Continuous-Flow Hydrogenation of 4-Phenylpyridine to 4-Phenylpiperidine with Integrated Product Isolation Using a CO₂ Switchable System

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Received: 07 April 2017; accepted: 22 April 2017

A process comprising a continuous-flow hydrogenation reaction integrated with selective water–organic solvent biphasic extraction using CO₂ as molecular switch to control partitioning was devised for the synthesis of arylpiperidines from arylpyridines. The selective hydrogenation of 4-phenylpyridine using heterogeneous carbon-supported metal catalysts was chosen as model reaction. A design-of-experiment approach was used for the identification of suitable reaction conditions under continuous-flow operation. A maximum selectivity for 4-phenylpiperidine of 96% was achieved at 87% conversion suppressing the deep hydrogenation to 4-cyclohexylpiperidine almost completely ($\leq 5\%$). The higher basicity of piperidines over pyridines was exploited for selective and reversible protonation of the product upon pressurization with CO₂ separating it quantitatively from the remaining starting material in a water–EtOAc biphasic system. This concept enabled a fully integrated and a salt-free synthetic process using a standard Pd/C catalyst for the hydrogenation coupled with the CO₂-triggered isolation of the desired product 4-phenylpiperidine in 81% yield and 98% purity.

Keywords: Continuous flow catalysis, selective hydrogenation of pyridine in the presence of a phenyl substituent, carbon dioxide as molecular switch, aqueous biphasic selective isolation of amines triggered by carbon dioxide, reversible formation of piperidium bicarbonate

1. Introduction

The piperidine group is one of the most common building blocks in natural products, and a number of bioactive compounds and drugs incorporate this 6-membered *N*-heterocycle [1]. Among the several methods affording substituted piperidine derivatives, the most widely used approach involves the hydrogenation of pyridines as easily accessible starting materials [2, 3]. First systematic studies on the catalytic hydrogenation of pyridine were published already in 1928 using PtO₂ (Adam's catalyst) [4]. In the 1960's, the group of Freifelder explored the reactivity of different noble metal catalysts (PtO₂, RuO₂, Rh/C, and Rh/Al₂O₃) focusing on expansion of the functional group tolerance in this reaction [5–10]. A major challenge remained the selective hydrogenation of pyridines in the presence of other aromatic groups and especially phenyl rings. Under harsh conditions (>250 °C and >130 atm), Re₂S₇ can selectively hydrogenate aryl-substituted pyridines to arylpiperidines [11, 12]. Heterogeneous Pt/C [13] and PtO₂ [14–17] were also used to hydrogenate arylpyridines at room temperature, and in all cases, the addition of acids was needed to avoid poisoning [18] of Pt catalysts. In general, Pt catalysts have shown little selectivity and fully hydrogenated cyclohexylpiperidines compounds were obtained, except for the case of sterically encumbered 2-phenylpyridines where 2-phenylpiperidine could be obtained in moderate to good yields of 60–90% [13–17]. Recently, Kappe et al. reported a detailed study on continuous-flow hydrogenation of pyridines using Pt/C or Rh/C and glacial acetic acid as solvent including one example of an aryl-substituted pyridine [19, 20]. The product isolation comprised dilution with CHCl₃, addition of K₂CO₃, filtration of the formed CH₃COOK, and solvent evaporation.

The implementation of sustainable processes is one of the top priorities of pharmaceutical and fine chemicals manufacturers. The use of more benign solvents [21] and the exploitation of transformations with minimal E-factor [22, 23] have been long identified as valuable options for reaching this target, following

the green chemistry principles [24–26]. More recently, the utilization of continuous-flow synthetic approaches with integrated product purification have been recognized as a particularly potent tool for achieving increased material efficiency, constant product specification, and safer handling [27]. Approximately three-fourths of the unit operations used in pharmaceutical companies are dedicated to purification and isolation of the reaction products [25]. The replacement of conventional workup technologies by more efficient and benign separation methodologies with a careful solvent selection [21] will positively impact also the cost-effectiveness of the overall manufacturing process [28].

In this context, the use of CO₂ in green chemical synthesis and processes has emerged as an important strategy [29]. Carbon dioxide offers low environmental risk in industrial processes since it is non-toxic and non-flammable. Most applications of CO₂ up to now exploit the solvent properties of CO₂ at high pressure and temperatures above the critical temperature as extracting agent, e.g., for caffeine and hops aroma, and, more recently, as mobile phase in continuous-flow catalytic processes [30]. Low-pressure (up to 5 bar) gaseous CO₂ can be used as a trigger to reversibly switch solvent properties for synthesis and purification [31, 32], as a pH-controlling agent in aqueous solutions, e.g., to remediate metal contaminated wastewater via precipitation of metal carbonates [33] and also to separate basic amines from less basic compound, e.g., piperidines from pyridines [34]. Such applications do not require any specialized high-pressure equipment as CO₂ is used at nearly ambient conditions.

