Triazolinedione-based Cross-linking of Plant Oils: an Introductory Organic Reactivity Laboratory Experiment

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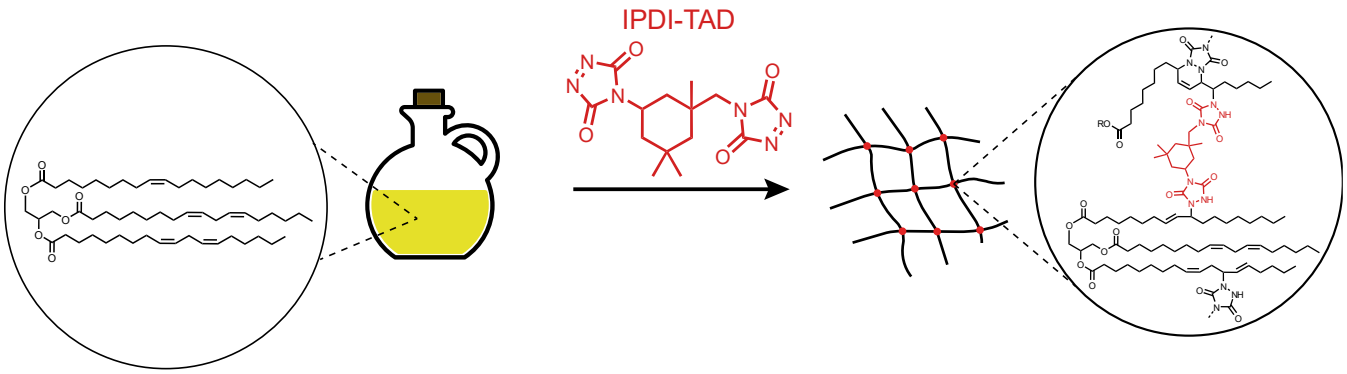
ABSTRACT

An undergraduate laboratory experiment has been developed for the synthesis of a reactive cross-linker that is useful in various highly visual demonstrations of organic reactivity, click chemistry and bio-based polymer synthesis. A triazolinedione-based cross-linker, which is known as a useful reagent for click chemistry, can be obtained from bio-based isophoronediisocyanate (IPDI) in three synthetic steps: two steps to elaborate a urazole precursor, and finally a mild oxidation of this urazole to the highly reactive triazolinedione click reagent. As triazolinediones are strong chromophores, progress of the oxidation step can be visually monitored by the appearance of a bright red-pink color. Students can either perform all three synthetic operations or just the final oxidation step, starting from a prepared batch of the precursor. Alternatively, for less experienced students, the reactive cross-linker or click reagent can be prepared beforehand by a lab assistant, and used as such. Students use the freshly prepared click reagent to covalently cross-link various unsaturated plant oils into a polymer network. The gelation of the plant oil into a “plant foil” can be visually monitored as the bright red-pink color of the cross-linker disappears over time. The purity of the synthesized cross-linking reagent can also be assessed by students using a simple titration experiment. Students can rely on various practical first and second year undergraduate lab skills, but at the same they arrive at a tangible and visual experience of chemical reactivity.



KEYWORDS

Second-Year Undergraduate, freshman, Multidisciplinary, Laboratory Instruction, Organic Chemistry, Polymer Chemistry, Analytical Chemistry, Hands-On Learning, Alkenes, Fatty Acids, Click chemistry, Heterocycles, Oxidation, Polymerization, Titration, bio-based materials synthesis

INTRODUCTION

A staple of introductory undergraduate laboratory experiments, and even a popular high school demonstration experiment, is the synthesis of nylon 6,6 via interfacial polymerization.[1a,b] Therein, a simple amide-forming condensation reaction is visualized by the formation of a long polyamide chain that – according to uninitiated students and pupils – almost magically appears from in between two dilute solutions. A diamine and a diacid-dichloride solution are carefully put into contact with each other, with the polyamide material being synthesized at their interface as fast they can pull away a nylon thread from in between these layers. It is a highly visual experience for students and brings home the message of chemical transformations in a very tangible and memorable way.

