Nucleophilic Reaction upon Electron-Deficient Pyridone Derivatives. X.[1] One-Pot Synthesis of 3-Nitropyridines by Ring Transformation of 1-Methyl-3,5-dinitro-2-pyridone with Ketones or Aldehydes in the Presence of Ammonia

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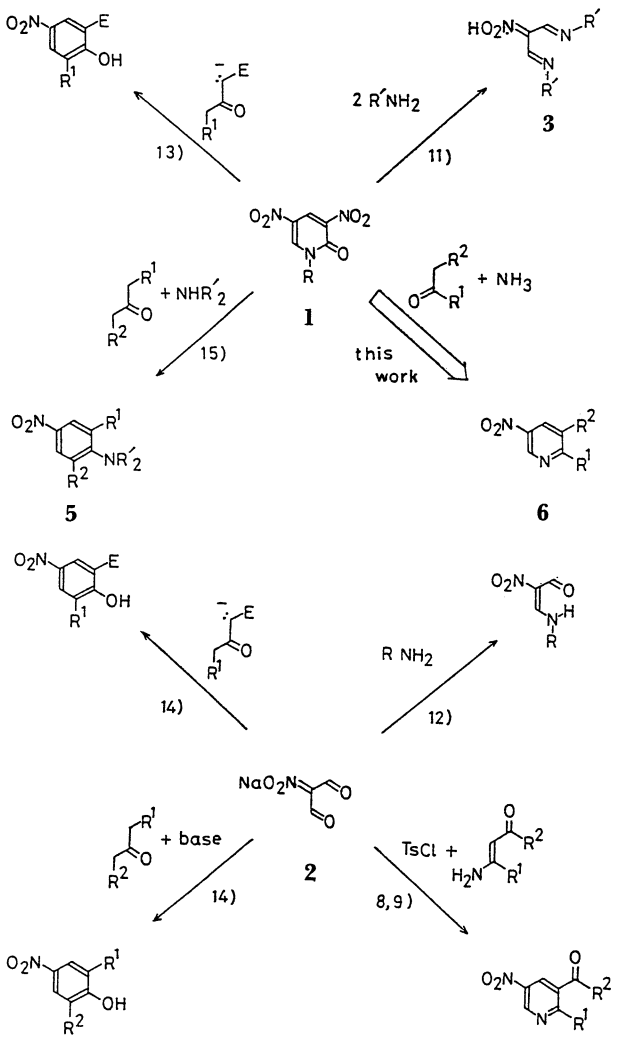
(Received March 22, 1990)

The reaction of 1-methyl-3,5-dinitro-2-pyridone (**1a**) with ketones or aldehydes in the presence of ammonia gave alkyl- and/or aryl-substituted 3-nitropyridines (**6**) in moderate to high yields. Enamines derived from the ketones gave better results than did the ketones themselves; on the other hand, those derived from the aldehydes gave no **6** at all. On the basis of deuterium-labeled experiments, a mechanism comprising competitive ring transformations of **1a** is proposed.

Alkyl- or aryl-substituted 3-nitropyridines (**6**) have been scarcely known. The nitration of mono- and dialkylpyridines give only traces of the expected products,[2,3] while that of aryl-substituted pyridines usually occurs at the aryl ring.[4] Recently, 2-(3,5-di-*t*-butyl-4-hydroxyphenyl)-5-nitropyridine was prepared as an interesting candidate for nonlinear optical materials[5] by coupling 2,6-di-*t*-butylphenol with 2-halo-5-nitropyridine;[6] the method[7] used, however, is not applicable to the preparation of other aryl-substituted 3-nitropyridines. An alternative approach to the syntheses of these compounds involves the construction of a pyridine ring. Some of the known methods are based on the condensation of sodium salt (**2**) of nitromalonaldehyde with α-acyl β-amino olefins and tosyl chloride[8] or with β-keto esters and ammonia.[8,9] These methods, however, are limited to the utilization of β-dicarbonyl compounds or their enamine derivatives, as the component of the C_2 unit of the pyridine ring.

In the course of our study on nucleophilic reactions upon 3,5-dinitro-2-pyridones (**1**),[1] we found that **1** often behaved as an activated and masked equivalent of sodium salt (**2**) of nitromalonaldehyde (Scheme 1), although **1** and **2** are quite different from one another regarding reactivity. Thus, the reaction of **1** with primary amines was followed by the elimination of α-nitroacetamides (**4**) to give diimines (**3**) of nitromalonaldehyde in good yields;[11] **2**, however, gave monoimines under the similar conditions.[12] The reaction of **1** with sodium salts of β-keto esters afforded *p*-nitrophenol derivatives more efficiently[13] than that of **2**.[14] Moreover, *p*-nitroaniline derivatives (**5**) were formed by the reaction of **1** with simple ketones in the presence of primary or secondary amines.[15]

These facts prompted us to develop a new synthesis using **1** as a novel equivalent of nitromalonaldehyde. We report here an elegant "one-pot" synthesis of 3-nitropyridines (**6**) by a ring transformation of 1-methyl-3,5-dinitro-2-pyridone (**1a**) with ammonia and such carbonyl compounds as aldehydes or ketones.



Scheme 1. Analogy of the reactions of **1** with those of **2** (E=CO_2Me; R, R^1, or R^2=H, alkyl, or aryl).

