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Synthesis of 4-Substituted 3,5-Dinitro-1,4-dihydropyridines by the Self-Condensation of β-Formyl-β-nitroenamine

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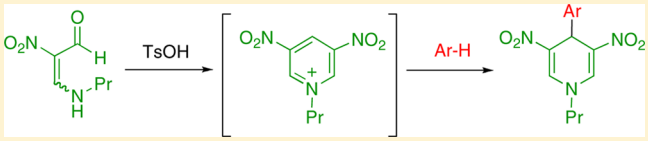
Supporting Information

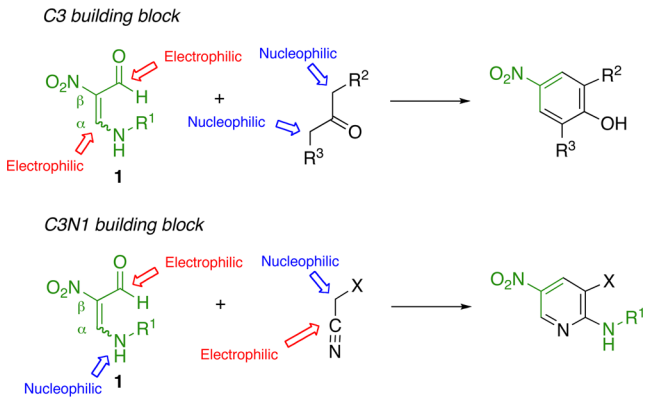
ABSTRACT: 3,5-Dinitro-1,4-dihydropyridines (DNDHPs) are readily constructed by the acid-promoted self-condensation of β-formyl-β-nitroenamines. In the DNDHPs, one molecule of the nitroenamine serves as a C3N1 building block and the other serves as a C2 block. This synthetic method does not require any special reagents and conditions. When the reaction is conducted in the presence of electron-rich benzene derivatives, arylation at the 4-position of DNDHP is achieved by trapping the 3,5-dinitropyridinium ion intermediate.



INTRODUCTION

Nitroenamines, one of the push−pull alkenes,[1] can undergo a wide variety of useful reactions such as electrophilic and nucleophilic addition−elimination,[2] Diels−Alder reaction,[2] and reduction.[3] However, only a few reports are found with regard to the reactions of functionalized nitroenamines because of their scarce availability.[4] We have been recently focusing attention to β-formyl-β-nitroenamines **1** having an additional functional group (CHO) as new building blocks for the syntheses of carbocyclic and heterocyclic compounds having a nitro group from the viewpoint of the following features (Scheme 1).[5] The formylnitroenamines **1** possess electrophilic formyl and α-vinyl carbons, and a nucleophilic amino nitrogen, in addition to an electron-withdrawing nitro group (Schemes 1). They are easily prepared from commercially available reagents by a few steps,[5a] and they are easily handled because of the high solubility in common organic solvents. Furthermore, the nitroenamines **1** can be safely stored without necessity of special conditions such as low temperature and inert gas atmosphere. We have reported that formylnitroenamines **1** serve as a double electrophilic C3 unit having a nitro group to afford nitrated diazoles,[6] isoxazole,[6] pyrimidines,[6] diazepines,[6] phenols[7] upon treatment with dinucleophiles such as hydrazines, hydroxylamine, guanidines, 1,2-diaminoethanes, and ketones, respectively. Formylnitroenamines **1** are also employed as the C3N1 building blocks, and multiply functionalized nitropyridones and aminonitropyridines are readily prepared under mild conditions.[8] In the present work, new reactivity of **1**, self-condensation leading to hitherto unknown 3,5-dinitro-1,4-dihydropyridines (DNDHPs), upon treatment with a Brønsted acid, is demonstrated. The DNDHP framework is constructed by formal [4 + 2] dimerization of **1**, in which a nucleophilic amino group and an electrophilic formyl group of **1** add to the electronically biased C−C double bond of another molecule of **1** (Scheme 2).

Scheme 1. Reactions of β-Formyl-β-nitroenamines 1 Using C3 and C3N1 as Building Blocks



1,4-Dihydropyridine (DHP) derivatives have been energetically studied because of their importance in medicinal chemistry and pharmacology.[9] Especially, DHPs have also drawn much attention as model compounds of coenzyme nicotinamide adenine dinucleotide (NADH).[10] Furthermore, the reducing ability of DHPs has been widely used in organic syntheses.[11] Among DHP derivatives, 4-arylated DHPs have been well studied on their bioactivity. For example, DHPs having an aryl group are also often found as the fundamental framework in drugs such as calcium antagonists[12] and for cardiovascular diseases,[13] and dimeric DHPs are used as the precursors for HIV-1 protease inhibitors.[14]

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Scheme 2. Self-Condensation of Nitroenamine 1

