Indian Journal of Chemistry
Vol. 63, June 2024, pp. 632-634
DOI: 10.56042/ijc.v63i6.10614

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

Shahnaz Begum[a,b] & China Raju Bhimapaka*[a,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, Kamla Nehru Nagar, Ghaziabad 201 002, Uttar Pradesh, India
E-mail: chinaraju@iict.res.in

Received 22 April 2024; accepted (revised) 22 May 2024

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.

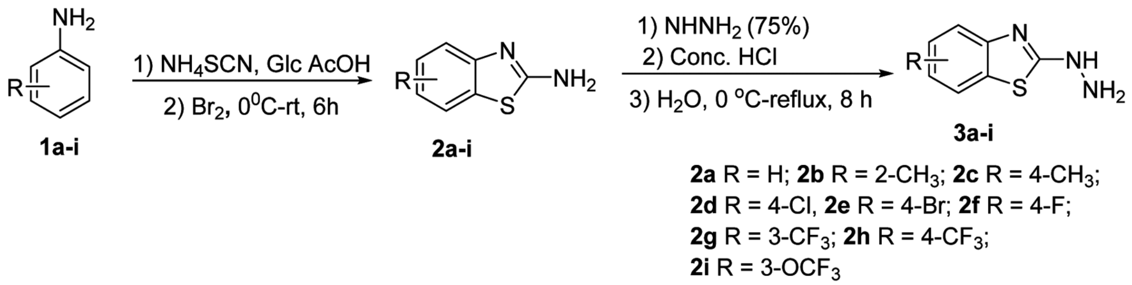
Keywords: 2-Hydrazinylbenzo[*d*]thiazoles, Benzo[*d*]thiazol-2-amines, Hydrazine hydrate

Hydrazinylbenzo[*d*]thiazoles are promising bio-active heterocycles known for their use in pharmaceutical and agrochemical industries[1-4]. This class of compounds namely hydrazinylbenzo[*d*]thiazoletriapine was identified as anti-cancer agents[5]. Further, 2-(2-(4-aryloxybenzylidene) hydrazinyl)benzothiazole derivatives were reported as anti-tubercular agents[6-8]. Benzothiazole based pyrene receptors[9-12] displayed fluorescent properties for the recognition of Zn^{2+}[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°C[13]. To the best of our knowledge, ethylene glycol is the only solvent used for the preparation of 2-hydrazinylbenzo[*d*]thiazole[14]. 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 heterocycles[15-17] includingbenzohydrazides[18]. 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**. NH_4SCN was added slowly to a pre-cooled aniline (**1a**) at 0°C followed by Glacial AcOH at the same temperature.



Scheme 1

Then, Br_2 in AcOH was added to the reaction mixture at 0°C and the reaction mixture was stirred at room temperature. This provided benzo[*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 $NH_2NH_2.H_2O$ (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 $NH_2NH_2.H_2O$ (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 $NH_2NH_2.H_2O$ (75% solution). The addition of Conc. HCl to the reaction is essential and the *p*H (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 $NH_2NH_2.H_2O$ (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 $NH_2NH_2.H_2O$ (75% solution) under optimized conditions to give compound **3j** in78% yield (Scheme 2).

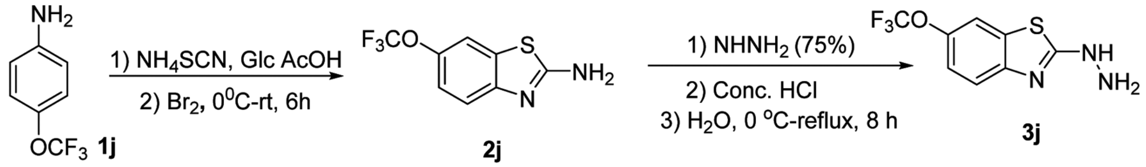
To further demonstrate the usefulness of the present method, the 2-hydrazinylbenzo[*d*]thiazole **3b** was prepared in five gram scale. Accordingly, benzo[*d*]thiazol-2-amine **2b** (5.0 g, 1.0 equiv) was reacted with $NH_2NH_2.H_2O$ (75% solution, 2.43 g, 2.5 equiv) in presence of conc. HCl (1.09 g, 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, NH_4SCN, Bromine, Glacial AcOH, Conc. HCl and $NH_2NH_2.H_2O$ 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 F_{254} (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. ^1H 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

NH_4SCN (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, Br_2 (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



Scheme 2

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 $NH_2NH_2.H_2O$ (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. Na_2SO_4 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.

Acknowledgements

Authors thank the Director, CSIR-IICT for providing research facilities. CSIR-IICT manuscript communication no. IICT/Pubs./2024/145.

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