A New and Efficient Synthesis of 2-Methyl-3-nitro-1,2-dihydropyridines by Heterocyclic Annulation Reactions of *sec*-Nitrodienamines with Acetaldehyde

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The *sec*-nitrodienamines 3 were prepared by reaction of the *tert*-nitrodienamine 1 with primary amines. The reaction of 3 with acetaldehyde afforded 2-methyl-3-nitro-1,2-dihydropyridines 5, providing a new and efficient heterocyclic annulation reaction.

Key words nitrodienamine; primary amine; acetaldehyde; 2-methyl-3-nitro-1,2-dihydropyridine; heterocyclic annulation reaction

In the preceding paper,[1] we reported the cycloaddition reactions of 1-(*N*,*N*-dimethylamino)-4-nitro-1,3-butadiene (*tert*-nitrodienamine **1**) with α,β-unsaturated carbonyl compounds and quinones, as well as the condensation reactions of **1** with Grignard reagents prepared from indoles and carbazole. We are interested in the reactivities of nitrodienamines containing enaminic, olefinic, and other attractive moieties as well as aminodienyl esters and aminoacrylates synthons, because of their electronic "push pull" character which can lead to interesting cycloaddition reactions.[2—4] Dihydropyridine chemistry is of interest from the point of view of pure research on heterocyclic compounds and also from a biological point of view.[5] The *sec*-nitrodienamines **3** were prepared by the reaction of the *tert*-nitrodienamine **1** with primary amines. The reactions of **3** with acetaldehyde afforded 2-methyl-3-nitro-1,2-dihydropyridines **5**, providing a new and efficient heterocyclic annulation reaction.

The 1-(*N*-alkylamino)-4-nitro-1,3-butadiene derivatives listed in Table 1, *sec*-nitrodienamines **3a**—**f**, were selected for investigation (Chart 1). The *sec*-nitrodienamines **3** were prepared by the reaction of the *tert*-nitrodienamine **1** with the corresponding primary amines, namely, 2-phenylethylamine (**2a**), benzylamine (**2b**), octylamine (**2c**), 2-(3,4-dimethoxyphenyl)ethylamine (**2d**), (4-pyridyl)methylamine (**2e**), and 2-(4-pyridyl)ethylamine (**2f**), respectively, under stirring at room temperature in benzene or tetrahydrofuran (THF) (Table 1).

First, we planned to prepare 2-methyl-3-nitro-1-phenethyl-1,2-dihydropyridine (**5a**) by a cycloaddition reaction of the *sec*-nitrodienamine **3a** with acetaldehyde. Expectedly, a heterocyclic annulation product, **5a**, was obtained in 92% yield by stirring **3a** with excess acetaldehyde in benzene in a sealed tube at room temperature. The structure of **5a** was proposed on the basis of the following spectroscopic analyses. The molecular formula of **5a** was found to be $C_{14}H_{16}N_2O_2$. The ^{1}H-NMR spectrum of **5a** showed the presence of two methylene protons at δ 2.93 (2H, t, J=7.0 Hz), 3.43—3.49 (1H, m), 3.65—3.71 (1H, m), and aromatic protons at δ 7.05—7.33 (5H, m) due to a phenethyl group, methyl protons at δ 1.19 (3H, d, J=6.2 Hz), a methine proton at δ 5.12 (1H, q, J=6.2 Hz), and three olefinic protons at δ 4.85 (1H, dd, J=7.4, 6.2 Hz), 6.46 (1H, d, J=6.2 Hz) and 7.58 (1H, d, J=7.4 Hz) due to a 1,2-dihydropyridine ring. The IR spectrum of **5a** showed absorption bands at 1616, 1514, 1481, 1435, 1358, and 1325 cm^{-1} due to nitro, two olefinic, and phenethyl groups. The nuclear Overhauser effect correlation spectroscopy (NOESY) of **5a** showed the presence of cross-peaks between the methylene protons of the phenethyl group at δ 3.43—3.71 (2H) and 2-methyl and 6-olefinic protons at δ 1.19 (3H) and 6.46 (1H) due to a 1,2-dihydropyridine ring, and a cross-peak between the methylene proton of the phenethyl group at δ 3.65—3.71 (1H) and a methine proton at δ 5.12 (1H). Therefore, it may be deduced that **5a** is a 1,2-dihydropyridine.

In a similar manner, several other substituted 2-methyl-3-nitro-1,2-dihydropyridines **5b**—**f** listed in Table 2 were prepared from the corresponding **3b**—**f** (Chart 1, Table 2).

