

Continuous-Flow Hydrogenation and Reductive Deuteration of Nitriles: a Simple Access to α,α -Dideutero Amines

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A simple and efficient continuous flow methodology has been developed for hydrogenation and reductive deuteration of nitriles to yield primary amines and also valuable α,α -dideutero analogues. Raney nickel proved to be a useful catalyst for the transformation of a wide range of nitriles under reasonably mild conditions with excellent deuterium incorporation (> 90%) and quantitative conversion. Among known model compounds, three new deuterated primary amines were prepared. The large-scale synthesis of deuterated tryptamine was also carried out to deliver 1.1 g product under flow conditions.

The exchange of a hydrogen atom for deuterium in a drug candidate molecule may improve its pharmacological profile.^[1] This is nicely exemplified by Austedo[®], the first deuterated drug marketed and also by numerous further representatives in various clinical trials.^[2] Given the importance of deuterated drugs, much effort has been undertaken to develop suitable methods for deuteration.^[3] In many cases, deuterium-containing materials are synthesized utilizing environmentally harmful and costly deuterium sources,^[4] such as LiAlD₄ or NaBD₄.^[5] Thus,

developing sustainable, inexpensive and simple methods can be crucial in this area. In H/D exchange reactions induced by heterogeneous metal catalysts, the most commonly used deuterium sources are D₂O, deuterated protic solvents and gaseous deuterium.^[6] In such reactions, the most widely used combinations of catalysts and deuterium sources are PtO₂-D₂-D₂O,^[7] Pd/C-D₂,^[8] and Rh/SiO₂-D₂.^[9]

Amines have a pivotal role in synthetic organic chemistry and they are widely present in pharmaceutical drugs and bioactive natural products and are frequently used in medicinal chemistry.^[10] Various methods have been developed to transform nitriles to amines, including metal hydride reductions,^[11] catalytic hydrogenations^[12] and dissolving metal reductions.^[13] Of these, catalytic hydrogenation is applied the most frequently. It is also the method of choice for the preparation of varied amines in industry. Hydrogenation of nitriles is generally performed in the presence of heterogeneous transition metal catalysts, such as nickel, cobalt, palladium or platinum.^[14]

Deuterated amines are relevant building blocks in the field of drugs, deuterium labelled probes and functional materials.^[15] However their synthesis is relatively rare in the literature. An important strategy to prepare deuterated amines is transfer deuteration.^[16] This method can be applied in the reductive amination of ketones or aldehydes in D₂O. Preformed imines can also undergo transfer deuteration in D₂O. These approaches, however, have several drawbacks. For example, only low degrees of deuterium incorporations were observed.^[16] From an environmental and industrial point of view, reductive deuteration of nitriles is an attractive strategy and valuable transformation for the synthesis of deuterated amines. An intriguing example was reported by An and co-workers. They exploited sodium-mediated electron transfer reactions for the synthesis of α,α -dideutero amines in the presence sodium dispersions in EtOD-d₁.^[15a]

Conventional deuterium labelling techniques involve serious difficulties. For example, D₂ gas as a deuterium source has high cost and imposes additional operational challenges.^[4] Catalytic H-D exchange reactions often require long reaction times, and alternatively, the costs of deuterated reagents and deuterated solvents as isotopic sources severely limit the practical applicability.^[17] Therefore, our research group established an individual flow-chemistry-based method for deuteration reactions by exchanging the hydrogen source to deuterated water in an H-Cube[®] system.^[18] In fact, heterogeneous catalytic hydrogenations and deuteration reactions can achieve important benefits from the features of flow chemistry,^[19] especially

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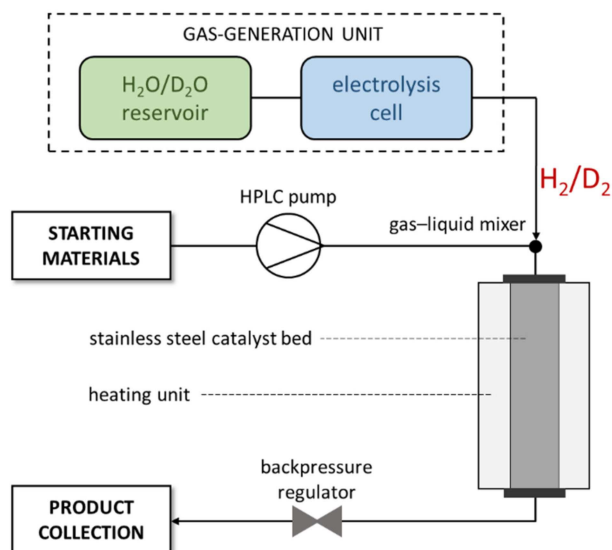


