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MICROWAVE-ASSISTED SCAVENGING OF ELECTROPHILES UTILIZING POLYMER-SUPPORTED SEQUESTRATION REAGENTS

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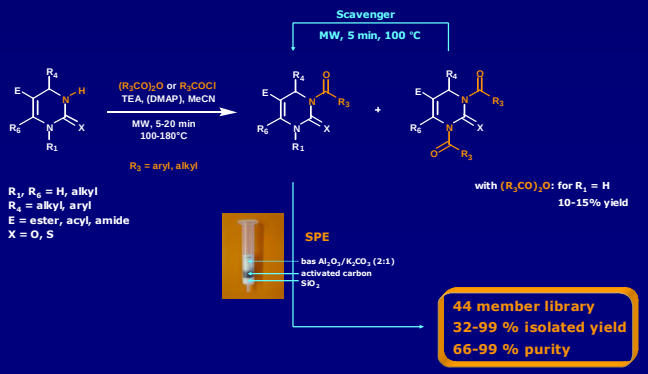
❶ Introduction

In recent work we have reported the automated generation of a diverse library of multifunctionalized dihydropyrimidines (DHPMs) utilizing a microwave-mediated solution phase Biginelli three component condensation [1]. Since most of the pharmacologically attractive DHPM derivatives are *N*3-acylated analogs [2], we became interested in developing a rapid method for accessing libraries containing this structural motif in high-throughput format. We now present the high-speed scaffold decoration of this library, introducing a new point of diversity at the *N*3 position [3]. Different scavenging techniques using polymer-supported sequestration agents are described for the purification steps in the synthesis of *N*3-acylated dihydropyrimidines.

[1] Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624
[2] Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879
[3] Dallinger, D.; Gorobets, N. Yu.; Kappe, C. O. *Org. Lett.* **2003**, *5*, 1205

❷ Microwave-Assisted *N*3-Acylation

➢ *Selective Acylations using Scavenging Techniques*



Dallinger, D.; Gorobets, N. Yu. Kappe, C. O. *Mol. Diversity* **2003**, *7*, 229

❸ Kinetic Analysis of Excess Bz_2O Scavenging using Supported Sequestration Reagents

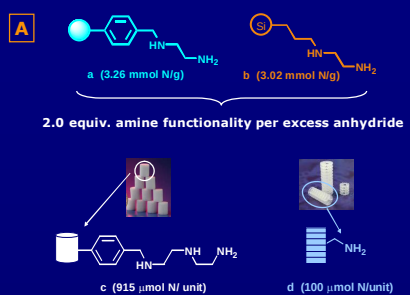
➢ In order to make this protocol amenable to a high-throughput format, several purification issues needed to be considered:
- Excess anhydride
- Acid and DMAP
- Bis-acylated Byproduct

➢ Several scavenging reagents A were evaluated both under rt and MW (80-100 °C) conditions (see data B and C on the right):
- Polystyrene-bound ethylenediamine
- Functionalized silica gel ethylenediamine
- StratoSpheres Plugs (diethylenetriaminomethyl)
- SynPhase Lanterns (aminomethyl)

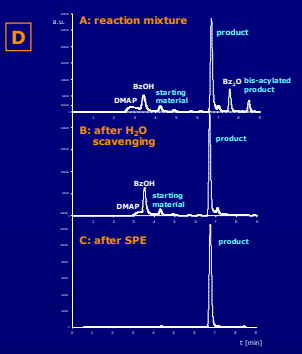
➢ Complete sequestration of Bz_2O was also achievable (MW: 10 min/ 100 °C) with Lanterns by mimicking the reaction conditions (without DHPM) but at a higher level of scavenger concentration (2.4 equiv.).

➢ Automation was possible using water as scavenger at 100 °C (removing excess anhydride and bis-acylated product) coupled with an SPE purification protocol (removing acid and DMAP, see HPLC chromatograms at 280 nm D on the right)

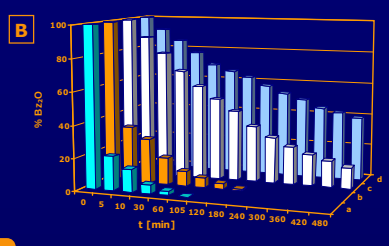
Scavengers



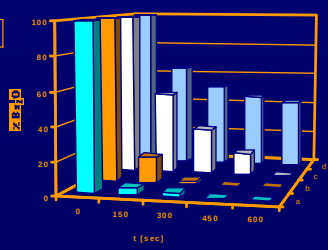
H_2O Scavenging, MW: 100°C, 5 min



Room Temperature (25 °C)



Microwave Heating (80-100 °C)



❹ Conclusion

- Kinetic investigations of 4 different polymer supported amine scavengers
- Reducing scavenging time from hours to minutes using microwave heating
- 44 member library of acylated DHPMs (80 % average yield)
- Shorter reaction times utilizing a microwave protocol
- Liquid handling possible using water as sequestration agent coupled with SPE

Acknowledgements

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