



## SYNTHESIS OF 6-ARYL-4-(4-CHLOROPHENYL)- IMINOTHIAZOLIDINO [3, 4-*c*] ISOXAZOLES AND THEIR ALKOXYPHthalIMIDE DERIVATIVES

NEHA DIXIT, V. K. SALVI and G. L. TALESARA\*

Synthetic Organic Chemistry Laboratory,  
Department of Chemistry, M.L. Sukhadia University, UDAIPUR – 313001 (Raj.), INDIA  
E.mail: gtalesara@yahoo.com

### ABSTRACT

4-Chlorophenylthiourea (1) reacted with chloroacetic acid in the presence of anhydrous sodium acetate to give 2-*p*-chlorophenyliminothiazolidin-4-one (2). The reactive methylene group present on the thiazolidinone ring at position-5 was condensed with various substituted benzaldehydes to give its arylidene derivatives (3a–c). These on reaction with hydroxylamine hydrochloride in acetic acid gave fused isoxazole compounds (4a–c). These are treated with  $\omega$ -bromoalkoxyphthalimides to give final compounds (5a–i). The structures of final compounds were characterized by  $^1\text{H}$  NMR, IR, mass spectra and elemental analysis.

**Keywords:** Chloroacetic acid, Condensation, Thiazolidinones, Isoxazole Alkoxyphthalimide.

### INTRODUCTION

The exploitation of a simple molecule with different functionalities for the synthesis of heterocycles is a worthwhile contribution in the chemistry of heterocycles. Isoxazoles are associated with a wide spectrum of biological activities<sup>1,2</sup>, such as antitubercular and antimicrobial<sup>3</sup> etc. Various thiazolidinones inhibit the bacterial enzyme in the biosynthesis of polymers<sup>4</sup> and exhibit a broad range of biological activities like anaesthetic<sup>5</sup>, fungicidal<sup>6</sup>, antituberculostatic<sup>7</sup>, hypnotic<sup>8</sup> etc. Several amino-oxy<sup>9</sup> compounds are well known for their interesting pharmacological activities<sup>10</sup>. In view of these facts, it was planned to synthesize bi-heterocyclic molecules containing amino-oxy moiety to get compounds with higher biological significance.

### EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra (KBr disc) were recorded on Perkin–Elmer 1800 FTIR spectrophotometer.  $^1\text{H}$  NMR spectra ( $\text{CDCl}_3$ ) were recorded on Perkin–Elmer R-32 (90 MHz)  $^1\text{H}$  NMR spectrometer using TMS as internal standard. Mass spectra were determined on Joel D-300 (EI) spectrometer. Purity of the

compounds was checked by TLC using silica gel-G plates and benzene-methanol and benzene-ethyl acetate as developing solvent and spots were exposed in an iodine chamber.

#### Synthesis of 4-chlorophenylthiourea (1)

4-Chloroaniline (0.1 mol) was dissolved in minimum amount of 1N hydrochloric acid and ammonium thiocyanate (0.2 mol) was added. The reaction mixture was refluxed for 6–7 hours. After cooling, the product was separated out as crystals. The crystals were filtered, washed with water and recrystallized with absolute ethanol. Yield (67%), m.p. 180°C.

#### Synthesis of 2-chlorophenyliminothiazolidin-4-ones (2)<sup>12</sup>

4-Chlorophenyl thiourea (1, 0.01 mol) and chloroacetic acid (0.01 mol) were dissolved in absolute alcohol and then anhydrous sodium acetate (0.02 mol) was added to it. The reaction mixture was heated to reflux for 8 hours. Excess amount of solvent was distilled off under reduced pressure and the reaction mixture was then poured into crushed ice. The solid thus obtained was filtered, washed with cold water, dried and recrystallized from absolute alcohol. Yield (62%), m.p. 208°C.

#### Synthesis of 5-benzylidene-2-p-chlorophenyliminothiazolidin-4-ones (3a)<sup>12</sup>

A mixture of benzaldehyde (0.02 mol), 2-p-chlorophenylimino-thiazolidin-4-one (2, 0.02 mol) and anhydrous sodium acetate (0.04 mol) was refluxed slowly in glacial acetic acid for 4–5 hours. After cooling, the solution was poured into ice-cold water and kept overnight. The resulting precipitate was filtered, washed with hot water, dried and recrystallized from alcohol. Similarly (3b) and (3c) compounds were also prepared.