Unfortunately, not all polymerization reactions lend themselves well to adaptation in an undergraduate lab experiment.[1c-g] Many classical polymerization methods require specific reactors, volatile and hazardous monomers, high temperatures, or inert and anhydrous conditions. In general, polymer synthesis requires very good student lab skills in order to ensure a successful experimental outcome. The concept of click chemistry aims to identify more simple, reliable and user-friendly processes to form bonds.[2] In 2014, Du Prez and Winne and co-workers introduced the use of triazolinedione-based *click chemistry* in the field of polymer synthesis,[3] which enables a facile and atom economic way to assemble complex and even dynamic molecular architectures from relatively simple building blocks without the need for any catalyst, initiator, special precautions or even pure starting materials.[4] Triazolinedione based click chemistry has found its way into many applications,[5] along with the more well-known, and Nobel prize winning triazole-based click chemistry.[6]

Herein, we report our efforts to incorporate the user-friendly triazolinedione-based click chemistry for macromolecular synthesis platform into an early-stage chemistry experiment for second year Bachelor students of chemistry. It combines the attractive visual features of polymer material synthesis with some sofomore organic reactivity, all integrated into the context of green or bio-based chemistry and renewable materials synthesis. This practical exercise can be implemented as a lab that combines skills from organic synthesis, titrimetric analysis and polymer synthesis. Alternatively, it can be tailored

for less experienced students and pupils as a very visual demonstration of polymer synthesis and click chemistry.

BACKGROUND

In 2015, Du Prez and Winne and coworkers reported that natural plant oils could be fully cross-linked into a thermoset network, using highly reactive triazolinedione-based cross-linking reagents (see Figure 1).[7] In that initial study, a wide range of simple vegetable oils, used in an unpurified supermarket consumer grade, were treated with bifunctional triazolinedione reagents, resulting in a fast network formation, due to the 'clicking together' of the unsaturated triglyceride fatty acid chains. The cross-linking reaction can be visually monitored by the disappearance of the distinctive and bright pink-red color of the triazolinedione reagent, and by the gelation of the oil (which usually preceeds the discoloration), which happens within a span of 5-15 minutes. By varying the relative amounts of cross-linker versus plant oil, and by varying the type of plant oil (degree of unsaturation), not only clear differences in the rate of gelation can be observed, but also differences in the properties of the obtained materials (increasing stiffness and brittleness for higher cross-linking degrees). Apart from a nice demonstration of the power of the triazolinedione 'click' reagents, as an efficient bond-forming reaction that works in high efficiency without having to take any special precautions, this type of experiment also seemed to be an ideal starting point to develop a novel teaching lab experiment. The synthesis of the cross-linking reagent is straightforward to perform, starting from a bio-based isocyanate monomer (isophorone diisocyanate). Its synthesis can be performed in a large batch by the instructors (10-20 gram), or – if time and student skills allow for this - in smaller batches by the students themselves. The cross-linking experiment itself is very straightforward, rapid, and highly visual. The use of different simple vegetable oils or other unsaturated plant based oils (such as terpenes) as fully renewable monomers, also opens up room for experimentation. Students can vary the amount of the cross-linker used, and they can also experiment with the exact mixture of plant oils that is used.

