SYNTHESIS AND CHARACTERIZATION OF SUBSTITUTED-2-AMINOBENZENETHIOLS

Savita Choudhary*and Vibha Shrivastav

*Department of Chemistry, S. K. Govt. College, Sikar

Abstract

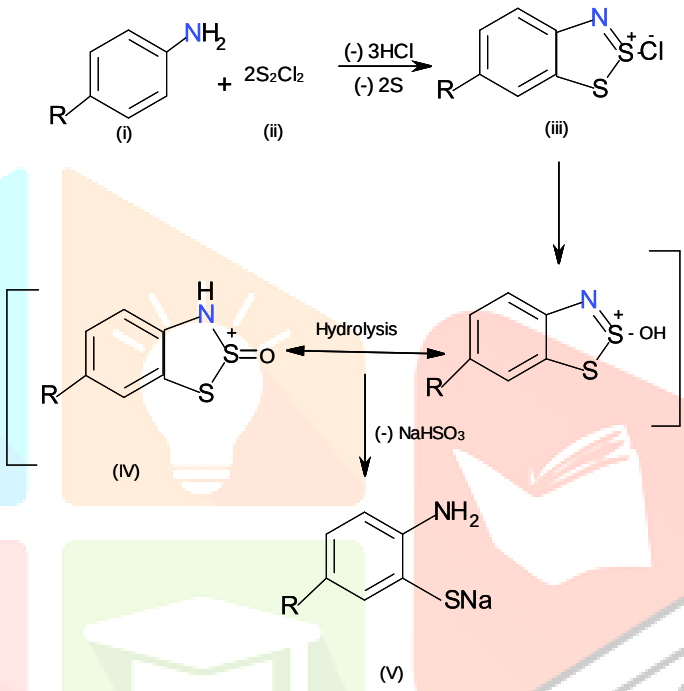
Wide spread applications of benzothiazines, triazolothiadiazines and phenothiazines in medicinal, industrial, biological and agricultural fields have stimulated our interest to synthesize 2-aminobenzo-thiazoles and 2-aminobenzenethiols which have been used as synthetic intermediates for the synthesis of a variety of pharmacologically important heterocyclic compounds. The aryl pharmacophore of benzenethiols and substituted triazolothiols exhibits a wide range of biological and pharmacological activities, such as anticonvulsant, antituberculosis, antiproferative, antitumor, antimicrobial, analgesic, vasodilator etc.In the present investigation we have synthesized a number of 2-aminobenzothiazoles and 2-aminobenzenethiols. The various methods have been reported in the literature for the synthesis of these compounds.

Key Words : Herz method, Thiocyanogenation, Bis – (o-nitrophenyl) disulfides.

2.1 HERZ METHOD

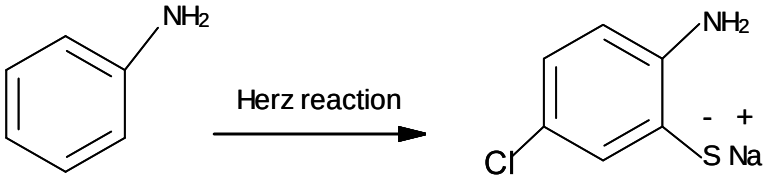
Richard Herz[17] has reported a method for the preparation of 2-aminobenzenethiols, which is now known as Herz reaction. In this method aryl amine (I) was treated with sulfur monochloride (II) to afford thiazathiolium chloride (III) (which is also called as Herz compound[1-18]) , which on alkaline hydrolysis provides sodium salt of 2-aminobenzenthiol. In this method, the replacement of chloride ion by hydroxyl group is followed by the cleavage of five membered ring of intermediate (IV) during hydrolysis to yield sodium salt of 2-aminobenzenethiols[19-23] (V) (scheme 2.1).

For the hydrolysis of Herz compound a number of methods have been reported, but sodium hydroxide is normally used. Hydrolysis by making alkaline with sodium carbonate and subsequent heating with sodium hydrogen sulphite have also furnished good results. In some cases the Herz compound was first converted into corresponding hydroxide[24] and then subjected to hydrolysis after recrystallization.