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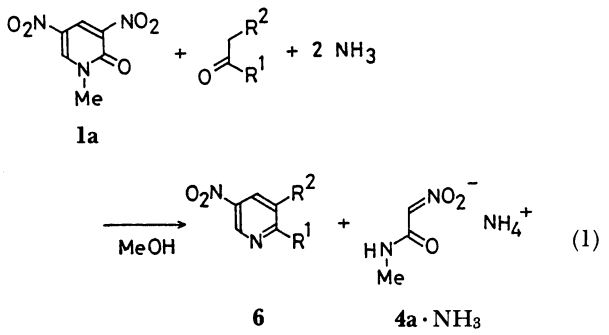


1a

6 4a·NH3 (1)

Results and Discussion

A methanolic solution of **1a**, cyclohexanone, and excess ammonia (1 M=1 mol dm^{-3}) was heated at 70 °C under atmospheric pressure for 3 h (condition A). After removing the solvent in vacuo, 5,6,7,8-tetrahydro-3-nitroquinoline (**6a**) was afforded in 83% yield as a benzene-soluble product. Ammonium salt of *N*-methyl-α-nitroacetamide (**4a**) was isolated in 67% yield as a benzene-insoluble counterpart. Methanol

Table 1. Synthesis of 3-Nitropyridines (**6**) from **1a**, Ammonia, and Carbonyl Compounds

Entry	Carbonyl compound	Reaction conditions[a)]	Product	R^1	R^2	Yield /%
	(Ketone with both α-and α′-hydrogens)					
1	Cyclohexanone	A	**6a**	$-(CH_2)_4-$		83
2	1-Morpholinocyclohexene	A	**6a**			90
3	Cyclohexanone	B	**6a**			28
4	Cyclohexanone	C	**6a**			50
5	Menthone	A	**6b**	$-CH(CH_2)_2CH-$		44
				C_3H_7-*i*	CH_3	
6	Menthone	B	**6b**			32
7	Cyclopentanone	A	**6c**	$-(CH_2)_3-$		27
8	1-Morpholinocyclopentene	A	**6c**			37
9	Cyclopentanone	B	**6c**			14
10	3-Methyl-2-butanone	A	**6d**	*i*-C_3H_7	H	36
11	3-Methyl-2-butanone	B	**6d**			21
	(Ketone without α′-hydrogen)					
12	Pinacolone	A	**6e**	*t*-C_4H_9	H	Trace
13	Pinacolone	B	**6e**			69
14	Acetophenone	A	**6f**	C_6H_5	H	44
15	α-Morpholinostyrene	A	**6f**			90
16	Acetophenone	B	**6f**			81
17	Propiophenone	A	**6g**	C_6H_5	CH_3	10
18	1-Morpholino-1-phenylpropene	A	**6g**			55
19	Propiophenone	B	**6g**			37
20	Tetralone	B	**6h**	-*o*-$C_6H_4(CH_2)_2-$		76
21	Desoxybenzoin	A	**6i**	C_6H_5	C_6H_5	Trace
22	Desoxybenzoin	B	**6i**			33
23	α-Morpholinostilbene	B	**6i**			66
24	*p*-Aminoacetophenone	B	**6j**	*p*-$C_6H_4NH_2$	H	44
25	*p*-Methoxyacetophenone	B	**6k**	*p*-$C_6H_4OCH_3$	H	64
26	*p*-Methylacetophenone	B	**6l**	*p*-$C_6H_4CH_3$	H	73
27	*p*-Cyanoacetophenone	B	**6m**	*p*-C_6H_4CN	H	30
28	*p*-Nitroacetophenone	B	**6n**	*p*-$C_6H_4NO_2$	H	27
29	2-Acetylpyridine	B	**6o**	2-Pyridyl	H	72
30	2,6-Diacetylpyridine	B[b)]	**6p**	c)	H	74[b)]
31	2-Acetylfuran	B	**6q**	2-Furyl	H	62
32	2-Acetylthiophene	B	**6r**	2-Thienyl	H	56
	(Aldehyde)					
33	Acetaldehyde	A or B	—			0
34	Acetaldehyde	C	**6s**	H	H	18
35	Propionaldehyde	A	**6t**	H	CH_3	Trace
36	1-Morpholinopropene	A	—			0
37	Propionaldehyde	C	**6t**			32
38	Butyraldehyde	C	**6u**	H	C_2H_5	41
39	Isovaleraldehyde	C	**6v**	H	*i*-C_3H_7	52

a) Conditions A: A solution of **1a** (2 mmol), a carbonyl compound (4 mmol) or an enamine (2.4 mmol), and ammonia (40 mmol) in methanol (40 ml) was heated at 70 °C for 3 h under atmospheric pressure. Conditions B: A solution of **1a** (2 mmol), a carbonyl compound (4 mmol) or an enamine (2.4 mmol), and ammonia (280 mmol) in methanol (40 ml) was heated at 120 °C for 3 h in a 200 ml autoclave. Conditions C: A solution of **1a** (2 mmol), an aldehyde (4 mmol), ammonia (20 mmol), and ammonium acetate (20 mmol) in methanol (40 ml) was heated at 100 °C for 3 h in a 200 ml autoclave. b) Yield of **6p** is based on the ketone (see Experimental). c) Structure of **6p** is shown in this text.

