L-Proline Catalyzed Condensation Reaction of Aldehyde or Carboxylic Acid with 2-Aminothiophenol under Solvent-Free and Microwave Irradiation

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Abstract

A series of 2-arylbenzothiazoles was synthesized from the condensation reaction of aryl aldehyde with 2-aminothiophenol in the presence of *L*-proline under solvent-free and microwave irradiation conditions. Aromatic acids and aliphatic acids also gave the desired products in good to moderate yields under the reaction conditions. The product yields of using carboxylic acids with 2-aminothiophenol were generally lower than those of using aldehydes. This microwave-assisted *L*-proline catalyzed reaction provides a green and inexpensive preparation method for synthesis of 2-arylbenzothiazoles.

***Key Words*:** 2-Arylbenzothiazole, 2-Aminothiophenol, *L*-Proline, Microwave Irradiation, Solvent-Free

1. Introduction

2-Arylbenzothiazole nucleus is of particular interest especially within the realm of medicinal [1–3] chemistry and material [4,5] industry because benzothiazoyl-moiety is the key structure of many natural products, drugs and optoelectronic materials. The reported synthetic methods of 2-arylbenzothiazoles in the literatures mainly fall into two categories: (1) the direct condensation reaction of 2-aminothiophenol with aldehydes [6–10], acyl chloride [11,12], carboxylic acids [13–16], esters [17, 18] and nitriles [19–21]; (2) potassium ferricyanide cyclization of thiobenzanilides [22–27]. Other recently reported methods [28] include Pd-catalyzed Suzuki-Miyaura reaction of arylboronic acid [29] with 2-bromobenzothiazole, Stille reaction of aryl iodide with 2-stannylbenzothiazole [30], and coupling reaction of aryl bromide [31] with benzothiazole. However, the most commonly used condensation reaction suffers from the reaction required extremely harsh conditions and often the products were isolated in poor yields. Cyclization method was restricted to the difficulties encountered in the synthesis of readily oxidizable 2-aminothiophenols bearing substituted groups. Thus, there is a need to develop a simple and an efficient method for the synthesis of 2-arylbenzothiazoles without multi-step process, hazardous and carcinogenic organic solvent and the use of expensive non-recovery catalyst. Herewith, we wish to report a facile *L*-proline catalyzed reaction for the synthesis of 2-arylbenzothiazole under solvent-free and microwave irradiation conditions (Figure 1).

2. Experiments and Results

Our previous studies showed that intramolecular cyclization of homoallyl alcohol to β-halogenated tetrahydrofuran was achieved in the presence of *L*-proline under both acidic and basic reaction conditions [32]. Solvent-free organic synthesis have attracted immense

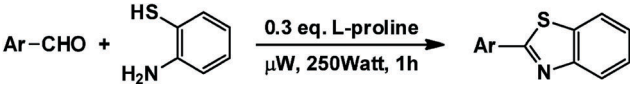

Figure 1. Condensation reaction of aryl aldehyde with 2-aminothiophenol.

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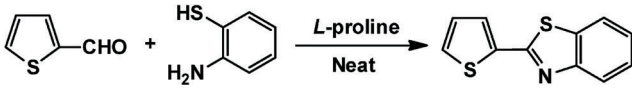
interest as environmentally benign methods. Thus, we further investigated the formation of 2-arylbenzothiazole by a direct condensation reaction of aryl aldehyde with 2-aminothiophenol in the presence of *L*-proline under solvent-free reaction condition. Using thiophenyl aldehyde as a model substrate, a reaction mixture of thiophenyl aldehyde (1.0 eq) and 2-aminothiophenol (1.5 eq) and *L*-proline (0.3 eq) was heated at 180 °C for 6 hours under solvent-free condition and 72% of 2-thiophenylbenzothiazole was obtained (Figure 2). The use of microwave irradiation to simplify and improve thermal reaction recently has become a very popular method, because it often leads to high yields and shorter reaction times. The product yield improved dramatically to 91% when 0.3 equivalent of *L*-proline was used under microwave irradiation. The quantitative amount of *L*-proline (0.1 eq. to 0.5 eq.) was introduced and investigated, and a 30 mol% of *L*-proline to substrate was shown to give the best results. The experimental results showed that the much shorter reaction time and higher efficiency were achieved when *L*-proline introduction and microwave irradiation were both employed.

