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# Synthesis of 2-(Substituted benzylsulfanyl)-4,5-dihydrothiazoles

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## ABSTRACT

A simple and convenient procedure for the preparation of 2-(substituted benzylsulfanyl)-4,5-dihydrothiazoles by the reaction of 4,5-dihydro-thiazole-2-thiol and benzyl bromides in methanol/$Na_2CO_3$ condition has been reported. This new method consistently has the advantage of excellent yields (84-93%) and short reaction time (3 h) at reflux temperature.
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## KEYWORDS

4,5-Dihydro-thiazole-2-thiol;
Benzylbromides;
Sodium carbonate;
2-(Substituted benzylsulfanyl)-4,5-dihydrothiazoles.

## INTRODUCTION

Thiazoles and its derivaties are biologically active compounds and an important group of heterocyclic systems found in many bioactive molecules[1]. Compounds containing this heterocyclic nucleus are also found in many bioactive substrates such as thiazole natural products[2], thiazole based amino acids[3] and peptide antibiotics[4] etc. Similarly, 4,5-dihydrothiazoles and their derivatives were also found to be potent antithro mbotic[5], nematocidal[6] and thiopenam[7] agents and oligo thiazoline and polyazole natural products[8,9]. Due to the wide biological significance, we wish to synthesize 2-(substituted benzylsulfanyl)-4,5-dihydrothiazoles.

A perusal of literature revealed that these compounds can be prepared by the reaction of 2-mercapto-4,5-dihydrothiazole with benzyl halides in the presence of a base[10]. Many methods employed for preparing thioethers include Pd(0) mediated alkylation[11], phase-transfer catalysis[12], bis(diphenylstanny) telluride[13], tin sulfides with aryl halides[14], ligand transfer reactions[15], clat catalysis[16], trifluoroacetic acid[17] and the use of strong base like n-BuLi has also been reported[18]. Recently use of CsF-Celite condition has also been reported for the S-alkylation[19].

Many of these processes suffer from one or more limitations, such as long reaction times, occurrence of several side reactions, drastic reaction conditions, low yields, and tedious work-up procedure. Therefore, the search continues for a better reagent for the synthesis of 2-(substituted benzylsulfanyl)-4,5-dihydrothiazoles in terms of mild reaction conditions. Now, we wish to report the synthesis of 2-(substituted benzylsulfanyl)-4,5-dihydrothiazoles by using sodium carbonate in methanol.

## EXPERIMENTAL

All chemicals were A. R. grade obtained from Qualigens, India. All the solvents were purified by standard techniques. Column chromatographic separations were carried out on silica gel 100-200 mesh size. I.R Spectra were scanned on FT/IR-4200 Type A, Spectrophotometer with Potassium bromide optics. NMR spectra were recorded on a 300 MHz and Mass spectra were recorded on a LC-MS.

The starting material, 4,5-dihydro-thiazole-2-thiol has been obtained from commercial suppliers.

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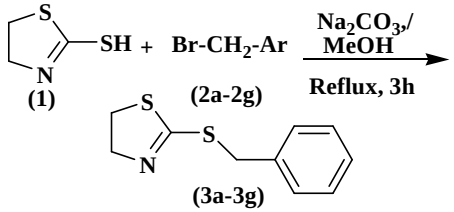
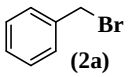
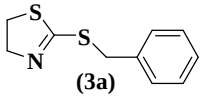
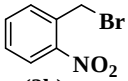
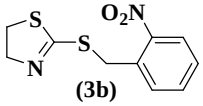
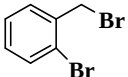
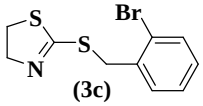
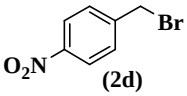
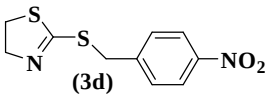
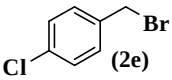
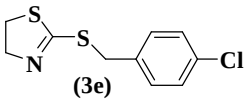
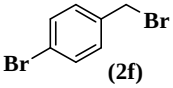
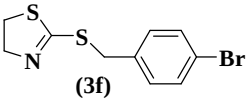
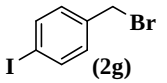
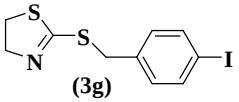