Table 2. Competitive Formation of 3-Nitropyridine (**6**) and 4-Nitroaniline (**5**)

Entry	Reagent	Reaction conditions[a)]	Products	Yields /%
40	Acetone	A	2-Methyl-5-nitropyridine (**6w**)	17
			4-Nitroaniline (**5a**)	34
41	Acetone	B	**6w**	9
			5a	29
42	2-Butanone	A	2,3-Dimethyl-5-nitropyridine (**6x**)	23[b)]
			2-Ethyl-5-nitropyridine (**6y**)	7[b)]
			2-Methyl-4-nitroaniline (**5b**)	43[b)]
43	2-Butanone	B	**6x**	20[b)]
			6y	2[b)]
			5b	53[b)]
44	3-Pentanone	A	2-Ethyl-3-methyl-5-nitropyridine (**6z**)	34
			2,6-Dimethyl-4-nitroaniline (**5c**)	47
45	3-Pentanone	B	**6z**	26
			5c	45

a) Notations of the conditions are same as shown in Table 1. b) The yields were determined by ^{1}H NMR spectra.

was the most suitable among the examined solvents. When pyridine or DMF was used as a solvent, dry ammonia gas had to be bubbled into the solvent during the reaction because of the low solubility of ammonia in these solvents.

Various ketones and aldehydes having α-methyl or α-methylene hydrogens reacted with **1a** in the presence of ammonia either under condition A or under other modified conditions, B or C (vide infra), to give alkyl- and/or aryl-substituted 3-nitropyridine derivatives (**6**). The results are summarized in Tables 1 and 2. These results show that the most suitable reaction conditions depend on the structure of the carbonyl compounds. In the case of aliphatic ketones having both α- and α'-hydrogens (Entry 1—11, 40—45), the mildest condition, A, gave the best results yielding 3-nitropyridines which had a 6-alkyl substituent with active α-hydrogens. The lower yields of the pyridines **6** under the other harder conditions, B and C, may be attributed to a further condensation of **6** with either the ketones or **1a**. On the other hand, when a ketone having no α'-hydrogen, such as aromatic ketones or pinacolone, were used as the C_2 component (Entry 12—32), the best results were obtained under the hardest condition, B: treatment of **1a** with the ketone in 7 M methanolic ammonia at 120 °C in an autoclave.

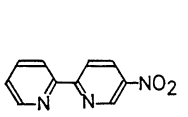
In reactions with **1**, enamines derived from the ketones and morpholine gave **6** in better yields than did the original ketones (Entry 2, 8, 15, 18, and 23). The yields of **6** were much improved in the cases of the less reactive aromatic ketones. Generally speaking, the enamines are more favorable reagents, although they are less available, especially those from methyl[16] or aromatic ketones.[17] Surprisingly, enamines derived from aldehydes and morpholine gave no **6** but, rather, unidentifiable resinous products (Entry 36).

Aliphatic aldehydes having α-methyl or α-methylene hydrogens did not yield any **6** under either condition A or B. Treatment of these aldehydes with **1a** and ammonia in the presence of ammonium acetate (condition C) afforded unsubstituted (**6s**) and 5-alkyl-substituted (**6t—6v**) 3-nitropyridines, respectively. Higher classes of the aldehydes gave **6** in better yields. These results suggest that self-condensation of the aldehyde reduces the yield of **6**.

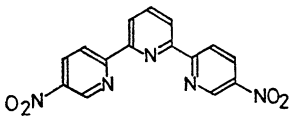
As expected from Scheme 1,[15] the competitive formation of 3-nitropyridines (**6**) and *p*-nitroanilines (**5**) was observed in the reaction of **1a** with ketones bearing either methyl or methylene hydrogens on both α- and α'-carbons (Table 2). Unfortunately, **6** was a minor product in every case, and it could be easily separated from the major product, **5**, by dissolving **6** in hexane. The reaction of **1a** with 2-butanone (Entry 42 and 43) gave two isomeric 3-nitropyridines (**6x** : **6y**=3 : 1) as well as **5b**. 3-Pentanone (Entry 44) gave better results than did acetone (Entry 40). These facts indicate that the ketones having α-methylene hydrogens are more reactive than those having α-methyl hydrogens in the case of aliphatic ketones. In the case of aromatic ketones, however, the ketones having α-methyl hydrogens (Entry 14—16) seem to be more reactive than those having α-methylene hydrogens (Entry 17—19).

Neither β-diketones, β-keto esters, nor their enamine derivatives gave the corresponding 3-nitropyridines, even under the strongest condition, B. It is interesting that these β-dicarbonyl compounds react well with sodium nitromalonaldehyde (**2**) to give 3-nitropyridine derivatives.[8,9] However, when a simple ketone, cyclohexanone, was treated with **2** under condition A, the yield of **6a** was only 6.5%. From these facts, it can be concluded that, for the synthesis of **6**, **1a** is a better reagent when simple aliphatic or aromatic ketones are used as the C_2 component of **6**, and **2** is suitable if the ketones having β-carbonyl groups are used.

