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Catalytic hydration of cyanopyridines using nickel(0)

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ABSTRACT

The homogeneous catalytic hydration of 2-, 3- and 4-cyanopyridines using 0.5 mol% of $[(dippe)Ni(\mu\text{-}H)]_2$ as catalyst precursor was achieved under heating. In the case of 4-cyanopyridine, production of isonicotinamide was observed at temperatures in the range of 80–120 °C. Heating to 180 °C resulted in formation of isonicotinic acid. In the case of 2- and 3-cyanopyridines the quantitative formation of their corresponding amides was achieved at 100 °C. The catalytic hydration of 2,6-dicyanopyridine was also undertaken in this work, in its case resulting in the synthesis of the mixed cyano/amide product, 2-cyanopyridine-6-carboxamide, at short reaction times.

1. Introduction

Nitriles play an important role in laboratory and in industry provided that the products that can be obtained from them exhibit several relevant applications [1]. In organic chemistry the addition of nucleophiles or electrophiles to a –CN bond is a way to form new C–C, C–N, C–O and C–S bonds [2]. The nitrile hydration reaction involves the nucleophilic addition of OH^- moieties to the CN carbon and the electrophilic addition of H^+ to the nitrogen atom in order to produce amides [3]. Under certain conditions, these may undergo subsequent hydrolysis to the corresponding carboxylic acid and ammonia in the case of primary amides, or alternatively to the NR′R″ amine (R′, R″ = H, alkyl or aryl) if the hydrolysis reaction is to take place over *N*-substituted amides. When undergone selectively, hydrolysis reactions may also yield important by-products for which industrial applications are also known and this indeed the case for amino acids [4]. Usually however, the selective preparation of amides is preferred for most industrial processes and this is exemplified by the synthesis of acrylamide from acrylonitrile [5] or the preparation of nicotinamide from 3-cyanopyridine (3-Cypy) [6].

Among the cyclic heterocyclic nitriles, cyanopyridines (CyPys) are usually the preferred substrates for the catalytic hydration reaction due to their small steric hindrance and overall greater reactivity [7]. To the best of our knowledge, the catalytic hydration of these substrates has been investigated to some extent using homogeneous [8–11] and heterogeneous transition-metal based catalysts [6,12] as well as enzymes [13], yet the ultimate applicability of these catalysts remains uncertain.

In the past years our group has intensively studied the chemistry of nickel compounds with a rigid backbone described by the general formula [(P–P)Ni(η^2-*N*,*C*-R)] (P–P = chelating alkyl diphosphine), that exhibit a η^2-coordinated aryl-, heteroaryl- or alkyl-nitrile [14]. These were probed to be active catalysts for the hydration of benzo (BN) and acetonitrile (AN) [14c] and more recently also, for the hydration of benzo- [14b] and alkyl-dinitriles [14a]. Herein, we report on the catalytic hydration of the 2-, 3- and 4-Cypys.

2. Results and discussion

2.1. Catalytic hydration of CyPys

The catalytic hydration of 2-, 3- and 4-Cyp was achieved under heating using 0.5 mol percent (mol%) of the nickel(I) compound, $[(dippe)Ni(\mu\text{-}H)]_2$ (**1**). Hydrations were performed using water at the 50:1 mol proportion of water to nitrile. Table 1 summarizes the results that were obtained with the three substrates in the range of 80 to 180 °C.

The results in Table 1 suggest that the hydration reactions are affected by the temperature at which the processes are performed as well as by the relative position of the nitrile in the corresponding Cypy. In the case of 4-Cypy, hydration at 180 °C resulted in

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Table 1
Catalytic hydration of CyPys using nickel(0).

