Synthesis of Methyl 2-Aryloxy-4-methyl-4-pentenoates and 2-Aryloxy-4-methyl-4-pentenals

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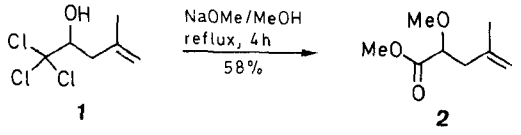
A convenient procedure for the preparation of the title compounds from 1,1,1-trichloro-4-methyl-4-penten-2-ol (**1**) and 1,1-dichloro-4-methyl-4-penten-2-ol (**8**), respectively, by treatment with unsubstituted and substituted sodium phenolates **5** is described.

α-Trichloromethyl alcohols, which can be readily prepared by various methods,[1-5] are versatile intermediates in organic syntheses. Under basic conditions, these compounds are transformed into several types of α-substituted carboxylic acids. Depending on the nature of the base used, α-alkoxy-,[6,7] α-hydroxy-,[8] α-chloro-,[9] and α-amino acids[10] can be prepared. The synthesis of α-aryloxycarboxylic acids by basic conversion of substituted α-trichloromethyl alcohols has attracted up to now only little attention.[11] Nevertheless, they are valuable intermediates in organic syntheses, e.g. for the preparation of drugs and plant protecting agents.[12]

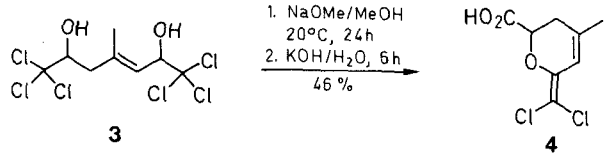
When studying the properties of 1,1,1-trichloro-4-methyl-4-penten-2-ol (**1**) and 1,1,1,7,7,7-hexachloro-4-methyl-3-hepten-2,6-diol (**3**), which are readily accessible by the reaction of trichloroacetaldehyde with 2-methylpropene,[13] we found that both compounds are converted to new products in the presence of sodium methoxide at elevated temperatures. Methyl 2-methoxy-4-methyl-4-pentenoate (**2**) is formed in the case of **1**. Syntheses of such methyl α-methoxycarboxylates and studies of the reaction mechanism have been reported earlier.[1,14]



1 2

The conversion of the trichloromethyl group takes place via an α,α-dichloroepoxide and an α-chloroacyl chloride as intermediates. The latter compound is attacked by methoxide ion producing α-methoxymethyl esters.[7] The corresponding α-methoxycarboxylic acid is obtained as a byproduct by the saponification of **2** during workup.

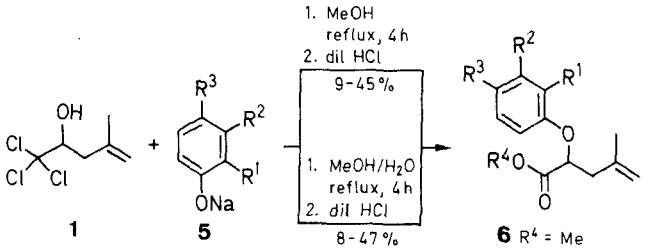
However, compound **3** undergoes an unexpected reaction with sodium methoxide yielding the cyclic compound **4**. The α-chloroacyl chloride formed in position 7 as an intermediate is apparently attacked by the hydroxy group in position 2 to give a 2,3-dihydro-2*H*-pyran. Finally, hydrochloric acid is eliminated to form a diene, and the ester is hydrolyzed to give **4**.



3 4

These experimental results demonstrate that a hydroxy group in a suitable position can act as a nucleophile in an intramolecular substitution of compounds bearing a trichloromethyl group. Compounds without a hydroxylic function at position 2 are only transformed into dichlorovinyl derivatives. Under these conditions, dialkoxydicarboxylic esters or acids were not detected. Thus, only compound **1** was used as the starting material for the synthesis of methyl 2-aryloxy-4-methyl-4-pentenoates.

