Novel ring transformation of nitropyrimidinone; synthetic equivalent of α-nitroformylacetic acid

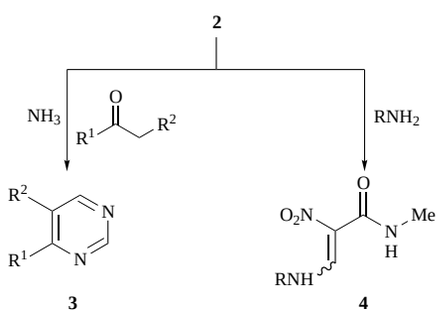
Nagatoshi Nishiwaki, Hui-Ping Wang, Kengo Matsuo, Yasuo Tohda and Masahiro Ariga*

Department of Chemistry, Osaka Kyoiku University, Asahigaoka 4-698-1, Kashiwara, Osaka 582, Japan

3-Methyl-5-nitropyrimidin-4(3*H*)-one reacts with ketones in the presence of ammonium salts to afford disubstituted pyrimidines and disubstituted 3-nitro-2-pyridones in a novel ring transformation reaction; nitropyrimidinone behaves as an activated diformylamine in the former case, and as a synthetic equivalent of α-nitroformylacetic acid in the latter case.

Diformylamine (diformamide) **1** (see Fig. 1), the simplest secondary amide, has not been extensively used in organic synthesis due to its low reactivity. Since the carbonyl group of **1** reveals carbamoyl properties rather than formyl properties, nucleophilic substitution predominantly occurs.[1] A unique example employing **1** as an aldehyde in an intramolecular Wittig reaction leading to a pyrrole derivative has, however, been reported.[2]

In our previous paper, we showed that 3-methyl-5-nitropyrimidin-4(3*H*)-one **2** reacts with ketones in the presence of NH_3 to give disubstituted pyrimidines **3** (Scheme 1).[3] In the ring transformation, pyrimidinone **2** behaves as the activated diformylamine. This reaction, however, requires severe conditions,† and is applicable only to restricted substrates.



Scheme 1

On the other hand, ring cleavage of pyrimidinone **2** with amines, not in the presence of ketones, readily proceeds to yield functionalized nitroenamines **4**.[4] This ring opening reaction is considered to prevent the pyrimidine synthesis. To avoid this aminolysis of **1**, less nucleophilic ammonium salts were employed as the nitrogen source for the ring transformation.

A solution of nitropyrimidinone **2** (155 mg, 1.0 mmol), acetophenone (0.23 ml, 2.0 mmol) and NH_4OAc (154 mg, 2.0 mmol) in MeOH (20 ml) was refluxed for 1 day. When the contents were cooled to room temperature, yellow needles precipitated. The collected crystalline product was identified as 3-nitro-6-phenyl-2-pyridone **5a** (R^1 = Ph, R^2 = H) from its spectral and analytical data. The filtrate was concentrated, and

† Pyrimidine **3a** was obtained in only 6% yield in the reaction of pyrimidinone **2** with acetophenone and NH_3 even though severe conditions (heating at 120 °C in a sealed tube for 3 h) were employed.[3]

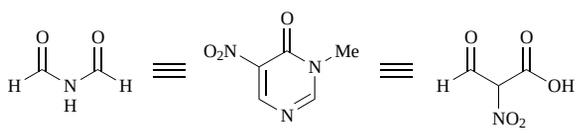


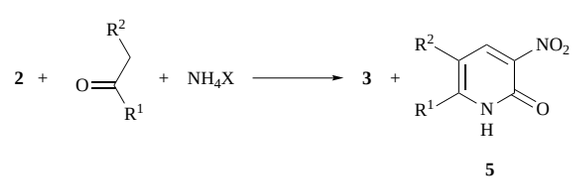
Fig. 1

Table 1 Reactions of pyrimidinone **2** with acetophenone[a]

Solvent	*t*/d	X^-	Yield (%) **3a**	**5a**	Recovery (%)
MeOH	1	AcO^-	47	48	0
MeOH	7[b]	AcO^-	35	33	32
EtOH	1	AcO^-	0	0	86
MeCN	1	AcO^-	0	5	95
DMF	1	AcO^-	trace	—	—
MeOH	3	$HCOO^-$	37	52	0
MeOH	3	$C_6H_4(COO^-)_2$	46	45	0
MeOH	3	$(COO^-)_2$	0	0	0
MeOH	3[c]	CO_3^{2-}	21	52[d]	0
MeOH	3	Cl^-	0	0	88
MeOH	3	BF_4^-	0	0	0

[a] *Reaction conditions:* **2** = 1 mmol; acetophenone = 2 mmol; NH_4X = 2 mmol; solvent = 20 ml; *T* = 65 °C. [b] *T* = Room temperature. [c] *T* = 50 °C. [d] Crude yield.

the residue was column chromatographed to give 4-phenylpyrimidine **3a** and a second crop of pyridone **5a** (Scheme 2).



