Макрогетероциклы
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DOI: 10.6060/mhc171261s

Synthesis of Starting Heterocycles: 2−Aminobenzothiazoles, 2−Aminothiazoles and 2−Aminobenzenethiols − Potential Precursors for Macroheterocycles

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This article reviews the synthetic methods used for obtaining of 2-aminobenzothiazoles, 2-aminothiazoles and 2-aminobenzenethiols – important precursors in synthetic organic chemistry and material science.

Keywords: Heterocycles, thiaaza heterocycles, 2-aminobenzothiazoles, 2-aminothiazoles, 2-aminobenzenethiols.

Получение 2−аминобензотиазолов, 2−аминотиазолов и 2−аминобензотиолов − прекурсоров для синтеза макрогетероциклов

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Тиазолы, тиолы и их производные используются в качестве исходных или промежуточных соединений для синтеза фармацевтических препаратов. В данном обзоре рассматриваются методы получения 2-аминобензотиазолов, 2-аминотиазолов, 2-аминобензотиолов, используемые в синтетической органической химии и материаловедении.

Ключевые слова: Гетероциклы, тиаазагетероциклы, 2-аминобензотиазолы, 2-аминотиазолы, 2-аминобензотиолы.

Introduction

Heterocycles have constituted important research area in organic chemistry. Heterocycles are widely used in the development of the modern raw material used for preparation of pharmaceuticals. Amongst the diverse heterocyclic systems, sulfur-nitrogen heterocycles [thiaaza based] are particularly interesting as far as their role in the field of biochemistry and medicinal chemistry. Thiazole, thiols and thiazine heterosystems have long been the subject of chemical research because thiazole, thiols and thiazine ring systems are important constituents of numerous bioactive natural/synthetic products and pharmaceuticals. A large number of heterocycles with thiazole and thiazine ring systems have emerged as potential pharmaceuticals with their use as antimicrobial,[1] anti-HIV,[2] antitumor,[3,4] antileishmanial,[5-7] anti-inflammatory,[8,9] antifungal,[10] *etc.* A number of 2-aminobenzothiazoles and 2-aminobenzenethiols which have been used as starting materials to synthesize structurally diverse heterocycles, pyrimidobenzothiazoles, 4*H*-1,4-benzothiazines, morpholinyl/piperazinyl substituted 4*H*-1,4-benzothiazines and pyrazolylbenzothiazines. In recent days, a variety of biomedical and industrial applications such as viral inhibition, fluorescence detection, photodynamic tumor therapy, polymerization, photonucleases, insecticides component

synthesis, synthesis of dyes *etc.* are mainly based on macroheterocycles.[11] Macroheterocycles present in various biodynamic natural systems and synthetic materials have been synthesized by either substituted thiazoles, thiols directly or as precursors.[12-13] This review includes the recent developments relating to the synthetic methods of 2-aminobenzothiazoles and 2-aminobenzenethiols, which have been used for the synthesis of a variety of therapeutically interesting heterocyclic compounds with diverse structural specificity.

Different methods have been reported in the literature for the synthesis of 2-aminobenzenethiazoles and 2-aminobenzenethioles. Some recently reported important methods have been briefly presented.

Herz method

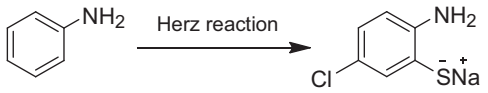
In this method, arylamine **I** is treated with sulfur monochloride **II** to afford thiazothiolium chloride **III**, Herz compound,[14] which on alkaline hydrolysis provides sodium salt of 2-aminobenzenethiol. In this method, the replacement of chloride ion by hydroxyl group is followed by the cleavage of five membered ring of **IV** during hydrolysis to yield sodium salt of 2-aminobenzenethiol **V** (Scheme 1).[15-19]

The Herz method has been reported to be successful in certain cases, but in some cases, it has some limitations.

