Eco-Friendly Synthesis of 2-Substituted Benzothiazoles Catalyzed by Cetyltrimethyl Ammonium Bromide (CTAB) in Water

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Una série de benzotiazóis 2-substituídos foi sintetizada pela condensação de 2-aminotiofenol com aldeídos (RCHO: R = Alquil, Aril, Heteroaril, 2-Arilformil) na presença de quantidade catalítica de brometo de cetiltrimetil amônio (CTAB) "on water". Assim, usando esse protocolo, 2-alquilbenzotiazóis foram sintetizados em altos rendimentos e 2-arylformilbenzotiazóis foram obtidos pela condensação de 2-aminotiofenol com arilformil aldeídos pela primeira vez.

A series of 2-substituted benzothiazoles have been synthesized by the condensation of 2-aminothiophenol with aldehydes (RCHO: R = Alkyl, Aryl, Heteroaryl, 2-Arylformyl) in the presence of a catalytic amount of cetyltrimethyl ammonium bromide (CTAB) "on water" by a one-pot procedure without additional organic solvents and oxidants. Thereinto, 2-alkylbenzothiazoles were synthesized in high yields and 2-arylformylbenzothiazoles were obtained from the condensation of 2-aminothiophenol with arylformyl aldehydes for the first time using the present protocol.

Keywords: 2-alkylbenzothiazole, 2-arylbenezothiazole, 2-arylformylbenzothiazole, cetyltrimethyl ammonium bromide (CTAB), water

Introduction

Benzothiazoles and their derivatives are very important group of heterocyclic bicyclic systems, which play a fundamental role in organic and bioorganic chemistry. They have potent antitumor activity and other important pharmaceutical utilities, such as their applications for treatment of autoimmune and inflammatory diseases, prevention of solid organ transplant rejection, epilepsy, analgesia, viral infections, cancer, and tuberculosis. Also, they can be used in industry as antioxidants and vulcanization accelerators that highlight their synthesis necessity.

The reported methods for the synthesis of 2-substituted benzothiazole (Scheme 1) involve two major routes: the condensation of 2-aminothiophenol with aldehydes, carboxylic acids, acid chlorides, or esters and by the cyclization of thiobenzanilides. Some other methods include microwave-mediated reaction of 2-aminothiophenol with β-chlorocinnamaldehydes, palladium-catalyzed Suzuki biaryl coupling of 2-halobenzothiazole with arylboronic acids, coupling of benzothiazoles with aryl bromides and the reaction between thiophenols and aromatic nitriles.

However, many of these methodologies are associated with one or more disadvantages such as (i) harsh reaction conditions, e.g., heating at 120 °C in xylene catalyzed by

![Scheme 1. Strategies for the synthesis of 2-substituted benzothiazoles.](image-url)
4-methoxy-TEMPO in presence of oxygen;\textsuperscript{18} heating in the presence of excess of PPA at 150-220 °C for 2-4 h;\textsuperscript{11} or P$_2$O$_5$/MeSO$_3$H at 70 °C for 10 h;\textsuperscript{13} microwave-assisted in ionic liquids\textsuperscript{23} or using excess of p-TsOH adsorbed on SiO$_2$/K$_2$O and graphite;\textsuperscript{27} treatment with stoichiometric amounts of oxidizing agents such as K$_5$Fe(CN)$_6$ at 90 °C under basic conditions;\textsuperscript{18} and excess of Mn(OAc)$_3$ in AcOH at 110 °C for 4 h;\textsuperscript{31} (ii) prolonged reaction time;\textsuperscript{32,47} (iii) additional reagents/catalysts, high boiling solvents that are difficult to recover;\textsuperscript{18,21,28} (iv) costly, air sensitive, and toxic substances;\textsuperscript{18} (v) requirement of excess strong oxidizing agents,\textsuperscript{18,19,21} etc. In many cases the acidic/metallic wastes are generated and mixed with the effluent water. On the other hand, the condensation reaction of 2-aminothiophenol with aliphatic aldehydes tend to attract little attention.\textsuperscript{21,33}

Thus, the development of environmentally benign, high yielding, and clean approaches for the synthesis of 2-substituted benzothiazoles is in demand.

The increasing concern about the tight legislation on the maintenance of greenness in synthetic processes\textsuperscript{51} led us to develop a method using a reagent that is less hazardous, non-toxic, cheap, and benign to the environment. Water as a reaction medium has gained importance in the development of sustainable chemistry.\textsuperscript{52}

As a common catalyst for phase transfer, cetyltrimethyl ammonium bromide (CTAB) is able to expedite the reaction between anion or nucleophile and neutral substrate via transferring one phase to another, making them collided with each other frequently.\textsuperscript{53}

In continuation of our efforts to develop green synthetic routes for the formation of C-C and carbon-heteroatom bond,\textsuperscript{54} we herein report a green, simple and practical method for the synthesis of 2-substituted benzothiazoles from the condensation of 2-aminothiophenol with aldehydes catalyzed by CTAB in water.

