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Graphical Abstract

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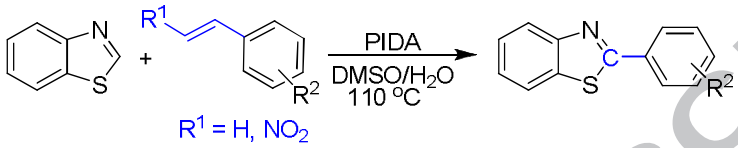

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Phenyliodonium diacetate mediated arylation of benzothiazoles with substituted styrenes

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ABSTRACT

A metal-free synthesis of 2-arylbenzothiazoles was achieved using phenyliodonium diacetate (PIDA) from benzothiazoles and styrenes or β-nitrostyrenes. This transformation tolerates various functional groups such as methoxy, hydroxy, fluoro, chloro and nitro groups.

2-Aryl benzothiazoles have received considerable interest due to their significant biological activities such as antitumor, antiviral and antimicrobial activities. Benzothiazoles **1** and **2** are potent ligands for the aryl hydrocarbon receptor (AhR),[1] whereas **3** and **4** have exhibited excellent antitumor activity.[2] The biologically active arylamine is generated from the prodrug (**5**),[3] which exhibits potent activity against human mammary tumor xenografts and is presently in clinical trials (Figure 1). Moreover, benzothiazoles are found in other molecules such as industrial dyes, functional materials, natural products, and agrochemical compounds.[4] Therefore, development of new methods for the synthesis of benzothizoles and its analogues has drawn much attention.

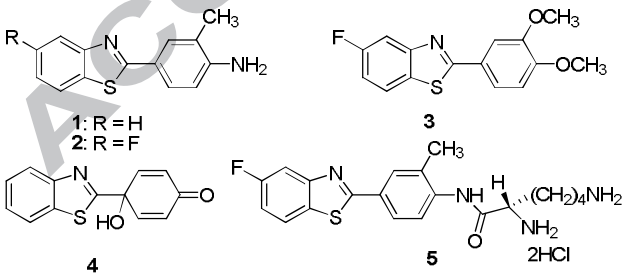

Figure 1. Chemical structures of benzothiazoles having antitumor activity.

Several methods have been reported for the formation of benzothiazoles including condensation of aminothiophenol with benzaldehydes,[5] nitriles,[6] carboxylic acids[7] and acyl chlorides[8] Scheme 1 a, b). However these methods have some limitations like high temperatures or strong acidic conditions. Other methods are based on transition metal (Pd or Cu) catalyzed decarboxylation of benzothiazole with benzoic acid, and phenyl acetic acid[9] and cyclization of thiobenzanilides using Jacobson method,[10] which actually requires several steps for starting material preparation. The direct arylation of benzothiazoles is an alternative and versatile method for the synthesis of 2-aryl benzothiazoles. These methods include transition metal catalyzed cross coupling reactions of benzothiazoles with arylsilanes,[11] aryl halides,[12] aryl boronic acids,[13] aryl triflates[14] and sodium sulfinates (Scheme 1, c).[15] These catalytic methods have drawn considerable interest, however, they suffer from the use of expensive transition metal catalysts. Recently, an iron catalyzed arylation of benzothiazoles (Scheme 1, d, condition 1) from aldehydes has been reported by Deng and co-workers.[16] The major limitation of the direct arylation of benzothiazoles using metal catalysts is the contamination of metal in the synthesized biologically active molecules or synthesized drug intermediates that is important in pharmaceutical industry. To avoid this, Yang and co-workers have developed a method to synthesize 2-substituted benzothiazoles from benzothiazole and aryl aldehydes using $K_2S_2O_8$ and this method is applicable for only electron rich aryl aldehydes (Scheme 1, d).[17] To overcome these problems, development of transition metal-free, direct and an efficient method for the synthesis of benzothiazoles from cost-effective staring materials needs to be explored. To the best of our knowledge, the preparation of aryl substituted benzothiazoles from benzothiazoles and styrenes is not known (Scheme 2).

