Formylnitroenamines: useful building blocks for nitrated pyridones and aminopyridines with functional groups†

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β-Formyl-β-nitroenamines **1** possess both an electrophilic formyl group and a nucleophilic amino group and, therefore, serve as C3N1 building blocks having a nitro group to afford nitropyridones and aminonitropyridines with a functional group at the 3-position. Upon treatment with malonic acid derivatives or β-keto esters, nitropyridones were obtained, whereas reactions with functionalized acetonitriles afford aminonitropyridines, *via* a formal transfer of an alkyl group from the ring nitrogen to the imino group. These procedures provide practical and useful methods for preparation of heterocycles with a nitro group.

Introduction

β-Formyl-β-nitroenamines **1** possess an electrophilic formyl group, an α-vinyl carbon, and a nucleophilic amino nitrogen, and therefore, can be used as useful building blocks for the syntheses of carbocyclic and heterocyclic compounds having a nitro group (Fig. 1). Moreover, the nitroenamines **1** are readily prepared in good yields from commercially available reagents with simple manipulations and are easily handled because of their thermal stability.[1] However, to the best of our knowledge they have not been employed for organic syntheses, except for a few instances.[2]

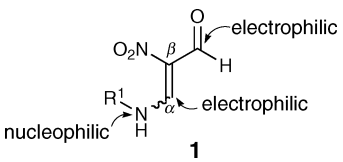
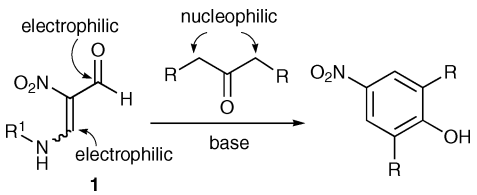


Fig. 1 β-Formyl-β-nitroenamines **1**.

In our previous work, we have shown that nitroenamines **1** serve as a new synthetic equivalent of nitromalonaldehyde;[3] reactions with dinucleophilic reagents occur at two electrophilic sites of **1**, the formyl and the α-vinyl carbons, leading to nitrated pyrazoles, pyrimidines, diazepines, phenols (shown in Scheme 1 as an example), etc.[1,4] On the other hand, nitroenamines **1** are expected to exhibit different reactivities which will lead to new methods for the syntheses of different types of functionalized nitro compounds. In the present work, we wish to demonstrate that nitroenamines **1** behave as the C3N1 building blocks having a nitro group by using the electrophilic formyl group and the nucleophilic amino group of **1**. Namely, we focus on the syntheses of *N*-substituted nitropyridones having a carbonyl group at the 3-position upon treatment of **1** with 1,3-dicarbonyl compounds, which have both a nucleophilic active methylene group and an electrophilic carbonyl group. We also wish to reveal a facile synthetic method for nitrated aminopyridines using combination of nitroenamines **1** and acetonitrile derivatives having a nucleophilic methylene group and an electrophilic cyano group.



Scheme 1 β-Formyl-β-nitroenamines **1** as C3 building blocks.

2-Pyridone is one of the important heterocyclic frameworks because of its characteristic chemical and physical properties, and it has drawn great attention of many researchers.[5,6] Among functionalized 2-pyridones, nitropyridones are often found as partial structures of alkaloids[7] and are used as precursors of anticancer and antibacterial agents.[8] The highly electron deficient nitropyridones also serve as the substrates for the Diels–Alder reaction[9,10] and for the ring transformation.[11] Much attention has been also paid to 2-pyridones having a carbonyl group at the 3-position as building blocks for synthesizing potassium channel activators[12] and antitumor agents such as camptothecin derivatives[13] and acronycine.[14] Meanwhile, pyridones having both a nitro and a carbonyl group have been shown to be applicable to medicines for ischemic heart diseases and hypertension,[15] and to the synthetic intermediates for inhibitors against receptors for α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)[16] and the 3-phosphoinositide-dependent protein kinase-1 (PDK1).[17] In view of the above aspects, pyridones having both a nitro and a carbonyl group are expected to serve as useful precursors of biologically active materials such as medicines and agricultural chemicals.

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Pyridones having both a nitro and a carbonyl group are generally synthesized by the nitration of carbonylated pyridone derivatives,[18] which are obtained by the oxidation of nicotinic acid derivatives[19] or the alkyl transfer of 2-alkoxypyridines.[20] However, these processes, which use harsh conditions, are not applicable to any functionalized pyridones which could not endure the acidic and oxidative conditions. Another preparative method, the condensation of sodium salt of nitromalonaldehyde with amides, has also been reported;[21] however, the salt should be handled with care,[3b] and the scope of usable amides for this reaction is limited. Therefore, the development of alternative facile methods for preparation of carbonylated nitropyridones that can be performed under mild conditions is strongly desired.

In the meantime, considerable attention has been paid to 2-amino-5-nitropyridines in view of their direct potential application to functional materials or intermediates for bioactive compounds[8d,21] and organic nonlinear optical materials.[22] However, it is difficult to synthesize this class of compounds from readily available materials in a few steps with simple manipulations. Most of the preparative methods involve nitration of 2-pyridone followed by transformation to 2-chloro-5-nitropyridine using phosphorus oxychloride or phosphorus pentachloride, which is then subjected to the nucleophilic substitution at the 2-position by amines.[8d,23] As another method, the ring transformation is also employed for preparation of aminonitropyridines,[24] but the starting materials are not easily available.

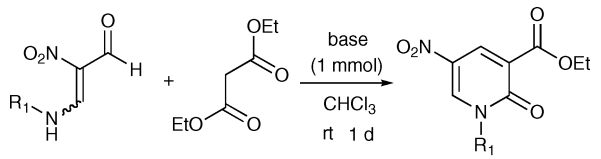
On the basis of the above background, we planned to develop facile synthetic method for nitropyridones and aminonitropyridines having a functional group at the 3-position, employing nitroenamines **1** as C3N1 building block in one pot.

Results and discussion

Nitroenamine **1a** (R^1 = *t*-Bu)[1] was allowed to react with diethyl malonate **2** (1 equiv.) in the presence of amines (1 equiv.) at 60 °C. When triethylamine was employed as the base, the reaction did not proceed, with quantitative recovery of **1a** and **2** even at high concentration (Table 1 entries 1 and 2). Though diethylamine did not bring about the reaction at ordinary concentrations (entry 3), when the reaction was conducted at high concentration (1 mmol of substrate/0.4 mL of solvent), the double condensation of **1a** took place to afford 1-*tert*-butyl-3-ethoxycarbonyl-5-nitro-2-pyridone (**3a**) in 50% yield (entry 4). In this reaction, the pyridone framework is constructed by the condensation of malonate with a formyl group of **1** and subsequent intramolecular nucleophilic substitution at the ester carbonyl group (Scheme 2).[25] Cyclic secondary amines such as morpholine and piperidine were more effective, and the latter amine was found to be the base of choice for the present reaction, giving **3a** up to 77% yield (entries 5–8). However, reducing the amount of piperidine diminished the yield of **3a** (entry 9).

Next, the scope of this reaction was studied. Nitroenamine **1b** (R^1 = Pr)[1] showed higher reactivity than **1a**, to give the corresponding *N*-propylpyridone **3b** in a moderate yield even at room temperature (Table 1, entry 10). The present reaction can also be used for preparing pyridones **3c–e** by using nitroenamines **1c–e** having an allyl, an acetal and an ester group, respectively, without any protection (entries 11–13). Modification of the 3-position was also possible. Reactions of nitroenamines **1a** and **1b**

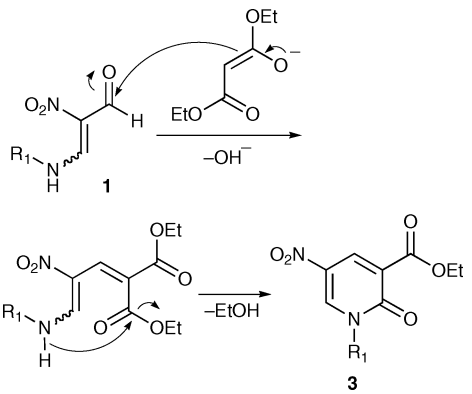
Table 1 Syntheses of pyridones **3** using different bases



1 (1 mmol) **2** (1 mmol) **3**

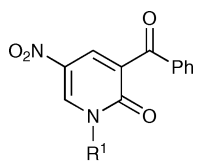
Entry	Starting material R¹		Base	Volume of solvent/mL	Product	Yield (%)
1[a]	**1a**	*t*-Bu	Et_3N	2	**3a**	0
2[a]	**1a**	*t*-Bu	Et_3N	0.4	**3a**	0
3[a]	**1a**	*t*-Bu	Et_2NH	2	**3a**	0
4[a]	**1a**	*t*-Bu	Et_2NH	0.4	**3a**	50
5[a]	**1a**	*t*-Bu	Morpholine	2	**3a**	13
6[a]	**1a**	*t*-Bu	Morpholine	0.4	**3a**	23
7[a]	**1a**	*t*-Bu	Piperidine	2	**3a**	31
8[a]	**1a**	*t*-Bu	Piperidine	0.4	**3a**	77
9[a,b]	**1a**	*t*-Bu	Piperidine	0.4	**3a**	57
10	**1b**	Pr	Piperidine	0.4	**3b**	78
11	**1c**	$-CH_2CH{=}CH_2$	Piperidine	0.4	**3c**	71
12	**1d**	$-CH(OMe)_2$	Piperidine	0.4	**3d**	75
13	**1e**	$-(CH_2)_2CO_2Et$	Piperidine	0.4	**3e**	30

[a] At 60 °C. [b] 0.5 mmol piperidine was employed as base.



Scheme 2 A plausible mechanism for the formation of pyridones **3**.

with ethyl benzoylacetate at 60 °C for 1 d afforded 3-benzoyl-5-nitro-2-pyridones **4a** and **4b** in 37% and 95% yields, respectively (Fig. 2).



4a: R^1 = *t*-Bu
4b: R^1 = Pr

Fig. 2 Structure of pyridone **4**.

