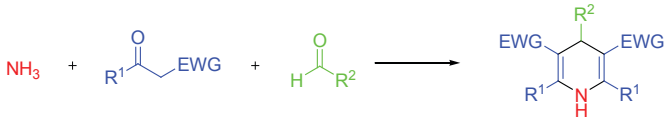
Reaction Optimization Using a Microwave Autosampler

Introduction

After identifying a novel reaction, the time consuming and often tedious process of reaction optimization begins, followed by substrate screening. While microscale reactions can 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. To overcome this process the CEM Explorer auto-sampler was developed, allowing researchers a more efficient way to survey and improve their chemistry.

Procedure

The Hantzsch dihydropyridine synthesis (Scheme 1) is a common multicomponent reaction in which ammonia, an aldehyde, and (most often) a β-keto ester undergo a series of condensations in a single flask. The resultant 1,4-dihydropyridine compound is frequently isolated, however, it can spontaneously oxidize to the corresponding substituted pyridine.



Scheme 1. General scheme for the Hantzsch dihydropyridine synthesis

Beginning with 28% ammonium hydroxide solution (1.0 equiv), ethyl acetoacetate (2.0 equiv), and benzaldehyde (1.0 equiv), the reaction was performed according to literature, general microwave conditions[1]. In our hands, the method produced erratic results (Table 1; entries 1 and 2) of inconsistent temperatures and poor conversions to product (significant starting material remained and only minor product was formed in both entries as visualized by TLC [30% EtOAc/Hex]). Since the initial reactions resulted in an elevated pressure (214-260 psi), lower temperatures were surveyed (entries 3-5). A decrease in the isolated yield of desired product was noted with higher temperature, corresponding to an increase in unidentified byproducts. Performing the reaction at 150 °C resulted in an 83% isolated yield. At lower temperatures, a significant amount of starting materials remained while the product yield dropped dramatically. A longer reaction time at 150 °C did not result in additional product formation, while incomplete conversion was seen with shorter reaction times (entries 6 and 7, respectively). The use of ethanol as a solvent (entry 8) or excess ammonia (entry 9) did not improve the amount of isolated product, so previous conditions were used (150 °C, 5 minutes). After a rapid optimization, the product was furnished in an 83% isolated yield (entry 4). While this series of reactions was performed without automation, it is easy to adapt a reaction plan of nine entries to the Explorer platform, saving time and energy.

Table 1. Optimization of microwave assisted Hantzsch dihydropyridine synthesis

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

[a] Isolated yield crude product [b] Reaction conditions: Fixed Power 45 W; 250 °C safe temperature; 300 psi; total time 100 s [c] Hold time

Once optimal conditions were determined (Standard Method; 150 °C; 5 min hold time), varied electronic and steric substrates were selected. To perform a small library synthesis, four 10-mL microwave reaction vials were prepared by adding the correct amounts of the specified reagents (Table 2; entries 2-5), and a stir bar to each vessel. All vials were capped and placed in an Explorer rack, then programmed with the optimized method.

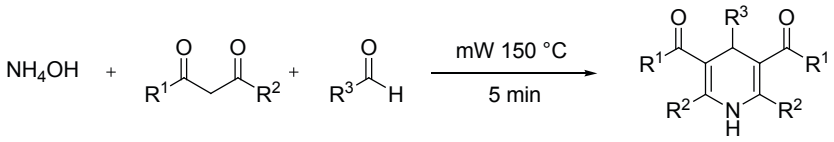
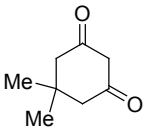


Table 2. Substrate scope of neat, microwave assisted Hanzsch dihydropyridine synthesis

Entry	R^1	R^2	R^3	Yield [%][a]
1	OEt	Me	Ph	83
2			Ph	99
3	OEt	Me	*p*-$MeOC_6H_4$	68[b]
4	OEt	Me	2-furyl	86
5	OEt	Me	2-pyridyl	60

[a] Isolated yield crude product [b] Reaction required 10 minutes

Varied 1,4-dihydropydirines were synthesized in moderate to good yields in a "hands-free" fashion, using the Explorer auto-sampler to run this small library of compounds in under an hour. Using the CEM Explorer 96, up to ninety-six combinations of starting materials can be prepared and screened in one session, making this instrument ideal for methodology, combinatorial chemistry, and reaction optimization.

[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):
CEM Corporation
PO Box 200
Matthews, NC 28106
800-726-3331
704-821-7015
Fax: 704-821-7894
info@cem.com
cem.com

France:
CEM µWave S.A.S.
Immeuble Ariane
Domaine Technologique de Saclay
4, rue Rene' Razel, 91892 ORSAY Cedex
33 (01) 69 35 57 80
Fax: 33 (01) 60 19 64 91
info.fr@cem.com

Germany, Austria, Switzerland:
CEM GmbH
Carl-Friedrich-Gauss-Str.9,
47475 Kamp-Lintfort
(49) 2842-9644-0
Fax: (49) 2842-9644-11
info@cem.de

Ireland:
CEM Technology (Ireland) Ltd.
Sky Business Centre,
9a Plato Business Park,
Damastown, Dublin 15
+353 (0) 1 885 1752
Fax: +353 (0) 1 885 1601
info.ireland@cem.com

Italy:
CEM S.R.L.
Via Dell' Artigianato, 6/8
24055 Cologno al Serio (Bg)
(39) 35-896224
Fax: (39) 35-891661
info.srl@cem.com

Japan:
CEM Japan K.K.
2-18-10 Takanawa, Minato-ku, Tokyo
108-0074
+81-3-5793-8542
Fax: +81-3-5793-8543
info@cemjapan.co.jp

United Kingdom:
CEM Microwave Technology Ltd.
2 Middle Slade, Buckingham Industrial
Estate, Buckingham MK181WA
(44) 1280-822873
Fax: (44) 1280-822873
info.uk@cem.com