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A Hydrazine-Free Wolff–Kishner Reaction Suitable for an Undergraduate Laboratory

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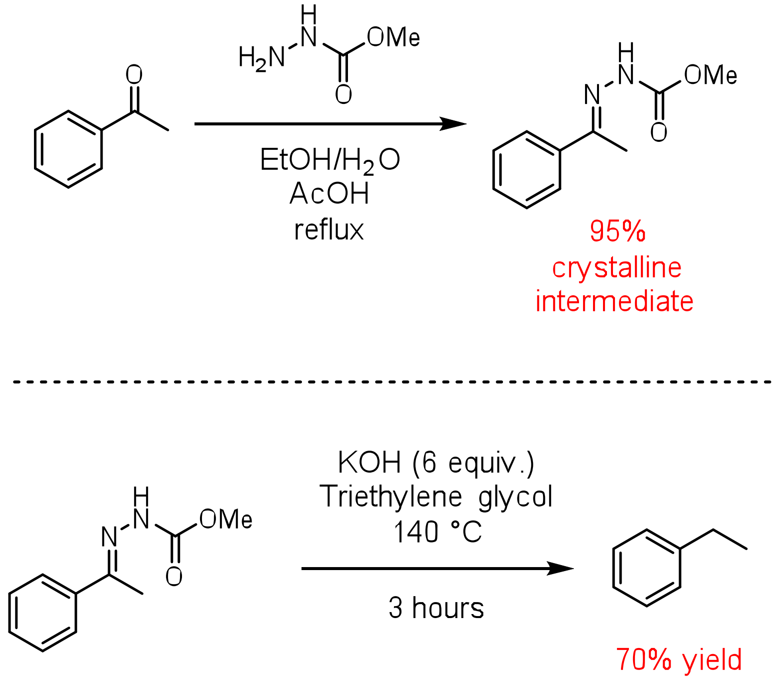
ABSTRACT

A Wolff–Kishner reaction that does not require hydrazine has been developed. The reaction sequence has two steps; formation of a carbomethoxyhydrazone from methyl hydrazinocarboxylate and acetophenone, then decomposition of this intermediate by treatment with potassium hydroxide in triethylene glycol. Purification is by filtration through a plug of silica encased in the barrel of a plastic syringe. The reaction sequence can be completed within a day-long laboratory class (8 hours).

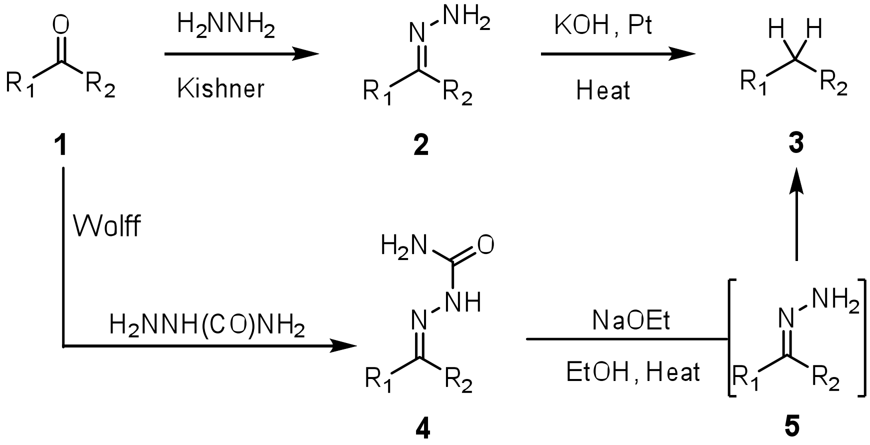
ABSTRACT GRAPHIC



KEYWORDS

Second year undergraduate, laboratory instruction, organic chemistry, safety/hazards, hands on learning/manipulatives, aldehydes/ketones, reduction, synthesis.

