HETEROCYCLES, Vol. 60, No. 2, 2003, pp. 303 - 308
Received, 12th November, 2002, Accepted, 12th December, 2002, Published online, 24th December, 2002

FACILE SYNTHESIS OF UNSYMMETRICAL 1,1-DIAMINO-2-NITROETHENES AND FUNCTIONALIZED AMIDOXIMES

Nagatoshi Nishiwaki,* Yoshikazu Okajima, Mina Tamura, Noriko Asaka, Kazushige Hori, Yasuo Tohda, and Masahiro Ariga*

Department of Chemistry, Osaka Kyoiku University, Asahigaoka 4-698-1, Kashiwara, Osaka 582-8582, Japan

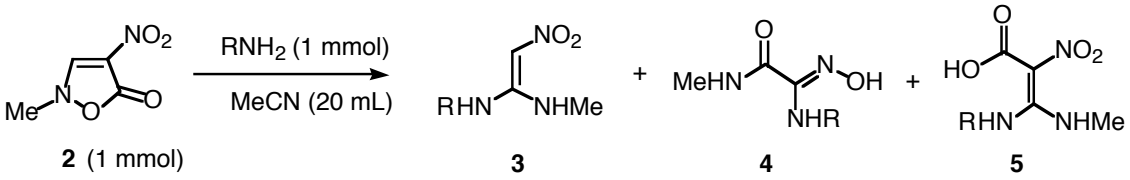
Abstract – Aminolysis of nitroisoxazolone affords unsymmetrical 1,1-diamino-2-nitroethenes and carbamoylamidoximes with simple experimental manipulations.

The "built-in" method of a functional unit is one of the important methodologies for the construction of polyfunctionalized compounds, and various kinds of building blocks have been developed. 1-Amino-2-nitroethene (nitroenamine), a typical push-pull alkene, reveals versatile reactivity such as electrophilic and nucleophilic addition-elimination as well as 1,3-dipolar cycloaddition and reduction.[1] 1,1-Diamino-2-nitroethenes (DANEs) are also used as synthetic intermediates for polyfunctionalized systems and as biologically active compounds.[1] DANEs are relatively easy to prepare. The condensation of nitromethane with carbon disulfide followed by alkylation leads to 1,1-bis(alkylthio)-2-nitroethene (**1**), which is then treated with amines to produce DANEs with symmetrical structure.[1c] On the other hand, preparation of unsymmetrical DANEs is somewhat troublesome. After one of the alkylthio groups in **1** is activated with conversion to monosulfoxide, successive substitution with different amines gives unsymmetrical DANEs *via* nitroketene *N*,*S*-acetal.[2] The addition of amine to isothiocyanate yielding *N*,*S*-acetal is also effective route.[3] Another alternative which can be employed involves the condensation of nitromethane with unsymmetrical ketene diimine.[4] However, these preparative methods for unsymmetrical DANEs are not always facile because of the difficulty of obtaining the starting materials.[1] Hence, it is highly desirable to develop a more efficient method for preparation of DANEs.

In our course of study on functionalized nitroenamines, we have established preparative methods using highly electron-deficient heterocyclic compounds. Isomeric *N*-substituted 5-nitropyrimidinones are

regarded as the masked form of functionalized nitroenamines. For example, aminolysis of nitropyrimidinones affords β-nitroenamines bearing a carbamoyl or a formyl group at the β-position,[5] which are transformed to pyridones, pyrazoles and macrocyclic compounds.[5,6] We recently showed nitroisoxazolone (**2**) behaves as a synthetic equivalent of the 1,3-dipolar nitroenamine affording 4-nitropyrrole-2-carboxylic acid derivatives.[7] Here, we anticipate that aminolysis of **2** furnishes DANE (**3**).

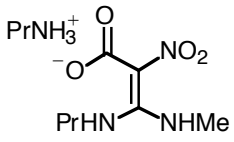
Table Reactions of isoxazolone **2** with amines



2 (1 mmol) **3** **4** **5**

R	Temp / °C		Yield/% 3	4	5
p-$MeOC_6H_4$	rt[a]	**a**	83	0	0
p-MeC_6H_4	rt[a]	**b**	76	0	0
p-$MeOC_6H_4$	50→80[b]	**a**	50	40	0
p-MeC_6H_4	50→80[b]	**b**	30	32	0
Ph	50→80[b]	**c**	15	44	0
p-ClC_6H_4	50→80[b]	**d**	26	6	0
p-$NO_2C_6H_4$	50→80[b]	**e**	13	34	0
Pr	50	**f**	0	78	5
i-Pr	50	**g**	0	87	0
t-Bu	50	**h**	0	81	0
$PhCH_2CH_2$	50	**i**	0	92	0
H[c]	50	**j**	0	86	0
Pr	rt	**f**	0	70	12
Pr[d]	0	**f**	0	17	33

a) At room temperature, 3 days.
b) Amine was added at 50 °C, then the mixture was heated at 80 °C for 5 h.
c) 2 equivalents of NH_3 were used.
d) 11 % of **6f** was obtained.