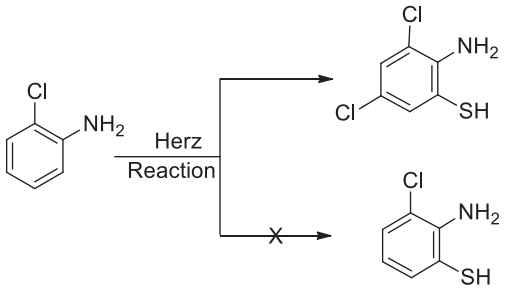
Limitations

When arylamine (unsubstituted at *para* position) is treated with sulfur monochloride, chlorination takes place at *para* position and therefore chlorinated product is obtained because of Herz reaction (Schemes 2-4).[20-26]

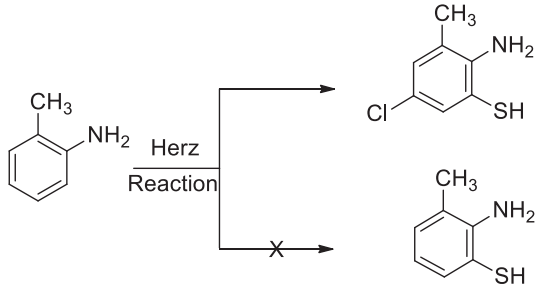
The preparation of 2-aminobenzenethiols by Herz method, therefore, requires the *para* position of arylamine to



Scheme 2.



Scheme 3.

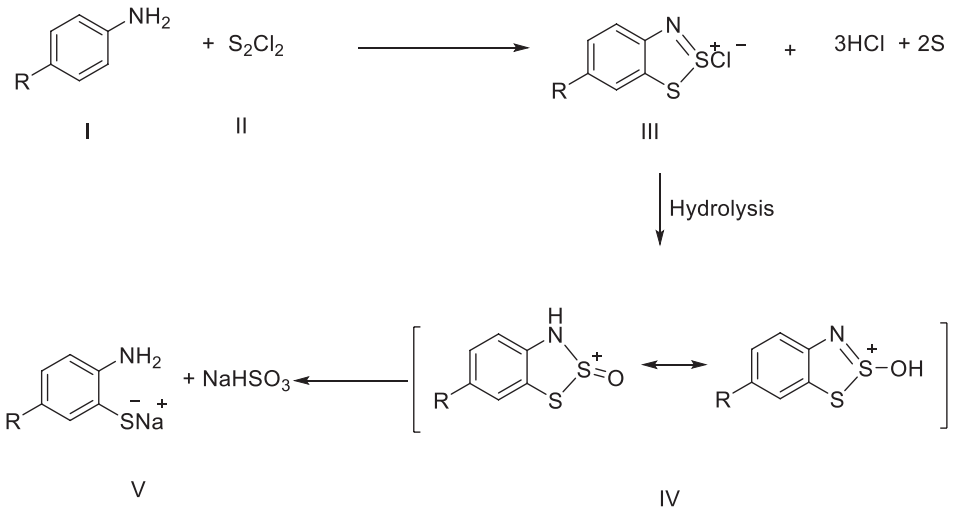


Scheme 4.

be occupied by such a group, which cannot be substituted by chloro group. The chloro group does not replace the groups such as ethoxy, phenoxy, methyl, methoxy, dimethylamino, bromo *etc.* during Herz reaction. However, some groups such as sulfonic acid, arsonic, carbonyl *etc.* at 5-position are relatively replaced.[27]

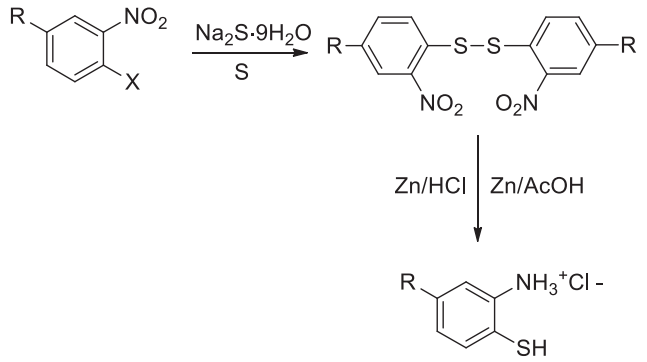
Reduction of bis-(o-nitrophenyl) disulfides

It involves two steps: In the first step, *bis*(*o*-nitrophenyl) disulfide is obtained by the reaction of halonitrobenzene with sodium polysulfide. The second step involves the reduction of *bis*(*o*-nitrophenyl) disulfide with zinc and acetic acid



