Nucleophilic Reaction of Electron-deficient Pyridone Derivatives. II. Ring Transformation of 1-Substituted 3,5-Dinitro-4-pyridones with Sodio β-Keto Esters

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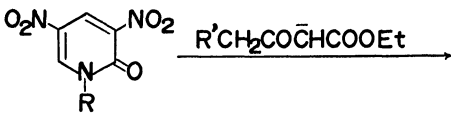
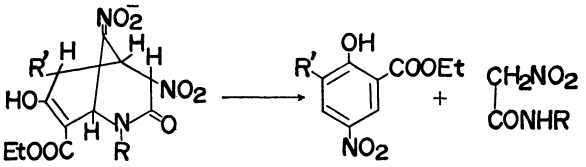
The reactions of 1-substituted 3,5-dinitro-4-pyridones [1-substituents: methyl (**1a**), 2-pyridyl (**1b**), 6-methyl-2-pyridyl (**1c**), and 4-pyridyl (**1d**)] with diethyl sodio-3-oxopentanedioate give 1-substituted 3,5-bis(ethoxycarbonyl)-4-pyridones and sodio-1,3-dinitro-2-propane. On the other hand, the reactions of the 4-pyridones (**1b, 1c,** and **1d**) with ethyl sodioacetoacetate give ethyl 4-hydroxy-3,5-dinitrobenzoate together with aminopyridine homologues, and that of **1a** gives furo[3,2-*b*]pyridine derivative. On the basis of the concept of soft and hard acids and bases, a stepwise nucleophilic attack of the anion of β-keto esters at the electrophilic center of the 2 and 6-positions or 2 and 3-positions of the 4-pyridones is proposed to interpret the variations of the reaction courses.

We have previously shown that 1-substituted 3,5-dinitro-2-pyridones give nitrophenol derivatives and *N*-substituted α-nitroacetamides. A reaction course of the reaction has been elucidated by the isolation of intermediately produced meta-bridging bicyclic addition compounds.[1)]





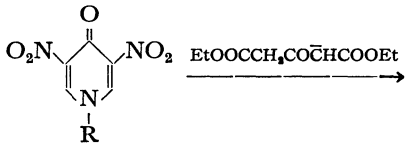
In this paper, we describe the reaction of 1-substituted 3,5-dinitro-4-pyridones with β-keto esters.

Results and Discussion

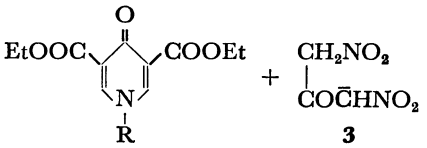
The reactions of 3,5-dinitro-1-methyl- (**1a**), 3,5-dinitro-1-(2-pyridyl)- (**1b**), 3,5-dinitro-1-(6-methyl-2-pyridyl)- (**1c**), and 3,5-dinitro-1-(4-pyridyl)-4-pyridone (**1d**) with the monosodium salts of β-keto esters were studied.

Treatment of **1a** with 1.5 equivalent amounts of diethyl sodio-3-oxopentanedioate (Na·DOPD) in pyridine gave 3,5-bis(ethoxycarbonyl)-1-methyl-4-pyridone (**2a**). The product **2a** showed strong absorption in the IR at 1735 and 1655 cm^{-1}, indicating the presence of ester carbonyl and pyridone carbonyl groups, respectively. The NMR spectrum of **2a** showed the presence of two ethyl groups. The other signals were very similar to that of the substrate **1a** except for the paramagnetic shift of the ring protons of about 1 ppm. The empirical formula of **2a**, $C_{12}H_{15}NO_5$, supports the structure indicated.

