

Synthesis of 1-Phenylthiourea: An Undergraduate Organic Chemistry Experiment Illustrating Carbonyl Transformations

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INTRODUCTION

The chemistry of carbonyl compounds is a fundamental part of undergraduate experiments and has been outlined in many undergraduate textbooks.^{1,2} Undergraduate students are routinely exposed to many experiments involving the chemistry of carbonyl-containing structures. These include carbonyl condensation reactions,³ carbonyl reactions in multistep syntheses,⁴ microwave-assisted synthesis of carbonyl compounds,⁵ carbonyl addition reactions⁶ and their stereochemistry⁷ and regiochemistry,⁸ and NMR⁹ and FT-IR¹⁰ spectroscopic studies. However, few of the experiments deal with reactions of carbonyl substitution and concomitant addition in a simple and applicable synthetic way.

One simple compound with the carbonyl group is urea, which was synthesized by Friedrich Wöhler in 1828 through heating of ammonium cyanate, thus marking an important milestone in organic chemistry.¹¹ Ammonium cyanate decomposes to ammonia and cyanic acid, which reacts to produce urea via nucleophilic addition followed by tautomeric isomerization. In a similar way, when ammonium thiocyanate is heated, it produces thiourea, the sulfur analogue of urea.¹² Substituted thioureas are important building blocks in organic synthesis, being used in the synthesis of many heterocyclic compounds, such as thiazoles,¹³ benzothiazoles,¹⁴ guanidines,¹⁵ and dihydropyrimidinthiones.^{16,17} Furthermore, recent studies have been performed to investigate the potential pharmacological activities of substituted thioureas, mainly

focusing on the development of novel antineoplastic, 18 anti-inflammatory, 19 and antimicrobial drugs. 20

Bearing in mind the importance of this group of molecules, numerous strategies have been developed for their preparation.²¹ One important route for the synthesis of substituted thioureas involves a two-step approach: the addition/ elimination reaction of benzoyl chloride (1) with thiocyanate ion (2) to generate benzoyl isothiocyanate (4) *in situ* by elimination of the weakest base from 3, and the addition of aniline (5), which reacts with 4 to produce 7. Intermediate 7 is submitted to alkaline hydrolysis in a second step, yielding the product 11 and benzoic acid 12 after workup.^{21,22} These steps and proposed mechanistic aspects of the synthesis are described in detail in Figure 1.

Because of the chemical diversity and the importance of the thiourea scaffold, we suggest here an experimental session in organic synthesis appropriate for lower-division undergraduate students in chemistry or pharmacy courses. The proposed thiourea synthesis occurs in two steps, and the synthesis and characterization can be successfully implemented in three

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Figure 1. Steps and mechanism involved in the synthesis of 1-phenylthiourea (11).

sessions of 3 hours each. The reactions involved in the synthesis are very useful examples to help students understand different concepts of carbonyl chemistry, such as (i) carbonyl substitution by the reaction between benzoyl chloride and ammonium thiocyanate and (ii) amide hydrolysis in an alkaline medium. Furthermore, this synthesis is useful for demonstrating concepts linked to thiocarbonyl addition, i.e., the reaction between an aroyl isothiocyanate and an aniline.

PEDAGOGICAL SIGNIFICANCE

This laboratory experimentation introduces students to several techniques and skills that may be covered concomitantly at some time in traditional organic chemistry experiments. The pedagogical goals of this proposal are (i) to apply in a laboratory experiment the academic knowledge of organic synthesis linked to carbonyl addition and substitution; (ii) to show students common separation techniques in organic synthesis laboratories, such as the effect of pH on ionization status and solubility, recrystallization, and filtration; (iii) to introduce the multistep synthesis concept; (iv) to introduce students to IR and NMR characterization; and (v) to show a historical perspective on the evolution of organic synthesis from the time of Wöhler's synthesis to the present day.

EXPERIMENTAL OVERVIEW

Session 1: Step 1

Initially, the three sessions are introduced to the concepts of both the synthesis and characterization of 1-phenylthiourea (11) (Scheme 1) and its importance and theoretical background. Then the students receive the physical data on each reagent and the molar proportion of the reaction so that they can calculate the appropriate quantities of reagents for the synthesis of intermediate 7. Step 1 is conducted following the detailed procedure provided in the Supporting Information. The reaction is monitored by thin-layer chromatography (TLC) until the aniline has been consumed. At the end of the reaction, the product is isolated by precipitation in water and vacuum filtration.

Session 2: Step 2

In the second session, the students must weigh intermediate 7, calculate the yield of the first step, and determine its melting point. A small portion must also be separated to use as a TLC standard and to record the FT-IR spectrum in the third session. Students have to calculate the reagent quantities for the second step of the synthesis and then set up and run the reaction following the detailed procedure provided in the Supporting Information. Upon reaction completion, the effect of the pH on the reaction workup and purification is evaluated. Some students are involved in the acidification of the reaction medium to pH 2 and others to pH 8. The effect of this treatment is analyzed and discussed through TLC analysis of the resultant precipitate. Then all of the students have to adjust the solution to pH 8. The filtrate is isolated by vacuum filtration and washed with water. If necessary, the product 11 can be recrystallized from ethanol.

