RESEARCH PAPER | CHEMISTRY | Volume : 4 | Issue : 2 | Feb 2014 | ISSN - 2249-555X

Cyclocondensation of 2-Acetylaminoacetanilide: Synthesis and Biological Evaluation of 4-Arylidene-1-Substituted Aryl-2-Styryl-2-Imidazoline-5-Ones.

KEYWORDS: Synthesis, 5-imidazolones, 2-acetylaminoacetanilide, anti-bacterial activity,

Dr Archana Taunk
Chemistry Department, R.D.National College, Linking Road, Bandra(w), Mumbai-50

Aditi Taunk
Chemistry Department, R.D.National College, Linking Road, Bandra(w), Mumbai-50

ABSTRACT *A series of 4-Arylidene-2-styryl-2-imidazoline-5-ones were synthesized by the cyclocondensation of 2-acetylaminactanilide which was prepared from N-acetylglycine. These products were characterized by the spectral and physical data and tested for their antibacterial activity against E.coli, S.paratyphe-B, B. subtilis and S. aureus.*

Introduction

Development of new synthetic routes in heterocycles has been fascinating, challenging & exciting area in synthetic Organic Chemistry. Among the various heterocyclic systems, substituted 2-imidazolin-5-one nucleus is of great importance because of its varied biological activities and different other applications. Imidazolines are useful intermediates in synthesis of natural products as well as common building blocks found in many biologically active molecules. They are reported to have remarkable pharmacological profile[1,2]. These imidazoles are also important because of its application in polymer chemistry[3,4] e.g.1-methyl-2-vinyl-1H-imidazole is used as the monomer but 2-ethenyl-1H-imidazole derivatives are very potent anti eubacterial agents[5]. In organic synthesis, imidazolin units are used as anticancer[6] ,anticonvulsant[7,8] ,antimicrobial [9-13] etc.

Materials and Methods

The usefulness of 2-imidazoline-5-ones as synthons has generated much interest in their chemistry in recent years. A number of methods have been reported for the synthesis of imidazolines but as a part of our investigation for developing efficient method for the synthesis of heterocyclic compounds, we report here a synthetic method for the preparation of 5-imidazolines from aromatic aldehydes and amines. Cyclisation of 2- acetylaminocinnamanilides (4) in the presence of acetic acid to the corresponding 2-methyl-imidazolin-5-ones (5) was unsuccessful as it was reported[14]. In order to verify this reaction we reinvestigated this reaction and have found that (5, Ar =Ph) had formed but on heating it decomposed. To convert the thermally unstable compound 5 which is generated in situ into a more stable compound, 2-acetylaminocinnamanilides (4) was cyclised in the presence of suitable aromatic aldehydes and 2-substituted styryl-2-imidazolin-5-ones (6) were obtained in good yields. The results are compiled in Table-1

Result and Discussion

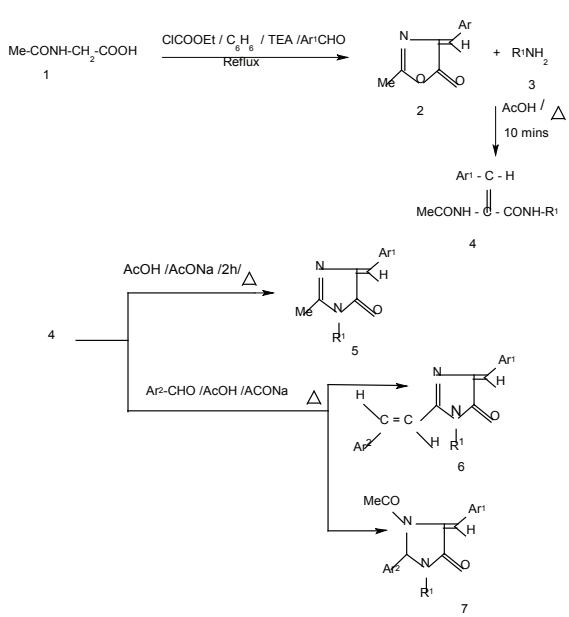
The formation of the products (6) is obviously due to the condensation of the activated methyl group of (5) with the aromatic aldehyde present in the reaction mixture. This procedure is also useful in the case of (6) carrying a free hydroxyl group but the reported method[15] requires very long time and the use of Schiff bases[16] for obtaining (6) involves additional step. The present one pot synthesis overcomes these difficulties. The starting materials are easily available and the reaction is quite fast the products were characterized by spectral data and elemental analysis. A series of 2-substituted styryl-2-imidazolin-5-ones were prepared and these were characterized on the basis of physical constant and spectral data.(Table 1).The alternative structure (7) was ruled out on the basis of spectral data. For example, in the PMR spectrum of the products, the signal for a methyl group was not discernible, whereas the peaks and coupling constants characteristic of the styryl moiety were conspicuous. The method is outlined in scheme 1.

