

A traceless perfluorooctylsulfonyl tag for deoxygenation of phenols under microwave irradiation

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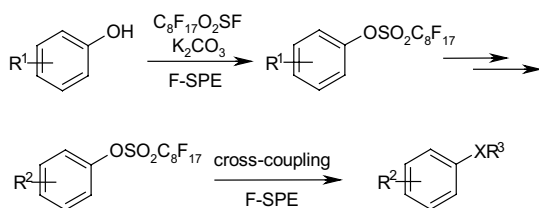
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Abstract—The perfluorooctylsulfonyl group is introduced as a traceless tag for solution-phase palladium-catalyzed deoxygenation reactions. The synthetic efficiency is improved by microwave irradiation for reaction and fluorous solid-phase extraction for separation. Further application of this traceless tag for multistep synthesis of substituted hydantoin and pyrimidine is also described.

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The development and application of fluorous protecting groups and tags as alternatives to solid-phase linkers have become an active research area.^{1–3} We recently reported the use of perfluorooctylsulfonates as fluorous tag for palladium-catalyzed cross-coupling reactions to form aryl C–S and C–C bonds.⁴ Commercially available phenols are converted to perfluorooctylsulfonates by reacting with perfluorooctylsulfonyl fluoride. The fluorous tagged intermediates are taken through several reaction steps to transform the R¹ to R² and finally detagged by microwave-assisted cross-coupling reactions (Scheme 1). The perfluorooctylsulfonyl group protects the hydroxy group during the multistep reac-



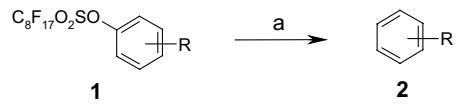
Scheme 1.

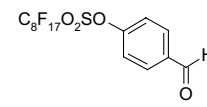
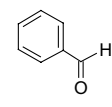
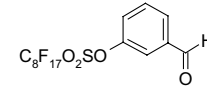
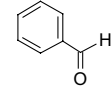
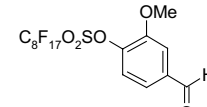
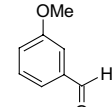
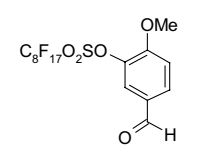
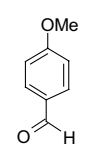
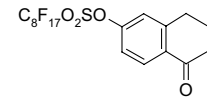
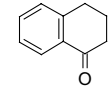
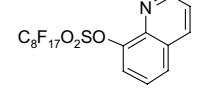
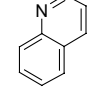
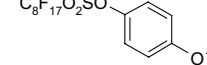
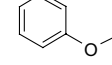
Keywords: Fluorous synthesis; Traceless tag; Perfluorooctylsulfonyl-fluoride; Solid-phase extraction; Microwave.

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tions and activates the hydroxy group for the cross-coupling reaction. This group also serves as a ‘phase tag’ for fluorous solid-phase extraction (F-SPE).⁵ We report here a new application of the perfluorooctylsulfonyl group as a traceless tag for the deoxygenation of phenols.

Traceless linkers have important applications in preparing molecules without residual functionality after solid-phase organic synthesis.^{6,7} This kind of linkers includes aryl silanes, alkyl selenides, alkyl sulfides sulfones and aryl triazenes.⁸ The Holmes group recently developed a perfluorosulfonyl fluoride resin (PS-NRC(O)CH₂CF₂CF₂OCF₂CF₂O₂SOF) as a traceless linker.⁹ This resin has a loading of 0.31–0.36 mmol/g and requires five steps to be synthesized. The perfluorooctylsulfonyl fluoride (C₈F₁₇SO₂F) we selected is commercially available, has a much higher ‘loading’ (2.5 mmol/g), and priced modestly (~\$0.60/g).¹⁰ More importantly, because of fluorous sulfonyl-tagged substrates are ‘light fluorous’ molecules, they usually have good solubility in common organic solvents and normal reactivity under general solution-phase conditions. The fluorous tag also has good thermal stability and low microwave absorption, it allows the use of microwave irradiation in the palladium-catalyzed deoxygenation reaction¹¹ to accelerate the reaction process. In a typical deoxygenation reaction,¹² fluorous sulfonate **1** was reacted with 5.0 equiv of formic acid using Pd(dppf)Cl₂ (dppf = 1,1’-bis(diphenylphosphino)ferrocene) as a catalyst, K₂CO₃ as a base, and 4:4:1 MePhH/Me₂CO/H₂O as a co-solvent. The mixture in a sealed microwave tube

