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THE ONE-POT CONVERSION OF PYRIMIDINONE DERIVATIVES INTO SUBSTITUTED PYRIMIDINES USING DIPHENYLPHOSPHINIC CHLORIDE UNDER A MILD CONDITION

Ken-ichi Tanji, Takeshi Yokoi, and Osamu Sugimoto*

Laboratory of Organic Chemistry, School of Food and Nutritional Sciences, University of Shizuoka, 52-1 Yada, Shizuoka 422-8526, Japan

osamu@smail.u-shizuoka-ken.ac.jp

Abstract – Pyrimidinone derivatives reacted with diphenylphosphinic chloride followed by addition of nucleophiles to afford substituted pyrimidine derivatives at a mild temperature (20-66 ^{o}C).

INTRODUCTION

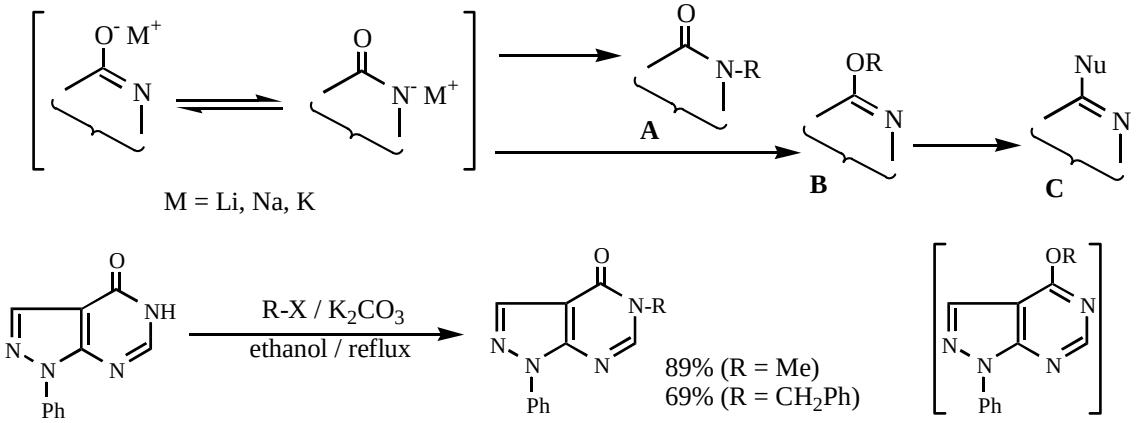
Since pyrimidine derivatives are highly reactive with nucleophiles such as amines, alkoxides, and carbanions, introduction of nucleophilic substituent into the pyrimidine ring is usually carried out by the reaction of halogenopyrimidine with nucleophiles.[1,2] The halogenopyrimidines, however, must be isolated before reaction with nucleophiles in many cases.[3-5] Silyloxyheteroaromatics, prepared by the reaction of hydroxyheteroaromatics with a silane reagent such as hexamethyldisilazane (HMDS), can be converted into aminoheteroaromatics,[6-9] but these reactions require a drastic condition (140-200 ^{o}C, 10-80 h). Thus, in order to overcome the inconvenience, we investigated the one-pot introduction of nucleophilic substituents into pyrimidine ring from the corresponding pyrimidinones under a mild condition, and report in this paper.

RESULTS AND DISCUSSION

Anion of 2- (or 4-) pyrimidinones may react with alkyl halide to give *N*-substituted product (**A**) or *O*-substituted product (**B**) (Scheme 1). When the substituent (-OR) at product (**B**) is a good leaving group, replacement of oxygen by nucleophiles may be expected to afford **C**. However, reaction of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one with alkyl halide in the presence of potassium

