

THE REACTION OF N-SUBSTITUTED DIHYDROPYRIMIDINES WITH KETENES

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Abstract — 1,4-Dihydro-4,4,6-trimethyl-1-phenylpyrimidine (1) was treated with ketenes prepared from acid chlorides and triethylamine in situ to afford N-acylated ring opened products 2. However, 1 was treated with diphenylketene generated from diphenylacetyl chloride and triethylamine to give the azetidin-2-one derivatives (4).

Previously, we have investigated the synthesis and properties of N-substituted dihydropyrimidines.¹ N-Substituted dihydropyrimidines whose double bonds are fixed have reactive structures in their ring, such as amidine, enamine, and aza-di- π -methane structure for 1,4-dihydropyrimidines, or amidine and conjugated aza-diene structure for 1,6-dihydropyrimidines. However, the reports concerning to the reaction of N-substituted dihydropyrimidines were limited only in three papers; 1,6-dihydropyrimidine reacted with methyllithium to yield 1,2,5,6-tetrahydropyrimidine,² and dihydropyrimidines reacted with metal hydride complexes to yield 1,3-diamines^{1c} or 1,2,3,4-tetrahydropyrimidines.³ In any cases, it was shown that the amidine moiety of dihydropyrimidines was a very reactive part.

The formation of azetidin-2-ones is the most widely investigated cycloaddition reactions of N-substituted imines and ketenes.⁴ Similarly, the C=N double bonds in amidines reacted with ketenes to afford 4-aminoazetidin-2-ones.⁵ Also, Sharma and Mehra reported on the synthesis of novel 1-aza-analogs of cepham, so-called 1-azacepham.⁶ Therefore, it is expected that dihydropyrimidines reacted with ketene in the amidine moiety to form the azetidin-2-one fused with the pyrimidine ring. In this paper, we describe the reaction of N-substituted dihydropyrimidines with ketenes.

RESULTS AND DISCUSSION

It is known that alkyl ketenes are generated from acid chlorides which have an α -hydrogen with tertiary amines.⁷ After isobutyryl chloride and triethylamine were mixed in ether, 1,4-dihydro-4,4,6-trimethyl-1-phenylpyrimidine (1) was added in situ. The product showing the following spectral data was obtained: in the ir spectrum, the absorption band at 3420 cm^{-1} owing to the N-H stretching was observed; the ^1H -nmr spectrum showed that the isopropyl group remained, and that two singlets appeared at δ 8.64 and 8.37 ppm. In ^{13}C -nmr spectrum, the peaks assignable to a formyl group appeared at δ 161.9 and 161.3 ppm. From these data and the formula shown as $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$, the product was considered to be 2 or 3. Since the mass spectrum showed fragment peaks which had formyl and phenyl groups on the same nitrogen atom (Fig. 1), the product was determined to be 2. Moreover, every peaks in the ^1H - and ^{13}C -nmr spectra were split to two peaks. It seemed that these peaks were caused by isomers by formyl group. Similar treatment of dihydropyrimidine (1) with other alkyl ketenes, gave not azetidin-2-one derivatives but the N-formyl compounds which are ring-opened compound of the pyrimidine ring between C-2 and N-3 (Scheme 1).

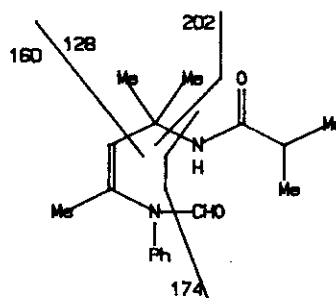
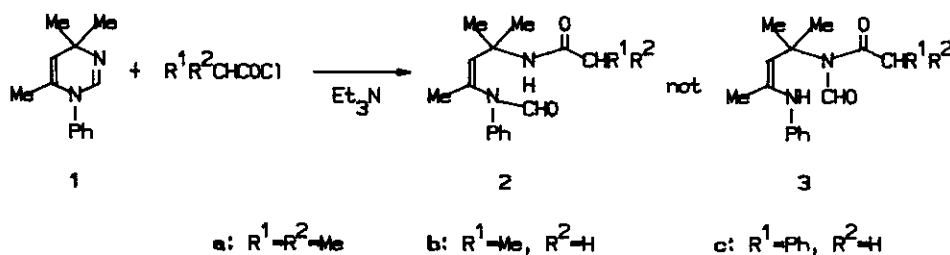


