

Some Oxidation Reactions of Isomeric Pyridinecarboxylic Acid Hydrazides

Rashid IQBAL*, Samia EBRAHIM and Muhammad ZIAULHAQ
*Department of Chemistry, Quaid-i-Azam University,
Islamabad-PAKISTAN*

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The oxidation reactions of the three isomeric pyridinecarboxylic acid hydrazides were studied using sodium metaperiodate, silver(I) oxide and potassium ferricyanide separately. Potassium ferricyanide emerged as an excellent reagent for preparation of 2-pyridinecarboxaldehyde and 3-pyridinecarboxaldehyde from the respective isomeric pyridinecarboxylic acid hydrazides. Oxidation with silver(I) oxide in each case yielded the corresponding 1,2-dipyridoylhydrazine, while sodium metaperiodate furnished different products with each isomeric pyridinecarboxylic acid hydrazide.

Introduction

Oxidation of isomeric pyridinecarboxylic acid hydrazides has long been a subject of interest, and a number of reports concerning it are found in the literature.

Wingfield et al¹ carried out oxidation of 3-pyridinecarboxylic acid hydrazide (II) with potassium ferricyanide. 3-Pyridinecarboxaldehyde was isolated as the phenylhydrazone in a yield of 60-65% , and regeneration to aldehyde was found to be difficult. In an improved method¹, the oxidation of 3-pyridinecarboxylic acid hydrazide was carried out with sodium metaperiodate in ammoniacal solution. Gautier² oxidized 3-pyridinecarboxylic acid hydrazide (II) with a theoretical amount of yellow mercuric oxide in ethanol in order to obtain 1,2-di-(3-pyridoyl) hydrazine. The oxidation of 4-pyridinecarboxylic acid hydrazide(III) has been carried out polarographically³. Oxidation of the three isomeric pyridinecarboxylic acid hydrazides with ordinary and active manganese dioxide was carried out at room temperature and under reflux⁴. Potassium ferricyanide, sodium metaperiodate and mercuric oxide were the reagents used for the oxidation of 3-pyridinecarboxylic acid hydrazide separately¹⁻³. However, the reactions were not carried out with the other two isomeric pyridinecarboxylic acid hydrazides.

The first aim of this study was to determine the feasibility of the reaction of 2-pyridinecarboxylic acid hydrazide(I) and 4-pyridinecarboxylic acid hydrazide with sodium metaperiodate and also with potassium ferricyanide in comparison to the previously reported reaction with 3-pyridinecarboxylic acid hydrazide. The second object was to discover whether these reactions can lead to the formation of isomeric pyridinecarboxaldehyde in good yield. In addition, the three isomeric pyridinecarboxylic acid hydrazides (I-III) were intended to be subjected to oxidation with a relatively mild oxidizing agent such as silver(I) oxide.

* For correspondence

Results and Discussion

The oxidation reactions of the three isomeric pyridine carboxylic acid hydrazides were studied using sodium metaperiodate, silver(I) oxide and potassium ferricyanide separately. The products obtained and their percentage yields are shown in Table 1. The results of these oxidation reaction studies show potassium ferricyanide to be an excellent reagent for the preparation of 2-pyridinecarboxaldehyde(Ic) and 3-pyridinecarboxaldehyde(IIc) from the respective hydrazide. The reaction with 4-pyridinecarboxylic acid hydrazide(III), however, did not furnish the corresponding aldehyde(IIIc). Similarly, oxidation with silver(I) oxide in each case yielded the corresponding 1,2-di(isomeric pyridoyl)hydrazine(Ib-IIIb). The oxidation reactions with sodium metaperiodate furnished different products with each isomeric pyridinecarboxylic acid hydrazide.

