A Direct and Selective Syntheses of α,α-Dichloro- and α-Chloro-ethyl Ketones by the Reaction of Alkyl Carboxylates with 1,1-Dichloroethyllithium

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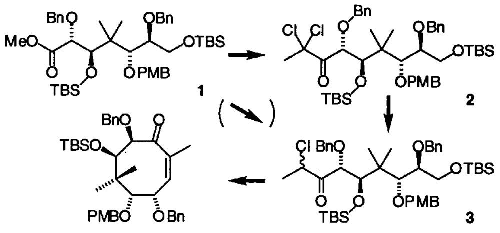
1,1-Dichloroethyllithium (**5**), generated by treating 1,1-dichloroethane (**4**) with lithium diisopropylamide (LDA) or *n*-butyllithium, reacted with alkyl carboxylates to afford the corresponding α,α-dichloro- or α-monochloro-ethyl ketones selectively in good to high yields. According to the above alkylation method, synthetic intermediates of Taxol, optically active α,α-dichloroethyl polyoxyketone **2** and α-chloroethyl polyoxyketone **3**, were respectively synthesized from optically active methyl polyoxycarboxylate **1** in good yields.

Total syntheses of Taxol and its derivatives were recently reported from our laboratory.[1] According to our strategy, the basic frameworks of taxoids were constructed from optically active polyoxy 8-membered ring compounds which were prepared by cyclization of chiral linear polyoxy compounds.



Scheme 1.

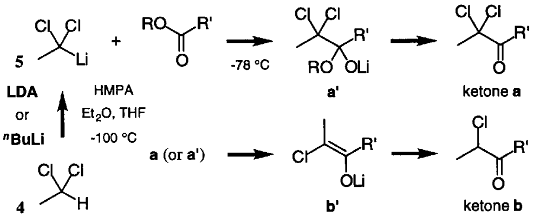
In the previous paper,[2] an improved method for the synthesis of chiral linear polyoxy compound was preliminarily reported, namely, i) intermediate methyl carboxylate **1** was prepared by starting from D-pantolactone, ii) the corresponding α,α-dichloroethyl polyoxyketone **2** was yielded by alkylation of **1** with 1,1-dichloroethyllithium (**5**), iii) α-chloroethyl polyoxyketone **3** was produced by partial reduction of **2** with ^{n}Bu$_3$SnH. It was noticed there that the alkylations of **1** with α-haloalkyllithiums[3-7] gave exclusively the corresponding monoalkylated ketones without accompanying the undesirable tertiary alcohols formed by double alkylations, whereas only the corresponding tertiary alcohol resulted when **1** was treated with MeLi. Concerning alkylation of alkyl carboxylates with alkyl metals, it was already reported that methyl or ethyl carboxylates containing heteroatom(s) at α-positions sometimes afforded the corresponding ketones without forming the tertiary alcohols.[7c,8,9] Further, Villieras et al. reported selective monoalkylations of methyl benzoate and 2-methylpropanoate with **5** prepared from 1,1-dichloroethane (**4**) and ^{s}BuLi.[4b,5a,7a]

In this communication, we would like to describe an effective method for the one-pot syntheses of α,α-dichloro- and α-monochloroethyl ketones from simple alkyl carboxylates such as methyl or ethyl carboxylates by the reaction with **5** which was prepared on treatment of **4** with LDA or ^{n}BuLi. Furthermore, relation between the structure of starting alkyl carboxylates and yields of the produced ketones, together with reaction conditions were examined in detail based on the reaction mechanism.

In the first place, alkylations of methyl benzoate with several alkyl metals such as EtMgBr, ^{n}BuLi and chloromethyllithium were studied in order to compare behavior of these alkylating reagents. When EtMgBr (2.0 eq.) and ^{n}BuLi (1.0 eq.) were used as alkylating reagents, only the corresponding tertiary alcohols were produced in ether and THF mixed solvents (EtMgBr; 56% at 0 °C, ^{n}BuLi; 39% at -78 °C). In the case of using chloromethyllithium[7b] (2.0 eq.), on the other hand, the corresponding monoalkylated α-chloromethyl ketone was selectively obtained in 93% yield at -78 °C under same reaction conditions. It was confirmed that reactions of simple alkyl carboxylates with in situ formed α-haloalkyllithium gave monoalkylated ketones preferentially while conventional alkylating reagents such as Grignard reagents, *etc.* gave tertiary alcohols.

