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Electrophilic Condensation of Pyrimidines with Cyclic Ketones

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Abstract: Electrophilic condensation of pyrimidines with cyclic ketones was investigated. As nucleophiles, the degree of ionization of pyrimidines in acidic media and the electron density on the C-5 determined the reactivity. An electron-rich nitrogen at the 4-position of cyclic ketones facilitated the reaction. This method is facile for the synthesis of 5-vinyl substituted pyrimidines as k_{cat} antifolates.

A series of 5-(3,4-dehydro-4-piperidinyl)pyrimidines (**1**) were desired as folate antimetabolites for antitumor purpose.[1] These compounds were designed as mechanism-based (k_{cat}) enzyme inhibitors which, upon metabolic oxidation by methylenetetrahydrofolate (MTHF) dehydrogenase, may generate a Michael acceptor for irreversible binding to the target enzyme along DNA *de novo* synthesis (Fig. **1**).[2] Due to the poor nucleophilicity of the C-5, reports for efficient synthesis of such C-5 vinyl substituted pyrimidines are rare.[3] The chemistry reported here uncovered some new observations along the synthesis of such pyrimidines. The degree of ionization, the nucleophilicity of the C-5 of pyrimidines and their reactivity toward electrophilic condensation with cyclic ketones were correlated.

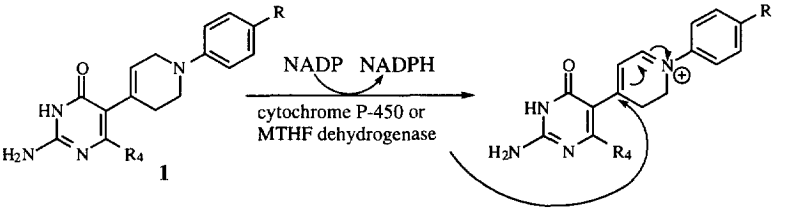
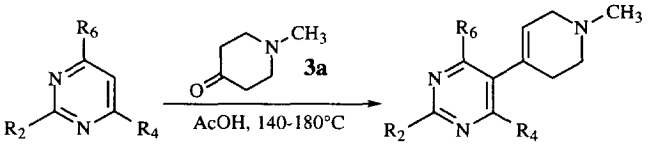


Fig. **1**

Electrophilic condensation of pyrimidines at C-5 with piperidones took place in acidic media. Nucleophilicity was represented as their chemical shift of ^{13}C NMR (Table **1**). Pyrimidines with poor electron density at C-5 failed to react with **3a** (entries **1-5**), while those with higher electron density were subject to the substitution reaction with fair to moderate yields (entries **6-7**, **10-12** and **14**). No reaction was observed for compounds **2h**, **2i**, and **2q**, possibly due to their poor solubility in acetic acid. As nonconjugated tautomer dominates, electrophilic reaction did not proceed for barbituric acid (**2r**) although it possesses high electron density at C-5.

Protonation of nucleophilic pyrimidines might prohibit the molecules from electrophilic reaction. Since the degree of ionization of a compound depends on its pK_a and the pH of reaction medium, the pKa[4] of pyrimidines and their reactivity were correlated. Although the substituents on pyrimidines **2m** and **2n** are similar and the chemical shifts of C-5 in ^{13}C NMR are almost identical (entries **12** and **13**, Table **1**), the reactivity of **2m** was much higher than that of **2n**. The lower basicity (pK_a 3.3 vs 6.5) and the consequent higher ratio of nonionic vs ionic form for **2m** might explain the result. Similar results were observed when **2m** and **2p** (entries **12** and **14**) were compared.

Table 1. Condensation of *N*-methylpiperidone (**3a**) with pyrimidines.[6]



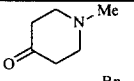
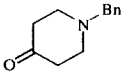
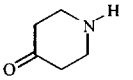
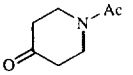
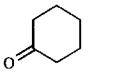
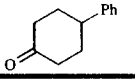
2a-r **1**

Entry	Pyrimidine	R_2	R_4	R_6	δ (ppm)[a]	pK_a[b]	**3a** (eq)	Reaction temp. (°C)	Reaction time (h)	Product (yield %)
1	**2a**	NH_2	OH	Me	110.74	--	1	140	24	NR[c]
2	**2b**	NH_2	H	H	110.50	3.54	1	140	24	NR
3	**2c**	OH	OH	H	100.00	9.4 12.5	1	140	24	NR
4	**2d**	Me	NH_2	Me	99.93	6.7	1	140	24	NR
5	**2e**	OH	OH	Me	98.50	1.2 9.7	1	140	24	NR
6	**2f**	NH_2	NH_2	H	95.66	7.4	2	180	10	**1f** (33)
7	**2g**	NH_2	NH_2	Me	93.30	7.7	2	180	10	**1g** (35)
8	**2h**	H	NH_2	OH	86.60	1.4 10.1	1	140	12	NR
9	**2i**	Me	NH_2	OH	82.80	--	1	140	12	NR
10	**2j**	H	Me	NH_2	82.60	6.0	1	140	10	**1j** (40)
11	**2k**	Me	NH_2	NH_2	79.58	6.4	1	140	10	**1k** (44)
12	**2m**	NH_2	NH_2	OH	76.56	3.3 10.8	1	140	3	**1m** (62)
13	**2n**	OH	NH_2	NH_2	75.60	6.5 12	1	140	12	NR
14	**2p**	NH_2	NH_2	NH_2	74.80	7.0	1	140	10	**1p** (43)
15	**2q**	OH	NH_2	OH	72.78	0.4 8.6 15.3	1	140	12	NR
16	**2r**	OH	OH	OH	39.22	3.9 12.5	1	140	24	NR

[a]Chemical shift of the C-5 of pyrimidines in ^{13}C NMR were determined in DMSO-D_6. [b]pK_a data were retrieved from reference 4. [c]NR denotes no reaction.

