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Studies on Pyrimidine Derivatives. XXXIII.[1] Synthesis of Alkyl Pyrimidinyl Ketones by Means of Nitrosation of Alkylpyrimidines

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The reaction of 4-alkylpyrimidines with propyl nitrite under acidic conditions followed by deoximation of the resulting ketoximes gave alkyl pyrimidinyl ketones in satisfactory yields. As compared with the direct oxidation of the alkylpyrimidines with selenium dioxide, the nitrosation followed by deoximation has some advantages for the synthesis of alkyl 4-pyrimidinyl ketones.

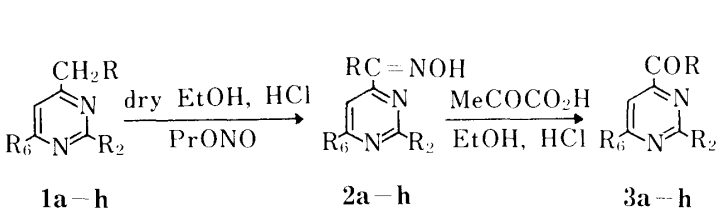
Keywords——alkylpyrimidine; pyrimidinyl ketone; ketoxime; deoximation; nitrosation; Meldrum's acid; Pinner reaction

As reported previously, the nitrosation of 2,4-dimethylpyrimidines with alkyl nitrite selectively proceeded at the 4-methyl group under basic conditions[2] or acidic conditions,[3] and in both cases 4-pyrimidinecarbaldehyde oximes were obtained as sole products. For example, when 2,4-dimethyl-6-phenylpyrimidine was treated with ethyl nitrite in liquid ammonia in the presence of potassium amide or in dry ethanol containing hydrogen chloride, 2-methyl-6-phenyl-4-pyrimidinecarbaldehyde oxime was obtained in 65—78% yields.

The 4-aldoximes thus obtained were fairly resistant to hydrolysis, and deoximation in an acidic medium in the presence of an appropriate carbonyl compound failed to give the free 4-pyrimidinecarbaldehydes.[3] On the other hand, it has been reported[4] that 4-methyl-6-methoxy-2-pyrimidinyl phenyl ketone was isolated by the deoximation of the corresponding ketoxime with sodium hydrogen sulfite in aqueous ethanol.

As an extension of the above findings, in the present paper, we describe the synthesis of alkyl 4-pyrimidinyl ketones by means of the nitrosation of 4-alkylpyrimidines followed by the deoximation of the resultant ketoximes.

When 4-alkylpyrimidines (**1a—i**) were allowed to react with two mole equivalents of propyl nitrite in dry ethanol containing hydrogen chloride at room temperature, the



a: R=Me, R_2=Me, R_6=H
b: R=Et, R_2=Me, R_6=H
c: R=Me, R_2=Ph, R_6=H
d: R=Et, R_2=Ph, R_6=H
e: R=Me, R_2=H, R_6=Ph
f: R=Et, R_2=H, R_6=Ph
g: R=Me, R_2=Me, R_6=Ph
h: R=Et, R_2=Me, R_6=Ph

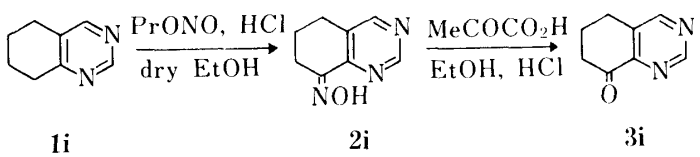


Chart 1

corresponding alkyl 4-pyrimidinyl ketone oximes (**2a—i**) were obtained in good yields. In the case of 2,4-dialkylpyrimidines (**1a**, **b**, **g**, **h**), the reaction took place at the 4-position exclusively. For example, the nitrosation of 4-ethyl-2-methylpyrimidine (**1a**) gave methyl 2-

TABLE I. Nitrosation of Alkylpyrimidines (**1a—i**)

