Asian Journal of Chemistry; Vol. 23, No. 11 (2011), 5133-5136

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Facile Synthesis of Bioactive 4*H*-[1,4]-Benzothiazines Under Solvent Free Conditions

G.S. KALWANIA*, S. CHOMAL and SAVITA CHOUDHARY

Department of Chemistry, S.K. Government College, Sikar-332 001, India

*Corresponding author: E-mail: gskalwania@yahoo.com

(*Received*: 15 March 2011; *Accepted*: 29 July 2011) AJC-10227

An efficient method for synthesis of 4*H*-[1,4]-benzothiazines under solvent free conditions has been developed. The oxidative condensation of 2-aminobenzenethiols with β-diketones/β-ketoesters in presence of catalytic amount of hydrazine hydrate yields the 4*H*-[1,4]-benzothiazines. The reaction is accelerated by microwave irradiation under solvent free conditions in presence of an energy transfer agent DMF to get the product in high yield. The 2-aminobenzenethiazole required for the synthesis of 4*H*-[1,4]-benzothiazines are also obtained by a new method instead of presently used time consuming and low yielding method. The structure of the synthesized compounds has been characterized by IR, NMR, mass spectral studies and elemental analysis.

Key Words: 4*H*-[1,4]-Benzothiazines, Microwave irradiation, Solvent free conditions, Energy transfer agent.

INTRODUCTION

Thiazine derivatives, 4*H*-[1,4]benzothiazines have structural resemblance with phenothiazine in having fold along the N-S axis[1] can be expected to posses the biological activities similar to phenothiazine derivatives. 1,4-Benzothiazines are known to exhibit various kinds of biological activities such as antipsychotic[2], antimicrobial[3], blood platelets aggregation inhibitors[4], Ca-antagonist[5], antihypertensive agents[6], anti-anginal[7], antiviral[8] and neuroleptic[9]. These are also used as dyestuffs, photographic developers[10], antioxidants[11] and UV-light absorbers. Besides these activities 1,4-benzothiazine nucleus[12,13] found in mammalian red hair and feathers as luciferin and rafamycin derivatives.

In view of multifarious applications of these bioactive thiazine derivatives, our main aim is to develop environmentally benign and eco-friendly method for synthesis of 4*H*-[1,4]-benzothiazine derivatives.

EXPERIMENTAL

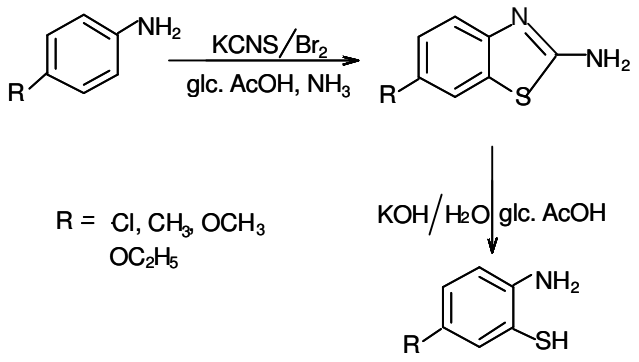
All the melting points are uncorrected. The purity of the compounds was checked on thin layer of silica gel in various non-aqueous solvent systems. Infrared spectra of all the synthesized compound have been scanned in KBr on Shimadzu FTIR. Affinity-1 and their NMR spectra were scanned on Varian Gemini 400 spectrometer (300 MHz) using TMS as an internal standard. The mass spectra were recoded on Jeol SX 102 spectrometer at 70 eV. The reactions were carried in domestic microwave oven.

Preparation of substituted 2-aminobenzenethiols: A mixture of potassium thiocyanate (0.06 mol) and *p*-substituted aniline (0.06 mol) was added into a precooled (5 ºC) glacial acetic acid (125 mL) and placed into freezing mixture. Now a bromine solution (0.02 mol of Br_2 in 20 mL glacial acetic acid) was added drop by drop with constant stirring so that temperature does not rise above 5 ºC and continue the stirring for additional 2.5 h. Filter the separated hydrochloride salt, washed with 5 mL acetic acid and dried. Dissolve the hydrochloride salt in hot water and neutralized with ammonia solution, filter the solid, washed with water and crystallized to get *p*-substituted 2-aminobenzothiazole.

