

FACILE AND GENERAL SYNTHESIS OF 8-SUBSTITUTED
2-METHYLTHIOPURIN-6-ONES

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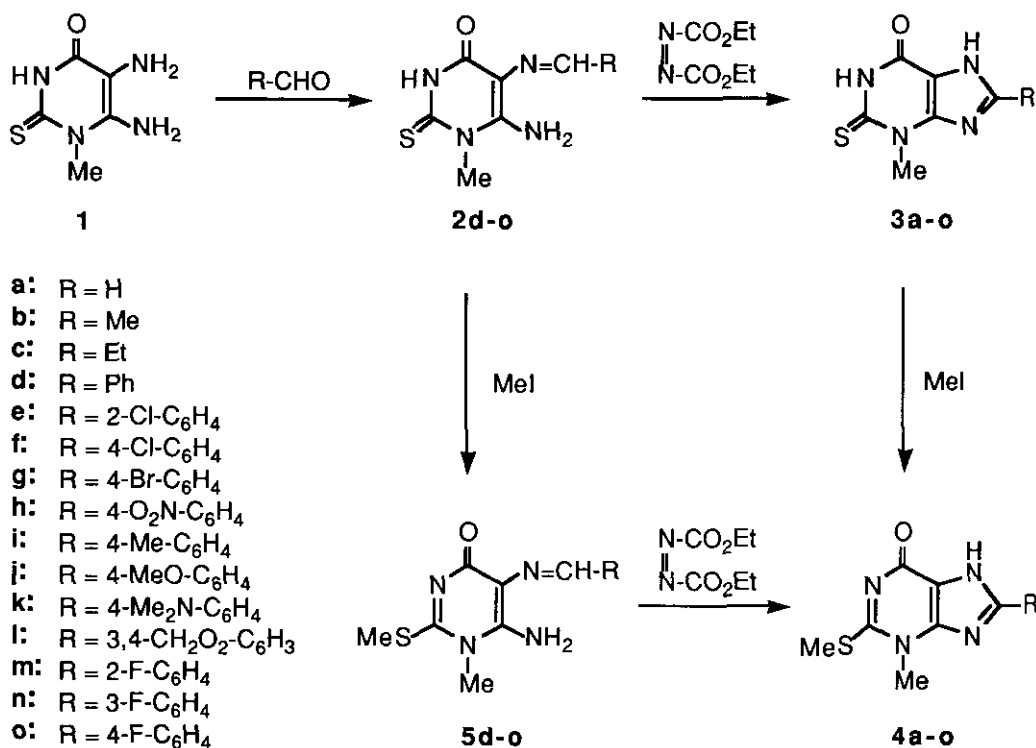
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Abstract --- A variety of 3-methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydropurine (**3a**) and its 8-substituted derivatives (**3b-o**) were synthesized by oxidative cyclization of the reaction product of 5,6-diamino-1-methyl-2-thiouracil (**1**) with an appropriate aldehyde or 6-amino-5-benzylideneamino-1-methyl-2-thiouracils (**2d-o**) in the presence of diethyl azodicarboxylate (DEAD). In addition, the oxidative cyclization of 4-amino-5-benzylideneamino-3-methyl-2-methylthiopyrimidin-6(3*H*)-ones (**5d-o**) in the presence of DEAD gave the corresponding 8-aryl-3-methyl-2-methylthio-6-oxo-3,6-dihydropurines (**4d-o**), which were identical with the compounds prepared by methylation of **3d-o**, respectively. 2-Methylthio-6-oxo-1,6-dihydropurine (**8a**) and its 8-alkyl and 8-aryl derivatives (**8b-h**) were synthesized from 4,5-diamino-2-methylthiopyrimidin-6(1*H*)-one (**6**) or 4-amino-5-benzylideneamino-2-methylthiopyrimidin-6(1*H*)-ones (**7d-h**) in a similar manner as above.

Studies on the synthesis of a number of purines structurally related to guanine and adenine

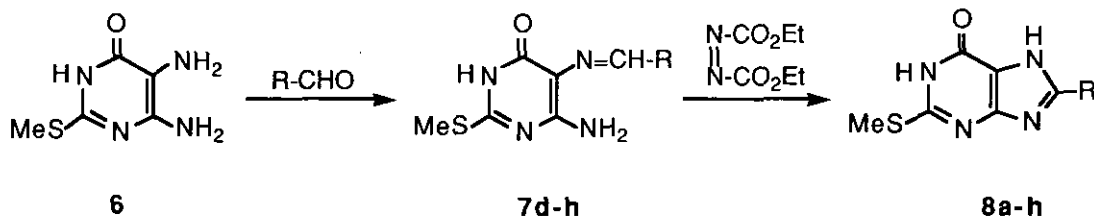
were undertaken in many laboratories in connection with investigation of the effects of structural modifications upon the activity of purine antagonists such as 6-mercaptopurine.^{1,2} In addition, such thiopurines have long been interest for their potential biological activities. Actually, the findings that 6-thioguanine acts as an inhibitor of the growth of *Lactobacillus casei*,^{1,3} embryonic tissue⁴ and a number of neoplasms, e.g., sarcoma 180⁵ and leukemia L 1210^{6,7} and 2-alkylthiopurines act as amplifiers of the antibiotic activity of phleomycin against *Escherichia coli* B,⁸ have aroused interest to us to determine whether similar effects would be observed for 8-substituted 2-thioxanthine derivatives.

2-Thioxanthine⁹ and 3-methyl-2-thioxanthine¹⁰ were previously prepared by the reaction of 5,6-diamino-2-thiouracil and 5,6-diamino-3-methyl-2-thiouracil with formamide, respectively. Such 5,6-diamino compounds should be useful as precursors for syntheses of a variety of thioxanthines and related compounds. However the 2-thioxanthine derivatives substituted by alkyl or aryl groups were little explored so far. This paper is concerned with the development of synthetic method for the preparation of the biologically interesting 8-substituted 3-methyl-2-methylthio-6-oxo-3,6-dihydropurines (**4b-o**) and 2-methylthio-6-oxo-1,6-dihydropurines (**8b-h**). That is, the key intermediates, 6-amino-5-benzylideneamino-1-methyl-2-thiouracils (**2d-o**), were prepared by treatment of 5,6-diamino-1-methyl-2-thiouracil (**1**)¹¹ with several aromatic aldehydes in dioxane at 80 °C (Scheme 1) (Table 1). The oxidative cyclization of the compounds (**2d-o**) thus obtained to the corresponding 8-aryl-3-methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydropurines (**3d-o**) was performed by heating at 100 °C with DEAD in dimethylformamide (DMF) in excellent yields (Table 2). On the other hand, the 8-unsubstituted and 8-alkyl derivatives (**3a-c**) were synthesized by the reaction of the compound (**1**) in the presence of an appropriate aldehyde and DEAD without isolation of the intermediates (**2a-c**). The methylation of **3a-o** with methyl iodide in 1N potassium hydroxide aqueous solution afforded the corresponding 3-methyl-2-methylthio-6-oxo-3,6-dihydropurine (**4a**) and its 8-substituted derivatives (**4b-o**) in high yields, respectively (Table 3). Moreover, heating 4-amino-5-benzylideneamino-3-methyl-2-methylthiopyrimidin-6(3*H*)-ones (**5d-o**), which were derived from **2d-o** with methyl iodide in 1N potassium hydroxide aqueous solution (Table 4), with DEAD in DMF, yielded similarly the cyclized compounds (**4d-o**), respectively (Table 3).



