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Mechanistic aspect of ring transformations in the reaction of 5-nitro-4-pyrimidinone with acetophenone derivatives and cycloalkanones depending on the electron density/ring size of the ketone

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ABSTRACT

3-Methyl-5-nitro-4-pyrimidinone undergoes two kinds of nucleophilic type ring transformations upon treatment with cycloalkanones in the presence of ammonium acetate, which affords 4,5-disubstituted pyrimidines and 5,6-disubstituted 3-nitro-2-pyridones. In order to improve the synthetic utility of this reaction, it is necessary to control the regioselectivity of these ring transformations. In the present work, we performed DFT calculation to realize the selectivity of two ring transformation products. In cases of adduct intermediates derived from cyclohexanone and cyclooctanone, the 2-attack proceeds preferably to give condensed pyrimidines. On the other hand, the adduct intermediate derived from cycloheptanone undergoes the 4-attack predominantly to afford condensed nitropyridone.

Ring transformation is one of the valuable methods for synthesizing ring systems which are not easily available by alternative methods. Although Diels–Alder type[1] and degenerated type ring transformations[2] have been widely employed in organic synthesis, nucleophilic type ring transformation[3] still remains being unexplored even now. It is demanded to establish the third method as a synthetic tool for a variety of purposes. Substrates suitable for the nucleophilic type ring transformation should have high electron deficiency and have a good leaving group as a partial structure.

From this viewpoint, we have studied ring transformation using the pyrimidinone **1** as a substrate. Indeed, the pyrimidinone **1** serves as a good substrate to undergo several kinds of nucleophilic type ring transformations constructing versatile azaheterocyclic frameworks.[4] When the pyrimidinone **1** is allowed to react with the ketone **2** in the presence of ammonium acetate, two kinds of three-component ring transformations proceed to afford the pyrimidine derivative **3** and the 3-nitro-2-pyridone derivative **4** (Table 1). Since both products involve important frameworks for the research of biologically active compounds and for the development of new medicines and agrochemicals, controlling of the selectivity of the reaction path is highly demanded.

In our previous work, substituted acetophenone derivatives were employed as reactants to obtain insights useful for controlling the selectivity. As a result, it was found that the selectivity is considerably influenced by electron density on the benzene ring. While acetophenone (**2b**) afforded almost the same amounts of two products **3b** and **4b**, the ratio of **4** increased when electron-rich ketones such as **2a** are used. Moreover, the formation of **3** preferably proceeded in the reactions of **1** with electron-poor ketones such as **2c** together with diminishing total yields.[5]

A plausible mechanism for these ring transformations is illustrated in Scheme 1. Initially, the enamine intermediate **5b** is formed by the addition of the enol **2b′** at the 6-position of **1**, followed by amination by ammonium acetate. The enamine **5b** is considered to serve as a common intermediate for both azaheterocyclic compounds, **3b** and **4b**. When the enamino group of **5b** attacks the 2-position, the pyrimidine **3b** is formed via the bicyclic intermediate (path A). On the other hand, the pyridone **4b** is similarly formed when the enamino group attacks at the 4-position (path B). The estimation of partial charges by DFT calculations using B3LYP/6-31++G** shown in parentheses reveals that the 4-position is more electron deficient than the 2-position. An electron-rich enamino group can attack both positions to afford the pyrimidine **3** via more stable intermediate (thermodynamic process). In the case of an electron-poor enamino group, only the 4-position is attacked to afford the pyridone **4** (kinetic process).

On the other hand, the ring transformation of the pyrimidinone **1** with cycloalkanones under the same conditions revealed somewhat different selectivities (Scheme 2 and Table 2).[5b] When the pyrimidinone **1** was subjected to the reaction with cyclopentanone (**2d**) or cyclohexanone (**2e**), the condensed pyrimidine **3d** or **3e**

