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ACTIVATION OF 1-METHYL-5-NITRO-2-PYRIMIDINONE BY DEAROMATIZATION USING A SECONDARY AMINE

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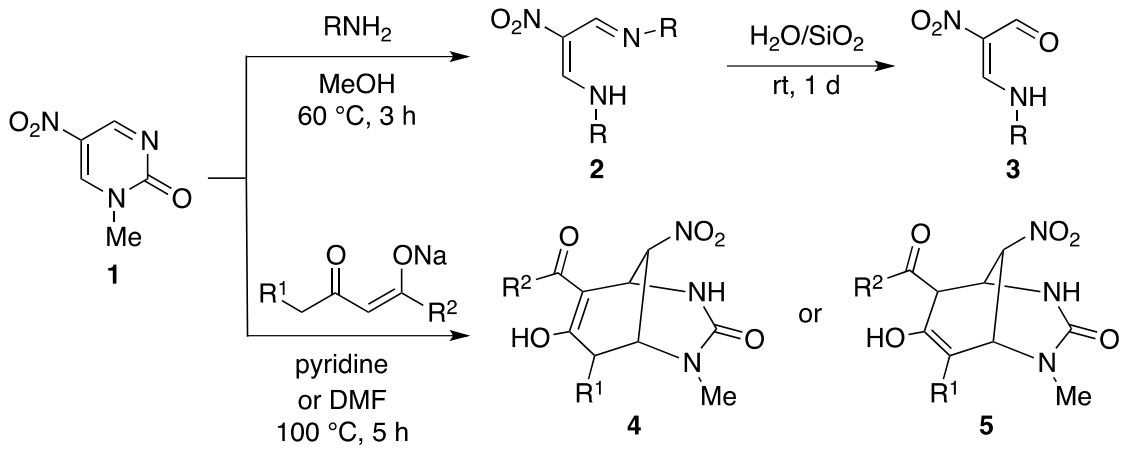
Abstract – Electron-deficient 1-methyl-5-nitro-2-pyrimidinone is easily attacked by methanol or pyrrolidine to afford the corresponding adducts, respectively, by which aromaticity of nitropyrimidinone is lost. Indeed, the amine-adduct higher reactivity than that of original structure to facilitate the reaction with 1,3-dicarbonyl compound leading to diazabicyclic compound at room temperature. The amine-adduct also underwent the ring opening reaction to furnish nitroenamines with (*Z*)-configuration.

INTRODUCTION

Highly electron-deficient heterocyclic compounds are often used in synthesis for polyfunctionalized compounds because the partial structure serves as a masked form of functionalized building block or its precursor.[1] 1-Methyl-5-nitro-2-pyrimidinone (**1**) is one of such compounds used for the present purpose that is easily prepared by condensation of *N*-methylurea and 1,1,3,3-tetramethoxypropane under acidic conditions followed by nitration.[2] The highly electron-deficient property of **1** facilitates the aminolysis to afford azadienamines (**2**)[3] used as unique bidentate ligands,[4] and half hydrolysis of **2** yields β-formyl-β-nitroenamines (**3**) which serve as a useful building block for versatile aza-heterocyclic compounds (Scheme 1).[3,5] Nitropyrimidinone (**1**) also reacts with enolate ions leading to diazabicyclic compounds (**4**) or (**5**) (Scheme 1).[2] Although the synthetic utility of **1** has been already revealed, some extent of aromaticity requires severe reaction conditions, which restricts the further synthetic application.

This paper is dedicated to Prof. Kiyoshi Tomioka's 70th birthday.

In order to overcome this problem, dearomatization of nitropyrimidinone (**1**) was studied.



Scheme 1. Chemical conversions of nitropyrimidinone (**1**)

RESULTS AND DISCUSSION

During the study on the reaction of nitropyrimidinone (**1**) with nucleophiles in methanol at 150 °C under microwave irradiation, yellow plates precipitated from the reaction mixture after cooling to room temperature followed by standing for 1 day. However, the ^{1}H NMR of this crystal showed only signals of **1** although their appearance were obviously different. As a result of X-ray crystallography, the crystalline product is confirmed to be dihydropyrimidine derivative (**6**) formed by addition of a methanol to **1**, and elimination of a methanol easily occurs upon dissolving into the organic solvent (Figure 1).

