Selva Kumar N. *et al.* / *International Journal of Pharmacy & Therapeutics*, 3(3), 2012, 255-258.

e- ISSN 0976-0342
Print ISSN 2229-7456

International Journal of Pharmacy & Therapeutics

Journal homepage: www.ijptjournal.com

IJPT

IMPROVED SYNTHESIS OF SOME IMIDAZOLINE AND OXAZOLINE DERIVATIVES USING LEAD II ACETATE; A NEW APPROACH

Selvakumar N[1*], Kottaimuthu A[2], Nepolean R[1], Chandramohan K[1], Nithya G[1], Jeyavalli A[1]

[1]Thanthai Roever College of Pharmacy, Perambalur, Tamilnadu – 621212, India.
[2]Department of Pharmacy, Annamalai University, Chidambaram, Tamilnadu – 608002, India.

ABSTRACT

A Series of imidazoline and oxazoline derivatives were prepared by using lead II acetate, which act as a cyclising agent is being reported. The synthesized compounds are primarily characterized by running TLC and melting point analysis. The structures of the synthesized compounds were confirmed by IR, ^{1}HNMR and MASS spectroscopy. The purity of the compound was confirmed by HPLC.

Key words: Imidazoline, Oxazoline, Lead II acetate.

INTRODUCTION

Imidazoline and oxazoline are heterocyclic nucleus, plays an important role in various medicines (MacInnes N *et al*., 2004; Gilchrist TL *et al*., 1985). Literature review reveals that Imidazoline and oxazoline derivatives have very broad Pharmacological activities such as Antihypertensive (Laubie M *et al*., 1985), (e.g. Clonidine), Anti-adrenegic (e.g.Oxymetazoline, Xylometazoline), Anticonvulsant, antibacterial activity (shanmugasundaram *et al*., 2009), Anti inflammatory (e.g. Deflazacort), (markham *et al*., 1995) Lead (II) acetate used to Conversion of Isocyanides into isothiocyanates, (Tanaka S *et al*., 1977). Elimination of H_2S (Bagudo *et al*., 2011), Preparation of cyclic Disulfides (Cragg R H *et al*., 1973). In this present work we have reported the cyclising reaction to develop the synthesis of imidazoline from corresponding substituted phenyl isothiocyanate and ethylenediamine using lead II acetate to produce imidazoline derivatives 4 (a-d). Oxazoline derivatives were obtained from various substituted phenyl isothiocyanate and ethanolamine using lead II acetate, as a cyclising agent 8 (a-d). The Structure of the entire synthesized compound has been characterized on the basis of IR, ^{1}H NMR, Mass, and the purity of the compound was confirmed by HPLC.

Corresponding Author

Selvakumar N
Email: sudhagarpharma@gmail.com

MATERIALS AND METHODS

The melting points of the compounds were checked by capillary method using Buchi melting point B-540 apparatus and are uncorrected. IR spectrum of the compounds was recorded using Perkin-Elmer FTIR spectrometer, from (4000cm-1) by KBR discs. ^{1}H NMR and spectra were recorded using Bruker NMR spectrometer, at 400 MHz in DMSO-d6. The chemical shifts were recorded in units (ppm) relative to

tetramethylsilane (Tms). Mass spectrum of the compounds was obtained using perkin- Elmer Mass –API –ES with both positive and negative mode of scanning. The purity of the compounds was determined by HPLC using the Waters –alliance 2695 instrument. The progress of the reaction was checked by thin layer chromatography (TLC), in a solvent-vapor saturated chamber on aluminum sheets with silica gel Merck, followed by visualization using short wavelength UV light (254 nm) to detect the compounds.

The starting materials 2,6-dichloro phenylisothiocyanate, 3,4-dichlorophenyl isothiocyanate, 4-chlorophenylisothiocyanate, phenylisothiocyanate used for synthesis were purchased from Lancaster Chemicals. Ethylenediamine, toluene, silica gel 60-120 mesh (column) were purchased from merck laboratories. Lead (II) acetate, Na-metal was supplied from s.d.fine chemicals. Ethanolamine was supplied from Rankem. Ethanol was supplied from Hayman and Jiagsu Hauxi. All the solvent used for purification was commercial grades.

