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Dehydrohalogenation of Substituted Diethyl Halocyclopropane-1,1-dicarboxylates

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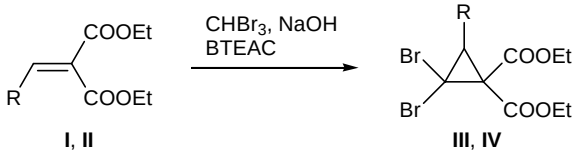
Abstract—The synthesis and dehydrohalogenation of diethyl halocyclopropane-1,1-dicarboxylates prepared from diethyl ethylidene- and benzylidenemalonates are described.

Halocyclopropane derivatives containing several electron-acceptor groups are convenient synthons in organic chemistry [1]. In the present work we studied dehydrohalogenation of diethyl halocyclopropanedicarboxylates prepared by cyclopropanation of diethyl ethylidene- and benzylidenemalonates **I** and **II** or by reaction of ethyl diazoacetate with diethyl benzylidenemalonate (**II**) with subsequent halogenation and denitrogenation of intermediate 4,5-dihydro-1*H*-pyrazole. By reaction of esters **I** and **II** with bromoform in the presence of sodium hydroxide and benzyltriethylammonium chloride as phase-transfer catalyst (reversed order of mixing the reactants) we obtained diethyl 2,2-dibromopropane-1,1-dicarboxylates **III** and **IV**, respectively (Scheme 1). Compound **III** was described previously in [2]; however; attempts to reproduce the procedure given therein were unsuccessful [3]. The ^{1}H NMR spectra of compounds **III** and **IV** contained signals from the cyclopropane ring CH proton at δ 2.56 (q, J = 7 Hz) and 3.84 ppm (s), respectively.

Scheme 1.



I, **II** **III**, **IV**

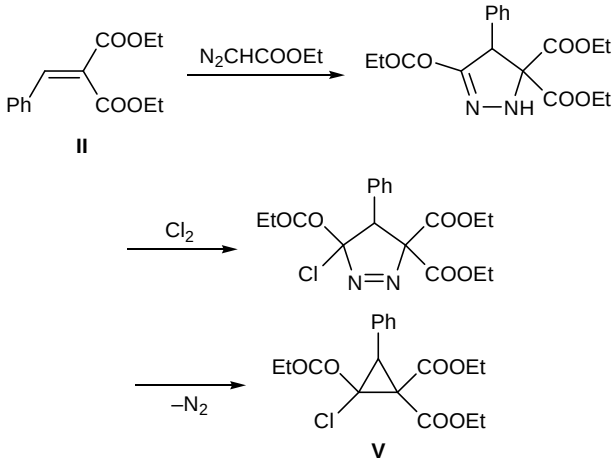
I, **III**, R = Me; **II**, **IV**, R = Ph.

We also examined dehydrohalogenation of chlorocyclopropane derivative **V** which was synthesized according to the scheme described in [4] (Scheme 2). The reactions of compounds **IV** and **V** with potassium *tert*-butoxide in tetrahydrofuran afforded the corresponding 2-cyclopropene-1,1-dicarboxylates **VI** and **VII** in 73 and 15% yield, respectively (Scheme 3).

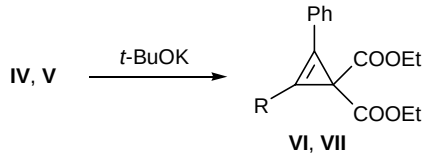
In the IR spectrum of compound **VII** we observed an absorption band at 1870 cm^{-1}, which belongs to stretching vibrations of the endocyclic double bond. Carbon atoms in the cyclopropane ring of compounds **VI** and **VII** gave the following signals in the ^{13}C NMR spectra: δ_C 85.7 and 37.4 (C^1), 113.2 and 99.2 (C^2), 40.0 and 120.7 ppm (C^3), respectively.

An analogous reaction with compound **III** resulted in formation of a mixture of products which, according

Scheme 2.



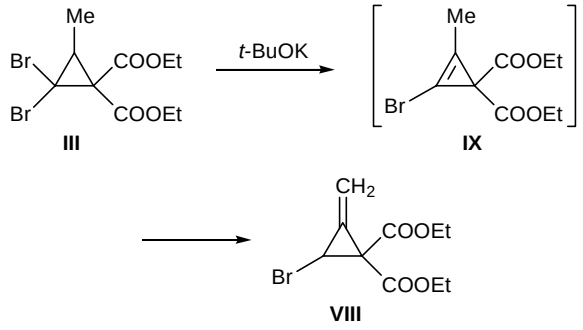
Scheme 3.



