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Laboratory Experiment

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Synthesizing Substituted 2-Amino-2-chromenes Catalyzed by Tertiaryamine-Functionalized Polyacrylonitrile Fiber for Students To Investigate Multicomponent Reactions and Heterogeneous Catalysis

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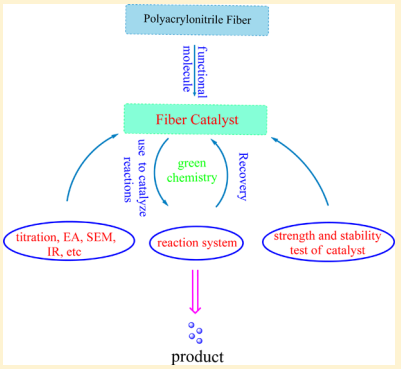
Supporting Information

ABSTRACT: A multistep experiment for a synthesis laboratory course that incorporates topics in organic synthesis, chemical analysis, and instrumental analysis was developed. Students prepared a tertiaryamine-functionalized polyacrylonitrile fiber (PAN_TF), and it was subsequently utilized as an immobilized catalyst in a three-component condensation reaction among an aromatic aldehyde, malononitrile, and α-naphthol in ethanol to synthesize substituted 2-amino-2-chromenes in one pot. The fiber catalyst exhibits the advantages of high yield, excellent recyclability and reusability, simple post-treatment, and environmental friendliness. Thus, students were able to apply the concept of green chemistry through catalysis. Moreover, this comprehensive experiment involves a number of unit operations, such as vacuum distillation, filtration, recrystallization, and acid−base titration, which can train the fundamental operation capability of students, and improve their experimental skills.



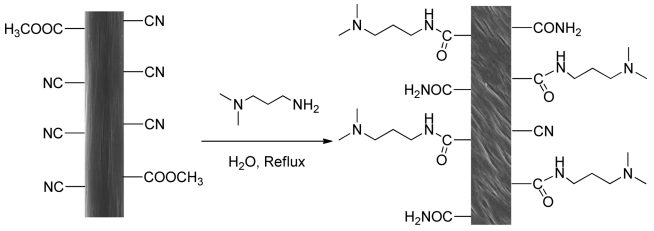
KEYWORDS: *Upper-Division Undergraduate, Organic Chemistry, Analytical Chemistry, Hands-On Learning/Manipulatives, Synthesis, Green Chemistry, Laboratory Instruction*

A study in this *Journal* has concluded that green chemistry concepts are so important in the undergraduate curriculum that these concepts should be combined with undergraduate laboratories at the practical level.[1] According to the strategy of sustainable development,[2] the applications of immobilized catalysts have been well-investigated to minimize waste production and maximize catalyst efficiency. A series of materials have been used as supports, such as silicas,[3] metal oxides,[4] polymers,[5] or zeolites,[6] etc. In comparison to traditional homogeneous catalysts, heterogeneous catalysts have the advantages of simpler post-treatment, easier recovery, and better reusability. Therefore, many efforts have been made to prepare heterogeneous catalysts based on solid materials.[7]

Commercially available polyacrylonitrile fiber (PANF) is based on the copolymer or homopolymer of acrylonitrile, so it contains an abundance of cyano groups, which is capable of being transformed into a myriad of functional moieties (carboxyl, amidoxime, amide, etc.).[8] PANF is also an ideal starting material for the preparation of heterogeneous catalysts, since it has properties including low cost (12 yuan or two dollars per kilogram), corrosion and mildew resistance, high strength (resistance to stretching about 10 cN for single silk), and low density. Therefore, PANF is a suitable material for the preparation of fiber catalysts.[9]

Multicomponent coupling reaction (MCR) is a method of obtaining complex target molecules directly in which three or more materials react in a reactor without separation of the intermediates. It has the advantages of simple operation, easily available materials, environmental friendliness, etc. Multicomponent coupling reactions include liquid phase and solid phase multicomponent reactions and have been successfully applied to the synthesis of pyrimidine ketone, pyrazole, isoquinoline, pyrimidine, etc.[10] Substituted 2-amino-2-chromenes have become an important class of heterocyclic compounds owing to their unique biological and pharmacological activities.[11] In this experiment, *N,N*-dimethyl-1,3-propanediamine was immobilized onto PANF (Scheme 1) through their primary amine groups to prepare tertiary amine-functionalized polyacrylonitrile fiber (PAN_TF). Subsequently, PAN_TF was utilized as a heterogeneous catalyst for the

