An improved method for the preparation of 2-hydrazinylbenzo[d]thiazoles from benzo[d]thiazol-2-amines

Shahnaz Beguma,b & China Raju Bhimapakaa,b

a Department of Natural Products & Medicinal Chemistry
CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India
b Academy of Scientific and Innovative Research (AcSIR), CSIR-HRDC Campus,
Postal Staff College Area Sector 19, Kaml Nehru Nagar, Ghaziabad 201 002, Uttar Pradesh, India
E-mail: chinaraju@iict.res.in

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2-Hydrazinylbenzo[d]thiazoles have been prepared by reacting benzo[d]thiazol-2-amines with hydrazine hydrate in presence of water and hydrochloric acid. The developed method is cost effective and viable compared to previous approaches.

Keywords: 2-Hydrazinylbenzo[d]thiazoles, Benzo[d]thiazol-2-amines, Hydrazine hydrate

Hydrazinylbenzo[d]thiazoles are promising bio-active heterocycles known for their use in pharmaceutical and agrochemical industries1-4. This class of compounds namely hydrazinylbenzo[d]thiazoletriapine was identified as anti-cancer agents5. Further, 2-(2-(4-aryloxybenzylidene) hydrazinyl)benzothiazole derivatives were reported as anti-tubercular agents6-8. Benzothiazole based pyrene receptors9-12 displayed fluorescent properties for the recognition of Zn2+3. Consequently, the synthesis of hydrazinylbenzo[d]thiazoles and their derivatives have attracted considerable attention.

The 2-hydrazinylbenzo[d]thiazole was prepared by reacting benzo[d]thiazol-2-amines with hydrazine hydrate in presence of ethylene glycol as the solvent at 140°C13. To the best of our knowledge, ethylene glycol is the only solvent used for the preparation of 2-hydrazinylbenzo[d]thiazole14. Ethylene glycol is not a good solvent when handling the large scale preparation of pharmaceutically important compounds. Exposure of ethylene glycol can be extremely dangerous, with significant morbidity and mortality if left untreated. Therefore, there is a need to develop the method by replacing the ethylene glycol solvent with other enviro friendly solvent like water. In the course of our research on heterocyclic compounds, we have reported various heterocycles15-17 includingbenzohydrazides18. As part of our research work on development of benzothiazole heterocycles; we have conducted the reactions between benzo[d]thiazol-2-amines and hydrazine hydrate in water provided hydrazinylbenzo[d]thiazoles and the results are discussed below.

Results and Discussion

Scheme 1 describes the preparation of benzo[d]thiazol-2-amines 2a-i starting from corresponding anilines 1a-i. NH4SCN was added slowly to a pre-cooled aniline (1a) at 0°C followed by Glacial AcOH at the same temperature.
Then, Br₂ in AcOH was added to the reaction mixture at 0°C and the reaction mixture was stirred at room temperature. This provided benz[d]thiazol-2-amine 2a as pale yellow solid in 75% yield (Scheme 1). The other benzo[d]thiazol-2-amines 2b-i were prepared from corresponding phenols 1b-i as per the above conditions. The compounds 2a-i were well characterized by spectral data and compared with the reported values\(^{19}\) (see Supporting Information).

The 2-hydrazinylbenzo[d]thiazoles 3a-i prepared from benzo[d]thiazol-2-amines 2a-i as depicted in Scheme 1. In an initial experiment, benzo[d]thiazol-2-amine (1.0 equiv 2a) was stirred with 1.0 equiv of NH₂NH₂.H₂O (75% solution) in methanol under reflux conditions (24 h). The reaction could not provide any compound. The repeated reaction with addition of Conc. HCl (1.0 equiv) under similar conditions provided the compound 3a in 59% yield as a pale yellow solid. Then, the reaction was carried out with 1.2 & 1.5 equiv of NH₂NH₂.H₂O (75% solution) in presence of water (4 mL) under reflux conditions. Interestingly, the compound 3a was obtained in 76% yield. The same reaction when repeated with ethylene glycol as the solvent in presence of Conc. HCl (1.0 equiv) provided the compound 3a in 70% yield under reflux conditions. Further, there is no improvement in the yield when the reaction was repeated with 2.0 equivalents of NH₂NH₂.H₂O (75% solution). The addition of Conc. HCl to the reaction is essential and the pH (9-10) was crucial to take place the reaction under reflux conditions. The water as the solvent worked well for this reaction to give the compound 3a in very good yields. The compound was confirmed based on spectral data (see ESI).

