Simple and Efficient Synthesis of *N*-Nitroethylenediamine Derivatives

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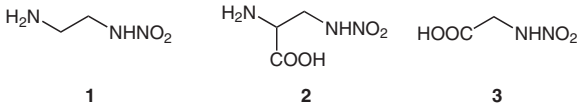
Abstract: A simple and efficient synthesis of *N*-nitroethylenediamine derivatives was carried out by reaction of 1-nitroimidazolidin-2-one with various nitrogen-, oxygen-, and sulfur-containing nucleophiles. The reactivity of primary and secondary amines, amino alcohols, hydrazines, amino acids, alcohols, and thiophenol was tested.

Key words: nucleophiles, ring opening, *N*-nitroethylenediamine derivatives, nitroamines

Ethylenediamines are an important class of organic compounds with many applications in industry and with extensive occurrence in nature.[1] They also serve as selective ligands in organic synthesis[2] and as synthons for heterocyclic compounds.[3] Relatively little attention has been paid to *N*-nitroethylenediamine (**1**) and its derivatives (Figure 1). These compounds belong to the nitroamine family that have importance as industrial and military explosives.[4,5] There are not many naturally occurring nitroamines, but *N*-nitroethylenediamine (**1**) and its derivative β-nitroaminoalanine (**2**) have been identified as metabolic products from mushroom *Agaricus silvaticus*.[6]

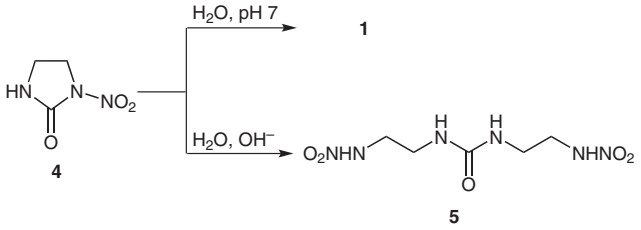
N-Nitroglycine (**3**), a metabolic product from the bacteria *Streptomyces noursei*, inhibits growing of *Escherichia coli*, *Pseudomonas tabaci*, and *Mycobacterium phlei*.[7] In the literature several rather complicated routes for the syntheses of *N*-nitroethylenediamine derivatives have been described.[6,8]



1 2 3

Figure 1

Our research is aimed at accessing intermediates for pyrazole-based cytostatics.[9] First, we reproduced the reaction of 1-nitroimidazolidin-2-one (**4**) with neutral water described previously.[10] *N*-Nitroethylenediamine (**1**) and an unknown compound were isolated, the latter being identified as **5**. Subsequently, we found that the same reaction carried out in alkaline aqueous solution led exclusively to **5** (Scheme 1).[11] These results encouraged us to test the reaction of **4** with various nucleophiles (Table 1). Reaction of compound **4** with primary and secondary amines in methanolic solution was carried out initially and compounds **6**–**30** were prepared in high yields. Reaction proceeded similarly with amino alcohols and hydrazines thus forming the corresponding products **31**–**40**. On the other hand, the reaction with guanidine and hydroxylamine resulted in formation of inseparable complex mixtures; whilst, in the case of anilines containing electron-withdrawing groups, the reaction failed completely. Alcohols reacted with **4** very slowly on heating but, in the presence of alkali, bases **41** and **42** formed in good yield and after short reaction time. Similarly, reaction with tertiary amines (e.g., triethylamine) or amides (e.g., acetamide) led to formation of **41** on prolonged heating in methanol. Thiophenol formed **43** in the presence of triethylamine.[12]



Scheme 1 Hydrolysis of compound **4** in neutral and alkaline solution

Aci–nitro tautomerism was proved by methylation of **30** using diazomethane; both N- and O-methylated products were isolated in a 1:2 ratio, respectively. Based on the above results and previous experience, we proposee that reaction begins with nucleophilic attack on the carbonyl group followed by ring opening.