No.	Yield (%)	mp (°C)	IR ($CHCl_3$) cm^{-1}	^{1}H-NMR (DMSO-d_6) δ
2a	67	191—192	3300—2400[a] (br)	2.21 (3H, s), 2.68 (3H, s), 7.70 (1H, d, J=5 Hz) 8.70 (1H, d, J=5 Hz), 12.00 (1H, s)
2b	60	162—163	3600	1.08 (3H, t, J=7 Hz), 2.67 (3H, s), 2.83 (2H, q, J=7 Hz) 7.70 (1H, d, J=5 Hz), 8.70 (1H, d, J=5 Hz), 11.90 (1H, s)
2c	92	169—170	3600	2.33 (3H, s), 7.4—7.8 (3H, m), 7.77 (1H, d, J=6 Hz) 8.3—8.6 (2H, m), 8.83 (1H, d, J=6 Hz), 12.13 (1H, s)
2d	92	147—148	3600	1.20 (3H, t, J=7 Hz), 3.00 (2H, q, J=7 Hz), 7.4—7.8 (3H, m) 7.80 (1H, d, J=6 Hz), 8.3—8.6 (2H, m), 8.90 (1H, d, J=6 Hz) 12.10 (1H, s)
2e	79	181—182	3600	2.30 (3H, s), 7.4—7.8 (3H, m), 8.0—8.4 (2H, m) 8.33 (1H, s), 9.30 (1H, s), 12.17 (1H, s)
2f	75	166—167	3600	1.11 (3H, t, J=7 Hz), 2.90 (2H, q, J=7 Hz), 7.5—7.7 (3H, m) 8.2—8.4 (2H, m), 8.45 (1H, s), 9.40 (1H, s), 12.20 (1H, s)
2g	97	129—130	3600	2.23 (3H, s), 2.75 (3H, s), 7.4—7.6 (3H, m) 8.0—8.3 (2H, m), 8.15 (1H, s), 12.20 (1H, s)
2h	80	123—125	3600	1.10 (3H, t, J=7 Hz), 2.76 (3H, s), 2.83 (2H, q, J=7 Hz) 7.4—7.7 (3H, m), 8.0—8.3 (2H, m), 8.05 (1H, s), 12.03 (1H, s)
2i	63	205—206[b] (dec.)	3600	1.6—2.1 (2H, m), 2.6—3.0 (4H, m), 8.73 (1H, s), 9.03 (1H, s) 12.00 (1H, s)

a) KBr. *b*) Lit.[6] mp 184 °C.

TABLE II. Alkyl 4-Pyrimidinyl Ketones (**3a—i**)

No.	Yield (%)		mp (°C) [bp (mmHg)]	IR ($CHCl_3$) cm^{-1}	^{1}H-NMR (CCl_4) δ
	Method A	Method B			
3a	29	32 (6)[a]	[100 (17)]	1708	2.63 (3H, s), 2.76 (3H, s), 7.65 (1H, d, J=5 Hz) 8.78 (1H, d, J=5 Hz)
3b	40	20 (15)	43—44	1710	1.18 (3H, t, J=7 Hz), 3.00 (3H, s), 3.38 (2H, q, J=7 Hz), 7.85 (1H, d, J=5 Hz), 9.02 (1H, d, J=5 Hz)
3c	64	0 (48)	83—84	1712	2.78 (3H, s), 7.3—7.5 (3H, m), 7.63 (1H, d, J=5 Hz), 8.3—8.6 (2H, m), 8.91 (1H, d, J=5 Hz)
3d	80	0 (65)	72—73	1715	1.73 (3H, t, J=7 Hz), 3.27 (2H, q, J=7 Hz) 7.3—7.6 (3H, m), 7.63 (d, J=5 Hz), 8.3—8.6 (2H, m), 9.90 (1H, d, J=5 Hz)
3e	81	28 (34)	52—53[b]	1710	2.72 (3H, s), 7.3—7.6 (3H, m), 8.0—8.2 (2H, m) 8.22 (1H, s), 9.28 (1H, s)
3f	66	16 (27)	[136 (3)][c]	1720	1.20 (3H, t, J=7 Hz), 3.20 (2H, q, J=7 Hz), 7.3—7.6 (3H, m), 8.0—8.4 (3H, m), 9.27 (1H, s)
3g	71	44 (20)	93—94[d]		
3h	95	39 (30)	95—97[e]		
3i	36	0 (0)	86—87	1710	2.1—2.5 (2H, m), 2.7—3.2 (4H, m), 8.90 (1H, s) 9.33 (1H, s)