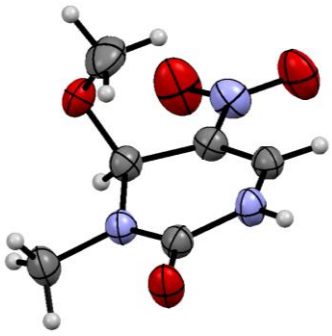
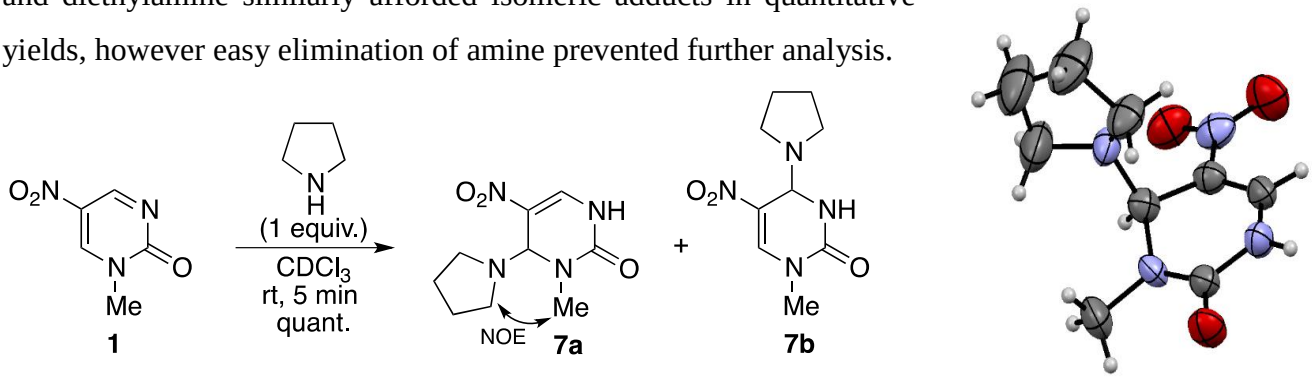


Figure 1. An ORTEP showing the 6-methoxy-1-methyl-5-nitropyrimidine-2(1*H*)-one (**6**) (color labels: gray, carbon; white, hydrogen; violet, nitrogen; red, oxygen). Thermal ellipsoids are drawn at the 50% probability level. Deposition number is CCDC-1813483.

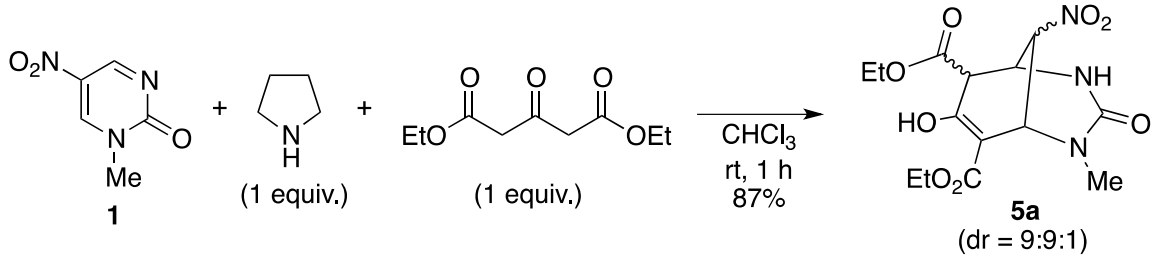
This result prompted us to study the reaction of nitropyrimidinone (**1**) with more nucleophilic amines. The formed adducts are considered to be enough stable for treating as a synthetic reagent for polyfunctionalized compounds. When pyrimidinone (**1**) reacted with pyrrolidine in deuterated chloroform at room temperature, addition reaction quantitatively occurred to afford two isomeric adducts (**7a**) and (**7b**) with 1:1 ratio. Although the formation of **7a** and **7b** was confirmed by ^{1}H and ^{13}C NMR spectra, these products were transformed to pyrimidinone (**1**) after evaporation. One isomer (**7a**) showed correlation between the methyl and pyrrolidino groups, **7a** was assigned to 6-adduct. Fortunately, single

crystal could be obtained when deuterated acetonitrile was used as a solvent, the structure of **7a** was confirmed by X-ray crystallography (Scheme 2). Other secondary amines such as piperidine, morphorine and diethylamine similarly afforded isomeric adducts in quantitative yields, however easy elimination of amine prevented further analysis.

