[Chem. Pharm. Bull. 30(5)1865—1867(1982)]

Studies on Pyrimidine Derivatives. XXVII.[1] Synthesis of 2- and 4-Pyrimidinyl Ketones by Means of the Hydration of Alkynylpyrimidines

KEN-ICHI TANJI, TAKAO SAKAMOTO, and HIROSHI YAMANAKA*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

(Received October 15, 1981)

In the palladium-catalyzed cross-coupling reaction of halopyrimidines with terminal acetylenes, 2- and 4-chloropyrimidines can be used as starting compounds, though their reactivity is inferior to that of 2- and 4-iodopyrimidines. The conversion of the 2- and 4-alkynylpyrimidines thus obtained into the corresponding pyrimidinylmethyl ketones was successfully achieved by consecutive treatment with piperidine and oxalic acid dihydrate.

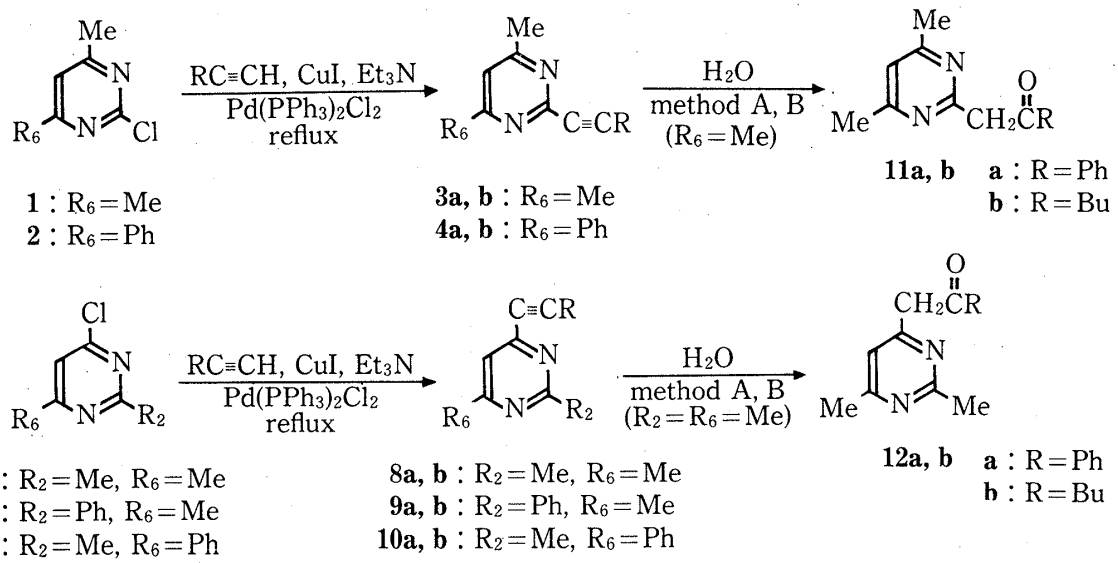
Keywords——chloropyrimidine; alkynylpyrimidine; pyrimidinylmethyl ketone; palladium catalyst; cross-coupling reaction; hydration of acetylenic bond

Previously we reported[2] that the cross-coupling reaction of 2- and 4-iodopyrimidines with terminal acetylenes in the presence of palladium(II) chloride-triphenylphosphine complex and cuprous iodide in triethylamine smoothly proceeded at room temperature to give the corresponding alkynylpyrimidines, and that 2-chloro-4,6-dimethylpyrimidine (**1**) remained almost intact when it was treated under identical conditions. On the other hand, Ohsawa *et al.* reported[3] that 3-chloropyridazines generally underwent the cross-coupling reaction on heating to give alkynylpyridazines. We reinvestigated the cross-coupling reaction in the pyrimidine series using 2- and 4-chloro derivatives instead of the iodopyrimidines, because 2- and 4-chloropyrimidines are most readily available among halopyrimidines. The present paper deals with the cross-coupling reaction of 2- and 4-chloropyrimidines under reflux conditions, and the synthesis of 2- and 4-pyrimidinylmethyl ketones by means of hydration of the pyrimidines having an acetylenic function thus obtained.

When a solution of 2-chloro-4,6-dimethylpyrimidine (**1**) and phenylacetylene in triethylamine was heated under reflux for 12 h in the presence of the palladium complex and cuprous iodide, 4,6-dimethyl-6-phenylethynylpyrimidine (**3a**) was obtained in 42% yield. In order to confirm the generality of this reaction, several chloropyrimidines such as **2**, **5**, **6**, and **7** were treated with phenylacetylene and 1-hexyne under the same conditions. In all cases, the corresponding alkynylpyrimidines (**3a**, **4a**, **b**, **8a**, **b**, **9a**, **b**, and **10a**, **b**) were obtained, although the yields of the products did not exceed those observed in the case of the iodopyrimidines.[2] This route to alkynylpyrimidines is synthetically convenient because 2- and 4-iodopyrimidines were usually prepared *via* the corresponding chloropyrimidines.

