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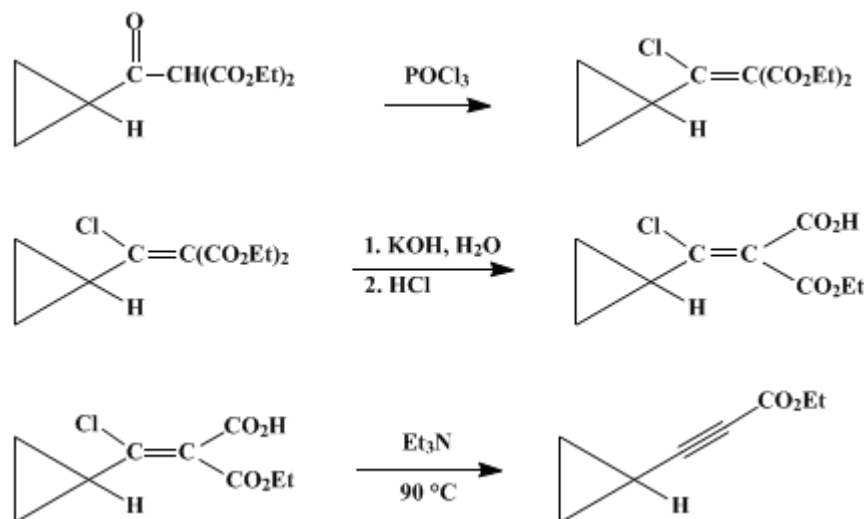
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UTILIZATION OF β -CHLORO ALKYLIDENE/ARYLIDENE MALONATES IN ORGANIC SYNTHESIS: ETHYL CYCLOPROPYLPROPIOLATE

[2-Propynoic acid, 3-cyclopropyl-, ethyl ester]



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1. Procedure

A. *Diethyl 2-chloro-2-cyclopropylethene-1,1-dicarboxylate*. A 1-L, two-necked flask equipped with magnetic stirrer, reflux condenser, and dropping funnel is charged with 166 g (0.73 mol) of *diethyl cyclopropylcarbonylmalonate* (Note 1) and 0.5 kg of *phosphorus oxychloride* (Note 2). The flask is cooled with a water bath, stirring is started and 135 g (0.73 mol) of *tributylamine* (Note 3) is added from the dropping funnel. The reaction is exothermic. When the addition is complete, the dropping funnel is replaced by a glass stopper and the water bath is replaced by an oil bath. The mixture is heated at 110°C with stirring for 5–6 hr.

Excess *phosphorus oxychloride* is removed as well as possible with a rotary evaporator under reduced pressure. The residue is cooled to room temperature and 300 mL of *diethyl ether* is added. The mixture is poured into a separatory funnel. *Hexane* is added until the two phases separate cleanly and the funnel is shaken vigorously. The phases are separated and the lower layer is extracted with three 250-mL portions of *ether* (Note 4). The combined organic layers are washed with 300 mL of cold aqueous 10% *hydrochloric acid* and 200 mL of aqueous 5% *sodium hydroxide* (Note 5) and then concentrated carefully with a rotary evaporator to give 136–156 g (70–87%) of crude *diethyl 2-chloro-2-cyclopropylethene-1,1-dicarboxylate*.²

B. The crude chloromalonate is dissolved in 100 mL of 95% *ethanol* and transferred to a 1-L, round-bottomed flask equipped with a magnetic stirring bar. Stirring is begun and a solution of *potassium hydroxide* in 350 mL of 95% *ethanol* (0.0035 mol of *potassium hydroxide* per gram of chloromalonate) (Note 6) is added dropwise from an additional funnel. A slightly exothermic reaction is noted. After the addition is complete, the mixture is stirred for 3 hr (or until the mixture is neutral to litmus; (Note 7)). Excess *ethanol* is removed with a rotary evaporator under reduced pressure and the residue is dissolved in 300 mL of water and extracted with 350 mL of *ether* (Note 8). The phases are separated and some ice is added to the aqueous phase. The cooled aqueous phase is acidified with concentrated *hydrochloric acid* and extracted with three 300-mL portions of *ether*. The *ether* phase is

dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure with a rotary evaporator to give 72–94 g (70–80%) of crude monoester.

C. Ethyl cyclopropylpropiolate. The crude product is transferred to a 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser. A solution of 0.70 mL of triethylamine (Note 9) per gram of crude monoester from Part B in about 200 mL of toluene is added. The mixture is heated using an oil bath at 90°C with stirring until the evolution of carbon dioxide has subsided, and is then heated for another hour (Note 10). The mixture is cooled to room temperature, and washed with 300 mL of aqueous 10% hydrochloric acid (Note 11) and finally with 300 mL of aqueous 5% sodium carbonate. The organic layer is dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure with a rotary evaporator. Fractional distillation of the residue gives the product, 87–95°C at 10 mm. The yield of the final step is 30–46 g (66–78%); the overall yield is 33–54% (Note 12).