Scheme 1

In a similar manner as above, the method was applied to the preparation of 2-methylthio-6-oxo-1,6-dihydropurine (**8a**) and its 8-substituted derivatives (**8b-h**) (Scheme 2). Namely, the compounds (**8a-c**) were synthesized by heating 4,5-diamino-2-methylthiopyrimidin-6(1H)-one (**6**) with an appropriate aldehyde and DEAD in dioxane at 80 - 90 °C, whereas the compounds (**8d-h**) were synthesized by heating 4-amino-5-benzylideneamino-2-methylthiopyrimidin-6(1H)-



Scheme 2

a: R = H, **b:** R = Me, **c:** R = Et, **d:** R = Ph, **e:** R = 4-Cl-C₆H₄,
f: R = 4-O₂N-C₆H₄, **g:** R = 4-Me-C₆H₄, **h:** R = 4-F-C₆H₄

Table 1. Yields and Analytical Data for 6-Amino-5-benzylideneamino-1-methyl-2-thiouracils (**2d-o**)

Compd. No.	R	Yield (%)	Mp (°C)	Appearance ^a	Formula	Analysis (%)		
						Calcd	(Found)	
						C	H	N
2d	Ph	92	280 - 282	yellow needles	C ₁₂ H ₁₂ N ₄ OS	55.36 (55.63)	4.64 (4.68)	21.52 (21.60)
2e	2-Cl-C ₆ H ₄	91	291 - 293 (decomp.)	yellow needles	C ₁₂ H ₁₁ N ₄ OCIS	48.89 (48.65)	3.76 (3.73)	19.00 (18.75)
2f	4-Cl-C ₆ H ₄	94	278 - 280 (decomp.)	yellow powder	C ₁₂ H ₁₁ N ₄ OCIS	48.89 (48.98)	3.76 (3.76)	19.00 (19.00)
2g	4-Br-C ₆ H ₄	92	277 - 279 (decomp.)	yellow prisms	C ₁₂ H ₁₁ N ₄ OBrS	42.48 (42.23)	3.26 (3.20)	16.51 (16.37)
2h	4-O ₂ N-C ₆ H ₄	92	> 330	red powder	C ₁₂ H ₁₁ N ₅ O ₃ S	47.20 (47.45)	3.63 (3.71)	22.93 (22.72)
2i	4-Me-C ₆ H ₄	93	269 - 271	yellow prisms	C ₁₃ H ₁₄ N ₄ OS	56.91 (56.83)	5.14 (5.26)	20.42 (20.36)
2j	4-MeO-C ₆ H ₄	93	252 - 254	yellow prisms	C ₁₃ H ₁₄ N ₄ O ₂ S	53.77 (53.63)	4.86 (5.01)	19.29 (19.27)
2k	4-Me ₂ N-C ₆ H ₄	91	> 260 (decomp.)	yellow powder	C ₁₄ H ₁₇ N ₅ OS	55.42 (55.28)	5.64 (5.77)	23.08 (23.31)
2l	3,4-CH ₂ O ₂ -C ₆ H ₃	93	273 - 275 (decomp.)	yellow needles	C ₁₃ H ₁₂ N ₄ O ₃ S	51.30 (51.11)	3.97 (3.98)	18.40 (18.53)
2m	2-F-C ₆ H ₄	94	276 - 278 (decomp.)	yellow needles	C ₁₂ H ₁₁ N ₄ OFS	51.78 (51.66)	3.98 (3.90)	20.13 (20.04)
2n	3-F-C ₆ H ₄	95	278 - 280 (decomp.)	yellow plates	C ₁₂ H ₁₁ N ₄ OFS	51.78 (51.51)	3.98 (3.91)	20.13 (20.11)
2o	4-F-C ₆ H ₄	94	279 - 281 (decomp.)	yellow needles	C ₁₂ H ₁₁ N ₄ OFS	51.78 (51.73)	3.98 (3.88)	20.13 (19.95)

^aAll compounds were recrystallized from 2-ethoxyethanol.

ones (**7d-h**), which were prepared by the reaction of **6** and an appropriate aromatic aldehyde in dioxane, with DEAD at 80 °C in good yields, respectively (Tables 5 and 6). The structural assignments of **2d-o**, **3a-o**, **4a-o**, **5d-o**, **7d-h**, and **8a-h** were based on the results of elemental analyses and spectroscopic data (Table 7).

Thus, the present methodology constitutes facile and general means of preparing a variety of 2-thioxanthine and its 8-substituted derivatives by the dehydrogenative cyclization of their precursors such as the Schiff's bases **2d-o**, **5d-o**, and **7d-h** using DEAD. The dehydrogenative

Table 2. Yields and Analytical Data for 3-Methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydropurine and Its 8-Alkyl and 8-Aryl Derivatives (3a-o)