Substituted 2-aminobenzenethiazole was refluxed with an aqueous solution of sodium hydroxide (5 times by weight of benzothiazole) until evolution of ammonia ceased. The contents were filtered and neutralized with glacial acetic acid. The separated yellowish semisolid benzenethiol was extracted with solvent ether. The evaporation of solvent ether and crystallization from methanol afforded the desired 2-amino-benzenethiol (**Scheme-I**).

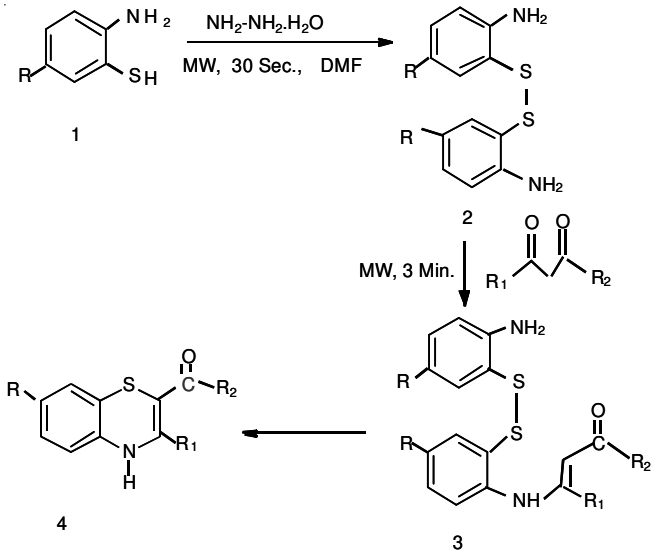
2-Amino-5-chlorobenzenethiol: m.p. 110 ºC; 2-amino-5-methylbenzenethiol: m.p. 90 ºC: 2-amino-5-methoxy-*o*-benzenethiol: m.p. 105 ºC; 2-amino-5-ethoxy-*o*-benzenethiol: m.p. 104 ºC.

Preparation of substituted 4*H*-[1,4]-benzothiazines: A mixture of substituted 2-aminobenzenethiol (10 mmol), catalytic amount of hydrazine hydrate (1 mmol) and DMF (5 mmol) as an energy transfer medium was exposed to microwave irradiation for 30 s. Now add β-diketone/β-ketoester



Scheme-I

(10 mmol) to the reaction mixture and again exposed to the microwave irradiation intermittently at 30 ºC for 3 min. After completion of reaction as monitored by TLC, the reaction mixture was cooled and transferred to crushed ice. The solid separated out was filtered, washed with 50 % ethanol and crystallized from ethanol (**Scheme-II**).



Scheme-II

Spectral data

4a: IR (KBr, ν_{max}, cm^{-1}): 3410 (N-H, s), 1685 (>C=O, s), 1460, 1350 (C-CH_3, m), 1230, 1035 (C-O-C, m), 855, 835 (adj. 2H in ring, m), 3000 (C-H aliph., s); PMR ($CDCl_3$): δ 6.85-6.3 (m, 3H, Ar.), 4.10 (q, 2H, CH_2 at C_2), 1.20 (t, 3H, CH_3 at C_2), 2.2 (s, 3H, CH_3 at C_3), 3.95 (q, 2H, CH_2 at C_7), 1.40 (t, 3H, CH_3 at C_7), 8.75 (s, 1H, N-H); mass: m/z 279 (M^+), 278 (M^+-H), 251 (M^+-C_2H_4), 250 (M^+-C_2H_5), 233 (M^+-C_2H_5OH), 234 (M^+-OC_2H_5), 222 (M^+-COC_2H_5), 205 (M^+-C_2H_5OH, CO).