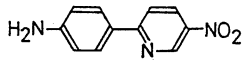
Most of the afforded 3-nitropyridines **6** are new compounds and some of them are expected to have



6o



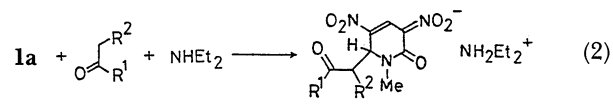
6p



6j

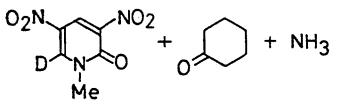
interesting properties. For example, 5-nitro-2,2′-dipyridine (**6o**) and 5,5″-dinitro-2,2′:6′,2″-terpyridine (**6p**) are ones of the most π-acidic 2,2′-dipyridines and 2,2′:6′,2″-terpyridines, which are interesting in terms of coordination chemistry, organometallic chemistry, and photochemistry.[18] 2-(4-Aminophenyl)-5-nitropyridine (**6j**) has a deep orange-red crystal form [λ_{max}(methanol)= 398 nm] due to its strong intramelocular charge-transfer; the other **6** are colorless or pale yellow.

When **1a** was treated with a 3 M ammonia solution in the absence of ketones at 70 °C for 3 h, the solution turned red, indicating the reversible formation of a Meisenheimer complex of **1a** with ammonia.[19] After removing the solvent in vacuo and allowing recrystallization, most of **1a** was recovered. On the other hand, the treatment of more electrophilic 3,5-dinitro-2-pyridones, such as 1-(2-pyridyl) (**1b**) or 1-(4-nitrophenyl) derivatives (**1c**), with ammonia alone or with ammonia and cyclohexanone gave neither **6** nor **3a**, these pyridones, however, were decomposed at once. Since **1b** and **1c** react with primary amines to give **3** much faster than **1a**,[11] the initial product of the reactions may be diimine (**3a**) of nitromalonaldehyde, which is more labile than free nitromalonaldehyde, itself.[10] Moreover, the treatment of **1a** with ketones having α-methylene or α-methyl hydrogens in methanol or other solvents in the presence of diethylamine gave a Meisenheimer adduct of **1a** with a ketonic nucleophile in good yields; however, no cleavage of the pyridone ring occurred (Eq 2).[19] These results show that the ring cleavage of **1a** in this reaction must be caused by cooperation with both ketones and ammonia and that **3a** is not an intermediate.



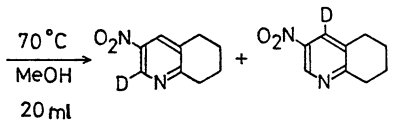
(2)

In order to clarify the reaction mechanism, 6-deuterio labeled dinitropyridone (**1d**) was treated under two different conditions. One was condition A in which cyclohexanone and excess ammonia were used (Eq 3). The other was a modified condition A in which a more nucleophilic enamine derivative and a 1.5 molar amount of ammonia were used (Eq 4). Under these conditions, mixtures of 2-deuterio- (**6α**) and 4-deuterio-3-nitropyridine derivatives (**6γ**) were afforded in different ratios; 58:42 under the former conditions and 81:19 under the latter. In both cases, the H-D exchanged product **6a** was not detected by the ^{1}H NMR spectra.[20] These results together indicate that the formation of **6α** and **6γ** (or **6**) proceeds competitively via different paths.



1d

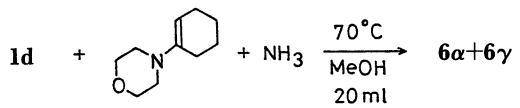
1 mmol 2 mmol 10 mmol



(3)

6α **6γ**

6α:6γ=58:42

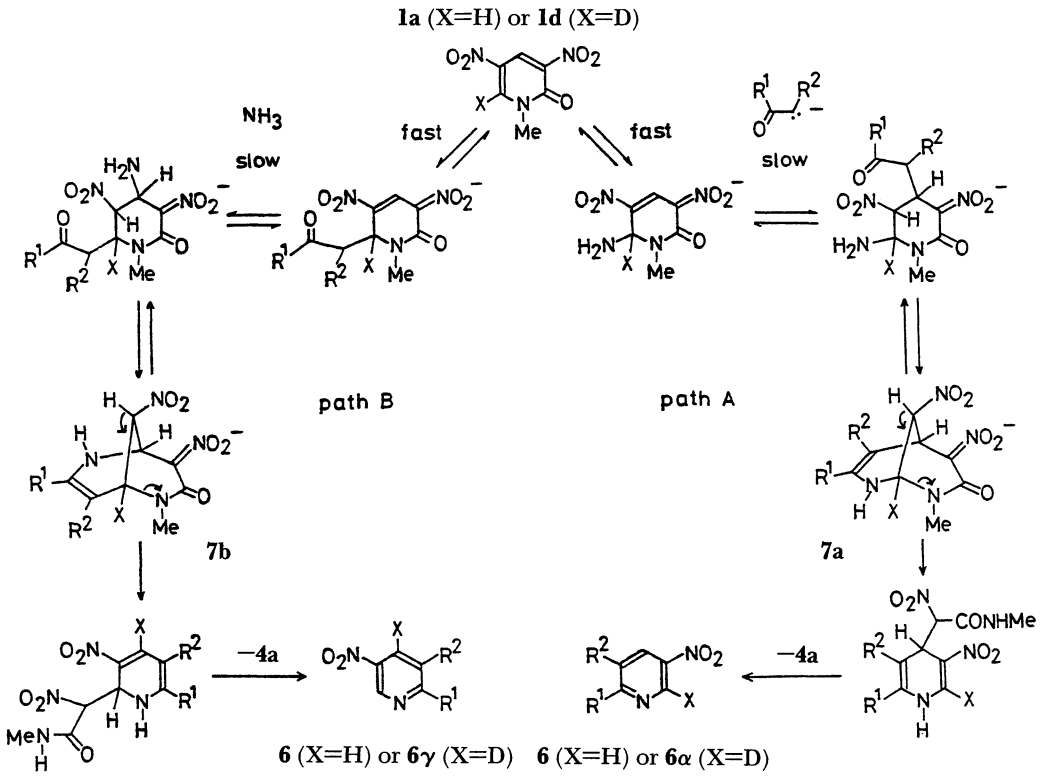


(4)

