SYNTHESIS AND CHARACTERIZATION STUDIES OF 3,4,5 -TRI-SUBSTITUTED 1,2,4 -TRIAZOLES.

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Abstract:

Synthesis of 3,4,5-tri-substituted 1,2,4-triazoles involving one step method has been developed. These have been obtained by the self cyclo-condensation of (2E)-N-phenyl-2-[(2E)-3-phenyl-1(arylamino)prop-2-en-1ylidene]hydrazine carbothioamide in refluxing alcohol medium for one hour. The condensation occurs with the evolution of H_2S gas. The various hydrazine carbothioamide were synthesized by carrying out the condensation of N-aryl-cinnamanilide and 4-phenyl thiosemicarbazide in chloroform medium. The structures of 3,4,5-tri-substituted 1,2,4-triazoles have been established on the basis of spectral studies including I.R., P.M.R., ^{13}C N.M.R. and Mass spectrometry. The 1,2,4-triazoles are further converted into their 1-acetyl derivatives by treating them with glacial acetic acid and acetic anhydride in 1:1 ratio. These compounds were evaluated for their in vitro antimicrobial activity.

Key Words: 1,2,4-triazoles, cinnamanilide, hydrazine carbothioamide, thiosemicarbazide, biological activity.

Introduction:

Heterocyclic compounds are widely distributed in nature and are essential for life. They play a vital role in the metabolism of all living cells. There are vast number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use. Triazole is one of the heterocyclic compound having a five membered ring of two carbon atoms and three nitrogen atoms. Triazole compounds containing three nitrogen atoms in the five-membered aromatic azole ring are readily able to bind with a variety of enzymes and receptors in biological system via diverse non-covalent interactions, and thus display versatile biological activities. The related researches in triazole-based derivatives as

medicinal drugs have been an extremely active topic, and numerous excellent achievements have been acquired. The synthesis of 1,2,4-triazole ring system was first of all reported by Bladin[1].

Triazoles and in particular 1,2,4-triazole nucleus have been incorporated into a wide variety of therapeutically interesting drug including anti-inflammatory, CNS stimulants, sedatives, anti-anxiety and antimicrobial agents [2-3]. Their antifungal activity is also documented[4-5]. The literature survey revealed that bis-1,2,4 triazoles, bis-1,2,3-triazoles have been reported by different routes[6-10].

Thus keeping in view the pharmacological activity of 1,2,4-triazole, we have synthesized a series of N-{(3Z)-4-aryl-5[(E)-2-phenylethenyl]-2,4-dihydro-3H-1,2,4-triazol-3-ylidene}amine.

Experimental:

The melting points (mp) are taken by using open capillary method and are uncorrected. The FT-IR spectra were recorded on Perkin –Elmer spectrophotometer using KBr disc. The ^{1}H NMR spectra are recorded on Brucker Avance 400 NMR Spectrometer using DMSO-d6 as a solvent and TMS as internal standard and the chemical shift are expressed in δ ppm values. EI-MS were recorded by direct insertion technique with a Hitachi Perkin Elmer RMU 6D mass spectrophotometer.

General procedure for 3,4,5-tri-substituted 1,2,4-triazoles (Ia-Id):

Cinnamanilide(0.01 mole) was refluxed with 4-phenyl thiosemicarbazide(0.01 mole) in chloroform medium for 2 hrs. to synthesize hydrazine carbothioamides. This hydrazine carbothioamide on refluxing with ethanol for 1 hr undergoes self cyclo-condensation with evolution of H_2S gas to obtain N-{(3Z)-4-phenyl-5[(E)-2-phenylethenyl]-2,4-dihydro-3H-1,2,4-triazol-3-ylidene}aniline (Ia).It was poured on cold water (200 ml) to get its solid form which was filtered, washed with water and re-crystallized from ethanol.