In summary, the course of hydrolysis of 1-nitroimidazolidin-2-one with water described earlier was reinvestigated, and we have prepared a number of *N*-nitroethylenediamine derivatives by simple reaction of an appropriate nucleophile with 1-nitroimidazolidin-2-one. Aci–nitro tautomerism has been proven by methylation.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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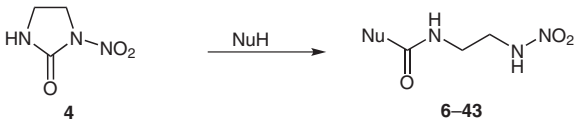
Table 1 Reaction of Compound **4** with Various Nucleophiles[12]



4 **6–43**

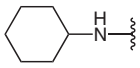
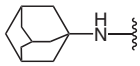
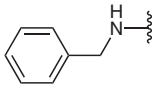
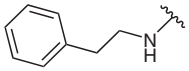
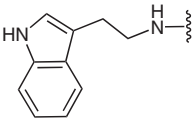
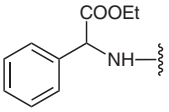
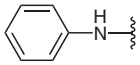
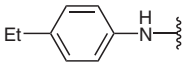
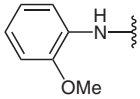
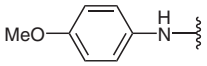
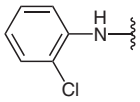
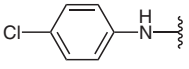
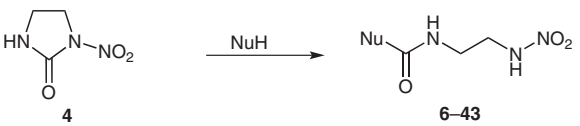
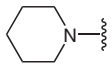
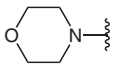
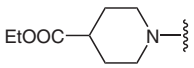
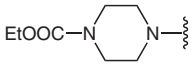
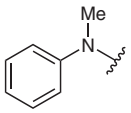
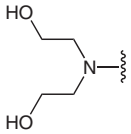
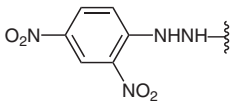
Compd	Nu	mp (°C)	Yield (%)
6	NH_2	97–99	80
7	*n*-BuNH	79–81	75
8	t-BuNH	117.5–119	81
9	$CH_3(CH_2)_7NH$	70–72	88
10	$CH_3(CH_2)_8NH$	88–90	77
11		120–122	80
12		204–206	75
13		147–149	77
14		92–94	74
15		153–155	67
16		124–126	74
17		159–160	73
18		139–141	71
19		148–150	68
20		146–148	83
21		167–169	79
22		186–188	74
23		90.5–93	51
24		120–122	48

Table 1 Reaction of Compound **4** with Various Nucleophiles[12] (continued)



4 **6–43**

Compd	Nu	mp (°C)	Yield (%)
25		151–153	76
26		103.5–105	59
27		95–97	83
28		133–135	80
29		168–170	77
30		124–125	81
31	$HOCH_2CH_2NH$	101–103	81
32	$HOCH_2CH_2CH_2NH$	80–82	80
33		98–100	85
34	NH_2NH	129–131	55
35	MeNHNH	153–155	68
36	PhNHNH	149.5–152	78
37		191–193	77
38	AcNHNH	157–159	72
39	MeOCONHNH	99–101	75
40	*t*-BuOCONHNH	132–134	71
41	MeO	86–87.5	77
42	*t*-BuO	90–92	53
43	PhS	109–111	51

Acknowledgment

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References and Notes

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(2) For recent examples, see: (a) Diaz-Valenzuela, M. B.; Philips, S. D.; France, M. B.; Gunn, M. E.; Clarke, M. L. *Chem. Eur. J.* **2009**, *15*, 1227. (b) Uchida, T.; Katsuki, T. *Tetrahedron Lett.* **2009**, *50*, 4741. (c) Fu, X.; Loh, W.-T.; Zhang, Y.; Chen, T.; Ma, T.; Liu, H.; Wang, J.; Tan, C.-H. *Angew. Chem. Int. Ed.* **2009**, *48*, 7387. (d) Yang, X.; Liu, H.; Fu, H.; Qiao, R.; Jiang, Y.; Zhao, Y. *Synlett* **2010**, 101.

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(11) **Procedure for the Preparation of 1,3-Bis[2-(nitroamino)-ethyl]urea (5)**
Starting material **4** (2.0 g, 15.26 mmol) was suspended in H_2O (10 mL). To this suspension was added dropwise 10% NaOH (10 mL); the starting material **4** dissolved. After 1 h stirring at laboratory temperature the reaction mixture was acidified with dilute HCl to pH 2. Product **5** crystallized from this solution in 72% yield (1.3 g) as colorless crystals. $C_5H_{12}N_6O_5$ (236.18); mp 161–163 °C. MS: *m/z* (rel. abundance) = 175.1 (14) $[NO_2NHCH_2CH_2NHCONHCH_2CH_2]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.16 (q, 4 H, *J* = 5.9 Hz, H4, H4′), 3.42 (t, 4 H, *J* = 5.9 Hz, H3, H3′), 6.19 (t, 2 H, *J* = 5.9 Hz, NH-5, NH-5′), 11.98 (br s, 2 H, NH-2, NH-2′). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 36.5, 45.5, 158.0.

