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Synthesis of Schiff Bases, Oximes and Hydrazones of 1,2,4-Oxadiazole and 1,2,4-Triazoles

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The synthesis of Schiff bases of aryl aldehydes with 4-aminooxadiazoline, 4-amino triazoles and 3-acetyl-1,2,4-triazole hydrazones is described. Oximes and hydrazones of differently substituted-3-acetyl-1,2,4-triazoles are also prepared in order to study their biological activity. The assignment of the structures of all synthesized compounds was based on spectral data (mass spectra, IR, ^1H and ^{13}C NMR).

Key Words: Nitrilimines, Triazoles, Oxadiazoles, Hydrazones, Oximes, Schiff bases.

INTRODUCTION

Azoles represent an important class of heterocycles that find many practical applications especially as antifungal reagents[1]. Certain oxadiazole derivatives are used as biocides, herbicides and antifungal agents[2]. Substituted 1,2,4-triazoles find many useful applications: Some of them are used as analytical and photographic reagents[3]. Recently, the synthesis of differently substituted oxadiazole and triazoles, mainly from the reaction of nitrilimines and nitrile oxides with different hydrazines, hydrazones and oximes are reported[4].

In this paper, the synthesis of some new 1,2,4-oxadiazole and 1,2,4-triazole derivatives and their Schiff bases, oximes and hydrazones are reported.

EXPERIMENTAL

Melting points were determined on Electrothermal mel. temp. apparatus and are uncorrected. IR spectra were obtained by using Perkin-Elmer 237 infrared spectrometer (KBr discs). ^1H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz instrument for solutions in $CDCl_3$ or DMSO-D_6 at 21°C, using TMS as an internal reference. Electron impact mass spectra were run on Finnigan Mat 8200 and 8400 spectrometers at 70 eV. Compounds **(3)**[5], hydrazonoyl halides **(6)**[6], hydrazone **(12a)**[7], triazoles **(15a–d)**[8], **(15e-i)**[9], **(17)**[10] were prepared as previously described.

Synthesis of 3-(4-chlorophenyl)-4-salicylideneamino-1,2,4-oxadiazospiro-[4.5]decane (5): Compound **3** (0.40 g, 0.0015 mol) and salicylaldehyde (0.25 g, 0.002 mol) in ethanol (50 mL) were refluxed for 2 h. The solvent was then concentrated to 20 mL. The precipitated compound **5** was filtered using suction filtration, washed with petroleum ether (40–60°C), collected and dried. m.p.

124°C; ^{1}H NMR DMSO-d_6 (ppm): 10.2 (s, 1H, OH), 8.6 (s, 1H, HC=N), 6.8–7.6 (m, 8H, aromatic), 1.0–2.1 (m, 10H, cyclohexane protons); ^{13}C NMR (Dept 135, Dept 90) (ppm): 157.4 (C=N), 152.1 (HC=N), 132.3, 130.2, 129.0, 128.6, 119.8, 116.6 (6 aromatic C—H), 155.9, 135.7, 124.8, 119.2 (4 aromatic C), 102.3 (spiro carbon), 32.9, 24.3, 22.7 ($3CH_2$); IR (KBr, cm^{-1}): 3250 ν(OH), 1616, 1599 ν(C=N); m.w. 369/371 ($C_{20}H_{20}ClN_3O_2$).

1-(2-Hydroxyphenyl)-4-methyl-2,3-diaza-1,3-pentadiene (13a): From 2.7 g (2 mol of **12a**): yield 1.7 g (44%); m.p. 62°C; ^{1}H NMR DMSO-d_6 (ppm): 11.6 (s, 1H, OH), 8.6 (s, 1H, HC=N), 6.9–7.6 (m, 4H, Ar), 2.02/1.98 (2s, 6H, $2CH_3$); ^{13}C NMR: 168.85 (C=N), 161.00 (HC=N), 159.16, 132.95, 132.01, 119.83, 118.67, 116.75 (6 aromatic carbons), 25.40, 18.85 ($2CH_3$); m.w. 176 ($C_{10}H_{12}N_2O$).

1-(4-Nitrophenyl)-4-methyl-2,3-diaza-1,3-pentadiene (13b): From 4.0 g (0.024 mol of **12b**): yield 2.3 g (46%), m.p. 80–83°C.

