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A highly efficient Pd–C catalytic hydrogenation of pyridine nucleus under mild conditions

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ABSTRACT

A synergistic Pd–C catalytic hydrogenation of 4-pyridinecarboxamides straightforward to 4-piperidinecarboxamide hydrochlorides was developed in the presence of $ClCH_2CHCl_2$. It provided a novel strategy for highly efficient hydrogenation of pyridine nuclear by using low-cost Pd–C catalyst under mild conditions.

1. Introduction

In recent years, piperidinecarboxamides have been gaining increasing importance because they have been recognized as key pharmacophores in drug discoveries. As shown in Chart 1, the clinical candidate TAK 220 (**1**) is a small-molecule CCR5 antagonist, part of the new class of anti-HIV-1 entry inhibitors.[1] BMS-387032 (**2**), a novel cyclin-dependent kinase 2 inhibitor, is currently in phase I clinical trials for anticancer therapy.[2] Elarofiban (**3**) has advanced into phase II clinical trials as a platelet GP IIb/IIIa antagonist with potential to become an oral antithrombotic drug.[3]

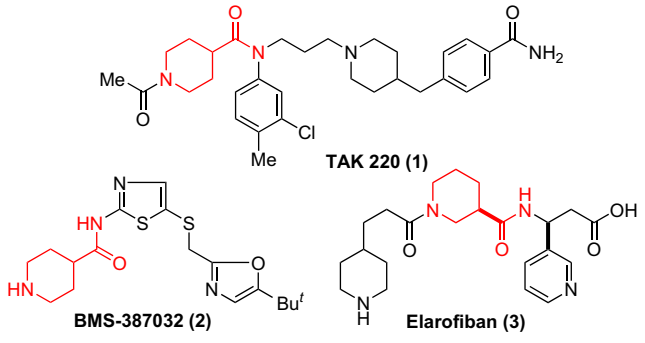
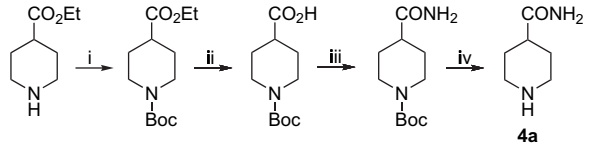


Chart 1.

In our recent project on chemical biology, a variety of 4-piperidinecarboxamides (**4**) were designed as key synthetic precursors. The investigation showed that they were mainly derived from 4-piperidinecarboxylates by a standard four-step route. As shown in Scheme 1, this route associated with two extra steps for the protection and deprotection of the amine group,[2,3a,4] even for the preparation of the most simple 4-piperidinecarboxamide (**4a**).[4c] Although many 4-pyridinecarboxamides (**5**) are commercially available products and the catalytic hydrogenation is characterized by economy, convenience, and environment-friendship, the preparation of **4** by catalytic hydrogenation of **5** in laboratory scale under mild conditions was an inefficient process, even though the expensive Pt[5] or Rh[6] catalysts were employed.



Scheme 1. Conditions: (i) Boc_2O, Et_3N; (ii) aq NaOH; (iii) $ClCO_2{}^iBu$, *N*-methylmorpholine, aq NH_3; (iv) 4.0 M HCl–EtOAc.

This problem clearly arose from the fact that the catalyst is deactivated by the coordination of the metal with the ring nitrogen of pyridine or piperidine.[7] It is well known that the formation of pyridine salt can completely block the coordination ability of the

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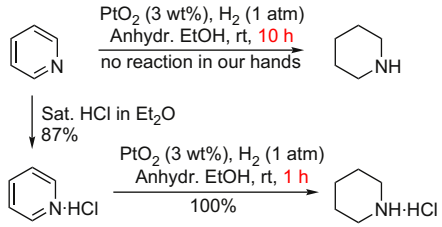
nitrogen and further polarize the pyridine nucleus. As shown in Scheme 2, Adams in 1928 had proved that the pre-formed pyridine hydrochloride can be hydrogenated directly into piperidine hydrochloride under extremely mild conditions.[8,9] Unfortunately, 4-pyridinecarboxamide hydrochlorides (**5**·HCl) were rarely used for this purpose. When we tried to prepare **5**·HCl by treatment of **5** with saturated solution of HCl in dry Et_2O, we found that it seriously suffered from the poor yields caused by the highly hygroscopic properties of those salts.