4b: IR (KBr, ν_{max}, cm^{-1}): 3340 (N-H, s), 1685 (>C=O, s), 1465, 1340 (C-CH_3, m), 1245, 1035 (C-O-C, m), 850, 820 (adj. 2H in ring, m); PMR ($CDCl_3$): δ 6.8-6.4 (m, 3H, Ar.), 3.95 (q, 2H, CH_2 at C-2, m), 2.25 (s, 3H, CH_3 at C-3), 1.25 (t, 3H, CH_3 at C-2), 4.4 (s, 3H, O-CH_3), 8.8 (s, 1H, N-H); mass: m/z 265 (M^+), 264 (M^+-H), 235 (M^+-CH_2O), 206 (M^+-CH_2O, C_2H_5), 178 (M^+-CH_2O, COC_2H_5), 250 (M^+-CH_3), 222 (M^+-CH_3, CO), 193 (M^+-CH_3, CO, C_2H_5), 165 (M^+-CH_3, CO, COC_2H_5).

4c: IR (KBr, ν_{max}, cm^{-1}): 3400 (N-H, s), 1665 (>C=O, s), 1230, 1050 (C-O-C, m), 855, 820 (adj. 2H in ring, m), 2920 (C-H, aliph., s); PMR ($CDCl_3$): δ 7.8-6.95 (m, 13H, Ar.), 4.5 (s, 3H, OCH_3), 8.7 (s,1H, N-H); mass: m/z 359 (M^+), 358 (M^+-H), 254 (M^+-COC_6H_5), 105 (COC_6H_5), 282 (M^+-C_6H_5), 77 (C_6H_5), 329 (M^+-CH_2O), 344 (M^+-CH_3), 316 (M^+-CH_3, CO), 252 (M^+-CH_2O, C_6H_5), 224 (CH_2O, COC_6H_5).

4d: IR (KBr, ν_{max}, cm^{-1}): 3460 (N-H, s), 1680 (>C=O, s), 1465, 1345 (C-CH_3, m), 1230, 1035 (C-O-C, m), 855, 825 (adj. 2H in ring, m), 2980 (C-H aliph., m); PMR ($CDCl_3$): δ 6.7-6.4 (m, 3H, Ar.), 4.15 (q, 2H, CH_2 at C-2), 2.25 (s, 3H, CH_3 at C-3), 1.95 (s, 3H, CH_3 at C-7), 1.25 (t, 3H, CH_3 at C-2), 8.8 (s, 1H. N-H); mass: m/z 249 (M^+), 248 (M^+-H), 220 (M^+-C_2H_5), 204 (M^+-OC_2H_5) , 192 (M^+-COC_2H_5), 221 (M^+-C_2H_4), 203 (M^+-C_2H_5OH), 175 (M^+-C_2H_5OH, CO).

4e: IR (KBr, ν_{max}, cm^{-1}): 3345 (N-H, s), 1695 (>C=O, s), 1470, 1330 (C-CH_3, s), 865, 820 (adj. 2H in ring, m), 3055 (C-H, Ar, m); PMR ($CDCl_3$): δ 7.3-7.0 (m, 13H, Ar.), 2.35 (s, 3H, CH_3 at C-7), 8.8 (s, 1H, NH); mass: m/z 343 (M^+), 342 (M^+-H), 238 (M^+-COC_6H_5), 105 (COC_6H_5), 266 (M^+-C_6H_5), 77 (C_6H_5), 161 (M^+-COC_6H_5, C_6H_5).

4f: IR (KBr, ν_{max}, cm^{-1}): 3380 (N-H, s), 1690 (>C=O, s), 1465, 1360 (C-CH_3, m), 735 (Cl, m), 1240, 1040 (C-O-C, m), 860, 825 (adj. 2H in ring, s), 2985 (C-H aliph., m); PMR ($CDCl_3$): δ 6.85-6.4 (m, 3H, Ar.), 4.05 (q, 2H, CH_2 at C-2), 2.25 (s, 3H, CH_3 at C-3), 1.25 (t, 3H, CH_3 at C-2), 8.7 (s, 1H, N-H); mass: m/z 269 (M^+), 268 (M^+-H), 241 (M^+-C_2H_4), 224 (M^+-C_2H_4, OH) or (M^+-OC_2H_5), 196 (M^+-$COOC_2H_5$), 240 (M^+-C_2H_5), 223 (M^+-C_2H_5OH), 212 (M^+-C_2H_5, CO).