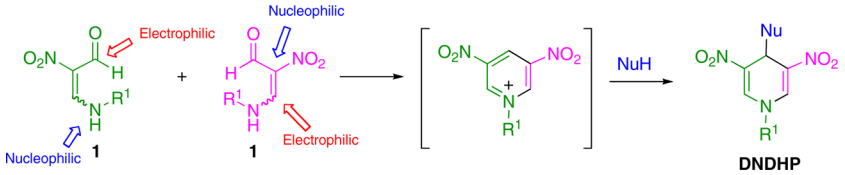
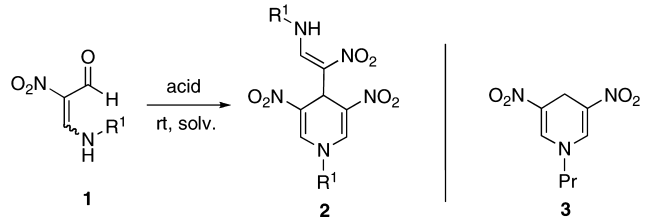


Table 1. Condensation of Three Molecules of Nitroenamines 1



entry		R^1	acid	solv	time (h)		yield (%)[a]
1	**1a**	Pr	AcOH	EtOH	24	**2a**	ND[b]
2	**1a**	Pr	CF_3COOH	EtOH	20	**2a**	1
3	**1a**	Pr	12 M HCl	EtOH	20	**2a**	80
4	**1a**	Pr	*p*-TsOH	EtOH	20	**2a**	90
5[c]	**1a**	Pr	*p*-TsOH	EtOH	20	**2a**	65
6[d]	**1a**	Pr	*p*-TsOH	EtOH	20	**2a**	ND[b,e]
7	**1a**	Pr	*p*-TsOH	MeCN	20	**2a**	ND
8	**1b**	*t*-Bu	*p*-TsOH	EtOH	48	**2b**	87
9	**1c**	$-CH_2CH_2CO_2Et$	*p*-TsOH	EtOH	48	**2c**	67
10	**1d**	Allyl	*p*-TsOH	EtOH	48	**2d**	65
11	**1e**	$CH_2CH(OMe)_2$	*p*-TsOH	EtOH	20	**2e**	quant

[a]Isolated yield based on the amount of **1** used. [b]Not detected. [c]A 0.5 equiv of acid was employed. [d]At 80 °C. [e]DNDHP **3** was obtained in 43% yield.

In general, a number of synthetic methods for DHPs have been established. Among them, the most common approach to DHPs involves nucleophilic addition of a carbanion or a hydride ion to pyridines or pyridinium salts. However, this method accompanies the difficulty in controlling the selectivity regarding the formation of 1,4-dihydro and 1,2-dihydropyridines.[15] As another method, Hantzsch reaction is important for constructing a 4-arylated DHP framework from an aromatic aldehyde and two β-keto esters in the presence of ammonia or ammonium salt.[16] Modified Hantzsch reactions are also developed, in which two of the four components are condensed beforehand.[17] Although these methods remain the most widely used protocols to access DHPs possessing various aryl groups at the 4-position, the substituents at the 3- and the 5-positions are limited to carbonyl functions such as ester and carbamoyl groups.[18] DHPs having one or two nitro groups at the 3- and/or the 5-positions cannot be prepared by the Hantzsch's method easily,[19] and other method has not been reported to the best of our knowledge except for a few literature dealing with reduction of nitropyridine.[20] Thus, development of a facile method for their preparation is desired.

Contrary to the preceding preparations, we present here a facile preparative method for 4-substituted 3,5-dinitro-1,4-dihydropyridines, which also features the regioselective introduction of a nitroenamino or an electron-rich aryl group to the 4-position.

RESULTS AND DISCUSSION

Synthesis of DNDHPs 2. First, we investigated the reaction conditions for the self-condensation of β-formyl-β-nitroenamines **1**. Nitroenamine **1a** was quantitatively recovered upon treatment with Brønsted acid such as acetic acid and trifluoroacetic acid in ethanol at room temperature (Table 1, entries 1 and 2). On the other hand, orange solid precipitated when concentrated hydrochloric acid was used (entry 3). In the ^{1}H NMR spectrum of the solid, signals due to the presence of two *N*-propyl groups were observed. While one of the *N*-methylene groups appeared at 3.58 ppm as a triplet, the other one at 3.44 ppm was observed as a doublet of triplet, indicating the presence of coupling between *N*-methylene and adjacent NH groups. A doublet signal assigned to a vinyl proton at 7.35 ppm with a coupling constant of 14.4 Hz was observed, which is the typical spectral feature of a nitroenamine framework.[5a] Furthermore, the presence of singlet signals at 5.23 (1H) and 7.87 ppm (2H) indicates a symmetrical 3,4,5-trisubstituted DHP ring. These assignments were also supported by the ^{13}C NMR spectrum, of which a salient feature involves signals due to two tertiary carbons at 37.9 and 151.4 ppm. The structure of the product was assigned to DNDHP **2a**, which consisted of three molecules of nitroenamine **1a**. Furthermore, single crystal X-ray structure analysis of **2a** showed the nitroenamine moiety at the 4-position adopted *Z*-form with an interatomic distance of 2.03 Å between O(6) and H(5), which would indicate a hydrogen bonding between the nitro and amino groups (Figure S1, Supporting Information).