Oxidation with sodium metaperiodate

Oxidation of 3-pyridinecarboxylic acid hydrazide yielded the corresponding aldehyde with the same yield and m.p. of its 2,4-dinitrophenylhydrazone derivative as reported earlier. Oxidation of 2-pyridinecarboxylic acid hydrazide(I) furnished a single product, 2-pyridinecarboxamide(Ia), whereas 4-pyridinecarboxylic acid hydrazide(III) on oxidation yielded a mixture of 4-pyridinecarboxaldehyde(IIIc) and 4-pyridinecarboxylic acid (IIIId) (Fig. 1). These results provide evidence that the reactivity of 2-pyridinecarboxylic acid hydrazide is different from that of the other two isomeric hydrazides. In view of the reaction mechanism suggested by Siedal et al⁶, and the formation of 2-pyridinecarboxamide (Ia) from 2-pyridinecarboxylic acid hydrazide in the present work, a strong electron attracting effect (similar to the nitro group) of the nitrogen atom in 2-pyridinecarboxylic acid hydrazide is confirmed. This effect appears to be much greater in intensity than the effect encountered in the 3-, and 4-pyridinecarboxylic acid hydrazides.

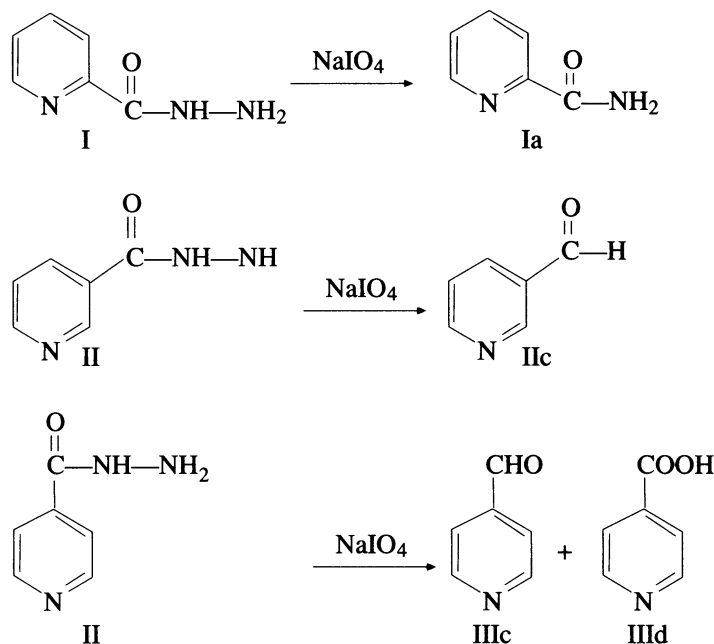


Figure 1

Oxidation with Silver(I) oxide

Oxidation of isomeric pyridinecarboxylic acid hydrazides (I-III) with silver(I) oxide were carried out at room temperature and under reflux separately. The products isolated were the corresponding 1,2-di(isomeric

pyridoyl) hydrazines (Ib, IIb and IIIb). The percentage yield and melting points of the products are given in Table 1. With silver(I) oxide, benzoic acid hydrazide is reported to yield a mixture of benzoic acid, benzaldehyde and 1,2-dibenzoylhydrazine⁵. In contrast, isomeric pyridinecarboxylic acid hydrozide in the present work yielded a single product, isomeric 1,2-dipyridoylhydrazine (Ib, IIb, IIIb). However, the formation of dibenzoylhydrazine solely from benzoic acid hydrazide is reported by oxidation with silver(II) oxide in benzene solvent⁷. Mackey et al.⁵ studied the oxidation of benzoic acid hydrazide with silver(I) oxide and explained the formation of products on the basis of a free radical mechanism. A free radical mechanism for the oxidation of isomeric pyridinecarboxylic acid hydrazide with silver(I) oxide is proposed in order to explain the formation of isomeric 1,2-dipyridoylhydrazines (Fig. 3). Silver(I) oxide first reacts with traces of water to yield silver cation and hydroxyl anion⁸. The presence of water is essential for the oxidation reaction of hydrazines with silver(I) oxide⁹. Initial abstraction of an electron followed by loss of a proton generates an unstable intermediate, 2-pyridoyldiimide (Id). This intermediate then undergoes a series of electron and proton loss to yield ultimately 2-pyridoyl radical(Ie). This may react with 2-pyridoyldiimide(Id) to furnish 1,2-dipyridoylhydrazine radical (If), which can further abstract a hydrogen atom either from the solvent or from the unreacted hydrazide to yield 1,2-di(2-pyridoyl)hydrazine(Ib). The same mechanism applies to the formation of the other two isomeric 1,2-dipyridoylhydrazines. Since only a single product, isomeric 1,2-dipyridoylhydrazine, (Ib-IIIb), has been obtained from oxidation of each isomeric hydrazide, it may be concluded that the position of the nitrogen atom in the pyridyl group has no significant effect in determining the nature of the product in this reaction.

