

Investigation of the Reaction of 6-Amino-3-methyl-4-oxo-3,4-dihydro-2-pyrimidinylhydrazine

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Abstract—The hydrazine derivative **2** has been utilized for the synthesis of three different fused 1,2,4-triazolo [4,3-a] pyrimidine derivatives **4**, **5** & **6** and a tetrazolo[1,5-a] pyrimidine derivative **7**. Reaction of **2** with the chalcone analogue 2-thenylidene-2'-acetothienone, gave the pyrazoline derivative **8**.

Keywords—Synthesis, fused-pyrimidines, triazoles, tetrazole, pyrazoline.

Hydrazine derivatives of aromatic and heterocyclic compounds are useful intermediates in the preparation of fused and hybridized ring systems¹⁻⁷). In analogy to these findings, it was of interest to investigate the synthesis and characterization of certain fused and hybridized derivatives of 6-amino-3-methyl-4-oxo-3,4-dihydro-2-pyrimidinyl-hydrazine **2**.

It is well established that the methylthio group attached to activated carbon can be substituted by weak basic nucleophiles⁷). Thus, 6-amino-3-methyl-2-methylthio-4-oxo-3,4-dihydro-pyrimidine (**1**⁸), was treated with hydrazine hydrate to obtain compound **2** (Scheme 1). Different triazoles from compound **2** have been prepared. Reaction of **2** with equimolar quantities of aromatic aldehydes in ethanol for 2 hr, yielded selectively, 1-arylidene-2-(6-amino-3-methyl-4-oxo-3,4-dihydro-2-pyrimidinyl) hydrazines **3a-d**. Treatment of **3a** with an acetic acid solution of bromine in presence of sodium acetate followed by pouring the reaction mixture into excess 0.5 N sodium hydroxide solution yielded 3-(4-chlorophenyl)-5-amino-8-methyl-7-oxo-7,8-dihydro-1,2,4-triazolo [4,3-a]pyrimidine **4**. The ¹H-NMR spectrum of compound **4** indicated the disappearance of the CH=N and NH protons of compound **3a** (Scheme 1). Alternatively, 5-formyl-amino-8-methyl-7-oxo-7,8-dihydro-1,2,4-triazolo [4,3-a] pyrimidine **5** was prepared by the action of formic acid on compound **2**. The structure of this fused system has been characterized by elemental and spectral analysis (see experimental part). On the other hand, reaction of compound **2** with carbon dis-

ulfide and potassium hydroxide yielded, 5-amino-8-methyl-7-oxo-7,8-dihydro-1,2,4-triazolo[4,3-a] pyrimidine-3-thiol **6**. The IR and ¹H-NMR spectra of compound **6** showed the disappearance of the characteristic bands of the NH and NH₂ of the hydrazine moiety. The N-aryl derivative of **6** was prepared by the action of *p*-chlorobenzoyl chloride in pyridine to afford **6a** (Scheme 1).

Fused tetrazoles could be prepared by the action of nitrous acid on hydrazine derivatives of cyclic systems in which a nitrogen atom is next to the carbon to which the hydrazine moiety is attached^{2,3,6,7}). The hydrazine derivative **2** can not be directly utilized for the synthesis of fused tetrazole derivative. Consequently, scheme 2 was applied to prepare the fused tetrazole derivative. Compound **1** was reacted with *p*-bromobenzaldehyde to form the Schiff's base **1a** from which compound **2a** was prepared by the action of hydrazine hydrate in a manner similar to that applied for the preparation of compound **2**. Finally, compound **2a** was then subjected to the action of nitrous acid in acetic acid to obtain 5-(4-bromobenzylidene)-amino-8-methyl-7-oxo-7,8-dihydro-tetrazolo[1,5-a] pyrimidine **7**. The IR and ¹H-NMR spectra of **7** showed the disappearance of the characteristic bands of the NH and NH₂ group of compound **2a**.

