Facile Synthesis of Functionalized Nitroenamines. III.[1,2] Aminolysis of 1-Methyl-5-nitropyrimidin-2(1*H*)-one

Nagatoshi Nishiwaki, Yasuo Tohda, and Masahiro Ariga*

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

(Received January 9, 1996)

The aminolysis of 1-methyl-5-nitropyrimidin-2(1*H*)-one furnished diimines of nitromalonaldehyde in good yields. One of the imino groups of the diimines was readily hydrolyzed on silica gel to give nitroenamines possessing a formyl group. These reagents behaved as the synthetic equivalent of unstable nitromalonaldehyde, affording azaheterocycles upon a treatment with hydrazines or diamines.

Nitroenamines[3] are typical push–pull alkenes; this structure means that these compounds can undergo such reactions as electrophilic and nucleophilic addition–elimination, 1,3-dipolar cycloaddition and reduction. Although functionalized nitroenamines are especially useful synthetic intermediates for polyfunctionalized systems, only a few preparative methods are known. The mainly employed synthetic method for them is the condensation of nitroacetic acid derivatives with dialkoxymethylamines or orthoformic esters. Since these starting materials are, however, not always readily available, there is a demand for a more effective approach to functionalized nitroenamines.

In the course of our investigation to explore electron-deficient dinitropyridones,[4] we directed our attention to the reactivities of their azaanalogs, nitropyrimidinones. The reaction of 3-methyl-5-nitropyrimidin-4(3*H*)-one (**1**) with ketones in the presence of NH_3 was found to be a useful method for preparing of disubstituted pyrimidines.[5] In this reaction, **1** behaved as a synthetic equivalent of activated diformylamine.

From an alternative point of view, three isomeric nitropyrimidinones (**1**, **2**, and **3**) could be regarded as being masked nitroenamines, respectively. Nitroenamines **4a** and **4b**, which possess a carbamoyl group, were obtained from **1** by treating with primary amines or hydrazines.[1] Functionalized nitroenamines (**5a** and **5b**) were also obtained from 1-methyl-5-nitropyrimidin-4(1*H*)-one (**2**) by hydration and a ring-opening reaction.[2] In this paper, the aminolysis of 1-methyl-5-nitropyrimidin-2(1*H*)-one (**3**)[6] is considered (Scheme 1).

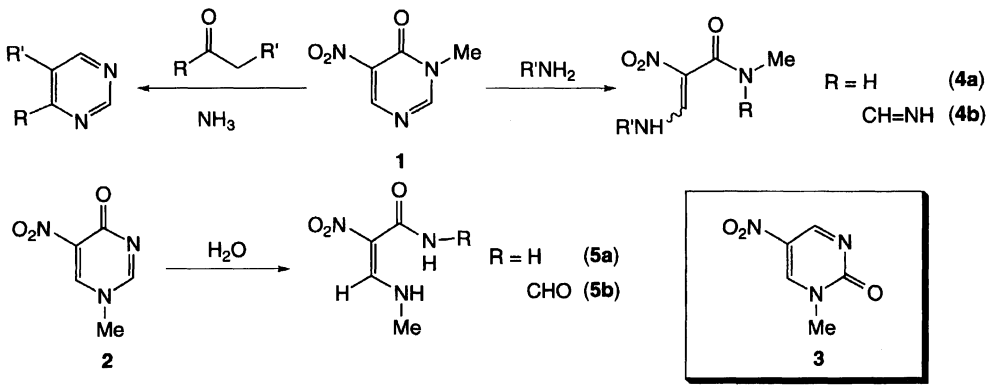
Results and Discussion

The nitration of 1-methylpyrimidin-2(1*H*)-one[7] gave 1-methyl-5-nitropyrimidin-2(1*H*)-one (**3**) together with the hydrated derivative **6**, indicating the high reactivity of **3** toward nucleophilic addition. It was considered that hydration occurred at the 6-position, not at the 4-position. This judgment is supported by the estimated nucleophilic susceptibilities[8] of **3** (Fig. 1). Pure pyrimidinone **3** was isolated by the dehydration of **6** with heating in polar solvents, such as MeCN, followed by recrystalization from PhH (Scheme 2).