Reaction conditions for the generation of **5**[4] were re-examined in detail concerning bases, solvents, additives, reaction time and temperature. It was then proven that LDA and ^{n}BuLi were quite suitable bases, whereas others such as LHMDS and LTMP gave poor results. The desired monoalkylated α,α-dichloroethyl ketone (ketone **a**) was obtained in 85% yield at -78 °C by the reaction of methyl benzoate with **5** generated from 2.5 molar amounts of **4** and 2.0 molar amounts of LDA at -100 °C in ether and THF mixed solvent containing HMPA (conditions A). Further, ketone **a** was also obtained in 91% yield at -78 °C from methyl benzoate on treatment with **5** prepared from 8.4 molar amounts of **4** and 4.2 molar amounts of ^{n}BuLi at -100 °C (conditions B). In the above reaction, *n*-butylated tertiary alcohol was not detected under the reaction conditions suggesting that ^{n}BuLi was quite quickly consumed to form **5**. However, in the absence of HMPA, generation of **5** by deprotonation of **4** with ^{n}BuLi was relatively slow and 46% of *n*-butylated secondary alcohol was produced by the reaction of benzaldehyde together with 44% of 2,2-dichloroethylated secondary alcohol. Since **5** is not stable and it decomposes immediately under the reaction conditions, an excess amount of the alkylating reagent is required to obtain the desired ketone **a** in good yield. When LDA was used as a base, on the other hand, the generation of **5** seems to take place gradually in accordance with the reaction proceeding. It is noted that the amounts of the above mentioned organometals such as LDA and ^{n}BuLi in the present alkylation depend on the rate of generation of **5**, an unstable intermediate, from **4**. In order to confirm the reaction intermediate, chlorotrimethylsilane was added to the reaction mixture of methyl benzoate and **5** prepared according to conditions A. There, methyl trimethylsilyl mixed acetal was trapped in good yield (88%) and it suggested that in situ formed lithium salt of hemiacetal **a'** would resist a further attack of **5** under the reaction conditions and no tertiary alcohol resulted (Scheme 2).

The desired ketones **a** were produced in high yields with complete selectivities from methyl 2-benzyloxypropanoate (**6**) and methyl 2-(*t*-butyldiphenylsiloxy)propanoate (**7**) by the use of **5** generated on treating **4** with each alkyl metal, LDA and ^{n}BuLi (from **6**; 85% and 73%, from **7**; 85% and 92%). As methyl trimethylsilyl mixed acetal was obtained in 70% yield by adding chlorotrimethylsilane to the reaction mixture of **7** and **5**, it was also revealed that an initially formed lithium salt of hemiacetal **a'** would resist the further attack of **5**.



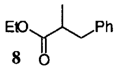
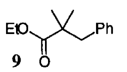
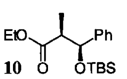
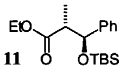
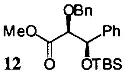
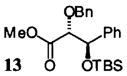
Scheme 2.

