Yields of Grignard Reagents in 4-Methyl-1,3-dioxane

By Robert B. Carlin[1] and L. Oliver Smith, Jr.

Since some of the components of solutions of Grignard reagents in ethyl ether are precipitated by 1,4-dioxane,[2] attempts were made to discover whether certain related compounds exhibit a similar precipitating action. Investigation disclosed that, while 1,3-dioxane has very much the same action on ether solutions of Grignard reagents as does 1,4-dioxane,[3] 4-methyl-1,3-dioxane not only fails to cause precipitation when added to solutions of Grignard reagents, but also acts as a solvent in which the Grignard reaction can be carried out. Inasmuch as 4-methyl-1,3-dioxane, b. p. 114°, is prepared easily, a number of Grignard reactions were carried out in this solvent, and the yields of Grignard reagents were determined. The results of these determinations, shown in Table I, indicate that 4-methyl-1,3-dioxane is as effective a solvent for the Grignard reaction as diethyl ether,[4-6] di-n-butyl ether[7] and ethyl orthosilicate.[8]

Since the titration method used to determine the quantity of reagent formed during a Grignard reaction does not actually prove the presence of a particular reagent, the identities of most of the Grignard reagents formed in the course of this work were established by treating them with phenyl isocyanate and isolating the corresponding anilides.

Experimental

4-Methyl-1,3-dioxane.—A stirred mixture of 500 g. of 1,3-butanediol (Carbide and Carbon Chemicals Corp.), 175 g. of paraformaldehyde and 10 ml. of concentrated sulfuric acid was heated to boiling, and most of the mixture was distilled. The dark residue was poured onto ice and salt, and the upper layer was washed with aqueous sodium bicarbonate, separated, distilled and the distillate combined with the main distillate. The aqueous layer of the latter was saturated with salt and then separated from the crude 4-methyl-1,3-dioxane, which was dried over potassium hydroxide and then distilled from sodium: b. p. 113.3–113.8° (740 mm.)[9]; d^{20}_4 0.9710; n^{20}D 1.4160; yield 503 g. (89%).

Before use as a solvent in quantitative studies of the Grignard reaction, 4-methyl-1,3-dioxane, prepared as described above, was further purified by preparing phenylmagnesium bromide in it. The pure solvent was recovered from solutions of this and all other Grignard reagents obtained in the course of this work by hydrolyzing the latter,

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(2) Schlenk and Schlenk, *Ber.*, **62**, 920 (1929).

(3) M. L. Hoefle, B.S. Thesis, University of Illinois, 1943.

(4) Gilman and McCracken, This Journal, **45**, 2462 (1923).

(5) Gilman and McCracken, *Rec. trav. chim.*, **46**, 463 (1927).

(6) Gzemski and Kilpatrick, *J. Org. Chem.*, **5**, 264 (1940).

(7) Marvel, Blomquist and Vaughn, This Journal, **50**, 2810 (1928).

(8) Andrianov and Gribanova, *J. Gen. Chem.*, **8**, 552 (1938); (*C. A.*, **32**, 7892 (1938)).

(9) Leutner, *Monatsh.*, **66**, 230 (1935), reported the b. p. 113–114° (745 mm.).

steam distilling, and separating the 4-methyl-1,3-dioxane, which was dried over potassium hydroxide and fractionally distilled from sodium.

Preparations of Grignard reagents in 4-methyl-1,3-dioxane were carried out and yields determined by means of a procedure essentially the same as that used by Marvel, Blomquist and Vaughn[7] for a similar study using di-n-butyl ether as the solvent. The only abnormalities encountered among the Grignard reactions studied in the course of the present work were shown by the two aryl halides and by β-bromostyrene, solutions of which had to be maintained at the boiling point until the reactions were complete.

Anilides.—A 15-ml. portion of solution of the Grignard reagent was withdrawn from the volumetric flask and treated with about 0.5 g. of phenyl isocyanate. After standing for five minutes, the mixture was treated with excess water, and the upper layer which formed was separated, steam distilled, and the residue allowed to cool. The crude anilide which separated was recrystallized from ethanol.

Results and Discussion

Table I shows the observed yields of Grignard reagents and the observed and reported melting points of the corresponding anilides.

Table I

Yields of Grignard Reagents in 4-Methyl-1,3-dioxane

Organic halide	Yield, %	M. p. of anilides, °C. Obs.	Reptd.
Ethyl bromide	92–93	103–104	105[c]
n-Propyl bromide	90–92	92	92[d]
Isopropyl bromide	81–88	103	103[d]
n-Butyl bromide	92–93	60.5–61.5[e]	63[d]
Isobutyl bromide	88–89	111	109.5[d]
s-Butyl bromide	83–86	108	108[d]
t-Butyl chloride	63[a]	Not obt.[f]	
Cyclohexyl bromide	86–87	142	146[d]
n-Heptyl bromide	88–89	52–53[e]	57[d]
Bromobenzene	81–86	161	161[g]
α-Bromostyrene	58–62	149.5	150[h]
β-Bromonaphthalene	76[b]	Not obt.[f]	

[a] Only successful experiment of several attempted. In four of these experiments, results of the titrations indicated that the main reaction was elimination of hydrogen chloride from the organic halide. [b] Single successful experiment. [c] Kelbe, *Ber.*, **16**, 1200 (1873). [d] Schwartz and Johnson, This Journal, **53**, 1063 (1931). [e] Recrystallized from petroleum ether (b. p. 50–60°). [f] Anilides were not isolated from mixtures of phenyl isocyanate with the Grignard reagents. [g] Wallach and Hoffmann, *Ann.*, **184**, 80 (1877). [h] Autenrieth, *Ber.*, **34**, 186 (1901).

