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New Access to Methyl Formylcyclopropanecarboxylates *via* Diethylaminotrimethylsilane Mediated Tandem Nucleophilic Reaction of Aldehyde with Methyl 2,3-Dihalopropanoate

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Abstract: Formylcyclopropanecarboxylates have been synthesized by diethylaminotrimethylsilane mediated tandem conjugate addition-alkylation of aldehydes to methyl α-haloacrylate generated *in situ* from methyl 2,3-dihalopropanoate.

Keywords: Aldehydes; Cyclopropanation; Halo esters; Michael reactions

Conjugate nucleophilic additions of α-carbons of naked aldehydes to electron deficient olefins have been quite limited because of the labile nature of aldehydes under a variety of reaction conditions. Although there have been several literature precedents to this efforts,[1] to the best of our knowledge, there are no precedents to isolate conjugate addition products directly. Thus, masked aldehydes such as trimethylsilyl enol ethers[2] or enamines[3] of aldehydes have been used often as latent synthones for such purpose. We recently reported a novel conjugate addition of naked aldehydes to vinylketones mediated by diethylaminotrimethylsilane (Et_2NTMS) to afford 5-ketoaldehydes.[4]

As a part of our ongoing interest to explore further the reactivity of aminosilane derivatives[4] as well as to expand nucleophilic tandem or cascade reactions in organic syntheses,[5] we delineate herein a tandem nucleophilic reaction which provides methyl formylcyclopropanecarboxylate **4** by Et_2NTMS mediated conjugate addition-alkylation of aldehydes **1** to methyl α-haloacrylate **6** generated *in situ* from methyl 2,3-dibromo- or 2,3-dichloropropanoate, **2** or **3** (Scheme 1).

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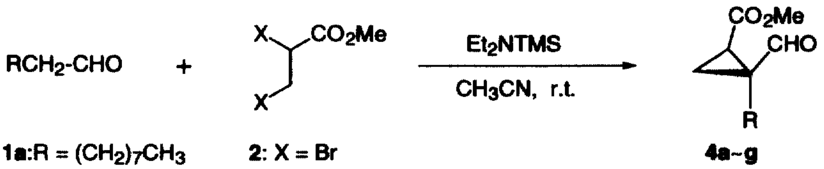
Scheme 1. Tandem Nucleophilic Reactions Leading to Formylcyclopropanecarboxylate



1a:R = $(CH_2)_7CH_3$
b:R = $(CH_2)_3CH_3$
c:R = Ph
d:R = $(CH_2)_3OTHP$
e:R = CH_2Ph
f:R = $(CH_2)_8OAc$
g:R = $(CH_2)_3OTBDMS$

2: X = Br
3: X = Cl

Reaction of decanal **1a** with methyl 2,3-dibromopropanoate **2** was investigated at first in order to optimize the reaction condition. Some of the representative results were listed in Table 1. Among the solvents investigated, acetonitrile (MeCN) gave the highest yield (entry 1). Contrary to the 1,4-addition of aldehyde to vinylketone,[4] the reaction without solvent gave the lowest yield (entry 3). The reaction condition was mild and subsequent work-up procedure was simple. The reaction was carried out by mixing aldehyde **1** and 2,3-dihalopropanoate **2** or **3** in the presence of 2.4 equiv. of Et_2NTMS at ambient temperature under nitrogen atmosphere, and evaporation of the solvent followed by flash column chromatography provided formylcyclopropnanecarboxylate **4**.

Table 1. Synthesis of Methyl Formylcyclopropanecarboxylate **4**

Entry[a]	Aldehyde	Dihaloester	Solvent	Times (h)	Product	Yield (%)[b, c]
1	**1a**	**2**	MeCN	1.5	**4a**	64 (1.4:1)
2	**1a**	**2**	CH_2Cl_2	2.5	**4a**	42 (1.4:1)[d]
3	**1a**	**2**	—	15.5	**4a**	41 (0.74:1)
4	**1b**	**2**	MeCN	1	**4b**	62 (2.1:1)
5	**1c**	**2**	MeCN	2	**4c**	30 (0.6:1)[d]
6	**1d**	**2**	MeCN	5	**4d**	30 (1.8:1)
7	**1e**	**2**	MeCN	20.5	**4e**	25 (1:1)
8	**1a**	**3**	MeCN	4	**4a**	65 (1.6:1)
9	**1b**	**3**	MeCN	4	**4b**	57 (2:1)
10	**1d**	**3**	MeCN	2	**4d**	61 (3.6:1:1)
11	**1e**	**3**	MeCN	3	**4e**	58 (1.3:1)
12	**1f**	**3**	MeCN	4	**4f**	64 (1.7:1)
13	**1g**	**3**	MeCN	11	**4g**	69 (1.2:1)

[a] 2.4 equiv. of Et_2NTMS was used.

[b] Yield is based on aldehyde **1**.

[c] A mixture of diastereomers was isolated. Ratios were determined by NMR.

[d] Diastereomers were separated by MPLC.

