Grignard Reactions in "Wet" Ether

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Students can run Grignard reactions in regular laboratory-grade ether and in equipment that has not been specially dried. The reaction begins within one minute and the product alcohol is ready for assay in one hour. This technique, which requires only the simplest of glassware and a low-power ultrasonic laboratory cleaner, is so robust that it deserves wider use. Because no particular care is needed to dry either the solvent or the equipment, large savings in time result for instructors and students.

Using this technique, the magnesium can be handled with the fingers during weighing. The diethyl ether can come from a half-full can of "anhydrous reagent ether" open for two months and in use in an undergraduate laboratory (even the can containing the Pasteur pipet and bulb lost by a student). The bromide and the ketone are from bottles suffering from numerous years of student use. The glassware is right off the shelf. The yield of product is typical of student reactions. This "non-dry" procedure has worked as described on the second day of a rain storm, with open laboratory windows, hoods pulling in the very humid air, and using glassware directly out of student desks.

The ultrasonic initiation of Grignard reactions (*1*) does not appear to have made the "mainstream" of use in current lab manuals. However, its theory and applications have been discussed in this *Journal* (*2*) and elsewhere (*3*), and, indeed, the use of ultrasonic initiation of the Grignard reaction has been reported in this *Journal* (*4*). The use of allyl bromide and acetophenone, mediated by zinc in water and THF, has recently been proposed (*5*) to circumvent the perceived problems with the need for anhydrous solvents, ultradry glassware, and slow initiation for Grignard reactions.

Experimental Procedure

CAUTION: All steps need to be conducted in a fume hood, as considerable amounts of ether will evaporate. The instructor should put water in an ultrasonic bath to a depth of about three inches. Several beakers filled with water to the same depth are placed in the bath to support students' test tubes. A beaker filled with cold tap water should be handy in case rapid cooling of the reaction is needed. Then:

1. Add 0.010 mol (0.25 g) of clean magnesium turnings to a 6″ test tube (tube A). Add 0.100 mol (1.41 g) of pure 1-bromobutane and 3.1 mL of anhydrous ether to a similar tube (tube B). Mix well. Note the level of liquid in tube B and place a line on tube A at this height.
2. Use a Pasteur pipet to add enough of the bromide–ether solution to tube A to partially cover the magnesium. Place this tube into a water-filled beaker in the ultrasonic bath and begin sonicating. CAUTION: Make sure the tube points away from other people! Watch the contents of the tube. When the liquid turns gray or white, remove the tube. The ether should begin to boil spontaneously. If it doesn't, put the tube back into the ultrasonic bath.
3. When the reaction starts boiling spontaneously, remove the tube from the ultrasonic bath. Add about 0.5 mL of pure ether. When the initial boiling has slowed, add more 1-bromobutane–ether solution at a rate to keep the reaction going moderately well. If the reaction slows, add another 0.5 mL of pure ether to make up for evaporation loss. If it goes too vigorously, place the tube in cool water.
4. After adding all of the bromide–ether solution, add enough ether to keep the liquid level to the mark on the test tube. When the reaction slows and almost all of the magnesium is gone, sonicate the mixture for a few minutes more.
5. Remove the tube from the ultrasonic bath. Pipet the solution into a dry 50-mL Erlenmeyer flask. Rinse the test tube once with 0.5 mL of ether and add the washings to the 50-mL flask. Cool the flask and its contents in an ice bath. Any magnesium remaining in the tube can be air-dried and weighed.
6. Any properly scaled standard procedure for adding the ketone to a Grignard reagent may be used at this point. CAUTION: It is important that the ether solution of the ketone be added dropwise into the 50-mL Erlenmeyer flask using cold reagents! The reaction with the ketone is *very* vigorous and material explodes from the open end of a test tube with a range of about two laboratory benches!

Results and Discussion

A standard laboratory ultrasonic parts cleaner of 125 W, 60 kHz has been used. A single unit of 3-L size is adequate for a lab section of 20 or more, with only slight crowding or waiting. Such a cleaner lists in laboratory supply catalogs for about $470. The water bath will heat up to about 35 °C in about an hour of continuous sonicating. Students should go to another hood after their reaction starts. A sizable amount of ether evaporates during sonication and reaction.

My students follow the general procedure above for forming Grignard reagents, and the scaled version of the ketone addition step from their regular laboratory manual. They are assigned alkyl or aryl bromides and ketones almost at random, but some care being taken by the instructor that the product will give a pattern in the NMR that a beginner can interpret (see list below). Students are responsible for adjusting the mass of reagents to the formula weights of their compounds and for predicting the IR and NMR of their product.

Compounds Used for Grignard Reaction

Bromides	*Ketones*
4-Bromotoluene	Cyclohexanone
Bromobenzene	2-Butanone
2-Bromopropane	3-Pentanone
3-Methyl-1-bromobutane	4-Methyl-2-pentanone
1-Bromobutane	Cyclopentanone
Bromoethane	2-Pentanone
1-Bromopropane	Benzophenone
2-Methyl-1-bromopropane	Acetophenone

Of these reagents, only *p*-bromotoluene has been slow, but it started as well as the others. Aldehydes work well, but their odor is unnecessarily strong. Virtually all students have an active Grignard reaction going within five minutes; most start within 45 seconds. In contrast, without sonication, 1-bromobutane does not begin reacting with magnesium for at least two minutes.

GC and IR assays of a typical reaction between 1-bromobutane and acetophenone show that some of the 1-bromobutane (2%) and some of the acetophenone (5%) remain. About 15% of the magnesium remains. Yields of alcohol of 60–80% are observed. The product distribution (via GC) is identical to the nonsonicated reaction (the alcohol, some unreacted ketone and bromide, and 15–30% of an unidentified material that is not *n*-octane dimer [GC] or an alkene [IR]).

What Are the Limits of This Procedure?

A reaction was performed using diethyl ether that had been shaken with water, the mixture then being allowed to stand for one hour. The ether was so wet that 1-bromobutane formed a cloudy mixture when it was added. The reaction of this mixture with magnesium proceeded satisfactorily after sonication for about 50 min. The yield of product alcohol was about 50% (GC).

The reaction of 1-bromobutane and magnesium started successfully within two minutes in undried either and undried equipment on the 10-g scale. The yield of alcohol was about 60%.

Old magnesium turnings with a black surface and just a small amount of brighter metal were also tried. The reaction started in the same time as the reaction with better quality magnesium. Alkyl chlorides in sodium-dried ether began reaction sooner with ultrasonication than without. However, the initiation time is greater than 30 minutes, impractical in the undergraduate laboratory. 1-Bromobutane in methyl *tert*-butyl ether did not react using the ultrasonic method. However, this less flammable solvent can be substituted for diethyl ether as the solvent for the aldehyde or ketone (*7*). Methyl *tert*-butyl ether and dichloromethane can be used in the extraction step, but some people find the odor of methyl *tert*-butyl ether to be objectionable and dichloromethane may be a weak carcinogen.

Summary

There is no question that thoroughly drying all components of a Grignard reaction will give better results, with or without ultrasonication. The use of the ultrasonicator will initiate Grignard reactions with organic bromides very rapidly with very little failure under conditions that prevail in undergraduate laboratories. The ultrasonicator also allows the use of much less expensive grades of ether, with no apparent penalty in product yield or quality.

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