The Reaction of Nucleophilic Reagents at the β-Position of 3-Bromo-4-nitropyridine *N*-Oxides

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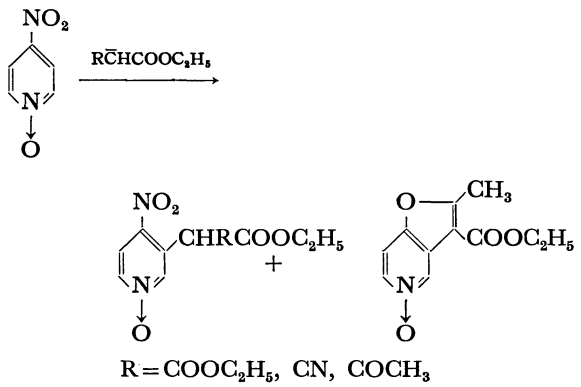
The reactions of 3-bromo-4-nitro-2-R_1-6-R_2-5-X-pyridine *N*-oxides (**1a**: R_1=H, R_2=Me, X=H; **1b**: R_1=R_2=Me, X=H; **1c**: R_1=R_2=H, X=Br) with diethyl sodiomalonate, ethyl sodiocyanoacetate, and ethyl sodioacetoacetate have been carried out. The treatment of **1a**, **1b**, and **1c** with diethyl sodiomalonate gives 3-[bis(ethoxycarbonyl)methyl]-4-nitro-2-R_1-6-R_2-5-X-pyridine *N*-oxides (**2a**, **2b**, and **2c**) and 4-[bis(ethoxycarbonyl)methyl]-3,5-dibromopyridine *N*-oxide (**3c**). With ethyl sodiocyanoacetate, 3-[cyano(ethoxycarbonyl)methyl]-4-nitro-2-R_1-6-R_2-pyridine *N*-oxides (**4a** and **4b**) and 4-[cyano(ethoxycarbonyl)methyl]-3,5-dibromopyridine *N*-oxide (**5c**) are obtained. With ethyl sodioacetoacetate, **1a** and **1c** give 3-[acetyl(ethoxycarbonyl)methyl]-6-methyl-4-nitropyridine *N*-oxide (**6a**) and/or 3-ethoxycarbonyl-2-methyl-6-R_1-7-X-furo[3,2-*c*]pyridine *N*-oxides (**7a** and **7c**), but **1b** is unaffected by ethyl sodioacetoacetate under the given conditions. The electronic and steric effects of methyl and bromo groups for the reactions are discussed.

The nucleophilic substitution reactions of pyridine homologues and their *N*-oxides have widely been studied for a long time,[1-4] but these studies dealt almost exclusively with the α or γ-position of the ring, with only a few exceptions.[5-7]

In the previous paper[8] of this series, the authors reported the nucleophilic substitution at the β-position of the pyridine ring. Thus, 3-bromo-4-nitropyridine *N*-oxide reacted with diethyl sodiomalonate, ethyl sodiocyanoacetate, and ethyl sodioacetoacetate to yield 3-[bis(ethoxycarbonyl)methyl]-4-nitropyridine *N*-oxide, 3-[cyano(ethoxycarbonyl)methyl]-4-nitropyridine *N*-oxide, and 3-[acetyl(ethoxycarbonyl)methyl]-4-nitropyridine *N*-oxide, respectively, and with ethyl sodioacetoacetate, when treated at a higher temperature, to yield 3-ethoxycarbonyl-2-methylfuro[3,2-*c*]pyridine *N*-oxide; the ring closure reaction was assumed to occur at the γ-position of the pyridine ring by the intramolecular nucleophilic attack of the mesomeric *O*-anion, which was produced by the loss of a proton from the substituted 3-methyl group of the intermediate, 3-[acetyl(ethoxycarbonyl)methyl]-4-nitropyridine *N*-oxide.