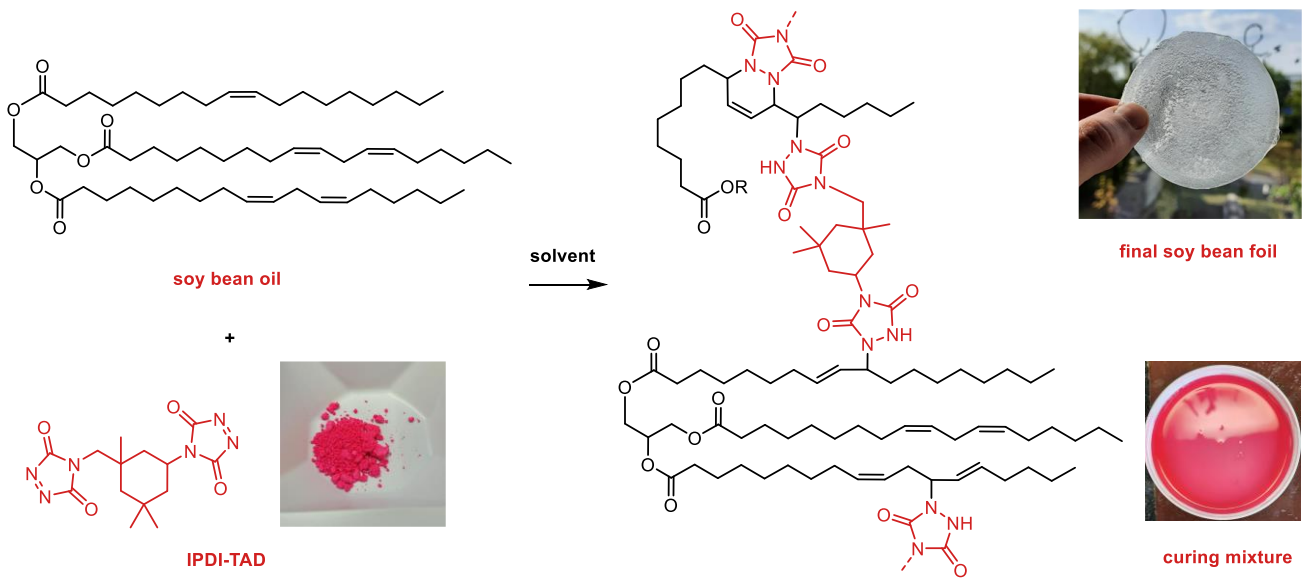


Figure 1: Example of a triglyceride that is cross-linked into a network using a bifunctional triazolinedione.

4-substituted-1,2,4-triazoline-3,5-diones (TADs) are generally considered to be the most reactive bench-stable dienophiles and enophiles.[5] They are highly reactive organic pi-acids, that prefer to react and bind with pi-electrons and alkenes rather than more classical 'lone pair' nucleophiles or bases. This chemoselectivity has led to multiple applications of triazolinedione-based click chemistry in synthesis,[8] polymer chemistry,[9] and bioorthogonal protein conjugation.[10] Although TADs are stable compounds, they need to be stored in strict absence of light and moisture, so in practice, TAD reagents are usually prepared directly before use from their corresponding urazole (or dihydrotriazolinedione, see Figure 2). Urazoles are fully bench stable, and can be oxidized to the corresponding TAD reagent in a single step. Although many oxidation methods are known for urazoles, most of them are quite hazardous and not very suitable for undergraduate lab course work. The original method used by Du Prez and others for the oxidation of the bisTAD, required the use of the hazardous 1,4-diazabicyclo[2.2.2]octane bromine complex (DABCO-Br).[3,7] As DABCO-Br slowly releases bromine (Br_2) when stored, it cannot be stored indefinitely, and its use in undergraduate labs is certainly a serious hazard, as bromine gas is acutely toxic. Alternative common urazole oxidation methods which have been used for student practicals are based on nitrogen dioxide gas (NO_2-N_2O_4),[11] or oxone.[12] For the purpose of this laboratory experiment, we adopted the use of trichloroisocyanuric acid (TCICA) as a safer oxidant.[12] TCICA is a commercially

available bench stable compound, and its use in the oxidation of urazoles is experimentally straightforward.[10] Additionally, TCICA can be considered as a relatively safe oxidant as it is actually also 'household chemical' available to a wide public, as it is used as a common active chlorine-based swimming pool cleaner and disinfectant.

