Synthesis of 2-Substituted 3-Nitro-1,2-dihydropyridines by Heterocyclic Annulation Reactions of a *sec*-Nitrodienamine with Aldehyde Compounds

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The reaction of a *sec*-nitrodienamine 3 with aldehyde compounds afforded 2-substituted 3-nitro-1,2-dihydropyridines 5, providing a heterocyclic annulation reaction.

Key words nitrodienamine; aldehyde; 2-substituted 3-nitro-1,2-dihydropyridine; heterocyclic annulation reaction

We are interested in the reactivities of *tert*-nitrodienamines [*ex.* 1-(*N*,*N*-dimethylamino)-4-nitro-1,3-butadiene **1**] and *sec*-nitrodienamines [*ex.* 4-nitro-1-(2-phenethylamino)-1,3-butadiene **3**] as potentially useful synthons in organic synthesis. The chemistry of nitrodienamines exploits in the enaminic, dienic, and electronic “push pull” character of these molecules, and leads to interesting cycloaddition reactions as well as aminodienyl esters and aminoacrylate synthons.[1—4] The reactions of a *sec*-nitrodienamine, 4-nitro-1-(2-phenethylamino)-1,3-butadiene **3**, with aldehyde compounds **4** afforded 2-substituted 3-nitro-1-(2-phenethyl)-1,2-dihydropyridines **5**, which provide a heterocyclic annulation reaction.

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] Regarding studies on dihydropyridines, we recently reported the synthesis of 1-substituted 2-methyl-3-nitro-1,2-dihydropyridines by the reaction of *sec*-nitrodienamines with acetaldehyde (**4a**) in good yield.[1d] Here, we describe full details of the heterocyclic annulation reactions of **3** with aldehydes **4** to prepare 2-substituted 3-nitro-1-(2-phenethyl)-1,2-dihydropyridines **5** (Chart 1). The *sec*-nitrodienamine **3** was prepared by the reaction of *tert*-nitrodienamine **1** with 2-phenethylamine in benzene at room temperature in 95% yield.[1d]

The reaction of **3** with propionaldehyde (**4b**) under neat refluxing conditions provided 2-ethyl-3-nitro-1-(2-phenethyl)-1,2-dihydropyridine (**5b**) in 82% yield. The structure of the product **5b** was confirmed on the basis of the following spectroscopic analyses. The molecular formula of **5b** was found to be $C_{15}H_{18}N_2O_2$. The ^{1}H-NMR spectrum indicated the presence of two methylene protons at δ 2.92 (2H, t, J=6.8 Hz), 3.58 (1H, dt, J=13.6, 6.8 Hz), 3.64 (1H, dt, J=13.6, 6.8 Hz), and aromatic protons at δ 7.09—7.26 (5H, m) due to a phenethyl group, ethyl protons at δ 0.91 (3H, t, J=7.7 Hz, Me) and 1.38—1.92 (2H, m), a methine proton at δ 5.05 (1H, t, J=4.6 Hz), and three olefinic protons at δ 4.83 (1H, dd, J=7.5, 6.4 Hz), 6.53 (1H, d, J=6.4 Hz) and 7.65 (1H, d, J=7.5 Hz) due to a 1,2-dihydropyridine ring. The IR spectrum of **5b** showed absorption bands at 1624, 1541, 1516, 1474, 1456, and 1360 cm^{-1} due to nitro, two olefinic, and phenethyl groups.

In a similar manner, several other 2-substituted 3-nitro-1-(2-phenethyl)-1,2-dihydropyridines **5c**—**g** listed in Table 1 were prepared from the corresponding **4c**—**g** (Chart 1, Table 1).

Unexpectedly, treatment of the *sec*-nitrodienamine **3** with 35% formaldehyde solution (**4h**) in tetrahydrofuran (THF) afforded 2-methyl-3-nitro-1-(2-phenethyl)-1,2-dihydropyridine (**5a**) and 3-nitro-2-(3-nitrophenyl)-1-(2-phenethyl)-1,2-dihydropyridine (**5i**) in 2% and 8% yields, respectively. The heterocyclic annulation reactions of **3** with aldehydes may be explained as follows. Initially, the hydrolysis reaction of **3** may generate acetaldehyde (**4a**) *via* intermediate **6a**, and self-condensation reaction of **3** may generate 3-nitrobenzaldehyde (**4i**) *via* intermediate **6i**. Then, the condensation reactions of **3** with **4a** and **4i**, followed by intramolecular ring closure with dehydration could lead to 1,2-dihydropyridines **5a** and **5i**, respectively, as shown in Chart 2.

