Simple and Convenient Synthesis of 2-(Substituted-benzylsulfanyl)-4,5-dihydrothiazoles and their Antimicrobial Activity Studies

Ramanatham Vinod Kumar* and Kotha V. S. R. Seshu Kumar

Janus Research Laboratories P. Ltd., Plot No: 5-9-285/1,1st floor, Rajiv Gandhi Nagar,
Prasanthi Nagar Extn., Kukatpally, Hyderabad (A.P.)-500 072, India.
E-mail: rvinodk@yahoo.com
Received November 8, 2004

A simple and convenient procedure for the preparation of 2-(substitutedbenzylsulfanyl)-4,5-dihydrothiazoles by the reaction of 4,5-dihydro-thiazole-2-thiol and benzyl bromides in acetone/K_2CO_3 condition has been reported.

J. Heterocyclic Chem., **42**, 1191 (2005).

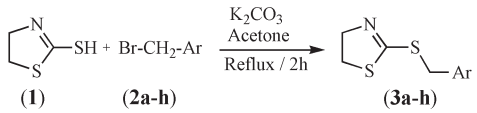
Introduction.

Thiazoles are an important group of heterocyclic systems found in many bioactive molecules, specifically in Vitamin-B1 [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 antithrombotic [5], nematocidal [6] and thiopenam [7] agents and oligo thiazoline and polyazole natural products [8,9]. We have previously reported the synthesis of 2-benzylsulfanylbenzothiazoles and their antimicrobial activities [10]. In continuation of our work on thiazole compounds, we now wish to report the synthesis of 2-benzylsulfanyl-4,5-dihydrothiazoles and their microbial activity studies.

Results and Discussion.

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 [11]. The yield of reactions depends on the solvent, basic catalyst and acidity of thiol. Generally these reactions require very long refluxing time and yields obtained are often very low [12]. Several other methods employed for preparing thioethers include Pd(0) mediated alkylation [13], phase-transfer catalysis [14], bis(diphenylstannyl)telluride [15], tin sulfides with aryl halides [16], ligand transfer reactions [17], clay catalysis [18], trifluoroacetic acid [19] and the use of strong base like *n*-BuLi has also been reported [20]. Recently use of CsF-Celite condition has also been reported for the S-alkylation [21]. Thus, it is evident from the literature that though there are several methods reported for the preparation of title compounds, yet there is no simple and efficient method for the synthesis of these important heterocyclics without the use of either expensive reagents, strong bases or PTC conditions. In this paper, we wish to report a simple but efficient methodology for the synthesis of 2-(substitutedbenzylsulfanyl)-4,5-dihydrothiazoles in excellent yields.

Reaction of 4,5-dihydro-thiazole-2-thiol, **1** with benzyl bromide (**2a**, Ar=Ph) at reflux in acetone, in the presence of anhydrous potassium carbonate as a base for 2 hr, gave the corresponding 2-benzylsulfanyl-4,5-dihydrothiazole (**3a**, Ar-=Ph) in 98 % yield (Figure 1). The product was identified with the spectral data and by comparison with the authentic sample [21]. Similary, compound **1** was reacted with other substituted benzyl bromides (**2b-2h**) under similar conditions to obtain the corresponding 2-(substituted-benzylsulfanyl)-4,5-dihydrothiazoles (**3b-3h**) in almost quantitative yields. (Table 1). All the new products were characterized by IR, ^{1}H-, ^{13}C-NMR spectral and analytical data. All the compounds synthesized herein were screened for their potential antimicrobial activities using disk diffusion method. The results are measured as the diameters of inhibition zones for each micro-organism and the details are presented in Table 2. Since, 2-(substituted-benzylsulfanyl)-4,5-dihydrothiazoles constitute an important class of heterocyclics found in bioactive compounds, the methodology described here may find useful applications in the synthesis of drug intermediates and other bioactive compounds containing this heterocyclic moiety.



(**1**) (**2a-h**) (**3a-h**)

Figure 1

Conclusion.