1 mmol 2 mmol 1.5 mmol **6α:6γ=81:19**

We propose a possible set of paths from **1a** (or **1d**) to **6** (or **6α** and **6γ**) involving two isomeric meta-bridged intermediates (**7a** and **7b**) (path A and path B in Scheme 2). Such a type of compounds has been isolated as the intermediates of the reactions of **1** to *p*-nitrophenols[13] or *p*-nitroanilines.[15] The intermediates, **7a** and **7b**, are formed by the consecutive addition of ketones and ammonia at the C-4 and C-6 positions of **1a**. On the basis of the structure of the Meisenheimer adducts of **1d** with *C*-, *N*-, *O*-nucleophiles,[19] it can be expected that the first addition of these nucleophiles in this reaction also occurs at the C-6 position of **1**. The second addition at C-4 of **1** may be much slower than the first one since the formation constants of such 1,3-adducts are generally smaller than those of the Meisenheimer adducts in many electron-deficient aromatics.[21] Consequently, we can assume that the product distribution between **6α** and **6γ** depends on the relative rate of the second nucleophilic addition of each path. This assumption implies that path A, which gives **6α**, is predominant when ketonic nucleophile is more active than ammonia. Since the actual nucleophilic species of the ketones are their enolate ions or/and their enamines derived from ammonia or morpholine, the effective concentration of such ketonic nucleophiles is higher in the case of Eq. 4 than in the case of Eq. 3. Thus, the predominant formation of **6α** in the case of Eq. 4 can be rationalized by this scheme.

In conclusion, the present reaction is one of the



Scheme 2. Dual path ways from **1a** (or **1d**) to 3-nitropyridines **6** (or 6α and **6γ**).

unique ring transformations of 1-methyl-3,5-dinitro-2-pyridone **1a**. Since **1a** is readily available (see Experimental) and nonexplosive, it is a useful reagent to prepare 3-nitropyridines with alkyl- and/or aryl-substituents at either the 5- and/or 6-positions.

Experimental

Elemental analyses were carried out using a Yanagimoto MT-3 CHN-corder. ^{1}H NMR spectra were measured using a Hitachi R-20 B spectrometer with TMS as an internal reference. IR spectra were collected with a Hitachi model 260-10 spectrophotometer. The melting points were measured by means of a Yanagimoto micro melting point apparatus.

1-Methyl-3,5-dinitro-2-pyridone (1a). 1-Methyl-2-pyridone was prepared from pyridine according to the known procedure,[22] and continuous extraction with chloroform gave it in 91% yield (lit,[22] 65—71%). Nitration of the pyridone (5.45 g) with nitric acid (d=1.38, 38 ml) in sulfuric acid (100 ml) at 100 °C for 4 h gave **1a** in 42%.[13] Similarly, 6-deuterio-1-methyl-2-pyridone[23] was nitrated to give 6-deuterio-1-methyl-3,5-dinitro-2-pyridone (**1d**) in 38% yield; pale yellow plates (water), mp 173 °C. ^{1}H NMR (DMSO-d_6): δ=3.69 (3H, s), 9.01 (1H, s). Found: C, 36.25; H, 2.18; N, 21.05%. Calcd for $C_6H_4DN_3O_5$: C, 36.01; H, 2.52; N, 21.00%.

Synthesis of 3-Nitropyridines (6) under the Condition A. A mixture of 0.40 g (2.0 mmol) of **1a**, 0.39 g (4.0 mmol) of cyclohexanone, and 40 ml of ammonia solution (1 M) in methanol was heated at 70 °C for 3 h under atmospheric pressure. The solvent was removed in vacuo and the residual oil was dissolved in benzene. A benzene-soluble portion was passed through a short silica-gel column. A benzene eluent gave a colorless solid, which was a mixture of **6a** and the starting ketone. The solid was recrystallized from methanol-water (1 : 4) to give 0.30 g (83%) of colorless plates (**6a**). Elemental analysis, melting points, and IR spectra of **6** are summarized in Table 3 and ^{1}H NMR spectra of **6** are shown in Table 4. A benzene-insoluble yellow solid (0.18 g, 67%) was identified as an ammonium salt of N-methyl-α-nitroacetamide (**4a**) by its ^{1}H NMR spectrum (DMSO-d_6): δ=2.69 (3H, d, J=4.6 Hz), 5.99 (1H, s), 6.15 (4H, m), 9.31 (1H, m). The solid was dissolved in 5 ml of water and just neutralized by dil. hydrochloric acid. A chloroform extract gave 0.05 g (20%) of N-methyl-α-nitroacetamide (**4a**), colorless plates, mp 61—64 °C. ^{1}H NMR (DMSO-d_6): δ=2.68 (3H, d, J=5.0 Hz), 5.23 (2H, s), 8.3 (1H, broad s). Found: C, 30.47; H, 5.19; N, 23.90%. Calcd for $C_3H_6N_2O_3$: C, 30.51; H, 5.12; N, 23.72%.

