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Functional Monomers and Polymers. 145. Synthetic Application Based on the Tautomerism of Polymer-Bound Purine and Pyrimidine Bases

Hiroshi Koshiba[a]; Koichi Kondo[a]; Kiichi Takemoto[a]
[a] Department of Applied Fine Chemistry, Faculty of Engineering Osaka University, Osaka, Japan

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FUNCTIONAL MONOMERS AND POLYMERS. 145.* SYNTHETIC APPLICATION BASED ON THE TAUTOMERISM OF POLYMER-BOUND PURINE AND PYRIMIDINE BASES

HIROSHI KOSHIBA, KOICHI KONDO, and KIICHI TAKEMOTO

Department of Applied Fine Chemistry
Faculty of Engineering
Osaka University
Yamadaoka 2-1 Suita, Osaka, Japan

ABSTRACT

Polymer-bound alkylthiopurine and -pyrimidine bases were prepared and used as the polymeric reagents for the reactions of nitrile, olefin, and enone formation. The corresponding low molecular weight compounds were also prepared for comparison. Differences in the reactivity of these reagents were related to the change in tautomerism of the purine and pyrimidine moieties.

INTRODUCTION

In previous papers we showed that the tautomerism of purine and pyrimidine bases supported on polymer main chains can be applied to ordinary organic reactions, such as dehydration and desulfhydration, which are also useful for ester and amide formation since the products obtained could be

*For Part 144 of this series, see K. Kondo and K. Takemoto, *Makromol. Chem. Rapid Commun., 7,* 549 (1986).

separated from the polymers employed by a simple filtration technique and reused [1, 2]. For a similar purpose, alkylthiopurine and -pyrimidine bases were used further for nitrile and olefin syntheses which were related to the change in the tautomerism [3, 4].

The present paper concerns a further synthetic study, based on polymer-bound alkylthiopurine and -pyrimidine bases, involving nitrile, olefin, and enone formation. Differences in the reactivity were kinetically studied by way of the hydrolysis of alkylthiopurine and -pyrimidine derivatives.

EXPERIMENTAL

Materials

Poly(isopropyl-2-phenethyl) fumarate (PIPF) (M_n 10^5), supplied by Nihon Yushi Chemical Co., was chloromethylated by a standard method similar to the preparation of chloromethylated polystyrene [5] (chlorine content, 1.98 mmol/g). IR(KBr): 2980(ν_{C-H}), 1730($\nu_{C=O}$), 1160(ν_{C-O}) cm^{-1}.

Polymer-Bound Benzylthiopurine and -Pyrimidine (1, 2; R = PIPF)

Chloromethylated PIPF (10 g) was allowed to react with adenine (2.7 g, 20 mmol) in the presence of potassium carbonate (2.8 g, 20 mmol) in DMF solution at 50°C for 5 days and poured into water. The resulting polymer was filtered off, washed with water, and dried (adenine content, 1.5 mmol/g). To 100 mL of 5 *N* hydrochloric acid containing PIPF-bound adenine (10.0 g) was added dropwise 50 mL aqueous sodium nitrite solution (6.9 g, 100 mmol), stirred at 30°C for 5 h, filtered, washed with water, and dried. The PIPF-bound hypoxanthine thus obtained (10.0 g) was refluxed with phosphorus pentasulfide (13.3 g, 60 mmol) in 100 mL pyridine for 5 h. After filtration the polymer was washed with water and 0.2 *N* aqueous sodium hydroxide solution and then dried. PIPF-bound thiopurine (10.0 g) was first mixed with potassium hydroxide (1.3 g, 20 mmol) in 100 mL methanol at room temperature for 1 h. To the mixture was added benzyl chloride (2.5 g, 20 mmol) and stirred for 5 h. The PIPF-bound benzylthiopurine obtained (1; R = PIPF) was filtered, washed with water, and dried (benzylthiopurine content, 1.20 mmol/g). IR(KBr): 2980(ν_{C-H}), 1730($\nu_{C=O}$), 1160(ν_{C-O}) cm^{-1}.