DNDHP **2a** was also obtained in a better yield when *p*-toluenesulfonic acid (TsOH) was employed as an acid (entry 4). The use of stoichiometric amount of TsOH was necessary for completion of the reaction because the acid is consumed by the salt formation with the amine formed during the reaction (entry 5). On the other hand, unsubstituted DNDHP **3** was isolated in 43% yield instead of **2a** when the reaction was

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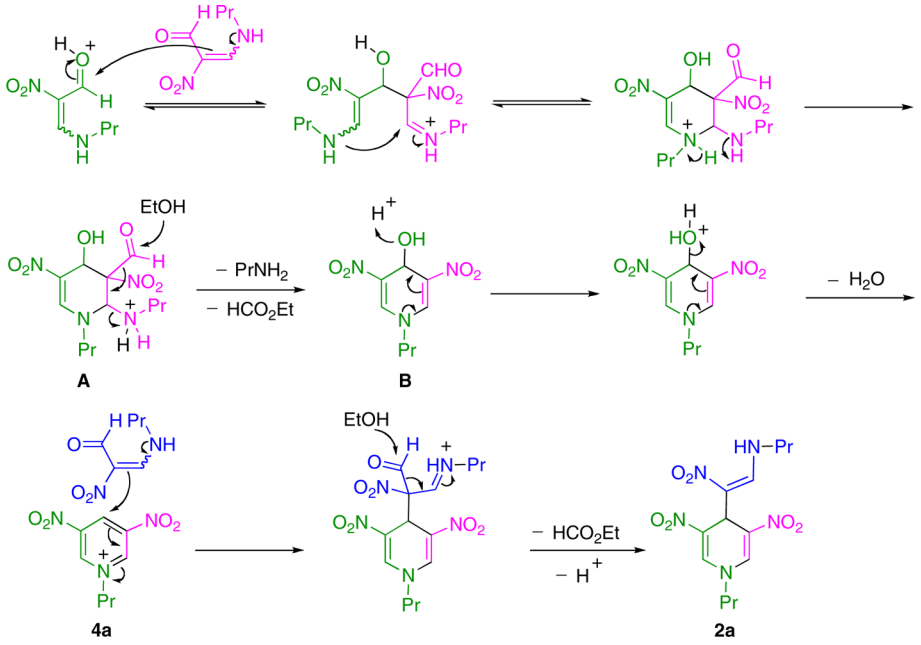
Scheme 3. Plausible Mechanism for the Formation of DNDHP 2a



conducted at reflux temperature (entry 6). Since DNDHP **3** was also formed in 60% yield when DNDHP **2a** was allowed to react with TsOH in ethanol at 80 °C, we assume **3** was formed via **2a** not directly by condensation of two molecules of **1a**.

The present reaction is significantly affected by solvent, and nitroenamine **1a** was recovered quantitatively when the reaction was conducted in acetonitrile at room temperature (entry 7). The substituents (R^1) at both the ring nitrogen and the substituent on the 4-position of DNDHPs **2** could be varied by the use of nitroenamines **1b–e** having a different substituent on the amino group (R^1), and a functional group such as an allyl, an ester, and an acetal could be introduced (entries 8–11).

A plausible mechanism for the formation of DNDHP **2a** is illustrated in Scheme 3. The DNDHP ring is constructed by a formal [4 + 2] condensation of two molecules of nitroenamine **1a**, in which the nucleophilic β-carbon of one nitroenamine attacks the activated formyl group of the other molecule, and the electrophilic α-carbon of the former is attacked by the amino group of the latter. The attack of ethanol to the formyl group in intermediate **A** induces deformylation and deamination to give alcohol **B** having a DNDHP framework. Dehydration of **B** results in the formation of pyridinium intermediate **4a**. The third nitroenamine attacks the 4-position of **4a**,[21] and subsequent deformylation again induced by an attack of ethanol leads to DNDHP **2a**. It is also possible to assume that the third nitroenamine directly replaces the water molecule from **B** by an S_N2 process without involving the intermediate **4a**. The formation of **3** is discussed in the subsequent section.

Since pyridinium ion has two electrophilic sites, i.e., the 2- and the 4-positions, two regioisomers, 1,4-dihydropyridines and 1,2-dihydropyridines, were typically obtained upon nucleophilic addition. However, only 1,4-dihydropyridines **2** were obtained in the present reactions. Density functional theory calculations at B3LYP/6-31G(d,p) level for the model compound, 3,5-dinitro-*N*-methylpyridinium ion **4f** (R^1 = Me), indicate that the coefficient of LUMO of the 4-position (0.41) is larger than that of the 2-position (−0.24). This explains that the selective C–C bond formation occurs at the 4-position because of the frontier orbital control.[21]