On the other hand, two types of pyridones **6** and **3** were obtained when amide esters **5**[26] were employed as the 1,3-dicarbonyl compounds (Fig. 3, Table 2, entry 1). When nitroenamine **1b** was treated with amide ester **5b** in the presence of piperidine, the product mixture exhibited two pairs of doublet signals at δ 8.80 and 8.83 (J = 3.2 Hz), 8.71 and 9.25 (J = 3.1 Hz) in the ^{1}H NMR spectrum, which were assigned to the protons at the

Table 2 Syntheses of pyridones **6** having carbamoyl group at 3-position

Entry	Starting materials				Base	Solvent	Products			
		R^1		R^2			**6**	Yield[a] (%)	**3**	Yield[a] (%)
1	**1b**	Pr	**5b**	Pr	Piperidine	$CHCl_3$	**6a**	37	**3b**	23
2	**1b**	Pr	**5c**	Allyl	Piperidine	$CHCl_3$	**6b**	26	**3c**	36
3	**1b**	Pr	**5c**	Allyl	Et_2NH	$CHCl_3$	**6b**	57	**3c**	19
4	**1b**	Pr	**5c**	Allyl	Et_2NH	MeCN	**6b**	53	**3c**	16
5	**1b**	Pr	**5c**	Allyl	Et_2NH	EtOH	**6b**	70	**3c**	15
6[b]	**1a**	*t*-Bu	**5c**	Allyl	Et_2NH	EtOH	**6c**	34[c]	**3c**	15
7	**1c**	Allyl	**5a**	*t*-Bu	Et_2NH	EtOH	**6d**	Quant.	**3a**	0
8	**1c**	Allyl	**5b**	Pr	Et_2NH	EtOH	**6e**	Quant.[d]	**3b**	0
9[b]	**1b**	Pr	**5d**	Ph	Et_2NH	EtOH	**6f**	45	**3f**	0
10[b]	**1b**	Pr	**5e**	*p*-$MeOC_6H_4$	Et_2NH	EtOH	**6g**	44	**3g**	0
11[b]	**1b**	Pr	**5f**	*p*-$NO_2C_6H_4$	Et_2NH	EtOH	**6h**	68	**3h**	0

[a] Yield estimated from ^{1}H NMR analysis (1,1,2,2-tetrachloroethane was used as an internal standard). [b] Reaction was conducted at 50 °C. [c] Isolated yield. [d] Isolated yield of **6e** was 77%.

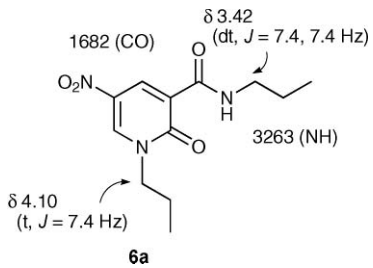


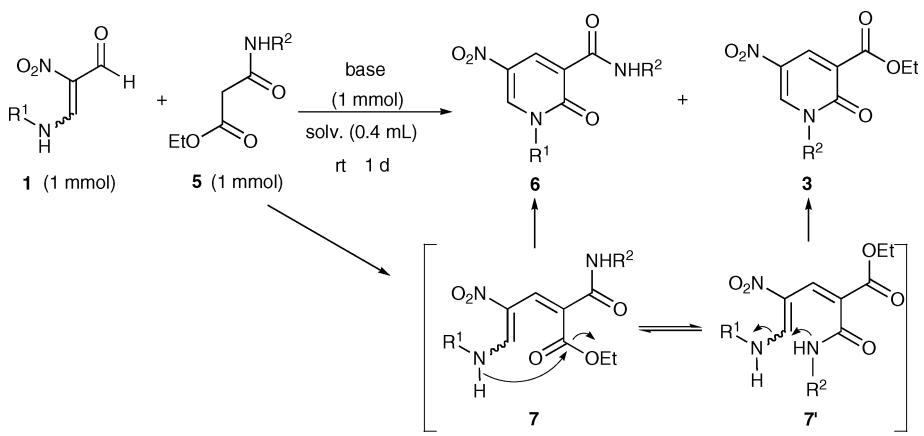
Fig. 3 Assignment of pyridone **6a**.

4- and the 6-positions of the pyridone ring, respectively. Pyridones **6a** and **3b** were isolated by chromatography on silica gel. Pyridone **6a** had two *N*-propyl groups, one of which was assigned to the *N*-propylcarbamoyl group because of the presence of coupling between the *N*-methylene group and the adjacent N-H. The other product was determined as pyridone **3b** as both signals of *N*-propyl and ethoxy groups were present.

It is considered that pyridone **6a** is constructed through a similar mechanism for the formation of pyridones **3**. Namely, the condensation of amide ester occurs at the formyl group of **1** to give intermediate **7**, whose amino group then attacks the ester function, leading to pyridone **6a**. In contrast, pyridone **3b** is produced *via* intermediate **7′**, a diastereomer of **7** presents under equilibrium. Here, the substitution by the amide group (R^2NHCO) of **7′** proceeds at the α-carbon of the enamino group to furnish pyridone **3b** (Scheme 3). In this case, although pyridone **3b** would be formed by substitution of the carbamoyl group with the amino group (R^1NH), this possibility is easily excluded by conducting the reaction of nitroenamine **1b** with amide ester **5c** (R^2 = allyl), in which only pyridone **6b** and **3c** were formed without any detectable pyridone **3b**.

The optimization of reaction conditions was studied using nitroenamine **1b** and amide ester **5c** (Table 2, entries 2–5). Diethylamine was more effective than piperidine, to afford pyridones **6b** and **3c** in higher total yields (entries 2 and 3). Acetonitrile and ethanol could be also used as the solvent instead of chloroform. Ethanol was slightly better with respect to total yield and the selectivity of pyridone **6b** (entries 3–5).

Syntheses of other pyridone derivatives **6** were performed under the conditions of entry 5. When nitroenamine **1a** was treated with **5c**, pyridone **6c** was formed in 34% yield together with pyridone **3a**, though heating was necessary (entry 6). It was considered that the bulkiness of the amino group of **1** hindered the cyclization forming a pyridone ring. On the other hand, *N*-allylnitroenamine **1c** reacted with both amide esters **5a** and **5b** to give the corresponding pyridones **6d** and **6e** in quantitative yields, respectively (entries 7 and 8). Furthermore, this procedure



Scheme 3 Reactions **1** with amide esters **5** to afford pyridones **6** and **3**.

is applicable to the preparation of pyridones **6f–6h** having an *N*-arylcarbamoyl group in moderate yields by using amide esters **5d–5f**, respectively (entries 9–11).

As mentioned above, 3-functionalized 5-nitropyridones **3**, **4** and **6** could be prepared by condensation of nitroenamines **1** and 1,3-dicarbonyl compounds. This result suggested that iminopyridine **10a** would result from the reaction of nitroenamine **1b** with malononitrile **8a**, but the isolated product was found to have a different structure. In the ^{1}H NMR spectrum of the product, a pair of doublet signals with a coupling constant of 2.5 Hz was observed at a low-field region, which were assigned to protons of the aromatic ring. The signal of the *N*-methylene group was observed as a doublet of triplet ($J = 6.6$ and 6.6 Hz), indicating the presence of coupling between *N*-methylene and NH groups. This observation obviously excluded the possibility of iminopyridine **10a** as the product. The structure of the product was assigned as aminopyridine **9a** that was produced as a result of formal rearrangement of the propyl group from the ring nitrogen to the imino group of **10a** (Scheme 4). Furthermore, the structure was also confirmed by single crystal X-ray structure analysis of the product[27] (see ESI†). The present reaction quantitatively proceeded to give aminopyridine **9a** even when other amines such as diethylamine and triethylamine were used (the data not shown), in contrast to the fact that the choice of amine was critical to synthesis of pyridone **3b**. Moreover, we found that aminopyridine **9a** was quantitatively obtained by only mixing nitroenamine **1b** and malononitrile **8a** without using any bases (Table 3, entry 1).[28]

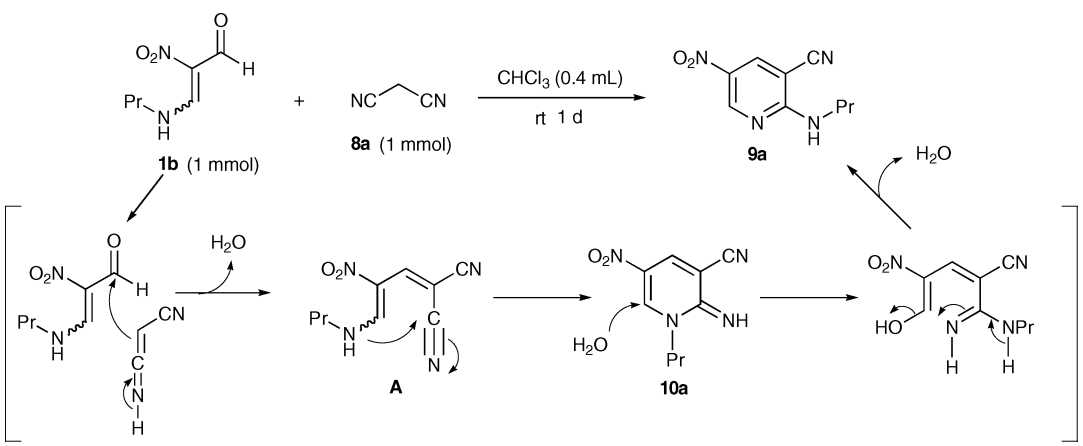
Formal transfer of an alkyl group from ring nitrogen of 1-alkyl-2-iminopyrimidine forming 2-alkylaminopyrimidine is often observed, which is known as the Dimroth rearrangement.[29] Accordingly, a plausible mechanism for the formation of **9a** is proposed as shown in Scheme 4. The attack of a nucleophilic keteneimine derived from malononitrile **8a** to the formyl group of nitroenamine **1b** followed by dehydration affords intermediate **A**, and subsequent intramolecular cyclization gives iminopyridine **10a**. The ring opening reaction of **10a** and recyclization proceed leading to aminopyridine **9a**. In this case, water formed during the condensation is considered to behave as the nucleophile to open the ring **10a**.