Compd. No.	R	Yield (%)	Mp (°C)	Appearance (Recryst. solv.)	Formula	Analysis (%)		
						Calcd	(Found)	
						C	H	N
3a ^a	H	72	> 330	colourless powder (water)	C ₆ H ₆ N ₄ OS			
3b ^b	Me	79	> 330	colourless powder (water)	C ₇ H ₈ N ₄ OS			
3c	Et	69	> 330	colourless leaves (water)	C ₈ H ₁₀ N ₄ OS	45.69 (45.55)	4.79 (4.90)	26.64 (26.82)
3d ^c	Ph	73	> 330	colourless powder (DMSO)	C ₁₂ H ₁₀ N ₄ OS			
3e	2-Cl-C ₆ H ₄	65	> 330	colourless powder (DMSO)	C ₁₂ H ₉ N ₄ OCIS	49.23 (49.18)	3.09 (3.21)	19.13 (19.31)
3f	4-Cl-C ₆ H ₄	71	> 330	colourless powder (DMSO)	C ₁₂ H ₉ N ₄ OCIS	49.23 (49.05)	3.09 (3.16)	19.13 (19.37)
3g	4-Br-C ₆ H ₄	73	308 (decomp.)	colourless powder (DMSO)	C ₁₂ H ₉ N ₄ OBrS	42.74 (42.86)	2.69 (2.72)	16.61 (16.55)
3h	4-O ₂ N-C ₆ H ₄	73	> 330	yellow powder (DMSO)	C ₁₂ H ₉ N ₅ O ₃ S	47.52 (47.38)	2.99 (2.75)	23.09 (23.31)
3i	4-Me-C ₆ H ₄	79	> 330	colourless powder (DMSO)	C ₁₃ H ₁₂ N ₄ OS	57.33 (57.58)	4.44 (4.41)	20.57 (20.35)
3j	4-MeO-C ₆ H ₄	79	> 330	colourless needles (DMSO)	C ₁₃ H ₁₂ N ₄ O ₂ S	54.15 (54.32)	4.19 (4.35)	19.43 (19.33)
3k	4-Me ₂ N-C ₆ H ₄	71	> 330	grey powder (DMSO)	C ₁₄ H ₁₅ N ₅ OS	55.79 (55.81)	5.01 (5.00)	23.23 (23.42)
3l	3,4-CH ₂ O ₂ -C ₆ H ₃	68	> 330	colourless powder (DMSO)	C ₁₃ H ₁₀ N ₄ O ₃ S	51.64 (51.88)	3.33 (3.09)	18.53 (18.55)
3m	2-F-C ₆ H ₄	68	> 330	colourless powder (DMSO)	C ₁₂ H ₉ N ₄ OFS	52.16 (51.92)	3.28 (3.32)	20.27 (20.07)
3n	3-F-C ₆ H ₄	75	> 330	colourless powder (DMSO)	C ₁₂ H ₉ N ₄ OFS	52.16 (52.31)	3.28 (3.33)	20.27 (20.17)
3o	4-F-C ₆ H ₄	77	> 330	colourless powder (DMSO)	C ₁₂ H ₉ N ₄ OFS	52.16 (52.19)	3.28 (3.07)	20.27 (20.39)

^aRef. 10. ^bRef. 12. ^cRef. 13.

Table 3. Yields and Analytical Data for 3-Methyl-2-methylthio-6-oxo-3,6-dihydropurine and Its 8-Alkyl and 8-Aryl Derivatives (4a-o)

Compd. No.	R	Yield (%) ^a		Mp (°C)	Appearance ^b (Recryst. solv.)	Formula	Analysis (%)		
		A	B				Calcd	Found	
							C	H	N
4a ^c	H	87		300 - 302	powder (water)	C ₇ H ₈ N ₄ OS			
4b ^d	Me	86		308 - 310	powder (water)	C ₈ H ₁₀ N ₄ OS			
4c	Et	85		280 - 282 (decomp.)	needles (water)	C ₉ H ₁₂ N ₄ OS	48.19 (48.20)	5.39 (5.42)	24.98 (24.76)
4d	Ph	89	74	323 - 325	leaves (DMF)	C ₁₃ H ₁₂ N ₄ OS	57.33 (57.29)	4.44 (4.36)	20.57 (20.44)
4e	2-Cl-C ₆ H ₄	90	68	284 - 286	leaves (DMF)	C ₁₃ H ₁₁ N ₄ OCIS	50.89 (50.88)	3.61 (3.82)	18.26 (18.38)
4f	4-Cl-C ₆ H ₄	92	82	> 330	needles (DMF)	C ₁₃ H ₁₁ N ₄ OCIS	50.89 (51.11)	3.61 (3.80)	18.26 (18.05)
4g	4-Br-C ₆ H ₄	92	81	329 (decomp.)	needles (DNF)	C ₁₃ H ₁₁ N ₄ OBrS	44.45 (44.68)	3.15 (3.09)	15.95 (15.99)
4h	4-O ₂ N-C ₆ H ₄	94	77	325 - 327 (decomp.)	powder (DMF)	C ₁₃ H ₁₁ N ₅ O ₃ S	49.20 (49.43)	3.49 (3.57)	22.06 (22.32)
4i	4-Me-C ₆ H ₄	91	75	> 320 (decomp.)	leaves (DMF)	C ₁₄ H ₁₄ N ₄ OS	58.72 (58.44)	4.92 (4.86)	19.56 (19.27)
4j	4-MeO-C ₆ H ₄	90	79	313 - 315 (decomp.)	leaves (DMF)	C ₁₄ H ₁₄ N ₄ O ₂ S	55.61 (55.33)	4.66 (4.61)	18.53 (18.32)
4k	4-Me ₂ N-C ₆ H ₄	92	83	> 330	leaves (DMF)	C ₁₅ H ₁₇ N ₅ OS	57.12 (56.98)	5.43 (5.71)	22.20 (22.29)
4l	3,4-CH ₂ O ₂ -C ₆ H ₃	88	72	> 330	powder (DMF)	C ₁₄ H ₁₂ N ₄ O ₃ S	53.15 (53.38)	3.82 (3.88)	17.71 (17.55)
4m	2-F-C ₆ H ₄	92	69	279 - 281	plates (DMF)	C ₁₃ H ₁₁ N ₄ OFS	53.78 (53.78)	3.81 (3.77)	19.29 (19.50)
4n	3-F-C ₆ H ₄	92	85	321 - 323 (decomp.)	leaves (DMF)	C ₁₃ H ₁₁ N ₄ OFS	53.78 (53.71)	3.81 (3.89)	19.29 (19.22)
4o	4-F-C ₆ H ₄	93	89	> 330	needles (DMF)	C ₁₃ H ₁₁ N ₄ OFS	53.78 (53.85)	3.81 (3.59)	19.29 (19.43)

^aSee Experimental, A : Method A; B : Method B. ^bAll compounds were obtained as colourless crystals without 4h (yellow) and 4k (pale yellow). ^cRef. 14. ^dRef. 12.

