# **Supplementary Information**

# Synthesis of 1-phenylthiourea: an undergraduate organic chemistry experiment illustrating carbonyl transformations

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# **TABLE OF CONTENTS**

Figure S1 – A: TLC analysis of the precipitate obtained at $pH = 8$ (left), the precipitate obtained at $pH = 2$ (right) and benzoic acid standard (middle); B: TLC analysis of intermediate 7 (right) and hydrolyzed product <b>11</b> (left). Mobile phase: diethyl ether
Figure S2 – <sup>1</sup> H NMR of product <b>11</b> in DMSO-d <sub>6</sub> , 400 MHz
Figure S3 – APT spectra of product 11 in DMSO- $d_6$
Figure S4 – Infrared spectra of intermediate $7$ (a) and product $11$ (b)
Figure S5 - Correlation between calculated and observed NMR shifts. The prediction of chemical shifts was performed using MestReNova 6.0.2-5475 (MestreLab Research S.L., 2009)
Questions for students 10
Student evaluation of experimental class
Reference

#### **CONSIDERATIONS ABOUT THE EXPERIMENTS FOR INSTRUCTORS**

#### **Chemicals and Equipment**

The chemicals of the experiment were of standard grade, obtained from commercial suppliers and used without further purification. Thin-layer chromatography (TLC) was conducted using Merck Silica Gel GF254 (0.25 mm thickness). For visualization, the TLC plates were either placed under ultraviolet light or stained with iodine vapor. Melting points were measured using a Fisatom model 431 equipment and were uncorrected. Infrared spectra data were collected using an IR Prestige-21 Shimadzu.

Samples for NMR were prepared by dissolving 15 mg of the product in 0.8–0.9 ml of DMSO- $d_6$  as indicated in the experimental section. <sup>1</sup>H NMR spectra were measured with 12 scans; relaxing time of 4 s and delay of 1 s. APT spectra were measured using 256 scans. <sup>1</sup>H and APT experiment were collected on a Bruker Ascend 400 NMR spectrometer, operating at 400 MHz for hydrogen and 100 MHz for carbon nuclei, using DMSO- $d_6$  as solvent. Tetramethylsilane (TMS;  $\delta = 0.00$  ppm) served as an internal standard for the NMR spectroscopy experiments.

# 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 burnings. 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 anilines where available, and the data may be found in previously published literature.<sup>1</sup>.

#### Organization

Students were organized in pairs due to the limitations of laboratory space. If possible, individual experimentation is preferable. In order to optimize the class time, a laboratory

technician can keep the oil bath (or heating mantle) at an adequate temperature for acetone reflux. This laboratory experiment addresses important concepts of organic chemistry linked to carbonyl chemistry, such as carbonyl addition and substitution reactions, melting point, NMR and FT-IR techniques. Instructors may use the free time during sessions to remind students of these subjects as well as teaching/recalling spectroscopy techniques. All starting materials used in this class are easily obtained from commercial sources.

#### Lab Session 1

A two neck round bottom flask (50 ml) was charged with ammonium thiocyanate (MW = 76.1 g/mol, 1.1 equiv., 11.0 mmol, 837 mg), acetone (15 mL) and benzoyl chloride (MW = 140.6 g/mol, d = 1.21 g/l, 1 equiv., 10.0 mmol, 1.16 ml) with magnetic stirring at room temperature. The round bottom flask was then coupled to a condenser and transferred to an oil bath or a heating mantle and heated at 60°C for 15 minutes. Then aniline (MW = 93.1 g/mol, d = 1.03 g/ml, 1 equiv., 10.0 mmol, 0.911 ml) solubilized in acetone (3 ml) was added dropwise and the heating of the solution was maintained for approximately 20 minutes. The reaction was monitored by TLC until aniline consumption. Following this, the reaction medium was poured into 50 ml of room temperature water and stirred vigorously and the precipitate formed was vacuum filtered and kept under reduced pressure. This intermediate is highly stable and can be stored for use in the next class.

## Lab Session 2

This class involves the preparation, isolation and purification of 1-phenylthiourea (11) through hydrolysis of intermediate 7 obtained in the lab session 1. Before proceeding, the students will be advised to save a small amount of the starting material for the purpose of TLC and FT-IR analysis.

