A Simple Iodine-promoted Synthesis of 2-Substituted Benzothiazoles by Condensation of Aldehydes with 2-Aminothiophenol

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Iodine is used to promote the condensation of 2-aminothiophenol with aldehydes in DMF, which affords corresponding 2-substituted benzothiazoles efficiently. Mild and manipulable procedure, use of available and less toxic oxidant, and shorter reaction times are the advantageous features of this method.

2-Substituted benzothiazoles are an important class of compounds in medicinal and industrial chemistry.[1] The benzothiazole nucleus constitutes the core unit of many antitumor drugs[2] and other pharmaceutic utilities,[3] some fluorescent[4] and photochromic[5] compounds, and some benzothiazoles have been found in some organism.[1] Thus, the synthesis of them is of considerable interests. The reported methods of benzothiazole synthesis involve two major routes: the condensation of 2-aminothiophenol with aldehydes,[6] carboxylic acids,[7] acid chlorides,[8] or esters[9] and by the cyclization of thiobenzanilides.[10] Other general methods include microwave-mediated reaction of 2-aminothiophenol with β-chlorocinnamaldehydes,[11] palladium-catalyzed Suzuki biaryl coupling of 2-bromobenzothiazole with arylboronic acids[12] and coupling of benzothiazoles with aryl bromides,[13] and the reaction between thiophenols and aromatic nitriles.[14] However, most of these methods suffer from one or more disadvantages such as high reaction temperature,[3d] harsh reaction condition,[10a] multistep process,[7a,7e] prolonged reaction time,[10c] requirement of excess of reagents,[6c,6d,11] and the use of costly,[6c] air sensitive[10b,12,13] catalysts, etc. Consequently, there is a need to develop a simple and mild protocol for synthesis of 2-substituted benzothiazoles without toxic oxidant.

Iodine is an inexpensive and readily available reagent and usually used as effective oxidant[15] and catalyst[16] in organic synthesis. We try to use it to promote the condensation of 2-aminothiophenol with aldehyde. When the mixture of 2-aminothiophenol and aldehyde was treated with iodine in a suitable solvent, the corresponding benzothiazole was afforded efficiently. To the best of our knowledge the employment of iodine in this area has not been reported previously.

In order to establish the optimum condition for this reaction, various ratio of iodine and various solvents were examined. Using 2-aminothiophenol and 4-chlorobenzaldehyde as a model, iodine was added in various ratio in DMF at 100 °C. As shown in Table 1, different results would be afforded in the presence of different ratio of iodine. Few desired products would be obtained in the absence of iodine. Substrates and intermediate could not be converted efficiently with too less iodine and more by-products would be obtained with too much iodine, higher yield was given in the presence of 50 mol % iodine. Four polar solvents were also investigated and the results summarized in Table 2 showed that DMF gave higher yield than others.

Table 1. Variation of ratio of iodine in condensation of 2-aminothiophenol with 4-chlorobenzaldehyde

Entry	I_2/mol %	Time/min	Yield[a]/%
1	0	60	Little
2	10	60	33
3	25	30	71
4	50	30	78
5	75	30	73
6	100	15	69
7	100	30	67

[a]All yields refer to isolated product.

Table 2. Variation of solvent in condensation of 2-aminothiophenol with 4-chlorobenzaldehyde

Entry	Solvent	Yield[a] /%
1	CH_3CH_2OH (reflux)	33
2	CH_3OH (reflux)	71
3	CH_3CN (reflux)	73
4	DMF (100 °C)	78

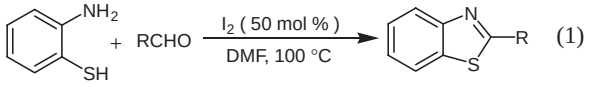
[a]All yields refer to isolated product.

Table 3. Condensation of 2-aminothiophenol with aldehydes promoted by iodine in DMF

Entry	R	Time/ min	Yield[a] /%	mp/°C[Lit]
1	C_6H_5	25	88	112–113[6d]
2	4-FC_6H_4	25	82	101–103[2a]
3	4-ClC_6H_4	30	78	112–114[6e]
4	2-BrC_6H_4	40	66	66–68[2a]
5	3-$O_2NC_6H_4$	35	78	183–185[6e]
6	2-HOC_6H_4	30	81	129–131[2a]
7	4-$H_3CC_6H_4$	30	80	83–85[2a]
8	4-$CH_3OC_6H_4$	30	71	120–122[2a]
9	Furyl	30	79	102–104[6d]
10	$C_6H_5CH{=}CH$	60	41	110–112[17]
11	$CH_3CH_2CH_2$	60	31	Liquid[18]

[a]All yields refer to isolated product, characterized by melting points, GC-MS, IR, and ^{1}H NMR spectroscopy.

Consequently the reaction was carried in DMF with 50 mol % iodine (Eq 1).



(1)

Various aldehydes were treated with 2-aminothiophenol in DMF in the presence of iodine (50 mmol %) at 100 °C to examine the generality of this procedure. Excellent results were obtained in most of the cases. The results were summarized in Table 3. Among them, benzaldehyde and substituted benzaldehydes gave higher yields than aliphatic aldehyde and α,β-unsaturated aldehyde.

In conclusion, a methodology has been developed for the synthesis of 2-substituted benzothiazoles via the condensation of 2-aminothiolphenol with aldehyde promoted by iodine.[19] Mild and manipulable procedure, use of available and less toxic oxidant, and shorter reaction times are the advantageous features of this method.

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19 General procedure for the synthesis of benzothiazole: 2-Aminothiophenol (25.0 mg, 0.2 mmol) and 4-chlorobenzaldehyde (28.0 mg, 0.2 mmol) were mixed in DMF (0.5 mL) thoroughly, then the solution of iodine (25.4 mg, 0.1 mmol) in DMF (0.5 mL) was added, heated and stirred at 100 °C for appropriate time (monitored by TLC). When the reaction was finished, the mixture was cooled to room temperature. Then, the solution of sodium thiosulfate (10%) was dropped into the mixture until the color of iodine was disappeared. The precipitate was filtrated and washed with water. After vacuum drying, the crude products was purified by column chromatography over silica gel (petroleum ether/ethyl acetate, 8:1) to afford the corresponding benzothiazole.

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