Fig. 1

Scheme 1

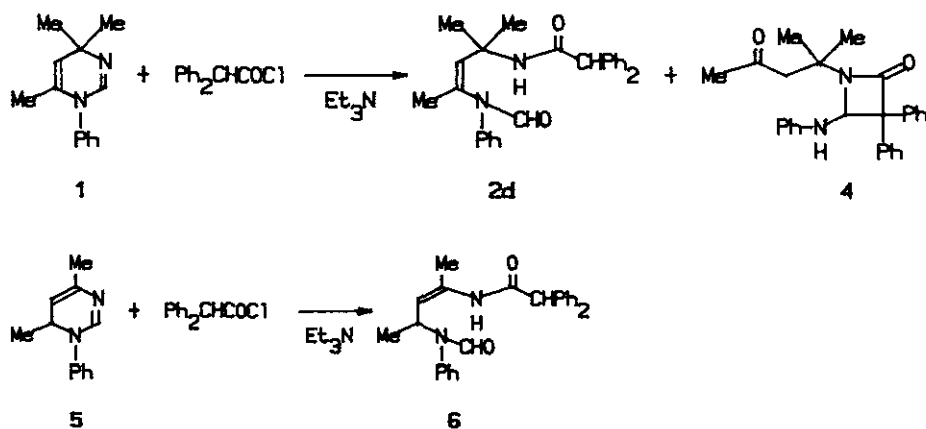


Next, the compound 1 was treated in situ with the yellow solution of diphenylketene, which was generated from the mixture of diphenylacetyl chloride and triethylamine in ether. The resulting products were ring-opened product 2d and an oily compound which showed the following spectral data. In the ir spectra, the

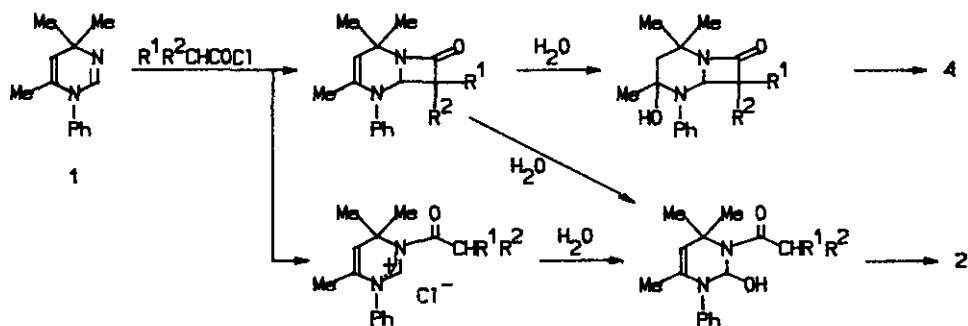
absorption band at 1715 cm^{-1} showed the existence of the azetidinone ring. In the ^1H -nmr spectra, a D_2O exchangeable doublet at $\delta\ 3.86\text{ ppm}$ was observed, which was attributed to N-H proton. Furthermore, the ^{13}C -nmr spectra showed the existence of carbon atoms assignable to ketone and amide. From these data, the product was determined to be 4-anilino-1-(4-oxo-2-methylpentan-2-yl)-3,3-diphenylazetidin-2-one (4). When 1,6-dihydro-4,6-dimethyl-1-phenylpyrimidine (5) was treated with diphenylketene, the product was the ring-opened *N*-formyl compound (6), not azetidin-2-one (Scheme 2).

The reaction mechanism was speculated as shown in Scheme 3. From the fact that an azetidine compound was formed, it seems that the azetidine ring fused with the

Scheme 2



Scheme 3



pyrimidine ring was first formed as an intermediate. However, during isolation, water attacked on the C-2 or C-6 carbon of the pyrimidine ring and then ring cleavage occurred to afford 2 or 4, respectively. When 2 was formed, the ring cleavage occurred to generate an anion on the more electron-negative nitrogen. In the case of aliphatic ketenes, which did not give azetidin-2-one compound, the reaction assumably proceeded in the N-acylated compound to afford N-formyl compounds.