The heterocyclic annulation reactions of *sec*-nitrodienamines **3** with acetaldehyde may be explained as follows. Initially, the condensation reaction of **3** with acetaldehyde may generate the intermediate **6**, followed by intramolecular ring closure with dehydration, which could lead to 1,2-dihydropyridines **5**, as shown in Chart 2.

These results provide a new and efficient method of synthesizing 2-methyl-3-nitro-1,2-dihydropyridines **5** by utilizing *sec*-nitrodienamines **3**.

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-200 or JASCO FT/IR-8000 spectrometer, and ^{1}H-NMR spectra on a JEOL EX-90 or JEOL JNM-α500 spectrometer with tetramethylsilane as an internal standard. MS were recorded on a JEOL JMS-D 300 spectrometer. Elemental

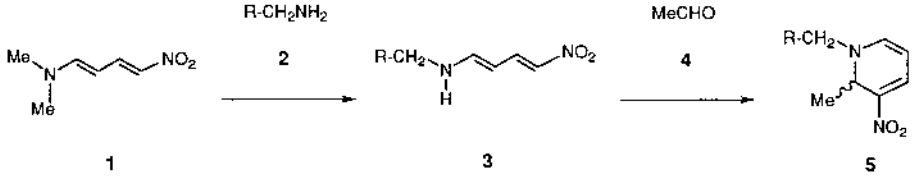

Chart 1

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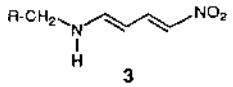
Table 1. The Reactions of *tert*-Nitrodienamine **1** with Primary Amines **2**[a)]



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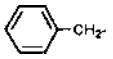
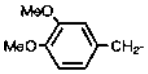
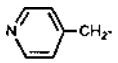
Starting amine	R	Reaction time (h)	Reaction product	Yield (%)	Appearance [solvent, mp (°C)]	^{1}H-NMR, δ (ppm)	IR (cm^{-1})
2a		3.5	**3a**	95	Dark yellow oil	2.91 (2H, t, *J*=6.8 Hz, methylene H), 3.46 (2H, t, *J*=6.8 Hz, methylene H), 5.33 (1H, t, *J*=12.3 Hz, olefinic H), 5.72 (1H, br s, NH), 6.97 (2H, d, *J*=12.3 Hz, olefinic H), 7.10—7.47 (5H, m, aromatic H), 7.77 (1H, t, *J*=12.3 Hz, olefinic H), [$CDCl_3$]	3281, 1615, 1543, 1497, 1454, 1350, (neat)
2b		3.5	**3b**	92	Dark yellow oil	4.34 (2H, d, *J*=5.1 Hz, methylene H), 5.51 (1H, br s, NH), 5.37 (1H, t, *J*=12.5 Hz, olefinic H), 6.97 (1H, d, *J*=12.5 Hz, olefinic H), 7.07 (1H, d, *J*=12.5 Hz, olefinic H), 7.78 (1H, t, *J*=12.3 Hz, olefinic H), 7.21—7.46 (5H, m, aromatic H), [$CDCl_3$]	3285, 1615, 1584, 1497, 1454, 1348, (neat)
2c	$Me(CH_2)_6$-	1.5	**3c**	95	Dark brown oil	0.88 (3H, t, *J*=6.2 Hz, Me), 1.09—1.49 (12H, m, methylene H), 3.18 (2H, t, *J*=6.7 Hz, methylene H), 5.34 (1H, t, *J*=12.3 Hz, olefinic H), 5.40 (1H, br s, NH), 7.00 (1H, d, *J*=12.3 Hz, olefinic H), 7.05 (1H, d, *J*=12.3 Hz, olefinic H), 7.82 (1H, t, *J*=12.3 Hz, olefinic H), [$CDCl_3$]	3279, 1614, 1584, 1550, 1464, 1430, (neat)
2d		3.5	**3d**	90	Dark yellow oil	2.85 (2H, t, *J*=6.8 Hz, methylene H), 3.36 (1H, d, *J*=6.8 Hz, methylene H), 3.47 (1H, d, *J*=6.8 Hz, methylene H), 3.86 (6H, s, OMe), 5.36 (1H, t, *J*=12.3 Hz, olefinic H), 5.79 (1H, br s, NH), 6.65—7.16 (5H, m, aromatic and olefinic H), 7.79 (1H, t, *J*=12.3 Hz, olefinic H), [$CDCl_3$]	3312, 1620, 1559, 1541, 1520, 1456, (neat)
2e		3.5	**3e**	87	Orange needles [AcOEt, 136—138]	4.43 (2H, s, methylene H), 5.42 (1H, t, *J*=12.4 Hz, olefinic H), 7.01 (1H, d, *J*=12.4 Hz, olefinic H), 7.29 (2H, d, *J*=5.9 Hz, aromatic H), 7.60 (1H, d, *J*=12.4 Hz, olefinic H), 7.90 (1H, t, *J*=12.4 Hz, olefinic H), 8.55 (2H, d, *J*=5.9 Hz, aromatic H), [DMSO-d_6]	3194, 1605, 1562, 1545, 1435, 1416, (KBr)
2f		2.5	**3f**	78	Red needles [AcOEt, 125—126 (dec.)]	2.85 (2H, t, *J*=6.7 Hz, methylene H), 3.45 (2H, t, *J*=6.7 Hz, methylene H), 5.52 (1H, t, *J*=12.3 Hz, olefinic H), 7.03 (1H, d, *J*=12.3 Hz, olefinic H), 7.29 (2H, d, *J*=5.8 Hz, aromatic H), 7.46 (1H, d, *J*=12.3 Hz, olefinic H), 7.91 (1H, t, *J*=12.3 Hz, olefinic H), 8.49 (2H, d, *J*=5.8 Hz, aromatic H), [DMSO-d_6]	3385, 1605, 1543, 1516, 1483, 1435, (KBr)

