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NOVEL SELECTIVE SYNTHESIS OF α-CHLOROMETHYL, α,α-DICHLOROMETHYL, and α,α,α-TRICHLOROMETHYL KETONES FROM ALDEHYDE UTILIZING ELECTROREDUCTION AS KEY REACTIONS[1]

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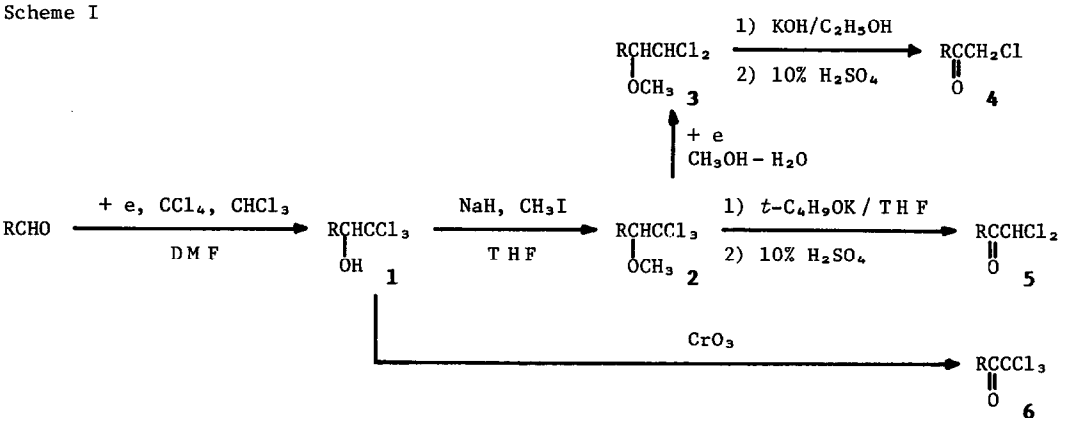
A variety of α-chloromethyl, α,α-dichloromethyl, and α,α,α-trichloromethyl ketones were synthesized from aldehyde utilizing cathodic reduction as key reactions.

Recently we have found a practically useful electroreductive anionic chain reaction in which aldehyde was efficiently converted into trichloromethylcarbinol **1**.[2] In our continuing study on the utilization of **1** in organic synthesis, it was found that **1** could selectively be transformed into α-chloromethyl **4**, α,α-dichloromethyl **5**, and α,α,α-trichloromethyl **6** ketones as the overall process is shown in Scheme I.

Scheme I



Although **4**, **5**, and **6** have been known to be reasonably important compounds as the starting material in organic synthesis, their simple and convenient synthetic methods have not always been found. Thus, the selective synthesis of **4** by chlorination of methyl ketone[3] or by the reaction of acyl chloride with diazomethane[4] is not necessarily a convenient procedure, and also there are actually no effective and simple methods of synthesizing a variety of **5**[5] and **6**. Our new methods shown in Scheme I afford, however, very simple and selective methods of synthesizing **4**, **5**, and **6** from a variety of aldehydes.

The reaction conditions of the electroreductive anionic chain reaction described in our previous report[2] were slightly modified to obtain satisfactory yield based on aldehyde. Thus, the molar ratio of aldehyde, carbon tetrachloride, and chloroform was 1 : 3 : 10, and

N,N-dimethylformamide was used as solvent instead of chloroform. Under these reaction conditions, cathodic reduction gave **1** in the yield of 62-92%.

α-Chloromethyl Ketone

A typical procedure is as follows: To a mixture of 24 mmol of NaH and 24 mmol of CH_3I in 10 ml of THF was added 20 mmol of **1** at 0 °C. After stirring for 1 h at 0 °C, excess water was added, and the solution was extracted with ether. The product **2** was isolated by distillation, the yield being 85-90%. Under the conditions of constant current (0.3 A) using a divided cell equipped with a platinum cathode and a carbon anode, the cathodic reduction of 10 mmol of **2** was carried out in 80 ml of 90% aqueous methanol containing 0.2M of ammonium nitrate until 2.5 *F*/mol of electricity was passed.[7,9] The dichloride **3** (10 mmol) was dissolved into 20 ml of ethanolic KOH (5 M), and the solution was refluxed until **2** was completely consumed. After usual working up, the crude product, that is enol ether, was dissolved into 20 ml of 50% aqueous dioxane containing 0.3 ml of conc. H_2SO_4. The solution was stirred for 2-3 h at room temperature to give α-chloromethyl ketone **4**.