To a solution of nitropyrimidinone **3** in MeOH, $PrNH_2$ was added, and heated under reflux for 3 h. The hexane extraction of the reaction mixture afforded 4,8-diaza-6-*aci*-nitroundeca-4,7-diene (**7a**) as a pale-yellow oil; the residual solid was NH_2COOMe. In the ^1H NMR of **7a**, each signal of the olefinic protons and each of the propyl groups were equally observed. Thus, this product was identified as the diimine of nitromalonaldehyde **7a**;[9,10] however, the possibility of azadiene **8** under equilibrium with fast conversion could not be completely excluded (Scheme 3).

We have reported that the same products were obtained in the reaction of 1-methyl-3,5-dinitropyridin-2(1*H*)-one (**9**) with primary amines in pyridine.[9] This reaction, however, suffered from the low solubility of **9**. In addition, the further formation of troublesome adduct **11**, which was derived from **9** and the eliminated anion of $NO_2CH_2CONHMe$ **10**, lowered the yield of diimine **7**. As compared with pyridone **9**, pyrimidinone **3** is more convenient to handle in terms of solubility into organic solvents. Pyrimidinone **3** reacted sufficiently with $PrNH_2$ under the same conditions in MeOH employed for pyridone **9** being intact. Since the anion **12** is the less reactive than **10**, and is thus trapped by MeOH to afford NH_2COOMe, no formation of an adduct corresponding to **11** was observed. Hence, pyrimidinone **3** would be the preferable precursor of **7** from these results (Scheme 4).

This aminolysis came to completion even at room temperature to furnish **7a** after 24 h. Diimines **7b** and **7c**[9] bearing *t*-butyl and *p*-methoxyphenyl groups were similarly prepared. In the latter case, severe conditions (reflux, 24 h) were necessary. Diamines such as $NH_2(CH_2)_2NH_2$ or $NH_2(CH_2)_3NH_2$ did not afford **7d** and **7e**, and the reaction mixtures were complicated. It is thought that the unreacted amino group caused further reactions. On the other hand, a pale-brown solid was precipitated in the reaction with $NH_2(CH_2)_6NH_2$. Based on the data of the mass spectrum (FAB, 395 ($M^+ + 1$))



Scheme 1.

and elemental analysis, it was determined to be the dimerized diimine **13f** ($n = 6$), which has a 22-membered ring. When a secondary amine, morpholine, was used, a mixture of regioisomers (**14a** and **14b**) was afforded in 56% yield, and ring-opened products were not obtained. The adduct **14a** is a thermodynamic-controlled product, and **14b** is a kinetic-controlled one. Based on the methyl hydrogen signals in the ^{1}H NMR, the ratio of both stereoisomers was a 1.2 : 1 (Scheme 5).

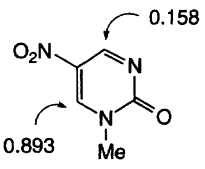
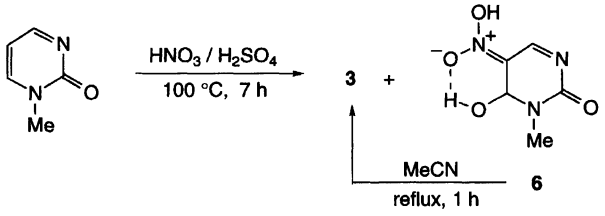


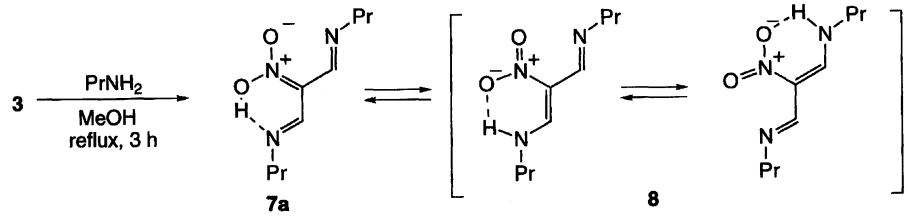
Fig. 1.