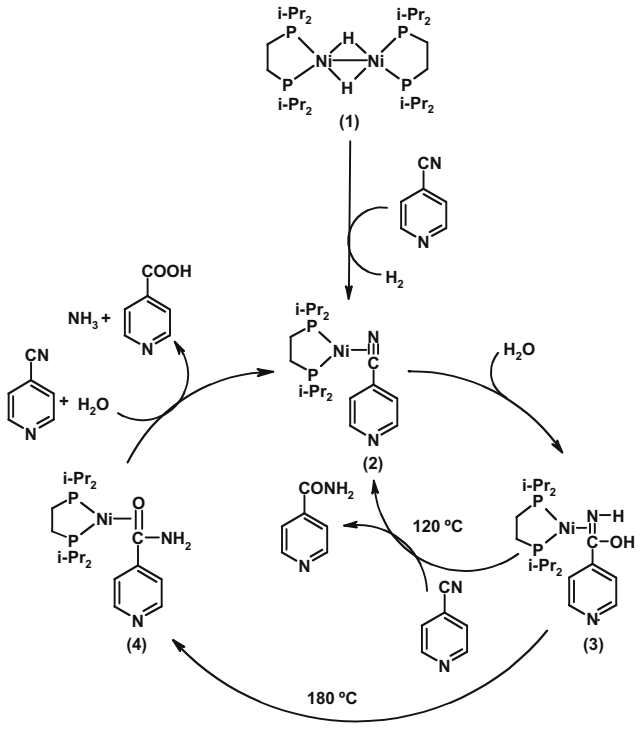
Entry	Substrate	T (°C)	Product	Yield (%)	TON[a]	TOF (TON/h)
1	4-Cypy	80	isonicotinamide	75	150	2.08
2	4-Cypy	100	isonicotinamide	80	160	2.22
3	4-Cypy	120	isonicotinamide	81	163	2.26
4[b]	4-Cypy	180	isonicotinic acid	74	149	2.06
5	3-Cypy	100	nicotinamide	88	177	2.45
6	2-Cypy	100	picolinamide	87	174	2.41

All entries in this table correspond to 72 h heating.
[a] Turnover numbers are calculated with respect to the amount of nickel(I) catalyst precursor.
[b] Formation of ammonia was confirmed in this experiment as a result of hydrolysis of isonicotinamide.

formation of isonicotinic acid and ammonia (entry 4) whereas heating to lower temperatures (80–120 °C, entries 1–3) yielded isonicotinamide, only. The catalytic activity increased slightly with a greater temperature, although heating to 180 °C changed the selectivity. In the case of 2- and 3-Cypy (entries 5 and 6) the quantitative formation of their corresponding amides (nicotinamide and picolinamide) was also achieved at 100 °C.

2.2. Mechanisms for hydration of CyPys

Similarly to previous results published by our group concerning the catalytic hydration of mono and dinitriles, the catalytic hydrations of Cypys are thought occur through nickel(0) intermediates that exhibit a η^2-coordination of a –CN bond to a [(dippe)Ni^0] moiety [14a–c]. Scheme 1 illustrates this proposal in the case of 4-Cypy, in which [(dippe)Ni(η^2-*N*,*C*-{4-py})] (**2**) is formed *in situ*. The synthesis and complete characterization of this compound has already been reported by our group as part of a series of stoichiometric reactions that preceded the use of these compounds for the catalytic hydration of nitriles [14e]. The addition of a water molecule to **2** presumably leads to an *N*-protonated hydroxy imine intermediate, [(dippe)Ni(η^2-*N*(H)=*C*(OH)-{4-py})] (**3**), within the catalytic cycle. The latter compound can follow two pathways depending on the particular temperature that is used for the process, the first one of which is proposed as the productive tautomerization of the coordinated iminic moiety that yields a free amide and regenerates the nickel(0) catalyst. We propose this route to occur at temperatures ⩽120 °C, in accordance to results in Table 1. Analogous pathways are proposed for the hydrations of 2-Cypy and 3-Cypy by analogy. Heating the system with 4-Cypy over 120 °C resulted in hydrolysis of isonicotinamide and thus, coordination of the carbonyl from this amide to [(dippe)Ni] is proposed as the second possible outcome of catalysis that in such case may allow a η^2-*O*,*C* intermediate, [(dippe)Ni(η^2-*O*,*C*(NH$_2$)-{4-py})] (**4**), to be formed also preceding the formation of the free carboxylic acid.



