

Synthesis and antimicrobial activity of some nitrogen heterobicyclic systems: Part III

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In search for a newer antimicrobial agents, some new nitrogen heterobicyclic systems **3-20** have been synthesized via condensation of the corresponding acetic acid hydrazide **2** with some oxygen compounds. The structures of these target compounds have been elucidated by elemental analysis and spectral data (IR, ¹H NMR and mass). The biocidal activity of the products have also been determined using gentamycin as standard antibiotic. Some compounds show equivalent activity to that of gentamycin towards *S. marcescens*.

Recently, we have reported the synthesis and antimicrobial, pharmaceutical and medicinal applications of some nitrogen heterocyclic systems¹⁻⁴. In continuation of our interest this field^{5,6}, we report here the synthesis of some more heterobicyclic systems which are likely to show enhanced biocidal effect.

The starting material *N*-triazino-2-acetic acid hydrazide derivative **2** was obtained⁷ by hydrazinolysis of the corresponding ethyl carboxylate derivative **1**.

Reaction of **2** with carbonyl compounds such as aldehydes, ketones, benzoin, *o*-acetylbenzoic and *o*-benzoylbenzoic acids in the presence of absolute ethanol with few drops of glacial acetic acid produced hydrazones **3a-g**, respectively (Scheme I). The structures of these compounds were deduced from elemental analyses and spectral data. The IR spectrum of **3a** showed characteristic bands at 3100, 3000-2980, 1680, 1600, 1550 and 700 cm⁻¹ attributed to NH, aromatic, aliphatic, C=O, CONH, exo C=N and C-Cl groups, while ¹H NMR spectrum of **3b** showed signals at δ 3.5, 4.7, 5.5, 7-8 and 10.5 ppm for CH₂, CH=N, NH, aromatic and OH protons.

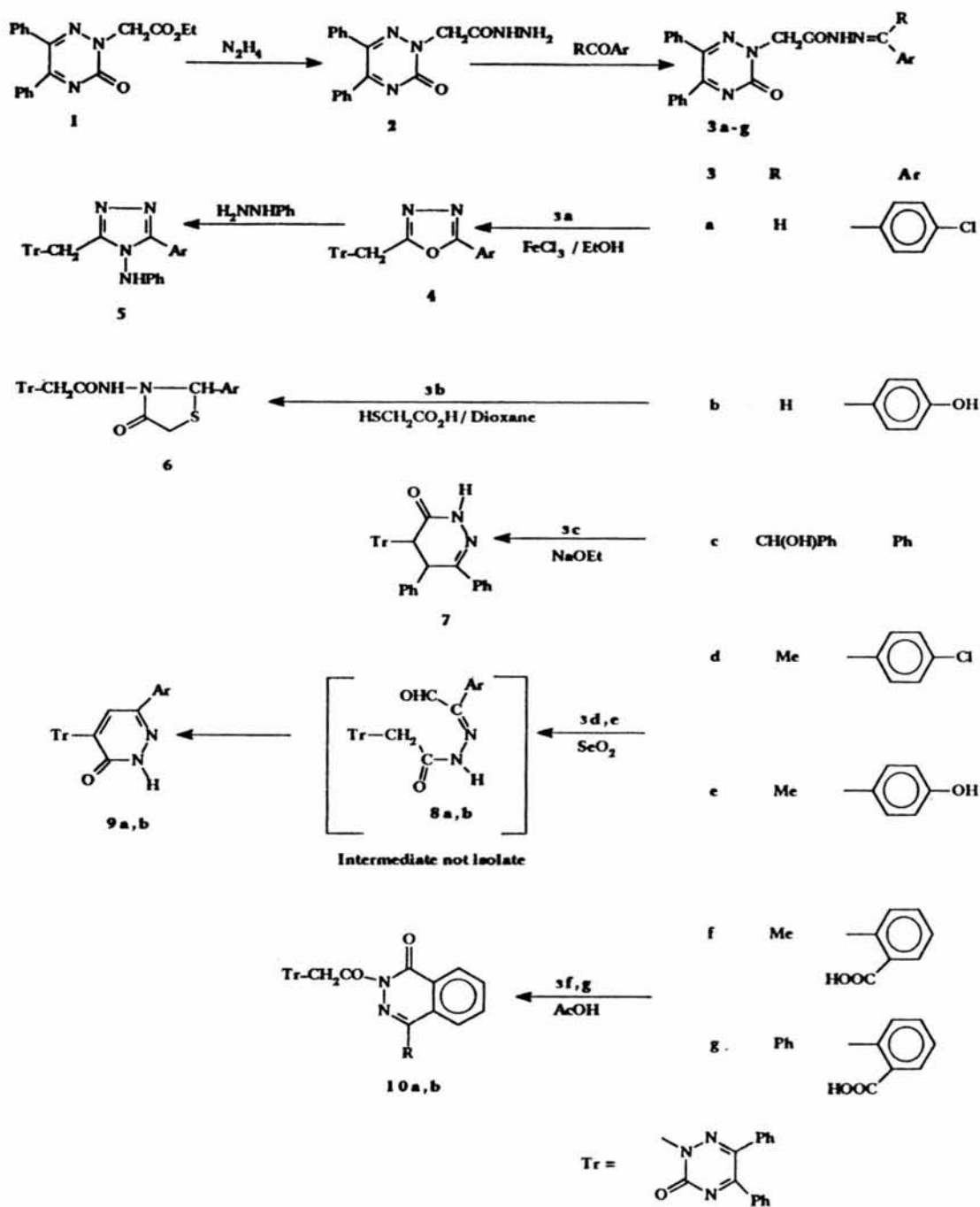
Treatment of **3a** with FeCl₃-ethanol⁸ afforded 2-aryl-5-(5, 6-diphenyl-3-oxo-1, 2, 4-triazin-2-ylmethyl)-1, 3, 4-oxadiazole **4** which on condensation with phenylhydrazine in the presence of absolute ethanol⁹ gave 3-aryl-4-anilino-5-(5, 6-diphenyl-3-oxo-1, 2, 4-triazin-2-ylmethyl)-1, 2, 4-triazole **5**. Moreover,