The Wolff–Kishner reaction, discovered independently by Kishner in 1911[1] and Wolff in 1912,[2] has become a standard method of reducing aldehydes and ketones to their corresponding methylene unit, although early work by Staudinger should not be forgotten[3] (Scheme 1). Modification of this initial work, by Huang-Minlon,[4] led to a procedure that was widely applicable to modern synthesis as well as a procedure suitable for an undergraduate practical class.[5] Further modifications have provided a range of variants, all of which have all proven useful.[5, 6]



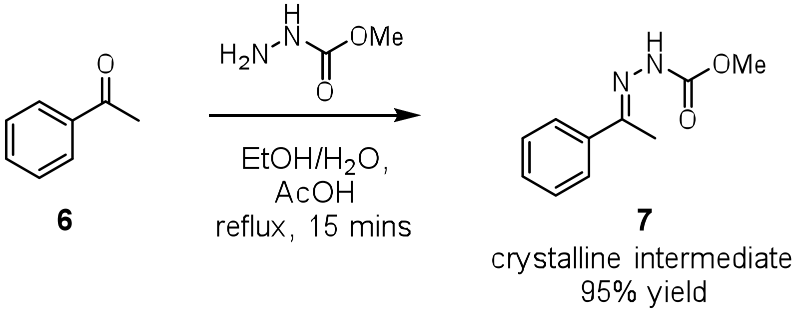
Scheme 1: General Wolff–Kishner Reaction

However, one significant draw-back of the Huang-Minlon variant of the Wolff–Kishner reaction is the requirement for hydrazine, an extremely toxic reagent, in stoichiometric quantities. Studies upon the effects of hydrazine have shown that acute expose leads to liver, kidney and CNS damage in humans. Chronic exposure by inhalation has shown effects in the liver, spleen and thyroid in animals as well as increased incidences of lung, nasal cavity and liver tumors. These effects have led the U.S. Environmental Protection Agency to deem hydrazine as Group 2B, a probable human carcinogen.[7] In terms of general research, this is not usually a problem because safeguards can be easily put in place to minimize exposure. However, in an undergraduate laboratory situation this is undesirable and the substitution of toxic hydrazine by another, less toxic, hydrazine equivalent is clearly an advantage. In order to address these issues, work towards developing an alternative procedure suitable for an undergraduate laboratory was undertaken that has ultimately led to the development of a generally applicable, hydrazine-free, Wolff-Kishner procedure.[8]

EXPERIMENTAL DETAILS

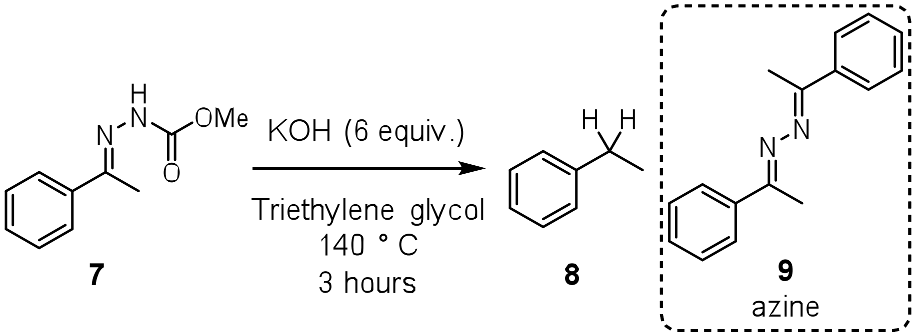
This experiment is designed for students who have already experienced a year of undergraduate practical chemistry, and, in our Department, sits within a 5-week organic chemistry laboratory course. For the duration of this course, students work in pairs in a day-long laboratory class (8 h). Before each laboratory class, students complete a risk assessment and are expected to complete an additional online test. During the tests students are asked a series of questions designed to encourage them to think about the reaction they are going to undertake, and ultimately enhance student engagement with the laboratory class. The pedagogic goals of this experiment are as follows: to encourage students to think about the toxicity of chemicals they are using and therefore the use of alternatives, to consider time management when undertaking an experiment, to introduce them to flash column chromatography, and to teach students to work with volatile compounds.

Students start by preparing the carbomethoxyhydrazone. This is achieved by addition of methyl hydrazinocarboxylate to acetophenone in ethanol with an acetic acid catalyst, then heating the reaction at reflux for 30 minutes, Scheme 2. After this time the reaction is cooled, the precipitated product collected by suction filtration through a Büchner funnel, washed with 95% EtOH and dried. The students collect IR and melting point data for this product. They are provided with ^{1}H NMR spectra (with and without D_2O shake) that they are expected to interpret fully as part of their laboratory report.



Scheme 2: Preparation of the carbomethoxyhydrazone intermediate **5**

The second step starts with students dissolving KOH in triethylene glycol, adding the carbomethoxyhydrazone in one portion and heating the reaction at 140 °C; slightly above the boiling point of ethyl benzene (136 °C), Scheme 3. After a short time, effervescence is observed that we attribute to CO_2 formation (see below).



