

Green synthesis of o-phenyl-benzothiazole



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Green Condensation of o-Aminothiophenol to o-Phenyl-benzothiazole

David Fairchild, Alex Irion, Dominic Russo, Luke Sanders

Abstract

Herein we describe a simple, efficient, and environmentally friendly synthesis of o-arylbenzothiazoles, such as o-phenyl-benzothiazole, under standard ambient temperature and pressure via reaction of o-aminothiophenols with aromatic aldehydes using glycerol as a solvent. The combined characteristics of glycerol allow it to act as both a green and biodegradable solvent, but its high polarity also catalyzes the reaction between various o-aminothiophenols and aromatic aldehydes, hence replacing the need for expensive, and often environmentally hazardous, solvents or catalysts.

- Land management
- Water conservation & clean-up

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Problem

Numerous o-arylbenzothiazoles can be found in a variety of biologically occurring compounds, and they are becoming an increasingly important family of antitumor agents (Kashiyama E et al., 1999)¹; moreover, these compounds exhibit biological activity as antituberculosis agents and antiparasitics (Yamamoto K et al., 1998)², but also serve as useful imaging agents for β -amyloid (Lee BC et al., 2011)³.

Traditionally, most o-arylbenzothiazoles are synthesized by either arylation of benzothiazole with aryl bromides and catalyzed by palladium (II) acetate, copper (I) bromide, or tri-tert-butylphosphine (Vattoly J. Majo, Jaya Prabhakaran, J. John Mann, J. S. Dileep Kumar, 2003)⁴ or via condensation of o-aminothiophenols by varying functional groups with a number of different catalysts including: trimethylsilyl chloride (S. V. Ryabukhin, A. S. Plaskon, D. M. Volochnyuk, & A. A. Tolmachev, 2006)⁵, manganese (II) oxide (Cecilia D. Wilfred & Richard J. K. Taylor, 2004)⁶, or 1-methyl-3-pentylimidazo-lium bromide (Brindaban C. Ranu, Ranjan Jana, & Suwendu S. Dey, 2004)⁷. Nevertheless, there have been several recent and more environmentally friendly procedures for synthesizing o-arylbenzothiazoles, such as with a mixture of sulfuric acid and silicon dioxide to act as a catalyst (Behrooz Maleki et al., 2010)⁸, or with p-toluenesulfonic acid in water (Najmedin AziziAlireza et al., 2009)⁹; however, many of these recent discoveries require high temperatures, lengthy reaction times, and sometimes result in relatively low yield. In addition, many of the catalysts employed in the traditional reactions are both economically and environmentally costly, thus often resulting in serious environmental pollution, which may affect important waterways for many ecological systems.

An important tenet of green chemistry is the minimal use of auxiliary substances and the use of innocuous solvents whenever possible; solvents play a major role in the environmental performance of chemical processes, but also impact cost, safety, and operational health. Thus, the purpose behind green solvents expresses the goal to minimize the environmental impact resulting from the use of solvents in chemical procedures; hence,

many of these solvents exhibit similar properties, including: low volatility, low cost, high reusability, low toxicity, low flammability, and high solvation power for both inorganic and organic compounds. Glycerol is one such compound that has recently garnered much attention as a result of these aforementioned qualities since it combines many of the characteristics of water with many of the benefits of ionic liquids. We have therefore chosen this project because the field of green chemistry is an ever-growing and an ever-more-important subfield of chemistry, and because a better and more efficient synthesis of o-phenylbenzothiazole and other o-arylbenzothiazoles will have practical applications toward minimizing potential environmental waste from the preparation of an increasingly important research pharmaceutical.

Hypothesis

If glycerol's high polarity and solvation ability were able to act as a functional group on aromatic aldehydes, then o-phenylbenzothiazole could be produced by simple condensation of o-aminothiophenol.

Experimentation

Due to the limited availability of many of the basic reagents required for this experiment, we plan on first synthesizing many of the preparatory reagents on a micro scale; these chemicals are more easily available in bulk, and, hence, the following procedures would be unnecessary in practice. The following preparations include:

1. Preparation of Nitrobenzene by Mixed Acid Nitration of Benzene

Nitrobenzene is produced by simple nitration of benzene with nitric acid and sulfuric acid acting as catalysts. A 500 ml flask is charged with a stir bar and 8 ml of concentrated 98% sulfuric acid and 84. 013 ml of concentrated 90% nitric acid is added slowly (note 1). Once the solution of acids cools, 182. 687 ml of benzene is slowly added to the flask (note 2).

