol. When we performed the alkylation of the 3-bromo ester in the presence of SmI_2 without isolation of a 3-bromo ketone, the desired cyclopropanol was obtained in excellent yield without contamination of the tertiary alcohol. We reported in a preliminary communication the subsequent alkylation and annulation of the 3-halo ester leading to 1-substituted cyclopropanols.[4] One of the most general procedures



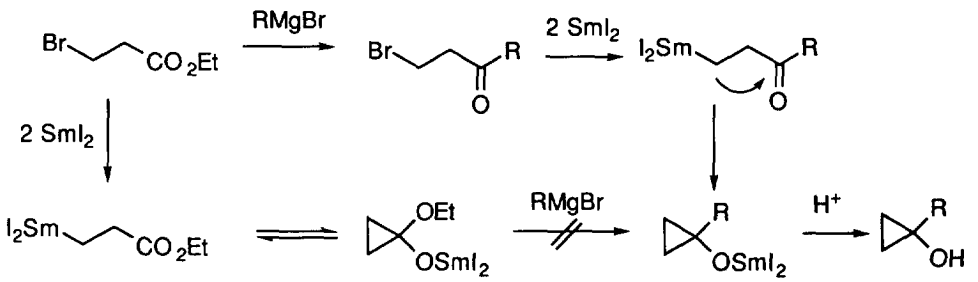
Scheme 1

† Graduate student from Tokyo Institute of Technology.

for the synthesis of a 1-substituted cyclopropanol is the direct alkylation of a cyclopropanone hemiacetal with a Grignard reagent (Scheme 1, route B).[5] A cyclopropanone hemiacetal is usually prepared from a 3-halo ester by way of 1-alkoxy-1-trimethylsiloxycyclopropane, it then takes three steps to obtain the 1-substituted cyclopropanol from a 3-halo ester. Our new procedure provided the one-step synthesis without preparation of a cyclopropanone hemiacetal (Scheme 1, route A).[6] In this report, we detail not only the alkylation-annulation reaction of the 3-halo ester with the organometallic reagent/SmI_2 couple but also the reaction with 4-, 5-, and 6-halo-substituted esters.

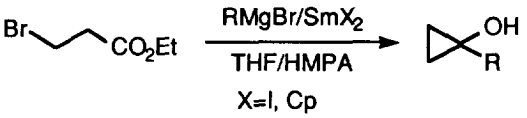
Results and Discussion

Reaction with 3-bromo ester. When ethyl 3-bromopropionate was reacted with one equivalent of Grignard reagent in the presence of two equivalents of SmI_2 in tetrahydrofuran (THF)/hexamethylphosphoric triamide (HMPA), the corresponding 1-substituted cyclopropanol was obtained in excellent yield (Scheme 1, route A). The typical results of the cyclopropanol synthesis are listed in Table 1. For aromatic Grignard reagents, the reaction can be carried out at room temperature and the yields of cyclopropanol are very satisfactory (runs 8-10, 13, and 15). On the other hand, aliphatic Grignard reagents must be added to the 3-bromo ester at low temperature (-78 °C), otherwise double alkylation of the ester became the main reaction resulting in a remarkable decrease in the yield of the cyclopropanol (runs 1, 4, and 6). HMPA was essential to the reaction. Reactions run without HMPA provided only a trace of the cyclopropanol, and a tertiary alcohol resulting from double alkylation of the ester was instead the major product. A slight excess of the 3-halo ester was always necessary to avoid double alkylation of the ester. The use of organolithium reagents instead of Grignard reagents resulted in lower yields of the cyclopropanol (runs 2 and 11). The reaction of ethyl 3-chloropropionate with phenylmagnesium bromide also produced 1-phenylcyclopropanol in 80% yield at room temperature. Samarocene [biscyclopentadienyl samarium(II); Cp_2Sm] has been reported to be an alternative divalent samarium reagent that is an efficient reagent for the Barbier reaction.[7] We applied Cp_2Sm to the reaction instead of SmI_2 and found that the coupled reagent of RMgBr/Cp_2Sm also accomplished the cyclopropanol synthesis in good to excellent yields. Quite interestingly, the Cp_2Sm promoted cyclopropanol formation reaction proceeded without HMPA. The results are also shown in Table 1.