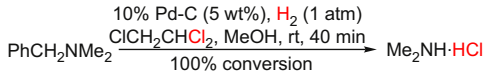


Scheme 2.

Herein, we report a novel synergistic Pd–C catalytic hydrogenation of **5** straightforward to **4**·HCl, in which the key intermediates **5**·HCl were formed stoichiometrically in situ during the hydrogenation. By using this method, a series of desired products **4**·HCl were prepared efficiently from **5** under mild conditions in a single flask.

2. Results and discussion

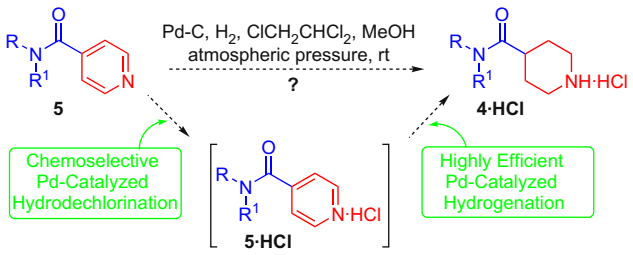
Pd–C is the most often used palladium-based catalyst with advantages of commercial availability, low cost, and easy regeneration. Comparing with Pt and Rh catalysts, it was a low active catalyst for the hydrogenation of pyridine nucleus and was rarely used for this purpose.[10] However, it is the most preferred catalyst of the hydrodechlorination, by which the C–Cl bonds in organochlorides can be cleaved to release HCl.[11] In practice, a base (inorganic bases or tertiary amines) was employed as both promoter and HCl acceptor in this conversion.[12] In our recent study,[13] a novel Pd–C catalytic hydrodechlorination of $ClCH_2CHCl_2$ was developed under mild conditions in the presence of a tertiary benzylamine. As shown in Scheme 3, it is an amine-controlled highly chemoselective process and an exactly equimolar amount of HCl was produced based on the amine.[13]



Scheme 3.

Thus, an in situ formation of **5**·HCl can be expected when **5** is used as a base in the Pd–C catalytic hydrodechlorination of $ClCH_2CHCl_2$, by which the pyridine nucleus in **5**·HCl is polarized to be more liable to catalytic hydrogenation. Therefore, we may further expect that a Pd–C catalytic hydrogenation of **5**·HCl will proceed to directly yield **4**·HCl in a single flask (Scheme 4).

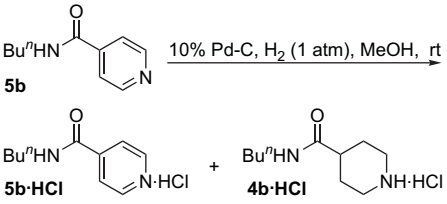
To prove our hypothesis, *N*-butyl-4-pyridinecarboxamide (**5b**) was used as a model substrate for the control experiments. As shown in Table 1, by using 40 wt % of Pd–C catalyst under the conventional conditions, **5b** was hydrogenated for 15 h to give *N*-butyl-4-piperidinecarboxamide (**4b**) in 84% selectivity as a mixture (entry 1). When the loading of Pd–C catalyst was reduced to 10 wt %, the same hydrogenation stopped after 11 h to give **4b** in 34% selectivity (entry 2). By addition of 1 equiv of aq HCl (37% solution), a minor improvement was observed (entry 3). It was not surprised that **5b** was quantitatively converted into **5b**·HCl when



Scheme 4.

the hydrogenation proceeded in a saturated HCl solution of MeOH because Pd–C catalyst was completely poisoned within 3 min (entry 4). To our delight, the desired product **4b**·HCl was obtained as a single product in 99% isolated yield in the presence of $ClCH_2CHCl_2$ (entry 5). This result coincided with that obtained by using **5b**·HCl as a substrate (entry 6).