Synthesis of 6 under the Condition B. A mixture of 0.40 g (2.0 mmol) of **1a**, 0.48 g (4.0 mmol) of acetophenone, and 40 ml of methanolic ammonia solution (7 M) was heated at 120 °C for 3 h in a 200 ml autoclave. After removing the solvent in vacuo, a residual oil was column-chromatographed over silica gel. The benzene eluent was washed with cold hexane to give 0.34 g (81%, mp 118—120 °C) of colorless prisms (**6f**).

Synthesis of 6 under the Condition C. A mixture of 0.40 g (2.0 mmol) of **1a**, 0.34 g (4 mmol) of isovaleraldehyde, 1.54 g (20 mmol) of ammonium acetate, and 40 ml of ammonia solution (0.5 M) in methanol was heated at 100 °C for 3 h in a 200 ml autoclave. After removing the solvent in vacuo, 20 ml of a saturated aqueous sodium chloride solution was added to the residual oil; the mixture was extracted by chloroform. The extract was dried with anhydrous sodium sulfate and passed through a silica-gel column. The first

Table 3. Melting Points, Analytical Data, and IR Spectra of 3-Nitropyridines **6**

Compound	Mp θ_m/°C	Found/%			Calcd/%			$\nu_{as}(NO_2)$	$\nu_s(NO_2)$
		C	H	N	C	H	N	cm^{-1}	cm^{-1}
6a	74 — 74.5	60.66	5.65	15.68	60.66	5.66	15.72	1513	1350
6b	Oil	66.50	7.75	11.86	66.64	7.74	11.96	1517	1352
6c	94.5— 95	58.63	4.93	17.09	58.53	4.91	17.07	1510	1350
6d	36 — 38.5	57.90	6.09	16.71	57.82	6.07	16.86	1520	1355
6e	26.5— 27	59.60	6.69	15.35	59.98	6.71	15.55	1527	1352
6f	120 —120.5	66.19	4.05	14.06	65.99	4.03	13.99	1520	1346
6g	74 — 74.5	67.30	4.80	13.02	67.28	4.71	13.08	1515	1343
6h	146 —150	69.14	4.49	12.54	69.01	4.46	12.38	1522	1340
6i	91 — 91.5	73.85	4.42	10.02	73.90	4.38	10.24	1520	1340
6j	220 —221	61.68	4.20	19.33	61.39	4.22	19.53	1520	1335
6k	131 —132	62.86	4.47	12.02	62.60	4.38	12.17	1520	1340
6l	129 —132	67.15	4.72	13.07	67.28	4.71	13.08	1520	1343
6m	209 —212	64.24	3.17	18.61	64.00	3.13	18.66	1520	1350
6n	220 —225	54.05	2.92	17.31	53.88	2.88	17.14	1516	1346
6o	173 —174	59.90	3.56	20.91	59.70	3.51	20.89	1518	1350
6p	271 —273	55.89	2.80	21.68	55.73	2.81	21.67	1524	1353
6q	164 —166	57.10	3.16	14.95	56.84	3.18	14.73	1510	1350
6r	170 —170.5	52.31	2.98	13.47	52.42	2.93	13.58	1515	1347
6s	38 — 40 (lit,[a] 41)	48.47	3.26	22.33	48.39	3.25	22.58	1533	1352
6t	95 — 96	52.15	4.38	20.42	52.17	4.38	20.28	1525	1358
6u	Oil	55.31	5.46	18.62	55.25	5.30	18.41	1530	1360
6v	49 — 49.5	57.88	6.06	17.04	57.82	6.07	16.86	1530	1360
6w	106 —108	52.44	4.47	20.07	52.17	4.38	20.28	1518	1350
6x	50.5— 51.5	55.15	5.19	18.38	55.25	5.30	18.41	1516	1346
6z	30 — 31.5	57.90	6.05	16.83	57.82	6.07	16.86	1515	1350

a) A. Kirpal and E. Reiter, *Ber.*, **58b**, 699 (1925).

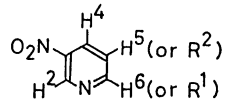
Table 4. ^1H NMR Spectra of 3-Nitropyridines (**6**)

