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CYCLOADDITION OF DICHLOROKETENE WITH FUNCTIONALIZED CYCLOALKENES. SYNTHESIS OF BICYCLO[4.2.0]OCTANONE-3-YL DERIVATIVES AND OF 3,4-DICARBOMETHOXY-1-METHYLBICYCLO[4.2.0]OCTAN-7-ONE.

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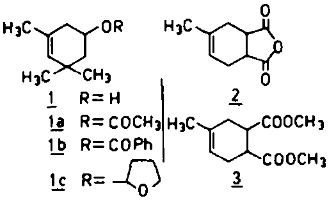
Abstract: Dichloroketene reacts with some cycloalkenes in which an ester function is in homoallylic or in an even more remote position with respect to sp^2 carbon atoms. In fact acetate and benzoate of 3,5,5-trimethylcyclohex-3-en-1-ol and 1,2-dicarbomethoxy-4-methyl-cyclohex-4-ene undergo 2+2 cycloaddition of dichloroketene to produce the corresponding bicyclo[4.2.0]octanone derivatives in 60-65% yield. In the latter case the process occurs regiospecifically to give 3,4-dicarbomethoxy-1-methylbicyclo[4.2.0]octan-7-one as product after dechlorination. The Hassner zinc dehalogenation method of generating dichloroketene is the best procedure.

The [2+2] cycloaddition of dichloroketene with cyclopentadienes and olefins is widely recognized[1] as a remarkably powerful method for construction of four membered rings. The α,α-dichlorocyclobutanone derivatives can be readily dechlorinated with zinc or subjected to other useful transformations[2].

Although this reaction has been the subject of intensive investigations, to date it has only seen limited applications with functionalized cycloalkenes[3-6]. The effectiveness of dichloroketene cycloadditions togheter with our interest in exploring new techniques for non photochemical synthesis of bicyclo[4.2.0]alkane derivatives, provided incentive for an investigation of cyclization process with cycloalkenes bearing activating functionality. We report here the results of a study concerning reactions of dichloroketene with cycloalkenes in which a supplementary function is in homoallylic, or in an even more remote position with respect to sp^2 carbon atoms. We chose compounds 1a-c, 2 and 3 as substrates for this study.



RESULTS

Dichloroketene,prepared *in situ* by dehalogenation of trichloroacetylchloride with activated zinc in presence of phosphorus oxychloride, reacted with compound 1a in refluxing diethyl ether. Work-up of mixture after 10-12 h provided 8,8-dichloro-1,5,5-trimethylbicyclo[4.2.0]octan-7-one-3-yl acetate (4) and 7,7-dichloro-1,5,5-trimethylbicyclo [4.2.0] octan-8-one-3-yl acetate (5) in 63% yield (Scheme 1). Bicyclo derivatives 4 and 5 proved to be rather unstable even when kept in refrigerator under nitrogen. They were dechlorinated with excess zinc dust in saturated methanol solution of ammonium chloride. After 6 h of reflux it was possible to obtain quantitative amounts of 1,5,5-trimethylbicyclo [4.2.0]octan-7-one-3-yl acetate (6) and the isomeric bicyclo[4.2.0]octan-8-one-3-yl acetate (7). Direct treatment of the reaction mixture between 1a and dichloroketene without separation of compound 4 and 5 produced compounds 6 and 7 in the same yield and without modification of the isomers ratio (ratio 6:7 = 1.78).

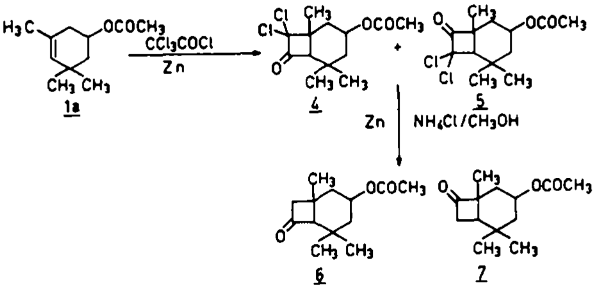


Fig.1

In the same conditions the benzoyl ester 1b underwent [2+2] cycloaddition of dichloroketene, and successively dehalogenation to give compounds 10 and 11 in 61% yield (ratio 10:11 = 1.85),(Scheme 2).