Once all the benzene is added, the contents of the flask are poured into an appropriate separatory funnel and the bottom aqueous layer is discarded. The crude nitrobenzene is then washed with 40ml of distilled water three times to remove excess acids; once complete, an appropriate round bottom flask (RBF) is charged with the bottom layer (crude nitrobenzene), and the top layer is discarded. A simple distillation of the crude nitrobenzene is performed collecting the fraction between 207° C and 211° C. This distillate is then dried with calcium chloride, and filtered off for future use yielding approximately 170. 37 ml of pure nitrobenzene (~83% theoretical yield based on nitric acid).

2. Preparation of Aniline by Reduction of Nitrobenzene

Aniline is synthesized by a modified procedure outlined in Vogel (5 , p. 892)10. 178. 065 g of tin powder, 140 ml of distilled water, and 564. 972 ml of 38% hydrochloric acid are charged into a two-way 1 L RBF along with a suitable stir bar. A thermometer and a pressure-equalizing additional funnel with 102. 636ml of the previously prepared nitrobenzene are clamped to the RBF. The RBF is placed on a hot plate and slowly heated and stirred while nitrobenzene is slowly added (note 3); upon completion, the solution is set up for reflux for 30 minutes. Thereafter, 39. 997 g of sodium hydroxide are added, and the solution is set up for steam distillation.

The collected distillate from the previous steam distillation is placed in a suitable separatory funnel, where it is washed with a saturated brine solution. The top layer of aniline is then placed in another suitable RBF and setup for simple distillation; this distillation is carried out until the temperature reaches 130° C. The collected distillate is then redistilled with the fraction between 180° C and 184° C collected (note 4). The final distillate of 90.336 ml (~97% yield based on nitrobenzene) is then poured into a suitable container for storage and future use.

3. Preparation of Acetanilide

Acetanilide is prepared by simple acetylation of the previously prepared aniline with acetic anhydride. 77.479 ml of the previously prepared aniline are charged into a 250 ml RBF, and 20 ml of water are added with an additional 2 ml of 38% hydrochloric acid so that the previous two layers mix; a stir bar is also charged in the flask. The solution of aniline hydrochloride is gently heated while stirring is begun. A mixture of 80.200 ml of acetic anhydride are added and 4.5 g of sodium acetate is quickly added all at once. Heat is removed, while vigorous stirring is maintained. The white acetanilide precipitate is then vacuum-filtered off and then washed with cold water, yielding approximately 110.96 g of product with a m. p. between 112° C to 115° C.

4. Preparation and Separation of o-Nitroaniline from Acetanilide

o-Nitroaniline is prepared by a slightly modified mixed acid nitration of acetanilide. 100g of the previously prepared dry acetanilide is charged into a two-neck 100 ml RBF along with a suitable stir bar. This set up is placed over

a magnetic stirrer (note 5), and a pressure-equalizing addition funnel containing 31.079 ml of 90% nitric acid, 2 ml of 98% sulfuric acid (note 6), and a thermometer are clamped to the RBF. The mixed acids are then slowly added drop-wise in 2 ml portions every ten minutes to allow for adequate cooling of the reaction.

Once the acid addition is complete, the addition funnel is removed, and 15 ml of ice water are added, heated to reflux allowing the nitroacetanilides to hydrolyze. After approximately 15 to 20 minutes, the reaction is allowed to cool; once cooled, an equimolar amount of sodium hydroxide (based on acetanilide) is very slowly added to the RBF. The crude mixture nitroacetanilides is then filtered off and dried.

This crude product is recrystallized from hot ethanol, thus allowing the p- and o- isomer to separate. The crystals are filtered off and stored for later use, however, the filtrate, which predominately contains o-nitroaniline, is set up for column chromatography with methylene chloride for further purification. Afterwards, the methylene chloride is allowed to evaporate off, yielding approximately 35.621 g of o-nitroaniline with a m. p. between 69° C and 75 ° C.