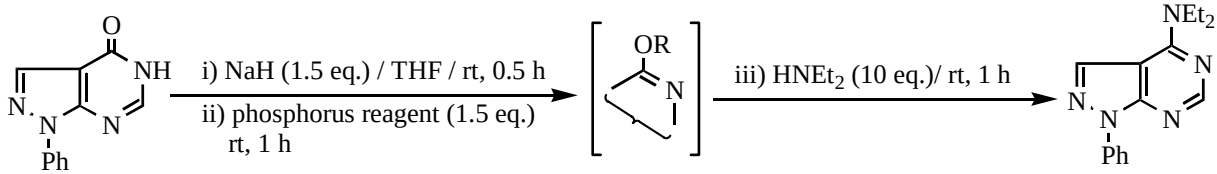
carbonate gave *N*-alkyl products. The same result was observed for the alkylation of the 9*H*-purine derivative.[10]

Scheme 1. Two binding sites (nitrogen and oxygen) at a reaction of nitrogen-containing hydroxyheteroaromatics



As it is well known that phosphorus reagents have a strong affinity for an oxygen atom, reaction of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one with some phosphorus reagents at an alkaline condition followed by addition of diethylamine was carried out. Four phosphorus reagents as shown in Table 1 were used in this reaction to afford the corresponding 4-diethylamino compound in 26-69% yield. It was found that the use of diphenylphosphinic chloride gave the best result. It should be noted that conversion of a hydroxypyrimidine derivative into the corresponding amino compound was accomplished at room temperature, whereas amination of silyloxyheteroaromatics[6-9] required generally 140-180 ^{o}C.

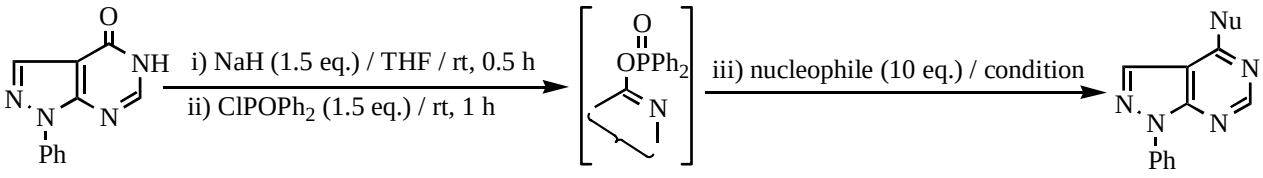
Table 1. Reaction of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one with phosphorus reagents followed by addition of diethylamine



Entry	Phosphorus reagent	R	Yield (%)
1	$ClPOPh_2$	$POPh_2$	69
2	$NCPO(OEt)_2$	$PO(OEt)_2$	55
3	$ClPO(OEt)_2$	$PO(OEt)_2$	28
4	ClPO(OPh)NHPh	PO(OPh)NHPh	26

Elongation of the time or heating at amination led to the increase of the yield (Entries 1-4 in Table 2). Other amines or a carbanion were also used in this reaction under reflux to afford the substituted product, and the yields were good to sparse (Entries 5-10).

Table 2. Reaction of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one with diphenylphosphinic chloride followed by addition of nucleophiles

