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Articles

Chlorination of Bicyclo[1.1.1]pentane Derivatives

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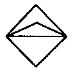
Several bridgehead-substituted bicyclo[1.1.1]pentanes have been chlorinated to yield the 2,2-dichloro derivatives as the exclusive products. Selective removal of one of the chlorine substituents has been accomplished with tri-*n*-butyltin hydride.

In connection with a synthetic program under way in our laboratory[2-5] we need to develop procedures for the functionalization of the methylene groups in bicyclo[1.1.1]pentanes and [*n*]staffanes (**1[*n*]**) carrying bridgehead substituents. These materials are readily available from the oligomerization of [1.1.1]propellane[6] (**2**), which in turn is accessible in two steps from commercial starting materials.[7,8]

Little can be found on this subject in the literature. The direct chlorination of bicyclo[1.1.1]pentane itself (**3**) with a limited concentration of chlorine[9] yielded an 11% yield of a complex mixture of chloro derivatives: 1-chloro (51%), 2-chloro (23%), 2,2-dichloro (11%), 1,3-dichloro (1%), and 1,2-dichloro (1%) substituted bicyclo[1.1.1]pentanes, and 3-chloro-1-methylenecyclobutane (12%). We now report the results of chlorination of several bridgehead-substituted bicyclo[1.1.1]pentanes. This yields single products in acceptable yields and is quite encouraging with respect to our ultimate goals.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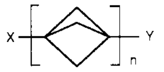


1[*n*]


3

Results

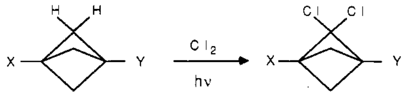
Our initial efforts were directed toward the bromination of the methylene bridges of 1,3-dibromobicyclo[1.1.1]pentane (**4a**). A wide variety of brominating agents were used to no avail.[10] In no case could the solution bromination be effected. An attempted oxidation with peroxydisulfate also yielded only unreacted starting material.

In contrast, photochemical chlorination at −15 °C with a $CFCl_3$ or CCl_4 solution of elemental chlorine smoothly produced essentially a single product, which contained two chlorine atoms and could be isolated in analytically pure form in 38% yield after three recrystallizations at −78 °C. The characteristic ^{13}C NMR shift of the CCl_2 group permitted a ready identification as **5a** once it was realized that the geminal proton coupling constants in the methylene bridges of **3** and its derivatives are very small.[9,11]

Table I. Photochlorination of Bridgehead-Substituted Bicyclo[1.1.1]pentanes

substrate	solvent	time, h	temp, °C	product	yield, %
4a	CCl_4	4	−10	**5a**	32
4a	$CFCl_3$	4	−10	**5a**	59
4b	CF_3CO_2H	21	+35	**5b**	67
4c	CCl_4	2	0	**5c**	75[a]
4c	CCl_4	4	0	**5c**	79[b]
4d	CCl_4	2	0	**5b**	55[c]
4e	CCl_4	2	−10	**5f**	29

[a] Yield based on GC/MS analysis of the diester **5d**, which was formed by treatment of the crude reaction mixture with absolute methanol. [b] NMR analysis showed the presence of an impurity (~21%), which was of a vinylic nature. The conversion was complete with no other impurities in evidence. [c] The crude chlorination mixture was immediately hydrolyzed to produce the diacid **5b**, which was identified by its NMR spectrum and by conversion to **5d** with oxalyl chloride followed by methanol. The yield refers to isolated **5d**.



4 **5**

a: X = Br; Y = Br
b: X = CO_2H; Y = CO_2H
c: X = COCl; Y = COCl
d: X = CO_2CH_3; Y = CO_2CH_3
e: X = H; Y = CO_2H
f: X = H; Y = CO_2CH_3

The chlorination of **4b** was similarly accomplished in high yield as were the reactions of **4c** and **4d**, yielding the dichloro derivatives **5** (Table I). While the use of trifluoroacetic acid as a solvent for preparative-scale reactions makes the chlorination of **4b** an odoriferous experiment, the high yield and the complete absence of byproducts in this case seem to make this substrate the molecule of choice for bridge functionalization.