Table 1
A highly efficient hydrogenation of **5b** into **4b**·HCl

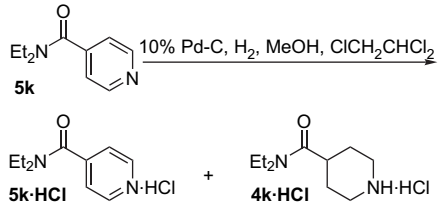


Entry	Substrate	Pd–C [wt %]	Additive [equiv]	Time [h]	Ratio of products[a]	Yield[b] [%]
1	**5b**	40	None	15	**5b**:**4b**=16:84	98
2	**5b**	10	None	11	**5b**:**4b**=66:34	97
3	**5b**	10	37% aq HCl (1.0)	11	**5b**·HCl:**4b**·HCl=60:40	96
4	**5b**	10	Satd HCl in MeOH	15	**5b**·HCl:**4b**·HCl=100:0	99
5	**5b**	10	$ClCH_2CHCl_2$ (1.2)	10	**5b**·HCl:**4b**·HCl=0:100	99
6	**5b**·HCl	10	None	9.5	**5b**·HCl:**4b**·HCl=0:100	99

[a] The ratio was determined by ^{1}H NMR.
[b] Isolated yield was obtained.

Thus, a novel synergistic Pd–C catalyzed highly efficient hydrogenation of **5b** into **4b**·HCl was achieved at room temperature and atmospheric pressure. To the best of our knowledge, this is the first procedure for highly efficient hydrogenation of pyridine nucleus by Pd–C catalyst under mild conditions. Since **4b**·HCl was obtained as a crystal product, the work-up procedure was as simple as a filtration.

Table 2
A highly efficient hydrogenation of **5k** into **4k**·HCl



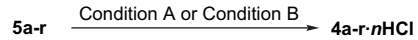
Entry	Pd–C [wt %]	Pressure	Temperature [°C]	Time [h]	Product ratio[a] **5k**·HCl:**4K**·HCl [%]	Yield[b]
1	10	Atmospheric	25	13	16:84	96
2	10	40 psi	25	16	4:96	97
3	10	50 psi	25	15	00:100	99
4	10	Atmospheric	35	23	00:100	99
5	10	Atmospheric	25	10	00:100	99
6	25	Atmospheric	25	17	00:100	99
7	50	Atmospheric	45	6	00:100	99

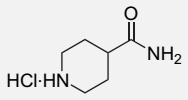
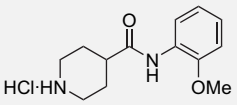
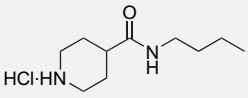
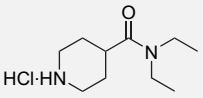
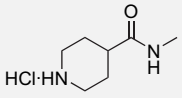
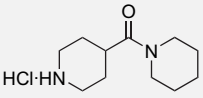
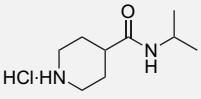
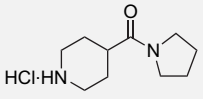
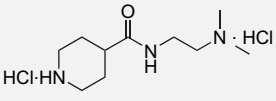
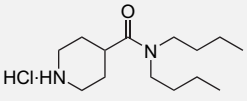
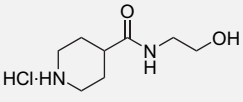
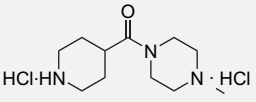
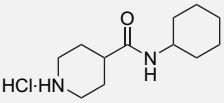
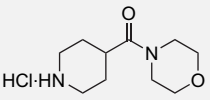
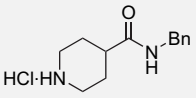
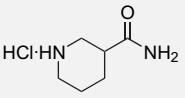
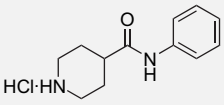
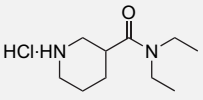
[a] The ratio was determined by ^{1}H NMR.
[b] Isolated yield was obtained.

