



CHEMICAL SYNTHESIS

Synthesis of Phenanthridine - Increasing Reaction Yields using Microwave Irradiation

Microwave irradiation (MWI) has been used extensively in organic synthesis.¹ It is perhaps best known for its ability to speed up chemical reactions and increase product yields. This is a particularly interesting phenomenon when MWI achieves these increases while under the same conditions (same temperature, time, and pressure) as the conventional heating method.² Microwave heating differs from conventional heating methods in that it heats from the inside out, rather than the outside in, as with thermal methods. Thus, MWI directly activates the precursor molecules as dielectric energy is transferred to any polar or ionic species much faster than conventional heating methods. This rapid energy exchange leads to faster rates and often higher yields with greater purity.

The CEM Discover[®], Figure 1, was employed in the synthesis of phenanthridine derivatives via a [2+2+2] cyclotrimerization between a diyne and alkyne by Professor Alexander Deiters and co-workers at North Carolina State University.³ Phenanthridine moieties are found in many biologically active molecules and have applications as anticancer and antibacterial agents or as commercial nucleic acid stains. The Discover was chosen for this application due to its ability to perform both open vessel (atmospheric pressure) and sealed vessel reactions. The open vessel option allows for scale up possibilities, use of standard round bottom flasks (up to 125 mL), and direct access to the sample during the reaction.⁴

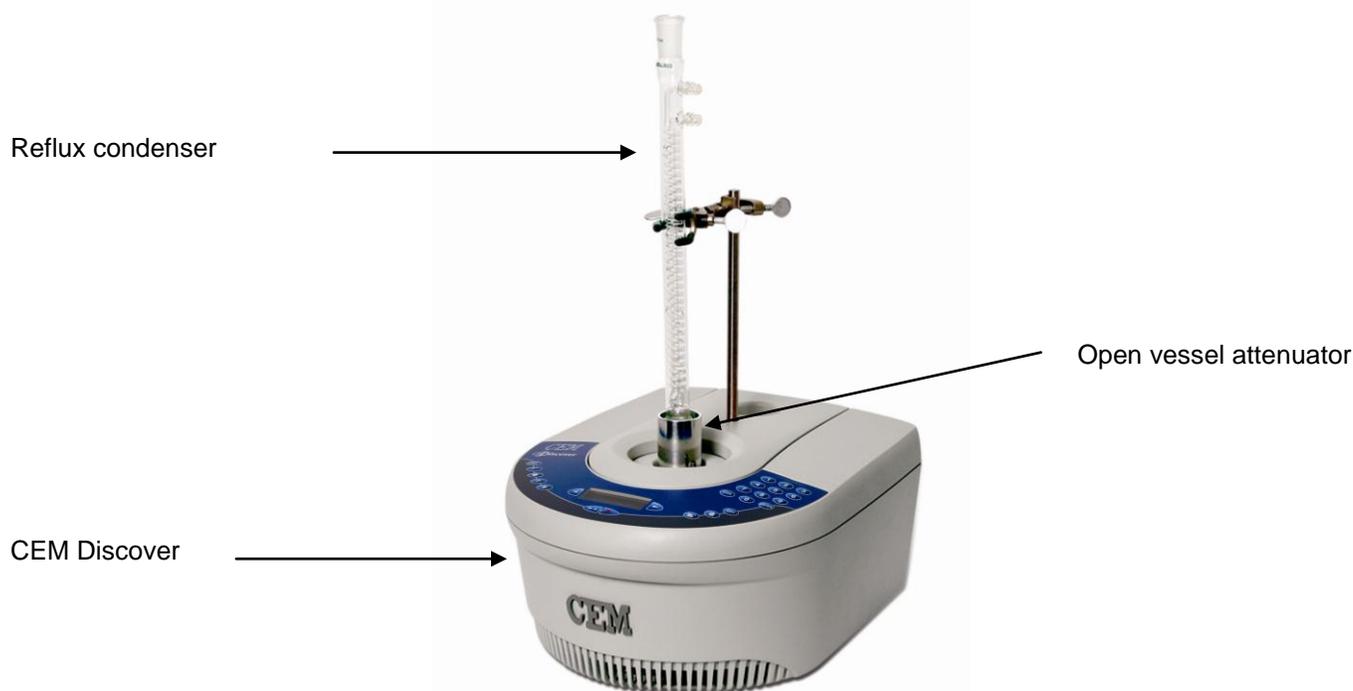
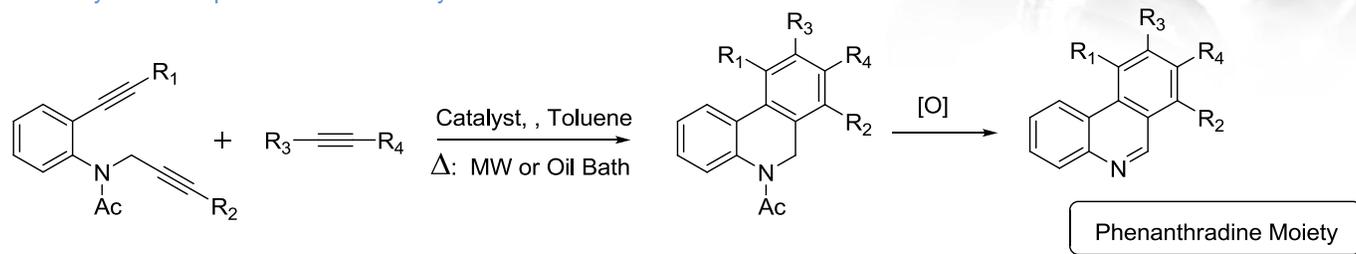