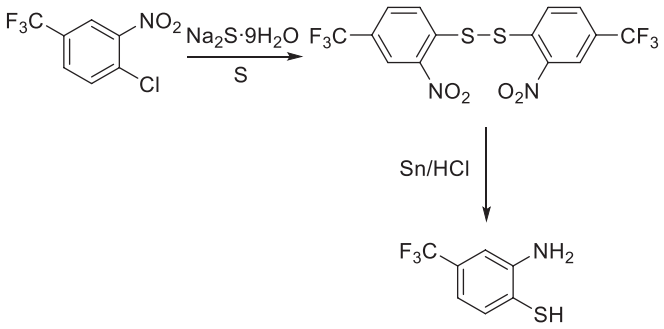
Scheme 1.

or with zinc and hydrochloric acid to provide zinc salt of 2-aminobenzenethiol.[28-32]



Scheme 5.

The reduction of diphenyl sulphides has also been reported with Sn/HCl.[33-35]



Scheme 6.

The reduction of diphenyl sulphide has also been reported recently by In/NH_4Cl in ethanol.[36]

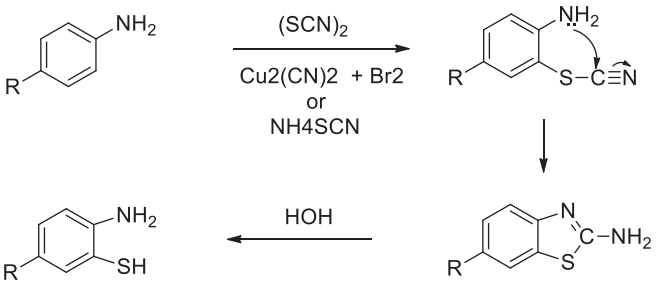
However, this method suffers from following drawbacks:

(i) Differently substituted *o*-halonitrobenzenes required in this method are not commercially available and their laboratory preparation is time consuming.
(ii) Separation of substituted 2-aminobenzenethiol hydrochloride from metallic chloride obtained during this method is very difficult.
(iii) Substituted dinitrodiphenyl sulfides are reduced into the corresponding 2-aminobenzenethiols by the reduction of disulfide as well as NO_2 group into –SH group and -NH_2 group, respectively.

Thiazolation

Following methods of thiazolation have been reported for the synthesis of 2-aminobenzothiazols and 2-aminobenzenethiols:

(A) Thiocyanogenation: Thiocyanogenation is the most widely used method for the synthesis of 2-aminobenzothiazoles and 2-aminobenzenethiols. Thiocyanogenation is carried out by thiocyanogen gas produced *in situ* by the reaction of Cu_2CN_2 and bromine or NH_4SCN/KCNS.[37-40] 2-Aminobenzenethiols are obtained by alkaline hydrolysis of the corresponding 2-aminobenzothiazoles (Scheme 7).



Scheme 7.

This method also has some limitations: 2-aminobenzothiazoles and 2-aminobenzenethiols cannot be easily synthesized by the thiocyanogenation reaction of arylamine with unoccupied *para* position, because thiocyanogenation occurs at both unoccupied *ortho* as well as *para* positions to the amino group.

(B) 2-Aminobenzothiazoles and 2-aminobenzenethiols can be conveniently prepared from aryl amines substituted or unsubstituted at *para* positions.[41-52]

