The Ethylene Ketal Protecting Group in Organic Synthesis

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Abstract:

"The multistep synthesis of 4-hydroxy-4,4-diphenyl-2-butanone from ethyl acetoacetate illustrates the use of a ketal protecting group. Reaction of ethyl acetoacetate with ethylene glycol with *p*-TsOH in toluene produced the ketal ester. Reaction of the crude ketal ester with two equivalents of phenyl magnesium bromide followed by an aqueous acid workup generated the tertiary alcohol and simultaneously removed the ketal protecting group to produce the hydroxyketone. Our procedure is a modification of a previously published synthesis whose end product was 4,4-diphenyl-3-buten-2-one, the dehydrated analog. Our modifications involved the exchange of toluene for carcinogenic benzene as the azeotropic solvent in the ketal forming step and the alteration in the Grignard workup from water to one with dilute acid. This shortens the experimental sequence by avoiding the isolation and subsequent deprotection of the hydroxyketal intermediate and avoids the complication of the concurrent dehydration. We engaged the students in a discussion about how minor variations in the Grignard workup procedure can affect which compound is formed and presented the students with the

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challenge of utilizing spectroscopic analyses to identify the final product.

Introduction:

Protecting groups can be very helpful in a lot of chemical procedures that are used commercially, because if a group needs to be masked during a synthesis, then this is a way to do it. In this experiment, the ethylene ketal masks a carbonyl group, to protect it from leaving during certain procedures where it could be reduced. The protecting group can be removed later to leave the desired functional group still attached. This experiment used the preparation of ethylene ketal using p-toluene-sulfonic acid . If the ethylene ketal were not used, then the ketones would have all been reduced during the synthesis. The protecting group was the only way to go about getting the desired product for this synthesis. There are three steps in this synthesis: preparation of ethyl acetoacetate ethylene ketal, preparation of keto-alcohol, and preparation of 4,4-diphenyl-3-buten-2-one. This paper should properly outline the procedure for the ethylene ketal protecting group in organic synthesis. It should also show how the results are subject to many variables. As in any chemical procedure, safety is an serious matter, and gloves, goggles, and appropriate clothing were and should be used during the synthesis. Part of the procedure included a Gringard synthesis. During this procedure, all glassware should be clean,

dry, and apart from the moisture and contaminants in the air.

Procedure/Experimental:

In the first step, preparation of ethyl acetoacetate ethylene ketal, the apparatus necessary was a stir plate, heating mantle to be placed on the stir plate, 100 ml round bottom flask in the mantle connected to a Dean-Stark connected to a reflux condenser. 15g of ethyl acetoacetate was added to the flask along with 7.5g of ethylene glycol, .065g of p-toluenesulfonic acid monohydrate, and 50 ml of toluene. It was refluxed until the theoretical amount of water was removed and the cooled to room temperature. The product was then washed with 17.5 ml of 10% sodium hydroxide and again with two 25 ml portions of water. The product was then dried over anhydrous potassium carbonate. This was a good stopping point, so the product was stored in the flask with a cap on it. The next stepped involved a distillation to purify the product. The apparatus necessary was a stir plate, a heating mantle on the stir plate, the 100 ml round bottom flask with product in it, in the mantle and connected to a distilling head, and thermometer adaptor with a thermometer in it. The head was connected to a condenser connected to a vacuum adapter connected to a 50 ml round bottom flask. The adapter was also connected to a vacuum flask. The product was stirred and heated, while the water ran through the condenser

- missing mol of chemicals used (x6)
- no equations
- no table of chemicals

and the vacuum was on. The distilled product was then flash evaporated. IR and NMR were run on the sample. The weight of the product was taken and this information can be found on the IR and NMR charts as well as in the results section of the paper. This was a good stopping point, so the product was capped and stored. The second step of the procedure, preparation of a keto-alcohol using Grignard, required thorough cleaning and high heating of the glassware and other tools to be used. The apparatus consisted of a stir plate, the round bottom flask with product in it connected to a connecting tube connected to both an addition funnel and a condenser connected to a drying tube. 2.6g of Magnesium turnings were added to the flask. A solution of 15.2g of bromobenzene in 25 ml of anhydrous ether were added dropwise to the product while it stirred. The product was refluxed for 25 minutes in a steam bath after all the solution was added. Then 25 ml of ether with ketal product were added to the flask. They were refluxed for 30 minutes. Then 50 ml of ice water was added to the product. This was a good stopping point in step two, so the product was capped and stored. When step two was continued, the product was washed with 25 ml of ether. The ether mixture was then removed, and this procedure was repeated. The combined ether layers were washed with 25 ml of water. The water layer was then discarded. The product was then weighed, dried

over magnesium sulfate, weighed again, flash evaporated, weighed again, cooled in an ice bath, vacuum filtrated, and then weighed a final time. All of the weights and observations can be found in the results portion of the paper. A sample for IR and NMR were turned in. The product was capped and stored for next time. The third step in the synthesis, preparation of 4,4-diphenyl-3-buten-2-one, was achieved with a much simpler apparatus: a stir plate, heating mantle, and a 100 ml flask connected to a condenser. 5g of the product was put into the 100 ml flask. 1.25 ml of concentrated hydrochloric acid, 50 ml of acetone, and 2.25 ml of water were also added to the flask. This mixture was refluxed for an hour. It was then diluted with 50 ml of water and cooled to room temperature. Then the mixture was extracted with two 25 ml portions of ether. The combined ether portions were washed with 25 ml of saturated sodium bicarbonate. Then the ether extractions were washed with 25 ml of water. This product was dried over magnesium sulfate. Then the product was flash evaporated. A sample for IR and NMR were turned in. The amount of final product was so nominal that it could not be purified by any means.

No NMR/IR tables or Analysis

Discussion/Results:

Once the first step was completed, the product weighed 18.014g. After the second step the final weight of the white crystals was 3.7g. The weight of

the product had already decreased six times from the first step to the second. TLC for after the third step showed one spot which indicated a pure final product, but the IR and NMR charts did not show this. However, after the third step there was so little product left that it could not be purified. The weight of the final product was nominal and still contaminated from glitches in previous procedures. The experiment probably could have been improved by more thorough cleanings of the glassware. A lot of product must have been lost if the times for purification went too long or the heat was turned up too high during refluxes. Moving the product into different glassware constantly, probably also lost a lot of the product.

References:

Abstract. Marsha R. Baar, Charles E. Russell, and Kristen L. Wustholz, http://jchemed.chem.wisc.edu/Journal/Issues/2005/Jul/abs1057.html, May 5, 2009.

Procedural Steps. D. R. Paulson, A. L. Hartwig, and G. F. Moran, The Ethylene Ketal Protecting Group in Organic Synthesis: An U ndergraduate Laboratory Experiment, 1-2.

missing information

not endnotes (-8)