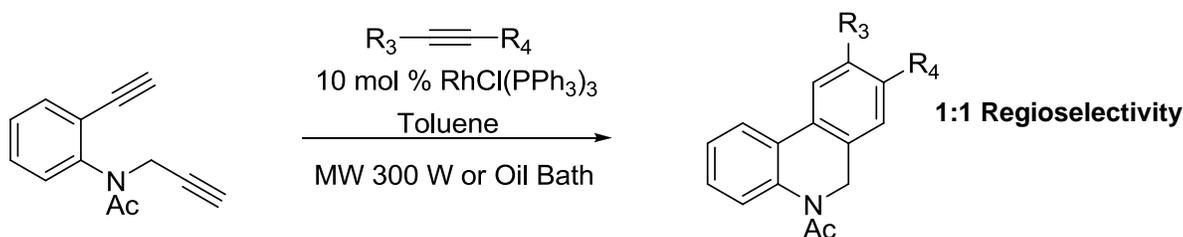
Figure 1. CEM Discover microwave in open vessel format

Scheme 1 outlines the general synthetic route to phenanthridines utilizing the above methodology. The cyclotrimerization proceeded under thermal conditions; however, MWI led to substantially enhanced yields in this step. Rh, Ni, Co, and Ru organometallic catalysts were surveyed under varying reaction conditions and concentrations until the optimal conditions were found. Oxidation after the cyclotrimerization with ceric ammonium nitrate gave the appropriate phenanthridine moiety.

Scheme 1. Synthesis of phenanthridine moiety



Terminal diynes ($R_1, R_2 = H$) were reacted with the mono- and di-substituted alkynes shown in Table 1. A catalyst screen revealed that Wilkinson's catalyst (10 mol%) delivered the highest yields. The reactions were conducted in a Discover microwave or an oil bath at an internal temperature of 130 °C. Reactions 7 – 9 were conducted in open vessel (commonly referred to as microwave reactions at reflux) at 110 °C. The synthesis of phenanthridine derivatives with mono-substituted alkynes proceeded smoothly with MWI as shown in entries 1 and 3. Yields of 91 % and 87 % were achieved after 10 min, while conventional heating obtained only a 34 % yield after 10 min. The oil bath temperature was held at 150 °C to ensure that the internal temperature of the conventional reaction was 130 °C, consistent with the MW reaction.