cycloaddition of **3b** with mercaptoacetic acid followed by cyclization in dry benzene-fused Na₂SO₄ furnished¹⁰ 4-thiazolidinone **6** (Scheme I).

The structures of compounds **4-6** were established on the basis of their elemental analyses and spectral studies. The IR spectrum of **4** revealed the presence of aromatic, aliphatic, carbonyl and C=N groups (3000-2900, 1700, 1580, 1570-1550 cm⁻¹) while that of **5** recorded the absorption bands at 3150, 3000, 2800, 1720 and 700 cm⁻¹ due to NH, aromatic, aliphatic, C=O and C-Cl groups. The ¹H NMR spectrum of **4** exhibited the signals attributed to CH₂, aromatic and NH—N< protons at δ 3.5, 7.8-8.5 and 12.7 ppm. The IR spectrum of **6** revealed the presence of OH, NH, C=O, CH₂, and C-S groups (3500-3100, 1700, 1680, 1480-1440, and 1100 cm⁻¹).

The original aim of the present work was to synthesize some more nitrogen heterobicyclic systems. Thus, compound **3c** underwent cyclization in sodium ethoxide resulting in the formation 4, 5-dihydro-5, 6-diphenyl-4-(5, 6-diphenyl-3-oxo-1, 2, 4-triazin-2-yl) pyridazin-3 (2*H*)-one **7** while normal oxidation of **3 d, e** using SeO₂ in dry dioxan¹¹ led directly to the formation of 4-(5, 6-diphenyl-3-oxo-1, 2, 4-triazin-2-yl)-6-arylpyridazin-3 (2*H*)-ones **9a,b** (Scheme I).

Structures of **7** and **9** were established from elemental analysis and spectral data. The IR spectrum of **7** showed characteristic bands due to OH, NH,



Scheme 1

C=O, C=N and phenyl groups (3200-3170, 1700, 1670, 1600-1580, 850, 800 cm^{-1}) while its ^1H NMR spectrum showed signals due to aliphatic, aromatic and NH protons at δ 6.6-8 and 11.7 ppm. The IR spectrum of **9a** showed a characteristic bands at 3210, 3020, 2850, 1720, 1640, 1440 and 700-680 cm^{-1} due to NH, aromatic, aliphatic, C=O, C=N and C-Cl functional groups. The ^1H NMR spectrum of **9a**

exhibited signals confirming the presence of CH=C, NH and aromatic protons at δ 4.1, 5.6, 7.2-7.8 and 7.9-8.2 ppm.