To understand the scope of this new microwave-assisted *L*-proline catalyzed solvent-free reaction, various aryl aldehydes were investigated under the reaction condition and the results are shown in Table 1.

As shown in Table 1, reactions using electron-poor (Entries 2, 3) or electron-rich (Entries 4, 5) aromatic aldehydes, or heteroaromatic aldehydes (Entries 9–12) gave the desired products in good to moderate yields. The pyridyl aldehydes (Entries 7, 8) gave better yield when *L*-proline was not introduced under the reaction condition.



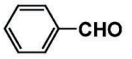
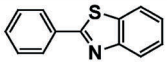
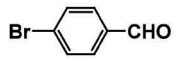
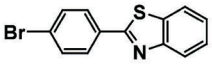
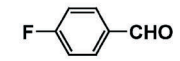
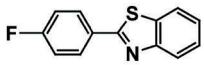
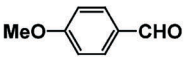
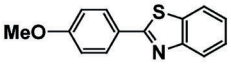
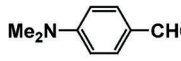
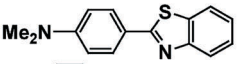
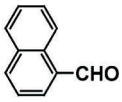
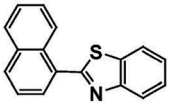
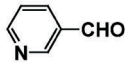
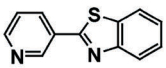
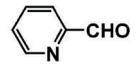
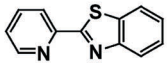
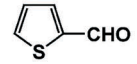
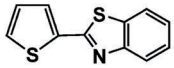
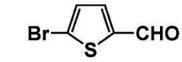
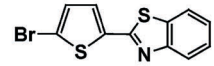
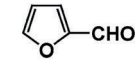
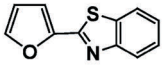
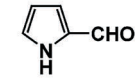
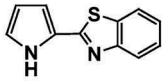
* In the absence of *L*-proline	
a. 180 °C, 12h	54%
b. μW, 250 Watt, 1h	63%
* In the presence of *L*-proline	
a. 180 °C, 6h	72%
b. μW, 100 Watt, 3h	79%
c. μW, 250 Watt, 1h	91%
d. 0.1 eq. L-proline, μW, 250 Watt, 1h	83%
e. 0.5 eq. L-proline, μW, 250 Watt, 1h	82%

Figure 2. Optimization of L-proline introduction.

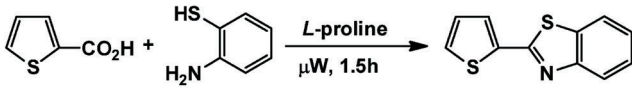
In order to expand the scope of this microwave-assisted *L*-proline catalyzed solvent-free reaction, carboxylic acid also was investigated for the formation of 2-arylbenzothiazole (Figure 3). A reaction mixture of thiophenyl acid (1.0 eq) and 2-aminothiophenol (1.5 eq) and *L*-proline (0.3 eq) was microwave irradiated for 1.5 hours under solvent-free condition and 60% of 2-thiophenylbenzothiazole was obtained. In order to estabilish the optimum conditions for this reaction, various ratio of *L*-proline and 2-aminothiophenol were examined. The quantitative amounts of *L*-proline (0.5 eq) and 2-aminothiophenol (3.0 eq) was shown to give the best results. Various carboxylic acids were investigated under the reaction condition and the results are shown in Table 2.

