Multi-step Synthesis and Purification

with the Combi*Flash* Torrent® and Redi*Sep*® Rf 3 kg columns

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Abstract

Many syntheses require ten or more steps to produce the desired compound. Since most organic synthesis steps fail to convert quantitatively to the desired product (with 40% loss being common), chemists need to synthesize and purify large quantities of early stage intermediates. Using 3 kg columns and 750 g solid load cartridges on the Combi*Flash* Torrent system allows facile purification of the intermediates with significant time savings compared to using small columns.

Overview

Multiple-step synthetic reactions often yield only a small amount of targeted compound. For example, if a ten-step reaction sequence begins with 150 grams of starting material and each step averages a 60% yield, the final yield is only 906 milligrams. Because of this typical loss of material, it is often necessary or desirable for multiple-step reactions to begin with a large quantity of material so that the synthesis can be accomplished without interruption. The Combi*Flash* Torrent is a system capable of purifying large quantities of product in the initial reaction steps, thereby expediting subsequent synthetic steps.

As the chemist progresses through the reaction sequence and material sizes decrease, there is a point where the Combi*Flash* Rf 200 becomes the more appropriate purification system. Figure 1 illustrates the typical purification range, where the upper green area shows the injected range for the Combi*Flash* Torrent systems while the lower blue area shows the usable range for the Combi*Flash* Rf 200.

This application note focuses on the purification of 3-(2-nitrophenyl amino) propionitrile to demonstrate the applicability of the Combi*Flash* Torrent system and the Redi*Sep* Rf 3 kg column. This purification is representative of “real world” purifications of similar compounds,[1,2] such as those used to synthesize quinolones.

The chromatograms (Figure 2, Crude and Flash) show peaks that elute closely to each other.

Experimental

2-Nitroaniline (304 g) was dissolved in 1500 mL reagent alcohol. Triton B (45 mL) was added and the mixture was heated to reflux. Acrylonitrile (420 mL) was added with stirring. The mixture was stirred overnight at reflux. The alcohol was evaporated and a tarry mixture (~550 g) was obtained.

A 150 g portion of this tarry mixture was dissolved in methanol and mixed with 600 g silica (75–150 µ, PN 60-3874-091). This created a 20% load on the silica in the solid load cartridge. The mixture was dried to a free-flowing powder and placed in a 750 g solid load cartridge (PN 69-3873-224). This created a 5% sample load on the 3 kg Redi*Sep* Rf silica column.

The sample was run on a Combi*Flash* Torrent (PN 68-5240-003) using a 3 kg Redi*Sep* Rf silica column (PN 69-2203-529). The standard 3 kg method was used. The detection wavelength was 254 nm; Solvent A was hexane and Solvent B was ethyl acetate.

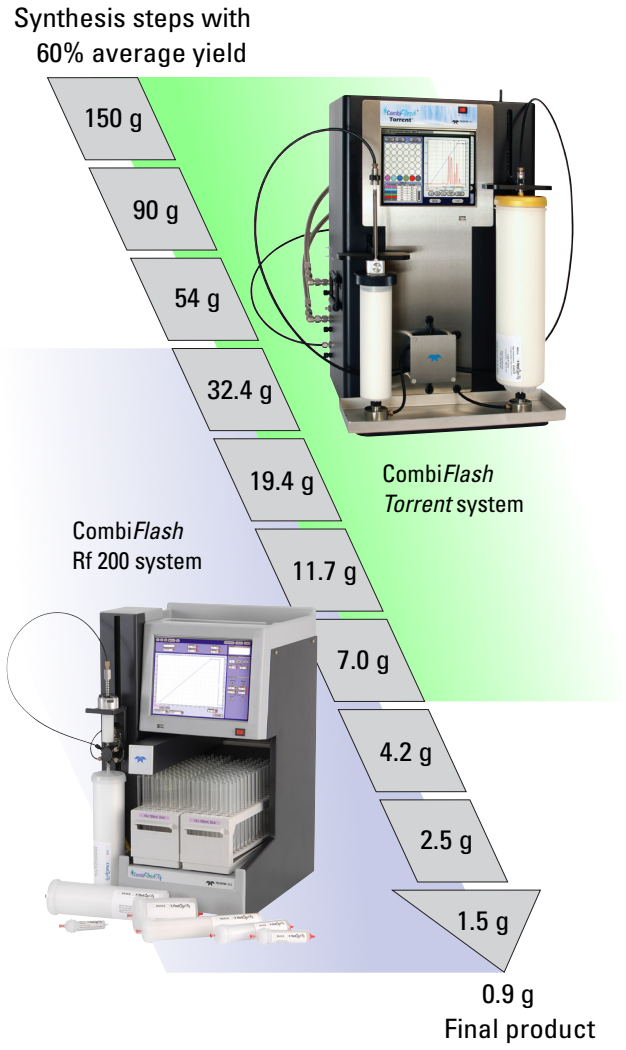

Figure 1: A ten-step synthesis beginning with 150 g and 60% average yield each step, gives 906 mg of final product.