4g: IR (KBr, ν_{max}, cm^{-1}): 3360(N-H, s), 1690 (>C=O, s), 740 (C-Cl, m), 850, 820 (adj. 2H in ring, m), 3060 (C-H, Ar. s); PMR ($CDCl_3$): δ 7.5-6.85 (m, 13H, Ar), 8.6 (s, !H, N-H); mass: m/z 363 (M^+), 362 (M^+-H), 258 (M^+-COC_6H_5), 105 (COC_6H_5), 286 (M^+-C_6H_5), 77 (M^+-C_6H_5), 181 (M^+-COC_6H_5, C_6H_5), 146 (M^+-COC_6H_5, C_6H_5, Cl).

4h: IR (KBr, ν_{max}, cm^{-1}): 3365 (N-H, s), 1675 (>C=O, s), 1460, 1340 (C-CH_3, m), 725 (C-Cl, m), 850, 830 (adj. 2H in ring, w), 3020 (C-H, Ar, m); PMR ($CDCl_3$): δ 7.6-7.0 (m. 8H, Ar.), 2.25 (s, 3H, CH_3 at C-3), 8.7 (s, 1H, NH); mass: m/z 301 (M^+), 300 (M^+-H), 196 (M^+-COC_6H_5), 105 (COC_6H_5), 224 (M^+-C_6H_5), 77 (C_6H_5), 161 (M^+-COC_6H_5, Cl).

4i: IR (KBr, ν_{max}, cm^{-1}): 3380 (N-H, s), 1680 (>C=O, s), 1460, 1340 (C-CH_3, m), 860, 825 (adj. 2H in ring, m), 2930 (C-H, aliph., s), 3030 (C-H, Ar., s); PMR ($CDCl_3$): δ 7.4-6.6 (m, 8H, Ar.),2.15 (s, 3H, CH_3 at C-3), 1.95 (s, 3H,CH_3 at C-7), 8.8 (s 1H, NH); mass: m/z 281 (M^+), 280 (M^+-H), 204 (M^+-C_6H_5), 77 (C_6H_5), 176 (M^+-COC_6H_5), 105 (COC_6H_5), 131 (M^+-COC_6H_5, HCS), 144 (M^+-COC_6H_5, S).

RESULTS AND DISCUSSION

Generally 1,4-benzothiazines were being synthesized by the reaction of 2-aminobenzenethiol with α-haloketones/ α-haloesters but the lachrymatory nature of the latter was the main draw back of that method. Latterly slightly improved method is being used by which 1,4-benzothiazines are prepared

by oxidative condensation of substituted 2-aminobenzenethiol with β-diketones/β-ketoesters in presence of DMSO. The latter is an aprotic dipolar solvent which acts as solvent and oxidant. It has several unfavourable properties and the product is difficult to separate out from it. Therefore, this method needs to be improved. Mechanism of the reaction of substituted 2-aminobenzenethiols with β-diketones/β-ketoesters reveals that the reaction proceeds in two steps. In the first step DMSO oxidizes 2-aminobenzenethiols[14] to the corresponding disulfides derivatives and the latter condense with β-diketones/β-ketoesters yielding 4*H*-[1,4]benzothiazines in the second step. From the literature survey it is observed that 2-aminobenzenethiols can be oxidized easily by hydrogen peroxide[15], DMSO-iodine[16], thallium acetate[17], sodium perborate[18], mixture of NO_2 and NO_3[19] and even environmental oxygen on standing in presence of small amount of base[20].

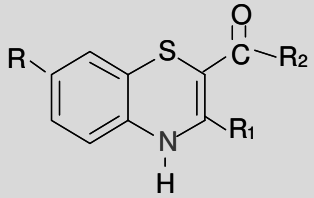
The literature survey[21] also reveals that benzenethiols are uncreative but in presence of catalytic amount of hydrazine hydrate and environmental oxygen at room temperature a quantitative amount of disulfide is obtained. Keeping this fact in mind the condensation of substituted 2-aminobenzenethiols is carried out with β-diketones/β-ketoesters in presence of catalytic amount of hydrazine hydrate in air. The reaction is accelerated by microwave irradiation under solvent free conditions in presence of an energy transfer agent DMF to get 4*H*-[1,4]-benzothiazine derivatives. The probable mechanism of the condensation reaction is drawn in **Scheme-II**. The physical and analytical data are summarized in Table-1. The 2-anminobenzenethiols required for synthesis of title compound are obtained by new method (**Scheme-I**) having two steps instead of time consuming and low yielding three step[22] method. In first step, substituted aromatic amines are converted directly into corresponding 2-aminobnzothiazoles instead of two steps in old methods and in second step 2-aminobenzothiazoles are hydrolyzed in corresponding 2-aminobenzenethioles. Presently we are trying to avoid direct use of environmentally hazardous bromine in the first step.

