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A new route to the synthesis of long-chain methyl α-chlorooxoalkanoates

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A reaction of long-chain methyl epoxyalkanoates with chlorotrimethylsilane in presence of triethylamine followed by Jones′ oxidation has resulted in the formation of respective chlorooxo derivatives. The reaction proceeds under mild conditions and in a short span of time. Thus, one pot synthesis of methyl chlorooxoalkanoates is assisted with high purity and good yield of the products. The pure products are characterized by IR, ^{1}H NMR, ^{13}C NMR and MS spectra.

Keywords: Methyl epoxyalkanoates, chlorotrimethylsilane, Jones′ oxidation, methyl α-chlorooxoalkanoates

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Haloketones are highly reactive compounds, which are eminently suitable for the synthesis of a great variety of physiologically active derivatives[1]. From time to time the potential usefulness of haloketones as synthetic intermediates has been emphasized in the literature[1,2] and hence they have attracted increasing interest. Haloketones are usually prepared by the halogenation of parent carbonyl compounds[3]. However, perusal of literature reveals that they are also prepared from substrates other than carbonyl compounds viz. olefins[4], α-halohydrins[5], epoxides[6] and some other substrates[7].

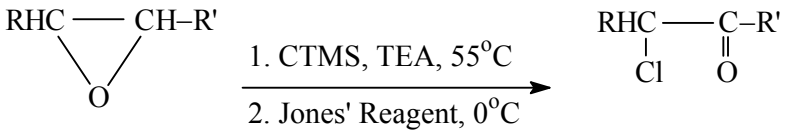
Among different substrates, epoxides proved to be an important base for the preparation of haloketones and has attracted considerable attention as the oxirane ring can be opened in almost all conditions: electrophilic, nucleophilic, neutral, gas phase, thermal and free radical conditions.

Denis and Krief[6] had developed a successful method for the preparation of α-haloketones from epoxides using bromotrimethylsilane. Halotrimethyl-silane in general is a versatile and commercially available reagent, widely used in different chemical transformations[8]. Chlorotrimethylsilane (CTMS) is used successfully as a reagent for the preparation of long-chain chlorohydrins[9] from epoxides in quantitative yield.

Though there are various methods for the preparation of the haloketones, very little work has been done on fatty substrates[10]. Keeping in view, the versatile nature of oxirane ring, use of CTMS as an epoxide ring opening reagent, lack of literature reports on the preparation of long-chain α-chloroketones (chlorooxo derivatives) and the ease of the reaction procedure, it is tried to prepare some of the long-chain methyl chlorooxoalkanoates from long-chain epoxyalkanoates using CTMS.

Reaction of methyl 10, 11-epoxyundecanoate **1** with CTMS followed by Jones′ oxidation gave product **2 (Scheme I)**. IR spectra of **2** clearly indicates the presence of oxo group by showing a peak at 1715 along with the ester peak at 1735 cm^{-1}. ^{1}H NMR spectra of the compound showed a singlet at δ 4.07 for C11 hydrogen, which indicates the presence of chloro group at the terminal position. ^{13}C NMR data also supported this finding by showing a signal at δ 48.20 for C_{11} i.e. carbon containing chloro group. Further the MS spectrum was showing structure depicting peaks at m/z 199 (M^{+}–Cl) and at m/z 105 (δ-cleavage of oxo group). These studies assigned the structure of methyl 11-chloro 10-oxoundecanoate.

Similarly reaction of methyl *cis*-9, 10-epoxy-octadecanoate **3** with CTMS followed by Jones′ oxidation furnished **4 (Scheme I)** an inseperable isomeric product. ^{1}H NMR study was recording a multiplet at δ 4.20 for C_9 or C_{10} methine proton along with a triplet at δ 2.63 for C_8 or C_{11} methylene protons, which confirmed the formation of the isomeric product. These findings were further



1,3 **2,4**

	R	R'
1,2	H	$(CH_2)_8COOCH_3$
3	$(CH_2)_7CH_3$	$(CH_2)_7COOCH_3$
4	$(CH_2)_7CH_3$ or $(CH_2)_7COOCH_3$	$(CH_2)_7COOCH_3$ or $(CH_2)_7CH_3$

Scheme I—Formation of methyl α-chlorooxoalkanoates

supported by ^{13}C NMR and MS spectral studies (Values are given in the experimental section). The MS peaks at m/z 141, 161/163, 185 and 205/207 is clearly confirming the presence of the isomeric product. On the basis of these findings compound **4** was characterized as an isomeric mixture of methyl 9-chloro (oxo)-10-oxo (chloro) octadecanoate.