Nitroenamines **1a**, **1c**, and **1d** reacted with malononitrile **8a** to afford aminopyridine **9b**, **9c**, and **9d**, respectively, having different substituent at the 2-position (Table 3, entries 2–4). We then tried to expand the scope of this method by using functionalized acetonitrile derivatives having an active methylene group. Cyanoacetates **8b** and **8c** similarly afforded nicotinic acid derivatives **9e**, **9f**, and **9g**, although piperidine was necessary to form enolate except for entry 6 (entries 5–7). In these cases, 3-cyano-5-nitro-2-pyridones were not detectable which would have resulted from the cyclization on the ester function. The reaction of **1d** with **8c** in the presence of piperidine gave aminopyridine **10h** accompanied by aminopyridine **10h′**, which was formed from **10h** by aminolysis with piperidine (entry 8). Less soluble cyanoacetamide **8d** afforded nicotinamide derivative **9i** in a quantitative yield by using tetrahydrofuran instead of chloroform (entry 9). Arylacetonitriles were also usable as the substrates of the present reaction to furnish aminopyridines having a (het)aryl group at the 3-position. While 2-pyridylacetonitrile **8e** similary leads to pyridylpyridine **9j**, potassium *tert*-butoxide was necessary to bring about the reaction of phenylacetonitrile **8f** (entries 10 and 11).[30,31] On the other hand, benzoylacetonitrile **8g** exhibits higher reactivity to give aminopyridine **9m** in a good yield without using any base at room temperature (entry 12).

The present reactions were superior to the conventional methods for the preparation of aminonitropyridines with regard to the following features. 1) Reactions proceed efficiently under mild conditions in one-pot to give the products **9** in excellent yields in most cases. 2) Modification of the substituents at the 2- and 3-positions is easily performed by selecting appropriate nitroenamines **1** and acetonitrile derivatives **8**.

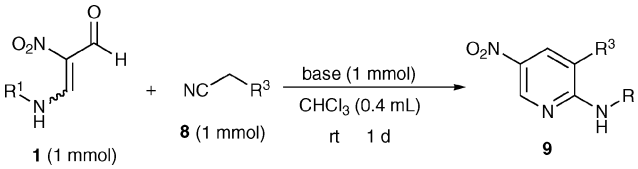
Conclusions

We have revealed the new reactivity of formylnitroenamines **1**, which means that they can be used as C3N1 building blocks for synthesizing (i) nitropyridones **3**, **4**, and **6** with a carbonyl group at the 3-position, upon treatment with malonates **2**, **5**, or ethyl benzoylacetate, and (ii) aminonitropyridines **9** with a functional group at the 3-position, when acetonitrile derivatives **8** are employed as reactants. In these reactions, modification of the pyridone and pyridine ring is readily achieved by selecting nitroenamines **1** and active methylene compounds. Furthermore, both preparative methods can be performed under mild conditions,

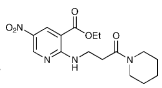


Scheme 4 Synthesis of aminopyridine **9a** from nitroenamine **1b** and **8a**.

Table 3 Syntheses of variety of aminopyridines **9**



Entry	Starting materials				Base	Product	Yield[a] (%)
		R^1		R^3			
1	**1b**	Pr	**8a**	CN	None	**9a**	Quant.
2[b]	**1a**	*t*-Bu	**8a**	CN	None	**9b**	74
3	**1c**	$-CH_2CH=CH_2$	**8a**	CN	None	**9c**	Quant.
4	**1d**	$-(CH_2)_2CO_2Et$	**8a**	CN	None	**9d**	Quant.
5[b]	**1a**	*t*-Bu	**8b**	CO_2Me	Piperidine	**9e**	85
6	**1b**	Pr	**8c**	CO_2Et	None	**9f**	93
7	**1c**	$-CH_2CH=CH_2$	**8c**	CO_2Et	Piperidine	**9g**	82
8	**1d**	$-(CH_2)_2CO_2Et$	**8c**	CO_2Et	Piperidine	**9h**	38[c]
9[d]	**1b**	Pr	**8d**	CO_2NH	Piperidine	**9i**	Quant.
10	**1b**	Pr	**8e**	2-Pyridyl	Piperidine	**9j**	90
11[b,d]	**1b**	Pr	**8f**	Ph	KOBu^t	**9k**	87
12	**1b**	Pr	**8g**	COPh	None	**9m**	97

[a] Isolated yield. [b] Reaction was carried out at 60 °C. [c] **9h′**  was also obtained in 13% yield. [d] THF was used as the solvent.

which require only simple experimental manipulations. These features should make the present procedures valuable, and enable them to replace conventional methods that require troublesome multi-step procedures.

Experimental

General

The melting points were determined on a Yanaco micro-melting-points apparatus, and were uncorrected. All the reagents and solvents were commercially available and used as received. The ^{1}H NMR spectra were measured on a Bruker DPX-400, Varian Mercury 300, or JEOL AL-400 spectrometer at 400 or 300 MHz, respectively, with TMS as an internal standard, and The ^{13}C NMR spectra were measured on a Bruker DPX-400 or JEOL AL-400 spectrometer at 100 MHz. Assignments of ^{13}C NMR spectra were performed by DEPT experiments. The UV-vis spectra were recorded on JASCO V-570. The IR spectra were recorded on a Horiba FT-200 IR spectrometer and a JASCO FT/IR-4200 Spectrophotometer. The mass spectra were recorded on a JEOL JMS-AX505HA or JEOL-DX-303-HF spectrometer. The elemental microanalyses were performed using a Yanaco MT-6 CHN corder. The X-Ray analysis was carried out with a Rigaku RAXIS-RAPID imaging plate diffractometer, using graphite monochromated Mo Kα radiation. The intensity data were computed by teXsan Single Crystal Structure Analysis Software Version 2.0 and structure solution and refinement were computed by SAPI91 and SHELXL-97, respectively.

3-(2-Propen-1-yl)amino-2-nitropropenal (1c). Nitroenamines **1c** was prepared according to the established method from nitropyrimidinone with 2 steps.[1] Nitropyrimidinone was prepared in 90% overall yield by the condensation of commercially available 1,1,3,3-tetramethoxypropane and *N*-methylurea in 12 M hydrochloric acid followed by nitration with fuming nitric acid (d = 1.52) in 18 M sulfuric acid. To a solusion of pyrimidinone (310 mg, 2.00 mmol) in methanol (40 mL) was added allylamine (375 µL, 5.00 mmol), and the mixture was heated under reflux for 3 h. After evaporation, the residue was extracted with hot hexane (3 × 30 mL), and evaporated under reduced pressure. Chloroform (5 mL) was added to the residue, and the solution was charged on silica gel (20 g) in a column and stood at room temperature for 1 d. Then, it was eluted with chloroform. The solvent was removed under reduced pressure to give nitroenamine **1c** (*E*/*Z* = 3/1, 144mg, 46%) as a brown oil (Found: C, 46.18; H, 4.97; N, 17.93. $C_6H_8N_2O_3$ requires C, 46.15; H, 5.16; N, 17.94%).

ν_{max}(neat)/cm^{-1} 1683 (CHO), 1658 (C=C), 1612 (C=C), 1506, 1317 (NO_2); δ_H(300 MHz, $CDCl_3$) 4.10 (2H$_E$, dd, *J* 5.7, 5.7, NHC*H*$_2$CH=CH$_2$), 4.17 (2H$_Z$, dd, *J* 5.4, 5.4, NHC*H*$_2$CH=CH$_2$), 5.35–5.45 (2H$_E$+2H$_Z$, m, NHCH$_2$CH=C*H*$_2$), 5.85–5.99 (1H$_E$+1H$_Z$, m, NHCH$_2$C*H*=CH$_2$), 7.91 (1H$_Z$, d, *J* 15.0, C=C*H*(NH)), 8.49 (1H$_E$, dd, *J* 3.6, 14.4, C=C*H*(NH)), 9.7 (1H$_Z$, br s, C=CH(N*H*)), 10.07 (1H$_Z$, s, C*H*O), 10.16 (1H$_E$, d, *J* 3.6, C*H*O) 10.5 (1H$_E$, br s, C=CH(N*H*)); δc(100 MHz, $CDCl_3$) 52.3 (CH_2), 52.5 (CH_2), 119.8 (CH_2), 119.9 (CH_2), 124.8 (C), 126.0 (C), 130.9 (CH), 150.4 (CH), 155.1 (CH), 182.9 (CH), 185.6 (CH), a tertiary carbon was not observed probably due to overlapping; *m*/*z* (EI) 156.0538 ($C_6H_8N_2O_3$ requires 156.0535), 156 (M$^+$, 20%), 41 (100).

Other nitroenamines **1a**, **1b**, **1d**, and **1e** were prepared in the same manner by using *t*-butylamine, propylamine, β-alanine ethyl ester hydrochloride, and 2,2-dimethoxyethylamine, respectively.

3-[(2-Ethoxycarbonyl)ethyl]amino-2-nitropropenal (1e). (*E*/*Z* = 3/1). 36% overall yield. White solid; mp 77–78 °C (recrystallized from ethanol, colorless needles). ν_{max}(KBr)/cm^{-1} 1719 (C=O),

1660 (CHO), 1603 (C=C), 1571, 1344 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.29 ($3H_E$+$3H_Z$, t, *J* 7.1, $CO_2CH_2CH_3$), 2.73 ($2H_E$, t, *J* 6.1, $NHCH_2CH_2$), 2.76 ($2H_Z$, t, *J* 6.0, $NHCH_2CH_2$), 3.77 ($2H_E$, dt, *J* 6.1, 6.1, $NHCH_2CH_2$), 3.83 ($2H_Z$, dt, *J* 6.0, 6.0, $NHCH_2CH_2$), 4.22 ($2H_E$+$2H_Z$, q, *J* = 7.1, $CO_2CH_2CH_3$), 7.96 ($1H_Z$, d, *J* 15.1, C=CH(NH)), 8.55 ($1H_E$, dd, *J* 3.6, 14.2, C=CH(NH)), 9.91 ($1H_Z$, br s, C=CH(NH)), 10.06 ($1H_Z$, s, CHO), 10.15 ($1H_E$, d, *J* 3.6, CHO) 10.69 ($1H_E$, br s, C=CH(NH)); δ_C(100 MHz, $CDCl_3$) 14.1 (CH_3), 34.3 (CH_2), 34.4 (CH_2), 46.5 (CH_2), 46.4 (CH_2), 61.6 (CH_2), 61.7 (CH_2), 150.7 (C), 155.6 (CH), 170.3 (C), 170.4 (C), 183.4 (CH), 186.3 (CH), one primary, one tertiary, and one quaternary carbons were not observed, probably due to overlapping of the signals at δ 14.1, 150.7, and 155.6 ppm, respectively; *m*/*z* (EI) 216.0720 ($C_8H_{12}N_2O_5$ requires 216.0746); *m*/*z* (FAB) 217 (M^++1, 100%).

