Samarium(II) Iodide-Mediated Synthesis of Chlorohydrins†

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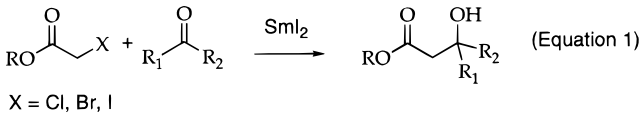
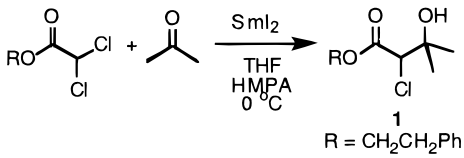
The reductive coupling between a carbonyl and an organic halide with samarium diiodide produces the corresponding alcohol efficiently, as first shown by Kagan et al. in their introductory paper on SmI_2.[1] It was also shown by several groups that these reactions did not proceed well when the carbonyl compounds were added subsequently to the halides and SmI_2.[1,2] A subset of these reactions, namely the samarium(II) iodide-mediated Reformatsky-type reaction of monohaloacetates with aldehydes and ketones (eq 1), is also well precedented.[1,3]



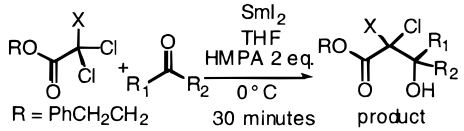
We have studied the SmI_2-mediated reaction of dichloroacetates with carbonyl compounds. The corresponding zinc-[4] and magnesium[5]-mediated reactions (eq 2) have been thoroughly studied,[6,7] but to the best of our knowledge, the use of SmI_2 as the reducing agent in this reaction has not been reported. Also, like the samarium(II) iodide-mediated Reformatsky-type reaction of monohaloacetates with aldehydes and ketones, the method described herein offers several advantages compared to the zinc-mediated reactions.[3b] For example, no activation agent (such as BF_3)[4a,5] is required, and the reaction time is considerably shorter for the SmI_2 reaction compared to the Zn reaction (typically 30 min for SmI_2 and 24 h for Zn).

Table 1. Reaction of Phenethyl Dichloroacetate, Acetone, and SmI_2



entry	conditions	yield (%)
1	Barbier procedure (acetone before SmI_2)	63
2	Grignard procedure (acetone after SmI_2)	0
3	"Barbier" + 2 equiv of HMPA	71
4	"Barbier" + 8 equiv of HMPA	33

Table 2. Reactivity of Phenethyl Dichloroacetate Derivatives and Carbonyl Compounds with SmI_2



entry	X	R_1	R_2	product	yield (%)
1	Me	Me	Me	**2**	55
2	Bn	Me	Me	**3**	66
3	Cl	Me	Me	**4**	65
4	H	Ph	Me	**6**[a]	45
5	H	Ph	Ph	**7**	0
6	H	Ph	H	**8**	0

[a] 1:1 mixture of diastereomers.

Table 1 summarizes the results we obtained using 2.5 equiv of samarium iodide and a mixture of phenethyl dichloroacetate and acetone in THF at 0 °C. A Barbier-type procedure (i.e., SmI_2 added last) afforded the chlorohydrin **1** in 63% yield (Table 1, entry 1) while the Grignard-type procedure (acetone added last) failed to provide any of the desired material (Table 1, entry 2). In the latter case, several decomposition products were obtained from which the only clearly identified product was phenethyl alcohol (ca. 25%). Chlorohydrin **1** was therefore obtained only when the carbonyl compound was added before SmI_2.[8] The addition of 2 equiv of HMPA (Table 1, entry 3) resulted in only a slightly improved conversion (71%), whereas the addition of a larger amount of HMPA (Table 1, entry 4) was detrimental to the formation of chlorohydrin **1**.

The reaction also proceeded in moderate to good yields with substituted dichloroacetates.[9] Under the optimized

† This paper is dedicated to Professor Yoshito Kishi on the occasion of his 60th birthday.

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(7) See also, tris(dimethylamino)phosphine: Hayon, A.-F.; Fehrentz, J.-A.; Chapleur, Y.; Castro, B. *Bull. Soc. Chim. Fr.* **1983**, *II*, 207.

(8) One recent report describes the successful reaction when the ketone was added last; however, see: Utimoto, K.; Takai, T.; Matsui, T.; Matsubara, S. *Bull. Soc. Chim. Fr.* **1997**, *134*, 365.

