[Contribution from the Department of Chemistry, Fresno State College]

3-SUBSTITUTED CYCLOHEXENES: EFFECT OF REVERSING THE MODE OF ADDITION OF THE REAGENTS IN THE ALKYLATION OF 3-BROMOCYCLOHEXENE

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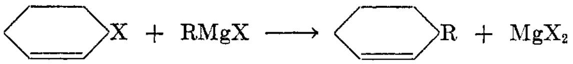
During the course of some work directed toward the synthesis of 3-alkyl and 3-aryl cyclohexenes we were led to the attractive method of Berlande (1) in which a 3-halocyclohexene is added to an appropriate Grignard reagent.



Individual procedures are not given for the compounds prepared by this method but the yields are said to be of the order of 70%. Although there can be no doubt as to the authenticity of the reported products, we have been unable after repeated attempts to approach these yields by the method described by Berlande.

It was in an attempt to obtain satisfactory yields of 3-substituted cyclohexenes that the present study was made.

Lespieau and Bourguel (2c, d) have observed in their report of the reaction of 2,3-dibromopropene with cyclohexylmagnesium bromide that the mode of addition of the reactants is of the utmost importance; the addition of the Grignard reagent to the halide resulted in higher yields than when the halide was added to the Grignard reagent.

We have now established that in at least four cases the yield of 3-alkyl (aryl) cyclohexene is markedly increased when the Grignard reagent is added to 3-bromocyclohexene at reflux temperature (the reverse of the procedure described by Berlande). Both modes of addition have also been carried out using the corresponding organolithium reagents; in these runs reversal of the addition has not consistently improved the yield. Check runs were made in every case; the results are summarized in Table I.

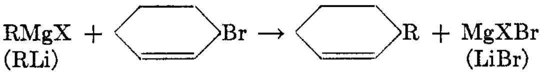
As shown in the first (Grignard) column, when the 3-bromocyclohexene was slowly added to the vigorously stirred, cold Grignard reagent only very low yields of 3-substitution products could be obtained and in the case of the isopropylmagnesium bromide none of the desired product was isolated.

Variations in the time of addition of the 3-bromocyclohexene to the cold isopropylmagnesium bromide or a period of reflux after addition was complete, failed to yield any detectable amount of the desired 3-isopropylcyclohexene; instead the product consisted mainly of unreacted 3-bromocyclohexene and 3,3′-bicyclohexenyl.

Since most of Berlande's work was done with 3-chlorocyclohexene instead of 3-bromocyclohexene, it was thought at first that this might be the source of our difficulty, although it might be expected that the bromo derivative should

TABLE I

YIELDS[a] OF 3-SUBSTITUTED CYCLOHEXENES FROM THE REACTIONS:



R	GRIGNARD RUNS			ORGANOLITHIUM RUNS	
	Halide to RMgX at 0°	Halide to RMgX at Reflux	RMgX to Halide at Reflux	Halide to RLi at Reflux	RLi to Halide at Reflux
n-C_4H_9—[c]	10, 11	25, 22	68, 65	52, 51	66, 70
i-C_3H_7—[b, c]	0, 0	27, 31	46, 45, 40	52, 56, 49	53, 50
tert-C_4H_9—[b]	17, 19	26,[d] 23[e]	29, 28	66,* 69	67,[d] 66[e]
p-$CH_3OC_6H_4$—	28, 27	45, 42	59, 64	57, 56	71, 71

[a] All yields have been converted to the nearest whole percentage and are based on the initial amount of 3-bromocyclohexene. [b]The isopropyl- and *tert*-butyl-lithium reagents were prepared in purified petroleum ether, b.p. 35–45° (see ref. 5); the 3-bromocyclohexene was diluted with anhydrous diethyl ether in all but one case, the 66*% *tert*-butyllithium run, in which the halide was diluted with petroleum ether, making this the only run carried out in the complete absence of diethyl ether. No appreciable effect on the ratio of products was observed. [c]Previously prepared by Berlande (1) using the Grignard reagent. [d]Wire stirrer. [e]Glass stirrer.

be the more reactive of the two compounds. However, when 3-chlorocyclohexene was added to isopropylmagnesium bromide at 0° none of the desired product was obtained and as much as 67% of unreacted 3-chlorocyclohexene could be recovered.