Scheme 1. Preparation of the Immobilized Fiber Catalyst PAN_TF



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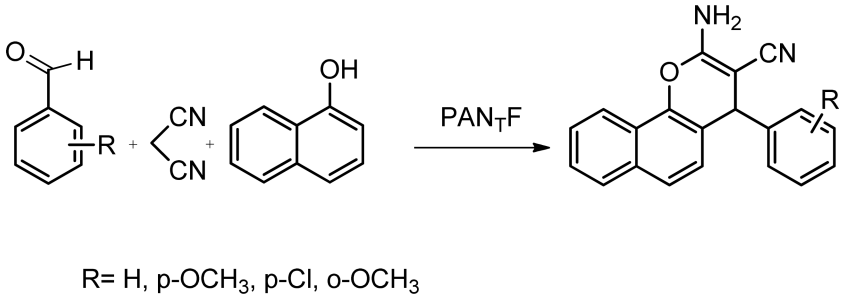
Scheme 2. Synthesis of Substituted 2-Amino-2-chromenes Catalyzed by PAN_TF



synthesis of substituted 2-amino-2-chromene (Scheme 2) in one pot without isolation of any intermediates. Then, the fiber catalyst was reused directly for the three-component reaction without any additional treatments to test its recyclability.

Pedagogically, this experiment seeks to achieve the following: (1) Have the students master the basic operations of chemical experiments such as reaction, filtration, extraction, recrystallization, distillation, and TLC monitoring, etc., and improve the comprehensive experimental skills of students; (2) have the students be familiar with the operation of instrumental analysis, such as Fourier transform infrared (FT-IR) spectroscopy, scanning electron microscopy (SEM), elemental analysis (EA), and ^{1}H NMR spectroscopy, and have the students apply chemical analysis methods such as titration to solve a practical problem; (3) have the students understand some current and important topics of chemistry such as green chemistry, multicomponent reaction, and heterogeneous catalysis. All student groups should prepare a laboratory report in the format of a journal article including introduction, experimental section, results and discussion, and conclusion. By asking questions and evaluating laboratory reports, we can assess the achievement of the pedagogic goals.

EXPERIMENTAL PROCEDURE

There were about 50 students doing the experiment in a laboratory course, and two students were assigned in one group according to their student ID. The total class hours of this experiment were 24 h (3 days, 8 class hours per day, 45 min per class hour), and the students would continuously conduct the experiments during these periods. Some descriptions and spectroscopic data for the compounds are in the Supporting Information.

Synthesis of PAN_TF (First Laboratory Class)

Dried PANF (1.3 g), *N,N*-dimethyl-1,3-propanediamine (20 mL), and deionized water (10 mL) were added to a 100 mL three-necked flask, and the mixture was stirred under reflux for some time (1 and 2.5 or 4 h). After the reaction, the modified fiber was filtered out, and washed with deionized water (250 mL, 60−70 °C) until the pH of the washing water was 7. The treated fiber was dried overnight under vacuum at 50 °C to give the functionalized *N,N*-dimethyl-1,3-propanediamine fiber (PAN_TF). Different experiment times were investigated by different groups, but the total experiment time of each group was about 6 h. More specifically, the groups whose experiment time was shorter should conduct two reactions (reaction time was 1 and 2.5 h, respectively). Also, the students whose experiment time was longer (reaction time was 4 h) can conduct only one reaction.

In this section, the students were taught to synthesize the fiber catalyst and could understand the heterogeneous process. At the same time, they would practice unit operations, such as reaction and filtration.

Determination of the Modification Extent (Second Laboratory Class)

The dried PAN_TF (0.500 g) was immersed into 25 mL of 0.100 mol/L HCl and stirred for 1−2 h at room temperature. The neutralized fiber was then filtered out, and washed with deionized water (250 mL, 60−70 °C). The HCl concentration of the remaining solution was determined by titration with 0.100 mol/L NaOH indicated with phenolphthalein. The exchange capacity was calculated on the basis of the consumption of the acid. Total experiment time for each group in this section was about 6 h.