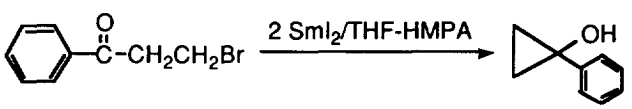
Scheme 2

Table 1. Cyclopropanol synthesis by the reaction of 3-bromo ester with Grignard reagent/SmX_2 couple.[a)]



Run	SmX_2	R in RMgBr	% Yield of Cyclopropanol[b)]
1	SmI_2	*n*-C_4H_9	99
2[c)]	SmI_2	*n*-C_4H_9	30
3[d)]	Cp_2Sm	*n*-C_4H_9	85
4	SmI_2	$(CH_3)_2CH$	85
5[d)]	Cp_2Sm	$(CH_3)_2CH$	40
6	SmI_2	Cyclohexyl	95
7	SmI_2	$(CH_3)_3SiCH_2$	95
8	SmI_2	C_6H_5	99
9[e)]	SmI_2	C_6H_5	70
10[d)]	SmI_2	C_6H_5	94
11[f)]	SmI_2	C_6H_5	88
12[d)]	Cp_2Sm	C_6H_5	84
13	SmI_2	4-$CH_3C_6H_4$	85
14[d)]	Cp_2Sm	4-$CH_3C_6H_4$	95
15	SmI_2	4-$CH_3OC_6H_4$	70
16[d)]	Cp_2Sm	4-$CH_3OC_6H_4$	99
17	SmI_2	*trans*-Styryl	95
18[d)]	Cp_2Sm	*trans*-Styryl	85

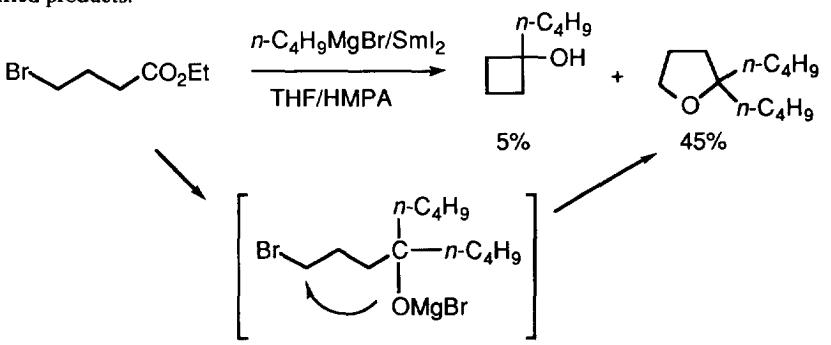
a) 3-Bromo ester (1.3 mmol), RMgBr (1.0 mmol), SmX_2 (2.0-2.5 mmol); THF-HMPA (20 ml-1 ml), see Experimental. b) Isolated as the 3,5-dinitrobenzoyl ester. c) *n*-BuLi was used instead of *n*-BuMgBr d)Without HMPA. e) The whole reaction was carried out at room temperature. f) PhLi was used instead of PhMgBr.



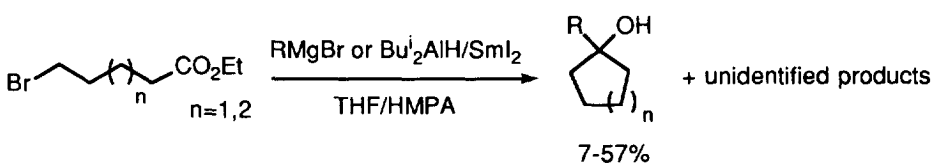
Scheme 3

The reaction pathway would involve the single addition of a Grignard reagent to the ester group of the 3-halo ester followed by the intramolecular Barbier-type reaction of a 3-bromo ketone by SmI_2 (Scheme 2); the 3-samarium ketone would intramolecularly cyclize to form the samarium cyclopropanoxide. Formation of 1-phenylcyclopropanol upon treatment of 3-bromopropiophenone with SmI_2 suggests that the 3-bromo ketone should be an intermediate (Scheme 3).[6c] Recently, Molander and Fadel independently reported the SmI_2 induced reductive acyl substitution of the halo-substituted esters and amides leading to cycloalkanones.[1a, 8] The cyclopropanone hemiacetals have been obtained from 3-halo amides. During our cyclopropanol formation reaction, intramolecular acyl substitution may first occur to form the acetal that could be alkylated by Grignard reagent. However, this reaction path may be ruled out because no cyclopropanol was produced when *n*-BuMgBr was added to the reaction solution where the 3-bromo ester was first treated with SmI_2 until the violet of the solution completely faded (this suggests the formation of the organosamarium intermediate)[9]; the tertiary alcohol (5-ethyl-5-nonanol) was the main product.