A yellow reisdue obtained after extraction of **2a** with chloroform was confirmed to be a monosodium salt of 1,3-dinitro-2-propanone (**3**), as follows. By coupling[2)] with 1 mol of benzenediazonium chloride at 0 °C, **3**



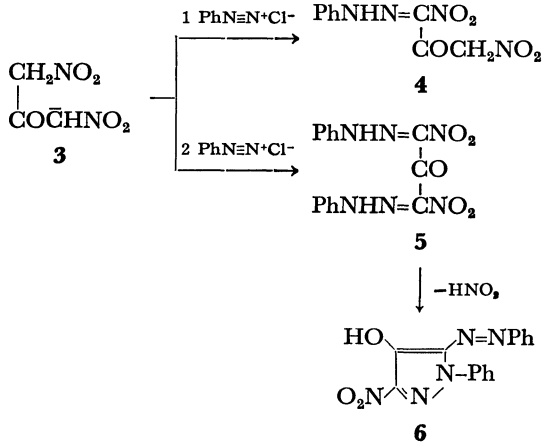
1 (a, b, c, d)



2a: Y. 84.9%
2b: Y. 66.35%
2c: Y. 58.5%
2d: Y. 61.5%

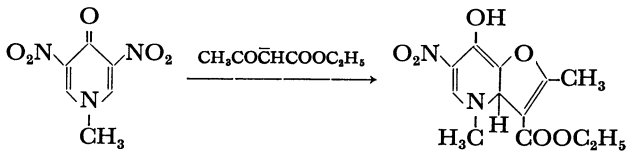
a: R=methyl
b: R=2-pyridyl
c: R=6-methyl-2-pyridyl
d: R=4-pyridyl

yielded yellow powder (**4**) of mp 167.0—168.0 °C, and with two moles of the chloride at 0 °C, another yellow powder (**5**) which decomposed at 138 °C. On the basis of their empirical formulae and their spectral properties, these products were identified as 1,3-dinitro-1-phenylhydrazono-2-propanone (**4**) and 1,3-dinitro-1,3-bis(phenylhydrazono)-2-propanone (**5**), respectively. The latter compound **5** was easily converted to 4-hydroxy-3-nitro-1-phenyl-5-(phenylazo)pyrazole (**6**) with loss of nitrous acid by heating in methanol



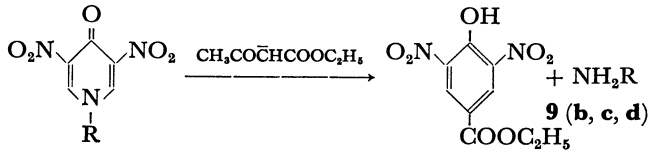
Similarly, treatment of **1b**, **1c**, and **1d** with Na·DOPD gave 3,5-bis(ethoxycarbonyl)-1-(2-pyridyl)- (**2b**), 3,5-bis(ethoxycarbonyl)-1-(6-methyl-2-pyridyl)- (**2c**), and 3,5-bis(ethoxycarbonyl)-1-(4-pyridyl)-4-pyridone (**2d**), respectively. **3** was also isolated from these reactions.

On the other hand, the reaction of **1a** with ethyl sodioacetoacetate (Na·EAA) offered different types of reaction products. First, by treatment of **1a** with Na·EAA in pyridine, colorless needles (**7a**) of mp 127.0—128.0 °C were obtained. The IR spectrum of the product showed the presence of an ester carbonyl group (1765 cm^{-1}) and a nitro group (1515, 1340 cm^{-1}). The NMR spectrum of **7a** indicated the presence of an ethoxyl group, 1.24 ppm (3H, t), 4.26 ppm (2H, q), a bridgehead proton, 6.51 ppm (1H, s), a highly deshielded proton, 8.69 ppm (1H, s), and a hydroxyl proton, 13.12 ppm (1H, s). The empirical formula of **7a** was consistent with $C_{12}H_{14}N_2O_6$. From the above data, 3-ethoxycarbonyl-7-hydroxy-2,4-dimethyl-6-nitro-3a,4-dihydrofuro[3,2-*b*]pyridine was assigned to **7a**.