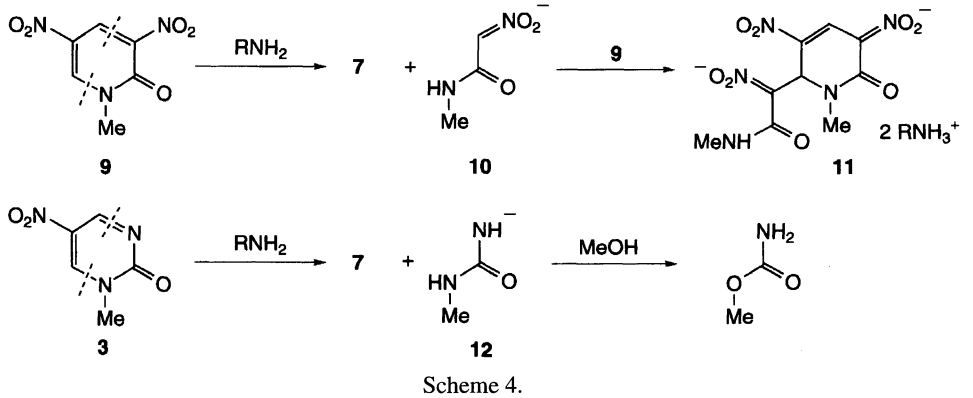
Scheme 2.

When products **7a** and **7b** were chromatographed on silica gel for purification, the half hydrolysis readily proceeded to furnish nitroenamines **15a** and **15b**. Also, diimine **7c**, having aromatic substituents, was sufficiently stable to be isolated by column chromatography. The other nitroenamines **15g—i** were similarly prepared from pyrimidinone **3** in good yields. It was found that nitroenamine **15a** was quantitatively reversed to compound **7a** by heating with $PrNH_2$ in MeOH. It was also possible to synthesize the unsymmetrically substituted product **7j** in 79% yield, since *t*-$BuNH_2$ was employed (Scheme 6).

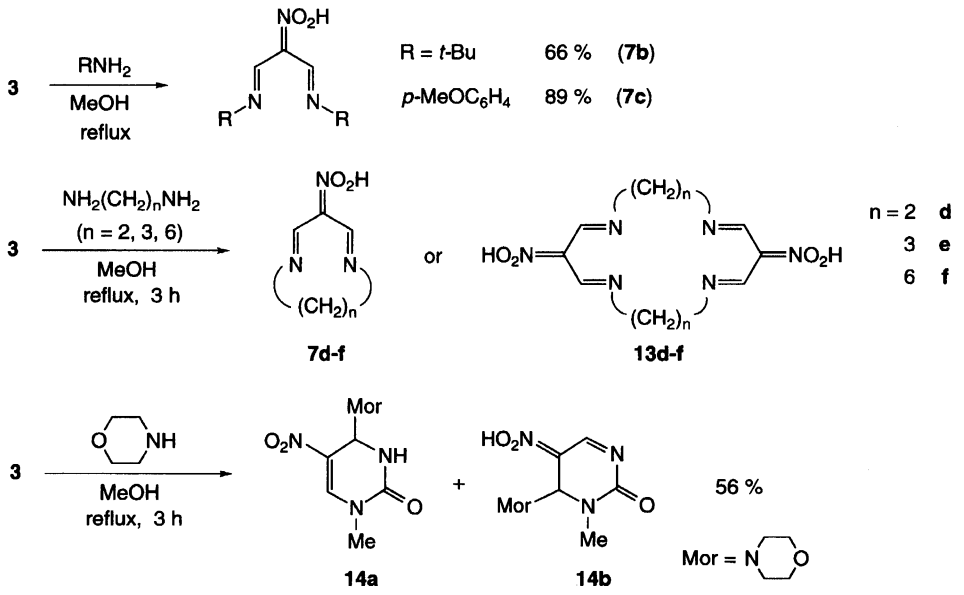
All of the structures of enamines **15** were confirmed by spectral and analytical data. The ^{1}H NMR data of *N*-methyl derivative **15h** were shown (Fig. 2). The large coupling