a) The figures in parenthesis show the percentages of starting alkylpyrimidines recovered.
b) Lit.[7] mp 53—53.5 °C. *c*) Lit.[7] bp 140—141 °C (5 mmHg).
d) Lit.[5] mp 94—95 °C. *e*) Lit.[5] mp 95—97 °C.

methyl-4-pyrimidinyl ketone oxime (**2a**) as a sole product. The proton magnetic resonance (^{1}H-NMR) spectrum of **2a** clearly demonstrated the ketoxime structure of this compound, showing two singlets at δ2.21 (3H, s) and δ2.68 (3H, s). The results obtained on the nitrosation of **2a**—**i** are listed in Tables I and III.

Next, the deoximation of **1a**—**i** to give alkyl 4-pyrimidinyl ketones (**3a**—**i**) was examined, and successful results were obtained. For example, when ethyl 2-methyl-6-phenyl-4-pyrimidinyl ketone oxime (**2h**) was heated with pyruvic acid in ethanolic hydrochloric acid (method A), ethyl 2-methyl-6-phenyl-4-pyrimidinyl ketone (**3h**) was obtained in 95% yield. The product (**3h**) was identical with an authentic specimen prepared by the reported method.[5] Except in the cases of **2a**, **b**, **i**, these ketoximes were converted into the corresponding ketones by method A in satisfactory yields (listed in Tables II and IV).

Judging from the results obtained on the oxidation of 4-methylpyrimidines with selenium dioxide in dioxane,[8] to afford the 4-pyrimidinecarbaldehydes in good yields, the oxidation of 4-alkylpyrimidines under similar conditions (method B) was expected to provide another practical procedure for the synthesis of 4-pyrimidinyl ketones. As shown in Table II however, the reaction of **1a**—**i** in dioxane–pyridine generally resulted in low yields of the ketones (**3a**, **b**, **e**—**h**) with recovery of considerable amounts of **1a**—**h**. Accordingly, the conversion of 8-hydroxyimino-5,6,7,8-tetrahydroquinazoline (**2i**) into 8-oxo-5,6,7,8-tetrahydroquinazoline (**3i**) is a good example of the advantage of the deoximation procedure for pyrimidinyl ketone formation.

The alkylpyrimidines employed in the investigation as substrates were synthesized as follows. The Pinner reaction[9] (the condensation of β-keto esters with amidines) is a convenient method for the introduction of alkyl groups into the 4-position, because the various β-keto esters can be readily prepared by the acylation of Meldrum's acid.[10] The synthesis of **1a**—**d** was accomplished by this route. Another method for the introduction is the palladium-catalyzed cross-coupling reaction of Grignard reagents and 4-chloropyrimidine derivatives.[11] The synthesis of **1g**, **h** was achieved by this method. The 4-alkyl-6-phenyl derivatives (**1e**, **f**) were synthesized from the corresponding benzoylketones according to the common pyrimidine formation procedure.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. ^{1}H-NMR spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ values. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

6-Ethyl-2-methyl-4(3*H*)-pyrimidinone,[1] 4-chloro-6-ethyl-2-methylpyrimidine,[1] 4-ethyl-2-methyl-6-phenylpyrimidine (**1g**)[1] and 5,6,7,8-tetrahydroquinazoline (**1i**)[12] were prepared according to the cited methods.