Decided differences in conditions under which the halides undergo reaction with magnesium in 4-methyl-1,3-dioxane were observed. Whereas the lower alkyl halides reacted spontaneously, solutions of cyclohexyl and n-heptyl bromides required brief heating in order to initiate reaction, and solutions of the aromatic bromides and β-bromostyrene had to be boiled continuously.

In general, good yields of anilides were obtained when solutions of the Grignard reagents were treated with phenyl isocyanate; therefore, cleavage of 4-methyl-1,3-dioxane, a cyclic formal, by the Grignard reagents could not have occurred in appreciable amount.

Further studies of 4-methyl-1,3-dioxane and similar compounds as solvents for the preparation and reactions of Grignard reagents are anticipated.

Summary

Solutions of several aliphatic and aromatic halides in 4-methyl-1,3-dioxane reacted with magnesium to produce good yields of Grignard reagents.


[CONTRIBUTION FROM THE SHELL DEVELOPMENT COMPANY]

The Catalytic Synthesis of Benzothiophene

BY R. J. MOORE AND B. S. GREENSFELDER

Recently,[1] new chemical methods for the synthesis of benzothiophene have been proposed to provide starting material for possible use in pharmaceuticals, and as a precursor of thioindigo. These processes are, however, inefficient and too expensive for commercial use. In the course of a general investigation of dehydrocyclization, a catalytic synthesis was developed by which good yields of benzothiophene can be obtained, using styrene and hydrogen sulfide as starting materials. The over-all reaction is described by the following equation
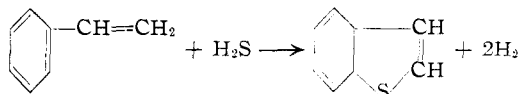
Experimental

The experiments discussed here were performed in a continuous flow reaction system at atmospheric pressure. The apparatus comprised a stainless steel catalyst tube heated by four sections of automatically controlled electric resistors and having the axial catalyst temperature profile flat within ±3°. The hydrocarbon was fed into the preheating section by a Hills–McCanna proportioning pump, while the gaseous reactants were measured by differential flowmeters. Reaction products were cooled to condense benzothiophene and unreacted styrene, and the vented product gases were sampled at intervals for analysis.

Ordinary commercial grade reactants were used, the styrene being only flash distilled to remove polymer and inhibitor. Hydrogen sulfide was charged directly from the cylinders as received.

Earlier work in these Laboratories showed in general that sulfur resistant dehydrogenation catalysts were suitable for this type of reaction; the most active of those tested was FeS/Al₂O₃ (ca. 5% iron on activated alumina). A suitable catalyst was prepared by sulfiding Alorco "Grade B" activated alumina at 600° with a mixture of two parts hydrogen sulfide and 1 part hydrogen at a rate of 100 vol./vol. catalyst/hr. until water no longer appeared as condensate. Usually one to two hours sufficed. Alternatively, activated alumina can be impregnated with ferric nitrate solution, and sulfided as above, after calcination to decompose the nitrate.

In order to minimize polymerization of the styrene, an excess of hydrogen sulfide was used, usually 4 moles of

hydrogen sulfide per mole of styrene. A mole ratio of 8:1 was found to increase conversion but handling the corresponding volume of excess gas in the laboratory was impracticable.

The preferred operating temperature is related to the contact time and to the activity of the catalyst. As shown by the following typical results for runs of four hours duration, a temperature of 600 to 625° appears to be satisfactory.

TABLE I

Temp., °C.	Contact time, seconds[a]	Conversion of styrene to benzothiophene. mole %
500	20	20 (estd.)
500	40	43
600	20	60
625	20	63

[a] Calculated on basis of 100% void in catalyst bed.

It was observed that the catalyst gradually accumulated a deposit of carbonaceous material and lost activity during processing. The average conversion over the initial ten-hour process period was only 45–50% compared with 60% for four hours; beyond this time the rate of production fell off sharply. The carbonaceous deposit could be removed by burning with air, but excessively long times were required at relatively low temperatures in order not to overheat the catalyst, and complete re-sulfiding of the catalyst was necessary. It was found, however, that regeneration could be completed in two to four hours if steam were charged at 400 vol./vol. catalyst/hr. with air at such a rate that the catalyst temperature did not exceed 675°. Under these conditions the ferrous sulfide was only partially oxidized.

With the exception of small amounts of benzene and tar-like polymer, the crude product consisted of benzothiophene and unreacted styrene. It was estimated that conversion efficiency (yield) was of the order of 90%. The benzothiophene product was readily purified by distillation, b. p. 221°, since neither the feed nor the side reaction products boil in this range. The distilled material had a melting point of 31°, and on recrystallization from ethanol, 31.2°. Analysis showed 23.6% sulfur, calculated 23.8%.

The hydrogen sulfide-free vent gas was found to be predominantly hydrogen, with a small admixture of ethylene and a saturated hydrocarbon, presumably ethane.

Discussion

While no extensive investigation of the mechanism of this reaction was carried out, several inferences can be drawn from the experimental results. Assuming that 2-phenylethyl mercaptan is an intermediate in the conversion, its formation could be achieved in at least two ways at 600°: firstly, at equilibrium there should be an appre-

(1) Hansch and Lindwall, J. Org. Chem., 10, 381 (1945); Buu-Hoï and Cagniant, Ber., 76B, 1269–1274 (1943); Tarbell and Fukushima, THIS JOURNAL, 68, 1456 (1946); Tarbell, Fukushima and Dam, ibid., 67, 1643 (1945).