An Improved Process for the Production of 5-Methyl-1,2,4-triazolo(3,4-b) benzothiazole as a Fungicide

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Abstract
In this study an improved process for the production of 5-Methyl-1,2,4-triazolo(3,4-b) benzothiazole fungicide (IV) is described. Firstly, (2-methylphenyl) thiourea (I), 2-amino-4-methylbenzothiazole (II) and 2-hydrazino-4-methylbenzothiazole (III) as intermediates consequently were prepared. Then IV is synthesized by the reaction of III with formic acid in the presence of p-toluenesulfonic acid catalyst. The purity of the synthesized compounds was confirmed by CHN analysis and the structures verified on the basis of IR, ¹H-NMR and mass spectral data.

Keywords: 2-amino-4-methylbenzothiazole, 2-hydrazino-4-methylbenzothiazole, (2-methyl-phenyl) thiourea, Benzothiazoles, Fungicide.

Introduction
Benzothiazoles are bicyclic ring system with multiple applications which have been the subject of great interest because of their biological activities. Literature review revealed the potent inhibition of human immunodeficiency virus type 1 (HIV-1) replication by HIV-1 protease inhibition, anti tumor, analgesic and anti-inflammatory, anti malaria, antifungal, anticandidal activities [1-5]. 2-methylphenyl thiourea (I), 2-amino-4-methylbenzothiazole (II) and 2-hydrazino-4-methylbenzothiazole (III) are the origin intermediates for the synthesis of 5-methyl-1, 2,4-triazolo (3,4b) benzothiazole (IV). It is a important fungicide for controlling of rice blast (pyricularia orazae) in transplanted and direct-seeded rice (Figure 1) [6]. There are various methods for production of aminobenzothiazoles from phenyl thioureas with chlorine in aprotic solvents in the presence of catalytic quantities of bromine or
preferably iodine which in these manners, the conversion to benzothiazoles with chlorine alone leads to products likewise chlorinated in the benzene ring [7-10].

In this research and by application of a surprising manner, the ring closure to the thiazole-compounds can be affected by using of bromine without any catalyst.

![Figure 1. Structure of intermediates and final compounds (I-IV).](image)

**Experimental**

*Materials and Methods*

All chemicals and solvents were obtained from Merck (Darmstadt, Germany) chemical company and were used without further purification. All melting points are uncorrected and were taken with an Electrothermal melting point apparatus (Electrothermal Eng. Ltd, Essex, UK). IR spectra were determined in KBr on a Shimadzu Dr-8031 instrument. The $^1$H NMR spectra of the synthesized compounds were measured in CDCl$_3$ solution and TMS as the internal standard using a Varian Mercury 400 MHz instrument. All Chemical shifts were reported as $\delta$ (ppm) values. The mass spectra were recorded on a LCQ ion trap mass spectrometer (Thermo Fisher. San Jose.CA, USA), equipped with an EI source. Elemental analyses were carried out using a Perkin-Elmer, CHN elemental analyzer model 2400 and were within ±0.4% of the theoretical values.

**Preparations (Scheme 1)**

*2-methylphenyl thiourea (I)*

In a vessel, 107.2 g of o-toluidine, 250 ml toluene and 106 g of 36% hydrochloric acid were charged with stirring. The mixture was heated to 75°C and 87.5 g ammonium thiocyanat was admixed with the mixture and the reaction was performed at 75 to 85°C for 2 hours. The resulting crystal was separated by filtration, washed with water and dried to obtain 160 g of 2-methylphenyl thiourea. The precipitate re-crystallized from ethanol [11].

Yield 96.4%, m.p: 149-150°C; IR (KBr, cm$^{-1}$); 3454, 2910, 1610, 1473, 1170, 901, 738; $^1$HNMR (CDCl$_3$, $\delta$ ppm), 2.136 (3H, s), 7.071 (1H, ddd), 7.006 (1H, ddd), 7.088 (1H, ddd), 6.848 (1H, ddd), Anal. Calcd. For C$_8$H$_{10}$N$_2$S: C, 57.85; H, 6.02; N, 16.86, Found: C, 57.70; H, 5.95; N, 16.80; Mass spectra, m/z=166.10 (100%).
2-amino-4-methylbenzothiazole (II)
73.5 g of 2-methylphenyl thiourea (I) obtained from the previous step was suspended in 300 g sulfuric acid 98% and while stirring, 32.5 g of sodium bromide was added. The 2-amino-4-methyl benzothiazole hydrobromide was crystallized out, whereby the hydrobromic acid development (removal) started. After completion of the hydrobromic acid removal by boiling at a reflux temperature, the reaction mixture was drained off and dried. Upon treating the hydrobromide with an aqueous NaOH 20% w/v solution; 2-amino-4-methyl benzothiazole was obtained. The precipitate re-crystallized from ethanol.
Yield 92.7%, m.p: 137.5 - 138.5°C, IR (KBr, cm\(^{-1}\)); 3339, 3038, 1615, 1473, 1270, 928, 750; \(^1\)HNMR (CDCl\(_3\), δ ppm) 2.162 (3H, s), 7.856 (1H, dd), 7.063 (1H, dd), 7.453 (1H, dd), Anal. Calcd. For C\(_8\)H\(_8\)N\(_2\)S: C, 58.55; H, 4.87; N, 17.06; Found: C, 55.40; H, 4.80; N, 17.00; Mass spectra, m/z=164.10 (100%).

