

Fluorous Multicomponent Reactions for Making Drug-Like Molecules

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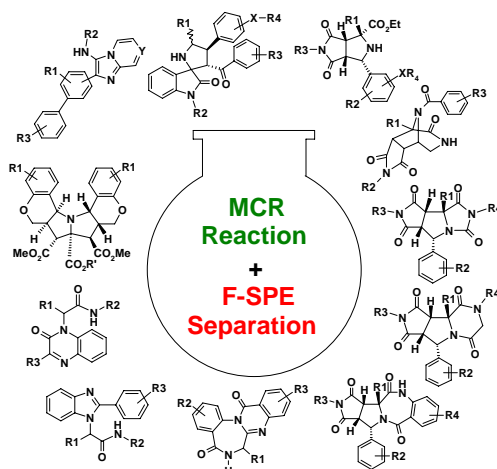
Introduction

Multicomponent reaction (MCR) is highly efficient for construction of complex molecules. Conducting post-MCR modification reactions further increases the molecular complexity and molecular diversity. In fluorous MCR (F-MCR),¹ one of the starting materials is attached to a fluorous tag and used as the limiting agent. After the MCR, the fluorous component is fished out from the reaction mixture and used for post-MCR modifications. The fluorous tag is finally removed by displacement or cyclization reactions. Fluorous solid-phase extraction (F-SPE) facilitates the separation process. Other techniques such as microwave irradiation can also be used to make the F-MCR even more efficient.

Fluorous synthesis of unique heterocyclic and natural product-like library scaffolds has been accomplished using following three general protocols:

- 1) Ugi/de-Boc/cyclization
- 2) MCR/Suzuki-type coupling
- 3) [3+2] Cycloaddition/de-tag/cyclization

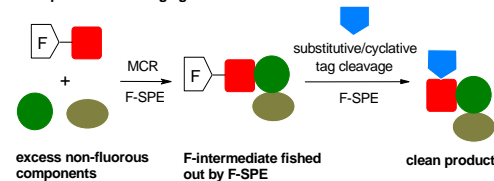
Representative Library Scaffolds



Zhang, W. *Comb. Chem. High Throughput Screening* 2007, 10, 219

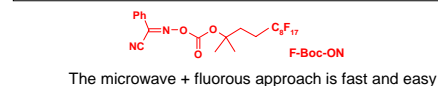
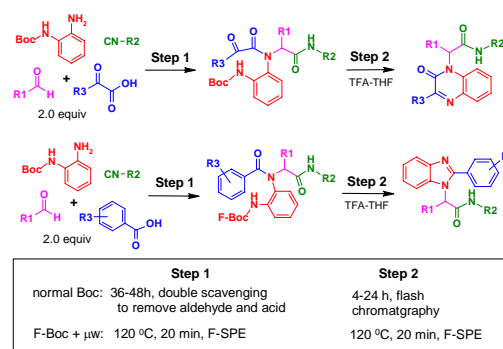
Concept of F-MCR