The infrared spectra of all the synthesized 4*H*-[1,4]-benzothiazines invariably showed a N-H stretching absorption peak in the region of 3410-3340 cm^{-1} and for C=O stretching absorption peak in the region of 1695-1665 cm^{-1}. The weak absorption bands in the region 1470-1330 cm^{-1} are attributed to C-CH_3 bending vibrations. In NMR spectra a broad singlet peak in the region of 8.70-8.80 δ is observed in all the synthesized compounds for N-H proton and multiplets in the region of 6.4-7.6 δ are due to aromatic ring protons. A singlet peak at about 4.4 δ is observed in methoxy derivatives due to OCH_3 group. Peaks for CH_3 and C_2H_5 groups are also observed in expected region and multiplicity. In mass spectra all 1,4-bebzothiazines having benzoyl group showed peak at m/z = M^+-105 (with high intensity), 105 ($C_6H_5CO^+$, base peak) and 77 ($C_6H_5^+$) by the loss of benzoyl group but didn't show any peaks corresponding to the M^+-$COCH_3$ or $COCH_3$ moiety, confirming the structure of these benzothiazines [**A**] rather than [**B**]. The 2-ethoxycarbonyl derivatives gave peaks at m/z = M^+-C_2H_4, M^+-C_2H_5, M^+-COC_2H_5 and M^+-OC_2H_5. All the analytical and physical data of the synthesized compounds are in good agreement with their literature[23,24] values.

Conclusion

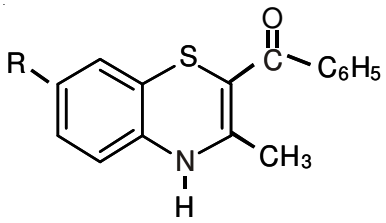
The oxidative condensation reaction of substituted 2-aminobenzenethiols and β-diketones/β-ketoesters, accelerated by microwave irradiation under solvent free conditions in presence of an energy transfer agent DMF, a catalytic amount of hydrazine hydrate and air is found to be strategically developed new good method for synthesis of 4*H*-[1,4]-benzothiazines in better yield. Certainly it is improved version of formerly used methods for synthesis of substituted 4*H*-[1,4]-benzothiazines and proved environmentally benign. 2-Aminobenzenetholes required for synthesis of 4*H*-[1,4]-benzothiazines are also prepared by newly developed method in two stages instead of presently used time consuming and low yielding method having three stages. We are trying to avoid the direct use of environmentally hazardous bromine in the first stage of synthesis for 2-aminobenzothiazoles by other means.

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF SUBSTITUTED 4*H*-[1,4]-BENZOTHIAZINES

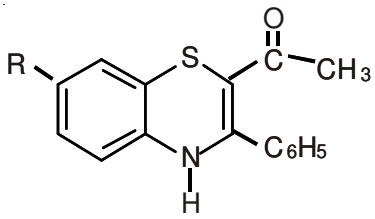


Compound	R	R1	R2	m.p. (ºC) Obs. (Lit.*)	Yield (%) Obs. (Lit.*)	N % Obs. (calcd.)
4a	OC_2H_5	CH_3	OC_2H_5	103 (101)	70(50)	5.0200(5.0179)
4b	OCH_3	CH_3	OC_2H_5	119 (116)	65 (45)	5.2868 (5.2830)
4c	OCH_3	C_6H_5	C_6H_5	172 (171)	82 (65)	3.9019 (3.8997)
4d	CH_3	CH_3	OC_2H_5	178 (178)	75 (50)	5.6196 (5.6224)
4e	CH_3	C_6H_5	C_6H_5	194 (195)	80 (60)	4.0820 (4.0816)
4f	Cl	CH_3	OC_2H_5	181 (180)	75 (60)	5.1936 (5.1948)
4g	Cl	C_6H_5	C_6H_5	87 (85)	85 (60)	3.8520 (3.8514)
4h	Cl	CH_3	C_6H_5	245 (247)	85 (72)	4.6406 (4.6434)
4i	CH_3	CH_3	C_6H_5	207 (208)	90 (71)	4.9902 (4.9822)

*Literature value corresponding to compounds synthesized by conventional method and reported in references 22 and 23.