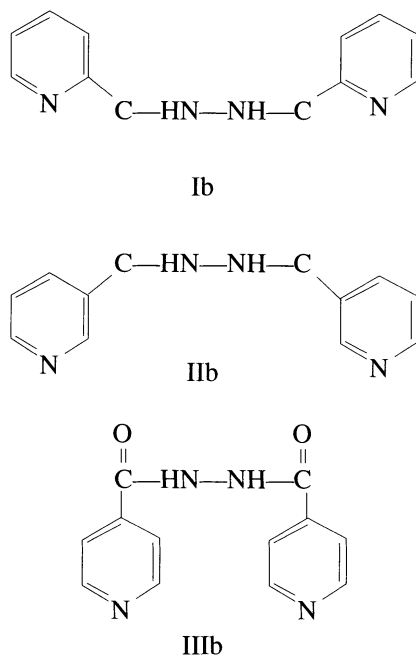


Figure 2

Oxidation with Potassium ferricyanide

Reactions were carried out at room temperature and under reflux. The melting points and percentage yield are given in Table 1. The reactions of 2- and 3-pyridinecarboxylic acid hydrazides (I, II) with potassium ferricyanide at room temperature and under reflux were found very successful since the desired respective aldehydes were obtained in yields ranging from good to excellent. The yield of 3-pyridinecarboxaldehyde(IIc) obtained was 42.3% when the reaction was carried out under reflux. However, when the reaction was carried

out at room temperature (25-28 °C) the yield isolated was 70.1%. No traces of 3-pyridinecarboxylic acid were detected when the reaction was performed under reflux. 4-Pyridinecarboxylic acid hydrazide(III) behaved differently in this reaction as it furnished 1,2-di-(4-pyridoyl)hydrazine(IIIb) under both reaction conditions. A proposed mechanism for the formation of 1,2-di-(4-pyridoyl)hydrazine(IIIb)⁹ is given in Figure 4. The mechanism assumes the formation of the corresponding aldehyde (IIIc) as a result of oxidation, which reacts with unstable intermediate, 4-pyridoyldiimide(IIIe) to form 1,2-di-(4-pyridyl)hydrezine(IIIb). As reported earlier¹⁰, these results indicate that 4-pyridinecarboxyldehde (IIIc) is more reactive than the other two isomeric aldehydes (Ic, IIc).