Some of the 4-arylmethylene-2-styryl-2-imidazolin-5-ones (6) reported here are known in the literature, but their synthesis are usually carried out in a step-wise fashion starting from the preparation of 2-oxazolin-5-one itself. In the present method all the steps are carried out in the same flask and it is useful in getting products having functionalized arylmethylene and styryl moieties. The condensation of the methylene and methyl groups takes place with the different aldehydes, thereby furnishing different arylidene moieties at the 4- position and in the styryl part of the molecule at 2-position.

EXPERIMENTAL

All chemicals used were of LR grade and the melting points reported were taken in an open capillary tube and are uncorrected. All yields refer to isolated product after purification. The products were confirmed by IR spectra. The ^{1}H NMR of the samples was also recorded.

Scheme 1



Antibacterial activity

All the synthesized compounds were screened for antimicrobial activity at, 50,100 and 200 µg/ml concentrations against the bacterial strains: against S. aureus, B. subtilis [Gram-positive bacteria] and E. coli, S. paratyphi-B [Gram-negative bacteria] by using agar diffusion method using standard literature protocol.[17,18] Known antibiotic Ciprofloxacin drug was used as standards for comparison of antibacterial activity un-

Volume : 4 | Issue : 2 | Feb 2014 | ISSN - 2249-555X

der the similar conditions. Dimethyl sulfoxide was used as a solvent to prepare the stock solution of the test compounds. The drug was allowed to diffuse for about 4h into the agar medium before adding the suspension of the test bacteria The plates were incubated at 37 °C for 48h and the results were recorded. The tests were carried out in duplicate. The zones of inhibition of the microbial growth produced by different concentration of test compounds were measured in millimeters (mm). The screening results indicate that compounds 6a and 6c were found less active against all the four strains used and 6f shows good activity against all the stains. Compound 6b were moderately active against E.coli and S.Paratyphi-B. while compound 6d showed moderate activity against S.aureus and S.paratyphi-B. Compound 6e were found to be moderately active against B. subtilis and E.coli. The results of this study is given in Table 2.

General Procedure

1) Preparation of 2-Acetyl aminocinnamanilide (4)

To a suspension of N-acetyl glycine (1.0 mol) in dry benzene (25 ml), triethylamine (2.2 mol) and ethyl chloroformate (1.1 mol) was added and the mixture was shaken at the room temperature until the triethylamine hydrochloride separates out. The mixture is refluxed for 10 min in presence of aromatic aldehyde (1.0 mole). After the filtration, the solvent is completely removed off under reduced pressure, to the residue aromatic amine (1.2 mol) and glacial acetic acid (10 ml) are added and refluxed for 10 mins. After the usual work-up the product was recrystallised from glacial acetic acid.

2) Preparation of 1-Aryl-4-substitutedbenzylidene-2-styryl-2-imidazolin-5-ones (6)

A mixture of 2–acetyl aminocinnamanilide (4, 1.0 mol) and aromatic aldehyde (1.1 mol) was heated under reflux in glacial acetic acid (15 ml/ g of anilide) for 2 hrs using freshly fused sodium acetate as a catalyst. After the usual work up product was recrystallised from ethanol or glacial acetic acid. The relevant data are given in table 1.