However, when *N*,*N*-diethylpyridinecarboxamide (**5k**) was used as a substrate under the similar conditions, **4k**·HCl was obtained as a mixture in 84% selectivity (Table 2, entry 1). This result may be caused by the fact that the electron-withdrawing ability of amide group was decreased by the secondary amine. Thus, the hydrogenation was optimized by varying the pressure, temperature, or catalyst loading. As shown in Table 2, **4k**·HCl was obtained as a single product in 99% yield by simply elevating the pressure (50 psi, entry 3) or the temperature (35 °C, entry 4). However, for the consideration of convenient performances in laboratory conditions, we preferred to increase the catalyst loading. Thus, a very satisfactory result was achieved at room temperature and atmospheric pressure by using 25 wt % of Pd–C catalyst (entry 6).

To determine the scope and generality of this novel method, different pyridinecarboxamides (**5a**–**r**) were tested with 25 wt % of Pd–C catalyst under atmospheric pressure (Condition A) or with 10 wt % of Pd–C catalyst under 50 psi hydrogen pressure (Condition B). As shown in Table 3, **5a**–**r** were hydrogenated into the corresponding piperidinecarboxamide hydrochlorides (**4a**–**r**·*n*HCl) in practically quantitative yields (entries 1–18). It was clearly observed that *N*-monosubstituted amides (**5a**–**j**) (entries 1–10) showed much higher reactivity than *N*,*N*-disubstituted amides (**5k**–**p**) (entries 11–16). It was noteworthy that the hydroxyl group stayed intact (entry 6) and the *N*-benzyl amide tolerated the conditions (entry 8). When the products with two amino groups, the corresponding dihydrochlorides (**4e**·**2**HCl and **4o**·**2**HCl) were formed automatically by

Table 3
Synergistic catalytic hydrogenation of **5a**–**r** to **4a**–**r**·*n*HCl[a]



Entry	Product [**4**·*n*HCl]	Time[b] [h]	Yield[c] [%]	Entry	Product [**4**·*n*HCl]	Time[b] [h]	Yield[c] [%]
1	 **(4a·HCl)**	11(10)	98(98)	10	 **(4j·HCl)**	13(14)	99(98)
2	 **(4b·HCl)**	5(4)	99(98)	11	 **(4k·HCl)**	17(15)	96(96)
3	 **(4c·HCl)**	8(7)	99(98)	12	 **(4l·HCl)**	16(14)	99(98)
4	 **(4d·HCl)**	7(10)	96(96)	13	 **(4m·HCl)**	16(14)	98(98)
5	 **(4e·2HCl)**	12(10)	99(99)	14	 **(4n·HCl)**	17(22)	99(97)
6	 **(4f·HCl)**	8(7)	98(97)	15	 **(4o·2HCl)**	35(26)	99(98)
7	 **(4g·HCl)**	9(12)	97(97)	16	 **(4p·HCl)**	20(18)	96(96)
8	 **(4h·HCl)**	9(7)	98(95)	17	 **(4q·HCl)**	21(19)	95(96)
9	 **(4i·HCl)**	5(6)	98(97)	18	 **(4r·HCl)**	46(40)	99(98)

[a] Condition A: 10% Pd–C (25 wt %), H_2 (1 atm), $ClCH_2CHCl_2$ (1.2 equiv) in MeOH at room temperature. Condition B: 10% Pd–C (10 wt %), H_2 (50 psi), $ClCH_2CHCl_2$ (1.2 equiv) in MeOH at room temperature.
[b] The number in the parenthesis is for Condition B.
[c] The isolated yield was obtained.

