Synthesis of 6-Substituted Purines From 3,7-Dimethyl-6-methylthio-2-oxopurine

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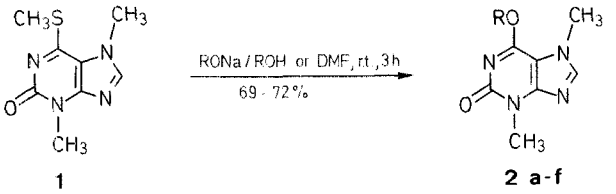
Nucleophilic substitution of 3,7-dimethyl-6-methylthio-2-oxopurine (**1**) with alcoholates or carbanions of active methylene compounds affords the corresponding 6-alkoxy- or 6-alkylidene-3,7-dimethyl-2-oxopurines, respectively, in good yields.

Nucleophilic substitution of purines at the 6-position is one of the useful methods for the synthesis of 6-substituted purine derivatives. 6-Chloropurine, 6-alkylthiopurine, and 6-methylsulfonylpurine undergo substitution by various nucleophiles such as amines,[1,2,3] alcoholates,[1,2] alkylthiolates[1] and carbanions[2,4] to afford the corresponding 6-substituted purines. However, only two examples of this kind of nucleophilic substitution by amines have been reported for 2-oxopurines.[5,6]

In this paper we wish to report the synthesis of 6-substituted purines by the nucleophilic substitution of 3,7-dimethyl-6-methylthio-2-oxopurine (**1**)[7] with alcoholates and active methylene compounds.

The methylthio group of **1** was easily substituted by treatment with alcoholates in alcohols (Method A) or one equivalent of alcoholates in dimethylformamide at room temperature (Method B) to give 6-alkoxypurines **2** (Scheme **A**). The structures of **2** were determined by their ^{1}H-NMR signals ($-O-CH_3$ or $-OCH_2-$) and IR spectra (no ν_{N-H} absorption) (Table 1). The structure of the allyl derivative **2e** was further confirmed by chemical conversion. On heating at 240 °C, 6-allyloxy-3,7-dimethyl-2-oxopurine (**2e**) underwent the Claisen rearrangement[8] to form 1-allyl-3,7-dimethyl-2,6-dioxopurine[9] in 69% yield.

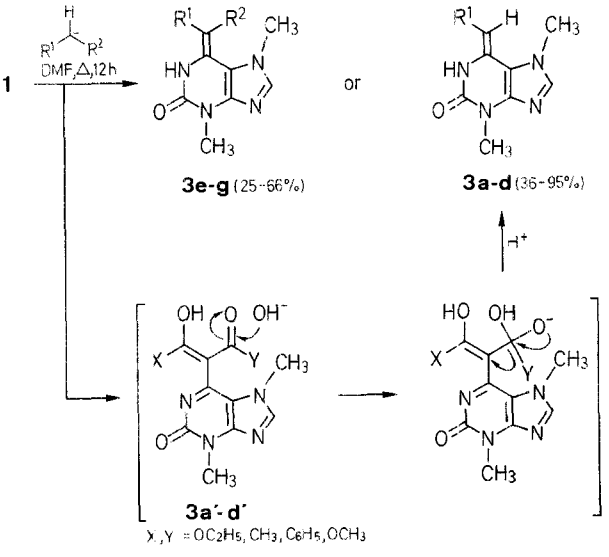


1 **2 a-f**

Scheme **A**

6-Alkoxy-2-oxopurines **2d–e** were obtained in high yields by using only one equivalent of the alcohol, and 3,7-dimethyl-6-methoxyethyl-2-oxopurine (**2f**) was obtained in 72% yield by using three equivalents of the respective alcohol. Thus method B using dimethylformamide as solvent was usefully applied for the reactions with high boiling or expensive alcohols such as benzyl alcohol and allyl alcohol etc.

There are no reports on the synthesis of 6-alkylidene-3,7-dimethyl-2-oxopurines. Alkylidene groups were also introduced in high yields by the reaction of **1** with active methylene compounds and sodium hydride in dimethylformamide under reflux conditions (Scheme **B**). The structure of **3** was determined by their ^{1}H-NMR and IR spectra (Table 2). In the IR spectra of **3a–e**, the carbonyl absorption of ester or acyl was observed at 1655–1675 cm^{-1}. This shows that the presence of the hydrogen bond between hydrogen at N-1 and the carbonyl of ester or acyl group. The geometry of double bond in **3a–e** is specified as *Z*. Also, the geometry of **3g** was determined as *Z*, considering the steric hindrance between the phenyl group and the methyl group at N-7.