Table 4. Yields and Analytical Data for 4-Amino-5-benzylideneamino-3-methyl-2-methylthiopyrimidin-6(3H)-ones (5d-o)

Compd. No.	R	Yield (%)	Mp (°C)	Appearance ^a	Formula	Analysis (%)		
						Calcd	(Found)	
						C	H	N
5d	Ph	80	274 - 276 (decomp.)	yellow prisms	C ₁₃ H ₁₄ N ₄ OS	56.91 (56.88)	5.14 5.29	20.42 20.34
5e	2-Cl-C ₆ H ₄	79	282 - 283	yellow powder	C ₁₃ H ₁₃ N ₄ OCIS	50.56 (50.58)	4.24 4.25	18.14 18.18
5f	4-Cl-C ₆ H ₄	80	> 280 (decomp.)	yellow leaves	C ₁₃ H ₁₃ N ₄ OCIS	50.56 (50.48)	4.24 4.28	18.14 18.04
5g	4-Br-C ₆ H ₄	83	279 - 280 (decomp.)	yellow leaves	C ₁₃ H ₁₃ N ₄ OBrS	44.20 (44.07)	3.70 3.68	15.86 15.66
5h	4-O ₂ N-C ₆ H ₄	82	309 (decomp.)	orange powder	C ₁₃ H ₁₃ N ₅ O ₃ S	48.89 (48.61)	4.10 4.04	21.93 21.76
5i	4-Me-C ₆ H ₄	84	258 (decomp.)	yellow needles	C ₁₄ H ₁₆ N ₄ OS	58.31 (58.32)	5.59 5.76	19.42 19.37
5j	4-MeO-C ₆ H ₄	82	273 - 275 (decomp.)	yellow leaves	C ₁₄ H ₁₆ N ₄ O ₂ S	55.24 (54.97)	5.29 5.33	18.40 18.47
5k	4-Me ₂ N-C ₆ H ₄	82	> 285 (decomp.)	yellow powder	C ₁₅ H ₁₉ N ₅ OS	56.76 (56.51)	6.03 6.20	22.06 21.87
5l	3,4-CH ₂ O ₂ -C ₆ H ₃	77	287 - 289 (decomp.)	yellow needles	C ₁₄ H ₁₄ N ₄ O ₃ S	52.81 (52.59)	4.43 4.36	17.59 17.46
5m	2-F-C ₆ H ₄	80	277 - 279	yellow leaves	C ₁₃ H ₁₃ N ₄ OFS	53.41 (53.48)	4.48 4.27	19.16 19.31
5n	3-F-C ₆ H ₄	82	> 284 (decomp.)	yellow powder	C ₁₃ H ₁₃ N ₄ OFS	53.41 (53.33)	4.48 4.50	19.16 19.16
5o	4-F-C ₆ H ₄	86	275 - 277 (decomp.)	yellow leaves	C ₁₃ H ₁₃ N ₄ OFS	53.41 (53.14)	4.48 4.40	19.16 19.37

^aAll compounds were recrystallized from DMF.

cyclization of such Schiff's bases containing mercapto or alkylthio group using other oxidizing agents such as lead tetraacetate was quite difficult. There are two examples^{18,19} for the preparation of xanthine derivatives by the similar method using DEAD so far.

EXPERIMENTAL

All melting points were taken using a Yanagimoto micro melting points apparatus and are uncorrected. Microanalyses were performed with a Yanagimoto MT-2 CHN elemental analyser.

Table 5. Yields and Analytical Data for 4-Amino-5-benzylideneamino-2-methylthio-pyrimidin-6(1*H*)-ones (**7d-h**)

Compd. No.	R	Yield (%)	Mp (°C)	Appearance ^a	Formula	Analysis (%)		
						Calcd	(Found)	
						C	H	N
7d	Ph	91	257 - 259	pale yellow powder	C ₁₂ H ₁₂ N ₄ OS	55.36	4.64	21.52
						(55.18)	4.77	21.32)
7e	4-Cl-C ₆ H ₄	93	266 - 268	yellow powder	C ₁₂ H ₁₁ N ₄ OCIS	48.89	3.76	19.00
						(48.78)	3.70	19.23)
7f	4-O ₂ N-C ₆ H ₄	95	295 - 297	orange powder	C ₁₂ H ₁₁ N ₅ O ₃ S	47.20	3.63	22.93
						(47.18)	3.81	23.12)
7g	4-Me-C ₆ H ₄	89	258 - 260	pale yellow powder	C ₁₃ H ₁₄ N ₄ OS	56.91	5.14	20.42
						(56.77)	5.32	20.65)
7h	4-F-C ₆ H ₄	91	267 - 269	pale yellow powder	C ₁₂ H ₁₁ N ₄ OFS	51.78	3.98	20.13
						(51.99)	4.12	20.02)

^aAll compounds were recrystallized from 2-ethoxyethanol.

Ir and ¹H-nmr spectra were measured with JASCO IRA-102 spectrophotometer and Hitachi R-1500 FT-NMR (60MHz) instrument with tetramethylsilane as an internal standard, respectively. The following abbreviations are used: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad.

General Procedure for Preparation of 6-Amino-5-benzylideneamino-1-methyl-2-thiouracils (**2d-o**)

A mixture of 5,6-diamino-1-methyl-2-thiouracil (**1**) (2 g, 11.6 mmol) and an appropriate aryl aldehyde (15.1 mmol) in dioxane (30 ml) was heated at 80 °C with stirring for 2 h. After cooling, the resulting solid was collected by filtration, washed with ethanol, dried, and recrystallized from 2-ethoxyethanol to afford the corresponding pure products (**2d-o**) (Table 1).

General Procedure for Preparation of 3-Methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydropurine and Its 8-Alkyl Derivatives (**3a-c**)

A mixture of 5,6-diamino-1-methyl-2-thiouracil (**1**) (2 g, 11.6 mmol) and an appropriate

Table 6. Yields and Analytical Data for 2-Methylthio-6-oxo-1,6-dihydropurine and Its 8-Alkyl and 8-Aryl Derivatives (8a-h)

Compd. No.	R	Yield (%)	Mp (°C)	Appearance ^a	Formula	Analysis (%)		
						Calcd	(Found)	
						C	H	N
8a ^b	H	72	> 310	colourless powder	C ₆ H ₆ N ₄ OS			
8b ^c	Me	74	314 (decomp.)	colourless powder	C ₇ H ₈ N ₄ OS			
8c	Et	67	279 - 281	colourless powder	C ₈ H ₁₀ N ₄ OS	45.69 (45.77)	4.79 (4.61)	26.64 (26.55)
8d	Ph	60	257 - 259	pale yellow powder	C ₁₂ H ₁₀ N ₄ OS	55.79 (55.91)	3.90 (3.95)	21.69 (21.55)
8e	4-Cl-C ₆ H ₄	62	260 - 262 (decomp.)	pale brown powder	C ₁₂ H ₉ N ₄ OClS	49.23 (49.41)	3.09 (3.10)	19.13 (19.43)
8f	4-O ₂ N-C ₆ H ₄	60	301 - 303 (decomp.)	pale orange powder	C ₁₂ H ₉ N ₅ O ₃ S	47.52 (47.68)	2.99 (3.05)	23.09 (23.11)
8g	4-Me-C ₆ H ₄	64	304 - 306 (decomp.)	pale yellow powder	C ₁₃ H ₁₂ N ₄ OS	57.33 (57.43)	4.44 (4.44)	20.57 (20.83)
8h	4-F-C ₆ H ₄	66	308 - 310	colourless powder	C ₁₂ H ₉ N ₄ OFS	52.16 (52.32)	3.28 (3.08)	20.27 (20.43)