When 3-bromocyclohexene was added over a one-hour period to the Grignard reagent at reflux temperature instead of 0° and maintained at that temperature for an additional two hours, an appreciable increase in yield of the desired 3-substitution product was observed (Table I, Column 2). A reversal of the mode of addition at reflux temperature, with other conditions unchanged, resulted in the further improvement shown in Column 3. The procedure used in these runs and also in the lithium runs shown in Column 5 was patterned after the classical method of Lespieau and Bourguel (2a).

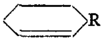
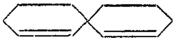
The use of the organolithium reagent in place of the Grignard reagent resulted in improved yields in nearly every case. Reversal of the mode of addition of the lithium reagent seemed to have little effect in the isopropyl and *tert*-butyl runs; the difference was quite marked, however, in the *n*-butyl and *p*-methoxyphenyl reactions. It would appear from these results that the Lespieau and Bourguel procedure using an organolithium reagent might be the preferred method for compounds of this type.

Although the isopropyl and *n*-butyl compounds have been previously reported by Berlande and the *tert*-butyl compound has been prepared by other methods, no previous report has been found of 3-(*p*-methoxphenyl)cyclohexene; the bond isomer, 1-(*p*-methoxyphenyl)cyclohexene has, however, been reported (3).

The complexity of the over-all reaction was reflected in the by-products

TABLE II

A COMPARISON OF YIELDS OF PRODUCTS ISOLATED IN TYPICAL GRIGNARD RUNS WITH 3-BROMOCYCLOHEXENE

R	MODE OF ADDITION[c]	RECOVERED HALIDE (3-Bromocyclohexene)			OTHER PRODUCTS[a]
n-C_4H_9—	Halide to RMgX	Trace	25	24	8 (RR)
	RMgX to Halide	Trace	68	12	6 (RR)
i-C_3H_7—	Halide to RMgX	Trace	27	54	None isolated
	RMgX to Halide	27	46	3	None isolated
i-C_3H_7—	Halide to RMgX at 0°	41	0	43	None isolated
	Halide[b] to RMgX at 0°	67[b]	0	20	None isolated
tert-C_4H_9—	Halide to RMgX	Trace	26	54	6 (RR)
	RMgX to Halide	Trace	29	33	1 (RR)
p-$CH_3OC_6H_4$—	Halide to RMgX	Trace	45	None isolated	36 (RH)[d]
	RMgX to Halide	Trace	64	None isolated	30 (RH)[d]

[a] A high-boiling residue of 0.5–2 g., which was not characterized, remained in most runs. [b] 3-Chlorocyclohexene was used instead of 3-bromocyclohexene. [c] Unless indicated otherwise the addition was made at reflux temperature. [d] Bianisole was also isolated in amounts equivalent to 15–20% of the *p*-bromoanisole used to prepare the Grignard reagent. The yields of *p*-methoxyphenylmagnesium bromide were usually 70–80%, and it was possible to isolate bianisole from the solution containing the reagent.

which were isolated. Table II lists the compounds obtained in representative Grignard runs.

In general, an increased yield of 3-substituted cyclohexene resulted in a decreased yield of the coupling product, 3,3′-bicyclohexenyl. The relatively small changes in the *n*-octane and bianisole fractions in the *n*-butyl and *p*-methoxyphenyl runs was probably due to the formation of these products, at least to a large degree, during the original preparation of the Grignard reagents. In general, no attempt was made to detect and characterize gaseous products. Most reactions showed evidence of unreacted organomagnesium or lithium reagent at the end of the reaction period.

The same products were usually obtained using the organolithium reagents although the bicyclohexenyl yields dropped to 5% or less. The recovered 3-bromocyclohexene ranged from trace amounts to 15%.

While it is unwise to propose a mechanism based upon the data so far obtained it would seem that the alkylation (or arylation) reaction proceeds best when the 3-bromocyclohexene is maintained in large excess. When the reverse condition exists, *i.e.* when the Grignard is in excess, the opposing coupling reaction resulting in bicyclohexenyl is favored at the expense of the alkylation.

It is interesting to note that the improvement in yield observed upon reversing the mode of addition in the case of the Grignard runs was in the order primary > secondary > tertiary while the *p*-methoxyphenylcyclohexene yield increase was comparable to the isopropylcyclohexene increase.

