FACILE SYNTHESIS OF FUNCTIONALIZED NITROENAMINES. II (1). RING OPENING REACTION OF HYDRATED 1-METHYL-5-NITROPYRIMIDIN-4(1*H*)-ONE

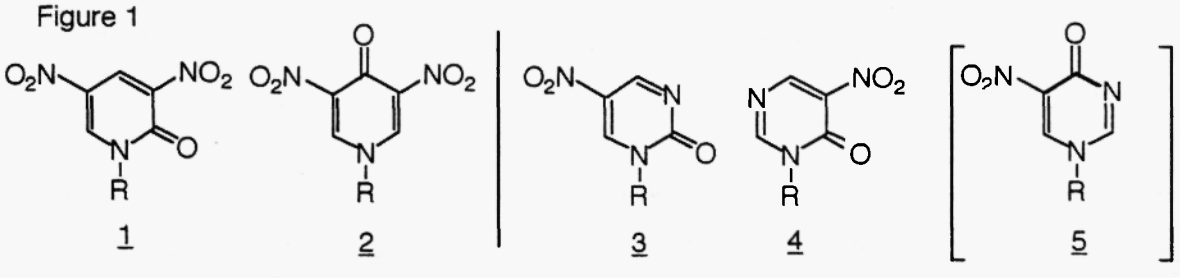
Nagatoshi Nishiwaki, Eriko Wakamura, Yukihiro Nishida, Yasuo Tohda and Masahiro Ariga*
Department of Chemistry, Osaka Kyoiku University,
Asahigaoka 4-698-1, Kashiwara, Osaka 582, Japan

Abstract: Three methods for synthesis of 1-methyl-5-nitropyrimidin-4(1*H*)-one 5a from 2-thiouracil 6 were investigated. It was found that the title compound 5a was readily hydrated and ring opening reaction proceeded to give nitroenamine 12a possessing a *N*-formylcarbamoyl group. Transformation of nitroenamine 12a to polysubstituted pyridin-2(1*H*)-one 13 was performed.

Introduction

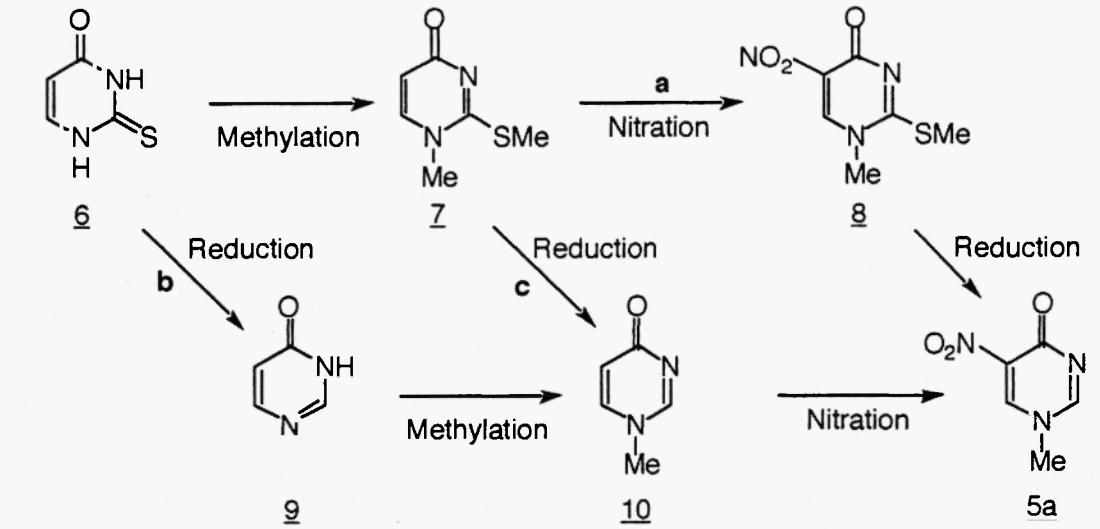
We have shown that the 1-substituted 3,5-dinitropyridin-2(1*H*)-ones 1 and -4(1*H*)-ones 2 are useful synthetic intermediates for polyfunctionalized systems (2, 3). Nitropyrimidinones 3 and 4 are the azahomologs of the former pyridones 1, and are also utilized for syntheses of various azaheterocycles (4, 5). While 1-substituted 5-nitropyrimidin-4(1*H*)-ones 5, the azahomologs of the latter pyridones 2, are hitherto unknown compounds to our best of knowledge (Figure 1).