Since the chloroketones **2** and **4** could be prepared cleanly and in high yield, it was of interest to determine the validity of this method to complicated substrate. A similar reaction of methyl 12-hydroxy *cis*-9,10-epoxyoctadecanoate **5** was performed and product **6** was obtained as inseperable isomeric product (**Scheme II**).

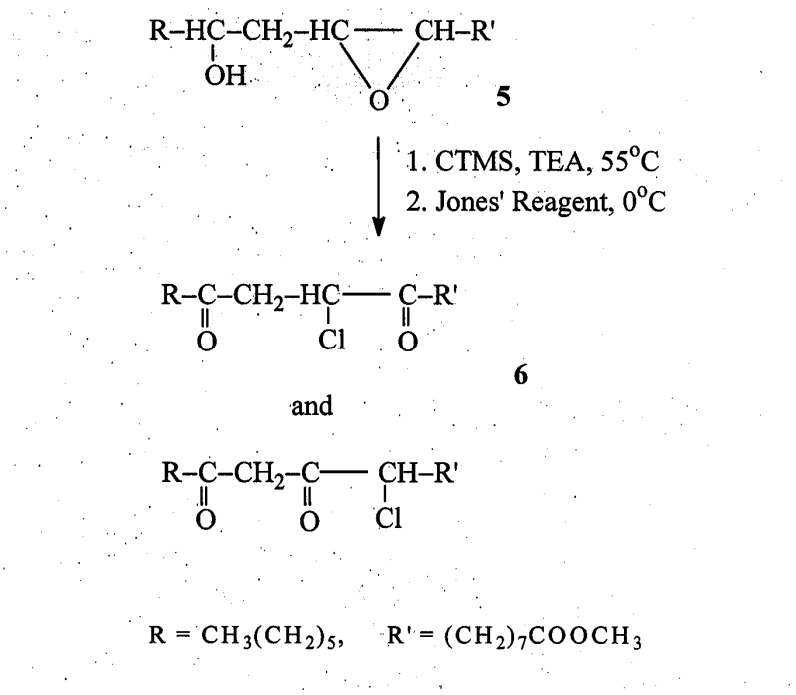
IR showed peak for oxo group at 1718 cm^{-1}. The ^1H NMR showed peak at δ 3.74 as multiplet, at 2.67 as a singlet ($O=\underset{|}{C}-CH_2-\underset{|}{C}=O$) and a distorted doublet at 2.64 ($O=\underset{|}{C}-CH_2-\underset{|}{C}H-Cl$), which were attributed to the formation of an isomeric product. ^{13}C NMR and MS spectra were also in accordance with these findings. The important structure confirming MS peaks were recorded at m/z 155, 175/177, 185 and 205/207. Other fragmentations are mentioned in the experimental section. These data lead to the formulation of **6** as an isomeric mixture of methyl 9(10) chloro-10(9), 12-dioxoundecanoate.

In case of methyl 12-hydroxy *cis*-9,10-epoxy-octadecanoate **5**, it was observed that mechanistically the reaction proceeds in the same way as in the case of **1** and **3** except, the hydroxy group present at C12 was also oxidized to oxo group during Jones′ oxidation, yielding a chlorodioxo derivative **6**.

Experimental Section

10-Undecenoic, *cis*-9-octadecenoic acids and CTMS were purchased from Fluka Chemicals (Switzerland). 12-Hydroxy *cis*-9-octadecenoic acid (ricinoleic acid) was isolated from the seed oil of *Ricinus cummunis* by using Gunstone's partition procedure[11]. Triethylamine (TEA), chromium trioxide and meta chloro perbenzoic acid (*m*-CPBA) were purchased from S.D. fine chemicals (India). Jones′ reagent was freshly prepared using chromium trioxide and concentrated sulphuric acid (Merck, India).

