Tetrahedron Letters 53 (2012) 6950–6953

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A robust one-pot synthesis of benzothiazoles from carboxylic acids including examples with hydroxyl and amino substituents

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ARTICLE INFO

Article history:
Received 13 July 2012
Revised 16 September 2012
Accepted 9 October 2012
Available online 16 October 2012

Keywords:
Benzothiazole
Substituted carboxylic acid
2-Aminothiophenol
Ionic liquid
Triphenyl phosphite

ABSTRACT

The cyclocondensation of 2-aminothiophenol and carboxylic acids to give benzothiazoles has been carried out under mild conditions using tetrabutylammonium bromide (TBAB) as the reaction medium and triphenyl phosphite as the catalyst. Shorter reaction times, rapid isolation of the products, and excellent yields are advantages of this method. The reaction is found to be general and quite tolerant to the nature of the substituted carboxylic acids.

Step economy is an important goal of simple, efficient, and protecting group free syntheses of organic compounds using readily available reagents. Unnecessary steps can be avoided if a reaction sequence is designed that does not need sequential separation and purification processes. Functionality tolerance, mild reaction conditions, short reaction times, economy, and simple work-up leading to the isolation of pure products are other key factors that must be taken into account. In line with these considerations we have focused on the development of a new method for the synthesis of 2-substituted benzothiazoles from substituted aromatic carboxylic acids under convenient reaction conditions.

2-Substituted benzothiazoles have attracted considerable interest due to their diverse biological and pharmaceutical properties such as antitumor,[1] antifungal,[2] anti-inflammatory,[3] antimicrobial,[4] antiviral,[5] and enzyme inhibitory activity.[6] Recently, radiolabeling of some derivatives of benzothiazoles has been developed for PET imaging in the diagnosis of Alzheimer's disease.[7] The increasing application of metal complexes of 2-(2-hydroxyphenyl)benzothiazolate (BTZ), which is an *N,O*-donor chelating ligand capable of forming multifunctional complexes in optoelectronics, and utilized for the synthesis of fluorogenic enzyme substrates, and fluorescent materials is well recognized.[8–10]

A range of methods is currently available for the synthesis of 2-substituted benzothiazoles including condensation-dehydration of 2-aminothiophenol with carboxylic acids,[11] aldehydes, alcohols,[12] and by cyclization of thiobenzamides.[13] While the reported methodologies are generally efficient, most require long reaction times, harsh reaction conditions including the use of corrosive acids (e.g., polyphosphoric acid, PPA) and heating in high boiling point solvents, and are associated with the generation of hazardous wastes, low functional group tolerance, and tedious work-up procedures.

We became aware of an earlier study[11c] that used ionic liquids for the synthesis of substituted benzothiazoles from carboxylic acids. However, the present studies use a simpler and less expensive ionic liquid and describe the preparation of hydroxyl and amino substituted benzothiazoles under mild and protecting group free conditions. Even in recent applications of these compounds harsh reaction conditions (PPA) were used for their synthesis.[14–16] Hence, there is a significant interest in developing more efficient, convenient, and environmentally benign methods that support different substitution patterns in the desired products.

In continuation of our studies on the development of synthetic methodologies,[17] we report an efficient and straightforward procedure for the synthesis of 2-arylbenzothiazoles from 2-aminothiophenol and a variety of substituted carboxylic acids under benign and metal-free conditions using triphenyl phosphite in the simple ionic liquid, tetrabutylammonium bromide (TBAB) (Scheme 1).

The key step in the synthesis involved the reaction of substituted aromatic carboxylic acids with 2-aminothiophenol. Acids

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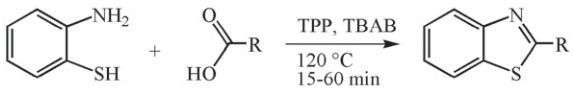
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.10.035



R = heteroaryl, substituted aryl (-OH, -NH_2, -halide, -CN, -NO_2).

Scheme 1. Formation of 2-substituted benzothiazoles from carboxylic acids.

containing both electron-donating [e.g., OH, NH_2, $N(CH_3)_2$] and electron-withdrawing groups (e.g., CN, NO_2) were successfully employed to prepare the corresponding benzothiazoles. These substituents had little effect on the product yields, the highest being obtained for quinaldic acid.