Figure 1



In this paper, investigation on synthetic routes for 5a (R = Me) from commercially available 2-thiouracil 6 involving three different order of combination of reductive desulfurization, methylation and nitration was described (Scheme 1). We also wish to deal the chemical transformation of nitroenamines 12 obtained by the ring opening reaction of 5a.

Scheme 1



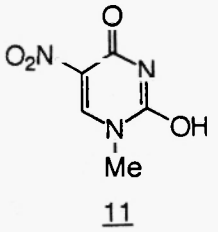
Results and Discussion

Method a

Methylation of thiouracil 6 with Me_2SO_4 was performed by Brown's method (6). 1-Methyl-2-methylthiopyrimidin-4(1*H*)-one 7 was effectively isolated in 48 % yield by the continuous extraction in addition to 2,3-dimethyl derivative (43 %) and 1,3-dimethyluracil (9 %).

Nitration of dimethylpyrimidinone 7 readily proceeded, but methylthio group at the 2-position was substituted by the hydroxy group to yield nitrouracil derivative 11 instead of 8 (Figure 2). To facilitate the elimination of the hydroxy group at the 2-position in the conversion to 5a, tosylation and acetylation of it were attempted. Nitrouracil 11 was too stable under the employed conditions (7) to be recovered. The other method for reduction at the 2-position of 11 are now under investigation.

Figure 2



11

Method b and c

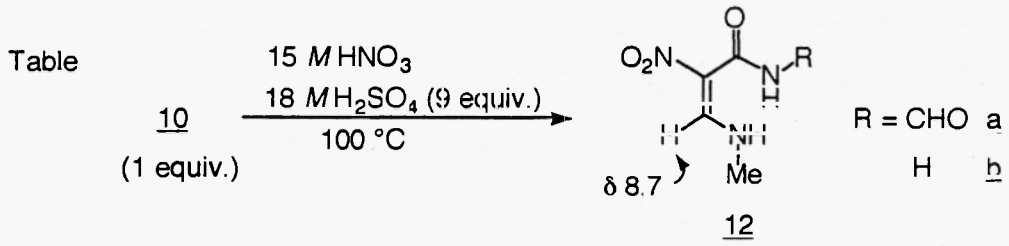
1-Methylpyrimidin-4(1*H*)-one 10 was obtained by methylation of pyrimidin-4(3*H*)-one 9 which was prepared by reduction of thiouracil 6 with Raney-Ni (8). It was reported that methylation of 9 affords two isomeric *N*-methylpyrimidinones, but desired 1-methyl derivative 10 is given in 5 % yield as the minor product (9). To promote the yield and selectivity of 10, reaction conditions (temperature, time, solvents, bases and methylating agents) were investigated. The yield of 10 could be raised to 23 % by dilution and by increasing molar ratio of base and MeI (10). Pyrimidinone 10 was obtained in 15 % yield based on 6 by method **b**.

As an alternative procedure to prepare pyrimidinone 10, dimethylated pyrimidinone 7 was desulfurized with Raney-Ni (method **c**). As a result, methylpyrimidinone 10 was afforded in 33 % yield based on 6 although it was not satisfactory yield.

Nitration of obtained methylpyrimidinone 10 was examined. Employment of NO_2BF_4, (HNO_3 + CF_3SO_3H) and fuming HNO_3 as nitrating agents caused no positive results and afforded only complex mixtures.

When the mixed acid (HNO_3 and H_2SO_4) was adopted, product 12a was isolated, whose empirical formula $C_5H_7N_3O_4$ was corresponded to the hydrated form of nitropyrimidinone 5a. The longer reaction time and the more HNO_3 gave the more product 12a (Table).

Table



HNO_3 / equiv.	Time / h	Yield of 12a / %
3.2	7	14 [a]
3.2	15	25
9.0	15	51

a) 10 was recovered in 65 % yield.

