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Combination of Microwave Reactions with Fluorous Separations in the Palladium-Catalyzed Synthesis of Aryl Sulfides

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Abstract

Coupling of microwave reactions with fluorous separations can dramatically increase the efficiency of high-speed synthesis. Described in this paper is a fluorous synthesis of aryl sulfides by palladium-catalyzed cross-coupling of aryl perfluoroalkylsulfonates ($C_8F_{17}O_2SOAr$) with thiols (RSH) under microwave irradiation. Fluorous solid-phase extractions (F-SPE) are employed for the purification of reaction mixtures. No fluorous solvents are involved in reaction and separation processes. The fluorous synthesis is further extended to the multi-step synthesis of substituted hydantoin and amide scaffolds.

Keywords

microwave reaction; fluorous synthesis; solid phase extraction; cross coupling; perfluoroalkylsulfonates; palladium catalysts; aryl sulfides

Microwave irradiation has been recognized as an alternative to conventional heating in organic synthesis.[1] With the enhanced efficiency, microwave reactions can finish in minutes and frequently with improvements in reaction selectivity and yield. Combination of microwave technology with tag-based separations[2] such as solid-phase[3] and fluorous synthesis provides a good opportunity to further improve the productivity in high-speed synthesis.

Fluorous synthesis is a complementary type of liquid-phase synthesis that employs perfluoroalkyl groups as a “phase tag” to facilitate the separation.[4] Fluorous tags have good thermostability and solution-phase reactivity, which are free from some constraints of polymer supports under microwave irradiation. Larhed, Hallberg and Curran first introduced fluorous strategy into microwave synthesis.[5] In their work of the Stille-coupling of organohalides with $PhSn(CH_2CH_2C_{10}F_{21})_3$, a “heavy fluorous” tag containing three $C_{10}F_{21}$ groups was employed to ensure the partition of the fluorous species during the fluorous liquid-liquid extraction. We recently explored the Suzuki coupling of fluorous aryl perfluorosulfonates with organoboronic acids[6] and found that perfluoroalkylsulfonates ($C_8F_{17}O_2SOAr$) had similar reactivity as the aryl triflates. The C_8F_{17} chain can be utilized as a fluorous tag for the F-SPE separation.[7]

Aryl triflates, just like halides, are important species for both solution-phase and solid-phase palladium-catalyzed reactions.[1c,8] The aryl triflates can easily be prepared from a large selection of commercially available phenols. Using aryl triflates as starting materials, Zheng and coworkers reported the synthesis of aryl sulfides under thermal conditions.[9] The reaction conditions were mild ($Pd(dba)_3$, Tol-BINAP, NaO*t*-Bu or NaHMDS, toluene, 100 °C), but reactions were relatively slow (12–24 h). Herein we report two improvements to this reaction: 1) use of microwave to speed up the reaction; and 2) use of fluorous tag to simplify the separation.

Two commercially available phenols were converted to the sulfonates **1** by reacting with $C_8F_{17}SO_2F$ under a general condition (K_2CO_3, DMF, 70 °C, 8h) (Scheme 1). The resulting F-sulfonates **1a** and **1b** were each reacted with four different thiols including aryl, benzyl, hexyl, and cyclohexyl thiols under microwave irradiation. We selected a Suzuki-type coupling condition according to a literature procedure[10] using Pd(dppf)Cl_2 (0.1 equiv) as a catalyst, K_2CO_3 (2.0 equiv) as a base, and acetone/toluene/H_2O (4:4:1) as a co-solvent. The reaction temperature was in the range of 100 to 150 °C and the reaction time was between 5–10 min. To prevent the unreacted thiol from contaminating the product in MeOH/H_2O fraction, a slight excess of F-sulfonate **1** was used in the coupling reaction. After an aqueous workup, the reaction mixture was loaded on the Fluoro*Flash*™ cartridge and purified by SPE. The product was collected at the 80:20 MeOH-H_2O elution, while unreacted F-sulfonate and the cleaved tag were retained on the cartridge. The fluorous species were washed out from the cartridge with a more fluorophilic solvent such as MeOH or acetone. The F-SPE cartridge can be conditioned and reused. Scheme 2 shows the structures and yields of aryl sulfides. The purities of the product after the F-SPE were greater than 90% by ^{1}H NMR analysis. Figure 1 shows a typical ^{1}H NMR spectrum of the product after the F-SPE separation.[11]