VI, R = Br; **VII**, R = CO_2Et.

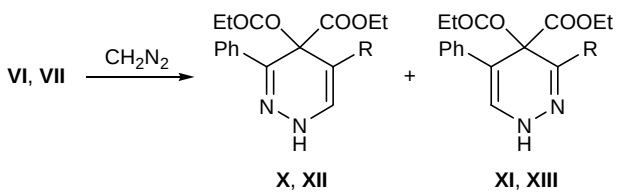
to the ^{1}H NMR data, contained 51% of compound **VIII**, 21% of initial diester **III**, and 28% of unidentified compounds (Scheme 4). We failed to separate this mixture into particular components owing to their ready polymerization, and it was used in further experiments without additional purification. The ^{13}C NMR spectrum of **VIII** contained signals from carbon atoms in the cyclopropane ring at δ_C 35.0 (C^2), 39.7 (C^1), and 130.1 ppm (C^3) and a signal from the exocyclic methylene carbon atom at δ_C 111.5 ppm. Methylenecyclopropane **VIII** is likely to be formed via isomerization of methylcyclopropene **IX**.

Scheme 4.



Cyclopropene derivatives **VI** and **VII** were brought into reaction with diazomethane. Treatment of **VI** with diazomethane in diethyl ether at room temperature (reaction time 48 h) gave a mixture of regioisomeric dihydropyridazines **X** and **XI** at a ratio of 1:1.3 (Scheme 5). In the ^{1}H NMR spectra of **X** and **XI**, signals from protons in the pyridazine ring were located at δ, ppm: **X**: 6.76 d (6-H, J = 2 Hz), 8.85 (NH); **XI**: 7.57 d (6-H, J = 3 Hz), 8.43 (NH). Under analogous conditions, the reaction of **VII** with diazomethane led to formation of triethyl 3-phenyl-1,4-dihydropyridazine-4,4,5-tricarboxylate (**XII**) and triethyl 5-phenyl-1,4-dihydropyridazine-3,4,4-tricarboxylate (**XIII**) at a ratio of 1.2:1 (overall yield 61%). The IR spectrum of the product mixture contained an absorption band at 3400 cm^{-1} due to stretching vibrations of the dihydropyridazine NH group. In the ^{1}H NMR spectrum of that mixture, we observed doublet signals

Scheme 5.

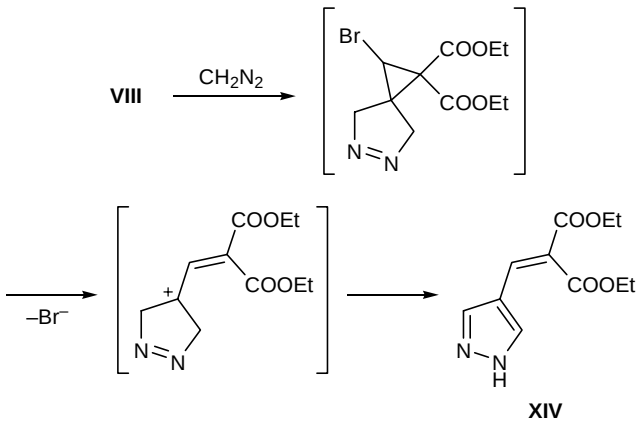


X, **XI**, R = Br; **XII**, **XIII**, R = CO_2Et.

from protons on C^6 and N^1, δ, ppm: **XII**: 7.02 d (6-H, J = 3 Hz), 11.14 d (NH, J = 3 Hz); **XIII**: 7.73 d (6-H, J = 4 Hz), 11.21 d (NH, J = 4 Hz).

The reaction of methylenecyclopropane **VIII** with diazomethane gave a complex mixture of products. By column chromatography we succeeded in isolating only individual pyrazole derivative **XIV** in 45% yield. The ^{1}H NMR spectrum of **XIV** contained singlet signals from the pyrazole ring prtons at δ 7.88, 8.06, and 11.81 ppm, as well as a signal at δ 6.86 ppm from the exocyclic olefinic proton. The formation of compound **XIV** may be illustrated by Scheme 6. According to this scheme, diazomethane adds at the exocyclic double bond in **VIII** to give spiro-fused dihydropyrazole derivative which loses bromide ion and undergoes opening of the three-membered ring, thus being converted into an allyl type cation. Elimination of proton from the latter yields pyrazole structure **XIV**.

Scheme 6.



EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer (Carl Zeiss) from 2% solutions in chloroform. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX-300 instrument at 300 and 75 MHz, respectively, from 2% solutions in $CDCl_3$. The elemental compositions were determined on a Hewlett–Packard 185 CHN analyzer. The melting points were measured on a Boetius device; uncorrected values are given. The purity of the compounds was checked, and the reaction mixtures were analyzed, by TLC using Silufol UV-254 plates.