A facile synthesis of isolated nitrogen heterobicyclic systems **10a** and **10b** has been achieved by refluxing **3 f,g** with glacial acetic acid in fused sodium acetate (Scheme 1). Compounds **10a,b** were also obtained by cyclocondensation of acetic

Table I—Physical characterisation data of the synthesized compounds 3-20

Compd	Crystallized	mp	Yield	Mol. formula	M ⁺	N
						Found/Calc. %
	from	°C	(%)			
3a	EtOH	201-203	80	C ₂₄ H ₁₈ Cl N ₅ O ₂	443	15.00/15.80
3b	EtOH	221-223	70	C ₂₄ H ₁₉ N ₅ O ₃	425	15.90/16.47
3c	EtOH	128-130	75	C ₃₁ H ₂₅ N ₅ O ₃	515	13.00/13.59
3d	Dioxan	145-147	70	C ₂₅ H ₂₀ Cl N ₅ O ₂	457	14.80/15.31
3e	Dioxan	230-231	60	C ₂₅ H ₂₁ N ₅ O ₃	439	15.10/15.95
3f	Dioxan	209-210	78	C ₂₆ H ₂₁ N ₅ O ₄	467	14.30/14.98
3g	Dioxan	215-217	68	C ₃₁ H ₂₃ N ₅ O ₄	529	12.75/13.23
4	Benzene	213-215	90	C ₂₄ H ₁₆ Cl N ₅ O ₂	441	15.30/15.87
5	Benzene	225-227	65	C ₃₀ H ₂₂ Cl N ₇ O	517	18.00/18.24
6	MeOH	208-210	90	C ₂₆ H ₂₁ N ₅ S ⁺ O ₄	499	13.15/14.02
7	Dioxan	171-173	78	C ₃₁ H ₂₃ N ₅ O ₂	497	13.80/14.08
9a	EtOH	212-213	90	C ₂₅ H ₁₈ Cl N ₅ O ₃	471	14.41/14.86
9b	DMF	220-221	95	C ₂₅ H ₁₇ N ₅ O ₃	435	16.00/16.09
10a	AcOH	170-172	80	C ₂₆ H ₁₉ N ₅ O ₃	449	15.10/15.59
10b	AcOH	185-187	90	C ₃₁ H ₂₁ N ₅ O ₃	511	13.00/13.69
11	Dioxan	230-231	79	C ₂₅ H ₂₁ N ₅ O ₃	439	15.10/15.94
12	Dioxan	214-215	75	C ₂₅ H ₁₉ N ₅ O ₂	421	16.01/16.62
14	Dioxan	240-242	60	C ₃₂ H ₂₅ Cl N ₆ O ₄	592	13.81/14.18
15	Dioxan	abov.300	50	C ₃₂ H ₂₃ Cl N ₆ O ₃	574	14.00/14.6
17	Benzene	210-211	55	C ₂₈ H ₂₄ N ₆ O ₅	524	15.05/16.03
18	Benzene	218-220	60	C ₂₈ H ₂₂ N ₆ O ₄	506	16.10/16.60
20	Dil.AcOH	220-222	85	C ₃₄ H ₂₄ N ₈ O ₃	593	18.11/19.05

All the compounds gave satisfactory C, H and Cl analysis.

¹Found: S, 5.71; Calcd.: S, 6.41%.

acid hydrazide **2** with *o*-acetyl/benzoylbenzoic acid in the presence of glacial acetic acid with fused sodium acetate for a long period¹².

