Synthesis of alkoxyphthalimide derivatives of 5-arylidene-2-(6'-chlorobenzothiazol-2'-yl-imino)-4-thiazolidinones

N. Dixit and G. L. Talesara*

Synthetic Organic Chemistry Research Laboratory, Department of Chemistry, M. L. Sukhadia University, Udaipur-313 001, India

E-mail: gtalesara@yahoo.com; nehadixit13@yahoo.co.in

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Thiazolidinones are important compounds due to their broad range of biological activities1. We have reported here some compounds with amino-oxo moiety containing thiazolylthiazolidinones.

Results and discussion

2-Amino-6-chlorobenzothiazole on reacting with benzoyl thiocyanate and hydrolysing the product with sodium hydroxide gave the corresponding thiocarbamide 2 in 68% yield. Cyclisation of 2 with chloroacetic acid in the presence of anhydrous sodium acetate in absolute alcohol furnished the corresponding thiazolidinone 3. IR, mass and NMR studies confirmed the formation of 3. The intense band at 1656 cm⁻¹ for this showed C=N stretching for the phenylimino group attached to the thiazolidinone nucleus while the ring C=O group appeared at 1710 cm⁻¹. Compound 3 on condensation with para-substituted benzaldehydes in acetic acid in presence of sodium acetate gave 4a-c. Formation of products was confirmed by disappearance of the IR band at 2939 cm⁻¹ and NMR signal at δ 4.4 (singlet) for the CH₃ group of the thiazolidinone nucleus in 3 and appearance of new IR band at 1642 cm⁻¹ and NMR signal at δ 6.4 (singlet) of C=CHAr in 4a. α-Bromoalkoxyphthalimides 5a-c were prepared by reported methods. Condensation of 4a-c with α-bromoalkoxyphthalimides 5a-c in absolute alcohol gave their alkoxyphthalimide derivatives 6a-c in good yields. IR, mass and NMR spectra confirmed the condensation of 5a-c with 4a-c at the N atom. Free stretching vibration band for -NH group at 3300–3100 cm⁻¹ which was present in its precursors 4a-c due to NHCO group, had disappeared and a strong band at 1300–1160 cm⁻¹ appeared for the C–N stretching of the CH₃NCO group confirmed the formation of a new C–N bond. Furthermore, C=O stretching of the thiazolidinone ring was still present which confirmed the formation of the final compounds.

Antimicrobial activity:

The titled compounds were screened for their antibacterial and antifungal activities using cup or well method². Antibacterial activity of compounds have been evaluated against four bacterial strains viz. B. subtilis, E. coli, K. pneumoniae and P. aeruginosa. Sterilized nutrient agar medium was poured in Petri dishes and after solidification, these Petri dishes were inoculated with 0.2 ml suspension of organism employing spread plate method³. Two wells were made in each Petri plate and filled with two different concentrations viz. 500 ppm and 1000 ppm. The zones of inhibition were recorded after 24 h of incubation. Almost all compounds showed low to moderate activity against K. pneumoniae and P. aeruginosa and majority of the compounds were inactive against E. coli and B. subtilis as compared to the standard drug (Ciprofloxacin) used.

Screening of the titled compounds for antifungal activity was carried out against two fungal strains viz. A. fumigatus and C. albicans using Fluconazole as a standard drug which showed that compounds 6a, 6g were highly ac-
tive against A. fumigatus and other were good active while compounds 6d, 6e and 6f were not exhibited activity against A. fumigatus but they were found to be moderately active against C. albicans. So these thiazolidinones are found to exhibit good antifungal activity rather then antibacterial activity. Although in the present findings, the antibacterial and antifungal activity could not be directly related to the structure yet some conclusions have been drawn.

### Experimental

Melting points were determined in open capillaries. IR spectra (KBr disc) were recorded on Perkin-Elmer 1800 and Shimadzu 8201 PC (4000–350 cm⁻¹) FTIR spectrophotometer. NMR spectra (CDCl₃) were recorded on Perkin-Elmer R-32 (90 MHz) NMR spectrometer using TMS as internal standard. Mass spectra were determined on Joel D-300 (EI) and Joel SX-102 (FAB) spectrometers. Purity of compounds was checked by TLC using silica gel-G plates and benzene-methanol or toluene-methanol as developing solvent and the spots were exposed in iodine chamber. Compounds 1 and 5a-e were prepared according to literature procedures.

### 2-(6'-Chlorobenzothiazol-2'-yl-imino)-4-thiazolidinone (3):

A mixture of N’-(6-chlorobenzothiazol-2-yl)thiourea (3.15 g), monochloroacetic acid (2 g) and anhydrous sodium acetate (1 g) refluxed in ethanol (20 ml) for 6–7 h. Excess of solvent was distilled off under reduce pressure and the residue was treated with water. The solid obtained was filtered, washed several times with hot water, dried and crystallized from alcohol. Yield 70%, m.p. 240°C.