using double amount of $ClCH_2CHCl_2$ (entries 5 and 15). Two examples of 3-pyridinecarboxamides (**5q**–**r**) were also tested and they worked well but with longer reaction time in comparison with their 4-substituted counterparts (entries 17 and 18). Unfortunately, 2-pyridinecarboxamide did not undergo a hydrogenation under our conditions. Finally, the hydrogenation of the parent compound pyridine was tested under the Condition A. We observed that there was no absorption of hydrogen in the absence of $ClCH_2CHCl_2$, while 96% isolated yield of piperidine hydrochloride was obtained in the presence of $ClCH_2CHCl_2$ in 23 h. These results further indicated that $ClCH_2CHCl_2$ is essential for this novel hydrogenation and the electron-withdrawing group substituted on the pyridine ring benefited rate of the hydrogenation.

3. Conclusions

In conclusion, a highly efficient catalytic hydrogenation of pyridinecarboxamides (**5**) to piperidinecarboxamide hydrochlorides (**4**·HCl) was developed. This novel method in fact is a synergistic catalytic process, in which the initial Pd–C catalytic hydrodechlorination of $ClCH_2CHCl_2$ was promoted by pyridinecarboxamide (**5**) to chemoselectively release HCl. Then, pyridinecarboxamide as an HCl acceptor captured HCl molecule to form the corresponding hydrochloride (**5**·HCl), by which the coordination ability of nitrogen in pyridine ring was blocked and the pyridine nucleus was polarized. Finally, pyridinecarboxamide hydrochloride (**5**·HCl) was hydrogenated to the corresponding piperidinecarboxamide hydrochloride (**4**·HCl). It provided a novel strategy for highly efficient hydrogenation of pyridine nucleus by Pd–C catalyst under mild conditions. Since the key intermediate **5**·HCl and the target product **4**·HCl were formed in situ during the hydrogenation in a single flask, the method proceeded with extremely convenient performance and work-up procedures.

4. Experimental section

4.1. General

*4.1.1. A typical procedure for the preparation of N-butyl-4-piperidinecarboxamide hydrochloride (**4b**·HCl).* The suspension of *N*-butyl-4-pyridinecarboxamide (**5b**, 178 mg, 1.0 mmol), 10% Pd–C (44.5 mg, 25 wt%), and $ClCH_2CHCl_2$ (160 mg, 1.2 mmol) in MeOH (30 mL) was hydrogenated (on an atmospheric pressure hydrogenator) at room temperature until the absorption of hydrogen ceased (5 h). After the Pd–C catalyst was filtered off, solvent was removed on a rotavapor. The residue was diluted with diethyl ether (10 mL) and **4b**·HCl (220 mg, 99%) was collected as a white crystal by filtration. Usually, the product was pure enough for any analytical purposes.

It had mp 106–108 °C (MeOH–Et_2O); IR: ν 3353, 3180, 2937, 1666 cm^{-1}; ^1H NMR: δ 3.44–3.39 (m, 2H), 3.12–3.07 (m, 2H), 3.04–2.99 (m, 2H), 2.59–2.50 (m, 1H), 1.99–1.93 (2H), 1.87–1.72 (m, 2H), 1.42–1.37 (m, 2H), 1.26–1.21 (m, 2H), 0.80 (t, 3H, J=7.22); ^{13}C NMR: δ 175.9, 43.2 (2C), 40.0, 39.1, 30.6, 25.2 (2C), 19.5, 13.2; MS m/z (%): 84 (100); calcd for $C_{10}H_{21}ClN_2O$: C, 54.41; H, 9.59; N, 12.69; found: C, 54.28; H, 9.67; N, 12.51.

The similar procedure was used to convert the substrates **5a**–**r** efficiently to the corresponding products **4a**–**r**·*n*HCl.

Acknowledgements

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Supplementary data

Experimental procedures and full spectroscopic data for **4a**–**r**·*n*HCl are given in the Supplementary data. Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2009.08.011.

References and notes

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