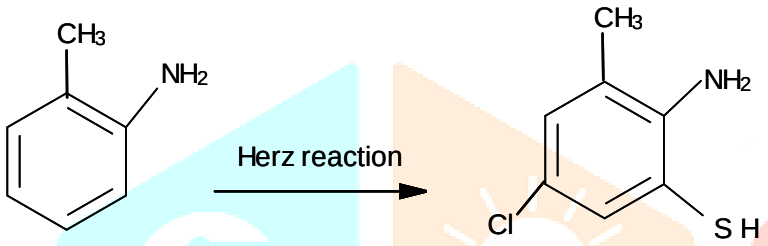
(Scheme: 2.1)

The Herz reaction has some limitations because it has been noted that anilines which are unsubstituted in para-position undergo chlorination at para-position by sulphur monochloride during the course of reaction. This is the reason that Farrington and Warburton[25] failed to isolate o-aminothiophenol from aniline by the Herz reaction, but obtained only 2-amino-5-chlorothiophenol (scheme 2.2).



(Scheme: 2.2)

Koing and Weinberg were also unsuccessful in preparing 2-amino-3-methylbenzenethiol but obtained 2-amino-5-chloro-3-methylbenzenethiol (scheme 2.3).

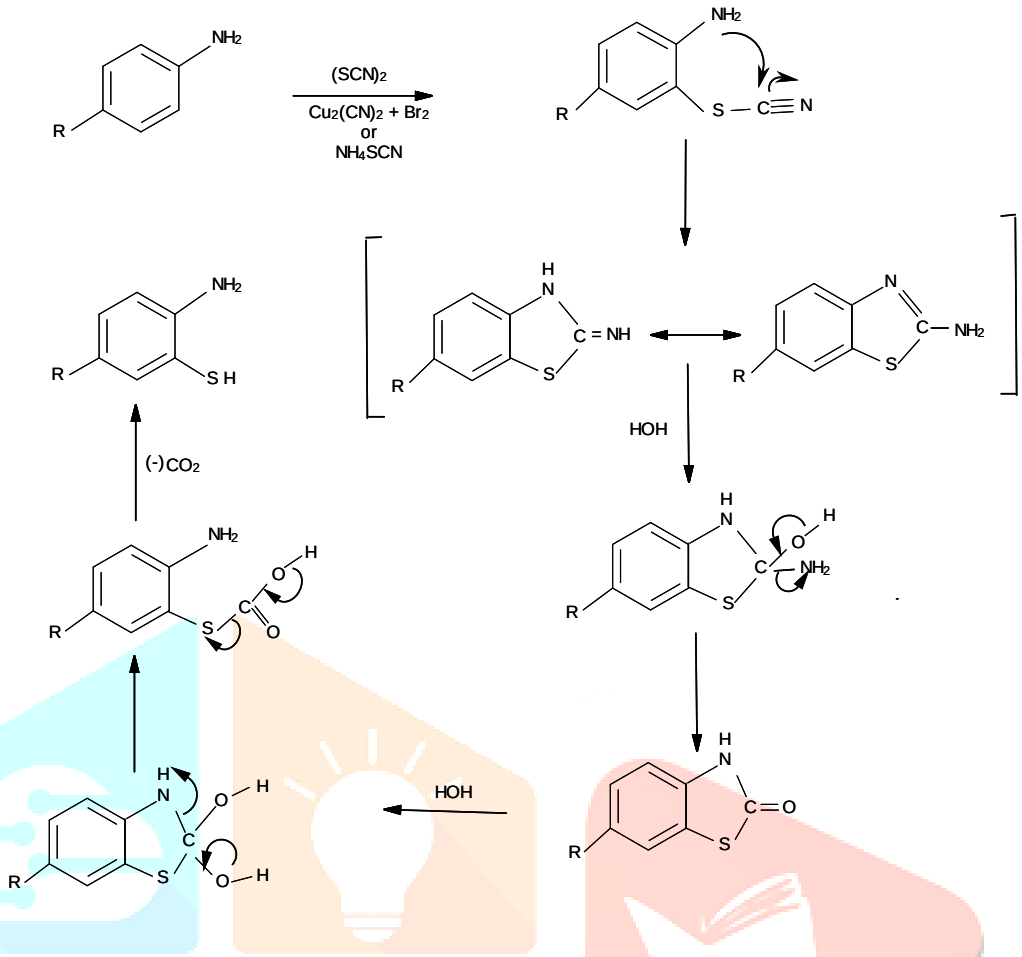


(Scheme: 2.3)

Therefore, the preparation of 2-aminobenzenethiols by Herz method, requires the para-position of arylamine to be occupied by such a group which cannot be substituted by chloro group. The chloro group does not replace the group such as ethoxy, phenoxy, methyl, methoxy, dimethylamino, bromo etc. during Herz reaction. However, some groups such as sulfonic acid, arsonic, carbonyl etc. at 5-positon are relatively replaced[26].