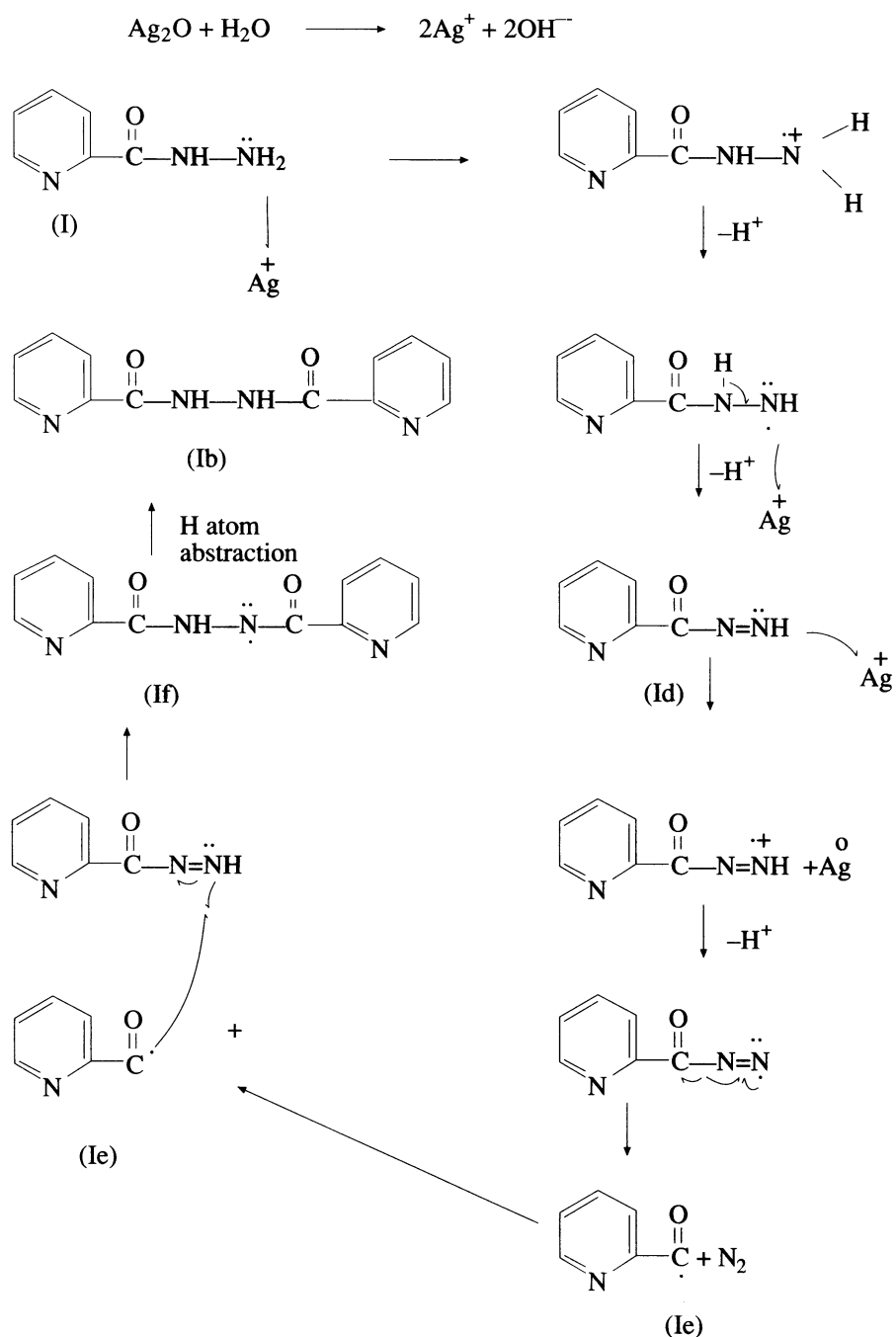


Figure 3

Table 1. Oxidation of isomeric pyridinecarboxylic acid hydrazides (I-III)

S.No.	Hydrazide Substrate No.	Oxidant	Reaction Conditions		Product/s		
			Temp(C°)	Time (hrs)	No.	m.p.(C°)	% yield
1	I	NaIO ₄	25-28	-	Ia	106	54.0
2	I	Ag ₂ O	25-28	192	Ib	220	33.0
3	I	Ag ₂ O	Reflux	2.5	Ib	220	41.3
4	I	K ₃ [Fe(CN) ₆]	25-28	288	Ic	-*	82.4
5	I	K ₃ [Fe(CN) ₆]	Reflux	18	Ic	-*	81.9
6	II	NaIO ₄	25-28	-	IIc	-*	54.2
7	II	Ag ₂ O	25-28	96	IIb	224	18.3
8	II	Ag ₂ O	Reflux	30	IIb	224	18.2
9	II	K ₃ [Fe(CN) ₆]	25-28	288	IIc	-*	70.1
10	II	K ₃ [Fe(CN) ₆]	Reflux	7.0	IIc	-*	42.3
11	III	NaIO ₄	25-28	-	IIIc,IIId	-,312	22.4,45.0
12	III	Ag ₂ O	25-28	192	IIIb	256	13.2
13	III	Ag ₂ O	Reflux	2.5	IIIb	256	52.1
14	III	K ₃ [Fe(CN) ₆]	25-28	144	IIIb	256	57.0
15	III	K ₃ [Fe(CN) ₆]	Reflux	11	IIIb	256	54.0

*Isolated product was a liquid

Characterization of the Isolated products

The purity of the isolated products was checked by TLC in two different solvent systems. Since all the products were already known, it was found suitable to identify them on the basis of their melting points, infrared spectra and the results of certain relevant chemical tests.