Table 1. Deoxygenation of fluorosulfonates


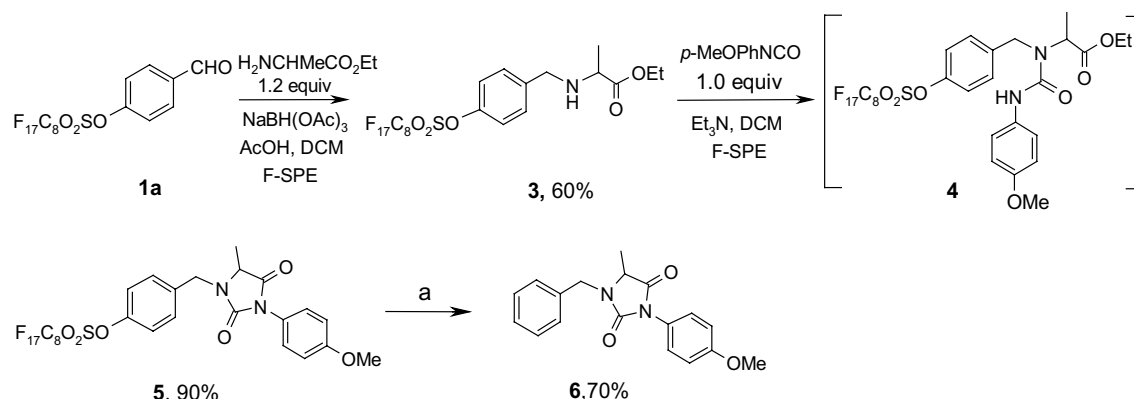
Entry	F-sulfonate 1	Product 2	Yield (%)
a			87
b			82
c			92
d			85
e			90
f			79
g			82

was irradiated in a single-mode cavity at 100 °C for 20 min. The reaction mixture was then loaded onto a FluoroFlash™ cartridge for F-SPE separation. The desired product **2** was eluted with 80:20 MeOH/H₂O, whereas the cleaved fluorosulfonate tag was retained on the cartridge. Reaction substrates listed in Table 1 include fluorosulfonates with aldehyde, ketone, benzyloxy, and heterocyclic substitutions. The yields were between 80% and 90% and purities were greater than 90% by LC-MS.

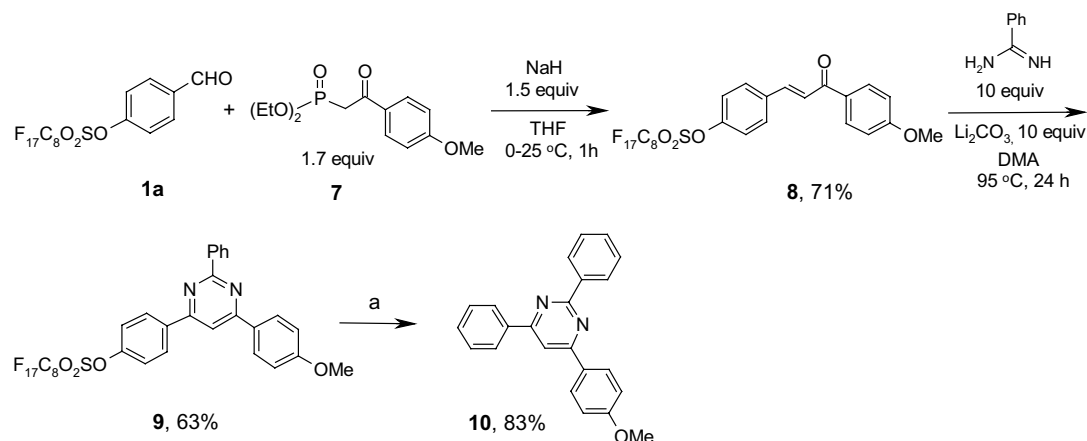
The utility of fluorosulfonate tags has been demonstrated in the synthesis of trisubstituted hydantoin **6** (Scheme 2). Fluorosulfonate **1a** was reacted with an amino ester under general reductive amination conditions to give **3** in 60% yield. Amine **3** was then treated with an isocyanate in the presence of Et₃N to form urea intermediate **4**, which spontaneously cyclized to generate the hydantoin ring of **5**. Microwave-assisted deoxygenation of fluorosulfonate **5** afforded trisubstituted hydantoin **6** in 70% yield. In this multistep synthesis, intermediates **3** and **5** and final product **6** were purified by F-SPE. The purity of product **6** was 90%.

The application of fluorosulfonate tag has been further demonstrated in the synthesis of triaryl-substituted pyrimidine **10** (Scheme 3).¹³ Fluorosulfonate **1a** was condensed with phosphonate **7** to form α,β -unsaturated ketone **8**. No significant amount of detached byproduct was observed under the basic condition. The cycloaddition of **8** with a benzamidine followed by the tag cleavage afforded the desired product **10** in 83% yield. Because of the relatively low solubility of intermediate **8** and **9** in organic solvents, these two fluorosulfonate compounds were purified by crystallization instead of F-SPE. Compound **8** was purified by crystallization with hexanes/Et₂O, whereas compound **9** was precipitated out by addition of water to the reaction mixture. Purification of fluorosulfonate intermediates by a simple, nonfluorinated method demonstrates the technical compatibility of fluorosulfonate synthesis.

In summary, the perfluorooctylsulfonyl fluoride has been introduced as a new traceless tag. Compared to its resin



Scheme 2. Reagents and conditions: (a) HCO₂H (5 equiv), Pd(dppf)Cl₂ (5 mol%), K₂CO₃ (2 equiv), MePhH/Me₂CO/H₂O (4/4/1), mw (150 w, 100 °C, 20 min), F-SPE.



Scheme 3. Reagents and conditions: (a) HCO₂H (29 equiv), Pd(dppf)Cl₂ (13 mol%), K₂CO₃ (3.3 equiv), MePhH/Me₂CO/H₂O (4/4/1), mw (150 w, 100 °C, 20 min).

analogues, this solution-phase fluororous tag is cheaper and readily available. It can be used in conjunction with F-SPE and conventional separation methods as well as microwave technology.

Acknowledgements

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