Direct and Selective Syntheses of α,α-Dichloroethyl Ketones or Their Ethyl Trimethylsilyl Mixed Acetals by the Reactions of Methoxymethyl or Ethyl Carboxylates with 1,1-Dichloroethyllithium in the Presence of Chlorotrimethylsilane

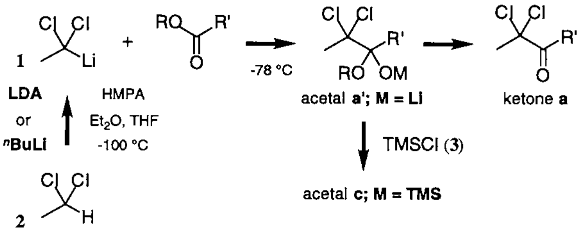
Isamu Shiina, Yumiko Imai, Masahiko Suzuki, Manabu Yanagisawa, and Teruaki Mukaiyama
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162-8601

(Received June 19, 2000; CL-000600)

1,1-Dichloroethyllithium (**1**), generated by treating 1,1-dichloroethane (**2**) with lithium diisopropylamide (LDA) or *n*-butyllithium, reacted with methoxymethyl carboxylates in the coexistence of chlorotrimethylsilane (**3**) to afford the corresponding α,α-dichloroethyl ketones in good yields. On the other hand, **1** reacted with ethyl carboxylates under the above reaction conditions to give 2,2-dichloro-1-alkyl-1-ethoxy-1-(trimethylsiloxy)propanes selectively in good yields.

An improved method for the synthesis of chiral linear polyoxy compound, one of the important synthetic intermediates of Taxol,[1] was preliminarily reported in the previous paper.[2] In the above synthesis, optically active methyl polyoxycarboxylate derived from D-pantolactone was directly converted to the corresponding α,α-dichloroethyl polyoxyketone or α-monochloroethyl polyoxyketone in high yield when treated with 1,1-dichloroethyllithium (**1**).[3] The latter reaction mechanism is assumed to proceed via initial formation of α,α-dichloroethyl polyoxyketone, followed by successive reductive dehalogenation with **1**. These methods were successfully applied to the syntheses of several α,α-dichloroethyl ketones (ketones **a**) and α-monochloroethyl ketones (ketones **b**) from alkyl benzoate, 2-alkoxypropanoate, 2-alkyl-3-phenylpropanoate, 2,2-dialkyl-3-phenylpropanoate, 3-alkoxy-2-alkyl-3-phenylpropanoate and 2,3-dialkoxy-3-phenylpropanoate.[3] However, their yields were not satisfactory when alkyl 3-phenylpropanoate and related alkyl carboxylates having methylene carbon at 2-position were employed due to facile enolization of the substrates.

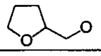
In this communication, we would like to describe an effective method for the one-pot syntheses of ketones **a** from alkyl carboxylates having methylene carbon at 2-position with **1**, prepared from 1,1-dichloroethane (**2**) and LDA or ^{n}BuLi. Further, a selective preparation of 2,2-dichloro-1-alkyl-1-ethoxy-1-(trimethylsiloxy)propanes (acetals **c**), ethyl trimethylsilyl mixed acetals of ketones **a**, by the reaction of alkyl carboxylates and **1** in the coexistence of chlorotrimethylsilane (**3**) is described.



Scheme 1.

In the first place, various alkyl 3-phenylpropanoates were synthesized and their alkylation with **1** was tried under the standard reaction conditions of using alkyl 2-substituted propanoate derivatives.[3] As shown in Table 1, alkylation of methoxymethyl 3-phenylpropanoate with **1**, generated from **2** and LDA (conditions A) or from **2** and ^{n}BuLi (conditions B), and alkylation of oxolan-2-ylmethyl 3-phenylpropanoate with **1** under conditions A gave the corresponding ketone **a**, 4,4-dichloro-1-phenylpentan-3-one, in fairly good yield.

Table 1. Yields of 4,4-dichloro-1-phenylpentan-3-one from alkyl 3-phenylpropanoates ($ROCOCH_2CH_2Ph$)

Entry	RO	Yield (Yield of recovered ester) / % LDA	 ^{n}BuLi
1	MeO	39 (48)	41 (18)
2	EtO	42 (60)	51 (30)
3	MOMO	73 (0)	59 (15)
4	MEMO	29 (0)	14 (3)
5		58 (11)	30 (28)

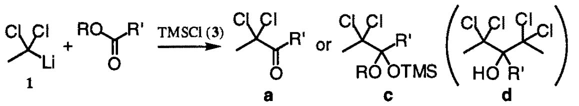
Next, several methoxymethyl and ethyl carboxylates were prepared and their reactions with **1** were systematically studied whose results are shown in the left column of Table 2. The reactions sometimes gave ketones **a** in fairly good yields, however, as shown in entries 5–9, 11, 13 and 15, the desired monoalkylated ketones **a** were obtained less than 39% yields and undesirable double alkylated products, tertiary alcohols **d**, were formed in up to 23% yields.

