A new synthesis of β-nitroenamines by amination of nitroolefins with methoxyamines

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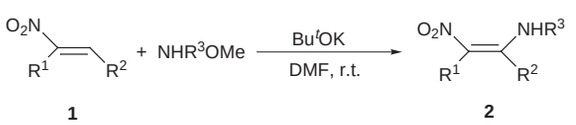
The amination of nitroolefins with methoxyamines in the presence of a base gives β-nitroenamines in good yields.

β-Nitroenamines have attracted an increasing interest as versatile intermediates in organic synthesis[1] due to their "push–pull" nature,[2] and are known to be part of the structure of many biologically active compounds such as antiulcerative pharmaceuticals (nizatidine,[3] ranitidine,[4] *etc.*) or some pesticides.[5] Although many synthetic approaches to these compounds have been explored,[1a,6] there has been no report on their direct synthesis from nitroolefins by nucleophilic substitution of vinylic hydrogen. Vicarious nucleophilic substitution (VNS)[7] of nitroarenes has been intensively studied and extended to electrophilic alkenes.[8] However, few examples concerning VNS amination in aliphatic systems are known. We have recently described the direct aminations of nitroarenes with methoxyamines by the VNS mechanism.[9] Herein we report a new amination of simple nitroolefins with methoxyamines to give β-nitroenamines.

We found that methoxyamines readily aminated nitroolefins in the presence of a base to afford β-nitroenamines, even in the case of nitroolefins with no leaving group at the β-position (Scheme 1). Metal catalysts were not required in this reaction,



1 **2**

Scheme 1

although they were necessary for the efficient amination of nitroarenes with methoxyamines.[9] The newly formed double bond of the products was determined to possess the *Z* configuration by the chemical shifts of the olefinic protons and/or NH protons in the ^{1}H NMR spectra.[10] When R^3 was H, they indicated the existence of two nonidentical broad peaks assignable as two NH protons of an amino group at 5.7–9.1 and 8.6–10.2 ppm in $CDCl_3$ due to intramolecular hydrogen bonding between the amino and nitro groups.

The general procedure for the reaction is as follows. A solution of the methoxyamine (2.5 mmol) and the nitroolefin (2 mmol) in DMF (2 ml) was added dropwise to a stirred solution of Bu^{t}OK (6 mmol) in DMF (8 ml) over 5 minutes at room temperature. After the solution was stirred for 0.1–3 h at the same temperature, the reaction was quenched with saturated aq. NH_4Cl, and the product was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated. The crude product obtained was purified by silica gel thin layer chromatography to afford the pure β-nitroenamine.

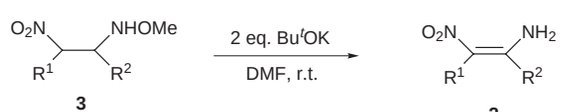
Representative results are shown in Table 1. Nitroolefins **1** having various alkyl and/or aryl groups could readily be converted into the corresponding β-nitroenamines **2**[11] in one step in good yields. Methylamination using *N*,*O*-dimethylhydroxylamine as the aminating agent also proceeded to give the expected product **2f**, although in lower yield than amination using a methoxyamine (entries 5 and 6). With a nitroolefin

Table 1 Amination of nitroolefins **1** with methoxyamines[a]

Entry		R^1	R^2	R^3	Yields[b] (%) of **2**
1	**a**	Me	H	H	61[c]
2	**b**	Me	Me	H	78[c]
3	**c**	$-(CH_2)_4-$		H	91
4	**d**	H	hexyl	H	87[c]
5	**e**	H	Ph	H	94
6	**f**	H	Ph	Me	51
7	**g**	H	3-$NO_2C_6H_4$	H	75
8	**h**	Me	3-ClC_6H_4	H	56
9	**i**	Me	3-$MeOC_6H_4$	H	59
10[d]	**j**	Me	3-HOC_6H_4	H	31
11[d]	**k**	Me	4-HOC_6H_4	H	0
12	**l**	Me	2-furyl	H	30[c]