^aAll compounds were recrystallized from 2-ethoxyethanol. ^bRef. 16. ^cRef. 17.

formaldehyde, acetaldehyde, or propionaldehyde (17.4 mmol) in dioxane (30 ml) was stirred at room temperature for 1 h. Then, to a stirred mixture was added DEAD (2.6 g, 15.1 mmol) and the mixture was heated at 80 - 90 °C for 5 h. After cooling, the resulting solid was collected by filtration, washed with ethanol, dried, and recrystallized from water to afford the corresponding pure products (3a-c) (Table 2)

General Procedure for Preparation of 8-Aryl-3-methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydropurines (3d-o)

A mixture of 2d-o (4 mmol) and DEAD (0.9 g, 5.2 mmol) in DMF (30 ml) was heated at 100 °C with stirring for 0.5 - 2 h. After cooling, the resulting solid was collected by filtration, washed with

Table 7. Nmr and Ir Spectral Data for 2d-o, 3a-o, 4a-o, 5d-o, 7d-h, and 8a-h

Compd. No.	Ir ν max KBr cm^{-1}	$^1\text{H-Nmr}$ ($\text{CF}_3\text{CO}_2\text{D}$ / TMS) ^a : δ (ppm), J (Hz)
2d	3370 (NH ₂) 3270 (NH ₂) 1632 (CO) 1610 (δ NH ₂)	3.84 (3H, s, NMe), 7.46 (5H, m, Ph- <i>m,p</i> H and D ₂ O exchangeable NH ₂), 7.95 (2H, m, Ph- <i>o</i> H), 9.75 (1H, s, NCH), 12.15 (1H, br s, D ₂ O exchangeable SH)
2e	3400 (NH ₂) 3290 (NH ₂) 1638 (CO) 1602 (δ NH ₂)	3.85 (3H, s, NMe), 7.44 (5H, m, Ar- <i>m,p</i> H and D ₂ O exchangeable NH ₂), 8.48 (1H, m, Ar- <i>o</i> H), 10.14 (1H, s, NCH), 12.22 (1H, br s, D ₂ O exchangeable SH)
2f	3400 (NH ₂) 3280 (NH ₂) 1632 (CO) 1604 (δ NH ₂)	3.81 (3H, s, NMe), 6.97 (2H, d, $J_{AB} = 8.76$, Ar- <i>m</i> H), 7.36 (2H, br s, D ₂ O exchangeable NH ₂), 7.88 (2H, d, $J_{AB} = 8.76$, Ar- <i>o</i> H), 9.68 (1H, s, NCH), 12.11 (1H, br s, D ₂ O exchangeable SH)
2g	3380 (NH ₂) 3260 (NH ₂) 1630 (CO) 1608 (δ NH ₂)	3.83 (3H, s, NMe), 7.53 (2H, br s, D ₂ O exchangeable NH ₂), 7.58 (2H, d, $J_{AB} = 8.76$, Ar- <i>m</i> H), 7.92 (2H, d, $J_{AB} = 8.76$, Ar- <i>o</i> H), 9.72 (1H, s, NCH), 12.16 (1H, s, D ₂ O exchangeable SH)
2h	3450 (NH ₂) 3340 (NH ₂) 1630 (CO) 1608 (δ NH ₂)	3.84 (3H, s, NMe), 7.69 (2H, br s, D ₂ O exchangeable NH ₂), 8.21 (4H, s, Ar-H), 9.82 (1H, s, NCH), 12.23 (1H, br s, D ₂ O exchangeable SH)
2i	3450 (NH ₂) 3370 (NH ₂) 1638 (CO) 1707 (δ NH ₂)	2.35 (3H, s, CMe), 3.84 (3H, s, NMe), 7.23 (2H, d, $J_{AB} = 8.22$, Ar- <i>m</i> H), 7.40 (2H, br s, D ₂ O exchangeable NH ₂), 7.82 (2H, d, $J_{AB} = 8.22$, Ar- <i>o</i> H), 9.71 (1H, s, NCH), 12.13 (1H, br s, D ₂ O exchangeable SH)
2j	3370 (NH ₂) 3280 (NH ₂) 1635 (CO) 1600 (δ NH ₂)	3.57 (3H, s, OMe), 3.83 (3H, s, NMe), 7.45 (2H, d, $J_{AB} = 8.82$, Ar- <i>m</i> H), 7.52 (2H, br s, D ₂ O exchangeable NH ₂), 7.98 (2H, d, $J_{AB} = 8.82$, Ar- <i>o</i> H), 9.73 (1H, s, NCH), 12.20 (1H, br s, D ₂ O exchangeable SH)
2k	3320 (NH ₂) 3170 (NH ₂) 1635 sh (CO) 1610 (δ NH ₂)	2.99 (6H, s, NMe ₂), 3.83 (3H, s, NMe), 6.72 (2H, d, $J_{AB} = 8.82$, Ar- <i>m</i> H), 7.26 (2H, br s, D ₂ O exchangeable NH ₂), 7.74 (2H, d, $J_{AB} = 8.82$, Ar- <i>o</i> H), 9.59 (1H, s, NCH), 12.06 (1H, br s, D ₂ O exchangeable SH)
2l	3350 (NH ₂) 3250 (NH ₂) 1630 sh (CO) 1603 (δ NH ₂)	3.83 (3H, s, NMe), 6.07 (2H, s, OCH ₂ O), 6.92 (1H, d, $J_{5',6'} = 8.22$, 5'-H), 7.22 (1H, dd, $J_{2',6'} = 1.80$, $J_{5',6'} = 8.22$, 6'-H), 7.44 (2H, br s, D ₂ O exchangeable NH ₂), 7.82 (1H, d, $J_{2',6'} = 1.80$, 2'-H), 9.65 (1H, s, NCH), 12.12 (1H, br s, D ₂ O exchangeable SH)
2m	3400 (NH ₂) 3280 (NH ₂) 1638 (CO) 1604 (δ NH ₂)	3.85 (3H, s, NMe), 7.22 - 7.53 (5H, m, Ar- <i>m,p</i> H and D ₂ O exchangeable NH ₂), 8.40 (1H, m, Ar- <i>o</i> H), 9.98 (1H, s, NCH), 12.19 (1H, br s, D ₂ O exchangeable SH)
2n	3380 (NH ₂) 3270 (NH ₂) 1636 (CO) 1614 (δ NH ₂)	3.84 (3H, s, NMe), 7.16 - 7.68 (5H, m, Ar-H and D ₂ O exchangeable NH ₂), 7.89 - 8.07 (1H, m, Ar- <i>o</i> H), 9.75 (1H, s, NCH), 12.18 (1H, s, D ₂ O exchangeable SH)
2o	3430 (NH ₂) 3320 (NH ₂) 1666 (CO) 1614 (δ NH ₂)	3.84 (3H, s, NMe), 7.23 (2H, dd, $J_{H,H} = 8.82$, $J_{H,F} = 8.76$, Ar- <i>m</i> H), 7.47 (2H, br s, D ₂ O exchangeable NH ₂), 8.01 (2H, ddd, $J_{H,H} = 8.82$, $J_{H,H} = 2.34$, $J_{H,F} = 5.82$, Ar- <i>o</i> H), 9.74 (1H, s, NCH), 12.16 (1H, br s, D ₂ O exchangeable SH)
3a	3130 (NH) 1680 (CO)	4.10 (3H, s, NMe), 8.97 (1H, s, 8-H)
3b	3060 (NH) 1680 (CO)	2.95 (3H, s, CMe), 4.03 (3H, s, NMe)

