N-HYDROXYAMIDE-CONTAINING HETEROCYCLES. PART 3.[1] THE RING TRANSFORMATION OF 1-BENZYLOXY-2(1*H*)-PYRIMIDINONES INTO 2-ISOXAZOLINES WITH HYDROXYLAMINE+

Akira Katoh,* Junko Ohkanda, Atsushi Tamura, Yuji Yoshiike, and Keiryo Mitsuhashi

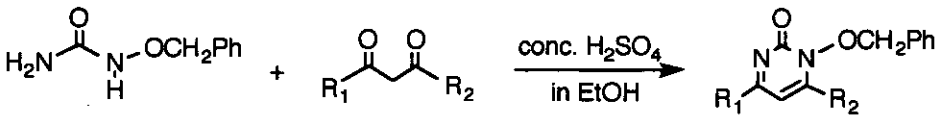
Department of Industrial Chemistry, Faculty of Engineering, Seikei University, Musashino, Tokyo, 180, Japan

Abstract --- *N*-Benzyloxyurea was treated with various β-diketones in the presence of sulfuric acid in EtOH to give the corresponding 1-benzyloxy-2(1*H*)-pyrimidinones. 1-Benzyloxy-2(1*H*)-pyrimidinones underwent the ring transformation with hydroxylamine to afford new 5-*N*-(benzyloxy)urea-attached 2-isoxazolines in addition to known isoxazoles. The MNDO molecular orbital calculation of 1-benzyloxy-4,6-dimethyl-2(1*H*)-pyrimidinone and the reaction mechanism are also discussed.

The synthesis of a variety of new heterocycles by the ring transformation of easily accessible heterocycles has been received considerable attention, and a number of papers have appeared in the literatures.[2,3] Recently, we have investigated the application of *N*-hydroxyamide-containing heterocycles to the peptide synthesis[4] and the property of their iron(III) complexes.[1] It has been reported that the ring transformation of 1-aryl-2(1*H*)-pyrimidinones with hydroxylamine afforded the corresponding isoxazoles in good yields.[5] The replacement of the aryl group at N-1 position of the pyrimidinone ring by the electron-withdrawing benzyloxy one would be expected to change the reactivity toward the nucleophile. In the course of our studies on *N*-hydroxyamide-containing heterocycles, we describe here the preparation of 1-benzyloxy-2(1*H*)-pyrimidinones and their ring transformation with hydroxylamine.

+Dedicated to Professor Alan R. Katritzky, University of Florida, on the occasion of his 65 th birthday.

1-Benzyloxy-2(1*H*)-pyrimidinones (**II**) were obtained by the condensation of *N*-benzyloxyurea and β-diketones under acidic conditions as shown in Scheme 1. The reaction with acetoacetaldehyde dimethylacetal gave a mixture of two structural isomers (**IIb** and **IIc**),[1] while 2,4-hexanedione afforded only one isomer, 1-benzyloxy-4-ethyl-6-methyl-2(1*H*)-pyrimidinone (**IId**).

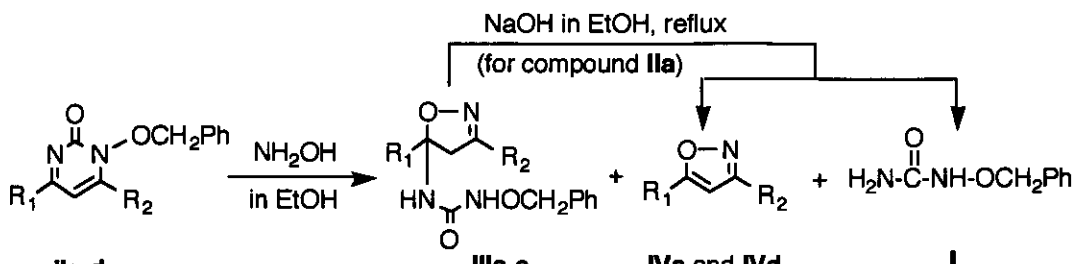


I **IIa-d**

IIa: R_1=R_2=Me (48%) **IIb**: R_1=Me, R_2=H (15%)
IIc: R_1=H, R_2=Me (6%) **IId**: R_1=Et, R_2=Me (19%)