Then the synthesis of 2- and 4-pyrimidinylmethyl ketones by hydration of the acetylenic group thus introduced was investigated. It was already known that the hydration of 2- and 4-phenylethynylquinoline[4] and 2-phenylethynylpyridines[5] in the presence of mercuric sulfate gave the corresponding phanacyl derivatives selectively (method A). On the other hand, Bestman *et al.*[6] reported that an acetylenic group with an electron-withdrawing substituent was readily transformed into a methyleneketone function by treatment with piperidine followed by hydrolysis of the resultant enamine with the aid of oxalic acid dihydrate (method B).

Thus, method B was compared with method A for the hydration of **3a**, **b** and **8a**, **b**. For example, the hydration of 4,6-dimethyl-2-(1-hexynyl)pyrimidine (**3a**) by method A afforded butyl 4,6-dimethyl-2-pyrimidinylmethyl ketone (**11b**) in 68% yield, whereas the same product (**11b**) was obtained in 73% yield by method B. As shown in Table II, the difference in the yields of pyrimidinylmethyl ketones (**11a** and **12a**, **b**) obtained by methods A and B was not



method A : $HgSO_4$, aq. H_2SO_4, acetone, reflux
method B : i) piperidine, toluene, reflux
ii) $(COOH)_2 \cdot 2H_2O$, Et_2O, EtOH, reflux

Chart 1

large. In the proton magnetic resonance (PMR) spectra of **11a, b** and **12a, b**, the existence of a characteristic tautomerism was recognized, indicating that an acylmethyl group is attached directly to the pyrimidine ring.

In our previous investigation, the synthesis of 2- and 4-pyrimidinylmethyl ketones from 2- and 4-chloropyrimidines was reported by two methods,[7,8] but the hydration described above appears to be a better procedure from the viewpoint of experimental simplicity.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. PMR spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in ppm downfield from tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet and m=multiplet.

Table I. Yields and Spectral Data for Cross-coupling Products of 2- and 4-Chloropyrimidines with Acetylenes

No.	Yield (%)	IR ($CHCl_3$) ν C≡C (cm^{-1})	PMR ($CDCl_3$) ppm
3a	42	2210	2.50 (6H, s), 6.92 (1H, s), 7.28—7.50 (3H, m), 7.51—7.84 (2H, m)
3b	45	2240	0.75—1.16 (3H, m), 1.30—1.98 (4H, m), 2.16—2.71 (2H, m), 2.60 (6H, s), 7.08 (1H, s)
4a	38	2220	2.60 (3H, s), 7.20—7.89 (9H, m), 8.00—8.33 (2H, m)
4b	56	2220	0.75—1.15 (3H, m), 1.33—1.95 (4H, m), 2.33—2.66 (2H, m) 2.59 (3H, s), 7.33—7.61 (4H, m), 7.86—8.14 (2H, m)
8a	53	2220	2.48 (3H, s), 2.68 (3H, s), 7.10 (1H, s), 7.18—7.68 (5H, m)
8b	44	2240	0.70—1.15 (3H, m), 1.35—1.95 (4H, m), 2.13—2.66 (2H, m) 2.45 (3H, s), 2.65 (3H, s), 7.00 (1H, s)
9a	57	2240	2.66 (3H, s), 7.16—7.82 (9H, m), 8.10—8.50 (2H, m)
9b	49	2240	0.70—1.15 (3H, m), 1.28—1.96 (4H, m), 2.33—2.80 (2H, m) 2.50 (3H, s), 7.00 (1H, s), 7.33—7.65 (3H, m), 8.18—8.64 (2H, m)
10a	38	2210	2.86 (3H, s), 7.31—7.87 (9H, m), 8.00—8.33 (2H, m)
10b	57	2220	0.68—1.13 (3H, m), 1.16—1.95 (4H, m), 2.31—2.62 (2H, m) 2.71 (3H, s), 7.32—7.66 (4H, m), 7.83—8.18 (2H, m)

