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Studies on Pyrimidine Derivatives. XXV.[1] Reaction of Pyrimidinyl Aldehydes and Ketones with Wittig Reagents

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The reaction of 2- and 4-pyrimidinecarbaldehydes with reagents such as ethoxycarbonyl- (**1**) and benzoyl-(triphenylphosphino)methanide (**2**) gave pyrimidines with an α,β-unsaturated carbonyl group. The reagents (**1, 2**) reacted with 2- and 4-acetylpyrimidines to give similar products, as expected. 4-(1-Chloroethyl)pyrimidines did not react with triphenylphosphine, though chloro-methylpyrimidines are know to give Wittig reagents.

Keywords——pyrimidinecarbaldehyde; methyl pyrimidinyl ketone; Wittig reaction; ethyl pyrimidineacrylate; phenyl pyrimidinylethenyl ketone

Previously, we reported[2] the synthesis of 4-pyrimidinecarbaldehydes by the oxidation of simply substituted methylpyrimidines with selenium dioxide in dioxane. Since the oxidation mentioned above was selective to the 4-methyl groups in a 2,4-dimethylpyrimidine series, the synthesis of the 2-aldehydes was achieved by similar oxidation of 2-pyrimidinemethanols,[3] which are easily prepared by the homolytic hydroxymethylation of 2-unsubstituted pyrimidines.[4] As a part of our investigation on the synthesis of pyrimidine derivatives containing a functionalized carbon-substituent,[5] the conversion of these aldehydes and related pyrimidinyl ketones into ethenylpyrimidines by means of the Wittig reaction was investigated, and the results are described in the present paper.

When 2-methyl-6-phenyl-4-pyrimidinecarbaldehyde (**3b**) was heated with (triphenylphosphino)ethoxycarbonylmethanide (**1**) in benzene under reflux, ethyl 2-methyl-6-phenyl-4-pyrimidineacrylate (**4b**) was obtained in 55% yield. In the proton magnetic resonance (PMR) spectrum of **4b**, the signal due to one of the olefinic protons on the side chain appears at 7.10 δ (1H, d) with a coupling constant of 16 Hz, together with signals corresponding to the other parts of the proposed structure. The above observed value evidently supports the ***trans***-acrylate structure of the product. The reaction of **3b** with (triphenylphosphino)benzoylmethanide (**2**) readily afforded 2-(2-methyl-6-phenyl-4-pyrimidinyl)ethenyl phenyl ketone (**5b**) in 52% yield, although the reaction of **3b** with (triphenylphosphino)butanide failed to give the expected product. Similarly, 2-phenyl-4-pyrimidinecarbaldehyde (**3a**) smoothly reacted with **1** and **2** to give ethyl 2-phenyl-4-pyrimidineacrylate (**4a**) and phenyl 2-(6-phenyl-4-pyrimidinyl)ethenyl ketone (**5a**) in 65 and 77% yield, respectively. No significant differences in