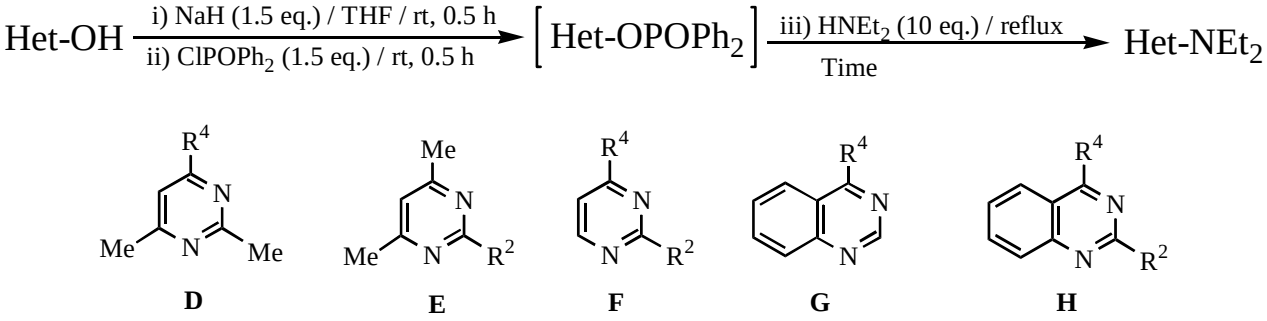


Entry	Nucleophile	Condition	Nu	Yield (%)
1	$HNEt_2$	rt, 1 h	NEt_2	69
2	$HNEt_2$	rt, 3 h	NEt_2	86
3	$HNEt_2$	rt, 7 h	NEt_2	93
4	$HNEt_2$	reflux, 2 h	NEt_2	91
5	piperidine	reflux, 2 h	piperidino	87
6	H_2N^nBu	reflux, 2 h	HNnBu	24
7	H_2NPh	reflux, 2 h	HNPh	32
8	NaCHPhCN	reflux, 2 h	CHPhCN	50
9	KCN	reflux, 2 h	CN	0
10	KCN	reflux, 2 h[a]	CN	11

[a] DMF was used as a solvent instead of THF.

Next, this method was applied to some pyrimidinone derivatives as shown in Table 3. The results of Table 1, Table 2, and Table 3 would propose two speculations. One is that pyrimidinediones are more reactive than pyrimidinones toward the amination, and the other is that the amination of pyrimidinone / pyrimidinediones preferably occur at the 2-position, whereas the amination of fused pyrimidinone / pyrimidinediones preferably occur at the 4-position.

Table 3. Reaction of pyrimidinone derivatives with diphenylphosphinic chloride followed by addition of diethylamine



Entry	Substrate	Time (h)	Product	Yield (%)
1	**D** (R^4=OH)	60	**D** (R^4=NEt_2)	0
2	**E** (R^2=OH)	2	**E** (R^2=NEt_2)	trace
3	**E** (R^2=OH)	96	**E** (R^2=NEt_2)	41
4	**F** (R^2=R^4=OH)	5	**F** (R^2=NEt_2, R^4=OH)	21
5	**G** (R^4=OH)	24	**G** (R^4=NEt_2)	trace
6	**H** (R^2=R^4=OH)	5	**H** (R^2=OH, R^4=NEt_2)	81

In conclusion, introduction of nucleophilic substituents into pyrimidine ring by the reaction of pyrimidinones and phosphorus reagents followed by addition of nucleophiles was accomplished under a mild condition.

EXPERIMENTAL

All melting points were not corrected. ^{1}H-NMR spectra were measured with HITACHI R-90H spectrometer using TMS as an internal standard.

Reaction of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one with methyl iodide: The mixture of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (2122 mg, 10.0 mmol), potassium carbonate (2073 mg, 15.0 mmol), methyl iodide (3800 mg, 26.8 mmol), and ethanol (100 mL) was heated to reflux for 3.5 h. Ethanol was removed under reduced pressure, and water was added to the residue. The solid was filtered and purified with silica gel chromatography (eluted with ethyl acetate-ethanol (10:1)) to give 5-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (2020 mg, 89%). White needles (recryst. from ethyl acetate). mp 212-213 ^{o}C. ^{1}H-NMR ($CDCl_3$) ppm: 3.61 (3H, *s*, CH_3), 7.27-7.64 (3H, *m*, phenyl-H), 7.92-8.13 (2H, *m*, phenyl-H), 8.01 (1H, *s*, C^3-H), 8.25 (1H, *s*, C^6-H). *Anal.* Calcd for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.77. Found: C, 63.82; H, 4.31; N, 24.68.

