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Regioselective N-nitrosation of dihydropyrimidinones with nitric oxide

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Abstract

N-Nitrosation of dihydropyrimidinones with nitric oxide occurred regioselectively, giving the corresponding N(3)-nitrosamides in high yields. The reaction most likely took place by a nucleophilic attack. Aprotic and polar solvents, such as CH_3CN and tetrahydrofurane (THF) greatly favored the reaction, whereas protic solvents with high dielectric constant, such as CH_3OH and water, disfavored it.

N-Nitroso compounds, in general, possess intriguing properties with an impact on medicine and biochemistry.[1] As such, it seems to be important to understand the formation mechanism for *N*-nitrosamines/amides. These compounds are traditionally prepared by the reaction of secondary amines/amides with nitrous acid formed in situ in aqueous acidic media,[2,3] where nitrosonium ion (H_2ONO^+, protonated nitrous acid) nitrosates secondary amines/amides via a series of proton/nitrosonium transfers. New approaches for the N-nitrosation of secondary and tertiary amines and amides using the complex [NO^+·Crown·H(NO_3)$^-$], a mixture of tin(IV) chloride and sodium nitrate, and PVP–N_2O_4 were reported.[4]

In conjunction with our continuing interest in reactions of nitric oxide (NO) with various organic molecules,[5] we recently found that NO nitrosated one of the secondary *N*-amido groups of dihydropyrimidinones, in which there were two different kinds of secondary *N*-amido groups, in high regioselectivity and in high yield. Itoh et al. studied the reaction of nitric oxide with amines[6] and amides[7] and different products were obtained. The reaction mechanism was assumed to be an N_2O_3-mediated hydrogen abstraction from the NH group. Calculations on the N-nitrosation of amines by NO_2 and NO, respectively, in various media such as alkaline solution, lipid, and gas phase suggested a free radical mechanism, in which NO_2 abstracted a hydrogen atom from the nitrogen of primary/secondary amines to form an intermediate complex of an aminyl radical and nitrous acid. The aminyl radical was then quenched by nitric oxide, leading to the formation of nitrosamine.[8] In the present work, yet, the reaction mechanism seems to take place by a nucleophilic attack of the nitrogen of an amine on N_2O_3.

In a typical procedure, 0.25 mmol of **1**, which was prepared following the method described in Ref. 9, was dissolved in 40 mL of dry CH_3CN at ambient temperature. The resulting solution was then degassed for 20 min. NO was carried by argon and purified by passing it through a series of scrubbing flasks containing 4 M NaOH, distilled water, and $CaCl_2$ in this order. Purified NO was bubbled through the stirred stock solution. In 3–5 h, after completion of the reaction, as indicated by TLC, evaporation of solvent gave almost pure product **2** in high yield (Scheme 1). Product **2** was further purified by column chromatography on silica gel and characterized by ^1H and ^{13}C NMR, MS, HRMS, and 1D NOE experiments with comparison to those of the mother molecules.[10] No side product was detected. The results are listed in Table 1.

Table 1 indicates that the nitrosation occurred regiospecifically at N(3). This observation may be rationalized in terms of the higher nucleophilic strength of N(3) compared to N(1), owing to a higher electron-withdrawing inductive effect on N(1) caused by both of a double carbon–carbon bond and a carbonyl group. This standpoint can be

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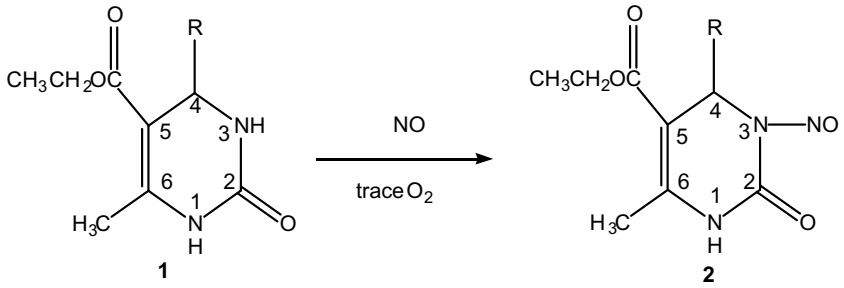


Scheme 1.