In this section, the students learned how to determine the degree of reaction, which is a commonly used method in scientific research.

Synthesis of 2-Amino-2-chromenes (Third Laboratory Class)

A mixture of aldehyde (5 mmol), malononitrile (5 mmol), and α-naphthol (5 mmol) was added to 40 mL of ethanol; PAN_TF (0.5 g, containing 0.94 mmol effective group, 24% percentage weight gain) was put into the mixture and refluxed for 1 h. The reaction was monitored with TLC. After completion of the reaction, the PAN_TF was filtered out and extracted for 3 h by ethanol using a Soxhlet apparatus to collect all the adsorbed products. The extracted ethanol was combined with the filtrate. After removal of the solvent by a rotary evaporator, the residue was recrystallized with ethanol to get 2-amino-2-chromenes. Also, the fiber could be reused without further treatment. Different aldehydes were investigated by different groups. The total experiment time of each group in this section was about 6 h.

In this section, students would apply organic chemistry unit operations to synthesize the target compound including filtration, extraction, recrystallization, TLC monitoring, etc. Moreover, they were instructed to utilize the modern instrumental analyses to characterize the compound, and they learned to apply comprehensive technologies in chemistry research.

HAZARDS

Students should wear gloves, safety goggles, and laboratory coats during all the experiments. All of the reactions should be performed in a well-ventilated equipment fume hood. *N,N*-Dimethyl-1,3-propanediamine, aromatic aldehyde, malononitrile, and α-naphthol can cause eye and skin irritation and are harmful if swallowed or inhaled. Hydrochloric acid and sodium hydroxide are corrosive and should be handled with care. Ethanol is a flammable and volatile organic solvent. The

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products can damage skin and eyes so the students should handle them with care avoiding inhalation or skin contact. Waste should be disposed in the appropriate waste containers.

RESULTS AND DISCUSSION

Synthesis and Optimization of PAN_TF

A fiber catalyst (PAN_TF) was prepared directly from polyacrylonitrile fiber and *N,N*-dimethyl-1,3-propanediamine in a one-step reaction. The extent of the modification was measured by the percentage weight gain and the acid exchange capacity of the fiber catalyst, which was strongly influenced by the reaction time and temperature. During the reaction time, the student will observe the phenomenon of the reaction, monitor the reaction degree by TLC every 30 min, and prepare for the post-treatments.

The modification degree can be calculated with an expression of the weight gain, where weight gain = (the weight of PAN_TF − the weight of PANF)/(the weight of PANF). In fact, the reaction condition was optimized as follows. The modification extent can be calculated with an expression: modification extent = $(V_o - V_t)C_{NaOH}/m$. V_o is the consumed volume of sodium hydroxide by initial HCl, and V_t is the consumed volume of sodium hydroxide by neutralized HCl. C_{NaOH} is the concentration of sodium hydroxide, and m is the weight of PAN_TF.

Table 1. Optimization of the Reaction Conditions

Time, h	Percentage Weight Gain, %[a]	Modification Extent, mmol/g[a]
1.0	8 ± 1	0.73 ± 0.1
2.5	24 ± 1	1.92 ± 0.1
4.0	40 ± 1	2.83 ± 0.1

[a]Both percentage weight gain and modification extent are derived from 25 sets of the experiments. Values for 1 standard deviation are also included.

The percentage weight gain increases with the elongation of the reaction time as shown in Table 1. With reaction for 1 h, the percentage weight gain is only 8%. The modification degree was too small to catalyze the reaction. When the reaction time was 4 h, the percentage weight gain is 40%. However, a higher percentage weight gain ratio would notably reduce the mechanical strength of PAN_TF.[12] So, students should choose the fiber catalyst with a percentage weight gain of 24% for the best catalyst.

Table 2. Elemental Analysis Results of PANF Elements

Sample[a]	C, %[b]	H, %[b]	N, %[b]
PANF	60.12 ± 0.50	5.49 ± 0.50	21.77 ± 0.50
PAN_TF	52.73 ± 0.50	7.65 ± 0.50	18.04 ± 0.50
PAN_TF-1	53.73 ± 0.50	7.52 ± 0.50	17.66 ± 0.50
PAN_TF-10	52.59 ± 0.50	7.27 ± 0.50	15.97 ± 0.50

[a]PAN_TF-1 results from PAN_TF reused 1 time; PAN_TF-10 results from PAN_TF reused 10 times [b]All data are derived from 25 sets of the experiments. Values for 1 standard deviation are also included.