1a **7a**

The reaction of **1b** with Na·EAA was carried out at 65—70 °C in pyridine. On work-up, ethyl 4-hydroxy-3,5-dinitrobenzoate (**8**)[3] and 2-aminopyridine (**9b**) were obtained. Similar results were observed in the reaction of **1c** and **1d** with Na·EAA; the products were **8** and either 2-amino-6-methylpyridine (**9c**) or 4-aminopyridine (**9d**).

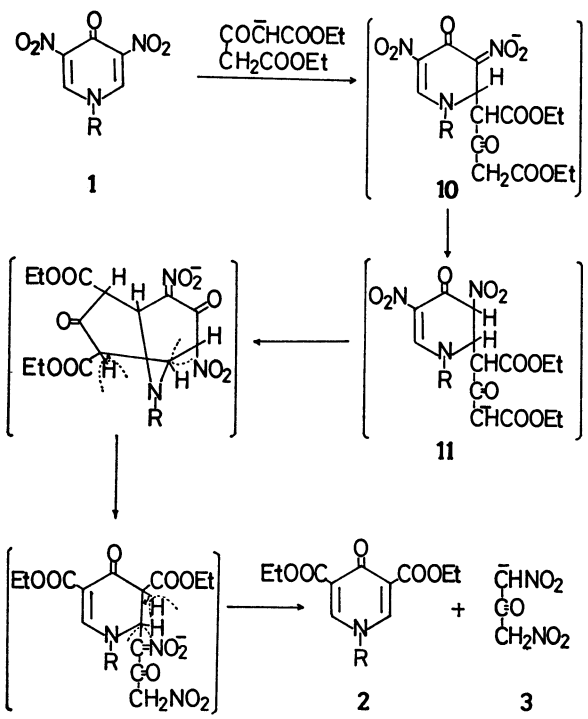


1 (b, c, d) **8** **9 (b, c, d)**

b: R=2-pyridyl
c: R=6-methyl-2-pyridyl
d: R=4-pyridyl

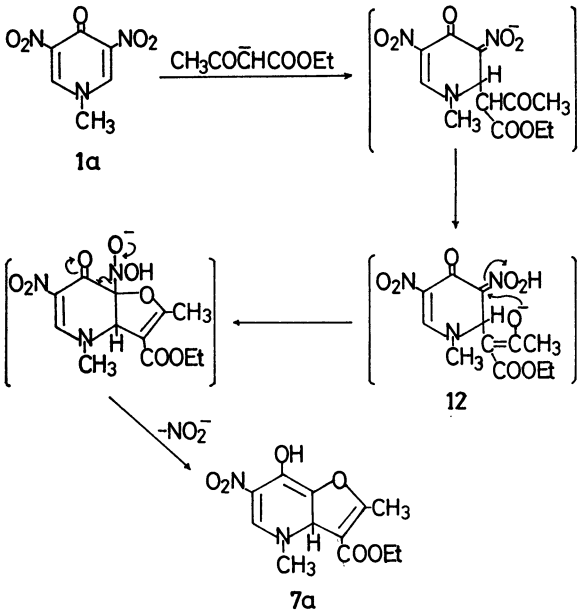
The formation of **2a**, **2b**, **2c**, and **2d** may proceed through a favorable nucleophilic attack of the nucleophile at the 2-position of the 4-pyridone to give the anion **10**, from which anion **11** can be derived by the prototropy. The successive steps to **2** and **3** may involve an intramolecular nucleophilic attack of an anion at the 6-position of the parent 4-pyridone. Scheme 1 may be proposed as one of the most likely reaction courses. The leaving carbanions may be considered to be soft leaving groups.

On the other hand, the formation of **7a** may proceed through the initial attack of a soft nucleophile of the enolate anion of ethyl acetoacetate ($CH_3COC^-HCOOEt$) at the softer 2-position of the 4-pyridone nucleus. The subsequent intramolecular nucleophilic attack of a harder *O*-anion of **12** at the 3-position of the parent



1 **10** **11** **2** **3**

Scheme 1.