\section*{Results and Discussion}

Initially, we investigated various conditions in the model reaction using 2-aminothiophenol with propionaldehyde in water and the results were summarized in Table 1. The results established that CTAB proved to be a superior catalyst among all the catalysts screened in this transformation. Then, the reaction was investigated with different amounts of CTAB. It was found that the yield was not significantly affected by adding amount of CTAB, 5 mol% of CTAB was sufficient, and excessive amount of catalyst did not increase the yield remarkably (Table 1, entries 6-8).

With the optimal conditions in hand, further investigations were carried out to expand the scope of other alky aldehydes and the results were summarized in Table 2. In all cases, it was found that alkyl aldehydes can react well with 2-aminothiophenol in good yields without using extra oxidants. It is noteworthy that the present protocol is superior to the previous method for the synthesis of 3a by heating in...
DMF at 100 °C catalyzed by 50 mol% of molecular iodine with the yields of 31% (Table 2, entry 1). Moreover, the 2-styrylbenzothiazole can react well with 2-aminothiophenol in high yield in short time (Table 2, entry 5).

Next, we examined the scope of the reaction of 2-aminothiophenol with a variety of aromatic aldehydes. As shown in Table 3, 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 3l with good yield in a long reaction time (Table 3, entry 7).

Furthermore, we also examined the condensation reaction of heteroaromatic aldehydes such as furfural, 2-thienyl aldehyde, 2-pyridyl aldehydes with 2-aminothiophenol (Table 3, entries 17-19). Similarly, the corresponding products were obtained with excellent yields.

Finally, we examined the reactivity of arylformyl aldehyde with 2-aminothiophenol in the presence of CTAB in water (Table 4). The results showed that arylformyl aldehyde exhibited analogous behavior to that of aromatic...
aldehyde and aliphatic aldehyde. To our knowledge, we reported the synthesis of 2-arylformylbenzothiazoles from the condensation of 2- aminothiophenol with arylformyl aldehyde for the first time.

A tentative mechanism for the formation of 2-substituted benzothiazoles was proposed. It may be assumed that the bromide ion of cetyltrimethyl ammonium bromide is hydrogen-bonding to –SH increasing the nucleophilicity of sulfur atom, which makes the thiolate anion as a stronger nucleophile towards efficient condensation with aldehydes followed by cyclization. The second step could be a rate determining step. That the actual oxidant is the oxygen of air, wherein in the atmosphere of nitrogen resulted in an extremely sluggish reaction insufficient for complete product formation even after 10 h. While the miceller environment formed by catalytic amount of resolved in water can accelerate the oxidation of thiazoline to thiazole.

In conclusion, we have developed a facile, efficient and green method for the synthesis of 2-substituted benzothiazoles by the condensation of alkyl, aryl, arylformyl aldehydes with 2-aminothiophenol in the presence of CTAB in water. Compared to previous reported methodologies, the present protocol features simple work-up, environmentally benign, high yields with alkyl aldehyde, no requirement of extra oxidants and use of the catalytic amounts of the cheap catalyst. Currently, studies on the extension of this protocol are ongoing in our laboratory.

Experimental

Melting points were recorded on Digital Melting Point Apparatus WRS-1B and are uncorrected. ¹H NMR and ¹³C NMR spectra were taken on a Bruker DPX300 spectrometer using CDCl₃ or DMSO-d₆ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts were given in δ relative to TMS, the coupling constants J are given in Hz. Mass spectrometric analysis was performed on GC-MS analysis (SHIMADZU GCMS-QP2010).

General procedure for the preparation of 2-substituted benzothiazoles

To a mixture of benzaldehyde (1 mmol) and 2-aminothiophenol (1.1 mmol), CTAB (0.05 mmol, 5 mol%) was added in water (5 mL) at reflux. After completion of the reaction, the product was extracted with ethyl acetate (3 × 10 mL), the organic layer washed with brine (3 × 10 mL), then dried over Na₂SO₄ and concentrated. The product was separated and purified by column chromatography on silica gel (300-400 mesh) using an ethyl acetate/petroleum ether mixture as the eluent to afford a pure product. When necessary, the products are purified through recrystallization from 95% ethanol.

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Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br, as PDF file.

References

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