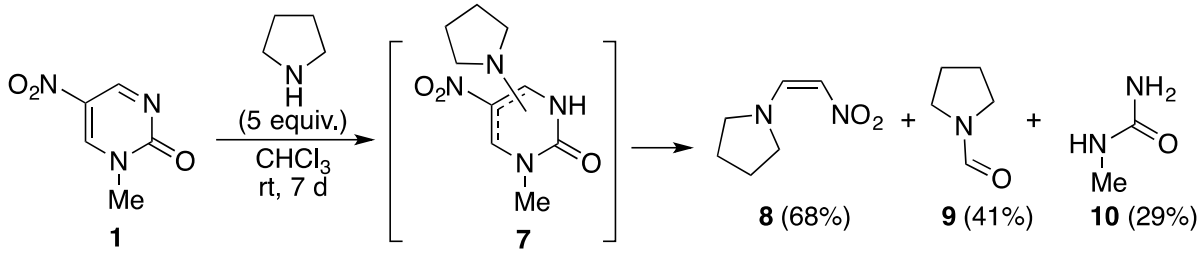


Scheme 2. Addition of pyrrolidine to nitropyrimidinone (**1**) and an ORTEP showing the 1-methyl-5-nitro-6-pyrrolidinopyrimidin-2(1*H*)-one (**7a**) (color labels: gray, carbon; white, hydrogen; violet, nitrogen; red, oxygen). Thermal ellipsoids are drawn at the 50% probability level. Deposition number is CCDC-1813484.

As shown in Scheme 1, when nitropyrimidinone (**1**) was heated with sodium enolate of diethyl acetonedicarboxylate in pyridine at 100 °C for 5 h, diazabicyclic compound **5a** (R^1 = CO_2Et, R^2 = OEt) was obtained in 76% yield.[2] Since nitropyrimidinone (**1**) shows aromaticity, severe conditions were necessary to undergo the reaction. Contrary to this, addition of pyrrolidine furnishes dearomatized adducts (**7a**) and (**7b**) to reveal higher reactivity than **1**. Indeed, **7a** and **7b** generated in situ reacted with diethyl acetonedicarboxylate even at room temperature, leading to **5a** in 87% yield (Scheme 3). In this reaction, stoichiometric amount pyrrolidine was necessary because formed **5a** consumed pyrrolidine by forming an ammonium salt.

