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Interfacing Microwave Synthesis with Enabling Technologies in Drug Discovery

Doris Dallinger and C. Oliver Kappe*

Institute of Chemistry, Organic and Bioorganic Chemistry, Karl-Franzens University Graz, Heinrichstrasse 28, A-8010-Graz, Austria
email: do.dallinger@uni-graz.at *website: http://www.maos.net*

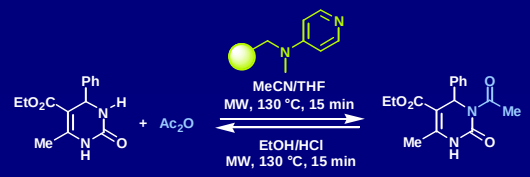
Introduction

Modern drug discovery steadily relies on high-speed organic synthesis and combinatorial chemistry techniques for the rapid generation of compound libraries. Microwave-assisted organic synthesis in combination with polymer-assisted solution phase (PASP) methods are powerful techniques that are frequently applied in both academia and industry.
Here we report on the rapid synthesis/decoration of privileged heterocyclic scaffolds, namely the dihydropyrimidine (DHPM) scaffold, by applying microwave heating in conjunction with PASP approaches. The use of resin-bound catalysts, reagents and scavengers as well as fluorous reagents in conjunction with microwave heating will be described for amidations, esterifications *via* a Mitsunobu protocol [1] and *N*-acylations [2].

[1] Desai, B.; Dallinger, D.; Kappe, C. O. *Tetrahedron* **2006**, *62*, in press.
[2] Dallinger, D.; Gorobets, N. Yu.; Kappe, C. O. *Org. Lett.* **2003**, *5*, 1205. Dallinger, D.; Gorobets, N. Yu.; Kappe, C. O. *Mol. Diversity* **2003**, *7*, 229.

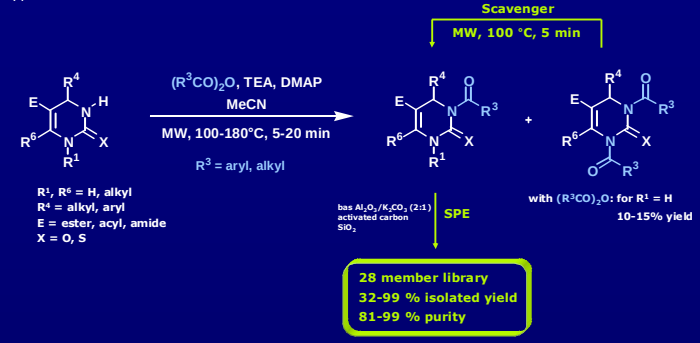
1 Polymer-supported catalysts

Acylation is used for a protection purpose at the *N*3-position of the DHPM. For ease of purification, polymer-bound DMAP is used as acylation catalyst.



2 Polymer-supported scavengers

In order to synthesize a library of *N*3-acylated DHPMs, we employed this high-throughput protocol which includes a scavenging step to remove both excess anhydride and bis-acylated byproduct.



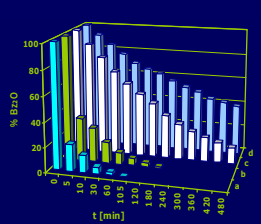
- **Several scavenging reagents A were evaluated both under rt and MW (80-100 °C) conditions (see data B and C):**

A

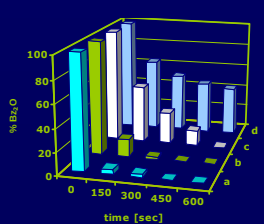
- **Polystyrene-bound ethylenediamine**
- **Functionalized silica gel ethylenediamine**
- **StratoSpheres Plugs (diethylenetriaminomethyl)**
- **SynPhase Lanterns (aminomethyl)**

Room Temperature (25 °C) ***Microwave Heating (80-100 °C)***

B

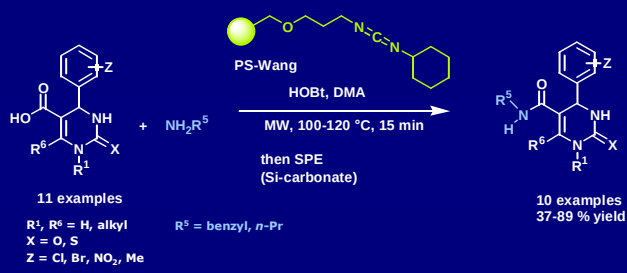


C



3 Polymer-supported reagents

Polymer-bound carbodiimide with subsequent SPE purification is used in this amidation protocol at the DHPM-C-5 position.



4 Fluorous reagents

To overcome the laborious purification of the Mitsunobu reaction, we decided on a fluorous approach using fluorous Mitsunobu reagents for the esterification at the DHPM-C-5 position.

5 Conclusion

The combination of MW heating with PASP methods is a powerful tool for organic synthesis. Not only an acceleration of reactions is possible but also the purification issue is simplified. Here we showed examples for the use of polymer-bound catalysts, scavengers and reagents as well as fluorous reagents to ease the sometimes laborious reaction work-up.

Acknowledgements

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