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## Studies on the Synthesis of 2-Aminothiophenol

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Among calcium channel blockers which are predominantly cardioselective, diltiazem is one which is equieffective with others but has a lower frequency of undesirable effects. The indigenous production of diltiazem is at the elementary stage and requires 2-aminothiophenol as an important intermediate, the demand of which is being met almost completely by import. The synthesis of this intermediate is attempted by four different routes.

**C**ALCIUM channel blockers are found to be useful in hypertension, myocardial infarction, congestive heart failure and angina pectoris. They are preferred for obstructive and non-obstructive cardiomyopathy<sup>1</sup>. Among calcium channel blockers which are predominantly cardioselective, diltiazem is one which is equieffective with others but has a lower frequency of undesirable effects<sup>2</sup>. This has increased the demand of diltiazem. Thus, there exists a tremendous scope for the development of its synthetic method. This requires easy availability of intermediates. 2-Aminothiophenol is one such important intermediate for diltiazem. The search for novel synthetic methods and optimization of synthetic procedures for such fine chemicals under indigenous conditions is therefore very valuable. The indigenous production of diltiazem is at the elementary stage. The major bulk of the drug required for formulation is imported. The demand for 2-aminothiophenol is met almost completely by import. In view of this, an approach was made to synthesise 2-aminothiophenol on the laboratory scale.

### EXPERIMENTAL

Purity of the synthesised compounds and the progress of the reactions were monitored by thin layer chromatography, using silica gel GF coated plates. The spots were detected either by placing the developed plates in a chamber, saturated with iodine vapours, or in an UV cabinet. The purity of the synthesised products was confirmed by

determining their physical constants (MP or BP) and by recording IR and NMR spectra of the same. All melting points were determined in open glass capillaries. IR absorption spectra were recorded on a JASCO FT/IR-5300 spectrophotometre, using KBr pellet method. NMR spectrum was recorded on a 300 MHz NMR spectrophotometre. The characteristic IR absorption bands and the physical constants are shown in Table 1.

The compound, 2-aminothiophenol, was synthesised by four different routes as shown in Fig.1. The starting material for all schemes was 2-chloronitrobenzene, a relatively cheaper raw material.

The first step in Schemes I, II and III was the synthesis of di-(2-nitrophenyl)-disulphide (2). Crystallised disodium sulphide, nonahydrate, Na<sub>2</sub>S. 9H<sub>2</sub>O [12 g, 0.05 M] was dissolved in water or alcohol [50 ml]. Sublimed sulphur [1.6 g, 0.05 m] was added to it and the mixture heated till all sulphur dissolved forming a brownish red solution of disodium disulphide. A solution of 2-chloronitrobenzene (1) [10.5 g, 0.066 M] was prepared in rectified spirit [17.5 ml] and the solution of disodium disulphide was added to it cautiously. The mixture was refluxed for two hours. On cooling, the solid that separated out was recrystallized from alcohol to obtain 6.8% of di-(2-nitrophenyl)-disulphide (2). The yield could be increased to 62.1 % by increasing the molar ratio of Na<sub>2</sub>S : S from 1 : 1 to 1 : 3 and by carrying out the reaction in aqueous medium instead of in alcoholic medium.

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Table 1 : Characteristic data obtained for 2-aminothiophenol

Scheme No.	Step No.	Compound No.	M.P./B.P.* o	Overall % yield	% yield	IR bands(cm <sup>-1</sup> )
I	1	2	192-193	-	62.10	1508, 1336 (C-N Str), 1105, 709 (C-S str), 652, 482 (S-S str)
	2	3	50-52	-	61.20	2530 (s-H str), 1510, 1336 (C-N str), 1113 (C-S str)
	3	4	230-231*	3.40	9.00	3464, 3358 (N-H str, Pri-amine), 1307 (C-N str), 2608 (S-H str), 1118 (C-S str)
II	2	5	59-62	-	69.50	1545, 1390 (C-N str), 1361 (S=O str), 1188 (C-S str)
	3	4	230-231*	4.00	9.04	Same as in Scheme I
III	2	4	231-232*	15.00	24.00	Same as in Scheme I
IV	1	4	230-231*	51.50	51.50	Same as in Scheme I

NMR spectrum of 2-aminothiophenol (4) showed the chemical shifts in ppm as  $\delta = 4.2$ (s, 1 H and  $\delta = 7.45$ -8.35 (m, 4 H)

Di-(2-nitrophenyl)-disulfide (2) was processed differently in each scheme. In Scheme I<sup>3,6</sup>, the disulfide (2) [10 g, 0.03 M] was reduced by sodium hydrosulfide (NaSH) which was formed by saturating NaOH solution [0.8 g, 0.02 M] with H<sub>2</sub>S and then refluxing them together. The reaction mixture was poured in 5 ml concentrated HCl. The precipitated 2-nitrothiophenol (3) was filtered and recrystallised from alcohol. In the third step, it was reduced by using Sn/HCl. The isolation of 2-aminothiophenol (4) from the reaction mixture was found to be difficult because of the pK<sub>a</sub> values of (4) as-pK = /< 2 ( $\pm 1$ ) and pK<sub>a</sub> = 7.9<sup>7</sup>. Hence, the reduction was carried out by using Zn/CH<sub>3</sub>COOH which gave 2-aminothiophenol in very poor yield (9%). The IR spectrum of (4) was compared with the IR spectrum of the authentic sample of 2-aminothiophenol obtained from Koch-Light Laboratories, England. The two spectra matched with each other.