The fluorous tag strategy can be better utilized in multi-step synthesis since all the intermediates bearing the fluorous tags can be purified by F-SPE.[14] The synthesis of substituted hydantoin **8** and amide **9** are two examples outlined in Scheme 3. Intermediate **5** was prepared by reductive amination of **1b.**[15] This compound was then reacted with an isocyanate to form substituted hydantoin **6** or with a benzoyl chloride to form amide **7**. Both **6** and **7** were purified by F-SPE. The non-fluorous compounds were collected in the 80:20 MeOH-H_2O fraction, while fluorous compounds were collected in the MeOH fraction. Similar fluorous palladium-catalyzed conditions described above were employed to convert F-sulfonates **6** and **7** to the corresponding sulfides **8** and **9,** respectively. The substituted hydantoin **10** and amide **11** possesses four points of diversity which are useful scaffolds for parallel and combinatorial synthesis (Scheme 4).

In summary, we have developed a new path to aryl sulfides by palladium-catalyzed cross coupling of fluorous sulfonates with thiols under microwave irradiation. The combination of microwave and fluorous technologies speeds up both the reaction and the purification processes.

Acknowledgements

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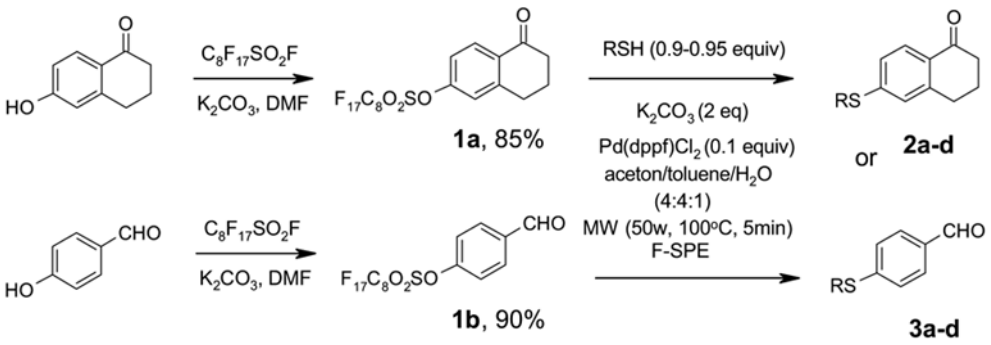
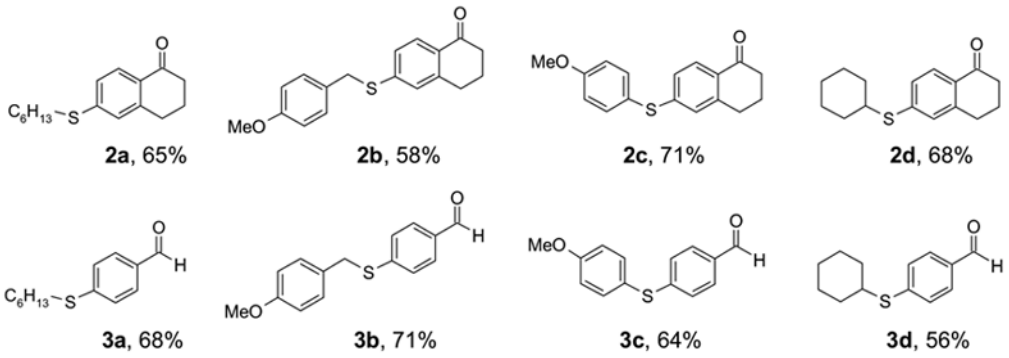
11. General procedures for fluorous palladium-catalyzed cross-coupling reactions under microwave irradiation. A septum-sealed microwave tube charged with F-sulfonate **1** (1.0 mmol), a thiol (0.95 mmol), Pd(pddf)Cl_2 (0.1 mmol), K_2CO_3 (2.0 mmol) in 0.5 mL of a co-solvent acetone-toluene-H_2O (4:4:1) was irradiated in a monomode microwave cavity (50w, 100–150 °C, 5–10 min). The reaction mixture was washed with 1 mL of H_2O. The organic layer was loaded onto a 5 g Fluoro*Flash*™ cartridge,[12] eluted with 10 mL of 80:20 MeOH-H_2O.[13] The collected fraction was concentrated to give an aryl sulfide. The fluorous species were washed out from the cartridge with 15–20 mL of MeOH. The cartridge can be conditioned for reuse.
12. Fluoro*Flash*™ SPE cartridges are available from FTI: www.fluorous.com
13. For more information on F-SPE, please log on to: http://www.fluorous.com/download/fspe.pdf
14. For fluorous tags in multi-step synthesis, see a) Zhang W, Lu Y. Fluorous Synthesis of Hydantoins and Thiohydantoins. Org Lett 2003;5:2555–2558. [PubMed: 12841779] b) Zhang W. Fluorous Synthesis of Disubstituted Pyrimidines. Org Lett 2003;5:1011–1014. [PubMed: 12659561]
15. Because the reaction mixture was relatively simple, intermediate **5** was purified by normal phase SPE instead of F-SPE.