PEDAGOGICAL GOALS AND LEARNING OBJECTIVES

This laboratory experiment is performed by second-year undergraduate students at the end of their third semester. The goal of the experiment is to let the students use some of the techniques they learned in the course of this semester, more specifically the synthesis of small organic molecules, and the analysis of reagents by titration. At the same time, they get an introduction to some of the concepts from polymer and thermoset material synthesis, as well as the use of renewable chemical feedstocks for the production of synthetic materials. Students also get to experience a 'hands on' example of the click chemistry concept and in the use of click reagents to directly functionalize and derivatize various biomolecules.

The experiment allows a student to visually monitor both the oxidation step (formation of the reagent) as well as the plant oil cross-linking process. They will also witness the gelation of the oil into a covalent network. In this way, they get more insight into chemical reactivity without having to go through the classical indirect ways to monitor reaction progress such as thin layer chromathography, LC-MS or infrared spectroscopy. By using various plant oils available from the supermarket or chemical vendors, and due to the very permissive nature of the cross-linking reaction in terms of stoichiometry, they can also be allowed to experiment with different formulations and ratios of reagent versus plant oil, without the need to be very precise. The bond formation is very robust, and the addition of a TAD reagent onto a fatty acid chain unsaturation (the ene reaction) does not consume the reactive double bond, but displaces it along the fatty acid alkyl chain, creating a new reactive site for additional cross-links (see Figure 1). Finally, the students are also asked to assess the purity of their prepared cross-linking agent by means of a simple titration experiment.

- Perform a multistep synthesis and isolate the target reagent in good yield
- Deduce curved-arrow mechanisms for all chemical transformations involved.
- Assess the reactivity of triazolinediones towards several reaction partners
- Perform a titration on an organic reagent

During the laboratory experiment the students need to keep careful records in a student lab book. Their report must contain the experimental hazards and risk assessment, and describe conducted experiments and observations. Additionally, students have to describe the mechanism of the reaction that is happening in their reports and answer a set of questions that probes them to think about the background and the chemical underpinnings of the experiment (such as the relation between the obtained material properties and experimental parameters). Finally, they have to calculate a purity of the synthesized reagent and critically assess the outcome of their gelation experiments in a written conclusion. These lab reports are graded by the supervisors that also guided the students during the practical.

EXPERIMENTAL OVERVIEW

The urazole **2** that is used for this experiment is a bisurazole derived from commercially available (and bio-based) isophorone diisocyanate (IPDI) **1**. The IPDI-Urazole **2** can be oxidized to the reactive cross-linker IPDI-TAD **3**. The synthesis of this IPDI-Urazole is rather straightforward to perform starting from the cheap isophorone diisocyanate as shown in Figure 2 (see Supporting Information). It can be prepared on multigram scale (20-50 gram batch) upfront for the students to use, or its two-step synthesis can be part of a preceeding synthesis lab experiment. For our practical, the students started from a batch of the bis-urazole **2** that was available on large scale in our laboratory.[13]

The experiments were preceded by an introductory explanation about the chemistry (see Supporting Information) and about the goal of the laboratory experiment. In this way the students were briefly introduced to the chemistry of triazolinediones, click chemistry, bio-based polymers, and polymer synthesis and thermoset cross-linking.