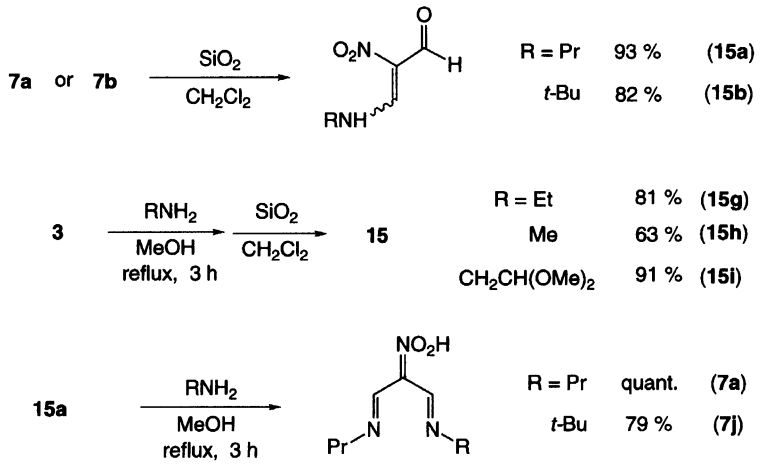
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

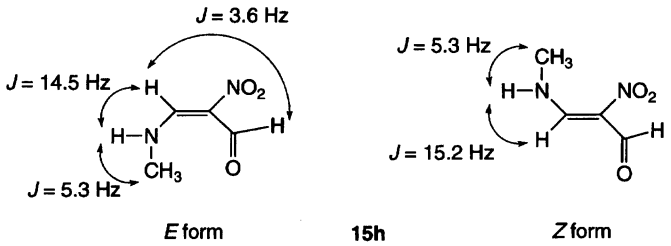
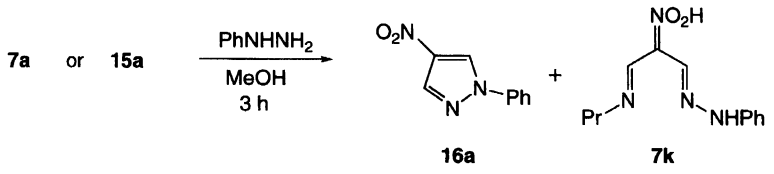


Fig. 2.

constants (14.5 and 15.2 Hz) are characteristic of the nitroenamine skeleton.[11] The exchange of the NH proton with D_2O was so slow that one day was necessary for completion. The isomer, having a long range coupling, was assigned to the *E* form, even though the value was large ($J = 3.6$ Hz). The *E*/*Z* ratio was approximately 3/1 in each case.

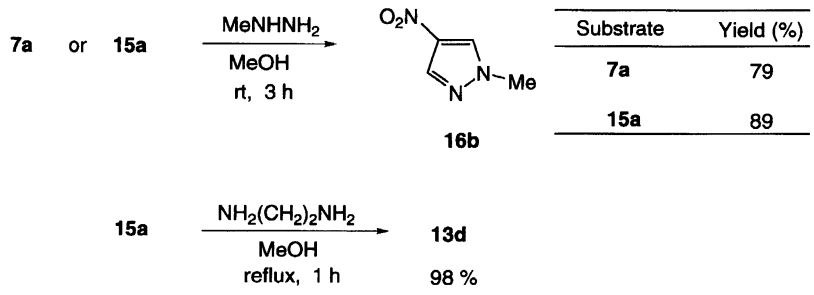
Although there have been many reports concerning the preparation of formylnitroenamines **15** by a treatment of sodium nitromalonaldehyde with equimolar amines, the structures of the products were subsequently corrected to the monoimine of nitromalonaldehyde.[12] Thus, the present reaction would be a facile synthetic method for nitroenamine **15** possessing a formyl group.

Diimine **7** and formylnitroenamine **15** are the derivatives of nitromalonaldehyde. Although nitromalonaldehyde is a useful building block for constructing of polyfunctionalized nitro compounds which would be difficult to prepare by any alternative procedure, it is too unstable to be isolated. As the synthetic equivalent of nitromalonaldehyde, its sodium salt has been employed from old times. Sodium nitromalon-



Substrate	Temp. (°C)	Ratio of **16a** / **7i**[a)]	Yield of **16a** (%)[b)]
7a	rt	33 / 67	–
	65	78 / 22	35
15a	rt	38 / 62	–
	65	82 / 18	52

a) determined by ^{1}H-NMR b) isolated yield



Substrate	Yield (%)
7a	79
15a	89

Scheme 7.

aldehyde, however, is used restrictively in only an aqueous media, and should be handled as an explosive material before purification.[12,13] Thus, an improvement in the other facile reagent substituting for nitromalonaldehyde is one of the important subjects. From this point of view, both reagents **7** and **15** obtained here could be utilized as the synthetic equivalent of nitromalonaldehyde in organic media, since they dissolve into almost all organic solvents.