2.2 THIOCYANOGENATION

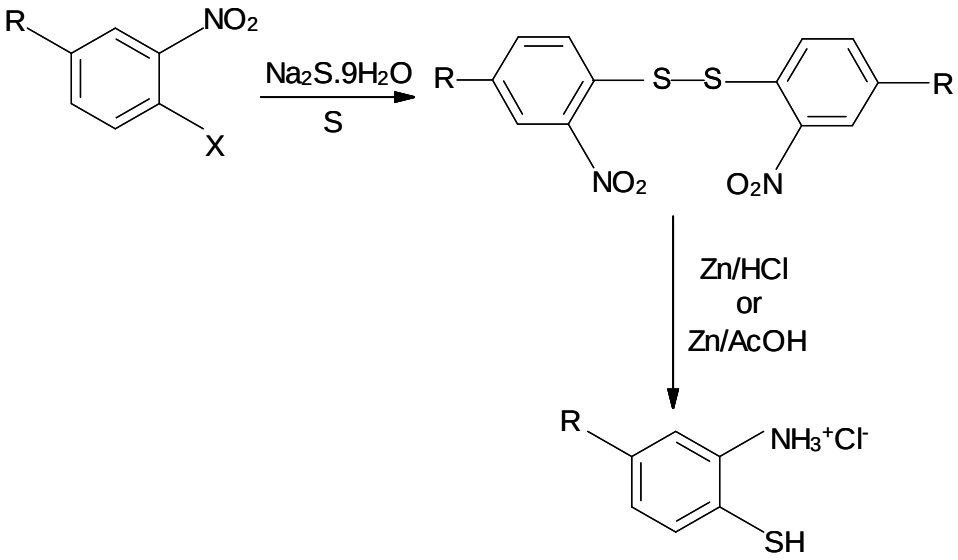
Another widely used method for the preparation of 2-aminobenzenethiol includes the hydrolytic cleavage of benzothiazoles. This method also has some limitations when para position in aniline is free. The thiocyanogenation at both ortho and para position to the amino group during the course of reaction is the serious drawback of this method. In some cases intermediates do not undergo cyclisation (scheme 2.4).



(Scheme: 2.4)

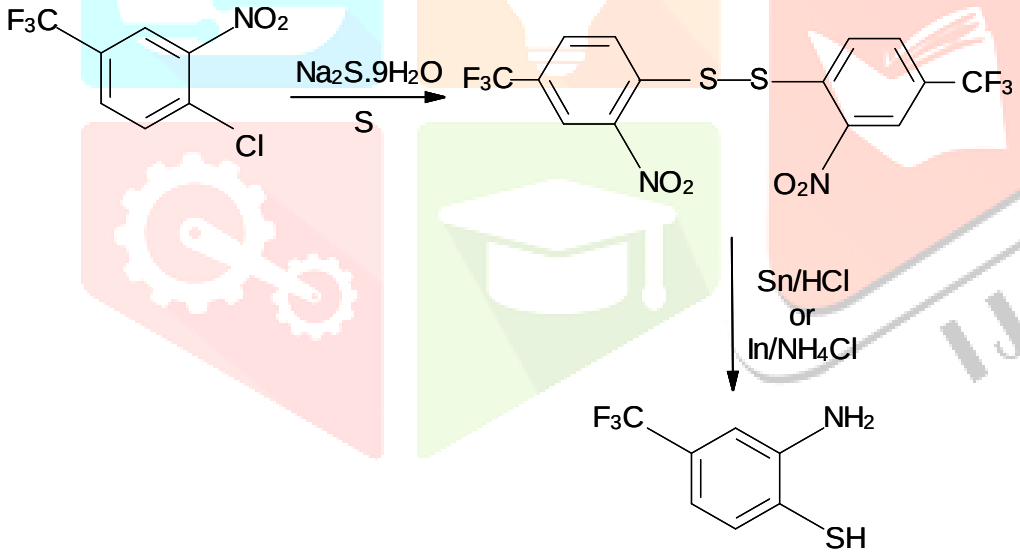
2.3 REDUCTION OF BIS – (o-NITROPHENYL) DISULFIDES