Oxidation of IPDI-Urazole

Each student can do the oxidation experiment individually, using non-dried glassware. Briefly, IPDI-Urazole **2** (1.00 g, 2.96 mmol, 1.00 equiv.) is brought into a 50 ml round bottom flask with a stirring bar, onto which 15 ml of acetonitrile was added. TCICA (458 mg, 1.97 mmol, 0.67 equiv.), was then added to the mixture followed by anhydrous Na_2SO_4 (1.68 g, 11.84 mmol, 4 equiv.). On this small scale, cooling of the reaction with a water or ice bath is not required as it is only mildly exothermic. The flask is then covered in aluminium foil to limit the exposure of the prepared IPDI-TAD to ambient light, which can initiate side reactions. After stirring at room temperature for 2 h the bright red/pink mixture is filtered over a glass filter into a pre-weighed 100 ml round bottom flask and the residue is washed with 5-10 ml acetonitrile. The deep red/pink filtrate is then concentrated *in vacuo* using a rotary evaporator until dry red-pink solids remain. The flask containing the IPDI-TAD was weighed again to determine the amount of IPDI-TAD (to determine the yield).

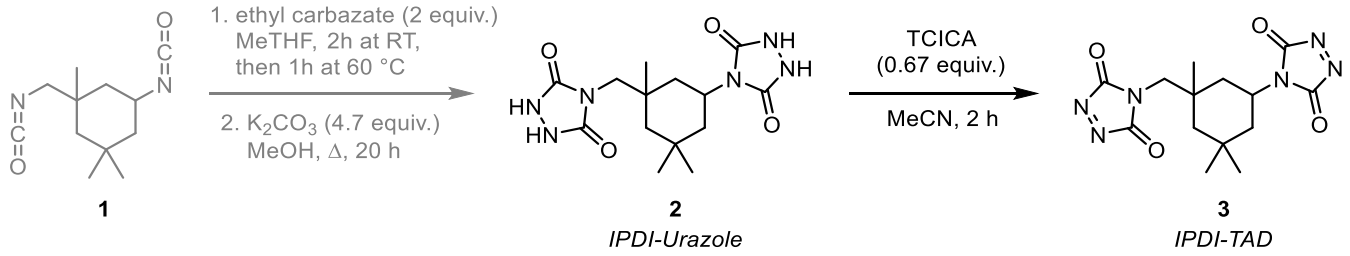


Figure 2: The synthesis of IPDI-TAD

Cross-linking the oil

250 mg of soy bean oil (or any other available plant oil, such as sunflower oil, olive oil, …) is added in a small plastic cup and dissolved in 2 mL dimethylcarbonate. Acetone can also be used as a solvent, although this is less efficient (as TADs have a slow background reaction with acetone, the use of this solvent can limit the success of the cross-linking, leading to a wider variation in results). Then, 125 mg of freshly prepared IPDI-TAD is added in a separate plastic cup or in a glass test tube, and dissolved in 2 mL dimethylcarbonate. The IPDI-TAD dissolves quite slowly and this may require some effort to arrive at a fully homogeneous solution. The mixture can be sonicated to facilitate this (if a sonication bath is present in the lab). Afterwards, the plastic cup (or test tube) with the click reagent 3 is added to that with the plant oil solution. The liquids should be thoroughly mixed for 1 minute and then poured into a

plastic lid, where it can be left to react until a foil is formed. After 30 minutes, the lids can be dried in an oven at 50 °C for 1 h, or they can be left for longer.

Titration of the IPDI-TAD

IPDI-TAD has a distinctive reddish/pink color that disappears upon reaction. Therefore, this color can also be used to determine the purity of the IPDI-TAD by means of a titration. While the students are waiting for their foil to dry, they can perform the titration. The students are offered a compound that is a naturally based furan (1,5-dimethylfuran) which is also a very good diene for a reaction with TAD, instantly resulting in the formation of a Diels-Alder adduct with TADs at room temperature. A simple stoichiometric calculations allows the students to assess the purity of their reagent after this titration experiment.

It is advised to let the students weigh out an exact amount (around 100 mg) of their synthesized IPDI-TAD **3** and dissolve it in acetonitrile in an Erlenmeyer flask, or round bottom flask with a stirring bar. They can use either a small burette or even a syringe to add the standard dimethylfuran solution, until all red color has disappeared. This reagent reacts instantaneously in a 1:1 ratio with TAD functionalities (so 2:1 for IPDI-TAD **3**), which is necessary for an accurate titration. Students can calculate their purity, and then critically compare this to the outcome of their cross-linking experiment (those with low purity will generally observe no or poor network gelation).