Diethyl 2,2-dibromo-3-methylcyclopropane-1,1-dicarboxylate (III). A mixture of 1 g (5.4 mmol) of diethyl ethylidenemalonate (**I**) [5], 0.7 ml (8.1 mmol) of bromoform, 0.1 g of benzyltriethylammonium

chloride, and 8 ml of methylene chloride was cooled with an ice–salt mixture, and 4 g of a 50% aqueous solution of sodium hydroxide was added dropwise under stirring, maintaining the temperature below 5°C. The cooling bath was removed, the mixture was stirred for 2.5 h at room temperature and diluted with an equal volume of water, and the organic phase was separated and washed with water. The aqueous phase was extracted with methylene chloride, the extracts were combined with the organic phase and dried over anhydrous magnesium sulfate, the solvent was evaporated, and the residue was subjected to column chromatography on silica gel using hexane–ethyl acetate (4:1) as eluent. Yield 0.74 g (38%), R_f 0.67. IR spectrum, ν, cm^{-1}: 1030, 1070, 1090, 1130, 1270, 1310, 1370, 1450, 1610, 1720 v.s, 2990. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.29–1.35 m (9H, CH_3), 2.56 q (1H, CH, J = 7 Hz), 4.25–4.34 m (4H, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.6 (CH_3), 14.5 (CH_3), 32.0 (C^2), 35.7 (CH), 45.0 (C^1), 62.4 (CH_2), 63.3 (CH_2), 163.7 (CO), 165.6 (CO).

Diethyl 2,2-dibromo-3-phenylcyclopropane-1,1-dicarboxylate (IV). Following an analogous procedure, from 10 g (40 mmol) of diethyl benzylidenemalonate (**II**) [6], 7.0 ml (80 mmol) of bromoform, 0.5 g of benzyltriethylammonium chloride, 80 ml of methylene chloride, and 32.0 g of 50% aqueous NaOH we obtained 5.0 g (30%) of diester **IV** (56% on the reacted **II**). mp 55–59°C, R_f 0.63 (hexane–ethyl acetate, 4:1). IR spectrum, ν, cm^{-1}: 1040, 1120, 1200, 1260, 1290, 1370, 1450, 1740 v.s, 2990, 3040. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.25 t (3H, CH_3, J = 7 Hz), 1.39 t (3H, CH_3, J = 7 Hz), 3.84 s (1H, CH), 4.16–4.32 m (2H, CH_2), 4.39 q (2H, CH_2, J = 7 Hz), 7.30–7.40 m (5H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.3 (CH_3); 14.5 (CH_3); 29.0 (C^2); 43.9 (CH); 46.7 (C^1); 62.6 (CH_2); 63.6 (CH_2); 128.5, 128.6, 129.7, 132.3 (C_{arom}); 163.4 (CO); 165.6 (CO).

Diethyl 2-bromo-3-phenylcyclopropene-1,1-dicarboxylate (VI). Potassium *tert*-butoxide, 0.29 g (2.6 mmol), was added under argon to a solution of 0.27 g (0.65 mmol) of ester **IV** in 5 ml of tetrahydrofuran, cooled to 0°C. The cooling bath was removed, and the mixture was stirred for 20 h at room temperature. The mixture was then treated with water, the organic layer was separated, and the aqueous layer was extracted with methylene chloride. The extracts were combined with the organic phase, dried over magnesium sulfate, and evaporated to isolate 0.16 g (73%) of compound **VI**. IR spectrum, ν, cm^{-1}: 800, 870, 940, 1030, 1070 s, 1090, 1160, 1180, 1260, 1280 s, 1370, 1390, 1450, 1470, 1620, 1740 s, 2930, 2950, 2990, 3030. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.28 t (6H, CH_3, J = 7 Hz), 4.24 q (4H, CH_2, J = 7 Hz), 7.40–7.50 m (3H, H_{arom}), 7.60–7.70 m (2H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.5 (CH_3); 40.0 (C^1); 61.3 (CH_2); 62.0 (CH_2); 85.7 (C^2); 113.2 (C^3); 123.6, 129.3, 130.0, 130.9 (C_{arom}); 169.4 (CO).