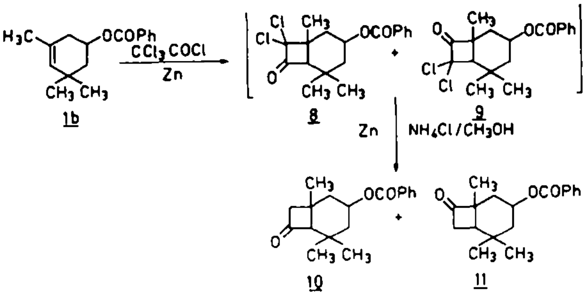


Fig.2

Similar treatment of 1,2-dicarbomethoxy-4-methylcyclohex-4-en (3) produced only 3,4-dicarbomethoxy-8,8-dichloro-1-methylbicyclo [4.2.0]octan-7-one (12) in 65% yield. Compound 12 underwent dehalogenation when treated with zinc dust in refluxing saturated solution of ammonium chloride and 3,4-dicarbomethoxy-1-methylbicyclo [4.2.0]octan-7-one (13) was separated in almost quantitative yield,(Scheme 3).

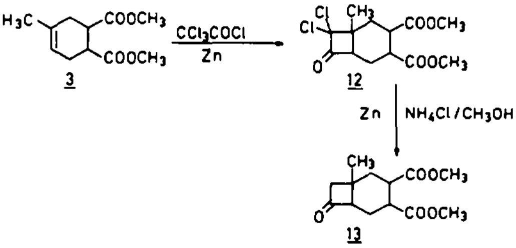


Fig.3

All compounds showed the expected spectral data (IR, ^1H NMR) and analytical properties. In addition Bayer-Williger oxidation with metachloroperbenzoic acid

(MCPBA) was performed on regioisomer 11 to have additional evidence for structural assignement. The bicyclolactone 14 was obtained in 90% yield.

10 14

It is noteworthy that dichloroketene, prepared *in situ* by dehydrohalogenation of dichloroacetylchloride with triethylamine, reacted with 1a and 1b in refluxing n-hexane to give complex mixtures. The IR spectra of these reaction mixtures showed a strong C=O absorption at 1805 cm^{-1}(cyclobutanone system) while the stretching absorption at 1730 cm^{-1} for the ester function was absent.

Reactions performed with tetrahydrofuranyl derivative 1c and on methyltetrahydrophtalic anhydride 2 were unsuccessful. Complex reaction mixtures were obtained and all our efforts to separate some significative product were unsuccessful.

We expected that our findings may encourage a much greater use of dichloroketene in non photochemical synthesis of bicyclo n.2.0 alkane derivatives.

EXPERIMENTAL

Proton NMR spectra were recorded at 60 MHz on a Varian EM360 L instrument and at 100 MHz on a Varian XL-100 operating in the CW mode. ^{1}H NMR shifts are given in parts per milion from Me_4Si in $CDCl_3$ solvent. IR spectra were recorded with a Perkin-Elmer 257 spectrophotometer. Microanalyses were performed by using C,H, N Analyzer Model 185 from Hewlett-Packard Co.. 3,5,5-Trimethylcyclohex-3-en-1-ol (1) was prepared in high yield by lithium aluminium hydride reduction of β-phorone, easily available by the method of Marx[8]. 1,2-Dicarbomethoxy-4-methylcyclohex-4-en (2) was prepared by esterification of the 1:1 adduct 3 of Diels Alder cycloaddition of isoprene and maleic anhydride[9]. The activation of zinc dust was performed according a procedure previously reported[10]. Analytical grade solvents (Carlo Erba)) were used without further purification.