[A]



[B]

ACKNOWLEDGEMENTS

One of the authors, G.S. Kalwania is thankful to the University Grant Commission, New Delhi for the financial support. The authors are also grateful to colleagues of the Department of Chemistry for their invaluable suggestions and administration of S.K. Government College, Sikar, India for providing the research facilities.

REFERENCES

1. M. Gordon, In ed.: M. Gordon, Psychopharmacological Agents, Medicinal chemistry, Academic Press, New York, Vol. 2, pp. 119-132 (1967).
2. J.C. Barker and M. Miller, *Br. J. Psychiatry*, **115**, 169 (1969).
3. A.K. Batt, H.G. Karadia and P.R. Shah, *Indian J. Heterocycl. Chem*., **13**, 281 (2004).
4. C. Brown and R.N. Davidson, *Adv. Heterocycl. Chem*., **38**, 135 (1985).
5. A. Ota, Y. Kawashima, H. Ohishi and T. Ishida, *Chem. Pharm. Bull*., **41**, 1681 (1993).
6. S. Florio and J.L. Leng, *J. Heterocycl. Chem*., **19**, 237 (1982).
7. A. Kanda and H. Hashimoto, *J. Pharmacol. (Japan)*, **63**, 121 (1993).
8. V.K. Pandey, S.K. Saxena and S.K. Bajpai, *Indian J. Chem*., **43B**, 1015 (2004).
9. G.P. Sarmiento, G.Y. Moltrasio and A.G. Moglioni, *ARKIVOC*, 33 (2009).
10. W.H. Strain and J.B. Dickey, US Patent, 2381935; *Chem. Abstr*., **40**, 1889 (1946).
11. C.R. Rasmussen, US Patent, 37877400; *Chem. Abstr*., **80**, 95987 (1974).
12. R.R. Gupta, Phenothiazines and 1,4-Benzothiazines Chemical and Biomedical Aspects, Elsevier, Amsterdam (1988).
13. H. Keyzer, G.M. Eskert, I.S.Forrest, R.R. Gupta, F. Gutmman and J. Molnar, Thiazines and Structurally Related Compounds, Proceedings of Sixth International Conference of Phenothiazines and Structurally Related Psychotic Compounds, Pasadena, CA, Kriger Publishing Co., Malbar, FL, USA (1992).
14. S. Miyano, N. Abe and K. Sumoto, *J. Chem. Soc. Chem. Commun*., 760 (1975).
15. B.J. Evans, J.T. Doi and W.K. Musker, *J. Org. Chem*., **55**, 2337 (1990).
16. W.E. Fristad and J.R. Peterson, *Synth. Commun*., **15**, 1 (1985).
17. S. Uemura, S. Tanaka and M. Okana, *Bull. Chem. Soc. (Japan)*, **50**, 220 (1977).
18. A. McKillop and D. Koyuncu, *Tetrahedron Lett*., **31**, 5007 (1990).
19. W.A. Pryor, D.F. Church, C.K. Govindan and G. Crank, *J. Org. Chem*., **47**, 156 (1982).
20. T.J. Wallace, A. Schriesheim and W. Bartok, *J. Org. Chem*., **28**, 1311 (1963).
21. S. Rajaram, G.S. Reddy and D.S. Iyengar, *Ind. J. Chem*., **38B**, 639 (1999).
22. R.R. Gupta, K.G. Ojha and M. Kumar, *J. Heterocycl. Chem*., **17**, 1325 (1980).
23. R.R. Gupta, G.S. Kalwania and R. Kumar, *Bull. Chem. Soc. (Japan)*, **57**, 2343 (1984).
24. R.R. Gupta, K.G. Ojha, G.S. Kalwania and M. Kumar, *Heterocycles*, **14**, 1145 (1980).