Session 3: Characterization of the Product

In the third session, the students have to calculate the yield of the second step of the synthesis as well as the global yield of the synthetic route. Then, the melting point of product **11** is determined, and **11** is characterized by ¹H NMR, attached proton test (APT) ¹³C NMR, and FT-IR spectroscopy by comparison with the spectra of intermediate 7. The product to be analyzed was maintained in vacuum since the preceding session. The samples were prepared, the ¹H and APT ¹³C spectra were obtained and processed, and their signals were analyzed and discussed. The observed chemical shifts were plotted against the values predicted by the MestReNova software. FT-IR spectra of both product **11** and intermediate 7 were also acquired.

HAZARDS

All reactants, products, and solvents must be handled in a manner consistent with the information available on their Material Safety Data Sheets. Eye protection, laboratory coats, and nitrile gloves must be used throughout the course of the experiment. Students should perform their experiments in a well-ventilated fume hood. In the second step, a slight characteristic odor may be detected, so it is recommended that the product isolation be performed under exhaustion conditions. Both hydrochloric acid and ammonium hydroxide are corrosive and may cause burning. Aniline is harmful if inhaled and is a potential methemoglobin-forming agent. Benzoyl chloride is hazardous if skin contact occurs (irritant). Dimethyl sulfoxide is readily absorbed through the skin and may carry other dissolved chemicals into the body. Acetone is a volatile and flammable solvent and can cause eye irritation. 1-Phenylthiourea (11) is toxic and must be handled with care. Both intermediate 7 and product 11 can cause skin irritation. The synthetic route was optimized for different less toxic

Scheme 1. Synthesis of 1-Phenylthiourea (11)



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anilines where available, and the data may be found in previously published literature.²²

RESULTS AND DISCUSSION

The experimental sessions were designed for students to enable them to review the basic concepts introduced in the prerequisite discipline (theoretical organic chemistry), linked to carbonyl addition and substitution, and to predict the scope of the planned synthetic route as well as the mechanisms, types of reactions, and limitations that occur in each step. The purification techniques, such as the effect of pH on ionization status and solubility as well as recrystallization and filtration concepts can also be explored and discussed in these sessions. The characterization of both the key intermediate and final product allows students both to practice and to discuss the theory behind such spectroscopic techniques. Students may apply prior knowledge of IR, ¹H NMR, and APT ¹³C NMR spectroscopy for interpretation of the product spectra. Additional methods for analysis of the reaction progress and product purity are TLC and melting point determination.

The students were divided into pairs, and at the end of the synthesis, the results were compared and discussed among all of the groups. The synthetic route to obtain product 11 is a two-step approach, and therefore, two practical sessions are needed, with each step being elaborated in one session; a third session intended for both characterization of the final product and evaluation of its purity. In the first session, the students must apply prior knowledge of stoichiometric calculations in order to find the measurable quantities of each component that will participate in the proposed experiment. Next, the synthesis is initiated by the reaction of benzoyl chloride with ammonium thiocyanate, which is followed by the addition of aniline to provide intermediate 7. In the first step, the students can check the chemical change by the yellow color that is formed in the reaction. After the addition of the nucleophilic aniline, the product formation and aniline consumption can be checked by TLC analysis. The workup consists of a simple precipitation in water and filtration at the end of the reaction, providing compound 7 with good purity, which can be checked by both melting point and TLC analysis. Here there is an opportunity to question students about the molar proportion of the reaction components, their physical properties such as solubility in aqueous media, and the possibility of using or not using an excess of each component involved in the workup as well as the expected product purity.

In the second session, students apply prior knowledge to calculate the yield of the first reaction and use the data to calculate the measurable quantities of the reagents for the basic hydrolysis of compound 7 in order to obtain the final monosubstituted thiourea 11. This reaction can be monitored through neutralization with NH₄Cl and microextraction of the TLC sample with diethyl ether, in accordance with Figure S1. Product 11 can be isolated by precipitation in water, controlling the pH of the mixture. 1-Phenylthiourea has a pK_{a} value of 9.62 and thus is ionized at the end of the hydrolysis (pH 14).²³ The hydrolysis byproduct, benzoic acid $(pK_a = 4.19)$ is present as sodium benzoate, so the reaction medium consists of a transparent solution of water.²⁴ In order to isolate product 11, it must be protonated to its neutral form by acidification of the crude reaction mixture in the workup. This reaction gives an opportunity to demonstrate the effect of pH control on the purity of the isolated compound during the workup. Some students are guided to acidify the reaction

medium to pH 2 using HCl and others to acidify the solution to pH 8 using NH₄Cl, where a massive precipitation occurs. The effect of this treatment is analyzed and discussed through TLC analysis of the precipitate formed. The analysis clearly shows that benzoic acid is a byproduct contaminant when the reaction mixture is treated with HCl, while it is not present in the mild acidification treatment. Thus, pH control can lead to product isolation with different degrees of purity and can avoid further purification steps. If necessary or as a pedagogical example, 11 can be recrystallized in ethanol into beautiful needlelike white crystals that crystallize in a short period of time (Figure 2). The yield ranges of both transformations as



