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Highly efficient microwave-assisted fluorous Ugi and post-condensation reactions for benzimidazoles and quinoxalinones

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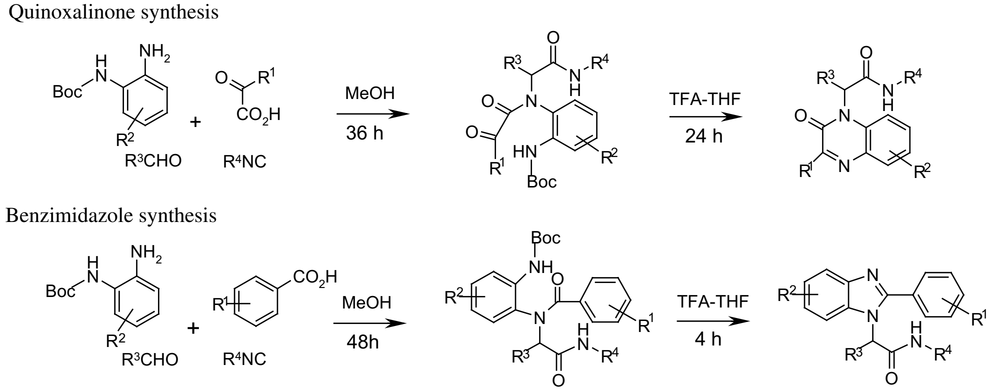
Abstract—The efficiency of an Ugi/de-Boc/cyclization strategy for construction of heterocyclic compounds has been improved through the incorporation of microwave and fluorous technologies. In the synthesis of substituted quinoxalinones and benzimidazoles, a fluorous-Boc protected diamine is employed for the Ugi reactions. Both the Ugi and the post-condensation reaction proceed rapidly under microwave irradiation and the reaction mixtures are purified by solid-phase extraction (SPE) over Fluoro*Flash*™ cartridges.

Multicomponent reactions (MCRs) have proven highly efficient in the assembly of diversified molecules.[1] The complexity of the initial products can be further increased by performing post-condensation modifications.[2] In order to access more diverse scaffolds, inputs of varying reactivity are used in the same array synthesis. To drive the underperforming inputs to completion, excess equivalents are often used leading to unreacted components, which complicate the intermediate purification for the post-condensation reaction. Recently Hulme and co-workers at Amgen reported an Ugi/de-Boc/cyclization sequence to construct heterocyclic cores of quinoxalinone and benzimidazole (Scheme 1).[3] The Ugi reactions gave good yields, but took 36–48 h to complete at room temperature. The condensation products were purified by double scavenging with immobilized tosylhydrazide and diisopropylethylamine to remove excess aldehydes and unreacted acids, respectively. Final products were generated by de-Boc/cyclization with TFA at room temperature for 4–24 h. We



Scheme 1.