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EXPERIMENTAL

Reagents. The 3-bromocyclohexene and 3-chlorocyclohexene were prepared from a fourfold excess of cyclohexene and the appropriate N-halo succinimide, using a slight modification of the method described by Ziegler (4). Enough of the bromo derivative was prepared at one time for two or three runs; the freshly distilled halide, b.p. 38–40° at 0.3 mm., n_D^{20} 1.5290, was stored under nitrogen in a glass stoppered flask and kept in the refrigerator. The compound was redistilled when a light amber color developed.

All of the Grignard reagents were prepared from the bromides with the exception of the *tert*-butyl reagent in which case *tert*-butyl chloride was used. The reagents were prepared under an atmosphere of dry nitrogen, filtered and standardized before use.

The lithium reagents were prepared directly from the halides — *n*-butyl bromide, *p*-methoxyphenyl bromide, isopropyl chloride, and *tert*-butyl chloride — using finely cut lithium ribbon in a dry nitrogen atmosphere. Diethyl ether was the solvent for the *n*-butyl and *p*-methoxyphenyl reagents and petroleum ether (b.p. 35–45°) was the solvent for the isopropyl and *tert*-butyl reagents (5). The reagents were filtered and standardized before use.

Apparatus. A standard three-necked, glass-jointed flask, fitted with a condenser, stirrer, and dropping-funnel was used for each reaction. The reaction product was usually distilled using a 25-cm. modified Widmer column at appropriate pressures ranging from 0.3 mm. to 20 mm. In the case of the *p*-methoxyphenyl runs (both Grignard and lithium) it was desirable to first effect a rough separation from the higher-boiling constituents using a two-bulb, low side-arm apparatus; this was followed by fractionation using the column. In every case, redistillation was continued until the refractive index approached that of the pure analytical sample.

The same rapid rate of stirring was maintained in each run and the same Hershberg type stirrer was used throughout the work. In two of the *tert*-butyl check runs (see Table I) an all glass stirrer was substituted for the wire stirrer without a significant effect on the yields.

The following detailed procedures are representative of those used to prepare the other cyclohexene derivatives.

3-(p-Methoxyphenyl)cyclohexene. Procedure A. Addition of the halide to the Grignard reagent at 0°. A solution of 13.4 g. (0.085 mole) of 3-bromocyclohexene in 25 cc. of dry ether was added at the rate of 75–85 drops per minute to 90 cc. of 0.998 *N* *p*-methoxyphenylmagnesium bromide. The reaction mixture was vigorously stirred and maintained at 0° during the addition, after which it was allowed to slowly reach room temperature. Dilute hydrochloric acid solution was slowly added and the ether layer was separated. After washing the ether solution with 5% sodium bicarbonate, and then with water, it was dried over sodium sulfate. Fractional distillation of the liquid which remained after removal of the ether gave 1.9 g. (20%) of anisole, b.p. 65–70° at 20 mm., n_D^{25} 1.5090; 4.0 g. (30%) of 3-bromocyclohexene, b.p. 50–60° at 0.6 mm., n_D^{25} 1.5320; 4.4 g. (28%) of *p*-methoxyphenylcyclohexene, b.p. 90–100° at 0.7 mm., n_D^{25} 1.5500; and 4 g. of residue from which some bianisole, m.p. 168–170° was crystallized.

Procedure B. Addition of the halide to the Grignard reagent at reflux temperature. When 10.3 g. (0.065 mole) of 3-bromocyclohexene in 25 cc. of dry ether was added dropwise to an equivalent amount of the Grignard reagent at reflux temperature instead of 0°, followed by two additional hours of refluxing, the following products were isolated from the resulting reaction mixture: 2.8 g. (36%) of anisole, a trace of 3-bromocyclohexene, 5.5 g. (45%) of 3-(*p*-methoxyphenyl)cyclohexene, b.p. 90–100° at 0.7 mm., n_D^{26} 1.5460, and 2 g. of residue.

Procedure C. Addition of the Grignard reagent to the halide at reflux temperature. When 100 cc. of 1 *N* *p*-methoxyphenylmagnesium bromide was added dropwise to a vigorously stirred solution of 16.3 g. (0.101 mole) of 3-bromocyclohexene in 25 cc. of dry ether at reflux temperature and the reaction mixture was refluxed for an additional two hours, fractional distillation of the product gave 3.3 g. (30%) of anisole and 12.1 g. (64%) of 3-(*p*-methoxyphenyl)cyclohexene. A high-boiling residue (3 g.) remained from which some bianisole was isolated.

