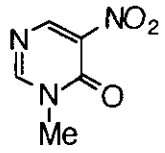
# NOVEL SYNTHESIS OF SUBSTITUTED PYRIMIDINES: A RING TRANSFORMATION OF 3-METHYL-5-NITROPYRIMIDIN-4(3*H*)-ONE

Nagatoshi Nishiwaki, Tomoko Matsunaga, Yasuo Tohda, and Masahiro Ariga*
Department of Chemistry, Osaka Kyoiku University,
Asahigaoka 4-698-1, Kashiwara, Osaka 582, Japan

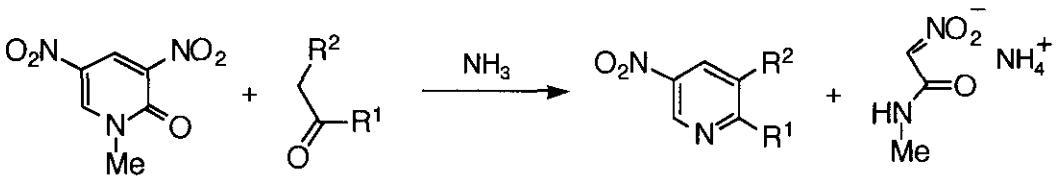
Abstract - A novel ring transformation of 3-methyl-5-nitropyrimidin-4(3*H*)-one with ketones in the presence of ammonia was found to be an elegant method for synthesizing 5,6-disubstituted pyrimidines. Tetrahydroquinazoline was readily obtained in good yields when cyclohexanone was employed as a substrate. The present reaction was applicable to cyclopentanone, acetophenone and *p*-nitroacetophenone to give the corresponding pyrimidine derivatives.

In heterocycles having the pyrimidine skeleton, there are many functional materials such as biologically active compounds. Pyrimidine rings have been generally constructed by the condensation of a C-C-C and a N-C-N units.[2] In the present paper, we provide a novel method for synthesis of pyrimidines including the condensation of a C-N-C and a C-C-N units, namely, nitropyrimidinone (**1**) plays a role of a precursor of the former and the carbonyl compounds and ammonia act as the latter. This type of general synthesis of pyrimidines has not been reported to our knowledge.




**1**

In our course of exploring the ring transformations of electron deficient pyridones, it was found that *N*-methyl-3,5-dinitro-2-pyridin-2(1*H*)-ones (**2**) would be an excellent precursor of 5,6-disubstituted 3-nitropyridines.[1]

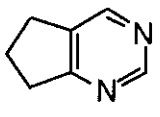


**2**

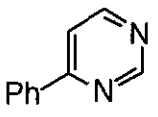
Nitropyrimidinone (**1**) was considered to show similar properties and reactivities to dinitropyridone (**2**). From these circumstances, the C(2)-N(1)-C(6) moiety of the 3-methyl-5-nitropyrimidin-4(3*H*)-one (**1**) is regarded as a synthetic equivalent of activated diformylamine and as a useful synthetic intermediate of 5,6-disubstituted pyrimidines.

3-Methyl-5-nitropyrimidin-4(3*H*)-one (**1**)[3] was easily prepared from 2-thiouracil by reduction,[4] methylation[4] and nitration with fuming $HNO_3$ in 18 *M* $H_2SO_4$ at 110 °C in 35 % overall yield. A solution of the nitropyrimidinone (**1**, 310 mg, 2.0 mmol) and cyclohexanone (393 mg, 4.0 mmol) in MeOH (40 ml) dissolving $NH_3$ gas (40 mmol) was heated at 100 °C in sealed tube for 3 h. MeOH was evaporated and the residual mixture was extracted with PhH (30 ml X 4). The organic layer was concentrated and was chromatographed on silica gel to give tetrahydroquinazoline[5] (**3**, 75 mg, 0.56 mmol, 28 %, eluted with PhH/AcOEt = 80/20) as a pale-yellow oil. A trace amount of *N*-methyl-α-nitroacetamide (**4**),[6] the other product of this ring transformation, was obtained together with methyl nitroacetate.

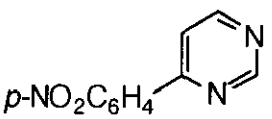
MeCN and MeOH were found to be suitable as solvents and 1-morpholino-1-cyclohexene showed similar reactivities to cyclohexanone in this ring transformation. The yield of quinazoline derivative (**3**) was raised to 85 % when the reaction was performed at 100 °C in a sealed tube, but a little carbonization was observed at higher temperature (> 120 °C). Pyrimidine derivatives (**5**),[5] (**6**)[7] and (**7**)[7] were also synthesized by utilizing cyclopentanone, acetophenone (or α-morpholinostylene) and *p*-nitroacetophenone as the substrates (Table).