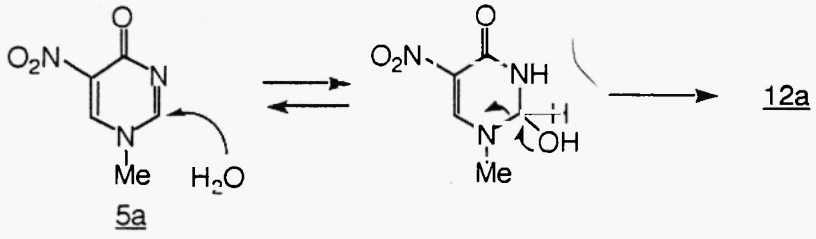
Functionalized Nitroenamines

During recrystalization, product 12a partially transformed into compound 12b whose empirical formula was $C_4H_7N_3O_3$. In the IR spectra of 12a, a pair of imide-type carbonyl absorptions (1716 and 1674 cm^{-1}) appeared, but only an absorption of conjugated amide was found at 1659 cm^{-1} in the case of 12b. Hence, it was concluded that compound 12b is the deformylated product of compound 12a. The quantitative conversion of 12a to 12b was also observed on heating under reflux in EtOH.

These two compounds showed doublet signals bearing large coupling constants (14.9 Hz) at δ 8.7 in the ^1H NMR. This means that the nitroenamine skeleton is contained in both of them (11, 12). Based on these spectral and analytical data, products 12a and 12b were determined as *N*-formyl-3-methylamino-2-nitropropenamide and 3-methylamino-2-nitropropenamide, respectively.

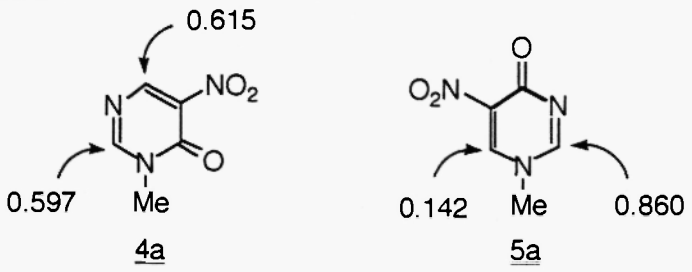
It is reasonable to consider that nitroenamine 12a was derived via temporally formed 5a as follows. Among the electrophilic 2, 4 and 6-positions of nitropyrimidinone 5a, the 2-position is attacked by H_2O since hydration at the other positions does not conduct 5a to 12a. The intermediate hydrated at the 2-position is so unstable that ring opening reaction easily occurs to furnish nitroenamine 12a (Scheme 2).

Scheme 2



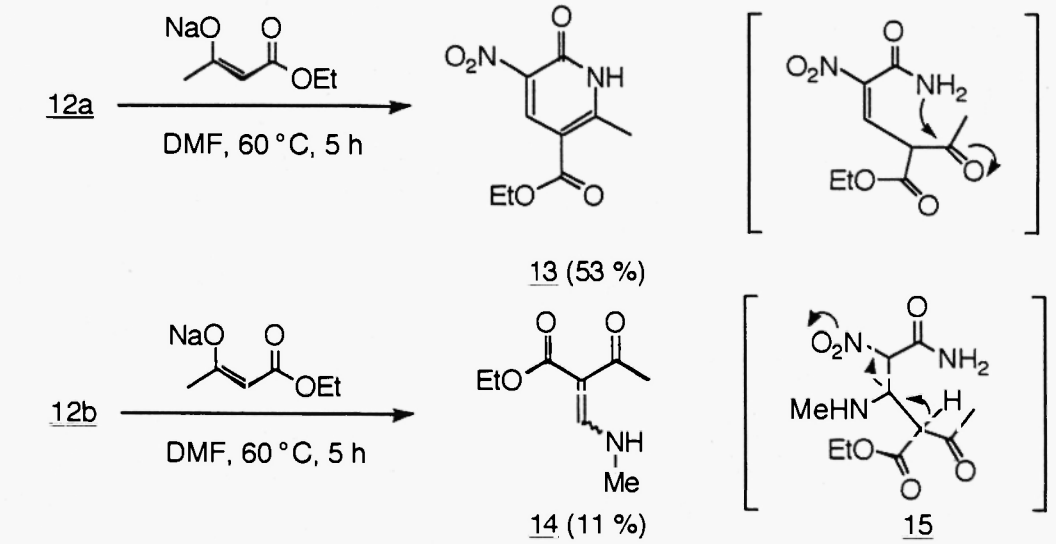
Nitropyrimidinones 3 and 4 are not hydrated under the conditions employed here though nitroenamine having a *N*-methaneimidoylcarbamoyl group was given by aminolysis of pyrimidinone 4 (1). The nucleophilic susceptibilities of 4a (R = Me) and 5a were estimated by the MOPAC (PM3) molecular orbital calculation using CAChe system (Figure 3). In the case of 4a, the 2- and 6-positions showed similar values indicating moderate electrophilicity. This is consistent with the fact that ring transformation readily proceeds when pyrimidinone 4a is reacted with bidentate nucleophiles (5). In contrast with 4a, the 2-position of 5a especially is highly electrophilic compared with other positions in the ring. This property would be a cause of unstability of 1-methyl-5-nitropyrimidin-4(1*H*)-one 5a. The present findings well explain the difference of reactivities between nitropyrimidinones 4 and 5.

