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A Publication
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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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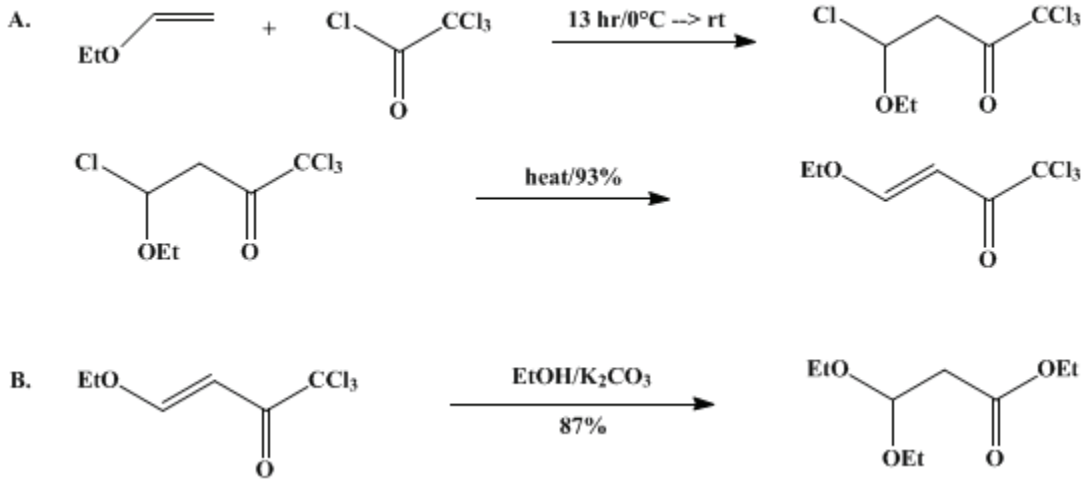
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.069.0238

Organic Syntheses, Coll. Vol. 8, p.254 (1993); Vol. 69, p.238 (1990).

SYNTHESIS OF ALKYL PROPANOATES BY A HALOFORM REACTION OF A TRICHLORO KETONE: ETHYL 3,3-DIETHOXYPROPANOATE

[Propanoic acid, 3,3-diethoxy-, ethyl ester]



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Checked by Daniel Romo and Albert I. Meyers.

1. Procedure

A. *1,1,1-Trichloro-4-ethoxy-3-buten-2-one* ***(4)***.[2] A 500-mL, two-necked, round-bottomed flask equipped with a pressure-equalizing addition funnel with drying tube, nitrogen inlet, and magnetic stirring bar is charged with trichloroacetyl chloride, **2** (173 g, 0.96 mol) (Note 1). Under nitrogen the flask is cooled with an ice bath to 0°C and ethyl vinyl ether (137 g, 181 mL, 1.90 mol, (Note 2)) is added within 1 hr to the well-stirred mixture. Stirring is continued for 12 hr, allowing the mixture to warm to room temperature without removing the cooling bath (Note 3). The addition funnel is replaced by a short Vigreux column and excess ethyl vinyl ether is removed at 20°C under reduced pressure (20 mm). The bath temperature is raised (to ca. 140°C) under reduced pressure (20 mm) to start elimination of hydrogen chloride, which is accompanied by formation of a deep black color and requires 1–2 hr for completion. Distillation of the residue under reduced pressure affords 193 g (92%) of **4**,[3] as a bright-yellow oil that fades to pale yellow on standing, bp 116–118°C/13 mm, n_D^{24} 1.5129 (Note 4) and (Note 5).

B. *Ethyl 3,3-diethoxypropanoate* ***(5)***. A 500-mL, two-necked, round-bottomed flask equipped with magnetic stirring bar, a reflux condenser with a drying tube, and a 250-mL pressure-equalizing addition funnel is charged with dry ethanol (200 mL, 3.4 mol) and anhydrous potassium carbonate (12 g, 87 mmol) and cooled with an ice–water bath. The addition funnel is charged with 1,1,1-trichloro-4-ethoxy-3-buten-2-one, **4** (200 g, 0.92 mol) and the addition is performed with stirring during 30 min. Stirring is continued for 10 hr at room temperature, petroleum ether or pentane (300 mL) is added, and the potassium carbonate is filtered off. After concentration under reduced pressure the residue is distilled through a short Vigreux column to yield 153 g (87%) of **5**, bp 92–95°C/15 mm, n_D^{24} 1.4117 (Note 6) and (Note 7).

