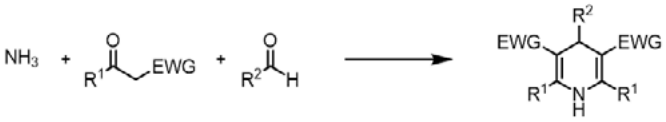
Reaction Optimization Using a Microwave Autosampler

Introduction

Upon discovery of a novel chemical transformation, the time-consuming and often-tedious process of reaction optimization begins (with substrate screening to follow). Though microscale reactions may be performed in parallel using a heating block, some reaction parameters cannot be adjusted easily in this format, consuming precious time for manually-performed, sequential reactions. The Autosampler 12 and 48 (developed in conjunction with the CEM Discover® 2.0 microwave reactor), however, provides researchers a more efficient means to optimize and screen their chemistry.



Scheme 1: The Hantzsch dihydropyridine synthesis.

To demonstrate the improved simplicity and efficiency offered by the Autosampler, a general microwave-assisted Hantzsch dihydropyridine synthesis (**Scheme 1**) was optimized and then applied in the synthesis of a small chemical library. In the Hantzsch dihydropyridine synthesis, ammonia, an aldehyde, and (most often) a β-keto ester undergo a series of condensations to afford a 1,4-dihydropyridine compound. Though frequently isolated, the dihydropyridine compound can spontaneously oxidize to the corresponding substituted pyridine.

Materials and Methods

Reagents

4-Anisaldehyde, aq. ammonium hydroxide (28%), benzaldehyde, 5,5-dimethyl-1,3-cyclohexanedione, ethanol, ethyl acetate, ethyl acetoacetate, 2-furaldehyde, hexanes, and 2-pyridinecarboxaldehyde were obtained from Sigma Aldrich (St. Louis, MO).

Procedure

Reaction Setup
A 10-mL vessel, equipped with stir bar, was charged with aldehyde (8.0 mmol, 1.0 equiv), 28% aq. ammonium hydroxide (1.0 mL, 8.0 mmol, 1.0 equiv.), and β-keto ester (16.0 mmol, 2.0 equiv.). Then, the vial was sealed with a Teflon-lined silicone cap and placed in the Autosampler queue rack. This procedure was repeated for each experiment prior to starting a queue of syntheses.

Method Programming
One-step Dynamic methods were programmed for the optimization and scope studies of the Hantzsch dihydropyridine synthesis. The reaction mixture was heated to a specified temperature for an indicated time period. (Additional Dynamic method parameters included: Maximum Pressure = 300 psi, Maximum Power = 300 W, PowerMax = Off, and Stirring = High.) A Dynamic method was created for each experiment and assigned to each preassembled reaction vessel position prior to starting a queue of syntheses.

Product Analysis
Upon cooling, the reaction solution was analyzed via thin-layer chromatography (30% EtOAc in hexanes). Crude product purity was determined by GC-MS.

Results

To start, general conditions from a microwave-assisted, literature-established[1] Hantzsch dihydropyridine synthesis were tested with ethyl acetoacetate and benzaldehyde. These "Fixed-Power" conditions produced erratic results, including inconsistent heating profiles, poor conversion to product, and elevated internal vessel pressure (215 – 260 psi) (**Table 1**, **entries 1 and 2**). From this point "Dynamic" methods were employed, maintaining steady heating profiles and reaction temperatures for each run.

To lower internal vessel pressure, lower reaction temperatures were surveyed (**Table 1**, **entries 3–5**). After 5 min at 170 °C, 68% conversion to product was observed, though high levels of unidentified byproducts were produced (**Table 1**, **entry 3**). Lowering reaction temperature to 150 °C yielded 83% conversion to product with minimal byproduct formation (**Table 1**, **entry 4**). Further dropping the reaction temperature to 130 °C dramatically lowered product conversion (**Table 1**, **entry 5**). From this point, a reaction temperature of 150 °C was deemed most suitable.

Extending the reaction time to 10 min at 150 °C had no effect on reaction outcome (**Table 1**, **entry 6**); 83% conversion to product with minimal side-product formation was observed after both 5 and 10 min reaction times. As expected, decreased conversion to product was observed with reduced reaction time (**Table 1**, **entry 7**). From this point a reaction time of 5 min was deemed most suitable.

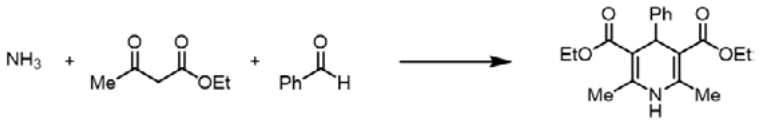


Table 1. Optimization of reaction temperature and time for the microwave-assisted Hantzsch dihydropyridine synthesis.