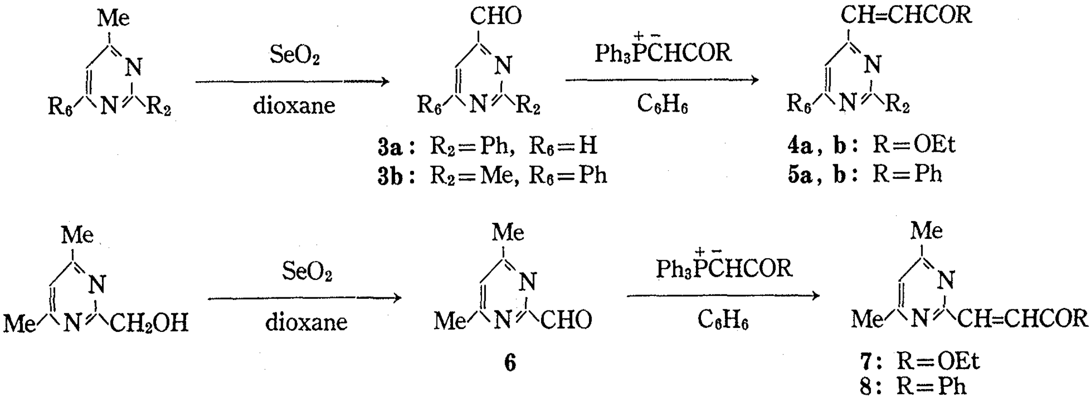


Chart 1

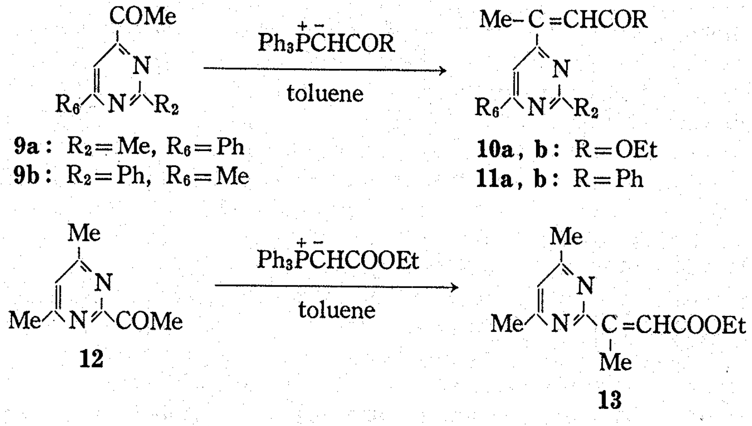
reactivity with the Wittig reagents were observed between the 4-aldehydes and 2-aldehydes. Namely, 4,6-dimethyl-2-pyrimidinecarbaldehyde (**6**) prepared by the oxidation of 4,6-dimethyl-2-pyrimidinemethanol was converted to ethyl 4,6-dimethyl-2-pyrimidineacrylate (**7**) and 2-(4,6-dimethyl-2-pyrimidinyl)ethenyl phenyl ketone (**8**) in yields (66 and 57%) comparable to those of **4a**, **b** and **5a**, **b**. The infrared (IR) spectra of these compounds (**7**, **8**), like those of **4** and **5**, show the presence of an α,p-unsaturated ester ($\nu_{C=O}$: 1710—1720) or ketone function ($\nu_{C=O}$: 1680), and the PMR spectra support their *trans*-olefin structures (J=16 Hz).

Table I. IR and PMR Spectral Data for Compounds **4a**, **b**, **5a**, **b**, **7**, and **8**

No.	IR ($CHCl_3$) $\nu_{C=O}$	PMR ($CDCl_3$) δ
4a	1720	1.40 (3H, t, J=8 Hz), 4.35 (2H, q, J=8 Hz), 7.10—7.70 (6H, m), 8.40—8.60 (2H, m), 8.90 (1H, d, J=5 Hz)
4b	1720	1.35 (3H, t, J=7 Hz), 2.85 (3H, s), 4.30 (2H, q, J=7 Hz), 7.10 (1H, d, J=16 Hz), 7.35—7.70 (4H, m), 7.95—8.20 (2H, m)
5a	1680	7.30 (1H, d, J=6 Hz), 7.40—7.80 (7H, m), 8.00—8.30 (3H, m), 8.50—8.85 (2H, m), 8.90 (1H, d, J=6 Hz)
5b	1680	2.80 (3H, s), 7 35—7 90 (8H, m), 8.00—8.30 (5H, m)
7	1710	1.33 (3H, t, J=8 Hz), 2.50 (6H, s), 4.30 (2H, q, J=8 Hz) 6.90 (1H, s), 7.15 (1H, d, J=16 Hz), 7.66 (1H, d, J=16 Hz)
8	1680	2.50 (6H, s), 6.92 (1H, s), 7.35—7.72 (4H, m), 7.90—8.30 (2H, m), 8.32 (1H, d, J=16 Hz)

Further investigation was made to extend this reaction to the introduction of branched olefin substituents. Thus, methyl 2-methyl-6-phenyl-4-pyrimidinyl ketone (**9a**) and methyl 6-methyl-2-phenyl-4-pyrimidinyl ketone (**9b**) were treated with **1** and **2**, respectively. In the case of **9a**, **b**, a rather higher reaction temperature seemed to be required. Namely, the reaction of **9a**, **b** with **1** in boiling benzene resulted in the recovery of the starting pyrimidinyl ketones, but the reaction in boiling toluene afforded the corresponding 4-propenylpyrimidines (such as **10a**, **b** and **11a**, **b**) in considerable yield. Similarly, 4,6-dimethyl-2-pyrimidinyl methyl ketone (**12**) was transformed into ethyl 3-(4,6-dimethyl-2-pyrimidinyl)crotonate (**13**) by reaction with **2** in boiling toluene.