Determination of the Modification Extent

The modification extent was determined by acid−base titration. The tertiary amine is being protonated by HCl for conversion into a quaternary ammonium salt, so the concentration of the less concentrated HCl solution gives the number of tertiary amine groups on the fiber. Table 1 shows that the modification extent increases with the elongation of the percentage weight gain.[13]

Characterization of the Fiber Catalyst

All of the characterization data of the fibers, including PAN_TF, PAN_TF-1 (PAN_TF reused for 1 time), and PAN_TF-10 (PAN_TF reused for 10 times) are for a percentage weight gain of 24%.

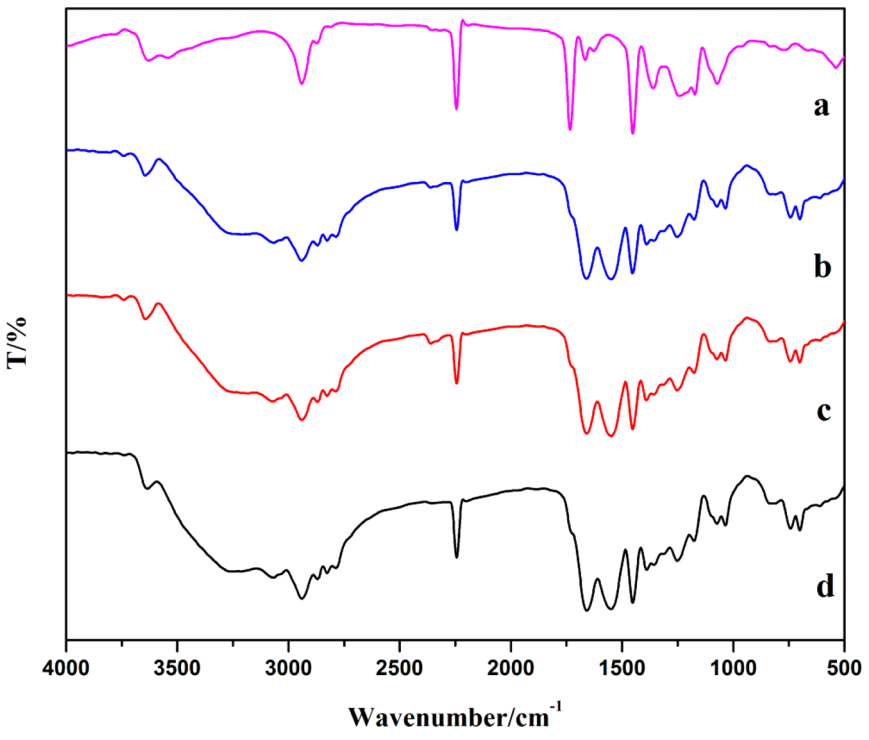

Figure 1. FTIR photograph of (a) PANF, (b) PAN_TF, (c) PAN_TF-1, and (d) PAN_TF-10.