Figure 3



In spite of high synthetic value of nitroenamines, facile methods to obtain functionalized ones have not been developed (13, 14). From this point of view, the present reaction would be a useful method for preparation of the functionalized enamines.

Equation



As an example of application of nitroenamines 12a and 12b, synthesis of the polysubstituted pyridone was studied. Nitroenamine 12a was reacted with the enolate ion of ethyl acetoacetate to yield 5-ethoxycarbonyl-6-methyl-3-nitropyridin-2(1*H*)-one 13. This product was formed by intramolecular cyclization after substitution of the *N*-methylamino group with the enolate ion. In contrast, treatment of 12b under the same conditions gave enamine 14, which was generated by loss of nitroacetamide from the Michael adduct 15 (Equation). It is, however, hard to conclude that the difference between 12a and 12b was shown in their reactivities since complex mixtures were formed in both reactions, and more detailed investigation would be necessary.

Some information about the reactivities of 1-substituted 5-nitropyrimidin-4(1*H*)-one 5 were obtained. Furthermore, the novel preparative method for functionalized nitroenamines 12a and 12b was found in the nitration of 1-methylpyrimidin-4(1*H*)-one 10.

Experimental

All melting points were determined on a Yanaco micro melting point apparatus and were uncorrected. IR spectra were recorded on a Horiba FT-200 infrared spectrometer and ^{1}H NMR spectra were obtained on a Hitachi NMR R-1200 at 60 MHz. Elemental microanalyses were performed using a Yanaco MT-3 CHN corder and all values were within ±0.4 % of the calculated values.

2-Hydroxy-1-methyl-5-nitropyrimidin-4(1H)-one 11 :

A solution of pyrimidinone (7, 2.0 g, 12.8 mmol) in fuming HNO_3 (10 ml, 104 mmol) was heated at 70 °C for 11 hours. After the reaction mixture was poured onto crushed ice (10 g), crystalline precipitates were collected by filtration, and recrystalized from H_2O to afford pyrimidinone (11, 1.72 g, 10.0 mmol, 79 %) as colorless needles. mp: 273-275 °C; IR (Nujol / cm^{-1}) 1701, 1507, 1316; ^{1}H NMR (d_6-DMSO) δ 3.32 (s, 3H), 9.35 (s, 1H), 11.9-12.2 (br, 1H); Anal. Calcd. for $C_5H_5N_3O_4$ C: 35.10, H: 2.95, N: 24.56; Found C: 34.95, H: 2.83, N: 24.51.

N-Formyl-3-methylamino-2-nitropropenamide 12a :

To a solution of methylpyrimidinone (10, 1.0 g, 9.1 mmol) in 18 *M* H_2SO_4 (4.5 ml, 81 mmol), 15 *M* HNO_3 (5.4 ml, 81 mmol) was added on a ice bath. The solution was heated at 100 °C for 15 hours. After the reaction mixture was poured onto crushed ice (10 g), the solution was adjusted at pH 3 with Na_2CO_3. Insoluble materials were filtered off, the filtrate was extracted with $CHCl_3$ (100 ml X 4). The organic layer was dried over ($MgSO_4$), and concentrated. The residue was recrystalized from EtOH to afford nitroenamine (12a, 0.80 g, 4.6 mmol, 51 %) as colorless needles. mp: 199-201 °C; IR (Nujol / cm^{-1}) 3270, 3199, 1716, 1674, 1495, 1344; ^{1}H NMR (d_6-DMSO) δ 3.31 (d, J = 5.0 Hz, 3H), 8.74 (d, J = 14.9 Hz, 1H), 9.28 (d, J = 10.0 Hz, 1H), 10.0-11.3 (br, 2H); Anal. Calcd. for $C_5H_7N_3O_4$ C: 34.69, H: 4.08, N: 24.27; Found C: 34.92, H: 4.02, N: 24.50.