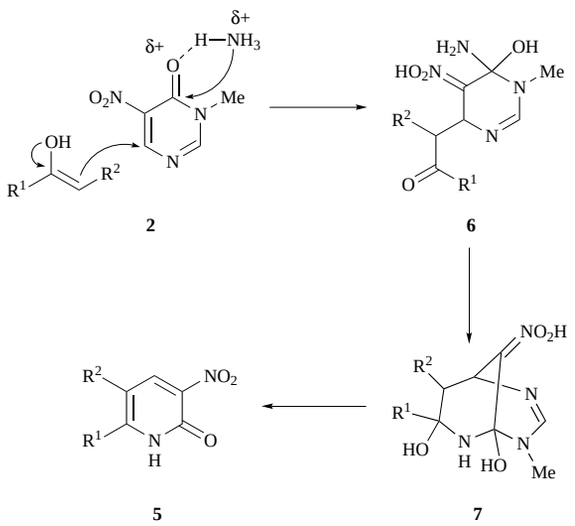
Scheme 2

Usage of NH_4OAc instead of NH_3† in the ring transformation reaction afforded pyrimidine **3a** under more mild conditions and in a considerably improved yield. Pyridone derivative **5a** was also isolated as the other product in moderate yield. Since 3-nitro-2-pyridone derivatives have recently attracted attention as anti-HIV drug intermediates, the present reaction would be a useful method for construction of this skeleton.[5] Although this transformation proceeded even at room temperature, refluxing the mixture brought about almost complete reaction after 1 day.

Several solvents and ammonium salts were also investigated. In cases when the reaction mixture became a homogeneous solution, both products **3a** and **5a** were obtained. Ammonium salts $(COONH_4)_2$, NH_4Cl and NH_4BF_4 were not effective owing to their insolubility (Table 1).

The present reaction was applied to other ketones. Acyclic or cyclic ketones also afforded ring transformed products **3** and/or **5**. A relationship between the ratio of the products (**3**:**5**) and the reaction conditions or the structure of the substrates could not be observed (Table 2). Further investigations to control this selectivity are in progress.

The two products **3a** and **5a** were formed as follows (Scheme 3). Coordination of NH_4^+ activates pyrimidinone **2**. The NH_3 generated attacks the carbonyl group at the 4-position, and the enol of the ketone attacks the 6-position of **2** to form adduct **6**. The intramolecular nucleophilic addition of adduct **6** gives bicyclic intermediate **7**, from which the amidine derivative is eliminated to give pyridone **5a**. Pyrimidine **3a** is the result of the ring transformation at the 2- and the 6-positions of **2** with liberation of nitroacetamide anion.[3]



Scheme 3

In conclusion, ring transformation of 3-methyl-5-nitropyrimidin-4-one **2** with a ketone in the presence of an ammonium salt can proceed to give substituted pyrimidines **3** and nitropyridone **5** in moderate yields. Nitropyrimidone **2** behaves as the activated diformylamine **1** in the former case, and as the synthetic equivalent of α-nitroformylacetic acid **8** in the latter case. Although ring transformations of nitropyrimidine derivatives have already been reported,[6] there are no examples of the use of 5-nitropyrimidin-4-ones. Hence, nitropyrimidinone **2** would be a useful precursor of azaheterocycles that are difficult to obtain by the alternative procedure.

Table 2 Syntheses of disubstituted pyrimidines **3** and pyridone **5**[a]

			Yield (%)	
	R^1	R^2	**3**	**5**
b	H	*m*-$NO_2C_6H_4$	—[b]	28
c	H	Me	—[b]	81[c]
d	H	Pr^i	—[b]	22
e	Me	Et	17	34
f	$-(CH_2)_3-$		46	trace
g	$-(CH_2)_4-$		49	0
h	$-(CH_2)_5-$		11	79

[a] *Reaction conditions:* **2** (1 mmol), substrate (2 mmol), NH_4OAc (2 mmol), MeOH (20 ml), 65 °C, 3 days. [b] Complex mixture. [c] Crude yield.

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