HAZARDS

For both experiments the proper PPE should be worn (lab coat, safety glasses and disposable gloves where needed) and it is strongly recommended to perform all experiments in a fume hood, even if only low hazard solvents are used such as acetone, acetonitrile and dimethyl carbonate. Hazards related to main compounds are given below, an elaborate hazards identification list is provided in the Supporting Information:

- **Trichloroisocyanuric acid (TCICA):** Even though trichloroisocyanuric acid is used as a disinfectant for swimming pools, higher levels of exposure can cause serious eye irritation and may cause respiratory irritation. It has the tendency to form chlorine gas (Cl_2), especially in acidic environment. For these reasons it is best to handle it inside a working fume hood.
- **Hydrogen chloride:** this gaseous by-product is generated in the oxidation step from TCICA and the IPDI-urazole. It will spontaneously evolve from the reaction mixture. It is important to perform the oxidation in a fume hood in an open reaction vessel and to make sure all volatiles have evolved before transferring the obtained solution to a rotary evaporator. In any case, the oxidation step should never be performed outside of a working fume hood to avoid exposure to this toxic and corrosive gas. Performing the oxidation in a closed vessel can lead to dangerous build up of pressure, so this should also be avoided. The addition of anhydrous sodium sulfate to the reaction mixture of the oxidation steps prevents the formation of hydrochloric acid from traces of water.
- **IPDI-TAD (3):** This is still an experimental chemical that has not been fully tested yet for hazards. As TADs are known to be reactive towards biomolecules such as proteins,[10] it is advised to be cautious when handling these reagents, so wearing standard nitrile lab gloves is advised when handling this liquid. Any unreacted residues of TAD or waste (acetone rinsings) can be quickly and efficiently neutralized using the solution of 2,5-dimethylfuran.

Note: This lab can be implemented as a generally safer experience than typical polymerizations if the oxidation reaction procedure (producing HCl gas) is performed beforehand by a supervisor on larger scale (see supporting information). This approach is not only safer for students, it is also very practical to cater for larger groups of students. These can perform the polymerization experiments on plant oils with minimal use of fume hoods (sharing one fume hood for 4-8 students on a turn base is quite feasible and has been implemented in our department). A more extensive discussion of the hazards associated with the synthesis of the IPDI-urazole compound is provided in the supporting information.

RESULTS AND DISCUSSION

The experiment was run by 20 students individually during a practical session over the course of one day (9:00-16:45). The total time they spent in the lab was between 5 and 6 hours, including a short introductory lecture. The experiment can also be split in two shorter practical sessions by storing the synthesized IPDI-TAD cross-linker at -20°C (lab freezer) after thorough drying. All students were successful in synthesising the IPDI-TAD with isolated yields ranging from 13% to 93% (see Figure 3). The students needed to do some calculations for the titration. Care has to be taken, because some students did not recognise at first that two equivalents of furan were needed for one equivalent of IPDI-TAD as there are two TAD functionalities present. The titration itself proceeded smoothly and students had a calculated purity varying from 57% to 100% (Figure 3c).