Next, alkylations of ethyl 2-methyl-3-phenylpropanoate (**8**) and ethyl 2,2-dimethyl-3-phenylpropanoate (**9**) with **5** were tried (Table 1, Entries 1 and 2). The corresponding α,α-dichloroethyl ketones (ketones **a**) were obtained in good yields under the conditions A while α-monochloroethyl ketones (ketones **b**) were exclusively produced in one-pot when **5**, generated according to conditions B, was used. In order to examine the difference between the above two reactions, an excess amount of **5**, prepared from 8.4 molar amounts of **4** with 4.2 molar amounts of LDA, was used for the reaction of **8**, and the corresponding ketone **b** was obtained in 42% yield. Further, reduction of 4,4-dichloro-2-methyl-1-phenylpentan-3-one (**14**), an example of ketones **a**, with **5** generated according to conditions A, proceeded smoothly to give the corresponding ketone **b**, 4-chloro-2-methyl-1-phenylpentan-3-one, in 68% yield. These indicate that the amount of **5** influences the yields of two ketones (ketone **a** and ketone **b**). Since dechlorinated enol silyl ether was obtained in 25% yield by the addition of *t*-butylchlorodimethylsilane to the reaction mixture of **14** and **5**, the above one-pot monochloroethylation of alkyl carboxylates was assumed to have taken place stepwise: that is, i) addition of **5** to alkyl carboxylates to form ketones **a**, and ii) successive dehalogenation of thus formed ketones **a** to form ketones **b** *via* lithium enolates **b'** by reduction with excess **5** (Scheme 2).

The results of monoalkylation using various simple alkyl carboxylates are summarized in Table 1. When alkyl 1,2-disubstituted carboxylates were treated with **5**, prepared from **4** under conditions A, the corresponding ketones **a** were selectively obtained (Entries 3-6). On the other hand, alkylations of **10**-**13** with **5**, prepared by conditions B (ratio; **4** / ^{n}BuLi = 2 / 1), gave the corresponding ketones **b** in good yields.

A typical experimental procedure is described for the reaction of **8** with **5** (conditions B): To a solution of HMPA (0.14 mL) in ether (3.0 mL) and THF (2.3 mL) was added a solution of ^{n}BuLi in hexane (1.57 M, 0.42 mL, 0.66 mmol). 1,1-Dichloroethane (**4**) (0.11 mL, 1.31 mmol) was added to the reaction mixture at -100 °C. After the reaction mixture was stirred for 30 min, a solution of **8** (30.0 mg, 0.156 mmol) in ether (0.8 mL) was added at -100 °C. The reaction mixture was stirred for 45 min at -78 °C and then saturated aqueous ammonium chloride was added. After usual work-up, the crude product was purified by TLC to afford the corresponding ketone **b** (21.4 mg, 65%) and recovered **8** (2.6 mg, 9%) as colorless oils (Entry 1).

Table 1. Yields of several monoalkylated ketones[a]

Entry	ROOCR'	α,α-Dichloroethyl Ketone (ketone **a**, conditions A)[b] α-Monochloroethyl Ketone (ketone **b**, conditions B)
1	 **8**	64 (12) 65 (9)[c]
2	 **9**	67 (26) 61 (26)[d]
3	 **10**	71 (5) 68 (10)[d]
4	 **11**	79 (0) 81 (11)[d]
5	 **12**	13 (45) 50 (14)[e]
6	 **13**	73 (0) 71 (3)[f]

[a] Isolated yield. The yields of recovered esters are shown in parentheses. [b] 2 molar amounts of LDA were used for the generation of **5**. [c] 4.2 molar amounts of ^{n}BuLi were used. [d] 5.2 molar amounts of ^{n}BuLi were used. [e] 15 molar amounts of ^{n}BuLi were used. [f] 20 molar amounts of ^{n}BuLi were used.

Finally, usefulness of the present method for the synthesis of α-haloethyl ketones from simple alkyl carboxylates was examined by taking Taxol intermediate **1**, an alkyl polyoxycarboxylate containing *anti*-configuration at C2,C3 positions, as a model. Expectedly, α,α-dichloroethyl polyoxyketone **2**, one of the intermediates of Taxol, was obtained in 54% yield (and 28% of **1** was recovered) when **1** was treated with **5** generated from **4** and LDA (14 eq., conditions A without HMPA). It is noteworthy that the one-pot and highly selective synthesis of intermediate of Taxol **3**, an α-monochloroethyl polyoxyketone, from **1** was attained in 91% yield on treatment with **5**, prepared from **4** and ^{n}BuLi (30 eq.).

Thus, α,α-dichloro- and α-monochloro-ethyl ketones were respectively synthesized in good to high yields by the alkylation of simple alkyl carboxylates with **5** generated from **4** using LDA and ^{n}BuLi.

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