In methanolic solution, the conversion of **1** in the presence of several substituted sodium phenoxides **5** yielded methyl α-aryloxycarboxylates **6**. The appropriate sodium phenoxide **5** was used in a fourfold excess and the reaction was performed at elevated temperatures. The reaction of **1** with nucleophiles under basic conditions involves the formation of an α-chloromethyl ester. Presumably, the corresponding phenyl ester is also produced in minor quantities. However, the presence of the base catalyzes the transesterification of the phenyl ester. This process is also supported by a large excess of methanol. In the presence of phenoxides in methanolic solution, two nucleophiles compete for reaction with the α-chloromethyl ester. An excess of phenol as compared to the amount of base diminishes the concentration of methoxide ions. Thus, phenoxide ions preferentially act as nucleophile in the substitution at position 2 yielding **6**.



1 5 **6** R^4 = Me **7** R^4 = H

	R^1	R^2	R^3		R^1	R^2	R^3
6a, 7a	H	H	H	**6d**	Me	H	H
6b, 7b	H	H	Me	**6e**	Cl	H	H
6c, 7c	H	Me	H	**6f, 7f**	Cl	H	Cl

The experimental results shown in Table 1 indicate a relation between the basicity of the phenol used and the yield of the product. Electron-withdrawing substituents in phenoxides decrease the yield while electron-donors promote the reaction due to a higher basicity of the phenoxide ion. In the same way, treatment of **1** with sodium phenoxides **5** in a mixture of methanol and water affords 2-aryloxy-4-methyl-4-pentenoic acids (**7**) after acidification (Table 1).

1,1-Dichloro-4-methyl-4-penten-2-ol (**8**) was prepared as reported,[15] by the electrochemical reduction of **1** at mercury cathode in 0.1 M lithium chloride in methanol with a working potential of −1.6 V versus saturated

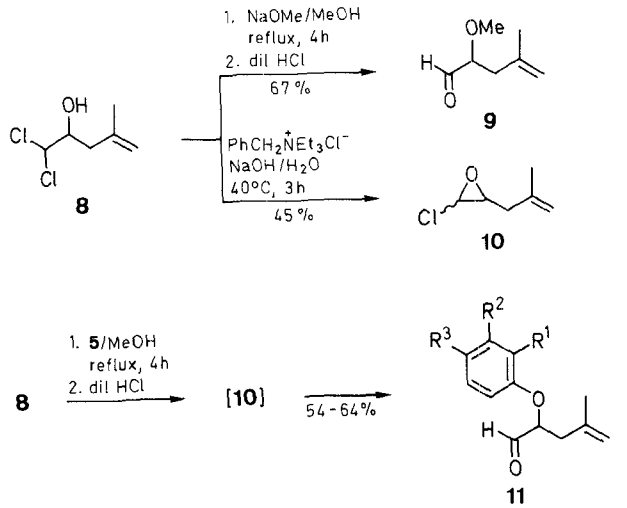
Table 1. Compounds **6** and **7** Prepared

