Fast and Efficient Deuteration in Continuous Flow Using the H-Cube® Advance Flow Reactor

INTRODUCTION

Deuterium-labeled compounds are widely used as research tools in chemistry. Their importance lies in a number of applications, such as proving **reaction mechanisms**, the investigation of a compound's **pharmacokinetic properties**, internal standards in **mass spectrometry**, and compound structure determination in **NMR spectroscopy**.

Conventional techniques for the synthesis of deuterated compounds utilize D_2 gas as a deuterium source. However, there are drawbacks to utilizing deuterium gas on a laboratory scale, such as the **handling of the gas** itself. Other methods have been employed to overcome this difficulty, such as **catalytic H–D exchange** reactions between **H_2** and **D_2O**. However, these methods are time-consuming and do not produce high purity D_2. They also require high pressure, the use of a special catalyst, or an excess amount of a strong base or acid[1].

The **H-Cube® Advance** continuous flow system is capable of generating deuterium gas from the **electrolysis of D_2O**, which is readily available in **99.98% purity** and is easy to handle.

TECHNIQUE

High-purity deuterated compounds can be generated in high yield as long as a few guidelines are followed. Removing H_2O from the water reservoir and the system is crucial. We recommend flushing in Manual operation mode.

Step 1: Clean and dry the inside of the water reservoir with a paper towel.

Step 2: Fill the water reservoir with D_2O. Place the free end of the water inlet tube into the reservoir.

Step 3: Select internal H_2 on the device's screen, and wait for the pressure in the electrolytic cell to build up.

Step 4: Prime the HPLC pump and both the solvent and reagent inlet tubes using a syringe adapter.

Step 5: Place the outlets into a product and waste vessel respectively.

Step 6: Tap the waste collection button ( ) on the screen. Start the HPLC pump at a set flow rate to wash the system with clean solvent.

Step 7: Set the desired gas flow rate and start the gas flow. Let the system run for approximately 10-15 minutes.

Step 8: Empty the water reservoir and refill it with fresh D_2O, making sure the system is completely purged of trace H_2O from previous runs.

After the system has been properly flushed, the reaction can be started.

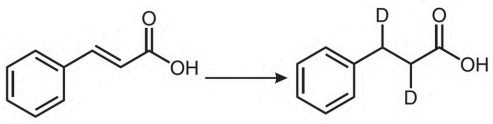
RECOMMENDATIONS

- Only use an **aprotic solvent** to avoid H–D exchange.
- Do not use hydrogen saturated catalysts such as **Raney catalysts** for the reaction.

LITERATURE

There are two literature examples of where the H-Cube® Advance has been utilized for the deuteration of compounds.

Fülöp et al. performed deuterations on a series of unsaturated compounds[1]. Optimum conditions were first explored using **cinnamic acid** as a standard. Early reactions using methanol and **10% Pd/C** led to only a **30% incorporation** of deuterium into the molecule. Changing from methanol to an aprotic solvent, **ethyl acetate**, increased **deuterium incorporation** to **70%**.

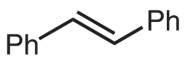
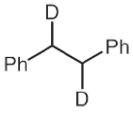
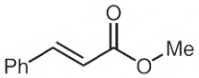
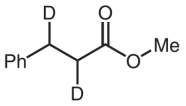
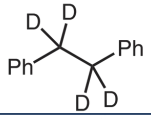
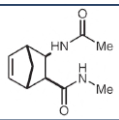
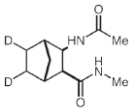


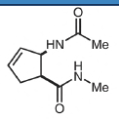
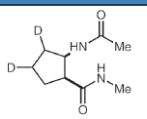
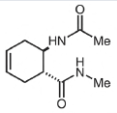
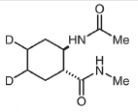
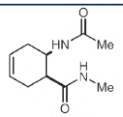
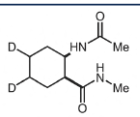
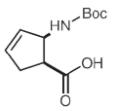
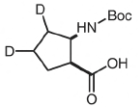
The catalyst was then changed to a less active catalyst (**5% Pd/$BaSO_4$**) to reduce the deuteration of the phenyl ring and selectively deuterate the double bond. This catalyst change increased **deuterium content** to **95%**. The reaction was carried out at room temperature. Pressures in the 40-60 atm. range and flow rates between 0.7-2 mL/min did not affect yield or deuterium levels.

Once the optimized conditions had been found, the same conditions were applied to a series of other unsaturated compounds. The results are displayed in Table 1.

As you can see from the results, the products were synthesized in near quantitative yield with a high deuterium incorporation. No purification was necessary. The structures included **foldamer building blocks**, so there is potential for structure elucidation via deuteration where bacteria labeling is not possible. The D_2O consumption was very low (4.41 µL/min), which is a much higher deuterium efficiency when compared to other methods.

The other paper is from Kappe et al. and describes the deuteration of **ethyl cinnamate**[2]. Using a flow rate of 1 mL/ min, 10% Pd/C, room temperature, and Full H_2 mode, the product was successfully synthesized in **92% yield** with a **95%** degree of **deuterization**.

Entry	Substrate	Product	D_2[a] (%)	Yield[b] (%)
1			99	99
2			97	98
3			93	97
4			96	98

Entry	Substrate	Product	D_2[a] (%)	Yield[b] (%)
5			96	99
6			95	99
7			97	95
8			98	98

[a] Deuterium content in %. [b] Isolated yield.

CONCLUSION

Utilizing D_2O instead of H_2O, the H-Cube® Advance is able to deuterate compounds in **high yield** and with a **deuteration incorporation** of **>95%**. These results offer up the H-Cube® Advance as a reliable alternative to other deuteration methods.

REFERENCES

[1] Mándity, I.M.; Martinek T.A.; Darvas, F.; Fülöp, F.; *Tet. Lett.*; **2009**; 50; 4372-4374.
[2] Irfan, M.; Petricci, E.; Glasnov, T.; Taddei, M.; Kappe, O.; *Eur. J. Org. Chem.*; **2009**; 1327-1334.

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