In conclusion, 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, commercial availability of large number of benzyl bromides or easy methods of their preparation makes this reaction a more attractive choice. All the compounds were tested for antimicrobial screening. However, only few compounds exhibited moderate activity against

Table 1

List of Various 2-(Substitutedbenzylsulfanyl)-4,5-dihydro-thiazoles Sythesized

Sr. No.	Starting Material	Aryl halide Used (**2**)	Product Obtained (**3**)	Yield (%)	M.P. (°C)
1	**1**	**2a**, Ar = C_6H_5-	**3a**, Ar = C_6H_5-	98	47- 48 (Lit [20]-48)
2	**1**	**2b**, Ar = 2-Br-C_6H_4-	**3b**, Ar = 2-Br-C_6H_4-	95	35 - 36
3	**1**	**2c**, Ar = 2-NO_2-C_6H_4-	**3c**, Ar = 2-NO_2-C_6H_4-	96	83 - 84
4	**1**	**2d,** Ar = 4-Br-C_6H_4-	**3d,** Ar = 4-Br-C_6H_4-	96	-
5	**1**	**2e,** Ar = 4-I-C_6H_4-	**3e,** Ar = 4-I-C_6H_4-	95	43 – 44
6	**1**	**2f,** Ar = 2,5-Br_2-C_6H_3-	**3f,** Ar = 2,5-Br_2-C_6H_3-	97	48 - 49
7	**1**	**2g,** Ar = 2-Br-3-Me-C_6H_3-	**3g,** Ar = 2-Br-3-Me-C_6H_3-	96	-
8	**1**	**2h,** Ar = 2-Br-5-I-C_6H_3-	**3h,** Ar = 2-Br-5-I-C_6H_3-	97	57 - 58

Table 2

Growth Inhibition Activity [a] of 2-substituted-benzylsulfanylbenzothiazoles **3a-3h** against *B. Subtilis, E. Coli, M. Luteus, P. Aeruginosa, C. Albicans* and *A. Niger in vitro*

Compd.	*B. subtilis*		*E. coli*		*M. Luteus*		*P. aeruginosa*		*C. albicans*		*A. niger*	
	AM1	AM11	AM1	AM11	AM1	AM11	AM1	AM11	AM1	AM11	AM1	AM11
3a	7.1	6.9	6.8	7.6	—	—	6.2	6.6	—	6.2	6.7	6.9
3b	—	—	—	—	—	—	—	—	7.1	6.0	—	—
3c	6.0	6.3	—	—	—	—	—	—	6.3	—	—	—
3d	—	—	6.3	6.8	—	—	7.2	8.2	6.7	7.0	—	7.2
3e	—	—	—	6.4	—	—	—	—	—	6.1	—	—
3f	6.0	7.2	6.9	7.1	—	—	6.3	—	—	6.9	7.3	—
3g	—	—	—	—	—	—	—	—	7.0	6.3	—	—
3h	—	7.0	7.6	6.6	—	—	—	—	8.0	6.7	7.6	6.0

[a] Diameter (in mm) of inhibition zones; AM1: Antibiotic medium N°1 (pH=6.5); AM11: Antibiotic medium N°11 (pH=7.9).

E. subtilis, *E. coli*, *P. aeruginosa, C. albicans and A. niger* in a preliminary screening.

EXPERIMENTAL

Melting points are uncorrected and were recorded on a MRVIS Series, Lab India Instrument**.**IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a JEOL 400 MHz spectrometer using TMS as internal standard. Elemental analysis was carried out on a Perkin–Elmer Series –II CHN Analyzer 2400. The starting material, 4,5-dihydro-thiazole-2-thiol has been obtained from commercial suppliers.

General Procedure.

A mixture of 4,5-dihydro-thiazole-2-thiol **1** (2 mmole), respective benzyl bromide (2 mmol), finely grounded anhydrous K_2CO_3 (4 mmol) in acetone was refluxed for 2 hr and the reactions were followed by method of tlc. The reaction mixture was then cooled to room temperature and filtered. Evaporation of the filtrate yielded the crude product. The crude products were purified by silica-gel flash column chromatography.