[a] Unless otherwise noted, the amination of **1** with NHR^3OMe (1.25 equiv.) was performed in the presence of Bu^{t}OK (3.0 equiv.) in DMF at room temperature for 0.1–3 h. [b] Isolated yields. [c] After completion of the reaction, the reaction mixture was applied to a silica gel short column directly without general work-up because of the instability of the product. [d] Five equivalents of Bu^{t}OK were used.

carrying a 3-nitrophenyl substituent, amination of the nitroolefin moiety preceded amination of the nitroaromatic nucleus. Amination of the nitrophenyl group did not occur, and 1-amino-2-nitro-1-(3-nitrophenyl)ethylene **2g** was obtained in 75% yield (entry 7). In the case of 1-(4-hydroxyphenyl)-2-nitropropene **1k**, no reaction occurred since a highly conjugated quinoid nitronate ion, which was inactive toward nucleophilic reaction, was formed by facile deprotonation of the hydroxy group in the presence of a base (entry 11). On the other hand, the amination of 1-(3-hydroxyphenyl)-2-nitropropene **1j** took place because such an inactive species could not be formed (entry 10). In the absence of a base, nitroolefins **1a**, **1b**, **1c**, **1d** and **1g** reacted with methoxyamine to give the corresponding 1,4-adducts, *O*-methyl-*N*-(β-nitroethyl)hydroxylamine derivatives **3**, quantitatively. This indicates that the 1,4-adduct of the methoxyamine with the nitroolefin could be one of the intermediates in this reaction. In fact, treatment of the isolated 1,4-adducts, **3c** and **3g**, with two equivalents of a base resulted in the corresponding β-nitroenamines, **2c** and **2g**, in 79 and 88% yields, respectively (Scheme 2). In this amination, more than



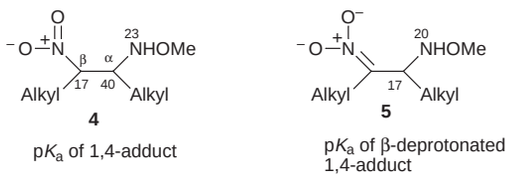
3
c: R^1,R^2 = -$(CH_2)_4$-
g: R^1 = H, R^2 = 3-$NO_2C_6H_4$

2
c: 79%
g: 88%
g: ca.50%(1 eq. Bu^{t}OK)

Scheme 2

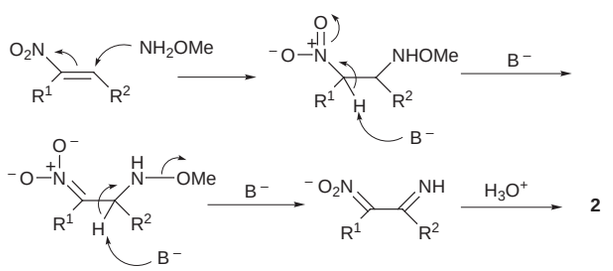
two equivalents of base were necessary to complete the reaction, because the reaction of **3g** with one equivalent of base gave **2g** in approximately 50% yield, and the starting material

was recovered in 40–50% yield. Predicted pK_a values of the 1,4-adduct in DMSO by CAMEO[12] are depicted in Scheme 3.



Scheme 3

The CAMEO predicts that the lowest pK_a value in the 1,4-adduct **4** is 17 at the β-position, and after deprotonation of the β-position, the pK_a value of the α-position is considerably lowered from the initial 40 to 17 as indicated in **5**. A similar tendency was observed in all cases, even when the α-substituent R^2 was aryl or hydrogen. This suggests that as soon as a base abstracts a β-proton in the 1,4-adduct, another equivalent of base can abstract an α-proton. Therefore, the amination would proceed *via* an α,β-dianion intermediate. The formation of α,β-dianions of nitroalkanes has been extensively studied by Seebach and co-workers, and many β-substitution reactions of nitroalkanes have been reported.[13] In the case of an ester derivative, methyl 3-(methoxyamino)propionate, derived from 1,4-addition of methoxyamine to methyl acrylate, a similar drop of the pK_a at the carbon center adjacent to the methoxyamino group was not predicted by the CAMEO. Accordingly, treatment of methyl 3-(methoxyamino)propionate with two equivalents of base did not give the methyl β-amino acrylate. A proposed reaction mechanism is illustrated in Scheme 4. After deprotonation of the β-position in the



Scheme 4

1,4-adduct, another equivalent of base abstracts an α-proton, and subsequent elimination of the methoxy group furnishes the product **2**.

