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Studies on Pyrimidine Derivatives. XXVI.[1] Synthesis of Derivatives containing a 1,3-Dicarbonyl Side Chain

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Pyrimidine derivatives containing a 1,3-dicarbonyl side chain at the 2- or 4-position were synthesized by the Claisen condensation of pyrimidine 2- or 4-carboxylic esters with ethyl acetate, acetophenone, and phenylacetonitrile. The keto–enol tautomerism of the products is also reported.

Keywords——methyl pyrimidinecarboxylate; Claisen condensation; pyrimidinyl-β-ketoester; pyrimidinyl-β-diketone; pyrimidinyl-β-ketonitrile; tautomerism

As a part of our work on the synthesis of pyrimidine derivatives, we reported the selective formation of 4-pyrimidinecarboxylic acids by the ouidation of 2,4-dimethyl compounds with selenium dioxide in pyridine.[2] In order to obtain 2-pyrimidinecarboxylic acids, methanolysis of the corresponding 2-pyrimidinecarboxamides is the preferred procedure, because the latter compounds are easily prepared by the direct homolytic amidation of 2-unsubstituted pyrimidines.[2,3] In both cases, the carboxylic acids thus prepared were isolated as their methyl esters for experimental convenience. In order to extend the utility of these esters, the Claisen condensations with ethyl acetate, acetophenone, and phenylacetonitrile were carried out, because pyrimidine derivatives with a 1,3-dicarbonyl side chain formed an unexplored family.

When methyl 2-methyl-4-pyrimidinecarboxylate (1) was reacted with ethyl acetate, acetophenone, and phenylacetonitrile in boiling toluene in the presence of sodium ethoxide, ethyl 3-(2-methyl-4-pyrimidinyl)-3-oxopropionate (3a), 1-(2-methyl-4-pyrimidinyl)-3-phenyl-

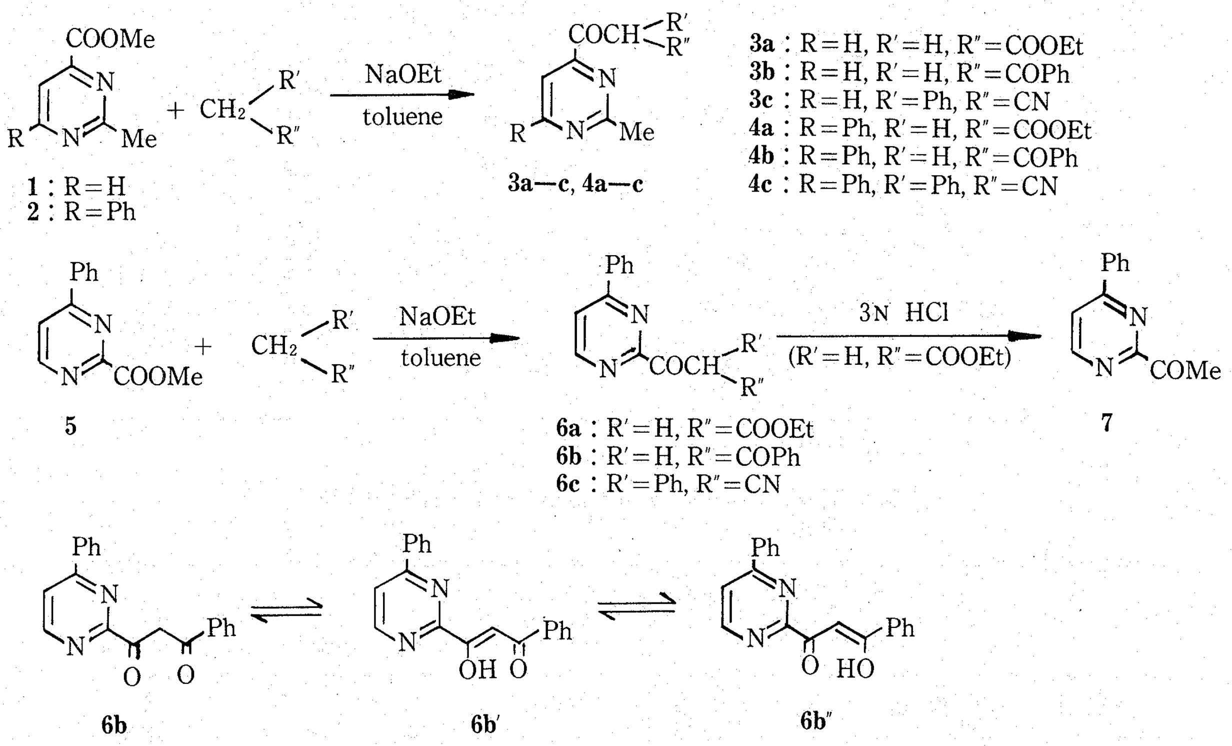

Chart 1

1,3-propanedione (**3b**), and 3-(2-methyl-4-pyrimidinyl)-3-oxo-2-phenylpropionitrile (**3c**) were obtained, respectively. Similarly, when methyl 2-methyl-6-phenyl-4-pyrimidinecarboxylate (**2**) was treated with the same reagents the 6-phenyl derivatives (**4a**—**c**) with a 1,3-dicarbonyl type side chain at the 4-position were obtained, as expected.