Figure 1. Schematic outline of the continuous-flow reactor (H-Cube®).

through the unprecedented level of control over the most important reaction conditions, the enhanced heat and mass transfer, and the improved mixing properties.^[20] However, in terms of safety the application of the H-Cube® system provides further advantages for lab-scale hydrogenations/deuterations as H₂ or D₂ gas is generated *in situ* by electrolysis.^[21]

Herein, we report a simple and sustainable method for the hydrogenation and reductive deuteration of nitriles producing primary amines and valuable α,α -dideutero analogues in a continuous-flow system with Raney nickel as heterogeneous catalyst.

Hydrogenation and reductive deuteration reactions were performed in an H-Cube® flow system, where the hydrogen source (H₂O) was changed to D₂O in the case of deuteration. The schematic representation of the reactor is shown in Figure 1. Raney nickel catalyst was charged into a stainless steel column, which ensured excellent ease of use. To avoid D–H exchange and to maximize deuterium incorporation in the reductive deuteration the use of an aprotic medium was necessary. Therefore, the reactions were carried out in EtOAc as solvent.

Our investigation was started by optimizing reaction conditions of nitrile reduction to primary amines using 4-phenylbutyronitrile as the model compound (Table 1). In this reaction, two key parameters – temperature and pressure – were optimized at a fixed flow rate of 1 mL/min. At 20 and 40 °C, practically no product formation was observed, while full conversion was detected at 60 °C and 80 °C (entries 1–4). As for the pressure, an efficient reaction required the use of at least 40 bar, because at lower pressure the conversion was merely 51 % (entries 5–8). Consequently, the optimal parameters of the reduction of 4-phenylbutyronitrile were 40 bar pressure and a temperature of 60 °C affording quantitative conversion and a selectivity of > 99%.

After the successful optimization of synthesis parameters, we investigated the reaction scope. A wide range of substituted

Table 1. Optimization of reaction conditions for the hydrogenation of 4-phenylbutyronitrile.

Entry	p [bar]	T [°C]	Conversion [%] ^[a]	Selectivity [%] ^[a]
1	40	20	0	–
2	40	40	traces	–
3	40	60	100	> 99
4	40	80	100	> 99
5	20	60	51	> 99
6	40	60	100	> 99
7	60	60	100	> 99
8	80	60	100	> 99

[a] Determined by ¹H NMR analysis of the crude product.

Table 2. Hydrogenation of diversely substituted aliphatic and aromatic nitriles to primary amines under optimized flow conditions.

Entry	Starting material	Product	Conv. [%] ^[a]	Sel. [%] ^[a]
1			100	> 99
2			100	> 99
3			100	> 99
4			100	> 99
5			100	> 99
6			100	> 99
7			100	> 99
8			100	> 99
9			100	> 99
10			100	> 99

[a] Determined by ¹H NMR analysis of the crude product.

aliphatic and aromatic nitriles were tested under optimum flow conditions (Table 2). Quantitative conversions and selectivity values of > 99% were observed for aromatic nitriles with electron-donating or electron-withdrawing functional groups

(entries 1 and 2). Similarly good results were found for linear or branched aliphatic nitriles bearing various substituents including (hetero)aromatic rings (entries 3–7). Nitriles with bulky substituents, such as adamantane-1-carbonitrile and diphenylacetoneitrile, were also nicely tolerated (entries 8 and 9). 3-(1-Piperidinyl)propanenitrile was successfully transformed into the corresponding amine (entry 10), yielding a significant intermediate for the synthesis of pharmaceutically relevant ω -piperidinoalkanamine derivatives with fluorescent moieties.^[22]

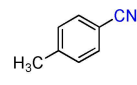
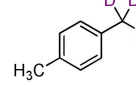
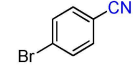
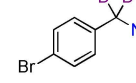
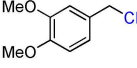
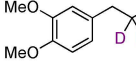
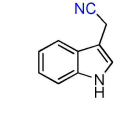
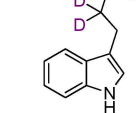
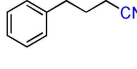
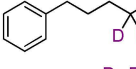
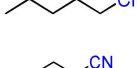
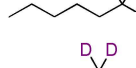
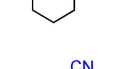
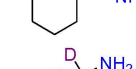

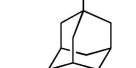
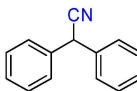
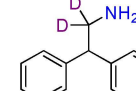
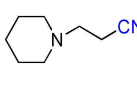
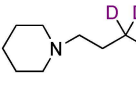
After successful hydrogenation experiments, we next turned our attention to continuous flow reductive deuterations to access α,α -dideutero amines. For this, the hydrogen source in the H-Cube[®] reactor was simply changed to D₂O, and reaction conditions optimized earlier for the hydrogenations were utilized without any change ($p=40$ bar, $T=60$ °C, 1 mL/min flow rate, Raney nickel as catalyst, EtOAc as solvent).

