PREPARATION OF CYCLOPROPA[4,5]PYRIDO[2,3-d]- AND PYRROLO[2,3-d]-PYRIMIDINE DERIVATIVES USING INTRAMOLECULAR CARBENE REACTIONS[1]

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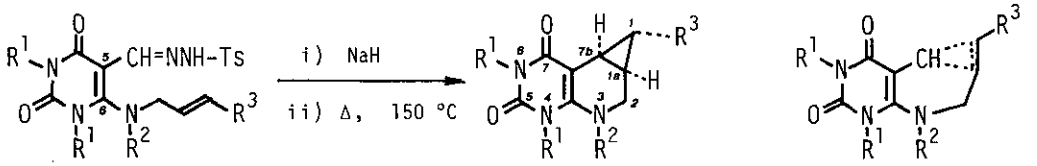
Abstract---- *Some cyclopropa*[4,5]pyrido[2,3-d]pyrimidine and pyrrolo[2,3-d]pyrimidine derivatives were obtained from the intramolecular carbene reactions of the pyrimidine system.

Much attention has been focused on fused pyrimidine derivatives from the viewpoints of synthetic interest and their biological potentiality.[2] Recently, we reported the preparation of fused pyrimidines such as pyrazolo[3',4':4,5]pyrido[2,3-d]pyrimidine,[3] pyrido[4,5-c]isoquinoline,[4] pyrido[3,4-d]pyrimidine,[5] and pyrrolo[3,4-d]pyrimidine.[6] These synthetic approaches *involve the* annulation of another ring system onto the preformed pyrimidine one. In the continuation of our *studies on fused pyrimidine derivatives*, we wish to report here a facile preparation of cyclopropa[4,5]pyrido[2,3-d]pyrimidine and pyrrolo[2,3-d]pyrimidine derivatives using intramolecular carbene reactions.

The treatment of 6-diallylamino-1,3-diphenyl-5-tosylhydrazonouracil (**1a**) with sodium hydride gave the sodium salt of **1a**, which was pyrolyzed at 150 °C to afford **2a** in 84% yield. The 1a,2,3,4,5,6,7,7b-octahydro-5,7-dioxo-1H-cyclopropa[4,5]pyrido[2,3-d]pyrimidine structure for **2a** was confirmed on the basis of analytical and spectral data; e.g., its ^{13}C nmr spectrum showed five sp^3-carbon signals at δ 6.7(d), 13.8(d), 18.8(t), 44.3(t), and 58.2(t). *Among them, the former* three signals were assignable to carbons of the cyclopropane ring. The ^1H nmr spectrum exhibited *characteristic signal* patterns for cis-1,2-disubstituted cyclopropane system;[7] δ 0.41(1-Hendo, ddd, J= 4, 5, 5 Hz), 1.08(1-Hexo, ddd, J= 9, 9, 5 Hz), 1.64(1a-H, m), 2.17(7b-H, ddd, J= 9, 9, 5 Hz).

Similar thermolysis of the sodium salts of 6-diallylamino- (**1b**),[2] 6-[N-methyl-(trans-cinnamyl)amino]- (**1c**),[2] 6-[N-benzyl-(trans-crotyl)amino]-1,3-dimethyl-5-tosylhydrazonouracil (**1d**)[2]

Table 1. Preparation of Cyclopropa[4,5]pyrido[2,3-d]pyrimidine Derivatives 2



1 **2**

2	R^1	R^2	R^3	Yield(%)[a]
2a	Ph	CH_2-CH=CH_2	H	84
2b	Me	CH_2-CH=CH_2	H	83
2c	Me	Me	Ph	93
2d	Me	CH_2-Ph	Me	58

a) *Based on isolated products.*

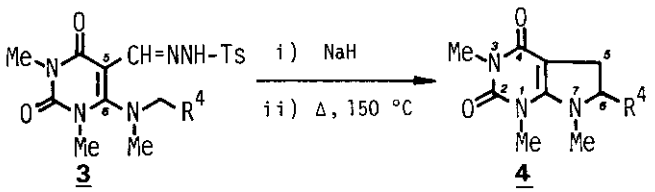
gave the corresponding cyclopropapyridopyrimidines **2b–d**, respectively. These results are summarized in Table 1.

The stereochemistries between 1-H and 1a-H of 2c and 2d were deduced to be trans from the analysis of coupling constants among the three methine protons on the cyclopropane ring (see experimental section). This means that the intramolecular [1+2]cycloaddition proceeds in a stereoselective manner and that the multiplicity of the carbenes are singlet.