It involves two steps. In the first step, bis-(o-nitrophenyl) disulfides is obtained by the reaction of halonitrobenzene with sodium polysulfide. The second step involves the reduction of bis-(o-nitrophenyl) disulfides with zinc and acetic acid or zinc and hydrochloric acid to provide zinc salt of 2-aminobenzenethiol[27-31] (scheme 2.5).



(Scheme: 2.5)

The reduction of diphenyl sulphides has also been reported with Sn/HCl[32-34.] and In/NH_4 Cl in ethanol[35](scheme 2.6).



(Scheme: 2.6)

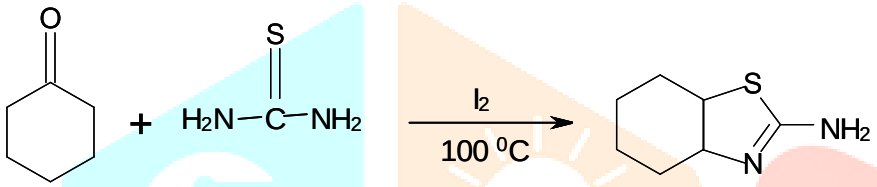
This method cannot be applied for the synthesis of nitroderivatives of 2-aminobenzenethiols because of simultaneous reduction of the nitro group during reduction of disulphide derivative into o-aminobenzenethiol.

2.4 HYDROLYSIS OF 2-AMINOBENZOTHIAZOLES

This method involves two steps. In the first step substituted aminobenzothiazole is prepared and than the latter hydrolysed to get 2-aminobenzenethiol. Various methods are reported for synthesis of 2-aminobenzothiazoles out of which some important are discussed here.

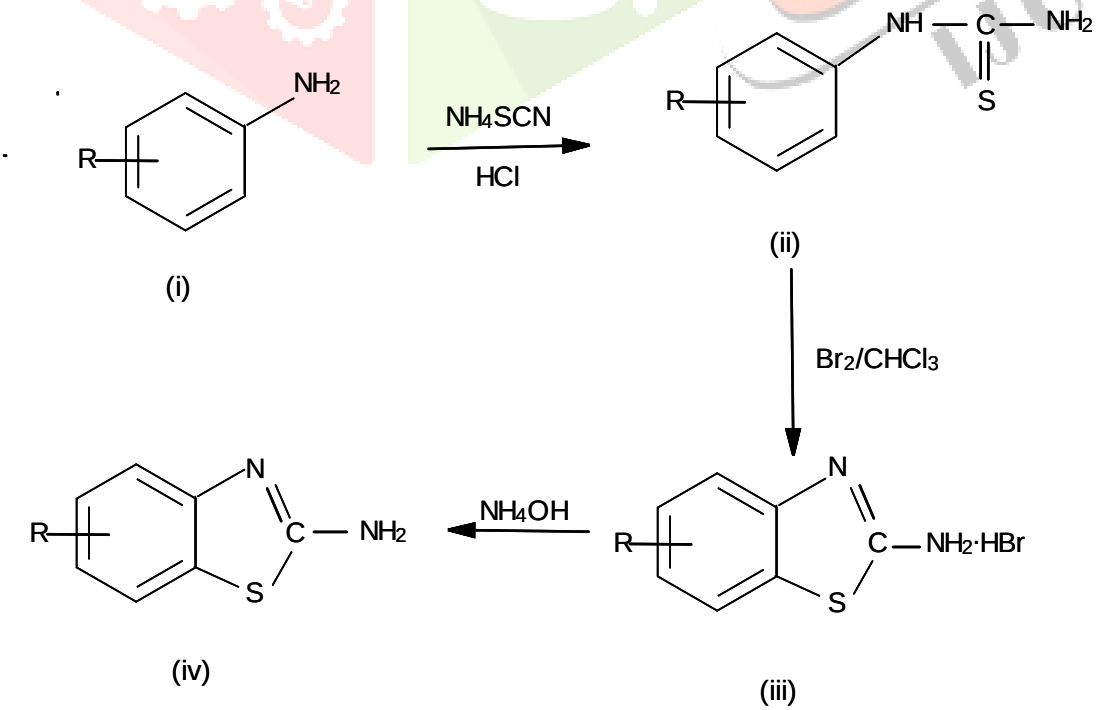
1. Synthesis of 2-aminobenzothiazoles

(1). 2-Aminobenzothiazoles have been prepared[36] by treating cyclo-hexanone with thiourea and iodine at 100^{0}C (scheme 2.7).