These results provide a method of synthesizing 2-substituted 3-nitro-1,2-dihydropyridines **5** by utilizing *sec*-nitrodienamine **3** with aldehyde compounds **4**.

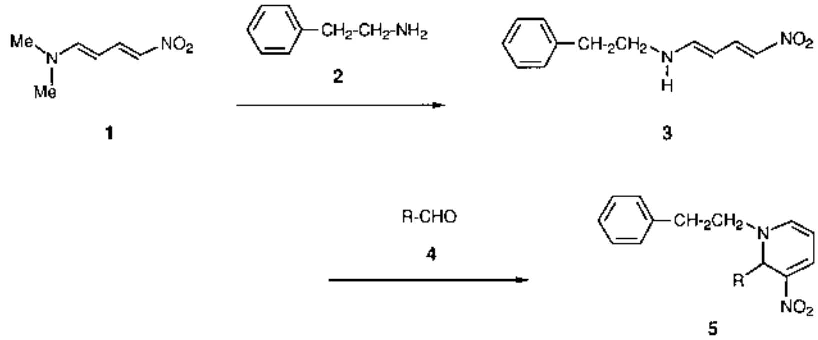

Chart 1

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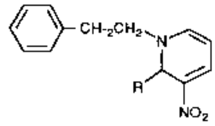
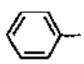
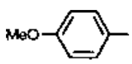
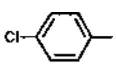
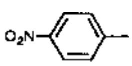
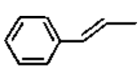
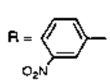
Table 1. The Heterocyclic Annulation Reactions of *sec*-Nitrodienamine **3** with Aldehyde Compounds **4**

