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Formation of Carbon–Carbon Double Bonds by the Reaction of Vicinal Dihalides with Sodium in Ammonia[1]

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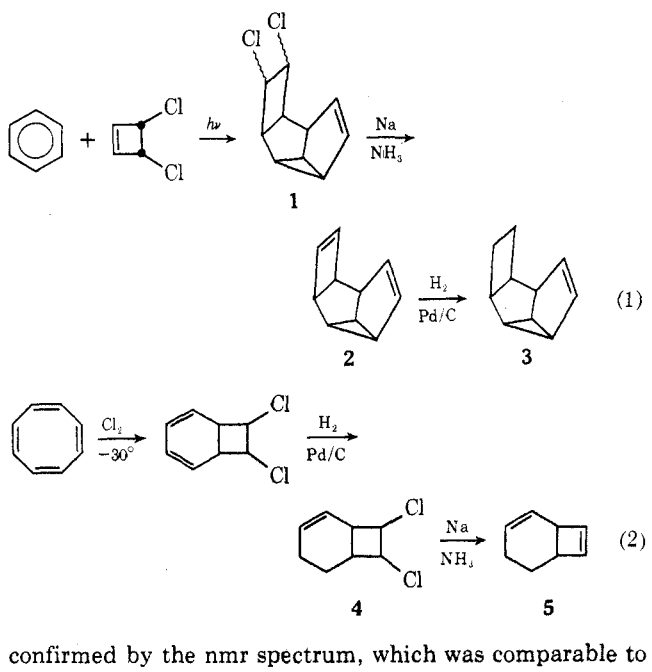
Recently we had need to transform vicinal dihalides to structures containing carbon–carbon double bonds.[3] One of the reagents we considered to be a prime candidate for effecting the dehalogenations was sodium in liquid ammonia. In surveying the literature, we found reports of such a reaction to be rare.[4-7] Much to our surprise, the treatises which deal with synthetic methods and reagents fail to illustrate,[8,9] or in most cases even reference, the reaction.[10-17] We have found the reaction of vicinal dihalides with sodium in ammonia to be very valuable in our work, and we believe that there should be more general awareness of the usefulness of this dehalogenation method.

Two synthetic sequences which illustrate our use of the method are shown by eq 1 and 2. When dichloride **1** was treated with excess sodium in ammonia for 1 hr, tetracyclo[5.3.0.$0^{2,10}$.$0^{3,6}$]deca-4,8-diene (**2**) was obtained in essentially quantitative yield. The structure **2** was established unequivocally by partial hydrogenation to known compound **3** of 3,6-endo configuration.[18] A similar dechlorination of **4** likewise gave a high conversion to bicyclo[4.2.0]octa-2,7-diene (**5**). The product structure was



confirmed by the nmr spectrum, which was comparable to those reported for **5**.[19,20]

The synthetic scope of the method was evaluated further with several simple vicinal dihalide systems. For example, treatment of 1,2-dichlorohexane, 1,2-dichlorocyclohexane, or 1,2-dichlorocyclooctane with sodium in ammonia for 1.5 hr gives >96% conversion to the corresponding alkene. Analogously, 1,2-dibromocyclohexane was transformed to cyclohexene (98%). When 1,2-dichlorocyclooctane was treated with sodium in ammonia for 10 min, a >95% conversion to cyclooctene was realized. We have not examined the question of the stereochemistry of the dehalogenations. However, an early mechanistic study indicates that the process is not stereospecific.[5,21]

It is often declared that dehalogenation of vicinal dihalides is of little synthetic value since the dihalides themselves are prepared from the alkenes.[12-14,16,23,24] Such statements are misleading in terms of synthetic usefulness. As illustrated by eq 1 and 2, dehalogenation can be an important part of a synthetic sequence which generates a structurally new double bond. Sodium in ammonia is an excellent reagent for this because the reaction is easily and rapidly completed, and the conversion to alkene is uniformly very high. For dehalogenation of **1** and **4** we found sodium in ammonia to be superior to the recently recommended arene–sodium reagents[22,25] in both convenience of procedure and in yield of isolated product.[3] It is clear that sodium in ammonia should be ranked among the best dehalogenating agents.[8-17,23-25]

Experimental Section[26]

