The Regioselective Alkylation of 4,6-Dimethyl-1-phenyl-2(1*H*)-pyrimidinone

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4,6-Dimethyl-1-phenyl-2(1*H*)-pyrimidinone (I) was treated with alkyl halides in the presence of sodium hydride at low temperature to afford only C-6 alkylated products III and IV in good yields. Further, the mono-, IIIa-d, and di-alkylated 2(1*H*)-pyrimidinones IVa-d were selectively obtained by changing the amount of alkyl halides.

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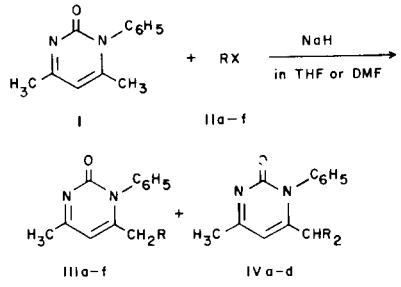
It has been known that methyl protons are activated by the adjacent aromatic ring, especially nitrogen containing heteroaromatic ring. For example, methyl protons of 2-methylpyridine [1] or 2-methylquinoline [2] are easily deprotonated by a base to yield a carbanion, which reacts with electrophiles to give the substitution products on the methyl group. While Batterham [3] and Stewart [4,5] reported that methyl protons of C-6 position of *N*-substituted 4,6-dimethyl-2(1*H*)-pyrimidinones were deuterated faster than those of C-4 position in the hydrogen-deuterium exchange reaction. However, to the best of our knowledge, only a paper concerning the regioselective reaction of C-4 and C-6 methyl protons have been reported [6]. On the other hand, unsymmetrical 2(1*H*)-pyrimidinones having the different substituents at C-4 and C-6 position in the pyrimidine ring are useful synthetic intermediates for other heterocyclic compounds [7,8].



In this paper, we wish to describe the regioselective alkylation of C-6 methyl protons of 4,6-dimethyl-1-phenyl-2(1*H*)-pyrimidinone with alkyl halides.

When 4,6-dimethyl-1-phenyl-2(1*H*)-pyrimidinone (I) was treated with an equimolecular amount of benzyl bromide (IIa) in the presence of large excess of sodium hydride in an ice/methanol bath (*ca.* −20°), two products, mp 238° (compound **A**) and mp 267° (compound **B**) were obtained. Compounds **A** and **B** had the formula, $C_{19}H_{18}N_2O$ and $C_{26}H_{24}N_2O$, respectively, from the elemental analysis. The ir spectrum of compounds **A** and **B** displayed a strong absorption band at 1655 cm^{-1} due to the C=O stretching. Previously Kashima *et al.* reported that the C-6 methyl protons were easily distinguishable from the C-4 methyl ones, that is, the C-6 methyl protons at δ 1.98 ppm of compound I exhibited the allyl coupling with a methine proton at C-5 position, while the C-4 methyl protons at δ 2.40 ppm appeared as a singlet [9]. From these data and the fact that the signal at δ 1.98 ppm of the starting material disappeared in both **A** and **B**, compound **A** was assigned to be 4-methyl-6-phenethyl-1-phenyl-2(1*H*)-pyrimidinone (IIIa), and compound **B** was 4-methyl-6-[2-(1,3-diphenyl)propyl]-1-phenyl-2(1*H*)-pyrimidinone (IVa). The total yield of IIIa and IVa was 54%, in the ratio of 83:17. Next, compound I was treated with two equimolecular amounts of IIa under the same condition to give two products IIIa and IVa in

Table 1

Product Distribution in the Reaction of I with II

	Alkyl halide II	Molar ratio I : II : NaH	Method	Products	Total yield (%)	Distribution III (%) : IV (%)
a	$C_6H_5CH_2Br$	1 1 20		IIIa + IVa	54	83 17
		31 2 20	A		52	20 80
b	4-$H_3CC_6H_4CH_2Br$	1 1 20	A	IIIb + IVb	51	86 14
		1 2 20	A		51	16 84
c	4-$BrC_6H_4CH_2Br$	1 1 20	A	IIIc + IVc	44	66 34
		1 2 20	A		42	12 88
d	3-$H_3CC_6H_4CH_2Br$	1 1 20	A	IIId + IVd	47	87 13
		1 2 20	A		50	14 86
e	CH_3I	1 6 1.5	B	IIIe	34	100 0
f	CH_3CH_2I	1 6 1.5	B	IIIf	35	100 0

Table 2

Analytical Data of Compounds IIIa-d and IVa-d

Compound No.	Mp (°C)	Formula	Analysis % Calcd./(Found) C	H	N
IIIa	238 dec	$C_{19}H_{18}N_2O$	78.59 (78.57)	6.24 (6.36)	9.64 (9.59)
IIIb	150.5-151	$C_{20}H_{20}N_2O$	78.91 (78.81)	6.62 (6.65)	9.20 (8.98)
IIIc	101-102	$C_{19}H_{17}BrN_2O$	61.80 (61.98)	4.64 (4.65)	7.58 (7.61)
IIId	118-119	$C_{20}H_{20}N_2O$	78.91 (78.91)	6.61 (6.64)	9.20 (9.10)
IVa	267 dec	$C_{26}H_{24}N_2O$	82.07 (81.86)	6.36 (6.33)	7.36 (7.43)
IVb	226-227	$C_{28}H_{28}N_2O$	82.31 (82.41)	6.90 (6.99)	6.85 (6.76)
IVc	227-227.5	$C_{26}H_{22}Br_2N_2O$	58.02 (58.10)	4.12 (4.18)	5.20 (5.29)
IVd	169-170	$C_{28}H_{28}N_2O$	82.31 (82.28)	6.90 (7.01)	6.85 (6.76)