Product	Yield (%)	mp (°C) or bp (°C)/mbar	Molecular Formula[a]	IR (neat/KBr) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/HMDS) δ, J (Hz)
6a	41	87/0.5	$C_{13}H_{16}O_3$ (220.3)	3070, 1760, 1650, 1495	1.84 (s, 3H), 2.69 (d, 2H, J = 6.7), 3.71 (s, 3H), 4.81 (t, 1H, J = 6.7), 4.9 (s, 2H), 6.86–7.39 (m, 5H)
6b	45	113/0.5	$C_{14}H_{18}O_3$ (234.3)	3070, 1770, 1620, 1490	1.83 (s, 3H), 2.28 (s, 3H), 2.67 (d, 2H, J = 6.6), 3.73 (s, 3H), 4.78 (t, 1H, J = 6.6), 4.87 (s, 2H), 6.80 (d, 2H, J = 8.5), 7.08 (d, 2H, J = 8.5)
6c	27	110/1	$C_{14}H_{18}O_3$ (234.3)	3070, 1740, 1640, 1490	1.86 (s, 3H), 2.33 (s, 3H), 2.70 (d, 2H, J = 6.7), 3.74 (s, 3H), 4.83 (t, 1H, J = 6.7), 4.91 (s, 2H), 6.66–7.27 (m, 4H)
6d	28	100/1	$C_{14}H_{18}O_3$ (234.3)	3070, 1760, 1660, 1490	1.90 (s, 3H), 2.35 (s, 3H), 2.77 (d, 2H, J = 6.7), 3.76 (s, 3H), 4.87 (t, 1H, J = 6.7), 4.95 (s, 2H), 6.70–7.25 (m, 4H)
6e	19	116/0.5	$C_{13}H_{15}ClO_3$ (254.7)	3070, 1760, 1660, 1495	1.82 (s, 3H), 2.70 (d, 2H, J = 6.5), 3.67 (s, 3H), 4.78 (t, 1H, J = 6.5), 4.85 (s, 2H), 6.71–7.37 (m, 4H)
6f	9	125/0.5	$C_{13}H_{14}Cl_2O_3$ (289.2)	3070, 1760, 1650, 1480	1.82 (s, 3H), 2.70 (d, 2H, J = 6.4), 3.70 (s, 3H), 4.67 (t, 1H, J = 6.4), 4.84 (s, 2H), 6.66–7.35 (m, 3H)
7a	40	37–39	$C_{12}H_{14}O_3$ (206.2)	3400, 1720, 1640, 1480	1.84 (s, 3H), 2.72 (d, 2H, J = 6.4), 4.82 (t, 1H, J = 6.4), 4.90 (s, 2H), 6.88–7.41 (m, 5H), 10.96 (s, 1H)
7b	47	42–43	$C_{13}H_{16}O_3$ (220.3)	3400, 1730, 1650, 1505	1.88 (s, 3H), 2.34 (s, 3H), 2.74 (d, 2H, J = 6.6), 4.82 (t, 1H, J = 6.6), 4.94 (s, 2H), 6.9 (d, 2H, J = 8.6), 7.14 (d, 2H, J = 8.6), 11.67 (s, 1H)
7c	26	57–59	$C_{13}H_{16}O_3$ (220.3)	3400, 1730, 1650, 1490	1.85 (s, 3H), 2.35 (s, 3H), 2.72 (d, 2H, J = 6.5), 4.82 (t, 1H, J = 6.5), 4.90 (s, 2H), 6.69–7.29 (m, 4H), 11.29 (s, 1H)
7f	8	82–84	$C_{12}H_{12}O_3$ (275.1)	3400, 1705, 1640, 1480	1.85 (s, 3H), 2.75 (d, 2H, J = 6.3), 4.80 (t, 1H, J = 6.3), 4.91 (s, 2H), 6.71–7.39 (m, 3H), 10.76 (s, 1H)

[a] Satisfactory microanalyses obtained: C ±0.4, H ±0.2, Cl ±0.4.

calomel electrode. This reduction procedure permits a selective conversion of a trichloromethyl group into a dichloromethyl group.[15] By conventional methods,[16] only a mixture of the fully reduced alcohol and the partially reduced alcohols was isolated.

Reaction of **8** with sodium methoxide gives 2-methoxy-4-methyl-4-pentenal (**9**). 1-Chloro-1,2-epoxides were proposed in the literature as intermediates for this reaction.[16,17] Such an epoxide **10** was isolated in the reaction of **8** with sodium hydroxide under phase-transfer conditions. Similarly **8** is converted by sodium phenoxides **5** to give α-aryloxyaldehydes **11**.



11	R^1	R^2	R^3
a	H	H	H
b	H	H	Me
c	H	Me	H

In comparison to base-induced conversions of **1**, the yield of aldehydes obtained by the reaction of **8** with bases are agreeable. However, the results show that both reactions are convenient methods for the synthesis of methyl 2-aryloxy-4-methyl-4-pentenoates and 2-aryloxy-4-methyl-4-pentenals.

^{1}H-NMR spectra and ^{13}C-NMR spectra were recorded on a Bruker AC-80 (80 MHz) or a Bruker WP-200 (200 MHz) spectrometer using hexamethyldisilane (HMDS) as internal standard. IR spectra were measured on Specord 71 IR spectrophotometer (VEB Carl Zeiss Jena). Elemental analyses were obtained on Carlo Erba elemental analyzer 1104.