R=$COOC_2H_5$, CN, $COCH_3$

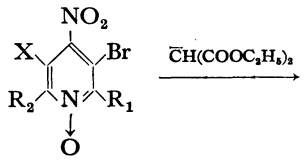
It seems of interest to investigate further the scope of this reaction. This paper deals with the reactions of the above nucleophiles with 3-bromo-6-methyl-4-nitropyridine *N*-oxide (**1a**), 3-bromo-2,6-dimethyl-4-nitropyridine *N*-oxide (**1b**), and 3,5-dibromo-4-nitropyridine *N*-oxide (**1c**). With the former two, the reactivity may be weakened by the inductive effects of the methyl groups located *ortho* and/or *para* to the site of the substitution, and the steric effect of the 2-methyl group also should be taken into consideration in the case of **1b**. With the latter, the resonance effect of the nitro group may be enfeebled by steric compression, and it is supposed that the nitro group, itself, may also be displaced by a nucleophilic substitution reaction.

Results and Discussion

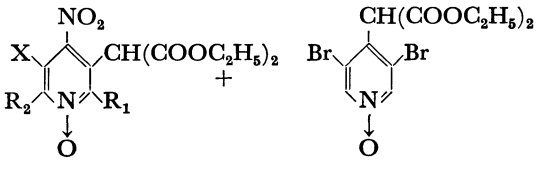
On the treatment of 3-bromo-6-methyl-4-nitropyridine *N*-oxide (**1a**), 3-bromo-2,6-dimethyl-4-nitropyridine *N*-oxide (**1b**), and 3,5-dibromo-4-nitropyridine *N*-oxide (**1c**) with diethyl sodiomalonate in diethyl carbonate at 50 °C, 3-substituted products, 3-[bis(ethoxycarbonyl)methyl]-6-methyl-4-nitropyridine *N*-oxide (**2a**), 3-[bis(ethoxycarbonyl)methyl]-2,6-dimethyl-4-nitropyridine *N*-oxide (**2b**), and 3-[bis(ethoxycarbonyl)methyl]-5-bromo-4-nitropyridine *N*-oxide (**2c**), respectively, were obtained in good yields. These were analogous to the results of the reaction of 3-bromo-4-nitropyridine *N*-oxide with diethyl sodiomalonate in our previous paper.[8] Besides, in the case of the reaction of **1c**, a small amount of **3c** was isolated in addition to **2c**. The compound, **3c**, had the empilical formula $C_{12}H_{13}NO_5Br_2$. The NMR spectra of **3c** showed nearly the same pattern as that of **2c** with exception of the paramagnetic shift of the methin proton in 0.68 ppm. The IR spectra of **3c** indicated the existence of a carbonyl group (1746 cm^{-1}) and an *N*-oxide (1260 cm^{-1}), and the lack of a nitro group. On the basis of these data, **3c** was proved to be 4-[bis(ethoxycarbonyl)methyl]-3,5-dibromopyridine *N*-oxide (**3c**).

The fact that the 4-substituted product, **3c**, was given, though in poor yield, indicated that the potential ability of the 4-nitro group as a leaving group was promoted by the inductive effect of the two bromine atoms, seated in both ortho places, on the nitro group.

The reactions of **1a**, **1b**, and **1c** with ethyl sodiocyanoacetate were performed at different temperature in pyridine. At 5 °C, 3-[cyano(ethoxycarbonyl)methyl]-6-methyl-4-nitropyridine *N*-oxide (**4a**) was obtained from **1a** in a good yield, but at this temperature, **1b** gave 3-[cyano(ethoxycarbonyl)methyl]-2,6-dimethyl-4-nitropyridine *N*-oxide (**4b**) in only 32% yield, and **1c** was



1 (a, b, c)



2 (a, b, c) 3c

a: R_1=H, R_2=Me, X=H
b: R_1=R_2=Me, X=H
c: R_1=R_2=H, X=Br

TABLE 1. REACTIONS WITH DIETHYL SODIOMALONATE

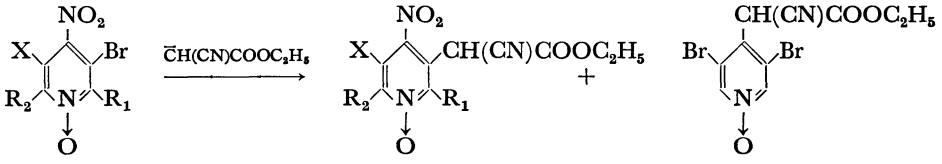
Substrates	Temp °C	Time h	Solvent	Products (Yields %)
1a	50	5	Diethyl carbonate	**2a** (97.3)
1b	50	5	Diethyl carbonate	**2b** (87.1)
1c	50	5	Diethyl carbonate	**2c** (88.9) **3c** (2.2)