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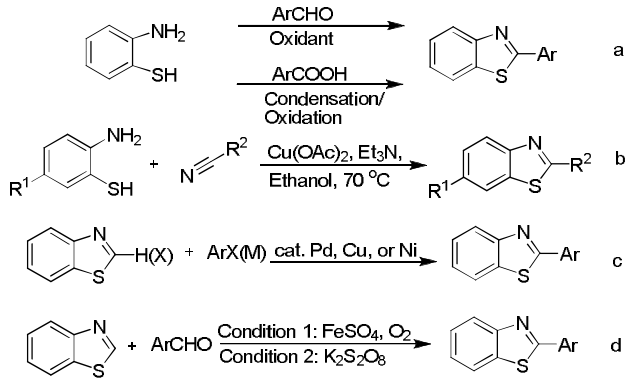
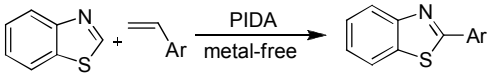


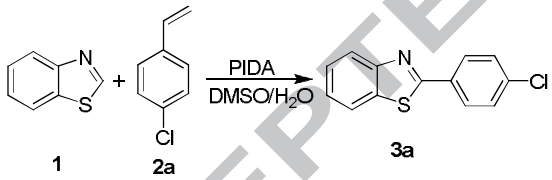
Scheme 1. Strategies for 2-arylbenzothiazole synthesis.



Scheme 2. Arylation of benzothiazoles using PIDA.

According to previous reports, phenyliodonium diacetate (PIDA) can oxidize alkenes into corresponding aldehydes[18] and aryl substituted benzothiazoles could be prepared through the condensation of benzothiazoles with aromatic aldehydes. Therefore, we conceived that 2-arylsubstituted benzothiazoles could be achieved directly from styrenes and benzothiazoles using PIDA. Initially, we tested this hypothesis by treating the benzothiazole with 4-chlorostyrene in the presence of PIDA as the model reaction to screen the various parameters. Reaction of 4-chlorostyrene with benzothiazole did not give the desired product in CH_3CN/H_2O and CH_3OH/H_2O at 70 °C for 14 h (Table 1, entries 1, 2). Later, the reaction was performed in DMSO and H_2O at 70 °C for 14 h, the desired

Table 1.Optimization of the reaction parameters for the synthesis of 2-(4-Chlorophenyl)benzothiazole[a]



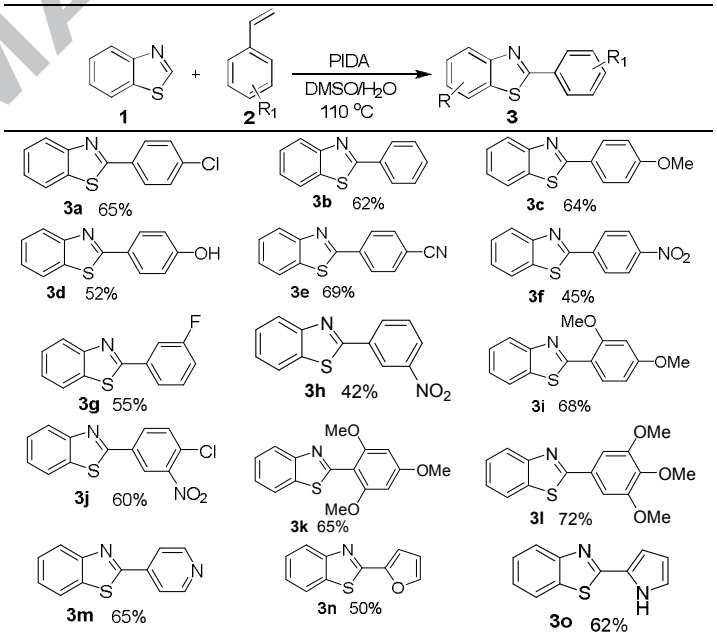
Entry	PIDA (equiv)	solvent	T (°C)	Yield (%)
1	1.2	CH_3OH/H_2O	70	0
2	1.2	CH_3CN/H_2O	70	0
3	1.2	DMSO/H_2O	70	10
4	1.2	DMSO/H_2O	90	30
5	1.2	DMSO/H_2O	110	40
6	1.2	DMSO/H_2O	130	40
7	2.4	DMSO/H_2O	110	60
8	3.0	DMSO/H_2O	110	65
9[b]	3.0	DMSO/H_2O	110	64
10		DMSO/H_2O	110	0

[a]benzothiazole (0.75 mmol), styrene (0.9 mmol), PIDA (2.25 mmol), DMSO/H_2O = 2:0.5 mL, 110 °C, 14 h. [b]DMSO/H_2O = 2:1 mL.