Triethyl 3-phenylcyclopropene-1,1,2-tricarboxylate (VII). Potassium *tert*-butoxide, 0.35 g (3.1 mmol), was added over a period of 30 min under argon to a solution of 0.94 g (2.6 mmol) of triethyl 2-chloro-3-phenylcyclopropane-1,1,2-tricarboxylate (**V**) [4] in 6 ml of tetrahydrofuran, cooled to 0°C. The cooling bath was removed, and the mixture was stirred for 40 min at room temperature, treated with water, and extracted with diethyl ether. The extract was washed with two portions of water, dried over magnesium sulfate, and evaporated, and the residue was subjected to column chromatography on silica gel using hexane–ethyl acetate (5:1, by volume) as eluent. Yield 0.13 g (15%), mp 44–45°C. IR spectrum, ν, cm^{-1}: 880, 1020, 1080, 1290 s, 1370, 1450, 1720 v.s, 1870, 2990. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.23 t (6H, CH_3, J = 7 Hz), 1.36 t (3H, CH_3, J = 7 Hz), 4.20 q (4H, CH_2, J = 7 Hz), 4.36 q (2H, CH_2, J = 7 Hz), 7.47 m (3H, H_{arom}), 7.81 m (2H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.5 (CH_3); 14.6 (CH_3); 37.3 (C^1); 61.9 (CH_2); 62.4 (CH_2); 99.2 (C^2); 120.7 (C^3); 123.6, 129.5, 132.5, 132.8 (C_{arom}); 158.0 (CO); 169.0 (CO). Found %: C 65.02, H 6.07. $C_{18}H_{20}O_6$. Calculated, %: C 65.05, H 6.07.

Diethyl 5-bromo-3-phenyl-1,4-dihydropyridazine-4,4-dicarboxylate (X) and diethyl 3-bromo-5-phenyl-1,4-dihydropyridazine-4,4-dicarboxylate (XI). Potassium *tert*-butoxide, 0.53 g (4.8 mmol), was added under argon to a solution of 0.50 g (1.2 mmol) of ester **IV** in 7 ml of tetrahydrofuran, cooled to 0°C. The cooling bath was removed, the mixture was stirred for 20 h at room temperature, and a solution of diazomethane prepared from 1.0 g (9.7 mmol) of *N*-nitroso-*N*-methylurea in diethyl ether was added. The mixture was kept for 48 h at room temperature and treated with water, the organic phase was separated, and the aqueous phase was extracted with methylene chloride. The extracts were combined with the organic phase, dried over magnesium sulfate, and evaporated, and the residue (0.46 g) was subjected to column chromatography using hexane–ethyl acetate (4:1) as eluent. We isolated 0.08 g (18%) of a mixture of diesters **X** and **XI**, R_f 0.21 (hexane–ethyl acetate, 4:1). IR spectrum, ν, cm^{-1}: **X**+**XI**: 820, 870, 1040, 1060, 1100, 1120, 1160,

1270, 1370, 1400, 1450, 1500, 1760 s, 2950, 2990, 3030, 3440. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: **X**: 1.14 t (6H, CH_3, *J* = 7 Hz), 3.85–4.05 m (2H, CH_2), 4.16 q (2H, CH_2, *J* = 7 Hz), 6.76 d (1H, CH, *J* = 2 Hz), 7.20–7.50 m (5H, H_{arom}), 8.85 br.s (1H, NH); **XI**: 1.13 t (6H, CH_3, *J* = 7 Hz), 3.85–4.05 m (2H, CH_2), 4.16 q (2H, CH_2, *J* = 7 Hz), 7.20–7.50 m (5H, H_{arom}), 7.57 d (1H, CH, *J* = 3 Hz), 8.43 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: **X**: 14.0 (CH_3); 62.9 (CH_2); 63.7 (C^4); 106.3 (C^5); 119.3, 128.4, 128.7, 128.8 (C_{arom}); 129.6 (CH); 136.7 (C^3); 167.8 (CO); **XI**: 14.0 (CH_3); 63.7 (C^4), 64.0 (CH_2); 106.3 (C^5); 119.3 (C^3); 125.9, 128.7, 128.8 (C_{arom}); 129.9 (CH); 136.7 (C_{arom}); 165.8 (CO).

