

Rapid, Two-Step Microwave-Assisted Synthesis of Acetaminophen



Introduction

Nearly any synthetic transformation can experience the benefits of microwave heating, which include shortened reaction times, decreased waste generation, and higher product purity. Small molecule synthesis, in particular, has seen great success with microwave irradiation;¹ from rearrangements to transition-metal catalysis, microwaves have proved an effective and efficient synthesis tool.² Hydrogenation, carbonylations, and other transformations requiring gaseous synthons can be performed readily but rely on reagents (often in excess) that generate gas in situ, which minimizes atom economy, complicates product purification, and leads to rapid increase of vessel pressure. The Gas Addition Kit for the Discover SP™ microwave (**Figure 1**), however, enables the safe, simple, and direct use of gaseous reagents with microwave irradiation.

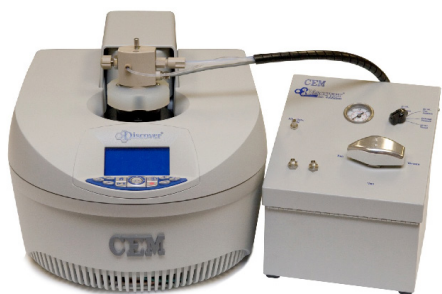


Figure 1: CEM Discover SP microwave with Gas Addition Kit.

To demonstrate the ease of microwave-assisted synthesis with gaseous reagent addition, a two-step synthesis of acetaminophen, a common pain medication, from 4-nitrophenol was developed (**Figure 2**). Using the Gas Addition Kit, hydrogenation of 4-nitrophenol was performed, and upon subsequent acetylation of the resulting 4-aminophenol, acetaminophen was afforded.

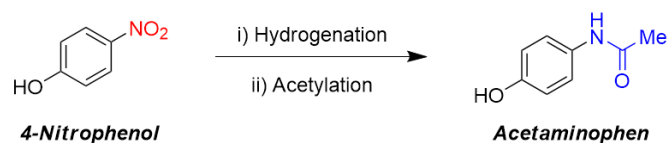


Figure 2: Synthesis of acetaminophen from 4-nitrophenol.

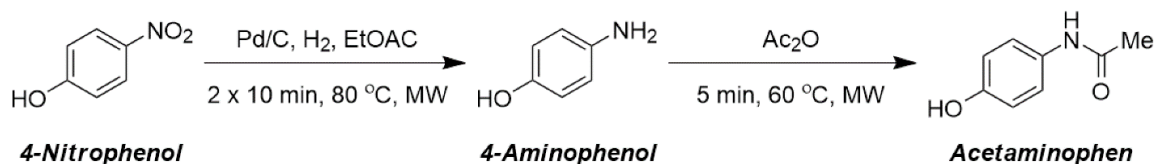
Materials and Methods

Reagents

Acetic anhydride, ethyl acetate, hexanes, 4-nitrophenol, and palladium on carbon (10 wt. %) were obtained from Sigma Aldrich (St. Louis, MO).

Procedure⁵

An oven-dried (180 °C) 10-mL vessel, equipped with stir bar, was charged with 4-nitrophenol (140 mg, 1.0 mmol, 1.0 equiv.), palladium on carbon (10 wt. %, 10 mg, 0.01 mmol, 1.0 mol %), and ethyl acetate (2.0 mL). Then, the vessel was placed in the Discover SP microwave cavity and fitted with the Gas Addition



Kit's attenuator cover assembly. The vessel was purged three times with H₂ (5 bar), pressurized to 5 bar and the solution heated to 80 °C at 150 W. After 10 min, the vessel was recharged with H₂ (5 bar), and heated to 80 °C for an additional 10 min. Upon cooling to room temperature, the solution was decanted into a new 10 mL vessel, equipped with stir bar, washing with ethyl acetate (1.0 mL).

Upon solution transfer, the vessel was charged with acetic anhydride (0.19 mL, 2.0 mmol, 2.0 equiv.) and sealed with a Teflon-lined silicon cap. The vessel was then placed in the Discover SP microwave cavity, where the solution was heated to 60 °C at 100 W for 5 min. Upon cooling to room temperature, the solution was loaded directly on a silica gel column, eluted with ethyl acetate/hexanes (2:1), and concentrated by rotary evaporation.

Results

Acetaminophen was produced as a white solid in 63% yield (95 mg, 0.63 mmol).

Conclusion

Acetaminophen was successfully synthesized using the Discover SP microwave reactor with Gas Addition Kit via a two-step hydrogenation/acetylation synthesis. First, the Pd-catalyzed, microwave-assisted reduction of 4-nitrophenol was

performed via H₂ gas addition to yield 4-aminophenol. Then, with acetic anhydride, the resulting free amine was acylated under microwave irradiation to yield acetaminophen, which was isolated in 63% yield after a simple purification step.

The entire synthesis, from the initial hydrogenation of 4-nitrophenol to the final isolation of acetaminophen, was completed in under 90 minutes, a 70% time-savings when compared to conventional hydrogenations of nitroarenes alone.⁴ Additionally, the Discover SP with Gas Addition Kit provides a safe and simple method for addition of gaseous reagents, avoiding hazardous H₂ balloons associated with conventional synthesis, and proving an effective tool for expedient, effective, and safe chemical synthesis.

References

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