3 c	3080 (NH) 1710 (CO)	1.62 (3H, t, J = 7.02, CH ₂ Me), 3.31 (2H, q, J = 7.02, CH ₂ Me), 4.05 (3H, s, NMe)
3 d	3130 (NH) 1673 (CO)	b
3 e	3175 (NH) 1687 (CO)	4.12 (3H, s, NMe), 7.50 - 7.97 (5H, m, Ar-H)
3 f	3125 (NH) 1683 (CO)	b
3 g	3100 (NH) 1675 (CO)	b
3 h	3100 (NH) 1673 (CO)	b
3 i	3170 (NH) 1665 (CO)	2.56 (3H, s, CMe), 4.13 (3H, s, NMe), 7.57 (2H, d, J _{AB} = 8.76, Ar-mH), 8.01 (2H, d, J _{AB} = 8.76, Ar-oH)
3 j	3180 (NH) 1674 (CO)	4.04 (3H, s, OMe), 4.14 (3H, s, NMe), 7.29 (2H, d, J _{AB} = 8.76, Ar-mH), 8.13 (2H, d, J _{AB} = 8.76, Ar-oH)
3 k	3150 (NH) 1678 (CO)	3.56 (6H, s, NMe ₂), 4.17 (3H, s, NMe), 7.96 (2H, d, J _{AB} = 8.76, Ar-mH), 8.45 (2H, d, J _{AB} = 8.76, Ar-oH)
3 l	3100 (NH) 1670 (CO)	4.12 (3H, s, NMe), 6.18 (2H, s, OCH ₂ O), 7.12 (1H, d, J _{5',6'} = 8.22, 5'-H), 7.51 (1H, d, J _{2',6'} = 2.34, 2'-H), 7.73 (1H, dd, J _{2',6'} = 2.34, J _{5',6'} = 8.22, 6'-H)
3 m	3180 (NH) 1690 (CO)	b
3 n	3140 (NH) 1680 (CO)	b
3 o	3120 (NH) 1670 (CO)	b
4 a	3090 (NH) 1620 (CO)	3.10 (3H, s, SMe), 4.20 (3H, s, NMe), 8.62 (1H, s, 8-H)
4 b	3120 (NH) 1615 (CO)	2.87 (3H, s, 8-Me), 3.07 (3H, s, SMe), 3.19 (3H, s, NMe)
4 c	3120 (NH) 1628 (CO)	1.55 (3H, t, J = 7.62, CH ₂ Me), 3.04 (3H, s, SMe), 3.22 (2H, q, J = 7.62, CH ₂ Me), 4.18 (3H, s, NMe)
4 d	3050 (NH) 1618 (CO)	3.12 (3H, s, SMe), 4.28 (3H, s, NMe), 7.70 (3H, m, Ph-m,pH), 8.17 (2H, m, Ph-oH)
4 e	3030 (NH) 1612 (CO)	3.14 (3H, s, SMe), 4.28 (3H, s, NMe), 7.55 - 7.70 (3H, m, Ar-m,pH), 8.24 (1H, m, Ar-oH)
4 f	3050 (NH) 1620 (CO)	3.14 (3H, s, SMe), 4.28 (3H, s, NMe), 7.62 (2H, d, J _{AB} = 8.76, Ar-mH), 8.16 (2H, d, J _{AB} = 8.76, Ar-oH)
4 g	3050 (NH) 1618 (CO)	3.13 (3H, s, SMe), 4.27 (3H, s, NMe), 7.79 (2H, d, J _{AB} = 8.76, Ar-mH), 8.08 (2H, d, J _{AB} = 8.76, Ar-oH)
4 h	3040 (NH) 1605 (CO)	3.15 (3H, s, SMe), 4.30 (3H, s, NMe), 8.51 (4H, s, ArH)
4 i	3050 (NH) 1610 (CO)	2.52 (3H, s, CMe), 3.09 (3H, s, SMe), 4.27 (3H, s, NMe), 7.49 (2H, d, J _{AB} = 8.22, Ar-mH), 8.08 (2H, d, J _{AB} = 8.22, Ar-oH)
4 j	3070 (NH) 1630 (CO)	3.10 (3H, s, SMe), 4.06 (3H, s, OMe), 4.27 (3H, s, NMe), 7.25 (2H, d, J _{AB} = 8.76, Ar-mH), 8.21 (2H, d, J _{AB} = 8.76, Ar-oH)
4 k	3060 (NH) 1600 (CO)	3.15 (3H, s, SMe), 3.56 (6H, s, NMe ₂), 4.29 (3H, s, NMe), 7.92 (2H, d, J _{AB} = 8.76, Ar-mH), 8.54 (2H, d, J _{AB} = 8.76, Ar-oH)
4 l	3080 (NH) 1585 (CO)	3.11 (3H, s, SMe), 4.26 (3H, s, NMe), 6.13 (2H, s, OCH ₂ O), 7.07 (1H, d, J _{5',6'} = 8.22, 5'-H), 7.66 (1H, d, J _{2',6'} = 1.80, 2'-H), 7.83 (1H, dd, J _{2',6'} = 1.80, J _{5',6'} = 8.22, 6'-H)
4 m	3050 (NH) 1615 (CO)	3.14 (3H, s, SMe), 4.30 (3H, s, NMe), 7.19 - 7.81 (3H, m, Ar-m,pH), 8.29 - 8.58 (1H, m, Ar-oH)
4 n	3050 (NH) 1620	3.17 (3H, s, SMe), 4.32 (3H, s, NMe), 7.32 - 8.08 (4H, m, Ar-H)

