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A NOVEL RING TRANSFORMATION OF NITROPYRIMIDINONE LEADING TO POLYFUNCTIONALIZED PYRIDONES

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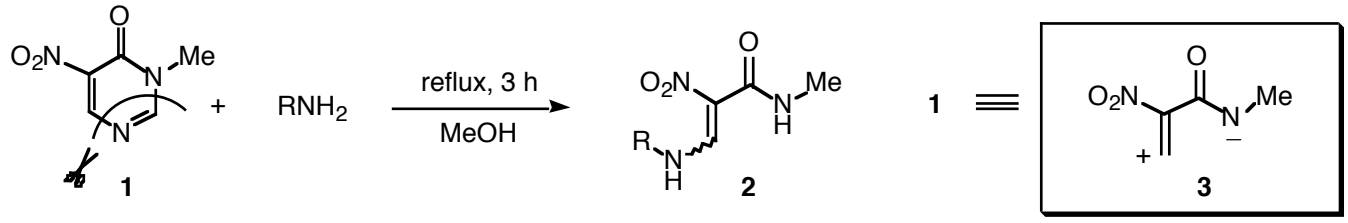
Abstract – Polyfunctionalized 2-pyridones are readily prepared by the ring transformation using 3-methyl-5-nitropyrimidin-4(3*H*)-one with active methylene compounds in the presence of piperidine.

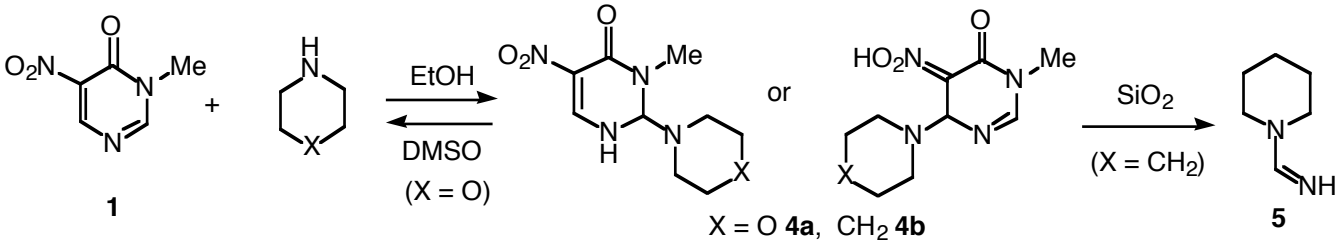
INTRODUCTION

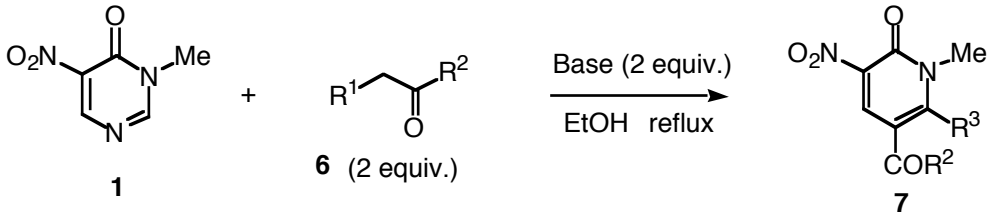
3-Methyl-5-nitropyrimidin-4(3*H*)-one (**1**) has been proved to show versatile reactivity.[1-4] Electron-deficient heterocyclic compounds having a good leaving group are useful substrate for the ring transformation.[5] Thus, pyrimidinone (**1**) is considered to cause the ring transformation effectively. Actually, the C2-N1-C6 moiety of **1** behaves as the synthetic equivalent of activated diformylamine to afford 4-aminopyridines,[1] pyrimidines[2] and 4-pyridones.[3] On the other hand, the C4-C5-C6 moiety of **1** behaves as that of α-nitroformylacetic acid leading to alkylated (or arylated) 3-nitro-2-pyridones.[2] Furthermore, the ring opening reaction of nitropyrimidinone (**1**) also proceeds on treatment with primary amines to furnish β-nitroenamines having a carbamoyl group (**2**) in which the acrylamide framework is derived from the N3-C4-C5-C6 moiety of **1**.[4] This result prompted us to develop a new ring transformation constructing polyfunctionalized 2-pyridones by the reaction of **1** with active methylene compounds in the presence of base. In this case, pyrimidinone (**1**) is regarded as the synthetic equivalent of dipolar β-nitroacrylamide (**3**).