The chlorination of bicyclo[1.1.1]pentane-1-carboxylic acid (**4e**) could occur either at one of the bridges or at the

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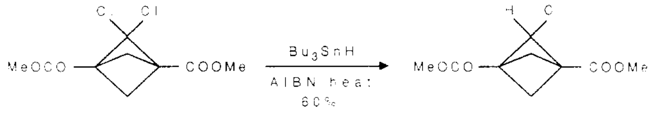
one free bridgehead position. The crude reaction mixture was treated with oxalyl chloride followed by methanol and analyzed by VPC. The major product (44%) was the 2,2-dichloro derivative **5f**. Smaller amounts of the chlorine-free ester **4f** (18%), of a suspected monochloro derivative (16%, an amount insufficient for complete characterization), and of a few additional minor components were detected as well. There was no evidence of more highly chlorinated products. The isolated yield of **5f** was 35%.

No significant amount of a firmly identified monochlorinated material was found in any reaction, even at small conversions. However, tri-*n*-butyltin hydride converts the dichlorinated (**5d**) into the monochlorinated (**6**) diester cleanly, judging by VPC analysis of the crude reaction mixture. Difficulty was experienced in the separation of the product from the tin polymer created during workup. Both solution and gas-phase chromatography cause losses due to partial decomposition of **6**. After sublimation and crystallization, analytically pure **6** was isolated in 23% unoptimized yield.



5d **6**

Attempts to force a higher degree of chlorination by increasing the reaction temperature and duration produced only rearrangement products and no bicyclo[1.1.1]pentanes with more than two chlorines and were therefore not pursued further.

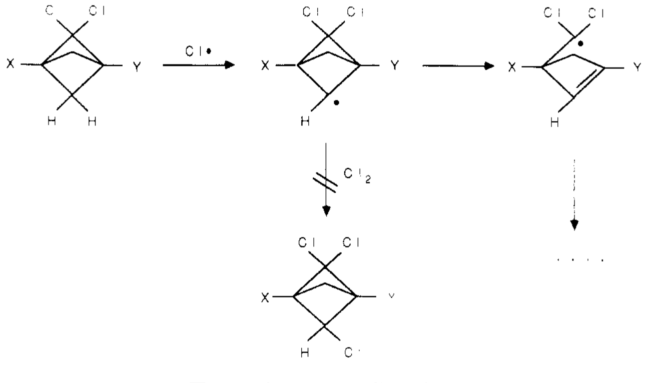
Discussion

The smooth conversion of bridgehead-substituted bicyclo[1.1.1]pentanes into their 2,2-dichloro derivatives is encouraging for our synthetic purposes. The absence of monochlorination, and the abruptness with which the photochlorination stops at the level of the dichloro derivative, simplify the separation procedures and increase the yield of the geminal dichloro compound. The ease with which one of the geminal chlorines is removed selectively promises ready access to other types of substitution in position 2.

The abstraction of a hydrogen atom from the methylene bridge of these bicyclo[1.1.1]pentane derivatives is clearly relatively difficult. The much higher rate of the second chlorination step is readily rationalized by reference to the radical-stabilizing effect of the first chlorine. The same effect explains the ease of the differential removal of only one of the geminal chlorine atoms by reaction with the tin hydride.

It is possible that the same radical-stabilizing effect of the chlorine substituent is responsible for the disappointing results of the attempts to introduce more than two chlorines. At the higher temperatures needed for the abstraction of a hydrogen atom from a second CH_2 group by a chlorine atom, made more difficult by the inductive and perhaps also the steric effect of the CCl_2 moiety, a strain-releasing ring opening to form a double bond and the stabilized $-CCl_2^{\bullet}$ radical apparently competes successfully with single chlorine atom abstraction from a Cl_2 molecule, which is probably slowed down by general steric crowding in the bicyclic system.

