Synthesis of some new tricyclic 1,4-benzothiazinones

M. B. Deshmukh*, S. S. Patil and A. R. Mulik

Department of Chemistry, Shivaji University, Kolhapur-416 004, India

E-mail : Mdeshmukh 1 @rediffmail.com

Manuscript received 31 January 2001, revised 17 August 2001, accepted 16 October 2001

2-Aminothiophenol on reaction with dimethyl oxalate and methyl 2-chloropropionate gives 1,4-benzothiazinone (1a, 1b) which when reacted with ethyl chloroacetate give *N*-ethoxycarbonylmethyl-1,4-benzothiazine-2,3-dione (2a₁). Compound 2 on reaction with hydrazine hydrate affords *N*-hydrazidomethyl-1,4-benzothiazine-2,3-dione (3). Compound 3 is cyclized in presence of ammonium acetate and acetic acid to give 5-methyl[1,2,4]triazino-6-oxo[3,4-*c*]-3(1*H*)-[1,4]benzothiazine (4b₁). Compound 1 on reaction with phosphorus oxychloride gives 3-chloro-1,4-benzothiazine-3-one (5a) which when reacts with ammonium sulfocyanide affords 1,4-benzothiazin-2-one-3-ylisocyanate (6a). Compound 6 when reacted with methyl cyanide gives the desired tricyclic compound 2-thio-6-methyl[1,3,5]triazolo[3,4-*c*]benzothiazine-2-one (7a).

Benzothiazine derivatives exhibit various biological activities¹. Here, we report the synthesis of some new tricyclic derivatives of benzothiazines. The strategy employed for the synthesis of desired heterocycles involved the *N*-alkylation of benzothiazinone (1) with alkyl halo-esters to form *N*-alkoxycarbonylalkylbenzothiazinones (2), which on reaction with hydrazine hydrate in methanol gave *N*-hydrazidoalkylbenzothiazin-3(*H*)-ones (3). Compounds 3 were further cyclized in presence of ammonium acetate in acetic acid to give 1,2,4-triazino[3,4-*c*][1,4]benzothiazin-3(1*H*)-ones (4). Compound 1 in refluxing POCl₃ gave 3-chloro-1,4-benzothiazines (5) which when reacted with ammonium sulfocyanide gave 1,4-benzothiazin-2-one-3-yl-isocyanate (6). Compound 6 when subjected to Diels-Alder reaction with alkyl cyanide gave the targetted 2-thio-6-alkyl [1,3,5]triazolo[3,4-*c*][1,4]benzothiazin-2-ones (7) (Scheme 1).

Results and Discussion

Benzothiazine-2,3-dione (1) was *N*-alkylated on reaction with ethylchloroacetate to form 2. The disappearance of NH signal in 1 and appearance of a triplet and a quartet at δ 1.1 and 4.15 respectively due to CH₃ and OCH₂ confirmed the formation of ester 2. Compound 2 on reaction with hydrazine hydrate gave compound 3, the formation of which was explained on the basis of the disappearance of ester C=O encountered at 1735 cm⁻¹ and appearance of amido C=O at 1680 cm⁻¹ in its IR spectrum. Compound 3 was cyclized in presence of ammonium acetate in acetic acid to get the tricyclic compound 4. The formation of 4 was explained on the basis of the presence of C=N band at 1610 cm⁻¹ in its IR spectrum. Further, compound 1 was converted into its 3-chloro derivative (5) by refluxing in POCl₃. The

Scheme 1

formation of 5 was ensured by the disappearance of bands due to N-H (3350) and C=O (1680 cm⁻¹) and appearance of C=O and C-Cl bands at 1620 (C=O) and 760 cm⁻¹ (C-Cl). Compound 5 on reaction with ammonium sulfocyanide yielded its isothiocyanate derivative 6, which was confirmed by the appearance of IR band at 2050 cm⁻¹ (-N=C=S). Compound 6 was reacted with substituted alkyl cyanides to form the targetted tricyclic triazolo derivative 7. The appearance of an additional signal at δ 2.188 in its

PMR spectrum and IR band at $1270\text{--}1190\text{ cm}^{-1}$ due to $\text{CH}_3\text{--C=N}$ and C=S .

N

Experimental

M.p.s. were determined in open capillary tubes and are uncorrected. IR spectra (KBr/nujol) were recorded on a Perkin-Elmer 783 spectrophotometer and PMR spectra ($\text{DMSO-}d_6/\text{CDCl}_3$) on a Bruker Ac 300F spectrometer (300 MHz) using TMS as an internal standard. Purity of the compounds was checked by TLC using silica gel G.