Scheme 1. Mechanistic proposal for the catalytic hydration of 4-Cypy at 120 and 180 °C, using nickel(0).

2.3. Reactivity of CyPys in hydration reactions at shorter time (12 h)

The catalytic hydrations of 2-, 3- and 4-Cypy were assessed at 12 h in an attempt at achieving optimized conditions with respect to the initial 72 h time that was used for all experiments in Table 1. Experiments were undertaken at 100 °C using 0.5 mol% of **1**. The results obtained showed an increasing trend in the formation the corresponding pyridine carboxamides as the –CN substituent occupied a farther position with respect to the nitrogen atom of the particular pyridine ring, 2-Cypy (38%) < 3-Cypy (63%) < 4-Cypy (75%) (see Fig. 1).

Initially, we expected 2- and 4-Cyp to be the more reactive substrates on the basis of the more favourable nucleophilic substitution reactions that may be effected at these positions as a result of the inductive effect of the heteroatom [15] and thus, we predicted 3-Cypy to exhibit the lowest conversion within the series. The fact that hydration of 3-Cypy was favoured over 2-Cypy after 12 h heating suggests that a certain kinetic difference in reactivity between these two may operate during the process at short reac-

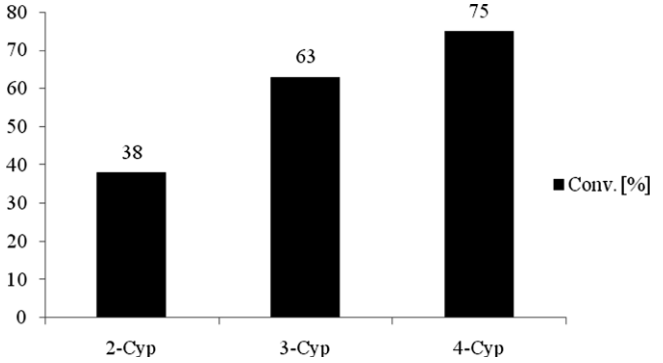


Fig. 1. Catalytic hydration of CyPys at 100 °C, for a period of 12 h using 0.5 mol% of **1**.

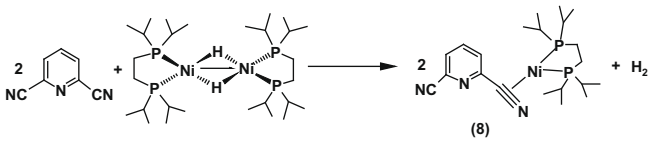
tion times. Alternatively, the hydrolysis product of 2-Cypy may be chelating to nickel and thus slowing down reactivity. The latter however is overcome by making use of a longer period of time as indeed, heating the systems to 100 °C for 72 h showed no significant difference in conversion with any of the three substrates, according to the results already shown in Table 1.

2.4. Catalytic hydration of 2,6-diCypy

The catalytic hydration of 2,6-diCypy was undertaken using 0.5 mol% of **1** at 100 °C. The results are showed in Table 2.

The results show that formation of 2-cyanopyridine-6-carboxamide or 2,6-pyridinedicarboxamide favours one product over the other when undergoing hydration at different reaction times (6–120 h). At shorter reaction times (6–36 h) production of the rare mixed cyano/amide compound takes place preferentially. When compared to the previous work using benzodinitriles, hydration of isophthalonitrile, which is similar to 2,6-diCypy, yielded the mixed product, 1,3-cyanobenzamide, at 120 °C after 72 h [14b]. Almost complete conversion to 2,6-pyridinedicarboxamide was achieved after 72 h (entries d and e). To the best of our knowledge, selective hydration of 2,6-diCypy towards 2-cyanopyridine-6-carboxamide and its higher by-products, 2,6-pyridinedicarboxamide and 2,6-pyridinedicarboxylic acid has only been achieved by an enzymatic route using nitrile hydratase/amidase from *Rhodococcus erythropolis* [16].

