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Research Article

Preparation of ^{18}O-labelled nicotinamide

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Summary

A method of preparing ^{18}O-labelled nicotinamide, involving cyanopyridine, $H_2{}^{18}O$, and 1,1′3,3′-tetramethylguanidine as a catalyst is described. The desired product is produced in 91% chemical yield and 97.5% isotopic incorporation. Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: nicotinamide; Vilsmeier reaction; alkaline hydrolysis; iminium ions; propyl benzenecarboximidoate

Introduction

Niacin, commonly known as nicotinamide, plays an important role in the biosynthesis of pyridine nucleotides. This nitrogen heterocyclic compound combines *in vivo* with the nucleotide adenosine to form nicotinamide adenine dinucleotide (NAD^+), which serves as a soluble electron carrier in biochemical reactions. Clinically, niacin maintains the normal function of the digestive system, reducing cholesterol levels, and even reducing dizziness and ringing in the ears. Other symptoms associated with niacin deficiency include general weakness and fatigue, loss of appetite, dermatitis, skin lesions, a swollen tongue, and dementia.

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Oxygen-labelled nicotinamide can be obtained by two synthetic strategies. The first of these is based on the exchange of the oxygen atom of the nicotinamide with ^{18}O-enriched water. In this approach a large excess of the labelled oxygen source is needed to assure high enrichment of the nicotinamide. The second strategy relies on the incorporation of the labelled oxygen from a readily accessible ^{18}O-enriched source into a mono-oxygenated precursor of nicotinamide. This enables more efficient use of the enriched substrate and high oxygen incorporation into the precursor. The synthesis of ^{14}C-nicotinamide,[1] (6-^{2}H) nicotinamide,[2,3] (1-^{15}N) nicotinamide,[4] 4-deutero-3-pyridi-necarboxamide,[5,6] (carboxyl ^{11}C) nicotinamide,[7] (6-^{13}C) nicotinamide,[8] and (4-^{13}C) nicotinamide[9] have been presented in the literature.

Results and discussion

Several approaches to the synthesis of nicotinamide have been presented in the literature.[1–19] Preparation of ^{18}O-labelled nicotinamide by treatment of unlabelled precursor with ^{18}O-labelled water in alkaline medium is possible due to the much faster oxygen exchange than hydrolysis.[10,11] In the reaction scheme presented in Figure 1, the intermediate [I] is assumed to give products or generate reactants and, provided that the oxygen atoms in I become equivalent by virtue of rapid proton transfers, this reverse step should lead to oxygen exchange.[10–13]

Under alkaline conditions the rate constants for the exchange and hydrolysis are then related to k_{-1} and k_2 by Equation (1):

$$k_e/k_h = k_{-1}/2k_2 \tag{1}$$

In acidic solution, the yield of labelled nicotinamide was negligible.[14] In the presence of hydrogen peroxide only a 19% yield was achieved.[10]

The synthesis of nicotinamide from thionicotinamide has been reported.[15] The superoxide group, generated by K_2O with the crown

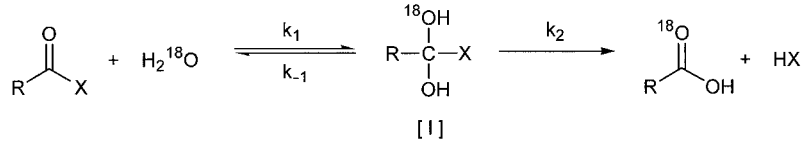


Figure 1. The mechanism of amide hydrolysis

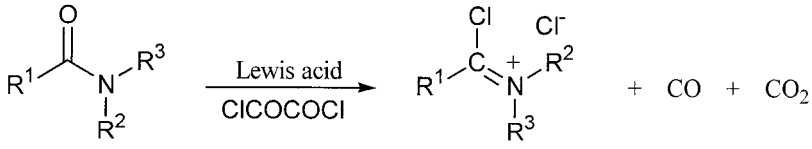


Figure 2. The Vilsmeier reaction scheme

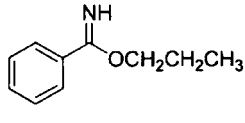
ether as the catalyst, was effective for the desulfurization of the thioamide group of thioisonicotinamide, its 2-ethyl derivative, and thionicotinamide to give the appropriate amides in 69, 61 and 71% yields, respectively. This yield is, however, too low to apply this synthetic route for labelling purposes.

The conversion of nicotinonitrile into nicotinamide has been reported in several publications. A good yield was reported by the use of ammonia under pressure, with 73% of the nitrile being converted into nicotinamide and the rest into nicotinic acid.[16] The inherent disadvantage associated with the use of alkali is the formation of acids as by-products with a corresponding decrease in yield and the necessity of separating the products formed. Our attempts to diminish the formation of acid were unsuccessful.

The Vilsmeier reaction (Figure 2) has long been used to convert amides to highly electrophilic iminium ions, which are susceptible towards attack of various nucleophiles including those as weak as aromatic rings.[17]

Iminium ions may be generated also in the reaction of nitriles with HCl and with oxalyl chloride. R^1, R^2 and R^3 could be different alkyl or aryl groups. We expected that such intermediates might provide a useful alternative route of activating nitriles towards nucleophilic attack by water. The reaction of amide and oxalyl chloride 1:1 gave the product in less than 20% yield.[18] Much better yields (70%) have been obtained from the reaction of 3-cyanopyridine with HCl.[19] We have studied the applicability of these procedures to oxygen-labelled nicotinamide. We used benzonitrile and HCl, as described by Veale *et al.* (Figure 3).