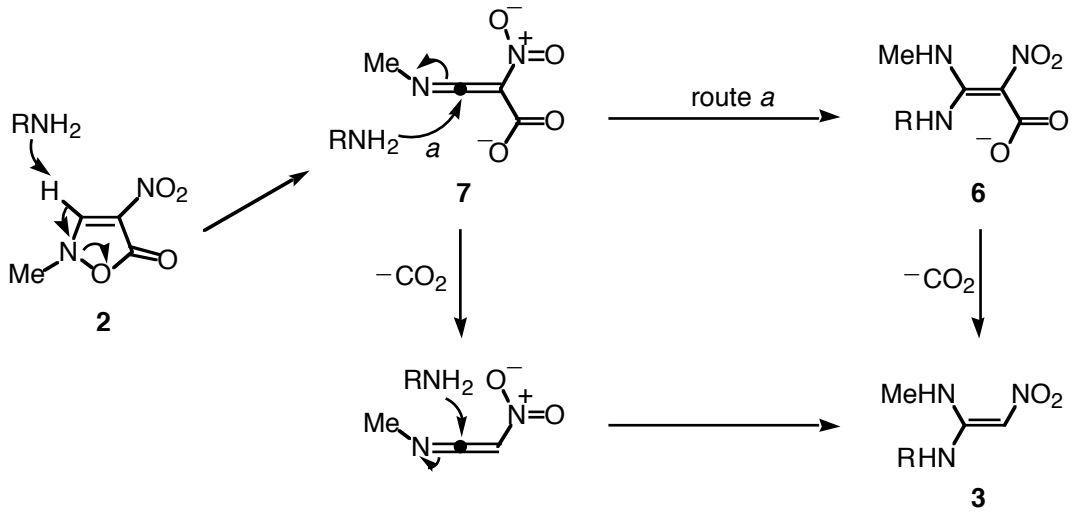
6f

To a solution of isoxazolone (**2**) in acetonitrile, *p*-methoxyaniline was added and the mixture stirred at room temperature. After removal of solvent, the reaction mixture was treated with column chromatography on silica gel to afford colorless prismatic crystal (**3a**). In the ^1H NMR spectrum, the signal of *N*-methyl group appeared as a doublet, which means that the exchanging rate of the adjacent *N*-hydrogen was markedly slow. In the lower field of the ^{13}C NMR and the DEPT spectra, two signals of

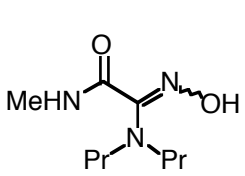
sp^2 carbons were observed at 98.2 ppm (tertiary carbon) and at 156.4 ppm (quaternary carbon). The large difference of chemical shifts corresponds to extremely biased electron density on the ethylene moiety. On the basis of spectral and analytical data,[7] **3a** was assigned as DANE (*E*-isomer), which was also confirmed with X-Ray crystallography.[7] Electron rich anilines afforded DANEs (**3a**) and (**3b**) in good yields, however starting materials were quantitatively recovered in cases of non-activated anilines. DANEs (**3c-e**) could be prepared under heated conditions, and gradual addition of anilines at 50 °C before heating at 80 °C was effective.

Heated conditions also furnished another products (**4a-e**). While elemental analyses of products (**3**) and (**4**) gave same empirical formulas, NMR spectra were quite different.[8] Three protons in **4** were found to be exchangeable with deuterium oxide in the ^{1}H NMR spectrum, and two signals of sp^2 carbons were observed at 145.7 and 161.7 ppm besides signals of a benzene ring (in the case of **4a**) in the ^{13}C NMR spectrum. This data indicates that the products (**4**) are amidoximes having a carbamoyl group, and the structure was finally confirmed with X-Ray crystallography using **4f** (*Z*-isomer).[9]

