Free Radical Synthetic Protocol for Benzothiazoles *via* Ring Opening of Benzotriazole: A Two-step Organic Chemistry Experiment for Undergraduate and Postgraduate Students

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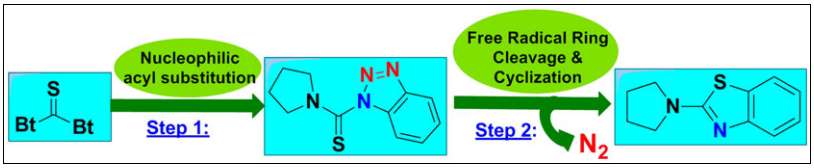

The utility and advantages of benzotriazole methodology have been described for the practical synthesis of benzothiazoles. The two-step synthetic procedure includes nucleophilic acyl substitution followed by benzotriazole ring cleavage under the free radical condition and subsequent cyclization *via* elimination of molecular nitrogen (N_2). This protocol requires cheap and readily available reagents, and moreover easy to handle, thus can be used to teach undergraduate and postgraduate students about the importance of benzotriazole moiety in organic synthesis, ring cleavage chemistry, cyclization reactions, and use of industrial waste in free radical reactions. Students can also learn some important and common techniques useful in organic chemistry such as monitoring of organic reaction using thin-layer chromatography and UV, microwave (MW) technique for the synthesis, and column chromatography for the product isolation and structure determination through NMR, MS, and IR spectral analysis of the pure compounds.

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INTRODUCTION

Benzotriazole methodology has emerged as a promising and successful tactic in synthetic chemistry [1,2]. Along with ease in introduction and removal, the compatibility of benzotriazole moiety with various reaction conditions makes it an ideal group for substitution reactions.[2] On the other hand, the rupture of benzotriazole ring *via* breaking of *N–N* and *C–N* bonds with assistance of suitable reagents leads to formation of different aromatic compounds such as benzothiazoles, amides, benzoxazoles, indoles, and benzimidazoles [3]. In addition to be a nontoxic, low-cost, and stable moiety, other advantages associated with benzotriazole such as simple introduction to a molecule, easy elimination, α-cation stabilization, and promotion of an anion or free radical formation at the α-position make the benzotriazole methodology even better than other synthetic techniques practiced so far. The wide substrate scope of this methodology has provided convenient and high-yielding synthesis of many valuable heterocyclic systems and other biologically significant molecules. Due to potential results and high yields associated with benzotriazole ring cleavage (BtRC) methodology, this protocol has been elaborately explored in synthesis of benzothiazoles by our group during past few years [4].

Benzothiazole heterocycles have extensively been used as a core moiety of different pharmaceutically relevant compounds particularly known for antidiabetic, antimicrobial, and antifungal activities [5]. The immunosuppressive drug frentizole, the antiparasitic tioxidazole, a human CCR1 and CCR3 receptor antagonist, the calcium channel blocker fostedil, and many others are the representative examples of drugs that consist of benzothiazole skeleton. These fascinating features of benzothiazole derivatives have compelled the chemists to develop new methodologies for their synthesis. Several earlier reported methods include $K_3[Fe(CN)_6]$ mediated cyclization of arylthioamide (Jacobson's method) [6], condensation of carbonyl compounds with 2-aminothiophenol [7], transition-metal catalyzed cyclization of thioformanilides under aromatic nucleophilic substitution [8] or radical conditions [9], and *via* thioamide intermediates derived from halo amides using P_4S_{10} or Lawesson's reagent [10]. Some disadvantages associated with these methods are use of toxic reagents, harsh reaction conditions, difficult work-up process, and toxic reaction wastes. Whereas BtRC mediated benzothiazole synthesis includes metal-free environmentally benign mild reaction conditions with easy work-up procedure and high yields.

Benzotriazole ring cleavage (BtRC) can take place either *via* Dimroth rearrangement or *via* free radical mechanism [11,12]. In Dimroth rearrangements, benzotriazole containing an electron withdrawing group at 1-position exists in thermal equilibrium with diazonium intermediate which participates in product formation *via* nucleophilic substitution. On the other

hand, the free radical path involves the generation of free radical with assistance of an initiator followed by eradication of nitrogen gas. The benefit of free radical process over Dimroth rearrangement comprises no need of electron withdrawing group.

