Tetrahedron Letters 59 (2018) 2189–2192

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis and spectroscopic studies of 3-carbamoylisonicotinic acid derivatives

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ARTICLE INFO

Article history:
Received 14 March 2018
Revised 17 April 2018
Accepted 24 April 2018
Available online 25 April 2018

Keywords:
Cyano group
Nitriles
Hydrolysis
Carboxylic acid
Isonicotinic acid
Pyridone

ABSTRACT

An unusual example of the selective hydrolysis of a cyano group to the corresponding carboxyl group under mild reaction conditions in the presence of a carboxamide group is reported. The reaction resulted in the formation of a rare combination of vicinal carboxamide and carboxyl groups on a pyridone ring. The structure of the synthesized products was thoroughly studied using one- and two-dimensional NMR experiments and the reaction pathway was monitored fluorometrically.

Cyano-containing organic molecules are convenient synthetic intermediates in organic synthesis. One of the most important reactions thereof is the hydrolysis of a carbonitrile group; this reaction proceeds with the formation of a carboxyl group or can be stopped at the formation of a carboxamide group. The hydrolysis of a cyano group to the carboxyl group generally takes place under harsh reaction conditions: this requires the use of concentrated strong acids or bases and high temperatures. For example, the hydrolysis of isonicotinonitrile derivatives to isonicotinic acid can be carried out with prolonged heating at reflux (for several hours) with aqueous and alcoholic solutions of sodium or potassium hydroxides;[1] concentrated sulfuric[2] or hydrochloric acids.[3]

Such harsh reaction conditions are inapplicable for the selective hydrolysis of cyano groups in the presence of other sensitive functional groups, for example, the carboxamide group, which is known to be more easily hydrolyzed than the cyano group.[4] Various approaches have been reported for cyano group hydrolysis under mild reaction conditions. For example, metal-mediated and metal-catalyzed hydrolysis,[4c,5] microbial hydrolysis,[6] assistance of the neighboring groups: a so-called *quasi*-hydrolysis,[7] CACHE-processes (carbonyl-assisted carbonitrile hydration effect),[7a,8] and an iminolactone-lactam rearrangement.[9]

Herein, we report the selective hydrolysis of a cyano group to the corresponding carboxyl group under comparatively mild reaction conditions in the presence of a carboxamide group. This reaction was applied to the synthesis of 2-oxo-isonicotinic acid derivatives, which find application in various fields. For example, they are promising fluorescent substances[10] and biologically active molecules, most of which are inhibitors of *Mycobacterium tuberculosis*.[11]

Under the action of a 1% aqueous solution of sodium hydroxide and heating at reflux for 2–3 min or heating at 40–50 °C for 30–60 min, 4-cyano-2-oxo-1,2-dihydropyridine-3-carboxamides **1a–g**[8] were converted to 3-carbamoyl-2-oxo-1,2-dihydropyridine-4-carboxylic acids **2a–g** in 72–97% yield (Scheme 1 and Table 1).[12] Unexpectedly, only the cyano group was transformed during the course of the reaction, and the carboxamide group remained untouched. It should be noted that reaction results in the formation of a rare combination of vicinal carboxamide and carboxyl groups on the pyridone ring.

The structures of the isonicotinic acids **2** were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, as well as mass spectrometry. A prominent feature of the ^{1}H NMR spectra of compounds **2** is the very large difference in the shifts (about 1.8 ppm) of proton signals for the carboxamide group (Fig. 1), which appear at 9.21–9.25 and 7.43–7.57 ppm (ESI, Table 1). The strong downshift of a single amide proton can be explained by the presence of hydrogen bonding with the oxygen of the pyrid-2-one fragment. Similar shifts of the amide proton were previously described for the starting 2-oxo-4-cyano-1,2-dihydropyridine-3-carboxamides **1**.[8]

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https://doi.org/10.1016/j.tetlet.2018.04.067
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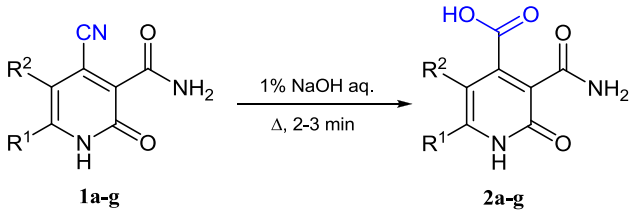
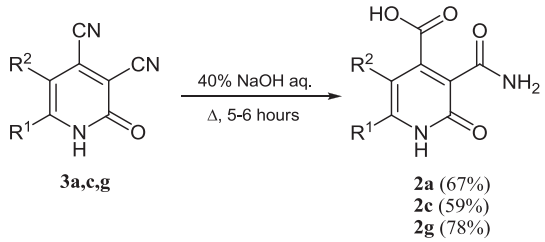


Scheme 1. Synthesis of 3-carbamoyl-2-oxo-1,2-dihydropyridine-4-carboxylic acid **2a–g**.



Scheme 2. Synthesis of 3-carbamoyl-2-oxo-1,2-dihydropyridine-4-carboxylic acid **2** from 2-oxo-1,2-dihydropyridine-3,4-dicarbonitrile **3**.