In this work, we present a selective continuous-flow hydrogenation system combined with a CO₂-switchable biphasic extraction to yield phenylpiperidines starting from phenylpyridines. Several commercially available drugs such as Ritalin[®], Aricept[®], and paroxetine contain piperidine moieties bearing aryl rings, and thus, the development of an integrated process selectively affording phenylpiperidines is of broad interest for the preparation of such derivatives.

2. Results and Discussion

The catalytic hydrogenation of 4-phenylpyridine (4PhPy) (Scheme 1) was chosen as model reaction for this study. The

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Scheme 1. Catalytic hydrogenation of 4-phenylpyridine

hydrogenation of 4PhPy (Scheme 1) in principle can yield two main products, the desired 4-phenylpiperidine (4PhPip) and the side product 4-cyclohexylpyridine (4CyPy). Both compounds can be further hydrogenated to the fully saturated 4-cyclohexylpiperidine (4CyPip). Thus, for the development of an efficient integrated process, it is necessary on the one hand to successfully address this selectivity issue with an effective catalyst using suitable conditions and, on the other hand, to develop an efficient separation procedure allowing for a facile product isolation.

Initial experiments to maximize 4PhPip yield and selectivity were performed in batch reactors. Different supported noble metal catalysts (Pd, Rh, Pt, and Ru) with a 5 wt% loading were investigated using ethyl acetate (EtOAc) as the solvent (Table 1). For all catalysts, carbon was chosen as support due to the promoting effect of carbonaceous materials for pyridine hydrogenation [8]. The Rh catalyst showed the highest activity for 4PhPy hydrogenation, and a conversion of 40% was obtained within 2 h, with selectivities of 85% for 4PhPip, 6% for 4CyPy, and 9% for the fully saturated side product (Table 1, entry 1). After 4 h, the reaction with Rh reached 50% conversion, while the selectivities remained nearly constant (Table 1, entry 2). The Pd catalyst showed a lower activity reaching 29% conversion after 4 h and selectivities of 84% for 4PhPip and 15% of 4CyPy (Table 1, entry 3). It is noteworthy that, prolonging the reaction time to 8 h, the formation of the fully hydrogenated product 4CyPip remained lower than 1% and, even when the reaction time was doubled again to 16 h, still less than 2% of 4CyPip was formed (Supporting Information, Table S3). Pt and Ru showed poor activities in the hydrogenation of 4PhPy as compared to Rh and Pd leading to $\leq 5\%$ conversion after 4 h (Table 1, entries 5 and 7). Additionally, the reaction using 5% Ru/C catalyst showed a significant formation of up to 15% of 4CyPip. The Pt-based catalyst, although being the most selective catalyst towards 4PhPip, showed only 7%

conversion even after a prolonged reaction time of 65 h, indicating a possible catalyst poisoning by the piperidine moiety [18] (Table 1, entry 8). The comparison of all reactions reaching ca. 40% conversion (Table 1, entries 1, 4, and 6) shows that Pd is the most suitable catalyst since it produces negligible quantities of 4CyPip at this stage.

Additionally, several phenylpyridine derivatives substituted with donating and withdrawing groups at the 4-position of the phenyl ring were hydrogenated in batch experiments using 10 wt% Pd/C as catalyst. The presence of substituents at the phenyl group decreased the reaction rates and increased the selectivity for the pyridine ring. The investigated substrates did not show a clear trend between the electronic character of the different substituents and the selectivity of the hydrogenation, but the high selectivity for the hydrogenation of the heteroaromatic moiety was retained in all cases (see Section 3.5 in the Supporting Information for further details).

After having identified a suitable solid catalyst for the selective hydrogenation of the heteroaromatic moiety in phenyl-pyridine derivatives at reasonably high conversion, we focused on devising a facile and clean isolation procedure for 4PhPip from the remaining starting material and small amounts of the side product. Taking advantage of different basicity of pyridines versus piperidines, a purification and isolation procedure based on a liquid–liquid extraction in a CO₂-switchable system was conceived as illustrated in Scheme 2 [35, 36]. The biphasic system comprises an organic solvent containing the product mixture and an aqueous layer. The admission of CO₂ to the system generates H₂CO₃ in the aqueous phase, and this weak acid protonates only the piperidine groups due to the highest basicity of this amine moiety over the pyridine (piperidine $pK_a = 11.12$; pyridine $pK_a = 5.23$) [37]. The formed piperidinium bicarbonate is then extracted into the aqueous phase, whereas the pyridine species remain in the organic phase.