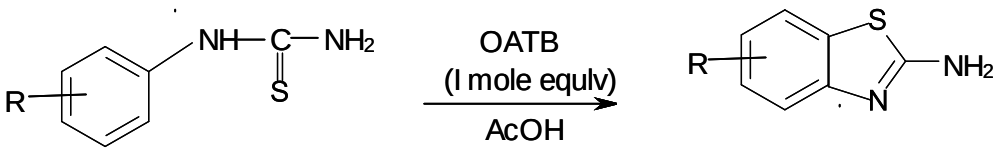
(Scheme: 2.7)

(2). In recently used method[37], benzene thiourea derivative on treatment with bromine and chloroform in ice cold solution followed by neutralization with sulphurous acid and ammonia solution provide 2-aminobenzothiazole (scheme 2.8).



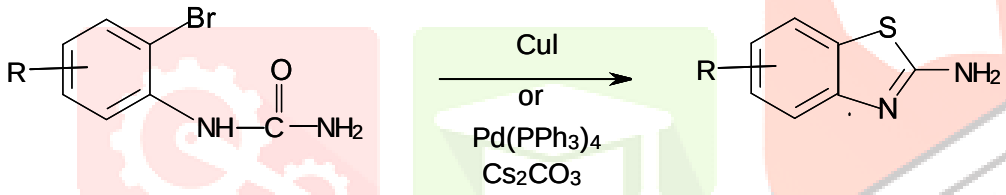
(Scheme: 2.8)

(3). Jordan et.el have been prepared 2-aminobenzothiazoles in quantitative yields by using organic ammoniumtribromide (OATB) (benzyltrimethyl-ammonium tribromide) as an alternative electrophilic bromine source in place of bromine and chloroform[38] (scheme 2.9).



(Scheme: 2.9)

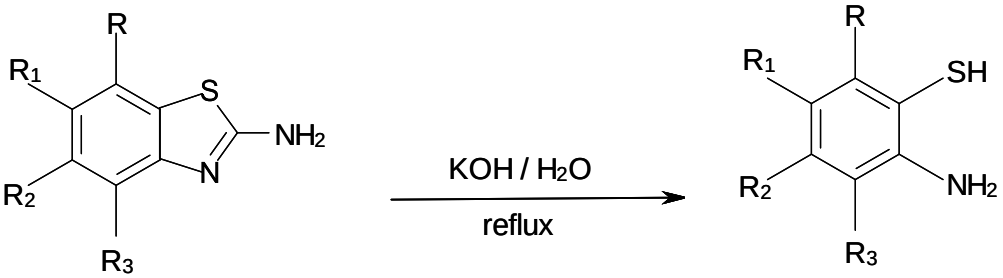
(4). Huang et.el have been prepared 2-aminobenzothiazoles recently by means of copper and palladium-catalyzed intramolecular C-S bond formation[39] (scheme 2.10).



(Scheme: 2.10)

2. Hydrolysis of 2-aminobenzothiazoles

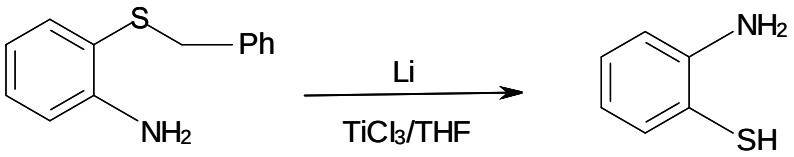
Synthesized 2-aminobenzothiazoles were hydrolysed to 2-aminobenzenethiol in second step by aqueous potassium hydroxide.