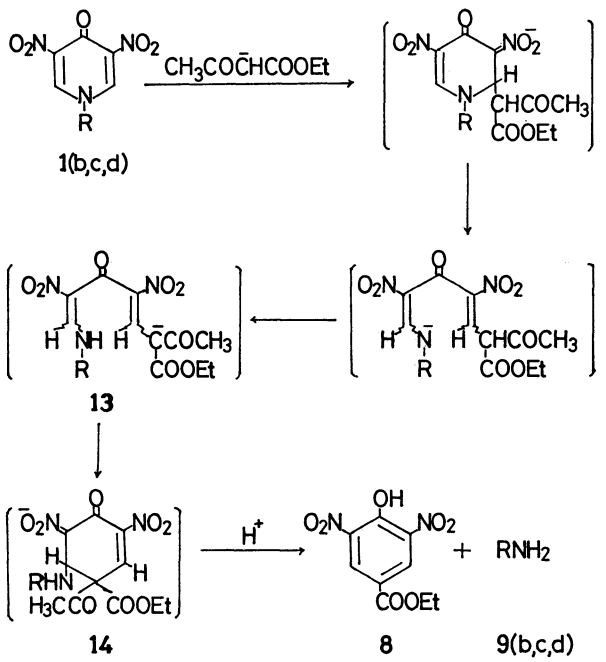
1a **12** **7a**

Scheme 2.

4-pyridone nucleus may lead to **7a** by loss of the harder nitrite anion (Scheme 2).

The course of the reaction of **1a** and Na·EAA is very similar to that of 3-bromo-4-nitropyridine *N*-oxide with Na·EAA.[4]

The probable course of the reaction of **1b**—**1d** with Na·EAA is shown in Scheme 3; the electron withdrawing interaction of the 5-nitro group of the parent 4-pyridone would allow the intramolecular nucleophilic attack of the carbanion **13** to lead to a cyclic intermediate **14**. Aromatization of **14** may give **8**



Scheme 3.

and **9**.

In the case of the reaction of **1a** with Na·EAA, the reason why the predominant attack of *O*-anion proceeds at the β-position which is substituted by the nitro group can be explained by the observation that the nature of the leaving group on the alkyl halides affects the proportion of *C* to *O* alkylation of the enolate ion. Sarthou *et al.*[5] concluded that the harder the leaving group, the lower the proportion of *C*-alkylation. A harder nitrite anion, however, classified as a border-line base, may be a favorable leaving group in the intramolecular nucleophilic substitution.

The difference between the reaction paths of **1a** with Na·EAA and those of **1b**—**1d** evidently depend upon the electronic behavior of the *N*-substituents of the 4-pyridone nucleus. The interaction of the electron donating 1-methyl group with the electron attracting β-nitro group may favor an initial attack of the soft end of the nucleophile at the 2-position of 4-pyridone nucleus without ring fission. The subsequent attack of the *O*-anion is promoted by the resonance interaction of the β-nitro group. On the other hand, the electron withdrawing 1-substituents such as 2-pyridyl and 4-pyridyl groups may reduce the resonance interaction of the 1-nitrogen atom with the β- or β′-nitro group; then the initial attack of the soft nucleophile at the somewhat harder 2-position of the 4-pyridone can not be allowed without the subsequent fission of the C_2–N bond.

In spite of the similar conditions, we find a remarkable difference of the reaction paths between the reaction of 1-substituted 3,5-dinitro-4-pyridones with Na·DOPD and those with Na·EAA. With 1-substituted 3,5-dinitro-4-pyridones and Na·DOPD, **2** were always obtained by the C_5 and C_3-anion heterolysis of the C_5–C_6 and C_2–C_3 bonds of the 4-pyridone nucleus. On the other hand, similar reactions with Na·EAA were affected not only by the nucleophile but also by the 1-substituted group.

Experimental

All the melting points are uncorrected. The IR spectra were obtained on a Hitachi EPI-S2 as Nujol muls. The NMR spectra were recorded on a Hitachi R 20-B with TMS as the internal standard.