Reaction of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one with benzyl bromide: The mixture of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (505 mg, 2.38 mmol), potassium carbonate (655 mg, 4.74 mmol), benzyl bromide (810 mg, 4.74 mmol), and ethanol (30 mL) was heated to reflux for 1.5 h. Ethanol was removed under reduced pressure, and the residue was treated with silica gel chromatography (eluted with dichloromethane-ethanol (10:1)) to give 5-benzyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (499 mg, 69%). White prisms (recryst. from hexane-ethyl acetate). mp 177-178 ^{o}C. ^{1}H-NMR ($CDCl_3$) ppm: 5.23 (2H, *s*, CH_2), 7.24-7.63 (8H, *m*, phenyl-H), 7.90-8.11 (2H, *m*, phenyl-H), 8.07 (1H, *s*, C^3-H), 8.27 (1H, *s*, C^6-H). *Anal.* Calcd for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.76; H, 4.68; N, 18.48.

Reaction of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one with phosphorus reagents followed by addition of nucleophiles (General procedure of Table 1 and Table 2): Suspension of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (500 mg, 2.36 mmol), and 60% sodium hydride (142 mg, 3.54 mmol) in THF (30 mL) was sirred at rt for 30 min. After phosphorus reagent (3.54 mmol) was added to the reaction mixture and the mixture was stirred for 1 h, nucleophile (23.6 mmol) was added and the mixture was stirred at the condition shown in Table 1 or Table 2. THF was removed under reduced pressure, and the residue was neutralized with 1 N sodium hydroxide solution, extracted with ethyl acetate. Ethyl acetate was removed under reduced pressure, and the residue was treated with silica gel chromatography (eluate : shown below) to give the corresponding product.

4-Diethylamino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine:[11] White solids. mp 80-81 ^{o}C (lit.,[11] 79-79.5 ^{o}C). Eluate: hexane-ethyl acetate (2:1). ^{1}H-NMR ($CDCl_3$) ppm: 1.34 (6H, *t*, J=7.0 Hz, CH_3*2), 3.79 (4H, *q*,

J=7.0 Hz, CH_2*2), 7.29-7.59 (3H, *m*, phenyl-H), 8.02 (1H, *s*, C^3-H), 8.10-8.21 (2H, *m*, phenyl-H), 8.44 (1H, *s*, C^6-H).

4-Piperidino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine:[12] White solids. mp 116-117 ^oC (lit.,[12] 113-114 ^oC). Eluate: hexane-ethyl acetate (2:1). ^{1}H-NMR ($CDCl_3$) ppm: 1.56-1.77 (6H, *m*, $CH_2CH_2CH_2$), 3.97-4.02 (4H, *m*, NCH_2*2), 7.31-7.61 (3H, *m*, phenyl-H), 8.12-8.19 (3H, *m*, phenyl and C^3-H), 8.44 (1H, *s*, C^6-H).

4-*n*-Butylamino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine:[11] White solids. mp 128-129 ^oC (lit.,[11] 118-120 ^oC). Eluate: hexane-ethyl acetate (2:1). ^{1}H-NMR ($CDCl_3$) ppm: 1.00 (3H, *t*, J=9.5 Hz, CH_3), 1.26-1.84 (4H, *m*, CH_2CH_2), 3.67 (2H, *q*, J=6.4 Hz, NCH_2), 5.49-5.58 (1H, *br*, NH), 7.31-7.61 (3H, *m*, phenyl-H), 8.06 (1H, *s*, C^3-H), 8.11-8.22 (2H, *m*, phenyl-H), 8.46 (1H, *s*, C^6-H).

4-Anilino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine:[11] White solids. mp 214-215 ^oC (lit.,[11] 208-210 ^oC). Eluate: hexane-ethyl acetate (2:1). ^{1}H-NMR ($CDCl_3$) ppm: 7.30-7.59 (10H, *m*, phenyl, NH, and C^3-H), 8.09-8.20 (2H, *m*, phenyl-H), 8.55 (1H, *s*, C^6-H).