Table 1
Synthesis of 3-carbamoyl-2-oxo-1,2-dihydropyridine-4-carboxylic acid **2a–f**.[a]

Substrate	R^1	R^2	Product	Yield **2** (%)[b]
1a	Me	Me	**2a**	88
1b	Me	Et	**2b**	81
1c	$(CH_2)_4$		**2c**	84
1d	$(CH_2)_2CH(t\text{-Bu})CH_2$		**2d**	97
1e	$(CH_2)_5$		**2e**	76
1f	$(CH_2)_6$		**2f**	72
1g	Ph	Me	**2g**	81

[a] Reagents and conditions: 4-cyano-2-oxo-1,2-dihydropyridine-3-carboxamide **1a–g** (1 mmol), 100 °C, 2–3 min, 1% NaOH (2 mL).[12]
[b] Isolated yield.

For comparison, the reaction of 2-oxo-1,2-dihydropyridine-3,4-dicarbonitriles **3**[8,13] was also carried out. In this case harsher reaction conditions (reflux, 5–6 h, 40% aqueous sodium hydroxide) were needed to produce the corresponding 3-carbamoyl-2-oxo-1,2-dihydropyridine-4-carboxylic acids **2** (Scheme 2).[14]

Such harsh reaction conditions for the reaction of pyridones **3** indicate that the cause of the abnormally facile cyano group hydrolysis in the case of compounds **1** is participation of the adjacent carboxamide in the transformation (Scheme 3). This is consistent with the theory of CACHE processes, where the carbonyl group assists with hydration of the cyano group.[8]

In the first stage, under the action of the base, deprotonation takes place which leads to intermediate **A**. The previously described reaction of pyridine derivatives with diethylamine, which gives salts under mild conditions, confirms the initial attack of the hydroxide anion at the NH-pyridone fragment.[15] Further, due to the intramolecular interaction of the vicinal functional groups, iminopyrrole ring **B** is formed. Hydrolysis of the imine fragment results in pyrrolopyridine **C**. Subsequently, the imide fragment in intermediate **C** is able to undergo ring-opening in two directions under the action of the hydroxide-anion. However, it was found that the reaction is extremely regiospecific; only the carbonyl group of imide **D** is attacked by the hydroxide-ion. This reaction direction is apparently due to the fact that the carbonyl group at the C-3 position effectively participates in delocalization of the anionic center, and so the hydroxide anion attacks the more electrophilic carbon atom at the C-4 position of fused pyrrolopyridine **D**. This leads to ring-opening of the imide ring and the formation of intermediate **E**. The final compound **2** is isolated after the neutralization of salt **E** by hydrochloric acid.

However, the selectivity of the ring-opening can be also related to the reversibility of decyclization and the further isolation of the more thermodynamically stable single product stabilized by hydrogen bonding. The harsher reaction conditions in the case of the reaction of 2-oxo-1,2-dihydropyridine-3,4-dicarbonitriles **3** with sodium hydroxide are due to the fact that there is no such facilitating effect and it is necessary to first transform the cyano group to the carboxamide group.[1–3]

Additionally, the proposed reaction pathway (Scheme 3) was confirmed by the reaction of 1*H*-pyrrolo[3,4-*c*]pyridine-1,3,4(2*H*,5*H*)-trione derivative **4**[16] (an analogue of intermediate **C**, Scheme 3) with a 1% aqueous solution of sodium hydroxide. After heating the reaction mixture for 1–2 min, the corresponding 3-carbamoyl-2-oxo-1,2-dihydropyridine-4-carboxylic acid **2e** was isolated in 92% yield (Scheme 4). This reaction also proceeds at room temperature and can be monitored fluorometrically.

Starting compound **4** possesses a medium intensive fluorescence in a water solution with the maximum at 515 nm.[16] In a 0.1 N solution of NaOH the fluorescence intensity decreases dramatically and a slight bathochromic shift of the emission maximum (about 5 nm) is observed. Apparently this is associated with salt formation. Moreover, a new shortwave peak in the fluorescence spectrum appears in the process of time; in the 0.1 N solution of NaOH it occurs in 1 min. Fluorescence measurements were carried out for compound **4** in a 0.01 N NaOH solution and after 30 min at room temperature the emission peak at 520 nm almost disappeared and a new peak at 448 nm emerged (Fig. 2). The value of the new shortwave maximum matches with the fluorescence maximum of compound **2e** in the 0.01 N solution of NaOH.

Previously, we reported that 2-oxo-4-cyano-1,2-dihydropyridine-3-carboxamides **1** exhibit fluorescent properties. It was shown that they are fluorescent in the blue region of the spectrum (448–454 nm), with fluorescence quantum yields of up to 0.87.[8]

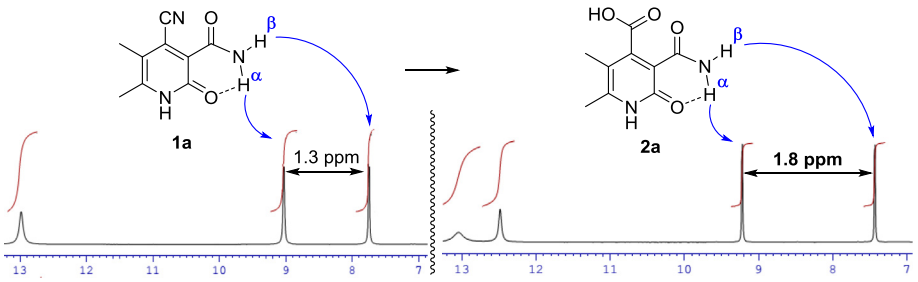


Fig. 1. Spectroscopic changes in the ^{1}H NMR spectra of compounds **1a** and **2a**.