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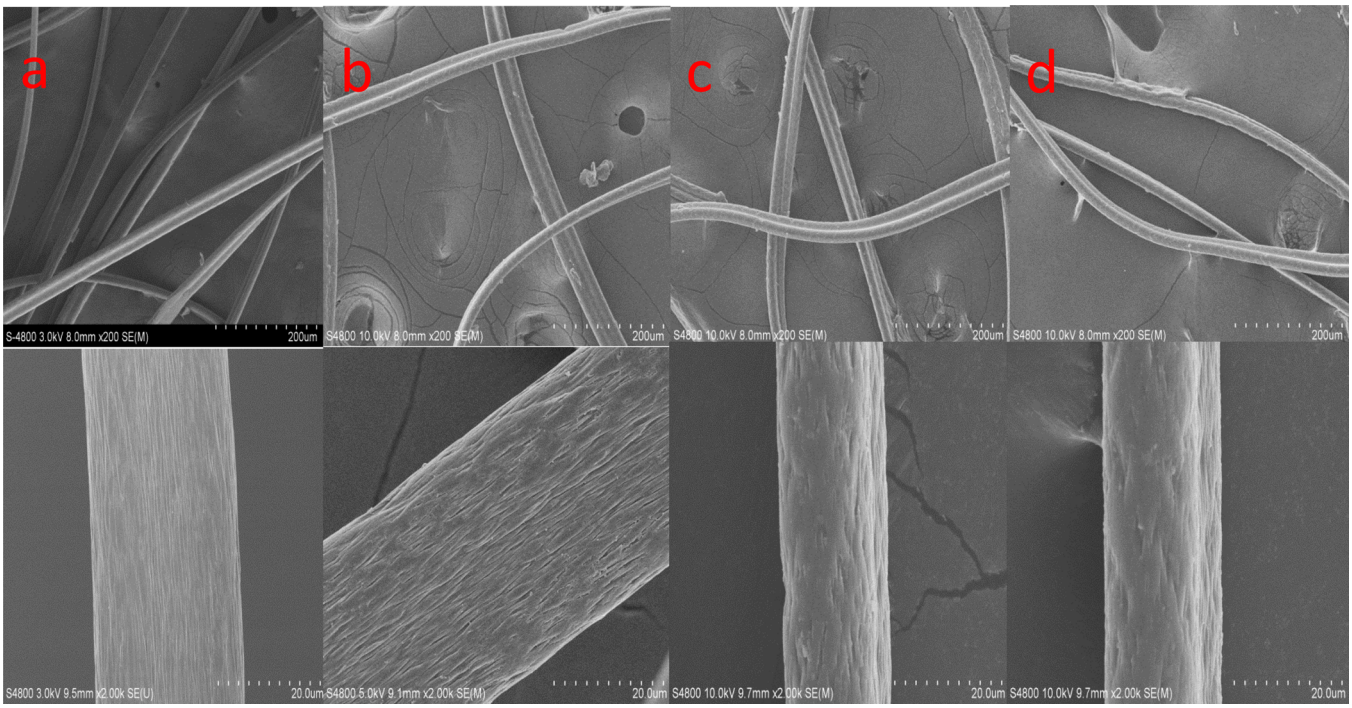

Figure 2. SEM images of (a) PANF, (b) PAN_TF, (c) PAN_TF-1, and (d) PAN_TF-10.

Table 3. Comparative Results of the Three-Component Condensation Reaction

	Melting Point Values (°C)		
R[a]	Experimental[b]	Literature	Yield, %[b,e,f,g]
H	208−210	205−207[c]	97 ± 3
p-OCH_3	182−184	205−207[c]	94 ± 3
p-Cl	224−225	233−235[c]	94 ± 3
o-OCH_3	188−189	204[d]	86 ± 3

[a]See Scheme 2. [b]Both the experimental values and the yields are derived from 25 sets of experiments. [c]See ref 14. [d]See ref 15. [e]Reactions were carried out with aldehyde (5 mmol), malononitrile (5 mmol), and α-naphthol(5 mmol) in the presence of PAN_TF (0.5 g, containing 0.94 mmol effective group) in ethanol (40 mL for each) under reflux for 1 h. [f]Isolated yield after recrystallization with ethanol. [g]Values for 1 standard deviation are also included.

All of the samples were pulverized by cutting and then prepared into KBr pellets. After unified teaching, each group was asked to operate the instrument and measure their samples in the second class according to their own experiment progress. The FTIR spectra of PANF, PAN_TF, PAN_TF-1, and PAN_TF-10 are shown in Figure 1, among which PAN_TF-10 is provided by teacher. The IR spectra of PAN_TFs with a percentage weight gain of 8% and 40% are almost the same as that of PAN_TF with a percentage weight gain of 24%

For the FTIR spectra of PAN_TF, PAN_TF-1, and PAN_TF-10, the new emerging broad peak at 3000−3700 cm^{-1} corresponds to the stretching vibrations of $-CONH_2$ groups. The C═O stretching vibration peak of the modified fiber occurring red shifts from 1730 to 1650 cm^{-1} suggests that the ester group forms an amide bond by virtue of ammonolysis. The IR spectra of PAN_TF-1 and PAN_TF-10 are almost the same as that of PAN_TF, which indicates that the functional fiber catalysts are still catalytically active after being recycled many times in the reaction.