3-Ethoxycarbonyl-5-nitro-1-propylpyridin-2(1*H*)-one (3b). Diethyl malonate (152 μL, 1.00 mmol) was added to a solution of nitroenamine **1b** (158 mg, 1.00 mmol) in chloroform (0.4 mL), and then piperidine (98 μL, 1.0 mmol) was added. The resultant mixture was heated under reflux for 1 d. After removal of the solvent under reduced pressure, the residual oily solid was purified by silica gel chromatography (eluted with hexane/ethyl acetate = 8/2) to give pyridone **3b** (198 mg, 78%) as a yellow oil (Found: C, 52.16; H, 5.81; N, 11.03. $C_{11}H_{14}N_2O_5$ requires C, 51.97; H, 5.55; N, 11.02%). Other pyridones **3a**, **3c–e**, and **6** were prepared in the same manner. ν_{max}(neat)/cm^{-1} 1739 (C=O), 1670 (C=O), 1571, 1344 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.02 (3H, t, *J* 7.1, $NCH_2CH_2CH_3$), 1.40 (3H, t, *J* 7.1, OCH_2CH_3), 1.87 (2H, tq, *J* 7.1, 7.3, $NCH_2CH_2CH_3$), 4.06 (2H, t, *J* 7.3, $NCH_2CH_2CH_3$), 4.40 (2H, q, *J* 7.1, OCH_2CH_3), 8.80 (1H, d, *J* 3.2, pyridone ring), 8.83 (1H, d, *J* 3.2, pyridone ring); δ_C(100 MHz, $CDCl_3$) 12.2 (CH_3), 15.5 (CH_3), 23.6 (CH_2), 54.7 (CH_2), 63.3 (CH_2), 120.9 (C), 130.2 (C), 138.6 (CH), 143.5 (CH), 159.3 (C), 164.4 (C); *m*/*z* (FAB) 255 (M^++1, 100%).

1-*tert*-Butyl-3-ethoxycarbonyl-5-nitropyridin-2(1*H*)-one (3a). Yellow oil. ν_{max}(neat)/cm^{-1} 1743 (C=O), 1706 (C=O), 1575, 1365 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.39 (3H, t, *J* 7.1, OCH_2CH_3), 1.77 (9H, s, $NC(CH_3)_3$), 4.39 (2H, q, *J* 7.1, OCH_2CH_3), 8.75 (1H, d, *J* 3.0, pyridone ring), 9.02 (1H, d, *J* 3.0, pyridone ring); δ_C(100 MHz, $CDCl_3$) 14.1 (CH_3), 28.4 (CH_3), 61.8 (C), 65.4 (CH_2), 120.6 (C), 128.6 (C), 136.2 (CH), 139.6 (CH), 159.1 (C), 163.3 (C); *m*/*z* (EI) 268.1056 ($C_{12}H_{16}N_2O_5$ requires 268.1059), 268 (M^+, 10%), 213 (100).

3-Ethoxycarbonyl-5-nitro-1-(2-propen-1-yl)pyridin-2(1*H*)-one (3c) (= 7ac, 7bc). Brown oil (Found: C, 52.47; H, 4.80; N, 10.96. $C_{11}H_{12}N_2O_5$ requires C, 52.38; H, 4.79; N, 11.11%). ν_{max}(neat)/cm^{-1} 1740 (C=O), 1708 (C=O), 1673 (C=C), 1570, 1345 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.40 (3H, t, *J* 7.0, OCH_2CH_3), 4.40 (2H, q, *J* 7.0, OCH_2CH_3), 4.70 (2H, d, *J* 6.3, $NCH_2CH{=}CH_2$), 5.43 (1H, d, *J* 16.9, $NCH_2CH{=}CHH$), 5.46 (1H, d, *J* 10.0, $NCH_2CH{=}CHH$), 5.99 (1H, ddt, *J* 6.3, 10.0, 16.9, $NCH_2CH{=}CHH$), 8.80 (1H, d, *J* 2.1, pyridone ring), 8.84 (1H, d, *J* 2.1, pyridone ring); δ_C(100 MHz, $CDCl_3$) 13.9 (CH_3), 52.5 (CH_2), 61.7 (CH_2), 119.3 (C), 121.7 (CH_2), 128.9(C), 129.9 (CH), 137.1 (CH), 141.5 (CH), 157.5 (C), 162.6 (C); *m*/*z* (FAB) 253 (M^++1, 100%).

3-Ethoxycarbonyl-1-(2,2-dimethoxy)ethyl-5-nitro-pyridin-2-(1*H*)-one (3d). Colorless oil (Found: C, 47.89; H, 5.19; N, 9.17. $C_{12}H_{16}N_2O_7$ requires C, 48.00; H, 5.37; N, 9.33%). ν_{max}(neat)/cm^{-1} 1743 (C=O), 1706 (C=O), 1572, 1347 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.40 (3H, t, *J* 7.1, OCH_2CH_3), 3.45 (6H, s, $NHCH(OCH_3)_2$), 4.15 (2H, d, *J* 5.1, $NCH_2CH(OCH_3)_2$), 4.41 (2H, q, *J* 7.1, OCH_2CH_3), 4.61 (1H, t, *J* 5.1, $NCH_2CH(OCH_3)_2$), 8.80 (1H, d, *J* 3.1, pyridone ring), 8.86 (1H, d, *J* 3.1, pyridone ring); δ_C(100 MHz, $CDCl_3$) 14.6 (CH_3), 53.1 (CH_2), 56.3 (CH_3), 62.4 (CH_2), 101.6 (CH), 119.5 (C), 129.4 (C), 138.2 (CH), 144.3 (CH), 158.7 (C), 163.3 (C); *m*/*z* (EI) 300 (M^+, 8%), 223 (100).

3-Ethoxycarbonyl-[1-(2-ethoxycarbonyl)ethyl]-5-nitropyridin-2-(1*H*)-one (3e). Yellow oil. ν_{max}(neat)/cm^{-1} 1738 (C=O, The shoulder was observed.), 1671 (C=O), 1573, 1345 (NO_2); δ_H(300 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.2, OCH_2CH_3), 1.40 (3H, t, *J* 6.9, OCH_2CH_3), 2.93 (2H, t, *J* 6.0, $NCH_2CH_2CO_2Et$), 4.14 (2H, q, *J* 7.2, OCH_2CH_3), 4.32 (2H, t, *J* 6.0, $NCH_2CH_2CO_2Et$), 4.40 (q, 2H, *J* 6.9, OCH_2CH_3), 8.84 (1H, d, *J* 3.3, pyridone ring), 9.03 (1H, d, *J* 3.3, pyridone ring); δ_C(100 MHz, $CDCl_3$) 14.1 (CH_3), 14.3 (CH_3), 32.0 (CH_2), 48.5 (CH_2), 61.4 (CH_2), 62.0 (CH_2), 119.4 (C), 137.6 (CH), 144.0 (CH), 158.0 (C), 162.8 (C), 170.9 (C), one quaternary carbon could not be observed probably due to overlapping; *m*/*z* (EI) 312.0936 ($C_{13}H_{16}N_2O_7$ requires 312.0958), 312 (M^+, 58%), 193 (100).

3-Benzoyl-1-*tert*-butyl-5-nitropyridin-2(1*H*)-one (4a). Colorless prisms (from $CHCl_3$) (Found: C, 63.92; H, 5.40; N, 9.33. $C_{16}H_{16}N_2O_4$ requires C, 63.99; H, 5.37; N, 9.32%); mp 222–224 °C. ν_{max}(KBr)/cm^{-1} 1668 (C=O), 1645 (C=O), 1563, 1336 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.76 (9H, s, $NC(CH_3)_3$), 7,47 (2H, dd, *J* 7.4, 7.8, benzene ring), 7.60 (1H, t, *J* 7.4, benzene ring), 7.81 (2H, d, *J* 7.8, benzene ring), 8.35 (1H, d, *J* 2.9, pyridone ring), 9.02 (1H, d, *J* 2.9, pyridone ring); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_3), 65.1(C), 128.6 (CH), 129.4 (CH), 129.6 (C), 130.2 (C), 133.3 (CH), 133.8 (CH), 136.2 (C), 138.3 (CH), 160.4 (C), 192.4 (C); *m*/*z* (FAB) 301 (M^++1, 10%), 105 (100).

3-Benzoyl-5-nitro-1-propylpyridin-2(1*H*)-one (4b). White solid; mp 125–126 °C. ν_{max}(KBr)/cm^{-1} 1675 (C=O), 1667 (C=O), 1569, 1341 (NO_2); δ_H(300 MHz, $CDCl_3$) 0.97 (3H, t, *J* 7.5, $NCH_2CH_2CH_3$), 1.82 (2H, tq, *J* 7.5, 7.5, $NCH_2CH_2CH_3$), 4.00 (2H, t, *J* 7.5, $NCH_2CH_2CH_3$), 7.43 (2H, dd, *J* 7.8, 7.8, benzene ring), 7.56 (1H, t, *J* 7.8, benzene ring), 7.76 (2H, d, *J* 7.8, benzene ring), 8.36 (1H, d, *J* 3.3, pyridone ring), 8.70 (1H, d, *J* 3.3, pyridone ring); δ_C(100 MHz, $CDCl_3$) 11.0 (CH_3), 22.5 (CH_2), 53.1 (CH_2), 128.5 (CH), 128.8 (C), 129.3 (CH), 129.4 (C), 133.7 (CH), 134.3 (CH), 136.1 (C), 140.9 (CH), 159.0 (C), 191.8 (C); *m*/*z* (EI) 286.0953 ($C_{15}H_{14}N_2O_4$ requires 286.0954), *m*/*z* (FAB) 287 (M^++1, 100%).

5-Nitro-1-propyl-3-(*N*-propylcarbamoyl)pyridin-2(1*H*)-one (6a). White solid; mp 97–98 °C. ν_{max}(neat)/cm^{-1} 3263 (NH), 1682 (br, C=O), 1539, 1342 (NO_2); δ_H(400 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.4, $NHCH_2CH_2CH_3$), 1.05 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$), 1.65 (2H, tq, *J* 7.4, 7.4, $NHCH_2CH_2CH_3$), 1.88 (2H, tq, *J* 7.4, 7.4, $NCH_2CH_2CH_3$), 3.42 (2H, dt, *J* 7.4, 7.4, $NHCH_2CH_2CH_3$), 4.10 (2H, t, *J* 7.4, $NCH_2CH_2CH_3$), 8.71 (1H, d, *J* 3.1, pridone ring), 9.25 (1H, d, *J* 3.1, pyridone ring), 9.25–9.30 (1H, br s, NH); δ_C(100 MHz, $CDCl_3$) 11.0 (CH_3), 11.6 (CH_3), 22.5 (CH_2), 22.7 (CH_2), 42.5 (CH_2), 53.5 (CH_2), 120.9 (C), 131.0 (C), 136.8 (CH),

140.4 (CH), 161.5 (C), 161.6 (C); *m/z* (EI) 267.1227 ($C_{12}H_{17}N_3O_4$ requires 267.1219), 267 (M^+, 20%), 209 (100).