2-Phenyl-2-(1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)acetonitrile:[13] White solids. mp 139-141 ^oC (lit.,[13] 127-129 ^oC). Eluate: dichloromethane-ethyl acetate (10:1). ^{1}H-NMR ($CDCl_3$) ppm: 6.55 (0.3H, *s*, CHCN), 7.23-7.66 (1H, *s*, C^3-H), 7.77 (1H, *s*, C^3-H), 7.82-8.04 (2H, *m*, phenyl-H), 8.50 (1H, *s*, C^6-H), 11.21-11.43 (0.7H, *br*, C=C=NH).

1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carbonitrile:[14] White solids. mp 191 ^oC (lit.,[14] 190.5-191.5 ^oC). Eluate: hexane-ethyl acetate (7:1). ^{1}H-NMR ($CDCl_3$) ppm: 7.41-7.69 (3H, *m*, phenyl-H), 8.16-8.26 (2H, *m*, phenyl-H), 8.51 (1H, *s*, C^3-H), 9.23 (1H, *s*, C^6-H).

Reaction of pyrimidinone derivatives with diphenylphosphinic chloride followed by addition of diethylamine (General procedure of Table 3): Suspension of pyrimidinone derivative (2.36 mmol) and 60% sodium hydride (142 mg, 3.54 mmol or 283 mg, 7.08 mmol) in THF (30 mL) was sirred at rt for 30 min. After diphenylphosphinic chloride (838 mg, 3.54 mmol or 1675 mg, 7.08 mmol) was added to the reaction mixture and the mixture was stirred for 1 h, diethylamine (1726 mg, 23.6 mmol or 3452 mg, 47.2 mmol) was added and the mixture was stirred at the condition shown in Scheme 3 or Scheme 4. THF was removed under reduced pressure, and the residue was neutralized with 1 N sodium hydroxide solution, extracted with ethyl acetate. Ethyl acetate was removed under reduced pressure, and the residue was treated with silica gel chromatography (eluate : shown below) to give the corresponding product.

2-Diethylamino-4,6-dimethylpyrimidine:[15] Yellow solids. mp 37-39 ^oC (lit.,[15] 41 ^oC). Eluate: hexane-ethyl acetate (20:1). ^{1}H-NMR ($CDCl_3$) ppm: 1.16 (6H, *t*, J=7.0 Hz, $CH_2C\underline{H}_3$), 2.25 (6H, *s*, C^4 andC^6-CH_3), 3.64 (4H, *q*, J=7.0 Hz, $C\underline{H}_2CH_3$), 6.18 (1H, *s*, C^5-H).

2-Diethylamino-4(3*H*)-pyrimidinone: White solids. mp 86-89 ^oC (whereas 4-diethylamino-2(1*H*)-pyrimidinone[16] melts at 280-281 ^oC). Eluate: dichloromethane-ethanol (15:1). ^{1}H-NMR ($CDCl_3$) ppm:

1.21 (6H, *t*, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.57 (4H, *q*, J=7.0 Hz, $C\underline{H}_2CH_3$), 5.68 (1H, *d*, J=6.3 Hz, C^5-H), 7.73 (1H, *d*, J=6.3 Hz, C^6-H). *Anal.* Calcd for $C_8H_{13}N_3O$: C, 57.47; H, 7.84; N, 25.13. Found: C, 57.19; H, 7.58; N, 25.15.

4-Diethylamino-2(1*H*)-quinazolinone: White solids. mp 221-224 ^oC (whereas 2-diethylamino-4(3*H*)-quinazolinone[17] melts at 177-180 ^oC). Eluate: ethyl acetate-ethanol (3:1). ^{1}H-NMR ($CDCl_3$) ppm: 1.40 (6H, *t*, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.77 (4H, *q*, J=7.0 Hz, $C\underline{H}_2CH_3$), 6.97-7.23 (1H, *m*, C^6-H), 7.38-7.48 (2H, *m*, C^7 and C^8-H), 7.61-7.74 (1H, *m*, C^5-H), 11.96-12.11 (1H, *br*, NH). *Anal.* Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.52; H, 6.95; N, 19.13.

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