3,5,5-Trimethylcyclohex-3-en-1-ol(1). A 500 ml three necked flask equipped with a condenser, additional funnel; magnetic stirrer, and N_2 inlet, was charged with 2.73 g ($7.2x10^{-2}$mol) of $LiAlH_4$ and dry diethyl ether (170 ml). The suspension was stirred under N_2 and a solution of 15 g ($10.8x10^{-2}$mol) of β-phorone[8] in dry diethyl ether (50 ml) was added dropwise during 1 h. When addition of solution was complete, the mixture was refluxed for half an hour. The cooled reaction mixture was treated with water (Caution!) and , successively, with a cold aqueous 5% HCl solution,washed with brine and dried(Na_2SO_4). The solvent was removed at reduced pressure to leave an oil weighing 15.2 g. Vacuum distillation afforded 14.6 g of product (96%): bp 80-82°C (6.0 mm$_{Hg}$); IR(neat) 3340(s),1670(m)cm^{-1}; ^{1}H NMR δ 5.1(s,1H),4.0(m,1H),2.2-1.5(m, 4H),1.6(s,3H),1.0(s,6H). Anal.Calcd for $C_9H_{16}O$: C,77.09; H,11.50. Found: C,76.95; H,11.42.

3,5,5-Trimethylcyclohex-3-en-1-yl acetate(1a).3,5,5-Trimethylcyclohex-3-en-1-ol (14.0 g, $9.9x10^{-2}$mol) dissolved in glacial acetic acid (30 ml) and acetic anhydride (30 ml) was treated at reflux under nitrogen. After 1 h the solution was cooled, added with diethyl ether (150 ml) and washed with water (3x70 ml) and successively with brine (3x30 ml). The organic phase was dried (Na_2SO_4) and the solvent was distilled under reduced pressure to give 17.10 g (94%) of 1a as a colorless liquid: bp 87-89°C(9.0 mm$_{Hg}$); IR(neat) 1740 (s), 1670 (m)cm^{-1}; ^{1}H NMR δ 5.1(s,1H),4.0(m,1H),2.1-1.7(m,4H),1.6 (s,3H).Anal.Calcd for $C_{11}H_{18}O_2$: C,72.49; H,9.96. Found: C,72.35; H,9.85.

3,5,5-Trimethylcyclohex-3-en-1-yl benzoate (1b).Benzoyl chloride (11.1,7.9x10^{-2} mol) in dry benzene (40 ml) was slowly added at 10-15°C with stirring to a solution of 3,5,5-trimethylcyclohex-3-en-1-ol (1) (10.0 g, 7.1x10^{-2}mol), pyridine (28.4 g, 36x10^{-2}mol) and benzene (100 ml). The reaction mixture was refluxed for 2 h , and then stirred for an additional hour at room temperature; 10% aqueous HCl was added until acidic pH was reached, and the organic phase was separated and washed with brine, dried (Na_2SO_4) and the solvent was distilled under reduced pressure. Distillation of residual oil yielded 11.03 g (63% yield) of 1b as a colorless liquid: bp 100-101° C(0.3 mm$_{Hg}$); IR(neat) 1720(s),1670(m) cm^{-1}; ^{1}H NMR δ 5.35(m,5H),5.2(s,1H),2.4-1.6(m,4H),1.6(s,3H),1.0(s,6H). Anal.Calcd for $C_{16}H_{20}O_2$: C,78.65; H,8.25. Found: C,78.72; H,8.37.

