One Pot Synthesis of Substituted Benzothiazoles from substituted aldehydes and 2-aminothiols using Phenyltrimethylammonium tribromide

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ABSTRACT

Substituted 2-phenylbenzo[d]thiazoles were synthesized by stirring a mixture of aldehyde and 2-aminothiol in CH₂Cl₂ at room temperature using Phenyltrimethylammonium tribromide as a catalyst. We show here that Phenyltrimethylammonium tribromide, a stable, crystalline organic ammonium tribromide, can be readily utilized as an alternative electrophilic bromine source. It is easier to control the stoichiometry of addition with an organic ammonium tribromide, which minimizes aromatic bromination caused by excess reagent. It brings about the efficient oxidative cyclization of benzaldehydes and 2-aminothiols to the corresponding benzothiazoles under mild conditions via condensation.

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Introduction

Despite improvements in survival rates, cancer and viral diseases remain the second leading cause of death in the western world. Therefore, an area of major pharmaceutical interest over the last several decades has been the development of small molecules with antitumor and antiviral activity. Two potential targets for compounds with antitumor and antiviral activity are DNA and different types of proteins like tyrosine kinases or topoisomerase I/II. Therefore, the design of new intercalators, groove-binders and discovery of specific inhibitors of proteins are two important approaches in the search for new chemotherapeutic agents.

Benzothiazole derivatives are widely found in bioorganic and medicinal chemistry with applications in drug discovery and development for treatment of autoimmune and inflammatory diseases in the prevention of solid organ transplant rejection, epilepsy, amyotrophic lateral sclerosis, analgesia, tuberculosis, viral infections, and cancer. They have also found applications in industry as antioxidants, vulcanization accelerators and as dopant in a light emitting organic electroluminescent device. As well as they are used as ligands for asymmetric transformations. A number of methods have been reported for the synthesis of these heterocycles which include condensation of carboxylic acids and their derivatives like orthoesters, nitriles, amides, aldehydes and esters with o-substituted aminoaromatics. Beckmann rearrangement of o-acetylphenol oximes and photocyclization of phenolic Schiff bases also produce these compounds. Synthetic routes that are common to the preparation of these heterocycles typically involve the reaction of a carboxylic acid or its derivatives with an appropriate 1, 2-phenylenediamine, 2-aminophenol or 2-aminothiophenol in the presence of a strong acid at elevated temperatures.

Alternatively, a two-step procedure is employed wherein the 1,2-phenylenediamine, 2-aminophenol or 2 aminothiophenol is treated with one equivalent of an acid chloride, and the resulting mono N-acylated product is subjected to cyclodehydration under a variety of conditions such as heating in aqueous acids by pyrolysis at 200–350°C etc. In addition to the harsh conditions employed in these cases, some side reactions such as Friedel–Crafts acylation and Fries rearrangement also take place leading to lowering of selectivities.

Hence, in the progress of solvent free reactions, the synthesis of substituted benzothiazoles in very good yields by using catalysts and ionic liquids has been reported in recent times.

Materials and Methods

As an alternative reagent to liquid bromine, organic ammonium tribromide such as Phenyltrimethylammonium tribromide, which is high molecular weight, stable, crystalline solid, is capable of delivering a stoichiometric amount of bromine where small amounts are necessary for micro scale reactions has been used. In this work a novel application of Phenyltrimethylammonium tribromide for the one-pot synthesis of substituted benzthiazoles from substituted benzaldehydes and 2-aminothiols as shown in Scheme 1.

A mixture of 4-cholorobenzaldehyde (1mmol) and 2-aminothiol (1mmol) in CH2Cl2 (10 ml) was stirred for 40 min at r.t. and the progress of the reaction was monitored by TLC. The solvent removed under reduced pressure. The residue was subjected to column chromatography (EtOAc–hexane, 1:5, silica gel) to obtain pure colorless product.

Reaction mechanism

A probable mechanistic pathway to explain the oxidative cyclisation of substituted benzaldehyde and 2-aminothiol reaction is depicted in (Scheme 2).
Phenyltrimethylammonium tribromide is a electrophilic bromine source 1. The condensation of substituted benzaldehyde and 2-aminothiol produces 2 as a transient intermediate, which is then attacked by the lone pair of amine to give 3 followed by rapid formation of 4.

**Result and Discussion**

The contemporary methods suffer from one or more of the following drawbacks such as strong acidic conditions, long reaction times, low yields of the products, tedious work-up; need to use excess amounts of reagent and the use of toxic reagents, catalysts and solvents. Therefore, there is a strong demand for a highly efficient and environmentally benign method for the synthesis of these heterocycles. In recent years, studies of low-waste routes and reusable reaction media for enhanced selectivity and energy minimization have occupied the interests of synthetic organic chemists. Phenyltrimethylammonium tribromide mediated oxidative cyclisation of 4-chlorobenzaldehyde and 2-aminothiophenol to 2-(4-chlorophenyl)benzo[d]thiazole was investigated. In a typical experiment to a mixture of 4-chlorobenzaldehyde (1mmol) and 2-aminothiophenol (1mmol) in CH₂Cl₂ (10ml),) was added and the reaction mixture was stirred for 40 minutes at room temperature. The reaction proceeds for the formation of oxidative cyclisation in satisfactory yield. The solvents tested for this reaction (CHCl₃, CH₂Cl₂, MeOH and MeCN), CH₂Cl₂ was found to be the most efficient for maximum yield of the oxidation product.

Next, we examined the scope of the reaction of 2-aminothiophenol with a variety of aromatic aldehydes. As shown in Table 1, it was observed that a series of aromatic aldehydes bearing either electron-donating or electron-withdrawing groups on aromatic ring were investigated. The substitution groups on the aromatic ring have no obvious effect on the yields and reaction time under the above optimal conditions. However, aldehydes with strongly electron-withdrawing groups on aromatic ring such as p-nitrobenzaldehyde gave the product of with good yield in a long reaction time.
Conclusion
Phenylltrimethylammonium tribromide is a stable, electrophilic bromine source for the conversion of substituted benzaldehyde and 2-aminothiol to substituted benzothiazoles under mild conditions in a variety of solvents with good yields. One of the key benefits for this reagent when compared with molecular bromine is ease of addition and handling, which minimizes the risk of forming brominated side products. We have extended the use of this reagent to a direct, one-pot synthesis of substituted benzaldehyde and 2-aminothiol to substituted benzothiazoles in the presence of a stoichiometric amount of Phenyltrimethylammonium tribromide.

Table (1): Formation of substituted benzothioles from substituted benzaldehydes and 2-aminothioles using PTAB in CH2Cl2

<table>
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<tr>
<th>Sr. No.</th>
<th>Comp. A</th>
<th>Comp. B</th>
<th>Product</th>
<th>% Yield</th>
<th>Time (min)</th>
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References


