

Regioselective N-nitrosation of dihydropyrimidinones with nitric oxide

Yinglin Shen, Qiang Liu, Guaili Wu, Longmin Wu *

State Key Laboratory of Applied Organic Chemistry, Department of Nuclear Science and Technology, Lanzhou University, Lanzhou 730000, PR China

Received 17 October 2007; revised 5 December 2007; accepted 7 December 2007

Available online 14 December 2007

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 CH₃CN and tetrahydrofuran (THF) greatly favored the reaction, whereas protic solvents with high dielectric constant, such as CH₃OH and water, disfavored it.
© 2007 Elsevier Ltd. All rights reserved.

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 (H₂ONO⁺, 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(NO₃)[−]], a mixture of tin(IV) chloride and sodium nitrate, and PVP–N₂O₄ were reported.⁴

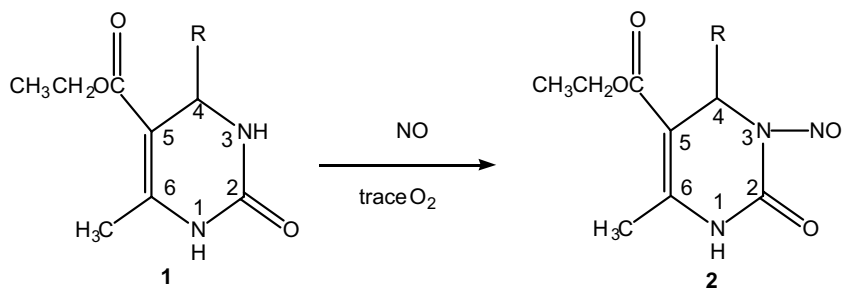
In conjunction with our continuing interest in reactions of nitric oxide (NO) with various organic molecules,⁵ we recently found that NO nitrosated one of the secondary N-amido groups of dihydropyrimidinones, in which there were two different kinds of secondary N-amido groups, in high regioselectivity and in high yield. Itoh et al. studied the reaction of nitric oxide with amines⁶ and amides⁷ and different products were obtained. The reaction mechanism was assumed to be an N₂O₃-mediated hydrogen abstraction from the NH group. Calculations on the N-nitrosation of amines by NO₂ and NO, respectively, in various media such as alkaline solution, lipid, and gas phase suggested a

free radical mechanism, in which NO₂ 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 N₂O₃.

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 CH₃CN 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 CaCl₂ 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 ¹³C 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 regioselectively 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

* Corresponding author. Tel.: +86 931 8912500; fax: +86 931 8915557.
E-mail address: nlaoc@lzu.edu.cn (L. Wu).



Scheme 1.

Table 1
Reaction of dihydropyrimidinones with NO in CH₃CN at ambient temperature

Substrate	R	Yield of 2 (%)
1a	4'-(OMe)-C ₆ H ₄	95
1b	4'-(Cl)-C ₆ H ₄	93
1c	4'-(NO ₂)-C ₆ H ₄	91
1d	Ph	93
1e		95
1f	<i>iso</i> -Butyl	94
1g	<i>n</i> -Propyl	94
1h	<i>iso</i> -Propyl	95
1i	Ethyl	94
1j	H	95
1k	PhCH=CH	0
1l	(CH ₃) ₂ C=CH	0

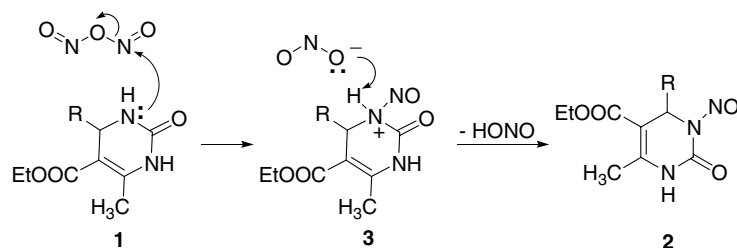
supported by ¹H NMR spectra of the substrate. ¹H NMR peak of N(1)–H of **1a** locates downfield at 9.17 ppm, whereas that of N(3)–H highfield at 5.09 ppm. This reveals that the reaction proceeds most likely via a nucleophilic mechanism. Otherwise, the nitrosation proceeded smoothly when R is aryl or 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. Pires¹² and Lewis¹³ studied the NO/O₂ system in the presence of phenol and morpholine, respectively, and concluded that N₂O₃ was the nitrosating entity. NO is readily oxidized by oxygen to NO₂ and then converted to N₂O₃.¹⁴ Displacement of the good leaving group nitrite ([−]ONO) from N₂O₃ 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 CCl₄, N(C₂H₅)₃, and benzene; (b) aprotic and polar solvents such as THF, CH₂Cl₂, and CH₃CN; and (c) protic solvents with high dielectric constant such as CH₃OH and H₂O.

Table 2 indicates that nonpolar solvents such as CCl₄ and N(C₂H₅)₃, in which dihydropyrimidinones and NO may be less soluble, disfavored the nitrosation, whereas aprotic, polar, and weakly nucleophilic solvents such as CH₃CN 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 CH₃OH and H₂O more favored the hydrogen bonding, but the reaction did not occur. It may be rationalized by a stronger hydrogen bonding (Scheme 3), which blocks N₂O₃ approaching N(3) of **1**. As such, the substrate molecule most likely undergoes a nucleophilic attack on N₂O₃, unlike a free radical mechanism. If not, it would afford N(1)-nitrosoamides instead of N(3)-nitroso

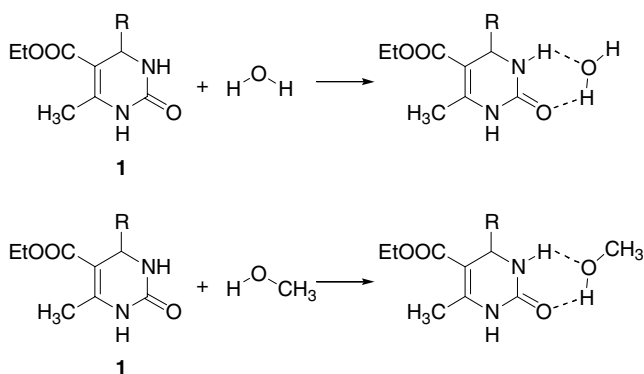


Scheme 2.