3-Methylamino-2-nitropropenamide 12b:

A solution of nitroenamine (12a, 85 mg, 0.5 mmol) in EtOH (10 ml) was heated for 7 hours under reflux. The solution was concentrated to afford nitroenamine (12b, 73 mg, 0.5 mmol, quant.) as pale yellow needles. mp: 188-189 °C; IR (Nujol / cm^{-1}) 3394, 3246, 1659, 1466, 1359; ^{1}H NMR (d_6-DMSO) δ 3.26 (d, J = 5.3 Hz,

3H), 7.2-7.7 (br, 1H), 7.8-8.4 (br, 1H), 8.68 (d, J = 14.9 Hz, 1H), 9.9-11.0 (br, 1H); Anal. Calcd. for $C_4H_7N_3O_3$ C: 33.10, H: 4.87, N: 28.96; Found C: 33.15, H: 4.79, N: 28.66.

5-Ethoxycarbonyl-6-methyl-3-nitropyridin-2(1H)-one 13:

To a solution of nitroenamine (12a, 300 mg, 1.7 mmol) in DMF (20 ml), a solution of sodium enolate of ethyl acetoacetate (2.1 mmol) in DMF (30 ml) was added at room temperature. The solution was heated at 60 °C for 5 hours. After the solvent was removed under reduced pressure, the residue was adjusted at pH 3 with 1 *M* HCl. Insoluble materials were filtered off, the filtrate was extracted with $CHCl_3$ (40 ml X 4). The organic layer was dried over ($MgSO_4$), and concentrated. The residue was chromatographed on SiO_2 column to afford pyridone (13, 205 mg, 0.91 mmol, 53 %, eluted with AcOEt) as colorless needles. mp: 219-220 °C; IR (Nujol / cm^{-1}) 1716, 1686, 1572, 1329; ^1H NMR ($CDCl_3$) δ 1.43 (t, J = 7.3 Hz, 3H), 2.92 (s, 3H), 4.44 (q, J = 7.3 Hz, 2H), 9.15 (s, 1H), 12.2-13.7 (br, 1H); Anal. Calcd. for $C_9H_{10}N_2O_5$ C: 47.79, H: 4.46, N: 12.39; Found C: 47.58, H: 4.45, N: 12.15.

References and Notes

(1) N. Nishiwaki, Y. Mizukawa, M. Ohta, R. Terai, Y. Tohda, M. Ariga, Heterocycl. Comm. in press
(2) M. Ariga, Y. Tohda, H. Nakashima, K. Tani, Y. Mori, E. Matsumura, Bull. Chem. Soc. Jpn. 64, 3544 (1991)
(3) Y. Tohda, M. Eiraku, T. Nakagawa, Y. Usami, M. Ariga, T. Kawashima, K. Tani, H. Watanabe, Y. Mori, Bull. Chem. Soc. Jpn. 63, 2820 (1990)
(4) J. J. Fox, T.-L. Su, L. M. Stempel, K. A. Watanabe, J. Org. Chem. 47, 1081 (1982)
(5) N. Nishiwaki, T. Matsunaga, Y. Tohda, M. Ariga, Heterocycles 38, 249 (1994)
(6) D. J. Brown, J. Chem. Soc., 211 (1955); 7 was obtained in 37 % yield.
(7) Tosylation; heated with tosyl chloride at 80 °C for 1 h in pyridine. Acetylation; treated with acetyl chloride in the presence of NEt_3 at room temperature for 3 h in DMF.
(8) D. J. Brown, J. Soc. Chem. Ind. 69, 353 (1950)
(9) L. Bauer, G. E. Wright, B. A. Mikrut, C. L. Bell, J. Heterocycl. Chem. 2, 447 (1965)
(10) Molar ratio and amount of EtOH described in the literature (9); 9 : KOH : MeI = 1 : 1 : 1.1, 0.75 ml / 1 mmol of 9. In the present work; 9 : KOH : MeI = 1 : 1.5 : 1.7, 2.0 ml / 1 mmol of 9.
(11) C. D. Bedford, A. T. Nielsen, J. Org. Chem. 44, 633 (1979)
(12) A. I. Fetell, H. Feuer, J. Org. Chem. 43, 497 (1978)
(13) V. V. Perekalin, E. S. Lipina, V. M. Berestovitskaya, D. A. Efremov, Nitroalkenes, Conjugated Nitro Compounds, Wiley, New York, 1994, pp 210-231
(14) S. Rajappa, Tetrahedron 37, 1453 (1981)

Received September 25, 1995