

Using Modern Instrumentation to Speed Synthesis Workflow

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Introduction

This poster highlights the use of an expedited workflow incorporating a microwave reactor for synthesis, high-speed solvent evaporator for work-up/chromatography sample prep, and automated flash chromatography for purification, which individually and combined minimize the time required to accomplish the manual synthesis tasks typically used.

Experimental Protocol

Reagents and Materials

Reagents: maleic anhydride, 1,3-cyclohexadiene (CHD), α -methylbenzylamine

Solvents: dichloromethane (DCM), methanol (MeOH), in-house deionized water.

Automation systems:
Biotage[®] Initiator+
Biotage[®] Selekt
Biotage[®] V-10 Touch

Flash chromatography:
12-gram Biotage[®] Sfär C18
Biotage[®] Sfär DLV system
Biotage[®] KP-C18-HS bulk media

Accelerating Workflow



According to the Arrhenius equation, reaction rates double with every 10 °C increase in temperature, Equation 1.

$$\text{Arrhenius Equation: } k = A e^{-\text{DG}^\ddagger/\text{RT}}$$

So, a conventional reaction requiring 12 hours at room temperature only needs 5 minutes when heated with a MW at 100 °C, a major time savings.

Automated flash chromatography along with a automated high-speed evaporator capable of removing DMSO, NMP, and other solvents, speeds the entire workflow and reduces the need for extraction and lyophilization.

Synthesis

A 2-step synthesis was conducted where the time needed to conduct each step from synthesis through purification and evaporation was measured.

Reaction 1 - maleic anhydride (130 mg, 1.3 mM) was added to a Biotage 2-5 mL MW reaction vial with magnetic stir bar. Dichloromethane (3 mL) was then added followed by 1,3-cyclohexadiene (200 mg, 2.5 mM). The microwave reaction ran for 10 minutes at 160 °C using a Biotage[®] Initiator+, Figure 1.

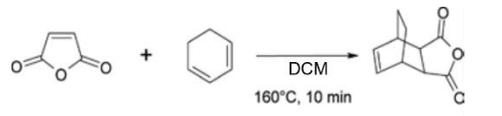


Figure 1. Diels-Alder reaction.

The reaction mixture was evaporated using a Biotage[®] V-10 Touch removing both the DCM (BP 39 °C) and excess CHD (BP 81 °C) in 11 minutes and provided a crude yield of 233 mg.

In the second reaction, the Diels-Alder product was reacted with α -methylbenzylamine for 5 minutes at 100 °C in 3 mL of DCM, Figure 2.

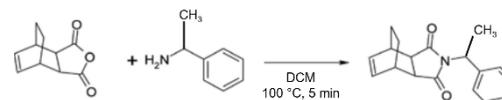


Figure 2. Acylation reaction.

The reaction product was evaporated in 4 minutes using the V-10 Touch yielding 405 mg.

Purification

The dried crude was prepared for dry loading by dissolving it in 5 mL of MeOH, adding 1.6 grams of bulk Biotage KP-C18-HS media, and evaporating on the V-10 Touch in 7 minutes. The dried media was added to an empty Biotage Sfär DLV.

After column equilibration (12-gram Biotage[®] Sfär C18), the DLV was attached and a 40-75% MeOH/H₂O gradient used for purification, Figure 3.

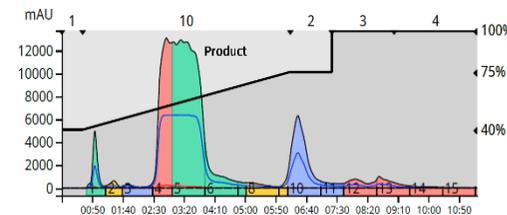


Figure 3. Crude reaction mixture reversed-phase purification using a 12-gram Biotage Sfär C18 column required only 11 minutes to purify 405 mg.

Fractions 4 and 5 (43 mL combined) were evaporated in a single vial using the V-10 Touch in 60 minutes yielding 262 mg of a pure, white solid, Figure 4.



Figure 4. Final product.

Manual synthesis workflow for these two reactions would require days¹ to accomplish, Table 1.

Table 1. Total workflow time comparison

Workflow	Total Manual	Total automated
Synthesis	13 hours	15 minutes
RxN Monitoring	10 minutes	0 minutes
Evaporate	60 minutes	15 minutes
Redissolve	1 minutes	1 minutes
Total RxN time	14.2 hours	31 minutes
Redissolve	1 minutes	1 minutes
Prep dry load	0 minutes	7 minutes
Prep HPLC/RP flash	60 minutes	11 minutes
Evaporate/lyophilize	12 hours	60 minutes
Total purification time	13 hours	1.3 hours
Total workflow time	27.2 hours	1.8 hours

Conclusions

Tools such as a microwave synthesizer, high-speed solvent evaporator, and automated flash chromatography system will reduce synthesis workflow time from days to hours thus improving productivity and completing projects more quickly.

¹ Internal communication