Methyl 4-phenyl-2-pyrimidinecarboxylate (**5**) also underwent the Claisen condensation smoothly with ethyl acetate, acetophenone, and phenylacetonitrile in a similar fashion. As shown in Table I and in the experimental section, the elemental analysis, infrared (IR), and proton magnetic resonance (PMR) data of all the products are in good agreement with the expected structures. In this series, the purification of one product, ethyl 3-oxo-3-(4-phenyl-2-pyrimidinyl)propionate (**6a**), by vacuum distillation failed because of its instability. Acid hydrolysis of **6a** afforded methyl 4-phenyl-2-pyrimidinyl ketone (**7**) whose structure is well supported by the observed spectral and elemental properties.

Furthermore, the PMR spectra of these nine products (**3a**—**c**, **4a**—**c**, and **6a**—**c**) revealed the existence of keto-enol tautomerism, as in the case of ethyl benzoylacetate and benzoylacetone. The keto-enol ratios in $CDCl_3$ solution, as roughly estimated by the measurement of the relative intensity of the methylene signals and the methine signals, are listed in Table II;, although in the cases of **3b**, **4b**, and **6b** the different formal enol forms (*e.g.*, **6b′** or **6b″**) could not be distinguished.

TABLE I. Yields, Melting Points, and the Results of Elemental Analyses of the Claisen Condensation Products

No.	Yield (%)	mp (°C)	Formula	Analysis(%) Calcd. (Found)		
				C	H	N
3a	73	77—79(EtOH)	$C_{10}H_{12}N_2O_3$	57.68	5.81	13.46
				(57.57	5.84	13.54)
3b	76	96—97(hexane)	$C_{14}H_{12}N_2O_2$	69.99	5.03	11.66
				(70.04	4.82	11.75)
3c	38	102—104(hexane)	$C_{14}H_{11}N_3O$	70.87	4.67	17.71
				(71.04	4.64	17.75)
4a	40	85—87(hexane)	$C_{16}H_{16}N_2O_3$	67.59	5.67	9.85
				(67.48	5.67	9.87)
4b	72	147—148(EtOH)	$C_{20}H_{16}N_2O_2$	75.93	5.10	8.86
				(76.20	5.15	8.72)
4c	44	112—113(hexane)	$C_{20}H_{15}N_3O$	76.66	4.83	13.41
				(76.83	4.75	13.34)
6a	79[a]					
6b	66	151—152(EtOH)	$C_{19}H_{14}N_2O_2$	75.48	4.67	9.27
				(75.73	4.71	9.25)
9c	41	133—134(hexane)	$C_{19}H_{13}N_3O$	76.24	4.38	14.04
				(75.98	4.29	13.88)
7	64	116—117(hexane)	$C_{12}H_{10}N_2O$	72.71	5.09	14.13
				(72.97	4.87	13.87)

[a] Tentatively calculated for the crude product.

TABLE II. Tautomerism between PmCOCHR′R″ and PmC(OH)=CR′R″ (Pm=pyrimidinyl)

	R′	R″	Compound 3		Compound **4**		Compound **6**	
			Keto (%)	Enol (%)	Keto (%)	Enol (%)	Keto (%)	Enol (%)
a	H	COOEt	50	50	60	40	60	40
b	H	COPh	0	100	0	100	0	100
c	Ph	CN	40	60	0	100	0	100

Experimental

All melting 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 values. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet.

Starting methyl pyrimidinecarboxylates were synthesized according to the cited methods: methyl 2-methyl-4-pyrimidinecarboxylate (**1**),[3] methyl 2-methyl-6-phenyl-4-pyrimidinecarboxylate (**2**),[3] and methyl 4-phenyl-2-pyrimidinecarboxylate (**5**).[4]

General Procedure for the Claisen Condensation with Methyl Pyrimidinecarboxylates——A mixture of methyl pyrimidinecarboxylate (0.0022 mol), NaOEt (0.0044 mol), an active methylene compound (0.0044 mol), and toluene (5 ml) was refluxed for 1 h. The solvent was removed under reduced pressure. The residue was diluted with H_2O, neutralized with 20% AcOH, and extracted with $CHCl_3$. The crude products were purified by silica-gel column chromatography using $CHCl_3$ as an eluant and by recrystallization from appropriate solvents.