RESULTS AND DISCUSSION

The reaction of pyrimidinone (**1**) with secondary amines was initially studied to confirm the leaving ability of the N1-C2 unit. When morpholine was added to a solution of nitropyrimidinone (**1**) in ethanol, white solid immediately precipitated. The empirical formula of this solid is $C_9H_{14}N_4O_4$, however, its ^{1}H NMR spectrum using DMSO-d_6 as the solvent shows a mixture of both starting materials. This fact indicates that pyrimidinone (**1**) and morpholine readily form adduct (**4a**) which splits into starting materials in a DMSO solution. On the other hand, piperidine reveals different behavior from morpholine, namely adduct (**4b**) is soluble in ethanol because of different polarity from **4a**. On treatment of the residual oil after evaporation with column chromatography, amidine (**5**) was isolated as yellow solid showing a singlet signal at 8.00 in the ^{1}H NMR spectrum (in $CDCl_3$). Since the N1-C2 moiety of **1** is transferred to piperidine accompanied by the fission of both C6-N1 and C2-N3 bonds, pyrimidinone (**1**) is found to be a good donor of the N-C-C-C unit with elimination of N1-C2 unit. So, the ring transformation of pyrimidinone (**1**) with active methylene compounds was conducted in the presence of piperidine as the base from a viewpoint of solubility of **4** into organic solvents.

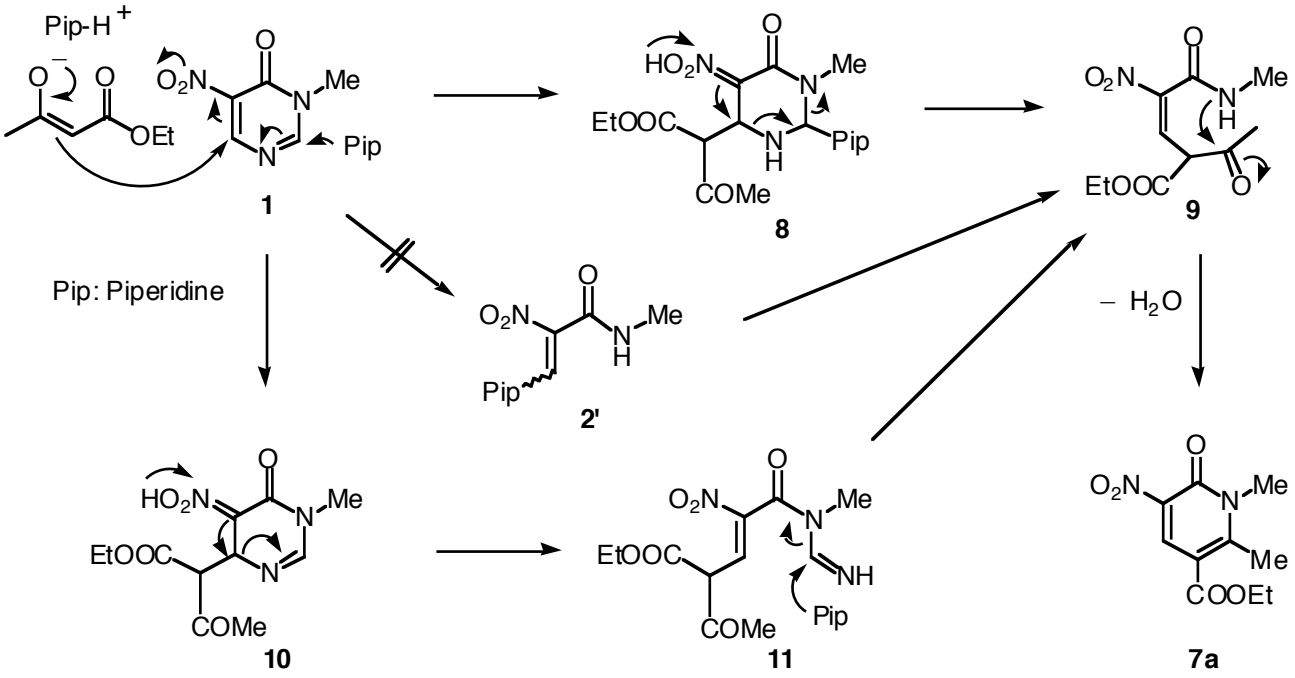




	R^1	R^2	Base	Time / h	R^3	Yield / %
a	MeCO	OEt	Piperidine	24	Me	67
b	PhCO	OEt	Piperidine	24	Ph	84
c	MeCO	Me	Piperidine	24	Me	0
d	PhCO	Me	Piperidine	24	Ph	0
e	COOEt	OEt	Piperidine	24	OH	31
e	COOEt	OEt	NaOEt	4	OH	78
f	CN	OEt	Piperidine	24	NH_2	67
f	CN	OEt	NaOEt	4	NH_2	70