3-Acetyl-4-salicylidenamino-5,5-dimethyl-1-(4-chlorophenyl)-1,2,4-triazole (10a): This compound was prepared using a procedure similar to that used for the synthesis of compound **5**. From 1.84 g (0.006 mol) of **6**: yield 1.8 g (63%), m.p. 130°C; ^{1}H NMR $CDCl_3$ (ppm): 11.1 (s, 1H, OH), 8.7 (s, 1H, HC=N), 6.9–7.4 (m, 8H, aromatic), 2.5 (s, 3H, CH_3), 1.7 (s, 6H, $2CH_3$), ^{13}C NMR: 189.16 (C=O), 159.1 (HC=N), 143.87 (C=N), 158.90, 140.21, 132.22, 131.73, 129.28, 129.07, 120.38, 119.47, 117.66, 117.14 (10 aromatic carbons), 90.21 (C_5 ring), 27.06 ($2CH_3$), 23.59 (CH_3); IR (KBr, cm^{-1}): 1674 ν(C=O); m.w. 370/372 ($C_{19}H_{19}ClN_4O_2$).

3-Acetyl-4-(4-nitrobenzylidine)-5,5-dimethyl-1-(4-chlorophenyl)-1,2,4-triazole (10b): From 1.84 g (0.006 mol) of **6**: yield 1.5 g (47%), m.p. 97–99°C; ^{1}H NMR DMSO-d_6 (ppm): 8.2 (d, 2H, $J = 9$ Hz, *p*-NO_2-Ph), 7.8 (d, 2H, $J = 9$ Hz, *p*-NO_2-Ph), 7.4 (m, 4H, *p*-Cl–Ph), 8.1 (s, 1H, CH=N), 2.5 (s, 3H, CH_3), 1.7 (s, 6H, $2CH_3$), ^{13}C NMR: 188.43 (C=O), 143.41 (C=N), 143.05 (HC=N), 147.68, 141.76, 140.18, 129.56, 127.64, 127.09, 124.52, 119.53 (8 aromatic carbons), 88.99 (C_5 ring), 27.74 ($2CH_3$), 24.52 (CH_3); IR (KBr, cm^{-1}): 1675 ν(C=O); m.w. 399/401 ($C_{19}H_{18}ClN_5O_3$).

Synthesis of Oximes and Hydrazones 16 (General procedure)

The oximes were obtained from the reaction of the respective triazole (0.002 mol) with hydroxylamine hydrochloride (0.01 mol) in the presence of sodium acetate (0.01 mol) in a mixture of ethanol-water (60 mL). The reaction mixture was refluxed for 24 h. A solid product separated upon concentration of the solvent; it was filtered using suction filtration, washed with petroleum ether (40–60°C), collected and dried.

The hydrazones were prepared similarly by mixing (0.002 mol of the respective triazole with (0.02 mol of 80% hydrazine hydrate) in ethanol. The reaction mixture was stirred for three days at room temperature. A solid product separated upon concentration of the solvent; it was filtered using suction filtration, washed with petroleum ether (40–60°C), collected and dried.

The following compounds were prepared using this procedure:

3-Acetyl-4-benzoylamino-1-(4-chlorophenyl)-5,5-dimethyl-4,5-dihydro-1,2,4-triazole oxime (16a): ^{1}H NMR DMSO-d_6 (ppm): 11.3 (s, 1H, OH), 10.3

(s, 1H, NH), 7.8–7.2 (m, 9H, aromatic protons), 2.0 (s, 3H, CH_3), 1.5 (s, 6H, $2CH_3$ at C5); ^{13}C NMR (Dept 135 + Dept 90): 167.61 (NC=O), 147.07 (C=N), 146.19, (C=NOH), 132.12, 129.11, 128.79, 128.15, 117.98 (5 aromatic C—H), 143.11, 133.37, 124.39 (3 aromatic C), 87.85 (C-5 carbon), 23.98 ($2CH_3$ at C5), 11.66 (CH_3C=N); IR (KBr, cm^{-1}): 3474 ν(OH), 3359 ν(NH), 1689 ν(NC=O); m.p. 175°C, yield (76%).