Scheme 3: Degradation of the carbomethoxyhydrazone intermediate **7**

The reaction is complete within 3 hours, at which point it is allowed to cool to ambient temperature and diluted with water. The product is extracted into diethyl ether, the organic phase dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Prior to solvent removal, students add a small volume of acetone (1 mL) as a safety measure in case there is any free-hydrazone present that could lead to azine **9** formation and, ultimately, hydrazine production upon concentration. Finally, purification is achieved by passing the crude material through a short plug of silica encased in a plastic syringe body,[9] eluting with pentane. The volatile product is isolated as a yellow oil. We attribute the yellow color to the formation of azine **9** (up to 5%) during the reaction itself, rather than after work-up. Students collect ^{1}H NMR data for this product and are provided with ^{13}C and DEPT135 NMR data that they are expected to interpret fully.

HAZARDS

Safety glasses, nitrile gloves, and a laboratory coat should be worn at all times in the laboratory and the reactions should all be undertaken in a fume cupboard. All hazardous materials should be used and disposed of in accordance with local health and safety rules. Acetophenone is harmful if swallowed and can cause serious eye irritation. Ethanol is highly flammable and can cause serious eye irritation. Methyl hydrazinocarboxylate cases skin irritation, serious eye irritation and may cause respiratory irritation. Glacial acetic acid is flammable and can cause severe skin burns and eye damage. The intermediate carbomethoxyhydrazone should be treated as toxic. Triethylene glycol has no known hazards but should be treated as toxic. Potassium hydroxide may be corrosive to metals, is harmful if swallowed and causes severe burns and eye damage. Ethyl benzene is highly flammable and harmful if inhaled. Diethyl ether is extremely flammable, harmful if swallowed and may cause drowsiness or dizziness. Magnesium sulfate has no known hazards but should be treated as toxic. Acetone is highly flammable, can cause serious eye irritation and may cause drowsiness or dizziness. Pentane is highly flammable, may be fatal if swallowed or inhaled, may cause drowsiness or dizziness and is toxic to aquatic life. Silica gel is harmful if inhaled and so should only be used in a fume cupboard. Deuterated chloroform is harmful if swallowed, causes skin and eye irritation, is toxic if inhaled, is a suspected carcinogen, is a teratogen, and can cause damage to organs through prolonged or repeated exposure. The second step of this reaction liberates a gas, therefore when stirring it is essential that the magnetic stirrer bar is large enough to allow effective stirring to occur. An oval stirrer bar is best for this. Concentration of the reaction should be undertaken in a fume hood to avoid any possible exposure to hydrazine.

RESULTS

Of the 40 students (20 pairs) who undertook the reaction, all prepared enough material to be able to characterize the intermediate carbomethoxyhydrazone. The average yield was 90% for this step, with student yields ranging from 72% to quantitative. The second step, degradation of the intermediate, was also successful and student yields ranged from 22% to 94%. The average yield for this step was 57%, comparable to the instructor yield of 70%.

During preparation of the carbomethoxyhydrazone, the product occasionally precipitated instantly after addition of the acetic acid. When this happened students were told to heat the reaction for 15 minutes then collect the precipitate. The yield of the intermediate obtained by students was good and all of them had reached this point after 2 hours. When students had yields greater than100% it was due to residual ethanol which evaporated if the sample was left open to air. Purity was also good, as the NMR data shows (see supporting information), and all melting points were in agreement with published data.[7] The instructors ensured that all students had started the reduction step before lunch to allow for the 3-hour heating step, during which time students collected data for their intermediate. It was important during the reaction that the KOH was pre-dissolved in the triethylene glycol otherwise the reaction did not run to completion in the time allocated. Approximately 10 minutes after initial addition of the carbomethoxyhydrazone intermediate to the basic solution, rapid bubbling was observed that we attribute to evolution of CO_2 from decomposition of the carbomethoxyhydrazone followed by slower formation of nitrogen (Figure 1). As the students used a 250 mL round-bottomed flask equipped with a large oval stirrer bar this did not cause any issues. If bubbling did become excessive, the flask was simply lifted out of the heat until the foam subsided, and then placed back onto the heat. Over time, the ethylbenzene product could be seen refluxing inside the flask, providing a visual cue that the reaction was proceeding.

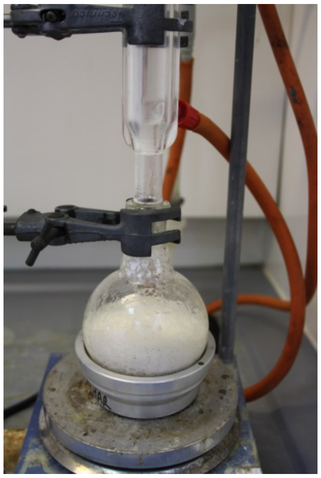


Figure 1: Bubbles formed during the reaction.