Synthesis of Arylated DNDHPs 6. Taking this mechanism into consideration, we expected that 4-arylated DNDHPs could be prepared by intercepting the intermediate pyridinium ion **4a** with electron-rich benzene derivatives. However, when nitroenamine **1a** was allowed to react with 1,3-dimethoxybenzene **5a** in the presence of TsOH at room temperature for 1 h, the major product was DNDHP **2a** (79% yield), accompanied by the formation of arylated product **6a** in 10% yield (Table 2, entry 1). On the other hand, the expected product **6a** was isolated in 64% yield in the reaction at 80 °C (entry 2). The ^{1}H NMR of **6a** exhibited the signals due to the 2,4-dimethoxyphenyl group in addition to the two singlet signals at 5.78 (1H) and 7.77 ppm (2H) due to the DNDHP ring. The reactions of other aromatic compounds **5b–5g** were conducted under the same conditions (entries 3–9). In the presence of phenols **5b–5d**, nitroenamine **1a** afforded the corresponding DNDHPs **6b–6d** in moderate yields (entries 3–5). DNDHP **6e** was not obtained when equimolar anisol **5e** was used. In this case, DNDHP **3** was formed in 26% yield instead. However, **6e** was obtained albeit in low yield by using an excess amount of **5e** (entries 6 and 7). Aniline derivative **5f** having a more electron-donating group underwent the reaction efficiently to afford DNDHP **6f** in 68% yield (entry 8). On the other hand, DNDHP **6g** was not obtained when less reactive benzene **5g** was employed (entry 9). In this case too, DNDHP **3** was formed in 20% yield. Interestingly, when DNDHP **2a** instead of **1a** was used as the starting material in the presence of **5a** under the same conditions, DNDHP **6a** was obtained in 60% yield.

Next, the mechanism for the formation of DNDHP **3** was studied. Alcohol often behaves as an important reducing agent in the biological system. For example, it is well-known that NAD^+ is reduced by an alcohol in the presence of dehydrogenase,[22] but only two reports dealing with the reduction of pyridine derivatives by an alcohol in the presence of Brønsted acid are known to the best of our knowledge.[23]

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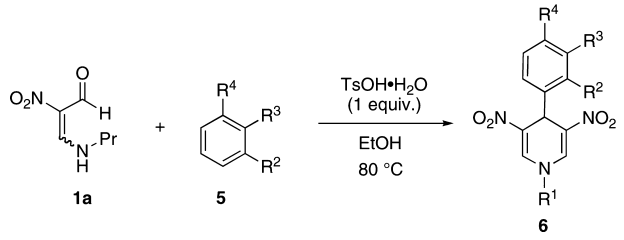
Table 2. Syntheses of Arylated DNDHPs 6



entry		5 R²	5 R³	5 R⁴	5 equiv	time (h)		yield of 6 (%)[a]
1[b]	**5a**	MeO	H	MeO	1.0	1	**6a**	10[c]
2	**5a**	MeO	H	MeO	1.0	1	**6a**	64
3	**5b**	Me	H	OH	2.0	2	**6b**	52
4	**5c**	H	Me	OH	1.0	20	**6c**	40
5	**5d**	H	H	OH	2.0	20	**6d**	27
6[d]	**5e**	H	H	OMe	1.0	5	**6e**	ND[e]
7[f]	**5e**	H	H	OMe	19	20	**6e**	16
8	**5f**	H	H	NMe_2	1.0	5	**6f**	68
9[g]	**5g**	H	H	H	1.0	20	**6g**	ND[e]

[a]Isolated yield based on nitroenamine **1a**. [b]Reaction was conducted at room temperature. [c]DNDHP **2a** was obtained in 83% yield. [d]DNDHP **3** was obtained in 26% yield. [e]Not detected. [f]The reaction was conducted with anisol **5e** as the solvent. [g]DNDHP **3** was obtained in 20% yield.

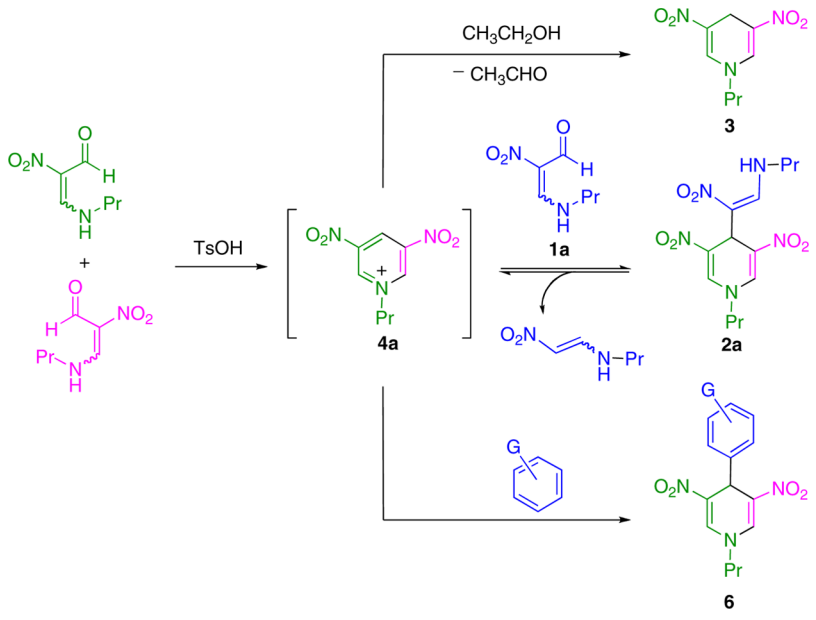
Hence, we considered that ethanol served as the hydride source to reduce pyridinium ion **4a** that is produced in the reaction of **1a** or from **2a** by fragmentation. Indeed, when ethanol-d_6 was employed as the solvent, monodeuteration took place at the 4-position of DNDHP **3**.