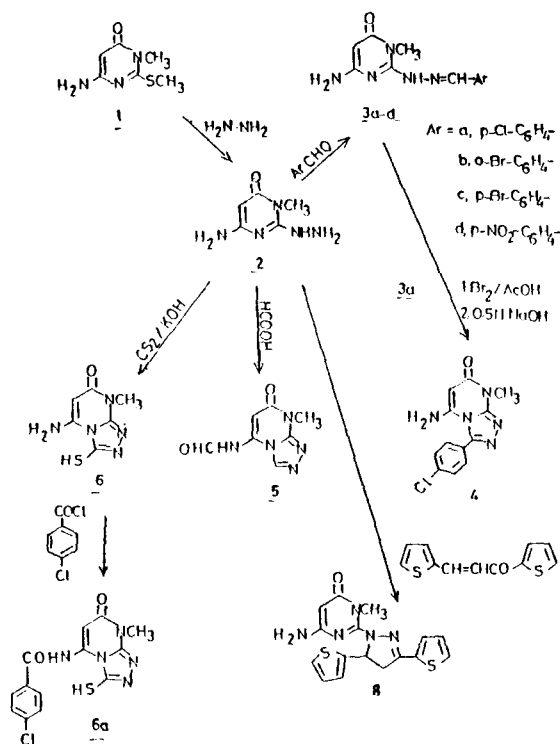
A single hybridized derivative **8** was prepared by the reaction of **2** with the chalcone analogue, 2-thenylidene-2'-acetothienone⁹). The structure of compound **8** was characterized by elemental and IR analysis (Scheme 1).

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EXPERIMENTAL

Melting points were determined on a Heine melt-



Scheme 1

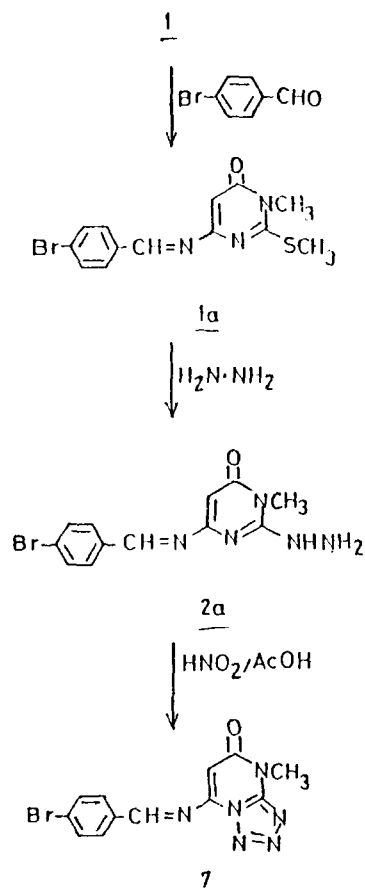
ing point apparatus and are uncorrected. IR spectra were recorded on a Pye Unicam SP 1000 spectrophotometer in KBr discs (ν , in cm^{-1}). ¹H-NMR spectra were measured in DMSO-*d*₆ with a JEOL FX 90 Q spectrometer and chemical shifts are given in δ values against TMS as the internal standard. Melting points, yield percentages, molecular formulae and elemental analysis of all compound are presented in Table I.

6-Amino-3-methyl-4-oxo-3,4-dihydro-2-pyrimidinylhydrazine 2

Compound 1 (0.01 mol, 1.71g) was heated under reflux with hydrazine hydrate (0.0122 mol, 0.6g) for 6 hr. The reaction product was then transferred to a filter paper, washed with ether and recrystallized from ethanol. IR: 1650 (CO), 2940 (CH) and 3180, 3320 (NH). ¹H-NMR: 2.49 (s, 2H, NH₂), 3.3 (s, 3H, CH₃), 4.97 (s, H, NH), 6.43 (s, 2H, NH₂ aromatic) and 7.54 (s, H, Ar-H).