(9) α-Methyl- and α-benzyl-substituted dichloroacetate were prepared from phenethyl dichloroacetate as described in: Villieras, J.; Perriot, P.; Bourgain, M.; Normant, J. F. *Synthesis* **1975**, 533. Phenethyl trichloroacetate was prepared from commercially available phenethyl alcohol and trichloroacetyl chloride.

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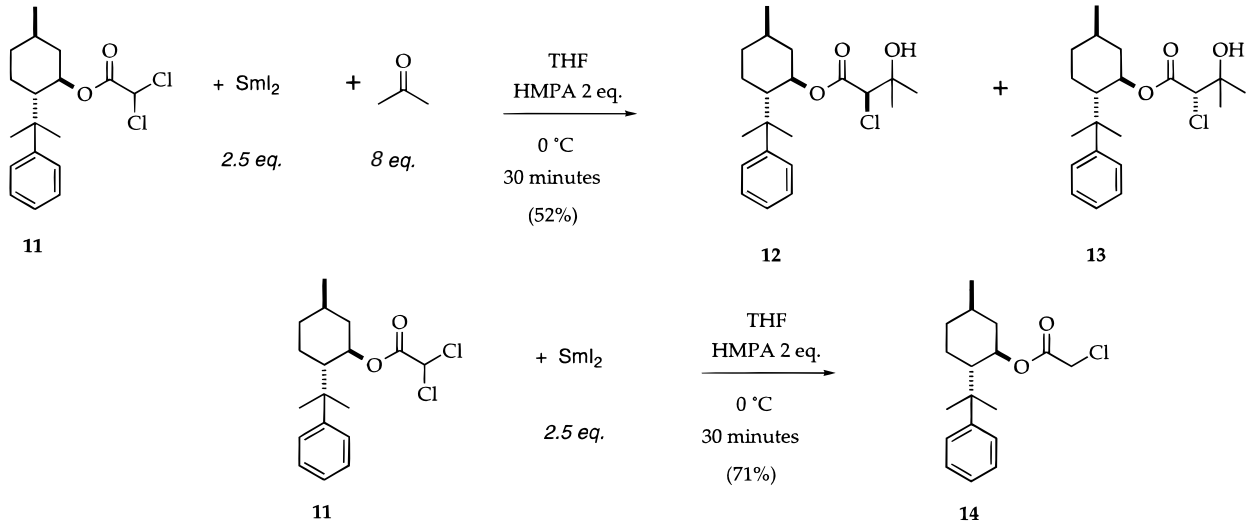
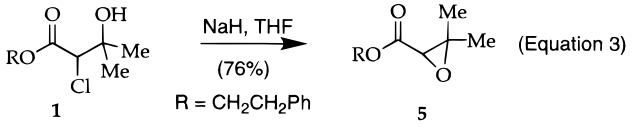
Scheme 1

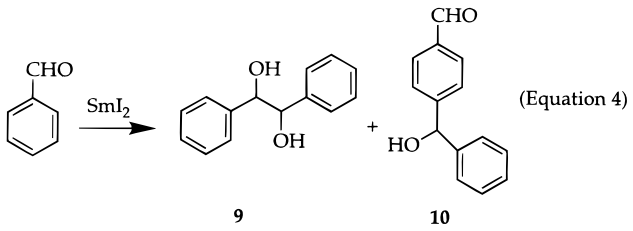


reaction conditions described above (Table 1, entry 3), compounds **2**, **3**, and **4** were obtained in 55%, 66%, and 65% yields, respectively (Table 2). It should be pointed out that none of the corresponding epoxides resulting from chlorohydrins **1**−**4** was isolated from the reactions described in Tables 1 and 2. On the other hand, when chlorohydrin **1** was treated with sodium hydride in THF at room temperature for 30 min, epoxide **5** was obtained in 76% yield (eq 3). However, all attempts to obtain



epoxide **5** directly from the SmI_2-mediated reaction failed. Some of these attempts included the following: (i) reaction run at 65 °C for 12 h (51% yield of **1** obtained) and (ii) reactions performed with large amount (10−25 equiv) of HMPA at 0 °C or refluxing THF for 12 h (yield of **1**, ∼20%). Presumably, the strong Sm−O bond prevents epoxide formation.