Scheme **B**

Table 1. 6-Alkoxy-3,7-dimethyl-2-oxopurines **2** Prepared

Product No.	R	Method[a]	Molecular Formula[b] or Lit. m.p. (°C)	Yield (%)	m.p. (°C) (solvent)	IR (KBr) (cm^{-1}) $\nu_{C=N}$	$\nu_{C=O}$	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)
2a	CH_3	A	245–246[11]	79	243 (dec.) (ethyl acetate/CH_2Cl_2)	1590	1635	3.65, 3.95, 4.14 (3s, 3H each, 2 × NCH_3 and OCH_3); 7.64 (s, 1 H_{arom})
2b	C_2H_5	A	261–263[11]	69	257 (ethanol)	1585	1630	1.44 (t, 3H, J = 14.4 Hz, OCH_2CH_3); 3.63, 3.95 (2s, 3H each, NCH_3); 4.63 (q, 2H, J = 21 Hz, OCH_2CH_3); 7.62 (s, 1 H_{arom})
2c	n-C_4H_9	A	216–217[11]	78	217–219 (ethanol)	1590	1630	0.88–1.92 (m, 7H, C_3H_7); 3.65, 3.97 (2s, 3H each, NCH_3); 4.57 (t, 2H, J = 12 Hz, OCH_2); 7.64 (s, 1 H_{arom})
2d	$C_6H_5CH_2$	B	$C_{14}H_{14}N_4O_2 \cdot 1/6H_2O$ (270.3)	~100	267.5–270 (ethanol)	1590	1630	3.67, 3.91 (2s, 3H each, NCH_3); 5.64 (s, 2H, OCH_2); 7.46 (s, 5 H_{arom}); 7.62 (s, 1 H_{arom})
2e	$H_2C{=}CHCH_2$	B	$C_{10}H_{12}N_4O_2$ (220.2)	69	259–.7–262.1 (ethanol)	1595	1640	3.64, 3.97 (2s, 3H each, NCH_3); 5.08 (d, 2H, J = 5.4 Hz, OCH_2); 5.24–5.60 (m, 2H, $-CH{=}CH_2$); 5.86–6.40 (m, 1H, $-CH{=}CH_2$); 7.64 (s, 1 H_{arom})
2f	$CH_3OCH_2CH_2$	B	$C_{10}H_{14}N_4O_3 \cdot 1/6H_2O$ (238.3)	72	228–230 (acetone)	1590	1640	3.42, 3.64, 3.96 (3s, 3H each, 2 × NCH_3 and OCH_3); 3.70–3.86 (m, 2H, OCH_2); 4.64–4.79 (m, 2H, CH_2OCH_3); 7.61 (s, 1 H_{arom})

[a] Method A: in alcohol.
Method B: in DMF.
[b] The microanalyses were in satisfactory agreement with calculated values: C ±0.29, H ±0.19, N ±0.29.