The melting point was taken in capillary tube in an electrically heated block and is uncorrected. Infrared spectra (IR), were obtained with Shimadzu 8201 PC spectrometer as neat films. Nuclear magnetic resonance (^1H NMR and ^{13}C NMR) spectra were recorded with Brucker DRX 300 spectrometer with $CDCl_3$ as the solvent. Chemical shifts are given in the δ scale, ppm downfield from tetramethylsilane (TMS) as internal standard. FAB, mass spectrum (MS) were recorded on a Jeol SX 102/DA-6000 mass spectrometer/Data system using Argon/Xenon (6KV, 10 mA) as the FAB gas.



Scheme II—Formation of methyl 9(10)-chloro-12,10(9)-dioxooctadecanoate **6**

Thin layer chromatographic plates (20 × 5 cm) were coated with a layer of silica gel G (0.25 mm thickness) and a mixture of pet. ether-diethyl ether-acetic acid (80:20:1, v/v) was normally used as the developing solvent. Components on the TLC plate were visualized by charring the sprayed plates with 20% aqueous solution of perchloric acid. All the reactions were monitored by TLC. Products were purified by column chromatography using silica (Merck, mesh 60-120) and a mixture of pet. ether and diethyl ether in different ratios as the eluting solvent.

Fatty acids were esterified by refluxing them with a large excess of anhydrous methanol in the presence of acid catalyst[12].

Esters were further epoxidized by using the method as described by Gunstone and co-worker[13] and Osman and co-workers[14] using *m*-CPBA to obtain **1**, **3** and **5**. All epoxides were tested for picric acid test and were further compared with authentic samples on TLC plates.

General procedure for the preparation of methyl α-chloroxoalkanoates

Methyl epoxy ester (**1** or **3** or **5**, 4 mmoles) in dichloromethane (6 mL) were added to a solution of CTMS (6 mmoles) and TEA (6.6 mmoles) in dichloromethane (12 mL) at 20°C. The solution was refluxed at 55°C till the maximum conversion takes place, and then cooled down to 0°C in an ice-bath. Freshly prepared Jones′ reagent [CrO_3 (16 mmoles), H_2SO_4 (98%) in water (5 mL)] was added to the reaction mixture and it was further stirred till the completion of the reaction at the same temperature. After quenching with water (20 mL) a reaction mixture was worked up in dichloromethane (20 × 30 mL). Organic extract was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. Crude products (**2**, **4**, **6**) were purified by column chromatography and were further tested for DNP and Beilstein tests.

Methyl 11-chloro-10-oxoundecanoate 2. Methyl 10,11 epoxy undecanoate **1** (856 mg, 4 mmoles) in CH_2Cl_2 (5 mL) was added at 20°C to a solution of CTMS (460 mg, 6 mmoles) and TEA (660 mg, 6.6 mmole) in CH_2Cl_2 (10 mL). The reaction mixture was heated and refluxed at 55°C for 3 hr, then cooled down to 0°C in an ice-bath. Freshly prepared Jones′ reagent [CrO_3 (1.6 g, 16 mmoles), H_2SO_4(Conc.) (1.4 mL) in water (4.5 mL)] was added and the reaction mixture was further stirred for 2 hr at this temperature. After quenching with water the reaction mixture was extracted with CH_2Cl_2 (2×30 mL). The organic extracts were dried over anhydrous sodium sulphate and the solvent was evaporated under reduced pressure to obtain the crude product. The