R–CHO

4



5

Starting amine	R	Reaction temp. (°C)	Reaction time (h)	Reaction product	Yield (%)	^{1}H-NMR ($CDCl_3$), δ (ppm)	IR (cm^{-1})
4a	Me–	25	1.2	**5a**	92	1.19 (3H, d, J=6.2 Hz, Me), 2.94 (2H, t, J=6.9 Hz, methylene H), 3.46 (1H, dt, J=13.9, 6.9 Hz, methylene H), 3.68 (1H, dt, J=13.9, 6.9 Hz, 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)
4b	Me–CH_2–	Reflux	39	**5b**	82	0.91 (3H, t, J=7.7 Hz, Me), 1.38—1.92 (2H, m, methylene H), 2.92 (2H, t, J=6.8 Hz, methylene H), 3.58 (1H, dt, J=13.6, 6.8 Hz, methylene H), 3.64 (1H, dt, J=13.6, 6.8 Hz, methylene H), 4.83 (1H, dd, J=7.5, 6.4 Hz, olefinic H), 5.05 (1H, t, J=4.6 Hz, methine H), 6.53 (1H, d, J=6.4 Hz, olefinic H), 7.09—7.26 (5H, m, aromatic H), 7.65 (1H, d, J=7.5 Hz, olefinic H)	1624, 1541, 1516, 1474, 1456, 1360, (neat)
4c		25	7	**5c**	59	2.89 (2H, t, J=6.8 Hz, methylene H), 3.35 (1H, dt, J=13.6, 6.8 Hz, methylene H), 3.60 (1H, dt, J=13.6, 6.8 Hz, methylene H), 4.82 (1H, dd, J=7.5, 6.7 Hz, olefinic H), 6.01 (1H, s, methine H), 6.59 (1H, d, J=6.7 Hz, olefinic H), 7.10 (2H, d, J=6.9 Hz, aromatic H), 7.23—7.35 (6H, m, aromatic H), 7.45 (2H, d, J=6.9 Hz, aromatic H), 7.75 (1H, d, J=7.5 Hz, olefinic H)	1620, 1505, 1495, 1460, 1420, 1590, (neat)
4d		25	26	**5d**	53	2.88 (2H, t, J=6.8 Hz, methylene H), 3.31 (1H, dt, J=13.6, 6.8 Hz, methylene H), 3.55 (1H, dt, J=13.6, 6.8 Hz, methylene H), 3.78 (3H, s, OMe), 4.80 (1H, dd, J=7.5, 6.3 Hz, olefinic H), 5.95 (1H, s, methine H), 6.57 (1H, d, J=6.3 Hz, olefinic H), 6.84 (2H, d, J=8.8 Hz, aromatic H), 7.06—7.30 (5H, m, aromatic H), 7.38 (2H, d, J=8.8 Hz, aromatic H), 7.74 (1H, d, J=7.5 Hz, olefinic H)	1605, 1585, 1515, 1500, 1495, 1485, (neat)
4e		25	15	**5e**	44	2.88 (2H, t, J=6.8 Hz, methylene H), 3.34 (1H, dt, J=13.6, 6.8 Hz, methylene H), 3.59 (1H, dt, J=13.6, 6.8 Hz, methylene H), 4.82 (1H, dd, J=7.5, 6.4 Hz, olefinic H), 5.97 (1H, s, methine H), 6.60 (1H, d, J=6.4 Hz, olefinic H), 7.08—7.43 (9H, m, aromatic H), 7.72 (1H, d, J=7.5 Hz, olefinic H)	1615, 1510, 1490, 1460, 1450, 1440, (neat)
4f		25	15	**5f**	57	2.91 (2H, t, J=6.8 Hz, methylene H), 3.43 (2H, dt, J=13.6, 6.8 Hz, methylene H), 4.90 (1H, dd, J=7.5, 6.4 Hz, olefinic H), 6.09 (1H, s, methine H), 6.69 (1H, d, J=6.4 Hz, olefinic H), 7.03—7.32 (5H, m, aromatic H), 7.60 (2H, d, J=8.8 Hz, aromatic H), 7.72 (1H, d, J=7.5 Hz, olefinic H), 8.17 (2H, d, J=8.8 Hz, aromatic H)	1620, 1520, 1485, 1455, 1445, 1395, (neat)
4g		25	39	**5g**	5	2.98 (2H, t, J=6.8 Hz, methylene H), 3.50 (1H, dt, J=13.6, 6.8 Hz, methylene H), 3.74 (1H, dt, J=13.6, 6.8 Hz, methylene H), 4.85 (1H, dd, J=7.3, 6.7 Hz, olefinic H), 5.65 (1H, d, J=7.0 Hz, methine H), 6.19 (1H, dd, J=15.9, 7.0 Hz, olefinic H), 6.62 (1H, d, J=6.7 Hz, olefinic H), 7.03—7.37 (11H, m, aromatic and olefinic H), 7.64 (1H, d, J=7.3 Hz, olefinic H)	1615, 1545, 1510, 1495, 1480, 1460, (neat)
4h	H–	25	1	**5a** R=Me–	2	1.19 (3H, d, J=6.2 Hz, Me), 2.94 (2H, t, J=6.9 Hz, methylene H), 3.46 (1H, dt, J=13.9, 6.9 Hz, methylene H), 3.68 (1H, dt, J=13.9, 6.9 Hz, 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)
				5i 	8	2.91 (2H, t, J=6.8 Hz, methylene H), 3.43 (1H, dt, J=13.6, 6.8 Hz, methylene H), 3.57 (1H, dt, J=13.6, 6.8 Hz, methylene H), 5.04 (1H, t, J=6.7 Hz, olefinic H), 6.05 (1H, s, methine H), 7.00 (1H, d, J=6.7 Hz, olefinic H), 7.22 (2H, d, J=7.9 Hz, aromatic H), 7.37—7.43 (3H, m, aromatic H), 7.53 (1H, t, J=7.9 Hz, aromatic H), 7.77 (1H, d, J=7.9 Hz, aromatic H), 7.81 (1H, d, J=6.7 Hz, olefinic H), 8.18 (1H, d, J=7.9 Hz, aromatic H), 8.30 (1H, s, aromatic H)	1668, 1620, 1529, 1454, 1392, 1352, (neat)