Plausible Mechanism for the Formation of DNDHPs 2, 3, and 6. On the basis of the above results, we propose a plausible mechanism for the formation of DNDHPs **2**, **3**, and **6** as shown in Scheme 4. When nitroenamine **1a** was treated with TsOH, two molecules of **1a** caused the formal [4 + 2] condensation to form pyridinium ion intermediate **4a**, and then **4a** is trapped by another molecule of **1a** leading to **2a**, which precipitates out at room temperature. When pyridinium ion **4a** is trapped with benzene derivatives **5**, arylated DNDHPs **6** are formed. However, another route to DNDHPs **6** can also be considered. While DNDHP **2a** is obtained prior to the formation of DNDHPs **6a** at room temperature even in the presence of benzene derivatives **5a** (Table 2, entry 1), only DNDHPs **6a** are obtained without detectable **2a** under heated conditions (entries 2–8). Furthermore, DNDHP **6a** was obtained by heating an ethanol solution of **2a** and **5a** with TsOH. These results suggest that DNDHPs **6** are formed via DNDHPs **2**, in which the nitroenamine moiety is eliminated to afford intermediate **4a**. Interceptions of **4a** with benzene derivatives **5** lead to arylated DNDHPs **6**. This consideration is consistent with the fact that the maximum yield of DNDHPs **6** was 68%. When the benzene derivatives **5** were not reactive, DNDHP **3** was formed by the reduction of pyridinium ions **4a** by ethanol. More details of the mechanism of the reaction are now under investigation.

CONCLUSION

The DNDHP framework with two nitro groups could be constructed from two molecules of **1** under acidic conditions, in which each **1** plays a different role. Namely, one nitroenamine **1** serves as the C3N1 unit and the other serves as the C2 unit. In this reaction, pyridinium ion **4** presents as the key intermediate, which is attacked by the third nitroenamine **1** to form the trimeric product, DNDHP **2**. Arylation at the 4-position of DNDHP was also achieved by trapping the intermediate **4** with electron-rich benzene derivatives **5** to furnish DNDHPs **6**. Furthermore, it was found that DNDHP **3** was formed as a result of the reduction of pyridinium ion **4** by ethanol. Our preparative method for DNDHPs reveals high synthetic value because special reagents and conditions are not necessary, and modification of the 4-position in dihydropyridine ring is readily achieved. These results provide useful information for the syntheses and applications of dihydropyridines in general.

Scheme 4. Formations of DNDHPs 2, 3, and 6 via the Dinitropyridinium Intermediate 4a



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EXPERIMENTAL SECTION

1,4-Dihydro-3,5-dinitro-4-[1-nitro-2-(propylamino)ethenyl]-1-propylpyridine (2a). *p*-Toluensulfonic acid monohydrate (95 mg, 0.50 mmol) was added to a suspension of nitroenamine **1a** (79 mg, 0.50 mmol) in ethanol (0.1 mL), and the resultant mixture was stirred at room temperature for one day. The yellow suspension changed to yellow solution, and orange solid was subsequently precipitated. The orange solid was collected by the filtration to give DNDHP **2a** (51 mg, yield 90%). Further purification was performed by recrystallization from chloroform. Orange prisms: mp 183−184 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.4 Hz, 3H), 1.07 (t, J = 7.3 Hz, 3H), 1.73 (tq, J = 6.7, 7.4 Hz, 2H), 1.88 (tq, J = 7.0, 7.3 Hz, 2H), 3.45 (dt, J = 6.7, 6.7 Hz, 2H), 3.59 (t, J = 7.0 Hz, 2H), 5.24 (s, 1H), 7.36 (d, J = 14.2 Hz, 1H), 7.88 (s, 2H), 9.70 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8 (CH_3), 10.9 (CH_3), 23.9 (CH_2), 37.9 (CH), 51.8 (CH_2), 58.3 (CH_2), 116.2 (C), 127.8 (CH), 138.1 (C), 151.4 (CH), One signal for the secondary carbon was not observed, probably because of overlapping; IR (neat, cm^{-1}) 1672 (C═C), 1645 (C═C), 1584, 1372 (NO_2), 1487, 1268 (NO_2); MS (FAB) m/z 342.1 (M^++1, 20%), 295.1 (7), 212.0 (100). Anal. Calcd for $C_{13}H_{19}N_5O_6$: C, 45.75; H, 5.61; N, 20.52. Found: C, 45.79; H, 5.63; N, 20.48.