As an example of the application of these reagents, the reactions of **7a** or **15a** with some bidentate nucleophiles, such as hydrazines and diamines, giving azaheterocycles, were studied. Since hydrazines were employed, the corresponding nitropyrazole derivatives **16a**,**b** were afforded.[14,15] In the case of $NH_2(CH_2)_2NH_2$, **13d** was quantitatively obtained, which was not obtained in a reaction with nitropyrimidinone **3** (Scheme 7). Although further investigations dealing with the other nucleophiles are necessary, these reagents (**7** and **15**) could be utilized as the synthetic equivalent of nitromalonaldehyde.

Experimental

The melting points were determined on a Yanaco micro-melting-point apparatus, and were uncorrected. All of the reagents and solvents were commercially available and used as received. MS spectra (EI, 70 eV) were recorded on a JEOL JMS-AX505HA or JEOL JMS-DX303 (**13d** and **13f**). IR spectra were recorded on a Horiba FT-200 infrared spectrometer and ^{1}H NMR spectra were measured on a Hitachi NMR R-1200 at 60 MHz or JEOL FT-NMR GSX at 270 MHz (**14**, **15g**, and **15h**) with TMS as an internal standard. Elemental microanalyses were performed using a Yanaco MT-3 CHN corder. None of the diimines **7** gave satisfactory analytical data, since further purification by column chromatography caused hydrolysis, affording nitroenamines **15**.

5, 6- Dihydro- 6- hydroxy- 1- methyl- 5- *aci*- nitropyrimidin-2(1*H*)-one (6). 1-Methylpyrimidin-2(1*H*)-one hydrochloride was prepared by an established method.[7] To a cold solution of pyrimidinone hydrochloride (2.0 g, 13.7 mmol) in 18 M H_2SO_4 (18 mL, 324 mmol, M = mol dm^{-3}), 15 M HNO_3 (3.3 mL, 49.5 mmol) was added and heated at 100 °C for 7 h. The reaction mixture was adjusted to pH 5 with Na_2CO_3. The solution was extracted with CH_2Cl_2 (100 mL×3). The organic layer was dried over $MgSO_4$ and concentrated to afford a mixture of nitropyrimidinone **3**[6] and **6** as a white solid. The ^{1}H NMR (DMSO-d_6) of the mixture is as follows. **3**: δ = 3.61 (s, 3H), 9.38 (d, J = 3.5 Hz, 1H), 9.65 (d, J = 3.5 Hz, 1H). **6**: δ = 2.98 (s, 3H), 5.90 (d, J = 7.3 Hz, 1H), 6.82 (d, J = 7.3 Hz, 1H, D_2O exchangeable), 8.12 (s, 1H), 10.2—11.0 (br, 1H, D_2O exchangeable). A solution of this mixture in MeCN (40 mL) was heated under reflux for 0.5 h, and concentrated to give pyrimidinone **3** (1.6 g, 10.5 mmol, 77%).

4,8-Diaza-6-*aci*-nitroundeca-4,7-diene (7a). To a solution of nitropyrimidinone (**3**, 310 mg, 2.0 mmol) in MeOH (40 mL), $PrNH_2$ (410 μL, 5.0 mmol) was added, and heated under reflux for 3 h. After removing the solvent, the residue was extracted with hexane (30 mL×3). The extract was concentrated to give **7a** (390 mg, 1.96 mmol, 98%, NMR pure) as pale yellow oil: IR (neat) 1649, 1601 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.97 (t, J = 6.7 Hz, 6H), 1.4—2.0 (m, 4H), 3.47 (t, J = 6.7 Hz, 4H), 8.77 (s, 2H), 10.1—12.0 (br, 1H); MS (EI) *m/z* 199 (M^+; 73), 182 (100), 170 (63), 113 (99), 43 (73). The residue was almost NH_2COOMe (86 mg, 1.14 mmol, 57%), which was confirmed by a comparison of the spectral data with those of a commercially available authentic sample. The other diimines **7b**,**c**[9] were prepared by a similar method.

