Synthesis and Characterization of 2-Amino-4-methylbenzothiazole as an Origin Intermediate for a Useful Fungicide Production

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Abstract

2-amino-4-methylbenzothiazole is an origin intermediate in the synthesis of 5-methyl-1,2,4-triazolo(3,4b)benzothiazole (Tricyclazole) as a useful fungicide. In this work, at the first step, (2-methylphenyl)thiourea was prepared with the reaction of o-toluidine and ammonium thiocyanate in toluene as a solvent. At the second step, the reaction was carried out from (2-methylphenyl)thiourea and chlorine as a ring closure reactant, without any catalysts. By the use of ethylene dichloride as an inert solvent, no ring chlorination takes place during the reaction. The purity of the synthesized compounds were judged by their C, N and H analysis and the structures were verified on the basis of IR, 1H-NMR and mass spectral data.

Keywords: Tricyclazole, Benzothiazoles, (2-methylphenyl) thiourea, Fungicide

1. 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 antiflammatory, antimalerial, antifungal, anticandidous activities. 2-amino-4-methylbenzothiazole (AMBT) (II) is an origin intermediate in the synthesis of 5-methyl-1,2,4-triazolo(3,4b)benzothiazole as a fungicide in the control of rice blast (pyricularia
Synthesis of 2-amino-4-methylbenzothiazole

orazae) in transplanted and direct-seeded rice. The various methods for production of aminobenzothiazoles from phenylthioureas with chlorine in aprotic solvents in the presence of catalytic quantities of bromine or preferably iodine have carried out that in these manners the conversion to benzothiazoles with chlorine alone leads to products which are likewise chlorinated in the benzene ring. But in accordance with the present work in a surprising manner the ring closure to the thiazole-compounds can be effected also by the action of chlorine without using a catalyst.

Figure 1: The compounds structure

2. Results and Discussion

In this work, at the first step, (2-methylphenyl)thiourea (I) produced according to a known manner from o-toluidine and ammonium rhodenate or sodium rhodenate. At the second step, the reaction was carried out from I and chlorine as a ring closure reactant, without any catalysts. By the use of ethylenedichloride, methylenechloride or nitro-benzene as an inert solvent, no ring chlorination takes place during the reaction. One weight unit of I was suspended in 3 to 4 times dilution of ethylene dichloride. The suspension was cooled to a temperature about 1°C and chlorine in quantities of 1 to 2 moles, related to one mole of I is introduced into the mixture while stirring. The product was removed from the resultant HCl-salt by treatment with sodium hydroxide solution. The reaction according to this work is shown by the following reaction scheme:

Scheme 1: synthesis process of the compounds

The hydrochloric acid, which is formed by the reaction, separated from the 2-amino-4-methyl benzothiazole preferably it is removed by boiling at reflux for 1 to 2 hours. After completion of the hydrochloric acid development (and removal), the 2-amino-4-methylbenzothiazolehydrochloride is filtered off. The hydrochloride is converted in water with a base or an alkali, preferably with caustic soda (NaOH) solution, into 2-amino-4-methylbenzothiazole (II) and the latter is filtrated off. The product, produced by the process of this work, is free of impurities and is obtained as a white crystalline powder in a high yield. The process according to this work permits the production of 2-
amino-4-methylbenzothiazole without the use of any or an additional catalyst, which, on its part, would have to be removed from the reaction mixture and isolated. Chlorination on the benzene ring does not take place, despite the absence of a catalyst.

In generally 2-aminobenzothiazole derivatives were prepared from the substituted aromatic amines which in the presence of ammonium thiocyanate forms substituted 1-phenylthiourea in acidic medium. This substituted 1-phenylthiourea cyclized into substituted 2-aminobenzothiazoles in the presence of oxidizing agent bromine water or chlorine. But in these manners the conversion to benzothiazoles with bromine or chlorine leads to products which are likewise chlorinated in the benzene ring and will be produced with unlikely impurities. In the present work, in a surprising manner, the ring closure to the thiazole-compounds can be effected also by the action of chlorine without by the using a catalyst and will be free of impurities. All the compounds obtained with good yield ranging from 92-96%. The homogeneity of the compounds was monitored by performing TLC by which \( R_f \) and \( R_m \) values were calculated. The solvent system used for all the compounds was toluene: methanol (8:2).

3. Experimental

3.1. Methods and Materials

All the chemicals and solvents were obtained from E-Merck (Darmstadt, Germany), 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 400,400MHz 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 El source. Elemental analyses were carried out using a Perkin-Elmer, CHN elemental analyzer model 2400 and were within \( \pm 0.4\% \) of the theoretical values.

3.2. Synthesis and characterization of (2-methylphenyl)thiourea

In a vessel, 107.2 g of o-toluidine and 250 ml toluene were charged and 106 g of 36% hydrochloric acid was 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°C to 85°C for 2 hours. The resulting crystal was separated by filtration and washed with water and dried to obtain 160 g of (2-methylphenyl) thiourea. The precipitate re-crystallized from ethanol. Yield 96.4%, mp: 149-150°C; IR (KBr, cm\(^{-1}\)); 3454 (NH), 2910 (Ar = C-H), 1610 (C=N), 1473 (CN), 1170 (C=S), 901,738 (Ar-H bending vibration); \(^1\)H NMR (CDCl\(_3\), \( \delta \) ppm), 2.136 (3H, s), 7.071 (1H, ddd, \( J=7.901 \), \( J=5.500 \), \( J=1.703 \)), 7.006 (1H, ddd,
3.3. Synthesis and characterization of AMBT

73.5 g of (2-methylphenyl)thiourea obtained in the previous step was suspended in 375 ml of ethylene chloride, and suspension was cooled to about 1°C, while stirring, 32.5 g of chlorine gas was conducted through a gas introduction pipe into the reaction mixture. The 2-amino-4-methylbenzothiazole hydrochloride was crystallized out, whereby the hydrochloric acid development (removal) started. After completion of the hydrochloric acid removal by boiling at a reflux temperature, the reaction mixture was drained off and dried. The yield amounted to 85 g of 2-amino-4-methylbenzothiazole hydrochloride. Upon treating the hydrochloride with an aqueous NaOH 20% w/v solution; 67.3 g of 2-amino-4-methylbenzothiazole was obtained. The precipitate recrystallized from ethanol. Yield 92.7%, mp: 137.5 - 138.5°C, IR (KBr, cm⁻¹); 3339 (NH), 3038 (Ar = C-H), 1615 (C=N), 1473 (CN), 1270 (C-S), 928,750 (Ar-H bending vibration); ¹H NMR (CDCl₃, δ ppm) 2.162 (3H), 7.856 (1H, dd, J=7.977, J=1.492), 7.063 (1H, dd, J=8.169, J=7.977), 7.453 (1H, dd, J=8.169, J=1.492), Anal. Calcd. For C₈H₈N₂S: 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%).

4. Conclusion

This work provides a new and particularly efficient environmentally safe process for preparing 2-amino-4-methyl benzothiazole with either elimination or prevention of by product impurities without using a catalyst during process. Other documents illustrate various processes for preparing AMBT which are not advantageous and environmentally safe as is the present invention. The product, produced by the process of this work, is free of impurities and is obtained as a white crystalline powder in a high yield. The process according to this work permits the production of 2-amino-4-methyl benzothiazole without the use of any or an additional catalyst which, on its part, would have to be removed from the reaction mixture and isolated. Furthermore, chlorination on the benzene ring does not take place, despite the absence of a catalyst.

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References and Notes