In a similar way, uracil was bound to PIPF, and by the reaction with phosphorus pentasulfide and treatment with benzyl chloride, PIPF-bound benzylthiopyrimidine (2; R = PIPF) was obtained (benzylthiopyrimidine content,

0.50 mmol/g). IR(KBr): 2980(ν_{C-H}), 1730($\nu_{C=O}$), 1660($\nu_{C=O}$), 1160-(ν_{C-O}) cm^{-1}.

The Polymeric reagents (**1, 2**) were insoluble in common organic solvents.

Low Molecular Weight Model Compounds

9-Methyl-6-benzylthiopurine (**1**, R = CH_3): 9-Methyl-6-thiopurine (1.7 g, 10 mmol) was mixed with potassium hydroxide (0.7 g, 10 mmol) in 70 mL methanol. To the solution, benzyl chloride was added (1.2 mL, 10 mmol), and stirred at room temperature for 4 h. The solvent was then evaporated *in vacuo,* the residue was washed repeatedly and recrystallized from methanol, which gave 9-methyl-6-benzylthiopurine (**1**; R = CH_3) in 93% yield, mp 137-138°C. IR(KBr): 3020(ν_{C-H}), 1580($\nu_{C=N}$) cm^{-1}. ^1H NMR(60 MHz, $CDCl_3$): δ8.73(s,1H), 7.88(s,1H), 7.2-7.4(m,5H), 4.66(s,2H), 3.73(s,3H).

Analysis. Calculated for $C_{13}H_{12}N_4S$ (256.34): C, 60.91; H, 4.73; N, 21.86; S, 12.51%. Found: C, 60.84; H, 4.73; N, 21.82; S, 12.31%.

Mass *m/e*: 256.

1-Methyl-4-benzylthio-2-pyrimidone (**2**, R = CH_3): 1-Methyl-4-thiouracil (1.4 g, 10 mmol) was mixed with potassium hydroxide (0.7 g, 10 mmol) in 50 mL methanol. Benzyl chloride (1.2 mL, 10 mmol) was added to the solution, and the mixture stirred at room temperature for 4 h. The solvent was evaporated *in vacuo*; the residue was washed with water and recrystallized from benzene, which gave 1-methyl-4-benzylthio-2-pyrimidinone (**2**, R = CH_3) in 77% yield, mp 158-159°C. IR(KBr): 2950(ν_{C-H}), 1680($\nu_{C=O}$), 1650-($\nu_{C=N}$), 1620($\nu_{C=C}$) cm^{-1}. ^1H NMR(60 MHz, $CDCl_3$): δ7.83-7.96(d,1H), 7.45(s,5H), 6.4-6.9(d,1H), 4.4(s,2H), 3.35(s,3H).

Analysis. Calculated for $C_{12}H_{12}N_2SO$ (232.31): C, 62.04; H, 5.22; N, 12.06; S, 13.80%. Found: C, 61.81; H, 5.25; N, 11.85; S, 13.62%.

Mass *m/e*: 232.

9-Methyl-6-(*p*-bromophenacyl)thiopurine (**6b**, R = CH_3): 9-Methyl-6-thiopurine (1.0 g, 6 mmol) was mixed with *p*-bromophenacyl bromide (1.7 g, 6 mmol) in the presence of 85% potassium hydroxide (0.5 g, 7 mmol) in 50 mL methanol at 40°C for 5 h. The solvent was evaporated *in vacuo,* the residue was filtered off, washed with water, and recrystallized from ethanol which gave **6** (R = CH_3) in 79% yield, mp 182-184°C. IR(KBr): 3080(ν_{C-H}), 2900(ν_{C-H}), 1670($\nu_{C=O}$), 1560($\nu_{C=N}$) cm^{-1}. ^1H NMR(60 MHz, DMSO-d_6): δ8.55(s,1H), 8.38(s,1H), 8.08-7.67(q,4H), 4.98(s,2H), 3.78(s,3H).

Analysis. Calculated for $C_{14}H_{11}N_4OSBr$(363.24): C, 46.29; H, 3.05; N, 15.43; S, 8.83, Br, 22.00%. Found: C, 46.18; H, 2.95; N, 15.33; S, 8.76; Br, 21.73%.

Mass *m/e*: 363.

In a similar way, PIPF-bound 6-(*p*-bromophenacyl)thiopurine (**1**, R = PIPF) was obtained (thiopurine content, 1.2 mmol/g).

