Polycyclic N-Hetero Compounds. XI.¹⁾ The Modified Vilsmeier Reaction of 4-Alkylpyrimidines

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Reactions of 4-alkylpyrimidines with formamide in the presence of phosphoryl chloride (called the modified Vilsmeier reaction) were described. 4-Methylpyrimidine derivatives (I, III) gave 4-pyrimidinylpyrimidines (II, IV) respectively but 4-methylenepyrimidine derivatives (V, VII) afforded 5-hydroxy-6-[4-(5-methylpyrimidinyl)]-2,4-diaza-heptenal (VI) or bis(5,6,7,8-tetrahydro-8-quinazolinyldenemethyl)amine (VIII) and 8-formylaminomethinyl-5,6,7,8-tetrahydroquinazoline (IX).

In the previous paper,³⁾ it was reported that condensation of 4-methyl-5-phenylpyrimidine with formamide in the presence of phosphoryl chloride (called the modified Vilsmeier reaction) afforded 5-phenyl-4-(5-pyrimidinyl)pyrimidine. Katoh, *et al.*⁴⁾ described that the Vilsmeier reaction (dimethylformamide-phosphoryl chloride) of 4-methylpyrimidine resulted double formylation at 4-methyl group, but direct one step pyrimidine ring formation of 4-methylpyrimidine derivatives with the modified Vilsmeier reaction has not been reported. To

Chart 1

- 1) Part X: T. Koyama, S. Fukuoka, T. Hirota, J. Maeyama, S. Ohmori, and M. Yamato, *Chem. Pharm. Bull.* (Tokyo), **24**, 591 (1976).
- 2) Location: 1-1, Tsushima-naka 1-chome, Okayama, 700, Japan.
- 3) T. Koyama, T. Hirota, Y. Shinohara, S. Matsumoto, S. Ohmori, and M. Yamato, *Chem. Pharm. Bull.* (Tokyo), **23**, 2029 (1975).
- 4) T. Katoh, H. Yamanaka, and H. Hiranuma, *Yakugaku Zasshi*, **90**, 870 (1970).

study the pyrimidine ring formation of the active alkyl groups of alkylpyrimidines, the present paper describes the modified Vilsmeier reaction of 4-alkylpyrimidines. As shown in Chart 1, 4,5-dimethylpyrimidine⁵⁾ (I), 4,6-dimethylpyrimidine⁶⁾ (III), 4-ethyl-5-methylpyrimidine⁵⁾ (V), and 5,6,7,8-tetrahydroquinazoline⁵⁾ (VII) were used as 4-alkylpyrimidines.

The modified Vilsmeier reaction of I expectedly afforded 5-methyl-4-(5-pyrimidinyl)-pyrimidine (II). The nuclear magnetic resonance (NMR) spectrum of II in deuteriochloroform exhibited disappearance of one methyl group and appearance of newly formed pyrimidine ring protons, that is, one-proton singlet at δ 9.41 (or 9.26, exact assignment of C_{2'} or C₂-proton was unconfirmed) attributable to C_{2'}-proton and two-proton singlet at δ 9.14 due to C_{4'}-, C_{6'}-protons.

Next, the similar reaction of III gave 6-methyl-4-(5-pyrimidinyl)pyrimidine (IV) but isolation of 4,6-di(5-pyrimidinyl)pyrimidine was unsuccessful. Similar to II in NMR, new pyrimidine ring protons were observed, one-proton singlet at δ 9.36 (C_{2'}-H) and two-proton singlet at δ 9.42 (C_{4'}-H, C_{6'}-H).

The modified Vilsmeier reaction of V afforded 5-hydroxy-6-[4-(5-methylpyrimidinyl)]-2,4-diaza-2-heptenal (VI). The infrared spectrum (IR) of VI showed O-H band at 3310 cm⁻¹ and broad C=O band at 1673 cm⁻¹ and its NMR spectrum in deuteriodimethyl sulfoxide exhibited one methyl group at δ 1.14 as doublet ($J=7$ Hz) attributable to C₇-protons, another methyl group at δ 2.28 as broad singlet for pyrimidine C_{5'}-methyl group, each one-proton multiplet at δ 3.48 and 5.78 for C₆ and C₅ proton respectively. Complicated multiplet signals at δ 7.83—8.85 may be due to NH, OH, vinyl proton, and formyl proton (perhaps partly enolated) and splitting of two pyrimidine ring protons suggested that varieties of prototropies and hydrogen bonds or transformations of double bonds. The pyrimidine ring protons were changed to two singlets with few drops of deuteriofluoroacetic acid and complicated signals of lower field to simplicity.