To a solution of **1** and ethyl acetoacetate (**6a**) in ethanol, piperidine was added and the resultant mixture was stirred at room temperature for 1 day. After removal of the solvent under reduced pressure, the residue was treated with column chromatography on silica gel to afford polysubstituted pyridone (**7a**)[4] in 49% yield. This result was actually better than those of morpholine (25% yield) and diethylamine (5% yield) under the same conditions. The yield of **7a** was improved up to 67% when the reaction mixture was heated under reflux.[6]

The present reaction was applicable to benzoylacetate (**6b**) to furnish corresponding pyridone (**7b**)[7] in a good yield, but pyridones (**7c**) and (**7d**) could not be obtained in reactions of **1** with 1,3-diketones (**6c**) and (**6d**). In the latter cases, reaction mixtures were complicated. The introduction of a hydroxyl and an amino group at the 6-position of pyridone was also possible when malonate (**6e**) and cyanoacetate (**6f**) were employed. Pyridones (**7e**)[8] and (**7f**)[9] were produced more effectively by use of sodium ethoxide as the base instead of piperidine, however, the use of sodium ethoxide in reactions for diketones and keto esters gave no corresponding pyridones. While **7e** and **7f** are stable due to a newly introduced electron-donating group, pyridones (**7c**) and (**7d**) are thought to be reactive under basic conditions due to two strong electron-withdrawing groups. It is considered that **7c** and **7d** cannot be isolated because further reactions such as decomposition or ring transformation proceed under the conditions employed here.



A plausible mechanism is illustrated above. The reaction is initiated with attack of ammonium enolate at the 6-position of **1** and piperidine adds to the 2-position of **1**. The ring opening reaction of **8** affords polyfunctionalized alkene (**9**) followed by cyclization with intramolecular attack of the carbamoyl group to the acyl one, and leading to pyridone (**7a**). There is another possibility that involves the ring opening

reaction of **10** just after addition of enolate, and the following substitution of the methaneimidoyl group of **11** by piperidine proceeds to give **9**. However, the mechanism via nitroenamine (**2'**) is excluded since aminolysis of **1** with secondary amines does not give corresponding nitroenamines having a dialkylamino group.[4]

Further study on application of this reaction to non-activated aliphatic ketones is in progress. The results will be shown in due course.

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6. Typical procedure. To a solution of pyrimidinone (**1**) (155 mg, 1.0 mmol) in ethanol (20 mL), were added ethyl acetoacetate (253 μL, 2.0 mmol) and piperidine (198 μL, 2.0 mmol), and the resultant mixture was heated under reflux for 1 day. After removal of the solvent, the residue was extracted with benzene (20 mL x 3), and the extract was concentrated. The residual reddish oil was treated with column chromatography on silica gel to afford **7a** (eluted with $CHCl_3$/AcOEt = 7/1, 162 mg, 0.67 mmol, 67%).
7. Spectral data for pyridone (**7b**). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, *J* = 7.1 Hz, 3H), 3.35 (s, 3H), 4.40 (q, *J* = 7.1 Hz, 2H), 7.22-7.27 (m, 2H), 7.54-7.61 (m, 3H), 8.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (q), 35.7 (q), 61.6 (t), 108.4 (s), 126.9 (d), 128.8 (s), 129.1 (d), 130.2 (d), 133.5 (s), 138.5 (d), 154.7 (s), 159.4 (s), 163.0 (s).
8. Spectral data for pyridone (**7e**). Colorless needles; mp 148-150 °C (recrystallized from EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (t, *J* = 7.1 Hz, 3H), 3.12 (s, 3H), 3.35 (br s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 8.81 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 15.9 (q), 27.8 (q), 60.7 (t), 100.7 (s), 121.7 (s), 142.3 (d), 158.9 (s), 160.3 (s), 166.1 (s).
9. Spectral data for pyridone (**7f**). Colorless needles (recrystallized from EtOH); mp 253-255 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (t, *J* = 7.1 Hz, 3H), 3.37 (s, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 8.72 (br s, 1H), 8.84 (s, 1H), 9.28 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.0 (q), 28.9 (q), 60.8 (t), 89.3 (s), 123.4 (s), 140.0 (d), 153.7 (s), 156.9 (s), 165.2 (s). Anal. Calcd for $C_9H_{11}N_2O_5$: C, 44.82; H, 4.60; N, 17.42. Found: C, 44.70; H, 4.50; N, 17.41.