product was formed in low yield. Further, we proceeded to screen the temperature and found that optimal temperature was 110 °C for arylation of benzothiazoles (Table 1 entries 3-6). The maximum yield was obtained when the amount of PIDA was increased from 1.2 equiv to 3.0 equiv (Table 1 entry 8). Without using PIDA, the reaction did not progress (Table 1 entry 10) indicating the necessity of phenyliodonium diacetate (PIDA). Similar yields were obtained when 0.5 mL or 1 mL of H_2O was added to DMSO (Table 1, entry 8, 9). On the basis of these results, the optimal reaction conditions emerged as benzothiazole (1 equiv), styrene (1.2 equiv), PIDA (3 equiv), DMSO (2 mL), H_2O (0.5 mL) at 110 °C for 14 h.

To evaluate the scope and limitations of this reaction with respect to styrenes, we performed the reactions of benzothiazoles with styrenes bearing electron withdrawing substituents (nitro, nitrile and halides) as well as electron donating substituents (methoxy and hydroxyl) under optimal conditions[19] and results are summarized in Table 2. These results showed that styrenes with wide variety of substituents afford 2-aryl substituted benzothiazoles in 42-72% yields. It should be pointed out that halides (Table 2, **3a**, **3g** and **3j**) are well tolerated on the benzene ring that could be utilized for further transformations through metal catalyzed coupling reactions. However, the reaction of benzothiazoles with nitrostyrenes afforded the desired products **3f** and **3h** in 45 and 42% yields respectively. The formation of aryl substituted benzothiazole with 4-hydroxystyrene indicated that free hydroxyl group tolerated well under these conditions. Furthermore, arylation of benzothiazoles with some heteroaromatic styrenes such as 2-vinylfuran, 2-vinylpyrrole and 4-vinylpyridine also provided the desired products in 50-62% yields (Table 2, **3m-3o**).

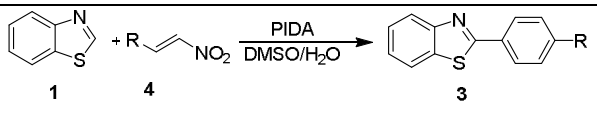
Table 2. Reaction of benzothiazoles with various substituted styrenes.[a,b]



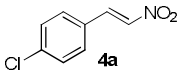
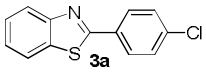
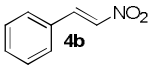
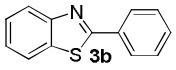
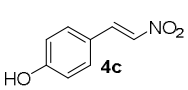
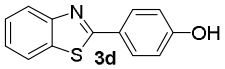
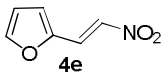
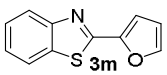
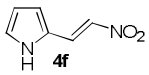
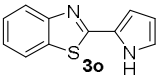
[a]conditions: benzothiazole (0.75 mmol), styrene (0.9 mmol), PIDA (2.25 mmol), DMSO/H_2O = 2:0.5 mL, 110 °C, 14 h. [b]All yields are isolated yields.

Next, we performed this reaction with *β*-nitrostyrenes and benzothiazole that also afford 2-aryl benzothiazoles[20] under optimal conditions and the results are shown in Table 3. The amount of *β*-nitrostyrenes used in this transformation is lesser compare with styrenes (Table 2). Initially we found that the treatment of (*E*)-1-chloro-4-(2-nitrovinyl)benzene with benzothiazole provided 2-(4-chlorophenyl)benzothiazole in 63% yield (Table 3, entry 1). Interestingly, functional groups such as chloro and methoxy tolerated well under these conditions. Heteroaromatic such as furanyl, and pyrrolyl substituted benzothiazoles were obtained in good yields with benzothiazole and corresponding nitrostyrenes. (Table 3, entries 4 and 5).