(3a) (68%); m.p. 220°C; (3b) (60%); m.p. 264°C; (3c) (55%); m.p. 270°C.

#### Synthesis of 6-phenyl-4-(4-chlorophenyl)-iminothiazolidino [3, 4-c] isoxazole (4a)

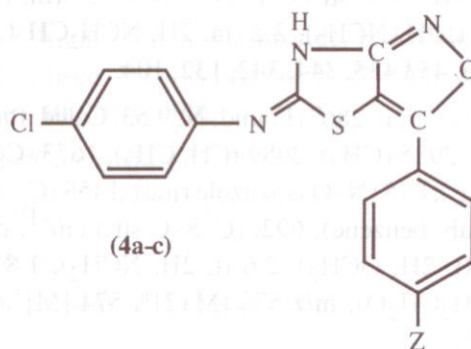
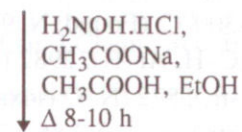
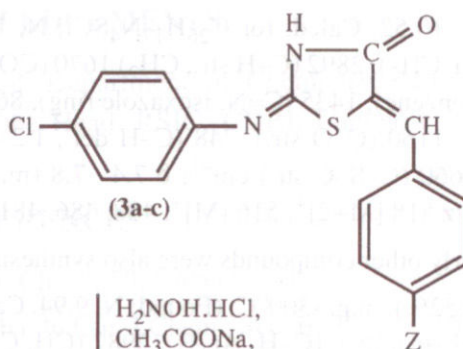
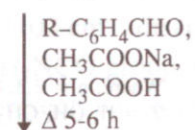
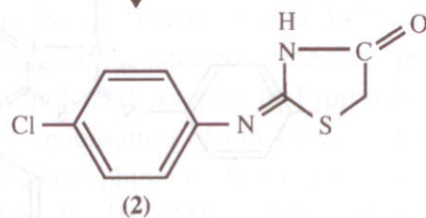
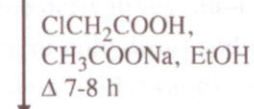
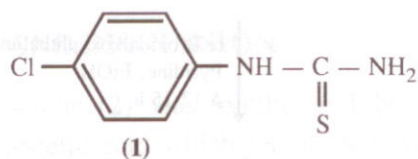
A mixture of 5-benzylidene-2-chlorophenyliminothiazolidin-4-one (3a, 0.01 mol) in ethanol and anhydrous sodium acetate (0.01 mol) dissolved in minimum amount of acetic acid, was added to a solution of hydroxylamine hydrochloride. The reaction mixture was refluxed for 8–10 hours. The product was isolated and recrystallized from ethanol.

(4a) (60%); m.p. 250°C.

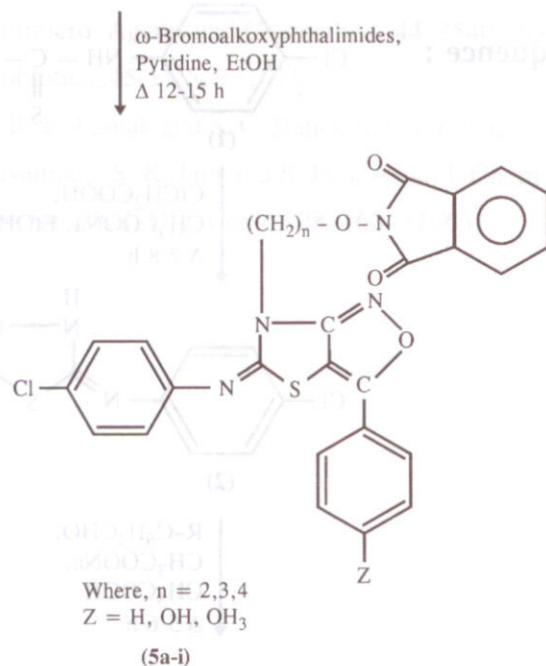
Similarly other compounds were prepared with minor modification in reaction conditions. (4b) (65%); m.p. 269°C; (4c) (63%); m.p. 258°C.