The synthesis was accomplished using a mixture of substituted aryl carboxylic acid and 2-aminothiophenol with triphenyl phosphite in the presence of the inexpensive ionic liquid, tetrabutylammonium bromide (TBAB) at 120 °C. The resulting viscous slurry was treated with methanol and the remaining solid filtered and washed with cold methanol and dried in vacuo.[18] This simple work-up procedure gave pure benzothiazole products without the need for further purification by column chromatography, apart from one case in which the product **12** was recrystallized.[19] The reaction time was in the range of 15–60 min, and the isolated product yields in the majority of cases were >65% (Table 1). Detailed synthetic procedures, spectroscopic (^{1}H NMR, MS, and FTIR) characterization data, and elemental analysis (CHN) data are provided in Supplementary data (SI). Similar results were obtained using bis-(2-aminophenyl) disulfide instead of 2-aminothiophenol, however, the latter is much less expensive and its use is more economical.

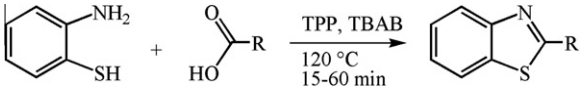
In comparison, the synthesis of a benzothiazole from pyridine carboxylic acid using more stringent reaction conditions, (i.e., heating in the presence of PPA at 160 °C for 4 h), has been reported, giving the product benzothiazole in only 31% yield. [20] In contrast, this product was obtained in 1 h, at 120 °C and in 70% yield using the method reported here (Table 1, entry 2). A further notable feature of this method is the ability to synthesize phenolic and 2-aminophenyl benzothiazoles without the need for protecting groups. Furthermore, aromatic carboxylic acids bearing various functionalities such as chloro, iodo, amino, and nitro tolerated the reaction and provided moderate to high yields of the corresponding benzothiazoles.

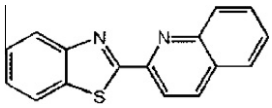
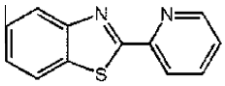
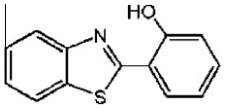
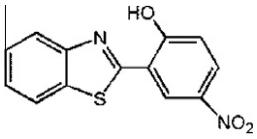
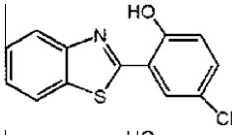
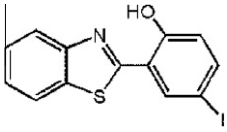
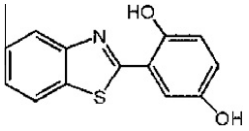
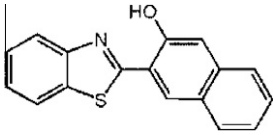
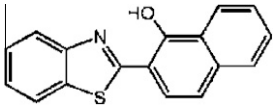
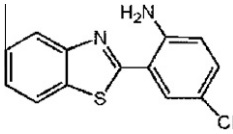
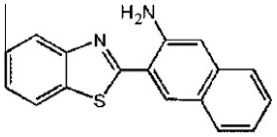
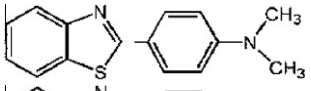
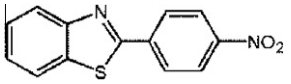
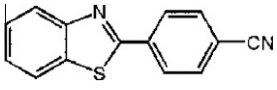
To the best of our knowledge, no synthetic procedure has been reported for 2-(2-aminonaphthyl)benzothiazole (Table 1, entry 11, 67%). The synthesis of 2-(2-amino-5-chlorophenyl)benzo-thiazole, (Table 1, entry 10, 61%), has also been reported previously in 13% yield, via two successive steps from 2-nitro-5-chlorobenzalde hyde.[21]

The application of 2-(2-aminophenyl)benzothiazole derivatives as fluorogenic substrates for the detection of enzyme activity in clinically important bacteria has been reported.[22] The present synthetic method opens a new avenue to the convenient synthesis of these compounds and the two 2-amino derivatives (Table 1, entries 10 and 11) merit consideration for similar applications.

This new methodology was also successfully utilized for the one-step synthesis of 2-(2-hydroxy-5-chlorophenyl)benzo-thiazole from 5-chlorosalicylic acid in high yield (Table 1, entry 5, 86%), the synthesis of which has been reported previously by a lengthy and complicated procedure in 46% yield.[23] Similarly, the synthesis of 2-(2-hydroxy-5-iodophenyl)benzothiazole (**6**) via iodination of 2-(2-hydroxyphenyl)benzothiazole in 61% yield has been reported.[24] There is no report on the synthesis of **6** from 2-aminothiophenol and iodine-substituted aldehydes or acids.

Table 1
Synthesis of various 2-substituted benzothiazoles



Entry	Product		Time (min)	Yield (%)
1		**1**	15	87
2		**2**	60	70
3		**3**	60	82
4		**4**	15	65
5		**5**	15	86
6		**6**	15	85
7		**7**	60	66
8		**8**	15	86
9		**9**	60	72
10		**10**	30	61
11		**11**	30	67
12		**12**	60	60
13		**13**	15	60
14		**14**	60	70