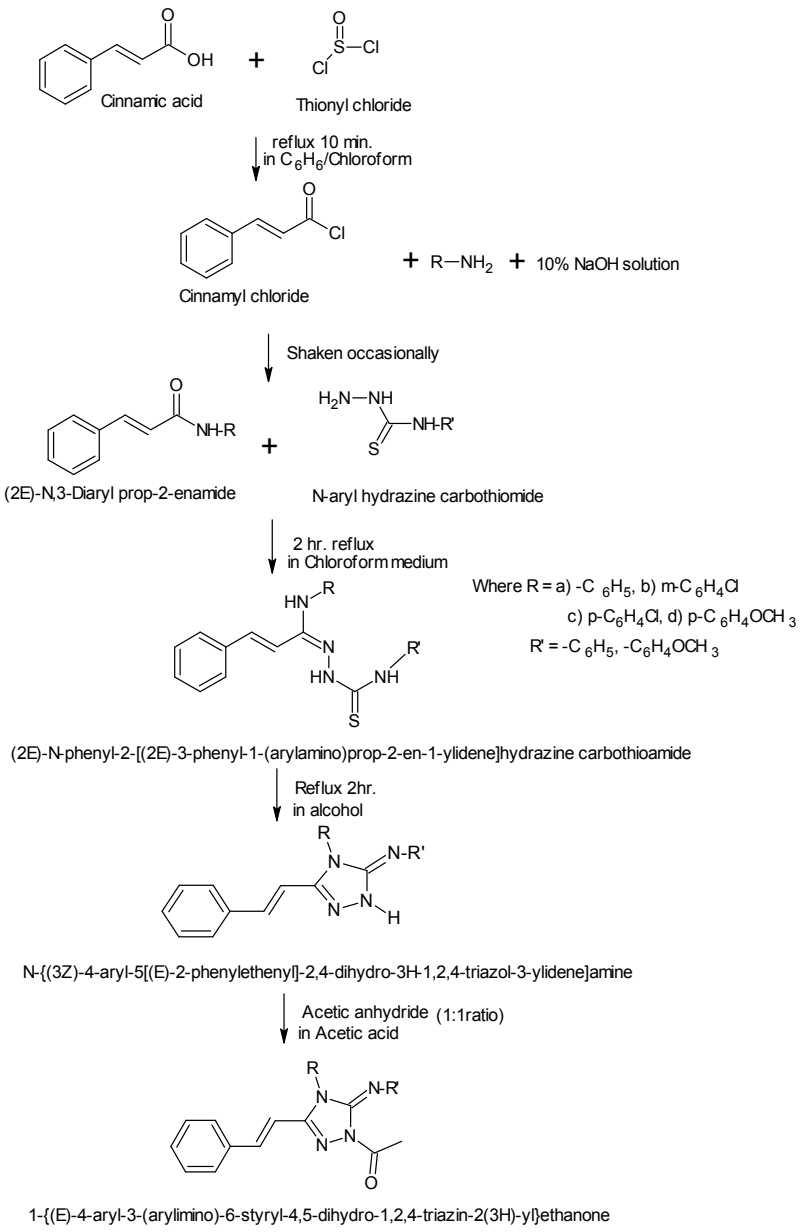

Fig 1: Reaction scheme of 3,4,5-tri-substituted 1,2,4-triazoles synthesis

N-{(3Z)-4-phenyl-5[(E)-2-phenylethenyl]-2,4-dihydro-3H-1,2,4-triazol-3- ylidene}aniline (Ia):

Yield 69 %, m.p. 150°C (Ethanol), Rf =0.56, FT-IR (KBr) cm^{-1}: 3294 (-NH), 3182.9-2791.3 (aromatic ring, str.), 1626.2 (C=N, str.), 1350-1294.4 (C-N, str.) 1250-1203.7 (N-N, str.). ^{1}HNMR δ: 7.73 (s,1H,-NH), 7.4-7.2 (m,15H,aromatic), 7.6-6.8 (d,2H,vinylic -CH=CH-). ^{13}CNMR (DMSO-d6):

163.85 (1C,C=N), 140.15-117.22 (18C,aromatic carbon atoms), 78.09-77.45 (vinylic carbon atoms). MS: m/z (%), 274 (15), 270 (30), 269 (100), 247 (13), 224 (29).