The side chain isomers in the products thus obtained could not be resolved except for **11b**.[6] When **11b** was chromatographed on a silica gel column using benzene as an eluant, two isomers [**11b′**: mp 71—73°C (13%); **11b″**: mp 132—134°C (19%)] were isolated. By comparing the chemical shifts of olefinic protons on the side chains with those of related compounds, *e.g.* methacrylate, compounds **11b′** (δ=8.00) and **11b″** (δ=6.60) were assigned as *E*-form and *Z*-form, respectively.



9a: R_2=Me, R_6=Ph
9b: R_2=Ph, R_6=Me

10a, **b**: R=OEt
11a, **b**: R=Ph

12

13

Chart 2

Table II. IR and PMR Spectral Data for Compounds **10a**, **b**, **11a**, **b′**, **b″**, and **13**

No.	IR($CHCl_3$) $\nu_{C=O}$	PMR ($CDCl_3$) δ
10a	1720	1.10 (3H, t, J=7 Hz), 2.12 (3H, s), 2.80 (3H, s), 4.05 (2H, q, J=7 Hz), 6.04 (1H, s), 7.35—7.90 (4H, m), 8.00—8.35 (2H, m)
10b	1720	1.08 (3H, t, J=7 Hz), 2.10 (3H, s), 2.60 (3H, s), 4.05 (2H, q, J=7 Hz), 6.02 (1H, s), 6.98 (1H, s), 7.33—7.60 (3H, m), 8.33—8.62 (2H, m)
11a	1660	2.70 (3H, s), 2.86 (3H, s), 7.34—7.66 (6H, m), 7.67 (1H, s) 7.85—8.30 (5H, m)
11b′	1665	2.55 (3H, s), 2.60 (3H, s), 7.20 (1H, s), 7.35—7.60 (6H, m), 7.90—8.10 (3H, m), 8.35—8.50 (2H, m)
11b″	1670	2.35 (3H s), 2.50 (3H, s), 6.60 (1H, s), 6.94 (1H, s) 7.20—7.60 (6H, m), 7.80—8.10 (4H, m)
13	1710	1.31 (3H, t, J=7 Hz), 2.50 (6H, s), 2.60 (3H, s), 4.20 (2H, q, J=7 Hz) 6.90 (1H, s), 7.16 (1H, s)

As shown in Chart 3, 2-methyl(phenyl)-6-phenyl(methyl)-4-(1-chloroethyl)pyrimidines (**15a**, **b**) are easily synthesized as follows. Sodium borohydride reduction of **9a**, **b** afforded the corresponding 1-(4-pyrimidinyl)ethanols (**14a**, **b**) in good yield, and these were readily converted into **15a**, **b** by treatment with phosphoryl chloride in chloroform. The chlorides (**15a**, **b**) were recovered unchanged when they were heated with triphenylphosphine in benzene or even in xylene, although the 4-chloromethylpyrimidines were reported[3] to react with triphenylphosphine to give the corresponding 4-pyrimidinylmethylphosphonium chlorides. Accordingly, the synthesis of derivatives with a branched olefin chain by means of the Wittig reaction is concluded to be restricted in application.

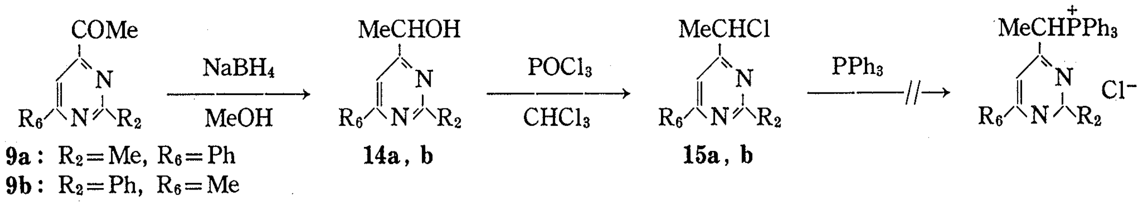


Chart 3

Experimental

All melting points and boiling points are uncorrected. 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 δ value. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet.