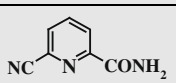
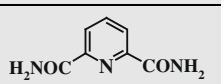
With the aim of obtaining additional information concerning coordination of 2,6-diCypy to [(dippe)Ni] that could be comparable to existing data over CyPys mentioned above, a stoichiometric reaction of this substrate with compound **1** was examined. Eq. (1) illustrates the reaction that took place at room temperature in benzene-d_6.



(1)

Examination of the corresponding $^{31}P\{^1H\}$ NMR spectrum of the reaction mixture confirmed the presence of two slightly broadened doublets centered at 79.2 and 65.8 ppm with ^2J(P,P) coupling constants of 62 Hz. The magnitude of the coupling constant is consistent with previous data for nickel(0) compounds that exhibit η^2-coordination of a CN bond to the metal center [14]. As such, we have assigned the doublets in the spectrum to the two asymmetric phosphorus environments in the compound, [(dippe)Ni(η^2-*N*,*C*-{2,6-$(CN)_2$-pyridine})], which was observed to be stable at room temperature and in deoxygenated solution for a period of 16 h. Evolution of this compound to the C–CN oxidative addition derivative, [(dippe)Ni(CN)(6-Cypy)] (**9**), was observed on standing after this time by the gradual apparition of two new doublets in the same spectrum, centered at δ 79.9 and 73.1 and displaying ^2J(P,P) coupling constants of 27 Hz. The magnitude of the latter coupling constant is also consistent with previous data for analogous compounds [14].

Table 2
Catalytic hydration of 2,6-diCypy using 0.5 mol% nickel(0) at 100 °C.

Entry	*t* (h)	Isolated products (%)	
			
		2-cyanopyridine-6-carboxamide	2,6-pyridinedicarboxamide
A	6	68	30
B	12	37	48
C	36	11	55
D	72	9	65
E	120	6	82

3. Conclusions

The catalytic hydrations of 2-, 3- and 4-cyanopyridine and 2,6-dicyanopyridine were achieved under reasonably mild conditions and in good yields using $[(dippe)Ni(\mu\text{-}H)]_2$ as catalyst precursor. The potential use of this catalyst in organic synthesis is envisioned from these results. In the case of 2,6-dicyanopyridine its hydration can be tuned to yield either the mixed cyano/amide product, 2-cyanopyridine-6-carboxamide or the fully hydrated one, 2,6-pyridinedicarboxamide, at different reaction times. The current work confirms that nickel(0) catalysts used for the nitrile hydration reaction are robust and remain active even after prolongued periods of heating time. Currently we work on further extending this chemistry to other heterocyclic nitriles.