4,5-Dichlorotetracyclo[5.3.0.$0^{2,10}$.$0^{3,6}$]dec-8-ene (1). The procedure used was a modification of the photochemical addition of benzene to cyclobutene.[18] A solution of 62.9 g (0.51 mol) of *cis*-3,4-dichlorocyclobutene[27] and 350 ml of benzene under a nitrogen atmosphere was irradiated (quartz) with a 450-W Hanovia medium-pressure mercury lamp for 20 hr. Progress of the reaction was followed by glpc (20% SE-30 on Chromosorb W, 15 ft × 0.125 in., programmed 70–130° at 6°/min). After this time the unreacted *cis*-3,4-dichlorocyclobutene and benzene were removed by vacuum distillation at 80° by gradually decreasing the pressure to 0.2 mm. This left a residue of 10.6 g of viscous brown oil. The distillate of reactants was again irradiated for 20 hr. A total of five of these cycles produced 46.8 g of crude photoadduct. Elution chromatography on 500 g of neutral alumina (pentane eluent) gave 19.1 g of **1** (31% based on the *cis*-3,4-dichlorocyclobutene consumed), mp 72.5–75°. An analytical sample was obtained by preparative glpc (15% FFAP on Chromosorb W, 10 ft × 0.375 in.): mp 77–78°; nmr (C_6D_6) δ 5.26 (d of d, 1 H), 5.02 (d of d, 1 H), 4.46 (apparent t, 1 H), 3.62 (br d, 1 H), 3.44 (apparent t, 1 H), 3.14 (m, 1 H), 2.68 (m, 1 H), 2.38 (apparent q, 1 H), 1.47 (apparent d of t, 1 H), 1.26 (apparent q, 1 H).

Anal. Calcd for $C_{10}H_{10}Cl_2$: C, 59.70; H, 5.01; Cl, 35.28. Found: C, 59.89; H, 4.88; Cl, 35.06.

Tetracyclo[5.3.0.$0^{2,10}$.$0^{3,6}$]deca-4,8-diene (2). A 4.0-g (0.174 g-atom) sample of freshly cut sodium (porcelain spatula) was added to 500 ml of dry ammonia which had been distilled from sodamide. To this stirred blue solution under a nitrogen atmosphere was added *via* a syringe 7.73 g (0.034 mol) of **1** in 75 ml of dry tetrahydrofuran. The reaction solution was stirred for 1 hr and then was quenched by cautiously adding ammonium chloride in small portions. Following this, 200 ml of ether and 800 ml of water were added. The aqueous mixture was extracted continuously with ether. The ether was removed from the dried extract ($MgSO_4$) by careful distillation, leaving 4.92 g (~98%) of **2**. A pure sample of **2** was obtained by preparative glpc (20% SE-30 on Chromosorb W, 10 ft × 0.375 in., 110°): ir (neat) 6.27 (C=C, cyclopentene),[28] 6.45 μ (C=C, cyclobutene);[28] nmr (C_6D_6) δ 6.18 (m, 1 H), 5.62 (d of d, 1 H), 5.50 (br d, 1 H), 5.00 (d of d, 1 H), 3.86 (m, 1 H), 3.70 (m, 1 H), 3.18 (apparent d of t, 1 H), 2.96 (apparent q, 1 H), 1.66 (apparent d of t, 1 H), 0.94 (apparent q, 1 H); high-resolution mass spectrum *m/e* 130.0790 (calcd for $C_{10}H_{10}$, *m/e* 130.0783).

Tetracyclo[5.3.0.$0^{2,10}$.$0^{3,6}$]dec-8-ene (3). A 40.1-mg (0.31 mmol) sample of **2** in 5 ml of ethyl acetate containing 30 mg of 5% palladium on carbon was partially reduced by the microhydrogenation procedure of Wiberg.[29] Stirring was stopped when

0.34 mmol of hydrogen (110%) had been absorbed (*ca.* 30 sec). Qualitative glpc analysis (15% FFAP on Chromosorb W, 8 ft × 0.125 in., 94°) showed one major and five minor products. The major product, which was collected by preparative glpc (20% SE-30 on Chromosorb W, 10 ft × 0.375 in., 110°), showed an nmr spectrum identical with that published for **3**:[18] nmr ($CDCl_3$) δ 5.80 (m, 2 H), 3.1 (br m, 3 H), 2.69 (br m, 1 H), 2.2–1.2 (series of m, 6 H).