Triethyl 3-phenyl-1,4-dihydropyridazine-4,4,5-tricarboxylate (XII) and triethyl 5-phenyl-1,4-dihydropyridazine-3,4,4-tricarboxylate (XIII). A solution of diazomethane in diethyl ether, prepared from 0.31 g (3.0 mmol) of *N*-nitroso-*N*-methylurea, was added to a solution of 0.088 g (0.3 mmol) of ester **VII** in diethyl ether, and the mixture was kept for 48 h at room temperature. The precipitate was filtered off and washed with cold diethyl ether. Yield of mixture **XII**/**XIII** 0.062 g (61%), mp 144–146°C. IR spectrum, ν, cm^{-1}: **XII**+**XIII**: 870, 1040, 1130, 1270, 1310, 1380, 1470, 1630, 1740 v.s, 3050, 3440. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: **XII**: 0.95 t (6H, CH_3, *J* = 7 Hz), 1.23 t (3H, CH_3, *J* = 7 Hz), 3.95 q (4H, CH_2, *J* = 7 Hz), 4.18 q (2H, CH_2, *J* = 7 Hz), 7.02 d (1H, CH, *J* = 3 Hz), 7.25–7.64 m (5H, H_{arom}), 11.14 d (1H, NH, *J* = 3 Hz); **XIII**: 0.95 t (6H, CH_3, *J* = 7 Hz), 1.19 t (3H, CH_3, *J* = 7 Hz), 3.95 q (4H, CH_2, *J* = 7 Hz), 4.09 q (2H, CH_2, *J* = 7 Hz), 7.20–7.64 m (5H, H_{arom}), 7.73 d (1H, CH, *J* = 4 Hz), 11.21 d (1H, NH, *J* = 4 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: **XII**: 14.0 (CH_3); 14.8 (CH_3); 56.2 (C^4); 60.7 (CH_2); 62.5 (CH_2); 96.7 (C^5); 124.2 (C^6); 128.6, 129.0, 134.7, 136.3 (C_{arom}); 141.7 (C^3), 165.9 (CO); 169.3 (CO); **XIII**: 14.0 (CH_3); 14.7 (CH_3); 56.2 (C^4), 62.2 (CH_2); 62.5 (CH_2); 114.4 (C^5); 124.9, 126.9, 127.3, 127.8 (C_{arom}); 134.6 (C^6); 136.4 (C^3); 164.1 (CO); 169.1 (CO). Found, %: C 60.97; H 5.90; N 7.47. $C_{19}H_{22}N_2O_6$. Calculated, %: C 60.95; H 5.92; N 7.48.

Reaction of diethyl 2,2-dibromo-3-methylcyclopropane-1,1-dicarboxylate (III) with potassium *tert*-butoxide. Potassium *tert*-butoxide, 1.25 g (11.2 mmol), was added under argon to a solution of 1.0 g (2.8 mmol) of diethyl ester **III** in 10 ml of tetrahydrofuran, and the mixture was stirred for 3.5 h at 40°C and treated with 10 ml of water. The organic layer was separated, and the aqueous layer was extracted with an equal volume of methylene chloride. The extract was combined with the organic phase, dried over magnesium sulfate, and evaporated. According to the ^{1}H NMR data, the residue, 0.7 g, contained 0.36 g (51%) of diethyl 2-bromo-3-methylenecyclopropane-1,1-dicarboxylate (**VIII**) and 0.15 g (21%) of initial compound **III**.

Compound **VIII**. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.27–1.36 m (6H, CH_3), 4.20–4.38 m (5H, CH_2, CH), 5.96 s (2H, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.4 (CH_3), 14.6 (CH_3), 35.0 (CH), 39.7 (C^1), 62.6 (CH_2), 62.8 (CH_2), 111.5 (CH_2), 130.1 (C^3), 164.5 (CO), 166.2 (CO).

Diethyl 2-(1*H*-pyrazol-4-yl)methylenemalonate (XIV). A solution of diazomethane in diethyl ether, prepared from 2.0 g of *N*-nitroso-*N*-methylurea, was added at room temperature to a mixture (see above) containing 0.35 g (1.3 mmol) of ester **VIII** in 10 ml of diethyl ether. The mixture was kept for 48 h at room temperature, and the solvent was distilled off. The residue, 0.71 g, was subjected to column chromatography using hexane–ethyl acetate (4:1) as eluent to isolate 0.138 g (45%) of ester **XIV**, mp 113–116°C. IR spectrum, ν, cm^{-1}: 870, 1020, 1040, 1080, 1160, 1200, 1270 s, 1300, 1380, 1400, 1470, 1740 s, 2990, 3040, 3450. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.36 t (3H, CH_3, *J* = 7 Hz), 1.37 t (3H, CH_3, *J* = 7 Hz), 4.36 q (2H, CH_2, *J* = 7 Hz), 4.41 q (2H, CH_2, *J* = 7 Hz), 6.86 s (1H, CH), 7.88 s (1H, CH), 8.06 s (1H, CH), 11.81 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.4 (CH_3), 63.1 (CH_2), 108.3 (CH), 124.9 (CH), 133.7 [=**C**$(CO_2Et)_2$], 134.0 (CH), 140.3 (C^4), 162.8 (CO), 165.0 (CO).

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