General Procedure for the Nitrosation of Alkylpyrimidines——Propyl nitrite (10 mmol) was added to a solution of an alkylpyrimidine (5 mmol) in dry EtOH (10 ml) containing dry HCl (*ca.* 50 mmol) under ice-cooling and stirring. After being stirred at room temperature for 2 h, the mixture was neutralized with 1 N $NaHCO_3$ and concentrated to dryness. The residue was washed with H_2O. The remaining solid was dried and recrystallized from an appropriate solvent (shown in Table I).

General Procedure for the Synthesis of Alkyl 4-Pyrimidinyl Ketones by Deoximation of the Ketoximes (Method A)——A mixture of an alkyl 4-pyrimidinyl ketone oxime (5 mmol) and pyruvic acid (10 mmol) in 95% EtOH (20 ml) containing conc. HCl (1 ml) was refluxed for 6 h. After removal of the solvent, the residue was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using C_6H_6 as an eluent. Distillation under reduced pressure or recrystallization of the crude product from an appropriate solvent gave a pure product as shown Table II.

General Procedure for the Synthesis of Alkyl 4-Pyrimidinyl Ketones by Oxidation with Selenium Dioxide (Method B)——A mixture of an alkylpyrimidine (5 mmol) and SeO_2 (5.5 mmol) in dioxane (15 ml) containing pyridine (5 drops) was refluxed for 2—5 h. The precipitated Se was filtered off, and the filtrate was evaporated to dryness. The residue was distilled under reduced pressure using a Kugelrohr apparatus. The crude product was purified by SiO_2 column chromatography. The results are listed in Table II, together with those obtained by Method A.

TABLE III. Appearance and Analytical Data for Alkyl 4-Pyrimidinyl Ketone Oximes (**2a—i**)

No.	Appearance (Recryst. solvent)	Formula	Analysis (%) Calcd (Found)		
			C	H	N
2a	Pale yellow needles (Acetone)	$C_7H_9N_3O$	55.61 (55.26	6.00 6.04	27.80 27.65)
2b	Pale yellow needles (Acetone)	$C_8H_{11}N_3O$	58.16 (57.76	6.71 6.61	25.44 25.18)
2c	Colorless needles (Ether–hexane)	$C_{12}H_{11}N_3O$	67.59 (67.30	5.20 5.19	19.71 19.41)
2d	Colorless needles (Ether–hexane)	$C_{13}H_{13}N_3O$	68.70 (69.02	5.77 5.90	18.49 18.23)
2e	Colorless needles (Acetone–$CHCl_3$)	$C_{12}H_{11}N_3O$	67.59 (67.17	5.20 5.11	19.71 19.58)
2f	Pale yellow needles (Ether)	$C_{13}H_{13}N_3O$	68.70 (68.27	5.77 5.78	18.49 18.41)
2g	Colorless needles (Ether–hexane)	$C_{13}H_{13}N_3O$	68.70 (68.79	5.77 6.01	18.49 18.19)
2h	Colorless needles (Hexane)	$C_{14}H_{15}N_3O$	69.69 (69.19	6.27 6.37	17.42 17.39)
2i	Colorless needles (MeOH–acetone)	$C_8H_9N_3O$	58.80 (58.73	5.56 5.49	25.75 25.85)

TABLE IV. Appearances and Analytical Data for Alkyl 4-Pyrimidinyl Ketone (**3a—f** and **3i**)