The modified Vilsmeier reaction of 5,6,7,8-tetrahydroquinazoline (VII) afforded bis(5,6,7,8-tetrahydro-8-quinazolinylidenemethyl)amine (VIII), identical with the specimen prepared from cyclohexanone and trisformylaminomethane⁷⁾ (mixed mp, IR, NMR, and thin-layer chromatography (TLC), and 8-formylaminomethyl-5,6,7,8-tetrahydroquinazoline (IX) which seems to be intermediate of formation of VIII. The IR spectrum of IX had C=O band at 1690 cm⁻¹ and N-H band at 3100 cm⁻¹ and its NMR spectrum exhibited three methylene multiplet at higher field, each one-proton broad doublet at δ 8.10 and 8.58 attributable to vinyl proton and formyl proton respectively which were changed to broad singlet with D₂O exchange and pyrimidine ring protons appeared at δ 8.39 and 8.87.

From the above results, in the case of 4-methylpyrimidine derivatives, 4-methyl group could be converted to pyrimidine ring but 4-methylene derivatives could not cyclize to pyrimidine.

Experimental

Melting points are uncorrected. NMR spectra were taken on a Hitachi Model R-22 spectrometer (90 MHz) with tetramethylsilane as an internal standard (δ value), s, singlet; d, doublet; m, multiplet; b, broad. IR spectra were recorded on a Nihon Bunko Model IR-G spectrometer in KBr disk. Mass spectra were taken on a Shimadzu LKB-9000 spectrometer with a direct inlet system. Ultraviolet spectra (UV) were taken on a Hitachi ESP-2 spectrophotometer in 99% EtOH.

General—To 20 mol of freshly distilled HCONH₂, 4—6 mol of POCl₃ was added dropwise during 40—60 min under stirring and cooling. Regardless vigorous exothermic and foaming reaction, the mixture was stirred for another 40—60 min (the modified Vilsmeier reagent). One mol of 4-alkylpyrimidines in 20 mol

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6) H. Bredereck, R. Gompper, and G. Morlock, *Chem. Ber.*, **90**, 942 (1957).

7) T. Koyama, T. Hirota, C. Bashoh, Y. Satoh, Y. Watanabe, S. Matsumoto, Y. Shinohara, S. Ohmori, and M. Yamato, *Chem. Pharm. Bull. (Tokyo)*, **23**, 2158 (1975).

of HCONH_2 was added to the above colloidal reagent and stirred at 65–80° until disappearance of starting materials.

The Modified Vilsmeier Reaction of 4,5-Dimethylpyrimidine (I)—To a modified Vilsmeier reagent prepared from 3.6 ml of HCONH_2 and 2.3 ml of POCl_3 (40 min-stirring after addition of POCl_3), 0.55 g of I in 3.6 ml of HCONH_2 was added in three portions and then stirred below 80° for 5 hr. The deep brown reaction mixture was dissolved in *ca.* five-fold of H_2O , made alkaline with NaHCO_3 and extracted with ether (for 15 hr). The ether layer was washed with sat. NaCl solution, dried (Na_2SO_4), and evaporated. The yellow solid residue was recrystallized from benzene to 106 mg (12.1%) of 5-methyl-4-(5-pyrimidinyl)pyrimidine (II) as pale yellow needles, mp 143–144°, identical with the specimen prepared from I and trisformylaminomethane⁷⁾ (mixed mp, IR, NMR, and TLC). For elemental analysis, the crystals were sublimed at 110–126° under reduced pressure (aspirator) to white crystals, mp 146°. *Anal.* Calcd. for $\text{C}_9\text{H}_8\text{N}_4$: C, 62.77; H, 4.68; N, 32.54. Found: C, 63.12; H, 4.65; N, 32.76. Mass Spectrum *m/e*: 172 (M^+). NMR (CDCl_3): 2.46 (3H, s, CH_3), 8.75 (1H, s, $\text{C}_6\text{-H}$), 9.14 (2H, s, C_4' , $\text{C}_6'\text{-H}$), 9.26, 9.41 (each 1H, s, C_2 , $\text{C}_2'\text{-H}$). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 208 (4.20), 223 (4.11), 263 (4.05).

The Modified Vilsmeier Reaction of 4,6-Dimethylpyrimidine (III)—To a modified Vilsmeier reagent prepared from 33 ml of HCONH_2 and 23 ml of POCl_3 (1 hr stirring), 4.5 g of III in 33 ml of HCONH_2 was added at once. The mixture was stirred at room temperature for 1 hr and then at 65° for 5 hr. To the reaction mixture, *ca.* five-fold of H_2O was added, made alkaline with Na_2CO_3 , and extracted with benzene, ether, and CHCl_3 successively. Each extract was washed with sat. NaCl solution, dried (Na_2SO_4), and evaporated. The residues of benzene and ether extracts were recrystallized from cyclohexane to 6-methyl-4-(5-pyrimidinyl)pyrimidine (IV) as pale yellow needles, mp 144°, combined yield 312 mg (6.0%). *Anal.* Calcd. for $\text{C}_9\text{H}_8\text{N}_4$: C, 62.77; H, 4.68; N, 32.54. Found: C, 63.13; H, 4.57; N, 32.36. Mass Spectrum *m/e*: 172 (M^+). NMR (CDCl_3): 2.62 (3H, s, CH_3), 7.62 (1H, bd, $J=2$ Hz, $\text{C}_5\text{-H}$), 9.24 (1H, bd, $J=2$ Hz, $\text{C}_2\text{-H}$), 9.36 (1H, s, $\text{C}_6\text{-H}$), 9.42 (2H, s, C_4' , $\text{C}_6'\text{-H}$). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 206 (4.38), 236 (4.34), 263 (4.30). The CHCl_3 extract had many spots on TLC and the isolation of pure compound was unsuccessful.