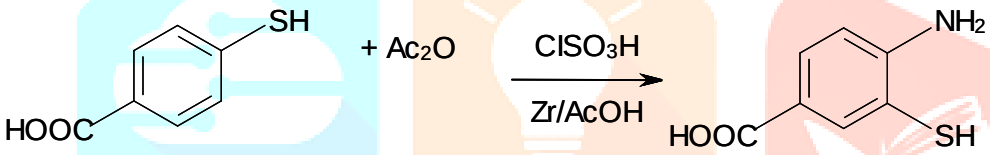
(Scheme: 2.11)

2.5 OTHER METHODS

There are some other methods reported recently for synthesis of 2-aminobenzenethiols as explained by schemes (2.12)[40] and (2.13)[41]



(Scheme: 2.12)



(Scheme: 2.13)

In the present investigation, a modified method having two steps instead of time consuming and low yielding three step[42] method is used for the synthesis of 2-aminobenzenethiols required for the synthesis 1,4-benzothiazine and phenothiazine derivatives.

2.6 EXPERIMENTAL

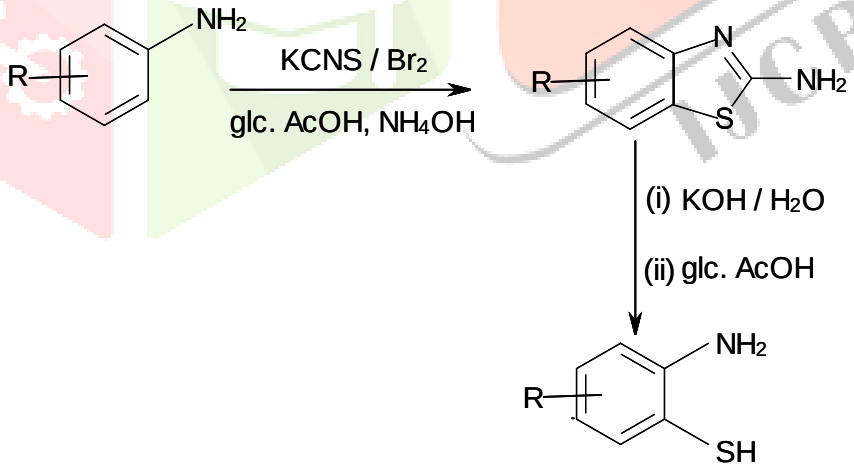
All the melting points are uncorrected. The purity of the compounds was checked on thin layer of silica gel in various non-aqueous solvent systems. Infrared spectra of all the synthesized compounds have been scanned in KBr on Shimadzu FTIR Affinity-1 and their NMR spectra scanned on Varian Gemini 400 spectrometer (300 MHz) using TMS as an internal standard.

1. Preparation of substituted 2-aminobenzothiazoles

A mixture of potassium thiocyanate (60 mmol) and substituted aniline (60 mmol) was added to a precooled (5ºC) glacial acetic acid (125 ml) and placed into freezing mixture. Now a bromine solution (20 mmol Br_2 in 20 ml glacial acetic acid) was added drop by drop with constant stirring so that temperature does not rise above 5ºC and continue the stirring for additional 2.5 h. The separated out solid hydrochloride salt was filtered, washed with 5 ml acetic acid and dried. The hydrochloride salt was dissolve in hot water and neutralized with ammonia solution. Finally the solid was filtered, washed with water and crystallized to get substituted 2-aminobenzothiazole.

2. Preparation of 2-aminobenzenethiol

Substituted 2-aminobenzothiazole was refluxed with an aqueous solution of potassium hydroxide (5 times by weight of benzothiazole) until evolution of ammonia ceased. The refluxed solution was neutralized with glacial acetic acid. The separated yellowish semisolid 2-aminobenzenethiol was extracted with solvent ether. The evaporation of solvent ether and crystallization from methanol afforded the desired 2-aminobenzenethiol (scheme 2.14).