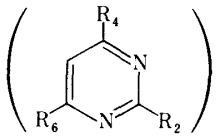
No.	Appearance (Recryst. solvent)	Formula	Analysis (%) Calcd (Found)		
			C	H	N
3a	Colorless liquid	$C_8H_{11}N_5O$[a] (Semicarbazone)	49.73 (49.74	5.74 5.76	36.25 36.02)
3b	Colorless prisms (Pentane)	$C_8H_{10}N_2O$	63.98 (63.68	6.71 6.81	18.65 18.65)
3c	Colorless prisms (Hexane)	$C_{12}H_{10}N_2O$	72.71 (72.23	5.09 5.05	14.13 13.83)
3d	Colorless needles (Hexane)	$C_{13}H_{12}N_2O$	73.56 (73.26	5.70 5.72	13.20 13.08)
3e	Colorless liquid	$C_{12}H_{10}N_2O$	72.71 (72.74	5.09 5.02	14.13 14.01)
3f	Colorless liquid	$C_{13}H_{12}N_2O$	73.56 (73.55	5.70 5.71	13.20 12.89)
3i	Pale yellow scales (Cyclohexane)	$C_8H_8N_2O$	64.85 (64.63	5.44 5.30	18.91 19.00)

a) Colorless needles (MeOH), mp 222—223 °C.

General Procedure for the Reaction of β-Ketoesters with Amidines——Sodium methoxide (100 mmol) in dry MeOH (100 ml) was added to a mixture of a β-ketoester (100 mmol) and an amidine hydrochloride (100 mmol) in dry MeOH (100 ml), and the mixture was stirred at room temperature for 12 h. After removal of the MeOH, the residue was heated at 120 °C under reduced pressure (20 mmHg) for 2 h and extracted with hot $CHCl_3$. The $CHCl_3$ extract was recrystallized from an appropriate solvent to give a pure product.

2-Methyl-6-propyl-4(3*H*)-pyrimidinone: The crude product obtained by the general procedure was recrystallized from EtOH to give colorless prisms, mp 99—101 °C (lit.[13] 89—91 °C). Yield 9.3 g (61 %). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200—2600 (br), 1680. ^{1}H-NMR ($CDCl_3$): 0.95 (3H, t, J=7 Hz), 1.3—2.0 (2H, m), 2.45 (3H, s), 2.50 (2H, t, J=7 Hz), 6.19 (1H, s),

TABLE V. Chloropyrimidines



R_2	R_4	R_6	Yield (%)	bp (°C) [mmHg]	^{1}H-NMR ($CDCl_3$) δ	Formula	Analysis (%) Calcd (Found)			
							C	H	Cl	N
Me	Cl	Pr	79	96—100 [16]	0.95 (3H, t, J=7 Hz), 1.4—2.1 (2H, m) 2.65 (3H, s), 2.70 (2H, t, J=7 Hz), 7.00 (1H, s)	$C_8H_{11}ClN_2$	56.31 (55.94)	6.50 (6.35)	20.78 (20.58)	16.42 (16.22)
Ph	Cl	Et	85	125—126 [2]	1.34 (3H, t, J=7 Hz), 2.82 (2H, q, J=7 Hz) 7.05 (1H, s), 7.3—7.6 (3H, m), 8.3—8.7 (2H, m)	$C_{12}H_{11}ClN_2$	65.90 (65.96)	5.07 (5.03)	16.21 (16.31)	12.81 (12.97)
Ph	Cl	Pr	91	135—137 [2]	0.95 (3H, t, J=7 Hz), 1.5—2.1 (2H, m) 2.70 (2H, t, J=7 Hz), 7.00 (1H, s) 7.3—7.6 (3H, m), 8.3—8.6 (2H, m)	$C_{13}H_{13}ClN_2$	67.10 (67.53)	5.63 (5.51)	15.23 (15.37)	12.04 (12.20)
Cl	Et	Ph	85	140—142 [2]	1.30 (3H, t, J=7 Hz), 2.76 (2H, q, J=7 Hz) 7.3—7.6 (4H, m), 7.8—8.1 (2H, m)	$C_{12}H_{11}ClN_2$	65.90 (66.31)	5.07 (5.07)	16.21 (16.17)	12.81 (12.57)
Cl	Pr	Ph	94	149—150 [2]	1.00 (3H, t, J=7 Hz), 1.6—2.1 (2H, m) 2.80 (2H, t, J=7 Hz), 7.4—7.6 (4H, m) 7.9—8.1 (2H, m)	$C_{13}H_{13}ClN_2$	67.10 (67.21)	5.63 (5.56)	15.23 (15.41)	12.04 (12.01)