Having obtained 3a in very good yield, we similarly prepared 2-hydrazinylbenzo[d]thiazoles 3b-i from corresponding benzo[d]thiazol-2-amines 2b-i with NH₂NH₂.H₂O (75% solution) under above optimized conditions. All the prepared compounds are well characterized by spectral data (see ESI). The known compounds have been compared with those reported in the literature, and unknown compounds have been well characterized by spectral data.

In this study, 5-(trifluoromethoxy)benzo[d]thiazol-2-amine (Riluzole, 2j)\(^{20}\) a FDA approved drug has been prepared starting from 4-(trifluoromethoxy)aniline 1j as per our established procedure. Thus obtained 2j was treated with NH₂NH₂.H₂O (75% solution) under optimized conditions to give compound 3j in 78% yield (Scheme 2).

To further demonstrate the usefulness of the present method, the 2-hydrazinylbenzo[d]thiazole 3b was prepared in five gram scale. Accordingly, benzo[d]thiazol-2-amine 2b (5.0 g, 1.0 equiv) was reacted with NH₂NH₂.H₂O (2.43 g, 2.5 equiv) in presence of conc. HCl (1.09 g, 1.0 equiv) and water (20 mL) as the solvent under above optimized conditions. This reaction provided compound 3b (4.14 g) in 76% yield.

**Experimental Section**

Anilines, NH₄SCN, Bromine, Glacial AcOH, Conc. HCl and NH₂NH₂.H₂O were procured from AVRA Laboratories. Solvents were procured from local suppliers. Reactions were monitored by thin layer chromatography (TLC) over pre-coated silica gel 60 F254 (mesh); spots were visualized under UV light. Column chromatographic separations were carried out over silica gel (60-120 mesh). Melting points were determined on a Mettler-Temp apparatus and are uncorrected. IR spectrum was recorded with a Thermo Nicolet Nexus 670 spectrometer. \(^1\)H and \(^13\)C NMR spectra were recorded on a Gemini 200 MHz and a Bruker Avance 300 MHz spectrometer. Chemical shifts are quoted in parts per million (δ, ppm) and are referenced to tetramethylsilane (TMS) as internal standard. EI-MS were obtained on 7070H spectrometer operating at 70 eV using a direct inlet system.

**General procedure for the preparation of benzo[d]thiazol-2-amines, 2a-k**

NH₄SCN (1.06 g, 0.014 mol) was added slowly to pre-cooled o-toluidine (1a, 1.0 g, 0.009 mol) at 0°C and followed by glacial AcOH (3.0 mL) drop-wise at the same temperature. Then, Br₂ (0.5 mL) in AcOH (5 mL) was added drop-wise to the reaction mixture at 0°C (color change was observed from brown to
yellow). The reaction mixture was slowly brought to RT and stirred for another 6 h. After completion of the reaction, crushed ice was added to the reaction mixture with continuous stirring and then treated with ammonia solution (25%, 20 mL) to give benzo[d]thiazol-2-amine 2a (1.14 g) as pale yellow solid in 75% yield.

General procedure for the preparation of 2-hydrazinylbenzo[d]thiazoles, 3a-k
Conc. HCl (0.22 g, 0.006 mol) was added drop-wise to a stirred solution of benzo[d]thiazol-2-amine (2a, 1.0 g, 0.006 mol) in water (8.0 mL) at RT followed by NH₂NH₂.H₂O (75% solution, 0.48 g, 0.015 mol) at the same temperature. The contents were refluxed and after completion of the reaction (TLC, at 4 h), the reaction mixture was extracted with chloroform and washed with water. After layer separation, the organic layer was dried over anhyd. Na₂SO₄ to give 2-hydrazinylbenzo[d]thiazole 3a (0.91 g) as a pale yellow solid in 76% yield.

Conclusion
In conclusion, 2-hydrazinylbenzo[d]thiazoles were prepared by reacting benzo[d]thiazol-2-amines with hydrazine hydrate in water under reflux conditions. The electron donating and withdrawing groups present on benzo[d]thiazoles were well tolerated and provided the corresponding 2-hydrazinylbenzo[d]thiazoles. The FDA approved Riluzole was also subjected to the reaction to give corresponding 2-hydrazinylbenzo[d]thiazole. The method has been developed with water as an environment friendly solvent and this method can be applied to any other pharmaceutically important compounds.

Supplementary Information
Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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