Synthesis and antimicrobial activity of 1,4- diaryl-5-miino-3-imidazolin-2-ones.

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Abstract

Fifteen new 1,4-diaryl-5-imino-3-imidazolin-2-ones have been prepared from α-oxonitriles and monochlorophenylureas. The present syntheses offer a simple and convenient method of preparation of the 5-imino-3-imodazotin-2-ones from readily available starting materials. The result of their antimicrobial screening indicate some of them possess significant activity.

Introduction

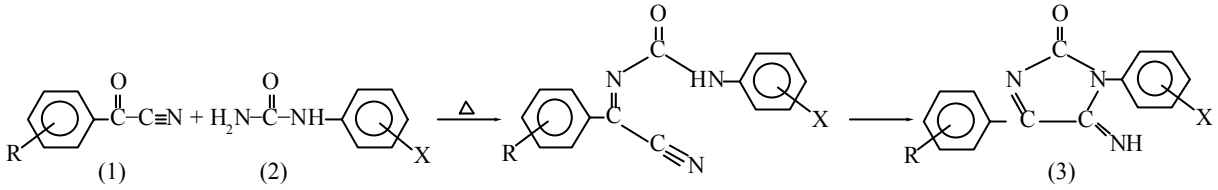
As part of our continuing program to investigate the potentialities of α-oxonitriles as synthons[1-4] and to study the antimicrobial activity of the products, we wish to report a facile synthesis of some new 1, 4-diaryl-5-imino-3-imidazolin-2-ones (3) from α-oxonitriles (1). Further, the fact that the chloro substituted arylureas possess remarkable antimicrobial property[5,6], prompted us to utilize the chlorophenylureas as one of the starting materials in the present work. The synthesis was carried out by heating α-oxonitriles with chlorophenyureas (2) just below their melting point. The synthetic approach to these compounds (3a-o) is outlined in scheme 1, and their characterization is based on their elemental analyses, IR and ^{1}H NMR data. The compounds synthesized were screened for their antimicrobial activities against seventeen different phathogenic strains of bacteria.

Experimental Methods

1-Chlorophenyl-4-aryl-5-imino-3-imidazolin-2-ones are prepared by heating an equimolecular mixture of α-oxonitriles and chlorophenylureas in the absence of any solvent just below the melting point of the reactants. The solidified reaction product was triturated with hot water and dried. Crystallized with ethanol.

α-oxonitriles were prepared by known methods[7]. The O-, m- and p- chlorophenylureas were prepared by following the procedure of kurzer[8]. All melting points were determined in open capillaries with a Gallenkamp apparatus and are uncorrected. The purity of compounds was routinely chechked by TLC using slica gel G (E.Merck) plates. The IR spectra were recoreded on a Jasco FT-IR 5300 spectrophotometer. The ^{1}H NMR spectra were recorded on a jelo FX-90 Q Fourier transform spectrometer (90 MH_z instrument) at the probe temperature 25°C with TMS as an internal standarde. Perkin- Elmer CHN analyzer 240C was used for elemental analyses.

The synthesized compounds were screened for their antimicrobial activity by Stockes disc-diffusion technique[9] at concentration of 40 μg/disc against seventeen strains of pathogenic microorganisms namely ***Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Citrobacter freundii, Proteus Vulgaris, Providencia rettgeri, Edwardsiella tarda, Salmonella typhu, Salmomella typhimurium, Strigella dysenteria, Vibrio***



Scheme 1. **Synthetic protocol of the compounds**

Comp. (3a-o)

X	R =	H	p-CH_3	m-CH_3	p-NO_2	p-Cl
p-Cl		3a	3b	3c	3d	3e
m-Cl		3f	3g	3h	3i	3j
o-Cl		3k	31	3m	3n	3o

cholerae 01 classical, Vibrio cholerae non 01, Vibrio parahaemolyticus, Aerominas hydrophila and Plesimonas shigelloides.

Results

The physical and spectral data of the compounds (3a-o) are given below.

(3a) Colourless, yield 56%, m.p. 232^0. IR (nujol): v 3500-3400 (NH), 1700 (C=0), 1660 (C=N), 1600, 1580,1500,1320,1280,750 cm^{-1}. ^1H NMR (DMSO-d_6): δ7.73-9.03 (M,9h, ArH), 11.63 (s, IH, NH, D_20 exchange) ppm. [Found:C, 63.6; H,3.4;N, 14.7. $C_{15}H_{10}ClN_3O$ requires C,63.4; H,3.5; N,14.8]

(3b) Colourless, yield 42% m.p. 296°. IR (nujol): v 3400, 1700, 1615, 1515, 760 cm^{-1}. ^1H NMR (DMSO-d_6): δ2.62 (s,3H, CH_3), 7.00-8.00 (m,8H, ArH), 9.06 (s, IH, NH, D_2O exchange) ppm.

(3c) Colourless, yield 42% m.p. 298°. IR (nujol): v 3300, 1690, 1640, 1600, 1560, 1500,1400,1240,750 cm^{-1}. ^1H NMR (DMSO-d_6-): δ2.31 (s,3H, CH_3), 7.50-8.44 (m, 8H, ArH), 9.00 s, IH, NH, D_2O (exchange) ppm. *Anal.* $C_{16}H_9ClN_4O_3$ (C,H,N).

(3d) Light grey, yield 51% m.p. 281°. IR (nujol): v 3360, 1700, 1640, 1600, 1560, 1500,1400,1240, 810, 750 cm^{-1}. ^1H NMR (DMSO-d_6): δ7.13-8.00 (m, 8H, ArH), 9.13 (s, IH, NH, D_2O (exchange) ppm. *Anal.*$C_{15}H_9ClN_4O_3$ (C,H,N).