Reaction with 4-, 5-, and 6-halo esters. We extended the alkylation-cyclization reaction to cyclobutanol, cyclopentanol, and cyclohexanol formation. Treatment of ethyl 4-bromobutyrate with *n*-BuMgBr/SmI_2 in THF/HMPA at -78 °C to room temperature provided only a poor yield of the desired cyclobutanol, and 2, 2-dibutyltetrahydrofuran was formed in 45 % yield. The tetrahydrofuran was formed by the double alkylation of the ester followed by the intramolecular S_N2 reaction (Scheme 4). Table 2 summarizes the reaction with the 5- and 6-halo esters. Alkylation-cyclization to form cyclopentanols occurred in moderate yields under the stated conditions (Scheme 5). The use of diisobutylaluminum hydride allows us to prepare the unsubstituted cyclopentanol. The reaction with the 5-halo ester gave only low yields of cyclohexanols and several unidentified products.

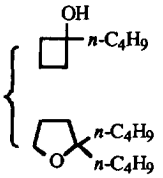
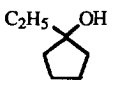
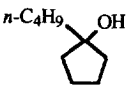
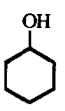
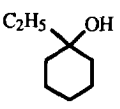
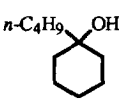
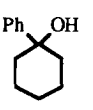


Scheme 4



Scheme 5

Table 2. The reaction of 4-, 5-, and 6-halo-substituted ester with organometallic reagents/SmI_2 couple.[a)]

Run	Substrate	Organometallic reagent	Pruduct(s)	Yield(%)[b)]
1	$Br(CH_2)_3CO_2Et$	*n*-C_4H_9MgBr		5 45
2[c)]	$Br(CH_2)_4CO_2Et$	Bu^i_2AlH		57
3		C_2H_5MgBr		52
4		n-C_4H_9MgBr		46
5		PhMgBr		26
6[c)]	$Br(CH_2)_5CO_2Et$	Bu^i_2AlH		58
7		C_2H_5MgBr		7
8		*n*-C_4H_9MgBr		15
9		PhMgBr		18

a) Substrate (1.25 mmol), RMgBr (1.0 mol), SmI_2 (2.2 mmol), THF-HMPA (20 ml-1 ml); -78 °C, 10 min, then rt, 2 h. b) GLC yield. c) Substrate (1.0 mmol), Bu^i_2AlH (1.5 mmol).

Experimental

General. ^1H NMR spectra were recorded on a JEOL JNM A-400 NMR (400 MHz) spectrometer as solutions in $CDCl_3$. The chemical shifts are reported in δ units downfield from the internal reference, Me_4Si. Infrared spectra were obtained with a JASCO Herschel FT/IR-230A spectrometer. GC/MS analyses were carried out on a Hewlett-Packard 5980/5972 instrument equipped with a capillary column (CBJ5-M30-025) (0.25 mm, 25 m) (helium as carrier gas). Elemental analyses were carried out using a Yanaco CHN CORDER MT-5. Column chromatography was performed on a Yamazen YFLC-254 and a Michael Miller column equipped with a UV detector using Merck Silica gel 60.

Materials. Samarium metal (99.9%) was purchased from Nippon Yttrium Co. Ltd., and scraped using a rasp under nitrogen and then used as powder (30-40 mesh). Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl just prior to use. 1,2-Diiodoethane was purchased from Tokyo Kasei Chemicals and used without further purification. Grignard reagents (0.9-1.1 M THF solution) were prepared from a reaction of organic halides with magnesium turnings and the concentrations were determined by titration. HMPA was purchased from Aldrich and distilled from CaH_2 and kept over molecular sieves 4A under nitrogen. All organic compounds were commercially available and used without purification, unless otherwise noted.

Preparation of SmI_2 solution. Under a nitrogen atmosphere, samarium metal (0.33 g, 2.2 mmol) was placed in a Schlenk tube containing a magnetic stirrer bar and septum inlet. To the samarium was added THF (20 ml) solution of 1,2-diiodoethane (0.56 g, 2.0 mmol) by a syringe through a septum at room temperature. The mixture was allowed to stir at room temperature for 2 h during which time the solution became blue-green.