Scheme 1

When 1-benzyloxy-4,6-dimethyl-2(1*H*)-pyrimidinone (**IIa**) was allowed to react with hydroxylamine hydrochloride in the presence of NaOH in abs. EtOH under reflux conditions, 5-*N*-(benzyloxy)urea-attached 2-isoxazoline (**IIIa**) was isolated at the first time in a 24% yield in addition to already known 3,5-dimethylisoxazole (**IVa**) and *N*-benzyloxyurea (**I**). The structure of **IIIa** was determined by ir, ^{1}H and ^{13}C nmr, and the elemental analysis. The C-4 methylene protons appeared as double doublets at 2.82 and 3.43 ppm having 18 Hz coupling constant. Two N-H protons of the urea moiety appeared separately at 6.02 and 7.03 ppm, both of which are D_2O exchangeable. Further, the 2-isoxazoline (**IIIa**) was converted into 3,5-dimethylisoxazole and *N*-benzyloxyurea upon refluxing the solution in the presence of NaOH in abs. EtOH, indicating that 2-isoxazoline(**IIIa**)is the reaction intermediate of the isoxazole. Similarly, 1-benzyloxy-4-methyl- (**IIb**) and 1-benzyloxy-6-methyl-2(1*H*)-pyrimidinones (**IIc**) underwent the ring transformation to afford 2-isoxazoline derivatives (**IIIb** and **IIIc**) in 15 and 24% yields, respectively (Scheme 2).



IIa-d **IIIa-c** **IVa** and **IVd** **I**

Scheme 2

On the reaction with 2(1*H*)-pyrimidinone (**IId**), the desired 2-isoxazoline could not be isolated. In ^{1}H nmr spectrum, however, one of two possible structural isomers of isoxazole, *i. e.*, 3-methyl-5-ethylisoxazole (**IVd**),[6,7] was detected in the crude reaction mixture, suggesting that hydroxylamine attacks regioselectively C-6 carbon of the pyrimidinone ring.

The LUMO coefficients of 1-benzyloxy-4,6-dimethyl-2(1*H*)-pyrimidinone (**IIa**) were estimated by the MNDO molecular orbital calculation, indicating that the LUMO coefficient of C-6 position is greater than that of C-4 one. (Figure 1)[8] Thus, the nucleophile was expected to attack preferentially C-6 carbon rather than C-4 one.

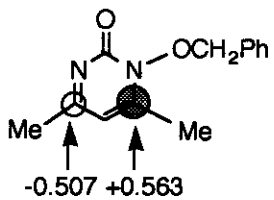
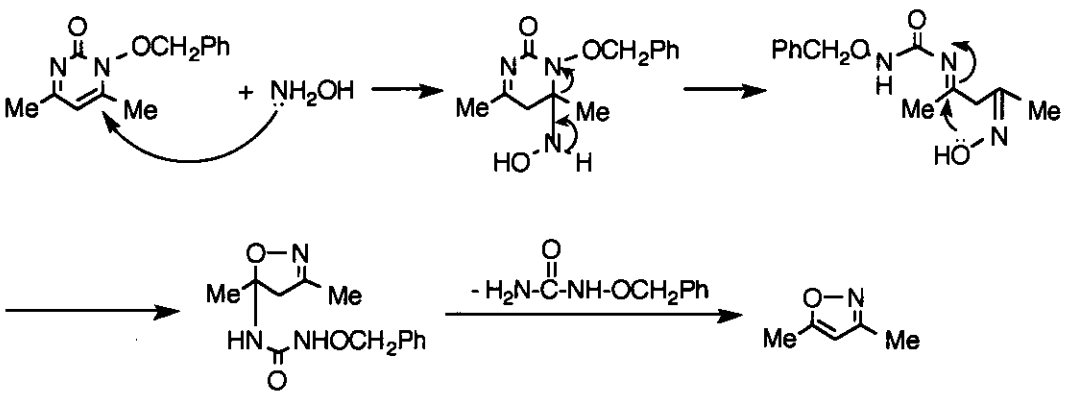


Figure 1. Estimated LUMO Coefficients by the MNDO Method

From these data, a reasonable reaction mechanism for the ring transformation are depicted in Scheme 3. A nitrogen lone pair of electron of hydroxylamine attacks predominantly C-6 position, and then the ring opening occurrs. The attack of a lone pair of oxygen at the imino carbon yields the 2-isoxazoline. The elimination of *N*-benzyloxyurea from 2-isoxazoline affords 3,5-dimethylisoxazole.