2. Notes

1. Diethyl cyclopropylcarbonylmalonate is prepared by the procedure of Price and Tarbell³ or Reynolds and Hauser.⁴ On scale-up the checkers found that a slight modification is necessary. The procedure of Price and Tarbell was used:³ 45 g (1.9 mol) of magnesium turnings, 1 mL of carbon tetrachloride, and approximately 20 mL of a solution of 281 mL (269 g, 1.9 mol) of diethyl malonate in 148 mL of absolute ethanol were combined. After the reaction begins, the addition of diethyl malonate solution is completed so that the reaction is maintained at a fairly vigorous rate. If the reaction subsides prior to the completion of the addition of the diethyl malonate solution, the addition is interrupted and a portion (300–400 mL) of the specified 550 mL of dry ether is added cautiously until the reaction resumes, whereupon the addition of the diethyl malonate solution is resumed. After the remainder of the diethyl malonate solution has been added and the reaction mixture cooled, the remaining dry ether is added cautiously and the mixture is worked up as described³ using 350 mL of dry benzene. The residue is dissolved in 550 mL of dry ether and treated as described by Reynolds and Hauser⁴ with 168 mL (194 g, 1.9 mol) of cyclopropanecarboxylic acid chloride in 230 mL of dry ether. After the addition is completed, an additional 40 mL of dry ether is added and the mixture is cooled and worked up as described⁴ using 2 L of aqueous 25% sulfuric acid, 800 mL of ether, 600 mL of saturated aqueous sodium bicarbonate, 200 mL of water, and 100 mL of brine. The crude product is distilled (85–95°C; 0.05 mm) and 362 g (1.6 mol, 86%) of a clear liquid is obtained. ¹H NMR δ : 1.01 (m, 2 H), 1.20 (m, 2 H), 1.31 (t, 6 H, $J = 7.1$), 2.12 (tt, 1 H, $J = 4.5, 7.8$), 4.28 (q, 4 H, $J = 7.1$), 4.58 (s, 1 H).
2. Commercial phosphorus oxychloride was used without purification.
3. Commercial tributylamine was used without purification.
4. Extraction with a mixture of ether and hexane is repeated until ether and the lower layer readily separate.
5. Tributylamine is liberated from the lower layer by addition of sodium hydroxide.
6. Commercial potassium hydroxide (minimum 85.5% of potassium hydroxide) was used. The yield is based on potassium hydroxide.
7. Dilution of 1 mL of the mixture in 5 mL of water gave pH 7–8.
8. The ether phase is dried with anhydrous sodium sulfate, filtered, and concentrated with a rotary evaporator to give 32–46 g of recovered starting material.
9. Commercial triethylamine was used without purification.
10. The checkers found that this process requires approximately 24 hr.
11. Triethylamine is liberated from the water phase by addition of sodium hydroxide.
12. Cyclopropylpropionic acid ethyl ester has the following spectra: ¹H NMR (CCl₄) δ : 0.84 and 0.93 (4 H, ring CH₂), 1.25 (t, 3 H, CH₃ ester), the ring-CH is hidden under the ester CH₃-triplet, 4.05 (q, 2 H, CH₂ ester); IR (CCl₄) cm⁻¹: 2220 (C \equiv C), m, 1710 (C=O), s, 1255 (C-O-C), s, 1030–1040 two bands (cyclopropyl), m, and 860–880 two bands (cyclopropyl), w; MS: M (calculated for C₈H₁₀O₂) 138.068, M⁺ is not readily detected, 94 (20%), 93 (100%), 66 (65%), 65 (53%), 63 (10%), 53 (15%), 40 (10%).

3. Discussion

Substituted cyclopropyl rings conjugated with a triple-bond system have recently received attention as C₅ building blocks.⁵ The procedure described here is a modification of the decarboxylation–elimination reaction for the preparation of α,β acetylenic acids from enol sulfonates of acyl

malonates.^{6,7,8} Addition of aqueous alkali to the enol sulfonate of diethyl cyclopropylcarbonylmalonate gives cyclopropylpropionic acid, but the yield is low.

The major advantages of this procedure over the enol sulfonate procedure lie in the availability of diethyl 2-chloro-2-cyclopropylethene-1,1-dicarboxylate from the corresponding acylmalonate and phosphorus oxychloride, and the fast, homogeneous, decarboxylative elimination reaction of the triethylamine salt of the half-ester in dry organic solvents. The conditions described here, with slight modifications (overnight treatment), have been used for a variety of β -chloro alkylidene/arylidene malonates as shown in Table I.