Table 3. Reaction of benzothiazoles with β-nitrostyrenes.[a,b]

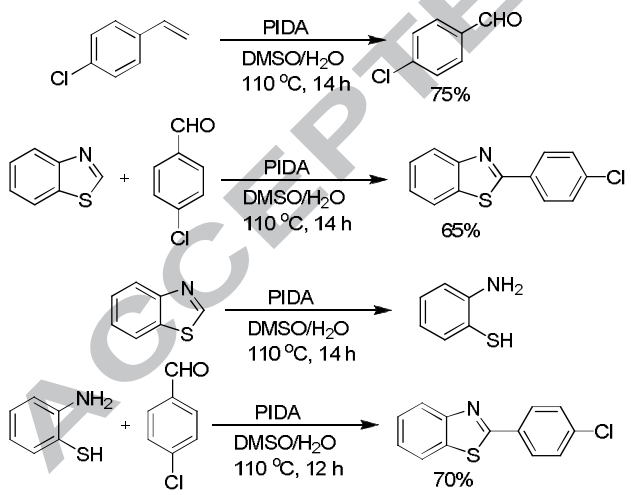


1 4 3

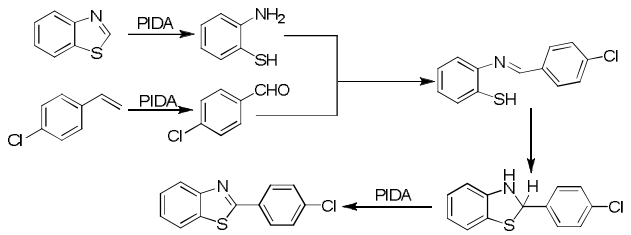
Entry	Substrate	Product	Yield (%)
1	 4a	 3a	63
2	 4b	 3b	62
3	 4c	 3d	59
4	 4e	 3m	59
5	 4f	 3o	62

[a] Conditions: benzothiazole (0.75 mmol), nitrostyrene (0.62 mmol), PIDA (2.25 mmol), DMSO/H_2O = 2:0.5 mL, 110 °C, 14 h. [b]All yields are isolated yields.

To elucidate the reaction mechanism, we have conducted some experiments as shown in Scheme 3. Treatment of chlorostyrene with PIDA under our standard conditions afforded the chlorobenzaldehyde in 75% yield. This was further supported by the reaction of benzothiazole with chlorobenzaldehyde to yield desired product in 65% yield. The reaction of benzaldehyde with both benzothiazole and aminothiophenol provided the desired product in good yield which indicated that this transformation might proceed via opening of benzothiazole ring. On this basis and the results of previous literature, a plausible mechanism was proposed as shown Scheme 4. Styrene was initially converted to the corresponding aldehyde, while benzothiazole gave ring opening product in the presence of PIDA. Next, the reaction of aminothiophenol with aldehyde produced imine which was further cyclized followed by oxidation to give the desired product.



Scheme 3. Detailed reaction study.



Scheme 4. Possible reaction mechanism.

In conclusion, we have developed a novel way for the synthesis of 2-substituted benzothiazoles using phnyliodonium diacetate (PIDA) employing benzothiazole and various styrenes at 110 °C in DMSO and H_2O. PIDA can oxidize benzothiazole and styrenes into 2-aminothiophenol and corresponding benzaldehydes *in situ* thus providing a variety of benzothiazoles. Particularly, this method was carried out without using any additive or base. This method is significant because it does not require any transitional metal catalysts, it is reasonably broad in scope and it is operationally simple. Finally, this method can be used in the synthesis of biologically active molecules having benzothiazloe scaffold.

Acknowledgments

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19. **General procedure for the synthesis 2-aryl benzothiazoles from styrenes**: To a solution of benzothiazole (0.75 mmol) and styrenes (0.9 mmol) in DMSO/H_2O (2:0.5 mL), PIDA (2.25 mmol) was added. The reaction mixture was heated at 110 oC for 14 h. After completion of the reaction indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated under vacuum to afford crude product which was purified by column chromatography (silica gel, hexane/ethyl acetate, 10:1) to give 2-aryl substituted benzothiazole.
20. **General procedure for the synthesis 2-aryl benzothiazoles from nitrostyrenes:** To a solution of benzothiazole (0.75 mmol) and β-nitrostyrenes (0.62 mmol) in DMSO/H_2O (2:0.5 mL), PIDA (2.25 mmol) was added. The reaction mixture was heated at 110 ^{o}C for 14 h. After completion of the reaction indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated under vacuum to afford crude product which was purified by column chromatography (silica gel, hexane/ethyl acetate, 10:1)to give 2-aryl substituted benzothiazole.

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Graphical Abstract

A metal free PIDA mediated arylation of benzothiazoles from styrenes or *β*–nitrostyrenes was developed. The reaction proceeded well for wide variety of substituted styrenes to give 2-aryl substituted benzothiazoles.