4. Experimental

4.1. General considerations

The synthesis of the catalyst precursor, $[(dippe)Ni(\mu\text{-}H)]_2$ (**1**) was performed under argon atmosphere in an MBraun glovebox (<1 ppm H_2O and O_2) according to the reported procedure [17]. All argon used in this work was supplied in high purity grade (99.998%) by Praxair. Deuterated solvents for NMR experiments were purchased from Cambridge Isotope Laboratories and were stored over 3 Å molecular sieves in the glovebox for at least 24 h before their use. All regular solvents were purchased from J.T. Baker in reagent grade. THF and hexanes were dried and distilled from sodium/benzophenone ketyl, according to standard procedures [18]. Ethanol was used for recrystallisation of hydration products and was used as received. All substrates for this work, 2-Cypy (99%), 3-Cypy (98%), 4-Cypy (98%) and 2,6-diCypy (97%) were purchased from Aldrich and were used without any additional purification. All the other chemicals, filter aids and chromatographic materials were reagent grade and were used as received. Catalysis experiments were performed either in a 300 mL stainless steel vessel, Parr Series 4560 Bench Top Mini Reactor, or under reflux using a Schlenk line. All the vessels or Schlenk flasks that were used for catalysis experiments were charged inside the glovebox. The water used for all hydrations was distilled and degassed following the standard freeze–pump–thaw procedure. Experiments for catalysis were performed by *in situ* preparation of the respective nickel(0) catalyst. The total amount of nitrile used was calculated on the basis of 0.5 mol% of the nickel(I) catalyst precursor **1** versus the total mol amount of substrate**.** NMR spectra of complexes and products were recorded at ambient temperature on a 300 MHz Varian Unity spectrometer. ^1H and $^{13}C\{^1H\}$ NMR spectra of hydration products were obtained using concentrated solutions of these dissolved in DMSO-d_6. ^1H and $^{31}P\{^1H\}$ NMR spectra of complex **8** was obtained using a concentrated solution of the nickel compound prepared *in situ*, in an inert solvent such as benzene-d_6. The sample was handled under argon, using a thin wall −0.38 mm WILMAD NMR tube equipped with a J. Young valve. ^1H and $^{13}C\{^1H\}$ chemical shifts (δ, ppm) are reported relative to either the residual proton or deuterated-carbon resonances of the solvent, respectively. $^{31}P\{^1H\}$ NMR spectra were recorded relative to external 85% H_3PO_4. All hydration products were purified by recrystalization and column chromatography and their characterization was made by direct comparison of the

^{1}H and ^{13}C{^{1}H} NMR spectra to expressly prepared standards and available literature [19]. Melting points of the products were obtained using an Electrothermal Digital Melting Point Apparatus, also compared to a standard whenever possible. Calculated ^{1}H and ^{13}C{^{1}H} NMR spectra were obtained using the ACD/HNMR and ACD/CNMR Predictors [20]. Elemental analyses and mass spectra (MS-EI$^+$) of the purified organic products were carried out by USAI-UNAM using an EA 1108 FISONS Instruments analyzer and a Jeol SX-102A mass spectrometer, respectively. Infrared spectra were obtained using a Perkin–Elmer 1600 FT spectrophotometer. All turnover numbers (TON) for the catalytic hydrations in this work were calculated as moles of isolated product over moles of nickel(I) catalyst precursor. Turnover frequencies (TOF) were calculated as TON over reaction time.

4.2. Reaction of 1 with 2,6-diCypy, preparation of [(dippe)Ni(η^2-N,C-{2,6-(CN)$_2$-py})] (8)

To a dark red benzene-d_6 solution (1 mL) of **1** (0.020 g, 0.030 mmol) was added 2 equiv. of 2,6-diCypy (0.008 g, 0.062 mmol), at room temperature. After mixing, extensive formation of $H_{2(g)}$ was observed; all of which was vented away into the glovebox. The mixture was left to stir for 1 h, after which time it was examined by NMR. After of 16 h stirring at room temperature, complex **8** evolved into its respective nickel(II) derivative [(dippe)Ni)(CN)(6-CN-py)] (**9**). NMR spectra of **8** in benzene-d_6 solution: ^{1}H, δ 7.82 (*s*, 1H, CH), 6.54 (*s*, 2H, CH), 2.2–1.9 (*m*, 4H, CH), 1.85–1.6 (*m*, 4H, CH_2), 1.2–0.92 (*m*, 24H, CH_3). ^{31}P{^{1}H}, δ 79.2 (*d*, $^2J_{P-P}$ = 62 Hz), 65.8 (*d*, $^2J_{P-P}$ = 63 Hz). NMR spectra of **9** in benzene-d_6: ^{1}H, δ 6.3–6.1 (*m*, 3H, CH), 2.2–1.9 (*m*, 4H, CH), 1.85–1.6 (*m*, 4H, CH_2), 1.2–0.92 (*m*, 24H, CH_3). ^{13}C{^{1}H}, δ 139.1 (*d*, J_{C-P} = 7.2 Hz, C), 137.9 (*s*, CH), 135.1 (*s*, coordinated CN), 130.3 (*s*, CH), 122.8 (*s*, CH), 119.8 (*s*, C), 116.3 (*s*, CN), 32.3 (s, CH), 30.5 (s, CH), 25.7–21.8 (*m*, CH_2), 20.1 (*s*, CH_3), 19.2 (*s*, CH_3), 19.6 (*s*, CH_3), 18.9 (*s*, CH_3). ^{31}P{^{1}H}, δ 79.9 (*d*, $^2J_{P-P}$ = 27 Hz), 73.1 (*d*, $^2J_{P-P}$ = 27 Hz).