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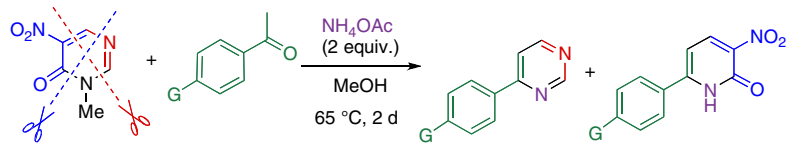
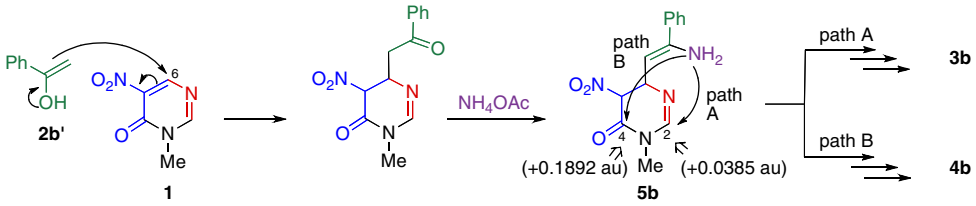
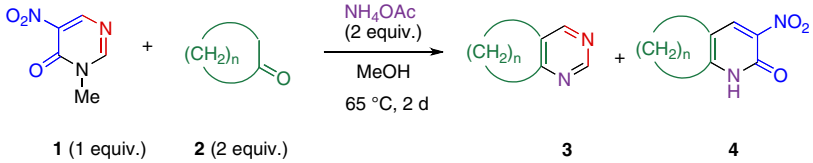
Table 1
Two ring transformations of pyrimidinone **1** with aromatic ketones **2**



G		Yield (%)	
		3	**4**
Me	**a**	25	75
H	**b**	49	51
NO_2	**c**	27	15



Scheme 1. Divergence of two ring transformations.



Scheme 2. Ring transformations of **1** with cycloalkanones leading to condensed products.

was afforded without the formation of a detectable amount of the corresponding pyridone **4d** or **4e**. To the contrary, condensed pyridone **4f** was predominantly formed in the reaction of **1** with cycloheptanone (**2f**). Furthermore, cyclooctanone (**2g**) afforded the pyrimidine **3g** as a major product together with a small amount of the pyridone **4g**. Surprisingly, when acetic acid was employed as the solvent instead of methanol in the reaction of **1** with **2f**, the selectivity was inverted to afford the pyrimidine **3f** exclusively. Although dramatic change in selectivity was observed, these results were not reasonably explained by only electron density. Then, we considered that the selectivity of the ring transformations by cycloalkanones would depend on activation energies from the enamine intermediates to the corresponding transition states to give bicyclic intermediates, because bicyclic compounds were sometimes isolated in the reactions of nitropyrimidinone or dinitropyridone with enolates of 1,3-dicarbonyl compounds,[6] which means that the formation of bicyclic intermediates is a crucial step in the ring transformation.

DFT calculations were performed using DFT B3LYP/6-31++G**. Although two tautomeric enamines, the 5-nitro form **5** and the 5-nitronic acid form **6**, were employed as starting structures, all calculations could give no reasonable transition state structures. This problem was settled by adding one water molecule in the transition state structures with hydrogen bonds (Fig. 1). Indeed, the solvent used for ring transformation is not dried, thus an enough amount of water would present in the reaction mixture. Calculation results are shown in Table 3.

Table 2
Ring transformations with cycloalkanones

n		Solv.	Yield (%)	
			3	**4**
3	**d**	MeOH	85	0
4	**e**	MeOH	71	0
5	**f**	MeOH	11	79
6	**g**	MeOH	67	17
5	**f**	AcOH	90	0

In the reaction with cyclohexanone (**2e**) as a reactant, the attack of the enamino group in nitro form **5e** at the 2-position is found to be the most advantageous (E_1). In the reaction with cyclooctanone (**2g**), the attack of the enamino group in the nitronic acid form **6g** at the 2-position shows the lowest activation energy (E_1). Both results reveal that the 2-attack (path A) occurs more easily to afford the bicyclic intermediate **7** and **8**, from which nitroacetamide is eliminated leading to the pyrimidine derivatives **3e** and **3g**.