The extraction did not provide any difficulties although students had to be reminded to allow the reaction to cool completely before addition of diethyl ether, and also to vent the separating funnel frequently, through the tap, during the work-up to prevent pressure build-up. Prior to solvent removal, students were instructed to add 1 mL of acetone to the crude material as a safety measure, just in case there was any residual hydrazone **2** present (as noted above, by self-condensation of **9** hydrazine would result). The solvent was removed with a rotary evaporator in a fume hood as an additional precaution. As part of the pre-laboratory test, students were asked to look up the boiling point of ethylbenzene then, using a nomograph, estimate its boiling point at 20 mmHg (as a reasonable approximation to the operating pressure inside our rotary evaporators). Responding to the students' estimated boiling point, during removal of the solvent students were asked to consider the value of having the water bath on the rotary evaporator cold, to avoid any product losses through evaporation.

^{1}H NMR spectra of the crude material obtained at this stage were recorded for some of the students' reactions and showed that they had proceeded to completion. In some cases there was minimal azine formation. This was evidenced by a bright yellow solid forming in the flask during solvent removal. Additionally, variable quantities of diethyl ether were present depending upon the care taken with rotary evaporation.

Purification was carried out by flash column chromatography through a short plug of silica encased in a 20 mL syringe.[9] A B19 air inlet adaptor was fitted inside the barrel so that the solvent could be eluted using bellows (Figure 2). Occasionally, there was an orange band at the base of the column.

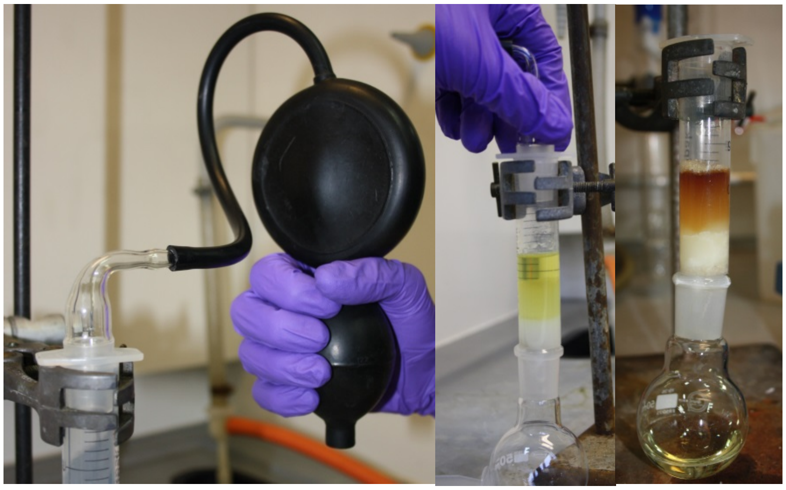


Figure 2: Photograph of silica gel column the students used to purify their product.

Removal of the solvent was achieved on a rotary evaporator and again students were reminded of the need to ensure the water bath was cold. In the students' product NMR spectra, the only impurities observed were residual pentane and, occasionally, traces of the azine that was formed during the heating step and could not be avoided (see Supporting Information). Low yields in some cases could be attributed to heating the water-bath, leading to losses due to the volatility of the product.

CONCLUSION

A Wolff–Kishner reaction that avoids the use of hydrazine has been developed and the pedagogic goals we set were achieved. All students were able to prepare the intermediate in high yield and purity and also prepared ethyl benzene within the allocated laboratory period, addressing the time management goal (8 h). The two distinct steps in the reaction sequence allow for the reaction to be split over a longer period if required.

The second step provided students with the chance to learn how to work with volatile compounds which provided a valuable assessment tool for practical ability; less diligent students achieved lower yields due to the volatility of the product. Purification through a silica gel plug taught students about flash column chromatography as a means for product purification, and the equipment we used was cheap and simple to set up.

In terms of safety, this reaction is advantageous because it avoids the use of hydrazine, an extremely toxic chemical.

ASSOCIATED CONTENT

Supporting Information [required for the manuscript types Laboratory Experiment and Activity]

Detailed reagent and supply list, protocols for laboratory instructors, student handouts and demonstration videos, and analytical data for products (including melting points, NMR data, and IR spectra). This material is available via the Internet at http://pubs.acs.org.

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