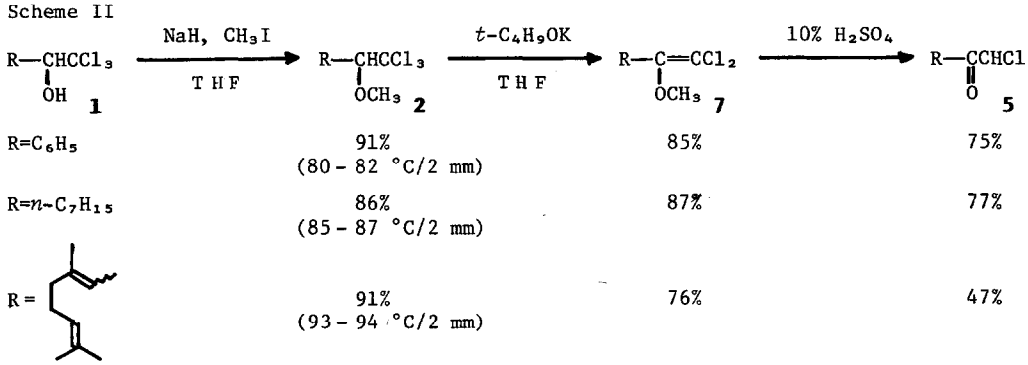
The results obtained with a variety of aldehydes are shown in Table I.

α,α-Dichloromethyl Ketone

The methyl ether **2** could easily be transformed into α,α-dichloromethyl ketone **5**. Followings are the typical procedure. Thus, to a suspension of 5.5 mmol of *t*-C_4H_9OK in 10 ml of THF was added 5 mmol of **2** at 0 °C. The mixture was stirred for 1 h, diluted with excess water, and extracted with ether. Enol ether **7** was isolated with column chromatography on silica gel.

The enol ether **7** (3 mmol) was refluxed in 50% aqueous dioxane (20 ml) containing 0.3 ml of conc. H_2SO_4 until hydrolysis was completed. After usual working up, **5** was purified by column chromatography on silica gel. Typical examples are shown in the following Scheme II.

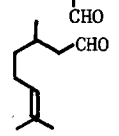
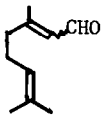
Scheme II



	1 → **2**	**2** → **7**	**7** → **5**
R=C_6H_5	91% (80 - 82 °C/2 mm)	85%	75%
R=*n*-C_7H_{15}	86% (85 - 87 °C/2 mm)	87%	77%
R=	91% (93 - 94 °C/2 mm)	76%	47%

Because of the difficulty of synthesizing **5**, the potentiality of **5** in organic synthesis is hitherto unknown. The Favorskii type rearrangement of **5** for instance, however, gave the corresponding α,β-unsaturated ester in an excellent yield. Typical procedure is as follows: To a solution of 3 mmol of CH_3ONa in 5 ml of methanol was added 1 mmol of **5**. The mixture was stirred at room temperature for 2-4 h, diluted with excess water, and extracted

Table I. Synthesis of α-Chloromethyl Ketone **4** from Aldehyde.