2-hydrazino-4-methylbenzothiazole (III)
70 g of 2-amino-4-methylbenzothiazole (II) obtained from the previous step and 23 g hydrazine monohydrate 100% were suspended in 400 ml of ethylene glycol (containing 44 g hydrazine monohydrate and 18 g hydrochloric acid). The mixture was heated with agitation to 120-130°C and stirred at a constant temperature for 2 hours. The reaction mixture was poured into ice water, drained off and dried. The precipitate re-crystallized from ethanol.
Yield 90.2%, m.p: 165–168°C, IR (KBr, cm\(^{-1}\)); 3423, 3128, 1632, 1486, 1275, 943, 770; \(^1\)HNMR (CDCl\(_3\), δ ppm) 2.162 (3H, s), 7.766 (1H, dd), 7.163 (1H, dd), 7.550 (1H, dd), Anal. Calcd. For C\(_8\)H\(_9\)N\(_3\)S: C, 53.81; H, 5.06; N, 23.44, Found: C, 53.70; H, 4.90; N, 23.21; Mass spectra, m/z=179.05 (100%).

5-Methyl-1,2,4-triazolo(3,4-b) benzothiazole (IV)
66.5 g of 2-hydrazino-4-methylbenzothiazole (III) obtained from the previous step was suspended in 200 ml of formic acid. The mixture was heated with agitation to 110°C and stirred at a constant temperature for 2 hours. The solvent was evaporated and the reaction mixture poured into ice water, drained off and dried. The precipitate re-crystallized from ethanol.
Yield 87.2%, m.p: 186–187 oC, IR (KBr, cm\(^{-1}\)); 3150, 1470, 1270, 943, 770, 480; \(^1\)HNMR (CDCl\(_3\), δ ppm) 2.25 (3H, s), 7.75 (1H, dd), 7.26 (1H, dd), 7.45 (1H, dd), 8.43 (1H, dd), Anal. Calcd. For C\(_9\)H\(_7\)N\(_3\)S: C, 57.12; H, 3.73; N, 22.21, Found: C, 56.95; H, 3.67; N, 22.10; Mass spectra, m/z=189.04 (100%).
Results and discussion
Benzothiazole is a privileged bicyclic ring system. Due to its potent and significant biological activities, it has great pharmaceutical importance; hence, synthesis of this compound is considerable interested. Benzothiazoles have many pharmacological activities such as antimicrobial, antifungal, antitumor, antiTB, antiHIV, anticancer and anti-inflammatory. Also, benzothiazole nucleus is associated with variety of antihistaminic activity which is probably due to presence of –N=C-S group. Some benzothiazoles have been reported to display diverse application as photostabilizer and metal complexing agents [12].

In this work an improved process for the production of 5-Methyl-1,2,4-triazolo(3,4-b) benzothiazole which is a useful fungicide in antifungal families, has been reported.

In view of industrial scale, significant advantage of this project is the synthesizing of all intermediates and final product together. Hereupon, at the first step, 2-methylphenyl thiourea (I) was synthesized from the reaction of o-toluidine and ammonium thiocyanat [13-15]. At the second step, 2-amino-4-methylbenzothiazole (II) was obtained from the cyclization of I with bromine which utilize sodium bromide as a catalyst and ring closure reactant [16,17]. In the third step, 2-hydrazino-4-methylbenzothiazole (III) was prepared by the reaction of amino compound (II) with 80% hydrazine hydrate in the presence of ethylene glycol and hydrochloric acid at 100-120°C. In the final step, 5-methyl [1, 2 ,4] triazolo [3,4-b] benzothiazole was prepared by the condensation process of hydrazino compound (III) with formic acid in presence of acid promotor catalyst at 100-140°C. The final product was isolated in aqueous slurry form by dumping solvent free molten stirrable mass in pre-cooled water. The chemical structure of
the synthesized compounds was established on the basis of physical, chemical and analytical data. The purity of the synthesized compounds were confirmed by CHN analysis and the structures verified on the basis of IR, $^1$H-NMR and mass spectral data.

**Conclusion**

It can be concluded that this work provides an improved and particularly efficient environmentally safe process for the preparation of 5-Methyl-1,2,4-triazolo(3,4-b) benzothiazole (IV) with high yield and low impurities which is concern to application of sodium bromide instead of bromine in the reaction that caused to either elimination or prevention of byproduct impurities.

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**References**