METHODS

Synthesis of imidazoline derivatives (4a – 4d)

Preparation of 1-(2-amino ethyl)-3(2,6dichloro-phenyl) thiourea (3a)

2, 6-Dichlorophenylisothiocyanate (1a) (1g, 0.0049 mole) was added to a solution of ethylenediamine (2) (0.98ml, 0.0147 mole) in toluene (50ml) at 0-5°C and the reaction mixture was stirred for one hour. The solid that formed was filtered, washed with hexane, dried under vacuum to afford title compound. (3a). The following intermediates were prepared according to procedure described above 1-(2-aminoethyl)-3-phenylthiourea (3b); 1-(2-aminoethyl)-3-(3, 4-dichlorophenyl)thiourea (3c); 1-(2-aminoethyl)-3-(4-chlorophenyl)thiourea (3d).

Preparation of N- (2, 6 dichlorophenyl) 4, 5 dihydro-1H- imidazol-2-amine (4a)

To a solution of 2,6-dichlorophenylthiourea **(3a)** (0.6g, 0.0022mole) in ethanol (50ml), aqueous solution of Lead (II) acetate (2.51g, 0.0068mole), was slowly added at room temperature and the reaction mixture was refluxed at 80 to 90°C for 9 hrs. The white turbidity was formed initially, turns to brown and finally to black precipitate. After completion of reaction as confirmed by TLC, the reaction mixture was filtered over a celite bed. The filtrate was concentrated under vacuum to afford the crude product which was purified by column chromatography using alumina as adsorbent and eluted with 100% dichloromethane. (4a).

Synthesis of Oxazoline Derivatives *(8a-8d)*

Preparation of 1-(2,6 dichlorophenyl)-3-(2-hydroxyethyl)thiourea (7a)

To a solution of ethanolamine (6) (0.36ml, 0.006moles), in toluene (30ml) was added, 2, 6-dichlorophenylisothiocyanate (5) (1g, 0.0074 mole) at 0-5^{o}C and was stirred for 45 minutes at same temperature. The solid thus formed was filtered, washed with hexane and dried under vacuum to afford the title compound. The product obtained was used as such in next step. (7a) The following intermediates were prepared according to procedure described above 1-(2-hydroxyethyl)-3-phenylthiourea (7b); 1-(3, 4-dichlorophenyl)-3-(2-hydroxyethyl)thiourea (7c); 1-(4-chlorophenyl)-3-(2-hydroxyethyl)thiourea (7d).

Preparation of N-(2,6-dichlorophenyl)- 4,5- dihydro-1,3 oxazol-2-amine (8a)

To a solution of 1-(2,6-dichlorophenyl)-3-(2-hydroxyethyl)thiourea (7a) (0.380g, 0.0014moles) in ethanol (30ml) was added freshly prepared solution of sodium ethoxide (sodium (0.68g, 0.0028 moles) in ethanol 10ml) at 80 – 90^{o}C and the reaction mixture was stirred at same temperature for 10 minutes. An aqueous solution of Lead (II) acetate (0.53g, 0.0014 moles) was added to above reaction mixture over 1 minute. The reaction mixture was refluxed for another 5 minutes and filtered. The filtrate is evaporated to dryness and the residue is partitioned between 1N HCl and dichloromethane .The aqueous phase is separated and made alkaline with concentrated aqueous ammonia. The resultant precipitate was filtered and dried under vacuum to give desired product (8a).

Table 1. The physic-chemical data of synthesized compound

SI. No	Comp. Code	Melting point (^{0}c)	% yield	Mol. Formula	Mol. Weight
1	4a	124-126	30	$C_9H_9C_{l2}N_3$	230
2	4b	201-206	49	$C_9H_{11}N_3$	162
3	4c	145-147	43	$C_9H_9C_{l2}N_3$	231
4	4d	149-151	24	$C_9H_{10}ClN_3$	196
5	8a	160-169	27	$C_9H_8C_{l2}N_2O$	231
6	8b	98-102	33	$C_9H_{10}N_2O$	163
7	8c	130-133	41	$C_9H_8C_{l2}N_20$	231
8	8d	149-151	44	$C_9H_9ClN_2O$	197

Table 2. Spectral data of the synthesized compounds

4a: IR (KBr cm^{-1}): 3438(-NH stretching); 2955(CH stretching); 1666 (C=N). **^{1}H NMR (DMSO**:, 400 MHz) δ 3.30(s, 4H); 6.09(s, 1H); 6.84(t, 2H); 7.28(d, 2H). **Mass:** m/z 234.1(M+4).