The lithium runs were carried out as described under B and C above. When the lithium reagent was added to the halide the yield rose to 71%.

An analytical sample of 3-(*p*-methoxyphenyl)cyclohexene was prepared by refluxing the fractionated product with sodium and then redistilling the product at reduced pressure (b.p. 160–161° at 22 mm.) until the refractive index remained constant; n_D^{29} 1.5445; d_4^{29} 1.0169.

Anal. Calc'd for $C_{13}H_{16}O$: C, 82.9; H, 8.6.
Found: C, 83.0; H, 8.6.

The *2,4-dinitrobenzenesulfenyl chloride* addition product prepared by the method described by Kharasch (6) crystallized in the form of fine yellow needles from benzene, m.p. 181.5–182.5°.

Anal. Calc'd for $C_{19}H_{19}ClN_2O_5S$: C, 53.8; H, 4.8.
Found: C, 53.9; H, 4.9.

Attempts to prepare the 2,4-dinitrobenzenesulfenyl chloride addition products of the other cyclohexene derivatives (Table I) met with only partial success. Although reaction occurred readily, the products (with the exception of that above) were mixtures of the two possible addition products.

Analytical samples of the other principal cyclohexene derivatives were also prepared by first refluxing the hydrocarbon with sodium followed by distillation. The by-products were identified by their physical constants.

3-n-Butylcyclohexene. The pure compound boiled at 76–78° (23 mm.); n_D^{26} 1.4529; d_4^{26} 0.8156. Reported (1) b.p. 178° (760 mm.); n^{25} 1.4530; d^{25} 0.830.

Anal. Calc'd for $C_{10}H_{18}$: C, 86.9; H, 13.1; M_R 45.71.
Found: C, 86.8; H, 13.0; M_R 45.80.

3-tert-Butylcyclohexene. The analytical sample boiled at 66–67° (23 mm.); n_D^{26} 1.4569; d_4^{26} 0.8280.

Anal. Calc'd for $C_{10}H_{18}$: C, 86.9; H, 13.1; M_R 45.71.
Found: C, 86.7; H, 13.0; M_R 45.46.

3-Isopropylcyclohexene. The boiling point of the pure compound was 65–66° at 30 mm. (150° at 751 mm.); n_D^{25} 1.4523; d_4^{25} 0.8216. Reported (1) b.p. 150° (760 mm.); n^{25} 1.4510; d^{25} 0.820.

Anal. Calc'd for C_9H_{16}: C, 87.0; H, 13.0; M_R 41.10.
Found: C, 86.6; H, 12.8; M_R 40.78.

SUMMARY

Significantly better yields of 3-substituted cyclohexenes were obtained in four cases in which the Grignard reagent was added at reflux to 3-bromocyclohexene than when the mode of addition was reversed. The effect was most pronounced when the Grignard was primary and diminished with the secondary and tertiary reagents. Corresponding runs using the lithium reagents gave improved yields; however, the effect of reversing the mode of addition of the reagents was not as marked as it was in the Grignard runs.

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REFERENCES

(1) BERLANDE, *Bull. soc. chim.*, **9**, 644 (1942).

(2) (a) LESPIEAU AND BOURGUEL, *Org. Syntheses*, Coll. Vol. I, 2nd Ed., 186 (1941); (*b*) LESPIEAU, *Bull. soc. chim.*, [4], **29**, 528 (1921); (c) BOURGUEL, *Ann. chim.*, [10], **3**, 191, 325 (1925); (d) JACOBS, *Org. Reactions*, **5**, 24 (1949).

(3) (a) MENTZER AND XUONG, *Bull. soc. chim. France*, 885 (1947); (b) BRAUN, ANTON, HAENSEL, AND WERNER, *Ann.*, **472**, 1 (1929).

(4) ZIEGLER, SPÄTH, SCHAAF, SCHUMANN, AND WINKELMANN, *Ann.*, **551**, 80 (1942).

(5) GILMAN, MOORE, AND BAINE, *J. Am. Chem. Soc.*, **63**, 2479 (1941).

(6) KHARASCH AND BUESS, *J. Am. Chem. Soc.*, **71**, 2724 (1949).