2,4-Di(*p*-bromophenacyl(thiopryimidine (**8b**): 2,4-Dithiouracil (1.0 g, 7 mmol) was mixed with *p*-bromophenacyl bromide (3.9 g, 14 mmol) in the presence of 85% potassium hydroxide (0.9 g, 14 mmol) in 50 mL methanol at 40°C for 5 h. The solvent was evaporated *in vacuo*, the residue was filtered, washed with water, and recrystallized from ethanol which gave **8b** in 90% yield, mp 156-158°C. IR(KBr): 2900($\nu_{C=H}$), 1660($\nu_{C=O}$) cm^{-1}. ^1H NMR(60 MHz, DMSO-d_6): δ8.23-8.12(d,1H), 7.8-7.55(q,8H), 7.11-7.12(d,1H), 4.72-4.61-(d,4H).

Analysis. Calculated for $C_{20}H_{14}N_2O_2S_2Br_2$ (538.27): C, 44.62; H, 2.62; N, 5.20; S, 11.92; Br, 29.69%. Found: C, 44.27; N, 5.17; S, 11.65; Br, 29.35%.

Mass *m/e*: 538.

1-Cyclohexyl-4-(*p*-bromophenacyl)thio-2-pyrimidinone (**7**, R = cyclohexyl): 1-Cyclohexyl-4-thiouracil (1.0 g, 5 mmol) was refluxed with *p*-bromophenacyl bromide (1.4 g, 5 mmol) in the presence of 85% potassium hydroxide (0.3 g, 5 mmol) in 30 mL ethanol for 1 h. After the solvent was evaporated *in vacuo*, the residue was recrystallized from 95% ethanol, which gave **7** in 70% yield, mp 72-73°C. IR(KBr): 3080(ν_{C-H}), 2930, 2850(ν_{C-H}), 1660($\nu_{C=O}$) cm^{-1}. ^1H NMR(60 MHz, $CDCl_3$): δ8.04-7.88(d,1H), 7.28-7.68(q,4H), 6.34-6.22(d,1H), 4.76(s,2H), 1.85-1.40(m,11H).

The compound was found to be heat sensitive and used directly for further reaction.

Nitrile Formation

1-Methyl-4-thiouracil (**4**; R = CH_3) (0.28 g, 2 mmol) was treated with methyl iodide (0.43 g, 3 mmol) in 30 mL acetone at room temperature for 30 min. Benzaldoxime (0.12 g, 1 mmol) was added to the solution and refluxed for 18 h. After the solvent was evaporated *in vacuo*, the residue was distilled *in vacuo* to give benzonitrile.

PIPF-bound thiouracil (**4**, R = PIPF) (4.0 g, 2 mmol) was stirred with methyl iodide (0.43 g, 3 mmol) in 50 mL acetone at room temperature for 30 min. Benzaldoxime (0.12 g, 1 mmol) was added to the mixture and refluxed for 18 h. After the polymer used was filtered and washed with acetone, the filtrate was condensed *in vacuo*. Benzonitrile was isolated from the residue by distillation. Other polymeric reagents were similarly treated to give benzonitrile.

Olefin Formation

The polymeric reagent (**2**; R = PIPF) (2 g, 1 mmol) was treated with *n*-butyllithium (*n*-hexane solution: 1.3 mL, 2 mmol) in 30 mL THF under nitrogen at -78°C for 2 h. Benzaldehyde (0.1 mL, 1 mmol) was added to the solution and stirred for 30 min at room temperature. After the reaction the polymer was filtered, the filtrate was treated with 50 mL aqueous saturated sodium chloride solution, and then extracted with ether. After evaporating the ether, the residue was heated with triethyl phosphite (1 mL, 5,8 mmol) at 90°C for 30 min and distilled *in vacuo,* which gave *trans*-stilbene in 5% yield.

Other benzylthio compounds were similarly treated, and *trans*-stilbene was isolated *in vacuo.*

Enone Formation

The polymeric reagent (**6**, R = PIPF) (1 g, 1.2 mmol) was refluxed with benzaldehyde (0.1 mL, 1 mmol) and tri-*n*-butylphosphine (0.3 mL, 1 mmol) in 50 mL benzene for 40 h. After the solvent was evaporated, the residue was distilled *in vacuo,* which gave enone in 55% yield.