3-Acetyl-4-benzoylamino-1-(4-chlorophenyl)-5,5-dimethyl-4,5-dihydro-1,2,4-triazole hydrazone (16b): ^1H NMR DMSO-d_6 (ppm): 10.2 (s, 1H, NH), 6.6 (s, 2H, NH_2), 7.8–7.2 (m, 9H, aromatic protons), 1.9 (s, 3H, CH_3), 1.5 (s, 6H, $2CH_3$ at C5); ^{13}C NMR (Dept 135 + Dept 90): 167.84 (NC=O), 148.52 (C=N), 133.83 (C=NNH_2), 131.86, 129.00, 128.74, 128.15, 117.51 (5 aromatic C—H), 143.50, 133.18, 123.54 (3 aromatic C), 87.02 (C-5 carbon), 23.89 ($2CH_3$ at C5), 11.71 (CH_3C=N); IR (KBr, cm^{-1}): 3419, 3291, 3150 ν(3NH), 1671 ν(NC=O); m.p. 188°C, yield (44%).

3-Acetyl-4-benzoylamino-1-(4-chlorophenyl)-1,2,4-triazaspiro[4.4]non-2-ene oxime (16c): Yield (62%); m.p. 158°C.

3-Acetyl-4-benzoylamino-1-(4-chlorophenyl)-1,2,4-triazaspiro[4.4]non-2-ene hydrazone (16d): ^1H NMR DMSO-d_6 (ppm): 10.3 (s, 1H, NH), 6.5 (s, 2H, NH_2), 7.8–7.2 (m, 9H, aromatic protons), 1.9 (s, 3H, CH_3), 1.7–2.2 (m, 8H, cyclopentane); ^{13}C NMR (Dept 135 + Dept 90): 168.7 (NC=O), 147.78 (C=N), 133.80 (C=NNH_2), 131.91, 129.58, 128.79, 128.14, 116.55 (5 aromatic C—H), 142.28, 133.28, 122.89 (3 aromatic C), 96.05 (C-5 carbon), 33.88, 25.16 (cyclopentane carbons), 11.58 (CH_3C=N); IR (KBr, cm^{-1}): 3425, 3282, 3155 ν(3NH), 1669 ν(NC=O); m.p. 150°C, yield (65%).

3-Acetyl-1-(4-chlorophenyl)-4,5-dihydro-4-methoxycarbonylamino-5,5-dimethyl-1H-1,2,4-triazole oxime (16e): ^1H NMR DMSO-D_6 (ppm): 11.5 (s, 1H, OH), 9.2 (s, 1H, NH), 7.3–7.2 (2d, 4H, aromatic protons), 3.6 (s, 3H, OCH_3), 2.0 (s, 3H, CH_3), 1.4 (s, 6H, $2CH_3$ at C5); ^{13}C NMR (Dept 135 + Dept 90): 157.86 (NC=O), 146.76 (C=N), 145.60, (C=NOH), 129.37, 118.32 (2 aromatic C—H), 143.19, 124.56 (2 aromatic C), 87.67 (C-5 carbon), 52.65 (OCH_3), 23.25 ($2CH_3$ at C5) 11.66 (CH_3C=N); IR (KBr, cm^{-1}): 3460 ν(OH), 3237 ν(NH), 1719 ν(C=O); m.p. 181°C, yield (62%).

3-Acetyl-1-(4-chlorophenyl)-4,5-dihydro-4-methoxycarbonylamino-5,5-dimethyl-1H-1,2,4-triazole hydrazone (16f): ^1H NMR DMSO-D_6 (ppm): 9.0 (s, 1H, NH), 7.3–7.2 (2d, 4H, aromatic protons), 6.7 (s, 2H, NH_2), 3.6 (s, 3H, OCH_3), 1.9 (s, 3H, CH_3), 1.4 (s, 6H, $2CH_3$ at C5); ^{13}C NMR (DEpt 135 + Dept 90): 158.06 (NC=O), 148.20 (C=N), 132.88, (C=NNH_2), 129.24, 117.67 (2 aromatic C—H), 143.63, 123.76 (2 aromatic C), 86.79 (C-5 carbon), 52.32 (OCH_3), 23.00 ($2CH_3$ at C5), 11.65 (CH_3C=N); IR (KBr, cm^{-1}): 3404, 3232 ν(NH), 1728 ν(C=O); m.p. 146°C, yield (80%).