1,5,12,16-Tetraaza-3,14-di-*aci*-nitrocyclododecosa-1,4,12,15-tetraene (13f). To a solution of $NH_2(CH_2)_6NH_2$ (128 mg, 1.1 mmol) in MeOH (20 mL), nitropyrimidinone (**3**, 155 mg, 1.0 mmol) was added, and heated under reflux for 3 h. During the

reaction, insoluble materials appeared. The precipitates were collected and dried under reduced pressure to afford **13f** (150 mg, 0.38 mmol, 76%) as a pale-brown solid: Mp 210—220 °C (decomp); IR (Nujol) 1645 cm^{-1}; MS (FAB) *m/z* 395 ($M^+ + 1$; 88), 289 (100), 190 (41). ^1H NMR could not measured as no solvent dissolving **13f** was found.

Found: C, 54.98; H, 7.62; N, 21.12%. Calcd for $C_{18}H_{30}N_6O_4$: C, 54.81; H, 7.67; N, 21.30%.

Adduct 14 of Pyrimidinone 3 with Morpholine. To a solution of nitropyrimidinone (**3**, 155 mg, 1.0 mmol) in MeOH (20 mL), morpholine (218 μL, 2.5 mmol) was added, and heated under reflux for 3 h. After concentration, the residue was recrystalized from PhH to give **14** (136 mg, 0.56 mmol, 56%) as yellow needles: Mp 162—165 °C; IR (Nujol) 3200—3600 (br), 1683, 1662 cm^{-1}; ^1H NMR (DMSO-d_6) δ = 2.4—2.6 (m, $4H_a + 4H_b$), 3.00 (s, $3H_b$), 3.18 (s, $3H_a$), 3.4—3.6 (m, $4H_a + 4H_b$), 5.23 (brs, $1H_a$), 5.45 (s, $1H_b$), 8.12 (s, $1H_b$), 8.49 (s, $1H_a$), 8.53 (brs, $1H_a$), 9.5—10.0 (br, $1H_b$), H_a and H_b stand for signals of each isomer. A measurement of ^1H-^1H 2D NMR nuclear Overhauser enhancements (NOEs) supported these assignments; the correlation between the methyl group and the olefinic proton was observed in the case of **14a**, and that between the methyl group and the methine proton was observed in the case of **14b**.

Found: C, 44.98; H, 5.80; N, 22.78%. Calcd for $C_9H_{14}N_4O_4$: C, 44.62; H, 5.83; N, 23.13%.

3-Propylamino-2-nitropropenal (15a). Diimine (**7a**, 200 mg, 1 mmol) was charged on a silica gel column (Merck, 20 g) and standed at room temperature for 0.5 h. CH_2Cl_2 elution (300 mL) was concentrated to yield nitroenamine (**15a**, 150 mg, 93%) as pale-yellow plates: Mp 52—53 °C; IR (neat) 3219, 1655, 1602, 1508, 1311 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.04 (t, $3H_E + 3H_Z$, J = 6.5 Hz), 1.5—2.0 (m, $2H_E + 2H_Z$), 3.3—3.7 (m, $3H_E + 3H_Z$), 8.03 (d, $1H_Z$, J = 16.0 Hz), 8.61 (dd, $1H_E$, J = 14.6, 3.8 Hz), 10.20 (s, $1H_Z$), 10.29 (d, $1H_E$, J = 3.8 Hz), 10.4—11.3 (br, $1H_E + 1H_Z$), H_E/H_Z = 74/26.

Found: C, 45.89; H, 6.53; N, 17.45%. Calcd for $C_6H_{10}N_2O_3$: C, 45.57; H, 6.37; N, 17.71%.

3-*t*-Butylamino-2-nitropropenal (15b). A similar treatment of **7b** (227 mg, 1.0 mmol) to that of **7a** afforded **15b** (141 mg, 0.82 mmol, 82%) as pale-yellow plates: Mp 107—108 °C; ^1H NMR ($CDCl_3$) δ = 1.49 (s, $9H_E + 9H_Z$), 7.94 (d, J = 15.9 Hz, $1H_Z$), 8.51 (dd, J = 14.9, 3.6 Hz, $1H_E$), 10.00 (s, $1H_Z$), 10.2—11.7 (br, $1H_E + 1H_Z$), H_E/H_Z = 79/21.