(12) **Representative Experimental Procedure for the Preparation of 1-(2-Hydroxyethyl)-3-[2-(nitroamino)-ethyl]urea (31)**
Starting material **4** (1.0 g, 7.63 mmol) was dissolved in MeOH (30 mL) and 2-aminoethanol (0.5 g, 8.18 mmol, 1.07 equiv) was added. The reaction mixture was heated to boiling and periodically analyzed using TLC (mobile phase: EtOAc). After 2 h the spot corresponding to **4** disappeared, the reaction mixture was concentrated to crystallization, and the crude product was filtered. Recrystallization from *i*-PrOH–toluene afforded **31** as colourless crystals (1.18 g, 81%). $C_5H_{12}N_4O_4$ (192.17); mp 101–103 °C. MS: *m/z* (%) = 131.0(16) $[HO(CH_2)_2NHCONHCH_2CH_2]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.03 (q, 2 H, *J* = 5.6 Hz, H-8), 3.15 (q, 2 H, *J* = 5.8 Hz, H-4), 3.17–3.40 (m, 4 H, H-3, H-9), 4.73 (br s, 1 H, OH), 6.03 (t, 1 H, *J* = 5.6 Hz, NH-7), 6.14 (t, 1 H, *J* = 5.8 Hz, NH-5), 11.0 (s, 1 H, NH-2). ^{13}C NMR, (75 MHz, DMSO-d_6): δ = 36.5, 42.0, 46.6, 61.1, 158.

Spectroscopic Data for Selected Products

1-[2-(Nitroamino)ethyl]urea (6)
$C_3H_8N_4O_3$ (148.12); mp 97–99 °C. MS: *m/z* (%) = 87.1 (100) $[NH_2CONHCH_2CH_2]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.14 (q, 2 H, *J* = 5.9 Hz, H-4), 3.41 (t, 2 H, *J* = 5.9 Hz, H-3), 5.57 (s, 2 H, NH_2), 6.10 (t, 1 H, *J* = 5.5 Hz, NH-5), 12.00 (s, 1 H, NH-2). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 36.4, 45.7, 158.7.

***N*-[2-(Nitroamino)ethyl]hydrazinecarboxamide (34)**
$C_3H_9N_5O_3$ (163.13); mp 129–131 °C. MS: *m/z* (%) = 163.9 (2) [M + H$^+$], 102.0(100) $[NH_2NHCONHCH_2CH_2]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.13–3.23 (m, 4 H, H-3, H-4), 5.96 (br s, 3 H, NH_2, NH-7), 6.46 (br s, 1 H, NH-5), 7.04 (s, 1 H, NH-2). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 37.55, 50.01, 160.33.

Methyl [2-(Nitroamino)ethyl]carbamate (41)
$C_4H_9N_3O_4$ (163.13); mp 86–87.5 °C. MS: *m/z* (%) = 163.7 (4) [M + H]$^+$, 102.1 (100) $[CH_3OCONHCH_2CH_2]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.15 (q, 2 H, *J* = 5.98 Hz, H-4), 3.43 (t, 2 H, *J* = 6.00 Hz, H-3), 3.52 (s, 3 H, CH_3), 7.25 (t, 1 H, *J* = 5.1 Hz, NH-5), 12.00 (s, 1 H, NH-2). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 37.57, 44.67, 51.36, 156.77.

***S*-Phenyl [2-(Nitroamino)ethyl]thiocarbamate (43)**
$C_9H_{11}N_3O_3S$ (241.26); mp 109–111 °C. MS: *m/z* (%): 180 (53) $[C_6H_5SCONHCH_2CH_2]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.30 (q, 2 H, *J* = 5.4 Hz, CH_2), 3.47 (t, 2 H, *J* = 5.4 Hz, CH_2), 7.36–7.47 (m, 5 H, ArH), 8.46 (t, 1 H, *J* = 5.4 Hz, NH), 12.07 (br s, 1 H, NH). ^{13}C NMR (300 MHz, DMSO-d_6): δ = 33.9, 37.9, 127.1, 128.8, 129.4, 134.8, 164.3.