Table 1

Compound	Ar^1	R^1	Ar^2	% Yield	M.P. in °C	IR (cm^{-1})	NMR in ppm
6a	Ph	Ph	4-OH, 3-OCH_3-C_6H_4	52.70	230	2921,2857,1706, 1615	-OCH_3 (3.5, s, 3H), -Ar-H (6.8 -7.5 m,12H), Ph-CH=C (6.4,d,1H), 2-CH=CH (7.9,d,1H) 2-CH=CH (8.2,d,1H) PhOH (8.88,s,1H)
6b	3-OCH_3-C_6H_4	4-Cl C_6H_4-	4-Br-C_6H_4	39.20	200	2929,2826, 1706,1620	-OCH_3 (3.8, s, 3H), -Ar-H (6.6 -7.3, m,12H), Ph-CH=C (6.4,d,1H), 2-CH=CH (7.9,d,1H) 2-CH=CH (8.2,d,1H)
6c	4-Br-C_6H_4	4-Br-C_6H_4	4-OH, 3-OCH_3-C_6H_4	42.30	242	3737,1717, 1619	-OCH_3 (3.6, s, 3H), -Ar-H (6.2 -7.3, m,11H), Ph-CH=C (6.4,d,1H), 2-CH=CH (7.9,d,1H) 2-CH=CH (8.2,d,1H) PhOH (8.88,s,1H)
6d	4-Br-C_6H_4	4-Cl-C_6H_4	2-OH-C_6H_4	36.39	215	2920,1717, 1623	-Ar-H (6.4 -7.3, m,11H), Ph-CH=C (6.4,d,1H), 2-CH=CH (7.8,d,1H) 2-CH=CH (8.4,d,1H) PhOH (8.68,s,1H)
6e	4-Br-C_6H_4	4-CH_3-C_6H_4	4-OH, 3-OCH_3-C_6H_4	45.20	230	3403,1710, 1637,2927	-OCH_3 (3.6, s, 3H), -CH_3 (.9.s,3H) -Ar-H (6.2 -7.06, m,11H), Ph-CH=C (6.4,d,1H), 2-CH=CH (7.8,d,1H) 2-CH=CH (8.4,d,1H) PhOH (8.78,s,1H)
6f	4-Br-C_6H_4	4-Cl-C_6H_4	3-NO_2-C_6H_4	42.20	225	2925,,2810, 1719,1620	-Ar-H (7.22- 8.07, m,12H), Ph-CH=C (6.4,d,1H), 2-CH=CH (7.8,d,1H) 2-CH=CH (8.4,d,1H)

Table 2

Antimicrobial activity of the compounds (Zone of inhibition in mm)

Compounds	B.subtilis			S.aureus			E.coli			S.paratyphi-B		
	50 ug/mL	100 ug/mL	200 ug/mL	50 ug/mL	100 ug/mL	200 ug/mL	50 ug/mL	100 ug/mL	200 ug/mL	50 ug/mL	100 ug/mL	200 ug/mL
6a	07	10	11	10	11	13	12	11	12	07	11	11
6b	08	11	13	09	12	14	16	15	17	14	14	14
6c	08	12	12	08	10	12	09	11	13	07	11	14
6d	09	08	07	15	16	17	11	10	10	15	16	15
6e	14	14	15	11	10	11	15	14	16	10	11	11
6f	15	16	16	16	17	18	18	14	15	17	17	18
Ciprofloxacin	31.41	31.42	31.41	30.40	30.42	30.42	35.43	35.42	35.53	31.15	31.14	31.16

Acknowledgement

We are thankful to the authorities of R.D. National and W.A. Science College for providing us with the necessary facilities. Our thanks to the IIT-Bombay for providing us with the NMR and IR spectra and UGC to give us financial grant to carry out the research work.