4b: IR: 3257 cm$^{-1,}$ -NH stretching; 2981 cm$^{-1,}$ CH stretching; 1652 cm$^{-1,}$ C=N stretching. **^{1}H NMR** : 3.76(s, 4H); 7.31(d, 2H); 7.39(t, 1H); 7.49(t, 2H). **Mass:** M+ peak at m/z 162.2.

4c: IR: 3438 cm$^{-1,}$ -NH stretching; 2955 cm$^{-1,}$ CH stretching; 1666 cm$^{-1,}$ C=N stretching. **^{1}H NMR:** 3.30(s, 4H); 6.09[s.1H); 6.84(t, 2H); 7.28 (d.2H). M+ peak at m/z 231.

4d: IR: 3412 cm^{-1} , -NH stretching ; 2924 cm^{-1} , CH stretching ; 1653 cm^{-1} ,C=N stretching. **^{1}H NMR:** .65(s, 4H); 7.27[d.2H); 7.50(d, 2H); 8.38(s, 1H); 10.58(s, 1H).**Mass:** M+ peak at m/z 196.1.

8a: IR: 3448 cm$^{-1,}$ -NH stretching; 3073 cm$^{-1,}$ CH stretching; 1697 cm^{-1}, C=N stretching 1234 cm^{-1} C-O stretching. **^{1}H NMR:** 3.50(t, 2H); 4.34[t.2H); 6.90(t, 1H); 7.31(d, 2H); 7.54(s, 1H). **Mass:** M+ peak at m/z 231.

8b: IR: 3353 cm$^{-1,}$ (-NH stretching;), 2873 cm$^{-1,}$ (CH stretching;), 1235 cm$^{-1,}$ (C-Ostretching **^{1}H NMR:** 3.73(t, 2H); 4.21[t.2H); 6.87(t, 1H); 7.21(t, 2H) 7.35(m, 1H); 7.49(s, 1H) **Mass:** M+ peak at m/z 163.1.

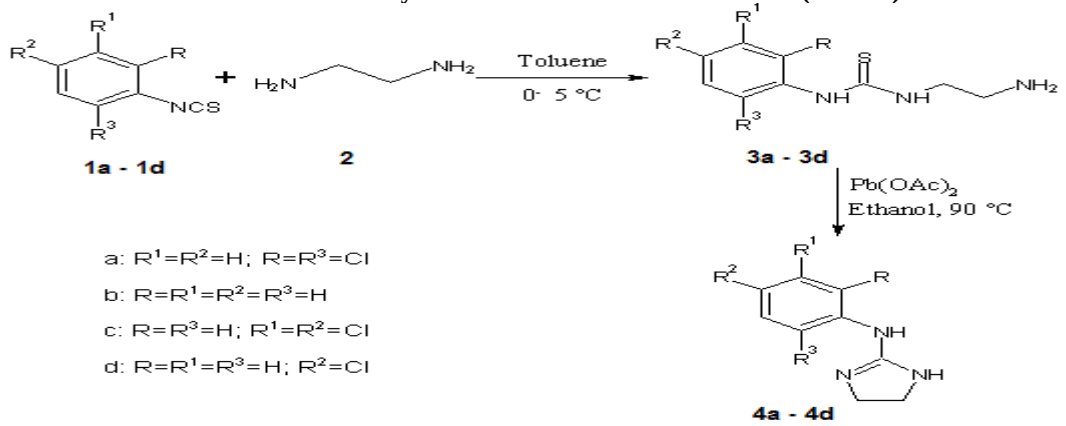
8c: IR: 3446 cm$^{-1,}$ -NH stretching; 2969 cm$^{-1,}$ CH stretching; 1681 cm$^{-1,}$ C=N stretching 1226 cm^{-1} C-O stretching.**^{1}H NMR:** 3.50(t, 2H); 4.37[t.2H); 6.97(s, 1H); 7.13(m, 2H); 7.5(s, 1H). **Mass:** M+ peak at m/z 231.

8d: IR : NH stretching; 2927 cm$^{-1,}$ CH stretching; 1693 cm^{-1} ,C=N stretching 1232 cm^{-1} C-O stretching.**^{1}H NMR** 3.74(s, 2H); 4.25(s.2H); 7.25(d, 2H); 7.54(s, 2H);.9.32(s,1H) **Mass:** M+ m/z 197.1.