3-Acetyl-1-(4-chlorophenyl)-4-ethoxycarbonylamino-1,2,4-triazaspiro[4.4]-non-2-ene oxime (16g): ^1H NMR $CDCl_3$ (ppm): 10.1 (s, 1H, OH), 8.3 (s, 1H, NH), 7.2–7.0 (2d, 4H, aromatic protons), 4.2 (q, 2H, OCH_2), 2.2 (s, 3H, CH_3), 2.2–1.7 (m 8H, cyclopentane), 1.2 (t, 3H, CH_3); ^{13}C NMR (Dept 135 + Dept 90): 158.93 (NC=O), 147.39 (C=N), 144.82, (C=NOH), 128.86, 117.88 (2 aromatic C—H), 141.29, 126.13 (2 aromatic C), 95.49 (C-5 carbon), 62.84 (OCH_2),

30.11, 24.32 (CH_2 from cyclopentane), 14.63 (CH_3), 10.68 (CH_3C=N); IR (KBr, cm^{-1}): 3460 ν(OH), 3237 ν(NH), 1719 ν(C=O); m.p. 145°C, yield (69%).

3-Acetyl-1-(4-chlorophenyl)-4-ethoxycarbonylamino-1,2,4-triazaspiro[4.4]-non-2-ene hydrazone (16h): ^1H NMR $CDCl_3$ (ppm): 7.0 (s, 1H, NH), 5.5 (s, 2H, NH_2), 7.2–7.1 (2d, 4H, aromatic protons), 4.2 (s, 3H, OCH_3), 2.0 (s, 3H, CH_3); 2.2–1.6 (m 8H, cyclopentane), 1.2 (t, 3H, CH_3); ^{13}C NMR (Dept 135 + Dept 90): 157.54 (NC=O), 146.01 (C=N), 138.53, (C=NNH_2), 128.75, 117.80 (2 aromatic C—H), 141.82, 125.36 (2 aromatic C), 96.17 (C-5 carbon), 61.93 (OCH_2), 33.70, 24.91 (CH_2 from cyclopentane), 14.68 (CH_3), 10.73 (CH_3C=N); IR (KBr, cm^{-1}): 3417, 3336, 3258 ν(NH), 1719 ν(C=O); m.p. 107°C, yield (36%).

3-Acetyl-5-methyl-1-(4-chlorophenyl)-1H-1,2,4-triazole hydrazone (18): This compound was prepared using a procedure similar to that reported for the synthesis of hydrazones **16**. ^1H NMR $CDCl_3$ (ppm): 7.5 (2d, 4H, Ar), 5.5 (s, 2H, NH_2), 2.4 (s, 3H, CH_3C=O), 2.2 (s, 3H, CH_3); 161.5, 153.5, 134.8 (3C=N), 139.6, 136.3 (2 aromatic C), 130.0, 126.1 (2 aromatic C—H), 13.7 (CH_3), 11.1 (CH_3C=N—NH_2); IR (KBr, cm^{-1}): 3451, 3289 ν(NH_2), 1619, 1590 ν(C=N); m.p. 175°C, yield (95%); m.w. 249/251 ($C_{11}H_{12}ClN_5$).

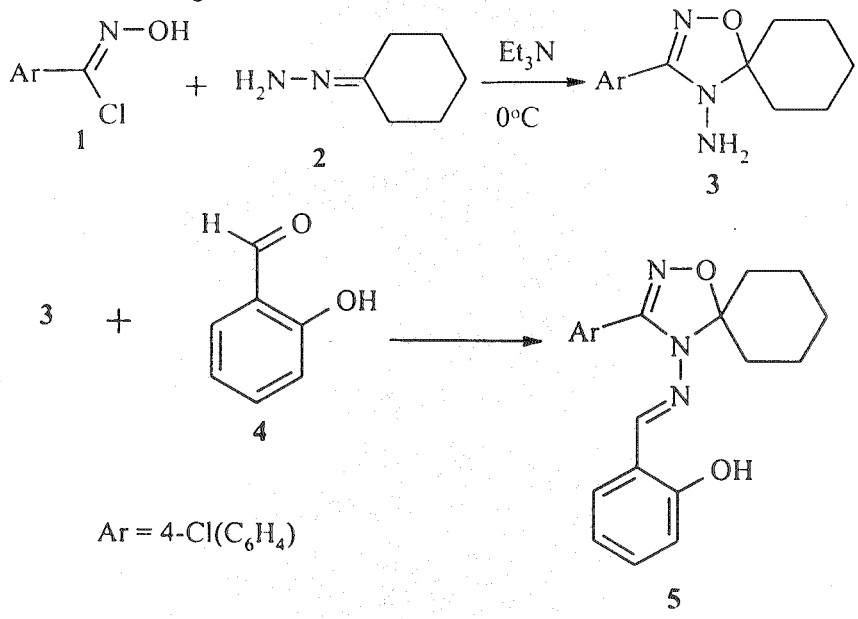
3-Acetyl-5-methyl-1-(4-chlorophenyl)-1H-1,2,4-triazole-2-hydroxybenzylidene-hydrazone (19): This compound was prepared by mixing the hydrazone **18** (0.6 g, 0.0024 mol) with salicylaldehyde (0.35 g, 0.0027 mol) in ethanol 50 mL. The mixture was refluxed for 2 h. The product precipitated upon cooling and concentration of the solvent. ^1H NMR $CDCl_3$ (ppm): 9.0 (OH), 6.9–7 (m, 8H, aromatic), 2.68 (s, 3H, CH_3), 2.70 (s, 3H, CH_3); ^{13}C NMR (Dept 135 + Dept 90): 165.5 (HC=N), 160.5, 159.9 (2C=N), 154.3, 136.0, 135.5, 118.2 (4 aromatic C), 133.6, 133.0, 130.1, 126.3, 119.9, 117.3 (6 aromatic C—H), 15.5, 13.7 (2 CH_3); IR (KBr, cm^{-1}): 3300 ν(OH), 1619, 1600 ν(C=N); m.p. 184°C, yield (75%); m.w. 353/355 ($C_{18}H_{16}ClN_5O$).