Other *p*-bromophenacylthio compounds (**6**; R = CH_3, **8b**) were similarly treated, and the enone was isolated.

In the case of Compound **7**, elimination of a sulfur atom took place. Compound **7** (0.1 g, 0.25 mmol) was refluxed with 2-methoxyethanol (5 mL) for 30 min; the precipitate was then filtered off and recrystallized from ethanol, which gave 1-cyclohexyl-4-(*p*-bromobenzoyl)methenylpyrimidinone (**9**) in 90% yield; mp 245-246°C. IR(KBr): 3080($\nu_{C=H}$), 2930, 2850(ν_{C-H}), 1680($\nu_{C=O}$), 1650($\nu_{C=O}$). ^{1}H NMR(60 MHz, $CDCl_3$): δ13.05(s,1H), 7.85-7.45(q,4H), 6.83-6.80(d,1H), 5.78-5.65(d,1H), 1.85-1.40(m,11H).

Analysis. Calculated for $C_{18}H_{19}N_2O_2Br$ (375.25): C, 57.61; H, 5.10; N, 7.47; Br, 21.29%. Found: C, 57.15; H, 4.95; N, 7.37; Br, 21.03%.

Mass *m/e*:375.

On thermal treatment of **7** with tri-*n*-butylphosphine, Compound **9** was obtained in excellent yield without forming enone.

Kinetic Studies of the Hydrolysis

Benzylthio compounds (**1**, R = CH_3; **2**, R = CH_3; and **8b**) were dissolved in ethanol and the concentrations adjusted to 110, 55, and 34 μmol/L, re-

spectively. The solution (20 mL) was mixed with 5 *N* aqueous sodium hydroxide solution (20 mL), diluted to 100 mL with ethanol, and kept at 40°C. At regular intervals the absorbance A at λ_{max} (**1**, 287; **2**, 303; **8b**, 303 nm) was measured, and the value of ln (A/A_0) was plotted with time. From the slope of the straight lines, the pseudo-first-order rate constant, k_1, was determined.

RESULTS AND DISCUSSION

Synthesis of Polymer-Bound Alkylthiopurine and -Pyrimidine Bases

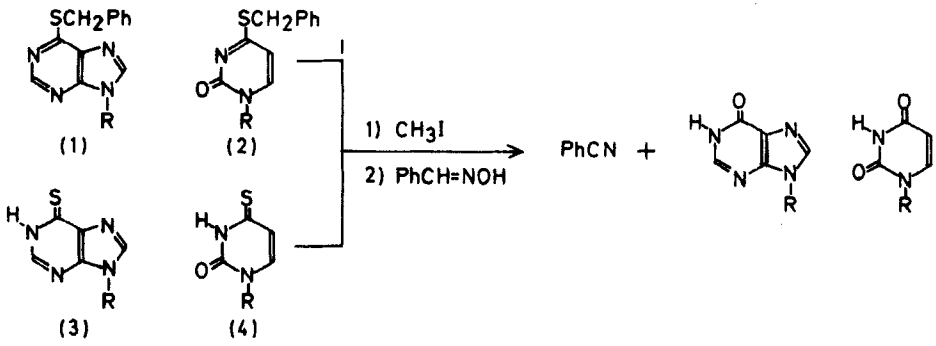
Polystyrene crosslinked with divinyl benzene has been widely used as a versatile polymeric support. Our preliminary study showed that alkylthiopurine and -pyrimidine supported on such polystyrene were sluggish in the olefin formation reaction, in contrast to the low molecular counterparts [4]. This might be ascribed to the formation of immobilized polymeric ion clusters [6]. In order to avoid such difficulties, a rodlike polymer, poly(isopropyl-2-phenethyl) fumarate (PIPF), was employed as the polymeric support for the present study. PIPF was at first chloromethylated and used for coupling with purine and pyrimidine bases.