Several selection criteria for the organic phase were defined. The solvent should be chosen from the industrially recommended solvent list [21]; it should be poorly miscible with water, and it should be suitable to be used as solvent already during the hydrogenation reaction. This last criterion allows integration of this procedure directly with the reaction step without the need of solvent replacement, thereby avoiding an additional process step and the use of additional solvent.

Therefore, water immiscible solvents of sufficiently high polarity were investigated for the hydrogenation of 4PhPy in batch using Pd supported on carbon (Pd/C) as the catalyst. 4-Methyl-2-pentanol (MiBC), 2-methyltetrahydrofuran (2-MeTHF), and EtOAc were found to provide suitable reaction media for the hydrogenation of 4PhPy using 10 wt% Pd/C (Table 2). Under the used reaction conditions (0.01 eq. 10 wt% Pd/C, 80 °C, 30 bar H₂), the highest catalytic activity was observed in MiBC,

Table 1. Catalyst screening for the hydrogenation of 4-phenylpyridine^a

Entry	Catalyst	Time (h)	Conv. ^b (%)
				<i>S</i> (4PhPip) ^{b,c} (%)	<i>S</i> (4CyPy) ^{b,c} (%)	<i>S</i> (4CyPip) ^{b,c} (%)
1	5 wt% Rh/C	2	40	85	6	9
2	5 wt% Rh/C	4	50	86	6	8
3	5 wt% Pd/C	4	29	84	15	<1
4	5 wt% Pd/C	8	41	87	12	<1
5	5 wt% Ru/C	4	4	69	19	12
6	5 wt% Ru/C	31	38	70	15	15
7	5 wt% Pt/C	4	5	100	0	0
8	5 wt% Pt/C	65	7	100	0	0

^aConditions: 0.5 M 4PhPy in EtOAc, 0.01 eq. cat (related to moles of metal), 80 °C, 30 bar H₂.

^bDetermined via ¹H-NMR.

^c*S* = selectivity.

Scheme 2. Principle for the separation of the piperidine product from the pyridine starting material and side product in a biphasic system using CO₂ as molecular switch **Table 2.** Solvent screening in batch hydrogenation of 4-phenylpyridine using 10 wt% Pd/C^a

Entry	Solvent	Time (h)	Conv. (%)	<i>S</i> (4PhPip) ^{b,c} (%)	<i>S</i> (4CyPy) ^{b,c} (%)	<i>S</i> (4CyPip) ^{b,c} (%)
1	EtOAc	24	49	90	9	<1
2	MiBC	10	48	85	15	Traces
3	MiBC	24	95	75	22	3
4	2-MeTHF	16	54	84	14	2
5	2-MeTHF	24	67	84	14	2

^aConditions: 0.5 M 4PhPy, 0.01 eq. 10 wt% Pd/C, 80 °C, 30 bar H₂.^bDetermined via ¹H-NMR.^c*S* = selectivity.

followed by 2-MeTHF and EtOAc (Table 2, entries 1, 2, and 4). In general, selectivities above 75% for 4PhPip were achieved in all cases, independently of the solvent and reaction times (Table 2, entries 1–5). The highest selectivity at ca. 49% conversion was reached in EtOAc with 90% (Table 2, entries 1, 2, and 4), and thus, this solvent was selected for further development.

In order to realize a fully integrated process, the hydrogenation reaction was carried out in continuous-flow mode and combined with the CO₂-triggered isolation procedure. The continuous-flow hydrogenation reactions were performed on an H-Cube Pro flow system (by Thales Nano) using commercial 10 wt% Pd/C catalyst cartridges provided by the same company (for detailed information, see Section 3.8 in Supporting Information). The reaction conditions were optimized using a design of experiments (DoE) approach with a central composite design varying the reaction temperature from 100 °C to 120 °C, the H₂ flow from 25 to 45 mL/min, and the substrate flow from 0.5 to 1.1 mL/min of 0.1 M 4PhPy in EtOAc at a total pressure of 30 bar. It was assured that EtOAc remains liquid within the given pressure and

temperature regime (see Supporting Information for full details). The conditions were varied every 10 min after steady state was achieved, and the same conditions were applied again randomly throughout the experiment to check the catalyst stability (see Section 3.8 in Supporting Information, Table S5). Target of the optimization procedure was the maximization of 4PhPy conversion, maximization of 4PhPip selectivity, and especially minimization of 4CyPip formation, whose separation from 4PhPip would be problematic because of the almost identical basicity.