Keywords: Fluorous synthesis; Microwave reaction; Multicomponent reaction; Ugi reaction; Solid-phase extraction; Quinoxalinone; Benzimidazole.
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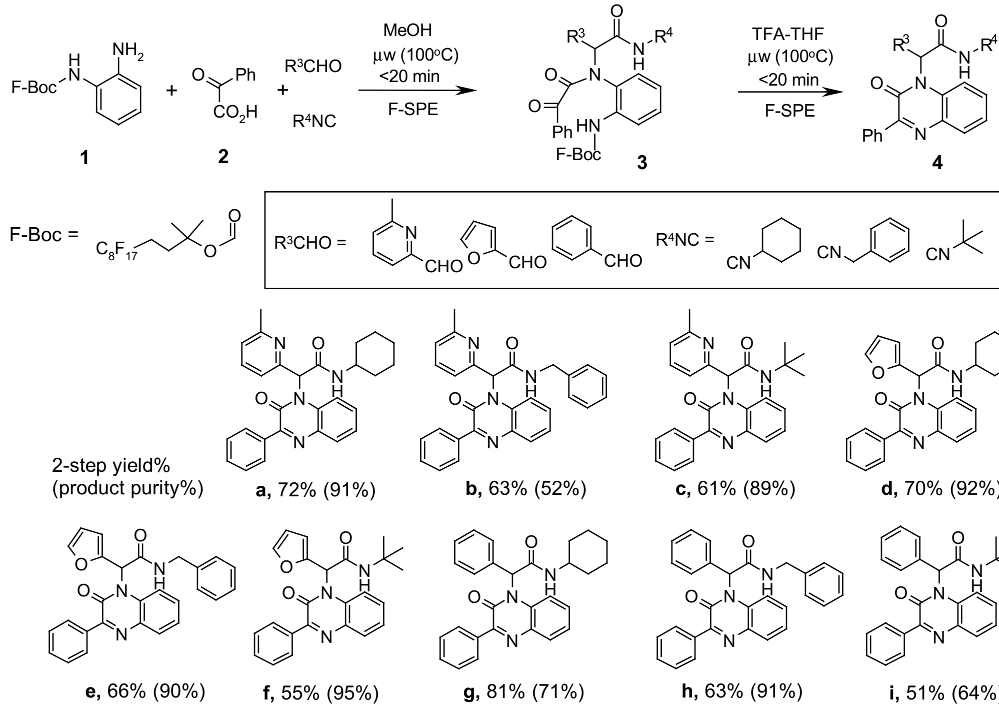
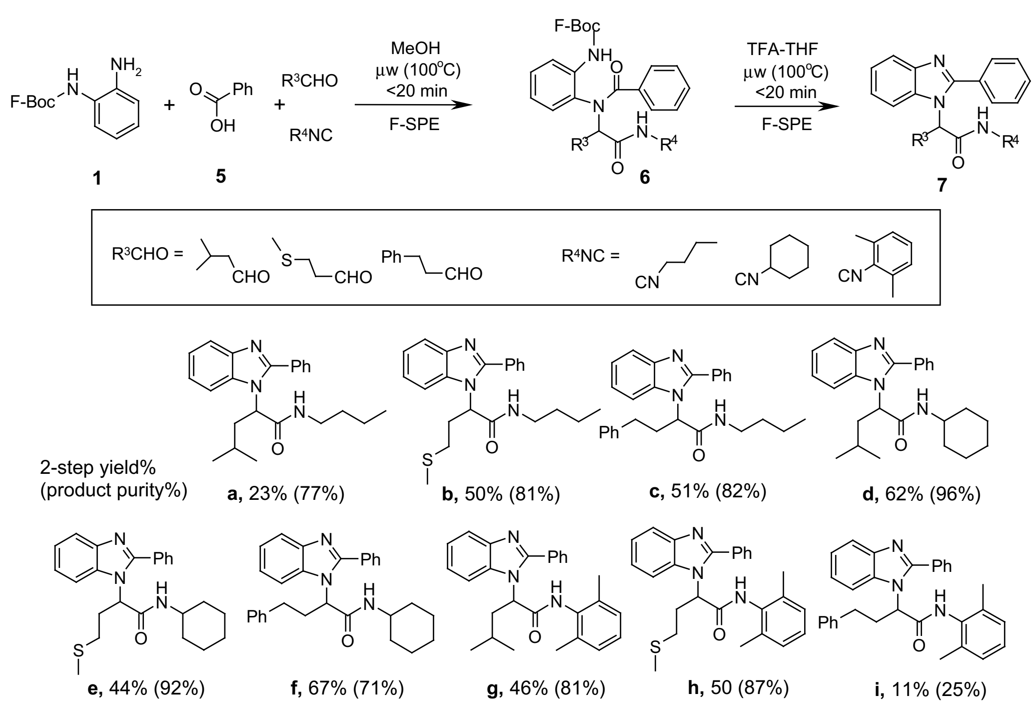


Scheme 2. Microwave-assisted fluorous Ugi/de-Boc/cyclization for quinoxalinones **4**.

report here a modified procedure that uses microwave irradiation to reduce the reaction time and uses fluorous SPE to simplify the purification of Ugi condensation products.[4,5]