5-Nitro-3-[*N*-(2-propen-1-yl)carbamoyl]-1-propylpyridin-2(1*H*)-one (6b). White solid (Found: C, 54.55; H, 6.00; N, 15.88. $C_{12}H_{15}N_3O_4$ requires C, 54.33; H, 5.70; N, 15.84); mp 94–95 °C. ν_{max}(neat)/cm^{-1} 3258 (NH), 1682 (br, C=O), 1530, 1335 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.04 (3H, t, *J* 7.3, $NCH_2CH_2CH_3$), 1.89 (2H, tq, *J* 7.3, 7.3, $NCH_2CH_2CH_3$), 4.09 (4H, m, $NCH_2CH_2CH_3$, $NHCH_2CH$=CHH), 5.18 (1H, dd, *J* 1.2, 10.4, $NHCH_2CH$=C*H*H), 5.27 (1H, dd, *J* 1.2, 17.1, $NHCH_2CH$=CH*H*), 5.93 (1H, ddt, *J* 5.4, 10.4, 17.1 Hz, $NHCH_2CH$=CHH), 8.76 (1H, d, *J* 3.1, pyridone ring), 9.13 (1H, d, *J* = 3.1, pyridone ring), 9.34–9.41 (1H, br t, N*H*); δ_C(100 MHz, $CDCl_3$) 11.0 (CH_3), 22.4 (CH_2), 42.1 (CH_2), 53.5 (CH_2), 116.4 (CH_2), 120.6 (C), 130.8 (C), 133.7 (CH), 137.0 (CH), 140.7 (CH), 161.4 (C), 161.6 (C); *m/z* (EI) 265 (M^+, 40%), 209 (32), 167 (45), 56 (100).

1-*tert*-Butyl-5-nitro-3-[*N*-(2-propen-1-yl)carbamoyl]pyridin-2(1*H*)-one (6c). Yellow solid; mp 156–158 °C. ν_{max}(KBr)/cm^{-1} 3299 (NH), 1684 (CO), 1673 (C=C), 1528, 1334 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.78 (9H, s, $NC(CH_3)_3$), 4.09 (2H, dd, *J* 6.0, 6.0, $NHCH_2CH$=CHH), 5.18 (1H, dd, *J* 1.6, 10.0, $NHCH_2CH$=C*H*H), 5.27 (1H, dd, *J* 1.6, 17.2 Hz, $NHCH_2CH$=CH*H*), 5.94 (1H, ddt, *J* = 6.0, 10.0, 17.2 Hz, $NHCH_2CH$=CHH), 8.99 (1H, d, *J* = 3.2 Hz, pyridone ring), 9.23 (1H, d, *J* 3.2, pyridone ring), 9.40 (1H, br m, N*H*); δ_C(100 MHz, $CDCl_3$) 28.5 (CH_3), 42.2 (CH_2), 65.7 (C), 116.3 (CH_2), 121.3 (C), 130.5 (C), 133.8 (CH), 136.3 (CH), 137.9 (CH), 161.8 (C), 162.7 (C); *m/z* (EI) 279.1208 ($C_{13}H_{17}N_3O_4$ requires 279.1219), 279 (M^+, 33%), 167 (100).

3-(*N*-*tert*-Butylcarbamoyl)-5-nitro-1-(2-propen-1-yl)pyridin-2(1*H*)-one (6d). Colorless prisms; mp 142–144 °C. ν_{max}(KBr)/cm^{-1} 3077 (NH), 1687 (br, C=O), 1559, 1357 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.46 (9H, s, $NHC(CH_3)_3$), 4.71 (2H, d, *J* 6.0, NCH_2CH=CHH), 5.38 (1H, d, *J* 17.2, NCH_2CH=C*H*H), 5.47 (1H, d, *J* 10.4, NCH_2CH=CH*H*), 5.99 (1H, ddt, *J* 6.0, 10.4, 17.2, NCH_2CH=CHH), 8.69 (1H, d, *J* 3.2, pyridone ring), 9.17 (1H, br s, N*H*), 9.23 (1H, d, *J* = 3.2 Hz, pyridone ring); δ_C(100 MHz, $CDCl_3$) 28.7 (CH_3), 51.5 (C), 52.9 (CH_2), 121.6 (CH_2), 121.9 (C), 130.0 (CH), 131.2 (C), 136.4 (CH), 139.6 (CH), 160.1 (C), 161.3 (C); *m/z* (EI) 279.1235 ($C_{13}H_{17}N_3O_4$ requires 279.1219), 279 (M^+, 7%), 207 (100%).

5-Nitro-1-(2-propen-1-yl)-3-(*N*-propylcarbamoyl)pyridin-2(1*H*)-one (6e). White solid; mp 64–65 °C. ν_{max}(KBr)/cm^{-1} 3280 (NH), 1682 (br, C=O), 1571, 1337 (NO_2); δ_H(400 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.2, $NHCH_2CH_2CH_3$), 1.64 (2H, tq, *J* 6.8, 7.2, $NHCH_2CH_2CH_3$), 3.41 (2H, dt, *J* 6.8, 6.8, $NHCH_2CH_2CH_3$), 4.73 (2H, d, *J* 6.4, NCH_2CH=CHH), 5.40 (1H, d, *J* 16.8, $NHCH_2CH$=C*H*H), 5.47 (1H, d, *J* 10.0, $NHCH_2CH$=CH*H*), 5.99 (1H, ddt, *J* 6.4, 10.0, 16.8, $NHCH_2CH$=CHH), 8.72 (1H, d, *J* 3.2, pyridone ring), 9.23 (2H, br m, pyridone ring, N*H*); δ_C(100 MHz, $CDCl_3$) 11.6 (CH_3), 22.7 (CH_2), 41.5 (CH_2), 52.9 (CH_2), 120.9 (C), 121.7 (CH_2), 130.0 (CH), 131.1 (C), 136.8 (CH), 139.8 (CH), 161.2 (C), 161.3 (C); *m/z* (EI) 265.1054 ($C_{12}H_{15}N_3O_4$ requires 265.1063), 265 (M^+, 12%), 167 (100).

5-Nitro-3-(*N*-phenylcarbamoyl)-1-propylpyridin-2(1*H*)-one (6f). Brown solid; mp 180–181 °C. ν_{max}(KBr)/cm^{-1} 3190 (NH), 1702 (C=O, The shoulder was observed.), 1554, 1343 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.06 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$), 1.92 (2H, tq, *J* 7.4, 7.4, $NCH_2CH_2CH_3$), 4.14 (2H, t, *J* 7.4, $NCH_2CH_2CH_3$), 7.16 (1H, t, *J* 7.4, benzene ring), 7.37 (2H, dd, *J* 7.4, 7.7, benzene ring), 7.72 (2H, d, *J* 7.7, benzen ring), 8.75 (1H, d *J* 3.2, pyridone ring), 9.34 (1H, d, *J* 3.2, pyridone ring), 11.4 (1H, br s, N*H*); δ_C(100 MHz, $CDCl_3$) 11.4 (CH_3), 22.8 (CH_2), 54.1 (CH_2), 120.9 (CH), 121.0 (C), 125.1 (CH), 129.5 (CH), 130.0 (C), 137.6 (CH), 138.0 (C), 141.0 (CH), 160.1 (C), 163.3 (C); *m/z* (EI) 301.1072 ($C_{15}H_{15}N_3O_4$ requires 301.1063), *m/z* (FAB) 302 (M^+, 100%).

3-[*N*-(4-Methoxyphenyl)carbamoyl]-5-nitro-1-propylpyridin-2(1*H*)-one (6g). Yellow powder (Found: C, 57.79; H, 5.33; N, 12.68. $C_{16}H_{17}N_3O_5$ requires C, 58.00; H, 5.17; N, 12.68%); mp 160–162 °C. ν_{max}(KBr)/cm^{-1} 3087 (NH), 1686 (br, C=O), 1555, 1340 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.06 (3H, t, *J* 7.3, $NCH_2CH_2CH_3$), 1.92 (2H, tq, *J* 7.3, 7.3, $NCH_2CH_2CH_3$), 3.82 (3H, s, OCH_3), 4.14 (2H, t, *J* 7.3, $NCH_2CH_2CH_3$), 6.91 (2H, d, *J* 9.0, benzene ring), 7.65 (2H, d, *J* 9.0, benzene ring), 8.74 (1H, d, *J* 3.2, pyridone ring), 9.33 (1H, d, *J* 3.2, pyridone ring), 11.2–11.3 (1H, br s, N*H*); δ_C(100 MHz, $CDCl_3$) 11.0 (CH_3), 22.5 (CH_2), 53.7 (CH_2), 55.5 (CH_3), 114.2 (CH), 121.0 (C), 121.9 (CH), 131.0 (C), 131.1 (C), 136.9 (CH), 140.5 (CH), 156.6 (C), 159.1 (C), 161.6 (C); *m/z* (EI) 331 (M^+, 100%).

5-Nitro-3-[*N*-(4-nitrophenyl)carbamoyl]-1-propylpyridin-2(1*H*)-one (6h). White solid (Found: C, 51.77; H, 4,14; N, 16.16. $C_{15}H_{14}N_4O_6$ requires C, 52.03; H, 4.07; N, 16.18%.); mp 277–279 °C. ν_{max}(KBr)/cm^{-1} 3069 (NH), 1690 (C=O), 1640 (C=O), 1550, 1350 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.07 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$), 1.92 (2H, tq, *J* 7.3, 7.4, $NCH_2CH_2CH_3$), 4.17 (2H, t, *J* 7.3, $NCH_2CH_2CH_3$), 7.92 (2H, d, *J* 9.1, benzene ring), 8.27 (2H, d, *J* 9.1, benzene ring), 8.81 (1H, d, *J* 3.1, pyridone ring), 9.36 (1H, d, *J* 3.1, pyridone ring), 11.4 (1H, br s, N*H*); δ_C(100 MHz, DMSO-d_6) 10.6 (CH_3), 21.6 (CH_2), 52.4 (CH_2), 118.3 (C), 119.8 (CH), 125.0 (CH), 130.4 (C), 136.6 (CH), 142.9 (CH), 143.7 (C), 144.5 (C), 160.6 (C), 161.3 (C); *m/z* (FAB) 346 (M^++1, 100%).