The elemental analysis data for PANF, PAN_TF, PAN_TF-1, and PAN_TF-10 are summarized in Table 2.

Compared to that for PANF, the carbon content of PAN_TF decreases remarkably, and the hydrogen content increases as expected; the important factor for explaining this behavior is that *N*,*N*-dimethyl-1,3-propanediamine has less carbon and more hydrogen than PANF. The carbon content of the PAN_TF-1 and PAN_TF-10 increases slightly, and the hydrogen and nitrogen contents of the fiber decrease slightly when compared with those of PAN_TF, which illustrates that no significant loss happens after being used many times. After unified explanation, each class was asked to provide two samples for EA characterization at the second class time.

The SEM images of PANF, PAN_TF, PAN_TF-1, and PAN_TF-10 are presented in Figure 2.

In the SEM photograph, we can see that the PANF has a smooth surface, and the surface becomes slightly rougher after ammoniation in the PAN_TF. The surfaces of PAN_TF-1 and PAN_TF-10 did not change very much when compared with that of PAN_TF, which accounts for the fact that the fiber catalyst still keeps its mechanical strength after being reused. After unified explanation, each class was asked to provide two samples for SEM characterization at the second class time.

Synthesis of 2-Amino-2-chromenes

This fiber catalyst can be utilized to catalyze a three-component condensation reaction among benzaldehyde, malononitrile, and α-naphthol in ethanol to synthesize substituted 2-amino-2-chromenes with excellent yields. At the end of this section, each group was required to measure the melting point, weigh the product for yield calculation, and hand in their product. Also, these results were also taken as the evaluation basis to assess the students. Each class was asked to provide one substituted 2-amino-2-chromene for a ^1H NMR test. The representative student ^1H NMR spectra are in the Supporting Information.

PAN_TF was used to synthesize several different substituted compounds (Table 3) in excellent yields ranging from 86% to

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97%. In the experiment, the students are divided into four big groups, and each big group is assigned to conduct one kind of substituted compound. The electronic effect and steric effect were investigated by students. For example, when R = *o*-OCH_3, it was obtained in a relatively low yield for the steric effect.

CONCLUSIONS

A laboratory experiment is presented for advanced organic chemistry students. Students synthesize and characterize PAN_TF and use it as supported catalyst in a three-component condensation reaction to synthesize substituted 2-amino-2-chromenes in one pot. The experimental procedure is straightforward and provides students with chances to train in modern laboratory methods and techniques. In this experiment, students are induced to recognize the role of catalysis in achieving green chemistry principles. In general, this experiment is a comprehensive one involving a number of unit operations, such as rotary distillation, filtration, recrystallization, and acid−base titration, which can train students in fundamental operations, and improve their experimental skills. Moreover, in this experiment, students were able to practice the preparation of a new heterogeneous catalyst, and to understand the advantages of the catalyst such as recyclability and reusability through the synthesis reaction, and recognize the role of the catalysis in green chemistry principles. For example, at the end of the reaction, the fiber catalyst can be easily separated from the reaction system by simple filtration and used directly in the next cycle.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00933.

Detailed experiment procedures and experimental data (PDF, DOCX)
Student handout (PDF, DOCX)
Structures and CAS numbers of relevant chemical species (PDF, DOCX)
Lab report rubric (PDF, DOCX)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Wong, T. C.; Sultana, C. M.; Vosburg, D. A. A green, enantioselective synthesis of warfarin for the undergraduate organic laboratory. *J. Chem. Educ.* **2010**, *87* (2), 194−195. (b) Ballard, C. E. Green reductive homocoupling of bromobenzene. *J. Chem. Educ.* **2011**, *88* (8), 1148−1151. (c) Ison, E. A.; Ison, A. Synthesis of well-defined copper N-heterocyclic carbene complexes and their use as catalysts for a "click reaction": A multistep experiment that emphasizes the role of catalysis in green chemistry. *J. Chem. Educ.* **2012**, *89* (12), 1575−1577.

(2) (a) Gironi, F.; Piemonte, V. Bioplastics and Petroleum-based Plastics: Strengths and Weaknesses. *Energy Sources, Part A* **2011**, *33* (21), 1949−1959. (b) Yang, D.; An, B.; Wei, W.; Jiang, M.; You, J.; Wang, H. A novel sustainable strategy for the synthesis of phenols by magnetic $CuFe_2O_4$-catalyzed oxidative hydroxylation of arylboronic acids under mild conditions in water. *Tetrahedron* **2014**, *70* (22), 3630−3634.