Figure 2. 1-Phenylthiourea crystals.

well as the melting points of both intermediate 7 and product 11 are listed in Table 1. As detailed below, both reactions were

Table 1. Data Obtained from the Multistep Synthesis of 1-Phenylthiourea (11)

	Reaction Time	Yield	
Reaction	$(\min)^a$	$(\%)^{a}$	Melting Point (°C) ^{abc}
Synthesis of 7	30-40	78-86	140-142 to 152 -155
Synthesis of 11	20-35	60-91	149-152 to 158-162
^a Ranges were ob	tained from 11 d	lifferent exp	periments. ^b Literature
lata for compoun	d 7: 147–149 °C.	²⁵ ^c Literatu	re data for compound
11: 152–154 °C. ²	26		

completed in a short period of time, and good yields of each product were obtained. All of the samples presented a melting point range of <5 °C. It may be highlighted here that these values are the lower and higher values obtained by the students in the melting point experiments, and the absence of a high level of accuracy may be linked to the mixed levels of experience of the students in the melting point determination.

In the third session, the students calculated the yield of the second transformation as well as the global yield of the synthetic route. 1-Phenylthiourea was analyzed through melting point determination and was fully characterized by FT-IR and NMR experiments. Figure S2 shows the ¹H NMR spectra, in which both NH and aromatic hydrogens can be observed. The APT ¹³C NMR experiment (Figure S3) shows the C aromatic carbon and the thiocarbonyl carbon in a contrasting phase to the CH aromatic carbons.²⁷ All of the signals are very characteristic, making the final product a good

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example for didactic NMR demonstration. In order to verify

their assignments, the students created graphs of ¹³C chemical shift found against the value predicted by MestReNova 6.03 software. One of these graphs is shown in Figure S5.

Figure S4 in shows the FT-IR spectra of compounds 7 and 11. Comparison of these spectra allowed the students to verify the main structural changes in the second synthetic step: (i) the absence of amide bands after hydrolysis and (ii) the modification in the NH region due to the appearance of the primary thioamide in product 11. The students were able to assign both the important bands in the FT-IR spectra and signals in the NMR experiments with the expected structures.

The time needed for the development of the entire session is compatible with three lab periods, and Table 2 shows the

 Table 2. Approximate Times Spent in Different Steps of the

 Experimental Sessions

	Time (min)					
Session	Setup	Reaction	Workup	Analysis	Total	
1	80	35	40	-	155	
2	45	30	60	30	165	
3	30	-	_	120	150	

approximate time spent in each step of the experimental session. Another particular aspect of this synthesis is that its procedures can be adapted for most undergraduate laboratories, including those with limited facilities, considering that the scope of this reaction may be extended by the use of different anilines with different substitution patterns.²² The students were assessed by analysis of their involvement, attitude, and motivation during the sessions as well as through the writing of a full report about the three sessions. They were also questioned about the theme of the experiment (see the Supporting Information) in order to guide literature research. There was also time dedicated to the discussion of the results and reporting. Similarly, the calculations and the relevant chemical information behind the experiments were used for examination questions in the discipline.

CONCLUSIONS

In this experiment, undergraduate students of organic chemistry synthesized 1-phenylthiourea using an accessible multistep synthetic route with inexpensive starting materials, most of which are available in the majority of organic chemistry laboratories. These reactions made it possible to demonstrate important basic concepts that are studied in an organic chemistry graduation course. The most important concepts explored in the proposed undergraduate experiment were various aspects of carbonyl chemistry, the effect of pH on solubility by modification of compound ionization and its relation to purification steps, and also recrystallization as a purification technique. In addition, this reliable methodology allowed students to synthesize interesting products in high yields by using a reproducible protocol. There are clear advantages and opportunities for demonstrating many concepts applied in various organic chemistry courses. The students set up, carried out, and monitored the reactions and isolated, purified, and characterized the intermediate and the final product of the synthesis, showing that this protocol can be easily conducted in practical sessions of organic chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.0c01114.

Spectroscopic data (FT-IR, ¹H NMR, and APT ¹³C NMR) of representative samples; TLC analyses of intermediate 7 and final product **11**; detailed comments for instructors; questions for students; student evaluation of experimental sessions (PDF, DOCX)

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Notes

The authors declare no competing financial interest.

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