In Scheme II, (2) was converted to 2-nitrobenzenesulphonyl chloride (5)<sup>8-11</sup>. Chlorine gas was passed through a hot mixture of (2) [4 g, 0.01 M], concentrated HCl [20 ml] and concentrated HNO<sub>3</sub> [4 ml]. Excess chlorine was absorbed into NaOH solution. Heating of

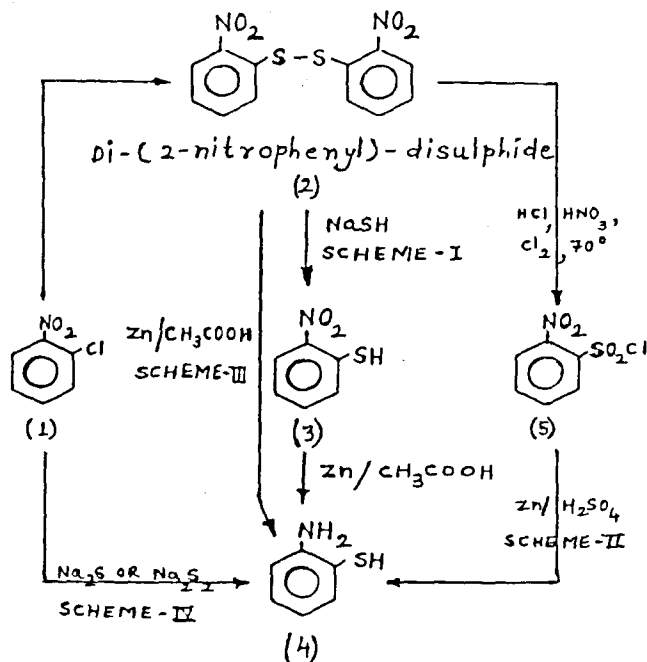


Fig. 1 : Various routes for the synthesis of 2-amino thiophenol

solution and passage of chlorine gas was continued for 1.5-2 hours. The precipitate of sulphonyl chloride (5) was immediately separated from the supernatant liquid and recrystallised from glacial  $\text{CH}_3\text{COOH}$  to obtain it in 69.5 % yield. In the third step, the nitro group and the sulphonyl chloride group<sup>12</sup> were reduced simultaneously by using compound (5) [0.75 g, 0.003 M], concentrated  $\text{H}_2\text{SO}_4$  [2.6 ml] and zinc powder [2.4 g], which resulted in 9.04 % yield of aminothiophenol.

In Scheme III, the disulphide linkage and the nitro group of (2) were reduced in one single step<sup>13</sup> by using Zn/ $\text{CH}_3\text{COOH}$  in different molar proportion than used in scheme I. In Scheme I, the molar ratio of Zn:2-nitrothiophenol (3) was 3.3:1 while in Scheme III, the ratio of Zn:disulphide (2) was 20:1. Zn dust (4 g) was added to the solution of (2) [1 g, 0.003 M] in glacial acetic acid [35 ml]. To obtain the free amine, the Zn salt of 2-aminothiophenol was suspended in water, the pH adjusted to 7 with 10 % NaOH and  $\text{H}_2\text{S}$  gas bubbled into the suspension. The resulting mixture was treated with ether to extract the free amine in 24 % yield.

In Scheme IV, 2-amimothiophenol (4) was synthesised from 2-chloronitrobenzene (1) in one single step<sup>14</sup>. This was attempted by using sodium sulphide nonahydrate ( $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ ) and also by using disodium disulphide ( $\text{Na}_2\text{S}_2$ ).

In the first procedure, a clear solution of  $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$  [4.8 g, 0.02 M] in water [20 ml] was prepared. The compound (1) [1.28 g, 0.008 M] was added to it in one single portion and the mixture refluxed for 8 hours. After about 4 hours, small amount of yellow coloured oil appeared in the reaction mixture due to the formation of 2-chloroaniline as the by-product. The reaction mixture was cooled after 8 hours and then extracted with ether (20 ml x 2) to remove 2-chloroaniline. The aqueous layer containing sodium salt of 2-aminothiophenol was saturated with NaCl and then acidified with glacial acetic acid [2.4 g, 0.04 M]. Addition of acetic acid should be done carefully in order to get maximum yield of 2-aminothiophenol. The product liberated in the form of oil was extracted several times in ether. Ether extract was dried and ether stripped off to obtain 2-aminothiophenol (4) in 48.5 % yield. In the second procedure, one step synthesis of 2-aminothiophenol was tried by using sodium disulfide. It was prepared by treating sodium sulfide (nonahydrate) with sublimed sulfur.  $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$  [0.53 g, 0.016 M] was added to sublimed sulphur in 3 portions over 15 minutes. Sodium disulfide thus prepared

was added to (1) [1.28 g, 0.008 M] in 50 % refluxing alcohol (20 ml) over the period of half an hour. After the addition was complete, the reaction mixture was further refluxed for 9-10 hours and then processed as in first procedure. The yield of the product could be increased to 51.5 %.

## RESULTS AND DISCUSSION

The overall percent yield of 2-aminothiophenol was calculated based on the very first starting material and is given in Table 1. Schemes I and II involved three step routes resulting in very low yields (3.4 % and 4.0 % respectively) of 2-aminothiophenol based on the same starting material, 2-chloronitrobenzene (1). Scheme III, involving a two step route, employed a direct reduction of di-(2-nitrophenyl)-disulphide (2) to 2-aminothiophenol (4) with slightly improved yield (15 %). However, Scheme IV was found to be the best among the four schemes since it was a single step reaction and gave highest yield (51.5 %).

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