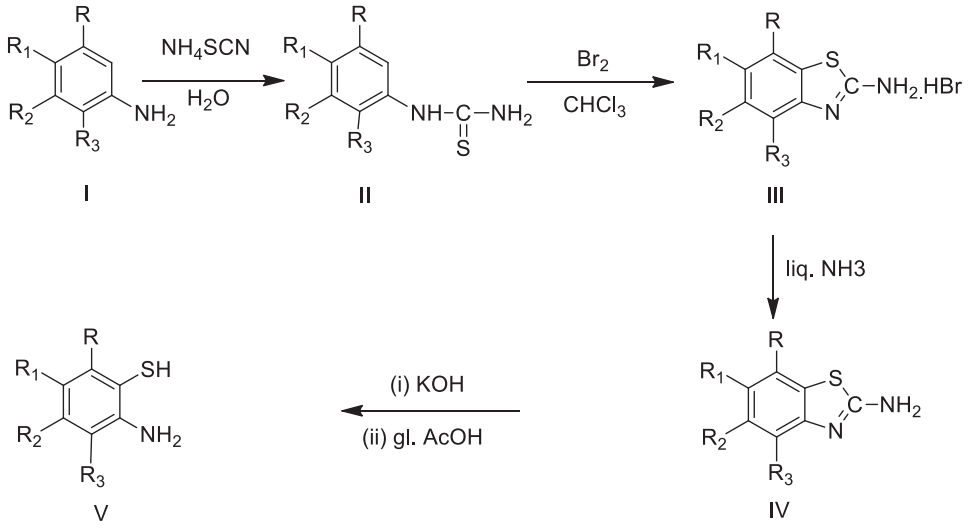
This method involves two steps: In the first step, hydrochloride of substituted arylamine is treated with KCNS or NH_4SCN to obtain corresponding phenylthiourea. The second step involves brominative cyclization of phenylthiourea by bromine and chloroform to provide the corresponding 2-aminobenzothiazole. The alkaline hydrolysis of substituted 2-aminobenzothiazole and subsequent neutralization by glacial acetic acid provides substituted 2-aminobenzenethiol (Scheme 8).

Synthesis of 2-aminobenzothiazoles and 2-aminothiazoles individually

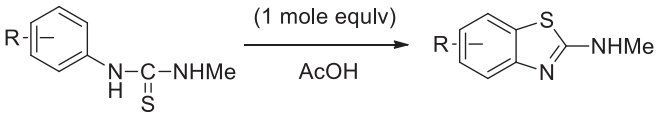
(i) Recently, 2-aminobenzothiazoles have been prepared in quantitative yields by using organic ammoniumtribromide (OATB) [benzyltrimethylammoniumtribromide] as an alternative electrophilic bromine source in place of bromine and chloroform.[53]
(ii) 2-Aminothiazoles have been prepared by treating arylamines with thiourea and bromine in acetic acid *via* bromide[54] (Scheme 9).
(iii) 2-Aminothiazoles have also been prepared by treating cyclohexanone with thiourea and iodine at 100 °C[55] (Scheme 10).
(iv) 2-Aminobenzothiazoles have also been prepared recently by means of copper and palladium-catalyzed intramolecular C–S bond formation[56] (Scheme 11).
(v) 2-Aminobenzothiazoles have also been synthesized by reaction of carbon chlorosulphide with 4-cynoaniline in the presence of NH_4OH/Dioxane[57] (Scheme 12).

Synthesis of 2-aminobenzenethiols individually

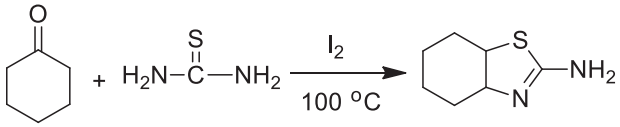
Some recently reported synthetic methods of 2-aminobenzenethiols are presented schematically. The reactants,



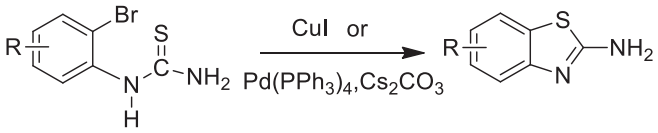
Scheme 8.



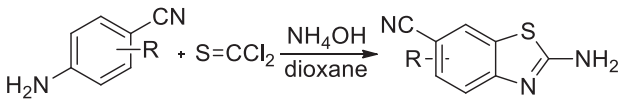
Scheme 9.



Scheme 10.

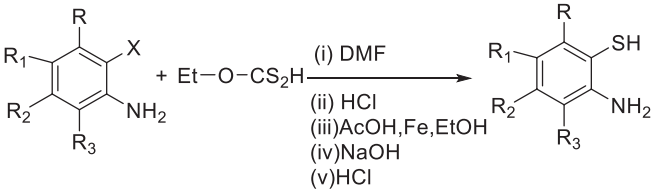


Scheme 11.



Scheme 12.