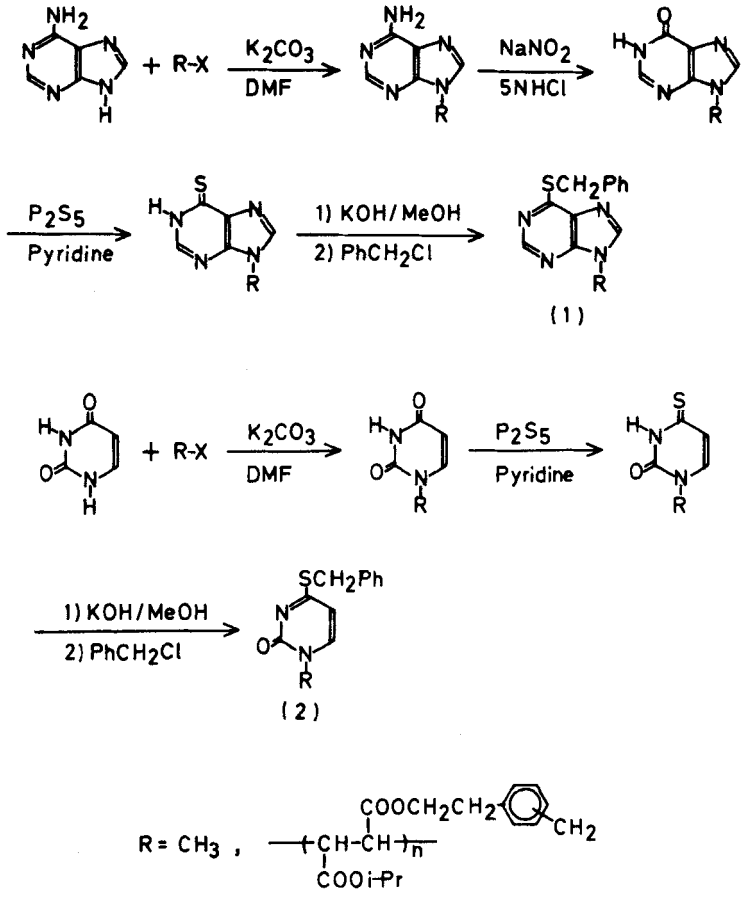
The chloromethylated PIPF (R-X) was reacted with adenine, followed by deamination, sulfurylation, and thioalkylation to give polymer-bound benzylthiopurine (**1**). In a similar way, uracil was converted to the polymer-bound benzylthiopyrimidinone (**2**) as shown in Scheme 1.

In parallel to the synthesis of these polymeric reagents, the corresponding low molecular compounds were also prepared (Scheme 2).

Nitrile Formation

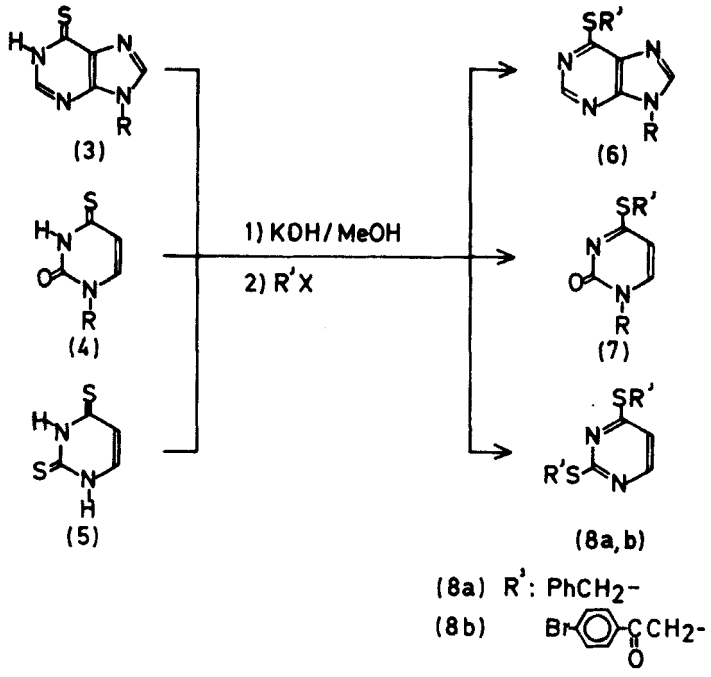
The reaction of a series of Compound **1** to **4** with benzaldoxime gave benzonitrile, together with the purine and pyrimidine derivatives.





