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The Ring Transformation of 3-Methyl-5-nitropyrimidin-4(3*H*)-one

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Abstract: 3-Methyl-5-nitropyrimidin-4(3*H*)-one readily reacts with carbonyl compounds to produce three kinds of ring transformations. The nitropyrimidinone behaves as the synthetic equivalent of activated diformylamine affording 3,5-difunctionalized 4-pyridones, 4,5-disubstituted pyrimidines and functionalized 4-aminopyridines. It also behaves like α-nitro-formylacetic acid to give 5,6-disubstituted 3-nitro-2-pyridones.

Keywords: Nitropyrimidinone, ring transformation, pyridone, pyrimidine, aminopyridine.

Introduction

Ring transformation has allowed syntheses of polyfunctionalized compounds that are not easily prepared by alternative procedures [1-3]. Although many compounds usable in this reaction have been reported, development of new key compounds is still an important project. In the course of our studies on ring transformation reactions, attention was paid to 3-methyl-5-nitropyrimidin-4(3*H*)-one (**1**), which is easily prepared from 2-thiouracil by reduction [4], methylation [4] and nitration [5]. The highly electron deficient structure of pyrimidinone **1** enables its reaction with bidentate nucleophiles, and the N3-C4-C5 unit is considered to be a good leaving group. Depending on these structural features, the ring transformation of **1** leads to several types of azaheterocyclic compounds. In the present paper, we would like to broadly introduce the synthetic utility of nitropyrimidinone **1**.

Results and Discussion

The reaction of nitropyrimidinone **1** with 1,3-dicarbonyl compounds **2** under basic conditions affords 3,5-difunctionalized 4-pyridones **3** (Scheme 1) [6]. Substrates **2a-b**, having two active methylene groups, effectively afford pyridones **3a-b** simply by mixing the reagents at 60 °C. This reaction is initiated with attack of the enolate anion of **2** to either of the electron deficient 2- or 6-positions, then the regenerated enolate attacks at the other site intramolecularly to give bicyclic intermediate **4**. The succeeding elimination of anionic nitroacetamide from **4** furnishes pyridone **3**. In this reaction, pyrimidinone **1** behaves as the synthetic equivalent of activated diformylamine, which has not been used in organic synthesis.

Scheme 1.
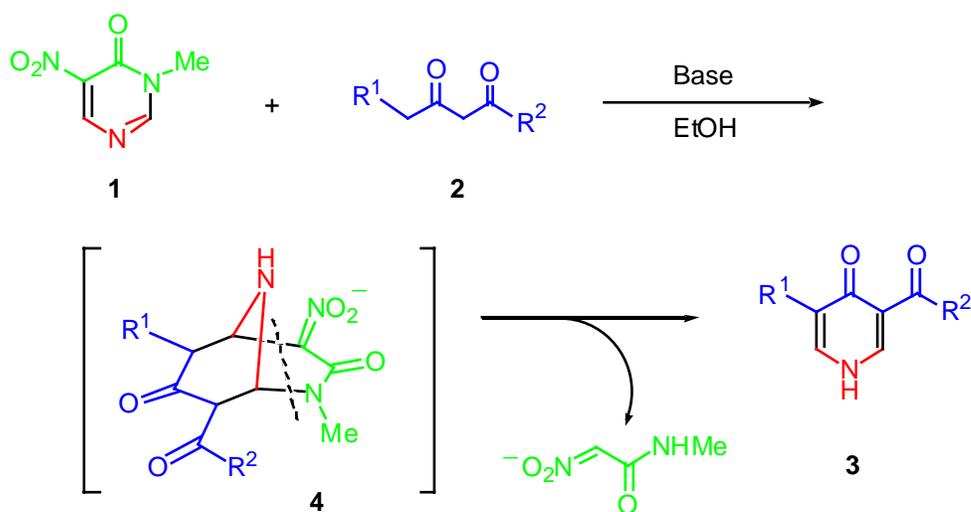
R^1	R^2		Base	Yield / %
COOEt	OEt	**a**	NEt$_3$	97
COMe	Me	**b**	NEt$_3$	80
H	OEt	**c**	NaOEt	44

When ketones **5** and ammonia are employed as the nucleophile, a similar ring transformation proceeds to afford 4,5-disubstituted pyrimidines **6** (Scheme 2) [7]. The main method used to construct the pyrimidine skeleton is the condensation of N-C-N and C-C-C units [8]. To the contrary, the present reaction involves a combination of three components (C-N-C + N + C-C), which suggests a new methodology for the pyrimidine chemistry, although this reaction suffers from low yields and severe conditions due to competitive aminolysis of **1** giving nitroenamine **7** [9].