3,5,5-Trimethyl-1-(tetrhydrofuranyloxy) cyclohex-3-ene(1c)^{10}.Amberlist H-15,H$^+$ form (1 g), was added to a cooled solution of compound 1 (9.79 g,6.9x10^{-2}mol) and dihydrofuran (26.4x10^{-2}mol) in CH_2Cl_2 (200 ml). after the mixture was stirred for 3 h at room temperature, the resin was taken away by decantation and the residue was washed with a 10% aqueous $NaHCO_3$, with saturated brine and finally dried (Na_2SO_4). The solvent was distilled at reduced pressure. Distillation of residual oil yielded 9.14 g (63% yield) of 1c as colorless liquid: bp 58-60°C (0.3 mm$_{Hg}$); IR(neat) 1670(m) cm^{-1}; ^{1}H NMR δ 5.35(s,1H),5.10(s,1H),3.9(m,3H),2.2 -1.6(m,8H),1.6(s,3H),1.0(s,6H). Anal.Calcd for $C_{13}H_{22}O_2$: C,74.24; H,10.54.Found: C,74.38; H,10.62.

1,2-Dicarbomethoxy-4-methylcyclohex-4-ene(3). Few drops of37% HCl were added to the solution of compound 2 (15 g,9.0 x10^{-2}mol) in MeOH (80 ml). The mixture was distilled at reduced pressure, diethyl ether was added and the ethereal solution was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated at reduced pressure to yield an oil. Fractional distillation produced 13.7 g(69% yield) of 3 as colorless liquid: bp 100-102°C(1.5 mm$_{Hg}$); IR(neat) 1735(s),1670(m) cm^{-1}; ^{1}H NMR δ 5.4(m,1H), 3.7(s,6H),3.0(m,2H),2.35(m,4H),1.75(s, 3H). Anal.Calcd for $C_{11}H_{16}O_4$: C,62.25; H,7.60. Found: C,62.32; H,7.68.

Cycloaddition of Dichloroketene with Compound 1a.Preparation of 8,8-Dichloro-1,5,5-trimethylbicyclo [4.2.0]octan-7-on-3-yl acetate (4) and 7,7-Dichloro-1,5,5-trimethylbicyclo[4.2.0]octan-8-on-3-yl acetate (5). A 250 ml three necked flask equipped with a condenser, addition funnel, magnetic stirrer and N_2 inlet was flame dried while purged with N_2. When cooled the flask was charged with activated zinc dust (5.0 g, 7.6x10^{-2}mol), compound 1a (3.0 g, 1.6x10^{-2}mol) and 60 ml of anhydrous ether. The suspension was stirred under N_2 at reflux and a solution of trichloroacetyl chloride (6.64 g, 3.65x10^{-2} mol) and phosphorus oxychloride (5.61 g, 3.5x10^{-2}mol) in 30 ml of anhydrous ether was added dropwise over a 3 h period. When the addition of the solution was complete, the mixture was refluxed with stirring for additional 10 h. The reaction mixture was cooled and then was filtered through a pad of Celite and the unreacted zinc washed with ether (2x50 ml). The ethereal solution was washed successively with water (2x25 ml), a cold saturated

$NaHCO_3$ solution (2x25 ml) and brine (2x 25 ml) and dried (Na_2SO_4). The solvent was removed at reduced pressure to leave 5.6 g of a mixture, which was chromatographed on a silica gel column (benzene-hexane, 8:2) eluting at first unreacted ester 1a and successively compound 4 (1.67 g, 35% yield) and compound 5 (1.31 g, 28% yield).

8,8-Dichloro-1,5,5-trimethylbicyclo[4.2.0]octan-7-on-3-yl acetate (4) was an oil: IR(neat),1805(s),1735(s)cm^{-1};^{1}H NMR δ 5.1(m,1H),3.40(bs,1H),2.10(s,3H),1.68(s,3H),1.22(s,3H),1.12(s,3H),3.1-1.9(m,4H). Anal.Calcd for $C_{13}H_{18}O_3Cl_2$: C,53.65; H,6.13. Found: C,53.74; H,5.97.