Isomeric Pyridinecarboxaldehydes (Ic-IIIc)

Isomeric pyridinecarboxaldehydes were characterized on the basis of positive silver mirror and positive Fehling solution tests, and an agreement of the observed melting points of their 2,4-dinitrophenylhydrazone derivatives with the literature values. In the infrared spectra of each isomeric aldehyde, a carbonyl absorption was observed in the region of 1716-1700 cm⁻¹ while aldehydic C-H stretching vibrations were present in the region 2801-2909 cm⁻¹.

4-Pyridinecarboxylic acid (IIId)

IIId was identified by comparison of the melting point and R_f value with the authentic sample. IR spectra exhibited a strong absorption due to νC=O at 1660 cm⁻¹. A broad peak at 3210-3180 cm⁻¹ was assigned to the hydroxyl group of carboxylic acid.

2-Pyridinecarboxamide (Ia)

The observed melting point was in accordance with the reported one. The evolution of ammonia on heating with aqueous sodium hydroxide indicated the presence of a carboxamide group. The IR spectra exhibited strong absorption at 1670 cm⁻¹ and 3200 cm⁻¹.

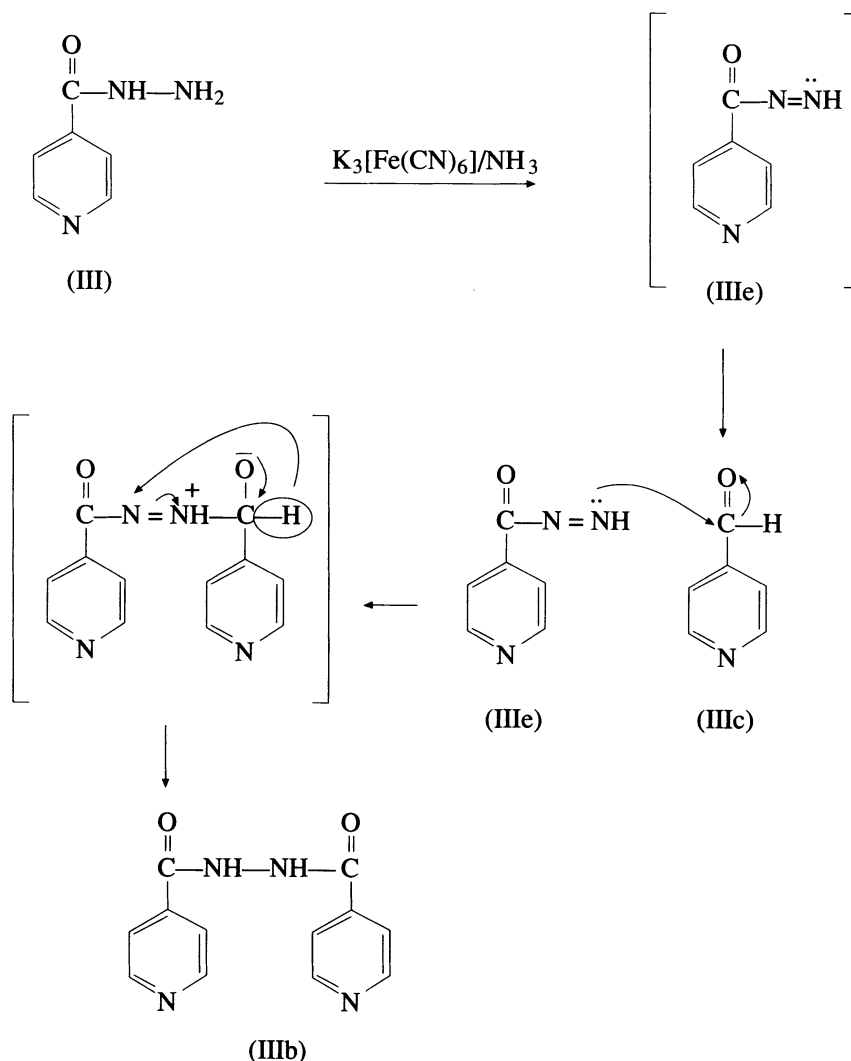


Figure 4

Isomeric 1,2-dipyridoylhydrazines (Ib-IIIb)