DNDHPs **2b**, **2c**, **2d**, and **2e** were synthesized by the same way.

1-*tert*-Butyl-1,4-dihydro-3,5-dinitro-4-[1-nitro-2-(*tert*-butylamino)ethenyl]pyridine (2b). Yellow solid: 54 mg, 0.14 mmol, yield 87%; mp 139−140 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.58 (s, 9H), 5.25 (s, 1H), 7.45 (d, J = 14.6 Hz, 1H), 8.12 (s, 2H), 9.92 (br d, J = 14.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8 (CH_3), 30.2 (CH_3), 38.5 (CH), 54,9 (C), 61.1 (C), 126.3 (C), 128.2 (C), 135.4 (CH), 147.7 (CH); IR (neat, cm^{-1}) 2979 (NH), 1671 (C═C), 1643 (C═C), 1589, 1370 (NO_2), 1504, 1353 (NO_2); MS (FAB) m/z 370.2 (M^++1, 52%), 226.1 (100). Anal. Calcd for $C_{15}H_{23}N_5O_6$: C, 48.77; H, 6.27; N, 18.96. Found: C, 48.95; H, 6.65; N, 18.67.

1,4-Dihydro-3,5-dinitro-1-[2-(ethoxycarbonyl)ethylamino]-4-[2-{2-(ethyoxycarbonyl)ethylamino}-1-nitroethenyl]pyridine (2c). Yellow solid: 51 mg, 0.11 mmol, yield 67%; mp 118−119 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H), 2.69 (t, J = 6.2 Hz, 2H), 2.85 (t, J = 6.2 Hz, 2H), 3.74 (dt, J = 6.2, 6.2 Hz, 2H), 3.93 (t, J = 6.2 Hz, 2H), 4.20 (q, J = 7.2 Hz, 2H), 4.22 (q, J = 7.2 Hz, 2H), 5.21 (s, 1H), 7.39 (d, J = 14.0 Hz, 1H), 7.96 (s, 2H), 9.72 (br d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3), 14.3 (CH_3), 34.9 (CH_2), 35.2 (CH_2), 37.7 (CH), 45.6 (CH_2), 51.5 (CH_2), 61.4 (CH_2), 61.6 (CH_2), 116.8 (C), 127.8 (C), 137.9 (CH), 150.7 (CH), 169.8 (C), 170.2 (C); IR (KBr/cm^{-1}) 1728 (C═O), 1710 (C═O), 1676 (C═C), 1508, 1380 (NO_2), 1482, 1275 (NO_2); MS (FAB) m/z 458 (M^++1, 11%), 270 (100). Anal. Calcd for $C_{17}H_{23}N_5O_{10}$: C, 44.64; H, 5.06; N, 15.31. Found: C, 44.28; H, 5.11; N, 15.19.

1,4-Dihydro-3,5-dinitro-1-(2-propenyl)-4-[2-(2-propenylamino)-1-nitroethenyl]pyridine (2d). Orange solid: 37 mg, 0.11 mmol, yield 65%; mp 141−143 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (dd, J = 5.7, 5.7 Hz, 2H) 4.24 (d, J = 6.0 Hz, 2H), 5.26 (s, 1H), 5.34 (d, J = 17.1 Hz, 1H), 5.35 (d, J = 10.4 Hz, 1H), 5.48 (d, J = 10.4 Hz, 1H), 5.52 (d, J = 17.1 Hz, 1H), 5.88−6.02 (m, 2H), 7.35 (d, J = 14.0 Hz, 1H), 7.88 (s, 2H), 9.7−9.8 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8 (CH), 51.7 (CH_2), 58.3 (CH_2), 119.3 (CH_2), 121.8 (CH_2), 128.0 (CH), 130.6 (C), 132.0 (C), 137.8 (CH), 151.0 (CH), one tertiary carbon could not be observed probably due to overlapping; IR (KBr/cm^{-1}) 1678 (C═C), 1655 (C═C), 1633 (C═C), 1591, 1381 (NO_2), 1481, 1278 (NO_2); MS (FAB) m/z 338 (M^++1, 40%), 210 (100). Anal. Calcd for $C_{13}H_{15}N_5O_6$: C, 46.29; H, 4.48; N, 20.76, Found: C, 46.26; H, 4.69; N, 20.57.