5. Preparation of o-Chloronitrobenzene from o-Nitroaniline

Hartman and Brethen (1923)¹¹ found that m-chloronitrobenzene can be synthesized by formation of the diazonium salt from m-nitroaniline. Based on their procedure, o-chloronitrobenzene is similarly synthesized from the previously prepared o-nitroaniline. A 500ml RBF is charged with 15 g of o-nitroaniline and with an equimolar amount of 38% hydrochloric acid, along

with an additional 250 ml of hot water, a stir bar, and an additional equimolar amount of hydrochloric acid, and this set up is then placed over a magnetic stirrer. The entire mixture is cooled, and 20 g of sodium nitrite are added slowly with heavy stirring; once this addition is complete, the solution is filtered to remove any amorphous solids.

A suitable two-neck RBF is charged with a mixture containing 14.251 g of cuprous chloride in 38% hydrochloric acid; a thermometer and powder addition funnel containing the previously prepared o-nitrobenzenediazonium chloride are clamped to the flask. o-Nitrobenzenediazonium chloride then is very slowly added to the flask over a period of one hour. After this addition is complete, the mixture is set up for reflux until nitrogen stops evolving from the flask, after which the solution is set up for simple steam distillation until no more o-chloronitrobenzene comes over. The distillate is cooled to allow the o-chloronitrobenzene to crystallize; this crude distillate is washed with sodium hydroxide and then with cold water, resulting in approximately 29 g of o-chloronitrobenzene (~62% theoretical yield based on o-nitroaniline).

6. Synthesis of o-Aminothiophenol by Sulfonation of o-Chloronitrobenzene

o-Aminothiophenol is synthesized by a modified procedure outlined in US Patent No. 3931321 (1976)¹². 10 g of the previously prepared o-chloronitrobenzene with 80 ml of water are charged into a 250 ml RBF. Paraffin oil is used instead of the special emulsion polymerizer outlined in the original patent; the mixture is strongly stirred, and an addition funnel containing solution 15.022 g of sodium sulfide and an equimolar amount of sodium hydroxide is clamped to the flask; the solution is added slowly over

10 minute intervals with periods of cooling in between. The mixture is heated between 100° C and 110° C for approximately two hours.

The product is set up for steam distillation until a clear distillate comes over. To this clear distillate, . 5 g of activated carbon is added, and the mixture is washed with cold toluene; for further work up, the product is then washed 38% hydrochloric acid until the pH is adjusted to six, and the mixture is poured into a separatory funnel from which the bottom aqueous layer is removed. Excess toluene is then removed by simple distillation, and this distillate is allowed to cool. Approximately 5. 461 g of o-aminothiophenol crystallizes (~78. 37% yield based on o-chloronitrobenzene) with a m. p. between 22° C and 25° C.

7. Synthesis of Benzaldehyde by Oxidation of Benzyl Alcohol

Benzaldehyde is synthesized by simple oxidation of benzyl alcohol. A two neck 500 mL RBF is setup with a ring stand and wire mesh pad. A Bunsen burner is then placed below the apparatus, and the RBF is charged with an appropriate stir bar and 103. 5 g of sodium persulfate dissolved in a minimum quantity of water. A pressure-equalizing funnel containing 30 ml of benzyl alcohol and a reflux condenser are clamped to the flask. This set up is then heated to reflux while benzyl alcohol is slowly added drip-wise; once all the benzyl alcohol is completely added, the Bunsen burner is extinguished, and replaced with a magnetic stirrer until the solution cools down.

Upon cooling, the RBF is setup for steam distillation. The distillate is then poured into a separatory funnel, and the bottom crude benzaldehyde is separated out; this crude product is then dried over magnesium sulfate.

Once dried, the benzaldehyde is placed in a suitable RBF and fractionally distilled under vacuum at approximately . 109 atm; the fraction between 91° C and 93° C is collected, leaving 19. 35 ml of pure benzaldehyde (~65% theoretical yield based on benzyl alcohol).

8. Synthesis of o-Phenyl-benzothiazole from o-Aminothiophenol and Benzaldehyde

2 g of the previously prepared o-aminothiophenol and 1. 695 g of benzaldehyde are charged into a 25 ml Erlenmeyer flask with 15 ml of glycerol. The reaction is heated for one hour. Afterwards, water is added until precipitate no longer fell out of solution; the precipitate is purified via recrystallization in hot ethanol, thus resulting in 3. 034 g of o-phenyl-benzothiazole with a m. p. between 112° C and 114° C.

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