Table 1
Reaction of dihydropyrimidinones with NO in CH_3CN at ambient temperature

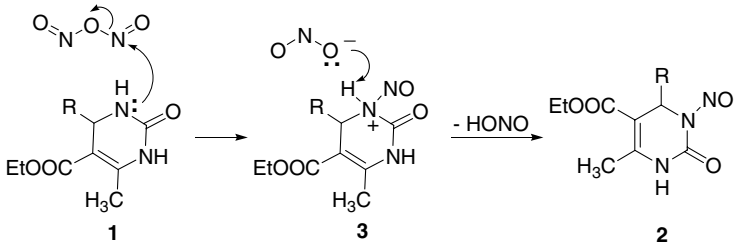
Substrate	R	Yield of **2** (%)
1a	4′-(OMe)–C_6H_4	95
1b	4′-(Cl)–C_6H_4	93
1c	4′-(NO_2)–C_6H_4	91
1d	Ph	93
1e		95
1f	*iso*-Butyl	94
1g	*n*-Propyl	94
1h	*iso*-Propyl	95
1i	Ethyl	94
1j	H	95
1k	PhCH=CH	0
1l	$(CH_3)_2C$=CH	0

supported by ^1H NMR spectra of the substrate. ^1H NMR peak of N(1)–H of **1a** locates downfield at 9.17 ppm, whereas that of N(3)–H highfield at 5.09 ppm. This reveals that the reaction proceeds most likely via a nucleophilic mechanism. Otherwise, the nitrosation proceeded smoothly when R is aryl or alkyl, whereas no reaction occurred when R was a vinyl as in the cases of **1k** and **1l**. The exceptions may be attributed to the lowering nucleophilicity of N(3) caused by a vinyl directly linked to C(4). A vinyl will exhibit a stronger electron-withdrawing inductive effect on N(3) than that of a phenyl. In addition, it is worth pointing out that the CH–N(NO) protons exhibited no diastereotopic nature in their ^1H NMR spectra.[5e,11]

In the reaction using NO as a reagent, there has been always a problem that the true active species is unidentified. In our experiments, we found no reaction occurred when the system was absolutely protected from air. Pires[12] and Lewis[13] studied the NO/O_2 system in the presence of phenol and morpholine, respectively, and concluded that N_2O_3 was the nitrosating entity. NO is readily oxidized by oxygen to NO_2 and then converted to N_2O_3.[14] Displacement of the good leaving group nitrite (^-ONO) from N_2O_3 by the Lewis base N(3) of dihydropyrimidinone with a stronger nucleophilicity leads to the formation of **3** (Scheme 2). Intermediate **3** then undergoes a deprotonation to give end product **2**.

The solvent effects on product yields were examined using **1a** as a substrate (Table 2) in various solvents, including: (a) aprotic and nonpolar solvents such as CCl_4, $N(C_2H_5)_3$, and benzene; (b) aprotic and polar solvents such as THF, CH_2Cl_2, and CH_3CN; and (c) protic solvents with high dielectric constant such as CH_3OH and H_2O.

Table 2 indicates that nonpolar solvents such as CCl_4 and $N(C_2H_5)_3$, in which dihydropyrimidinones and NO may be less soluble, disfavored the nitrosation, whereas aprotic, polar, and weakly nucleophilic solvents such as CH_3CN and THF, in which dihydropyrimidinones and NO may be relatively soluble, favored the reaction. Polar solvents can stabilize ions through a charge dispersion interaction. The more important role of polar solvents is to form hydrogen bonds between *N*-amido hydrogen and solvent, which will enhance the nucleophilicity of *N*-amido.[15] Although protic solvents with high dielectric constant such as CH_3OH and H_2O more favored the hydrogen bonding, but the reaction did not occur. It may be rationalized by a stronger hydrogen bonding (Scheme 3), which blocks N_2O_3 approaching N(3) of **1**. As such, the substrate molecule most likely undergoes a nucleophilic attack on N_2O_3, unlike a free radical mechanism. If not, it would afford N(1)-nitrosoamides instead of N(3)-nitroso

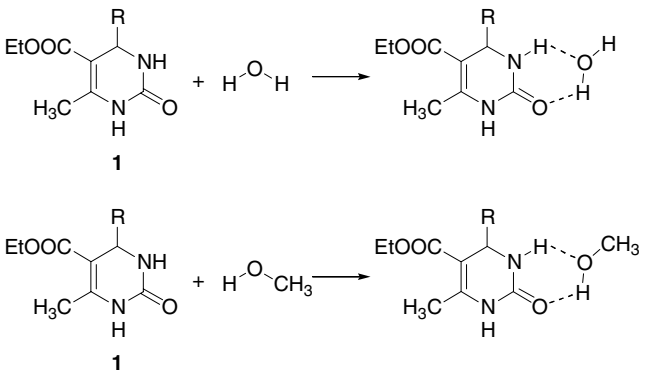


Scheme 2.