We also studied the reactivity of other carbonyl compounds with SmI_2 and phenethyl dichloroacetate. Aromatic ketones and aldehydes reacted sluggishly (Table 2, entries 4−6), as was the case with Kagan's original samarium Barbier procedure,[1] and with the exception of acetophenone, the expected products were not obtained. In fact, when samarium(II) iodide was added to a mixture of acetophenone and phenethyl dichloroacetate, a (1:1) diastereomeric mixture of chlorohydrin **6** was obtained in a low 45% yield (Table 2, entry 4). Several unidentified byproducts were also observed. On the other hand, we did not isolate any of the desired expected product **8** when the reaction was carried out with benzaldehyde (Table 2, entry 6). In this case, several unidentified products were obtained along with dimers **9** and **10** (20% combined yield, eq 4). Diol **9** originates from the precedented samarium iodide-induced pinacol coupling,[10] whereas dimer **10** was recently reported by Fang and coworkers.[11]



We have also examined the reaction of (1*S*,2*R*,5*S*)-(−)-8-phenylmenthyl dichloroacetate (**11**) with acetone and samarium iodide (Scheme 1). No asymmetric inductionwas observed, and a 1:1 mixture of **12** and **13** was obtained in 52% combined yield. Nevertheless, the use of chiral dichloroacetate **11** allowed us to make an observation on the stability of the species obtained when a dichloroacetate was treated with SmI_2. Unlike all reactions reported in Tables 1 and 2 that resulted in complex reaction mixtures when no carbonyl compounds was added, exposure of **11** to SmI_2 without acetone provided chloroacetate **14** in 71% yield. The corresponding monochloroacetates were not isolated when Grignard-type (ketone added last or no ketone added) procedures were used in the reactions described in the aforementioned Tables 1 and 2. It should also be pointed out that attempts to carry out the reaction between **11** and SmI_2 in which acetone is added last (Grignard procedure) provided none of the expected products **12** and **13**, even at higher temperature. In these cases, monochlorinated product **14** was obtained in good yield. Consequently, it would seem that steric hindrance around the dichloroacetate-derived reactive species dictates its stability. There is a possibility that less hindered dichloroacetates form a species more reactive toward self-condensation processes similar to those we[12] and others[13] have reported. These self-condensation processes would in turn generate reactive species, hence providing a complex reaction mixture. In other words, the reactive intermediate, be it radical,[3d] transient anion,[3d] or organosamarium,[2b] is more stable when generated from **11**, compared to when generated from any of the other dichloroacetates described in this report.

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Failure to provide products in related Grignard procedures has been rationalized as favoring the radical−ketyl coupling mechanism.[3d] Considering, however, the complexity of the mechanistic possibilities of reductions of halides and radicals with SmI_2 that has been recently reviewed by Curran et al.,[2b] the mechanism of the samarium iodide-mediated coupling of dichloroacetate remains unclear until further evidence becomes available.

Experimental Section

Phenethyl 3-Chloro-2-hydroxy-2-methylbutanoate (1). To a solution of phenethyl dichloroacetate (200 mg, 0.86 mmol), acetone (0.5 mL, 6.9 mmol), and HMPA (0.33 mL, 1.9 mmol) at −78 °C was added a 0.1 M THF solution of samarium iodide (20.6 mL, 2.4 mmol) (purchased from Aldrich). The mixture was warmed to 0 °C and stirred at 0 °C for 30 min. A 5% solution of $NaHCO_3$ (30 mL), ether (30 mL), and hexanes (30 mL) were added, and the separated aqueous layer was extracted with 1:1 ether−hexanes (3 × 50 mL), dried (anhyd $MgSO_4$), filtered, and evaporated. Flash chromatography of the residue (EtOAc/hexanes 1:8) yielded 156 mg (71%) of **1**: IR (neat) 3560, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.25 (5H, 2m), 4.42 (2H, t, J = 7.0 Hz), 4.18 (1H, s), 3.50 (1H, br s), 2.99 (2H, t, J = 7.0 Hz), 1.30 (3H, s), 1.29 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 168.7, 136.9, 128.7, 128.4, 126.6, 71.6, 66.3, 64.2, 34.6, 26.3, 25.4; MS m/z 257 (15), 153 (100). Anal. Calcd for $C_{13}H_{17}ClO_3$: C, 60.82; H, 6.67. Found: C, 60.81; H, 6.82.

Phenethyl 3-chloro-2,3-dimethyl-2-hydroxybutanoate (2): IR (neat) 3560, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.24 (5H, m), 4.42 (2H, t, J = 7.0 Hz), 3.16 (1H, s), 3.00 (2H, t, J = 7.0 Hz), 1.73 (3H, s), 1.30 (3H, s), 1.26 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 171.4, 136.9, 128.7, 128.4, 126.6, 75.4, 74.4, 66.7, 34.6, 25.0, 24.8, 24.2; MS (m/z) 271 (7), 253 (4), 197 (9), 135 (32), 105 (100). Anal. Calcd for $C_{14}H_{19}ClO_3$: C, 62.11; H, 7.07. Found: C, 62.49; H, 6.67.