The direction of the chlorination of the monoacid **4e**, with the 2,2-dichloro derivative again as the major product, was unexpected. Chlorocarbonylation of the parent hydrocarbon with oxalyl chloride yields predominantly the bridgehead-substituted product,[9] and in both reactions, an abstraction of a hydrogen atom by a chlorine atom is expected to be the first reaction step. Perhaps this is simply a reflection of the effect of different reaction conditions on a nearly balanced competition between abstraction of hydrogens in positions 1 and 2, but it is also possible that some more subtle mechanistic points are involved, and the issue deserves further investigation.



Experimental Section

All solvents were reagent grade and used as received except where noted. 1,3-Dibromobicyclo[1.1.1]pentane (**4a**),[12] bicyclo[1.1.1]pentane-1,3-dicarboxylic acid (**4b**),[8] and bicyclo[1.1.1]pentane-1-carboxylic acid (**4e**)[3] were prepared by literature methods. Melting points are uncorrected. ^1H NMR spectra were determined in $CDCl_3$ solution at 90 MHz on a Varian EM 390 instrument or at 360 MHz on a NT 360 instrument with TMS as internal standard. ^{13}C NMR spectra were measured on the latter instrument, except for **5a**, measured at 500 MHz on a QE 500 instrument. Infrared spectra were recorded on a Nicolet 60SXR FTIR instrument. VPC separations were performed using a 6 ft 20% SE-30 column. VPC analysis used a 6 ft OV 101 and SE-30 columns. All elemental analyses were performed by Atlantic Microlab.

Chlorination of 1,3-Dibromobicyclo[1.1.1]pentane (5a). A 250-mL three-neck round-bottom flask was equipped with a reflux condenser and a Teflon inlet for chlorine gas. The flask was then dried by heating under a stream of argon. An argon atmosphere was maintained throughout the reaction. Into the flask was placed 1.008 g of **4a**, 200 mL of carbon tetrachloride, 6.5 g of anhydrous calcium carbonate (to suppress acid-initiated reactions), and a spinbar. The vessel was then placed in a −10 °C bath, and chlorine was passed into the solution until saturated. Irradiation was effected with a 275-W incandescent lamp for a total of 4 h when VPC analysis revealed a nearly complete reaction. Removal of the solvent at reduced pressure provided a viscous oil, which solidified on standing. This oil was recrystallized three times from pentane at −78 °C, affording 0.428 g (32% yield) of analytically pure material, mp 67.5–69.2 °C. In another run a yield of 59% (98.7% purity by VPC) was realized with use of $CFCl_3$ as solvent: ^1H NMR δ 2.61 (br s, 2 H), 3.06 (br s, 2 H); ^{13}C NMR δ C1 44.15 (p, $J = 4.45$ Hz), C4 58.64 (dddd, $J_1 = 159.1$, $J_2 = 157.2$, $J_3 = 12.6$, $J_4 = 8.3$ Hz), C2 97.07 (tt, $J_1 = 25.2$, $J_2 = 7.8$ Hz); IR (neat solid) 800, 952, 1181 cm^{-1}; EIMS m/z 261 (0.4, M − Cl), 259 (0.8, M − Cl), 257 (0.3, M − Cl), 219 (0.7, M − Br), 217 (5.7, M − Br), 215 (12.8, M − Br), 213 (8.1, M − Br), 180 (13), 179 (15), 178 (9), 177 (11), 136 (63), 135 (31), 134 (100), 133 (40), 101 (18), 99 (59), 73 (41), 63 (40). Anal. Calcd for $C_5H_4Cl_2Br_2$: C, 20.37; H, 1.37; halogens as a Cl, 48.11 or as a Br, 108.42. Found: C, 20.32; H, 1.41; Cl, 48.07 or Br, 108.34.