3-Acetyl-1-(4-chlorophenyl)-4-ethoxycarbonylamino-1,2,4-triazaspiro[4.6]-undec-2-ene 2-hydroxybenzylidenehydrazone (20): This compound was prepared by reacting the triazole **15i** (0.002 mol) with excess hydrazine hydrate (0.02 mol). The reaction mixture was stirred for 24 h at room temperature. The solvent and the excess hydrazine were then completely evaporated. Salicylaldehyde (0.02 mol) in 40 mL ethanol was then added to the oily crude product, and the reaction mixture was refluxed for 2 h. Concentration of the solvent gives the pure product. ^1H NMR in $CDCl_3$: 8.6 (s, 1H, OH), 5.5–7.6 (m, 8H, aromatic), 6.8 (s, 1H, NH), 4.2 (q, 2H, OCH_2), 2.0 (s, 3H, CH_3), 2.6–1.1 (m, 12H, cycloheptane protons), 1.2 (t, 3H, CH_3); ^{13}C NMR (Dept 135 + Dept 90): 165.1 (HC=N), 163.6, 160.4 (2C=N), 146.1, 141.8, 133.8, 117.5 (4 aromatic C), 133.5, 132.6, 129.6, 122.1, 119.9, 117.4 (6 aromatic C—H), 92.8 (C-5 ring spiro carbon), 62.4 (OCH_2), 39.2, 30.8, 24.1 (cycloheptane carbons), 15.0, 14.5 ($2CH_3$); IR (KBr, cm^{-1}): 3350 ν(OH), 3252 ν(NH), 1724 ν(COO), 1622, 1615 ν(C=N); m.p. 141°C, yield = (55%); m.w.: 510/512 ($C_{26}H_{31}ClN_6O_3$).

RESULTS AND DISCUSSION

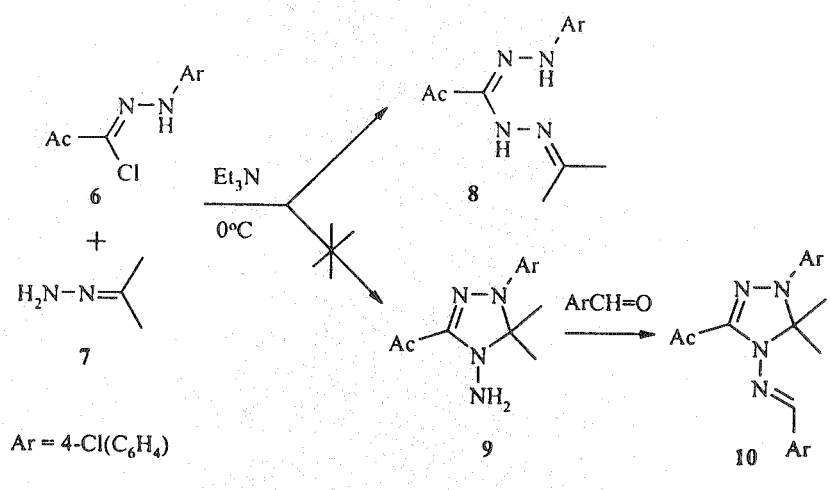
The reaction of hydoxamoyl chloride (**1**) with cyclohexanone hydrazone (**2**) was reported to give the cycloaddition 4-amino-1,2,4-oxadiazolines (**3**)[4]. Conden-

sation of this compound with salicylaldehyde gave the corresponding Schiff base **5** (**Scheme-1**). Structural assignment of the resulting product was based on spectral data including IR, MS and NMR.