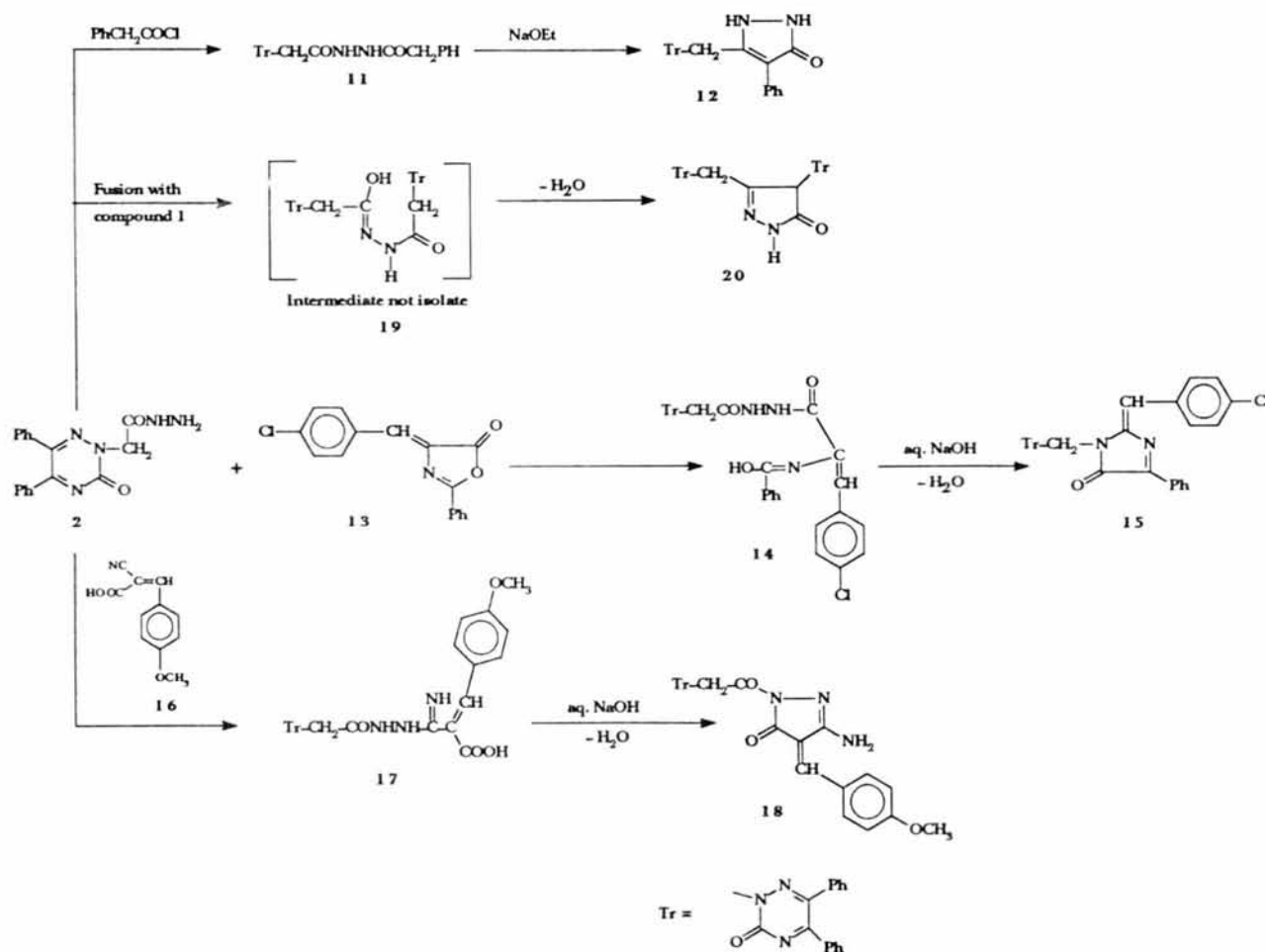
The IR spectra of **10a,b** showed absorption bands at 3020-2980 (aromatic and aliphatic), 1780, 1700, 1650 (3 C=O), 1560-1540 (C=N), 1480-1440 (deformation of CH₂) and 900, 800 cm⁻¹ (phenyl groups), while ¹H NMR spectrum of **10a** lent further support to structure and showed signals at δ 3.6, 7.3-7.9 and 8.1-8.3 ppm attributed to CH₂ and aromatic protons.