3,5-Dinitro-1-methyl-4-pyridone (1a). Five grams of 1-methyl-4-pyridone[6] was dissolved in 50 ml of fuming sulfuric acid (30% SO_3), then 25 g of potassium nitrate was added in portions with cooling. The mixture was heated at 110 °C for 5 h and then poured onto crushed ice. Crystalline precipitates were recrystallized from water to give 4.8 g (52.1%) of **1a**, mp 214.0—215.0 °C. IR: 1680 cm^{-1} (C=O), 1550, 1360 (NO_2). NMR (DMSO-d_6): δ 3.90 (3H, s), 8.95 (2H, s). Found: C, 36.11; H, 2.63; N, 20.89%. Calcd for $C_6H_5N_3O_5$: C, 36.19; H, 2.53; N, 21.10%.

3,5-Dinitro-1-(2-pyridyl)-4-pyridone (1b). A mixture of 2-bromopyridine and sodium salt of 4-hydroxypyridine in DMSO was heated at 150 °C for 8 h to give 1-(2-pyridyl)-4-pyridone in 76.9% yield. This pyridone was treated with 10 equimolar amounts of potassium nitrate in fuming sulfuric acid (30% SO_3) at 130 °C for 10 h to give **1b** in 31.4% yield; mp 219.5—220.0 °C (water). IR: 1675 cm^{-1} (C=O), 1520, 1360 (NO_2). NMR (DMSO-d_6): δ 7.60 (1H, m), 8.12 (2H, m), 8.62 (1H, dd), 9.59 (2H, s). Found: C, 45.65; H, 2.20; N, 21.47%. Calcd for $C_{10}H_6N_4O_5$: C, 45.81; H, 2.31; N, 21.37%.

3,5-Dinitro-1-(6-methyl-2-pyridyl)-4-pyridone (1c). 1-(6-Methyl-2-pyridyl)-4-pyridone, prepared from sodium salt of 4-hydroxypyridine and 2-bromo-6-methylpyridine, was worked up according to the preceding method to give **1c** in 24.0% yield; mp 245.0—246.0 °C (aqueous acetic acid). IR: 1675 cm^{-1} (C=O), 1520, 1360 (NO_2). NMR (DMSO-d_6): δ 3.31 (3H, s), 7.4 (1H, m), 7.8 (2H, m), 9.61 (2H, s). Found: C, 47.99; H, 2.88; N, 19.90%. Calcd for $C_{11}H_8N_4O_5$: C, 47.83; H, 2.92; N, 20.24%.

3,5-Dinitro-(4-pyridyl)-4-pyridone (1d). 1-(4-Pyridyl)-4-pyridone[7] was treated as above to give **1d** in 36.2% yield; mp 242.0—243.0 °C (water). IR: 1680 cm^{-1} (C=O), 1520, 1315 (NO_2). NMR (DMSO-d_6): δ 7.81 (2H, dd), 8.82 (2H, dd), 9.31 (2H, s). Found: C, 45.49; H, 2.23; N, 21.37%. Calcd for $C_{10}H_6N_4O_5$: C, 45.81; H, 2.31; N, 21.37%.

Reaction of 3,5-Dinitro-1-methyl-4-pyridone (1a) with Na·DOPD. To a solution of 1.0 g of **1a** in 100 ml of pyridine was added a pyridine solution (20 ml) of Na·DOPD, prepared from 0.17 g of sodium and 1.7 g of diethyl 3-oxopentanedioate, with cooling. The mixture was heated at 50 °C for 5 h. The solvent was evaporated under reduced pressure, and the residue was extracted with $CHCl_3$. After the solvent was distilled off, the residual cake was rinsed with a small amount of diethyl ether, and recrystallized from benzene to give 1.08 g (84.9%) of 3,5-bis(ethoxycarbonyl)-1-methyl-4-pyridone (**2a**); colorless plates, mp 138.0—139.0 °C. IR: 1735 cm^{-1} (C=O), 1655 (C=O). NMR ($CDCl_3$): δ 1.31 (6H, t), 3.73 (3H, s), 4.28 (4H, q), 7.92 (2H, s). Found: C, 56.70; H, 5.95; N, 5.26%. Calcd for $C_{12}H_{15}NO_5$: C, 56.92; H, 5.93; N, 5.53%.

