

Automated, Microwave Assisted Alkene Synthesis via Wittig Reaction: Unattended Library Synthesis on Chemspeed SWAVE Synthesizer

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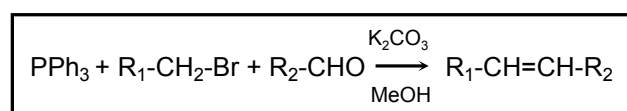
General

The Wittig reaction is an efficient method for alkene synthesis, which can be completed up to ten times faster via microwave irradiation compared to conventional heating.

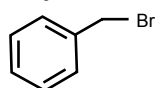
Objective

- Fully unattended, automated synthesis via Wittig reaction in 24 vials on the SWAVE.
- Compare the reactivity of different alkyl halides and aldehydes.
- Assess the existence of a “cooling while heating (cwh) effect”.

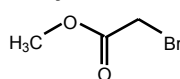
Reaction sketch



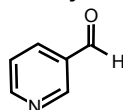
Alkyl halide 1



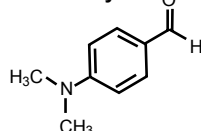
Alkyl halide 2



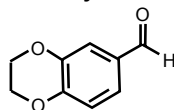
Aldehyde 1



Aldehyde 2



Aldehyde 3



Experimental Set-Up

- 3 aldehydes x 2 alkyl halides 6 compounds
- Cooling while heating on / off 12 samples
- Each sample duplicated 24 samples
- Automated sequential workflow:
 - Precise* dispensing of solid and liquid reagents
 - Cap, crimp, transport vial to microwave
 - Heat for 5 min at 150°C with magnetic stirring
 - Prepare next reaction mixture while heating
 - Transport vial back from microwave to rack and transport next vial to microwave
 - Decap all vials at the end of the application

*Examples:

	Target amount	Actual dosing range
Aldehyde 2	89.5 mg	89.7 - 91.0 mg
PPh ₃	393.4 mg	393.1 - 394.6 mg



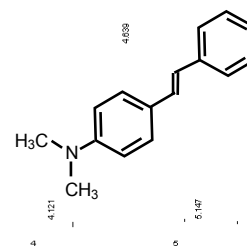
Chemspeed SWAVE synthesizer

Results

- All samples were analysed by LC/MS and yields determined by the internal standard method.
- The average yield (%) of every two replicates is reported in the following table.

	Alk. hal. 1 cwh off	Alk. hal. 2 cwh off	Alk. hal. 1 cwh on	Alk. hal. 2 cwh on
Aldehyde 1	63	86	61	84
Aldehyde 2	60	72	63	68
Aldehyde 3	51	63	57	61

Yield of each replicate:
59% and 61% (cwh off)
62% and 64% (cwh on)



- Bromoacetate (alk. hal. 2) is more active than benzyl bromide (alk. hal. 1): the nucleophilic substitution of Br⁻ by PPh₃ is indeed facilitated by the α-carbonyl group.
- Lower yields are obtained with Aldehyde 3 compared to the other aldehydes, which can be explained by -I and -M effects.
- Cooling while heating doesn't have any significant effect.

Conclusion

Microwave assisted synthesis of 24 samples via Wittig reaction was successfully automated and performed in 4 hours using only 1/16th of the vial capacity of the SWAVE.

Results are in accordance with literature and theory [1].

References

- [1] www.biotagepathfinder.com - Wittig Olefin Synthesis

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