It was concluded that the amidine moiety of 1,4-dihydropyrimidines reacted with diphenylketene to yield the azetidin-2-one derivatives. However, the pyrimidine ring was not stable enough during purification. In the reaction of dihydropyrimidine with alkanolic acid chlorides in the presence of triethylamine, N-acylated ring-opened products were obtained.

EXPERIMENTAL

Melting points, measured on a Yanagimoto micro melting point apparatus, were uncorrected. The ir spectra were recorded on a Jasco IRA-1 infrared spectrophotometer. The ^1H -nmr and ^{13}C -nmr spectra were recorded on Hitachi R-24 and JEOL-100 spectrometer, respectively, using TMS as an internal standard. The mass spectra were recorded on a Hitachi M-80 gas chromatograph mass spectrometer, a JEOL DX-300 mass spectrometer, and a VG ZAB-HF mass spectrometer.

Reaction of Dihydropyrimidines with the Mixture of Acid Chloride and Triethylamine.

General Procedure. To a solution of an acid chloride (2 mmol) in 20 ml of dry diethyl ether on an ice-methanol bath, triethylamine (2.2 mmol) was added. After 2 h, a diethyl ether solution (10 ml) of a dihydropyrimidine (1 or 5, 1 mmol) was added to the resulting mixture in situ. The reaction mixture was stirred for 3 h on an ice bath, and at room temperature for 15 h. It was evaporated in vacuo and chromatographed on silica gel with hexane-ethyl acetate (2:1 or 3:1) mixture.

2-(N-Formylanilino)-4-isobutyrylamino-4-methyl-2-pentene (2a).

Yield 80 %; mp 86-87°C (from benzene-hexane); ir (CHCl_3): 3420, 1660 cm^{-1} ; ^1H -nmr (CDCl_3): δ 1.04 and 1.06 (d, 6H, $J=6.9$ Hz), 1.45 (s, 6H), 1.84 (s, 3H), 2.0-2.4 (m, 1H), 5.8-5.9 (m, 2H), 7.2-7.7 (m, 5H), 8.64 and 8.37 (s, 1H); ^{13}C -nmr (CDCl_3):

δ 19.4 (q), 22.3 and 23.1 (q), 26.6 (q), 28.5 (q), 35.8 and 35.6 (d), 52.7 and 52.4 (s), 121.1 and 122.9 (d), 126.0 and 125.5 (d), 129.7 and 128.9 (d), 130.4 and 132.3 (s), 135.1 and 134.8 (d), 139.7 and 137.6 (s), 161.9 and 161.3 (d), 176.2 (s); ms (CI): m/z 289 $[M+1]^+$, 261, 202, 174, 160 (100 %), 128.

Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.38; N, 9.71.

Found: C, 70.79; H, 8.45; N, 9.59.

2-(N-Formylanilino)-4-propionyl-4-methyl-2-pentene (2b).

Yield 80 %; bp $93^\circ/10^{-4}$ mmHg; ir (liquid film): 3300, 1650 cm^{-1} ; 1H -nmr ($CDCl_3$): δ 1.02 and 1.04 (t, 3H, $J=7.3$ Hz), 1.45 (s, 6H), 1.86 (s, 3H), 1.9-2.1 (m, 2H), 5.8 (br, 2H), 7.2-7.7 (m, 5H), 8.63 and 8.37 (s, 1H); ^{13}C -nmr ($CDCl_3$): δ 9.6 and 9.5 (q), 22.3 and 23.3 (q), 28.6 and 26.7 (q), 29.9 (t), 52.6 (s), 120.9 and 122.9 (d), 125.9 and 125.5 (d), 129.7 and 128.9 (d), 130.5 and 132.4 (s), 135.0 and 134.6 (d), 139.8 and 137.7 (s), 161.3 and 161.9 (d), 172.9 (s); ms (EI): m/z 274 (M^+), 161, 160 (100 %), 118, 77, 58; exact mass (EI) (M^+): Calcd. for $C_{16}H_{22}N_2O_2$: 274.1676. Found: 274.1655.