7,8-Dichlorobicyclo[4.2.0]octa-2,4-diene. This dichloride was prepared in 54% yield from cyclooctatetraene and chlorine by the previously described method: bp 102–104° (2 mm);[30] nmr ($CDCl_3$) δ 5.2 (m, 4 H), 4.67 (t, 1 H), 4.45 (t, 1 H), 3.5 (br m, 1 H), 3.0 (br m, 1 H). On the basis of the nmr spectrum, our compound appears to be the *trans*-7,8-dichloro isomer.[31]

7,8-Dichlorobicyclo[4.2.0]oct-2-ene (4). A solution of 9.6 g (0.055 mol) of 7,8-dichlorobicyclo[4.2.0]octa-2,4-diene in 150 ml of a 50:50 methanol–ethyl acetate mixture and 50 mg of 5% palladium on carbon was partially reduced in a Parr shaker. The shaker was stopped when 0.055 mol of hydrogen had been absorbed (*ca.* 5 min). The solution was filtered, the solvent was removed, and the residue was distilled to give 6.8 g (73%) of **4**, bp 115–116° (30 mm). An analytical sample was obtained by preparative glpc (20% SE-30 on Chromosorb W, 20 ft × 0.25 in.): nmr ($CDCl_3$) δ 5.94 (m, 2 H), 4.7–3.9 (9-line m, 2 H), 3.4–1.3 (series of m, 6 H).

Anal. Calcd for $C_8H_{10}Cl_2$: C, 54.29; H, 5.65; Cl, 40.06. Found: C, 54.48; H, 5.85; Cl, 39.89.

Bicyclo[4.2.0]octa-2,7-diene (5). A 0.85-g (0.037 g-atom) sample of freshly cut sodium was added to 200 ml of ammonia. To this stirred solution under a nitrogen atmosphere was added 1.5 g (0.008 mol) of **4** in 100 ml of dry ether. The reaction solution was stirred for 1.5 hr and then was quenched with ammonium chloride. After this, 400 ml of water was added and the mixture was continuously extracted with ether. The ether extract was dried ($MgSO_4$) and the solvent was removed by careful distillation, leaving 0.74 g (83%) of **5** which was >97% pure by glpc (20% SE-30 on Chromosorb W, 10 ft × 0.125 in., 70°): nmr (C_6D_6) δ 6.08 (d, 1 H), 5.9 (m, 3 H), 3.2 (br m, 2 H), 2.3–1.2 (series of m, 4 H).[19,20]

Reaction Scope Studies. The vicinal dihalides 1,2-dichlorohexane, 1,2-dichlorocyclohexane, 1,2-dichlorocyclooctane, and 1,2-dibromocyclooctane were prepared in the usual way by addition of halogen to the corresponding alkene at low temperature.[32] In all cases the dihalides were purified and had physical and spectral properties in agreement with the indicated structures. Dehalogenations were carried out by the procedure given above for the formation of **5**. The conversion of dihalide to alkene was quantitatively measured by glpc using appropriate *n*-alkane internal standards and detector response factors obtained from standardized solutions.

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Registry No.—1, 41326-65-2; **2**, 50987-22-9; **3**, 31750-01-3; **4**, 50987-23-0; **5**, 3786-98-9; benzene, 71-43-2; *cis*-3,4-dichlorocyclobutene, 2957-95-1; cyclooctatetraene, 629-20-9; *trans*-7,8-dichlorobicyclo[4.2.0]octa-2,4-diene, 34719-15-8.

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Cleavage of Protecting Groups with Boron Tribromide

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Boron halides have been used for the cleavage of methyl ethers,[1,2] benzhydryl esters,[3] *tert*-butyloxycarbonyl amine protecting groups,[4,5] and hindered esters.[6] A recent report[7] that benzyloxycarbonyl amine protecting groups can be removed quantitatively with boron tribromide prompts us to report on our observations using this reagent in peptide chemistry. We observed that, in addition to the removal of *N*-*tert*-butyloxycarbonyl and *N*-benzyloxycarbonyl protecting groups, boron tribromide in methylene chloride gave rapid conversion of methyl, ethyl, *tert*-butyl, benzyl, and *p*-nitrobenzyl esters to their corresponding acids. The alkaline conditions usually employed to hydrolyze methyl and ethyl esters enhances the chances of racemization. The sensitivity of the *N*-benzyloxycarbonyl group[8] and the seryl peptide bond[9-11] to strongly basic conditions also render that method unattractive for general usage.

The products after boron tribromide treatment were isolated by ion-exchange chromatography, found to be analytically pure, and were obtained in yields of 60–90% after crystallization. Optical purity of the products was ascertained to be >99.9% using the procedure of Manning and Moore.[12] Table I summarizes the results obtained for the deprotection of a variety of substrates with boron tribromide. Many of the widely used amino acid side chain protecting groups[13] [Ser(Bzl), Tyr(Bzl), Tyr(Cl_2Bzl), Thr(Bu^t), Glu(OMe), Glu(OEt), Glu(OBzl), Asp(OBu^t), and Lys(Z)] were also removed by boron tribromide, whereas certain other groups [Arg(Tos), Cys(Bzl), and His(im-Bzl)] were unaffected. Although Arg(Tos) was not