a) All reactions were run at room temperature.

analyses were recorded on a Yanaco CHN-corder MT-3. Wakogel C-200 (silica gel) and Merck Kieselgel G nach Stahl (silica gel) and NH-DM 1020 (basic 100 Å type silica gel, Fuji Silysia Chemical, Ltd.) were used for column chromatography and thin layer chromatography (TLC), respectively. All runs were carried out under an argon atmosphere.

General Procedure for Reactions of *tert*-Nitrodienamine 1 with Primary Amines 2 A solution of the *tert*-nitrodienamine **1** (40 mg, 0.28 mmol) and an amine **2** (0.83—3.49 mmol) in benzene (8 ml) or THF (4 ml) was stirred at room temperature for an appropriate period until the disappearance of **1** (checked by TLC). The reaction mixture was concentrated under a vacuum, then the residue was subjected to silica gel column chromatography with appropriate solvents. The isolated yield of **3** is based on **1**. The reaction conditions and properties of the prepared compounds **3** are shown in Table 1.

4-Nitro-1-phenethylamino-1,3-butadiene (**3a**): Amine **2a**: 119 mg (0.98 mmol). Reaction solvent: benzene. Solvent for chromatography: 20% ethyl acetate in hexane. Product **3a**: 58 mg. HR-MS *m/z*: Calcd for $C_{12}H_{14}N_2O_2$ (M^+): 218.1081. Found: 218.1056.

1-Benzylamino-4-nitro-1,3-butadiene (**3b**): Amine **2b**: 106 mg (1.02 mmol). Reaction solvent: benzene. Solvent for chromatography: 20% ethyl acetate in hexane. Product **3b**: 50 mg. HR-MS *m/z*: Calcd for $C_{11}H_{12}N_2O_2$ (M^+): 204.0900. Found: 204.0933.

4-Nitro-1-octylamino-1,3-butadiene (**3c**): Amine **2c**: 450 mg (3.49 mmol). Reaction solvent: benzene. Solvent for chromatography: 50% ethyl acetate in hexane. Product **3c**: 61 mg. CI-MS *m/z*: 227 ($M^+ + 1$).

1-[2-(3,4-Dimethoxyphenyl)ethylamino]-4-nitro-1,3-butadiene (**3d**): Amine **2d**: 151.7 mg (0.83 mmol). Reaction solvent: benzene. Solvent for chromatography: 20% ethyl acetate in hexane. Product **3d**: 75 mg. HR-MS *m/z*: Calcd for $C_{14}H_{18}N_2O_4$ (M^+): 278.1265. Found: 278.1230.

4-Nitro-1-(4-pyridyl)methylamino-1,3-butadiene (**3e**): Amine **2e**: 242 mg (2.24 mmol). Reaction solvent: THF. Solvent for chromatography: 10% methanol in ethyl acetate. Product **3e**: 50 mg. *Anal*. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.33; H, 5.49; N, 20.41.