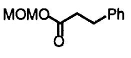
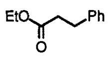
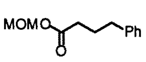
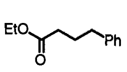
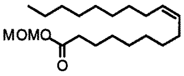
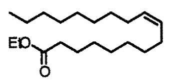
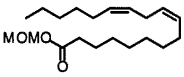
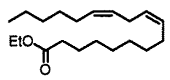
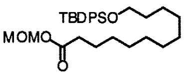
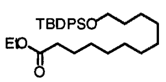
In the previous communication, it was shown that the acetal **c** was obtained in good yield when **3** was added to the reaction mixture of methyl 2-benzyloxypropanoate and **1**.[3,4] This result suggested that in situ formed lithium salt **a'** resisted a further attack of **1** under the above reaction conditions to prevent the formation of tertiary alcohol **d**. In order to examine the effect of **3**, the reaction of alkyl carboxylates having methylene carbon at 2-position and **1** was tried in the coexistence of **3**.

When alkylation of methoxymethyl 3-phenylpropanoate with **1** formed under either conditions A or B was tried in the coexistence of **3**, the corresponding ketone **a** was obtained in good yield as expected (See the right column of Table 2, Entries 1 and 2). On the other hand, the corresponding acetal **c** was exclusively produced in one-pot when ethyl 3-phenylpropanoate was employed as a substrate (Entries 3 and 4). In order to show the generality of the present protocol, monoalkylation by the use of various alkyl carboxylates having methylene carbon at 2-position was studied and the results are summarized in the right column of Table 2. When methoxymethyl 3-phenylpropanoate, 4-phenylbutanoate, oleate, linoleate and 12-(*t*-butyldiphenylsiloxy)dodecanoate were treated with **1** in the presence or absence of **3**, the corresponding ketones **a** were selectively obtained. It is noteworthy that the addition of **3** increased the yields up to acceptable level to all cases (Entries 1-2, 5-6, 9-10, 13-14 and 17-18). On the other hand, alkylations of ethyl 3-phenylpropanoate, 4-phenylbutanoate, oleate, linoleate and 12-(*t*-

butyldiphenylsiloxy)dodecanoate with **1** in the presence of **3** selectively gave the corresponding acetals **c** in good yields (Entries 3-4, 7-8, 11-12, 15-16 and 19-20). The above two conditions were compared in detail, and conditions A turned out to give better yields by 22% to the maximum.

Table 2. Yields of several monoalkylated ketones and acetals

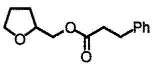
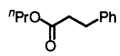


Entry	Ester	Base	Yield of **a** or **c** (Yield of Recovered Ester) / %		
			without TMSCl		with TMSCl
1		LDA	**a** 73 (0)	➡	**a** 78 (9)
2		^{n}BuLi	**a** 59 (15)	➡	**a** 80 (17)
3		LDA	**a** 42 (60)	➡	**c** 83 (11)
4		^{n}BuLi	**a** 51 (30)	➡	**c** 75 (15)
5		LDA	**a** 20 (19) plus **d** 21	➡	**a** 73 (19)
6		^{n}BuLi	**a** 25 (38) plus **d** 8	➡	**a** 68 (24)
7		LDA	**a** 16 (26) plus **d** 7	➡	**c** 86 (11)
8		^{n}BuLi	**a** 35 (38) plus **d** 3	➡	**c** 66 (24)
9		LDA	**a** 10 (36) plus **d** 15	➡	**a** 69 (18)
10		^{n}BuLi	**a** 24 (33)	➡	**a** 55 (35)
11		LDA	**a** 23 (0) plus **d** 21	➡	**c** 70 (27)
12		^{n}BuLi	**a** 46 (30)	➡	**c** 48 (21)
13		LDA	**a** 15 (39) plus **d** 18	➡	**a** 73 (12)
14		^{n}BuLi	**a** 59 (13)	➡	**a** 70 (16)
15		LDA	**a** 39 (0) plus **d** 23	➡	**c** 81 (12)
16		^{n}BuLi	**a** 51 (0)	➡	**c** 59 (28)
17		LDA	**a** 40 (15)	➡	**a** 75 (6)
18		^{n}BuLi	**a** 52 (11)	➡	**a** 64 (10)
19		LDA	**a** 51 (9)	➡	**c** 81 (13)
20		^{n}BuLi	**a** 30 (48)	➡	**c** 75 (17) plus **a** 7