Spectral Data of Compounds.

2-(2-Bromobenzylsulfanyl)-4,5-dihydro-thiazole (**3b**).

This compound has the following properties: IR (KBr): 3060, 2967, 1575, 1465, 1402, 1302, 1275, 1203, 1053, 999, 925 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS): δ 3.39 (t, *J*= 8.0 Hz, 2H), 4.22 (t, *J* = 8.0 Hz, 2H), 4.48 (s, 2H), 7.11 (t, *J*=7.6Hz, 1H), 7.25 (d, *J*=7.6Hz, 1H), 7.52 (m, 2H); ^{13}C-NMR (100MHz/$CDCl_3$): 35.77, 37.18, 64.11, 124.68, 127.51, 129.12, 131.28, 132.89, 136.41, 164.94.

Anal. Calcd. for $C_{10}H_{10}BrNS_2$: C, 41.67; H, 3.50; N, 4.86. Found: C, 41.68; H, 3.52; N, 4. 89.

2-(2-Nitrobenzylsulfanyl)-4,5-dihydrothiazole (**3c**).

This compound has the following properties: IR (KBr): 3012, 2848, 1608, 1574, 1444, 1350, 1249, 1170, 1060, 968 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS): δ 3.38 (t, *J*= 8.0 Hz, 2H), 4.20 (t, *J* = 8.0 Hz, 2H), 4.67 (s, 2H), 7.43 (t, *J* = 6.8Hz, 1H), 7.55 (t, *J* = 7.0Hz, 1H), 7.69 (d, *J* = 8.0Hz, 1H), 8.02 (d, *J* = 8.0Hz, 1H); ^{13}C-NMR (100MHz/$CDCl_3$): 33.68, 35.87, 63.96, 125.10, 128.50, 132.78, 133.42, 133.56, 148.24, 164.68.

Anal. Calcd. for $C_{10}H_{10}N_2O_2S_2$: C, 47.22; H, 3.96; N, 11.01. Found: C, 46.96; H, 4.02; N, 11.04.

2-(4-Bromobenzylsulfanyl)-4,5-dihydrothiazole (**3d**).

This compound has the following properties: IR ($CHCl_3$): 3042, 2936, 2848, 1899, 1570, 1485, 1432, 1408, 1303, 1244, 1193, 1102, 1070, 995 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS): δ 3.39 (t, *J*= 8.0 Hz, 2H), 4.21 (t, *J* = 8.0 Hz, 2H), 4.28 (s, 2H), 7.23 (d, *J* = 8.4Hz, 2H), 7.42 (d, *J* = 8.4Hz, 2H); ^{13}C-NMR (100MHz/$CDCl_3$): 35.71, 36.16, 64.11, 121.38, 130.71, 131.65, 135.95, 164.89.

Anal. Calcd. for $C_{10}H_{10}BrNS_2$: C, 41.67; H, 3.50; N, 4.86. Found: C, 41.69; H, 3.48; N, 4.84.

2-(4-Iodobenzylsulfanyl)-4,5-dihydro-thiazole (**3e**).

This compound has the following properties: IR (KBr): 2933, 1908, 1573, 1483, 1396, 1303, 1192, 1056, 968 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS): δ 3.39 (t, *J*= 8.0 Hz, 2H), 4.20 (t, *J* = 8.0 Hz, 2H), 4.27 (s, 2H), 7.10 (d, *J* = 8.4Hz, 2H), 7.61 (d, *J* = 8.0Hz, 2H); ^{13}C-NMR (100MHz/$CDCl_3$): 35.70, 36.23, 64.09, 92.92, 130.93, 136.58, 137.59, 164.79.

Anal. Calcd. for $C_{10}H_{10}INS_2$: C, 35.83; H, 3.01; N, 4.18. Found: C, 35.96; H, 3.12; N, 4.01.