1-Arylidene-2-(6-amino-3-methyl-4-oxo-3,4-dihydro-2-pyrimidinyl)hydrazines 3a-d

Compound 2 (0.01 mol, 1.55g) was heated under



Scheme 2

reflux with the appropriate aromatic aldehyde (0.01 mol) in ethanol (20 ml) for 2 hr. The solid separated after cooling was collected by filtration and crystallized from ethanol. IR: **3a-d**, 1470, 1570, 1610, 1655, 2950, 3200, and 3350 (1340, 1560 for NO₂ of compound **3d**), ¹H-NMR: **3a**, 3.3 (s, 3H, CH₃), 4.5 (s, H, NH), 6.7 (s, 2H, NH₂), 7.35-7.45 (d, 2H, Ar-H), 7.75-7.85 (d, 2H, Ar-H), 8.3 (s, H, Ar-H) and 9.9 (s, H, CH=N). **3c**, 3.3 (s, 3H, CH₃), 4.55 (s, 1H, NH), 6.7 (s, 2H, NH₂), 7.55-7.65 (d, 2H, Ar-H), 7.7-7.8 (d, 2H, Ar-H), 8.3 (s, 1H, Ar-H) and 9.95 (s, 1H, CH=N).

3-(4-Chlorophenyl)-5-amino-8-methyl-7-oxo-7,8-dihydro-1,2,4-triazolo [4,3-a]pyrimidine 4

A solution of bromine (0.05 ml) in glacial acetic acid (0.5 ml) was added to a mixture of anhydrous sodium acetate (0.9g) and compound **3a** (0.001 mol, 0.28g) in acetic acid (5 ml). The reaction mixture was allowed to stir at ambient temperature for 30 min. and

Table I. Melting points, yield percentages, molecular formulae and elemental analysis of compound 1-8

Comp. no.	mp. (°C)	Yield (%)	Molecular formulae	Elemental analysis (%)		
				Calcd.	Found	
2	257-9	65	C ₅ H ₉ N ₅ O	C	38.71	38.9
				H	5.81	5.7
				N	45.16	45.2
3a	271-2	85	C ₁₂ H ₁₂ ClN ₅ O	C	51.89	51.9
				H	4.32	4.2
				N	25.22	25.4
3b	255-7	70	C ₁₂ H ₁₂ BrN ₅ O	C	44.72	44.6
				H	3.73	3.8
				N	21.74	21.8
3c	269-71	85	C ₁₂ H ₁₂ BrN ₅ O	C	44.72	44.8
				H	3.73	3.6
				N	21.74	21.9
3d	285-7	90	C ₁₂ H ₁₂ N ₆ O ₃	C	50.00	49.8
				H	4.17	4.3
				N	29.17	29.4
4	230-32	50	C ₁₂ H ₁₀ ClN ₅ O	C	52.27	52.7
				H	3.63	3.7
				N	25.41	25.7
5	> 320	60	C ₇ H ₇ N ₅ O ₂	C	43.52	43.3
				H	3.63	3.8
				N	36.27	36.4
6	302-4	70	C ₆ H ₃ N ₅ O ₅	C	36.55	36.7
				H	3.55	3.4
				S	16.24	15.9
6a	280-2	85	C ₁₃ H ₁₀ ClN ₅ O ₂ S	C	46.50	46.5
				H	2.98	2.8
				N	20.86	20.8
1a	215-7	65	C ₁₃ H ₁₂ BrN ₃ OS	C	46.15	46.2
				H	3.55	3.5
				Br	23.67	23.6
2a	233-35	75	C ₁₂ H ₁₂ BrN ₅ O	C	44.72	44.6
				H	3.73	3.8
				N	21.74	21.9
7	210-12	60	C ₁₂ H ₉ BrN ₆ O	C	43.24	43.4
				H	2.7	2.6
				N	25.23	25.4
8	241-3	70	C ₁₆ H ₁₄ N ₅ OS ₂	C	53.93	53.7
				H	3.93	4.1
				S	17.98	17.8

poured into excess ice cooled 0.5 N NaOH (20 ml). The product separated was collected by filtration, washed with water, dried, and recrystallized from methanol. IR: 1570, 1640, 2940 and 3230. ¹H-NMR: 3.45 (s, 3H, CH₃), 6.6 (s, 2H, NH₂), 7.2-7.43 (d, 2H, Ar-H), 7.65-7.88 (d, 2H, Ar-H) and 8.48 (s, 1H, Ar-H).