Excellent deuterium incorporations, quantitative conversions and high selectivities were observed for a wide variety of nitriles in their reduction to the corresponding α,α -dideutero amines (Table 3). The reaction was successful for aromatic nitriles possessing electron-donating or electron-withdrawing functional groups (entries 1 and 2), and as well as for diversely substituted aliphatic nitriles (entries 3–10), including adamantane-1-carbonitrile and diphenylacetoneitrile (entry 8 and 9). Deuterated amines in Table 3 entries 8, 9 and 10, are new materials, not known in the literature.

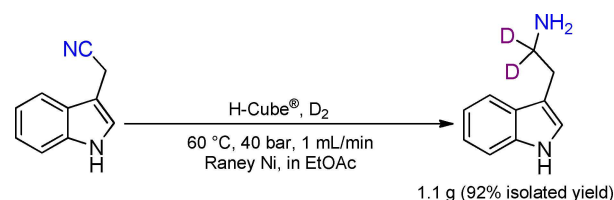
Finally, we investigated the applicability of the continuous flow reductive deuteration method for the gram-scale synthesis of deuterated tryptamine (Scheme 1). Tryptamine is a pharmaceutically active compound, found in trace amounts in the brain of mammals and it is believed to play a significant role as neurotransmitter or neuromodulator in the brain.^[23] Samples were taken and conversion and selectivity were determined in every hour to obtain a clear view of catalyst activity (Figure S1 in the Supporting Information). We were delighted to find that the Raney nickel catalyst worked for 20 hours without loss of activity and change in selectivity during this time. Deuterated tryptamine was formed with quantitative conversion, >99% chemoselectivity and deuterium incorporation ratios of $\geq 95\%$ in all samples investigated. In the scale-out experiment, we managed to produce 1.1 g of the deuterated product which corresponded to an isolated yield of 92%.

A novel continuous-flow method has been developed for hydrogenation and reductive deuteration of nitriles with Raney nickel catalyst under mild conditions. The applicability of the reactions was demonstrated with a wide range of nitriles with varied substitution patterns affording outstanding conversions, selectivities and deuterium incorporations. Importantly, valuable α,α -dideutero amines were achieved in a simple, safe and sustainable manner utilizing heterogenous catalysis, EtOAc as environmentally-benign solvent and D₂O as electrolytic deuterium source. The preparative capabilities of the synthesis method were tested with a large-scale deuteration experiment producing 1.1 gram of deuterated tryptamine.

Table 3. Reductive deuteration of diversely substituted aliphatic and aromatic nitriles to α,α -dideutero amines under optimized flow conditions.

$\text{R-CN} \xrightarrow[\text{Raney Ni, in EtOAc}]{\text{H-Cube}^{\text{®}}, \text{D}_2, 60 \text{ }^{\circ}\text{C}, 40 \text{ bar}, 1 \text{ mL/min}}$ $\text{R}-\overset{\text{D}}{\underset{\text{D}}{\text{C}}}-\text{NH}_2$				
Entry	Starting material	Product ^[a]	Conv. [%] ^[b]	D [%] ^[c]
1			100	> 99
2			100	> 99
3			100	90
4			100	> 99
5			100	90
6			100	91
7			100	95
8			100	96
9			100	98
10			100	90

[a] Chemoselectivity was > 99% in all reactions. [b] Determined by ¹H NMR analysis of the crude product. [c] Deuterium contents (represent deuterium incorporation rate over incidental hydrogenation).



Scheme 1. Gram-scale synthesis of deuterated tryptamine under flow conditions.

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2016-00038], the EU-funded Hungarian Grant [EFOP-3.6.1-16-2016-00008], and the Ministry of Human Capacities, Hungary Grant, 20391-3/2018/FEKUSSTRAT. SBÖ acknowledges the Premium Post Doctorate Research Program of the Hungarian Academy of Sciences. Financial support is highly appreciated. We are grateful to Prof. Árpád Molnár for proofreading our manuscript.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: amines · continuous flow chemistry · deuteration · nitriles · Raney nickel

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