Albeit quantitative analysis was hampered by slight catalyst deactivation, the DoE approach allowed identification of optimized conditions (110 °C, substrate flow of 0.5 mL/min, and H₂ flow of 26 mL/min). Figure 1 shows the reaction profile of a typical continuous-flow experiment performed under such conditions. At the beginning of the experiment a minor deactivation of the catalyst was observed and the conversion decreased from 92% after 10 min to 85% after 60 min. This deactivation might be caused by the adsorption of basic piperidines to partially block catalytically active Pd sites. After this induction period, conversion remained practically constant in the next hour. Remarkably, a very high selectivity towards the desired product 4PhPip was achieved under these conditions and remained nearly constant over the total time on stream. After 10 min, the selectivity towards 4PhPip reached 93% and slightly increased up to 95% after 60 min. The amount of 4CyPy was about 6% after 10 min and decreased further to about 4% after 60 min. The same trend followed the formation of the fully saturated 4CyPip (slightly above 2% at the beginning of the experiment, less than 2% after 60 min). It is noteworthy that the selectivities towards 4PhPip achieved in the continuous-flow experiments significantly surpassed the

Figure 1. Hydrogenation of a 0.1 M solution of 4-phenylpyridine in EtOAc over 10 wt% Pd/C at 110 °C, at a substrate flow of 0.5 mL/min, H₂ flow of 26 mL/min, and 30 bar system pressure (full data in Section 3.7 in Supporting Information). Legend: ◆ conversion; ■ *S*(4PhPip) = selectivity for 4Php; ● *S*(4CyPy) = selectivity for 4CyPy, and ▲ *S*(4CyPip) = selectivity for 4CyPip

Figure 2. Process scheme for the selective continuous-flow hydrogenation of 4-phenylpyridine in EtOAc integrated with product isolation using a CO₂-switchable aqueous biphasic extraction

values obtained in the batch experiments (cf. Tables 1 and 2), underlining the superiority of this methodology. The productivity of the reaction step expressed as space-time yield is $1.5 \text{ g}_{\text{product}}/\text{mL}_{\text{catalyst}} \text{ h}^{-1}$. Similar results have been obtained in a distinct experiment over a prolonged time-on-stream of 4 h (see Section 3.8 in Supporting Information), showing full conversion and a selectivity of 90–92% for 4PhPip in the first 2 h. Reduced conversions of 95–87% were observed in the third and fourth hour-on-stream, whereas the selectivity towards 4PhPip increased to up to 96%.

A portion of a product mixture collected from a continuous-flow experiment (see Section 3.8 in Supporting Information) containing small amounts of starting material, 4CyPy, and 4CyPip was purified using the method described above. Water was added to the ethyl acetate solution, and the mixture was stirred for 5 min under CO₂ atmosphere (5 bar). Thereby, 4PhPip was quantitatively extracted in the water phase as the corresponding piperidinium bicarbonate. Then, the water phase was separated and the pressure was released. After evaporation of the aqueous phase, 4PhPip was obtained with a total isolated yield of 81% with 98% purity (Figure 2). It is important to note that the product was obtained as free base due to the reversibility of the protonation step. No additional salt was produced because the bicarbonate is decomposed and CO₂ is removed together with water during the evaporation step. Moreover, after the phase separation, the ethyl acetate phase mostly containing unreacted starting material could be recirculated, resulting in a highly integrated and salt-free overall process.

3. Conclusion

We have demonstrated the selective hydrogenation of 4-phenylpyridine to the corresponding 4-phenylpiperidine using a commercially available Pd/C heterogeneous catalyst and EtOAc as ecologically benign solvent [38, 39]. The continuous-flow hydrogenation of 4-phenylpyridine to 4-phenylpiperidine was optimized using a DoE approach. High conversion (85–92%) and selectivities (94–99%) were obtained at a space-time yield of $1.5 \text{ g}_{\text{product}}/\text{mL}_{\text{catalyst}}/\text{h}$. The reaction step was combined with an isolation method using CO₂ as molecular switch for the selective extraction of the desired piperidine derivative from the organic to the water phase. This effective purification method does not involve by design the formation of a by-product (salt) and can be directly integrated with the reaction step using the same organic phase throughout the process. Under optimized conditions, 4-phenylpiperidine was obtained with 98% purity with a total isolated yield of 81%. This atom-efficient and green methodology may hold significant potential for the synthesis of pharmaceutically relevant arylpiperidines.