4.3. Catalysis

4.3.1. Hydration of 4-Cypy at 80 and 100 °C, formation of isonicotinamide

In a glovebox, Schlenk flasks were charged in different runs with **1** (0.035 g, 0.054 mmol), 4-Cypy (1.14 g, 0.010 mol) and water (10 mL, 0.55 mol). The mixtures were heated in a silicon oil bath under argon, connected to an inert-gas/vacuum double manifold, during 72 h. A white solid residue was recovered from the flasks and was recrystallised from hot ethanol using hexanes. Yield of isonicotinamide at 80 °C, after work-up: 75% of white solid (0.99 g, 0.008 mol) with a TON of 150 and a TOF of two cycles per hour. Yield of isonicotinamide at 100 °C, after work-up: 80% of white solid (1 g, 0.0087 mol) with a TON of 160 and a TOF of two cycles per hour. M.p. of isonicotinamide: 155–157 °C. MS-EI$^+$: m/z = 122 (molecular ion). Losses: m/z = 106 (–NH_2), 78 (–$CONH_2$). *Anal.* Calc. for $C_6H_6N_2O_1$ (isonicotinamide): C, 59.0; H, 4.9; N, 22.9. Found: C, 59.2; H, 5.1; N 22.8%. NMR spectra for isonicotinamide in DMSO-d_6: ^{1}H, δ 8.71–8.70 (*d*, 2H, CH), 8.2 (*s*, br, H, NH_2), 7.77–7.75 (*d*, 3H, CH and NH_2). ^{13}C{^{1}H}, δ 166.6 (*carbonyl*), 150.3 (*s*, CH), 141.4 (*s*, C), 121.5 (*s*, CH).

4.3.2. Hydration of 4-Cypy at 120 °C, formation of isonicotinamide

In a glovebox, a reactor vessel was charged with **1** (0.035 g, 0.054 mmol), 4-Cypy (1.14 g, 0.010 mol) and water (10 mL, 0.55 mol). The mixture was heated to 120 °C for 72 h. After this time, heating was stopped and the vessel allowed to cool down to room temperature. A white solid residue was recovered from the reactor vessel and recrystallised from hot ethanol as described above. Yield of isonicotinamide at 120 °C, after work-up: 81% of white solid (1.1 g, 0.0088 mol) with a TON of 163 and a TOF of two cycles per hour.