(Scheme: 2.14)

In present investigation following 2-aminobenzenethiols have been synthesized:

(1). 2-Amino-5-chlorobenzenethiol

(2). 2-Amino-5-methylbenzenethiol

(3). 2-Amino-5-methoxybenzenethiol

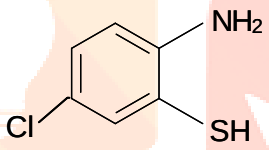
(4). 2-Amino-5-ethoxybenzenethiol

(5). 2-Amino-5-bromobenzenethiol

Physical and spectral data of the synthesized 2-aminobenzenethiols

(1). 2-Amino-5-chlorobenzenethiol

Molecular Formula : C_6H_6NSCl



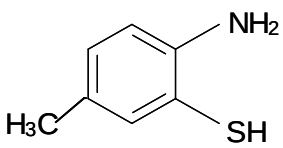
Yield :35%, M.P. 110^{O}C

IR (KBr, ν_{max}, cm^{-1}) : 3350, 3295 (N-H str.), 2470 (S-H str.), 735 (C-Cl str.)

^{1}H NMR ($CDCl_3$) δ : 7.15-6.75 (3H, m, Ar-H), 4.35 (2H, s, NH_2), 2.75 (1H, s, SH) .

(2). 2-Amino-5-methylbenzenethiol

Molecular Formula : C_7H_9NS



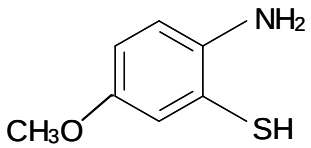
Yield : 62%, M.P. 90-92^{O}C.

IR (KBr, ν_{max}, cm^{-1}) : 3420, 3340 (N-H str.), 2510 (S-H str.), 1420,1360 (C-H bending).

^{1}H NMR ($CDCl_3$) δ : 7.25-6.65 (3H, m, Ar-H), 4.30 (2H, s, NH_2) 2.30 (3H, s, CH_3), 2.50 (1H, s, SH)

(3). 2-Amino-5-methoxy benzenethiol

Molecular Formula : C_7H_9NOS



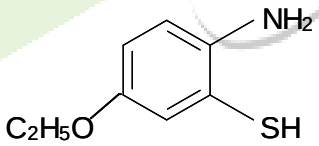
Yield : 55% , M.P. 105^{o}C.

IR (KBr, ν_{max}, cm^{-1}) : 3365-3285 (N-H str.), 2370 (S-H str.), 1410, 1350 (C-H bending), 1270 (O-C str.)

^{1}H NMR ($CDCl_3$) δ : 7.35-6.90 (3H, m, Ar-H) , 4.65 (2H, s, NH_2), 3.50 (3H, s, CH_3), 2.30 (1H, s, SH).

(4). 2-Amino-5-ethoxy benzenethiol

Molecular Formula : $C_8H_{11}NOS$



Yield : 45%, M.P. 104^{0}C

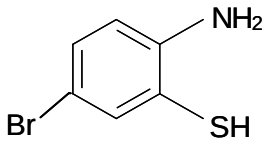
IR (KBr, ν_{max}, cm^{-1}) : 3350-3285 (N-H str.), 2345 (S-H str.), 1400-1370 (C-H bending), 1310 (O-C str.)

^{1}H NMR ($CDCl_3$) : 7.25-6.85 (3H, m, Ar-H) 4.55 (2H, s, NH_2), 3.80

(2H, q, CH_2 at C_5), 1.35 (3H, t, CH_3 at C_5) 2.25 (1H, s, SH).

(5). 2-Amino-5-bromobenzenethiol

Molecular Formula : C_6H_6NSBr



Yield : 32%, M.P. 111-113°C

IR (KBr, ν_{max}, cm^{-1}) : 3400, 3290 (N-H str.), 2475 (S-H str.), 810 (C-Br str.).

^1H NMR ($CDCl_3$) : 7.30-6.80 (3H, m, Ar-H), 4.45 (2H, s, NH_2), 2.85 (1H, s, SH).

Spectral Analysis :

The structures of synthesized substituted 2-aminobenzenethiols have been confirmed by spectral analysis. In IR spectra, two sharp bands in the region 3450 - 3300 cm^{-1} and 3330-3240 cm^{-1} are assigned to asymmetric and symmetric vibrations of primary amino group respectively. Weak band due to S-H stretching vibration is observed in the region 2450-2530 cm^{-1}. The IR bands due to C-Cl, C-Br are observed at 735 and 810 cm^{-1} respectively.

^1H NMR spectra of synthesized compounds exhibits singlet at δ 4.30-4.70 due to NH_2 protons. Multiplet due to aromatic protons appeared in the region δ 7.50-6.60. The singlet observed at δ 2.25-2.85 is attributed to SH proton.

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