4-Nitro-1-[2-(4-pyridyl)ethylamino]-1,3-butadiene (**3f**): Amine **2f**: 347 mg (2.34 mmol). Reaction solvent: THF. Solvent for chromatography: 13% methanol in ethyl acetate. Product **3f**: 48 mg. CI-MS *m/z*: 220 ($M^+ + 1$).

General Procedure for Reactions of *sec*-Nitrodienamine 3 with Acetaldehyde A solution of a *sec*-nitrodienamine **3** (0.214 mmol) and acetaldehyde (0.4 ml, 7.16 mmol) in THF (3 ml) in a sealed tube was stirred at room temperature for an appropriate period until the disappearance of **3** (checked by TLC). The reaction mixture was concentrated under a vacuum, then the residue was subjected to silica gel column chromatography. The reaction conditions and properties of the prepared compounds **5** are shown in Table 2.

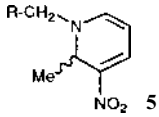
2-Methyl-3-nitro-1-phenethyl-1,2-dihydropyridine (**5a**): Substrate **3a**: 47 mg. Solvent for chromatography: 20% ethyl acetate in hexane. Product **5a**: 48 mg. HR-MS *m/z*: Calcd for $C_{14}H_{16}N_2O_2$ (M^+): 244.1212. Found: 244.1217.

1-Benzyl-2-methyl-3-nitro-1,2-dihydropyridine (**5b**): Substrate **3b**: 44 mg. Solvent for chromatography: 20% ethyl acetate in hexane. Product **5b**: 47 mg. HR-MS *m/z*: Calcd for $C_{13}H_{14}N_2O_2$ (M^+): 230.1053. Found: 230.1051.

2-Methyl-3-nitro-1-octyl-1,2-dihydropyridine (**5c**): Substrate **3c**: 48 mg. Solvent for chromatography: 20% ethyl acetate in hexane. Product **5c**: 50 mg. HR-MS *m/z*: Calcd for $C_{14}H_{24}N_2O_2$ (M^+): 252.1835. Found: 252.1818.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-2-methyl-3-nitro-1,2-dihydropyridine (**5d**): Substrate **3d**: 60 mg. Solvent for chromatography: 20% ethyl acetate in hexane. Product **5d**: 57 mg. HR-MS *m/z*: Calcd for $C_{16}H_{20}N_2O_4$ (M^+): 304.1420. Found: 304.1388.

Table 2. The Heterocyclic Annulation Reactions of *sec*-Nitrodienamines **3** with Acetaldehyde **4**[a)]