4.3.3. Hydration of 4-Cypyat 180 °C, formation of isonicotinic acid

A reactor vessel was charged in the glovebox with **1** (0.035 g, 0.054 mmol), 4-Cypy (1.14 g, 0.010 mol) and water (10 mL, 0.55 mol). The mixture was heated to 180 °C under vigorous stirring for 72 h, after which time the reactor vessel was left to cool down. All the ammonia (NH_3) generated in the vessel during the reaction was bubbled into concentrated hydrochloric acid producing NH_4Cl. After complete venting of the gas, the vessel was opened and a white solid residue recovered and subjected to purification. The product was purified by sublimation. Yield of isonicotinic acid, after work-up: 74% white solid (0.995 g, 0.008 mol) with a TON of 149 and a TOF of two cycles per hour. M.p. of isonicotinic acid: 200–250 °C (sublimes). MS-EI$^+$: m/z = 123 (molecular ion). Losses: m/z = 106 (–OH), 78 (–COOH). *Anal.* Calc. for $C_6H_5N_1O_2$ (isonicotinic acid): C, 58.4; H, 4.1; N, 11.3. Found: C, 58.9; H, 4.5; N, 11.2. NMR spectra for isonicotinic acid in DMSO-d_6: ^{1}H, δ 8.77–8.76 (*d*, 2H, CH), 7.82–7.80 (*d*, 2H, CH). ^{13}C{^{1}H}, δ 166.4 (carbonyl), 150.7 (*s*, CH), 138.4 (*s*, C), 122.9 (*s*, CH).

4.3.4. Hydration of 3-Cypy at 100 °C, formation of nicotinamide

A Schlenk flask was charged in the glovebox with **1** (0.035 g, 0.054 mmol), 3-Cypy (1.14 g, 0.010 mol) and water (10 mL, 0.55 mol). The mixture was heated to 100 °C in an oil bath under inert atmosphere, connected to an inert-gas/vacuum double manifold, for 72 h. A white solid residue was progressively formed during this time and recovered from the flask by dissolving it in hot ethanol. The product was recrystallised by dropwise addition of cold hexane. Yield of nicotinamide at 100 °C, after work-up: 88% of white crystals (1.18 g, 0.0096 mol), with a TON of 177 and a TOF of two cycles per hour. M.p. of nicotinamide: 129–131 °C. *Anal.* Calc. for $C_6H_6N_2O_1$ (nicotinamide): C, 59.0; H, 4.9; N, 22.9. Found: C, 59.4; H, 4.9; N, 22.2%. NMR spectra for nicotinamide in DMSO-d_6: ^{1}H, δ 9.0 (*s*, H, CH), 8.69–8.68 (*d*, H, CH), 8.22–8.20 (*m*, br, 2H, CH and NH_2), 7.6. (*s*, br, H, NH_2), 7.6–7.4 (*m*, H, CH). ^{13}C{^{1}H}, δ 166.5 (*carbonyl*), 151.9 (*s*, CH), 148.7 (*s*, CH), 135.1 (*s*, CH), 129.7 (*s*, C), 123.4 (*s*, CH).

4.3.5. Hydration of 2-Cypy at 100 °C, formation of picolinamide

A Schlenk flask was charged in the glovebox with **1** (0.035 g, 0.054 mmol), 2-Cypy (1.14 g, 0.010 mol) and water (10 mL, 0.55 mol). The mixture was heated to 100 °C following the procedure described above, for 72 h. Yield of picolinamide at 100 °C, after work-up: 87% of white solid (1.15 g, 0.0094 mol), with a TON of 174 and a TOF of two cycles per hour. M.p. of picolinamide: 105–108 °C. *Anal.* Calc. for $C_6H_6N_2O_1$ (picolinamide): C, 59.0; H, 4.9; N, 22.9. Found: C, 57.7; H, 5.0; N, 22.1%. NMR spectra for picolinamide in DMSO-d_6: ^{1}H, δ 8.63–8.61 (*m*, H, CH), 8.1 (*br s*, H, NH_2), 8.0–7.9 (*m*, 2H, CH), 7.6. (*s*, br, H, NH_2), 7.6–7.5 (*m*, H, CH). ^{13}C{^{1}H}, δ 166.0 (*carbonyl*), 150.2 (*s*, C), 148.4 (*s*, CH), 137.6 (*s*, CH), 126.4 (*s*, CH), 121.9 (*s*, CH).