Phenethyl 3-benzyl-3-chloro-2-hydroxy-2-methylbutanoate (3): IR (neat) 3560, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.20 (8H, m), 7.16 (2H, m), 4.31 (2H, m), 3.78 (1H, d, J = 14.0 Hz), 3.51 (1H, br s), 3.14 (1H, d, J = 14.0 Hz), 2.73 (2H, t, J = 7.0 Hz), 1.44 (3H, s), 1.35 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 170.9, 136.9, 135.5, 130.5, 128.7, 127.8, 127.0, 126.6, 81.4, 75.6, 66.8, 41.2, 34.4, 26.1, 24.6; MS (m/z) 347 (6), 289 (4), 195 (19), 154 (25), 136 (21), 105 (100). Anal. Calcd for $C_{20}H_{23}ClO_3$: C, 69.26; H, 6.68. Found: C, 69.02; H, 6.61.

Phenethyl 3,3-dichloro-2-hydroxy-2-methylbutanoate (4): IR (neat) 3550, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.26 (5H, m), 4.50 (2H, t, J = 7.0 Hz), 3.32 (1H, br s), 3.04 (2H, t, J = 7.0 Hz), 1.46 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.2, 136.5, 128.8, 128.5, 126.7, 65.4, 60.1, 59.1, 34.8, 24.1, 18.0; MS (m/z) 293 (3), 291 (5), 135 (6), 117 (11), 105 (100). Anal. Calcd for $C_{13}H_{16}Cl_2O_3$: C, 53.63; H, 5.54. Found: C, 53.56; H, 5.54.

Phenethyl 2,3-epoxy-2-hydroxy-2-methylbutanoate (5): IR (neat) 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.30 (5H, m), 4.42 (2H, t, J = 7.0 Hz), 3.30 (1H, s), 2.98 (2H, t, J = 7.0 Hz), 1.40 (3H, s), 1.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 168.5, 137.6, 128.7, 128.4, 126.5, 71.6, 66.3, 64.2, 34.6, 26.3, 25.4; MS (m/z) 221 (9), 154 (43), 137 (36), 105 (100). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.98; H, 7.42.

Phenethyl 3-chloro-2-hydroxy-2-phenylbutanoate (6): IR (neat) 3560, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm, high R_f diastereomer, 7.44 (10H, m), 4.51 (1H, s), 4.32 (2H, t, J = 7.0 Hz), 3.33 (1H, s), 2.86 (2H, t, J = 7.0 Hz), 1.63 (3H, s), low R_f diastereomer, 7.40 (10H, m), 4.55 (1H, s), 4.10 (2H, t, J = 7.0 Hz), 3.94 (1H, s), 2.86 (2H,m), 1.63 (3H, s); ^{13}C NMR (two diastereomers) (75 MHz, $CDCl_3$) δ ppm 169.1, 168.5, 143.1, 142.6, 136.8, 136.7, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 127.6, 127.5, 126.6, 126.5, 125.1, 124.9, 74.8, 74.7, 66.4, 66.2, 64.8, 62.7, 34.5, 34.2, 26.7, 26.2; MS (m/z) 319 (3), 303 (8), 301 (22), 154 (31), 105 (100). Anal. Calcd for $C_{18}H_{19}ClO_3$: C, 67.82; H, 6.01. Found: C, 67.74, H, 6.13.

(1*S*,2*R*,5*S*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 3-chloro-2-hydroxy-2-methylbutanoate (12) and (13): IR (neat) 3560, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.25 (8H, m), 7.12 (2H, m), 4.80 (2H, m), 3.39, 3.32, 3.27, 2.55 (4H, s), 2.15−0.9 (46H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 168.5, 167.7, 151.5, 151.0, 127.9, 127.8, 125.6, 125.3, 125.1, 125.0, 124.9, 76.8, 76.6, 71.4, 71.3, 65.4, 62.5, 50.4, 49.7, 41.1, 40.4, 39.5, 39.4, 34.2, 31.1, 27.9, 27.3, 27.0, 26.4, 26.3, 26.1, 25.9, 25.5, 25.1, 24.4, 21.5; MS (m/z) 367 (36), 333 (100), 313 (31), 247 (87). Anal. Calcd for $C_{21}H_{31}ClO_3$: C, 68.74; H, 8.52. Found: C, 68.91; H, 8.82.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **1**−**6**, **12**, and **13** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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