Reductive Amination Reaction with UV-Transparent Compounds

This application describes how Isolera™ Dalton was used to fractionate completely non-UV absorbing starting materials and products of reaction from a classic reductive amination reaction. The method was also effective at separating the major over-alkylated by-product of reaction, thus ensuring product purity.

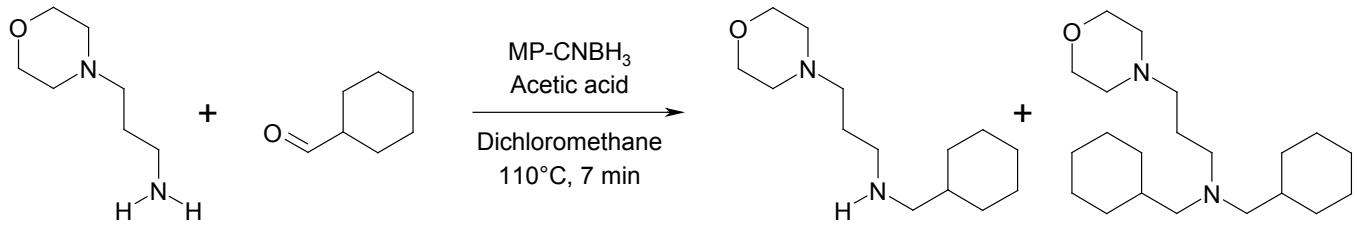

Figure 1. Structures of compounds described.

Reductive amination continues to be a powerful tool for chemistry. It facilitates the synthesis of amines, which are key components in many drug compounds and natural products. There are many strategies to quickly and effortlessly synthesize amines, however it is not always easy or possible to purify reaction mixtures as the components may not be UV active. In some cases side reactions may lead to closely related by-products which are difficult to differentiate using only UV based methods.

In this example, Isolera™ Dalton was used to fractionate completely non-UV absorbing starting materials and products from a classic reductive amination reaction. A resin bound cyanborohydride reagent was used to greatly facilitate the work flow by eliminating the need for traditional work-up, and the mixture applied to flash chromatography purification methods. The method was also effective at separating the major over-alkylated by-product of reaction, thus ensuring product purity.

Experimental

523 mg (2.39 mmol/g, 1.25 mmol) MP-cyanoborohydride was weighed into a 2–5 mL reaction vial. 2.5 mL dichloromethane, 73 µL (72.1 mg, 0.5 mmol) 4-(3-aminopropyl)morpholine, 73 µL (67.3 mg, 0.6 mmol) cyclohexanecarboxaldehyde, and 142 µL (2.5 mmol) acetic acid were added and the vial was heated to 110 °C for 7 minutes using a Biotage® Initiator Sixty. After the reaction, the solid phase reagent was filtered off and washed with 3 x 5 mL dichloromethane. The combined organic fractions were washed with 10 mL saturated Na_2CO_3 and 10 mL purified water. The aqueous washings were re-extracted with 10 mL dichloromethane and the combined organic solutions were dried over Na_2SO_4 and concentrated to give 126.9 solid material.

Chromatographic Method

The raw material from the synthesis was dissolved in 1.5 mL dichloromethane and purified using Isolera™ Dalton.

- 10 g Biotage® SNAP Ultra cartridge
- Dichloromethane (1% triethylamine) – methanol (1% triethylamine); 30–100% over 5 CV
- λ-All monitoring (200–800 nm)
- Mass collection based on positive ionization with m/z 241.2 (corresponding to the product) and 337.4 (corresponding to the dialkylated by-product)