Scheme-1

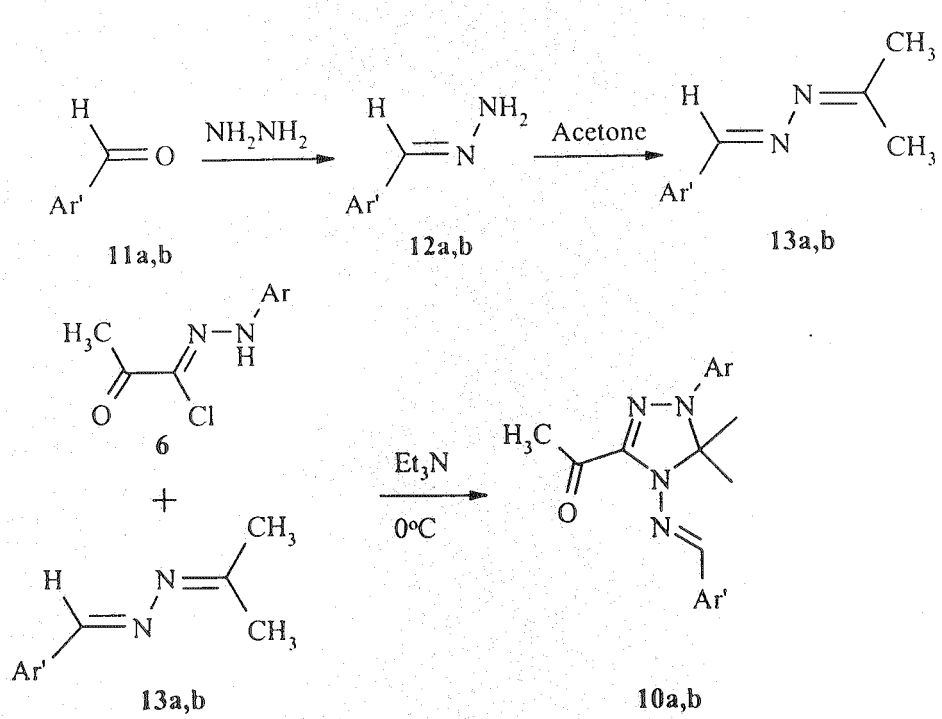
The similar reaction of nitrilimines **6** with hydrazones **7** gave, however, the acyclic adducts **8** rather than the amino triazoles **9**[11] and hence, the Schiff bases



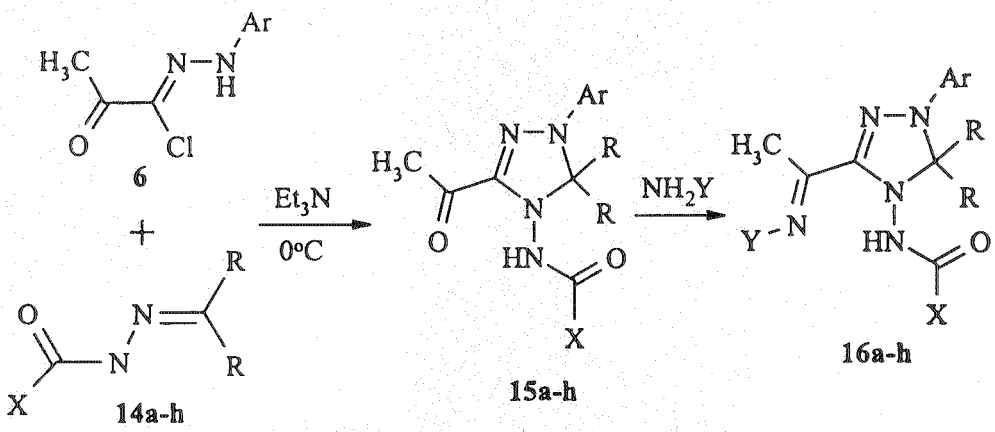
Scheme-2

10 cannot be prepared using this approach (**Scheme-2**).