1,4-Dihydro-1-(2,2-dimethoxy)ethyl-4-[2-(2,2-dimethoxy)-ethylamino]-1-nitroethenyl-3,5-dinitropyridine (2e). Yellow solid: 74 mg, 0.17 mmol, yield quant.; mp 133−134 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (dd, J = 4.7, 6.3 Hz, 2H), 3.46 (s, 6H), 3.51 (s, 6H), 3.64 (d, J = 4.7 Hz, 2H), 4.45 (t, J = 4.7 Hz, 1H), 4.59 (t, J = 4.7 Hz, 1H), 5.24 (s, 1H), 7.37 (d, J = 14.1 Hz, 1H), 7.90 (s, 2H), 9.4−9.5 (br dt, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.6 (CH), 53.3 (CH_2), 57.2 (CH_3), 57.9 (CH_3), 104.8 (CH), 105.1(CH), 124.0 (C), 126.2 (C), 129.8 (CH), 140.7 (CH) A signal of secondary carbon was not observed, probably because of overlapping; IR (KBr/cm^{-1}) 1678 (C═C), 1592, 1375 (NO_2), 1498, 1287 (NO_2); MS (FAB) m/z 443 (M^+, 8%), 387 (66). 258 (100). Anal. Calcd for $C_{15}H_{23}N_5O_{10}$: C, 41.57; H, 5.34; N, 16.16, Found: C, 41.56; H, 4.95; N, 15.79.

1,4-Dihydro-3,5-dinitro-1-propylpyridine (3). Red solid: 24 mg, 0.11 mmol, yield 43%; mp 148−149 °C (dec); UV/vis (MeCN, c = 6.20 × 10^{-5}) λ_{max} (ε) 463 (9652) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, J = 7.4 Hz, 3H), 1.77 (tq, J = 7.1, 7.4 Hz, 2H), 3.45 (t, J = 7.1 Hz, 2H), 3.92 (s, 2H), 7.67 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5 (CH_3), 23.2 (CH_2), 24.3 (CH_2), 57.2 (CH_2), 125.8 (C), 136.1 (CH); IR (KBr/cm^{-1}) 1678 (C═C), 1592, 1381 (NO_2); MS (EI) m/z 213 (M^+, 36%), 212 (44), 196 (84), 166 (91), 120 (100). Anal. Calcd for $C_8H_{11}N_3O_4$: C, 45.07; H, 5.20; N, 19.71, Found: C, 44.97; H, 4.87; N, 19.67.

1,4-Dihydro-4-(2,4-dimethoxyphenyl)-3,5-dinitro-1-propylpyridine (6a). 1,3-Dimethoxybenzene **5a** (66 μL, 0.50 mmol) was added to a suspension of nitroenamine **1a** (79 mg, 0.50 mmol) in ethanol (0.1 mL), and *p*-toluensulfonic acid monohydrate (95 mg, 0.50 mmol) was subsequently added to the reaction mixture. The resultant mixture was stirred at 80 °C for one hour. During the reaction, the color of the reaction mixture changed to orange, from yellow, and orange solid was subsequently precipitated. After cooling the mixture to the room temperature, the orange solid was collected by the filtration to give DNDHP **6a** (56 mg, yield 64%). Orange solid: mp 212−213 °C (dec); UV/vis (MeCN, c = 4.81 × 10^{-5}) λ_{max} (ε) 452 (11855) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, J = 7.4 Hz, 3H), 1.87 (tq, J = 7.1, 7.4 Hz, 2H), 3.56 (t, J = 7.1 Hz, 2H,), 3.77 (s, 3H), 3.78 (s, 3H), 5.78 (s, 1H), 6.40 (d, J = 2.3 Hz, 1H), 6.45 (dd J = 2.3, 8.4 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4 (CH_3), 24.2 (CH_2), 36.8 (CH), 55.9 (CH_3), 56.3 (CH_3), 58.1 (CH_2), 96.1 (C), 99.7 (CH), 105.2 (CH), 120.3 (C), 133.0 (CH), 135.9 (CH), 159.7 (C), 161.4 (C); IR (KBr/cm^{-1}) 1673 (C═C), 1499, 1279 (NO_2); MS (EI) m/z 349 (M^+, 30%), 196 (100). Anal. Calcd for $C_{16}H_{19}N_3O_6$: C, 55.01; H, 5.48; N, 12.02, Found: C, 54.71; H, 5.30; N, 12.01.

DNDHPs **6b**, **6c**, **6d**, **6e**, and **6f** were synthesized by the same way.

1,4-Dihydro-3,5-dinitro-4-(4-hydroxy-2-methylphenyl)-1-propylpyridine (6b). Orange solid: 42 mg, 0.13 mmol, yield 52%; mp 261−263 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.93 (t, J = 7.3 Hz, 3H), 1.74 (tq, J = 7.1, 7.3 Hz, 2H), 2.50 (s, 3H), 3.75 (t, J = 7.1 Hz, 2H), 5.72 (s, 1H), 6.49 (d, J = 2.4 Hz, 1H), 6.54 (dd, J = 2.4, 8.3 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 8.29 (s, 2H), 9.30 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.3 (CH_3), 18.7 (CH_3), 22.9 (CH_2), 34.3 (CH), 55.7 (CH_2), 113.2 (CH), 116.2 (CH), 129.2 (CH), 131.3 (C), 133.4 (C), 136.6 (CH), 137.6 (C), 156.2 (C); IR (KBr/cm^{-1}) 3387−3500 (br, OH), 1587, 1308 (NO_2); MS (EI) m/z 319 (M^+, 7%), 212 (100). Anal. Calcd for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37; N, 13.16, Found: C, 56.61; H, 5.07; N, 13.10.