In each case the melting point was in accordance with value in the literature. In the IR spectra, the carbonyl stretching absorptions were observed at 1670 cm^{-1} , while secondary amide group stretching absorptions were present at $3400\text{-}3300\text{ cm}^{-1}$. In the mass spectra, the molecular ion peak was present at m/z 242. The base peak was due to the fragment $C_5H_4NCO]^+$. The other prominent peaks observed were at m/z 212, 184 and 106.

Experimental

The melting points of the compounds were determined on a Gallenkamp melting point apparatus. IR spectra were recorded on a Hitachi model 270-50 Infrared spectrophotometer. Mass spectra were recorded on Varian Mat CH-5. The isomeric hydrazides were prepared by a previously reported method.

Oxidation with Sodium metaperiodate

To a stirred and chilled solution of 11g of sodium metaperiodate in 150 ml of water, 100ml of ammonium hydroxide (33%) was added slowly. A solution of 0.047 moles (6.5g) of respective isomeric pyridinecarboxylic acid hydrazide in 75 ml of 8 % aqueous ammonium hydroxide was added to the stirred ice-cold periodate solution as rapidly as was permitted by the gas evolution. Stirring and cooling of the reaction mixture were continued for five minutes before allowing the mixture to stand for an additional fifteen minutes. A solution of 12g of barium acetate in 50 ml of H₂O was then added to the reaction mixture, which resulted in precipitation of a solid. The solid was filtered off and the filtrate was neutralized to pH 7 using dilute acetic acid. This neutral solution was then saturated with a sufficient amount of sodium chloride and filtered. The filtrate thus obtained was used for isolation of the products by a different method for each isomeric hydrazide.

In the oxidation of 2-pyridinecarboxylic acid hydrazide(I), the filtrate was extracted with chloroform (3 × 30 ml). Evaporation of the solvent led to a crude red solid residue which was recrystallized from ethyl acetate to yield white crystalline 2-pyridinecarboxamide (2.1 g). The aqueous layer was dried under reduced pressure and extracted with hot ethanol (2 × 100 ml). The ethanolic layer was concentrated and extracted with chloroform (2 × 25 ml). Following evaporation the solid residue left was recrystallized from ethyl acetate. White crystals of 2-pyridinecarboxamide (Ia) (1g) were obtained.

In the oxidation of 3-pyridinecarboxylic acid hydrazide(II), the filtrate was extracted with chloroform (2 × 30 ml), and upon evaporation yielded 3-pyridinecarboxaldehyde (IIc), (2.74 g, 54.2%).

In the oxidation of 4-pyridinecarboxylic acid hydrazide(III), the aqueous layer was extracted with diethyl ether (3 × 30 ml). Removal of the solvent yielded 4-pyridinecarboxaldehyde(IIIc) (1.14 g, 22.4%). The aqueous layer was evaporated to dryness under reduced pressure. The solid obtained was extracted with hot ethanol (2 × 100 ml). After complete evaporation of ethanol, the off-white solid obtained was recrystallized with petroleum ether (40-60°), yielding 4-pyridinecarboxylic acid (IIId), 52.6 g, 45%).

Oxidation of Isomeric Pyridinecarboxylic acid hydrazides (I-III) with Silver(I) oxide

The three isomeric pyridinecarboxylic acid hydrazides were subjected to oxidation with silver(I) oxide in ethanol at two different reaction conditions: i) at room temperature (25-28°C) and ii) under reflux.

At room temperature

The respective pyridinecarboxylic acid hydrazide 0.0072 mole (1g), was dissolved in 25 ml of absolute ethanol. Silver(I) oxide, 0.0077 mole (1.8g), was added to the respective hydrazide solution in a beaker and stirred for an appropriate period of time period (Table 1) and monitored by TLC. Upon completion of the reaction, the mixture was filtered and excess ethanol was removed under reduced pressure. The crude product obtained was recrystallized from an appropriate solvent (Table 1).