Starting pyrimidines were synthesized according to the literature except for 2-phenyl-4-pyrimidinecarbaldehyde (**3a**), as follows: 2-methyl-6-phenyl-4-pyrimidinecarbaldehyde (**3b**),[2] 4,6-dimethyl-2-pyrimidinecarbaldehyde (**6**),[3] methyl 2-methyl-6-phenyl-4-pyrimidinyl ketone (**9a**),[7] methyl 6-methyl-2-phenyl-4-pyrimidinyl ketone (**9b**),[7] and 4,6-dimethyl-2-pyrimidinyl methyl ketone (**12**).[7]

2-Phenyl-4-pyrimidinecarbaldehyde (**3a**)——A mixture of 4-methyl-2-phenylpyrimidine (1.7 g, 0.01 mol), SeO_2 (1.11 g, 0.01 mol), and dioxane (60 ml) was refluxed for 5 h. After removal of the precipitated selenium by filtration, the dioxane was evaporated off under reduced pressure. The residue was purified by silica gel chromatography using C_6H_6 as an eluant. Recrystallization from hexane gave colorless needles, mp 116—117°C (lit.[8] mp 118°C). Yield 1.45 g (79%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720. PMR ($CDCl_3$) δ: 7.33—7.66 (4H, m), 8.30—8.60 (2H, m), 8.95 (1H, d, J=5 Hz), 10.05 (1H, s).

General Procedure for the Wittig Reaction of Pyrimidinecarbaldehydes——A solution of a 2- or 4-pyrimidinecarbaldehyde (0.003 mol) and (triphenylphosphino)ethoxycarbonylmethanide (**1**) (0.003 mol) or (triphenylphosphino)benzoylmethanide (**2**) (0.003 mol) in dry C_6H_6 (10 ml) was refluxed for 2—4 h. The solvent was evaporated off under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was purified by silica gel column chromatography using $CHCl_3$ as an eluant and by recrystallization from appropriate solvents.

Table III. Yields, Melting Points, and Analytical Data for Compounds **4a**, **b**, **5a**, **b**, **7**, and **8**

No.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
4a	65	78—80 (hexane)	$C_{15}H_{14}N_2O_2$	70.85	5.55	11.02
				(70.94	5.60	11.09)
4b	55	74—75 (hexane)	$C_{16}H_{16}N_2O_2$	71.62	6.01	10.44
				(71.37	5.86	10.32)
5a	77	112—114 (hexane)	$C_{19}H_{14}N_2O$	79.70	4.93	9.78
				(80.10	5.04	9.72)
5b	52	117—119 (hexane)	$C_{20}H_{16}N_2O$	79.98	5.37	9.33
				(80.03	5.75	9.00)
7	66	55—56 (hexane)a)				
8	57	183—185 (EtOH)	$C_{15}H_{14}N_2O$	75.60	5.92	11.76
				(75.90	5.97	11.67)

a) Lit.9) mp 54—56°C.

Table IV. Yilds, Melting[Boiling] Points, and Analytical Data for Compounds **10a**, **b**, **11a**, **b′**, **b″**, and **13**

No.	Yield (%)	mp [bp] (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
10a	75	65—66 (hexane)	$C_{17}H_{18}N_2O_2$	72.32	6.43	9.92
				(72.21	6.40	9.91
10b	57	75—77 (hexane)	$C_{17}H_{18}N_2O_2$	72.32	6.43	9.92
				(72.08	6.30	9.72)
11a	40	100—102 (hexane)	$C_{21}H_{18}N_2O$	80.23	5.77	8.91
				(80.42	5.92	8.87)
11b′	13	71—73 (hexane)	$C_{21}H_{18}N_2O$	80.23	5.77	8.91
				(80.41	5.76	8.83)
11b″	19	132—134 (hexane)	$C_{21}H_{18}N_2O$	80.23	5.77	8.91
				(80.32	5.75	8.87)
13	41	[130—135 (2 mmHg)]	$C_{12}H_{16}N_2O_2$	65.43	7.32	12.72
				(65.20	7.37	12.43)