Chlorination of Bicyclo[1.1.1]pentane-1,3-dicarboxylic Acid (4b). A cylindrical Pyrex reactor was fit with a Teflon chlorine inlet tube and an argon purge. The system was cooled by an internal water cooling coil and stirred magnetically. The temperature could be conveniently maintained by this arrangement at 35 °C under irradiation with a 275-W incandescent lamp at a distance of 5 cm. Into this system were placed 1.265 g of **4b**

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(12) Prepared by addition of bromine to **2**: Friedli, A. C.; Kaszynski, P.; Michl, J., unpublished results.

and 500 mL of trifluoroacetic acid. The solution was saturated with chlorine and irradiated for 21 h at which time NMR analysis showed a 98/2 ratio of **5b** to **4b**. Evaporation of the solvent at reduced pressure provided 1.950 g of beige solid, which failed to show a sharp melting point. No convenient method was found that would allow purification for analysis, and the entire sample was therefore converted to the diester **5d** by reaction with oxalyl chloride followed by methanol. The yield of **5d** was 67%, based on unreacted starting material at 71% conversion: mp 42.0–42.5 °C; ^{1}H NMR δ 2.48 (s, 2 H), 3.01 (s, 2 H), 3.81 (s, 6 H); ^{13}C NMR δ 49.60, 52.35, 52.80, 91.40, 164.86; IR (CS_2) 864, 1063, 1204, 1302, 1744 (C=O) cm^{-1}; EIMS *m/z* 224 (0.8, M − MeOH), 222 (4.6, M − MeOH), 220 (7.1, M − MeOH), 196 (2.7, M − COOMe), 194 (14.6, M − COOMe), 192 (23.3, M − COOMe), 99 (34), 73 (33), 59 (100). Anal. Calcd for $C_9H_{10}Cl_2O_4$: C, 42.70; H, 3.95; Cl, 28.04. Found: C, 42.76; H, 3.95; Cl, 27.99.

Chlorination of 1,3-Bis(chlorocarbonyl)bicyclo[1.1.1]pentane (4c). The chlorination of **4c** was conducted in the same manner as that of **4b**. The crude yield was nearly quantitative. Due to instability at VPC conditions no analytical sample could be obtained, although ^{1}H NMR analysis of crude material showed complete conversion to an 80/20 mixture of **5c** and an unidentified impurity with vinylic-type resonances. The crude mixture was therefore converted directly to the diester **5d** by the addition of absolute methanol and provided material identical with that described above.

Chlorination of Dimethyl Bicyclo[1.1.1]pentane-1,3-dicarboxylate (4d). Upon chlorination in the manner described above for **4a**, complete loss of the methyl groups was noted by ^{1}H NMR analysis. The crude mixture was hydrolyzed immediately, and the acidic product was isolated by removal of the solvent at reduced pressure. The diacid **5b** was isolated in 55% yield. The structure was established by esterification using oxalyl chloride followed by methanol, which gave material identical with **5d**.

Chlorination of Bicyclo[1.1.1]pentane-1-carboxylic Acid (4e). The acid **4e** (0.357 g) was chlorinated as above in carbon tetrachloride solvent saturated with chlorine. A white solid (0.488 g) was isolated and immediately converted to the methyl ester **5f** with oxalyl chloride followed by methanol. This produced 0.298 g of crude material, 44% of which was shown to be **5f**. The overall yield of **5f** isolated by VPC was 22%. No impurities were detected by VPC on SE-30. A second experiment on a 0.524-g scale led to a 35% yield of VPC-purified material: ^{1}H NMR δ 2.23 (br s, 2 H), 2.81 (br s, 2 H), 3.12 (s, 1 H), 3.81 (s, 3 H); ^{13}C NMR δ 46.07, 47.57, 52.04, 56.98, 92.00, 165.18; IR (neat film) 859, 1155, 1209, 1343, 1725, 1743 cm^{-1}; EIMS *m/z* 161 (7, M − Cl), 159 (20.5, M − Cl), 127 (10), 101 (30), 99 (81), 73 (35), 59 (100). Anal. Calcd for $C_7H_8Cl_2O_2$: C, 43.09; H, 4.10; Cl, 36.37. Found: C, 43.15; H, 4.08; Cl, 36.25.

