An Improved Extraction Strategy for Polar Solvent Reactions

With many reactions today being performed using polar, high boiling point solvents such as DMSO, the post-synthesis work-up is not trivial. With a boiling point of 189 °C, DMSO is among the most difficult solvents to evaporate thus requiring chemists to extract with an immiscible solvent with a lower boiling point. However, with most solvents being soluble in DMSO, water must be added before the addition of a suitable extractant such ad DCM. This is the approach many chemists follow for this situation.

The typical extraction device is a glass separatory funnel, which all chemists know how to use. However, there are drawbacks to the separatory funnel.

- Fragility
- Emulsion formation
- Gas/pressure evolution
- Phase interface recognition
- Flow rate restrictions
- Apparatus cleanliness/maintenance

Biotage has addressed these limitations by developing efficient and recyclable polypropylene Phase Separators, Figure 1. These vessels contain a hydrophobic frit which allows dense organic solvents such as DCM to flow while retaining water thus eliminating the glass separatory funnel drawbacks.

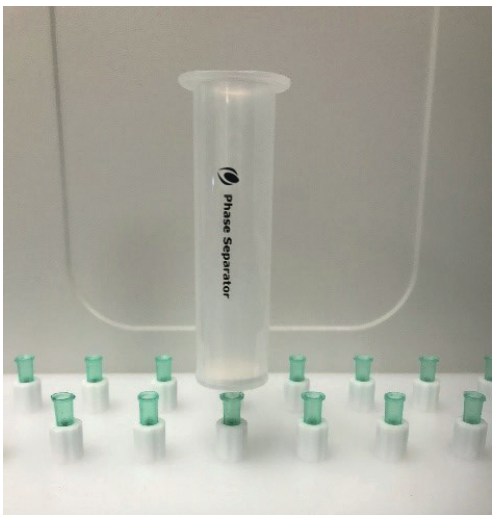

Figure 1. ISOLUTE® Phase Separator mounted on a Biotage® Gravity Rack.

The ISOLUTE® Phase Separator eliminates the need to monitor flow rate and the organic/aqueous phase interface. Because the reaction mixture can be mixed with water and DCM in the reaction vessel, there is no need to vent pressure or even be concerned with emulsions.

To show their effectiveness, the phase separators were used to extract the reaction product of a succinic acid and benzylamine reaction in DMSO from several by-products, Figure 2.

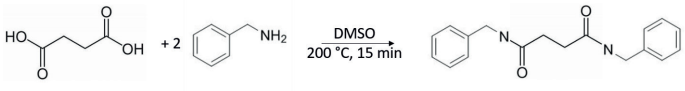

Figure 2. Reaction of succinic acid and benzylamine in DMSO using a Biotage® Initiator+ microwave reactor.

Materials and Methods

Synthesis and Work-up

Reactor:	Biotage® Initiator+ with 2–5 mL reactor vial
Solvent:	DMSO
Reagents:	Succinic acid (1 eq), benzylamine (2 eq)
Reaction:	15 minutes at 200 °C
Extraction:	ISOLUTE® Phase separator, 25 mL, with Biotage® Gravity Rack

Evaporation

System:	Biotage® V-10 Touch Rapid Solvent Evaporator

Purification

System:	Biotage® Selekt
Column:	Biotage® Sfär C18 12 gram
Dry Load Vessel:	Biotage® Sfär C18 Samplet®
Load Amount:	~21 mg
Solvent A:	Water, deionized
Solvent B:	Methanol
Flow Rate:	30 mL/min.
Equilibration:	10% B for 2 CV
Gradient:	10% B for 1 CV 10–100% B in 10 CV 100% B for 2 CV
Detection:	UV 200–400 nm

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Results and Discussion

To evaluate the DMSO reaction mix complexity, a 0.1 mL aliquot was loaded onto a 12 g Sfär C18 column (prior to extraction). The results indicated two major retained compounds and several by-products, Figure 3.

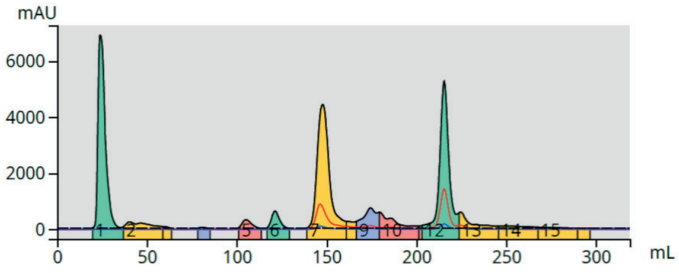

Figure 3. Reversed-phase flash chromatography of the DMSO crude reaction mix prior to extraction shows two major products (fractions 7 and 12) and many by-products. Fraction 1 is DMSO.

To evaluate the ISOLUTE® phase separator's efficiency, a 0.5 mL aliquot was transferred to a 20 mL scintillation vial. To this vial was added ~5 mL of water and 3 mL of DCM. The contents were mixed and poured into a Phase Separator attached to a Biotage® Gravity Rack.

Within seconds the dense DCM extract was collected into a scintillation vial. The crude reaction vial was rinsed again with both water and DCM, transferred to the Phase Separator, and the DCM portion collected. The entire extraction process required only about 2 minutes.

Since DCM is not a suitable injection solvent for reversed-phase, the extract was evaporated on a Biotage® V-10 Touch followed by re-dissolution in a 1:1 mix of methanol and acetone (1 mL). Purification (0.1 mL of re-dissolved extract) was repeated and the results showed removal of most interfering by-products, Figure 4.

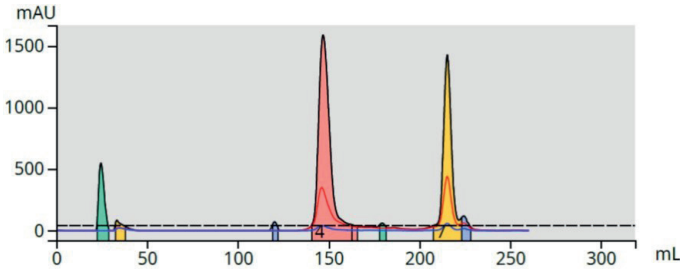

Figure 4. Flash chromatography of the DCM extract (dried and re-dissolved in 1:1 methanol/acetone) using reversed-phase shows removal of many of the reaction by-products.

Conclusion

Reactions conducted in high boiling point solvents pose work-up and evaporation challenges requiring a substantial time investment. Biotage Phase Separators simplify and speed compound extraction with equal, if not better, efficiency compared to glass separatory funnels. After use, phase separators can be dried and recycled with other polypropylene lab waste.

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