Results and Discussion

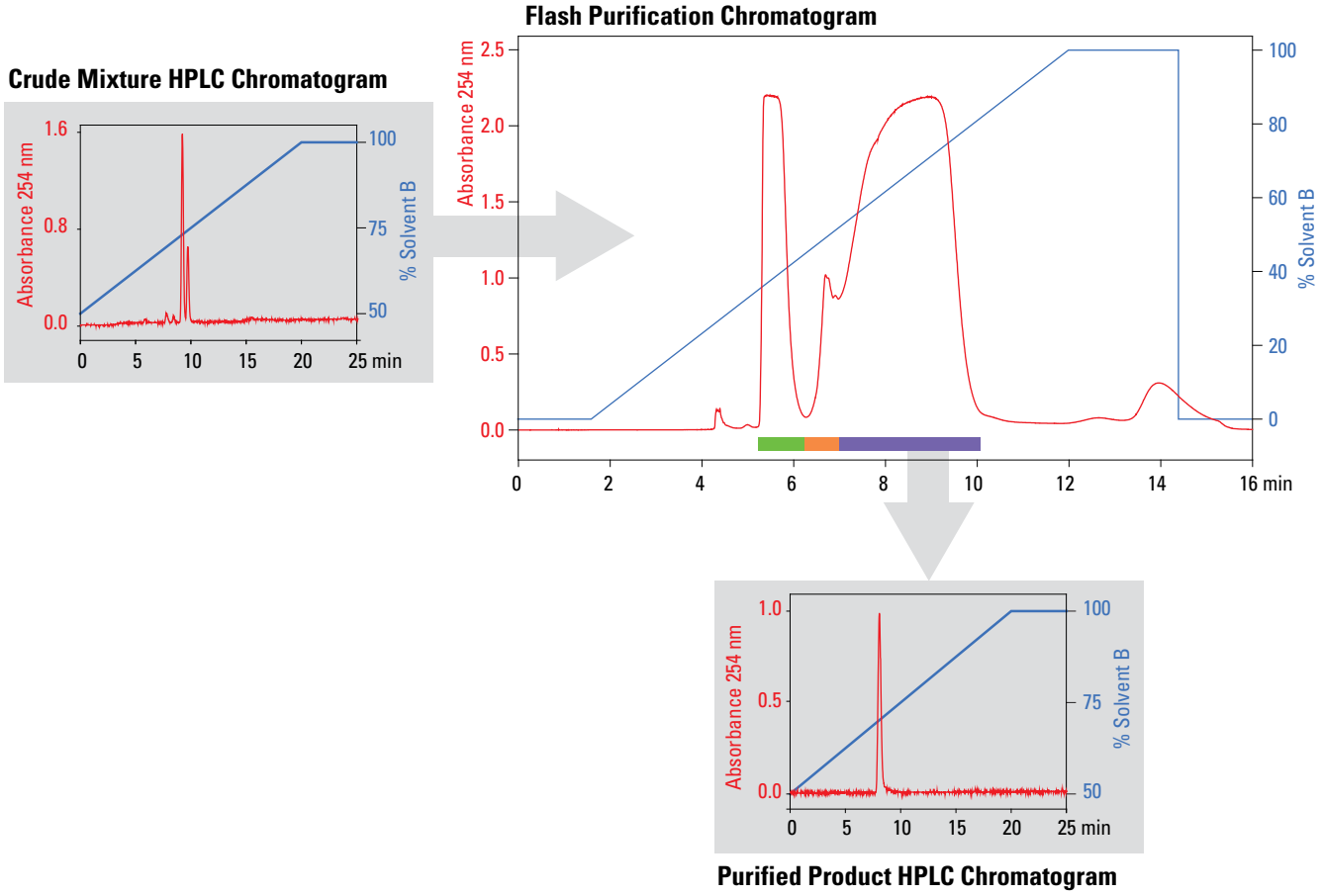

Figure 2: Purification of 3-(2-nitrophenyl amino) propionitrile using a Combi*Flash* Torrent, Redi*Sep* Rf 3 kg silica column, and 750 g solid load cartridge. HPLC chromatograms indicate purity of crude and purified product.

The Combi*Flash* Torrent system purified 150 g of crude material in 1.75 hours. Running the same material using 330 g silica column would require 1.5 hours per run, but the chemist would only be able to purify 16.5 g material each time. It would require 13.5 hours using the 330 g column to purify the same amount of material that can be purified in a single run on the Combi*Flash* Torrent with a 3 kg column.

Conclusion

The Combi*Flash* Torrent is able to support a 3 kg column, sufficient to purify over 150 g sample in a single run, saving days of purification compared to using smaller columns. The compounds elute cleanly for subsequent synthesis steps. The Combi*Flash* Torrent system saves time by allowing easy purification of a large amount of synthesized intermediate compounds.

For later synthesis steps which produce smaller sample loads, run the purifications on the Combi*Flash* Rf 200 system.

References

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2. Chen, W.; Lin, Z.; Ning, M.; Yang, C.; Yan, C.; Xie, Y.; Shen, X.; Wang, M-W. Aza analogues of equol: Novel ligands for estrogen receptor ß. *Bioorg & Med Chem.* **15**, 2007, 5828-5836

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