General Procedure for the Wittig Reaction of Methyl Pyrimidinyl Ketones——A solution of a methyl 2- or 4-pyrimidinyl ketone (0.003 mol) and **1** (0.003 mol) or **2** (0.003 mol) in dry toluene (10 ml) was refluxed for 10 h. The solvent was evaporated off under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude products were purified by recrystallization (compound **10b**) or by silica gel column chromatography using $CHCl_3$ (compound **10a** and **11a**) or C_6H_6 (compound **11b**) and by recrystallization from hexane or by distillation under reduced pressure (compound **13**).

1-(2-Methyl-6-phenyl-4-pyrimidinyl)ethanol (14a)——A mixture of **9a** (3 g, 0.014 mol), sodium borohydride (0.52 g, 0.014 mol), and EtOH (30 ml) was refluxed for 5 h. The EtOH was evaporated off under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was purified by distillation under reduced pressure to give a colorless liquid, bp 160—165°C (3 mmHg), which was used without analysis in the next step. Yield 2 g (66%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400. PMR ($CDCl_3$) δ: 1.52 (3H, d, $J=7$ Hz), 2.72 (3H, s), 4.14—4.52 (1H, br), 4.85 (1H, q, $J=7$ Hz), 7.34—7.62 (4H, m), 7.85—8.17 (2H, m).

1-(6-Methyl-2-phenyl-4-pyrimidinyl)ethanol (14b)——A mixture of **9b** (3 g, 0.014 mol), sodium borohydride (1.06 g, 0.028 mol), and EtOH (100 ml) was refluxed for 1 h. The EtOH was evaporated off under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was purified by distillation under reduced pressure to give a colorless liquid, bp 160—163°C (3 mmHg). Yield 2.5 g (83%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420. PMR ($CDCl_3$) δ: 1.62 (3H, d, $J=6$ Hz), 2.65 (3H, s), 4.00—4.50 (1H, br), 4.90 (1H, q, $J=6$ Hz), 7.10 (1H, s), 7.35—7.70 (3H, m), 8.35—8.65 (2H, m). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.73; H, 6.45; N, 13.26.

4-(1-Chloroethyl)-2-methyl-6-phenylpyrimidine (15a)——A mixture of **14a** (1.5 g, 0.007 mol) and $POCl_3$ (15 ml) was refluxed for 2 h, and then excess $POCl_3$ was evaporated off under reduced pressure. The residue was diluted with H_2O, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The crude product was distilled under reduced pressure to give a colorless liquid, bp 145—147°C (3 mmHg). Yield 1.3 g (80%). PMR ($CDCl_3$) δ: 1.84 (3H, d, $J=7$ Hz), 2.75 (3H, s), 5.00 (1H, q, $J=7$ Hz), 7.35—7.63 (3H, m), 7.65 (1H, s), 7.90—8.28 (2H, m). *Anal.* Calcd for $C_{13}H_{13}ClN_2$: C, 67.10; H, 5.59; Cl, 15.27; N, 12.04. Found: C, 67.03; H, 5.62; Cl, 14.99; N, 11.81.

4-(1-Chloroethyl)-6-methyl-2-phenylpyrimidine (15b)——A mixture of **14b** (2.5 g, 0.012 mol) and $POCl_3$ (15 ml) was refluxed for 4 h, and then excess $POCl_3$ was evaporated off under reduced pressure. The residue was diluted with H_2O, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The crude product was distilled under reduced pressure to give a colorless liquid, bp 140—145°C (3 mmHg). Yield 2 g (74%). PMR ($CDCl_3$) δ: 1.95 (3H, d, $J=6$ Hz), 2.65 (3H, s), 5.10 (1H, q, $J=6$ Hz), 7.30 (1H, s), 7.35—7.65 (3H, m), 8.30—8.65 (2H, m). *Anal.* Calcd for $C_{13}H_{13}ClN_2$: C, 67.10; H, 5.59; Cl, 15.27; N, 12.04. Found: C, 66.98; H, 5.56; Cl, 15.04; N, 12.17.

References and Notes

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