SCHEME 1

Thiopyrimidine derivatives were found to be more reactive than thiopurine derivatives (**2** > **1**; **4** > **3**) (Table 1). The presence of methyl iodide in the reaction system accelerated nitrile formation. The reaction did not take place in the absence of methyl iodide in the cases of **3** and **4**. This result was similar to the case of the nitrile-formation reaction based on *N,N*-dimethylthioamide [7]. For benzylthiopurine and -pyrimidine derivatives (**1**, **2**), the reaction took place even in the absence of methyl iodide, which reflects that alkylthiopurine and -pyrimidine derivatives are readily attacked by nucleo-

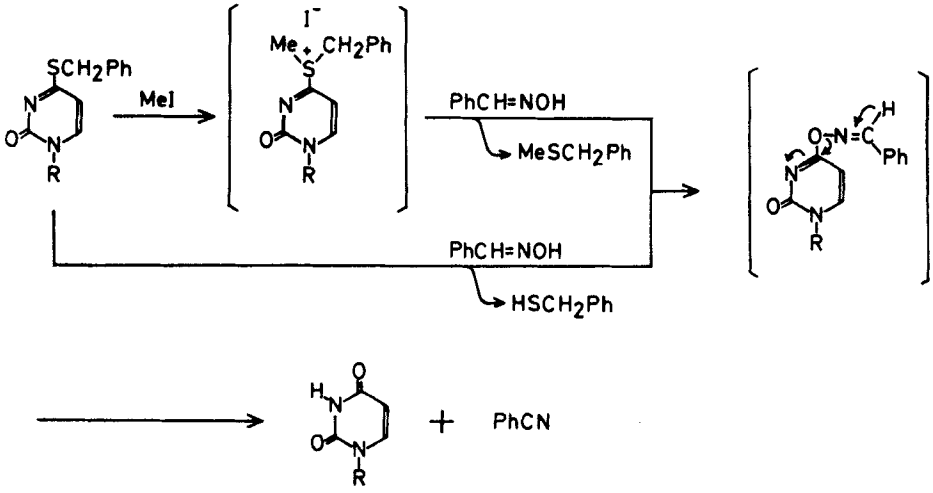


SCHEME 2

TABLE 1. Benzonitrile Formation

		Reagent			
R	Method	1	2	3	4
CH_3	I[a]	66%	83%	54%	76%
	II[b]	31	45	—	—
PIPF	I	40	59	50	63

[a]Treated with methyl iodide.
[b]Without methyl iodide treatment.



SCHEME 3

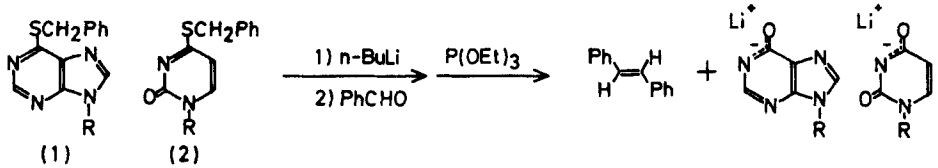
philic reagents, as can be seen in the usual adenine and cytosine synthesis [8]. The nitrile formation is shown as Scheme 3, which includes two reaction paths.

In the case of polymer-bound benzylthiopurine and -pyrimidine, the product could be separated by a simple filtration, and the reuse of the polymer was feasible.

Olefin Formation

Meyers and Ford reported earlier about olefin formation based on alkylthioxazolines [9]. Our earlier report also concerns their application on alkylthio-purine and -pyrimidine derivatives [4].

Benzylthiopurine or -pyrimidine derivatives (**1**, **2**) were further treated with *n*-butyllithium, followed by the addition of benzaldehyde and triethylphosphite, which gave *trans*-stilbene.