Pyrazole compounds have a marked biological activity^{13,14}. This prompted us to prepare some new substituted pyrazoles and evaluate their antimicrobial activity. The target pyrazoles **12**, **18** and **20** and also imidazole **15** were obtained by the treatment of acetic acid hydrazide **2** with *N*-phenylacetyl chloride (in DMF), oxazolone **13** (in aqueous ethanol¹⁵) and α -cyanoethylene **16** (in ethanol-piperidine) followed by cyclization in basic medium. Finally, fusion of

compounds **1** with **2** at 200°C gave 3-(5, 6-diphenyl-3-oxo-1, 2, 4-triazin-2-yl methyl)-4-(5,6-diphenyl-3-oxo-1, 2, 4-triazin-2-yl)-4, 5-dihydropyrazol-5 (*1H*) one **20** without isolation¹⁶ of the intermediate **19** (Scheme II). Formation of the pyrazoles **12**, **18** and **20** was confirmed by their positive Knorr's colour test¹⁷.

The structural assignments of compounds **12-20** were based on elemental analyses and spectral data. The IR spectra of these compounds showed the presence of C=O (1700, 1680, 1650), arylidene (1600, 1570), methylene (2900-2800) and their deformation (1470, 1440) bands in addition to NH at (3100-3000) (**12**, **20**) and NH₂ band at 3300 cm⁻¹ (**18**). The ¹H NMR spectra of **11-15** indicated the presence of signals at δ 2.65, 3.7, 7.3-8.1 and 8.8 ppm attributed to CH₂, CH of pyrazol-4-yl, aromatic and NH protons; in addition signals appeared at δ 6.6 (exocyclic =CH, **15,18**) and 12.7 (NH₂, **18**).

The mass spectrum of **20** showed a molecular ion



Scheme II

peak at m/z 592 (0.1%) corresponding to the molecular formula weight, a peak at m/z 344 (5%) corresponding to the loss of 5,6-diphenyl-3-oxo-1,2,4-triazin-2-yl moiety and the base peak at m/z 178 due to diphenylene acetylene radical ion¹⁸ that corroborate the assigned structure.

Antimicrobial activity. In a program to obtain new potent antimicrobial agents, the synthesized compounds were evaluated against the bacteria, *S. aureus*; *S. marcescens*; *B. subtilis*; *C. albine*; *E. coli* and *M. lutea* in DMF as solvent at concentration 4 mg/mL. Gentamycin antibiotic was used as standard for the antibacterial activity. The cup diffusion techniques were performed¹⁹ and the results obtained are recorded in **Table II**.

From the results obtained, it is obvious that all the compounds show promising antimicrobial activity while the presence of phenolic moiety especially when attached to heterocyclic ring augments the

antibacterial activity remarkably. On the other hand, compounds having acetamido structure are more active than the compounds bearing CH_2 group (**3a**, **3f**, **5**, **9** and **12**). Also, thiazolidinones **6** are in general more active than other five-membered heterocyclic systems²⁰ (**12** and **15**) towards *S. aureus* while hydroxypyrimidine **9a** shows a sharp fall in the activity toward *M. lutea* than other tested compounds.

Finally, compound **10** exhibits antibacterial activity equivalent to that of gentamycin toward *S. marcescens* (**Table II**).

Experimental Section

General. Melting points reported are uncorrected. IR spectra (KBr) were recorded on a FTIR 1650 spectrophotometer (γ_{max} in cm^{-1}), ^1H NMR spectra in $\text{DMSO}-d_6$ with TMS as internal standard (δ , ppm) on a Tesla BS-467 (60 MHz) spectrometer (JEOL), and mass spectra on a Gas chromatographic GCMS qp 1000_{ex} Shimadzu instrument at 70 eV.

Table II—Antibacterial activities of some compounds^a at 4 mg/mL concentration (diameter of inhibition zones in mm)

Compd.	<i>S. aureus</i>	<i>S. marcescens</i>	<i>B. subtilis</i>	<i>C. albicans</i>	<i>E. coli</i>	<i>M. lutea</i>
3c	16	24	-	14	17	-
3f	12	23	12	15	16	-
4	-	23	-	11	12	-
5	20	21	-	13	18	-
6	22	20	12	12	13	16
7	13	21	12	13	14	12
9a	-	22	-	12	15	18
10a	16	25	14	13	14	13
12	11	24	-	12	13	-
13	11	22	16	11	12	13
18	-	21	15	11	11	13
DMF	-	12	-	-	-	-
(Control)						
Gentamycin	28	27	24	22	28	30

Preparation of 2-carboxyhydrazone-5, 6-1, 2, 4-triazin-3-ones 3 a-g. A mixture of **2** (0.01 mole) and the appropriate carbonyl compound (0.01 mole) in ethanol (50 mL) and glacial acetic acid (1 mL) was refluxed for 1hr, cooled and the resultant solid filtered, and recrystallized to give **3a-g** (Table I).