General experimental procedure for the reaction of halo-substituted ester with organometallic reagent in the presence of SmI_2. To the SmI_2 solution of THF (2.0 mmol) was added HMPA (1.0 ml) and the solution turned violet. The resulting solution was cooled to -78 °C and ethyl 3-bromopropionate (0.23 g, 1.3 mmol) was added to the solution of SmI_2. After less than 10-15 seconds, *n*-butylmagnesium bromide (1.0 M THF; 1.0 ml, 1.0 mmol) was successively injected by a syringe through a rubber septum over a period of 60 seconds. The resulting mixture was stirred at -78 °C for 15 min, then the solution was allowed to warm to room temperature for an additional 1-2 h, during which time the color of the solution turned yellow-green. After aqueous workup, the mixture was extracted with diethyl ether (25 ml × 2) and dried ($MgSO_4$). GC/MS analysis revealed the formation of 1-butylcyclopropanol as the main product. Evaporation of the solvent left a yellow oil which was treated with 3,5-dinitrobenzoylchloride (0.23 g, 1.0 mmol) in pyridine (0.25g, 3 mmol) at room temperature overnight.[6a] The benzoyl ester was subjected to column chromatography on silica gel (hexane/chloroform =5/1). For the reaction with ethyl 4-bromobutyrate, 5-bromopentanoate, and 6-bromohexanoate, products and yields were determined by GC/MS analyses using authentic samples.

1-*n*-Butylcyclopropyl 3,5-dinitrobenzoate. Yield 0.30 g, 0.99 mmol, 99%, mp 88-89 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 0.62-2.10 (m, 10H), 9.13 (s, 2H), 9.21(s, 1H). ^{13}C NMR: δ 11.9, 13.9, 22.5, 28.0, 33.9, 62.9, and 3,5-dinitrobenzoyl group (122.2, 129.3, 134.5, 148.7, 162.2). Anal. Calcd for $C_{14}H_{16}O_6N_2$: C, 54.54; H, 5.23. Found: C, 54.49, H, 5.21.

1-Isopropylcyclopropyl 3,5-dinitrobenzoate. Yield 85%, mp. 110.5-111.5 °C. ^1H NMR (400

MHz, $CDCl_3$): δ 0.88-1.05 (m, 10H), 2.28 (sept, J=6.9 Hz, 1H), 9.13 (s, 2H), 9.21(s, 1H). ^{13}C NMR: δ 9.73, 18.8, 31.0, 67.2, and 3,5-dinitrobenzoyl group. Anal. Calcd for $C_{13}H_{14}O_6N_2$: C, 53.06; H, 4.80. Found: C, 52.91, H, 4.69.

1-Cyclohexylcyclopropyl 3,5-dinitrobenzoate. Yield 95%, mp 119-120 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 0.8-1.4 (m, 10H), 1.6-2.0 (m, 4H), 9.13 (s, 2H), 9.21(s, 1H). ^{13}C NMR: δ 9.61, 25.9, 26.0, 26.1, 29.2, 29.3, 40.7, 66.5, and 3,5-dinitrobenzoyl group. Anal. Calcd for $C_{16}H_{18}O_6N_2$: C, 57.65; H, 5.14. Found: C, 57.08, H, 5.35.

1-Phenylcyclopropyl 3,5-dinitrobenzoate. Yield 99%, mp 120.0-120.6 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.2-1.6 (m, 4H), 7.2-7.6 (m, 5H), 9.13 (s, 2H), 9.21(s, 1H). ^{13}C NMR: δ 14.3, 62.9, 127.0, 127.9, 128.4, 138.3, and 3,5-dinitrobenzoyl groups (122.3, 129.3, 138.3,148.5, 162.1). Anal. Calcd for $C_{16}H_{13}O_6N_2$: C, 58.54; H, 3.69. Found: C, 58.66; H, 3.58.