recovered intact. At 50 °C **1b** was converted to **4b** in a satisfactory yield, but **1c** was still unaffected, **1c** berely underwent the reaction at 75 °C to give 3,5-dibromo-4-[cyano(ethoxycarbonyl)methyl]pyridine *N*-oxide (**5c**). However, 5-bromo-3-[cyano(ethoxycarbonyl)methyl]-4-nitropyridine *N*-oxide (**4c**), analogous to **4a** and **4b**, was not obtained. The yield of **5c** was not enhanced even if the reaction temperature was raised.

With ethyl sodioacetoacetate, **1a** gave 3-[acetyl-(ethoxycarbonyl)methyl]-6-methyl-4-nitropyridine *N*-oxide (**6a**) at the lower temperature (35 °C), and when the reaction was followed by further treatment at the higher temperature (75 °C), the anticipated 3-ethoxycarbonyl-2,6-dimethylfuro[3,2-*c*]pyridine *N*-oxide (**7a**) was obtained. The identity of both products was confirmed by the IR, NMR, and elemental analytical data, and by analogy with the results in the previous paper.[8] Similarly, 7-bromo-3-ethoxycarbonyl-2-methylfuro[3,2-*c*]pyridine *N*-oxide (**7c**) was easily obtained by treatment of **1c** with ethyl sodioacetoacetate at 35 °C, and 5-bromo-3-[acetyl(ethoxycarbonyl)methyl]-4-nitropyridine *N*-oxide (**6c**), analogous to **6a**, was not isolated even under the mild conditions in which a part of **1c** was recovered. The reaction of **1b** with ethyl sodioacetoacetate was examined under several conditions, but resulted in either the recovery of the starting material or the formation of resinous matters.

Examination of the above results as a whole reveals that **1a** is more liable to undergo the reaction with the anions than **1b**. Thus, whereas **1a** can be allowed to react under as mild conditions as 3-bromo-4-nitropyridine *N*-oxide[8] allows, **1b** required more severe conditions to give the same results. These facts are consistent with the results which are expected by considering the electronic effects of the second substituents (2 and/or 6-methyl groups). The inductive and steric effects of the 2-methyl group of **1b** appear to play an important role in preventing the formation of the 3-substituted product on treatment with ethyl sodioacetoacetate. The nucleophilicity of ethyl sodioacetoacetate is intermediate between those of ethyl sodiomalonate and ethyl sodiocyanoacetate (the pK_a value of these esters are about 11, 13, and 9, respectively). The steric requirement of ethyl sodioacetoacetate is also located between those for the other (stericaly favorable -CN,>-$COCH_3$,>-$COOC_2H_5$). Taking into account the operation of these characters a and effects, the lower reactivity of **1b** with ethyl sodioacetoacetate may be reasonable.

It appears that **7a** and **7c** are formed *via* **6a** and **6c**, as shown in the following scheme. This is quite analogous to the formation of 3-ethoxycarbonyl-2-methylfuro[3,2-*c*]pyridine *N*-oxide in the previous paper.[8] This account is supported by the facts that 3-[acetyl(ethoxycarbonyl)-methyl]-4-nitropyridine *N*-oxide was converted to

