AN UNUSUAL SYNTHESIS OF NICOTINAMIDES

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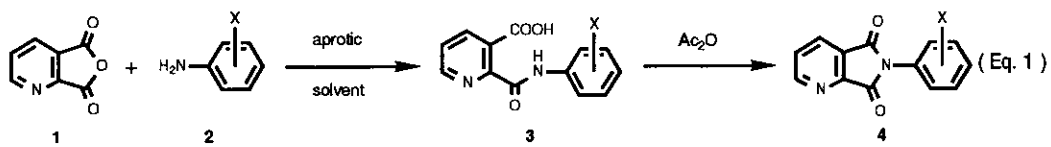
Abstract - Reaction of 2,3-pyridinedicarboxylic anhydride (**1**) with a substituted aniline (**2**) in acetic acid gave rise to a mixture of two products. These two products were identified as the cyclic imide (**4**) and nicotinamide (**5**). A mechanistic scheme consistent with empirical observations is proposed.

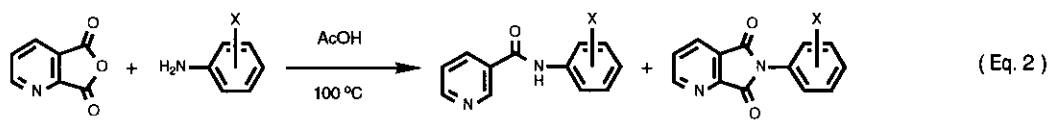
Dedicated to Prof. Edward C. Taylor on the occasion of his 70th birthday.

Pyridine-2,3-dicarboximides (**4**) are typically prepared in stepwise fashion by initial formation of nicotinic acid derivative (**3**), as the major or exclusive product resulting from attack at the more reactive C-2 carbonyl of anhydride (**1**), and subsequent cyclization with acetic anhydride (Eq. 1).[1]



1 **2** **3** **4** (Eq. 1)

In connection with Herbicide Discovery efforts at Cyanamid, we recently attempted to effect this overall transformation in one step by heating equimolar amounts of components (**1**) and (**2**) in glacial acetic acid at 100 °C for 16 h, and found that the major product was not the desired cyclic imide (**4**), but the nicotinamide (**5**) (Eq. 2). Since to our knowledge this observation had not been reported,[2] a number of additional examples were investigated, the results of which are summarized in the following Table.



1 **2** **5** major **4** minor (Eq. 2)

Although in all cases the nicotinamide (**5**) predominates, a proportionately higher amount of imide (**4**) is produced when aniline (**2**) is substituted with electron-donating substituents. For example, 4-methoxy-2-methylaniline furnishes nearly a 1:1 mixture while 2-nitroaniline yields almost exclusively the corresponding nicotinamide (see Table).

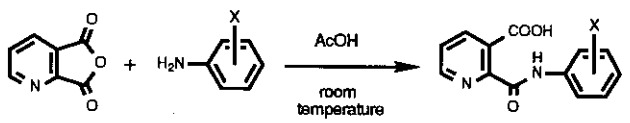
Table. Product Distributions[a,b]

substituent (X)	nicotinamide (5)	cyclic imide (4)	total yield (%)
H	86	14	92
p-methoxy	75	25	89
m-methoxy	90	10	86
o-methoxy	84	16	92
p-nitro	87	13	87
m-nitro	71	29	90
o-nitro	98	2	78
p-methyl	66	33	87
m-methyl	66	33	95
o-methyl	75	25	93
p-fluoro	82	18	88
m-fluoro	91	9	93
o-fluoro	18	82	97
p-fluoro,*m*-nitro	80	20	96
o-methoxy,*m*-nitro	83	17	85
p-methoxy,*o*-methyl	56	44	92
p-nitro,*m*-trifluoromethyl	75	25	74

[a]All reactions were conducted for ~16 h employing 1 molar equivalent of anhydride in 50 mM glacial AcOH at 100 °C. [b]Ratios were determined by hplc after the consumption of starting amine.

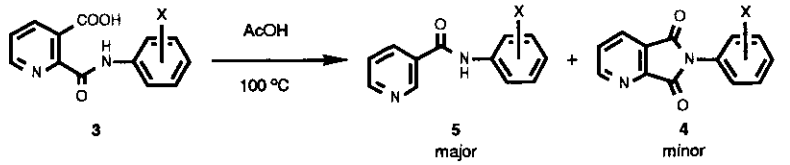
The following additional observations that relate to this transformation were made:

1) Nicotinic acid derivative (**3**) is cleanly formed at room temperature in acetic acid (Eq. 3) and can be detected in the initial stages of reaction at elevated temperature. This is consistent with previously reported regioselective attack of anilines at the C-2 carbonyl of anhydride (**1**) in aprotic solvents.[3]



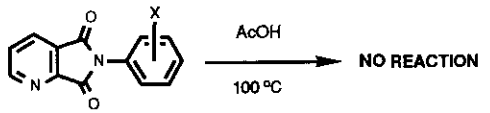
1 **2** **3** (Eq. 3)

2) Nicotinic acid derivative (**3**) was isolated and independently subjected to the same conditions as described in Eq. 2, i.e., glacial acetic acid at 100 °C (Eq. 4). The same products were obtained but the product distribution was different from that obtained in Eq. 2. Although the nicotinamide (**5**) predominated, a relatively smaller amount of cyclic imide (**4**) was detected. This suggests that under the conditions described in Eq. 2, some aniline attack at C-3 of anhydride (**1**) occurred followed by decarboxylation.[4]