Methyl 2-methoxy-4-methyl-4-pentenoate (2):
To a solution of Na (9.5 g, 0.41 mol) in anhydrous MeOH (250 mL) heated to about 60 °C is added dropwise, the alcohol **1** (20.3 g, 0.1 mol), and the mixture is refluxed for 4 h. After the mixture has cooled, MeOH is removed under reduced pressure and the residue is treated with water and dil HCl. The aqueous solution is extracted with CH_2Cl_2 (2 × 100 mL), the combined organic layers are washed with water (50 mL) and dried (Na_2SO_4). Removal of the solvent gives an oil which is distilled under reduced pressure; yield: 9.2 g (58%); bp 36–38 °C/1.3 mbar.

$C_8H_{14}O_3$ (158.2) calc. C 60.76 H 8.86
found 60.65 9.30

IR (neat): ν = 1750, 1640, 1200, 1120 cm^{-1}.

^{1}H-NMR ($CDCl_3$/HMDS): δ = 1.49 (s, 3H), 2.15 (d, 2H, J = 6.6 Hz), 3.09 (s, 3H), 3.45 (s, 3H), 3.64 (t, 1H, J = 6.6 Hz), 4.47 (s, 1H), 4.53 (s, 1H).

6-Dichloromethylene-3,6-dihydro-4-methyl-2*H*-pyran-2-carboxylic Acid (4):
A solution of **2** (19.3 g, 0.055 mol) in MeOH (50 mL) is added dropwise to a stirred solution of NaOMe (17.8 g, 0.33 mol) in

Table 2. Compounds **9** and **11** Prepared

Product	Yield (%)	bp (°C)/ mbar	Molecular Formula[a]	IR (neat) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/HMDS), δ, J (Hz)
9	67	45/16	$C_7H_{12}O_2$ (128.2)	3040, 1730, 1650	1.75 (s, 3H), 2.35 (d, 2H, J = 6.95), 3.43 (s, 3H), 3.69 (m, 1H, J_1 = 2.1, J_2 = 6.95), 4.80 (m, 2H), 9.63 (d, 1H, J = 2.1)
11a	53	76/0.7	$C_{12}H_{14}O_2$ (190.2)	3040, 1735, 1650, 1500	1.81 (s, 3H), 2.59 (d, 2H, J = 6.6), 4.65 (m, 1H, J_1 = 6.6, J_2 = 2.3), 4.89 (s, 2H), 6.86–7.34 (m, 5H), 9.69 (d, 1H, J = 2.3)
11b	63	98/0.7	$C_{13}H_{16}O_2$ (204.3)	3040, 1740, 1640, 1510	1.83 (s, 3H), 2.30 (s, 3H), 2.33 (d, 2H, J = 6.5), 4.62 (m, 1H, J_1 = 6.5, J_2 = 2.3), 4.88 (s, 1H), 4.91 (s, 1H), 6.84 (d, 2H, J = 8.4), 7.1 (d, 2H, J = 8.4), 9.70 (d, 1H, J = 2.3)
11c	58	86/0.7	$C_{13}H_{16}O_2$ (204.3)	3040, 1735, 1640, 1495	1.84 (s, 3H), 2.34 (s, 3H), 2.59 (d, 2H, J = 6.6), 4.65 (m, 1H J_1 = 6.6, J_2 = 2.3), 4.89 (s, 1H), 4.91 (s, 1H), 6.67–7.21 (m, 4H), 9.70 (d, 1H, J = 2.3)

[a] Satisfactory microanalysis obtained: C ±0.4, H ±0.2.

MeOH (80 mL). The mixture is maintained for 3 h at 30 °C and stirring is continued at r.t. for 1 d. The mixture is then poured into ice-water (300 mL) containing KOH (6.7 g, 0.12 mol). After 6 h, the solution is acidified with 1 M H_2SO_4. The organic products are extracted with Et_2O (3 × 100 mL), the combined organic layers are washed with brine (50 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. The resultant solid is recrystallized from toluene; yield: 5.8 g (47%); mp 126–27 °C.

$C_8H_8Cl_2O_3$ (223.0) calc. C 43.08 H 3.61 Cl 31.78
found 43.05 3.89 31.56

IR (KBr): ν = 3400, 1720, 1645, 1590, 1340, 1300, 1100, 940 cm^{-1}.