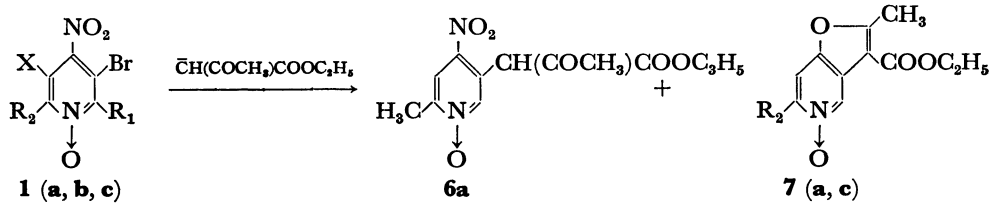


1 (a, b, c) 4 (a, b) 5c

a: R_1=H, R_2=Me, X=H; b: R_1=R_2=Me, X=H; c: R_1=R_2=H, X=Br

TABLE 2. REACTIONS WITH ETHYL SODIOCYANOACETATE

Substrates	Temp °C	Time h	Solvents	Products (Yields %)		
1a	5	5	Pyridine	**4a** (91.5)		
1b	5	5	Pyridine	**4b** (32.1)		**1b** (59.0)
1b	5	10	Pyridine	**4b** (48.8)		**1b** (43.0)
1b	50	5	Pyridine	**4b** (93.0)		
1c	5	5	Pyridine			**1c** (88.0)
1c	50	5	Pyridine			**1c** (84.0)
1c	75	10	Pyridine		**5c** (14.1)	**1c** (78.0)
1c	95	5	Pyridine		**5c** (13.2)	**1c** (48.0)
1c	75	5	DMF		**5c** (12.0)	**1c** (69.0)



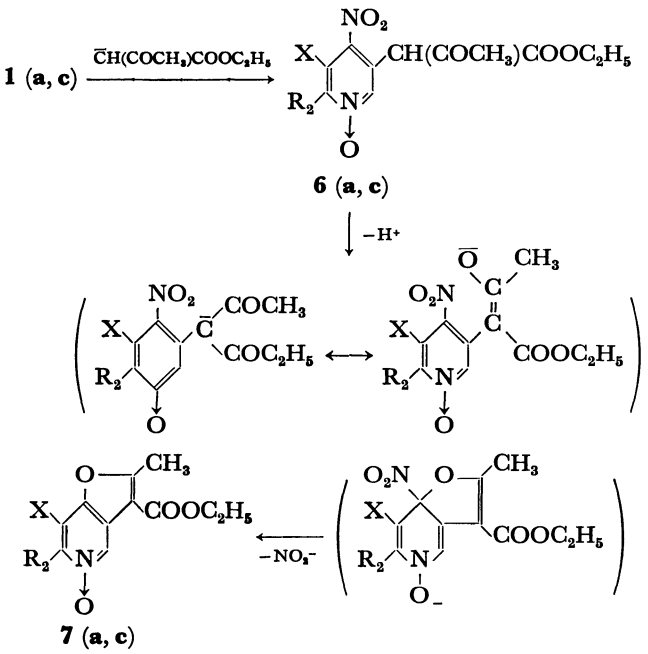
1 (a, b, c) **6a** **7 (a, c)**

a: R_1=H, R_2=Me, X=H; b: R_1=R_2=Me, X=H; c: R_1=R_2=H, X=Br

Table 3. Reactions with ethyl sodioacetoacetate

Substrates	Temp °C	Time h	Solvents	Products (Yield %)		
1a	35	5	Diethyl carbonate	**6a** (86.8)		
1a	35 75	5 5	Diethyl carbonate		**7a** (94.2)	
1b	35	5	Diethyl carbonate			**1b** (89.0)
1b	60	5	Diethyl carbonate			**1b** (78.0)
1b	90	10	Diethyl carbonate			**1b** (74.0)
1b	90	10	Pyridine			**1b** (75.0)
1b	110	10	Pyridine			**1b** (54.0)
1b	130	10	DMF			**1b** (38.0)
1c	35	5	Diethyl carbonate		**7c** (68.6)	**1c** (5.0)
1c	50	5	Diethyl carbonate		**7c** (94.4)	
1c	5—10	5	Diethyl carbonate		**7c** (41.2)	**1c** (43.0)
1c	35	5	Pyridine		**7c** (63.6)	**1c** (6.0)

3-ethoxycarbonyl-2-methylfuro[3,2-*c*]pyridine *N*-oxide either by treating with dilute ethanolic sodium ethoxide or only the prolonged storage.



a: R_2=Me, X=H; b: R_2=H, X=Br

On reaction of **1c** with ethyl sodioacetoacetate, an anticipated **6c** as an intermediate for **7c** was not isolated even under the mild conditions in which the starting material was recovered as shown in Table 3. This result may be interpreted as follows. The nitro group in the anticipated product, **6c**, was not coplanar with the pyridine ring on account of the steric hindrance by a bromine atom and newly introduced group situated at both *ortho* positions to the nitro group, and **6c**, even if formed, becomes labile and converts to **7c** as soon as it is formed.