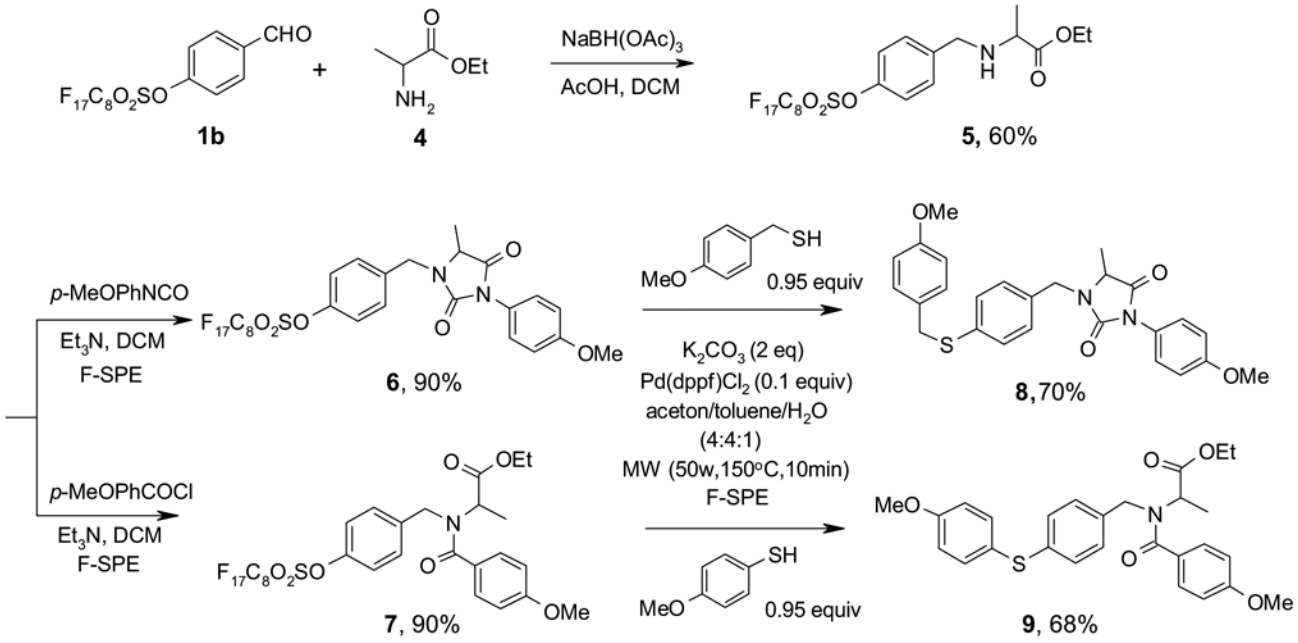
Figure 1.
^{1}H NMR ($CDCl_3$) spectrum of **2b** after F-SPE



Scheme 1.
Microwave –assisted fluorous synthesis of aryl sulfides **2** and **3**.

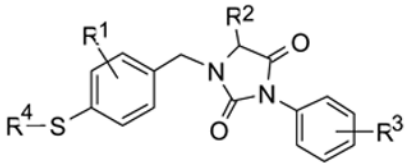


Scheme 2.
Structures and yields of aryl sulfides



Scheme 3.

F-Sulfonate-tagged multi-step synthesis of substituted hydantoin **8** and amide **9**



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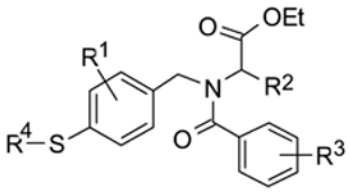

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Scheme 4.