2-(N-Formylanilino)-4-methyl-4-phenylacetyl-amino-2-pentene (2c).⁸

Yield 40 %; ir ($CHCl_3$): 3400, 1660 cm^{-1} ; 1H -nmr ($CDCl_3$): δ 1.34 (s, 6H), 1.79 (s, 3H), 3.20 (d, 1H, $J=6.0$ Hz), 3.37 (d, 1H, $J=6.0$ Hz), 5.67 (br s, 1H), 5.80 (br s, 1H), 7.0-7.5 (m, 10H), 8.23 and 8.18 (s, 1H); ms (EI): m/z 336 (M^+), 161 (100 %), 160, 118, 91, 77; exact mass (CI) $[M+1]^+$: Calcd. for $C_{21}H_{25}N_2O_2$: 337.1918. Found: 337.1903.

2-(N-Formylanilino)-4-methyl-4-diphenylacetyl-amino-2-pentene (2d).

Yield 31 %; mp $130-132^\circ C$ (from benzene-hexane); ir (KBr): 3290, 1690, 1640 cm^{-1} ; 1H -nmr ($CDCl_3$): δ 1.41 (s, 6H), 1.83 (s, 3H), 4.67 (s, 1H), 5.73 (s, 1H), 5.83 (s, 1H), 7.0-7.6 (m, 15H), 8.30 (s, 1H); ^{13}C -nmr ($CDCl_3$): δ 22.3 (q), 26.5 (q), 28.2 (q), 53.4 (s), 59.2 (d), 120.9 (d), 122.9 (d), 125.5, 125.9, 126.9, 128.5, 128.7, 129.6, 129.9, 130.9 (d), 135.1 (s), 139.6 (d), 161.4 (s); ms (EI): m/z 412 (M^+), 202, 167, 160 (100 %), 118, 99, 77; exact mass (CI) $[M+1]^+$: Calcd. for $C_{27}H_{29}N_2O_2$: 413.2231. Found: 413.2220.

4-Anilino-1-(4-oxo-2-methylpentan-2-yl)-3,3-diphenylazetidin-2-one (4).⁸

Yield 31 %; ir (liquid film): 3350, 1730 cm^{-1} ; ^1H -nmr (CDCl_3): δ 1.43 (s, 3H), 1.45 (s, 3H), 2.03 (s, 3H), 2.88 (d, 1H, $J=17$ Hz), 3.12 (d, 1H, $J=17$ Hz), 3.86 (d, 1H, $J=11$ Hz, D_2O exchangeable), 5.99 (d, 1H, $J=11$ Hz), 6.5-6.8 (m, 3H), 7.1-7.5 (m, 12H); ^{13}C -nmr (CDCl_3): δ 25.7 (q), 27.4 (q), 31.2 (q), 51.4 (t), 54.0 (s), 71.6 (s), 71.9 (d), 113.9 (d), 118.9 (d), 127.2 (d), 127.3 (d), 127.5 (d), 128.5 (d), 128.7 (d), 129.5 (d), 137.3 (d), 139.1 (s), 144.5 (s), 168.4 (s), 206.4 (s); ms (EI): m/z 412 (M^+), 309, 271, 194 (100 %), 165, 43; exact mass (CI) $[\text{M}+1]^+$: Calcd. for $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_2$: 413.2231. Found: 413.2178.

4-(N-Formylanilino)-2-diphenylacetyl-amino-2-pentene (6).⁸

Yield 49 %; ir (liquid film): 3260, 1650 cm^{-1} ; ^1H -nmr (CDCl_3): δ 1.00 (d, 3H, $J=6.8$ Hz), 2.22 (d, 3H, $J=1.0$ Hz), 4.59 (dd, 1H, $J=1.0$ and 6.8 Hz), 5.10 (s, 1H), 5.1-5.3 (m, 1H), 7.1-7.5 (m, 15H), 8.09 (s, 1H), 9.69 (br s, 1H); ^{13}C -nmr (CDCl_3): δ 18.9 (q), 20.8 (q), 45.6 (d), 59.0 (d), 114.8 (d), 126.9, 127.8, 128.2, 128.4, 128.8, 129.3, 137.2 (s), 139.7 (s), 163.6 (d), 170.8 (s); ms (EI): m/z 398 (M^+), 277, 165, 128 (100 %), 121, 93, 84, 83; exact mass (CI) $[\text{M}+1]^+$: Calcd. for $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_2$: 399.2074. Found: 399.2109.

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- The Compounds were liquid but were too unstable to be obtained exact bps.

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