Table 3. HPLC data of synthesized compound

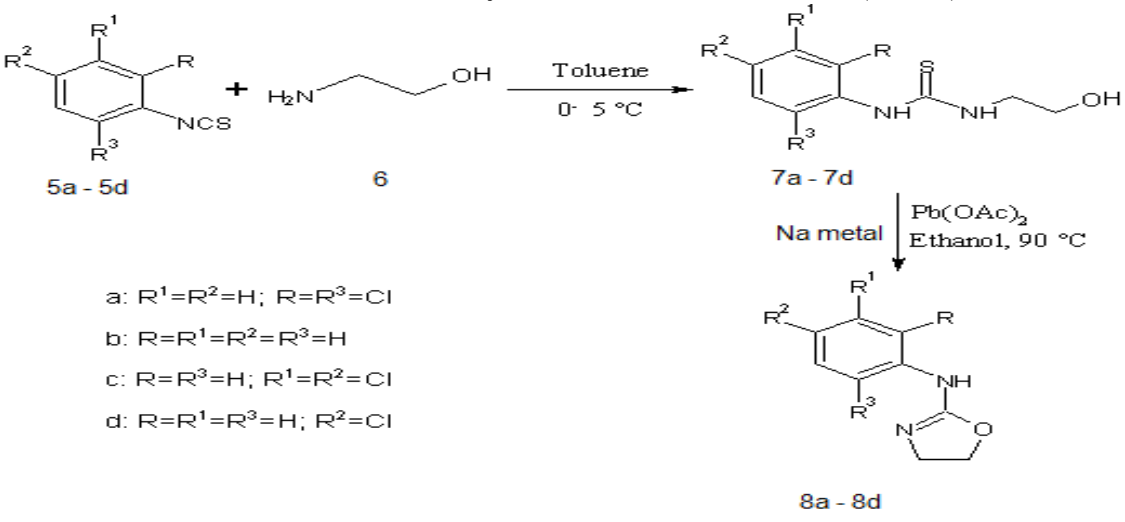
SI. NO	Comp. code	HPLC (% of purity)
1	4a	97.9
2	4b	96.7
3	4c	99.7
4	4d	93
5	8a	99.3
6	8b	92.3
7	8c	99.5
8	8d	100

Scheme I. Synthesis of Imidazoline derivatives (4a – 4d)



Scheme I

Scheme II. Synthesis of oxazoline derivatives (8a – 8d)



Scheme II

RESULTS AND DISCUSSION

We have established a new methodology for synthesizing Imidazoline and oxazoline containing compounds using lead (II) acetate. Eight different compounds of Imidazoline and Oxazoline derivatives were synthesized and characterized by IR, 1HNMR and Mass spectral properties. The purity of the synthesized compounds was determined by HPLC.

ACKNOWLEDGEMENT

Authors are thankful to Dr. B. Gopalan, Executive Directive and Chief Scientific Officer, Orchid Research Laboratories, Chennai for providing laboratory facilities to carry out the research work, Dr. Gajendra Singh Chief Scientist, New Drug Discovery, Orchid Research Laboratories, Chennai for encouragement to do the research work successfully. And my heartfelt thanks to Dr. Sukumar Sakamuri. Director, New Drug Discovery, Orchid Research Laboratories, Chennai for providing all the facilities to complete the research work.

REFERENCES

Bagudo BU Garba, Dangoggo SM. The Qualitative Evaluation of Biogas Sample Generated from Selected Organic Wastes. *Archives of Applioed Science Research*, 3(5), 2011, 549-555.

Cragg RH, Weston AF. Lead dithiolates: their use in the synthesis of cyclic disulphides. *Tetrahedron Letters*, 1973 655-656.

Gilchrist TL. The Bath Press Heterocyclic Chemistry, 1985.

Laubie M, Drouillat M, Dabiré H, Cherqui C, Schmitt H. Ventrolateral medullary pressor area: site of hypotensive and sympatho-inhibitory effects of (+/-) 8-OH-DPAT in anaesthetized dogs. *Eur J Pharmacol.*, 160(3), 1989, 385-394.

MacInnes N, Duty S. Loco motor effects of imidazoline I2-site-specific ligands and monoamine oxidase inhibitors in rats with a unilateral 6-hydroxydopamine lesion of the nigrostriatal pathway. *Brt jour of pharmacology*, 143(8), 2004, 952-959.

Markham A, Bryson HM. Deflazacort. A Review of Its Pharmacological Properties and Therapeutic Efficacy. *Drugs*, 50(2), 1995, 317-33.

Shanmugasundaram P, Vijayakumar Devadass H. Synthesis and Biological Activities Of Novel Imidazoline Derivatives. *Rasayan J.Chem*., 2, 2009, 890-894.