Present scheme of benzothiazole synthesis *via* BtRC route consists of two successive reactions. In the first step, the substitution of one of the two benzotriazole rings of *bis*-(benzotriazole) methanethione with pyrrolidine ring in basic medium proceeds rapidly to produce (1*H*-benzo[*d*][1,2,3]triazol-1-yl)(pyrrolidin-1-yl) methanethione in excellent yield. The second step includes free radical cleavage of benzotriazole ring initiated through tributyltin hydride (Bu_3SnH) in the presence of radical initiator azobisisobutyronitrile (AIBN). The resulting free radical gets cyclized by elimination of molecular nitrogen (N_2). In place of Bu_3SnH or TMS-H, poly(methylhydrosiloxane), an industrial waste can also be used as a radical reagent [13]. Although there are a number of addition [14], substitution [15], elimination [16], and free radical reactions [17] available in literature for chemistry education point of view which can be performed by the students in laboratory, none of them envelopes the main concepts of organic reactions to the benefits of undergraduate and postgraduate students. For improving the basic concept of organic chemistry among undergraduate students, there are only limited studies dealing with the cyclization reactions, for example, cyclization of the monoterpene citronellal to isopulegol [18]. Furthermore, for introducing the concept of the ring cleavage chemistry, a separate reaction, that is, the electrocyclic ring opening of halocyclopropanes is performed by students [19]. In contrast to the earlier practiced experiments, the present scheme includes an easy experimental demonstration of free radical reaction for undergraduate students and embraces substitution reaction, ring cleavage chemistry, free radical reaction, elimination, and cyclization, all in a single reaction protocol, which we wish to report herein.

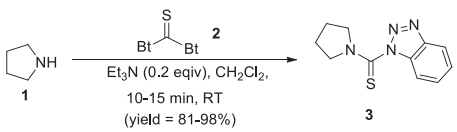
EXPERIMENTAL

Students may work alone or with lab mates. This laboratory exercise can easily be performed in three 2- to 3-h lab sessions. Basic requirements of the reaction setup, safety precautions, and reaction metrics are introduced in a pre-lab session. In the first lab session, a 15-min nucleophilic substitution reaction is carried out, and the product is isolated after an easy work-up and column chromatographic purification (SiO_2). The reaction product is dried and weighed and % yield is calculated. The product is analyzed by melting point determination and by extensive spectroscopic techniques including ^{1}H-NMR and ^{13}C-NMR and IR spectroscopy. In the second lab session, the second step (BtRC) of two-step synthesis is started and the reaction is monitored by TLC (*Rf* = 0.5, 35% ethyl acetate/*n*-hexane). In the third lab session, work-up is performed and product is purified by column chromatography. After drying and weighing, the isolated product is analyzed by ^{1}H-NMR and ^{13}C-NMR spectroscopy, IR spectroscopy, and melting point determination for identity and purity. The yield of each step as well as the overall yield is calculated. See Supporting Information for experimental details.

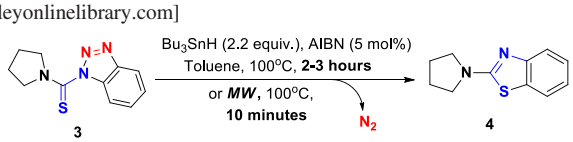
Synthesis of 1-(1-pyrrolidinyl thioxomethyl)-1*H*-benzotriazole 3. A synthetic scheme for the first step of two-step synthetic route is shown in Scheme 1 and Scheme 2. Students are familiar with the concept of nucleophilic acyl substitution reaction and the role of an easily substituted group to facilitate this reaction [14]. Here, we used pyrrolidine as a nucleophile in the presence of triethylamine to substitute one of the easily removable benzotriazole moieties of *bis*(benzotriazolyl) methanethione **2**. Thus, thiocarbamoyltion reaction of secondary amine pyrrolidine **1** (1.0 equiv) with *bis*-benzotriazole methanethione **2** (1.0 equiv) in the presence of Et_3N (0.2 equiv) in anhydrous CH_2Cl_2 at room temperature leads to synthesis of 1-(1-pyrrolidinyl thioxomethyl)-1*H*-benzotriazole **3** in quantitative yield in a very short span of time (10–15 min) (Scheme 1). The resulting adduct 1-(1-pyrrolidinyl thioxomethyl)-1*H*-benzotriazole **3** is highly stable and can be easily controlled for the attack by another amine molecule. Thus, no bi-substituted product is observed in this first step. The structure of compound 1-(1-pyrrolidinyl thioxomethyl)-1*H*-benzotriazole **3** is elucidated using extensive spectral studies (IR, MS, ^{1}H-NMR, and ^{13}C-NMR).