2-(2, 5-Dibromobenzylsulfanyl)-4,5-dihydrothiazole (**3f**).

This compound has the following properties: IR (KBr): 3086, 2847, 1567, 1456, 1405, 1304, 1238, 1198, 1084, 1029, 993 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS): δ 3.42 (t, *J*= 8.0 Hz, 2H), 4.24 (t, *J* = 8.0 Hz, 2H), 4.42 (s, 2H), 7.25 (dd, *J* = 10.4 & 2.4Hz, 1H), 7.40 (d, *J* = 8.4Hz, 1H), 7.67 (d, *J* = 2.0Hz, 1H); ^{13}C-NMR (100MHz/$CDCl_3$): 35.87, 36.59, 64.02, 121.18, 123.29, 132.06, 134.09, 134.14, 138.75, 164.54.

Anal. Calcd. for $C_{10}H_9Br_2NS_2$: C, 32.72; H, 2.47; N, 3.82; Found: C, 32.86; H, 2.18; N, 3.76.

2-(2-Bromo-3-methylbenzylsulfanyl)-4,5-dihydrothiazole (**3g**).

This compound has the following properties: IR ($CHCl_3$): 3050, 2944, 2848, 1935, 1571, 1461, 1379, 1261, 1190, 1025, 964 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS): δ 2.41 (s, 3H), 3.38 (t, *J*= 8.0 Hz, 2H), 4.23 (t, *J* = 8.0 Hz, 2H),4.52 (s, 2H), 7.13 (d, *J*=4.8Hz, 2H), 7.32 (t, *J*=4.6Hz, 1H); ^{13}C-NMR(100MHz/$CDCl_3$): 23.83**,** 35.70, 38.10, 64.13, 126.92, 127.26, 128.68, 130.02, 136.69, 138.91, 165.08.

Anal. Calcd. for $C_{11}H_{12}BrNS_2$: C, 43.71; H, 4.00; N, 4.63. Found: C, 43.82; H, 4.08; N, 4.44.

2-(2-Bromo-5-Iodobenzylsulfanyl)-4,5-dihydro-thiazole (**3h**).

This compound has the following properties: IR (KBr): 3077, 1904, 1559, 1456, 1404, 1375, 1306, 1235, 1198, 1075, 996 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS): δ 3.42 (t, *J*= 8.0 Hz, 2H), 4.25 (t, *J* = 8.0 Hz, 2H), 4.40 (s, 2H), 7.26 (d, *J*=3.6Hz, 1H), 7.42 (dd, *J*=8.0 & 2.0Hz, 1H), 7.85 (d, *J*=2.0Hz, 1H); ^{13}C-NMR(100MHz/$CDCl_3$): 35.81, 36.52, 63.85, 92.33, 124.51, 134.40, 138.02, 138.79, 139.99, 165.01.

Anal. Calcd. for $C_{10}H_9BrINS_2$: C, 29.00; H, 2.19; N, 3.38. Found: C, 28.86; H, 2.31; N, 3.20.

Antimicrobial Activity of Compounds **3a-3h**.

Test disks (6mm in diameter) impregnated with 100µg of the appropriate sample were used to test both antibacterial and antifungal activities at pH 6.5 and 7.9 respectively. Disks were applied on the surface of plates containing each 25 ml of Antibiotic medium N°1 (pH=6.5) or N°11(pH=7.9), inoculated with 10^6 CFU/ml of the microorganisms. The following strains were used to test the activities: *Bacillus subtilis* ATCC 6633 CCM-A-10, *Escherichia coli* ATCC 11105 CCM-A-424, *Micrococcus luteus* ATCC 9341 CCM-A-45, *Pseudomonas aeruginosa* ATCC 9027 CCM-A-39, *Candida albicans* ATCC 10231 and *Aspergillus niger* ATCC 16404. Growth inhibition was tested after a 24 hour incubation at 37 °C. All the results are expressed as the diameter (in mm) of inhibition zones, and are shown in Table 2.