(3e) Colourless, yield 45% m.p. 288°. IR (nujol): v 3320, 1700, 1640, 1600, 1580, 760 cm^{-1}. *Anal.*$C_{15}H_9Cl_2N_3O$ (N,H,N).

(3f) Colourless, yield 52% m.p. 190°. IR (nujol): v 3400–3100, 1700, 1650, 1610, 1560, 780, 760, cm^{-1}. *Anal.*$C_{15}H_{10}ClN_3O$ (C,H,N).

(3g) Colourless, yield 52% m.p. 235^0. IR (nujol): v 3400, 1690, 1640, 1590, 840, 720cm^{-1}. ^1H NMR (DMSO-d_6): δ2.37 (s,3H, CH_3), 7.03-8.44 (m,8H, ArH), 9.19 (s, IH, NH, D_2O exchange) ppm. *Anal.*$C_{15}H_{12}ClN_3O$ (C,H,N).

(3h) Colourless, yield 53% m.p. 210^0. IR (nujol): v 3300, 1680, 1640, 1590, 1560, 790,750cm^{-1}. ^1H NMR (DMSO-d_6): δ2.44 (s,3H, CH_3), 6.66-8.22 (m,8H, ArH), 9.33 (s, IH, NH, D_2O exchange) ppm. *Anal.*$C_{16}H_{12}ClN_3O$ (C,H,N).

(3i) Light violet, yield 58% m.p. 232^0. IR (nujol): v 3420, 1740, 1640, 1610, 1580, 765cm^{-1}. *Anal.*$C_{15}H9ClN_4O_3$ (C,H,N).

(3j) Colourless, yield 58% m.p. 198-200^0. IR (nujol): v 3450-3300, 1680, 1640, 1600, 1550, 1500, 1380, 1280,750cm^{-1}. ^1H NMR (DMSO-d_6): δ6.88-7.93 (m,8H, ArH), 9.80 (s, IH, NH, D_2O exchange) ppm *Anal.*$C_{15}H_gCl_2N_3O$.

(3k) Colourless, yield 58% m.p. 208^0. IR (nujol): v 3320, 1700, 1640, 1600, 1560, 800, 740cm^{-1}. ^1H NMR (DMSO-d_6): δ7.00-8.11 (m,9H, ArH), 9.04 (s, 1H, NH, D_2O exchange) ppm *Anal.*$C_{15}H_{10}ClN_3O$ (C,N,H).

(3l) Grey, yield 52% m.p. 165^0. IR (nujol): v 3320, 1690, 1650, 1600, 1550, 1380, 1320, 1260, 1220, 740cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.66 (s, 3H, ArH), 9.04 (s, 1H, NH, D_2O exchange) ppm *Anal.*$C_{15}H_{10}ClN_3O$ (C, H, N).

(3m) Pink, yield 51% m.p. 178-180^0. IR (nujol): v 3300, 1680, 1650, 1580, 1540,780, 740cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.61 (s, 3H, CH_3), 7.00-8.22 (m, 8H, ArH), 9.11 (s 1H, NH, D_2O exchange) ppm. *Anal.*$C_{16}H_{12}ClN_3O$ (C, H, N).

(3n) Grey, yield 60%, m.p. 118-120°. IR (nujol): v 3350, 1700, 1660, 1600, 1560, 855, 755 cm^{-1}. Anal. $C_{15}H_9ClN_4O_3$ (C,H,N).

(3o) Colourless, yield 65%, m.p. 220°. IR (nujol) : v 3300, 1680, 1630, 1605, 1580, 840, 740 cm^{-1}.

Discussion

The product (**3**) is formed by the condensation of the carbonyl group of aroyl cyanide (**1**) and primary amino group of monochlorophenylurea (**2**) forming an unstable intermediate followed by its cyclization to give the heterocycle. The acyl cyanides (**1**) containing electron withdrawing para substituents in the benzene ring e.g. Chloro, nitro) undergo the reaction smoothly giving better yields of the imidazol-2-ones. Electron-releasing groups (e.g.m -and p-methyl) exhibit

lower reactivity towards chlorophenylurea and require prolong heating to form (**3**). The raction however, fails with o-toluoyl cyanide as well as p-anisoyl cyanide to give the expected 3-imidazolin-2-one.

The IR, ^{1}H NMR and microanalytical data of the heterocycles (**3a-o)** are in accordance with their proposed structures. The IR spectra of the compounds in nujol show absorption bands at 3450-3250 cm^{-1} for NH stretching, at 1740-1680 cm^{-1} for C=O stretch, at 1660-1630 cm^{-1} for C=N stretch and at 1605-1550 cm^{-1} for the aromatic ring. The ^{1}H NMR spectra in DMSO-d_6 exhibit a D_2O exchangeable singlet at δ 11.63-9.00 ppm for the imino proton besides aromatic ring proton. The microanalytical values for C,H,N are within ± 0.3% of the theoretical values.

It is found from the antimicrobial screening that the compounds (**3a-d, 3k-m and 3n)** are resistant to all the tested microbes. Only compounds **(3e,g-j and 3I)** are found sensitive to one or more tested microorganisms. It is also found that compounds (**3f-3j)** having a chloro substituent at *meta* position of the phenyl ring are most sensitive as compared with those at ortho or *para* position.

Conclusion

The present syntesis offer a simple and convenient method of preparation of TLC-pure 5 - iminolin-3-imidazolin-2-ones of considerable biological activity, from readily available starting materials. So, this research work has further explored the potentiality of α-oxonitrile as synthon in heterocyclic synthesis.

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