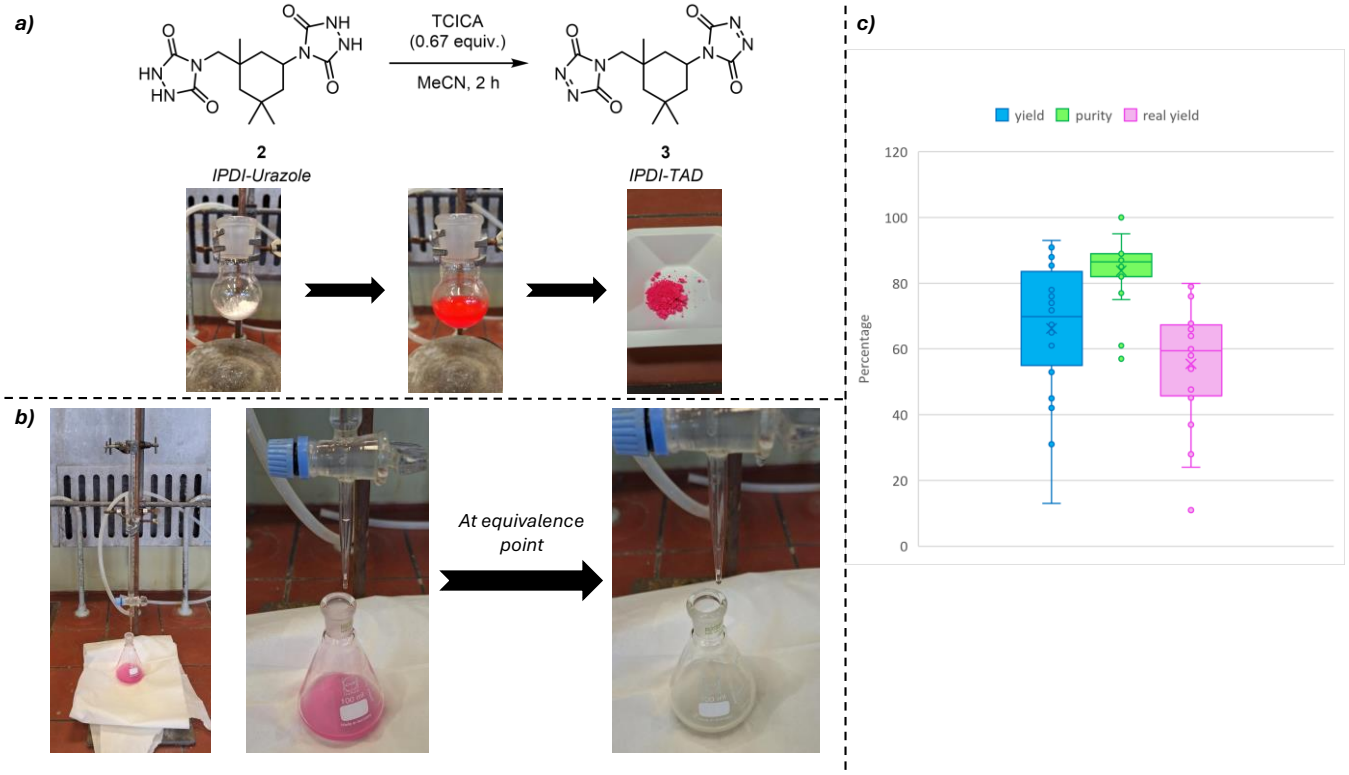


Figure 3 a) IPDI-Urazole (2) oxidation to IPDI-TAD (3), b) Titration setup in which a stock solution of dimethylfuran is used to titrate the synthesisd IPDI-TAD, c) Boxplot ot the results of the students.

The cross-linking of plant oil was straightforward to perform, but gave mixed results for the students, as could be expected from the wide range in purity of the obtained IPDI-TAD reagent. Another important variable was the homogeneity of the solution of the TAD reagent. Quite few students obtained materials (or not fully cured gels) with dark pink-red 'spots' of concentrated IPDI-TAD, making the plant oil based

material they obtained rather heterogeneous. Some samples took overnight drying before a clear 'foil' could be peeled off the lid. When time and materials allows, students were encouraged to experiment with various ratio of plant oil and IPDI-TAD reagent. In particular the use of nerol and geraniols (as polyunsaturated monoterpenes) was very suitable here. These plant oils have trisubstituted olefins and react much more rapidly with TAD, giving an instant gelation, even when acetone is used as a solvent. Some of the soy bean oil derived 'plant foils' turned out to be opaque or off-white to brown rather than the expected transparent material with the same aspect and color as the neat plant oil. This is usually related to the fact that the students did not obtain a pure or sufficiently dried TAD reagent. The same problem was not observed in another lab practical where the oxidation and drying of the IPDI-TAD reagent was performed by a lab assistant prior to the student exercise. This approach is less challenging for students, and gives them more freedom to experiment with different plant oils. Moreover, such a lab can be done in a single afternoon, even with high school students.