Under reflux

0.0145 moles (2g) of the respective isomeric pyridinecarboxylic acid hydrazide was dissolved in absolute ethanol (40 ml). 0.0155 moles (3.6g) of silver(I) oxide moles (3.6g) was added to hydrazide solution. The reaction mixture was then refluxed with stirring and monitored by TLC. Upon completion of the reaction, the

mixture was filtered and the excess ethanol was distilled off. The crude product obtained was recrystallized from an appropriate solvent (Table 1).

Oxidation of Isomeric Pyridinecarboxylic acid hydrazide with Potassium ferricyanide

The oxidation reaction of each of the three isomers was carried out both at room temperature and under reflux.

At room temperature

To a solution of 0.015 moles (2.1g) of respective isomeric pyridinecarboxylic acid hydrazide in 16ml of water at room temperature was added a solution of potassium ferricyanide 0.0272 moles (9g) in 45 ml of aqueous ammonium hydroxide (33%). After the evolution of a colourless gas, an additional 0.0136 moles (4.5g) of potassium ferricyanide in 23ml of aqueous ammonium hydroxide (33%) was added. The reaction mixture was stirred thoroughly with a magnetic stirrer at room temperature and was monitored by TLC. The work up for isolation of the reaction products for different hydrazides is described below:

The reaction mixture of 2-pyridinecarboxylic acid hydrazide was evaporated under reduced pressure. The solid obtained was extracted with hot acetone (2 × 3ml). Evaporation of acetone yielded 2-pyridinecarboxaldehyde(Ic) 1.34g, 82.4%.

In case of 3-pyridinecarboxylic acid hydrazide, the reaction mixture was extracted with diethyl ether (3 × 10ml) and dried over anhydrous sodium sulfate. Removal of ether yielded 3-pyridinecarboxaldehyde(IIc) 1.14g, 70.1%.

The reaction mixture of 4-pyridinecarboxylic acid hydrazide was evaporated to dryness under reduced pressure. The solid obtained was extracted with hot ethyl acetate. Removal of ethyl acetate by evaporation furnished a solid 1,2-di-(4-pyridoyl) hydrazine(IIIb), which was recrystallized from water, 2.1 g, 57%.

Under Reflux

To a solution of 0.015 moles (2.1g) of respective isomeric pyridinecarboxylic acid hydrazide in 16ml of water at room temperature was added a solution of potassium ferricyanide 0.0272 moles (9g) in 45 ml of aqueous ammonium hydroxide (33%). After evolution of gas an additional 0.0136 moles (4.5g) of potassium ferricyanide in 23 ml of aqueous ammonium hydroxide (33%) was added. The reaction mixture was then subjected to reflux with stirring for a specific time (Table 1) followed by TLC. Work up for each isomer is given below:

In the case of 2-pyridinecarboxylic acid hydrazide, the reaction mixture turned from yellow to green as the reaction proceeded. After completion, the reaction mixture was evaporated to dryness under reduced pressure. The solid obtained was treated with hot acetone (3 × 30ml). Following evaporation of the organic solvent, a light yellow liquid was left behind identified as 2-pyridinecarboxaldehyde(Ic), 1.34g, 81.9%.

In the case of 3-pyridinecarboxylic acid hydrazide, the initial yellow colour turned brownish green and ultimately green. The reaction mixture was filtered and the filtrate was extracted with diethyl ether (3 × 25ml), dried over anhydrous sodium sulfate. Evaporation of the solvent resulted in an oily liquid identified as 3-pyridinecarboxaldehyde(IIc), 0.68g, 42.3%.

The reaction mixture of 4-pyridinecarboxylic acid hydrazide was evaporated to dryness under reduced pressure. The orange solid obtained was treated with hot ethyl acetate (4 × 30ml). The organic layer was

dried over anhydrous sodium sulfate. Following filtration, evaporation of ethyl acetate furnished white crystals of 1,2-di-(4-pyridoyl) hydrazine(IIIb), which was recrystallized from water 2.0g, 54%.

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