**5**

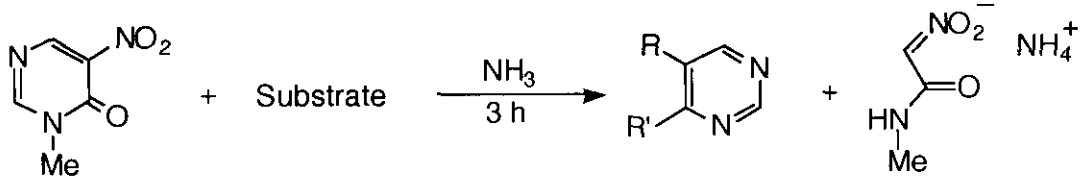


**6**



**7**

Table Ring Transformation of Nitropyrimidinone (**1**)




**1** **4**

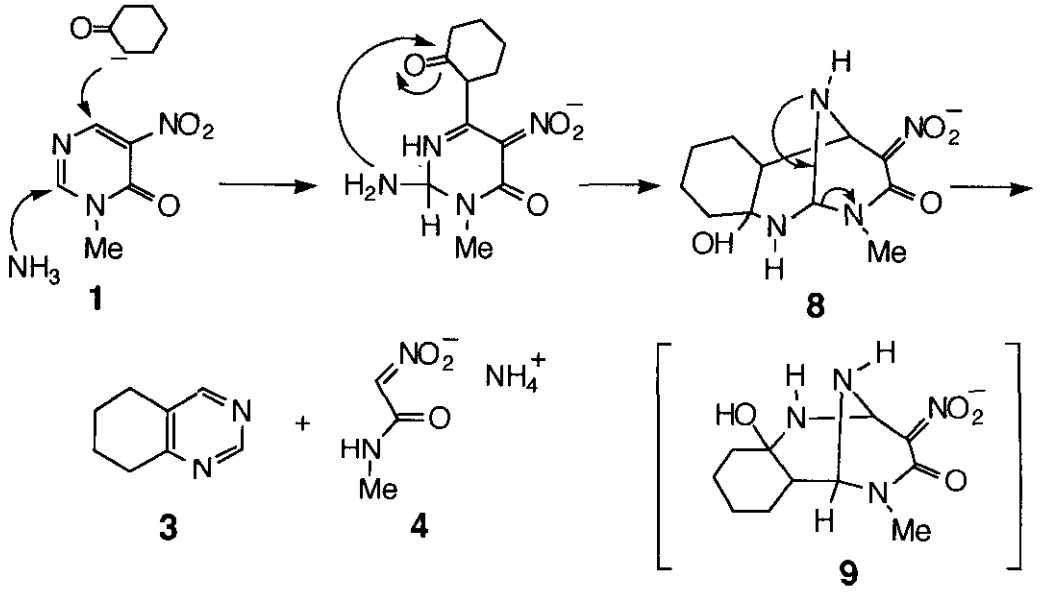
| run | Substrate | Solv. | Temp. (°C) | Product | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | A | MeOH | 65 | **3** | 45 |
| 2 | A | " | 100[b] | " | 54 |
| 3 | A | " | 120[b] | " | 29 |
| 4 | B | " | 65 | " | 55 |
| 5 | B | " | 100[b] | " | 71 |
| 6 | A | MeCN | " [b] | " | 85 |
| 7 | B | " | " [b] | " | 78 |
| 8 | C | " | " [b] | **5** | 31 |
| 9 | D | MeOH | 120[b] | **6** | 6 |
| 10 | E | MeCN | 100[b] | " | 25 |
| 11 | F | " | 130[b] | **7** | 14 |

Substrate A : Cyclohexanone, B : 1-Morpholinocyclohexene,
C : Cyclopentanone, D Acetophenone, E : α-Morpholinostylene,
F . *p*-Nitroacetophenone

a) by $^1$H-nmr b) in sealed tube

On the basis of the ring transformation of **2**, the present reaction was considered to proceed as follows. The bicyclic intermediate (**8**) or (**9**) was produced by intramolecular nucleophilic addition of the adduct of the nitropyrimidinone (**1**), cyclohexanone and ammonia. Nitroacetamide (**4**) was eliminated from these intermediates to give the substituted pyrimidine (**3**) (Scheme).

Scheme A Plausible Path



As mentioned above, a ring transformation of 3-methyl-5-nitropyrimidin-4(3*H*)-one (**1**) provided substituted pyrimidines. Although further investigations on the reaction conditions and the application to other carbonyl compounds are necessary, we considered that this reaction has a great possibility to be a valuable preparative method leading to various pyrimidines.

## REFERENCES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3. 3-Methyl-5-nitropyrimidin-4(3*H*)-one (**1**); yellow needles (from EtOH); mp 103-104 °C; ir (Nujol) 1685, 1522, 1359 $cm^{-1}$; $^1H$-nmr (60 MHz, $CDCl_3$) δ 3.63 (s, 3H), 8.38 (s, 1H), 8.84 (s, 1H).
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