F-component as limiting agent

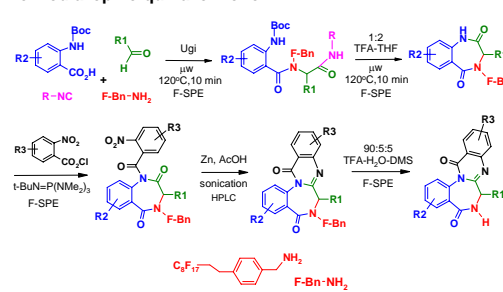


I. Ugi/De-Boc/Cyclization Protocol

Quinoxalones and benzimidazoles²



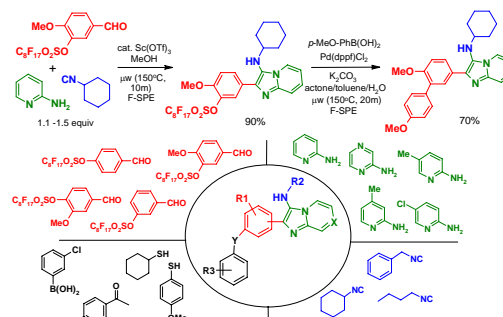
Benzodiazepine-quinazolinone³



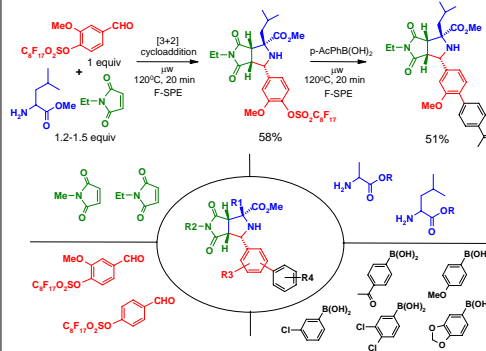
A common scaffold for many natural alkaloids such as circumdatins, benzomalvin, asperlicin, sclerotigenin.

II. MCR/Suzuki Coupling Protocol

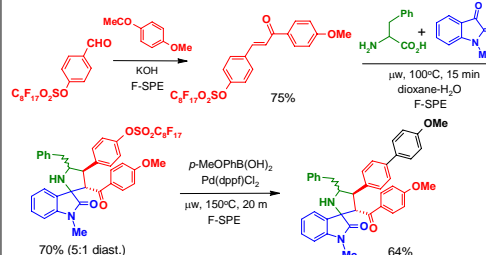
Imidazo[1,2-a]pyridines and imidazo[1,2-a]pyrazines⁴



Diaryl-substituted proline derivatives⁵



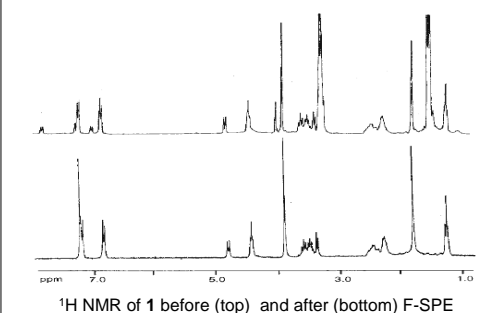
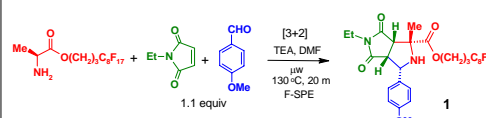
Spirocyclics



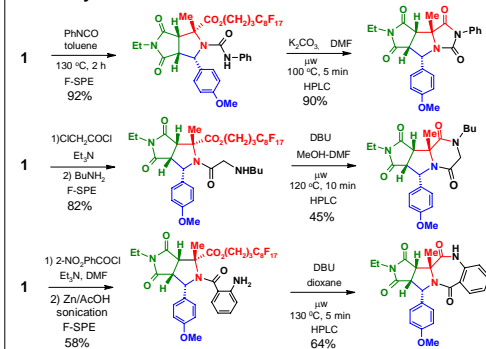
Fluorous sulfonyl tag has three functions:

- 1) Protection of the hydroxyl group
- 2) Introduction of fluorous tag for F-SPE
- 3) Activation of the hydroxyl group for cross-coupling reactions.

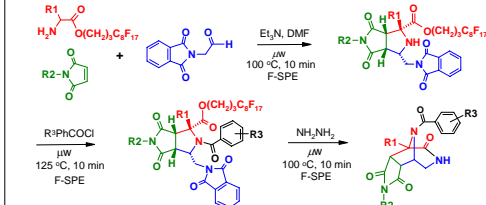
III. [3+2]Cycloaddition/De-Tag/Cyclization Protocol



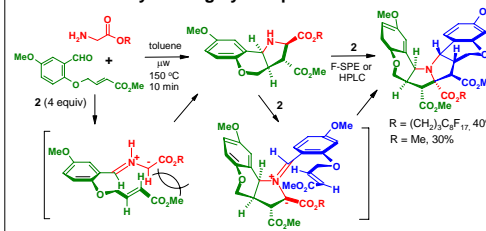
Hydantoin-, piperazinedione-, and benzodiazepine-fused heterocyclic scaffolds⁶



Bridged-tricyclic ring



A Novel hexacyclic ring by one-pot reaction⁷



Generates four new rings, six bonds, and seven diastereocenters

Conclusion

Fluorous chemistry can nicely embrace with MCR and microwave reactions to significantly improve efficiency for making drug-like molecules and exploring new chemistry.

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References:

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