2-*tert*-Butylamino-3-cyano-5-nitropyridine (9b). Malononitrile **8a** (66 mg, 1.0 mmol) was added to a solution of nitroenamine **1a** (172 mg, 1.00 mmol) in chloroform (0.4 mL). The resultant mixture was heated under reflux for 1 d. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel eluted with chloroform to give product **9b** (163 mg, 74%) as a white solid. mp 133–135 °C. ν_{max}(neat)/cm^{-1} 3330 (NH), 2231(CN), 1542, 1328 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.53 (9H, s, $NHC(CH_3)_3$), 5.79 (1H, br s, $NHC(CH_3)_3$), 8.44 (1H, d, *J* 2.7, pyridine ring), 9.15 (1H, d, *J* 2.7, pyridine ring); δ_C(100 MHz, $CDCl_3$) 30.0 (CH_3), 55.8 (C), 93.0 (C), 116.2 (C), 135.5 (C), 138.3 (CH), 150.7 (CH), 160.8 (*C*); *m/z* (FAB) 221.1051 ($C_{10}H_{12}N_4O_2$ requires 221.1039), 221 (M^++1, 100%).

Other pyridines **9a**, **9c**, **9d**, **9e**, **9f**, **9g**, **9h**, **9i**, **9j**, **9k**, and **9m** were prepared in the same manner.

3-Cyano-5-nitro-2-(propylamino)pyridine (9a). White solid (Found: C, 52.72; H, 5.03; N, 26.94. $C_9H_{10}N_4O_2$ requires C, 52.42; H, 4.89; N, 27.17%.); mp 126–128 °C. λ_{max}(MeCN)/nm 344 (ε/dm^3 mol^{-1} cm^{-1} 19 171); ν_{max}(neat)/cm^{-1} 3336 (NH), 2231

(CN), 1590, 1333 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.02 (3H, t, *J* 7.4, $NHCH_2CH_2CH_3$), 1.72 (2H, tq, *J* 6.2, 7.4, $NHCH_2CH_2CH_3$), 3.50 (2H, dt, *J* 6.2, 6.2, $NHCH_2CH_2CH_3$), 6.1–6.3 (1H, br s, $NHCH_2CH_2CH_3$), 8.48 (1H, d, *J* 2.6, pyridine ring), 9.14 (1H, d, *J* 2.6, pyridine ring); δ_C(100 MHz, $CDCl_3$) 11.3 (CH_3), 22.4 (CH_2), 44.0 (CH_2), 90.6 (C), 114.8 (C), 134.3 (C), 137.3 (CH), 150.2 (CH), 160.0 (C); *m*/*z* (FAB) 207 (M^++1, 100%).

3-Cyano-5-nitro-2-(2-propen-1-ylamino)pyridine (9c). White solid (Found: C, 53.18; H, 3.93; N, 27.38. $C_9H_8N_4O_2$ requires C, 52.94; H, 3.95; N, 27.44%.); mp 111–112 °C. ν_{max}(neat)/cm^{-1} 3334 (NH), 2229 (CN), 1620 (C=C), 1594, 1305 (NO_2); δ_H(400 MHz, $CDCl_3$) 4.29 (2H, dd, *J* 5.7, 5.7, $NHCH_2CH$=CHH), 5.28 (1H, dd, *J* 1.1, 10.3, $NHCH_2CH$=C*H*H), 5.31 (1H, dd, *J* 1.1, 18.4, $NHCH_2CH$=CH*H*), 5.94 (1H, ddd, *J* 5.7, 10.3, 18.4, $NHCH_2CH$=CHH), 6.0–6.3 (1H, br t, $NHCH_2CH$=CHH), 8.50 (1H, d, *J* 2.5, pyridine ring), 9.18 (1H, d, *J* 2.5, pyridine ring); δ_C(100 MHz, $CDCl_3$) 44.4 (CH_2), 91.1 (C), 114.5 (C), 118.1 (CH_2), 132.5 (CH), 134.8 (C), 137.2 (CH), 150.1 (CH), 159.6 (C); *m*/*z* (FAB) 205 (M^++1, 100%).

3-Cyano-2-[2-(ethoxycarbonyl)ethylamino]-5-nitropyridine (9d). White solid (Found: C, 50.20; H, 4.75; N, 20.94. $C_{11}H_{12}N_4O_4$ requires C, 50.00; H, 4.58; N, 21.20%.); mp 133–134 °C. ν_{max}(neat)/cm^{-1} 3338 (NH), 2225 (CN), 1724 (C=O), 1592, 1332 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.2, OCH_2CH_3), 2.70 (2H, t, *J* 6.1, $NHCH_2CH_2$), 3.95 (2H, dt, *J* 6.1, 6.1, $NHCH_2CH_2$), 4.21 (2H, q, *J* 7.2, OCH_2CH_3), 6.5–6.8 (1H, br t, $NHCH_2CH_2$), 8.49 (1H, d, *J* 2.6, pyridine ring), 9.15 (1H, d, *J* 2.6, pyridine ring); δ_C(100 MHz, $CDCl_3$) 14.2 (CH_3), 33.6 (CH_2), 37.6 (CH_2), 61.2 (CH_2), 91.5 (C), 114.3 (C), 134.7 (C), 137.2 (CH), 149.9 (CH), 159.6 (C), 171.9 (C); *m*/*z* (FAB) 265 (M^++1, 100%).

2-*tert*-Butylamino-3-methoxycarbonyl-5-nitropyridine (9e). Pale yellow solid; mp 106–108 °C. ν_{max}(KBr)/cm^{-1} 3314 (NH), 1698 (C=O), 1594, 1347 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.53 (9H, s, $NHC(CH_3)_3$), 3.92 (3H, s, OCH_3), 8. 88 (1H, d, *J* 3.6, pyridine ring), 9.13 (1H, d, *J* 3.6, pyridine ring); δ_C(100 MHz, $CDCl_3$) 28.9 (CH_3), 52.5 (CH_3), 53.1 (C), 104.6 (C), 133.5 (C), 135.5 (CH), 149.7 (CH), 159.6 (C), 166.9 (C); *m*/*z* (EI) 253.1071 ($C_{11}H_{15}N_3O_4$ requires 253.1063), 253 (M^+, 13%), 238 (100).

3-Ethoxycarbonyl-5-nitro-2-(propylamino)pyridine (9f). White solid (Found: C, 52.10; H, 6.06; N, 16.44. $C_{11}H_{15}N_3O_4$ requires C, 52.17; H, 5.97; N, 16.59%.); mp 68–69 °C. λ_{max}(MeCN)/nm 353 (ε/dm^3 mol^{-1} cm^{-1} 20 723); ν_{max}(neat)/cm^{-1} 3323 (NH), 1697 (C=O), 1594, 1344 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.02 (3H, t, *J* 7.4, $NHCH_2CH_2CH_3$), 1.43 (3H, t, *J* 7.1, OCH_2CH_3), 1.71 (2H, tq, *J* 7.0, 7.4, $NHCH_2CH_2CH_3$), 3.59 (2H, dd, *J* 7.0, 7.0, $NHCH_2CH_2CH_3$), 4.39 (2H, q, *J* 7.1, OCH_2CH_3), 8.80–8.87 (1H, br, $NHCH_2CH_2CH_3$), 8.89 (1H, d, *J* 2.9, pyridine ring), 9.14 (1H, d, *J* 2.9, pyridine ring); δ_C(100 MHz, $CDCl_3$) 11.9 (CH_3), 14.6 (CH_3), 22.9 (CH_2), 43.7 (CH_2), 62.2 (CH_2), 105.1 (C), 134.2 (C), 136.0 (CH), 151.0 (CH), 160.5 (C), 166.7 (C); *m*/*z* (FAB) 254 (M^++1, 100%).

3-Ethoxycarbonyl-5-nitro-2-(2-propen-1-ylamino)pyridine (9g). White solid (Found: C, 52.77; H, 5.36; N, 16.73. $C_{11}H_{13}N_3O_4$ requires C, 52.59; H, 5.22; N, 16.73%.); mp 80–82 °C. ν_{max}(neat)/cm^{-1} 3316 (NH), 1692 (C=O), 1592, 1303 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.44 (3H, t, *J* 7.1, OCH_2CH_3), 4.29 (2H, dd, *J* 5.6, 5.6, $NHCH_2CH$=CHH), 4.40 (2H, q, *J* 7.1, OCH_2CH_3), 5.21 (1H, dd, *J* 1.0, 10.5, $NHCH_2CH$=C*H*H), 5.28 (1H, dd, *J* 1.0, 17.1, $NHCH_2CH$=CH*H*), 5.98 (1H, ddt, *J* 5.6, 10.5, 17.1, $NHCH_2CH$=CHH), 8.7–9.0 (1H, br s, $NHCH_2CH$=CHH), 8.91 (1H, d, *J* 2.7, pyridine ring), 9.12 (1H, d, *J* 2.7, pyridine ring); δ_C(100 MHz, $CDCl_3$) 15.5 (CH_3), 45.1 (CH_2), 63.2 (CH_2), 106.3 (C), 118.0 (CH_2), 134.8 (CH), 135.5 (C), 137.0 (CH), 151.8 (CH), 161.2 (C), 167.6 (C); *m*/*z* (FAB) 252 (M^++1, 100%).

3-Ethoxycarbonyl-2-[2-(ethoxycarbonyl)ethylamino]-5-nitropyridine (9h). White solid (Found: C, 50.20; H, 5.70; N, 13.58. $C_{13}H_{17}N_3O_6$ requires C, 50.16; H, 5.50; N, 13.50%.); mp 120–123 °C. ν_{max}(neat)/cm^{-1} 3325 (NH), 1728 (C=O), 1695 (C=O), 1591, 1344 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.2, OCH_2CH_3), 1.42 (3H, t, *J* 7.1, OCH_2CH_3), 2.69 (2H, t, *J* 6.2, $NHCH_2CH_2$), 3.95 (2H, dt, *J* 6.2, 6.2, $NHCH_2CH_2$), 4.20 (2H, q, *J* 7.2, OCH_2CH_3), 4.39 (2H, q, *J* 7.1, OCH_2CH_3), 8.90 (1H, d, *J* 2.9, pyridine ring), 9.14 (1H, d, *J* 2.9, pyridine ring), 9.15–9.20 (1H, br t, $NHCH_2CH_2$); δ_C(100 MHz, $CDCl_3$) 14.2 (CH_3), 14.3 (CH_3), 33.7 (CH_2), 37.0 (CH_2), 60.9 (CH_2), 61.9 (CH_2), 105.3 (C), 134.3 (C), 135.7 (CH), 150.3 (CH), 159.9 (C), 166.0 (C), 172.4 (C); *m*/*z* (FAB) 312 (M^++1, 100%).