Table 2
Solvent effects on the reaction of **1a** with NO[a]

Solvent	Conversion (%)	Yield of **2** (%)
CCl_4	0	0
$N(C_2H_5)_3$	0	0
Benzene	75	73
THF	>99	93
CH_2Cl_2	90	88
CH_3CN	>99	94
CH_3OH	0	0
H_2O	0	0

[a] All the reactions were carried out with 0.15 mmol of **1a** in 20 mL solvent for 3 h.



Scheme 3.

compounds because N(1)-aminyl radical intermediate complex is more stable than N(3)-aminyl radical intermediate complex due to a large conjugated system.

In conclusion, we present herein an approach for regioselective N-nitrosation of dihydropyrimidinons with NO. Its main advantages are readily available starting materials, convenient performance under mild conditions and high yields.

Acknowledgment

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9. Ranu, B. C.; Hajra, A.; Dey, S. S. *Org. Process Res. Dev.* **2002**, *6*, 817. *Data for* **1a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, t, $J = 7.0$ Hz), 2.24 (3H, s), 3.71 (3H, s), 3.98 (2H, q, $J = 7.0$ Hz), 5.09 (1H, s, N(3)–H), 6.88 (2H, d, $J = 8.5$ Hz), 7.15 (2H, d, $J = 8.6$ Hz), 7.68 (1H, s), 9.17 (1H, s, N(1)–H).
10. *Data for representative products* **2a**: Yellow solid, mp 192–193 °C; IR (KBr) ν_{max} 3256, 3159, 2976, 1741, 1709, 1648, 1510, 1385, 1304, 1243, 1202, 1097, 1026, 835, 792, 653 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (3H, t, $J = 7.2$ Hz), 2.51 (3H, s, CH_3), 3.78 (3H, s), 4.13 (2H, q, $J = 7.2$ Hz), 6.45 (1H, s), 6.79 (2H, d, $J = 8.6$ Hz), 7.24 (2H, d, $J = 8.6$ Hz), 8.54 (1H, s, N(1)–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.05, 18.26, 53.50, 55.19, 60.73, 106.14, 113.93, 128.68, 129.80, 143.93, 150.51, 159.54, 164.19; MS (EI, 70 eV) *m*/*z* 319 (M^+), 289, 261, 217, 183, 137, 134, 119, 110, 103, 89, 77; HR-ESI-MS *m*/*z* calcd for $C_{15}H_{18}N_3O_5$ (M+Na) 342.1060, found: 342.1058. 1D NOE: Irradiation of CH_3 proton at δ 2.51 enhanced N(1)–H proton at δ 8.54 by 7%. Compound **2f**: Yellow solid, mp 150–151 °C; IR (KBr) ν_{max} 3242, 3140, 2967, 2878, 1722, 1646, 1541, 1391, 1310, 1249, 1219, 1086, 1024, 991, 771 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, d, $J = 6.3$ Hz), 0.95 (3H, d, $J = 6.3$ Hz), 1.15 (1H, m), 1.35 (5H, m), 2.45 (3H, s, CH_3), 4.23 (2H, m), 5.76 (1H, t, $J = 6.9$ Hz), 8.94 (1H, s, N(1)–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.14, 18.12, 21.86, 23.07, 24.28, 43.59, 47.80, 60.73, 107.12, 144.91, 151.51, 164.42; MS (EI, 70 eV) *m*/*z* 269 (M^+), 239, 224, 212, 183, 154, 137, 110, 96, 68; HR-ESI-MS *m*/*z* calcd for $C_{12}H_{19}N_3O_4$ (M+Na) 292.1268, found: 292.1270; 1D NOE: irradiation of N(1)–H proton at δ 8.94 enhanced CH_3 proton at δ 2.45 by 6.4%.
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