sorb P, 8 ft or 10% SE-30 on 60–80 Chromosorb P, silanized with dimethyldichlorosilane, 9 ft) and the quotients of the peak areas from four or more injections were observed as apparent values of the rate constant quotient, k_1/k_2. A detector sensitivity factor was determined with a standard mixture. Each observed rate constant quotient was corrected for detector sensitivity and the corrected values were averaged for each competition.

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Registry No.—**1a,** 1120-56-5; **1b,** 1528-30-9; **1c,** 1192-37-6; **2a,** 54788-75-9; **2b,** 54788-76-0; **2c,** 15997-13-4; dichlorocarbene, 1605-72-7; cyclohexanone, 108-94-1; methyltriphenylphosphonium bromide, 1779-49-3; ethyl trichloroacetate, 515-84-4; phenyl(bromodichloromethyl)mercury, 3294-58-4.

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Aspects of Direct Bridgehead Methylation

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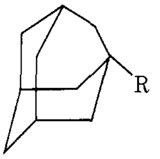
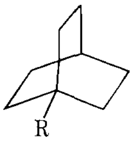
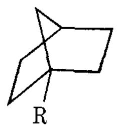
We recently required a method of synthesizing the hydrocarbons (I–III, R = CH_3) via direct quaternization of the readily available tertiary bromides. One attractive route appeared to be coupling of the appropriate halide with Grignard reagents. Despite several, largely unsuccessful, attempts[1,2] at direct alkylation of bridgehead halides,



I



II

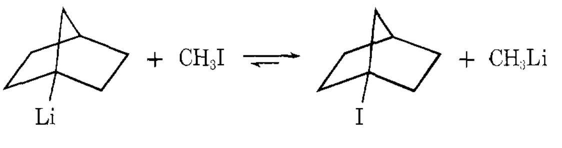


III

Schleyer and coworkers[3] recently described the preparation of 1-methyladamantane in high yield by treatment of 1-bromoadamantane with methylmagnesium bromide (molar ratio 1:3) in ether contained in a pressure bottle heated to 100°. These workers further reported that methylmagnesium iodide can also be used, and suggested that the method may be applicable to related alicyclic compounds.

We repeated the experiments outlined by von Schleyer's group and similarly obtained the desired product (I, R = CH_3) in high yield (Table I). However, we found that use of methylmagnesium iodide under the same conditions gave a 3:1 mixture of 1-methyladamantane and adamantane, which are difficult to separate by VPC but which could easily be detected and analyzed by NMR (^{13}C and proton). In an attempt to apply this method to the other bridgehead bromides (II and III, R = Br) we found that longer reaction times were necessary in order to convert bicyclooctyl bromide into the methyl derivative (II, R = CH_3). Use of methylmagnesium iodide led to extensive reduction of the halide and afforded the hydrocarbons (II, R = CH_3 and R = H) in essentially equal proportions. Accordingly, this route to 1-methylbicyclo[2.2.2]octane is very attractive if methylmagnesium bromide is used as the coupling reagent.[4] As indicated in Table I, prolonged heating of 1-bromobicyclo[2.2.1]heptane in ether at 100° gave only a trace (5%) of the coupled product (III, R = CH_3), the remainder of the product being starting material. Obviously, under these conditions the coupling reaction is extremely slow, and the Grignard reagent preferentially reacts with the solvent (as confirmed by conducting a "blank" experiment).

As a possible alternative to the synthesis of 1-methylbicyclo[2.2.1]heptane, the lithio derivative (III, R = Li) was heated with methyl iodide in ether (and also hexane). The product was found to consist entirely of 1-iodobicyclo[2.2.1]heptane arising from simple halogen–metal exchange (eq 1) in which the position of equilibrium lies almost completely to the right. Similar treatment of 1-bicyclo[2.2.1]heptylmagnesium halide, whose preparation has recently been successfully performed[5] and which was not expected to undergo exchange, yielded only bicyclo[2.2.1]heptane.



(1)

The use of trimethylaluminum in the quaternization of tertiary acyclic halides has been shown[6] to be widely applicable and proceeds without the intervention to any appreciable extent of unwanted side reactions. In any case, although coupling of this kind involving bridgehead halides has not previously been reported, it seemed reasonable that in the systems under examination here, competing reactions, such as elimination, would be highly unlikely. The solvent found to be most appropriate in the study[7] of the acyclic halides was methyl chloride, in which coupling occurs rapidly at very low temperatures.

Accordingly, we treated the bromides (I–III, R = Br)

Table I
Coupling Reactions of the Bridgehead Bromides

Compd	Reagent	Molar ratio reagent/compd	Temp, °C	Reaction time, hr	Product, %		
					Coupling	Reduction	Halide
I (R = Br)	CH_3MgBr^a	3.0	100	1	76		
I (R = Br)	CH_3MgI^a	1.5	95	1	69	22	9[c]
I (R = Br)	CH_3MgI^a	1.5	110	3	72	28	
I (R = Br)	$(CH_3)_3Al^b$	1.0	−70	0.5	82	8	
II (R = Br)	CH_3MgBr^a	3.0	95	18	82		18[d]
II (R = Br)	CH_3MgI^a	2.0	110	18	46	44	8[e]
II (R = Br)	$(CH_3)_3Al^b$	1.0	−70	0.5	98	≤2	
III(R = Br)	CH_3MgBr^a	3.0	110	18	≤5		95[f]
III (R = Br)	$(CH_3)_3Al^b$	1.0	100	24			100[f]

[a] In ether solution. [b] In CH_2Cl_2 solution. [c] 1-Iodoadamantane. [d] 1-Bromobicyclo[2.2.2]octane. [e] 1-Iodobicyclo[2.2.2]octane. [f] 1-Bromobicyclo[2.2.1]heptane.

with trimethylaluminum in methylene chloride. The results are summarized in Table I.