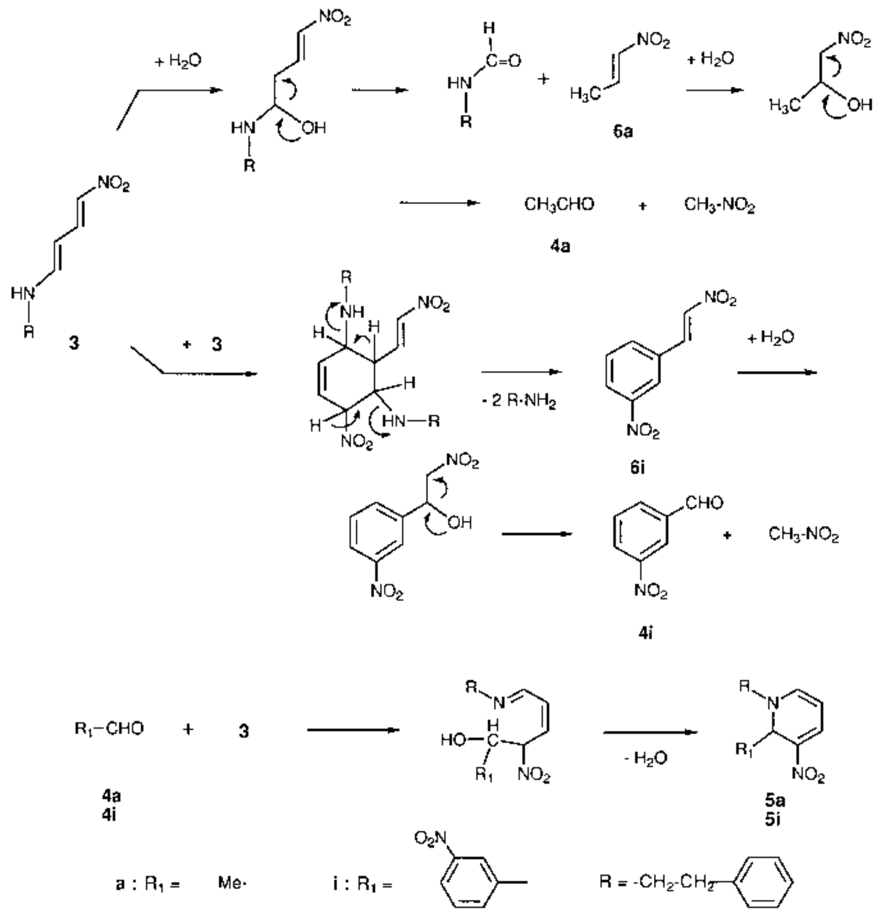


Chart 2

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 internal standard. MS were recorded on a JEOL JMS-D 300 spectrometer. Silica gel 60 (Cica-Merck) 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 reactions were carried out under an argon atmosphere.

General Procedure for Reactions of 4-Nitro-1-(2-phenethylamino)-1,3-butadiene (3) with Aldehyde Compounds 4 A solution of *sec*-nitrodienamine **3** (40 mg, 0.183 mmol) with the aldehyde compound **4** and 2-phenethylamine (2 drops) in a liquid reaction mixture (no solvent) or THF (3 ml) in a sealed tube was stirred at room temperature or refluxed for an appropriate period until the disappearance of **3** (checked by TLC). The reaction mixture was concentrated under vacuum, and the residue subjected to silica gel column chromatography. The isolated yield of **5** is based on **3**. The reaction conditions and properties of the prepared compounds **5** are shown in Table 1.

2-Methyl-3-nitro-1-(2-phenethyl)-1,2-dihydropyridine (**5a**):[1d] Aldehyde **4a**: 0.4 ml (7.16 mmol). Reaction solvent: THF. Solvent for chromatography: 20% ethyl acetate in hexane. Product **5a**: 41 mg, dark red oil. ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 15.4, 35.9, 52.5, 56.4, 93.5, 126.7, 127.1, 128.7, 128.8, 133.2, 137.1, 146.6. This product was identical with an authentic sample on the basis of IR, MS and NMR spectral comparisons.

2-Ethyl-3-nitro-1-(2-phenethyl)-1,2-dihydropyridine (**5b**): Aldehyde **4b**: 1063 mg (18.3 mmol). Reaction solvent: no solvent. Solvent for chromatography: 15% ethyl acetate in hexane. Product **5b**: 39 mg, dark red oil. High-resolution EI MS *m/z*: Calcd for $C_{15}H_{18}N_2O_2$ (M^+): 258.1367. Found: 258.1357.

3-Nitro-1-(2-phenethyl)-2-phenyl-1,2-dihydropyridine (**5c**): Aldehyde **4c**: 1942 mg (18.3 mmol). Reaction solvent: no solvent. Solvent for chromatography: 20% ethyl acetate in hexane. Product **5c**: 33 mg, dark red oil. High-resolution EI MS *m/z*: Calcd for $C_{19}H_{18}N_2O_2$ (M^+): 306.1368. Found: 306.1371.