^{1}H-NMR (acetone-d_6/HMDS): δ = 1.91 (d, 3H, J = 1.5 Hz), 2.60 (d, 2H, J = 5.6 Hz), 4.82 (t, 1H, J = 5.6 Hz), 6.30 (q, 1H, J = 1.5 Hz), 10.2 (s, 1H).

^{13}C-NMR (acetone-d_6/HMDS): δ = 30.02, 38.94, 80.49, 121.24, 146.28, 153.37, 160.59, 177.85.

MS (70 eV): m/z = 222 (M^+, 100), 204 ($M^+ - H_2O$, 15), 187 (M^+ – Cl, 17), 177 $M^+ - CO_2H$, 67), 176 ($M^+ - HCO_2H$, 80), 169 (M^+ – Cl-H_2O, 51), 143 (71), 113 (68), 97 (35).

Methyl 2-Aryloxy-4-methyl-4-pentenoates 6; General Procedure:
To a stirred solution of Na (9.5 g, 0.41 mol) in anhydrous MeOH (250 mL) is added dropwise a solution of the corresponding phenol (0.42 mol) in MeOH (100 mL). The solution is heated to about 60 °C and the alcohol **1** (20.3 g, 0.1 mol) is added dropwise to it. The mixture is refluxed for 4 h. After the mixture has cooled, MeOH is removed under reduced pressure and the residue is treated with water and dil HCl. The aqueous solution is extracted with CH_2Cl_2) (2 100 mL), the combined organic layers are washed with water (50 mL), and dried (Na_2SO_4). Removal of the solvent gives an oil, which is distilled under reduced pressure (Table 1).

2-Aryloxy-4-methyl-4-pentenoic Acids 7; General Procedure:
Aq 4.1 M NaOH (100 mL) is added to a mixture of the appropriate phenol (0.45 mol) and MeOH (150 mL). Subsequently, the reaction and workup are carried out as described for the preparation of α-aryloxycarboxylic esters **6**. After removal of phenol by distillation under reduced pressure, purification of acids is carried out by recrystallisation from heptane.

2-Methoxy-4-methyl-4-pentenal (9):
To a solution of Na (2.75 g, 0.12 mol) in anhydrous MeOH (100 mL) is added dropwise the alcohol **8** (10 g, 0.06 mol), and the reaction and workup are carried out as described for the preparation of α-aryloxycarboxylic esters **6**.

***cis/trans*-1-Chloro-1,2-epoxy-4-methyl-4-pentene (10):**
To a solution of the alcohol **8** (10 g, 0.06 mol) in CH_2Cl_2 (60 mL) are added benzyltriethylammonium chloride (10 g, 0.054 mol) and a solution of NaOH (23 g, 1 mol) in water (100 mL). The mixture is stirred vigorously for 3 h at about 40 °C, cooled and the organic layer is washed with water repeatedly. After drying (Na_2SO_4) and removal of solvent, the crude product is distilled under reduced pressure; yield: 3.5 g (45%); bp (16 mbar) 35 °C/16 mbar.

C_6H_9ClO (132.5) calc. C 54.36 H 6.79 Cl 26.76
found 54.03 7.00 26.31

IR (neat): ν = 3100, 1660, 1250 cm^{-1}.

^{1}H-NMR ($CDCl_3$/HMDS); *trans*: δ = 1.80 (s, 3H), 2.43 (d, 2H, J = 6.0 Hz), 3.27–3.02 (m, 1H), 4.83 (s, 2H), 5.15 (d, 1H, J = 2.8 Hz).

cis: δ = 1.76 (s, 3H), 2.25 (d, 2H, J = 5.7 Hz), 3.27–3.02 (m, 1H), 4.83 (s, 2H), 4.84 (d, 1H, J = 1.1 Hz).

2-Aryloxy-4-methyl-4-pentenals 11; General Procedure:
To a solution of Na (2.75 g, 0.12 mol) in anhydrous MeOH (100 mL) is added dropwise the corresponding phenol (0.13 mol). The mixture is heated to about 60 °C and the alcohol **8** (10 g, 0.06 mol) is added dropwise to it. The mixture is refluxed for 5 h and worked up as given under the general procedure for the preparation α-aryloxycarboxylic esters **6** (Table 2).

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