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

Solvent	Conversion (%)	Yield of 2 (%)
CCl ₄	0	0
N(C ₂ H ₅) ₃	0	0
Benzene	75	73
THF	>99	93
CH ₂ Cl ₂	90	88
CH ₃ CN	>99	94
CH ₃ OH	0	0
H ₂ O	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 dihydropyrimidinones with NO. Its main advantages are readily available starting materials, convenient performance under mild conditions and high yields.

Acknowledgment

Project No. 20572040 was supported by National Natural Science Foundation of China.

References and notes

- (a) White, E. H.; Darbeau, R. W.; Chen, Y.; Chen, D.; Chen, S. *J. Org. Chem.* **1996**, *61*, 7986; (b) Darbeau, R. W.; Gible, R. E.; Pease, R. S.; Siso, L. M.; Heurtin, D. J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1084.
- Williams, D. L. H. *Nitrosation Reactions and the Chemistry of Nitric Oxide*; Elsevier: Amsterdam, 2004; Chapter 2.
- Zolfigol, M. A. *Synth. Commun.* **1999**, *29*, 905.
- (a) Zolfigol, M. A.; Zebarjadian, M. H.; Chehardoli, G.; Keypour, H.; Salehzadeh, S.; Shamsipur, M. *J. Org. Chem.* **2001**, *66*, 3619; (b) Céleriès, B.; Párkányi, C. *Synthesis* **2006**, 2371; (c) Iranpoor, N.; Firouzabadi, H.; Pourali, A.-R. *Synthesis* **2003**, 1591.
- (a) Yang, D. S.; Lei, L. D.; Liu, Z. Q.; Wu, L. M. *Tetrahedron Lett.* **2003**, *44*, 7245; (b) Liu, Z. Q.; Li, R.; Yang, D. S.; Wu, L. M. *Tetrahedron Lett.* **2004**, *45*, 1565; (c) Liu, Z. Q.; Fan, Y.; Li, R.; Zhou, B.; Wu, L. M. *Tetrahedron Lett.* **2005**, *46*, 1023; (d) Liu, Z. Q.; Zhou, B.; Liu, Z. L.; Wu, L. M. *Tetrahedron Lett.* **2005**, *46*, 1095; (e) Peng, L. J.; Liu, Z. Q.; Wu, L. M. *Tetrahedron Lett.* **2007**, *48*, 7418.
- Itoh, T.; Nagata, K.; Matsuya, Y.; Miyazaki, M.; Ohsawa, A. *J. Org. Chem.* **1997**, *62*, 3582.
- Itoh, T.; Nagata, K.; Matsuya, Y.; Miyazaki, M.; Ohsawa, A. *Tetrahedron Lett.* **1997**, *38*, 5017.
- Zhao, Y. L.; Stephen, L.; Garrison, C. G.; William, D. J. *Phys. Chem. A* **2007**, *111*, 2200.
- Ranu, B. C.; Hajra, A.; Dey, S. S. *Org. Process Res. Dev.* **2002**, *6*, 817. Data for **1a**: ¹H NMR (300 MHz, CDCl₃) 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).
- 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; ¹H NMR (200 MHz, CDCl₃) δ 1.22 (3H, t, J = 7.2 Hz), 2.51 (3H, s, CH₃), 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₅H₁₈N₃O₅ (M+Na) 342.1060, found: 342.1058. 1D NOE: Irradiation of CH₃ 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; ¹H NMR (300 MHz, CDCl₃) 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, CH₃), 4.23 (2H, m), 5.76 (1H, t, J = 6.9 Hz), 8.94 (1H, s, N(1)-H); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₂H₁₉N₃O₄ (M+Na) 292.1268, found: 292.1270; 1D NOE: irradiation of N(1)-H proton at δ 8.94 enhanced CH₃ proton at δ 2.45 by 6.4%.
- Zolfigol, M. A.; Shirini, F.; Choghamarani, A. G.; Taqian-Nasab, A.; Keypour, H.; Salehzadeh, S. *J. Chem. Res. (S)* **2000**, 420.
- Pires, M.; Rossi, M. J.; Ross, D. S. *Int. J. Chem. Kinet.* **1994**, *26*, 1207.
- Lewis, R. S.; Tannenbaum, S. R.; Deen, W. M. *J. Am. Chem. Soc.* **1995**, *117*, 3933.
- (a) Nelsen, J. R.; Eur. Pat. App. EP 301 191 (CA 111: 80345q); (b) Greenwood, N. N.; Earnshaw, A. In *Chemistry of the Elements*; Pergamon Press: Oxford, 1990; Vol. 508, Chapter 11; (c) Upchurch, G. R.; Welch, G. N.; Loscalzo, J. *Adv. Pharmacol.* **1995**, *34*, 343; (d) von Gratzel, M.; Taniguchi, S.; Henglein, A. *Ber. Bunsenges. Phys. Chem.* **1970**, *74*, 488.
- Ghosh, K. K.; Satnami, M. L.; Sinha, D.; Vaidya, J. *J. Mol. Liq.* **2005**, *116*, 55.