Experimental

All the melting points were uncorrected. The IR spectra were obtained on a Hitachi Infrared Spectrophotometer, EPI-S2, as Nujol mulls with the exception of some liquid samples. The NMR spectra were recorded on a Hitachi High Resolution NMR Spectrometer, 20-B, with TMS as the internal standard.

3-Bromo-6-methyl-4-nitropyridine N-*Oxide (**1a**).* 3-Bromo-6-methylpyridine[9] was treated according to the manner described in our paper[8] to give 3-bromo-6-methylpyridine *N*-oxide (mp 117.5—118 °C) in 86.8% yield. 3-Bromo-6-methyl-4-nitropyridine *N*-oxide (**1a**) (mp 137.5—138 °C) was obtained from 3-bromo-6-methylpyridine *N*-oxide by application of Jujo's method[10] in 76.3% yield.

3-Bromo-2,6-dimethyl-4-nitropyridine N-*Oxide (**1b**).* 3-Bromo-2,6-dimethylpyridine[11] was managed in the same manner as above to give 3-bromo-2,6-dimethyl-4-nitropyridine *N*-oxide **1b** (mp 111.5—113 °C) in 64.8% total yield.

3,5-Dibromo-4-nitropyridine N-*Oxide (**1c**).* 3,5-Dibromopyridine[12] was treated as above to give 3,5-dibromopyridine *N*-oxide in 93.5% yield. The *N*-oxide was treated as reported in the literature[13] to give 3,5-dibromo-4-nitropyridine *N*-oxide **1c** in 91.3% yield.

*General Procedure of the Reaction of **1a**, **1b**, and **1c**.* To a solution of the pyridine **1** in a three necked flask were added three equimolar amounts of sodium salt in appropriate solvents dropwise over a period of an hour, at 15—20 °C with few exceptions, then the mixture were stirred at the required temperature for 5—10 h. The solvent was evaporated under reduced pressure, and the solution were neutralized with dil hydrochloric acid to pH 3—4; when diethyl carbonate is used as a solvent, the evaporation of the solvent may be omitted. The resulting mixture was extracted with chloroform. After drying over anhydrous sodium sulfate the solvent was distilled off, and the residual oil disolved in a small

amount of chloroform and refined through a silica gel (Wakogel C-300) column.

The Reaction of ***1a*** *with Diethyl Sodiomalonate.* A diethyl carbonate solution of 1.0 g of 3-bromo-6-methyl-4-nitropyridine *N*-oxide (**1a**) was treated as general procedure with a solution of diethyl sodiomalonate which had been formed from 0.3 g of sodium and 2.2 g diethyl malonate in 50 ml of diethyl carbonate. After the elution of diethyl malonate with chloroform on the chlomatograph, evaporation of the ethereal elute gave 1.30 g of 3-[bis(ethoxycarbonyl)methyl]-6-methyl-4-nitropyridine *N*-oxide (**2a**) as an oily syrup. Found: C, 49.90; H, 4.92; N, 8.37%; Calcd for $C_{13}H_{16}N_2O_7$: C, 50.00; H, 5.16; N, 8.97%. IR: 1750 cm^{-1} (C=O), 1525 and 1345 (NO_2), 1240 (N→O). NMR ($CDCl_3$): δ 1.27 (6H, t) 4.25 (4H, q), 2.52 (3H, s), 5.26 (1H, s), 8.02 (1H, s), 8.25 (1H, s).