Found: C, 49.14; H, 7.28; N, 15.90%. Calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.03; N, 16.27%.

3-Ethylamino-2-nitropropenal (15g). An aqueous $EtNH_2$ solution was used. Colorless plates: Mp 85—86 °C; ^1H NMR ($CDCl_3$) δ = 1.39 (t, J = 7.3 Hz, $3H_Z$), 1.40 (t, J = 7.3 Hz, $3H_E$), 3.58 (q, J = 7.3 Hz, $2H_E$), 3.68 (q, J = 7.3 Hz, $2H_Z$), 7.95 (d, J = 15.5 Hz, $1H_Z$), 8.52 (dd, J = 14.5, 3.0 Hz, $1H_E$), 9.0—9.9 (br, $1H_Z$), 10.06 (s, $1H_Z$), 10.15 (d, J = 3.0 Hz, $1H_E$), 10.6—11.6 (br, $1H_E$), H_E/H_Z = 73/27.

Found: C, 42.06; H, 5.72; N, 19.13%. Calcd for $C_5H_8N_2O_3$: C, 41.67; H, 5.59; N, 19.44%.

3-Methylamino-2-nitropropenal (15h). An aqueous $MeNH_2$ solution was used. Colorless plates: Mp 154—155 °C; ^1H NMR ($CDCl_3$) δ = 3.32 (s, $3H_E$), 3.39 (s, $3H_Z$), 7.92 (d, J = 15.2 Hz, $1H_Z$), 8.50 (dd, J = 14.5, 3.6 Hz, $1H_E$), 9.3—9.8 (br, $1H_Z$), 10.06 (s, $1H_Z$), 10.15 (d, J = 3.6 Hz, $1H_E$), 10.2—10.8 (br, $1H_E$), H_E/H_Z = 76/24.

Found: C, 37.23; H, 4.64; N, 21.29%. Calcd for $C_4H_6N_2O_3$: C, 36.93; H, 4.65; N, 21.53%.

3-(2,2-Dimethoxyethylamino)-2-nitropropenal (15i). Colorless plates: Mp 75—76 °C; ^1H NMR ($CDCl_3$) δ = 3.51 (s, $6H_Z + 6H_E$), 3.64 (d, J = 6.2 Hz, $2H_Z + 2H_E$), 4.55 (t, J = 6.2 Hz, $1H_Z + 1H_E$), 8.04 (d, J = 16.0 Hz, $1H_Z$), 8.58 (dd, J = 14.8, 3.6 Hz, $1H_E$), 10.22 (s, $1H_Z$), 10.31 (d, J = 3.6 Hz, $1H_E$), 8.9—11.0 (br, $1H_Z + 1H_E$), H_E/H_Z = 67/33.

Found: C, 41.47; H, 5.92; N, 13.49%. Calcd for $C_7H_{12}N_2O_5$: C, 41.18; H, 5.92; N, 13.72%.

Conversion of 15a into 7a. To a solution of nitroenamine (**15a**, 158 mg, 1.0 mmol) in MeOH (15.8 mL), $PrNH_2$ (100 μL, 1.2 mmol) was added and refluxed for 1 h. The reaction mixture was concentrated under reduced pressure to afford diimine (**7a**, 197 mg, 1.0 mmol) as pale yellow oil.

3,7-Diaza-2,2-dimethyl-5-*aci*-nitrodeca-3,6-diene (7j). A similar treatment of **7a** (227 mg, 1.0 mmol) with *t*-$BuNH_2$ afforded **7j** (168 mg, 0.79 mmol, 79%) as a pale-yellow oil: ^1H NMR ($CDCl_3$) δ = 0.99 (t, J = 6.5 Hz, 3H), 1.38 (s, 9H), 1.5—2.0 (m, 2H), 3.48 (t, J = 6.5 Hz, 2H), 8.79 (s, 1H), 8.85 (s, 1H), 10.2—10.4 (br, 1H); MS (EI) *m/z* 213 (M^+; 25), 154 (26), 140 (51), 139 (41), 113 (31), 98 (35), 57 (100), 41 (77).