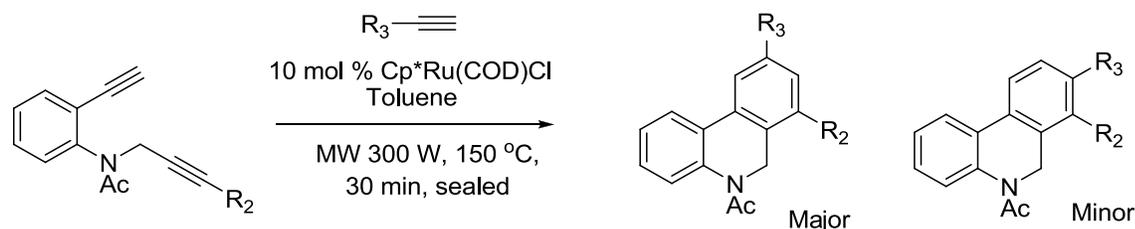
Ex	R ₃	R ₄	Yield (%)	Heat	Temp (°C)	Time	Vessel
1	Bu	H	91	MW	130	10 min	sealed
2	Bu	H	34	Oil Bath ^a	130	10 min	sealed
3	Ph	H	87	MW	130	10 min	sealed
4	Et	Et	30	MW	130	60 min	sealed
5	CH ₂ OCH ₃	CH ₂ OCH ₃	33	MW	130	60 min	sealed
6	CH ₂ OTBS	CH ₂ OTBS	34	MW	130	60 min	sealed
7	Et	Et	64	MW	110	60 min	open
8	CH ₂ OCH ₃	CH ₂ OCH ₃	56	MW	110	60 min	open
9	CH ₂ OTBS	CH ₂ OTBS	65	MW	110	60 min	open

Table 1. Synthesis of phenanthridine with mono- and di-substituted alkynes with terminal diyne

^a Oil bath temperature of 150 °C

Symmetrical di-substituted alkynes led to diminished yields, as the lower reactivity of these alkynes caused the formation of diyne dimers and trimers instead of desired product formation. Professor Deiters and co-workers alleviated this problem by running the reactions in an open vessel format. Alkynes were slowly added (via syringe pump) to the diyne-toluene-catalyst mixture while at 110 °C. The resultant yields were essentially doubled (entries 7 – 9) when compared to the sealed vessel reactions (entries 4 – 6).

Regio-control was accomplished by switching to a bulkier catalyst and increasing the steric effects of the R_2 and R_3 substituents as shown in Table 2. Increased size of R_2 improved the regioselectivity substantially, but decreased the yield (compare entry 1 to 5 and entry 4 to 7) even with a higher reaction temperature. Increased bulk of R_3 only decreased the yield; it did not affect the regioselectivity. For example, increasing the bulk of R_3 from Bu to *t*-BuOTBS decreased the yield from 91 to 78 %, while maintaining the same regio-control of 4:1. The yields were dramatically decreased when conventional heating was used, as shown in entries 2 and 6. The reaction in entry 6 did not occur under conventional heating methods.



Ex	R_2	R_3	Yield (%)	Regio	Heat
1	Me	Bu	91	4:1	MW
2	Me	Bu	31	4:1	Oil Bath ^a
3	Me	CH ₂ NHBoc	55	4:1	MW
4	Me	(CH ₂) ₃ OTBS	78	4:1	MW
5	TMS	Bu	85	95:5	MW
6	TMS	Bu	-	-	Oil Bath ^a
7	TMS	(CH ₂) ₃ OTBS	49	95:5	MW

Table 2. Regio-controlled synthesis of functionalized phenanthridine

^a Oil bath temperature of 165 °C

Professor Deiters and his co-workers developed a synthetic route to functionalized phenanthridines via a [2+2+2] cycloaddition. In several cases, MWI dramatically increased the isolated yield of the cyclotrimerization step when compared to conventional heating methods. The flexibility of being able to perform a reaction in either an open or sealed vessel format gave Prof. Deiters and his co-workers the ability to add all reagents at the start of the reaction and take advantage of a high temperature/high pressure environment or add reagents during the reaction, reducing byproduct formation.

References

- 1) For reviews, see Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*. Wiley-VCH, Weinheim, 2005.; Appukkuttan, P.; Van der Eycken, E. *Eur. J. Org. Chem.* **2008**, 1133 – 1155.; Kappe, C. O. *Chem. Soc. Rev.* **2008**, 37, 1127 – 1139.
- 2) Hull, K. L.; Anani W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, 128, 7134 – 7135. Wunderlich, S.; Knochel, P. *Org. Lett.* **2008**, 10, 4075 – 4077, Thanh, G. V.; Loupy, A. *Tetrahedron Lett.* **2003**, 44, 9091 – 9094.
- 3) Sripada, L.; Teske, J. A.; Deiters, A. *Org. Biomol. Chem.* **2008**, 6, 263 – 265. DOI: [10.1039/b716519f](https://doi.org/10.1039/b716519f)
- 4) For more information, see <http://www.cem.com/discover-sp.html>