Pedagogical outcome. The students that performed both the synthesis, titration and cross-linking experiments were also given questions to answer in their lab reports (where they detailed yield, purity and observations). These question sets are provided in the Supporting Information. The students received a score out of 20 on their overall lab performance, with half of the mark on how well they performed and came prepared to the lab and followed safe practices, and the other half on the written student report. Awarded scores for the entire semester's performance ranged from 11/20 to 16/20. The report for this practical was not graded based on the purity and yield that was reported, but on its completeness, and correctness of answers to questions as well as the soundness of the conclusions. Extra credit was awarded to students that could make a connection in their report between various experimental outcomes (such as purity and gelation). While the student assessments (scores) for the lab report were generally in line with those of other organic chemistry practicals, the student scores for the work floor/attitude evaluation showed an improved trend, as students were generally better prepared and clearly showed higher engagement levels according to their usual lab supervisors. Many students also started to 'experiment' automatically at the end of the practical, playing with different parameters to see how they could affect the material synthesis, and engaging their supervisors about the scientific aspects of their practical. The students were also surveyed about their lab experience. Some students

indicated that they struggled to understand the exact chemistry that was happening, as they had not yet seen this reaction type in lecture courses, but they still found the lab more engaging than a classical organic synthesis experiment. Even when the plant oil cross-linking experiment was performed by visiting high school students in our department, they reported a positive learning experience, and the same tendency to start to experiment could be observed in this relatively unexperienced student population.

In our experience, the oxidation of the urazole towards the TAD is a good test of general student lab skills, as both the titration experiment and the cross-linking experiment allow a very quantitative and qualitative assessment of the outcome of the synthesis of the TAD reagent. If desired, a simple quantitative assessment of lab skills is thus also possible based on numerical outcomes, although this was not implemented by us here, given the relatively junior nature of these students in terms of organic synthesis experience.

CONCLUSION

The laboratory experiment reported here is well appreciated by students, and can be readily tailored to diverse audiences. The oxidation step used herein also clearly presents is a safer and more practical alternative to the previous reported oxidation methods.[11,12] The practical provides hands on experience of relatively complex concepts such as polymer cross-linking, click chemistry, and bio-based plastics. It is also a very visual experience of organic reactivity in general, while the technical difficulty of the experiments is very low. This leaves time and opportunity for students to critically think about their experiments, and even to design their own experiments. All students were successful in arriving at a cross-linked material, and several students showed original thinking in adapting the formulations to arrive at different outcomes and different bio-based plastics. Depending on the practical skills level of the students the experiment can be extended to a multiple day practical, including the synthesis of IPDI-Urazole (2) starting from the diisocyanate as reprented in Figure 2. Conversely, the practical can be shortened to a half day experiment, if the IPDI-TAD reagent is prepared beforehand by a lab assistant (it can be easily stored for several days without special precautions). In this simplified version, student populations can be easily scaled to larger groups, and to teams of students (40-80 students). Creative

315 expansion is easily achieved by switching from soybean oil to other unsaturated plant oils, leading to diverse outcomes.[7] We thus expect that this lab exercise can be of value for a wide range of student audiences.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.XXXXXXX.

Synthesis of the IPDI-urazole (**1**), notes for Instructors, handouts for the students, NMR spectra of the IPDI-urazole (**1**) (DOCX)

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