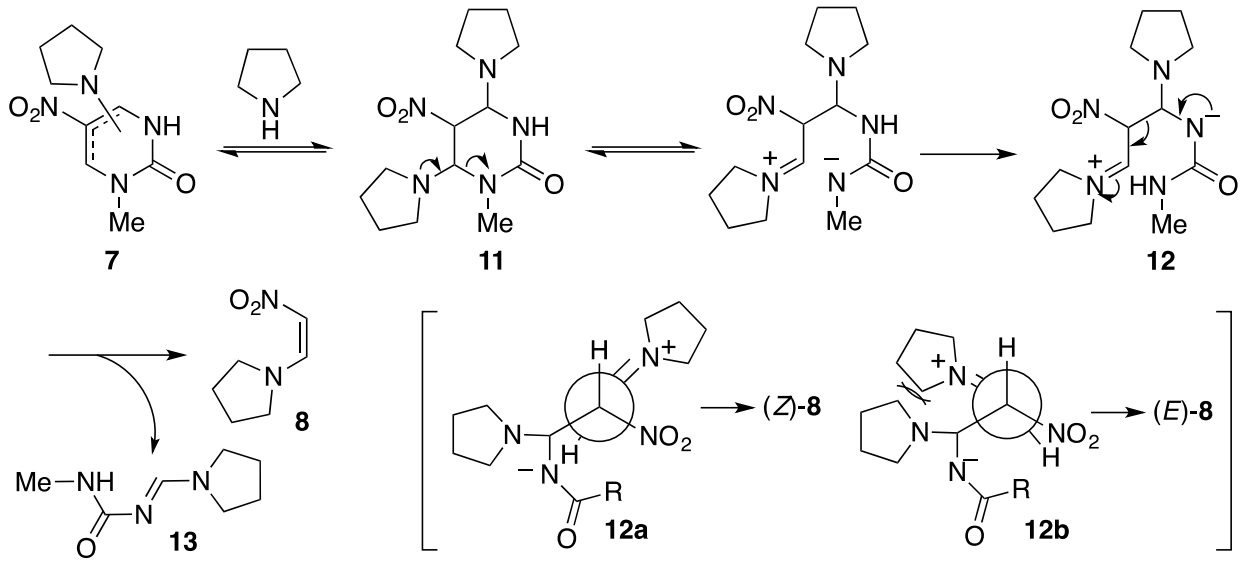


Scheme 3. Synthesis of diazabicyclic compound (**5a**) under mild conditions



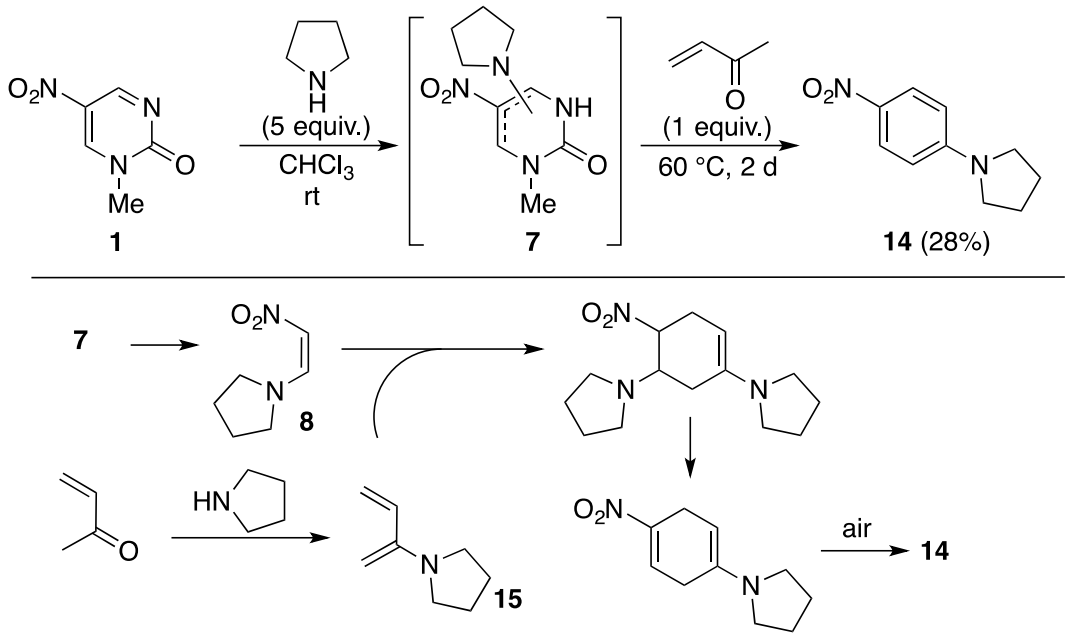
Scheme 4. Ring opening reaction of adduct (**7**) leading to nitroenamine (**8**), *N*-formylpyrrolidine (**9**) and *N*-methylurea (**10**). Yields were determined based on pyrimidinone (**1**).

When adducts (**7a**) and (**7b**) were stood in acetonitrile at room temperature for 1 day, the ring opening reaction also proceeded to afford nitroenamine (**8**),[6] *N*-formylpyrrolidine (**9**) and *N*-methylurea (**10**) in 17%, 16% and 12% yields, respectively. For this reaction, chloroform was found to be more suitable solvent, and using excess amounts of pyrrolidine and longer reaction time was effective to increase the yield of **8** up to 68% (Scheme 4). A plausible mechanism for formation of **8** is shown in Scheme 5. Adducts (**7**) is attacked by an additional pyrrolidine to afford tetrahydropyrimidine derivative (**11**). Each C–N bond easily cleavages because of the aminal structure, among which the C–N bond at the 6-position is considered to be more easily cleaved because of the steric repulsion between the methyl and pyrrolidino groups. After the ring opening reaction, the subsequent C–N bond cleavage yields nitroenamine (**8**) by elimination of urea (**13**), which is hydrolyzed to afford **9** and **10**, respectively. During the second cleavage of intermediate (**12**), conformer (**12a**) is more preferable than **12b** because of less steric repulsion between two pyrrolidino groups to afford (*Z*)-**8**.



Scheme 5. A plausible mechanism for the formation of nitroenamine (**8**)

The generated nitroenamine (**8**) in situ was easily trapped by cycloaddition. To a solution of adducts (**7**) in chloroform, equimolar methyl vinyl ketone was added, and the resultant solution was heated at 60 °C for 2 days. After concentration of the reaction mixture, the residue was subjected to silica gel column chromatography to afford 1-nitro-4-pyrrolidinobenzene (**14**)[7] in 28% yield (Scheme 6). In this reaction, dienamine (**15**) is generated from methyl vinyl ether and pyrrolidine in situ, which undergoes the cycloaddition with nitroenamine (**8**). However, side reactions of **8** also proceeded under heated conditions to diminish the reaction efficiency. Subsequent aromatization accompanied by elimination of pyrrolidine and air-oxidation furnishes nitroaniline (**14**).