Table II. Yields and Spectral Data for 2- and 4-Pyrimidinylmethyl Ketones

No.	Yield (%) Method A	Yield (%) Method B	IR ($CHCl_3$) cm^{-1} ν_{OH}	IR ($CHCl_3$) cm^{-1} $\nu_{C=O}$	PMR ($CDCl_3$) ppm
11a	70	46			
11b	68	73	3400	1725	0.75—1.14 (3H, m), 1.30—1.95 (4H, m), 2.17—2.74 (2H, m) 2.40 (2.4H, s), 2.43 (3.6H, s), 4.00 (1.2H, s), 5.51 (0.4H, s)6.65 (0.4H, s), 6.91 (0.6H, s), 14.14—14.34 (0.4H, broad)
12a	60	55			
12b	67	55	3400	1720	0.67—1.06 (3H, m), 1.17—1.97 (4H, m), 2.16—2.67 (2H, m), 2.34 (1.3 H, s), 2.48 (1.7H, s), 2.54 (1.3H, s), 2.66 (1.7H, s) 3.80 (1.1H, s), 5.18 (0.45H, s), 6.38 (0.45H, s), 6.92 (0.55H, s), 14.10—15.33 (0.45H, broad)

Table III. Elemental Analyses for **4a,b**, **10a,b**, **11b**, and **12b**

No.	mp [bp (mmHg)] (°C)	Formula	Analysis Calcd (%) C	H	N	Found (%) C	H	N
4a	87—89 (Hexane)	$C_{19}H_{14}N_2$	84.42	5.22	10.36	84.68	5.27	10.46
4b	[165—170 (3)]	$C_{17}H_{18}N_2$	81.56	7.25	11.19	81.23	7.22	11.35
10a	90—92 (Hexane)	$C_{19}H_{14}N_2$	84.42	5.22	10.36	84.34	5.18	10.27
10b	[170—175 (3)]	$C_{17}H_{18}N_2$	81.56	7.25	11.19	81.62	7.31	11.06
11b	[140—145 (3)]	$C_{12}H_{18}N_2O$	69.87	8.80	13.58	70.08	8.88	13.46
12b	[120—125 (3)]	$C_{12}H_{18}N_2O$	69.87	8.80	13.58	69.60	8.82	13.45

General Procedure for Cross-coupling Reaction of 2- and 4-Chloropyrimidines with Terminal Acetylenes——A mixture of a chloropyrimidine (0.01 mol), a terminal acetylene (0.012 mol), $Pd(PPh_3)_2Cl_2$ (0.2 mmol), CuI (0.2 mmol), and Et_3N (20 ml) was refluxed for 12 h. The solvent was evaporated off under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ layer was purified by SiO_2 column chromatography using $CHCl_3$ as an eluent and by subsequent recrystallization from hexane or distillation under reduced pressure.

General Procedure for Hydration of Alkynylpyrimidines——Method A: A solution of an alkynylpyrimidine (0.005 mol) and $HgSO_4$ (0.005 mol) in 70% aq. acetone containing 95% H_2SO_4 (1.0 g) was refluxed for 6 h. The solvent was evaporated off under reduced pressure and the residue was purified by SiO_2 column chromatography using $CHCl_3$ as an eluent and by subsequent recrystallization from hexane or distillation under reduced pressure.

Method B: A solution of an alkynylpyrimidine (0.01 mol) and piperidine (0.02 mol) in toluene (20 ml) was refluxed for 60 h. The solvent was evaporated off under reduced pressure. The residue was dissolved in a mixture of oxalic acid dihydrate (0.012 mol), ether (20 ml), and EtOH (3 ml), and the solution was refluxed for 6 h. After removal of the solvent by evaporation, the residue was diluted with H_2O, made alkaline with $NaHCO_3$, and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ layer was purified as described above.

References and Notes

1) Part XXVI: T. Sakamoto, K. Tanji, and H. Yamanaka, *Chem. Pharm. Bull.*, **30**, 1033 (1982).
2) K. Edo, T. Sakamoto, and H. Yamanaka, *Chem. Pharm. Bull.*, **26**, 3840 (1978).
3) A. Ohsawa, Y. Abe, and H. Igeta, *Chem. Pharm. Bull.*, **28**, 3488 (1980).
4) S. Konno, M. Shiraiwa, and H. Yamanaka, *Chem. Pharm. Bull.*, **29**, 3554 (1981).
5) L. Marion, R. Lavigne, and L. Lemay, *Can. J. Chem.*, **29**, 347 (1951).
6) H.J. Bestmann and C. Geisman, *Ann.*, **1977**, 282.
7) H. Yamanaka, S. Konno, T. Sakamoto, S. Niitsuma, and S. Noji, *Chem. Pharm. Bull.*, **29**, 2837 (1981).
8) S. Konno, M. Yokoyama, A. Kaite, I. Yamatsuta, S. Ogawa, M. Mizugaki, and H. Yamanaka, *Chem. Pharm. Bull.*, **30**, 152 (1982).