In the case of **1d**, another type of product was detected (yield; below 5%), although it was not isolated as a pure form. The ^{1}H nmr spectrum of this compound in the reaction mixture showed the existence of N-crotyl group indicating that the attack of the carbene took place on the N-benzyl moiety. This suggested that another reaction of the singlet carbene, e.g., the insertion reaction into C-H bond, would compete with the [1+2]cycloaddition. So, the synthetic utility of the C-H insertion reaction of singlet carbenes was also investigated.

On heating of the sodium salts of 6-diethylamino-1,3-dimethyl-5-tosylhydrazonouracil (**3a**) in diglyme gave only unseparable mixture of products, as expected.[8] On the other hand, the insertion reaction of carbenes into activated C-H bonds proceeded smoothly; the thermolysis of the sodium salts of 6-(N-methylbenzylamino)- (**3b**), 6-[N-methyl-(2-furfuryl)amino]- (**3c**), 6-[N-methyl-(2-pyridyl)methylamino]-1,3-dimethyl-5-tosylhydrazonouracil (**3d**) gave 6-substituted 1,2,3,4,6,7-hexahydro-1,3,7-trimethyl-2,4-dioxo-5H-pyrrolo[2,3-d]pyrimidines **4b–d** in good yields (Table 2).

Table 2. Preparation of Pyrrolo[2,3-d]pyrimidine Derivatives 4



3 4

4	R^4	Yield(%)[a]
4b	Ph	84
4c	2-Furyl	68
4d	2-Pyridyl	77

a) Based on isolated products.

EXPERIMENTAL[9]

The new starting materials 1a and 3a-d were prepared by the similar procedure to the reported one[2] and gave satisfactory analytical and spectral data.

Thermolysis of the sodium salts of tosylhydrazonouracils 1 and 3. General Procedure: the treatment of 6-diallylamino-1,3-diphenyl-5-tosylhydrazonouracil (**1a**)(1.0 mmol) with sodium hydride (1.2 equiv.) in anhydrous diglyme (15 ml) at room temperature for 4 h under nitrogen atmosphere gave the sodium salt of **1a**, which was heated at 150 °C for 30 min. After cooling, the precipitates were filtered off and filtrate was evaporated to dryness. The residue was extracted with dichloromethane (3 x 30 ml) and the organic layer was washed with water. The solvent was evaporated to give an oily product, which was treated with a short silica gel column (chloroform/ethyl acetate= 3/1) to afford **2a** in 84% yield.

3-Allyl-1a,2,3,4,5,6,7,7b-octahydro-5,7-dioxo-4,6-diphenyl-1H-cyclopropa[4,5]pyrido[2,3-d]pyrimidine (**2a**): colorless needles (ethanol); mp 196-197 °C; ir(KBr) cm^{-1}: 1700, 1640(CO); ^1H nmr ($CDCl_3$): 0.41(ddd, 1H, 1-H, J= 5, 5, 4 Hz), 1.08(ddd, 1H, 1-H, J= 9, 9, 5 Hz), 1.64(m, 1a-H), 2.17(ddd, 1H, 7b-H, J= 9, 9, 4 Hz)), 3.02(dd, 1H, 3-H, J= 15, 8 Hz), 3.37(dd, 1H, 3-H, J= 15, 5 Hz), 3.06(d, 2H, $-CH_2-$, J= 3Hz), 4.2-4.7(m, -CH=), 4.8-5.0(m, $=CH_2$), 7.1-7.3(m, phenyl); ^{13}C nmr($CDCl_3$): 6.8, 13.8, 18.8, 44.3, 58.2, 100.5, 119.1, 128.5, 128.7, 129.2, 132.7, 135.8, 137.3, 150.4, 151.8, 163.2; ms m/z: 371(M^+). Found: C, 74.36; H, 5.77; N, 11.09. Calcd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31.

3-Allyl-1a,2,3,4,5,6,7,7b-octahydro-4,6-dimethyl-5,7-dioxo-1H-cyclopropa[4,5]pyrido[2,3-d]pyrimidine (**2b**): colorless needles (ethanol); mp 71-72 °C; ir(KBr) cm^{-1}: 1690, 1620(CO); ^1H nmr ($CDCl_3$): 0.19(ddd, 1H, 1-H, J= 5, 5, 4 Hz), 1.09(ddd, 1H, 1-H, J= 9, 9, 5 Hz), 1.67(m, 1a-H), 2.07(ddd, 1H, 7b-H, J= 9, 9, 4 Hz), 3.30, 3.37(2s, $-CH_3$), 3.0-3.7(overlapping, $-CH_2-$ x 2), 5.2-5.4(m, $=CH_2$), 5.7-6.0(m, -CH=); ms m/z: 292(M^+). Found: C, 63.03; H, 6.84; N, 16.73. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99.