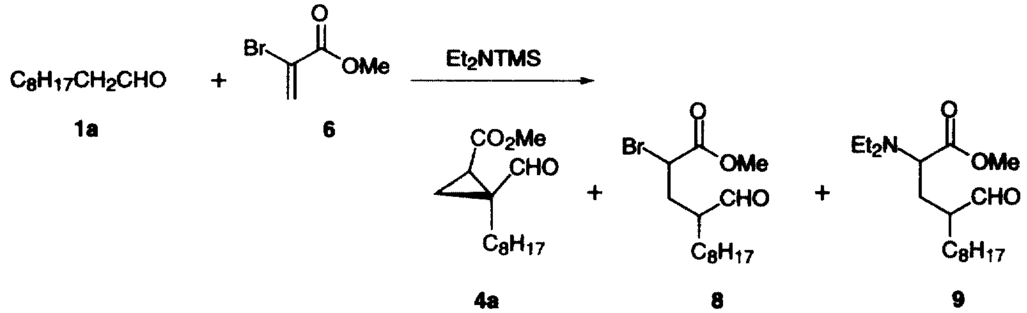
Product **4** was a mixture of diastereomers, some of which were separable by medium pressure LC (MPLC) and we could assign relative stereochemistry by nOe experiment as represented in Figure 1. Though there is no major difference in reactivity between 2,3-dibromo- and 2,3-dichloropropanoates, **2** and **3**, reaction of **3** with dihydrocinnamaldehyde **1e** gave improved yield as shown in entry 11. Present reaction conditions are so mild that the aldehyde **1d**, **1f** or **1g** having tetrahydropyranyl, acetoxy or TBDMS group gave the desired cyclopropane derivatives **4d**, **4f** or **4g** (Entry 6, 10, 12 and 13). Reaction of decanal **1a** with other dihalocompounds such as 3,4-dibromobutan-2-one, 1,2-dibromopentan-3-one or 2,3-dibromopropionitrile gave poor (5 to 40%) yield of cyclopropane derivatives, probably due to instability of α-bromo-α,β-unsaturated moieties.

Figure 1. Slected nOe correlations.

4c (a major diastereomer) **4c** (a minor diastereomer)

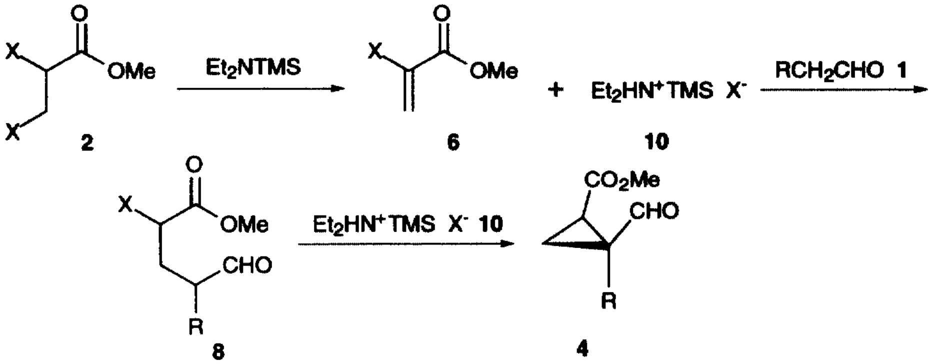
Methyl α-bromoacrylate **6** is a reactive Michael partner[6] and has been employed successfully for cascade Michael-Michael-alkylation reaction to construct a tricyclic framework[7] in a one pot operation (bicyclo annulation). Reaction of decanal **1a** with methyl α-bromoacrylate **6** in the presence of Et_2NTMS afforded a mixture of methyl 2-formyl-2-octylcyclopropanecarboxylate **4a** (25%), methyl 2-bromo-4-formyldodecanoate **8** (24%) and methyl 2-diethylamino-4-formyldodecanoate **9** (20%) (Scheme 2). Treatment of the resulting methyl 2-bromo-4-formyldodecanoate **8** with Et_2NTMS provided the aminoester **9** in 67% yield.

Scheme 2



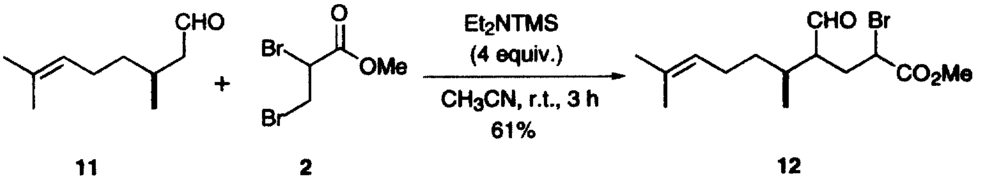
Although the exact role of Et_2NTMS is still ambiguous, the present cyclopropanation proceeds *via* 1,4-conjugate addition of a naked aldehyde to methyl α-haloacrylate generated *in situ* by the dehydrohalogenation of methyl 2,3-dibromopropanoate **2** or **3** with Et_2NTMS, followed by an intramolecular alkylation of an aldehyde enolate to furnish formylcyclopropane derivative **4** (Scheme 3). Different from a conjugate addition to pre-formed α-bromoacrylate **6**, ammonium bromide **10** may play some role to drive the reaction towards cyclopropanoate **4**. Facile generation of methyl α-bromoacrylate **6** *in situ* was confirmed by NMR experiment after mixing methyl 2,3-dibromopropanoate **2** and Et_2NTMS in $CDCl_3$.

Scheme 3. Reaction pathway of cyclopropanation



Reaction of citronellal **11** with methyl 2,3-dibromopropanoate **2** in the presence of 4 equiv. of Et$_2$NTMS in MeCN gave methyl 2-bromo-4-formyl-5,9-dimethyl-8-decenoate **12** in 61% yield (Scheme 4). Absence of cyclopropane derivative indicates that the second intramolecular nucleophilic substitution of aldehyde is sensitive to steric hindrance.

Scheme 4



In summary, we have shown that in presence of Et$_2$NTMS, the reaction of aldehyde **1** with methyl 2,3-dihalopropanoate **2** or **3** furnished methyl formylcyclopropanecarboxylate **4** by the tandem Michael-alkylation under milder reaction condition.

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