(3) Notestein, J. M.; Iglesia, E.; Katz, A. Grafted Metallocalixarenes as Single-Site Surface Organometallic Catalysts. *J. Am. Chem. Soc.* **2004**, *126* (50), 16478−16486.

(4) Lim, C. W.; Lee, I. S. Magnetically recyclable nanocatalyst systems for the organic reactions. *Nano Today* **2010**, *5* (5), 412−434.

(5) Yan, P.; Jing, H. Catalytic Asymmetric Cycloaddition of Carbon Dioxide and Propylene Oxide Using Novel Chiral Polymers of BINOL-Salen- Cobalt(III) Salts. *Adv. Synth. Catal.* **2009**, *351* (9), 1325−1332.

(6) Llopis, F. J.; Sastre, G.; Corma, A. Xylene isomerization and aromatic alkylation in zeolites NU-87, SSZ-33, *β*, and ZSM-5: molecular dynamics and catalytic studies. *J. Catal.* **2004**, *227* (1), 227−241.

(7) (a) Bloomfield, A. J.; Sheehan, S. W.; Collom, S. L.; Anastas, P. T. Performance Enhancement for Electrolytic Systems through the Application of a Cobalt-based Heterogeneous Water Oxidation Catalyst. *ACS Sustainable Chem. Eng.* **2015**, *3* (6), 1234−1240. (b) Min, B. K.; Friend, C. M. Heterogeneous Gold-Based Catalysis for Green Chemistry: Low-Temperature CO Oxidation and Propene Oxidation. *Chem. Rev.* **2007**, *107* (6), 2709−2724. (c) Weckhuysen, B. M.; Keller, D. E. Chemistry, spectroscopy and the role of supported vanadium oxides in heterogeneous catalysis. *Catal. Today* **2003**, *78* (1−4), 25−46. (d) Corma, A.; Garcia, H. Silica-Bound Homogenous Catalysts as Recoverable and Reusable Catalysts in Organic Synthesis. *Adv. Synth. Catal.* **2006**, *348* (12−13), 1391−1412.

(8) (a) Chang, X.; Yang, X.; Wei, X.; Wu, K. Efficiency and mechanism of new poly(acryl-phenylamidrazone phenylhydrazide) chelating fiber for adsorbing trace Ga, In, Bi, V and Ti from solution. *Anal. Chim. Acta* **2001**, *450* (1−2), 231−238. (b) Li, G.; Zhang, L.; Li, Z.; Zhang, W. PAR immobilized colorimetric fiber for heavy metal ion detection and adsorption. *J. Hazard. Mater.* **2010**, *177* (1−3), 983−989. (c) Moroi, G.; Bilba, D.; Bilba, N. Thermal degradation of mercury chelated polyacrylamidoxime. *Polym. Degrad. Stab.* **2004**, *84* (2), 207−214. (d) Gong, B.; Li, X.; Wang, F.; Xu, H.; Chang, X. Synthesis of polyacrylacylaminourea chelating fiber and properties of concentration and separation of trace metal ions from samples. *Anal. Chim. Acta* **2001**, *427* (2), 287−291.

(9) (a) Li, G.; Xiao, J.; Zhang, W. Efficient and reusable amine-functionalized polyacrylonitrile fiber catalysts for Knoevenagel condensation in water. *Green Chem.* **2012**, *14* (8), 2234−2242. (b) Shi, X.-L.; Tao, M.; Lin, H.; Zhang, W. Application of the polyacrylonitrile fiber as a support for the green heterogeneous base catalyst and supported phase-transfer catalyst. *RSC Adv.* **2014**, *4* (109), 64347−64353.