Entry	Temperature (°C)	Time (mm:ss)	Conversion (%)
1[a]	198	1:40	---
2[a]	188	1:40	---
3	170	5:00	68
4	150	5:00	83
5	130	5:00	53
6	150	10:00	83
7	150	3:00	70
8[b]	150	5:00	73
9[c]	150	5:00	59

[a]*Method Programming: A one-step Fixed Power method was programmed to mimic literature precedence. Method parameters included: Power = 45 W, Maximum Temperature = 250 °C, Maximum Pressure = 300 psi, PowerMax = Off, and Stirring = High.*
[b]*Ethanol (2.0 mL) added during reaction setup.*
[c]*Additional aq. NH_3 (1.0 mL) added during reaction setup.*

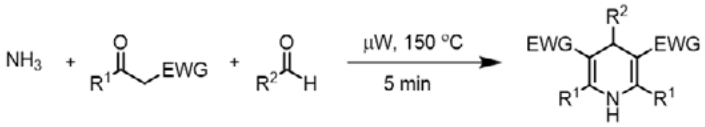


Table 2. Substrate scope for the microwave-assisted Hantzsch dihydropyridine synthesis.

Entry	β-Keto Ester	Aldehyde	Conversion (%)
1	Ethyl Acetoacetate	Benzaldehyde	83
2[a]	Ethyl Acetoacetate	4-Anisaldehyde	68
3	Ethyl Acetoacetate	2-Furaldehyde0	86
4	Ethyl Acetoacetate	2-pyridinecarboxaldehyde	60
5	5,5-Dimethyl-1,3-cyclohexanedione	Benzaldehyde	99

[a]*Reaction Time = 10 min*

In an attempt to further increase product yield, ethanol was investigated as a solvent; product conversion, however, suffered a 10% decrease (**Table 1**, **entry 8**). Furthermore, addition of an extra equivalent of aq. ammonium hydroxide was tested, but also met with a sizable decrease in product yield (**Table 1**, **entry 9**). Upon conclusion of these studies, a neat reaction at 150 °C for 5 min was deemed best suited for library synthesis. The nine condition-screening reactions were completed hands-free in under 2 hours.

Upon determination of optimal reaction conditions, the Hantzsch dihydropyridine synthesis was performed with a selection of electronically and sterically varied substrates. 4-Anisaldehyde, 2-furaldehyde, and 2-pyridinecarboxaldehyde (with ethyl acetoacetate) successfully underwent conversion to product in 68%, 86%, and 60% yield, respectively (**Table 2**, **entries 2–4**). Notably, when switching the β-keto ester to 5,5-dimethyl-1,3-cyclohexanedione, the transformation underwent quantitative conversion to product (**Table 2**, **entry 5**). The 4 substrate-screening reactions were completed hands-free in under 1 hour.

Conclusions

The Autosampler 12 and 48 enable a simple and efficient approach to reaction optimization and substrate scope investigation. In this study, a general microwave-assisted Hantzsch dihydropyridine synthesis was optimized and applied to varying substrates. First, a queue of 9 optimization reactions was run, revealing that heating at 150 °C for 5 min yielded the best synthesis results. Then, a queue of 4 varying β-keto ester and aldehyde combinations were subjected to these optimal conditions, successfully affording the product dihydropyridine products.

The Autosampler takes the efficiency and convenience of the Discover 2.0 microwave reactor one-step further; up to 48 reaction combinations can be prepared, queued, and run in a single session, making this instrument ideal for method development, combinatorial chemistry, and reaction optimization.

References

(1) Torchy, S.; Cordonnier, G.; Barbry, D.; Vanden Eynde, J. J. “Hydrogen Transfer from Hantzsch 1,4-Dihydropyridines to Carbon-Carbon Double Bonds under Microwave Irradiation.” *Molecules*. **2002**, *7,* 528–533.

United States (Headquarters)
800-726-3331
704-821-7015
info@cem.com

France
33 (01) 69 35 57 80
info.fr@cem.com

Germany, Austria, Switzerland
(49) 2842-9644-0
info@cem.de

Ireland
+353 (0) 1 885 1752
info.ireland@cem.com

Italy
(39) 35-896224
info.srl@cem.com

Japan
+81-3-5793-8542
info@cemjapan.co.jp

United Kingdom
(44) 1280-822873
info.uk@cem.com

www.cem.com