TABLE VI. Reduction of Chloropyrimidines

No.	Method	Yield (%)	bp (°C) [mmHg]	^{1}H-NMR (CCl_4) δ	Formula	Analysis (%) Calcd (Found)		
						C	H	N
1a	D	79	89 [60]	1.25 (3H, t, J=7 Hz), 2.60 (3H, s) 2.75 (2H, q, J=7 Hz), 6.85 (1H, d, J=5 Hz), 8.40 (1H, d, J=5 Hz)	$C_{13}H_{13}N_5O_7$ (Picrate)[a]	44.45 (44.47)	3.73 (3.73)	19.94 (19.79)
1b	D	88	98 [50]	0.95 (3H, t, J=7 Hz), 1.4—2.1 (2H, m), 2.60 (3H, m), 2.65 (2H, t, J=7 Hz), 6.85 (1H, d, J=5 Hz) 8.40 (1H, d, J=5 Hz)	$C_{14}H_{15}N_5O_7$ (Picrate)[b]	46.03 (46.26)	4.14 (4.43)	19.17 (19.43)
1c	C	96	113—115 [2]	1.22 (3H, t, J=7 Hz), 2.67 (2H, q, J=7 Hz), 6.75 (1H, d, J=5 Hz) 7.3—7.6 (3H, m), 8.4—8.6 (3H, m)	$C_{12}H_{12}N_2$	78.23 (78.50)	6.57 (6.69)	15.21 (15.01)
1d	C	98	130 [2]	0.95 (3H, t, J=7 Hz), 1.5—2.1 (2H, m), 2.70 (2H, t, J=7 Hz) 6.80 (1H, d, J=5 Hz), 7.3—7.6 (3H, m), 8.4—8.7 (3H, m)	$C_{13}H_{14}N_2$	78.75 (78.44)	7.27 (7.27)	14.13 (13.94)
1e	C	96	124 [2][c]	1.30 (3H, t, J=7 Hz), 2.75 (2H, q, J=7 Hz), 7.3—7.6 (4H, m) 7.9—8.2 (2H, m), 9.03 (1H, s)				
1f	C	96	130—131 [2][d]	1.00 (3H, t, J=7 Hz), 1.5—2.1 (2H, m), 2.75 (2H, t, J=7 Hz) 7.3—7.6 (4H, m), 7.9—8.2 (2H, m) 9.03 (1H, s)				

a) Yellow needles (ether), mp 113—115 °C. *b*) Yellow needles (ether), mp 90—92 °C.
c) Lit.[15] bp 162—165 °C (12 mmHg). *d*) Lit.[15] bp 175—177 °C (20 mmHg).

12.5—13.5 (1H, br).

6-Ethyl-2-phenyl-4(3*H*)-pyrimidinone: The crude product obtained by the general procedure was recrystallized from ether to give colorless needles, mp 169—170 °C. Yield 17.6 g (88%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200—2800 (br), 1670. ^{1}H-NMR ($CDCl_3$): 1.28 (3H, t, J=7 Hz), 2.65 (2H, q, J=7 Hz), 6.38 (1H, s), 7.4—7.6 (3H, m), 8.1—8.4 (2H, m) 12.5—14.0 (1H, br). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.73; H, 6.19; N, 13.73.