7,7-Dichloro-1,5,5-trimethylbicyclo[4.2.0]octan-8-on-3-yl acetate (5) was an oil: IR(neat) 1805(s),1735(s)cm^{-1};^{1}H NMR δ4.95(m,1H),3.28(bs,1H)2.12(s,3H),1.62(s,3H),1.28(s,3H),1.04(s,3H),3.1-1.95(m,4H). Anal.Calcd for $C_{13}H_{18}O_3Cl_2$: C,53.65;H,6.13; Found: C,53.69; H,6.18.

Dechlorination of Dichlorobicyclo 4.2.0 octane Derivatives 4 and 5.Preparation of 1,5,5-Trimethylbicyclo[4.2.0]octan-7-on-3-yl acetate (6) and 1,5,5-Trimethyl bicyclo[4.2.0]octan-8-on-3-yl acetate (7) The mixture of compound 4 and 5 (4 g,1.36 x10^{-2}mol) and zinc dust(8.0 g,12.3x10^{-2} mol) was added to saturated methanolic solution of NH_4Cl (60 ml) in a 100 ml flask equipped with a condenser. The suspension was refluxed for 4 h, cooled and filtered. Methanol was evaporated at reduced pressure and the residue was dissolved with diethyl ether. The ethereal solution was washed with water and brine and dried (Na_2SO_4). The solvent was removed at reduced pressure to leave an oil (2.82 g,92%) which was chromatographed on a silica gel column (benzene-ethyl acetate,97:3), eluting at first compound 6 (1.78 g) and successively compound 7 (1.04 g).

1,5,5-Trimethylbicyclo[4.2.0]octan-7-on 3-yl acetate (6) was anoil: IR(neat) 1775(s),1730(s)cm^{-1};^{1}H NMR δ5.12(m,1H),2.70(s,3H),2.04(s,3H),1.54(s,3H),1.18(s,3H),1.08(s,3H),2.0-1.5(m,4H).Anal.Calcd for $C_{13}H_{20}O_3$: C,69.61; H,8.99. Found: C,70.03 H,9.07.

1,5,5-Trimethylbicyclo[4.2.0]octan-8-on 3-yl acetate (7) was an oil: IR(neat) 1775(s),1730(s)cm^{-1};^{1}H NMR δ5.0(m,1H), 2.75-2.55(m,3H),2.00(s,3H),1.52(s,3H), 1.22(s,3H),1.04(s,3H),2.5-1.0(m,4H). Anal.Calcd for $C_{13}H_{20}O_3$: C,69.61; H,8.99. Found: C,69.85; H,8.75.

Cycloaddition of Dichloroketene with Compound 1b.Preparation of 1,5,5-Trimethylbicyclo[4.2.0]octan-7-on-3-yl benzoate (10),and 1,5,5-Trimethylbicyclo[4.2.0]octan-8-on-3-yl benzoate (11). According to the previously reported procedure, a mixture of dichlorobicyclo[4.2.0]octanones 8 and 9 obtained as unstable liquid from activated zinc dust (6.0 g,9.1x10^{-2}mol), compound 1b (4.64 g,1.9x10^{-2}mol) trichloroacetylchloride (8.36 g,4.6x10^{-2}mol) and phosphorus oxychloride (4.2 ml,4.6x10^{-2}). The crude mixture was dechlorinated by treatmentwith zinc dust (6.0 g,9.1x10^{-2} mol) in saturated methanolic solution of NH_4Cl. Usual work-up of reaction yielded 3.91 g of an oil which was chromatographed on a silica gel column (benzene-ethyl acetate, 97:3) eluting at first unreacted ester 1b, compound 11 (1.20 g) and successively compound 10 (0.80 g).

1,5,5-Trimethylbicyclo[4.2.0]octan-7-on-3 yl benzoate (10) was a wite solid: mp 76-78°C; IR(KBr) 1770(s),1705(m)cm^{-1};^{1}H NMR δ 8.15-8.00(m,2H),7.65-7.30(m,3H),5.42(m,1H),2.75(s,3H),2.35-1.70(m,4H),1.55(s,3H),1.20(s,3H),1.10(s,3H).Anal. Calcd for $C_{18}H_{22}O_3$: C,75.49; H,7.74. Found: C,75.84; H,7.81.