### 5-Benzylidene-2-(chlorobenzothiazol-2'-yl-imino)-4-thiazolidinone (4):

A mixture of benzaldehyde (0.1 M), thiazolidinone 3 (0.1 M) and anhydrous sodium acetate (0.2 M) was refluxed slowly in acetic acid for 4 h. After cooling, the solution was poured into ice-cold water and kept overnight. The resulting precipitate was filtered, washed with hot water, dried and crystallized from alcohol. Yield 62%, m.p. 240°C.

### Note

| Compd. | 6a | 6b | 6c | 6d | 6e | 6f | 6g | 6h | 6i | Standard |
|--------|----|----|----|----|----|----|----|----|----|----------|
| B. subtilis | - | - | + | + | + | + | ++ | + | + | +++ |
| K. pneumoniae | + | + | + | + | + | + | + | + | + | +++ |
| P. aeruginosa | - | - | + | + | + | + | + | + | + | +++ |
| E. coli | ++ | ++ | + | + | + | + | + | + | + | +++ |
| A. fumigatus | - | - | - | - | + | + | + | + | + | +++ |
| C. albicans | - | - | - | - | + | + | + | + | + | +++ |

Table 1. Antibacterial and antifungal activities of compounds 6a to i.

Standard used : Antibacterial activity - Ciprofloxacin; Antifungal activity – Fluconazole.

| Zone of inhibition in mm | Activity |
|-------------------------|----------|
| 3> (no activity) | |
| 3-5 = (mild activity) | |
| 5-10 = ++ (moderate activity) | |
| 10-15 = +++ (strong activity) | |

A solution of ammonium thiocyanate (9 g) in acetone (50 ml) was taken inside a three necked flask provided with a reflux condenser, a dropping funnel and a mechanical stirrer. Benzoyl chloride (13 ml) was added dropwise with stirring. A solution of 2-amino-6-chlorobenzothiazole (0.1 M) in acetone (50 ml) was added dropwise so that the solution was refluxed at its own temperature. The whole reaction mixture was poured into cold water (1 L) and the resulting precipitate was filtered off and hydrolysed by boiling with solution of NaOH (30 g) in water (300 ml). It was filtered and the filtrate was acidified with conc. HCl and made basic with ammonium hydroxide. The solid obtained was filtered, dried and crystallized from alcohol. Yield 65%, m.p. 220°C.

A mixture of N’-(6-chlorobenzothiazol-2-yl)thiourea (3.15 g), monochloroacetic acid (2 g) and anhydrous sodium acetate (1 g) refluxed in ethanol (20 ml) for 6–7 h. Excess of solvent was distilled off under reduce pressure and the residue was treated with water. The solid obtained was filtered, washed several times with hot water, dried and crystallized from alcohol. Yield 70%, m.p. 240°C.

### 3-(N-Ethoxyphthalimido)-5-benzylidene-2-(6'-chlorobenzothiazol-2'-yl-imino)-4-thiazolidinone (6a):

A mixture of compound 4 (0.01 M), ω-bromoethoxyphthalimide (0.01 M), absolute alcohol (20 ml) and pyridine
Similarly other compounds were prepared.

6b (62%), m.p. 268°C (Found : N, 9.69). C_{27}H_{37}N_{4}O_{5}S_{2}Cl requires : N, 9.71%; \( \nu_{\text{max}} \) 3020, 1648, 1689, 1695, 2895, 1380, 740, 685 cm\(^{-1}\); \( \delta \) 7.7 (4H, m, ArH), 7.1-6.9 (7H, m, ArH), 5.4 (1H; br, s, OH), 6.2 (1H, s, C=CHAr), 3.1 (2H, t, OCH\(_{2}\)), 2.8 (2H, t, NCH\(_{2}\)); \( \nu_{\text{z}} \) 578 (M\(^{++}\) + 2), 576 (M\(^{++}\)), 386, 190, 142, 50; 6e (58%), m.p. 278°C (Found : N, 9.48%); \( \nu_{\text{max}} \) 3010, 1650, 1685, 1670, 2898, 1385, 750, 685 cm\(^{-1}\); \( \delta \) 7.6 (4H, m, ArH), 7.2-6.9 (7H, m, ArH), 5.4 (1H, br, s, OH), 6.2 (1H, s, C=CHAr), 3.2 (2H, t, OCH\(_{2}\)).

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(0.02 M) was refluxed for 13 h. Excess of solvent was removed under reduced pressure. After cooling, the product separated was collected by filtration and recrystallized from absolute alcohol. Yield 60%, m.p. 260°C (Found : N, 9.96, C_{27}H_{37}N_{4}O_{5}S_{2}Cl requires : N, 9.99%); \( \nu_{\text{max}} \) 3028, 1650, 1710, 1680, 2890, 1385, 745, 685 cm\(^{-1}\); \( \delta \) 7.6 (4H, m, ArH), 7.2-6.9 (8H, m, ArH), 6.3 (1H, s, C=CHAr), 3.1 (2H, t, OCH\(_{2}\)), 2.8 (2H, t, NCH\(_{2}\)); \( \nu_{\text{z}} \) 562 (M\(^{++}\) + 2), 560 (M\(^{++}\)), 370, 190, 132, 77, 76, 50.