DI-ISOPROPYL ETHER AS A SOLVENT IN THE GRIGNARD REACTION

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Solvents other than diethyl ether were tried in the earliest days of the Grignard reaction and found to be at times successful. The higher ethers, in particular di-isoamyl ether and anisole, were early used. Ether-like substances such as dimethyl sulfide, dimethyl selenide, dimethyl telluride and dimethyl sulfone have been used although the yields are reported as low [1]. Other authors report the use of quinoline, pyridine, dimethyl aniline, and other tertiary amines either as solvents or as catalysts [1]. Hydrocarbons such as benzene, toluene, xylene, and petroleum ether have been found at times to increase, at others to decrease, the yields [2]. In a study of the luminescence occurring during Grignard reactions, Evans and Diepenhorst used as solvents for the reagent diethyl, dinormal propyl, di-isopropyl, dinormal butyl, dinormal amyl, di-isoamyl, diphenyl, resorcinol, dimethyl, methyl phenyl (anisole), ethyl phenyl (phenetole), benzyl ethyl, alpha naphthyl methyl, alpha naphthyl ethyl, alpha naphthyl isoamyl, beta naphthyl methyl, beta naphthyl ethyl, beta naphthyl isoamyl ethers, and di methyl aniline. Tschelinzeff reports the use of paracymene and of other hydrocarbons of the terpenic, aromatic, and aliphatic series [3]. The Grignard reagent was insoluble in benzene although the yield was high. Other substances reported as used were ethyl normal propyl ether and ethyl normal propyl sulfide, 1, 3 dioxan, 1, 4 dioxan, 1, 4 di thian, di isoamyl sulfoxide, diphenyl sulfoxide, diphenyl sulfone, and even carbon tetrachloride [4].

In very few cases, however, do the authors report definite yields, and in most cases no comment whatever is offered as to the yields.

Majima and Kotake [5] studied the relative yields in the case of indole magnesium iodide using diethyl ether and anisole, finding that the former solvent is better when the Grignard reagent is allowed to react with acyl halides while the latter is better in reactions with aldehydes and ketones. Thus indole magnesium iodide with benzaldehyde gives respectively 20 per cent and 61.6 per cent while with acetyl chloride the yields are respectively 93 per cent and 61 per cent in the two solvents.

Gilman and McCracken [2] studied the effect of hydrocarbon ethyl ether mixtures, finding that the yields of Grignard reagent were reduced by addition of hydrocarbon from 10 to 30 per cent in some cases and increased 5 per cent in other cases.

Marvel and Blomquist [6] made quantitiative studies of the yields of Grignard reagents in dinormal butyl ether and found that these yields were equal or nearly equal to those obtained when diethyl ether was used as the solvent. They recommended dinormal butyl ether in place of diethyl ether, in many cases citing as advantages its higher boiling point which gives a higher reaction temperature and a greater recovery of solvent, and the ease of preparation of the anhydrous compound without the use of sodium metal.

As di-isopropyl ether has become an article of commerce, the authors believed that it might be more successfully substituted for diethyl ether than might dibutyl, inasmuch as it should have some of the advantages of dibutyl ether without the excessively high boiling point and rather high cost. Di-isopropyl ether at present sells for about ten to fifteen cents a pound. Recovery of solvent would be much greater, and the danger of fire much less than in the case of diethyl ether. However, so far as our results go at present, di-isopropyl ether does not measure up to the hopes we hold out for it.

The di-isopropyl ether was the commercial grade put out by the Carbide and Carbon Chemicals Corporation and contained according to the specifications only very small amounts of isopropanol. This product was purified in three ways; first, by washing with saturated sodium chloride three times, drying over calcium chloride, distilling, drying, over metallic sodium, and distilling, collecting the 67-68° fraction; second, by washing six times with water, drying over calcium oxide, filtering, drying over sodium and using directly; third, washing three times with eight normal sulfuric, twice with saturated sodium chloride, twice with three normal sodium hydroxide, drying over burnt lime, distilling, refluxing over sodium, distilling and collecting the fraction 67-68° (practically 100 per cent came over in this fraction). So far as our work shows, these three methods are equivalent.

Methyl iodide and magnesium failed to react in di-isopropyl ether in the presence of a crystal of iodine in spite of heating and shaking over a period of several hours. Hepworth reports a similar result using benzene as the solvent [4].

Ethyl iodide reacted well at first with magnesium in di-isopropyl ether but a white solid was formed which soon coated over the magnesium. 7.8 grains (1/20 mole) of ethyl iodide was refluxed with 1.4

grains magnesium in 25 cubic centimeters of the ether for an hour or more after reaction had started. The mixture was then made up to 50 cc. of which 10 cc. taken out for titration required 4.5 cc. of half normal hydrochloric acid. This corresponds to a yield of 22.5 per cent of the theoretical quantity of Grignard reagent. In diethyl ether the yield was 86 per cent and in dibutyl it was 75 per cent.

The reaction of 1/20 mole portions of ethyl bromide was tried in ethyl, isopropyl, and butyl ethers as solvents. The yield of ethyl magnesium bromide was determined by the acid titration and the gas evolution methods [7]. In case of isopropyl ether, a mercury seal mechanical stirrer was used to shake off the white coating forming over the magnesium; the other two were run without the stirrer.

	Diethyl ether	di-isopropyl ether	dibutyl ether
	Per cent	Per cent	Per cent
Acid titration	75, 85, 88	67.5	74, 75
Gas evolution	49, 55	33	38

Isoamyl iodide and magnesium started to react in isopropyl ether but the magnesium soon became coated over with an adhesive layer and reaction ceased in spite of shaking and heating..

Brom benzene and magnesium and isopropyl ether with a crystal of iodine were shaken together for several hours without evidence of reaction. Even after the first signs of reaction appeared, the action did not go on. A 1/20 mole reaction mixture in a three neck flask fitted with a mercury mechanical stirrer was started by means of some previously prepared ethyl magnesium bromide. Soon the magnesium became coated with a black solid. After stirring and refluxing for nearly three hours, the yield of Grignard reagent as found by acid titration to be only 34 per cent.

Dimethyl ethyl carbinol and ethyl phenyl carbinol were prepared by the action of one-tenth molar quantities of acetone and benzaldehyde or the Grignard reagent prepared from one-tenth molar quantities of ethyl bromide in ethyl ether and in isopropyl ether. In both cases the yields obtained from the latter solvent were considerably less than half those obtained from the former.

From this preliminary study it seems that di-isopropyl ether is not a suitable solvent for the Grignard reaction. The authors intend to study the question further.

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