Scheme 3

In conclusion, 1-benzyloxy-2(1*H*)-pyrimidinones underwent the ring transformation with hydroxylamine to give new 5-*N*-(benzyloxy)urea-attached 2-isoxazolines.

EXPERIMENTAL

Melting points were taken on a Mel-Temp apparatus in open capillaries and are uncorrected. Ir and uv spectra were recorded on a JASCO A-100 and a Ubest-50 spectrophotometers, respectively. ^{1}H and ^{13}C nmr spectra were obtained on a JEOL GX-270 spectrometer and are reported in ppm (δ) downfield from internal Me_4Si. Thin layer chromatography (tlc) analysis was performed on a silica gel 60F-254 with a 0.2 mm layer thickness. Column chromatography was carried out with Merck Kieselgel 60 (230-400 mesh). Combustion analysis was performed on a Yanaco MT-3 CHN corder. *N*-Benzyloxyurea (**I**) was prepared according to the literature.[9,10] 1-Benzyloxy-4,6-dimethyl-2(1*H*)-pyrimidinone (**IIa**), 1-benzyloxy-4-methyl- (**IIb**) and 1-benzyloxy-6-methyl-2(1*H*)-pyrimidinone (**IIc**) were also prepared according to the literature.[1]

1-Benzyloxy-4-ethyl-6-methyl-2(1*H*)-pyrimidinone (IId): To a solution of *N*-benzyloxyurea (**I**) (1.66 g, 10 mmol) and 2,4-hexanedione (1.42 g, 12 mmol) in EtOH (15 ml) was added conc. H_2SO_4 (1.2 ml) cautiously at room temperature. The reaction mixture was refluxed for 2 h. After evaporation of the solvent, H_2O (10 ml) was added to the residue. The aqueous solution was adjusted to pH 10 with 4N NaOH solution and then extracted with $CHCl_3$ (80 ml x 3). The organic layer was washed with H_2O (60 ml), saturated NaCl solution (60 ml), and then dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel with AcOEt to give the product (**IId**, 0.19 g) in a 19% yield, mp 105-108 °C; uv λ_{max} (log ε in EtOH): 205 (4.27) and 305 nm (3.83); ir (KBr): υ_{max} 1660 cm^{-1} (C=O); ^{1}H nmr ($CDCl_3$): δ 1.24 (3H, t, J=7 Hz, 4-$CH_2\underline{CH_3}$), 2.12 (3H, s, 6-CH_3), 2.58 (2H, q, J=7 Hz, 4-$\underline{CH_2}CH_3$), 5.31 (2H, -OCH_2Ph), 5.94 (1H, s, 5-H), and 7.37-7.45 ppm (5H, m, Ph). *Anal.* Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.55; H, 6.65; N, 11.39.

Reaction of 2(1*H*)-Pyrimidinone (IIa) with Hydroxylamine: A mixture of 1-benzyloxy-4,6-dimethyl-2(1*H*)-pyrimidinone (**IIa**) (368 mg, 1.6 mmol), hydroxylamine hydrochloride (665 mg, 9.6 mmol), and NaOH (405 mg, 9.6 mmol) in abs EtOH (30 ml) was refluxed for 21 h. After removal of the solvent, the residue was dissolved in H_2O (50 ml) and extracted with $CHCl_3$ (100 ml). The organic layer was washed with H_2O (50 ml) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel with $CHCl_3$:acetone:EtOH (100:5:1) mixture to give