The reactivity of cyclic ketones was also investigated (Table **2**). Reaction of *N*-alkyl-4-piperidones (**3a-3c**) with pyrimidine **2m** proceeded fairly well, while no reaction was observed between *N*-acetyl-4-piperidone (**3d**) and **2m**. Cyclohexanones (**4a, 4b**) did not react with **2m** either. Wysocka proposed the formation of an active cation (**3C**, Fig. **2**) from 4-piperidones upon hydration under acidic conditions.[5] We postulate here that the same intermediate (**3C**) formed from *N*-alkyl-4-piperidones **3a**, **3b** and **3c** under acidic conditions behaved as an electrophile for nucleophilic attack by pyrimidines in the way as depicted in Fig. **2**.

Table 2. Reaction of pyrimidine **2m** with cyclic ketones.

Cyclic ketone	Structure	Reaction time (h)	Product (yield %)
3a		3	**1m** (62)
3b		3	**1s** (55)
3c		3	**1t** (71)
3d		12	NR
4a		12	NR
4b		12	NR

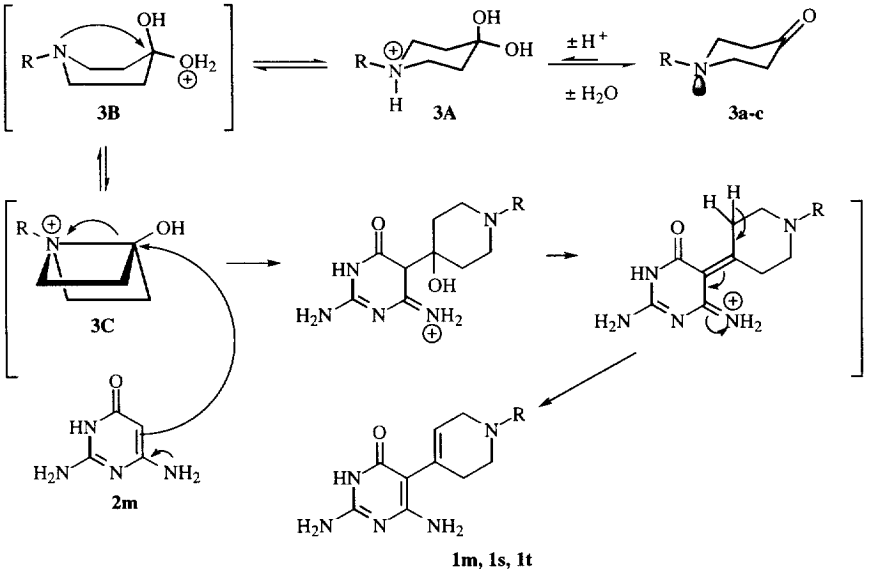


Fig. **2**

In summary, this report uncovers some new observations on electrophilic condensation between pyrimidines and cyclic ketones. The reaction proceeded mainly in acidic media. The degree of ionization of pyrimidines in acetic acid and the electron density on the C-5 determine the reactivity. Cyclic ketones or piperidones with poor electron density on the nitrogen failed to react with active pyrimidines. An electron-rich nitrogen at the 4-position of cyclic ketones facilitated the reaction. This method is facile for the synthesis of a series of novel 5-(3,4-dehydro-4-piperidinyl)pyrimidines as k_{cat} antimetabolites of methylene-tetrahydrofolate for antitumor purpose.

General Prodecure: A mixture of pyrimidine (4.0 mmol) and cyclic ketone (4.0-8.0 mmol) in glacial acetic acid (25 mL) was placed in a close vessel and heated to 140-180°C for required time. After reaction, the solution was condensed in vacuum and the residue was purified with column chromatography to furnish the product.[6]

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References and Notes

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5. Wysocka, W. *Heterocycles*, **1982**,*19*, 1-5.
6. Representative data for 5-(*N*-methyl-3,4-dehydro-4-piperidinyl)-2,4-diamino-6-hydroxypyrimidine (**1m**): mp 305-306°C; IR (KBr): 3400 (br), 1670, 1635, 1605, 1560, 1450, 1410 cm^{-1}; ^1H NMR (400 MHz, DMSO-D_6): δ=6.13 (2H, s, NH_2), 5.50 (2H, s, NH_2), 5.39 (1H, s, =CH), 2.95 (2H, d, J=2.4, =CH-$\underline{CH_2}$), 2.53-2.49 (4H, m, Me-N-$\underline{CH_2}$-$\underline{CH_2}$-C=), 2.27 (3H, s, N-Me) 1.86 (3H, s, CH_3COO^-); ^{13}C NMR (100 MHz, DMSO-D_6): δ=172.45 ($CH_3\underline{C}OO^-$), 160.98 (pyrimidine-C^4), 160.90 (pyrimidine-C^6), 153.57 (pyrimidine-C^2), 130.92 ($\underline{C}$=CH), 123.94 (C=$\underline{C}$H), 90.54 (pyrimidine-C^5), 54.07 (=CH-$\underline{CH_2}$-N), 51.74 ($\underline{CH_2}$-C=CH), 45.19 (N-Me), 28.20 (N-$\underline{CH_2}$-CH_2), 21.54 ($\underline{C}H_3COO^-$); mass spectrum, m/z (relative intensity) 221 (M^+, 12), 206 (5), 96 (19), 60 (100); EI HRMS, $C_{10}H_{15}N_5O$ (M^+): calcd. 221.1276, found 221.1279.

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