BtRC route for the cyclization *via* free radical mechanism leading to benzothiazoles. The triazole ring of benzotriazole moiety undergoes ring cleavage by free radical mechanism. Moreover, the generated free radical can

Scheme 1. Synthesis of 1-(1-pyrrolidinyl thioxomethyl)-1*H*-benzotriazole **3**.



Scheme 2. Synthesis of 2-(pyrrolidin-1-yl)benzo[*d*]thiazole **4** *via* benzotriazole ring cleavage (BtRC) under conventional and microwave irradiation (*MW*) route. [Color figure can be viewed at wileyonlinelibrary.com]



be cyclized again by an intramolecular attack of a free radical site to afford another hetrocyclic moiety. This concept has been used to synthesize 2-(pyrrolidin-1-yl)benzo[*d*]thiazole **4** *via* free radical ring cleavage followed by cyclization of 1-(1-pyrrolidinyl thioxomethyl)-1*H*-benzotriazole.

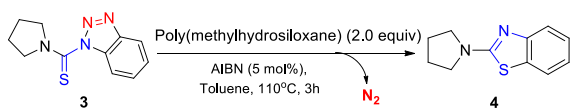
Thus, a reaction of 1-(1-pyrrolidinyl thioxomethyl)-1*H*-benzotriazole **3**, Bu_3SnH (2.2 equiv), and AIBN (5 mol%) in toluene as solvent at 100°C produces a biradical *via* *β*-scission of *N–N* bond of benzotriazole and affords 2-(pyrrolidin-1-yl)benzo[*d*]thiazole **4** *via* cyclative elimination of molecular nitrogen (N_2) (Scheme 2). This BtRC methodology shows notable compatibility with microwave conditions. The reaction of benzotriazolemethanethione **3** with stannanyl/silyl hydride (2.2 equiv) and AIBN (5 mol %) in anhydrous toluene under microwave irradiation (CEM Discover LabMate) at 100°C for 10 min affords corresponding benzothiazole **4**. The reaction mixture is concentrated *in vacuo*, extracted with CH_2Cl_2, washed with water, and dried over anhydrous Na_2SO_4. The organic layer is concentrated *in vacuo* and purified by flash column chromatography (SiO_2) to afford benzothiazole **4** in pure form. Spectral data and m.p. of the isolated product **4** are matched with the previous one obtained under conventional heating condition. Thus, the reaction completes within 10 min under microwave irradiation and is considered important one for the radical cyclization.

An inexpensive, biodegradable, and nontoxic polymethylhydrosiloxane, which is a silicon industry by-product, has been considered as a green alternative reagent for the wide applications in organic synthesis [14]. Thus, the BtRC reaction of 1-(1-pyrrolidinyl thioxomethyl)-1*H*-benzotriazole **3** in the presence of poly(methylhydrosiloxane) (2.0 equiv of weight) and AIBN (5 mol%) in toluene as solvent at 100°C affords 2-(pyrrolidin-1-yl)benzo[*d*]thiazole **4** *via* cyclative elimination of molecular nitrogen (N_2) in almost quantitative yield (Scheme 3). This methodology may be considered as environmentally benign.

MECHANISM

Mechanism of the two-step synthetic route is explained in a pre-lab session which highlights the formation of thioamide bond by nucleophilic acyl substitution reaction of pyrrolidine and *bis*(benzotriazolyl)methanethione, role of AIBN and tributyl tin hydride (Bu_3SnH) in free radical generation, free radical opening of benzotriazole ring *via* *β*-scission of *N–N* bond and ring closure by cyclative molecular nitrogen elimination leading to formation of benzothiazole ring.