pure compound **2** was eluted on a column of silica gel with pet. ether-diethyl ether (90:10, v/v) as the eluent. Removal of solvent gave white solid which was crystallized with cold pet. ether (920 mg, 73.6%, m.p. 42°C). Anal. Found: C, 57.99; H, 8.25. Calcd. for $C_{12}H_{21}O_3Cl$: C, 58.06; H, 8.46%; IR (film): 1735 and 1715 cm^{-1} (ester carbonyl and C=O a part of absorption peaks merged together); ^1H NMR (δ, $CDCl_3$) 4.07 s (2H, C_{11} methylene protons), 3.68 s (3H, $COOCH_3$), 2.58 t (*J*=7.5 Hz, 2H, C_9 methylene protons), 2.30 t (*J*=7.5 Hz, 2H, CH_2 α to $COOCH_3$) 1.60 br m (4H, C_3 and C_8 methylene protons), 1.30 br s (8H, chain $-CH_2-$); ^{13}C NMR (δ_c, $CDCl_3$) 202.80, 174.00, 51.40, 48.20, 29.00, 28.98, 24.80, 23.50; Mass spectrum m/z (%) 250/248 (M^+, 10, 32), 249 (48), 219/217 (21, 65), 213 (15), 199/197(2,8), 154 (100), 119 (19), 105 (19).

Methyl 9-chloro(oxo)-10-oxo(chloro) octadecanoate 4. In a similar way as described above, methyl *cis*-9,10-epoxy octadecanoate **3** was treated with CTMS and TEA followed by Jones′ oxidation and was worked-up in a similar way as for product **2**. The crude product was chromatographed over a column of silica using pet. ether-diethyl ether (90:10, v/v) as the solvent to obtain the pure product **4** a colourless liquid (954 mg, 69%) and was further tested for DNP and Beilstein test. Anal. Found: C, 65.86; H, 10.06. $C_{19}H_{35}O_3Cl$ requires C, 65.90: H, 10.11%; IR (neat) 1730 ($COOCH_3$), 1720 cm^{-1} (C=O); NMR:δ, $CDCl_3$) 4.20 m (C_9 or C_{10} methine protons), 3.67 s (3H $COOCH_3$), 2.63 t (*J*=7.5 Hz C_8 or C_{11} methylene protons), 2.30 t (*J*=7.5 Hz, CH_2 α to $COOCH_3$), 1.66 br m (methylene protons β to $COOCH_3$ and C=O) and 1.27 br, s (chain $-CH_2-$) and 0.88 distorted t (3H, terminal $-CH_3$); ^{13}C NMR (δ_c, $CDCl_3$) 203.20, 173.72, 63.75, 51.44, 38.58, 38.45, 34.01, 31.78, 29.29, 29.09, 28.94, 28.25, 26.04, 25.97, 24.83, 23.65, 23.53, 22.62, 14.06; Mass spectrum m/z (%) 348/346 (M^+, 17,52), 347(73), 315(100), 316(21), 311(15), 207/205 (3.1, 10.2), 185(23), 163/161(3.7,11.0), 154(17), 141(44), 125(17).

Methyl 9(10)-chloro-10(9), 12-dioxooctadecanoate 6. Following the same procedure as used for the above two substrates, methyl 12-hydroxy 9,10-epoxy octadecanoate (**5**, 1.312 g, 4 mmoles) was introduced into the solution of CTMS (460 mg, 6 mmoles) and TEA (660 mg, 6.6 mmoles) in CH_2Cl_2 (10 mL) followed by Jones′ reagent. After refluxing for 4.5 hr at 55°C, the reaction mixture was worked up in CH_2Cl_2 as described earlier to obtain the crude product, which was then purified by column, using pet. ether-diethyl ether (80:20, v/v) as the solvent to yield **6**, a colourless liquid (964 mg, 67%). DNP and Beilstein tests were further performed. Anal. Found: C, 63.29; H, 9.13. Calcd. for $C_{19}H_{33}O_4Cl$: C, 63.33; H, 9.16%; IR (neat) 1738 ($COOCH_3$), 1718 cm^{-1}(C=O); ^1H NMR (δ,$CDCl_3$) 3.74 m (C_9 or C_{10} methine proton, merged in part with ester protons), 3.67 s (3H,$COOCH_3$), 2.67 s and 2.64 dist. d merged in part with 2.67 (C_{11} methylene protons), 2.45 t (*J*=7.5 Hz, CH_2 α to $COOCH_3$), 1.27 br s (chain $-CH_2-$), 0.88 distorted t (3H, terminal CH_3); ^{13}C NMR (δ_c, $CDCl_3$) 202.40, 203.80, 174.98, 62.98, 51.43, 42,78, 39.72, 39.68, 34.03, 31.56, 29.03, 28.96, 28.73, 25,23, 24.85, 23.79, 23.70, 22.45, 14.00; Mass spectrum m/z (%) 362/360 (M^+, 14, 58), 328(13), 325(15), 295(100), 277 (15), 207/205 (8.3,22.1), 203(10), 177/175 (9.8,27), 169(20.9), 154(29), 141(10.8), 139(21), 137(22), 136(30), 125(17), 113(29.8), 111(14).