Fluorous synthesis combines the characteristics of solution-phase reaction with phase-tag separation.[6] The functional group protection and substrate attachment with fluorous reagents have been employed in parallel and mixture syntheses.[7,8] Common protecting groups such as Boc,[8b] PMB,[8d] Cbz,[8f,h] and silane[8e] for solution-phase synthesis as well as Wang[8d] and Marshall[9c] resins for solid-phase synthesis now have fluorous analogs. To improve the efficiency of the Ugi/de-Boc/cyclization synthesis, we replaced the normal Boc group with the fluorous-Boc group to protect the diamine.[10]



Scheme 3. Microwave-assisted fluorous Ugi/de-Boc/cyclization for benzimidazoles **7**.

The fluorous component was used as the limiting agent in the Ugi reaction. The desired condensation products containing the F-Boc group were easily separated from the reaction mixture by fluorous SPE. Thus, a mixture of F-Boc protected diamine **1** with a slight excess amount of acid **2**, aldehyde, and isonitrile in MeOH was irradiated under microwaves at 100 °C for 10–20 min. The reaction mixture was loaded onto a Fluoro*Flash*™ cartridge for F-SPE.[11] The MeOH fraction was collected and concentrated to give the desired condensation products **3** or **6**. Compounds **3** or **6** were then treated with 50:50 TFA–THF under microwave irradiation at 100 °C for 10–20 min to give quinoxalinones **4** or benzimidazoles **7**.[12] The final products were purified by F-SPE and purities were checked by LC-MS (254 nm). The synthesis of quinoxalinones **4** is shown in Scheme 2, which has nine examples of Ugi reactions involving the reactions of *ortho*-*N*-^{F}Boc phenylene diamine **1**, phenylglyoxylic acid **2**, three different aldehydes, and three different isocyanides. Another nine examples for the synthesis of benzimidazoles **7** using diamine **1**, benzoic acid **5**, three different aldehydes, and three different isocyanides are shown in Scheme 3.

Compared to the original Ugi/de-Boc/cyclization procedures, which take 1–2 days, the fluorous/microwave approach has more favorable reaction and purification conditions: less than 20 min for each reaction and no need of the double scavenging step. This general strategy can be applied to other MCR and post-condensation reactions.

Acknowledgements

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10. *ortho*-*N*-^{F}Boc phenylene diamine **1** was prepared by the reaction of 1.2 equiv of phenylene diamine with 1.0 equiv of F-BocON (available from Fluorous Technologies, Inc. www.fluorous.com) in THF at room temperature for 2 h. The crude product was purified by F-SPE.
11. For more information on F-SPE and Fluoro*Flash*™ cartridges, please log onto: http://fluorous.com/download/an_spe.pdf.
12. General procedures for fluorous Ugi condensation reaction: A mixture of *ortho*-*N*-^{F}Boc phenylene diamine (0.1 mmol, 1 equiv), acid (1.1 equiv), aldehyde (1.5 equiv), and isonitrile (1.1 equiv) in 0.5 mL of MeOH was irradiated under microwave at 100 °C for 10–20 min (including 2 min ramp time). The concentrated reaction mixture (~0.2 mL) was loaded onto a 2-g Fluoro*Flash*™ cartridge for SPE.[11] The MeOH fraction was collected and concentrated to give the condensation product. General procedures for de-Boc/cyclization reaction: The Ugi

condensation product (0.1 mmol) was mixed with 0.2 mL of 1:1 TFA/THF and irradiated under microwave at 100 °C for 10–20 min (including 2 min ramp time). The reaction mixture was neutralized with 1.0 N aq NaOH. The concentrated organic layer (∼0.2 mL) was loaded onto a 2-g Fluoro*Flash*™ cartridge for SPE. The 80:20 MeOH/H_2O fraction was collected and concentrated to give the final product. The analytical data (^{1}H NMR and MS) of the representative compounds such as **4a** was consistent with that reported in literature.[3b]