The model experiments involving reaction of benzonitrile with HCl in alcohol gave the required imidoyl ester.



Moreover, only unreacted substrate was isolated in experiments involving methylene chloride instead of expected imidoyl chloride.

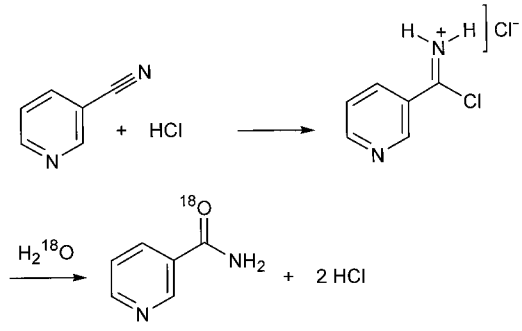


Figure 3. The synthesis of nicotinamide via an iminium ion

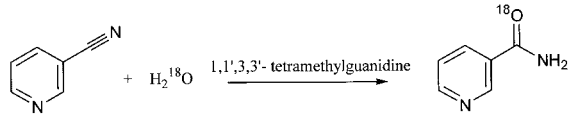


Figure 4. The hydrolysis of nicotinonitrile

It is well known that the action of KOH or NaOH on nitriles leads directly to the formation of the corresponding acids. The amides, postulated as intermediate products in this reaction, are obtained efficiently when hydrogen peroxide is added to the mixture. For example, the use of amonium hydroxide gave nicotinamide in 70% yield, but the high excess of the labelled water necessary for efficient hydrolysis strongly diminishes the isotopic efficiency of the method.[16] In order to reduce the requirement for labelled water we improved the procedure through the use 1,1′,3,3′-tetramethyl-guanidine (TMG) as catalyst (Figure 4).

TMG was chosen as a base because it is volatile and can be easily removed from the final product by evaporation or lyophilization. Moreover, the absence of any exchangable oxygen atom does not lower the enrichment of the labelled water. Overall the chemical and isotopic yields in our method were 91 and 97.5%, respectively, making this procedure an excellent way for preparing ^{18}O–labelled nicotinamide.

Experimental

Alkaline hydrolysis of nicotinamide

Four samples each containing nicotinamide (100 mg, 0.83 mM) in water (1 ml) and 10, 20, 40 and 100 µl of $Ba(OH)_2$, respectively, were heated in

a water bath for 1 h. After cooling the water was evaporated off. The products were dried over P_2O_5 and recrystallized from ethyl acetate. 50, 39, 21 and 0 mg of amide were produced, respectively. ^{1}H-NMR (250 MHz, ^2H_2O): $\delta = 4.89$ ppm (s, 2H) R–N$\underline{H_2}$, 7.53–8.87 ppm (m, 4H) ring [H-2 8.87 ppm; H-4 8.2 ppm; H-5 7.6 ppm; H-6 8.7 ppm]. ^{13}C-NMR (62.9 MHz, ^2H_2O): $\delta = 151.60$ ppm C-2, 128.89 ppm C-3, 136.19 ppm C-4, 124.40 ppm C-5, 147.40 ppm C-6, 170.16 ppm –C = O.

Propyl benzenecarboximidoate

A solution of benzonitrile (3 g, 29 mM) in propanol (3 ml) was cooled to 0°C and saturated with dry HCl gas for 2 h. The reaction mixture was allowed to warm to room temperature and stand for 16 h. The solvent was then evaporated off. The white solid product was dried over P_2O_5. 4.37 g of product (27 mM, 92%) was obtained. ^{1}H-NMR (250 MHz, ^2H_2O): $\delta = 1.15$ ppm (t, 3H, $J = 7$ Hz) R–C$\underline{H_3}$, 1.95–2.09 ppm (m, 2H) R–C$\underline{H_2}$–$\underline{Me}$, 4.84–4.89 ppm (t, 2H, $J = 7$ Hz) RO–C$\underline{H_2}$–$\underline{Et}$, 7.32–8.43 ppm (m, 5H) ring, 11.94 and 12.66 ppm (2 × s, 1H) $\underline{H}$–N.

^{18}O-labelled nicotinamide

A solution of 3-cyanopyridine (Aldrich) (270 mg, 2.6 mM) and 1,1′,3,3′-tetramethylguanidine (Aldrich) (13.8 mg, 15 µl) in $H_2^{18}O$ (40% enrichment, Technabexport, Russia) (300 µl) was heated in water bath for 1 h. Water and 1,1′3,3′-tetramethylguanidine were then removed by lyophilization. The residue was crystallized from benzene, yielding 245 mg (91%) of ^{18}O-nicotinamide, m.p. 129–130°C (39% ^{18}O from FAB mass spectrometry). ^{1}H-NMR (250 MHz, ^2H_2O): $\delta = 4.89$ ppm (s, 2H) R–N$\underline{H_2}$, 7.53–8.87 ppm (m, 4H) ring [H-2 8.87 ppm; H-4 8.2 ppm; H-5 7.6 ppm; H-6 8.7 ppm]. ^{13}C-NMR (62.9 MHz, ^2H_2O): $\delta = 151.69$ ppm C-2, 129.16 ppm C-3, 136.33 ppm C-4, 124.02 ppm C-5, 147.51 ppm C-6, 170.58 ppm –C = O.

Acknowledgements

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