Both 1-bromoadamantane and 1-bromobicyclo[2.2.2]octane reacted rapidly, even at −70°, and at that temperature methylation was complete in 15 min. The products were obtained in excellent yield, and although 1-methyladamantane was contaminated with a small quantity of reduction product, 1-methylbicyclo[2.2.2]octane was obtained almost completely pure. Unfortunately, 1-bromobicyclo[2.2.1]heptane again proved to be inert and was unaffected by trimethylaluminum even when heated at 100° for 24 hr.

Experimental Section

1-Bromoadamantane, purchased from Koch-Light Laboratories Ltd., was recrystallized and sublimed. 1-Bromobicyclo[2.2.2]octane was synthesised from 2-methoxybuta-1,3-diene,[8] following the route described by Morita and coworkers.[9] 1-Bromobicyclo[2.2.1]heptane was prepared from 1-carboxybicycloheptane[10] using dibromomethane as solvent in the Cristol–Firth modification[11] of the Hunsdiecker reaction. All reactions described below were performed under an atmosphere of nitrogen.

Methylation with Grignard Reagents. 1-Bromoadamantane. The procedure adopted was that outlined by von Schleyer and coworkers,[3] except that, in order to effect complete consumption of substrate, it was found necessary to heat the reaction for longer periods than specified (Table I). The identity of the products was established by comparison of their spectral properties with those of authentic specimens.

1-Bromobicyclo[2.2.2]octane. The reactions were performed as for 1-bromoadamantane, except that the period of heating was extended to 18 hr. The results are displayed in Table I. VPC analysis (10 ft × 0.125 in. 10% QF-1 at 40°) cleanly separated 1-methylbicyclo[2.2.2]octane and bicyclo[2.2.2]octane, whose physical properties were consistent with those reported.

1-Bromobicyclo[2.2.1]heptane. A. A 3 *M* solution of methylmagnesium bromide in ether (2.8 ml) and 1-bromobicyclo-[2.2.1]heptane (0.5 g) were heated at 110° for 18 hr. After work-up (no residual Grignard reagent detected) the product was analyzed by VPC–mass spectrometry and shown to consist of 5% of 1-methylbicycloheptane (*m/e* 110) and 95% of 1-bromobicycloheptane. When the bromide (1.0 g) in cyclohexane (10 ml) was converted into the lithio derivative[12] and treated with methyl iodide (0.8 g) in ether (10 ml) for 2 hr at 35°, the product isolated after work-up consisted solely of 1-iodobicyclo[2.2.1]heptane (VPC and spectral analysis).

B. Following the reported procedure[5] for the preparation of the 1-bicyclo[2.2.1]heptyl Grignard reagent, anhydrous magnesium chloride (1.71 g, 0.018 mol), freshly cut potassium (1.33 g, 0.034 g-atom), predried potassium iodide (2.82 g, 0.017 mol), and anhydrous THF (40 ml) were placed in a flame-dried 100-ml three-necked flask equipped with a magnetic follower, condenser, and septum, and protected under a nitrogen atmosphere. The stirred solution was boiled under reflux for 3 hr, after which 1-bromobicyclo[2.2.1]heptane (1.75 g, 0.01 mol) in THF (3 ml) was injected and the mixture was heated at 67° for 6 hr, when VPC analysis of an aliquot quenched with dilute HCl indicated that all the bromide had been consumed. Methyl iodide (2.84 g, 0.02 mol) was added to the cooled mixture, which was stirred for 3 hr at room temperature. No alkylation was evident (VPC). The mixture was heated at 65° for 5 hr, cooled to 0°, and treated with gaseous CO_2. After the usual work-up, the product was isolated and shown (VPC–mass spectrometry) to be bicyclo[2.2.1]heptane. Neither the 1-methyl nor the 1-carboxy derivative was detected. Similar results were obtained when the reaction mixture was heated in a pressure bottle.

Methylation with Trimethylaluminum. General Procedure.[13] Trimethylaluminum (1.1 g, 0.015 mol) was added to dry methylene chloride (10 ml) in a 100-ml two-necked flask equipped with a stirring bar, condenser, and septum, and the stirred solution was maintained at −70° under a nitrogen atmosphere. The bridghead bromide (0.015 mol) in methylene chloride (5 ml) was injected and the mixture was allowed to warm to 0° over 0.5 hr. After excess trimethylaluminum had been destroyed by careful addition of methanol, the mixture was washed with 5% HCl (3 × 10 ml) and water (2 × 10 ml), and then dried ($MgSO_4$). Solvent was removed through an 3-in. column packed with helices and the residue was analyzed by NMR and VPC–mass spectrometry. The products were purified by sublimation and recrystallization.

Both 1-bromoadamantane and 1-bromobicyclo[2.2.2]octane reacted rapidly under the conditions specified above and the products obtained are shown in Table I. A small-scale run (sealed NMR tube) monitored by NMR indicated that reaction was complete in 15 min at −70°.

1-Bromobicyclo[2.2.1]heptane was unaffected under these conditions or when the reaction mixture was heated in a bomb at 100° for 24 hr. At the higher temperature the only noticeable reaction was that between trimethylaluminum and the solvent.

Registry No.—I (R = Br), 768-90-1; II (R = Br), 7697-09-8; III (R = Br), 13474-70-9; methyl bromide, 74-83-9; methyl iodide, 74-88-4; trimethylaluminum, 75-24-1.

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