2. Notes

1. Trichloroacetyl chloride (obtained from Fluka Chemical Corporation) was distilled immediately before use.

2. Ethyl vinyl ether (obtained from Fluka Chemical Corporation) was used from a freshly opened bottle containing a stabilizer (0.1% diethylaniline) without purification. The stabilizer seems to be important (see (Note 7)).
3. An exothermic reaction was observed after removing the ice bath.
4. Distillation should not be performed at a lower pressure.
5. The synthesis of **4** can be carried out on a large scale: a run using 1.8 kg of trichloroacetyl chloride gave **4** in 97% yield. The spectral properties are as follows: IR (neat) cm^{-1}: 2990 (C-H), 1710 (C=O), 1600 (C=C), 835 (C-Cl); ^1H NMR (60 MHz, $CDCl_3$) δ: 1.38 (t, 3 H, J = 7, OCH_2CH_3), 4.08 (q, 2 H, J = 7, OCH_2CH_3), 6.13 (d, 1 H, J = 12.4, 3-H), 7.87 (d, 1 H, J = 12.4, 4-H).
6. Distillation should be performed only within the indicated temperature range. Approximately 20 mL of a dark residue remains after distillation. The spectral properties are as follows: IR (neat) cm^{-1}: 2990, 2940 (C-H), 1740 (C=O), 1115, 1060 (C-O); ^1H NMR (60 MHz, $CDCl_3$) δ: 1.18 (t, 6 H, J = 7, OCH_2CH_3), 1.25 (t, 3 H, J = 7, $CO_2CH_2CH_3$), 2.62 (d, 2 H, J = 6, 2-H), 3.30–3.80 (2 AB systems, 4 H, 2 OCH_2CH_3), 4.13 (q, 2 H, J = 7, $CO_2CH_2CH_3$), 4.93 (t, 1 H, J = 6, 3-H).
7. In a similar way, methyl 3,3-dimethoxypropanoate can be prepared using trichloroacetyl chloride and methyl vinyl ether as starting materials. However, in this case, using methyl vinyl ether without a stabilizer, it is necessary to perform the reaction in the presence of pyridine; otherwise extensive polymerization of the vinyl ether takes place.
Procedure. A 1000-mL, three-necked, round-bottomed flask equipped with a pressure-equalizing addition funnel with drying tube, intensive condenser (cryostat temp., −5°C) with nitrogen inlet, and mechanical stirrer, is charged with **2** (270 g, 1.48 mol); pyridine (117 g, 1.48 mol) is added within 15 min under vigorous stirring at room temperature. Under nitrogen, the flask is cooled with an ice bath to −10°C and liquid methyl vinyl ether (112 g, ca. 145 mL, 1.93 mol) is added through a coolable addition funnel (ca. −10°C) within 30 min to the well-stirred mixture. Stirring is continued for 12 hr, allowing the mixture to warm to room temperature without removing the cooling bath. After addition of water (250 mL) and extraction with diethyl ether (2 × 200 mL), the combined organic layers are washed with brine (2 × 50 mL), dried (Na_2SO_4), and the solvent evaporated under reduced pressure. Distillation (20-cm Vigreux column) of the residue under reduced pressure affords 267 g (88%) of 1,1,1-trichloro-4-methoxy-3-buten-2-one as a colorless liquid, bp 102°C at 10 mm, n_D^{20} 1.5238. The spectral properties are as follows: IR (neat) cm^{-1}: 2940, 2840 (C-H), 1710 (C=O), 1600 (C=C); ^1H NMR (60 MHz, $CDCl_3$) δ: 3.80 (s, 3 H, OCH_3), 6.03 (d, 1 H, J = 12, 3-H), 7.77 (d, 1 H, J = 12, 4-H). Solvolysis of 1,1,1-trichloro-4-methoxy-3-buten-2-one with methanol to give methyl 3,3-dimethoxypropanoate can be performed according to the procedure given for **5**.

3. Discussion

The synthesis of ethyl 3,3-diethoxypropanoate **(5)** described here implies acylation of an enol ether followed by a haloform reaction. The procedure is superior to other methods, which afford mixtures of acetals and acrylates,[4] give only moderate yields,[5,6,7] require the troublesome use of ketene[8] or expensive ethyl propiolate,[9,10,11] need palladium(II) catalysis,[12] or equipment for electrochemical reactions.[13]

Ethyl 3,3-diethoxypropanoate **(5)** is the stable, protected derivative of the unstable 3-formylpropanoate. It can be stored at room temperature for several months without decomposition. It is a useful starting material, especially for the synthesis of heterocycles such as coumarins,[14] isoxazoles,[15] pyrimidines,[16] porphyrins,[17] and thiadiazines.[18] Also spermine metabolites,[19] steroids,[20] herbicides,[21] antihypertensives,[22] photographic sensitizers,[23] cephalosporins,[24] lycopodium alkaloids,[25] nucleic acids,[5] and pentaerythritol[26] as well as related alcohols can be obtained from **5**. Thus ester **5** can be reduced to the corresponding alcohol, which yields 3-hydroxypropanal with acidic conditions;[26] elimination of ethanol gives 3-ethoxyacrylate.[27] Of great interest is also the formylation of **5** to give ethyl 2-formyl-3-oxopropanoate or, starting from methyl 3,3-dimethoxypropanoate, methyl 2-formyl-3-oxopropanoate.[10,28] The latter compound has been used in the synthesis of iridoids,[28] ipecacuanha alkaloids,[29] 1,4-dihydropyridines,[29] NADH analogs,[30] dihydropyrans,[31] and branched amino sugars.[32]

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride (7647-01-0)

methanol (67-56-1)

diethyl ether (60-29-7)

Na_2SO_4 (7757-82-6)

nitrogen (7727-37-9)

pyridine (110-86-1)

diethylaniline (91-66-7)

Pentane (109-66-0)

Pentaerythritol (115-77-5)

methyl vinyl ether (9003-09-2)

ethyl vinyl ether (109-92-2)

ethyl propiolate (623-47-2)

trichloroacetyl chloride (76-02-8)

vinyl ether (109-93-3)

Palladium(II)

methyl 2-formyl-3-oxopropanoate

methyl 3,3-dimethoxypropanoate (7424-91-1)

Ethyl 3,3-diethoxypropanoate,
Propanoic acid, 3,3-diethoxy-, ethyl ester (10601-80-6)

1,1,1-Trichloro-4-ethoxy-3-buten-2-one (83124-74-7)

1,1,1-trichloro-4-methoxy-3-buten-2-one (138149-14-1)

3-formylpropanoate

3-hydroxypropanal (2134-29-4)

3-ethoxyacrylate

ethyl 2-formyl-3-oxopropanoate