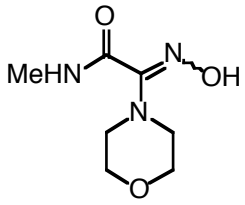
Reactions of isoxazolone (**2**) with aliphatic amines completed just after adding amine, and amidoximes (**4f-j**) were obtained in high yields. In each reaction, formation of DANEs (**3f-j**) was not detected. It is notable that sterically hindered *t*-butylamine can be employed without problem. The present reaction is also applicable to secondary amines. Dipropylamine and morpholine afforded amidoximes (**4k**) and (**4l**) in 74 and 76 % yields as a mixture of *E*/*Z* isomers, respectively. In the reaction using propylamine, a small amount of polyfunctionalized acrylic acid (**5f**) was obtained. When propylamine was added at lower temperature, larger amounts of **5f** and ammonium salt (**6f**) were produced. As the ammonium salt (**6f**) is quantitatively converted to **5f** by acidification with hydrochloric acid, the yield of **5f** is consequently improved up to 44 %.



Scheme 1 A plausible mechanism for the present reaction

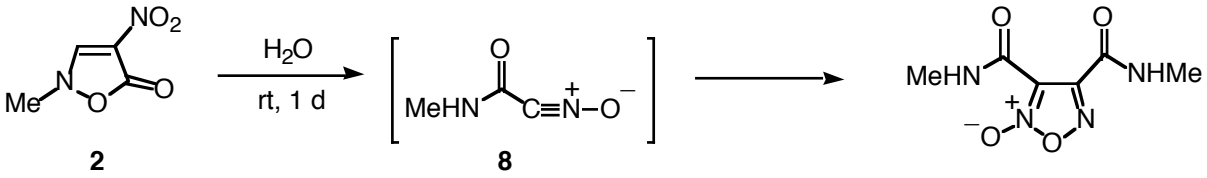


4k



4l

A plausible mechanism forming DANE (**3**) is illustrated in Scheme 1. Deprotonation at the 3-position of **2** gives ketene imine carboxylate (**7**).[10,11] The amination at the cumulene carbon and decarboxylation give DANE (**3**). Isolation of **5f** and **6f** supports this conclusion. On the other hand, a satisfactory explanation for the formation of amidoxime (**4**) is still to be determined. Since isolated DANE (**3a**) was not transformed to amidoxime (**4a**) under the same conditions used for preparation of **4a** from **2**, we consider that DANE (**3a**) is not a precursor for amidoxime (**4a**). In our previous work, we have found that carbamoylnitrile oxide (**8**) is easily generated by treatment of isoxazolone (**2**) using only water at room temperature in the absence of base (Scheme 2).[12] Hence, amidoxime (**4**) might be an adduct of amine with nitrile oxide (**8**).



2 **8**

Scheme 2 Generation of nitrile oxide (**8**) from isoxazolone (**2**)

In summary, unsymmetrical DANEs (**3**) are readily prepared with aminolysis of nitroisoxazolone (**2**). Furthermore, aminolysis of **2** leads to functionalized amidoxime (**4**) which is also a useful precursor for polyfunctionalized compounds such as 1,2,4-oxadiazole.[13] We are now studying chemical transformations of building blocks (**3**-**5**), and results will be shown in due course.

REFERENCES AND NOTES

1. Reviews for nitroenamines, and references are cited therein. a) S. Rajappa, *Tetrahedron*, 1999, **55**, 7065; b) V. V. Perekalin, E. S. Lipina, V. M. Berestovitskaya, and D. A. Efremov, 'Nitroalkenes, Conjugated Nitro Compounds,' Wiley, New York, 1994, pp. 210-249; c) S. Rajappa, *Tetrahedron*, 1981, **37**, 1453.