The Modified Vilsmeier Reaction of 4-Ethyl-5-methylpyrimidine (V)—To a modified Vilsmeier reagent prepared from 32.6 ml of HCONH_2 and 22.5 ml of POCl_3 (stirring for 40 min), 5.0 g of V in 32.6 ml of HCONH_2 was added to the reagent at once and then stirring was continued at 70–80° for 4 hr. The reaction mixture was dissolved in *ca.* three-fold of H_2O , made alkaline with Na_2CO_3 , and extracted with CHCl_3 (for 38 hr). The CHCl_3 layer was washed with H_2O , dried (Na_2SO_4), and evaporated. The benzene-insoluble fraction of the residue was chromatographed over silica gel with CH_2Cl_2 . After elution of CH_2Cl_2 , the acetone: EtOH (9:1) eluate was recrystallized from acetone to 1.01 g (11.1%) of 5-hydroxy-6-[4-(5-methylpyrimidinyl)]-2,4-diazahex-2-heptenal (VI) as light brown fine crystals, mp 150–152°. For elemental analysis, the crystals were recrystallized from acetone three times to colorless plates, mp 152–153°. *Anal.* Calcd. for $\text{C}_{10}\text{H}_{14}\text{O}_2\text{N}_4$: C, 54.04; H, 6.35; N, 25.21. Found: C, 53.83; H, 6.23; N, 25.20. Mass Spectrum *m/e*: 222 (M^+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3310 (broad N-H, O-H), 1675 (C=O). NMR ($\text{Me}_2\text{SO}-d_6$): 1.14 (3H, d, $J=7$ Hz, $\text{C}_7\text{-CH}_3$), 2.28 (3H, bs, $\text{C}_5'\text{-CH}_3$), 3.48 (1H, m, $\text{C}_6\text{-H}$), 5.78 (1H, m, $\text{C}_5\text{-H}$), 7.83–8.85 (4H, m, NH, OH, CHO, CH=N , two protons were disappeared with D_2O exchange), 8.55, 8.97 (each 1H, d, pyrimidine ring-H, each signal to singlet with few drops of CF_3COOD).

The Modified Vilsmeier Reaction of 5,6,7,8-Tetrahydroquinazoline (VII)—To a modified Vilsmeier reagent prepared from 19 ml of HCONH_2 and 11 ml of POCl_3 (stirring for 1 hr), 3.23 g of VII in 19 ml of HCONH_2 was added in three portions and then stirred below 75° for 2.5 hr. The reaction mixture was dissolved with H_2O , made alkaline with Na_2CO_3 , and extracted with CHCl_3 . The CHCl_3 layer was washed with H_2O , dried (Na_2SO_4), and evaporated. The crystalline residue was repeatedly recrystallized from EtOH to 17 mg (0.4%) of 8-formylaminomethynyl-5,6,7,8-tetrahydroquinazoline (IX) as colorless granules, mp 171–173°. *Anal.* Calcd. for $\text{C}_{10}\text{H}_{11}\text{ON}_3$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.60; H, 5.76; N, 22.40. Mass Spectrum *m/e*: 189 (M^+). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1690 (C=O). NMR (CDCl_3): 1.87, 2.51, 2.73 (each 2H, m, C_6 , C_5 , $\text{C}_7\text{-H}$), 8.10 (1H, bd, $J=12$ Hz, $=\text{CH-N}$, changed to broad singlet with D_2O), 8.39 (1H, bs, $\text{C}_4\text{-H}$), 8.58 (1H, bd, $J=9$ Hz, CHO, changed to broad singlet with D_2O), 8.87 (1H, bs, $\text{C}_2\text{-H}$). The oily residue of the mother liquid was chromatographed over alumina. Evaporation of the ether eluate was left crystals and which was recrystallized from benzene and EtOH alternatively to yield 0.85 g (23.1%) of bis(5,6,7,8-tetrahydro-8-quinazolinylidenemethyl)amine (VIII) as light brown needles, mp 190–192°, identical with the specimen prepared from VII and trisformylaminomethane⁷⁾ (mixed mp, IR, NMR, and TLC).

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