In a round bottom flask (50 ml) fitted with a condenser, intermediate **7** (approximately 2.3 g, MW = 256.32 g/mol, 8.90 mmol) is added to a sodium hydroxide aqueous solution (2.5 M, 15 ml) and stirred at 90°C for approximately 20 minutes. The reaction flask is then cooled to room temperature. This reaction can be monitored using TLC by both neutralization with NH<sub>4</sub>Cl and micro extraction of the TLC sample with ethyl acetate. Upon reaction completion, the effect of the pH value on reaction work up and purification is evaluated. Some students are guided to acidify the reaction medium to pH 2 using HCl, while others are guided to acidify to pH 8 using saturated NH<sub>4</sub>Cl. The effect of this treatment is analyzed and discussed through TLC analysis of the precipitate formed (Figure S1). All the students must then adjust to pH 8 (by using Na<sub>2</sub>CO<sub>3</sub>). The

filtrate is isolated by vacuum filtration and washed with water. If necessary, the 1-phenylthiourea **11** can be recrystallized from ethanol. The base and acid addition can be performed using a Pasteur pipette and the pH checked with pH indicator strips. In general, only a few milliliters of acid or base are spent during this procedure. During these procedures, it is very important that the instructor reminds the students about the use of nitrile gloves, protecting glasses and coat, and the use of an exhaust system.

After the pH adjustments, the precipitate can be analyzed by TLC using diethyl ether as eluent on silica plates. The intermediate **7** present a Rf value of 0.90 and the product **11** a Rf value of 0.50. The intermediate **7** and the product **11** show a high degree of purity without extra purification processes, according to Figure S1.

If necessary, the product can be recrystallized using ethanol. This recrystallization is viable during the class because the product crystalizes in a few minutes. For the recrystallization process, the product is solubilized in a minimum amount of boiling ethanol with stirring. When all material is solubilized, the recipient is left to cool to room temperature. The crystals can be isolated by drainage of the supernatant, followed by washings of the crystals with small amounts of cold ethanol.



**Figure S1** – **A**: TLC analysis of the precipitate obtained at pH = 8 (left), the precipitate obtained at pH = 2 (right) and benzoic acid standard (middle); **B**: TLC analysis of intermediate **7** (right) and hydrolyzed product **11** (left). Mobile phase: diethyl ether.

#### Lab Session 3

In the third class, the students will be instructed to check the yield of their reactions, their purity by melting point determination and characterize their products by spectroscopic techniques. The product to be analyzed is kept under vacuum between the classes. 1-Phenylthiourea (15 mg) is carefully weighed in a NMR tube. To this sample, a deuterated DMSO (0.80-0.90 mL) is carefully added, by using a Pasteur pipete. In a short time (in less than 30 minutes for both), the <sup>1</sup>H and APT spectra were obtained. The students then process their adquired FIDs in MestReNova 6.0 software and analyzed the signals.

The instructor can discuss the two groups of signals observed in <sup>1</sup>H NMR: (*i*) the signals corresponding to the aromatic ring; and (*ii*) the signals corresponding to the hydrogens that are linked to the nitrogens. In the APT experiment, the characteristic carbon of C=S appears near 181 ppm and the aromatic carbons may be observed at 139 ppm. The instructor must remind the students about the chemical equivalence of some carbons due to the symetry of the aromatic ring, which results in only three CH aromatic signals. The <sup>1</sup>H NMR spectrum is shown in Figure S2, while the APT spectrum is shown in Figure S3.

After the students discuss the chemical shifts of each signal, they can simulate the <sup>13</sup>C chemical shifts in the MestReNova software. The accuracy of the calculated assignments is evaluated when the students plot the observed chemical shifts against the values predicted by the software MestReNova. In all the cases, a good correlation between the predicted and observed chemical shift was found. An example of this analysis is shown in Figure S4.

The students also performed a FT-IR spectra of the product **11** and the intermediate **7** (Figure S5). The simple observation of the carbonyl stretching frequencies allowed for confirmation of the hydrolysis reaction. Amide C=O stretching vibrations are absent in the product **11** after hydrolysis and present in intermediate **7**. In addition, changes in the wavenumber region corresponding to NH stretching can be observed. In the product, a new NH<sub>2</sub> group appears when compared with intermediate **7** in which only the two NH groups are found.

#### Reresentative product data obtained

*1-phenylthiourea* (**11**): *mp*. 150-154 °C, yield 82%. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): 7.14 − 7.08 (*m*, 1H); 7.36 − 7.29 (*m*, 2H); 7.42 − 7.37 (*m*, 2H); 9.68 (*s*, 1H). APT <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): 123.04 (2xCH), 124.40 (CH), 128.70 (2xCH), 139.07 (C), 181.00 (C).











Figure S4 – Infrared spectra of intermediate 7 (a) and product 11 (b).



**Figure S5** - Correlation between calculated and observed NMR shifts. The prediction of chemical shifts was performed using MestReNova 6.0.2-5475 (MestreLab Research S.L., 2009).