#### Synthesis of 3-N-ethoxyphthalimido-6-phenyl-4-(4-chlorophenyl)-iminothiazolidino [3, 4-c] isoxazole (5a)

A mixture of compound (4a, 0.01 mol), ω-bromoalkoxy-phthalimide (0.01 mol), absolute alcohol (20 mL.) and pyridine (0.02 mol) was refluxed for 12 hours. Solution was filtered and the excess of solvent was removed under reduced pressure. On cooling, the precipitate separated was collected by filtration and then recrystallized by ethanol. (5a) (61%); m.p. 260°C

**Reaction sequence :**





(Found: N, 10.52. Calcd. for  $\text{C}_{26}\text{H}_{17}\text{N}_4\text{SCl}$ ; N, 10.85%);  $\nu_{\text{max}}$  3098 (C-H str., ArH), 2942 (C-H asym.  $\text{CH}_2$ ), 2892 (C-H str.,  $\text{CH}_2$ ), 1670 (CO-N-CO str.), 1640 (C=N), 826 (C-H def., 1, 4-disub. benzene), 1435 (C=N, isoxazole ring), 860 (N-O, isoxazole ring), 768 (Ar-Cl), 1384 (N-O str.), 1160 (C-O str.), 748 (C-H def., 1,2-disub. benzene), 702 (C-H def., monosub. benzene), 660 (C-S-C str.)  $\text{cm}^{-1}$ ;  $\delta$  7.4–7.8 (m, 13H, ArH), 3.2 (t, 2H,  $\text{OCH}_2$ ), 2.8 (t, 2H,  $\text{NCH}_2$ );  $m/z$  518  $[\text{M}+2]^+$ , 516  $[\text{M}]^+$ , 488, 486, 481, 441, 439, 405, 326, 190, 132, 127, 125.

Similarly other compounds were also synthesized by changing reagents and reflux time.

**(5e)** : (52%), m.p. >300°C; (Found: N, 9.94. Calcd. for  $\text{C}_{27}\text{H}_{19}\text{N}_4\text{O}_5\text{SCl}$ ; N, 10.25%);  $\nu_{\text{max}}$  3456 (O-H str.), 3036 (C-H, Ar-H), 2982 (CH,  $\text{CH}_2$ ), 1672 (CO-N-CO), 1636, (C=N), 1349 (N-O str.), 1181 (C-O str.), 872 (N-O isoxazole ring), 760 (Ar-Cl), 735 (C-H def., 1,2-disub. benzene), 683 (C-S-C str.)  $\text{cm}^{-1}$ ;  $\delta$  7.85–7.35 (m, 12H, ArH), 6.0 (br, s, 1H, OH), 2.9 (t, 2H,  $\text{OCH}_2$ ); 2.5 (t, 2H,  $\text{NCH}_2$ ), 2.2 (m, 2H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{O}$ );  $m/z$  548  $[\text{M}+2]^+$ , 546  $[\text{M}]^+$ , 518, 516, 511, 455, 453, 435, 344, 342, 132, 104.

**(5i)** : (56%), m.p. 286° (Found: N, 9.53. Calcd. for  $\text{C}_{29}\text{H}_{23}\text{N}_4\text{SO}_5\text{Cl}$ ; N, 9.75%);  $\nu_{\text{max}}$  3038 (C-H Ar-H), 2985 ( $\text{CH}_3$ ), 2989 (CH,  $\text{CH}_2$ ), 1673 (CO-N-CO), 1376 (N-O str.), 1645 (C=N), 1178 (C-O str.), 875 (N-O isoxazole ring), 1458 (C=N isoxazole ring), 760 (Ar-Cl), 816 (C-H def. 1,4-disub. benzene), 692, (C-S-C str.)  $\text{cm}^{-1}$ ;  $\delta$  7.34–7.82 (m, 12H, ArH), 3.6 (s, 3H,  $\text{OCH}_3$ ), 2.8 (t, 2H,  $\text{OCH}_2$ ); 2.6 (t, 2H,  $\text{NCH}_2$ ), 1.8 (m, 2H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{O}$ ); 1.6 (m, 2H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$ );  $m/z$  576  $[\text{M}+2]^+$ , 574  $[\text{M}]^+$ , 546, 544, 539, 469, 467, 463, 356, 218, 132, 127, 125.