N-{(3Z)-4-(2-chloro phenyl)-5[(E)-2-phenylethenyl]-2,4-dihydro-3H-1,2,4-triazol-3- ylidene}aniline (Ib):

Yield 74%, m.p.117 ^{o}C (Ethanol), Rf=0.45, FT-IR (KBr) cm^{-1}: 3284 (-NH), 3184-2792 (aromatic ring, str.), 1630 (C=N, str.), 1350-1290 (C-N, str.) ,1254-1206

(N-N, str.). ^{1}HNMR δ: 10.8 (s,1H,-NH), 7.6-7.2 (m,14H,aromatic), 7.1-6.7(d,2H,vinylic -CH=CH-). MS: m/z (%), 151 (15), 258 (30), 269 (100),303 (20).

N-{(3Z)-4-(4-chloro phenyl)-5[(E)-2-phenylethenyl]-2,4-dihydro-3H-1,2,4-triazol-3- ylidene}aniline (Ic):

Yield 68%, m.p. 119 ^{o}C (Ethanol), Rf=0.43, FT-IR (KBr) cm^{-1}: 3358 (-NH), 3105-2788 (aromatic ring, str.), 1618 (C=N,str.), 1350-1291 (C-N,str.) ,1250-1202 (N-N,str.). ^{1}HNMR δ: 8.76 (s,1H,-NH), 7.6-6.8 (m,14H,aromatic), 7.2-6.4(d,2H,vinylic -CH=CH-). MS: m/z (%), 202 (30), 269 (100),303 (15),274(20),328(10),360(5).

N-{(3Z)-4-(4-methoxy phenyl)-5[(E)-2-phenylethenyl]-2,4-dihydro-3H-1,2,4-triazol-3- ylidene}aniline (Id):

Yield 70%, m.p. 142 ^{o}C (Ethanol), Rf=0.61, FT-IR (KBr) cm^{-1}: 3280 (-NH), 3085-2712 (aromatic ring, str.), 1624 (C=N, str.), 1348-1285 (C-N, str.) ,1250-1202 (N-N, str.), 1220(C-O). ^{1}HNMR δ: 9.8 (s, 1H,-NH), 7.7-6.7 (m, 14H, aromatic), 7.1-6.4(d, 2H, vinylic -CH=CH-), 3.7(3H,-OCH_3).MS: m/z (%), 131(5) ,254(70), 269(100), 338(10).

1-{(E)-4-phenyl-3-(phenylimino)-6-styryl-4,5-dihydro-1,2,4-triazin-2(3H)-yl} (Ia_1):

Yield 69%, m.p.156 ^{o}C(Ethanol),Rf=0.62, FT-IR (KBr) cm^{-1}: 3132-2890 (aromatic ring, str.), 1628 (C=N, str.), 1350-1286 (C-N, str.) ,1247-1208 (N-N, str.), 1250(C-O). ^{1}HNMR δ: 7.7-6.9 (m,15H,aromatic), 6.6-6.4(d,2H,vinylic -CH=CH-), 1.2(s,3H,$COCH_3$). MS: m/z (%), 103(5), 114(10), 131(40), 224(100), 269(20), 338(30),354(45).