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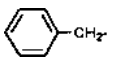
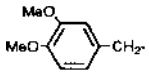
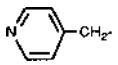
Starting amine	R	Reaction time (h)	Reaction product	Yield (%)	Appearance	^{1}H-NMR ($CDCl_3$), δ (ppm)	IR (cm^{-1})
3a		1.2	**5a**	92	Dark red oil	1.19 (3H, d, J=6.2 Hz, Me), 2.93 (2H, t, J=7.0 Hz, methylene H), 3.43—3.49 (1H, m, methylene H), 3.65—3.71 (1H, m, methylene H), 4.85 (1H, dd, J=7.4, 6.2 Hz, olefinic H), 5.12 (1H, q, J=6.2 Hz, methine H), 6.46 (1H, d, J=6.2 Hz, olefinic H), 7.05—7.33 (5H, m, aromatic H), 7.58 (1H, d, J=7.4 Hz, olefinic H).	1616, 1514, 1481, 1435, 1358, 1325, (neat)
3b		1.5	**5b**	95	Dark red oil	1.21 (3H, d, J=6.2 Hz, Me), 4.42 (1H, d, J=16.4 Hz, methylene H), 4.61 (1H, d, J=16.4 Hz, methylene H), 4.98 (1H, dd, J=7.4, 6.2 Hz, olefinic H), 5.07 (1H, q, J=6.2 Hz, methine H), 6.77 (1H, d, J=7.4 Hz, olefinic H), 7.26—7.43 (5H, m, aromatic H), 7.62 (1H, d, J=6.2 Hz, olefinic H).	1618, 1514, 1481, 1450, 1437, 1360, (neat)
3c	$Me(CH_2)_6$-	1.5	**5c**	93	Dark red oil	0.88 (3H, t, J=5.5 Hz, Me), 1.02—1.92 (12H, m, methylene H), 1.20 (3H, d, J=6.2 Hz, Me), 3.06—3.61 (2H, m, methylene H), 4.94 (1H, dd, J=7.3, 6.2 Hz, olefinic H), 5.16 (1H, q, J=6.2 Hz, methine H), 6.71 (1H, d, J=6.2 Hz, olefinic H), 7.61 (1H, d, J=7.3 Hz, olefinic H).	1620, 1518, 1480, 1460, 1441, 1360, (neat)
3d		1.5	**5d**	88	Dark red oil	1.19 (3H, d, J=6.2 Hz, Me), 2.93 (2H, t, J=7.0 Hz, methylene H), 3.29—3.86 (2H, m, methylene H), 3.81 (3H, s, OMe), 3.85 (3H, s, OMe), 4.85 (1H, dd, J=7.4, 6.2 Hz, olefinic H), 5.12 (1H, q, J=6.2 Hz, methine H), 6.46 (1H, d, J=6.2 Hz, olefinic H), 7.05—7.33 (3H, m, aromatic H), 7.58 (1H, d, J=7.4 Hz, olefinic H).	1620, 1610, 1558, 1541, 1520, 1456, (neat)
3e		1.0	**5e**	88	Dark red oil	1.23 (3H, d, J=6.3 Hz, Me), 4.41 (1H, d, J=16.1 Hz, methylene H), 4.42 (1H, d, J=16.1 Hz, methylene H), 5.01 (1H, q, J=6.3 Hz, methine H), 5.04 (1H, dd, J=7.4, 6.2 Hz, olefinic H), 6.72 (1H, d, J=6.2 Hz, olefinic H), 7.18 (2H, d, J=5.9 Hz, aromatic H), 7.63 (1H, d, J=7.4 Hz, olefinic H), 8.63 (2H, d, J=5.9 Hz, aromatic H).	1618, 1559, 1541, 1520, 1456, 1362, (neat)
3f		1.0	**5f**	89	Dark red oil	1.20 (3H, d, J=6.2 Hz, Me), 2.94 (2H, t, J=6.9 Hz, methylene H), 3.12—3.90 (2H, m, methylene H), 4.86 (1H, dd, J=7.4, 6.2 Hz, olefinic H), 5.16 (1H, q, J=6.2 Hz, methine H), 6.42 (1H, d, J=6.2 Hz, olefinic H), 7.07 (2H, dd, J=4.3, 1.7 Hz, aromatic H), 7.57 (1H, d, J=7.4 Hz, olefinic H), 8.53 (2H, dd, J=4.3, 1.7 Hz, aromatic H).	1605, 1543, 1516, 1483, 1435, 1362, (neat)

a) All reactions were run at room temperature.

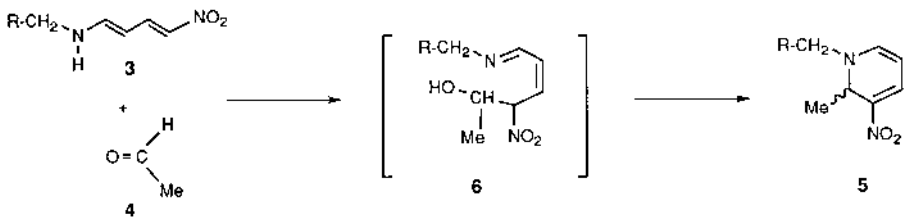


Chart 2

2-Methyl-3-nitro-1-(4-pyridylmethyl)-1,2-dihydropyridine (**5e**): Substrate **3e**: 44 mg. Solvent for chromatography: 10% methanol in ethyl acetate. Product **5e**: 44 mg. HR-MS *m/z*: Calcd for $C_{12}H_{13}N_3O_2$ (M^+): 231.1008. Found: 231.1026.

2-Methyl-3-nitro-1-[2-(4-pyridyl)ethyl]-1,2-dihydropyridine (**5f**): Substrate **3f**: 47 mg. Solvent for chromatography: 20% methanol in ethyl acetate. Product **5f**: 47 mg. HR-MS *m/z*: Calcd for $C_{13}H_{15}N_3O_2$ (M^+): 245.1164. Found: 245.1214.

References

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5) *a*) Hantzsch A., *Justus Liebigs Ann. Chem.*, **215**, 1—82 (1882); *b*) Eisner U., Kuthan J., *Chem. Rev.*, **72**, 1—42 (1972); *c*) Kuthan J., Kurfürst A., *Ind. Eng. Chem. Prod. Res. Dev.*, 191—261 (1982); *d*) Stout D. M., Meyers A. I., *Chem. Rev.*, **82**, 223—243 (1982).