The Reaction of ***1b*** *with Diethyl Sodiomalonate.* From 1.0 g of 3-bromo-2,6-dimethyl-4-nitropyridine *N*-oxide (**1b**), 1.15 g of 3-[bis(ethoxycarbonyl)methyl]-2,6-dimethyl-4-nitropyridine *N*-oxide (**2b**) was obtained as an oily syrup. Found: C, 51.66; H, 5.70; N, 8.19%. Calcd for $C_{14}H_{18}N_2O_7$: C, 51.38; H, 5.54, N. 8.56%. IR: 1745 cm^{-1} (C=O), 1530 and 1340 (NO_2), 1245 (N→O). NMR ($CDCl_3$): δ 1.26 (6H, t), 4.24 (4H, q), 2.54 (3H, s), 2.58 (3H, s), 5.21 (1H, s), 7.84 (1H, s).

The Reaction of ***1c*** *with Diethyl Sodiomalonate.* From the reaction of 1.0 g of **1c** with diethyl sodiomalonate, 1.12 g of 3-[bis(ethoxycarbonyl)methyl]-5-bromo-4-nitropyridine *N*-oxide (**2c**) was obtained from ethereal elution; mp 79—80 °C (acetone–diisopropyl ether). Found: C, 38.08; H, 3.37; N, 7.16%. Calcd for $C_{12}H_{13}N_2O_7Br$: C, 38.22; H, 3.47; N, 7.43%. IR: 1760 cm^{-1} (C=O), 1560 and 1355 (NO_2), 1240 (N→O). NMR ($CDCl_3$): δ 1.29 (6H, t), 4.26 (4H, q), 5.64 (1H, s), 8.37 (2H, s). From the succesive acetone–ether elution was obtained 0.03 g of 4-[bis(ethoxycarbonyl)methyl]-3,5-dibromopyridine *N*-oxide (**3c**); mp 124—125 °C (diisopropyl ether). Found: C, 34.72; H, 3.04; N, 3.16%; Calcd for $C_{12}H_{13}NO_5Br_2$: C, 35.02; H, 3.16; N, 3.40%. IR: 1746 cm^{-1} (C=O), 1254 (N→O). NMR ($CDCl_3$): δ 1.28 (6H, t), 4.26 (4H, q), 5.32 (1H, s), 8.40 (2H, s).

The Reaction of ***1a*** *with Ethyl Sodiocyanoacetate.* From 1.0 g of **1a**, 1.04 g of 3-[cyano(ethoxycarbonyl)methyl]-6-methyl-4-nitropyridine *N*-oxide (**4a**) was obtained: mp 177—177.5 °C (ethanol). Found: C, 49.62; H, 4.01; N, 15.63%. Calcd for $C_{11}H_{11}N_3O_5$: C, 49.81; H, 4.18; N, 15.84%. IR: 2230 cm^{-1} (CN), 1746 (C=O), 1260 (N→O). NMR ($CDCl_3$): δ 1.33 (3H, t), 4.32 (2H, q), 2.52 (3H, s), 5.51 (1H, s), 8.13 (1H, s) 8.43 (1H, s).

The Reaction of ***1b*** *with Ethyl Sodiocyanoacetate.* Under the suitable conditions, 50 °C, 3-[cyano(ethoxycarbonyl)-methyl]-2,6-dimethyl-4-nitropyridine *N*-oxide (**4b**) was obtained in 93.0% yield: mp 118.5—119.0 °C (acetone–diisopropyl ether). Found: C, 51.53; H, 4.46; N, 14.80%. Calcd for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.69; N, 14.80%. IR: 2224 cm^{-1} (CN), 1745 (C=O), 1530 and 1342 (NO_2), 1270 (N→O). NMR ($CDCl_3$): δ 1.32 (3H, t), 2.54 (3H, s), 2.60 (3H, s), 4.30 (3H, q), 6.50 (1H, s), 7.97 (1H, s). The starting material, **1b**, when it was recovered, was obtained from chloroform elution following after the reagemt.