1,4-Benzothiazin-2,3-dione (1a) : A mixture of 2-aminothiophenol (2.915 g, 0.017 mol) and dimethyl oxalate (2.06 g, 0.017 mol) in methanol (20 ml) was refluxed for 5 h and then cooled. The separated solid was crystallized from DMF to get **1a** (1.0 g, 32%), m.p. 260° ; ν_{max} $3220\text{--}3140$ (NH), 1680 (C=O), 1600 cm^{-1} (C=C); δ 6.35–7.1 (4H, m, ArH), 10.45 (1H, s, CONH). **1b** was prepared by refluxing a mixture of 2-aminothiophenol (2 g, 0.016 mol) and methyl 2-chloropropionate (1.96 g, 0.016 mol) in 33% NaOH (17.5 ml) on a water-bath for 5 h. The reaction mixture was then cooled, neutralized with dil. HCl, and the resulting solid was washed with water and crystallized from 80% ethanol, (70%), m.p. 125° ; ν_{max} 3220 (NH), $1700\text{--}1650\text{ cm}^{-1}$ (cyclic C=O); δ 1.5 (3H, d, CH_3), 3.5–3.6 (1H, q, CH), 6.95–7.35 (4H, m, ArH), 9.2–9.3 (1H, s, NH).

N-Ethoxycarbonylmethyl-1,4-benzothiazine-2,3-dione (2a₁) : To a mixture of **1a** (0.734 g, 0.0045 mol) and ethyl chloroacetate (1.12 g, 0.009 mol) in acetone (15 ml), potassium carbonate (1 g) was added. The reaction mixture was refluxed on an oil-bath for 36 h, then cooled, filtered and the solvent removed under reduced pressure and the crude compound was column chromatographed using benzene as an eluent. The solvent was removed to get the solid (1.0 g, 89%), m.p. 98° ; ν_{max} $1740\text{--}1700$ (ester C=O), $1700\text{--}1670\text{ cm}^{-1}$ (cyclic C=O); δ 1.1 (3H, t, J 7 Hz, CH_3), 4.15 (2H, q, J 7 Hz, OCH_2), 5.2 (2H, s, N- CH_2), 7.15–7.5 (4H, m, ArH); **2a₂** oil (0.71 g, 40%); ν_{max} 1740 (ester CO), $1700\text{--}1670\text{ cm}^{-1}$ (cyclic amido CO); δ 1.1 (3H, t, J 7 Hz, CH_3), 1.5 (3H, d, J 7 Hz, CHCH_3), 3.2 (1H, q, J 7.5 Hz, CH), 4.18 (2H, q, J 7 Hz, OCH_2), 5.15 (2H, s, N- CH_2), 7.15–7.5 (4H, m, ArH); **2b₁** oil (1.0 g, 84%); ν_{max} $1740\text{--}1735$ (ester CO), 1680 cm^{-1} (cyclic amido CO); δ 1.5 (3H, d, J 7 Hz, CH-CH_3), 3.2 (1H, q, J 7 Hz, CH), 4.15 (2H, q, J 7.5 Hz, OCH_2), 5.15 (2H, s, N- CH_2), 7.1–7.5 (4H, m, ArH); **2b₂** oil (0.9 g, 84%); ν_{max} $1740\text{--}1730$ (ester CO), 1680 cm^{-1} (cyclic amido CO); δ 1.1 (3H, t, J 7 Hz, CH_3), 1.5 (3H, d, J 7 Hz, CH_3), 4.18 (2H, q, J 7.5 Hz, OCH_2), 5.1 (1H, q, J

7 Hz, NCH), 7.15–7.55 (4H, m, ArH).

N-Hydrazidomethyl-1,4-benzothiazin-2,3-dione (3a₁) : A mixture of **2a₁** (0.1 g, 0.00037 mol) and hydrazine hydrate (0.02 g, 0.00037 mol) in methanol (10 ml) was refluxed on a steam-bath for 3 h, then concentrated, cooled and filtered to obtain the product (0.08 g, 85%), m.p. 125° ; ν_{max} 3300 (NH), $1700\text{--}1630$ (cyclic and acyclic C=O), 1600 cm^{-1} (C=C); δ (DMSO- d_6) 4.6 (2H, s, NH_2), 5.1 (2H, s, N- CH_2), 7.15–7.5 (4H, m, ArH), 10.45 (1H, s, exchangeable with D_2O , CONH); **3b₁** (85%), m.p. 125° , ν_{max} $3350\text{--}3150$ (NHNH₂), 1685 (acyclic amido CO), $1670\text{--}1655\text{ cm}^{-1}$ (cyclic CO); δ 1.5 (3H, d, J 7 Hz, CH_3), 3.2 (1H, q, J 7 Hz, CH), 4.2 (2H, s br, NH_2 exchangeable with D_2O), 7.1–7.55 (4H, m, ArH), 11.5 (1H, s br, CONH, exchangeable with D_2O); **3b₂** (62%), m.p. 127° ; ν_{max} 3400 (NHNH₂), $1690\text{--}1670$ (cyclic and acyclic C=O), 1600 cm^{-1} (C=C); δ 1.12 (3H, t, J 7 Hz, CH_3), 1.5 (3H, d, J 7 Hz, CH_3), 3.3 (1H, q, J 7 Hz, CH), 4.18 (2H, s br, NH_2 exchangeable with D_2O), 5.1 (1H, q, J 7 Hz, N-CH), 7.15–7.5 (4H, m, ArH), 11.5 (1H, s br, CONH exchangeable with D_2O).