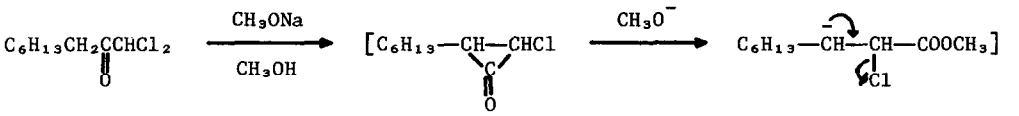
Aldehyde	Yield (%)[a] (bp °C/mmHg or mp °C)		
	1	**3**	**4**[b]
$CH_3(CH_2)_2CHO$	88 (84 - 85/18)	61 (88 - 90/50)	59 (85 - 88/75)
$CH_3(CH_2)_6CHO$	92 (98-101/2)	84 (90 - 95/2)	73 (98-100/15)
$CH_3(CH_2)_3CH(CHO)CH_2CH_3$	86 (68 - 70/1)	54 (105-110/6)	70 (78 - 80/15)
	62 (99-101/1)	68 (103-105/1)	73 (115-118/5)
$PhCH_2CH_2CHO$	89 (103/1)	70 (85/1)	81 (83 - 85/1)
	76 (95 - 97/1)	80 (108-110/2)	90 (100-102/1)
PhCH=CHCHO	86 (120/1)	50 (123-125/2)	73 (56 - 57)[c]
PhCHO	88 (138-139/15)	74 (76 - 78/1)	70 (96 - 98/15)
o-CH_3O—C_6H_4CHO	91 (120-122/2)	64 (125-126/2)	72 (63 - 65)[c]
m-CH_3O—C_6H_4CHO	91 (126-128/2)	75 (116-117/1)	69 (70 - 72)[c]
p-CH_3O—C_6H_4CHO	90 (122-124/1)	76 (125-126/2)	72 (96 - 98)[c]

[a] Isolated yield.

[b] All the compounds gave satisfactory spectroscopic and elemental analyses.

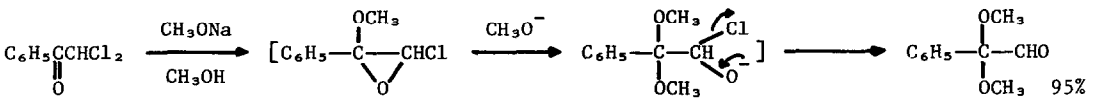
[c] Melting point.

with ether. The product was isolated by distillation using Kugel Rohr.



90%

Treatment of phenyl dichloromethyl ketone under the same reaction conditions described above gave α-ketoaldehyde in an excellent yield.



α,α,α-Trichloromethyl Ketone

The oxidation of **1** with Jones reagent gave the corresponding α,α,α-trichloromethyl ketone in the reasonable yield.

$R = C_6H_5$	76%
$R = C_7H_{15}$	70%

Acknowledgment

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References and Notes

(1) Electroorganic Chemistry. 61.

(2) T. Shono, H. Ohmizu, S. Kawakami, S. Nakano, and N. Kise, *Tetrahedron Lett.*, **22**, 871 (1981).

(3) (a) Y. Jasor, M. Gaudry, and A. Marquet, *Bull. Soc. Chim. Fr.*, **1973**, 2735.
(b) J. F. W. Keana and R. R. Schumaker, *Tetrahedron*, **26**, 5191 (1970).
(c) For review see: J. F. Stoddart Ed., " Comprehensive Organic Chemistry", Pergamon Press Ltd., Oxford, (1970), Vol. 1, pp. 1036-1039.

(4) J. W. Thorpe and J. Warkentin, *Can. J. Chem.*, **51**, 927 (1973).

(5) The synthesis of α,α-dichloromethyl ketone using the reaction of *N*-chlorosuccinimide with the ketimine of methyl ketone having a particular structure is not a versatile and practical method.[6]

(6) W. Coppens and N. S. Schamp, *Bull. Soc. Chim. Belg.*, **81**, 643 (1972).

(7) Cathodic reduction of some simple trichloroalkanes to dichlorides has been studied using mercury as the cathode, though using mercury as cathode is highly inconvenient in practical organic synthesis.[8]

(8) M. Nagao, N. Sato, T. Akashi, and T. Yoshida, *J. Am. Chem. Soc.*, **88**, 3447 (1966).

(9) The electroreduction of **1** instead of **2** yielded two types of product, namely **1'** and **1''**, depending on the reaction conditions. Both products were, however, not able to be transformed into **4**. The synthesis of **1'** and **1''**, and their use in organic synthesis will be reported elsewhere.

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