2-(4-Methoxyphenyl)-3-nitro-1-(2-phenethyl)-1,2-dihydropyridine (**5d**): Aldehyde **4d**: 2492 mg (18.3 mmol). Reaction solvent: no solvent. Solvent for chromatography: 15% ethyl acetate in hexane. Product **5d**: 32 mg, dark red oil. High-resolution EI MS *m/z*: Calcd for $C_{20}H_{20}N_2O_3$ (M^+): 336.1471. Found: 336.1453.

2-(4-Chlorophenyl)-3-nitro-1-(2-phenethyl)-1,2-dihydropyridine (**5e**): Aldehyde **4e**: 515 mg (3.66 mmol). Reaction solvent: THF. Solvent for chromatography: 40% hexane in chloroform. Product **5e**: 28 mg, dark red oil. High-resolution EI MS *m/z*: Calcd for $C_{19}H_{17}N_2O_2Cl_1$ (M^+): 340.0979. Found: 340.0986.

3-Nitro-2-(4-nitrophenyl)-1-(2-phenethyl)-1,2-dihydropyridine (**5f**): Aldehyde **4f**: 24 mg (0.16 mmol). Reaction solvent: THF. Solvent for chromatography: 40% hexane in chloroform. Product **5f**: 37 mg, dark red oil. High-resolution EI MS *m/z*: Calcd for $C_{19}H_{17}N_3O_4$ (M^+): 351.1218. Found: 351.1248.

3-Nitro-1-(2-phenethyl)-2-(*trans*-2-phenylvinyl)-1,2-dihydropyridine (**5g**): Aldehyde **4g**: 484 mg (3.66 mmol). Reaction solvent: THF. Solvent for chromatography: 40% hexane in chloroform. Product **5g**: 3 mg, dark red oil. CI-MS *m/z*: 333 ($M^+ + 1$).

2-Methyl-3-nitro-1-(2-phenethyl)-1,2-dihydropyridine (**5a**)[1d] and 3-Nitro-2-(3-nitrophenyl)-1-(2-phenethyl)-1,2-dihydropyridine (**5i**): Aldehyde **4h**: 47.2 μl (35% formaldehyde, 0.60 mmol). Reaction solvent: THF. Solvent for chromatography: 20% ethyl acetate in hexane. First eluated product **5a**: 1 mg, dark red oil. This product was identical with an authentic sample on the basis of IR, MS and NMR spectral comparisons. Second eluated product **5i**: 2 mg, dark red oil. CI-MS *m/z*: 352 ($M^+ + 1$). (The *sec*-nitrodienamine **3** was almost completely decomposed under these conditions.)

References

1) *a*) Takeuchi N., Ohki J., Tobinaga S., *Chem. Pharm. Bull.*, **36**, 481—487 (1988); *b*) Takeuchi N., Tanabe M., Hagiwara M., Goto K., Koike T., Tobinaga S., *Heterocycles*, **38**, 613—627 (1994); *c*) Koike T., Hagi-

wara M., Takeuchi N., Tobinaga S., *ibid*., **45**, 1271—1280 (1997); *d*) Koike T., Shinohara Y., Tanabe M., Takeuchi N., Tobinaga S., *Chem. Pharm. Bull*., **47**, 1246—1248 (1999); *e*) Koike T., Takeuchi N., Hagiwara M., Yamazaki K., Tobinaga S., *Heterocycles*, **51**, 2687—2695 (1999).
2) Rajappa S., *Tetrahedron*, **37**, 1453—1480 (1981).
3) *a*) Severin T., Ipach I., *Chem. Ber*., **109**, 3541—3546 (1976); *b*) *Idem*, *ibid*., **111**, 692—697 (1978).
4) *a*) Koike T., Tanabe M., Takeuchi N., Tobinaga S., *Chem. Pharm. Bull*., **45**, 243—248 (1997); *b*) *Idem*, *ibid*., **45**, 27—31 (1997); *c*) *Idem*, *ibid*., **45**, 1117—1119 (1997); *d*) Koike T., Takeuchi N., Tobinaga S., *ibid*., **46**, 1497—1500 (1998); *e*) *Idem*, *ibid*., **47**, 128—130 (1999).
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*., **1982**, 191—261; *d*) Stout D. M., Meyers A. I., *Chem. Rev*., **82**, 223—243 (1982).