Compound	R^1	R^2	Solvent	Chemical shift[a] (δ)				
				H^2	H^4	H^5	H^6	Other protons
6a	$-(CH_2)_4-$		$CDCl_3$	9.15, d ($J_{2,4}$=2.5 Hz)	8.15, d	—	—	1.7—2.2 (4H, m), 2.7—3.2 (4H, m).
6b[b]	$-CH(CH_2)_2CH-$ (C_3H_7-*i*, CH_3)		CCl_4	9.13, d ($J_{2,4}$=2.6 Hz)	8.11, d	—	—	0.68 (3H, d, J=6.5 Hz), 1.06 (3H, d, J=6.7 Hz), 1.34 (3H, d, J=7.0 Hz), 1.6—2.2 (4H, m), 2.5—3.3 (3H, m).
6c	$-(CH_2)_3-$		$CDCl_3$	9.28, d ($J_{2,4}$=2.4 Hz)	8.26, m	—	—	2.26 (2H, quintet, J=7.5 Hz), 3.1 (4H, m).
6d	*i*-C_3H_7	H	CCl_4	9.30, d ($J_{2,4}$=2.7 Hz, $J_{4,5}$=9.0 Hz)	8.34, dd	7.28, d	—	1.32 (6H, d, J=6.7 Hz), 3.16 (1H, septet, J=6.7 Hz).
6e	*t*-C_4H_9	H	CCl_4	9.32, dd ($J_{2,4}$=2.7 Hz, $J_{4,5}$=9.2 Hz, $J_{2,5}$=0.6 Hz)	8.35, dd	7.46, dd	—	1.38 (9H, s).
6f	C_6H_5	H	$CDCl_3$	9.48, dd ($J_{2,4}$=2.5 Hz, $J_{4,5}$=8.8 Hz, $J_{2,5}$=0.7 Hz)	8.50, dd	7.90, dd	—	7.4—7.6 (3H, m), 7.9—8.1 (2H, m).
6g	C_6H_5	CH_3	$CDCl_3$	9.18, d ($J_{2,4}$=2.5 Hz)	8.23, d	—	—	2.46 (3H, s), 7.4 (5H, m).
6h	$-o-C_6H_4(CH_2)_2-$		$CDCl_3$	9.31, d ($J_{2,4}$=2.5 Hz)	8.26, d	—	—	3.03 (4H, 2), 7.3—7.5 (3H, m), 8.3—8.5 (1H, m).
6i	C_6H_5	C_6H_5	$CDCl_3$	9.49, d, ($J_{2,4}$=2.5 Hz)	8.52, d	—	—	7.2—7.4 (10H, m).
6j	*p*-$C_6H_4NH_2$	H	DMSO-d_6	9.28, d ($J_{2,4}$=2.7 Hz, $J_{4,5}$=9.2 Hz)	8.45, dd	7.96, d	—	5.85 (2H, m), 6.68 (2H, d, J=8.4 Hz), 7.96 (2H, d, J=8.4 Hz).
6k	*p*-$C_6H_4OCH_3$	H	$CDCl_3$	9.38, d ($J_{2,4}$=2.5 Hz, $J_{4,5}$=9.0 Hz)	8.41, dd	7.76, d	—	3.86 (3H, s), 6.99 (2H, d, J=8.8 Hz), 8.02 (2H, d, J=8.8 Hz).

Table 4. (Continued)

Compound	R^1	R^2	Solvent	Chemical shift[a] (δ) H^2	H^4	H^5	H^6	Other protons
6l	*p*-$C_6H_4CH_3$	H	$CDCl_3$	9.44, d ($J_{2,4}$=2.8 Hz)	8.46, dd ($J_{4,5}$=9.0 Hz)	7.97, d	—	2.44 (3H, s), 7.28 (2H, d, J=8.2 Hz), 7.97 (2H, d, J=8.2 Hz).
6m	*p*-C_6H_4CN	H	$CDCl_3$	9.53, dd ($J_{2,4}$=2.6 Hz)	8.60, dd ($J_{4,5}$=8.6 Hz, $J_{2,5}$=0.7 Hz)	7.97, dd	—	7.83 (2H, d, J=8.6 Hz), 8.23 (2H, d, J=8.6 Hz).
6n	*p*-$C_6H_4NO_2$	H	$CDCl_3$	9.56, d ($J_{2,4}$=2.7 Hz)	8.63, dd ($J_{4,5}$=8.8 Hz)	8.01, d	—	8.34 (4H, s).
6o	2-Pyridyl	H	$CDCl_3$	9.46, dd ($J_{2,4}$=2.0 Hz)	8.4—8.7, m ($J_{2,4}$=1.0 Hz)	8.4—8.7, m	—	7.39 (1H, ddd, J=7.5, 4.7 and 1.4 Hz), 7.88 (1H, td, J=7.5 and 1.8 Hz), 8.4—8.7 (2H, m).
6p	c)	H	$CDCl_3$	9.53, dd ($J_{2,4}$=2.5 Hz)	8.65, dd ($J_{4,5}$=8.6 Hz, $J_{2,5}$=0.7 Hz)	8.82, dd	—	8.68 (2H, d, J=7.8 Hz), 8.10 (1H, t, J=7.8 Hz).
6q	2-Furyl	H	$CDCl_3$	9.37, d ($J_{2,4}$=2.6 Hz)	8.48, dd ($J_{4,5}$=8.8 Hz)	7.80, d	—	6.61 (1H, dd, J=3.5 and 1.8 Hz), 7.30 (1H, d, J=3.5 Hz), 7.64 (1H, d, J=1.8 Hz).
6r	2-Thienyl	H	$CDCl_3$	9.36, dd ($J_{2,4}$=2.6 Hz)	8.45, dd ($J_{4,5}$=8.8 Hz, $J_{2,5}$=0.8 Hz)	7.76, dd	—	7.18 (1H, dd, J=5.0 and 3.7 Hz), 7.59 (1H, dd, J=5.0 and 1.1 Hz), 7.76 (1H, dd, J=3.7 and 1.1 Hz).
6s	H	H	CCl_4	9.41, d ($J_{2,4}$=2.5 Hz)	8.47, dd ($J_{4,5}$=8.4 Hz, $J_{5,6}$=4.6 Hz, $J_{4,6}$=1.6 Hz)	7.50, dd	8.88, dd	
6t	H	CH_3	$CDCl_3$	9.27, d ($J_{2,4}$=2.3 Hz)	8.30, m	—	8.76, m	2.51 (3H, s).
6u	H	C_2H_5	CCl_4	9.20, d ($J_{2,4}$=2.4 Hz)	8.24, m ($J_{4,6}$=1.9 Hz)	—	8.69, d	1.38 (3H, t, J=7.4 Hz), 2.84 (2H, q, J=7.4 Hz).
6v	H	*i*-C_3H_7	$CDCl_3$	9.27, d ($J_{2,4}$=2.4 Hz)	8.33, t ($J_{4,6}$=2.3 Hz)	—	8.80, d	1.36 (6H, d, J=7.1 Hz), 3.14 (1H, septet, J=7.1 Hz).
6w	CH_3	H	$CDCl_3$	9.33, d ($J_{2,4}$=2.7 Hz)	8.37, dd ($J_{4,5}$=8.5 Hz)	7.35, d	—	2.70 (3H, s).
6x	CH_3	CH_3	CCl_4	9.06, d ($J_{2,4}$=2.3 Hz)	8.12, d	—	—	2.42 (3H, s), 2.59 (3H, s).
6y	C_2H_5	H	$CDCl_3$	9.34, d ($J_{2,4}$=2.5 Hz)	8.39, dd ($J_{4,5}$=8.5 Hz)	7.36, d	—	1.36 (3H, t, J=7.5 Hz), 2.98 (2H, q, J=7.5 Hz).
6z	C_2H_5	CH_3	CCl_4	9.11, d ($J_{2,4}$=2.5 Hz)	8.12, d	—	—	1.32 (3H, t, J=7.5 Hz), 2.44 (3H, s), 2.88 (2H, q, J=7.5 Hz).