1,4-Dihydro-3,5-dinitro-4-(4-hydroxy-3-methyl)phenyl-1-propylpyridine (6c). Reddish orange solid: 32 mg, 0.10 mmol, yield 40%; mp 200−203 °C (dec); UV/vis (MeCN, c = 4.14 × 10^{-5}) λ_{max} (ε) 449 (10338) nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.92 (t, J = 7.3 Hz, 3H), 1.74 (tq, J = 7.0, 7.3 Hz, 2H), 2.06 (s, 3H), 3.76 (t, J = 7.0 Hz, 2H), 5.35 (s, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.89 (dd, J = 2.2, 8.2 Hz, 1H), 6.94 (d, J = 2.2 Hz, 1H), 8.31 (s, 2H), 9.34 (br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.2 (CH_3), 16.9 (CH_3), 23.9 (CH_2), 39.3(CH), 56.6 (CH_2), 115.1(CH), 124.5 (C), 127.4 (CH), 131.1 (CH), 132.5 (C), 133.5 (C), 137.5 (CH), 155.8 (C); IR (KBr/cm^{-1}) 3419 (OH), 1674 (C═C), 1493, 1268 (NO_2); MS (EI) m/z 319 (M^+, 7%), 288 (31), 212 (100). Anal. Calcd for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37; N, 13.16, Found: C, 56.32; H, 5.31; N, 13.02.

1,4-Dihydro-3,5-dinitro-4-(4-hydroxyphenyl)-1-propylpyridine (6d). Orange solid: 21 mg, 0.07 mmol, yield 27%; mp 226−230 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.92 (t, J = 7.2 Hz, 3H), 1.74 (tq, J = 7.2, 7.6 Hz, 2H), 3.76 (t, J = 7.6 Hz, 2H), 5.38 (s, 1H), 6.68 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 8.29 (s, 2H), 9.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.2 (CH_3), 23.9 (CH_2), 39.3 (CH), 56.6 (CH_2), 115.8 (CH), 130.1 (CH), 132.6 (C), 133.4

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(C), 137.6 (CH), 157.7 (C); IR (KBr/cm^{-1}) 3390 (OH), 1671 (C=C), 1493, 1277 (NO_2); MS (EI) m/z 305 (M^+, 30%), 288 (31), 212 (100); HRMS (EI, magnetic field) calcd for $C_{14}H_{15}N_3O_5$ requires 305.1012, found 305.1015.

1,4-Dihydro-3,5-dinitro-4-(4-methoxyphenyl)-1-propylpyridine (6e). Orange solid: 13 mg, 0.04 mmol, yield 16%; mp 143−145 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, J = 7.3 Hz, 3H), 1.85 (tq, J = 7.1, 7.3 Hz, 2H), 3.58 (t, J = 7.1 Hz, 2H), 3.77 (s, 3H), 5.60 (s, 1H), 6.82 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.7 Hz, 2H), 7.82 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1 (CH_3), 23.9 (CH_2), 39.2 (CH), 55.6 (CH_3), 58.0 (CH_2), 114.3 (CH), 129.9 (CH), 133.0 (C), 133.9 (C), 134.9 (CH), 159.7 (C); IR (KBr/cm^{-1}) 1675 (C=C), 1504, 1278 (NO_2); MS (EI) m/z 319 (M^+, 12%), 212 (23), 97 (100); HRMS (EI, magnetic field) calcd for $C_{15}H_{17}N_3O_5$ 319.1168, found 319.1160.

1,4-Dihydro-4-(4-dimethylamino)phenyl-3,5-dinitro-1-propylpyridine (6f). Purple solid: 56 mg, 0.17 mmol, yield 68%; mp 238−239 °C (dec); UV/vis (MeCN, $c = 3.73 \times 10^{-5}$) λ_{max} (ε) 446 (10759) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, J = 7.4 Hz, 3H), 1.86 (tq, J = 7.0, 7.4 Hz, 2H), 2.91 (s, 6H), 3.57 (t, J = 7.0 Hz, 2H), 5.54 (s, 1H), 6.62 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H), 7.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8 (CH_3), 23.6 (CH_2), 38.6 (CH), 40.4 (CH_3), 57.6 (CH_2), 112.2 (CH), 128.4 (C), 129.1 (CH), 133.8 (C), 134.2 (CH), 150.2 (C); IR (neat/cm^{-1}) 1671 (C=C), 1491, 1279 (NO_2); MS (FAB) m/z 332 (M^++1, 100%). Anal. Calcd for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.06; N, 16.85, Found: C, 57.68; H, 5.90; N, 16.90.

■ ASSOCIATED CONTENT

Supporting Information

Information of X-ray analysis for **2a** and of calculation for **4g**, crystal data (CIF), and copies of ^{1}H and ^{13}C NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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