(10) (a) Wang, H.-J.; Mo, L.-P.; Zhang, Z.-H. Cerium Ammonium Nitrate-Catalyzed Multicomponent Reaction for Efficient Synthesis of Functionalized Tetrahydropyridines. *ACS Comb. Sci.* **2011**, *13* (2), 181−185. (b) Liu, H.-L.; Jiang, H.-F.; Zhang, M.; Yao, W.-J.; Zhu, Q.-H.; Tang, Z. One-pot three-component synthesis of pyrazoles through a tandem coupling-cyclocondensation sequence. *Tetrahedron Lett.* **2008**, *49* (23), 3805−3809. (c) Kumar, A.; Maurya, R. A. Organocatalysed three-component domino synthesis of 1,4-dihydropyridines under solvent free conditions. *Tetrahedron* **2008**, *64* (16), 3477−3482. (d) Maggi, R.; Ballini, R.; Sartori, G.; Sartorio, R. Basic alumina catalysed synthesis of substituted 2-amino-2-chromenes via three-component reaction. *Tetrahedron Lett.* **2004**, *45* (11), 2297−2299.

(11) (a) Das, S. G.; Doshi, J. M.; Tian, D.; Addo, S. N.; Srinivasan, B.; Hermanson, D. L.; Xing, C. Structure−Activity Relationship and Molecular Mechanisms of Ethyl 2-Amino-4-(2-ethoxy-2-oxoethyl)-6-

DOI: 10.1021/acs.jchemed.5b00933
J. Chem. Educ. XXXX, XXX, XXX−XXX

phenyl-4H-chromene-3-carboxylate (sHA 14−1) and Its Analogues. *J. Med. Chem.* **2009**, *52* (19), 5937−5949. (b) Erichsen, M. N.; Huynh, T. H. V.; Abrahamsen, B.; Bastlund, J. F.; Bundgaard, C.; Monrad, O.; Bekker-Jensen, A.; Nielsen, C. W.; Frydenvang, K.; Jensen, A. A.; Bunch, L. Structure−Activity Relationship Study of First Selective Inhibitor of Excitatory Amino Acid Transporter Subtype 1:2-Amino-4-(4-methoxyphenyl)-7-(naphthalen-1-yl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (UCPH-101). *J. Med. Chem.* **2010**, *53* (19), 7180−7191. (c) Kumar, D.; Reddy, V. B.; Sharad, S.; Dube, U.; Kapur, S. A facile one-pot green synthesis and antibacterial activity of 2-amino-4H-pyrans and 2-amino-5-oxo-5,6,7,8-tetrahydro-4H-chromenes. *Eur. J. Med. Chem.* **2009**, *44* (9), 3805−3809. (d) Ough, M.; Lewis, A.; Bey, E. A.; Gao, J.; Ritchie, J. M.; Bornmann, W.; Boothman, D. A.; Oberley, L. W.; Cullen, J. J. Efficacy of beta-lapachone in pancreatic cancer treatment: Exploiting the novel, therapeutic target NQO1. *Cancer Biol. Ther.* **2005**, *4* (1), 102−109.

(12) Shi, X.-L.; Yang, H.; Tao, M.; Zhang, W. Sulfonic acid-functionalized polypropylene fiber: highly efficient and recyclable heterogeneous Bronsted acid catalyst. *RSC Adv.* **2013**, *3* (12), 3939−3945.

(13) Zhen, Y.; Lin, H.; Wang, S.; Tao, M. A Water−Ethanol On−Off Fiber Catalyst for the Synthesis of Substituted 2-Amino-2-Chromenes. *RSC Adv.* **2014**, *4* (50), 26122−26128.

(14) Saha, A.; Payra, S.; Banerjee, S. On water synthesis of pyran-chromenes via a multicomponent reactions catalyzed by fluorescent t-ZrO_2 nanoparticles. *RSC Adv.* **2015**, *5* (123), 101664−101671.

(15) Maalej, E.; Chabchoub, F.; Oset-Gasque, M. J.; Esquivias-Pérez, M.; González, M. P.; Monjas, L.; Pérez, C.; de los Ríos, C.; Rodríguez-Franco, M. I.; Iriepa, I.; Moraleda, I.; Chioua, M.; Romero, A.; Marco-Contelles, J.; Samadi, A. Synthesis, biological assessment, and molecular modeling of racemic 7-aryl-9,10,11,12-tetrahydro-7H-benzo-[7,8]chromeno[2,3-b]quinolin-8-amines as potential drugs for the treatment of Alzheimer's disease. *Eur. J. Med. Chem.* **2012**, *54*, 750−763.

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J. Chem. Educ. XXXX, XXX, XXX−XXX