SCHEME 1

**TABLE 1: Synthesis of 2-(substituted benzylsulfanyl)-4,5-dihydrothiazoles**

| S.no. | Benzyl bromide | Product | Yield (%)[a] |
|---|---|---|---|
| 1. |  (2a) |  (3a) | 94 |
| 2. |  (2b) |  (3b) | 93 |
| 3. |  (2c) |  (3c) | 91 |
| 4. |  (2d) |  (3d) | 92 |
| 5. |  (2e) |  (3e) | 90 |
| 6. |  (2f) |  (3f) | 88 |
| 7. |  (2g) |  (3g) | 84 |

[a]Yields refer to the Isolated yields

## General procedure for the synthesis of 2-(substituted benzylsulfanyl)-4,5-dihydrothiazoles

A mixture of 4,5-dihydro-thiazole-2-thiol (1, 2 mmol), benzyl bromides (2a-2g, 2 mmol) and finely grounded anhydrous sodium carbonate (5 mmol) in methanol was stirred at reflux temperature for 3h. The completion of reaction was monitored by TLC. After completion of reaction, evaporate the solvent and add 20 ml of ethyl acetate and water. The organic layer was separated, concentrated and the crude product was purified by silica gel column chromatography using ethyl acetate-n-hexane (1:9) as eluent to afford the desired products **(3a-3g)**. Entry 1-7 spectral data is in full agreement with the reported literature[20]. Some of the compounds spectral data is given below.

### Entry (3b)

2-(2-Nitro benzylsulfanyl)-4,5-dihydrothiazole : IR(KBr): $\nu_{max}$ 3030, 2860, 1600, 1574, 1444, 1358, 1240, 1170, 1050, 960 $cm^{-1}$; $^1H$ NMR ($CDCl_3$/TMS): δ 3.38 (t, J= 8.0 Hz, 2H), 4.25 (t, J=8.0 Hz, 2 H), 4,60 (s, 2H), 7.38 (t, J=7.0 Hz, 1H), 7.54 (t, J=7.0 Hz, 1H) 7.68 (d, J=8.0, 1H), 8.01 (d, J=8.0, 1H); Anal.Cald. for $C_{10}H_{10}N_2O_2S_2$: C, 47.22; H, 3.96; N, 11.01. Found: C, 47.25; H, 3.90, N, 11.00.

### Entry (3c)

2-(2-Bromo benzylsulfanyl)-4,5-dihydrothiazole: IR(KBr): $\nu_{max}$ 3062, 2965, 1575, 1468, 1400, 1308, 1278, 1052, 995, 928 $cm^{-1}$; $^1H$ NMR (CDCl3/TMS): δ 3.38 (t, J= 8.0Hz, 2H), 4.25 (t, J=8.0 Hz, 2 H), 4.49 (s, 2H), 7.10 (t, J=7.6 Hz, 1H), 7.26 (d, J=7.6 Hz, 1H), 7.53 (m, 2H); Anal.Cald. for $C_{10}H_{10}BrNS_2$: C, 41.67; H, 3.50; N, 4.86. Found: C, 41.62; H,3.48, N, 4.85.

## RESULTS AND DISCUSSION

Initially, we studied the synthesis of 2-(substituted benzylsulfanyl)-4,5-dihydro-thiazole (3a, Ar=Ph), using of 4,5-dihydro-thiazole-2-thiol (1) and benzyl bromide **(2a)** at reflux temperature in methanol in the presence of anhydrous sodium carbonate as base for 3 h to get the 2-(substituted benzylsulfanyl)-4,5-dihydro-thiazoles in 94% yield. The product was identified with spectral data and by comparision with the authentic sample[20].

Similarily 4,5-dihydro-thiazole-2-thiol was reacted with other substituted benzyl bromides **(2b-2g)** under similar conditions to give the corresponding 2-(substituted benzylsulfanyl)-4,5-dihydrothiazole **(3b-3g)** in excellent yields (TABLE 1).

All the products were characterised by I.R, $^1H$-NMR, LC-Mass and analytical data. 2-(substituted benzylsulfanyl)-4,5-dihydrothiazoles are important class of heterocycles, and this methodology may find useful applications in the synthesis of drug intermediates and other bio active compounds. It is noteworthy which the survival of a variety of sensitive groups, worked

well without formation of any side products under the reaction conditions.

In conculsion, we have reported a convenient and useful methodology for the synthesis of 2-(substituted benzylsulfanyl)-4,5-dihydrothiazoles in excellent yields. The advantage of this methodology is the use of very mild reaction conditions, which can tolerate various functional groups that can be used for further synthetic manipulations. Further, commericial availiability of large number of benzyl bromides or easy methods of their preparation makes this reaction a more attractive choice.

## ACKNOWLEDGMENTS

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