a) Notations of the protons are shown as follows:

6 = 

b) Absorptions of a major diastereoisomer. Those of the minor isomer are shown in experimental section.
c) Structure of **6p** is shown in the text.

benzene eluent gave 0.04 g of a yellow oil which consisted of polymers of the starting aldehyde. The second benzene eluent gave 0.174 g (1.05 mol) of **6v**.

Reaction of 1a with Menthone and Ammonia. A mixture of 0.40g (2.0 mmol) of **1a**, 0.62 g (4.0 mmol) of menthone, and 40 mmol of ammonia in 40 ml of methanol was heated at 70 °C for 3 h. After removing the solvent, the residual oil was passed through a short silica-gel column. A benzene eluent was concentrated to about 20 ml and extracted with 12 M hydrochloric acid (20 ml). The aqueous layer was neutrized by sodium carbonate and then extracted with benzene. The extract was dried over sodium sulfate. After removing the solvent, the residual oil was distilled by a short-pass distillation apparatus at 110—120 °C (oven temperature)/7 Pa to give 0.27 g (44%) of analytically pure **6b**. ^{1}H NMR spectra of **6b** reveals that it is an diastereomeric mixture (86 : 14). Chemical shifts of the major isomer are shown in Table 4, and those of the minor isomer are as following. ^{1}H NMR (CCl_4): δ=0.61 (3H, d, J=6.5 Hz), 1.04 (3H, d, J=6.7 Hz), 1.39 (3H, d, J=6.7 Hz), 1.6—2.2 (4H, m), 2.5—3.3 (3H, m), 8.21 (1H, d, J=2.6 Hz), 9.13 (1H, d, J=2.6 Hz).

Reaction of 1a with 2-Butanone and Ammonia. To a

mixture of 0.40 g (2.0 mmol) of **1a** and 0.27 g (4.0 mmol) of 2-butanone, 40 ml of methanolic ammonia (40 mmol) was added. The mixture was heated at 70 °C for 3 h under atmospheric pressure. After removing the solvent, residual oil was dissolved in benzene and passed through a silica-gel column. The first benzene eluent gave 0.110 g (36%) of **5b**; the second benzene eluent gave 0.044 g of a mixture of **5b**, **6x**, and **6y**. The mixture was treated with 5 ml of cold hexane. A hexane soluble portion gave 0.022 g (14%) of a mixture of **6x** and **6y**. From the NMR spectrum of the mixture, it was assigned as being a 1 : 1 mixture of **6x** and **6y**. The third benzene eluent gave 0.051 g (17%) of **6x** as pale-yellow prisms.

Reaction of 1d with Ammonia and 1-Morpholinocyclohexene (Eq. 4). A mixture of 0.20 g (1.0 mmol) of **1d**, 0.33 g (2.0 mmol) of 1-morpholinocyclohexene, and 1.5 mmol of ammonia in 20 ml of methanol was heated at 70 °C for 3 h. After the usual work up, 0.13 g (total yield 73%) of a mixture of **6α** and **6β** was yielded. Colorless plates, mp 73—74.5 °C (methanol-water 1 : 3). Found: C, 60.15; H, 5.13; N, 15.78%. Calcd for $C_9H_9DN_2O_2$: C, 60.32; H, 5.63; N, 15.63%. ^{1}H NMR (CCl_4): δ=1.92 (4H, m), 2.94 (4H, m), 8.05 [0.81H, s, H(4) of **6α**], 9.00 [0.19H, s, H(2) of **6γ**].

One Pot Synthesis of 2,6-Bis(5-nitro-2-pyridyl)pyridine (6p). A mixture of 0.16 g (1 mmol) of 2,6-diacetylpyridine, 0.44 g of **1a**, and 100 ml of 7 M methanolic ammonia was heated at 120 °C for 3 h in a 200 ml autoclave. After cooling the mixture, 0.24 g (mp 255—267 °C, 74%) of crude **6p** was obtained as brown prisms. Recrystallization from benzene gave an analytically pure sample. Ivory powder, mp 271—273 °C.

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