A new approach for the synthesis of Schiff bases **10** is presented as: aryl aldehyde hydrazones **12** were first prepared[7]. Condensation of these hydrazones with acetone gave the corresponding 1-aryl-4-methyl-2,3-diaza-1,3-pentadiene (**13**). The reaction of nitrilimines with **13** gave the target Schiff bases **10**. Structural assignment of the resulting product was also based on spectral data including IR, MS, and NMR (**Schemes 2 and 4**).



Scheme-3



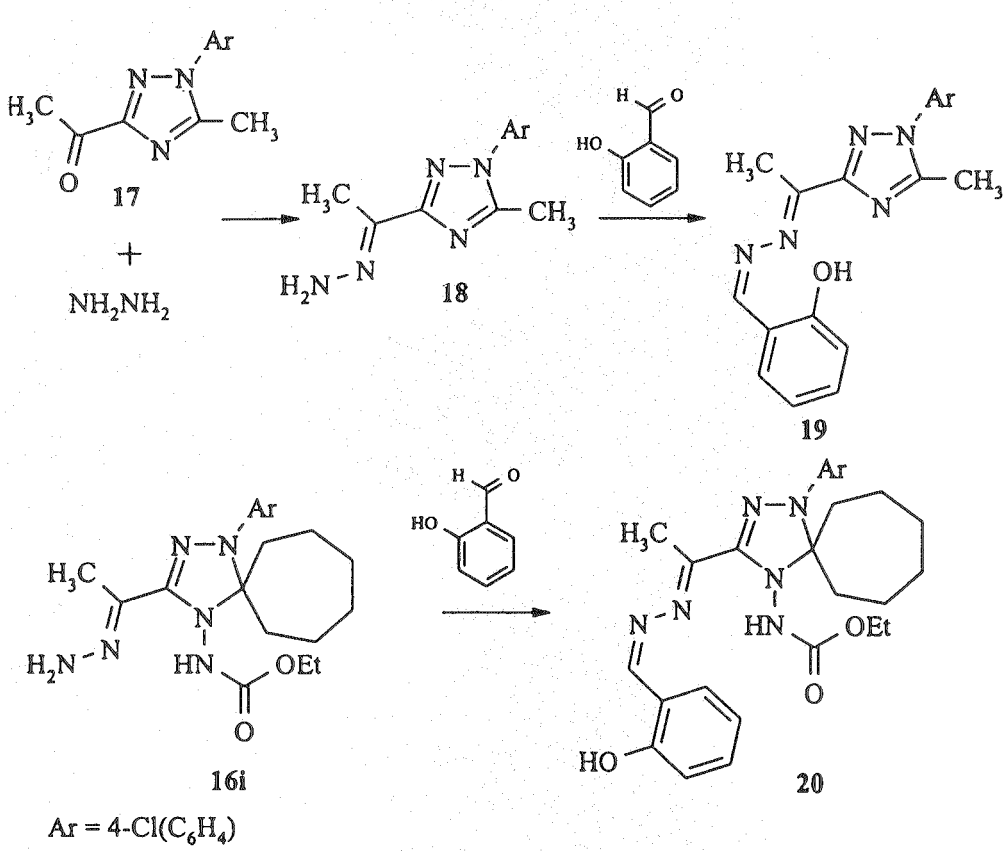
15 / 16	a	b	c	d	e	f	g	h	i
R, R	Me/Me	Me/Me			Me/Me	Me/Me			
X	Ph	Ph	Ph	Ph	OMe	OMe	OEt	OEt	OEt
Y	OH	NH_2	OH	NH_2	OH	NH_2	OH	NH_2	NH_2

Scheme-4

Differently substituted triazoles **15** were recently prepared[8, 9]. Oximes and hydrazones **16** of these triazoles prepared in order to study their biological activitycompounds gave spectral data in consistence with their suggested structures.

Schiff base **19** of the triazole hydrazone **18** with salicylaldehyde, and that of triazole hydrazone **16i** with salicylaldehyde were also prepared (**Scheme-5**), and their structures were proved using spectral data analysis. These derivatives can serve as good bidentate ligands, which can react with different metals giving complexes that may find biological activity or used as catalysts.

All the above compounds are to be investigated for any antibacterial or antifungal effects.



Scheme-5

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