The residual powder which did not dissolve in $CHCl_3$ was washed with ethanol, and was dissolved in 50 ml of cold water. To this solution 10 g of sodium acetate was added, then aqueous benzenediazonium chloride solution formed from 0.5 g of aniline and 0.4 g of sodium nitrite was added dropwise at 0 °C. The precipitates were collected by filtration and were rinsed with methanol to give 0.40 g (31.7%) of 1,3-dinitro-1-phenylhydrazono-2-propanone (**4**); mp 167.0—

168.0 °C. IR: 3200 cm^{-1} (N–H), 1720 (C=O), 1530, 1330 (NO_2). NMR (acetone-d_6): δ 6.10 (2H, s), 7.25—7.80 (5H, m), 12.40 (1H, b, s). Found: C, 43.43; H, 3.14; N, 23.54%. Calcd for $C_9H_8N_4O_5$: C, 42.86; H, 3.20; N, 22.22%.

When three equimolar amounts of benzenediazonium chloride were used, 1,3-dinitro-1,3-bis(phenylhydrazono)-2-propanone (**5**) was obtained in 35.7% yield; dec. 138 °C. IR: 3230 cm^{-1} (N–H), 1700 (C=O), 1530, 1350 (NO_2). NMR (acetone-d_6): δ 7.1—7.7 (10H, m), 12.48 (2H, b. s). Found: C, 50.68; H, 3.10; N, 23.64%. Calcd for $C_{15}H_{12}N_6O_5$: C, 50.56; H, 3.39; N, 23.59%.

*3,5-Bis(ethoxycarbonyl)-1-(2-pyridyl)-4-pyridone (**2b**).* One gram of **1b** was treated according to the manner described above to give 0.8 g (66.3%) of **2b**; colorless prisms (benzene), mp 150.0—151.0 °C. IR: 1715 cm^{-1} (C=O), 1665 (C=O). NMR ($CDCl_3$): δ 1.32 (6H, t), 4.31 (4H, q), 7.4 (2H, m), 7.9 (1H, m), 8.53 (1H, dd), 8.93 (2H, s). Found: C, 61.03; H, 4.96; N, 8.98%. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86%.

*3,5-Bis(ethoxycarbonyl)-1-(6-methyl-2-pyridyl)-4-pyridone (**2c**).* From 1.0 g of **1c**, 0.75 g (58.5%) of **2c** was obtained; colorless prisms (benzene), mp 168.5—169.5 °C. IR: 1750 cm^{-1} (C=O), 1675 (C=O). NMR ($CDCl_3$): δ 1.42 (6H, t,) 2.62 (3H, s), 4.33 (4H, q), 7.2 (2H, m), 7.82 (1H, t), 8.81 (2H, s). Found: C, 62.02, H, 5.56; N, 8.54%. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48%.

*3,5-Bis(ethoxycarbonyl)-1-(4-pyridyl)-4-pyridone (**2d**).* From 1.0 g of **1d**, 0.75 g (61.9%) of **2d** was yielded; colorless plates (benzene), mp 201.0—202.0 °C. IR: 1755 cm^{-1} (C=O), 1650 (C=O). NMR ($CDCl_3$): δ 1.32 (6H, t), 4.33 (4H, q), 7.39 (2H, dd), 8.34 (2H, s), 8.82 (2H, dd). Found: C, 60.98; H, 5.11; N, 8.67%. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86%.

*4-Hydroxy-3-nitro-1-phenyl-5-(phenylazo)pyrazole (**6**).* A mixture of 0.1 g of **5** and 100 ml of methanol was refluxed for 2h, and the solvent was evaporated to half volume. 0.08 g (93.2%) of **6** was precipitated; red needles (methanol), mp 218.0—219.0 °C. IR: 3400 cm^{-1} (O–H), 1590 (C=N), 1520, 1345 (NO_2). Found: C, 58.32; H, 3.43; N, 22.63%. Calcd for $C_{15}H_{11}N_5O_3$: C, 58.25; H, 3.59; N, 22.65%.