1-(4-Methylphenyl)cyclopropyl 3,5-dinitrobenzoate. Yield 85%, mp 121.5-122.5 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.2-1.5 (m, 4H), 2.32 (s, 3H), 7.16 (d, J=8.6 Hz, 2H), 7.39 (d, J=8.4Hz, 2H), 9.13 (s, 2H), 9.21(s, 1H). ^{13}C NMR: δ 13.9, 14.2, 21.0, 62.9, and several aromatic peaks. Anal. Calcd for $C_{17}H_{15}O_6N_2$: C, 59.65; H, 4.12. Found: C, 59.24; H, 3.98.

1-(4-Methoxylphenyl)cyclopropyl 3,5-dinitrobenzoate. Yield 70%, mp 119.9-120.8 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.2-1.5 (m, 4H), 3.78 (s, 3H), 6.85 (d, J=8.9 Hz, 2H), 7.50 (d, J=8.8Hz, 2H), 9.0-9.2 (m, 3H). ^{13}C NMR: δ 13.5, 55.2, 62.9, and several aromatic peaks. Anal. Calcd for $C_{17}H_{15}O_6N_2$: C, 59.65; H, 4.12. Found: C, 59.24; H, 3.98.

1-trans-Styrylcyclopropyl 3,5-dinitrobenzoate. Yield 95%, mp 140-141 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.2-1.5 (m, 4H), 6.34 (d, 1H, *J*=16.0 Hz), 6.46(d, 1H, *J*=16.0 Hz), 7.1-7.4 (m, 5H), 9.13 (s, 2H), 9.21(s, 1H). ^{13}C NMR: δ 14.6, 61.5, 128.7, 129.6 and 3,5-dinitrobenzoyl groups (122.3, 129.2, 133.4, 148.7, 162.3). Anal. Calcd for $C_{18}H_{14}O_6N_2$: C, 61.01; H, 3.98. Found: C, 61.09; H, 3.85.

1-Trimethylsilylmethylcyclopropyl 3,5-dinitrobenzoate. Yield 95%, mp 119.9-120.8 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 0.043 (s, 9H), 0.81(t, 1H), 1.08(t, 1H), 1.38 (s, 2H), 9.13 (s, 2H), 9.21(s, 1H). ^{13}C NMR: δ -0.69, 13.6, 23.2, 61.6, and several aromatic peaks. Anal. Calcd for $C_{14}H_{18}O_6N_2Si$: C, 78.20; H, 13.12. Found: C, 77.94; H, 13.23.

2,2-Di-*n*-butyltetrahydrofurane. The title compound was prepared by the reaction of ethyl 4-bromobutyrate with SmI_2/*n*-BuMgBr. ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H), 1.1-1.6 (m,.12H), 1.64 (t, 2H, *J*=6.9 Hz), 1.83 (quint, 2H, *J*=6.9 Hz), 3.79 (t, 2H, *J*=6.9 Hz). ^{13}C NMR: δ 14.0, 23.3, 26.2, 26.5, 35.0, 38.2, 67.1, 84.8. IR (neat): 1465, 1057 cm^{-1}. Anal. Calcd for $C_{12}H_{24}O$: C, 49.69; H, 5.36. Found: C, 49.68; H, 5.23.

Preparation of biscyclopentadienyl samarium(II) (samarocene). This procedure is a slight modification of the procedure of Kagan et al.[7] Under nitrogen, to the SmI_2 (2.5 mmol) in THF(10 ml) was added sodium cyclopentadienide (1.0 M THF solution, 5.0 ml, 5.0 mmol) at room temperature with stirring. The resulting mixture was stirred at room temperature for 10 min, and heated at reflux for 10 min. The solution was allowed to stand at room temperature during which time samarocene precipitated. The supernatant was removed by a syringe and the precipitate was washed with THF (10 ml) for two times.

General experimental procedure for the reaction of Grignard reagent with ethyl 3-bromopropionate in the presence of samarocene. To the THF (15 ml) solution of samarocene (2.5

mmol) was added ethyl 3-bromopropionate (0.23 g, 1.3 mmol) at -78 °C. *n*-Butylmagnesium bromide (1.0 M THF; 1.0 ml, 1.0 mmol) was successively injected by a syringe through a rubber septum over a period of 1 min. The resulting mixture was stirred at -78 °C for 15 min, and then the solution was allowed to warm to room temperature for 60 min, during which time the color of the solution turned to yellow-brown. After aqueous workup, the mixture was extracted with diethyl ether (25 ml × 2) and dried ($MgSO_4$). The cyclopropanol was isolated as the 3,5-dinitrobenzoyl ester.

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