4. Experimental Section

4.1 Batch Hydrogenation of 4-Phenylpyridine. 4-Phenylpyridine (155 mg, 1.00 mmol, 1 eq.) and a carbon-supported noble metal catalyst (5 wt% Rh/C, 20.6 mg; 5 wt% Pd/C, 21.3 mg; 5 wt% Ru/C, 20.2 mg; 5 wt% Pt/C, 39.0 mg, or 10 wt% Pd/C, 10.6 mg; 10.0 μmol of metal, 0.01 eq.) were weighed into a glass inlet for a 10 mL autoclave, and the solvent (2.0 mL; EtOAc, MiBC or 2-MeTHF) was added. The dispersion was stirred until 4-phenylpyridine was completely dissolved. The autoclave was purged with hydrogen and then pressurized at the desired pressure. The reaction was started via placing the autoclave into a heating cone, which was previously heated to reaction temperature, and switching on the magnetic stirrer. After the reaction, the autoclave was cooled in ice water. The pressure was carefully released, and the solution was analyzed via proton nuclear magnetic resonance (NMR) spectroscopy according to Section 2.1 in Supporting Information. The mass balance could be closed for all performed reactions. The results are given in Tables 1 and 2.

4.2 Continuous-Flow Hydrogenation of 4-Phenylpyridine over 10 wt% Pd/C. The continuous-flow reactions were carried out using a H-Cube Pro System equipped with a 30 mm catalyst cartridge containing about 82 mg 10 wt% Pd/C as delivered by Thales Nano. The system was operated with pure EtOAc at a liquid flow of 0.3 mL/min, a hydrogen flow of 60 mL/min, at 100 °C, and a system pressure of 30 bar to activate the catalyst for 1 h. Afterwards, the system parameters were changed to 110 °C, a solvent flow of 0.5 mL/min, and a hydrogen flow of 26 mL/min. When the system reached a steady state, the EtOAc was exchanged by a solution of 4-phenylpyridine (6.22 g, 0.400 mol) in EtOAc (359 g, 401 mL) (substrate concentration of 0.1 mol/L). The system was operated with the substrate solution for 10 min before the first sample was taken to rinse the neat solvent out of the system. Afterwards, samples were collected after different time intervals (see Table S6 and S7 in Supporting Information and Figure 1). For each sample, about 6 mL of product solution was collected. The samples were analyzed according to Section 2.1 in Supporting Information.

4.3 Isolation of 4-Phenylpiperidine from a Reaction Solution Using Carbon Dioxide. A reaction solution as obtained from the continuous-flow hydrogenation of 4-phenylpyridine was used. The reaction solution (45.82 g, 51 mL) contained 4-phenylpyridine (102 mg, 0.659 mmol), 4-phenylpiperidine (666 mg, 4.13 mmol), 4-cyclohexylpyridine (21.2 mg, 0.131 mmol), and 4-cyclohexylpiperidine (12.5 mg, 0.0748 mmol) as determined by ¹H-NMR spectroscopy. First, the solvent was reduced using a rotary evaporator at 40 °C and 270 mbar. The resulting solution (15.69 g, 17.5 mL) was

transferred in a 100 mL glass autoclave (Büchi Miniclave), and water (17.5 mL) was added. The autoclave was pressurized with CO₂ (5 bar). The dispersion was stirred for 5 min at room temperature (about 22 °C), while the pressure was kept at 5 bar. Afterwards, the phases were allowed to separate for 20 min, and the water phase was taken out of the autoclave via a septum while the system was kept under 5 bar CO₂ atmosphere. Water was carefully removed using a rotary evaporator at 40 °C and 70 mbar, yielding a white solid. The solid was dried in a desiccator under vacuum for 4 days. 4-Phenylpiperidine was obtained as a white solid in 98% purity (GC, see Section 3.9 in Supporting Information). Yield was 653 mg (4.05 mmol, 98%).

Supporting Information

Electronic Supplementary Material (ESM) associated with this article is available in the online version at doi: 10.1556/1846.2017.00003.

Acknowledgments. We thank the Ministry for Innovation, Science, and Research of the State North Rhine-Westphalia (project “Conticat”) and Novartis for financial support and Dr. Thomas Tacke (Evonik AG) for the kind donation of a sample of Pd/C. P.M. thanks the Alexander von Humboldt Foundation for funding.

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