In conclusion, we have demonstrated that a new amination of simple nitroolefins with methoxyamines gives β-nitroenamines in good yields. To the best of our knowledge, this is the first example of a direct synthesis of β-nitroenamines from nitroolefins bearing no leaving groups. β-Nitroenamines can react with both electrophiles and nucleophiles to furnish various useful polyfunctionalised compounds, since they are "push–pull" alkenes. We are continuing to investigate the scope and application of the present amination using methoxyamines.

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Notes and references

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11 ^{1}H NMR spectral data are as follows (*J* values in Hz). **2a**: δ_H(270 MHz, $CDCl_3$) 2.07 (s, 3H), 6.03 (br s, 1H), 7.02 (t, 1H, *J* 11.55), 8.62 (br s, 1H). **2b**: δ_H(270 MHz, $CDCl_3$) 2.12 (s, 3H), 2.18 (s, 3H), 7.94 (br s, 1H), 10.08 (br s, 1H). **2c**: δ_H(270 MHz, $CDCl_3$) 1.63–1.78 (m, 4H), 2.53 (t, 2H, *J* 6.27), 2.62 (t, 2H, *J* 6.27), 6.73 (br s, 1H), 9.69 (br s, 1H). **2d**: δ_H(270 MHz, $CDCl_3$) 0.89 (m, 3H), 1.30 (m, 6H), 1.61 (m, 2H), 2.24 (m, 2H), 6.54 (s, 1H), 6.67 (br s, 1H), 9.22 (br s, 1H). **2e**: δ_H(270 MHz, $CDCl_3$) 6.64 (br s, 1H), 6.81 (s, 1H), 7.45–7.59 (m, 5H), 9.29 (br s, 1H). **2f**: δ_H(270 MHz, $CDCl_3$) 2.99 (d, 3H, *J* 5.61), 6.58 (s, 1H), 7.34–7.39 (m, 2H), 7.47–7.54 (m, 3H), 10.22 (br s, 1H). **2g**: δ_H(400 MHz, DMSO-d_6) 6.93 (s, 1H), 7.79 (t, 1H, *J* 8.05), 8.09 (m, 1H), 8.40 (m, 1H), 8.45 (m, 1H), 9.09 (br s, 1H), 9.38 (br s, 1H). **2h**: δ_H(400 MHz, $CDCl_3$) 1.96 (s, 3H), 5.72 (br s, 1H), 7.29 (td, 1H, *J* 1.51, 7.39), 7.39–7.50 (m, 3H), 9.56 (br s, 1H). **2i**: δ_H(270 MHz, $CDCl_3$) 1.96 (s, 3H), 3.84 (s, 3H), 6.00 (br s, 1H), 6.89–7.03 (m, 3H), 7.38 (t, 1H, *J* 7.92), 9.69 (br s, 1H). **2j**: δ_H(270 MHz, DMSO-d_6) 1.85 (s, 3H), 6.79–6.93 (m, 3H), 7.31 (t, 1H, *J* 7.92), 8.72 (br s, 1H), 9.83 (br s, 1H). **2l**: δ_H(270 MHz, $CDCl_3$) 2.39 (s, 3H), 6.62 (dd, 1H, *J* 1.65, 3.63), 6.89 (d, 1H, *J* 3.63), 7.65 (d, 1H, *J* 1.65), NH_2 n.d.

12 CAMEO is an interactive computer program, which predicts the products of organic reactions given starting materials and conditions, as well as pK_a values for organic compounds, developed by W. L. Jorgensen. See A. J. Gushurst and W. L. Jorgensen, *J. Org. Chem.*, 1986, **51**, 3513.

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