4.3.6. Hydration of 2,6-diCypy, formation of 2-cyanopyridine-6-carboxamide and 2,6-pyridinedicarboxamide

Schlenk flasks were charged in separate runs with **1** (0.0024 g, 0.0037 mmol), 2,6-diCypy (0.1 g, 0.774 mmol) and water (10 mL, 0.55 mol), in the glovebox. The mixtures were refluxed at 100 °C under argon atmosphere for different periods of time, being 6, 12, 36, 72 and 120 h. The crude mixtures were purified by column chromatography eluting over silica gel with an 80:20 (v/v) mixture of ethyl acetate and hexane. 2-cyanopyridine-6-carboxamide was eluted as the first fraction; elution with ethanol allowed recovery of 2,6-pyridinedicarboxamide as the second one. The two products were vacuum dried for 4 h. Yield of 2-cyanopyridine-6-carboxam-

ide produced after 6 h, after work-up: 68% of a white crystalline solid (0.0771 g, 0.052 mmol). Yield of 2-cyanopyridine-6-carboxamide produced after 12 h, after work-up: 37% of a white crystalline solid (0.042 g, 0.28 mmol). Yield of 2-cyanopyridine-6-carboxamide produced after 36 h, after work-up: 11% of a white crystalline solid (0.012 g, 0.081 mmol). Yield of 2-cyanopyridine-6-carboxamide produced after 72 h, after work-up: 9% of a white crystalline solid (0.0104 g, 0.068 mmol). Yield of 2-cyanopyridine-6-carboxamide produced after 120 h, after work-up: 6% of a white crystalline solid (0.0064 g, 0.043 mmol). M.p. of 2-cyanopyridine-6-carboxamide: >200 °C (sublimes). NMR spectra for 2-cyanopyridine-6-carboxamide in DMSO-d_6: ^{1}H, δ 8.8–8.2 (*m*, 3H, CH), 7.7 (*s*, br, 2H, NH_2). $^{13}C\{^1H\}$, δ 164.5 (*carbonyl*), 151.8 (*s*, C), 139.7 (*s*, CH), 131.4 (*s*, C), 131.3 (*s*, CH), 125.8 (*s*, CH), 117.1 (*s*, CN). IR (KBr disc, cm^{-1}): 3399 and 3201 (NH_2), 2238 (CN), 1709 (*carbonyl*), 836–450 (Ar). Yield of 2,6-pyridinedicarboxamide produced after 6 h, after work-up: 30% of a white crystalline solid (0.0383 g, 0.023 mmol). Yield of 2,6-pyridinedicarboxamide produced after 12 h, after work-up: 48% of a white crystalline solid (0.060 g, 0.38 mmol). Yield of 2,6-pyridinedicarboxamide produced after 36 h, after work-up: 55% of a white crystalline solid (0.070 g, 0.42 mmol). Yield of 2,6-pyridinedicarboxamide produced after 72 h, after work-up: 65% of a white crystalline solid (0.0829 g, 0.50 mmol). Yield of 2,6-pyridinedicarboxamide produced after 120 h, after work-up: 82% of a white crystalline solid (0.1051 g, 0.63 mmol). M.p. of 2,6-pyridinedicarboxamide: >250 °C (sublimes). *Anal.* Calc. for $C_7H_7N_3O_2$ (2,6-pyridinedicarboxamide): C, 50.9; H, 4.2; N, 25.4. Found: C, 50.2; H, 4.3; N, 24.6. NMR spectra for 2,6-pyridinedicarboxamide in DMSO-d_6: ^{1}H, δ 8.8 (*br s*, H, NH_2), 8.2–8.1 (*m*, 3H, CH), 7.7 (*br s*, H, NH_2). $^{13}C\{^1H\}$, δ 165.6 (*carbonyl*), 149.1 (*s*, C), 139.4 (*s*, CH), 124.4 (*s*, CH). IR (KBr disc, cm^{-1}): 3420 and 3244 (NH_2), 1686 (*carbonyl*), 843–548 (Ar).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ica.2009.07.002.

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