REFERENCES AND NOTES

[1a] J. V. Metzger (Ed.), *Thiazole and its Derivatives*, Wiley-Interscience, New York, 1979; [b] J. V. Metzger in A. R. Katritzky and C. W. Rees (Eds.), *Comprehensive Heterocyclic Chemistry*, Pergamon Press, Oxford, 1984,Vol. **6**, 235; [c] R. Tanaka and I. Shinkai in H. Suschitzky and E. F. V. Scriven (Eds.), *Progress in Heterocyclic Chemistry*, Pergamon Press, Oxford, 1989-1994, Vols. **1-6**; J. V. Metzger, *Chem. Heterocycl. Compds*., **34**, 1 (1979).

[2a] Z. Jin, Z. Li and R. Huang, *Natural Product Reports*, **19**, 454 (2002); [b] P. Catsoulacos and Ch. Camoutsis, *J. Heterocyclic Chem.*, **18**, 1485 (1981).

[3] A. Bertram and G. Pattenden, *Synlett*, **12**, 1873 (2001).

[4] Y-M. Li, J. C. Milne, L.L. Madison, R. Kolter and C. T. Walsh, *Science*, **274**, 1188 (1996).

[5] A. K. Saxena, S. K. Pandey, P. Seth, M. P. Singh, M. Dixit, A. Carpy, *Bioorg & Med. Chem.*, **9**, 2025 (2001).

[6] A. J. Martinez,U S Pat., 4584306, 1986; *Chem. Abstr*., **105**: 60598x (1986).

[7] E. Schaumann, W. R. Foerster and G. Adiwidjaja, *Angew. Chemie*., **96**, 429 (1984).

[8] S. Hoppen and U. Koert, *Organic Synthesis Highlights IV*, 218 (2000).

[9] P. Wipf and S. Venkatraman, *Synlett*, **1**, 1 (1997).

[10] R. Vinod Kumar, K. V. S. R. Seshu Kumar and K. Raja Gopal, *J. Heterocyclic Chem.*, **42**, 153 (2005).

[11] For a review, see: M. E. Peach in The Chemistry of Thiol Groups, S. Patai (Ed.), Thiols as nucleophiles; John Wiley & Sons, London, 721 (1974).

[12] S.-I. Yunoki, K. Takimiya, Y. Aso and T. Otsubo, *Tetrahedron. Lett.*, **38**, 3017 (1997).

[13] C. Goux, P. Lhoste and D. Sinou, *Tetrahedron.Lett*., **33**, 8099 (1992).

[14] A. W. Herriott and D. Picker, *J. Am. Chem.Soc*., **97**, 2345 (1975).

[15] C.-J. Li and D. N. Harpp, *Tetrahedron.Lett*., **33**, 7293 (1992).

[16] M. Kosugi, T. Ogata, M. Terada, H. Sano and T. Migata, *Bull. Chem. Soc. Jpn*, **58**, 3657 (1985).

[17a] F. D. Toste and I. W. J. Still, *Tetrahedron.Lett*., **36**, 4361 (1995); [b] F. D. Toste F. Laronde and I. W. J. Still, *Tetrahedron.Lett*., **36**, 2949 (1995).

[18] T.-S. Li and A.-X. Li, *J. Chem. Soc., Perkin Trans*.-1, 1913 (1998).

[19] L. S. Richter, J. C. Marsters and T. R. Gadek, *Tetrahedron.Lett*., **35**, 1631 (1994).

[20a] E. Fujita, Y. Nagao, K. Seno, S. Takeo and T. Miyasaka, *J. Chem. Soc., Perkin Trans. 1*, ,914 (1981); [b] J. Yin and C. Pidgeon, *Tetrahedron. Lett*., **38**, 5953 (1997).

[21] S. T. A. Shah, K. M. Khan, A. M. Heinrich and W. Voelter, *Tetrahedron. Lett*., **43**, 8281 (2002).