TABLE I
 α,β -ACETYLENIC ESTERS FROM β -CHLOROALKYLIDENE MALONATES

$\begin{array}{c} \text{Cl} \\ \\ \text{R}-\text{C}=\text{C}(\text{COOH})\text{COOEt} + \text{N}(\text{Et})_3 \longrightarrow \text{R}-\text{C}\equiv\text{C}-\text{COOEt} + \text{HCl} \cdot \text{N}(\text{Et})_3 + \text{CO}_2 \end{array}$	
R	Yield (%)
Phenyl	
$\begin{array}{c} \text{Cl} \\ \\ \text{Phenyl}-\text{C}=\text{C}(\text{COOH})\text{COOEt} + \text{N}(\text{Et})_3 \longrightarrow \text{Phenyl}-\text{C}\equiv\text{C}-\text{COOEt} + \text{HCl} \cdot \text{N}(\text{Et})_3 + \text{CO}_2 \end{array}$	80
2-Thienyl	
$\begin{array}{c} \text{Cl} \\ \\ \text{S} \text{---} \text{C}=\text{C}(\text{COOH})\text{COOEt} + \text{N}(\text{Et})_3 \longrightarrow \text{S} \text{---} \text{C}\equiv\text{C}-\text{COOEt} + \text{HCl} \cdot \text{N}(\text{Et})_3 + \text{CO}_2 \end{array}$	90
$p\text{-NO}_2\text{-C}_6\text{H}_4$	
$\begin{array}{c} \text{Cl} \\ \\ \text{O} \parallel \\ \text{NO}_2 \text{---} \text{C}_6\text{H}_4 \text{---} \text{C}=\text{C}(\text{COOH})\text{COOEt} + \text{N}(\text{Et})_3 \longrightarrow \text{O} \parallel \text{NO}_2 \text{---} \text{C}_6\text{H}_4 \text{---} \text{C}\equiv\text{C}-\text{COOEt} + \text{HCl} \cdot \text{N}(\text{Et})_3 + \text{CO}_2 \end{array}$	70
Isopropyl	
$\begin{array}{c} \text{Cl} \\ \\ \text{H}_3\text{C} \text{---} \text{CH} \text{---} \text{C}=\text{C}(\text{COOH})\text{COOEt} + \text{N}(\text{Et})_3 \longrightarrow \text{H}_3\text{C} \text{---} \text{CH} \text{---} \text{C}\equiv\text{C}-\text{COOEt} + \text{HCl} \cdot \text{N}(\text{Et})_3 + \text{CO}_2 \end{array}$	67
<i>tert</i> -Butyl	
$\begin{array}{c} \text{Cl} \\ \\ \text{H}_3\text{C} \text{---} \text{C} \text{---} \text{C}=\text{C}(\text{COOH})\text{COOEt} + \text{N}(\text{Et})_3 \longrightarrow \text{H}_3\text{C} \text{---} \text{C} \text{---} \text{C}\equiv\text{C}-\text{COOEt} + \text{HCl} \cdot \text{N}(\text{Et})_3 + \text{CO}_2 \end{array}$	70

Sometimes the acetylenic ester rearranges to the corresponding allenic ester. For example, when the triethylamine salt of 3-chloro-2-ethoxycarbonyl-4-phenyl-2-hexenoic acid is refluxed in toluene, the allenic ester and acetylenic ester are obtained in a ratio of 3 : 7 (total yield 70%). There are alternative routes to cyclopropylpropionic acids and esters, such as adding butyllithium to corresponding acetylenes and treating the product with carbon dioxide or methyl chloroformate.⁵

References and Notes

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Appendix

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

brine

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether,
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

magnesium turnings (7439-95-4)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

carbon dioxide (124-38-9)

Phosphorus Oxychloride (21295-50-1)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

diethyl malonate (105-53-3)

butyllithium (109-72-8)

methyl chloroformate (79-22-1)

hexane (110-54-3)

triethylamine (121-44-8)

tributylamine (102-82-9)

Ethyl cyclopropylpropiolate,
2-Propynoic acid, 3-cyclopropyl-, ethyl ester (123844-20-2)

diethyl cyclopropylcarbonylmalonate (7394-16-3)

Diethyl 2-chloro-2-cyclopropylethene-1,1-dicarboxylate (123844-18-8)

cyclopropanecarboxylic acid chloride (4023-34-1)

cyclopropylpropiolic acid

triethylamine salt of 3-chloro-2-ethoxycarbonyl-4-phenyl-2-hexenoic acid