1,5,5-Trimethylbicyclo[4.2.0]octan-8-on 3-yl benzoate (11) was an oil: IR(neat) 1780(s),1175(m)cm^{-1};^{1}H NMR δ 8.15-7.98 (m,2H)),7.65-7.30(m,3H)),5.30(m,1H),2.76 -2.58(m,3H),2.50-1.30(m,4H),1.60(s,3H), 1.30(s,3H),1.12(s,3H).Anal.Calcd for $C_{18}H_{22}O_3$: C,75.49; H,7.74.Found: C,75.61; H,7.35.

Cycloaddition of Dichloroketene with Compound 3. Preparation of 3,4-Dicarbomethoxy-8,8-dichloro-1-methylbicyclo[4.2.0]octan-7-one (12). Compound 3 (4.03g,1.9x10^{-2}mol) was treated with activated zinc dust (6.0,9.1x10^{-2}mol),trichloroacetylchloride (5.0 ml,4.6x10^{-2}mol) and phosphorus oxychloride (4.2 ml,4.6x10^{-2}mol) according to the previous procedure to yield 3,4-dicarbomethoxy-8,8-dichloro-1-methylbicyclo 4.2.0 octan-7-one (12)(3.98 g,65% yield) as pale yellow crystals:mp 67-68°C;IR(KBr) 1795(s),1740(s)cm^{-1};^{1}H NMR δ 3.70(s,3H),3.62(m,1H),3.38-3.18(m, 2H),2.68-1.90(m,4H),1.42(s,3H). Anal. Calcd for $C_{13}H_{16}Cl_2O_5$: C,48.31; H,5.56. Found: C,48.48; H,5.67.

Preparation of 3,4-Dicarbomethoxy-1-methylbicyclo[4.2.0]octan-7-one (13). Compound 12 (2.0 g,0.6x10^{-2}mol) was dechlorinated by treatment with zinc dust (3.0 g,4.55x10^{-2}mol) in saturated methanol solution of NH_4Cl (20 ml).After 4h at reflux, usual work-up of reaction mixture furnished 1.42 g of compound 13 as an oil that was purified by silica gel column chromatography (Et_2O-hexane 1:1): IR(neat)1775(s),1735(s) cm^{-1};^{1}H NMR δ 3.76(s,6H),3.30-3.00(m,2H),2.70-1.55(m, 5H),1.4(s,3H). Anal.Calcd for $C_{13}H_{18}O_5$: C, 61.40; H,7.14. Found: C,61.27; H,7.65.

Lactone of cis-2-Hydroxy-4-benzoyloxy-2,6,6-trimethyl-1-acetic Acid (14). To a solution of compound 10 (0.40 g,0.14x10^{-2}mol) in chloroform (10 ml) cooled at 0°C was added MCPBA (0.26 g,0.15x10^{-2}mol). The reaction mixture was stirred for 24 h at 0°C. The product was extracted with ether and washed with 10% aqueous sodium sulfite and saturated sodium carbonate. The ether layer was dried over $MgSO_4$ and the solvet was removed in vacuo. Compound 14 (0.340 g, 90% yield) is a solid: mp 102-104°C; IR(KBr): 1725(s),1715(s) cm^{-1}; ^{1}H NMR δ 8.16-7.00(m,2H),7.60-7.20(m,3H), 5.30(m,1H),3.90(s,1H),2.35(s,2H),1.90-1.60 (m,4H),1.4(s,3H),1.30(s,3H),1.18(s,3H). Anal.Calcd for $C_{18}H_{22}O_4$: C,71.54; H,7.34. Found: C,71.74; H,7.42.

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