Synthesis of Azaheterocycles (16 and 13d). To a solution of diimine **7a** or nitroenamine **15a** (1.0 mmol) in MeOH (10 mL), hydrazine or diamine (1.1 mmol) was added, and stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure to afford **16**[14] or **13d**.

1,5,8,12-Tetraaza-3,10-di-*aci*-nitrocyclotetradeca-1,4,8,11-tetraene (13d). Colorless solid: Mp 200—215 °C (decomp); ^1H NMR (DMSO-d_6) δ = 3.65 (s, 8H), 8.62 (s, 4H), 9.8—11.2 (br, 2H); MS (EI) *m/z* 282 (M^+; 5), 141 (100), 81 (44), 66 (90).

Found: C, 42.68; H, 5.02; N, 30.07%. Calcd for $C_{10}H_{14}N_6O_4$: C, 42.55; H, 5.00; N, 29.77%.

We would like to thank Mr. Hiroshi Moriguchi, Faculty of Engineering, Osaka University for measuring the mass spectra. The present work was supported by a Grant-in Aid for Scientific Research Nos. 05640605 and 07855107 from the Ministry of Education, Science and Culture, and supported by Daiichi Pharmaceutical Co., Ltd. Award in Synthetic Organic Chemistry, Japan.

References

1) N. Nishiwaki, Y. Mizukawa, M. Ohta, R. Terai, Y. Tohda, and M. Ariga, *Heterocycl. Commun.*, **2**, 21 (1996).

2) N. Nishiwaki, E. Wakamura, Y. Nishida, Y. Tohda, and M. Ariga, *Heterocycl. Commun.*, in press.

3) V. V. Perekalin, E. S. Lipina, V. M. Berestovitskaya, and D. A. Efremov, "Nitroalkenes Conjugated Nitro Compounds," Wiley, New York (1994), p. 210; S. Rajappa, *Tetrahedron*, **37**, 1453 (1981).

4) Y. Tohda, T. Kawahara, M. Eiraku, K. Tani, N. Nishiwaki, and M. Ariga, *Bull. Chem. Soc. Jpn.*, **67**, 2176 (1994).

5) N. Nishiwaki, T. Matsunaga, Y. Tohda, and M. Ariga, *Heterocycles*, **38**, 249 (1994).

6) V. L. Rusinov, O. N. Chupakhin, and H. C. van der Plas, *Heterocycles*, **40**, 441 (1995); J. J. Fox, T.-L. Su, L. M. Stempel, and K. A. Watanabe, *J. Org. Chem.*, **47**, 1081 (1982).

7) J. J. Fox and D. V. Praag, *J. Am. Chem. Soc.*, **82**, 486 (1960).

8) The nucleophilic susceptibilities were estimated by the MOPAC (PM3) molecular orbital calculation using CAChe system.

9) Y. Tohda, M. Ariga, T. Kawashima, and E. Matsumura, *Bull. Chem. Soc. Jpn.*, **60**, 201 (1987).

10) J. Alcazar, I. Almena, M. Begtrup, and A. de la Hoz, *J.*

Chem. Soc., Perkin Trans. 1, **1995**, 2773.

11) C. D. Bedford and A. T. Nielsen, *J. Org. Chem.*, **44**, 633 (1979); A. I. Fetell and H. Feuer, *J. Org. Chem.*, **43**, 497 (1978); O. S. Wolfbeis, *Chem. Ber.*, **110**, 2480 (1977).

12) P. E. Fanta and R. A. Stein, *Chem. Rev.*, **60**, 261 (1960), and references cited in.

13) P. E. Fanta, *Org. Synth.*, Coll. Vol. 4, 844 (1963).

14) J. H. Boyer, "Nitroazoles The C–Nitro Derivatives of Five-Membered N- and N,O-Heterocycles," VCH, Weinheim (1986), p. 186.

15) The reaction of the sodium salt with hydrazines in aqueous solution was reported, but yields of pyrazoles **16** were not given: H. B. Hill and J. Torrey, Jr., *Am. Chem. J.*, **22**, 89 (1899).