Table 3

The IR and NMR Spectra of 6-Substituted 4-Methyl-1-phenyl-2(1*H*)-pyrimidinones (IIIa-d and IVa-d)

Compound No.	IR Spectra (C=O, cm^{-1})	^{1}H-NMR Chemical Shift δ (ppm)
IIIa [a]	1655	2.39 (s, 3H), 2.4-2.8 (m, 4H), 6.19 (s, 1H), 6.8-7.6 (m, 10H)
IIIb	1655	2.22 (s, 3H), 2.33 (s, 3H), 2.3-2.7 (m, 4H), 6.10 (s, 1H), 6.7-7.5 (m, 9H)
IIIc	1650	2.35 (s, 3H), 2.2-2.7 (m, 4H), 6.16 (s, 1H), 6.5-7.5 (m, 9H)
IIId	1650	2.20 (s, 3H), 2.33 (s, 3H), 2.35-2.7 (m, 4H), 6.05 (s, 1H), 6.4-7.5 (m, 9H)
IVa [b]	1655	2.50 (s, 3H), 2.79 (broad s, 5H), 6.0-6.2 (m, 2H), 6.46 (s, 1H), 6.8-7.4 (m, 13H)
IVb	1650	2.27 (s, 6H), 2.45 (s, 3H), 2.68 (broad s, 5H), 6.2-6.4 (m, 2H), 6.47 (s, 1H), 6.7-7.5 (m, 11H)
IVc	1660	2.48 (s, 3H), 2.73 (broad s, 5H), 6.3-6.6 (m, 2H), 6.40 (s, 1H), 6.6-6.8 (m, 4H), 7.2-7.6 (m, 7 H)
IVd	1650	2.20 (s, 6H), 2.41 (s, 3H), 2.68 (broad s, 5H), 6.0-6.2 (m, 2H), 6.25 (s, 1H), 6.4-7.2 (m, 11H)

[a] ^{13}C-nmr: δ (ppm) 25.3 (t), 33.7 (t), 34.8 (t), 104.1 (d), 126.4 (d), 127.6 (d), 127.9 (d), 128.4 (d), 128.9 (d), 129.6 (d), 137.0 (s), 138.9 (s), 156.8 (s), 159.2 (s), 175.8 (s). [b] ^{13}C-nmr: δ (ppm) 25.7 (q), 41.5 (t), 46.4 (d), 102.7 (d), 126.9 (d), 127.9 (d), 128.2 (d), 128.6 (d), 128.9 (d), 129.3 (d), 136.7 (s), 137.7 (s), 163.5 (s), 175.5 (s).

52% yield, but the ratio was 20:80. Finally compound I was treated with three equimolecular amounts of IIa. However, the expected tri-alkylated product could not be obtained. It may be attributable to the steric effect around the C-6 position. The reaction of compound I with other alkyl halides was examined, and the results are summarized in Tables 1, 2, and 3. Compounds IIIe and IIIf were determined by comparison with authentic samples [10].

In conclusion, the regioselective alkylation of the C-6 methyl protons of 4,6-dimethyl-1-phenyl-2(1*H*)-pyrimidinone becomes possible by treatment with alkyl halides in the presence of sodium hydride at low temperature. Furthermore, the mono- and di-alkylated 2(1*H*)-pyrimidinones are selectively obtained by changing the amount of alkyl halides.

EXPERIMENTAL

The melting points were uncorrected. The ir spectra were recorded on a Jasco IRA-1 infrared spectrophotometer. The ^{1}H- and ^{13}C-nmr spectra were recorded on a Hitachi R-24 or a JEOL-100 spectrometer using TMS as an internal standard.

6-Substituted 4-Methyl-1-phenyl-2(1*H*)-pyrimidinones (IIIa-f and IVa-d).

Method A.

Compound I (2 mmoles) in dry tetrahydrofuran (10 ml) was stirred for 2 hours in the presence of sodium hydride (0.8 g, 60% in oil, 20 mmoles) in an ice/methanol bath, and then the aklyl halide II (2 or 4 mmoles) in dry tetrahydrofuran (10 ml) was added dropwise. After stirring for another 2 hours, the reaction mixture was poured onto ice (40 g). The aqueous solution was extracted with dichloromethane (2 × 40 ml). The organic layer was dried with anhydrous magnesium sulfate, and evaporated off. The crude products were purified by column chromatography on silica gel with chloroform/acetone/ethanol (100:20:4), then recrystallization from benzene/hexane mixture.

Method B.

Compound I (1 mmole) in dry dimethylformamide (8 ml) was added dropwise to the solution of the alkyl halide II (6 mmoles) and sodium hydride (0.06 g, 1.5 mmoles) in dry dimethylformamide (3 ml) in an ice/-methanol bath. After stirring for an hour, the reaction mixture was poured onto ice (20 g). The resulting solution was extracted with dichloromethane (2 × 20 ml). The organic layer was washed with water (7 × 80 ml) to remove dimethylformamide, dried, and evaporated off. The crude products were worked up according to Method A.

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