Volume : 4 | Issue : 2 | Feb 2014 | ISSN - 2249-555X

REFERENCE

1. V. Parscha et. Al.. Synthesis and pharmacological evaluation of imidazole derivatives of | some non-steroidal anti-inflammatory drugs.. JICS. 2008; 85: 321. | 2. K Shankar et al. .. Novel imidazole congeners as anti-inflammatory agents. JICS. 1992; 69: 594. | 3. M Ueda, K Kino, K Yamaki, Y Imai. . Preparation and properties of polyamides from 2,2' -p-phenylenebis-5-oxazolones with diamines...J Polym Sci Polym chem Ed. 1978; 16: 155. | 1978: 89: 2486. | 4. G Markert, H Penneniss, Angew. .. Inhomogeneous [polymer] networks due to incompatibility.....Makromol Chem 1978; 72: 199. C.A.1979; 90: 6812. | 5. Rottenberg AS, Panzer HP, Schmitt JL, Card RJ. US Patent 4410706, 1983; C.A., 1984, 100, 34542. Preparation of 2-vinylimidazoles by dehydrogenation of 2-ethylimidazoles and 2-ethylimidazolines | 6. I Krezel. ... New derivatives of imidazole as potential anticancer agents....Farmaco. 1998; 53 (5): 342. | 7. HT Nguyen, Ce Destrad, J Malthete. .. Phasmids and Polycatenar Mesogens...Adv Mater 1997; 9: 375. | 8. H Joshi, P Upadhyay, D Karia and AJ Baxi. .. Synthesis of some novel imidazolinones as potent anticonvulsant agents.Eur J Med Chem. 2003; 38(9): 837 | 9. H Miyachi, H Kiyota, M Segawa... Novel imidazole derivatives with subtype-selective antimuscarinic activity (1)... Bio Med Chem Lett 1998; 1807. | 10. NC Desai, D Dave, MD Shah, GD Vyas. .. Synthesis and antibacterial activity of some novel 4-oxo-1,3-thiazolidines, 2-oxoazetidines and 5-oxoimidazolines.. IJ Chem 2000; 39(B): 277. | 11. KV Hirpara, SP Patel, KA Parikh, AS Bhimani, HH Parekh..Preparation, Characterisation and Antimicrobial Activities of Some Novel Nitriles and ImidazolinesJ Sci Islam Rep Iran. 2004;15:135. | 12. G Aydogan and M Kutlu... Mutagenic activities of ten imidazole derivatives in Salmonella typhimurium. Biologia. 2007; 62: 6. | 13. NC Desai, AM Bhavsar and BB Baldaniya.. Synthesis and antimicrobial activity of 5-imidazolinone derivatives... Ind J Pharm Sci 2009; 71(1).90-4 | 14. J.K.Baldwin,J.Chem.Soc., Rules for ring closure, Chem. Commun.,1976, 734 | 15. P Kumar, HD Mishra, AK Mukerjee... Condensation of 2-Substituted 5-Oxo-4,5- dihydro-1,3-oxazoles with Imines and Their Corresponding Carbonyl Compounds.... Synthesis. 1980; 836. | 16) M.S. Reddy, P. Hanumanthu, and C.V. Ratnam, "Condensation of 4-benzylidene-2-methyl oxazolin-5-one with Schiff bases: Formation of 1-Aryl-4-benzylidene-2-styryl imidazolin-5-ones" Indian J. Chem., 1982, 21B, 646.222 | 17) "The Antimicrobial Suceptibility Test : Principal and Practice" By A. Berry, Pub.Illus, | Lea & Febgier Phildelphia, Pa. USA, 180, 1976. | 18) National Committee for Clinical Laboratory Standards (NCCLs). Standard methods | for dilution antimicrobial susceptibility tests for bacteria, which grows aerobically. | Nat. Comm. Lab. Stands. Villanova, 1982, pp. 242.