The Reaction of ***1c*** *with Ethyl Sodiocyanoacetate.* In this case ethyl sodiocyanoacetate was added at 75 °C over a period of 5 h, then the mixture was managed according to the general procedure. From 1.0 g of 3,5-dibromo-4-nitropyridine *N*-oxide (**1c**), after the collection of unreacted **1c** from ether–acetone elution 0.18 g of 4-[cyano(ethoxycarbonyl)methyl]-3,5-dibromopyridine *N*-oxide (**5c**) was obtained: mp 182—183 °C (ethanol). Found: C, 33.14; H, 2.29; N, 7.84%. Calcd for $C_{10}H_8N_2O_3Br_2$: C, 33.00; H, 2.22; N, 7.70%. IR: 2235 cm^{-1} (CN), 1745 (C=O), 1246 (N→O). NMR ($CDCl_3$): δ 1.33 (3H, t), 4.32 (2H, q), 5.52 (1H, s), 8.30 (1H, s).

The Reaction of ***1a*** *with Ethyl Sodioacetoacetate at 35 °C.* One gram of **1a** was treated with ethyl sodioacetoacetate according to the general procedure; the reaction temperature was kept at 35 °C for 5 h, and from ethereal elution 1.05 g of 3-[acetyl(ethoxycarbonyl) methyl]-6-methyl-4-nitropyridine *N*-oxide (**6a**) was obtained as yellow leaflets; mp 106—107 °C (diethyl ether). Found: C, 51.18; H, 4.87; N, 9.78%. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.08; H, 5.00; N, 9.93%. IR: 1720 cm^{-1} (C=O), 1730 (C=O), 1560 and 1335 (NO_2), 1260 (N→O). NMR ($CDCl_3$): δ 1.12 (3H, t), 1.93 (3H, s), 2.54 (3H, s), 4.11 (2H, m), 7.96 (1H, s), 8.04 (1H, s), 12.98 (1H, s).

The Reaction of ***1a*** *with Ethyl Sodioacetoacetate at 75 °C.* The reaction mixture of the above reaction was further heated at 75 °C for an additional 5 h. The resulting mixture was treated by the same procedure, and from the alcoholic elute, 0.9 g of 3-ethoxycarbonyl-2,6-dimethylfuro[3,2-*c*]-pyridine *N*-oxide (**7a**) was obtained as colorless prisms; mp 120—121 °C (ethanol). Found: C, 61.44; H, 5.58; N, 5.57%. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.58; N, 5.95%. IR: 1720 cm^{-1} (C=O), 1246 (N→O). NMR ($CDCl_3$): δ 1.42 (3H, t), 2.58 (3H, s), 2.74 (3H, s), 4.38 (2H, q), 7.28 (1H,s), 8.83 (1H, s).

The Reaction of ***1c*** *with Ethyl Sodioacetoacetate.* When the reaction was carried out at 50 °C, 7-bromo-3-ethoxycarbonyl-2-methylfuro[3,2-*c*]pyridine *N*-oxide (**7c**) was obtained from ethanol elution as colourless prisms; mp 194—195 °C (acetone). Found: C, 44.07; H, 3.24; N, 4.48%. Calcd for $C_{11}H_{10}NO_4Br$: C, 44.02; H, 3.36; N, 4.67%. IR: 1705 cm^{-1} (C=O), 1250 (N→O). NMR ($CDCl_3$): δ 1.43 (3H, t), 2.83 (3H, s), 4.42 (2H, q), 8.28 (1H, s), 8.70 (1H, s).

3-Ethoxycarbonyl-2-methyl[3,2-c]pyridine N-Oxide. The mixture of 0.5 g of 3-[acetyl(ethoxycarbonyl)methyl]-4-nitropyridine *N*-oxide and 0.2 g of sodium ethoxide in 100 ml of ethanol was heated at 50 °C for 5 h. The deep violet color of the mixture faded with time. The solvent was evaporated, and the residue was neutralized with dil hydrochloric acid to pH 4, then extracted with chloroform. After drying over anhydrous sodium sulfate, evaporation of the solvent gave 0.22 g (53.4%) of 3-ethoxycarbonyl-2-methylfuro-[3,2-*c*]pyridine *N*-oxide, semihydrate; mp 150 °C, which was identified by mixed melting point determination and by comparing the IR and NMR spectra data with those of an authentic sample.[8]

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