1a,2,3,4,5,6,7,7b-Octahydro-3,4,6-trimethyl-5,7-dioxo-1-phenyl-1H-cyclopropa[4,5]pyrido[2,3-d]-pyrimidine (**2c**): colorless needles (ethanol); mp 157-158 °C; ^1H nmr($CDCl_3$): 1.68(dd, 1H, 1-H, J= 5, 4 Hz), 2.04(m, 1H, 1a-H), 2.43(dd, 1H, 7b-H, J= 9, 4 Hz), 2.85, 3.32, 3.35(3s, $-CH_3$), 3.2-

3.4(overlapping, $-CH_2-$), 7.2-7.4(m, phenyl); ms m/z: 295(M^+). Found: 68.56; H, 6.40; N, 13.97. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.66; H, 6.44; N, 14.13.

3-Benzyl-1a,2,3,4,5,6,7,7b-octahydro-1,4,6-trimethyl-5,7-dioxo-1H-cyclopropa[4,5]pyrido[2,3-d]-pyrimidine (**2d**): pale yellow oil; ir(NaCl) cm^{-1}: 1690, 1630(CO); ^1H nmr($CDCl_3$): 0.60(m, 1H, 1-H), 1.17(d, $-CH_3$, J= 6 Hz), 1.22(m, 1a-H), 1.78(dd, 7b-H, J= 9, 4 Hz), 3.37, 3.43(2s, $-CH_3$), 2.9-3.4(overlapping, $-CH_2-$), 4.15, 4.33(2d, 1H each, $-CH_2-$, J= 16 Hz), 7.2-7.6(m, phenyl); ms m/z: 311(M^+). Found: C, 69.18; H, 6.93; N, 13.71. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.50.

1,2,3,4,6,7-Hexahydro-1,3,7-trimethyl-2,4-dioxo-6-phenyl-5H-pyrrolo[2,3-d]pyrimidine (**4b**): colorless needles (ethanol); mp 86-88 °C; ir(KBr) cm^{-1}: 1700, 1620(CO); ^1H nmr($CDCl_3$): 2.93, 3.32, 3.55(3s, $-CH_3$), 2.70(dd, 1H, 5-H, J= 15, 8 Hz), 3.37(overlapping, 1H, 5-H), 4.52(dd, 1H, 6-H, J= 9, 8 Hz), 7.2-7.4(m, phenyl); ms m/z: 271(M^+). Found: C, 66.20; H, 6.29; N, 15.41. Calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49.

6-(2-Furyl)-1,2,3,4,6,7-hexahydro-1,3,7-trimethyl-2,4-dioxo-5H-pyrrolo[2,3-d]pyrimidine (**4c**): colorless needles (ethanol); mp 114-115 °C; ir(KBr) cm^{-1}: 1690, 1620(CO); ^1H nmr($CDCl_3$): 3.00, 3.30, 3.48(3s, $-CH_3$), 3.05(dd, 1H, 5-H, J= 16, 8 Hz), 3.37(overlapping, 1H, 5-H), 4.58(dd, 6-H, J= 9, 8 Hz), 6.2-6.4(m, 2H, furyl), 7.41(br s, 1H, furyl); ms m/z: 261(M^+). Found: C, 60.09; H, 5.87; N, 16.25. Calcd for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08.

1,2,3,4,6,7-Hexahydro-1,3,7-trimethyl-2,4-dioxo-6-(2-pyridyl)-5H-pyrrolo[2,3-d]pyrimidine (**4d**): colorless needles (ethanol); mp 235-236 °C; ir(KBr)cm^{-1}: 1690, 1620(CO); ^1H nmr($CDCl_3$): 2.83 (dd, 1H, 5-H, J= 14, 9 Hz), 3.03, 3.27, 3.56(3s, $-CH_3$), 3.48(overlapping, 1H, 5-H), 4.66(dd, 1H, 6-H, J= 9, 3 Hz) 7.1-7.5, 7.6-7.8, 8.4-8.6(3m, pyridyl); ms m/z: 272(M^+). Found: C, 62.02; H, 5.77; N, 20.41. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58.

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9) The general experimental procedures were the same as in Part I.[3]

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