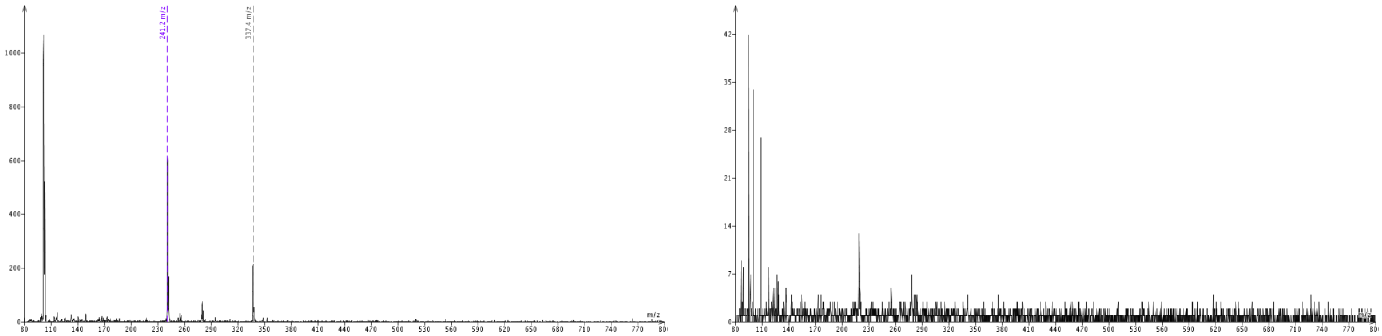

Figure 2. Mass spectrum from positive (left) and negative (right) ionization.

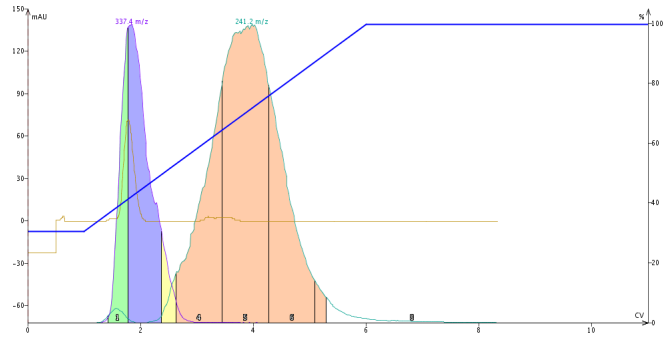

Figure 3. Isolera™ Dalton chromatogram.

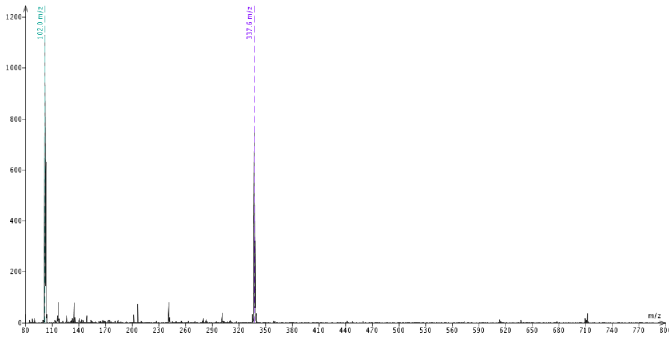

Figure 4. Mass spectrum of fractions 1+2 (dialkylated by-product) 31.3 mg, 0.09 mmol, 18 %.

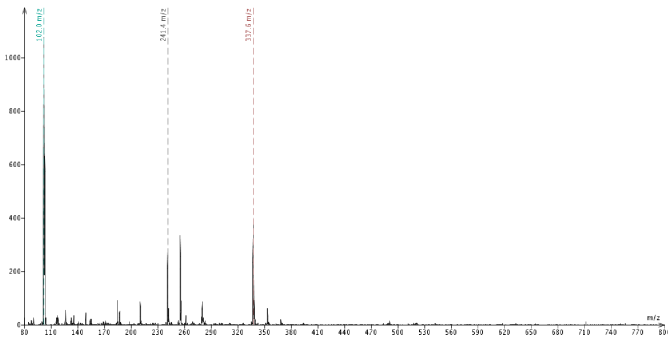

Figure 5. Mass spectrum of fraction 3 (mixed fraction) 3 mg.

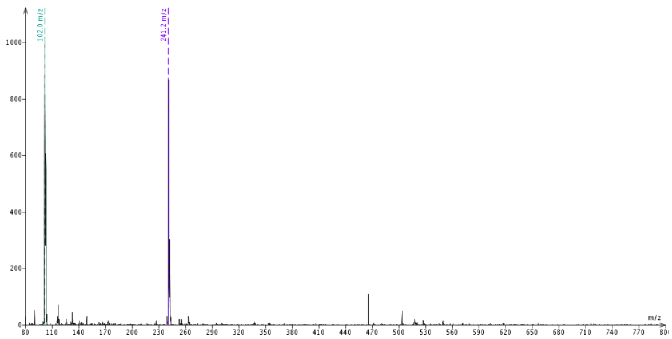

Figure 6. Mass spectrum of fractions 4–7 (product) 77.4 mg, 0.32 mmol, 64%.

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