Table 2. 6-Alkylidene-3,7-dimethyl-2-oxopurines **3** Prepared

Active Methylene Component	Product No.	R^1	R^2	Molecular Formula[a]	Yield (%)	m.p. (°C)	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)
Diethyl malonate	**3a**	$COOC_2H_5$	–	$C_{11}H_{14}N_4O_3$ (250.3)	95	260.5 (dec.)	1630 (C=O); 1660 (COO); 3095 (NH)	1.30 (t, 3H, J = 15 Hz, OCH_2CH_3); 3.48 3.87 (2s, 3H each, NCH_3); 4.21 (q, 2H, J = 22.5 Hz, OCH_2CH_3), 4.98[b] (s, 1H, –CH=); 7.41 (s, 1 H_{arom})
Ethyl acetoacetate	**3a**				63			
Methyl acetoacetate	**3b**	$COOCH_3$	–	$C_{10}H_{12}N_4O_3$ (236.2)	41	257 (dec.)	1630 (C=O); 1660 (COO); 3100 (NH)	3.47, 3.73, 3.87 (3s, 3H each, NCH_3); 4.99 (s, 1H, –CH=); 7.43 (s, 1 H_{arom})
Acetyl-acetone	**3c**	$COCH_3$	–	$C_{10}H_{12}N_4O_2$ (220.2)	75	274–276 (dec.)	1635 (C=O); 1675 (C=O); 3100 (NH)	2.19 (s, 3H, $COCH_3$); 3.51, 3.94 (2s, 3H each, NCH_3); 5.48 (s, 1H, –CH=); 7.53 (s, 1 H_{arom})
Benzoyl-acetone	**3c**				9			
Benzoyl-acetone	**3d**	COC_6H_5	–	$C_{15}H_{14}N_4O_2$ (282.3)	36	267.5–270 (dec.)	1625 (C=O); 1670 (C=O); 3095 (NH)	3.46 3.99 (2s, 3H each, NCH_3); 6.11 (s, 1H, –CH=); 7.35–7.94 (m, 6H, 6 H_{arom})
Methyl cyanoacetate	**3e**	$COOCH_3$	CN	$C_{11}H_{11}N_5O_3$ (261.2)	66	250–252 (dec.)	1615 (C=O); 1655 (COO); 2190 (CN); 3380 (NH)	3.75, 4.02 4.41 (3s, 3H each, 2 × NCH_3, OCH_3); 8.16 (s, 1 H_{arom})[c]
Malono-nitrile	**3f**	CN	CN	$C_{10}H_8N_6O$ (228.2)	74	270–272.5 (dec.)	1725 (C=O); 2200 (CN); 3080 (NH)	3.78, 4.38 (2s, 3H each, NCH_3); 8.60 (s, 1 H_{arom})[d]
Benzyl cyanide	**3g**	C_6H_5	CN	$C_{15}H_{13}N_5O$ (279.3)	25	268.5–270	2172 (CN); 3240 (NH)	3.50, 4.30 (2s, 3H each, NCH_3); 7.45 (s, 5 H_{arom}); 8.28 (s, 1 H_{arom})[c]

[a] The microanalyses were in satisfactory agreement with calculated values: C ±0.23, H ±0.08, N ±0.27.
[b] This signal disappeared on addition of D_2O.
[c] Measured in $CF_3COOH-CDCl_3$.
[d] Measured in CF_3COOH.

The products **3a–d** were formed by deesterification or deacylation after the hydrolysis of the primary products **3a′–d′** under basic conditions (Scheme **B**).

The new method is valuable for the synthesis of the novel compounds with a carbon chain at the 6-position of the purine ring. This nucleophilic substitution at 6-position was performed by the direct substitution of methylthio group.[10]

6-Alkoxy-3,7-dimethyl-2-oxopurines 2; General Procedure:

Method A: Sodium (57 mg, 2.5 mmol) is added to the appropriate alcohol (50 ml). After stirring for 1 h, 3,7-dimethyl-6-methylthio-2-oxopurine (**1**; 1.05 g, 5 mmol) is added to the alcoholate solution. Stirring is continued for 3 h at room temperature. After the solvent is removed under reduced pressure, water (50 ml) is added to the residue. After neutralization with 10%-hydrochloric acid, the aqueous layer is extracted with chloroform (3 × 20 ml). The organic layer is dried with magnesium sulfate and evaporated under reduced pressure to give 6-alkoxy-3,7-dimethyl-2-oxopurines **2a–c** which are recrystallized from suitable solvent (Table 1).

Method B: Sodium hydride (60% dispersion in mineral oil, 88 mg, 2.2 mmol) is added to a solution of the appropriate desired alcohol (2 mmol) in dimethylformamide (10 ml) with cooling in an ice bath. After evolution of hydrogen has ceased, 2-oxopurine **1** (420 mg, 2 mmol) is added to the solution and stirred for 3 h at room temperature. Then the solvent is removed under reduced pressure and water (40 ml) is added to the residue. After neutralization with 10%-hydrochloric acid, the aqueous layer is extracted with chloroform (3 × 10 ml) and the organic layer is dried with magnesium sulfate. The solvent is removed under reduced pressure and the 6-alkoxy-3,7-dimethyl-2-oxopurines **2** obtained are recrystallized from suitable solvent (Table 1).

6-Alkylidene-3,7-dimethyl-2-oxopurines 3; General Procedure:

Sodium hydride (60% dispersion in mineral oil, 88 mg, 2.2 mmol) is added to a solution of the appropriate active methylene compound (2 mmol) in dimethylformamide (10 ml) with cooling in an ice bath. After completion of hydrogen evolution, 2-oxopurine **1** (420 mg, 2 mmol) is added to the solution and stirred for 12 h under reflux. After the mixture is cooled to room temperature, 6-alkylidene-3,7-dimethyl-2-oxopurine is precipitated. The precipitate is filtered, washed with ethanol and recrystallized from ethanol (Table 2).

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