Scheme 3. Synthesis of 2-(pyrrolidin-1-yl)benzo[*d*]thiazole **4** *via* benzotriazole ring cleavage (BtRC) with an use of poly (methylhydrosiloxane). [Color figure can be viewed at wileyonlinelibrary.com]

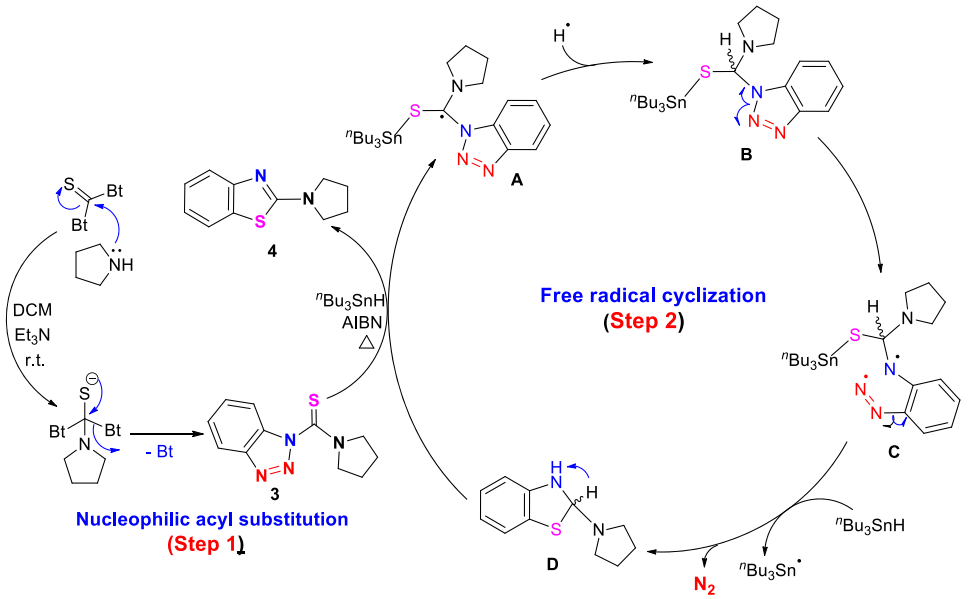


First of all, AIBN initiates the process by the generation of 2-cyanoprop-2-yl radical, which rapidly reacts with Bu_3SnH producing a tin radical ($Bu_3Sn^{\bullet}$) [20]. This newly formed radical attacks on thione functionality of thiocarbonyl and generates radical intermediate **A**. The intermediate **A** further generates a radical intermediate **B** by consequently introduction of a tin radical and $H^{\bullet}$. Intermediate **B**, on benzotriazole ring opening transforms into biradical intermediate **C**, which on elimination of nitrogen molecule and subsequent attack of sulfur, produces **D** [21]. Loss of molecular hydrogen (H_2) from intermediate **D** through oxidative aromatization at the cost of 2σ-bond to a resulted π-bond in final product produces title benzothiazole (Scheme 4). The mechanism of this BtRC reaction leading to benzothiazole is also supported by density functional theory (DFT) [4b].

SAFETY PRACTICE AND SUSPECTED HAZARDS

Protective equipments such as safety goggles, lab coat, and gloves must be used while performing experiments. All the reactions should be carried out using standard laboratory safety precautions in a fume hood. Reagents, solvents, products, and wastes must be manipulated and dispensed in a fumehood. *Bis*(1-benzotriazolyl) methanethione is harmful if swallowed; causes skin, eye, and respiratory irritation. Triethylamine is a highly flammable liquid. It is harmful if swallowed, in contact with skin causes severe burns, if inhaled causes respiratory irritation, and causes damage in contact with eyes. Toluene is a highly flammable liquid and may be fatal if inhaled. It causes skin irritation and may cause drowsiness or dizziness. Chloroform-*d* and dichloromethane are fatal if swallowed or inhaled, cause skin and eye irritation, and are suspected of causing cancer. Tributyltin hydride is a flammable liquid and toxic if swallowed, harmful in contact with skin, causes skin and eye irritation, and causes damage to organs through prolonged or repeated exposure. AIBN may cause fire, fatal if swallowed, and it is harmful to aquatic life with long lasting effect. Silica gel causes irritation to respiratory track and digestive track and should never be used without mask and other safety measures. Prolonged or extensive exposure to silica gel may cause Silicosis. Iodine vapors cause skin and eye irritation and are corrosive in nature. UV rays cause skin and eye irritation and are responsible

Scheme 4. Reaction mechanism leading to benzothiazole from corresponding thioacyl benzotriazole derivative *via* cleavage of benzotriazole ring (BtRC) under free radical condition. [Color figure can be viewed at wileyonlinelibrary.com]



for skin cancer and many ocular disorders. Ethyl acetate and hexane are highly flammable solvents and must be kept away from any source of heat and spark.