4 o	3050 (NH) 1600 (CO)	3.14 (3H, s, SMe), 4.28 (3H, s, NMe), 7.32 (2H, dd, $J_{H,H} = 8.82$, $J_{H,F} = 8.22$, Ar- <i>m</i> H), 8.25 (2H, ddd, $J_{H,H} = 8.82$, $J_{H,H} = 2.34$, $J_{H,F} = 5.28$, Ar- <i>o</i> H)
5 d	3420 (NH ₂) 3250 (NH ₂) 1622 (CO) 1603 (δ NH ₂)	2.85 (3H, s, SMe), 3.95 (3H, s, NMe), 7.60 - 8.38 (5H, m, Ph-H), 9.19 (1H, s, NCH)
5 e	3420 (NH ₂) 3270 (NH ₂) 1623 (CO) 1600 (δ NH ₂)	2.84 (3H, s, SMe), 3.93 (3H, s, NMe), 7.58 - 8.03 (3H, m, Ar- <i>m,p</i> H), 8.37 (1H, m, Ar- <i>o</i> H), 9.69 (1H, s, NCH)
5 f	3370 (NH ₂) 3260 (NH ₂) 1623 sh (CO) 1607 (δ NH ₂)	2.84 (3H, s, SMe), 3.93 (3H, s, NMe), 7.80 (2H, d, $J_{AB} = 8.76$, Ar- <i>m</i> H), 8.25 (2H, d, $J_{AB} = 8.76$, Ar- <i>o</i> H), 9.17 (1H, s, NCH)
5 g	3370 (NH ₂) 3250 (NH ₂) 1622 (CO) 1603 (δ NH ₂)	2.84 (3H, s, SMe), 3.93 (3H, s, NMe), 7.85 - 8.08 (4H, m, Ar-H), 9.17 (1H, s, NCH)
5 h	3380 (NH ₂) 3250 (NH ₂) 1624 (CO) 1608 (δ NH ₂)	2.82 (3H, s, SMe), 3.94 (3H, s, NMe), 8.09 - 8.60 (4H, m, Ar-H), 9.55 (1H, s, NCH)
5 i	3420 (NH ₂) 3250 (NH ₂) 1624 (CO) 1602 (δ NH ₂)	2.51 (3H, s, CMe), 2.84 (3H, s, SMe), 3.93 (3H, s, NMe), 7.67 (2H, d, $J_{AB} = 8.22$, Ar- <i>m</i> H), 8.18 (2H, d, $J_{AB} = 8.22$, Ar- <i>o</i> H), 9.02 (1H, s, NCH)
5 j	3420 (NH ₂) 3250 (NH ₂) 1620 sh (CO) 1600 (δ NH ₂)	2.83 (3H, s, SMe), 3.93 (3H, s, NMe), 4.14 (3H, s, OMe), 7.31 (2H, d, $J_{AB} = 9.36$, Ar- <i>m</i> H), 8.26 (2H, d, $J_{AB} = 9.36$, Ar- <i>o</i> H), 8.75 (1H, s, NCN)
5 k	3400 (NH ₂) 3250 (NH ₂) 1620 sh (CO) 1592 (δ NH ₂)	2.81 (3H, s, SMe), 3.45 (6H, s, NMe ₂), 3.91 (3H, s, NMe), 7.26 (2H, d, $J_{AB} = 9.36$, Ar- <i>m</i> H), 8.02 (2H, d, $J_{AB} = 9.36$, Ar- <i>o</i> H), 8.47 (1H, s, NCH)
5 l	3420 (NH ₂) 3270 (NH ₂) 1622 (CO) 1598 (δ NH ₂)	2.82 (3H, s, SMe), 3.92 (3H, s, NMe), 6.32 (2H, s, OCH ₂ O), 7.20 (1H, d, $J_{5',6'} = 8.22$, 5'-H), 7.74 (1H, d, $J_{2',6'} = 1.80$, 2'-H), 7.90 (1H, dd, $J_{2',6'} = 1.80$, $J_{5',6'} = 8.22$, 6'-H), 8.72 (1H, s, NCH)
5 m	3420 (NH ₂) 3280 (NH ₂) 1632 (CO) 1608 (δ NH ₂)	2.84 (3H, s, SMe), 3.93 (3H, s, NMe), 7.36 - 7.76 (2H, m, Ar- <i>m,p</i> H), 8.01 - 8.35 (2H, m, Ar- <i>o,m</i> H), 9.32 (1H, s, NCH)
5 n	3380 (NH ₂) 3270 (NH ₂) 1638 (CO) 1610 (δ NH ₂)	2.85 (3H, s, SMe), 3.94 (3H, s, NMe), 7.62 - 8.07 (4H, m, Ar-H), 9.28 (1H, s, NCH)
5 o	3370 (NH ₂) 3250 (NH ₂) 1612 (CO) 1600 (δ NH ₂)	2.84 (3H, s, SMe), 3.94 (3H, s, NMe), 7.52 (2H, dd, $J_{H,H} = 8.82$, $J_{H,F} = 8.76$, Ar- <i>m</i> H), 8.41 (2H, ddd, $J_{H,H} = 8.82$, $J_{H,H} = 2.34$, $J_{H,F} = 5.28$, Ar- <i>o</i> H), 9.15 (1H, s, NCH)
7 d	3450 (NH ₂) 3260 (NH ₂) 3120 (NH) 1600 (CO, δ NH ₂)	2.78 (3H, s, SMe), 7.78 - 8.25 (5H, m, Ph-H), 9.30 (1H, s, NCH)

