Highly Stereoselective C-Silylation and Alkylation of 1-Chlorocyclopropanecarboxylic Ester Using SmI_2

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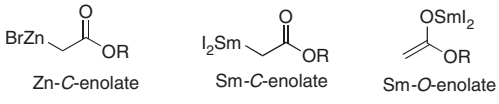
Highly stereoselective SmI_2-promoted substitutions of alkyl 1-chlorocyclopropanecarboxylate **1** using TMSCl or alkyl halide proceeded to give trans adduct **2** or **3** in moderate to high yield with excellent trans stereoselectivity (trans-add/cis-add = >99/1) in the presence of HMPA in THF. Silylation occurred on the α-carbon of the ester with excellent regio- and stereoselectivity (C-silylation/O-silylation = >99/1, trans-add/cis-add = >99/1).

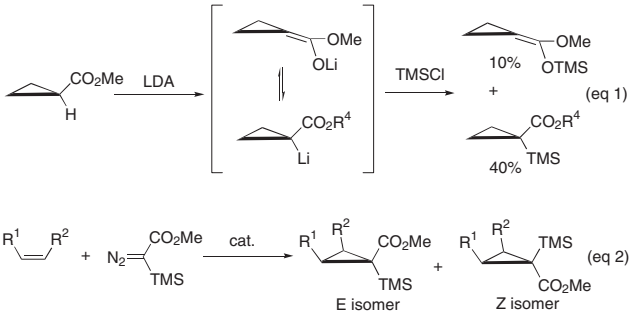
Structural studies of the Reformatsky reagent derived from α-haloesters revealed that the Zn–enolate is present in the *C*-enolate form (Scheme 1).[1] Hence, in SmI_2-promoted Reformatsky-type reactions, most proposed mechanisms proceed through an *O*-enolate.[2] Few examples of *C*-enolate have been reported.[3] Recently, we reported highly stereoselective SmI_2-promoted Reformatsky-type reactions of 1-chlorocyclopropanecarboxylic ester **1** with aldehydes, ketones, and acyl chlorides.[4] In that report, we proposed an ambiguous mechanism via *O*- or *C*-enolate form of ester.

On the other hand, silylation of the Li–enolate of methyl cyclopropanecarboxylate afforded mixture of O- and C-silylated products in moderate yield (Scheme 2, eq 1).[5,6] As the literature pointed out, in the case of ethyl cyclopropanecarboxylate, trimethylsilylation proceeds in moderate yield due to the self-Claisen condensation and further reaction. In addition, cyclopropanation of monosubstituted or cis-disubstituted olefin with diazo(trimethylsilyl)acetate affords a mixture of E and Z isomers with moderate to good selectivity (Scheme 2, eq 2).[7]

Here we report the highly stereoselective C-trimethylsilylation and alkylation of 1-chlorocyclopropanecarboxylic ester using SmI_2. Based on the regio- and stereoselectivity, a plausible mechanism in such reactions is also disclosed.

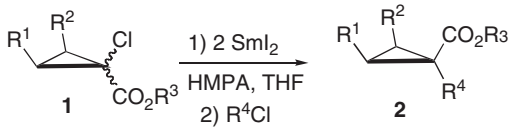


Scheme 1.



Scheme 2.

Table 1. Highly regio- and stereoselective SmI_2-promoted trimethylsilylation of alkyl 1-chlorocyclopropanecarboxylates **1**[a,b]



trans-add/cis-add = >99/1[c]
C-TMS/O-TMS = >99/1

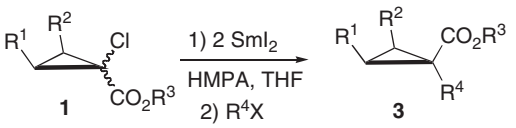
Entry	Substrate[d]	R^1	R^2	R^3	R^4	Product	Yield[e] /%
1	**1a**	Ph	H	Me	TMS	**2a**	94
2	**1a**	Ph	H	Me	TBDMS	**2a′**	0
3	**1b**	Ph	H	Et	TMS	**2b**	84
4	**1c**	$-(CH_2)_4-$		Me	TMS	**2c**	92
5	**1d**	$-(CH_2)_4-$		Et	TMS	**2d**	51
6	**1e**	$-(CH_2)_4-$		*i*-Pr	TMS	**2e**	47

[a]Reactions were carried out at −78 °C (Entries 1–4) or 0 °C (Entries 5 and 6) under an Ar atmosphere. [b]TMSCl or TBDMSCl was added after generation of Sm–enolate. [c]In this case, trans-add means trans-adduct. Ratios were determined from ^{1}H NMR spectra. [d]A mixture of *cis*-**1** and *trans*-**1** (cis/trans = 3/1) was used for the reactions of **1a** and **1b**, whereas *cis*-**1** was used for the reactions of **1c**–**1e**. [e]Isolated.

Initially, we investigated the reaction of alkyl 1-chlorocyclopropanecarboxylates[8] **1a**–**1e** with TMSCl or TBDMSCl.[9] Table 1 lists the results of the silylation. Salient features were as follows: every case of R^1-monosubstituted- and 2,3-*cis*-disubstituted-1-chlorocyclopropanecarboxylates **1a**–**1e** underwent the desired trimethylsilylation to give C-trimethylsilylated products **2a**–**2e** with excellent selectivity (C-/O-silylation = >99/1, trans-add/cis-add = >99/1) (Entries 1 and 3–6). No O-trimethylsilylated compound was obtained. The structures of **2a**–**2e** were determined by analogy with known compounds,[7a] based on spectral data. A similar reaction of **1a** with TBDMSCl did not proceed, and work up of enolate with water yielded a hydrodechlorinated product (Entry 2). This was caused by the stereocongestion of TBDMSCl in the S_N2 reaction. In the case of ethyl ester **1b**, the trimethylsilylation proceeded in high yield (Entry 3). This result is not consistent with a similar reaction of ethyl cyclopropanecarboxylate using LDA, KH, or NaH.[6] In addition, the trimethylsilylation of esters **1d** and **1e** at 0 °C afforded **2d** and **2e**, respectively, in moderate yield (Entries 5 and 6). Similar reactions at −78 °C or rt decreased the yield of silylation.