A typical experimental procedure is described for the reaction of methoxymethyl 3-phenylpropanoate with **1** (conditions A): To a solution of diisopropylamine (0.043 mL, 0.31 mmol) in ether (2.9 mL) and THF (2.5 mL) was added a solution of ^{n}BuLi in hexane (1.50 M, 0.205 mL, 0.308 mmol). After the reaction mixture had been stirred for 30 min at 0 °C, HMPA (0.067 mL, 0.39 mmol) was added. 1,1-Dichloroethane (**2**) (0.032 mL, 0.38 mmol) was added to the reaction mixture at –100 °C. After the reaction mixture had been stirred for 30 min, a solution of methoxymethyl 3-phenylpropanoate (30.0 mg, 0.154 mmol) in ether (0.8 mL) and **3** (0.058 mL, 0.46 mmol) were successively 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 **a** (27.9 mg, 78%) and recovered ester (2.7 mg, 9%) as colorless oils (Table 2, Entry 1).

Yields and selectivities of reactions using oxolan-2-ylmethyl and *n*-propyl 3-phenylpropanoate were further examined (See Table 3). Similar to the case of using ethyl 3-phenylpropanoate, the corresponding acetal **c** was obtained in good yield when *n*-propyl 3-phenylpropionate was treated with **1** which was generated under conditions A (Entry 3). A mixture of ketone **a** and its acetal **c** resulted in both reactions of oxolan-2-ylmethyl 3-phenylpropanoate under conditions A or B (Entries 1 and 2) and *n*-propyl 3-phenylpropionate under conditions B (Entry 4). Thus, it is noted that methoxymethyl and ethyl carboxylates are effectively employed in the synthesis of the above mentioned two respective products in selective manner.

Table 3. Yields of 4,4-dichloro-1-phenylpentan-3-one and its acetal

Entry	Ester	Base	Yield of **a** or **c** (Yield of Recovered Ester) / %		
			without TMSCl		with TMSCl
1		LDA	**a** 58 (11)	➡	**a** 39 (0) plus **c** 41
2		^{n}BuLi	**a** 30 (28)	➡	**a** 46 (15) plus **c** 22
3		LDA	**a** 34 (0)	➡	**c** 70 (14)
4		^{n}BuLi	**a** 41 (45)	➡	**c** 30 (48) plus **a** 11

The pathway and selectivities of the present reaction are explained as follows; ethyl and methoxymethyl carboxylates are similarly activated firstly by the coordination of the carbonyl oxygen to **3**, and then lithium salts of hemiacetals are smoothly produced by the nucleophilic addition of **1** to alkyl carboxylates. As sketched in Figure 1, the transmetallation of intermediate from lithium to silicone in **a'-1** would hardly take place because lithium is rigidly restrained by a 5- and 6-membered fused ring structure.[5] On the other hand, the transmetallation of intermediate **a'-2** which forms less stable single 5-membered chelate ring proceeds preferentially to give acetal **c**.

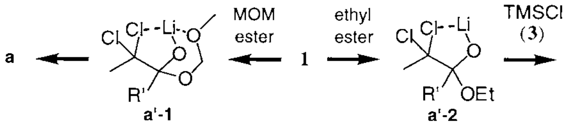


Figure 1.

Thus, α,α-dichloroethyl ketones (ketones **a**) or its ethyl trimethylsilyl mixed acetals (acetals **c**) were respectively synthesized in good yields by the alkylation of methoxymethyl or ethyl carboxylates with **1** in the presence of **3**.

This work was supported by Grant-in-Aids for Scientific Research from the Ministry of Education, Science, Sports, and Culture.

References and Notes

1 T. Mukaiyama, I. Shiina, H. Iwadare, M. Saitoh, T. Nishimura, N. Ohkawa, H. Sakoh, K. Nishimura, Y. Tani, M. Hasegawa, K. Yamada, and K. Saitoh, *Chem. Eur. J.*, **5**, 121 (1999).
2 I. Shiina, J. Shibata, Y. Imai, R. Ibuka, H. Fujisawa, I. Hachiya, and T. Mukaiyama, *Chem. Lett.*, **1999**, 1145.
3 I. Shiina, Y. Imai, A. Kagayama, and T. Mukaiyama, *Chem. Lett.*, **2000**, 190. See also, preparation and utilization of 1,1-dichloroethyllithium: J. Villiéras and M. Rambaud, *C. R. Acad. Sci., Ser. C*, **291**, 105 (1980), and references cited therein.
4 J. Barluenga, B. Pedregal, and J. M. Concellón, *Tetrahedron Lett.*, **34**, 4563 (1993), and references cited therein.
5 Structures of lithium salts of hemiacetals were suggested by DFT calculation. Details of the structures will be discussed in full paper.