#### Questions for students

1. Search the literature for alternative approaches to 1-phenylthiourea synthesis

1-phenylthiourea can be obtained by the heating of the desired arylamine with ammonium thiocyanate in acid media with water as solvent. <sup>[a]</sup>

$$R \stackrel{\text{II}}{=} \stackrel{\text{NH}_2}{\longrightarrow} \stackrel{\text{NH}_2}{\xrightarrow} \stackrel{\text{NH}_4\text{SCN, HCl}}{\xrightarrow} R \stackrel{\text{II}}{=} \stackrel{\text{NH}_2}{\xrightarrow} \stackrel{\text$$

Another method to obtain 1-phenyl(thio)ureas is by reflux of (thio) urea with the desired arylamines and acid. To avoid the formation of di-substituted byproducts, the (thio)urea must be used in excess. <sup>[b]</sup>



2. Explain the changes in pH after hydrolysis and correlate the observed purity of the isolated compound

Benzoic acid shows a pKa value of 4.19 <sup>[c]</sup> and the predicted 1-phenylthiourea pKa value is 9.62.<sup>[d]</sup> At pH 2, both compounds will be present as water insoluble neutral species, while at pH 8, benzoic acid will be present in its water-soluble salt form and 1-phenylthiourea in its water insoluble neutral form. Filtration of the reaction medium at pH 2 isolates the product contaminated with benzoic acid, while filtration at pH 8 isolates only 1-phenylthiourea.

3. Use the literature to identify reactions which employ 1-phenylthiourea as the starting material Thioureas can be used as building blocks in the Biginelli reaction to produce N1 aryl dihydropirimidin-2-thiones analogues, as shown below by employing chlorotrimethylsilane (TMSCI) as reaction promoter. <sup>[e]</sup>



2-aminothiazole derivatives can be obtained by the reaction of 1-phenylthiourea and a  $\alpha$ -bromoketone in refluxing ethanol.<sup>[a]</sup>



4. Why is the carbon of intermediate **4** (PhCON=C=S) easily attacked by nucleophiles such as the amino group of aniline?

Nitrogen and sulfur atoms are more electronegative than carbon. They deal better with negative charges and have the tendency to form polar bonds where the electrons are closer to them than carbon. This means that the carbon atom is highly electron deficient and can interact with nucleophiles such as anilines.

[a] European Journal of Medicinal Chemistry 87 (2014) 643e656

[b] Indo Global Journal of Pharmaceutical Sciences, 2013; 3(1): 33-39

[c] https://pubchem.ncbi.nlm.nih.gov/compound/benzoic\_acid#section=Top access 15/02/2019

[d] https://pubchem.ncbi.nlm.nih.gov/compound/Phenylthiourea#section=Top access 15/02/2019

[e] Tetrahedron Letters 59 (2018) 2759-2762

#### Student evaluation of experimental class

 The didactic material and laboratory protocol produced was relevant for the classes
 a. strongly disagree (0, 0%)\*1

b. disagree (0, 0%)

c. neutral (1, 6%)

d. agree (8, 44%)

e. strongly agree (9, 50%)

2. The professor instructions were adequate for the successful development of the experimenta. strongly disagree (0, 0%)b. disagree (0, 0%)

c. neutral (0, 0%)

d. agree (7, 39%)

e. strongly agree (11, 61%)

3. In my opinion the experiment was successfully completed
a. strongly disagree (0, 0%)
b. disagree (1, 6%)
c. neutral (1, 6%)
d. agree 9, 50%)

e. strongly agree (7, 39%)

b. disagree (1, 6%)
c. neutral (5, 28%)
d. agree (6, 33%)
e. strongly agree (6, 33%)

5. In my opinion, these experiments are more interesting than other experiments developed in this course.
a. strongly disagree (0, 0%)
b. disagree (2, 11%)
c. neutral (6, 33%)
d. agree (7, 39%)
e. strongly agree (3, 17%)

6. I would recommend that theseexperiments continue being developed in the organic synthesis course next semester.a. strongly disagree (0, 0%)b. disagree (0, 0%)

c. neutral (1, 6%)

d. agree (8, 44%)

e. strongly agree (9, 50%)

 Write here your comments and suggestions for improvement of this class. No suggestions.

\*(number of students, % of total students)

4. These experimental classes helped me to understand concepts from other disciplines a. strongly disagree (0, 0%)

<sup>&</sup>lt;sup>1</sup> Reported as absolute number followed by percentage

## Reference

1. I. Gonçalves, L. Rockenbach, G. das Neves, G. Göethel, F. Soares do Nascimento, L. Porto Kagami, F. Figueiró, G. Oliveira de Azambuja, A. de Fraga Dias, A. Amaro, L. de Souza, I. da Rocha Pitta, D. Avila, D. Kawano, S. Garcia, A. M. d. O. Battastini and V. L. Eifler-Lima, *Medicinal Chemistry Communications*, 2018, **2018**, 995-1010.