N-benzyloxy-*N'*-(3,5-dimethyl-2-isoxazolin-5-yl)urea (**IIIa**); R_f=0.26; mp 93-94 °C; λ_{max} (log ε in EtOH): 207 (4.07) and 258 nm (2.16); ir (KBr) υ_{max}: 3200, 1660, 1533, 754, and 711 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.63 (3H, s, 5-CH_3), 1.97 (3H, s, 3-CH_3), 2.82 and 3.43 (2H, dd, J=18 Hz, 4-CH_2), 4.77 (2H, s, -OC$\underline{H_2}$Ph), 6.02 (1H, br s, D_2O exchangeable, NH), 7.03 (1H, br s, D_2O exchangeable, NH), and 7.40 ppm (5H, m, Ph); ^{13}C nmr ($CDCl_3$) δ: 13.2 (q), 25.6 (q), 49.0 (t), 78.7 (t), 92.1 (s), 128.8 (d), 129.0 (s), 129.4 (d), 135.3 (s), 156.9 (s), and 158.2 ppm (d). *Anal.* Calcd for $C_{13}H_{17}N_3O_3$: C, 59.32; H, 6.46; N, 15.70. Found: C, 59.32; H, 6.49; N, 15.69. 3,5-Dimethylisoxazole (**IVa**) and *N*-benzyloxyurea (**I**) were identified with authentic samples by ^1H nmr and the mixed melting method, respectively.

***N*-Benzyloxy-*N'*-(5-methyl-2-isoxazolin-5-yl)urea (IIIb)**:[11] a viscous oil; R_f=0.4 [$CHCl_3$:acetone:-EtOH (100:10:2)]; yield: 15%; ir (neat) υ_{max} 1691, 1520, 775, and 741 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.65 (3H, s, 5-CH_3), 2.85 and 3.54 (2H, dd, J=18 Hz, 4-CH_2), 4.78 (2H, s, -OC$\underline{H_2}$Ph), 6.01 (1H, br s, NH), 6.95 (1H, br s, NH), 7.16 (1H, s, 3-H), and 7.35-7.45 ppm (5H, m, Ph).

***N*-Benzyloxy-*N'*-(3-methyl-2-isoxazolin-5-yl)urea (IIIc)**:[11] a viscous oil; R_f=0.32 [$CHCl_3$:acetone:-EtOH (100:10:2)]; yield: 24%; ir (neat) υ_{max} 1691, 1522, 781, and 737 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.02 (3H, s, 3-CH_3), 2.48-2.58 (1H, dd, J=5 and 17 Hz, 4-CH_2), 3.15-3.25 (1H, dd, J=8 and 17 Hz, 4-CH_2), 4.76 and 4.85 (2H, dd, J=11 Hz, -OC$\underline{H_2}$Ph), 6.1-6.2 (2H, m, NH and 5-H), 7.07 (1H, br s, NH), and 7.3-7.5 ppm (5H, m, Ph).

REFERENCES AND NOTES

1. Part 2. J. Ohkanda, T. Tokumitsu, K. Mitsuhashi, and A. Katoh, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 841.
2. H. C. van der Plas, in "*Ring Transformations of Heterocycles*", Vol.1 and 2, Academic Press, New York, 1973.
3. A. Katoh, T. Nishio, and C. Kashima, *Heterocycles*, 1987, **26**, 2223 and references cited therein.
4. A. Katoh, J. Ohkanda, Y. Itoh, and K. Mitsuhashi, *Chem. Lett.*, 1992, 2009.
5. C. Kashima, A. Katoh, Y. Yokota, and Y. Omote, *Chem. Pharm. Bull.*, 1981, **29**, 2516.

6. C. Kashima, S. Tobe, N. Sugiyama, and M. Yamamoto, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 310.
7. H. Feuer and S. Markofsky, *J. Org. Chem.*, 1964, **29**, 935.
8. MOPAC Ver.5.00 (QCPE No. 445): J. J. Stewart, *QCPE Bull.*, 1989, **9**, 10; T. Hirano, *JCPE Newsletter*, 1989, **1**, 36; Revised as Ver.5.01 by J. Toyoda, for Apple Macintosh.
9. J. I. G. Cadogan and A. G. Rouley, *Synth. Commun.*, 1977, 365.
10. Y. Endo, K. Shudo, and T. Okamoto, *Synthesis*, 1980, 461.
11. An attempt to purify products (**IIIb** and **IIIc**) by column chromatography was unsuccessful due to their partial decomposition.

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