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Scaffold Decoration at the *N*3-Position of Dihydropyrimidine Derivatives by Microwave-Assisted Solution Phase Synthesis

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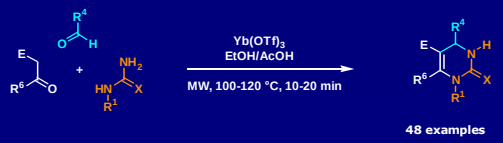
Introduction

The exploration of privileged structures like dihydropyrimidines (DHPMs) in drug discovery is a rapidly emerging theme in medicinal chemistry [1]. We now report on the high-speed scaffold decoration of a previously made DHPM library [2], introducing new points of diversity at the *N*3-position by acylation [3] and arylation respectively. In the library synthesis of *N*3-acylated DHPMs, different scavenging techniques using polymer-supported sequestration agents are described for the purification steps. In both synthesis and purification microwave flash heating was utilized, reducing reaction times from hours to minutes. In order to introduce *novel* diversity in the *N*3-position of the DHPM-scaffold, *N*3-arylations were performed by applying classical Cu (I)-catalyzed Goldberg reaction conditions under microwave heating.

[1] Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879; Kappe, C. O. *QSAR Comb. Sci.* **2003**, 22, 630. [2] Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624
[3] Dallinger, D.; Gorobets, N. Yu.; Kappe, C. O. *Mol. Diversity* **2003**, *7*, 229.

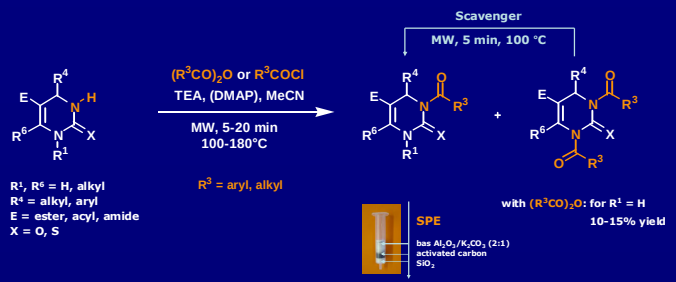
❶ Microwave-Assisted *N*3-Acylation

Library Generation via the Biginelli Reaction



48 examples

Selective Acylations using Scavenging Techniques



44 member library
32-99 % isolated yield
66-99 % purity

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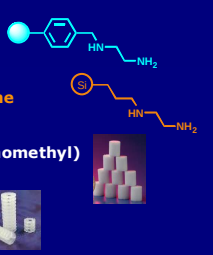
❷ Scavenging Kinetics of Excess Bz_2O

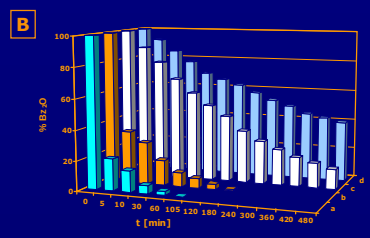
- Several scavenging reagents [A] were evaluated both under rt and MW (80-100 °C) conditions (see data [B] and [C]):

[A]
- Polystyrene-bound ethylenediamine
- Functionalized silica gel ethylenediamine
- StratoSpheres Plugs (diethylenetriaminomethyl)
- SynPhase Lanterns (aminomethyl)



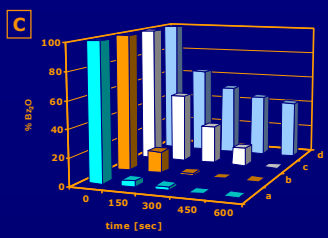
Room Temperature (25 °C)

[B]



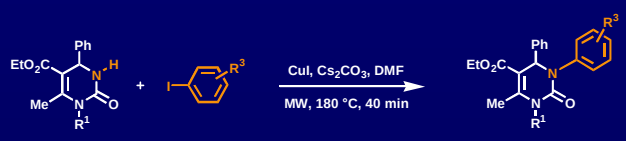
Microwave Heating (80-100 °C)

[C]



❸ *N*3-Arylation via the Goldberg Reaction

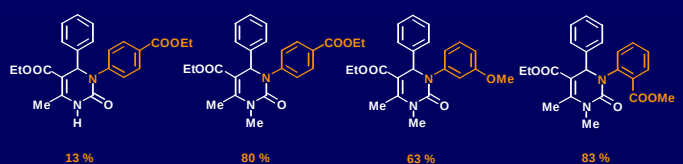
*N*3-aryl DHPMs were synthesized by applying standard Goldberg reaction conditions under microwave heating using only 5 equiv of DMF as solvent [4].



R1 = H, Me

R3 = H, 4-COOEt, 2-COOEt, 4-COMe, 4-Cl, 4-Me, 4-NO2, 3-OMe

10 examples
13-83 % yield



[4] Lange, A. et al. *Tetrahedron Lett.* **2002**, *42*, 1101

❹ Conclusion

- 44 member library of *N*3-acylated DHPMs (80 % average yield)
- Kinetic investigations of 4 different polymer supported amine scavengers
- Reducing scavenging time from hours to minutes using microwave heating
- Introduction of *novel* diversity at the *N*3-position by arylation applying the Goldberg reaction
- 10 examples of *N*3-arylated DHPMs
- Shorter reaction times utilizing a microwave protocol

Acknowledgements

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