Scheme 2.
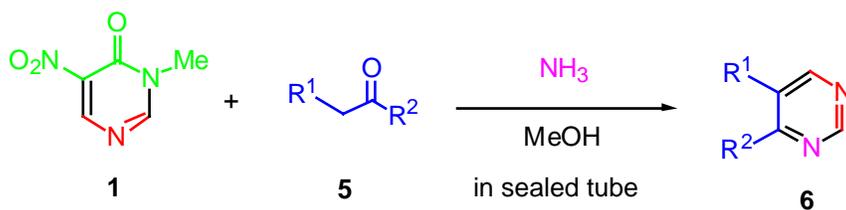
R^1	R^2		Temp. / °C	Yield / %
H	Ph	**a**	120	6
—(CH$_2$)$_4$—		**b**	100	54
—(CH$_2$)$_3$—		**c**	100	31
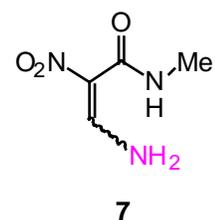
Scheme 3.
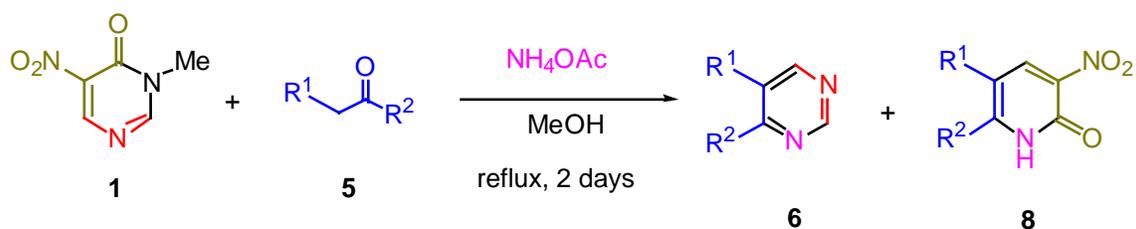
R^1	R^2		Yield / %		6 / 8
			6	**8**	
H	Ph	**a**	49	51	49 / 51
H	*p*-MeOC$_6$H$_4$	**d**	14	65	18 / 82
H	*p*-NO$_2$C$_6$H$_4$	**e**	34	10	77 / 23
—(CH$_2$)$_4$—		**b**	71	0	100 / 0
—(CH$_2$)$_5$—		**f**	11	79	12 / 88

The yields of pyrimidines **6** are considerably improved under milder conditions by using less nucleophilic ammonium acetate as the nitrogen source, instead of ammonia, to avoid undesired aminolysis (Scheme 3). In this reaction, 5,6-disubstituted 3-nitro-2-pyridone derivatives **8** are also

isolated [7]. Activation of the carbonyl group at the 4-position of **1** causes another ring transformation. The 4- and the 6-positions of **1** react with nucleophiles, in which pyrimidinone **1** behaves as the synthetic equivalent of α-nitroformylacetic acid. Since both skeletons **6** and **8** are important for drug design [10], the present reaction should prove useful to synthetic chemists working in this area.

The yields of products and their ratio (**6** / **8**) are influenced by the structural features of the ketones **5**. In the case of *p*-substituted acetophenones, electron-donating groups increase the ratio of pyridone **8**, and electron-withdrawing ones reverse the ratio. Similar contrasting results are observed in the reactions of cyclic ketones. While cyclohexanone **5b** leads to pyrimidine **6b**, pyridone **8f** is the main product in the case of cycloheptanone **5f**.

In order to synthesize more functionalized systems, the reaction of pyrimidinone **1** with 1,3-dicarbonyl compounds **2** in the presence of ammonium acetate was conducted. As a result, functionalized 4-aminopyridines **9** were unexpectedly obtained (Scheme 4) [11]. The ring transformation occurs at the 2- and the 6-positions, and the carbonyl group of **2** is converted to an amino group. This reaction is similarly applicable to ketoamide **2d**, chloroacetone **2e** and 2-hexanone. As ammonium acetate causes no change on pyridone **3c**, it is considered that the introduction of the amino group is not performed after formation of **3**. This reaction is a useful and simple procedure for preparation of functionalized 4-aminopyridines **9** instead of conventional troublesome multistep methods [12,13].

Scheme 4.
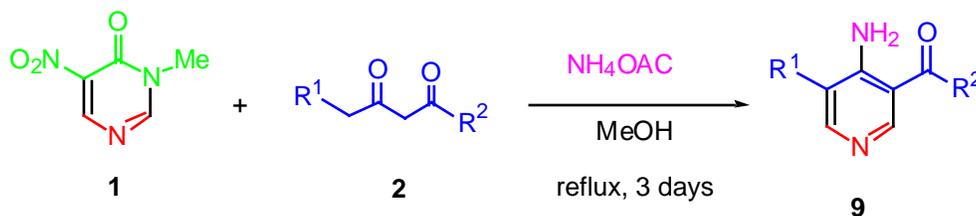
R^1	R^2		Yield / %
H	OEt	**c**	97
H	CONH$_2$	**d**	31
H	Cl	**e**	17

Conclusions

Nitropyrimidinone **1** behaves as the two synthetic equivalents, activated diformylamine and α-nitroformylacetic acid. The ring transformation of pyrimidinone **1** leads to several kinds of azaheterocyclic compounds. Furthermore, all of reactions demonstrated here are performed with simple experimental manipulations. Hence, it is concluded that synthetic utility of **1** is quite high as a useful precursor for polyfunctionalized systems.
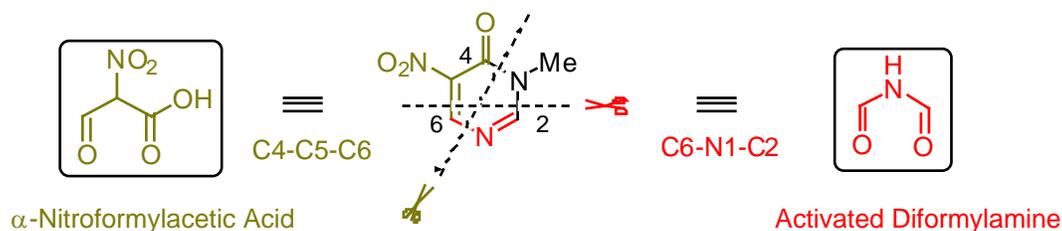
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