5-Methyl-[1,2,4]-triazino-6-oxo[3,4-c]-3(1H)-[1,4]-benzothiazine (4b₁) : A mixture of **3b₁** (0.06 g, 0.00024 mol) and ammonium acetate (0.11 g, 0.0014 mol) in acetic acid (5 ml) was refluxed in an oil-bath till yellow colour of reaction mixture changed to dark-brown. Then the reaction mixture was poured on crushed-ice and neutralized with ammonia. The separated solid was washed with water and crystallized from ethanol, (0.05 g, 87%), m.p. 145° , ν_{max} $3400\text{--}3200$ (NH), $1740\text{--}1630$ (cyclic and acyclic C=O), 1600 cm^{-1} (C=N); δ 1.1 (3H, d, J 7 Hz, CH_3), 3.2 (1H, q, J 7 Hz, CH), 5.18 (2H, s, N- CH_2), 7.15–7.55 (4H, m, ArH), 11.4 (1H, s br, CONH exchangeable with D_2O); **4a₁** (78%); ν_{max} $3180\text{--}3100$ (NH), $1690\text{--}1640$ (cyclic C=O), 1595 cm^{-1} (C=O); δ 5.1 (2H, s, N- CH_2), 7.0–7.55 (4H, m, ArH), 10.5 (1H, s, exchangeable with D_2O , CONH).

3-Chloro-1,4-benzothiazine-2-one (5a) : A mixture of **1a** (0.268 g, 0.0015 mol) and phosphorus oxychloride (0.0044 mol) was refluxed on an oil-bath at $130\text{--}140^\circ$ for 5 h, then cooled, concentrated and poured on crushed-ice. The separated solid was washed with water and crystallised from benzene, (0.2 g, 68%), m.p. 275° ; ν_{max} 1710 (lactone C=O and amido C=O), 1620 (C=N), 760 cm^{-1} (C-Cl); δ 7.1–7.5 (4H, m, ArH).

1,4-Benzothiazin-2-one-3-yl isocyanate (6a) : A mixture of **5a** (0.035 g, 0.003 mol) ammonium sulfocyanide (0.228 g, 0.003 mol) in acetone (5 ml) was stirred under reflux for 1.5 h, then cooled, filtered and concentrated under vacuum. The residue was washed with water and

crystallised from ethanol, (46%), m.p. 190°; $\nu_{\max}$ 1705 (C=O), 1620 (C=N), 1600 (C=C), 2050 cm^{-1} (N=C=S); δ 7.1–7.55 (4H, m, ArH).

2-Thio-6-methyl[1,3,5]triazolo[3,4-c][1,4]benzothiazin-2-one (7a) : To a solution of **6a** (0.06 g, 0.0003 mol) in ethanol (5 ml), methyl cyanide (0.02 g, 0.0005 mol) was added and the mixture refluxed on a steam-bath for 5 h, then cooled, the solvent removed under reduced pressure and the residual oily mass triturated with ice-water to get reddish-brown product (0.05 g, 64%), m.p. 139°; $\nu_{\max}$ 1730 (C=O), 1270–1190 (C=S), 1600 cm^{-1} (C=N); δ (DMSO- d_6) 2.18 (3H, s, =C-CH₃), 7.0–7.6 (4H, m, ArH).

Acknowledgement

The authors thank R.S.I.C., Punjab University, Chandigarh for PMR and IR analyses.

References

- 1 M. B. Hogale and A. C. Uthale, *Indian J. Chem., Sect. B*, 1990, **29**, 590; V. L. Cizej and U. Urleb, *J. Heterocycl. Chem.*, 1996, **33**, 97 and the references cited therein; M. B. Deshmukh (Hogale), J. S. Jadhav and S. H. Patil, *J. Indian Chem. Soc.*, 1997, **74**, 52; S. H. Mashraqui, M. M. Biswas and K. R. Nivalkar, *Indian J. Chem., Sect. B*, 1996, **35**, 1031; A. Napolitano, S. Memoli and G. Prota, *J. Org. Chem.*, 1999, **64**, 3009; V. K. Ahluwalia, R. Aggarwal and R. Kumar, *Indian J. Chem., Sect. B*, 1994, **33**, 65; B. R. Chaudhari, D. B. Shinde and M. S. Shingare, *Indian J. Heterocycl. Chem.*, 1995, **4**, 187.