3-Ethoxycarbonyl-2-[(3-oxo-3-pyperidino)propylamino]-5-nitropyridine (9h′). White solid (Found: C, 55.01; H, 6.53; N, 16.03. $C_{16}H_{22}N_4O_5$ requires C, 54.85; H, 6.33; N, 15.99%.); mp 66–68 °C. ν_{max}(neat)/cm^{-1} 3338 (NH), 1685, 1633 (C=O), 1538, 1344 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.40 (3H, t, *J* 7.1, OCH_2CH_3), 1.52–1.57 (4H, m, CH_2 at 3-position of piperidino group), 1.61–1.64 (2H, m, CH_2 at 4-position of piperidino group), 2.67 (2H, t, *J* 6.1, $NHCH_2CH_2$), 3.3–3.7 (4H, m, CH_2 at 2-position of piperidino group), 3.99 (2H, dt, *J* 6.1, 6.1, $NHCH_2CH_2$), 4.39 (2H, q, *J* 7.1, OCH_2CH_3), 8.89 (1H, d, *J* 2.7, pyridine ring), 9.13 (1H, d, *J* = 2.7, pyridine ring), 9.32 (1H, br t, $NHCH_2CH_2$); δ_C(100 MHz, $CDCl_3$) 16.7 (CH_3), 26.9 (CH_2), 27.9 (CH_2), 28.8 (CH_2), 35.0 (CH_2), 39.8 (CH_2), 45.1 (CH_2), 48.8 (CH_2), 64.3 (CH_2), 107.7 (C), 136.5 (C), 138.2 (CH), 152.7 (CH), 162.2 (C), 168.9 (C), 171.6 (C); *m*/*z* (FAB) 351 (M^++1, 60%), 307 (100).

3-Carbamoyl-5-nitro-2-propylaminopyridine (9i). White solid (Found: C, 47.92; H, 5.28; N, 24.96. $C_9H_{12}N_4O_3$ requires C, 48.21; H, 5.39; N, 24.99%); mp 169–170 °C. λ_{max}(MeCN)/nm 360 (ε/dm^3 mol^{-1} cm^{-1} 17 824); ν_{max}(neat)/cm^{-1} 3390 (NH), 1647 (C=O), 1531, 1303 (NO_2); δ_H(400 MHz, DMSO-d_6) 0.92 (3H, t, *J* 7.5, $NHCH_2CH_2CH_3$), 1.60 (2H, tq, *J* 6.5, 7.5, $NHCH_2CH_2CH_3$), 3.50 (2H, dt, *J* 6.5, 6.5, $NHCH_2CH_2CH_3$), 7.7–7.8 (1H, br, CONHH), 8.4–8.5 (1H, br, CONHH), 8.79 (1H, br d, pyridine ring), 9.04 (1H, br d, pyridine ring), 9.8 (1H, br t, $NHCH_2CH_2CH_3$); δ_C(100 MHz, DMSO-d_6) 11.2 (CH_3), 21.8 (CH_2), 42.3 (CH_2), 107.5 (C), 132.3 (CH), 132.9 (C), 148.8 (CH), 159.7 (C), 168.4 (C); *m*/*z* (FAB) 225 (M^++1, 100%).

5-Nitro-2-propylamino-3-(2-pyridyl)pyridine (9j). Yellow solid (Found: C, 60.20; H, 5.51; N, 21.70. $C_{13}H_{14}N_4O_2$ requires C, 60.45; H, 5.46; N, 21.69%.); mp 114–115 °C. λ_{max}(MeCN)/nm 370 (ε/dm^3 mol^{-1} cm^{-1} 18 745); ν_{max}(KBr)/cm^{-1} 1542, 1327 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.05 (3H, t, *J* 7.3, $NHCH_2CH_2CH_3$), 1.75 (2H, tq, *J* 7.0, 7.3, $NHCH_2CH_2CH_3$), 3.64 (2H, dt, *J* 7.0, 7.0, $NHCH_2CH_2CH_3$), 7.32 (1H, dd, *J* 5.0, 6.6, pyridine ring), 7.86 (1H, dd, *J* 6.6, 8.2, pyridine ring), 7.90 (1H, d, *J* 8.2, pyridine ring), 8.63 (1H, d, *J* 5.0, pyridine ring), 8.67 (1H, d, *J* 2.3,

pyridine ring), 9.09 (1H, d, *J* 2.3, pyridine ring), 10.62 (1H, br s, N*H*$CH_2CH_2CH_3$); δ_C(100 MHz, $CDCl_3$) 12.1 (CH_3), 22.9 (CH_2), 43.8 (CH_2), 113.7 (C), 121.8 (CH), 122.8 (CH), 130.6 (CH), 134.4 (C), 137.9 (CH), 147.4 (CH), 147.6 (CH), 155.4 (C), 159.6 (C); *m*/*z* (EI) 258 (M^+, 20%), 229 (100), 183 (40).

5-Nitro-3-phenyl-2-(propylamino)pyridine (9k). Yellow oil (Found: C, 65.47; H, 5.82; N, 16.21. $C_{14}H_{15}N_3O_2$ requires C, 65.35; H, 5.88; N, 16.33%). λ_{max}(MeCN)/nm 371 (ε/dm^3 mol^{-1} cm^{-1} 16 300); ν_{max}(neat)/cm^{-1}. δ_H(400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.4, $NHCH_2CH_2CH_3$), 1.61 (2H, tq, *J* 7.0, 7.4, $NHCH_2CH_2CH_3$), 3.49 (2H, dt, *J* 7.0, 7.0, $NHCH_2CH_2CH_3$), 5.2–5.4 (1H, br t, N*H*$CH_2CH_2CH_3$), 7.39–7.46 (2H, m, benzene ring), 7.48–7.52 (3H, m, benzene ring), 8.02 (1H, d, *J* 2.4, pyridine ring), 9.04 (1H, d, *J* 2.4, pyridine ring); δ_C(100 MHz, $CDCl_3$) 11.8 (CH_3), 22.9 (CH_2), 44.0 (CH_2), 121.8 (C), 129.1 (CH), 129.4 (CH), 130.1 (CH), 132.0 (CH), 135.8 (C), 136.0 (C), 146.1 (CH), 159.1 (C); *m*/*z* (EI) 257 (M^+, 60%), 228 (100), 182 (74).

3-Benzoyl-5-nitro-2-(propylamino)pyridine (9m). White solid (Found: C, 63.27; H, 5.46; N, 14.53. $C_{15}H_{15}N_3O_3$ requires C, 63.15; H, 5.30; N, 14.73%.); mp 120–121 °C. λ_{max}(MeCN)/nm 358 (ε/dm^3 mol^{-1} cm^{-1} 19 669); ν_{max}(neat)/cm^{-1} 3278 (NH), 1637 (C=O), 1541, 1315 (NO_2); δ_H(400 MHz, $CDCl_3$) 1.05 (3H, t, *J* 7.4, $NHCH_2CH_2CH_3$), 1.76 (2H, tq, *J* 6.8, 7.4, $NHCH_2CH_2CH_3$), 3.68 (2H, dt, *J* 6.8, 6.8, $NHCH_2CH_2CH_3$), 7.51–7.57 (2H, m, benzene ring), 7.59–7.64 (3H, m, benzene rimg), 8.57 (1H, d, *J* 2.7, pyridine ring), 9.19 (1H, d, *J* 2.7, pyridine ring), 9.5–9.7 (1H, br t, N*H*$CH_2CH_2CH_3$); δ_C(100 MHz, $CDCl_3$) 11.9 (CH_3), 22.8 (CH_2), 43,8 (CH_2), 112.3 (C), 129.2 (CH), 129.4 (CH), 132.8 (CH), 133.4 (C), 138.3 (C), 139.0 (CH), 151.3 (CH), 161.0 (C), 196.2 (C).

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References and notes

1 (*a*) N. Nishiwaki, T. Ogihara, T. Takami, M. Tamura and M. Ariga, *J. Org. Chem.*, 2004, **69**, 8382–8386; (*b*) N. Nishiwaki, Y. Tohda and M. Ariga, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 1997–2002.

2 S. M. Kvitko, V. V. Perekalin and N. V. Buivsl, *Z. Org. Khim.*, 1966, **2**, 2253–2255.

3 For synthetic equivalents of nitromalonaldehyde:(*a*) R. Jędrysiak, M. Sawicki, P. Wagner and J. Suwiński, *Arkivoc*, 2007, **vi**, 103–111; (*b*) P. E. Fanta and R. A. Stein, *Chem. Rev.*, 1960, **60**, 261–266.

4 Y. Nakaike, Y. Kamijo, S. Mori, M. Tamura, N. Nishiwaki and M. Ariga, *J. Org. Chem.*, 2005, **70**, 10169–10171.

5 (*a*) J. M. Mellor, in *Second supplements to the 2nd edition Rodd's Chemistry of Carbon Compounds*, ed. M. Sainsbury, Elsevier, Amsterdam, 1998, vol. 4, pp. 1-116; (*b*) O. Plunkett, M. Sainsbury, in *Second supplements to the 2nd edition Rodd's Chemistry of Carbon Compounds*, ed. M. Sainsbury, Elsevier, Amsterdam, 1998, vol. 4, pp. 365-421; (*c*) D. L. Comins, S. P. Joseph, in *Comprehensive Heterocyclic Chemistry*, ed. A. Mckillop, Pergamon, New York, 1996, vol. 5, pp. 92-131; (*d*) G. Jones, in *Comprehensive Heterocyclic Chemistry*, ed. A. Mckillop, Pergamon, New York, 1996, vol. 5, pp. 167-244; (*e*) M. Balasubramanian, J. G. Keay, in *Comprehensive Heterocyclic Chemistry*, vol. 5, ed. A. Mckillop, Pergamon, New York, 1996, vol. 5, pp. 245-300.