Scheme 6. Cycloaddition of nitroenamine (**8**) and dienamine (**15**) leading to nitroaniline (**14**)

In summary, nitropyrimidinone (**1**) was found to obtain high reactivity upon treatment with pyrrolidine, which dearomatized adducts (**7**). Indeed, adducts (**7**) underwent the reaction with diethyl acetonedicarboxylate under mild conditions to afford bicyclic compound (**5a**). Furthermore, ring opening reaction leads to nitroenamine (**8**), which is converted to 1-nitro-4-pyrrolidinobenzene (**14**) in one-pot reaction. These results will be useful insights for researchers using less reactive aromatic heterocyclic compounds.

EXPERIMENTAL

Synthesis of amine-adduct (7)

To a solution of nitropyrimidinone (**1**, 15.5 mg, 0.1 mmol) in deuterated chloroform (0.4 mL), pyrrolidine (8 μL, 0.1 mmol) was added. The ^{1}H and ^{13}C NMR spectra showed the quantitative formation of adduct (**7**) as a mixture of regioisomers with 1:1 ratio, however, elimination of pyrrolidine easily occurred when the solution was concentrated to afford **1** again. Thus, the following NMR data were analyzed using a mixture of adducts (**7a**) and (**7b**). ^{1}H NMR (400 MHz, $CDCl_3$) 6-adduct (**7a**): δ 1.77 (br s, 4H), 2.67–2.78 (m, 4H), 3.09 (s, 3H), 5.69 (br s, 1H), 8.00 (br s, 1H); 4-adduct (**7b**): δ 1.77 (br s, 4H), 2.67–2.78 (m, 4H), 3.30 (s, 3H), 5.70 (br s, 1H), 8.00 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9 (CH_2), 24.5 (CH_2), 34.4 (CH_3), 36.2 (CH_3), 46.1 (CH_2), 47.3 (CH_2), 65.6 (CH), 71.2 (CH), 122.9 (C), 124.5 (C), 134.6 (CH), 139.2 (CH), 152.7 (C), 152.9 (C).

Synthesis of bicyclic compound (5a)

To a solution of nitropyrimidinone (**1**, 78 mg, 0.5 mmol) in $CHCl_3$ (6.5 mL), were added pyrrolidine (40 μL, 0.5 mmol) and diethyl acetonedicarboxylate (90 μL, 0.5 mmol), and the resultant mixture was stirred

at room temperature for 1 h. After washing with 1 M hydrochloric acid (10 mL × 1), the solvent was removed under reduced pressure. The residue was extracted with hexane (10 mL × 2), and concentrated to afford bicyclic compound (**5a**, 151.9 mg, 0.43 mmol, 86% yield)[2] as a white solid. Although formation of three diasteromers was confirmed in the ^{1}H NMR, these could not be separated and assigned because of similar property and spectra.

Aminolysis of nitropyrimidinone (1)

To a solution of nitropyrimidinone (**1**, 31 mg, 0.2 mmol) in $CHCl_3$ (2 mL), pyrrolidine (80 μL, 1.0 mmol) was added, and the resultant mixture was stood at room temperature for 7 d. After the solvent was removed under reduced pressure, the residue was subjected to column chromatography on silica gel to afford nitroenamine (**8**, 19 mg, 0.136 mmol, 68%, eluted with EtOAc) as a brown solid, and a mixture of *N*-formylpyrrolidine (**9**) and *N*-methylurea (**10**) (eluted with MeOH, the yields were determined by ^{1}H NMR).

Synthesis of nitroaniline (14)

To a solution of nitropyrimidinone (**1**, 31 mg, 0.2 mmol) in $CHCl_3$ (2 mL), pyrrolidine (80 μL, 1.0 mmol) was added, and the resultant mixture was heated at 60 °C for 1 d. Then, methyl vinyl ketone (40 μL, 0.4 mmol) was added, and the mixture was heated at 60 °C for 2 d. After the solvent was removed under reduced pressure, the residue was treated with column chromatography on silica gel to afford nitroaniline (**14**, eluted with hexane : EtOAc =1 : 1, 11 mg, 0.056 mmol, 28% yield)[7] as a yellow oil.

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