Next we investigate the SmI_2-promoted alkylation of alkyl 1-chlorocyclopropanecarboxylates **1a**–**1e** with alkyl halide. As expected, alkylation of methyl ester **1a** using MeI, and allylbromide proceeded smoothly (Table 2, Entries 1 and 2). Alkylation of **1a** with BnBr and EtI afforded **3c** and **3d**, respectively, in

Table 2. Highly stereoselective SmI_2-promoted alkylation of alkyl 1-chlorocyclopropanecarboxylates **1**[a,b]



trans-add/cis-add = >99/1[c]

Entry	Substrate[d]	R^1	R^2	R^3	R^4	Product	Yield[e] /%
1	**1a**	Ph	H	Me	Me	**3a**	92
2	**1a**	Ph	H	Me	Allyl	**3b**	89
3	**1a**	Ph	H	Me	Bn	**3c**	40
4	**1a**	Ph	H	Me	Et	**3d**	19
5	**1a**	Ph	H	Me	*i*-Pr	**3e**	0
6	**1b**	Ph	H	Et	Me	**3f**	78
7	**1c**	$-(CH_2)_4-$		Me	Me	**3g**	88
8	**1d**	$-(CH_2)_4-$		Et	Me	**3h**	39
9	**1e**	$-(CH_2)_4-$		*i*-Pr	Me	**3i**	34

[a]Reactions were carried out at −78 °C (Entries 1–7) or 0 °C (Entries 8 and 9) under an Ar atmosphere. [b]R^4X was added after generation of Sm–enolate. [c]In this case, trans-add means trans-adduct. Ratios were determined from ^1H NMR spectra. [d]A mixture of *cis*-**1** and *trans*-**1** (cis/trans = 3/1) was used for the reactions of **1a** and **1b**, whereas *cis*-**1** was used for the reactions of **1c**–**1e**. [e]Isolated.

moderate to low yield with many inseparable by-products (Entries 3 and 4). In the case of BnBr, the self-coupling of BnBr mainly occur to give dibenzyl. Alkylation using *i*-PrI did not occur because of stereocongestion in the S_N2 reaction (Entry 5). It should be noted that reactions proceeded with nearly complete trans selectivity (trans-add/cis-add = >99/1) for every case examined.[10] In the case of ethyl ester **1b**, the methylation proceeded in good yield (Entry 6). This result is also inconsistent with a similar reaction of ethyl cyclopropanecarboxylate using LDA, KH, or NaH.[5] Methylation of 2,3-*cis*-disubstituted cyclopropanecarboxylic ester **1c** proceeded smoothly to afford **3g** in high yield (Entry 7). A similar reaction of ethyl or isopropyl esters **1d** and **1e** at 0 °C afforded **3h** and **3i**, respectively, in moderate yield (Entries 8 and 9). Similar reactions at −78 °C or rt decreased the yield of alkylation.

Because of the excellent C-selectivity of the present trimethylsilylation, we proposed a plausible mechanism via *O*- or *C*-enolate (Scheme 3). SmI_2–enolate reacted with TMSCl on only the trans-face to afford **2** due to the stereocongestion between R^1 (and/or R^2) and TMSCl. Based on the fact that no *O*-TMS-product was obatained,[11] a SmI_2–*O*-enolate might not be generated or should exist as a particular intermediate[12] that can not react with TMSCl on oxygen atom. The mechanism remains an open problem.

In conclusion, we developed a stereoselective synthesis of cyclopropane derivatives utilizing a highly stereoselective SmI_2-promoted C-silylation and alkylation of 1-chlorocyclopropanecarboxylic esters. The present method is a new avenue for the stereoselective synthesis of highly substituted cyclopropylcarbonyl compounds.

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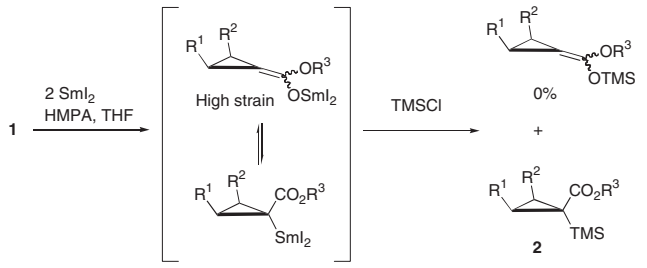

Scheme 3.

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6 Trimethylsilylation of Li–enolate of methyl acetate or isobutyrate with TMSCl provides O-silylated product as a major product. However, a similar reaction of methyl cyclopropanecarboxylate preferentially affords C-silylated product (*O*-TMS/*C*-TMS = 1/4), because of the highly strained structure of Li–*O*-enolate.

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8 Alkyl 1-chlorocyclopropanecarboxylates **1** were prepared by the same method of previous report and a modified method: see Supporting Information.

9 Procedures were described in Supporting Information, which is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

10 The structures of **3a**–**3i** were determined by analogy with known compounds based on their spectral data: see Supporting Information.

11 This result is inconsistent with the trimethylsilylation of Li–enolate of cyclopropanecaboxylic ester (Scheme 2, eq 1).

12 Planar or pyramidal *O*-enolate: see H.-U. Reissig, I. Böhm, *J. Am. Chem. Soc.* **1982**, *104*, 1735.

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