Reduction of 5d with Tri-*n*-butyltin Hydride. Into a 25-mL round-bottom flask were placed 500 mg of **5d**, 690 mg of tri-*n*-butyltin hydride, and 15 mL of benzene, which was freshly distilled from sodium. A small amount of AIBN was added, and the mixture was refluxed under an argon atmosphere for 2 h. The solvent was evaporated, and the residue was dissolved in diethyl ether and an equal volume of excess aqueous potassium fluoride. Over a period of 2 days further portions of KF were added to the stirred solution. The layers were separated, and the resulting white powder was carefully sublimed (60 °C, 26 Torr) and recrystallized from hexanes at −78 °C to give 101 mg (23%) of an analytically pure sample: mp 40–40.5 °C; ^{1}H NMR δ 2.16 (dd, J_1 = 10 Hz, J_2 = 3 Hz, 1 H), 2.39 (dd, J_1 = 7 Hz, J_2 = 3 Hz, 1 H), 2.58 (d, J = 3 Hz, 1 H), 3.11 (dd, J_1 = 10 Hz, J_2 = 3 Hz, 1 H), 3.72 (s, 6 H), 4.51 (d, J = 7 Hz, 1 H); ^{13}C NMR δ 43.99, 48.16, 48.70, 52.08, 70.46, 166.77; IR (CS_2) 787, 813, 1207, 1299, 1742 cm^{-1}; EIMS *m/z* 183 (10, M − Cl), 160 (7.6, M − COOMe), 158 (23.4, M − COOMe), 100 (16), 95 (33), 65 (75), 59 (100). Anal. Calcd for $C_7H_8ClO_2$: C, 49.44; H, 5.07; Cl, 16.22. Found: C, 49.52; H, 5.09; Cl, 16.31.

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Registry No. **4a**, 82783-71-9; **4b**, 56842-95-6; **4c**, 115913-31-0; **4d**, 115913-32-1; **4e**, 22287-28-1; **5a**, 119327-49-0; **5b**, 119327-50-3; **5c**, 119327-51-4; **5d**, 115913-32-1; **5f**, 106813-54-1; **6**, 119327-52-5.

Electron-Transfer-Induced Rearrangements of Phenylated Tricyclo[4.2.0.0^{2,5}]octane and 1,5-Cyclooctadiene

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The hitherto unknown examples of cation radical isomerizations of tricyclo[4.2.0.0^{2,5}]octane and 1,5-cyclooctadiene derivatives are reported. Photoreaction of 1,2,5,6-tetraphenyltricyclo[4.2.0.0^{2,5}]octane (**1**) with 9,10-dicyanoanthracene (DCA) afforded 1,2,5,6-tetraphenyl-1,5-cyclooctadiene (**2**) and 1,2,5,6-tetraphenyltricyclo[3.3.0.0^{2,6}]octane (**3**). Upon a similar irradiation, **2** was converted to **3**. Likewise, other electron acceptors, such as tetracyanoethylene (TCNE), 1,2,4,5-tetracyanobenzene (TCNB), and tris(*p*-bromophenyl)aminium hexachloroantimonate, catalyzed these reactions. Quenching experiments using 1,2,4,5-tetramethoxybenzene (TMB) and naphthalene (NAP) supported the occurrence of cation radical isomerizations among **1**, **2**, and **3**.

Recently organic photoinduced electron-transfer chemistry has provided many interesting examples of ion radical reactions in solution that are comparable to redox reactions induced by electrochemical methods or chemical reagents.[4] Cyanoaromatics, quinones, and some cationic salts, such as pyrylium and iminium salts, are known to serve as electron-accepting sensitizers.[4] Single electron transfer

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