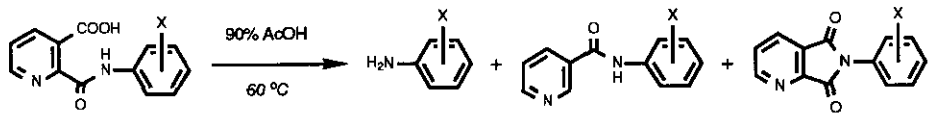
3 5 major 4 minor (Eq. 4)

3) When imide (**4**) was heated in glacial acetic acid at 100 °C, no reaction occurred (Eq. 5). This suggests that, in the overall transformation described in Eq. 2, there is a role played by the water liberated in the dehydration of **3** to **4**.



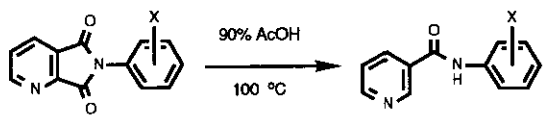
4 (Eq. 5)

4) When nicotinic acid derivative (**3**) was treated with 90% acetic acid (aq.) at 60 °C (18 h), the usual products (**4**) and (**5**) as well as unreacted **3** were observed along with a significant amount of aniline (**2**) (Eq. 6), presumably arising *via* direct hydrolysis of starting material.



3 2 5 4 (Eq. 6)

5) Reaction of the cyclic imide (**4**) in 90% acetic acid (aq.) effected partial hydrolysis to yield the nicotinamide (**5**) as the major product (Eq. 7).



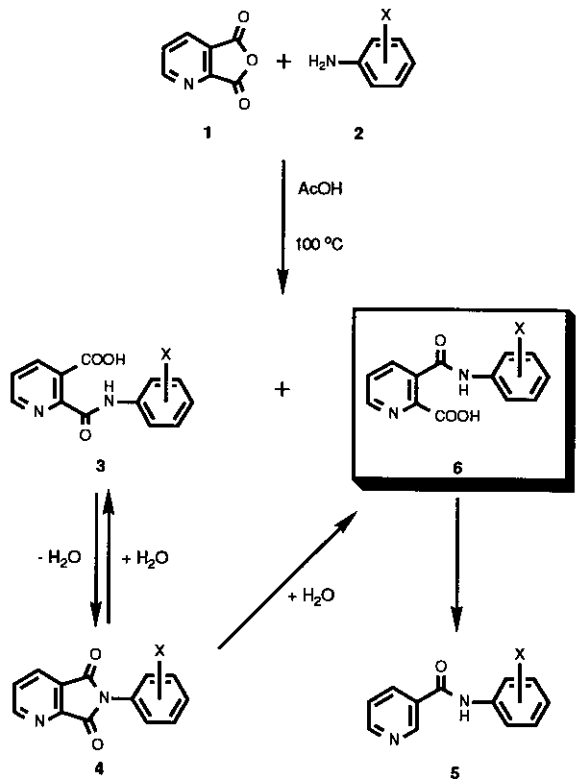
4 5 (Eq. 7)

Although it is not our intent to prove a reaction mechanism, all the preceding observations are consistent with the reaction Scheme shown below. Key to the production of major product (**5**) is the generation of picolinic acid derivative (**6**), which irreversibly decarboxylates and shifts the equilibrium in favor of the nicotinamide (**5**). Picolinic acid derivative (**6**) can arise either by direct attack at C-3 on anhydride (**1**), or *via* equilibration of nicotinic acid derivative (**3**) through imide (**4**). No attempt was made to determine the relative role of each in the overall production of major product (**5**). It would appear that water plays a critical role in this equilibration, and its concentration affects the overall product distribution.

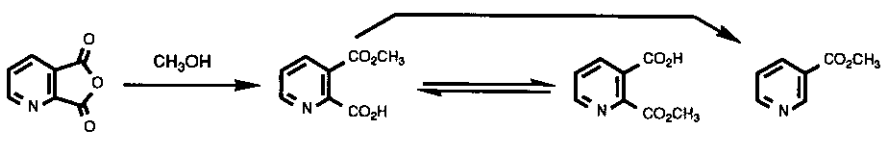
The reaction of anilines (**2**) with 2,3-pyridinedicarboxylic anhydride (**1**) to directly produce nicotinamides (**5**), although synthetically useful, does not offer any advantages over existing methods such as coupling of nicotinoyl chloride with the requisite aniline.[5] Moreover, the corresponding cyclic imides (**4**) are best prepared by forming the half-amide of quinolinic acid and cyclizing with acetic anhydride.[1] The preferential formation of nicotinamides (**5**) in glacial acetic acid

at 100 °C can be understood in terms of an irreversible decarboxylation which drives a set of equilibrium reactions in this direction.

Scheme



Precedent for equilibration in a similar system is the following transformation in which heating **1** in methanol gives the 3- and 2-methyl carboxypyridinecarboxylates (**7**) and (**8**).[6] The proportion of **7** increases as the heating is prolonged, favorably disposing the free carboxyl group for smooth decarboxylation to nicotinate (**9**) (Eq. 8). In both the nicotinamide and nicotinate cases, the reaction course is ultimately determined by the extent of decarboxylation occurring at the C-2 position.



(Eq. 8)

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