RESULTS AND DISCUSSION

The pedagogic goals of this experiment are mainly focused on (1) understanding of basic protocols of organic synthesis, discussion, and comprehension of chemical literature for information and carrying out a chemical synthesis task as a team work for UG and PG students; (2) understanding of some basic concepts of organic chemistry such as nucleophilic acyl substitution, free radical mechanism, ring cleavage, and cyclization; (3) understanding of feasible role and importance of some reagents and groups in organic synthesis such as tributyl tinhydride and AIBN for free radical reactions and benzotriazole as good leaving group; (4) understanding the concepts of green chemistry to know the significance of utilization of industrial waste in organic synthesis; and (5) application of column chromatography (SiO_2) for the purification of developed organic compound.

To achieve these goals, the pre-lab and post-lab exercises (Supporting Information), answering questions in a handout (Supporting Information) as well as the two-step synthesis experiment is mandatory for every student. Through the answers given by students and the experimental results achieved by them, the assessment of the extent of success of our pedagogic aims can be performed. A detailed knowledge of nucleophilic acyl substitution reaction, role, and importance of benzotriazole moiety as a good leaving group, free radical reaction and mechanism of free radical cyclative cleavage of benzotriazole ring is assessed through pre-lab exercises completed by students. Also, it helps students to take interest in independent consultation of chemical literature for useful information. The experiment was made to perform by five batches of 10 students each since last 2.5 years, and we could successfully achieve these pedagogical goals in 80–90% cases in each batch.

The handout provided in Supporting Information contains information about chemicals and equipments related to this synthetic protocol, probable hazards, and the experimental procedures.

Synthesis of 1-(1-pyrrolidinyl thioxomethyl)-1*H*-benzotriazole: a nucleophilic acyl substitution. Thin-layer chromatography (TLC) analysis (30% ethyl acetate/*n*-hexane) of the reaction mixture under UV/iodine showed gradual disappearance of the starting material spot (Rf = 0.7) and appearance of a new product spot (Rf = 0.5) with time. This TLC analysis helped students to observe consumption of starting material *bis*-benzotriazole methanethione (BtCSBt, **2**) and formation of the reaction product with time. The absence in the TLC (using solvent system, 30% ethyl acetate/hexane) of a spot from the starting material after 15 min gives evidence that the starting material has been consumed. After completion of reaction, the purification of product was performed by flash chromatography (SiO_2). Isolated yield of reaction product was achieved by students in the range of 81–98%. The structure of product **3** was confirmed after analysis of ^{1}H-NMR and ^{13}C-NMR spectra, IR spectra, and melting point determination.

Free radical ring cleavage followed by cyclization. The progress of reaction was observed by students by means of TLC analysis (35% ethyl acetate/*n*-hexane) under UV or iodine by disappearance of 1-(1-pyrrolidinyl thioxomethyl)-1*H*-benzotriazole spot (*Rf* = 0.6) and appearance of new benzothiazole product **4** spot (at *Rf* = 0.5, 35% ethyl acetate/*n*-hexane). Students reported the full consumption of starting compound after 2 h. Toluene in reaction mass was removed using rotary evaporator at 55°C temperature and 100-mbar pressure. Students isolated the product in the next lab session by flash chromatography and reported yields ranging 70–89%. The structure of product **4** was confirmed by students analyzing ^{1}H-NMR and ^{13}C-NMR spectra, IR spectra, and melting point determination.

A careful comparison of the ^{1}H-NMR (300 MHz, $CDCl_3$) of *bis*-benzotriazole methanethione (**1**) and its reaction product **3** (*Step 1*) simply reveals about the appearance of supplementary signals in compound **3** at δ 4.01 and 3.86 (each t, J = 6.6 Hz) attributed to methylene protons (2 x NCH_2) in addition to two more signals at δ 2.10 and 1.98 each correspond for two protons (2 x NCH_2CH_2) that confirm about the successful conversion of starting material **1** to its coupling product **3**. Likewise, appearance of signals in ^{1}H-NMR of benzothiazole product **4** in different pattern both in aromatic region (attributed to four aryl protons) and at δ 3.53 (t, J = 6.6 Hz, 4H) and δ 2.01 (m, 4H) attributed to eight pyrrolidine protons (2 x CH_2) was found in close agreement about the successful conversion of compound **3** to **4** *via* BtRC under free radical condition (*Step 2*). Thus, both the steps can be easily analyzed, and reaction product has been well characterized by careful comparison of ^{1}H-NMR ($CDCl_3$, 300 MHz) of compounds **1**, **3**, and **4** (Fig. 1) (see Supporting Information for the characterization of developed compounds by extensive spectral analysis).