6 (*a*) M. Ando, T. Wada and N. Sato, *Org. Lett.*, 2006, **8**, 3805–3808; (*b*) R. Li, L. Xue, T. Zhu, Q. Jiang, X. Cui, Z. Yan, D. McGee, J. Wang, V. R. Gantla, J. C. Pickens, D. McGrath, A. Chucholowski, S. W. Morris and T. R. Webb, *J. Med. Chem.*, 2006, **49**, 1006–1015; (*c*) K. Ikegai and T. Mukaiyama, *Chem. Lett.*, 2005, **34**, 1496–1497; (*d*) S. V. Ryabukhin, A. S. Plaskon, D. M. Volochnyuk and A. A. Tolmachev, *Synlett*, 2004, 2287–2290; (*e*) V. Rusinov, O. N. Chupakhin and H. C. van der Plas, *Heterocycles*, 1995, **40**, 441–475.

7 G. Laurent, R. Benoit, C. Daniel, G. Laurence and H. Jean-Pierre, *Tetrahedron*, 2007, **63**, 9456–9464.

8 (*a*) D. C. Pryde, G. N. Maw, S. Planken, M. Y. Platts, V. Sanderson, M. Corless, A. Stobie, C. G. Barber, R. Russell, L. Foster, L. Barker, C. Wayman, P. Van Der Graaf, P. Stacey, D. Morren, C. Kohl, K. Beaumont, S. Coggon and M. Tute, *J. Med. Chem.*, 2006, **49**, 4409–4424; (*b*) J. V. N. V. Prasad, F. E. Boyer, L. Chupak, M. Dermyer, Q. Ding, K. Gavardinas, S. E. Hagen, M. D. Huband, W. Jiao, T. Kaneko, S. N. Maiti, M. Melnick, K. Romero, M. Patterson and X. Wu, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5392–5397; (*c*) P. Wang, J. Du, S. Rachakonda, B.-K. Chun, P. M. Tharnish, L. J. Stuyver, M. J. Otto, R. F. Schinazi and K. A. Watanabe, *J. Med. Chem.*, 2005, **48**, 6454–6460; (*d*) P. F. H. Freeman, *U.S. Pat.*, 197042858, 1970.

9 Nitropyridones emplyed as dienophiles in Diels–Alder reaction: R. Fujita, K. Watanabe, Y. Nishiuchi, R. Honda, H. Matsuzaki and H. Hongo, *Chem. Pharm. Bull.*, 2001, **49**, 601–605.

10 Nitropyridones emplyed as dienes in Diels–Alder reaction: Y. Tohda, K. Tani, N. Yamawaki, M. Ariga, N. Nishiwaki, K. Kotani and E. Matsumura, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 1222–1228.

11 N. Nishiwaki, H. Tatsumichi, M. Tamura and M. Ariga, *Lett. Org. Chem.*, 2006, **3**, 629–633.

12 R. Bergmann and R. Gericke, *J. Med. Chem.*, 1990, **33**, 492–504.

13 (*a*) K. Hiroya, K. Kawamoto and T. Sakamoto, *Synlett.*, 2006, 2636–2640.

14 J. Reisch, L. Mester and S. M. El-Moghazy Aly, *J. Chem. Soc. Perkin Trans. 1*, 1983, **33**, 219–223.

15 Y. Uchida, M. Ogawa, N. Iibuchi, T. Morita, *PCT Int. Appl.*, WO 2003033471, 2003.

16 S. Nagato, K. Ueno, K. Kawano, Y. Norimine, K. Ito, T. Hanada, M. Ueno, H. Amino, M. Ogo, S. Hatakeyama, Y. Urawa, H. Naka, A. Groom, L. Rivers, T. Smith, *PCT Int. Appl.*, WO 2006/109876, 2006.

17 K. E. Lind, K. Cao, E. Y.- S. Lin, T. B. Nguyen, B. T. Tangonan, D. A. Erlanson, K. Guckian, R. L. Simmons, W.-C. Lee, L. Sun, S. Hanses, N. Pathan, L. Zhang, *PCT Int. Appl.*, WO 2008005457, 2008.

18 (*a*) O. M. Guicherit, E. A. Boyd, S. A. Bruton, S. Price, J. H.-A. Stibbard, C. H. MacKinnon, *PCT Int. Appl.*, WO 2006050506, 2006; (*b*) J. Lee, S. J. Kirincich, M. J. Smith, D. P. Wilson, B. C. Follows, Z.-K. Wan, D. M. Joseph-Mccarthy, D. V. Erbe, Y.-L. Zhang, W. Xu, S. Y. Tam, *PCT Int. Appl.*, WO 2005081960, 2005; (*c*) A. Monge, V. Martinez-Merino, M. A. Simon and C. Sanmatin, *J. Heterocyclic Chem.*, 1992, **29**, 1545–1549.

19 The syntheses of 3-carbonylated-2-pyridones: (*a*) The oxidation of nicotinic acid derivatives; H. Suante and M. K. Mahanti, *Heterocyclic Commum.*, 2003, **9**, 489–492; R. Fujita, K. Watanabe, W. Ikeura, Y. Ohtake, H. Hongo, Y. Harigaya and H. Matsuzaki, *Tetrahedron*, 2001, **57**, 8841–8850; F. Trecourt, F. Marsais, T. Gungor and G. Queguiner, *J. Chem. Soc. Perkin Trans. 1*, 1990, 2409–2415; S. Rozen and D. Hebei, *Heterocycles*, 1989, **28**, 249–258; (*b*) The rearrangement of *O*-alkylpyridine: G. R. Newkome, D. K. Kohli and T. Kawato, *J. Org. Chem.*, 1980, **45**, 4508–4511.

20 P. E. Fanta and R. A. Stein, *J. Am. Chem. Soc.*, 1955, **77**, 1045–1046.

21 (*a*) V. Makarov, O. B. Riabova, A. Yuschenko, N. Urlyapova, A. Daudova, P. F. Zipfel and U. Möllmann, *J. Antimicrob. Chemother.*, 2006, **57**, 1134–1138; (*b*) A. Chetia, M. Longchar, K. C. Lekhok and R. C. Boruah, *Synlett*, 2004, 1309–1311; (*c*) J. M. Klunder, M. Hoermann, C. L. Cywin, E. David, J. R. Brickwood, R. Schwartz, K. J. Barringer, D. Pauletti, C.-K. Shih, D. A. Erickson, C. L. Sorge, D. P. Joseph, S. E. Hattox, J. Adams and P. M. Grob, *J. Med. Chem.*, 1998, **41**, 2960–2971; (*d*) Y. Morisawa, M. Kataoka, N. Kitano and T. Matsuzawa, *J. Med. Chem.*, 1977, **20**, 129–133.

22 (*a*) P. J. Langley, R. T. Bailey, F. R. Cruickshank, A. R. Kennedy, S. Lochran, D. Pugh, J. N. Sherwood, A. Viikki and J. D. Wallis, *J. Mater. Chem.*, 2001, **11**, 1047–1056; (*b*) H. Koshima, M. Hamada, I. Yagi and K. Uosaki, *Cryst. Growth Des.*, 2001, **1**, 467–471.

23 J. M. Bakke, H. Svensen and R. Trevisan, *J. Chem. Soc. Perkin Trans. 1*, 2001, 376–378.

24 P. Barczynski and H. C. van der Plas, *J. Org. Chem.*, 1982, **47**, 1077–1080.

25 The fact that secondary amines such as diethylamine, morphorine, piperidine induced the formation of the pyridones suggests that the present reaction proceeds *via* an iminium salt intermediate formed by condensation between the formyl group of **1** and an amine. The

formation of the reactive iminium ion is considered to enable the condensation with malonic acid derivatives **2** and **5**.

26 Y. Nakaike, N. Taba, S. Itoh, Y. Tobe, N. Nishiwaki and M. Ariga, *Bull. Chem. Soc. Jpn.*, 2007, **80**, 2413–2417.

27 Crystal data for compounds **9a**. $C_9H_{10}N_4O_2$, $M = 206.21$, triclinic, $a = 4.5625(6)$, $b = 10.2315(19)$, $c = 11.4327(17)$ Å, $\alpha = 107.479(5)$, $\beta = 100.889(8)$, $\gamma = 101.507(5)°$, $V = 480.82(13)$ Å^3, $T = 113.2$ K, Mo-Kα radiation, $\lambda = 0.71075$ Å, space group $P\bar{1}$ (no. 2), $Z = 2$, measured/independent reflections: 7811/2180, $R_1 = 0.0356$ for 1946 data with $I > 2\sigma(I)$, $wR_2 = 0.1097$ (all data).

28 There are some reports that describe condensations of acetonitrile derivatives with carbonyl compounds without any base. Most of them were conducted at high temperatures, but the mechanism was not discussed: (*a*) G. Kaupp, M. R. Naimi-Jamal and J. Schmeyers, *Tetrahedron*, 2003, **59**, 3753–3760; (*b*) D. F. Perepichka, M. R. Bryce, A. S. Batsanov, E. J. L. McInnes, J. P. Zhao and R. D. Farley, *Chem. Eur. J.*, 2002, **8**, 4656–4669; (*c*) A. J. Fatiadi, *Synthesis*, 1978, 165–204; (*d*) A. J. Fatiadi, *Synthesis*, 1978, 241–282.

29 (*a*) O. N. Chupakhin, V. L. Rusinov, A. A. Tumashov, E. O. Sidorov and I. V. Karpin, *Tetrahedron Lett.*, 1992, **33**, 3695–3696; (*b*) M. Wahren, *Z. Chem.*, 1969, **9**, 241–252; (*c*) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1965, 5542–5551; (*d*) M. Wahren, *Z. Chem.*, 1966, **6**, 181.

30 In contrast to **8a** and **8g**, with less acidic acetonitrile derivatives **8b**, **8c**, **8d**, **8e**, and **8f**, bases such as piperidine or potassium *tert*-butoxide were used to generate the corresponding anionic nucleophiles.

31 When triethylamine was employed as the tertiary amine in the reaction of **1a** and **8e** for 1 d at room temperature, aminopyridine **9j** was formed in only 10% yield with 27% recovery of **1a**, which indicates that piperidine serves not only as the base forming anionic nucleophiles but also as the activator of the formyl group of nitroenamine **1** by converting to iminium ion[25].