(1) (2)

TABLE 2. Stilbene Formation

	Reagent	
R	1	2
CH_3	63%	81%
$C_6H_5CH_2$	75	–
PIPF	2	5

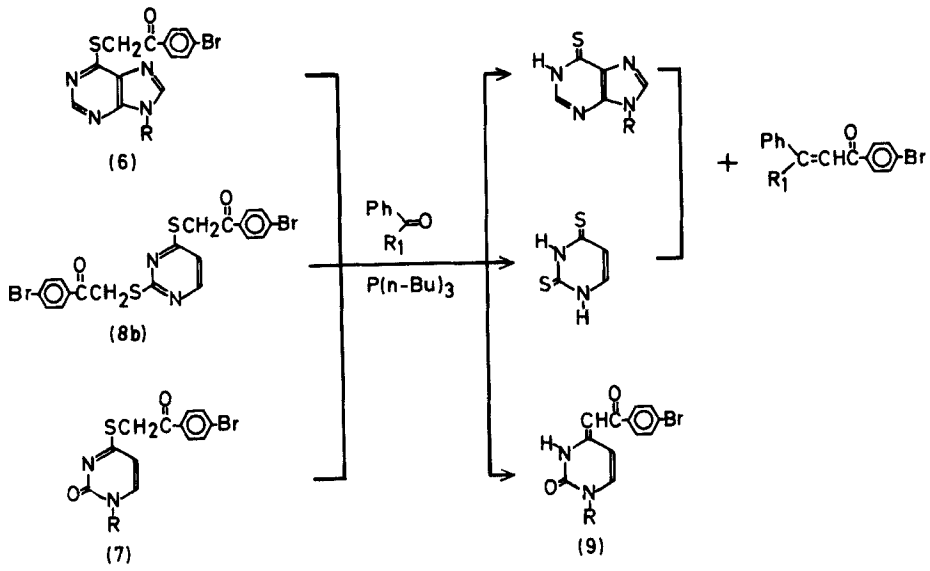
From the reactions with low molecular counterparts, benzonitrile was obtained in satisfactory yields, while the yield was found to be substantially lower for polymeric reagents (Table 2). This could be explained by the production of inactive carbanions on the polymer in the latter case. Nevertheless, some advantages of PIPF as a polymer support over polystyrene was observed for the stilbene-formation reaction; the reaction did not take place with polystyrene-bound reagents.

Enone Formation

The enone formation reaction, starting from 2-phenacylthiobenzothiazole in the presence of *n*-butylphosphine, has been reported by Ueno et al. [10]. Phenacylthiopurine and -pyrimidine derivatives (**6**, **7**, **8**) were similarly expected to yield enones. The reactions of Compounds **6**, **7**, and **8** with carbonyl compounds in the presence of tri-*n*-butylphosphine was rather complicated (Scheme 4): **6** was found to be more reactive than **8b**, which may be explained by thermal stability of the conjugated six-membered ring in the latter case (Table 3). Compound **7** showed quite unique behavior in this treatment, and the removal of the sulfur atom took place preferentially, giving no enone compounds. This reaction is similar to the case of phenacyl thiopyrimidine, which is thermally converted to the sulfur-free pyrimidine derivative [11].

Hydrolysis of Benzylthiopurine and -Pyrimidine Bases

The nitrile, olefin, and enone formation reactions described here revealed conclusively that *N*-substituted alkylthiopyrimidine derivatives seem to be more reactive than other ones. In regard to the different reactivities of alkylthiopurine and -pyrimidine derivatives toward nucleophiles, the hydrolysis was studied kinetically.



SCHEME 4

The benzylthiopurine and -pyrimidine derivatives (**1**; **2**, R = CH_3; **8a**) were treated with an excess amount of aqueous sodium hydroxide solution, and the pseudo-first-order rate constant for hydrolysis was determined spectrophotometrically. The results are summarized in Table 4.

The rate constant k_1 decreased in the order **2** > **1** > **8a** (Table 4). The results were in fair agreement with the different reactivities observed for nitrile,

TABLE 3. Enone Formation

	Carbonyl compound	
Reagent	C_6H_5CHO	$(C_6H_5)_2C{=}O$
6; R = CH_3	73%	70%
PIPF	55	64
8b	10	15

TABLE 4. Value of k_1 for the Hydrolysis

Reagent	k_1, min^{-1}
1; R = CH_3	3.2×10^{-3}
2; R = CH_3	8.4×10^{-2}
8a	4.6×10^{-4}

olefin, and enone formation. Compound **2**, which was more labile toward the attack by nucleophiles, tends to be converted to the more stable lactam form from the active lactim form. The less reactive **8a**, like aromatic compounds, is inert toward nucleophilic attack.

The differences in reactivity could thus be related to the change in the tautomeric character of purine and pyrimidine bases.

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