*Reaction of **1a** with Na·EAA.* To a solution of 0.5 g of **1a** in 25 ml of pyridine was added a solution of Na·EAA, prepared from 0.17 g of sodium and 1.10 g of ethyl acetoacetate, in 25 ml of pyridine with cooling. The mixture was heated at 65—70 °C for 5 h. Pyridine was evaporated under reduced pressure, the residue was acidified to pH 3 with dil. HCl, extracted with $CHCl_3$. After the extract was dried over anhydrous sodium sulfate, the solvent was distilled off, and the residual syrup was chromatographed on a silica gel column. From the chloroform elute, 0.17 g (16.2%) of 3-ethoxycarbonyl-7-hydroxy-2,4-dimethyl-6-nitro-3a,4-dihydrofuro[3,2-*b*]pyridine (**7a**) was obtained; colorless needles (ethanol–diisopropyl ether), mp 127.0—128.0 °C. Found: C, 51.12; H, 4.90; N, 9.69%. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 5.00; N, 9.93%.

*Reaction of **1b** with Na·EAA.* A mixture of 0.5 g of **1b** and Na·EAA, prepared from 0.13 g of sodium and 0.8 g of ethyl acetoacetate, in 50 ml of pyridine was heated at 65—70 °C for 5 h. Pyridine was evaporated under reduced pressure. To the residue ethanol was added and evaporated to dryness. The residue was extracted with $CHCl_3$. Evaporation of $CHCl_3$ gave crude 2-aminopyridine (**9b**), which was purified by column chromatography on silica gel, using diethyl ether for eluent, to give 0.11 g (61.5%) of pure sample. The chloroform insoluble layer was acidified with dil. HCl to pH 3, extracted with $CHCl_3$, and dried over anhydrous sodium sulfate. The solvent was distilled off and the residue was chromatographed on a silica gel column. From the benzene elute, 0.33 g (65.0%) of ethyl 4-hydroxy-3,5-dinitrobenzoate (**8**) was obtained; pale yellow needles (petroleum benzine), mp 88.0—89.0 °C (lit. mp 87 °C).[3] IR: 3300 cm^{-1} (O–H), 1730 (C=O), 1540, 1340 (NO_2). NMR ($CDCl_3$): δ 1.40 (3H, t), 4.41 (2H, q), 8.94 (2H, s), 11.0 (1H, b. s). Found: C, 42.37; H, 3.43; N, 10.79%. Calcd for $C_9H_8N_2O_7$: C, 42.19; H, 3.15; N, 10.94%.

When the reaction mixtrue was worked up without preceeding extraction with $CHCl_3$, 0.53 g (85.3%) of salt of 2-aminopyridine with **8** was obtained; yellow needles (ethanol), mp 217.0—218.0 °C. IR: 3400, 3250, 3200 cm^{-1} (N–H), 1720 (C=O), 1560, 1340 (NO_2). NMR (DMSO-d_6): δ 1.28 (3H, t), 4.21 (2H, q), 7.7—8.1 (2H, m), 8.7—9.2 (2H, m) 8.5—10.0 (3H, br), 9.20 (2H, s). Found: C, 48.32; H, 3.67; N, 16.29%. Calcd for $C_{14}H_{14}N_4O_7$: C, 48.00; H, 4.03; N, 16.00%.

*Reaction of **1c** with Na·EAA.* A similar treatment of 0.5 g of **1c** with Na·EAA gave 0.12 g (66.9%) of 2-amino-6-methylpyridine (**9c**) and 0.35 g (72.9%) of **8**.

*Reaction of **1d** with Na·EAA.* From 0.3 g of **1d**, 0.1 g (55.95%) of 4-aminopyridine (**9c**) and 0.26 g (51.0%) of **8** were obtained.

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