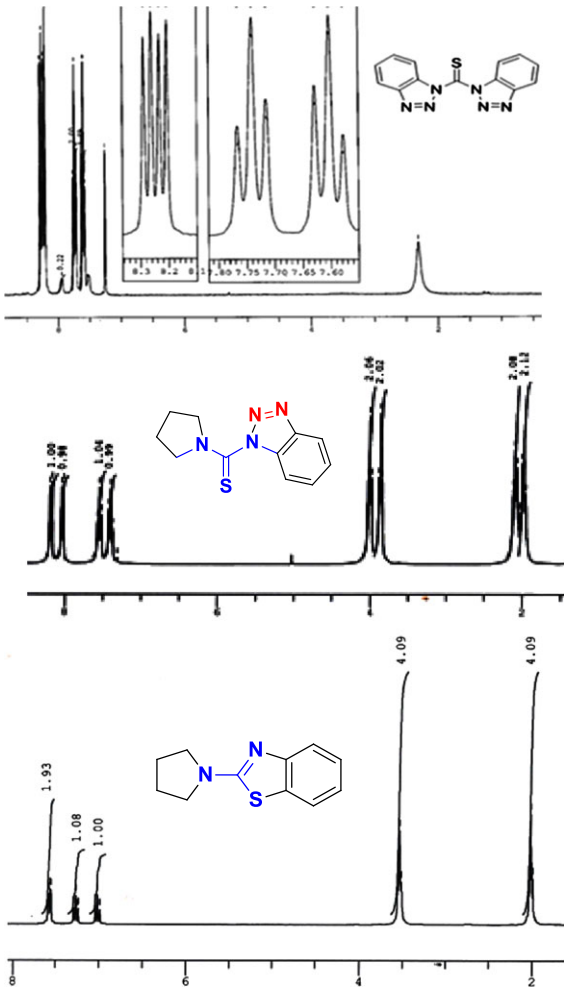


Figure 1. ^{1}H-NMR (300 MHz, $CDCl_3$) of compound **1**, coupling product **2** and BtRC product **4**. [Color figure can be viewed at wileyonlinelibrary.com]

A brief discussion on the role of benzotriazole moiety in organic synthesis was conducted, and most of the students were able to properly understand the significance of benzotriazole methodology in the synthesis of heterocyclic compounds. The use of AIBN and tributyltin hydride in free radical reactions and mechanism of ring cleavage and cyclization reaction was also discussed well with students. A discussion on mechanism of this reaction exhibited the level of interest and analytical approach of students. Some students proposed really appreciating alternatives of the cyclization step using Lewis acid instead of tributyltin hydride and AIBN.

In post-lab sessions, all the students could give correct details of mechanistic consideration of the two reactions. After consulting chemical literature, majority students considered the benzotriazole moiety as an efficient, promising, and versatile tool in organic synthesis, and most of them understood significance of benzothiazole synthesis. By considering the ^{1}H-NMR and ^{13}C-NMR spectra of developed compounds students determined the number of signals, multiplicity, and coupling constants. All the students could appropriately assign the characteristic peaks of the compounds using a chemical shift table provided to them, and they successfully differentiated the NMR and IR spectra of compounds **3** and **4** on the basis of characteristic peaks (Supporting Information).

CONCLUSIONS

Benzotriazole methodology is a facile, inexpensive, and promising method for the synthesis of heterocyclic. This experiment offers an exposure for students

towards understanding of role of benzotriazole moiety in synthesis of benzothiazole ring *via* mode of nucleophilic acyl substitution, free radical ring cleavage, and cyclization reactions. A group of students became aware of role of AIBN and tributyltin hydride in free radical reactions and understood their mechanisms. This experiment provided an opportunity for students to learn organic synthesis skills, ability of analytical thinking and solving synthesis problems independently as well as by team work.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies with human participants or animals performed by any of the authors.

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SUPPORTING INFORMATION

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