On the other hand, activation energy for the 4-attack (path B) is the smallest (E_3) when cycloheptanone (**2f**) is employed as a reactant, although this process is endothermic and energy difference from the 2-attack (E_1) is quite small. The small difference between E_3 and E_1 also means that reaction path is readily chan-

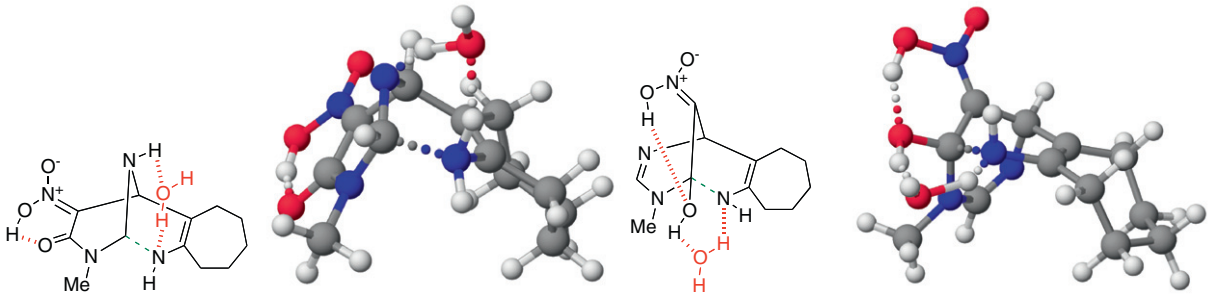
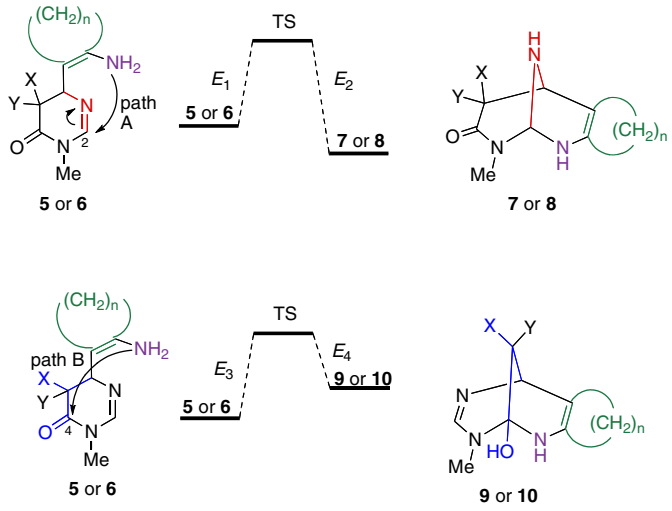


Figure 1. Transition states between **6f** and **8f** (left) and between **6f** and **10f** (right).

Table 3
Energy correlations (kcal mol^{-1}) when the enamino group attacks at the 2-position or at the 4-position (water molecule is omitted)



n	X	Y	Enamine	Product	E_1	E_2
4	NO_2	H	**5e**	**7e**	23.44	25.07
4	$=NO_2H$		**6e**	**8e**	27.60	29.27
5	NO_2	H	**5f**	**7f**	26.38	28.82
5	$=NO_2H$		**6f**	**8f**	27.71	29.54
6	NO_2	H	**5g**	**7g**	25.43	28.58
6	$=NO_2H$		**6g**	**8g**	21.34	28.76

n	X	Y	Enamine	Product	E_3	E_4
4	NO_2	H	**5e**	**9e**	25.75	12.47
4	$=NO_2H$		**6e**	**10e**	33.40	4.71
5	NO_2	H	**5f**	**9f**	26.30	12.78
5	$=NO_2H$		**6f**	**10f**	34.31	4.74
6	NO_2	H	**5g**	**9g**	25.16	12.21
6	$=NO_2H$		**6g**	**10g**	34.31	4.65

ged when reaction conditions are varied. Indeed, the reaction of the pyrimidinone **1** with cycloheptanone (**2f**) in acetic acid undergoes another ring transformation to afford the pyrimidine **3f** exclusively.

In summary, the regioselectivity of the ring transformation of the pyrimidinone **1** with acetophenone derivatives could be realized by considering partial charges of **1**. On the other hand, the regioselectivity depending on the ring size of cycloalkanones could be realized from the viewpoint of activation energies in the processes forming bicyclic intermediates. Since the present reaction includes complex processes, we cannot exclude another possibility. However, this insight for controlling ring transformations would be helpful information for designing new ring transformations.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.020.

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