7 e	3440 (NH ₂)	2.76 (3H, s, SMe), 7.74 (2H, d, J _{AB} = 8.82, Ar- <i>m</i> H), 8.14 (2H, d, J _{AB} = 8.82, Ar- <i>o</i> H), 9.31 (1H, s, NCH)
	3260 (NH ₂)	
	3120 (NH)	
	1598 (CO, δ NH ₂)	
7 f	3450 (NH ₂)	2.75 (3H, s, SMe), 8.17 - 8.60 (4H, m, Ar-H), 9.81 (1H, s, NCH)
	3270 (NH ₂)	
	3120 (NH)	
	1602 (CO, δ NH ₂)	
7 g	3450 (NH ₂)	2.63 (3H, s, Me), 2.79 (3H, s, SMe), 7.62 (2H, d, J _{AB} = 8.22, Ar- <i>m</i> H), 8.10 (2H, d, J _{AB} = 8.22, Ar- <i>o</i> H), 9.12 (1H, s, NCH)
	3260 (NH ₂)	
	3120 (NH)	
	1602 (CO, δ NH ₂)	
7 h	3460 (NH ₂)	2.78 (3H, s, SMe), 7.46 (2H, dd, J _{H,H} = 8.82, J _{H,F} = 8.22, Ar- <i>m</i> H), 8.31 (2H, ddd, J _{H,H} = 8.82, J _{H,H} = 1.74, J _{H,F} = 5.22, Ar- <i>o</i> H), 9.27 (1H, s, NCH)
	3270 (NH ₂)	
	3130 (NH)	
	1601 (CO, δ NH ₂)	
8 a	3120 (NH)	2.77 (3H, s, SMe), 9.14 (1H, s, 8-H)
	3050 (NH)	
	1702 (CO)	
8 b	3120 sh (NH)	2.75 (3H, s, SMe), 2.98 (3H, s, 8-Me)
	3040 (NH)	
	1672 (CO)	
8 c	3120 sh (NH)	1.63 (3H, t, J = 7.62, CH ₂ Me), 2.75 (3H, s, SMe), 3.33 (2H, q, J = 7.62, CH ₂ Me)
	3030 (NH)	
	1678 (CO)	
8 d	3140 (NH)	2.86 (3H, s, SMe), 7.73 (3H, m, Ph-H), 8.24 (2H, m, Ph-H)
	3110 (NH)	
	1674 (CO)	
8 e	3140 (NH)	2.85 (3H, s, SMe), 7.65 (2H, d, J _{AB} = 8.82, Ar- <i>m</i> H), 8.18 (2H, d, J _{AB} = 8.82, Ar- <i>o</i> H)
	3100 sh (NH)	
	1660 (CO)	
8 f	3150 (NH)	2.81 (3H, s, SMe), 8.42 (2H, d, J _{AB} = 9.36, Ar- <i>m</i> H), 8.67 (2H, d, J _{AB} = 9.36, Ar- <i>o</i> H)
	3100 (NH)	
	1680 (CO)	
8 g	3160 sh (NH)	2.57 (3H, s, CMe), 2.79 (3H, s, SMe), 7.60 (2H, d, J _{AB} = 8.82, Ar- <i>m</i> H), 8.07 (2H, d, J _{AB} = 8.82, Ar- <i>o</i> H)
	3140 (NH)	
	1660 (CO)	
8 h	3140 (NH)	2.79 (3H, s, SMe), 7.48 (2H, dd, J _{H,H} = 8.76, J _{H,F} = 7.62, Ar- <i>m</i> H), 8.23 (2H, ddd, J _{H,H} = 8.76, J _{H,H} = 2.34, J _{H,F} = 4.74, Ar- <i>o</i> H)
	3098 (NH)	
	1662 (CO)	

^aCompounds (2d-o) were measured in DMSO-d₆. ^bThis compound was not sufficiently soluble in any solvents at room temperature.

ethanol, dried, and recrystallized from dimethyl sulfoxide (DMSO) to afford the corresponding pure products (3d-o) (Table 2).

General Procedure for Preparation of 3-Methyl-2-methylthio-6-oxo-3,6-dihydropurine and Its 8-Alkyl and 8-Aryl Derivatives (4a-o)

Method A

A mixture of **3a-o** (2 mmol) and methyl iodide (0.85 g, 6 mmol) in 1N aqueous KOH (8 ml, 8 mmol) was stirred at 5 - 15 °C for 1.5 - 2 h. The resulting solution was neutralized with glacial acetic acid to afford the corresponding products (**4a-o**), which were washed with water, dried, and recrystallized from water or DMF (Table 3).

Method B

A mixture of **5d-o** (2 mmol) and DEAD (0.45 g, 2.6 mmol) in DMF (20 ml) was heated at 100 °C with stirring for 0.5 - 1.5 h. After cooling, the resulting solid was collected by filtration, washed with ethanol, dried, and recrystallized from DMF to afford the corresponding pure products (**4d-o**) (Table 3).

General Procedure for Preparation of 4-Amino-5-benzylideneamino-3-methyl-2-methylthiopyrimidin-6(3H)-ones (**5d-o**)

A mixture of **2d-o** (4 mmol) and methyl iodide (1.7 g, 12 mmol) in 1N aqueous KOH (12 ml, 12 mmol) was stirred at 5 - 15 °C for 1 - 1.5 h. The resulting solid was collected by filtration, washed with water, dried, and recrystallized from DMF to afford the corresponding pure products (**5d-o**) (Table 4).

General Procedure for Preparation of 4-Amino-5-benzylideneamino-2-methylthiopyrimidin-6(1H)-ones (**7d-h**)

A mixture of 4,5-diamino-2-methylthiopyrimidin-6(1H)-one (**6**) (2 g, 11.6 mmol) and an appropriate aryl aldehyde (17.4 mmol) in dioxane (30 ml) was heated at 80 °C with stirring for 2 h. After cooling, the resulting solid was collected by filtration, washed with ethanol, dried, and recrystallized from 2-ethoxyethanol to afford the corresponding pure products (**7d-h**) (Table 5).

General Procedure for Preparation of 2-Methylthio-6-oxo-1,6-dihydropurine and Its 8-Alkyl Derivatives (**8a-c**)

A mixture of 4,5-diamino-2-methylthiopyrimidin-6(1H)-one (**6**) (2 g, 11.6 mmol) and an appropriate formaldehyde, acetaldehyde, or propionaldehyde (17.4 mmol) in dioxane (30 ml) was stirred at room temperature for 1 h. Then, to a stirred mixture was added DEAD (2.6 g, 15 mmol)

and the mixture was heated at 80 - 90 °C for 8 h. After cooling, the resulting solid was collected by filtration, washed with ethanol, dried, and recrystallized from 2-ethoxyethanol to afford the corresponding pure products (**8a-c**) (Table 6).

General Procedure for Preparation of 8-Aryl-2-methylthio-6-oxo-1,6-dihydropurines (8d-h**)**

A mixture of **7d-h** (4 mmol) with DEAD (3.48 g, 20 mmol) was heated at 100 - 110 °C with stirring for 2 - 4 h. After cooling, the mixture was diluted with ethanol to get the solid, which was collected by filtration, washed with ethanol, dried, and recrystallized from 2-ethoxyethanol (Table 6).

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