2-Phenyl-6-propyl-4(3*H*)-pyrimidinone: The crude product obtained by the general procedure was recrystallized from C_6H_6 to give colorless needles, mp 150—151 °C (lit.[14] mp 141 °C). Yield 18.2 g (85%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200—2800 (br), 1670. ^{1}H-NMR ($CDCl_3$): 1.01 (3H, t, J=7 Hz), 1.5—2.1 (2H, m), 2.56 (2H, t, J=7 Hz), 6.31 (1H, s), 7.4—7.8 (3H, m), 8.1—8.5 (2H, m), 13.0—14.0 (1H, br).

4-Ethyl-6-phenyl-2(1*H*)-pyrimidinone: A mixture of 1-phenylpentane-1,3-dione (17.6 g, 100 mmol) and urea (9 g, 150 mmol) in EtOH (50 ml) containing conc. HCl (15 ml) was refluxed for 48 h. After removal of the solvent, the residue was neutralized with 3 N Na_2CO_3. The resulting solid was filtered off and recrystallized from EtOH to give colorless needles, mp 199—200 °C. Yield 14 g (70%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200—2600 (br), 1650. ^{1}H-NMR ($CDCl_3$): 1.36 (3H, t, J=7 Hz), 2.77 (2H, q, J=7 Hz), 6.43 (1H, s), 7.1—7.3 (3H, m), 7.6—8.0 (2H, m), 13.5—14.0 (1H, br). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.85; H, 6.06; N, 13.93.

6-Phenyl-4-propyl-2(1H)-pyrimidinone: The crude product was obtained according to the above method from 1-phenylhexane-1,3-dione (19 g, 100 mmol) and urea (9 g, 150 mmol). Recrystallization from EtOH gave colorless prisms, mp 164—165 °C. Yield 13.7 g (64%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200—2600 (br), 1650. ^{1}H-NMR ($CDCl_3$): 1.02 (3H, t, J=7 Hz), 1.5—2.2 (2H, m), 2.67 (2H, t, J=7 Hz), 6.60 (1H, s), 7.2—7.6 (3H, m), 7.8—8.2 (2H, m), 13.6—14.1 (1H, br). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.76; H, 6.67; N, 12.85.

General Procedure for the Chlorination of Pyrimidinones with Phosphoryl Chloride——A mixture of a pyrimidinone and excess $POCl_3$ was refluxed for 1—3 h. After removal of the excess $POCl_3$, the residue was poured into ice-conc. ammonia, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was passed through a short Al_2O_3 column with $CHCl_3$ as an eluent and the product was distilled under reduced pressure to give a clorless liquid.

General Procedure for the Reduction of Chloropyrimidines——i) Hydrogenation over Palladium Charcoal (Method C): A mixture of a chloropyrimidine (100 mmol), 5% Pd-C (2 g), conc. ammonia (10 ml), and MeOH (150 ml) was shaken in an H_2 atmosphere. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was extracted with $CHCl_3$. Distillation under reduced pressure gave a colorless liquid.

ii) Reduction with Zinc and Aqueous Ammonia (Method D): A mixture of a 4-chloropyrimidine (100 mmol), Zn dust (50 g), saturated NaCl aq. solution (100 ml) containing 5% ammonia, and C_6H_6 (50 ml) was refluxed for 12 h with vigorous stirring. The Zn was filtered off and the filtrate was separated to a C_6H_6 layer and an aqueous layer. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was distilled under reduced pressure to give a colorless liquid.

2-Methyl-6-phenyl-4-propylpyrimidine (1h)——According to the reported procedure,[11] **1h** was prepared from 4-chloro-2-methyl-6-phenylpyrimidine (10.2 g, 50 mmol) and PrMgBr in dry ether as a colorless liquid, bp 128—130 °C (2 mmHg). Yield 7.0 g (66%). ^{1}H-NMR (CCl_4): 1.60 (3H, t, J=7 Hz), 1.5—2.1 (2H, m), 2.60 (2H, t, J=7 Hz), 2.67 (3H, s), 7.20 (1H, s), 7.2—7.5 (3H, m), 7.9—8.1 (2H, m). *Anal.* Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.09; H, 7.68; N, 12.98.

References and Notes

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