## RESULTS AND DISCUSSION

2-p-Chlorophenyliminothiazolidin-4-one (**2**) was synthesized by the reaction of 4-chlorophenyl thiourea (**1**) with chloroacetic acid which on condensation with various substituted aldehydes gave corresponding arylidene derivatives (**3a-c**). Reaction of (**3a-c**) with hydroxylamine hydrochloride in the presence of anhydrous sodium acetate furnished cyclisation reaction to form isoxazole ring in the compounds (**4a-c**). IR, mass and  $^1\text{H}$  NMR studies confirmed their formation. The intense bands around  $1455\text{ cm}^{-1}$  for  $\text{C}=\text{N}$  stretching and  $880\text{ cm}^{-1}$  for  $\text{N}-\text{O}$  stretching for the isoxazole ring were present and  $\text{C}=\text{O}$  stretching around  $1700\text{ cm}^{-1}$  was absent in their IR spectra.  $\omega$ -Bromoalkoxyphthalimides were prepared by reported methods<sup>13</sup>. Condensation of (**4a-c**) with  $\omega$ -bromoalkoxyphthalimides in absolute ethanol gave their alkoxyphthalimide derivatives (**5a-i**) in moderate to good yields and this was confirmed by IR,  $^1\text{H}$  NMR and mass spectral studies. Free stretching vibration for  $\text{NH}$  group around  $3300\text{--}3100\text{ cm}^{-1}$  disappeared and a strong band at  $1200\text{--}1300\text{ cm}^{-1}$  for  $\text{C}-\text{N}$  stretching of the  $\text{CH}_2\text{NCO}$  group appeared. Vibration bands for  $\text{N}-\text{O}$  and  $\text{C}=\text{N}$  of isoxazole ring were still present, which confirmed the formation of final compounds.

## ACKNOWLEDGEMENTS

The authors are thankful to the Head, Department of Chemistry, M.L. Sukhadia University, Udaipur for facilities and to the Head, RSIC, CDRI, Lucknow for spectral studies and elemental analysis.

## REFERENCES

1. M. Scobie and M. D. Theadosil, J. Org. Chem., **59**, 7008 (1994).
2. K. V. Reddy, S. G. Rao and A. V. Subba, Indian, J.Chem., Sec. B, **37**, 677 (1998).
3. K. H. Popat, K. S. Nimavat, U. V. Kachhadia and H. S. Joshi, J. Indian Chem. Soc., **80**, 707 (2003).
4. C. J. Andres, J. J. Bronson, S. V. D' Andrea, M. S. Deshpande, P. J. Falk, K. A. Grant Young, W. E. Harte, H. T. Ho, P. E. Misco, J. G. Robertson, D. S. Yaxiiongsum and A. W. Walsh, Bioorg. Med. Chem. Lett., **10**, 715 (2000).
5. S. L. Dalal and J. J. Trivedi, J. Indian Chem. Soc., **37**, 408 (1960).
6. P. N. Bhargava and L. C. Tiwari, Curr. Sci., **41**, 717 (1973).
7. Larnnartz, Z. Natureforsch, **2**, 7 (1947).
8. W. J. Doran and H. A. Shonle, J. Org. Chem., **8**, 193 (1938).

9. J. B. Bradely, Antimicro. Agents and Chemother., **44**, 2540 (2000).
10. P. Mamalis, Xenobiotica, **45**(1), 569 (1975).
11. S. K. Srivastava, R. B. Pathak and S. C. Bahel, Indian J. Chem., **30B**, 620 (1991).
12. P. Mishra, K. P. Namdeo, S. K. Jain and S. Jain, Asian J. Chem., **11**(1), 55 (1999).
13. L. Bauer and K. S. Suresh, J. Org. Chem., **28**, 1604 (1963).

Accepted : 2.1.05