Oxidative cyclization of 3a: Formation of 2,5-disubstituted-1,3,4-oxadiazole 4. Compound **4** was obtained as colourless crystals by oxidative cyclization of the arylidenehydrazone **3a** with FeCl₃ as described earlier¹⁵.

Synthesis of N¹-anilino-2, 5-disubstituted-1, 3, 5-triazole 5. Equimolar mixture of **4** and phenylhydrazine in absolute ethanol (100 mL) was refluxed for 6hr concentrated, one drop of conc HCl added to it and poured onto ice. The solid thus obtained was recrystallized to give **5** (Table I).

Synthesis of pyridazinone derivative 7. A mixture of **3c** (0.01 mole) and sodium ethoxide (0.5 g Na in 50 mL abs. ethanol) was refluxed for 4hr, cooled and poured onto ice-HCl. The resulting solid was crystallized to give **7** (Table I).

Oxidative cyclization of 3d,e: Formation of 4,6-disubstituted pyridazin-3(2H)-ones 9a,b. A suspension of **3d,e** (0.01 mole) in dry dioxan (100 mL) with SeO₂ (5 g) was refluxed for 8hr, filtered while hot and concentrated. The resulting solid was crystallized to give **9a,b** (Table I).

Synthesis of phthalazinone derivatives 10 a,b.

(a) A mixture of **3f,g** (0.01 mole) in glacial acetic acid (50 mL) and fused sodium acetate (5g) was refluxed for 2hr, cooled and diluted with cold water. The solid thus, obtained was recrystallized to give **10a,b** (Table I).

(b) A mixture of **2** (0.01 mole) with 2-acetylbenzoylbenzoic (0.01 mole) in glacial acetic acid (100 mL) was refluxed for 4hr, cooled and poured onto ice. The solid obtained was recrystallized to give **10a,b** (Table I).

Mps and mixed melting pointing of the compounds from method **a** and **b** gave no depression.

Preparation of N¹,N²-diacetylhydrazine derivative 11. A mixture of **2** (0.01 mole) and phenylacetyl chloride (0.01 mole) in DMF (20 mL) was refluxed for 1hr, cooled and poured onto ice. The solid obtained was filtered and recrystallized to give **11** (Table I).

1, 2-Dihydro-4, 5-disubstituted pyrazol-3 (2H)-one 12. A mixture of **11** (0.01 mole) and sodium ethoxide (0.5 g Na in 50 mL absolute ethanol) was refluxed for 4hr, cooled and poured onto ice-HCl. The solid thus obtained was recrystallized to give **12** (Table I).

Formation of acid hydrazido derivative 14. A mixture of **2** (0.01mole) and oxazolone **13** (0.01 mole) in aqueous ethanol (80%, 50 mL) was refluxed for 6hr, and cooled. The precipitated solid was filtered and crystallized to give **14** (Table I).

Synthesis of imidazolone derivative 15. A mixture of **14** (0.01 mole) and aqueous sodium hydroxide (2N, 100 mL) was refluxed for 4hr, cooled and neutralized with dilute HCl. The solid thus obtained was recrystallized to give **15** (Table I).

Addition of 2 with α -cyanoethylene derivatives 16 : Formation of 17. Equimolar mixture of **2** and **16** in ethanol (100 mL) with piperidine (0.5 mL) was refluxed for 12 hr, cooled and concentrated, and then diluted. The solid obtained was filtered and crystallizes to give **17** (Table I).

Basic cyclization of 17: Formation of 18. A mixture of **17** (0.01 mole) and aqueous sodium hydroxide (1%, 100 mL) was refluxed for 2hr, cooled, and neutralized with dilute acetic acid. The solid obtained was recrystallized to give **18** (Table I).

Synthesis of 3, 4-disubstituted-4, 5-dihydro-pyrazol-5 (1H)-one 20. Equimolar amounts of compounds **1** and **2** were fused under reflux at 200°C for 2hr and cooled. The precipitated solid was triturated with methanol and crystallized to give **20** (Table I).

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