Methyl 4-Phenyl-2-pyrimidinyl Ketone (7)——A mixture of ethyl 3-oxo-3-(4-phenyl-2-pyrimidinyl)-propionate (**6a**) (1.0 g, 0.0037 mol) and 3 N HCl (15 ml) was refluxed for 1 h and then extracted with $CHCl_3$. The crude product was purified by silica gel column chromatography using $CHCl_3$ as an eluant. Recrystallization from hexane gave colorless needles, mp 116—117°C. Yield 0.5 g (82%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1713. PMR ($CDCl_3$) δ: 2.83 (3H, s), 7.46—7.65 (3H, m), 7.82 (1H, d, $J=6$ Hz), 8.09—8.30 (2H, m), 8.94 (1H, d, $J=6$ Hz). *Anal.* Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.97; H, 4.87; N, 13.87.

TABLE III. IR and PMR Spectral Data for the Claisen Condensation Products

No.	IR($CHCl_3$) cm^{-1}	PMR ($CDCl_3$) δ
3a	1750 1705	1.28 (1.5H, t, $J=7$ Hz), 1.31 (1.5H, t, $J=7$ Hz), 2.85 (3H, s), 4.00—4.50 (2H, m) 4.10 (1H, s), 6.45 (0.5H, s), 7.60 (0.5 H, d, $J=5$ Hz), 7.68 (0.5H, d, $J=5$ Hz) 8.72 (0.5H, d, $J=5$ Hz), 8.85 (0.5H, d, $J=5$ Hz), 12.15 (0.5H, s)
3b	1630	2.85 (3H, s), 7.33—7.65 (4H, m), 7.80 (1H, d, $J=5$ Hz), 7.95—8.20 (2H, m) 8.85 (1H, d, $J=5$ Hz), 15.05—16.20 (1H, broad)
3c	2200 1720	2.85 (3H, s), 6.45 (0.4H, s), 7.30—7.70 (3H, m), 7.83—8.10 (2H, m) 8.65 (1H, d, $J=5$ Hz), 8.93 (1H, d, $J=5$ Hz), 9.30—10.35 (0.6H, broad)
4a	1750 1720	1.28 (1.9H, t, $J=7$ Hz), 1.35 (1.1H, t, $J=7$ Hz), 2.84 (3H, s), 4.00—4.50 (2H, m) 4.16 (1.2H, s), 6.48 (0.4H, s), 7.33—7.84 (3H, m), 7.95—8.34 (3H, m) 12.32 (0.4H, s)
4b	1630	2.85 (3H, s), 7.34—7.82 (7H, m), 8.00—8.35 (5H, m), 14.85—16.25 (1H, broad)
4c	2200 1720	2.91 (3H, s), 7.33—7.67 (7H, m), 7.85—8.12 (2H, m),8.13—8.40 (2H, m) 9.10 (1H, s)
6a	1745 1720	1.15 (1.8H, t, $J=8$ Hz) 1.32 (1.2H, t, $J=8$ Hz), 4.16 (1.2H, s), 3.95—4.82 (2H, m) 6.52 (0.4H, s), 7.33—7.55 (3H, m), 7.66 (0.4H, d, $J=5$ Hz), 7.81 (0.6H, d, $J=5$ Hz) 8.00—8.35 (2H, m), 8.84 (0.4H, d, $J=5$ Hz), 8.92 (0.6H, d, $J=5$ Hz), 12.29 (0.4H, s)
6b	1630	7.35—7.86 (8H, m), 7.95—8.42 (4H, m), 8.93 (1H, d, $J=5$ Hz), 15.08—16.66 (1H, broad)
6c	3220 2200	7.30—7.65 (6H, m), 7.72 (1H, d, $J=5$ Hz), 7.84—8.11 (2H, m), 8.12—8.51 (2H, m) 8.84 (1H, d, $J=5$ Hz), 9.00—9.65 (1H, broad)
7	1713	2.83 (3H, s), 7.46—7.65 (3H, m), 7.82 (1H, d, $J=6$ Hz), 8.09—8.30 (2H, m) 8.94 (1H, d, $J=6$ Hz)

References and Notes

1) T. Sakamoto, K. Tanji, and H. Yamanaka, *Chem. Pharm. Bull.*, **30**, 610 (1982).
2) T. Sakamoto, T. Ono, T. Sakasai, and H. Yamanaka, *Chem. Pharm. Bull.*, **28**, 202 (1980).
3) T. Sakasai, T. Sakamoto, and H. Yamanaka, *Heterocycles*, **13**, 235 (1979).
4) T. Sakamoto, T. Sakasai, and H. Yamanaka, *Chem. Pharm. Bull.*, **28**, 571 (1980).