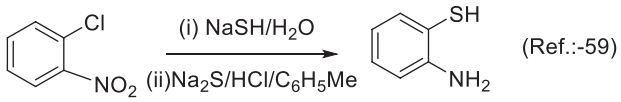
(i)



X=Halo, NO_2, alkylsulphonyloxy (Ref:-58)

Scheme 13.

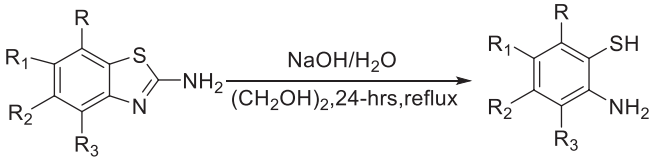
(ii)



(Ref.:-59)

Scheme 14.

(iii)



(Ref.:-60)

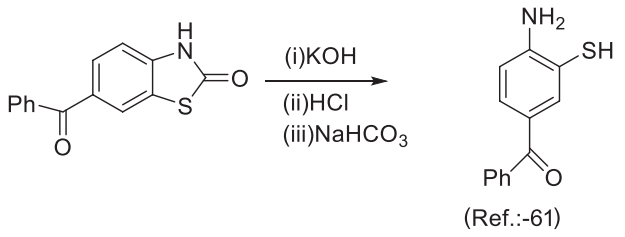
Scheme 15.

reagents and solvents along with reaction conditions are given in the schematic presentation of synthetic methods[58-66] (Schemes 13-21).

Conclusion

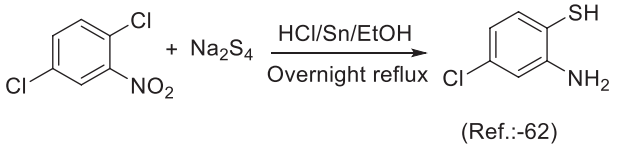
The data available in this review give an idea that thiazoles, thiols containing molecules constitute a chief category of heterocycles. A study of thiazoles, benzenethiols and their derivatives exposed a huge interest to the chemist/researchers in designing possible biological active compounds, which exhibit various pharmacological activities. I expect that this review will help to researchers for synthesis

(iv)



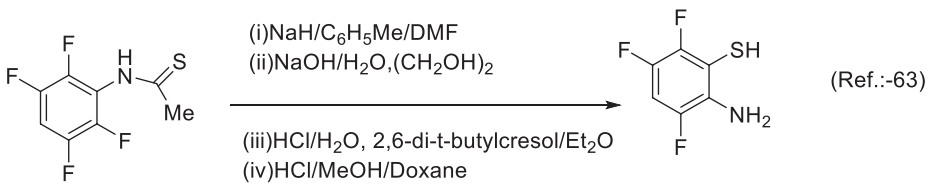
Scheme 16.

(v)



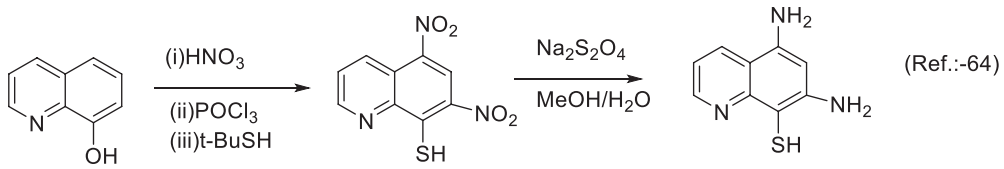
Scheme 17.

(vi)



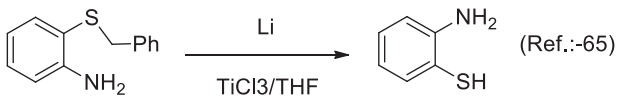
Scheme 18.

(vii)



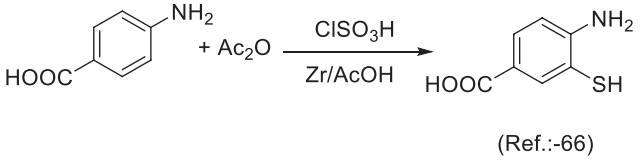
Scheme 19.

(viii)



Scheme 20.

(ix)



Scheme 21.

of specific heterocycles to produce various commercially important materials.

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Received 20.12.2017
Accepted 15.06.2018