As shown in Table 2, reactions using electron-poor (Entry 2) or electron-rich (Entries 3, 4) aromatic acids, or heteroaromatic acids (Entries 6–8), or aliphatic acids

Table 1. Synthesis of 2-Arylbenzothiazoles

Entry	Aldehyde	Product	Yield[a]
1			99%
2			90%
3			80%
4			96%
5			45% 22%[b]
6			94%
7			99%[b]
8			65%[b]
9			91%
10			59%[c]
11			71%
12			52%

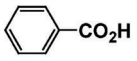
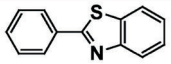
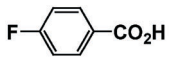
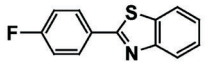
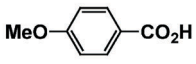
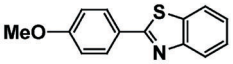
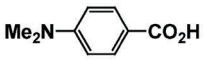
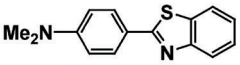
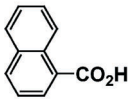
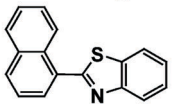
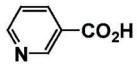
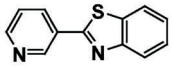
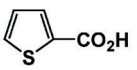
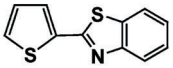
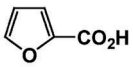
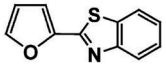
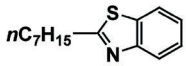
a. The yields were determined after chromatographic purification.
b. In the absence of *L*-proline.



a. 0.3 eq. *L*-proline, 1.5 eq. 2-aminothiophenol 60%
b. 0.3 eq. *L*-proline, 2.0 eq. 2-aminothiophenol 63%
c. 0.5 eq. *L*-proline, 2.0 eq. 2-aminothiophenol 67%
d. 0.5 eq. *L*-proline, 3.0 eq. 2-aminothiophenol 72%

Figure 3. Optimization of condensation reaction condition.

Table 2. Synthesis of 2-Arylbenzothiazoles[a]

Entry	Carboxylic Acid	Product	Yield[b]
1			86%
2			66%
3			66%
4			12% 5%[c]
5			64%
6			45% 46%[c]
7			72%
8			57%
9	CH_3-$(CH_2)_6$-CO_2H	nC_7H_{15} 	80%

a. 3.0 eq. of 2-aminothiophenol and 0.5 eq. of *L*-proline were introduced.
b. The yields were determined after chromatographic purification.
c. In the absence of *L*-proline.

(Entry 9) gave the desired products in good to moderate yields. The product yields of using carboxylic acids with 2-aminothiophenol were generally lower than those of using aldehydes. A representative procedure for synthesis of 2-arylbenzothiazoles as follows: Aldehyde (1.0 mmol), 2-aminothiophenol (1.5 mmol) and *L*-proline (0.3 mmol) were added in a pressure tube with a threaded Teflon cap and the reaction mixture was microwave irradiated for one hour at 250 Watts, 200 psi conditions. The reaction mixture was cooled to room temperature and the resulted arylbenzothiazole was purified on a flash chromatograph with silica gel and ethyl acetate/hexane as eluant. All reagents were purchased from Aldrich and Riedel-deHaen and all were used directly without further purification. The microwave irradiation reaction was carried out in CEM Discover microwave reactor.

3. Conclusion

2-Arylbenzothiazoles were synthesized from the condensation reaction of aryl aldehydes or carboxylic acids with 2-aminothiophenol in the presence of *L*-proline under solvent-free and microwave irradiation conditions. This microwave-assisted *L*-proline catalyzed reaction provides a green and an inexpensive preparation method for synthesis of 2-arylbenzothiazoles which are the important synthetic intermediates for synthesis of biologically active compounds and industrial materials.

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