1-{(E)-4-(2-chloro phenyl)-3-(phenylimino)-6-styryl-4,5-dihydro-1,2,4-triazin-2(3H)-yl} (Ib_1):

Yield 73%, m.p.124 ^{o}C(Ethanol),Rf=0.59, FT-IR (KBr) cm^{-1}: 3180-2960 (aromatic ring, str.), 1656 (C=N, str.), 1348-1258 (C-N, str.) ,1245-1216 (N-N, str.), 1280(-C-O). ^{1}HNMR δ: 7.5-6.9 (m,14H,aromatic), 6.7-6.5(d,2H,vinylic -CH=CH-),1.7(s,3H,-$COCH_3$).MS: m/z (%),M^+ :414 910),131(40) ,224(15),258(100),311(35),338(40).

Biological Assay:

Antibacterial Activity:

The synthesized compounds were screened for their antibacterial activities against pathogenic bacteria i.e. *Escherichia coli* using cup plate diffusion method. The test compounds were dissolved in DMSO at a concentration of 100 μg/ml, 50 μg/ml, 25 μg/ml, 12.5 μg/ml using Streptomycin as standard drug.

Antibacterial activity of N-{(3Z)-4-aryl-5[(E)-2-phenylethenyl]-2,4-dihydro-3H-1,2,4-triazole-3-ylidene}amine (Ia - Id) and 1-{(E)-4-aryl-3-(arylimino)-6-styryl-4,5-dihydro-1,2,4-triazin-2(3H)-yl}eathanone (Ia_1 and Ib_1) against E.coli using streptomycin as a standard drug is given below:

Concentration	**Compounds**						
	Ia	**Ib**	**Ic**	**Id**	**Ia_1**	**Ib_1**	**Streptomycin**
100 μg/ml	S10mm	S22mm	S10mm	S12mm	S10mm	S18mm	S26mm

50 μg/ml	R	S20mm	S10mm	S10mm	R	S14mm	S18mm
25 μg/ml	S12mm	S16mm	S10mm	R	R	S12mm	S14mm
12.5 μg/ml	R	S14mm	S10mm	R	R	S10mm	S12mm

(Diameter of inhibition zone in mm)

R : Resistant (below 10mm)

S : Sensitive (Bacteriocidal) (10mm above)

Table 1: Antimicrobial activity of Ia to Ib_1 against E-coli.

Results and Discussion:

The starting compound (2E)-N, 3-diphenylprop-2-enamide was synthesized by known methods from cinnamyl chloride and aniline[11]. This compound refluxed with N-phenyl hydrazine carbothioamide in chloroform medium to form (2E)-N-phenyl-2[(2E)-3-phenyl-1-(phenylamino) prop-2-ene-1-ylidene] hydrazine carbothioamide. It undergoes self cyclo-condensation by refluxing with alcohol for 1 hr and has resulted in the formation of N-{(3Z)-4-phenyl-5[(E)-2-phenylethenyl]-2,4-dihydro-3H-1,2,4-triazol-3- ylidene}aniline (Ia). These synthesized compound have been well characterized by IR, NMR and Mass Spectrometry.

Conclusion:

In the present work, N-{(3Z)-4-aryl-5[(E)-2-phenylethenyl]-2,4-dihydro-3H-1,2,4-triazol-3-ylidene}amines and their acetyl derivatives were synthesized and evaluated their in vitro antimicrobial activity. Biological result indicated that the new N-{(3Z)-4-(2-chloro phenyl)-5[(E)-2-phenylethenyl]-2,4-dihydro-3H-1,2,4-triazol-3- ylidene}aniline (Ib) and 1-{(E)-4-(2-chloro phenyl)-3-(phenylimino)-6-styryl-4,5-dihydro-1,2,4-triazin-2(3H)-yl} (Ib_1) shows greater pharmacological significance. Hence the compounds Ib and Ib_1 might be promising new antimicrobial agents.

Acknowledgments:

The authors are grateful to the Director, SAIF, Chandigarh for providing necessary spectral analysis; the Head , Department of Botany, RTM Nagpur University, Nagpur, for biological activity; and the Head , Department of Chemistry, RTM Nagpur University, Nagpur, for providing necessary laboratory facilities.

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