5-Formylamino-8-methyl-7-oxo-7,8-dihydro-1,2,4-triazolo[4,3-a]pyrimidine 5

A mixture of compound 2 (0.005 mol, 0.78g) and formic acid (5 ml) was heated under reflux for 1 hr. The mixture was then poured onto crushed ice and

the solid separated was collected by filtration and recrystallized from DMF. IR: 1650, 1640, 2730, 2800, 2950 and 3260. ¹H-NMR: 3.3 (s, 3H, CH₃), 8.3 (s, 1H, Ar-H), 8.8 (s, 1H, Ar-H), 9.2 (s, 1H, CHO) and 11.1 (s, 1H, NH).

5-Amino-8-methyl-7-oxo-7,8-dihydro-1,2,4-triazolo[4,3-a]pyrimidine-3-thiol 6

Compound 2 (0.01 mol, 1.55g), carbon disulfide (5 ml) and KOH (0.5g) in ethanol (50 ml) was heated under reflux for 5 hr. The solvent was then distilled under vacuum and the remaining solid was acidified with 0.1 N HCl. The solid separated by filtration, was

recrystallized from methanol. IR: 1560, 1650, 2940, 3210. ¹H-NMR: 3.1 (s, 1H, NH), 3.3 (s, 3H, CH₃), 6.8 (s, 2H, NH₂) and 8.4 (s, 1H, Ar-H).

5-(4-Chlorobenzoylamino)-8-methyl-7-oxo-7,8-dihydro-1,2,4-triazolo[4,3-a]pyrimidine-3-thiol 6a

A mixture of compound **6** (0.005 mol, 0.99g) and 4-chlorobenzoylchloride (0.0055 mol, 0.87g) in pyridine (15 ml) was heated under reflux for 30 min. The mixture after cooling was poured onto ice cooled water, and the solid separated was collected by filtration and recrystallized from methanol. IR: 1420, 1490, 1590, 1640, 1700, 2950, 3100. ¹H-NMR: 3.3 (s, 3H, CH₃), 7.6-7.75 (d, 2H, Ar-H), 8.0-8.15 (d, 2H, Ar-H), 8.28 (s, 1H, Ar-H), and 11.0 (s, 1H, NH).

6-(4-Bromobenzylidene)amino-3-methyl-2-methylthio-3,4-dihydro-4-oxopyrimidine 1a

A mixture of compound **1** (0.01 mol, 1.71g), 4-bromobenzaldehyde (0.01 mol, 1.85g) and few drops of piperidine in ethanol (30 ml) was heated under reflux for 10 hrs. The solid separated by filtration after cooling was collected and recrystallized from ethanol. IR: 1570, 1630, 1650 and 2960.

6-(4-Bromobenzylidene)amino-3-methyl-4-oxo-3,4-dihydro-2-pyrimidinyl hydrazine 2a

The title compound was prepared in manner similar to that used in the preparation of **2**. The product was recrystallized from ethanol. IR: 1560, 1610, 1660, 2940, 3180 and 3320.

5-(4-Bromobenzylidene)amino-8-methyl-7-oxo-7,8-dihydro-tetrazolo[1,5-a]pyrimidine 7

To an ice-cold solution of compound **2a** (0.005 mol, 1.61g) in acetic acid (40 ml), was added a solution of sodium nitrite (0.0055 mol, 0.38g) in water (5 ml), drop-wise with stirring. The reaction mixture was allowed to stir for further 2 hr, and the solid obtained was collected by filtration washed with water dried and crystallized from ethanol. IR: 1590, 1650, 1670 and 2940. ¹H-NMR: 3.3 (s, 3H, CH₃), 7.3-7.4 (d, 2H, Ar-H), 7.6-7.7 (d, 2H, Ar-H) and 8.3 (s, 1H, Ar-H).

1-(6-Amino-3-methyl-7-oxo-3,4-dihydro-2-pyrimidinyl)-3,5-bis-(2-thienyl)-2-pyrazoline 8

A mixture of compound **2** (0.01 mol, 1.55g) and 2-thenylidene-2-acetothienone (0.01 mol, 2.2g) in ethanol (30 ml) was heated under reflux for 5 hr. The

solid separated after cooling was collected by filtration and recrystallized from methanol. IR: 1570, 1615, 1670 and 2940.

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