Conclusion

Preparation of α-haloketones from substrates such as olefins or epoxides is generally carried out in two steps: first by converting the starting material into its halohydrin followed by the oxidation of the hydroxyl group. Here it is considered that the present method might be useful, easy and one-pot alternative method over conventional methods for converting epoxides or their precursor olefins into α-haloketones. The prepared compounds can be used as intermediates for the synthesis of certain useful compounds.

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References

1 Mangold H K, *Chem Phys Lipids*, 11, **1973**, 244.

2 Back H S, Yoo B W, Keum S R, Yoon C M, Kim S H & Kin J H, *Synth Commun,* 30, **2000**, 31; Takuma Y, Katsurda M & Suginome H, *Jpn, Kokai Tokkyo Koho*, J P, 128, **2002**, 722; Calter M A & Zhu C, *Org letter*, 4, **2002**, 205.

3 Brummond K M & Gesenberg K D, *Tetrahedron Lett,* 40, **1999**, 2231; Nishiyama T, Ono Y, Kurokawa S & Kimura S, *Chem Pharm Bull*, 48, **2000**, 1999; Bakarert A, Barberan O & Brion J D, *Tetrahedron Lett*, 41, **2000**, 2903.

4 Ascole R D, D' Auria M, Mucciliarelli L, Piancatelli G & Scelttri A, *Tetrahedron Lett*, 21, **1981**, 4521.

5 Corey E J, Yi K Y & Matsuda S P T, *Tetrahedron Lett*, 33, **1992**, 2319; Olah, G A, Vankar Y D & Arvanaghi M, *Tetrahedron Lett*, **1979**, 3653.

6 Denis J N & Krief A, *Tetrahedron Lett*, 22, **1981**, 1429; Raina S, Bhuniya D & Singh V K, *Tetrahedron Lett*, 33, **1992**, 6021.

7 Tillyer R, Frey L F, Tschen D M & Dolling U H, *Synlett*, **1996**, 225; Krohn K, Steingroever K & Vinke I, *J Prackt Chem*, 341, **1999**, 62; Wang X, Thottathil J K & Polniaszek R P, *Synlett*, **2000**, 202; Chambers R D & Hutchinson J, *J Flourine Chem*, 89, **1998**, 229.

8 Rauf A, Ahmad M S (Jr) & Osman S M, *J Oil Techn Assoc* (India), 31, **1981**, 135.

9 Olah G A & Narang S C, *Tetrahedron*, 38, **1982**, 2225; Kraus G A & Frazier K, *J Org Chem*, 45, **1980**, 257.

10 Hussain S R, Ahmad F, Ahmad M & Osman S M, *J Am Oil Chem Soc*, 61, **1984**, 954; Khan M, Ahmad S, Ahmad M S (Jr) & Osman S M, *Indian J Chem*, 25B, **1986**, 321.

11 Gunstone F D, *J Chem Soc*, **1954**, 1611.

12 Christie W W, in *Lipids Analysis* (Pergamon Press: Oxford), **1973**, p. 88.

13 Gunstone F D & Jacobsberg F R, *Chem Phys Lipids*, 9, **1972**, 26.

14 Rauf A, Ahmad M S (Jr) & Osman S M, *J Oil Techn Assoc* (India), 13, **1981**, 135.