2. R. C. Young, R. C. Mitchell, T. H. Brown, C. R. Ganellin, R. Griffiths, M. Jones, K. K. Rana, D. Saunders, I. R. Smith, N. E. Sore, and T. J. Wilks, *J. Med. Chem.*, 1988, **31**, 656.
3. H. Schäfer, B. Bartho, and K. Gewald, *J. Prakt. Chem.*, 1977, **319**, 149.
4. F. Moimas, C. Angeli, G. Comisso, P. Zanon, and E. Decorte, *Synthesis*, 1985, 509.
5. a) N. Nishiwaki, Y. Mizukawa, R. Terai, Y. Tohda, and M. Ariga, *Arkivoc*, 2000, **1**, 103; b) N. Nishiwaki, Y. Tohda, and M. Ariga, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 1997.
6. N. Nishiwaki, T. Ogihara, M. Tamura, N. Asaka, K. Hori, Y. Tohda, and M. Ariga, *Heterocycles*, 2002, **57**, 425.
7. Crystal data for **3a**: $C_{10}H_{13}N_3O_3$, M = 209.22, triclinic, space group P-1, a = 7.4114(8) Å, b = 10.716(1) Å, c = 6.7851(7) Å, α = 91.721(8)°, β = 93.354(8)°, γ = 82.311(9)°, V = 533.0(1) Å^3, D = 1.304 g/cm^3, Z = 2, F(000) = 296.00, μ = 0.97 cm^{-1}. A colorless prismatic crystal of dimensions 0.30 x 0.20 x 0.30 mm was mounted at a glass fiber and used for measurement at 293 K on a Rigaku AFC7R four-circle diffractometer employing graphite monochromated MoKα radiation (λ = 0.71069 Å) using the $\omega/2\theta$ scan technique. The 2455 unique reflections were corrected for Lorents and polarization effects. The structure was solved by direct methods (SIR88). The final full-matrix least squares refinement, based on $|F|^2$ using 1446 reflections ($I > 2.00\sigma(I)$) and 197 parameters, converged with R = 0.047 and Rw = 0.076. Spectral and Analytical data: mp 212-214 °C; ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ 2.9-3.0 (br d, 3H), 3.78 (s, 3H), 5.8-6.2 (br, 1H), 7.00 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 8.7-9.2 (br, 1H), 9.8-10.2 (br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS) δ 28.3, 55.3, 98.2, 114.6, 128.1, 156.4, 158.1; IR (Nujol / cm^{-1}) 1628, 1568, 1513, 1377. Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.59; 5.94; 18.79.
8. Spectral and Analytical data for **4a**: colorless needles; mp 150-152 °C; ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ 2.63 (d, J = 4.7 Hz, 3H), 3.68 (s, 3H), 6.75 (d, J = 9.6 Hz, 2H), 6.78 (d, J = 9.6 Hz, 2H), 7.97 (s, 1H), 8.27 (br d, J = 4.7 Hz, 1H), 10.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS) δ 25.7, 55.0, 113.5, 120.6, 133.8, 145.7, 154.2, 161.7; IR (Nujol / cm^{-1}) 3500-3000 (br), 1633. Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.93; 5.95; 18.82.
9. Crystal data for **4f**: $C_6H_{13}N_3O_2$, M = 159.19, orthorhombic, space group Aba2, a = 11.572(6) Å, b = 11.603(5) Å, c = 27.823(6) Å, V = 3735(4) Å^3, D = 1.132 g/cm^3, Z = 16, F(000) = 1376.0, μ = 0.86 cm^{-1}. A colorless plate crystal of dimensions 0.10 x 0.30 x 0.30 mm was measured in the same way for **3a**. The 1209 unique reflections were corrected for Lorents and polarization effects. The structure was solved by direct methods (MITHRIL90). The final full-matrix least squares refinement, based on $|F|^2$ using 780 reflections ($I > 2.00\sigma(I)$) and 199 parameters, converged with R = 0.069 and Rw = 0.090. Spectral and Analytical data: mp 79-81 °C; ^{1}H NMR (400 MHz, $CDCl_3$,

TMS) δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.55 (tq, *J* = 7.4, 7.2 Hz, 2H), 2.82 (d, *J* = 5.0 Hz, 3H), 3.46 (t, *J* = 7.2 Hz, 2H), 5.0-5.9 (br, 1H), 7.15 (br d, *J* = 5.0 Hz, 1H), 7.6-8.4 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 11.0, 24.6, 26.1, 45.6, 147.3, 161.9; IR (Nujol / cm^{-1}) 3700-3200 (br), 3400-3250, 1678, 1635. Anal. Calcd for $C_6H_{13}N_3O_2$: C, 45.27; H, 8.23; N, 26.40. Found: C, 44.92; 8.37; 26.59.

10. N. Nishiwaki, M. Nakanishi, T. Hida, Y. Miwa, M. Tamura, K. Hori, Y. Tohda, and M. Ariga, *J. Org. Chem.*, 2001, **66**, 7535.
11. R. H. Prager and C. M. Williams, *Heterocycles*, 1999, **51**, 3013, and references are cited therein.
12. N. Nishiwaki, T. Uehara, N. Asaka, Y. Tohda, M. Ariga, and S. Kanemasa, *Tetrahedron Lett.*, 1998, **39**, 4851.
13. A. R. Gangloff, J. Litvak, E. J. Shelton, D. Sperandio, V. R. Wang, and K. D. Rice, *Tetrahedron Lett.*, 2001, **42**, 1441.